



**Finanziato dall'Unione Europea**  
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**UNIVERSITÀ  
DEGLI STUDI  
DI BRESCIA**

*DIPARTIMENTO DI INGEGNERIA MECCANICA E INDUSTRIALE*

*DOTTORATO DI RICERCA IN INGEGNERIA MECCANICA E INDUSTRIALE*

SSD: IINF-04/A

CICLO  
XXXVIII

# **ADVANCED CONTROL STRATEGIES FOR TOTAL INTRAVENOUS ANESTHESIA**

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# Abstract

La somministrazione dell'anestesia generale rappresenta un compito clinico complesso e critico dal punto di vista della sicurezza, che richiede una regolazione continua degli effetti farmacologici in presenza di significativa variabilità inter-paziente, dinamiche farmacologiche ritardate, incertezza nelle misurazioni e disturbi legati all'intervento chirurgico. Nonostante l'ampia diffusione dei sistemi di infusione a target controllato, la gestione dell'anestesia dipende ancora in larga misura dall'esperienza del clinico e da interventi manuali. I sistemi di controllo in anello chiuso rappresentano una soluzione promettente per migliorare l'accuratezza della regolazione, ridurre il carico di lavoro e aumentare la sicurezza del paziente. Tuttavia, la loro adozione clinica è ancora limitata da problematiche legate alla robustezza, alla fedeltà dei modelli, all'affidabilità dei segnali e all'integrazione nel flusso operativo dell'anestesista.

La presente tesi analizza strategie di controllo per la medicina personalizzata, con particolare attenzione al controllo in anello chiuso della profondità ipnotica (Depth-of-Hypnosis, DoH) durante anestesia totalmente endovenosa. L'attività di ricerca integra modellazione farmacocinetica-farmacodinamica, progettazione dei controllori, analisi di robustezza e validazione sperimentale, con l'obiettivo di affrontare i principali limiti degli approcci attualmente disponibili. Il controllo classico Proporzionale-Integrale-Derivativo (PID) viene analizzato come soluzione di riferimento, mentre diverse estensioni vengono investigate al fine di valutarne i potenziali benefici in termini di robustezza e prestazioni.

I controllori PID a ordine frazionario (FOPID) vengono studiati per analizzare il compromesso tra la maggiore flessibilità di taratura e la complessità implementativa. Inoltre, strutture predittive di ordine superiore, tra cui i controllori Proporzionale-Integrale-Derivativo e Accelerativo (PIDA) e i controllori frazionari PIDD<sup>2α</sup>, vengono analizzate per quantificare i miglioramenti prestazionali ottenibili nella regolazione della profondità ipnotica in presenza di incertezza e rumore di misura. L'impatto della scelta del modello farmacologico viene esaminato in dettaglio, evidenziando l'influenza delle dinamiche dipendenti dall'età e dell'eterogeneità della popolazione sul comportamento del sistema in anello chiuso.

Vengono inoltre proposte strategie di personalizzazione basate su informazioni demografiche del paziente che, attraverso estese campagne di simulazione, mostrano una riduzione della dispersione prestazionale e un miglioramento della robustezza, in particolare nei pazienti anziani. Per affrontare il problema dell'inaffidabilità delle misure di DoH, viene sviluppata un'architettura di soft-sensor model-based che integra filtraggio di Kalman e indicatori di

qualità del segnale, dimostrando migliori prestazioni di regolazione in condizioni di degrado delle misure. Sono inoltre introdotte architetture di controllo “clinician-in-the-loop”, che consentono al medico di modulare in maniera controllata il bilanciamento farmacologico e l’aggressività del controllore senza compromettere stabilità e sicurezza del sistema.

Le soluzioni selezionate vengono validate mediante scenari di simulazione realistici ed esperimenti clinici in vivo, dimostrando un’efficace regolazione della profondità ipnotica, un comportamento emodinamico stabile e un funzionamento sicuro del sistema. Nel complesso, questa tesi sostiene una visione collaborativa dell’anestesia in anello chiuso, nella quale algoritmi di controllo, modelli fisiologici ed esperienza clinica coesistono sinergicamente, contribuendo con metodologie e principi progettuali orientati a un’automazione della somministrazione anestetica sicura, interpretabile e personalizzata.

# Abstract

The administration of general anesthesia is a complex and safety-critical clinical task that requires continuous regulation of pharmacological effects in the presence of significant patient variability, delayed drug dynamics, measurement uncertainty, and surgical disturbances. Despite the widespread use of target-controlled infusion systems, anesthesia management remains largely dependent on clinician experience and manual intervention. Closed-loop control offers a promising pathway to improve regulation accuracy, reduce workload, and enhance patient safety. However, its clinical adoption is still limited by challenges related to robustness, model fidelity, signal reliability, and integration within the anesthesiologist's workflow.

This thesis investigates control system strategies for personalized medicine, with a specific focus on closed-loop control of Depth-of-Hypnosis (DoH) during total intravenous anesthesia. The research combines pharmacokinetic–pharmacodynamic modeling, controller design, robustness analysis, and experimental validation to address key limitations of existing approaches. Classical Proportional–Integral–Derivative (PID) control is analyzed as a baseline solution, while several extensions are investigated to evaluate potential robustness and performance benefits.

Fractional-order PID (FOPID) controllers are studied to assess the trade-off between increased tuning flexibility and implementation complexity. In addition, higher-order predictive structures, including Proportional–Integral–Derivative–Acceleration (PIDA) and fractional PIDD<sup>2 $\alpha$</sup>  controllers, are analyzed to quantify the achievable performance improvements in Depth-of-Hypnosis regulation under uncertainty and measurement noise. The impact of pharmacological model selection is examined in detail, highlighting the influence of age-dependent dynamics and population heterogeneity on closed-loop behavior. Personalization strategies based on patient demographic information are proposed and shown, through extensive simulation studies, to reduce performance dispersion and improve robustness, particularly in elderly patients. To address the unreliability of DoH measurements, a model-based soft-sensor architecture integrating Kalman filtering and signal quality information is developed, demonstrating improved regulation under measurement degradation. Clinician-in-the-loop control architectures are also introduced, enabling controlled adjustment of drug balance and controller aggressiveness without compromising stability or safety.

Selected solutions are validated through realistic simulation scenarios and in vivo clinical

experiments, demonstrating effective Depth-of-Hypnosis regulation, stable hemodynamic behavior, and safe operation. Overall, this thesis supports a collaborative vision of closed-loop anesthesia in which control algorithms, physiological models, and clinical expertise coexist, contributing methodological insights and practical design principles toward the safe, interpretable, and personalized automation of anesthesia delivery.

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# Chapter 1

## Introduction

General anesthesia (Brown et al., 2010) is a fundamental medical practice that enables patients to safely undergo surgical procedures by inducing a reversible state of unconsciousness (Mashour and Pryor, 2015), analgesia (Proudfoot, 1995), and muscle relaxation (Brull et al., 2020). Despite standardized clinical protocols and decades of pharmacological research, anesthesia administration remains a complex and highly demanding task. The anesthesiologist must continuously balance multiple drugs (Bouillon, 2008), monitor delayed and noisy physiological signals, and respond promptly to surgical stimuli and patient-specific reactions. This complexity is further amplified by pronounced inter- and intra-patient variability (Sahinovic et al., 2018), nonlinear pharmacodynamics, and the absence of reliable direct measurements for some anesthetic components.

In current clinical practice, total intravenous anesthesia is commonly administered using open-loop strategies or target-controlled infusion systems (Bibian et al., 2005), which rely on pharmacokinetic–pharmacodynamic (PKPD) models to compute infusion profiles (Struys et al., 2011). While these approaches have proven effective and safe, they do not explicitly exploit feedback from the patient’s physiological response and may suffer from model mismatch, delayed drug effects, and limited adaptability. As a result, maintaining an adequate Depth-of-Hypnosis throughout the surgical procedure requires continuous manual intervention and considerable clinician workload.

Closed-loop control has emerged as a promising solution to address these limitations by automatically adjusting drug delivery based on real-time feedback signals (Ghita et al., 2020), such as the bispectral index scale (BIS) (Rosow and Manberg, 2001; Avidan et al., 2008). From a control engineering perspective, anesthesia represents a challenging regulation problem characterized by long and uncertain delays, nonlinear dynamics, strong disturbances, measurement degradation, and strict safety constraints. At the same time, any automation strategy must remain interpretable, reliable, and compatible with clinical practice, preserving the anesthesiologist’s authority and decision-making role.

Within this context, control systems for personalized medicine offer a structured framework to improve anesthesia delivery. By integrating patient-specific modeling, robust feedback control, and state estimation techniques, closed-loop anesthesia systems have the potential

to enhance regulation accuracy, reduce variability, and improve patient safety. However, their widespread adoption is still hindered by unresolved issues related to model selection, robustness across heterogeneous populations, measurement reliability, and the practical integration of automation into the clinical workflow.

In addition, while classical Proportional-Integral-Derivative controllers (Visioli, 2006) remain the most widely adopted solution due to their simplicity and transparency, their limited predictive capability may constrain performance in systems characterized by long delays and strong disturbances, such as anesthesia (Yousefi et al., 2019; Schiavo et al., 2023, 2020, 2021). This has motivated the investigation of extended control structures, including fractional-order controllers (Copot et al., 2017; Hegedus et al., 2022; Paolino et al., 2023b, 2025b) and predictive architectures (Pawlowski et al., 2023), which can offer additional degrees of freedom for shaping closed-loop dynamics while retaining an interpretable structure suitable for clinical use.

This thesis addresses these challenges by investigating control strategies for closed-loop anesthesia with a specific focus on Depth-of-Hypnosis regulation during total intravenous anesthesia. The work combines pharmacological modeling, controller design, robustness analysis, and experimental validation to contribute toward safe, interpretable, and clinically meaningful automation in anesthesia.

## 1.1 Research Purposes

The main purpose of this research is to study and develop control system strategies for closed-loop anesthesia that are robust to patient variability, grounded in clinically relevant models, and suitable for real-world implementation. Rather than proposing a single optimal controller, the thesis adopts a comprehensive and systematic approach to analyze how different design choices affect performance, robustness, and clinical usability. The specific research objectives are:

- Investigate the role of pharmacokinetic–pharmacodynamic modeling in closed-loop anesthesia control, with particular emphasis on population-based versus individualized representations and age-dependent dynamics;
- Evaluate classical PID control as a baseline solution for Depth-of-Hypnosis regulation, assessing its robustness and limitations in heterogeneous patient populations;
- Analyze fractional-order PID controllers as an extension of classical PID, quantifying their potential advantages and trade-offs in terms of performance, robustness, and implementation complexity;
- Develop personalization strategies for controller tuning based on patient demographic information, aiming to reduce performance dispersion and improve safety, especially in vulnerable populations such as elderly patients;

- Address the problem of unreliable Depth-of-Hypnosis measurements by integrating model-based estimation and signal quality information into the feedback loop;
- Design clinician-in-the-loop control architectures that allow controlled adjustment of system behavior—such as drug balance or controller aggressiveness—without compromising stability or robustness;
- Validate selected control solutions through realistic simulation studies and in vivo clinical experiments.

Through these objectives, the thesis aims to contribute both methodological insights and practical design principles for closed-loop anesthesia, supporting the broader vision of personalized medicine where automation enhances, rather than replaces, clinical expertise.

## 1.2 Outline

The remainder of the thesis is structured as follows. Chapter 2 presents the preliminary knowledge required to understand the subsequent contributions. It introduces general anesthesia from a clinical perspective, describes pharmacokinetic–pharmacodynamic modeling of anesthetic drugs, and reviews the control-theoretic tools employed throughout the thesis, including PID and fractional-order control, model predictive control, and Kalman filtering. Chapter 3 summarizes the scientific contributions of the thesis by presenting the included papers. For each article, the main objectives and key findings are outlined, highlighting their role within the overall research framework.

Chapter 4 provides a comprehensive discussion of the results, synthesizing insights across all contributions. The implications for closed-loop anesthesia and personalized medicine are analyzed, and overarching conclusions are drawn regarding robustness, model selection, measurement reliability, and clinician interaction.

The thesis concludes with the bibliography, followed by the full texts of the included papers.

# Chapter 2

## Generalities

This chapter provides an overview of the fundamental concepts required to understand the scientific contributions presented in the subsequent chapters.

General anesthesia is presented, focusing on describing its clinical procedure and the anesthesiologist workload. Particular attention is paid to open- and closed-loop anesthesia control solutions. In any control architecture, two main components can be identified: the controller and the system (or process) being controlled. In the context of anesthesia, the system corresponds to the patient undergoing surgery for medical reasons. The patient's response to drug administration is typically modeled using pharmacological frameworks that describe drug distribution and effects. Precisely, in most of the literature, the patient model is employed to tune the controller, conduct simulations, and assess control performance. With regard to the controller, the literature offers a broad range of solutions and control strategies. Although control systems are still relatively uncommon in anesthesia applications, they are widely adopted in industrial domains. Among these, the PID controller remains one of the most prevalent, owing to its simplicity, robustness, and ease of implementation. Finally, this chapter introduces the essential background underlying both modeling and control theory, which form the foundation for the discussions developed in the subsequent sections.

### 2.1 General Anesthesia

General anesthesia (Brown et al., 2010) is an essential medical practice that enables patients to safely undergo surgical procedures by suppressing pain perception and consciousness (Mashour and Pryor, 2015). Specifically, it is a pharmacologically induced and fully reversible state characterized by three primary effects, namely hypnosis, analgesia, and muscles relaxation (Brown et al., 2010). Hypnosis induces loss of consciousness and memorization, preventing undesired intra-operative awareness episodes. Analgesia suppresses pain sensation by inhibiting the physiological response to noxious stimuli. Muscles relaxation prevents involuntary muscle contraction that could interfere with the surgeons tasks. In clinical practice, anesthesia can be administered via two main approaches: in-

halation or intravenous injection (Vuyk et al., 2020). Throughout the following chapters, the term anesthesia will always refer to intravenous administration.

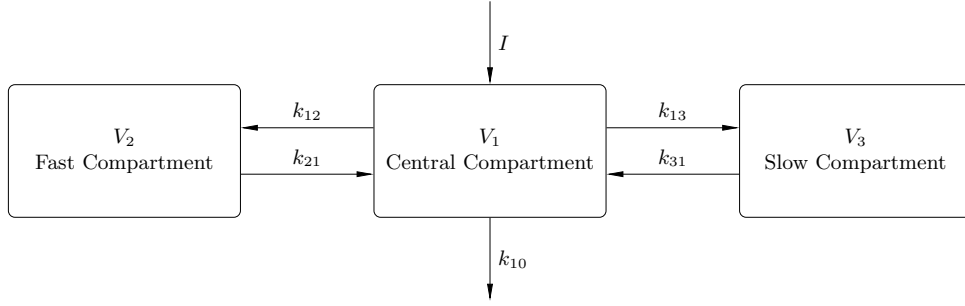
In total intravenous anesthesia, the desired Depth-of-Hypnosis is reached by the administration of multiple drugs, each responsible of one effect. Clinically, the most popular drugs are propofol (hypnotic agent) (Mashour and Pryor, 2015), remifentanyl (analgesic or opioid agent) (Proudfoot, 1995), and curare (muscles blockade) (Brull et al., 2020). Drugs co-administration needs particular attention since in the literature it is well known that the simultaneous administration of different type of drugs could increase or decrease the effect of every single drug (Bouillon, 2008; Bouillon et al., 2002). Precisely, the presence of an opioid increases the effect of the hypnotic drug and also of its side effects. Then it is clear that the anesthesiologist must guarantee an adequate regulation of each drug for the whole surgical procedure (Oberfrank et al., 2020).

From a clinical and procedural perspective, anesthesia is typically divided into three main phases according to the patient's level of sedation, that are:

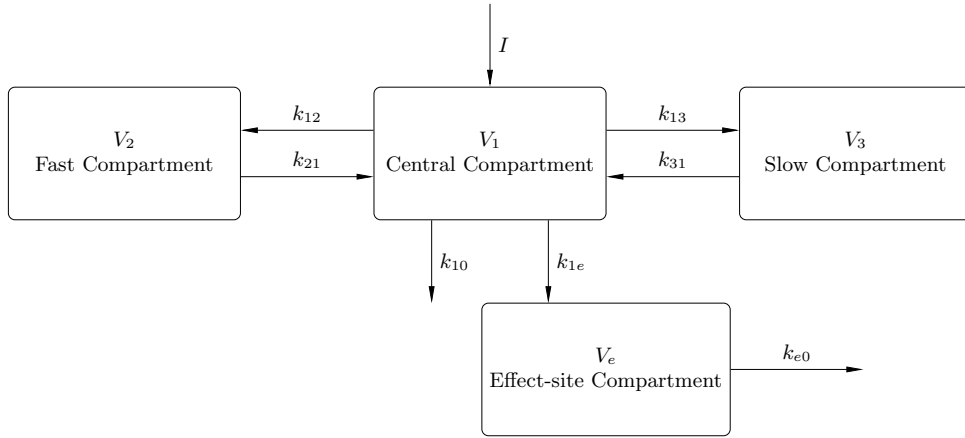
- *induction*: it is the first phase. Here, the patient's consciousness state is forced from an alert to an anesthetized one. Mechanical ventilation must be provided to the patient to guarantee correct breathing, therefore, intubation must be performed during this first phase. Usually induction lasts less than 10 minutes to minimize patient stress;
- *maintenance*: it is the longest and most demanding phase since the surgery is performed there. Precise amounts of anesthetic agents are continuously administered to maintain an adequate level of unconsciousness, while avoiding both under- and over-dose. Throughout this stage, the anesthesiologist constantly adjusts drug infusion rates based on the intensity of surgical stimuli, ensuring patient stability until the surgery is completed;
- *emergence*: it is the last phase. Once the surgery ends, all the surgical devices are turned off to facilitate the arousal procedure. Here, skin closure is performed and once the patient shows clear signs of wakefulness, regaining to breath autonomously, the mechanical ventilation is stopped.

The anesthesiologist, beside using clinical dose guidelines, checks some measurable (i.e. brain activity, heart rate, blood pressure) and non-measurable (i.e. lacrimation, spasm) physiological signs to properly adjust drug flow rate. Clearly, administering anesthesia is very challenging and the anesthesiologist's experience plays a central role in the success of the whole surgical procedure.

Among the indicator listed before, monitoring brain activity gives a quick and intuitive information of the patient's consciousness (Liu et al., 2024). The BIS (Avidan et al., 2008) is one of the most common measuring system that sense and process brain waves. Precisely, the BIS map the consciousness state of the patient into a scale that ranges from 100 to 0, where 100 correspond to a fully awake patient while 0 indicates that there is no brain



**Figure 2.1:** Three-compartment model.  $k_{ij}$  [ $\text{s}^{-1}$ ] are the inter-compartmental constants and represent the drug transfer rate from compartment  $i$  to  $j$ .



**Figure 2.2:** Four-compartment model.

activity. Anesthesia aims to settle the BIS value as close as possible to 50, but more generally, guidelines says that values within 40 to 60 are acceptable and clinically safe. Concerning analgesia, to date, there are not clinically established sensing instruments. This, together with the complexity of the whole surgical environment, pones a strong limitation for the anesthesiologist and contribute in increasing the clinician effort and workload.

In the last decade, several engineering solutions have been proposed by researchers to provide anesthesiologists with safe devices which can help them during their daily job (Bibian et al., 2005; Ghita et al., 2020). From a control engineering point of view it is possible to identify two broad groups, respectively open- and closed-loop control systems. An overview of the most relevant regulation solutions is presented in Section 2.3.

## 2.2 Pharmacological Models

When developing a clinically relevant and safe automatic anesthesia administration device, it is essential to take into account the dose-effect relationship (Kim et al., 2015). In pharmacology, this interaction is described through pharmacokinetic (PK) and pharmacodynamic (PD) models (Struys et al., 2011). Pharmacokinetics describes the relationship between the administered drug dose and its concentration in plasma (Absalom et al., 2009), while pharmacodynamics links drug plasmatic concentration with the therapeutic effect of

the drug.

As stated before, pharmacokinetics models the relationship between drug dose and drug concentration in plasma. In the literature, compartmental models are the most preferred solution to model drug behavior (Holz and Fahr, 2001). Compartmental models are intuitive empirical representations that estimate drug concentration over time in response to administration. Fig. 2.1 shows a schematic representation of a standard PK model. They are typically made up of three compartments, each corresponding to a hypothetical compartment exhibiting homogeneous properties, namely infusion point (i.e. blood), rapid distribution (i.e. muscles), slow distribution (i.e. fat). The central compartment, that is the blood, represents the volume in which the drug is injected. Initially, the drug tends to spread through the compartment with faster dynamics, such as muscle tissue. Once the concentration in the fast compartment becomes higher than the one in the central compartment, the drug will change its course and it will start flowing in the slow compartment. In the end, drug will be eliminated through metabolism ( $k_{10}$ ) only when the central concentration level is below both fast and slow compartment concentration.

Pharmacodynamics describes the relationship between the drug concentration in the central compartment (the blood) and its physiological effect. This relationship is modeled through an additional fictitious volume known as effect-site compartment. Therefore, the overall four-compartment PKPD model corresponds to that shown in Fig. 2.2. From a control systems engineering perspective, the effect-site compartment provides an estimate of the lag time elapsed from the drug administration to the onset of the clinical effect. Here, the drug transfer rate between the central compartment and the effect-site is called  $k_{1e}$ , while, the elimination from the effect-site compartment is  $k_{e0}$ .

Mathematically, concerning pharmacokinetics, it is possible to describe the drug quantity in each compartment by using a system of differential equation, in which, given the drug infusion rate over time  $u(t)$ , the drug mass  $x_i(t)$  result to be:

$$\begin{cases} \dot{x}_1 = -(k_{10} + k_{12} + k_{13})x_1 + k_{21}x_2 + k_{31}x_3 + \frac{1}{V_1}u \\ \dot{x}_2 = k_{12}x_1 - k_{21}x_2 \\ \dot{x}_3 = k_{13}x_1 - k_{31}x_3 \end{cases} \quad (2.1)$$

where  $\dot{x}_i$  are the time derivative of  $x_i$ . Here, it is important to underline that  $x_1$  represents the drug mass contained in  $V_1$ . Therefore, the drug concentration in plasma  $C_p$  is computed by:

$$C_p(t) = \frac{x_1(t)}{V_1} [\text{mg L}^{-1}]. \quad (2.2)$$

The PK model parameters can be described either in terms of transfer rates, namely  $k_{ij}$ , or volumes and clearance, namely  $V_i$  and  $Q_i$ . In the case of a three-compartmental model

the relations between transfer rates and volumes are the following:

$$\begin{aligned}
 k_{10} &= \frac{CL}{V_1 60} \\
 k_{12} &= \frac{Q_2}{V_1 60} \\
 k_{13} &= \frac{Q_3}{V_1 60} \\
 k_{21} &= \frac{Q_2}{V_2 60} \\
 k_{31} &= \frac{Q_3}{V_3 60}
 \end{aligned} \tag{2.3}$$

where  $V_1$ ,  $V_2$ , and  $V_3$  [L] are the compartmental volumes, while  $CL$ ,  $Q_2$ , and  $Q_3$  [L min<sup>-1</sup>] are the clearances. The systemic clearance  $CL$  represents the irreversible elimination of drug from the central compartment due to metabolism and/or excretion (i.e. via liver or kidney). The distribution clearance  $Q_i$  quantifies the bidirectional exchange of drug between the central compartment and another tissue group with distinct perfusion or binding characteristics. They reflect how quickly the drug equilibrates between plasma and each group.

Pharmacodynamics is commonly modeled with a nonlinear system. Precisely, the PD relationship is usually represented by using a sigmoid function known as the Hill function (Goutelle et al., 2008). Given the drug concentration at the effect site over time  $C_e(t)$  [mg L<sup>-1</sup>], the clinical effect  $E(t)$  [BIS] results:

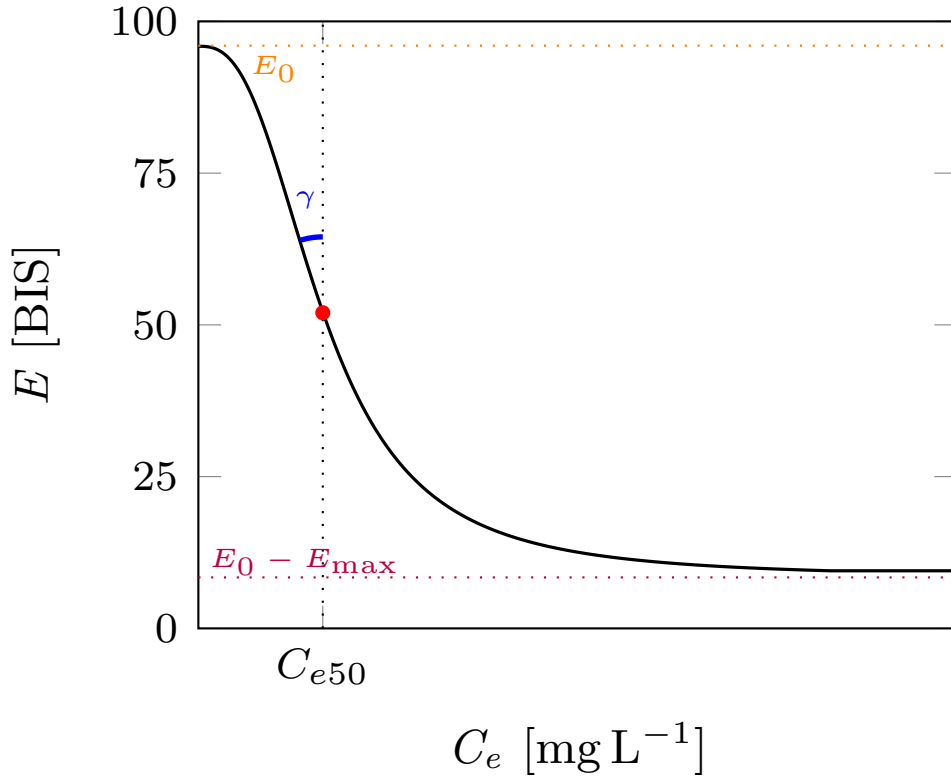
$$E(t) = E_0 - E_{\max} \left( \frac{C_e^\gamma(t)}{C_{e50}^\gamma + C_e^\gamma(t)} \right) \tag{2.4}$$

where  $E_0$ [BIS] is the baseline BIS value associated to a drug-free patient state, usually assumes values close to 100 [BIS]. The difference between  $E_0$  and  $E_{\max}$  models the maximum achievable clinical effect.  $C_{e50}$  is the drug concentration needed to provoke 50% of the maximal clinical effect. In the end,  $\gamma$  (gamma) represent the slope of the sigmoid curve computed in  $C_{e50}$ . An illustration of a Hill function can be seen in Fig. 2.3.

The effect site concentration  $C_e$  is computed starting from the plasmatic concentration  $C_p$ . Precisely, their relationship is:

$$\dot{C}_e = k_{e0}(C_p - C_e). \tag{2.5}$$

In conclusion, it is important to underline that the model's structure depends on the mathematical formulation adopted during its design phase and every model is designed for the administration of one or more specific drugs. Consequently, the model parameters are computed in a certain way according to the model used. The ones employed throughout this research are described in Sections 2.2.1 and 2.2.2.



**Figure 2.3:** Hill function illustration. Orange horizontal dotted line:  $E_0$  value. Purple horizontal dotted line:  $E_0 - E_{\max}$  amount.

### 2.2.1 Schnider Model

Over the past decade, the model presented by (Schnider et al., 1998, 1999) has gained popularity among researcher and became the reference for the sector since it has been widely used in development of both open- and closed-loop control strategies achieving promising results. This PKPD model allows to predict the BIS transient produced by the administration of the hypnotic drug propofol. The model is based on the compartmental structure described in Section 2.2 and was developed using data coming from a group of patients aged from 26 to 81 years, and with a weight and height ranging from 44-123 [kg] and 155-196 [cm], respectively. According to (Schnider et al., 1998, 1999) the PKPD parameters are computed as follows:

$$lbm = \begin{cases} 1.1 \cdot WGT - 128 \left( \frac{WGT}{HGT} \right), & \text{males} \\ 1.07 \cdot WGT - 148 \left( \frac{WGT}{HGT} \right), & \text{females} \end{cases}$$

| Parameter     | Value   |
|---------------|---------|
| $\theta_1$    | 4.27    |
| $\theta_2$    | 18.9    |
| $\theta_3$    | 238     |
| $\theta_4$    | 1.89    |
| $\theta_5$    | 1.29    |
| $\theta_6$    | 0.836   |
| $\theta_7$    | -0.391  |
| $\theta_8$    | 0.0456  |
| $\theta_9$    | -0.0681 |
| $\theta_{10}$ | 0.0264  |
| $\theta_{11}$ | -0.024  |

**Table 2.1:**  $\theta$  values taken from (Schnider et al., 1998, 1999).

$$V_1 = \theta_1$$

$$V_2 = \theta_2 - \theta_7(AGE - 53)$$

$$V_3 = \theta_3$$

$$CL = \theta_4 + \theta_8(WGT - 77) + \theta_9(lbm - 59) + \theta_{10}(HGT - 177)$$

$$Q_2 = \theta_5 + \theta_{11}(AGE - 53)$$

$$Q_3 = \theta_6$$

$$k_{e0} = \frac{0.456}{60}$$

$$k_{1e} = k_{e0}$$

To compute the other drug transfer rates it is sufficient to replace the values in Eq. (2.3). The values of  $\theta$  are listed in Table 2.1.

### 2.2.2 Eleveld Model

(Eleveld et al., 2018) designed a PKPD model that can predict the BIS evolution produced by propofol administration. Sensibly, like for every model, the ability to represent the reality hardly depends from the population involved during the training phase. The Eleveld model has been designed by taking into account 1033 patients with different gender, age, and physical characteristics. Moreover, the training sample included young children, children, adults, and elderly people. For this reason this model is thought to be representative of a broad population.

During the design phase, a male subject of 70 kg, 35 yr, and 170 cm has been used as reference to obtain all the models equations and parameters. Thus, the PK model equations

results to be:

$$f_{Al-Sallami} = \begin{cases} \left[ 0.88 + \frac{1 - 0.88}{1 + \left(\frac{AGE}{13.4}\right)^{-12.7}} \right] \cdot \left[ \frac{9270 \cdot WGT}{6680 + 216 \cdot BMI} \right], & \text{males} \\ \left[ 1.11 + \frac{1 - 1.11}{1 + \left(\frac{AGE}{7.1}\right)^{-1.1}} \right] \cdot \left[ \frac{9270 \cdot WGT}{8780 + 270 \cdot BMI} \right], & \text{females} \end{cases}$$

$$f_{opiates}(x) = \begin{cases} 1, & \text{absence of opiates} \\ e^{(x \cdot AGE)}, & \text{presence of opiates} \end{cases}$$

$$f_{ageing}(x) = e^{(x \cdot (AGE - AGE_{ref}))}$$

$$f_{sigmoid}(x, E50, \gamma) = \frac{x^\gamma}{(x^\gamma + E50^\gamma)}$$

$$f_{central}(x) = f_{sigmoid}(x, \theta_{12}, 1)$$

$$f_{CLmaturation} = f_{sigmoid}(PMA, \theta_8, \theta_9)$$

$$f_{Q3maturation} = f_{sigmoid}(AGE + 40 \text{ weeks}, \theta_{14}, 1)$$

$$V_{1arterial} [L] = \theta_1 \cdot \frac{f_{central}(WGT)}{f_{central}(WGT_{ref})} \cdot e^{(\eta_1)}$$

$$V_{1venous} [L] = V_{1arterial} \cdot (1 + \theta_{17} \cdot (1 - f_{central}(WGT)))$$

$$V_2 [L] = \theta_2 \cdot \frac{WGT}{WGT_{ref}} \cdot f_{ageing}(\theta_{10}) \cdot e^{(\eta_2)}$$

$$V_3 [L] = \theta_3 \cdot \frac{f_{Al-Sallami}}{f_{Al-Sallami,ref}} \cdot f_{opiates}(\theta_{13}) \cdot e^{(\eta_3)}$$

$$CL [L \min^{-1}] = \begin{cases} \theta_4 \cdot \left( \frac{WGT}{WGT_{ref}} \right)^{0.75} \cdot \frac{f_{CLmaturation}}{f_{CLmaturation,ref}} \cdot f_{opiates}(\theta_{11}) \cdot e^{(\eta_4)}, & \text{males} \\ \theta_{15} \cdot \left( \frac{WGT}{WGT_{ref}} \right)^{0.75} \cdot \frac{f_{CLmaturation}}{f_{CLmaturation,ref}} \cdot f_{opiates}(\theta_{11}) \cdot e^{(\eta_4)}, & \text{females} \end{cases}$$

$$Q_{2arterial} [L \min^{-1}] = \theta_5 \cdot \left( \frac{V_2}{V_{2ref}} \right)^{0.75} \cdot (1 + \theta_{16} \cdot (1 - f_{Q3maturation})) \cdot e^{(\eta_5)}$$

| Parameter | Inter-individual variability | Variance ( $\omega^2$ ) |
|-----------|------------------------------|-------------------------|
| $\eta_1$  | $V_1$                        | 0.610                   |
| $\eta_2$  | $V_2$                        | 0.565                   |
| $\eta_3$  | $V_3$                        | 0.597                   |
| $\eta_4$  | $CL$                         | 0.265                   |
| $\eta_5$  | $Q_2$                        | 0.346                   |
| $\eta_6$  | $Q_3$                        | 0.463                   |

**Table 2.2:** PK  $\eta$  values taken from Eleveld et al. (2018).

| Parameter     | Interpretation                       | Units         | Estimated Values |
|---------------|--------------------------------------|---------------|------------------|
| $\theta_1$    | $V_{1ref}$                           | L             | 6.28             |
| $\theta_2$    | $V_{2ref}$                           | L             | 25.5             |
| $\theta_3$    | $V_{3ref}$                           | L             | 273              |
| $\theta_4$    | $CL_{ref}$ (males)                   | $L \min^{-1}$ | 1.79             |
| $\theta_5$    | $Q_{2ref}$                           | $L \min^{-1}$ | 1.75             |
| $\theta_6$    | $Q_{3ref}$                           | $L \min^{-1}$ | 1.11             |
| $\theta_8$    | $CL_{maturation}$ E50                | weeks         | 42.3             |
| $\theta_9$    | $CL_{maturation}$ slope              |               | 9.06             |
| $\theta_{10}$ | Smaller $V_2$ with age               |               | -0.0156          |
| $\theta_{11}$ | Lower $CL$ with age                  |               | -0.00286         |
| $\theta_{12}$ | Weight for 50% of maximal $V_1$      | kg            | 33.6             |
| $\theta_{13}$ | Smaller $V_3$ with age               |               | -0.0138          |
| $\theta_{14}$ | Maturation of $Q_3$                  | weeks         | 68.3             |
| $\theta_{15}$ | $CL_{ref}$ (females)                 | $L \min^{-1}$ | 2.10             |
| $\theta_{16}$ | Higher $Q_2$ for maturation of $Q_3$ |               | 1.30             |
| $\theta_{17}$ | $V_1$ venous samples (children)      |               | 1.42             |
| $\theta_{18}$ | Higher $Q_2$ venous samples          |               | 0.68             |

**Table 2.3:** PK  $\theta$  values taken from (Eleveld et al., 2018).

$$Q_{2venous} [L \min^{-1}] = Q_{2arterial} \cdot \theta_{18}$$

$$Q_3 [L \min^{-1}] = \theta_6 \cdot \left( \frac{V_3}{V_{3ref}} \right)^{0.75} \cdot \frac{f_{Q3maturation}}{f_{Q3maturation,ref}} \cdot e^{(\eta_6)}$$

The symbols  $\theta$  are estimated model parameters while  $\eta$  are random variables representing inter-individual variability. Their values are shown in Tables 2.2 and 2.3. Parameters  $AGE$ ,  $PMA$ , and  $WGT$  represents the patient's age [years], PMA [weeks], and weight [kg] respectively. Symbols and functions with the subscript *ref* are related to the reference patient, whereas, the subscript *arterial* and *venous* indicates in which way blood has been sampled. Concerning pharmacodynamics, like for the Schnider model, the relationship between the effect-site concentration and the BIS is represented with the Hill function. The PD equations are:

$$C_{50} [\mu g mL^{-1}] = \theta_1 \cdot f_{ageing}(\theta_7) \cdot e^{\eta_1}$$

| Parameter  | Interpretation                         | Units                 | Estimated Values |
|------------|----------------------------------------|-----------------------|------------------|
| $\theta_1$ | $C_{50}$                               | $\mu\text{g mL}^{-1}$ | 3.08             |
| $\theta_2$ | $k_{e0}$ for arterial samples          | $\text{min}^{-1}$     | 0.146            |
| $\theta_3$ | Baseline BIS value                     |                       | 93.0             |
| $\theta_4$ | PD sigmoid slope ( $C_e > C_{50}$ )    |                       | 1.47             |
| $\theta_6$ | Increase in delay with age             |                       | 0.0517           |
| $\theta_7$ | Decrease in $C_{50}$ with age          |                       | -0.00635         |
| $\theta_8$ | $k_{e0}$ for venous samples            | $\text{min}^{-1}$     | 1.24             |
| $\theta_9$ | PD sigmoid slope ( $C_e \leq C_{50}$ ) |                       | 1.89             |
| $\eta_1$   | $C_{50}$                               |                       | 0.242            |
| $\eta_2$   | $k_{e0}$                               |                       | 0.702            |

**Table 2.4:** PD model parameters taken from (Eleveld et al., 2018).

$$k_{e0} = \begin{cases} \theta_2 \cdot \left( \frac{WGT}{WGT_{ref}} \right)^{-0.25} \cdot e^{\eta_2}, & \text{arterial samples} \\ \theta_8 \cdot \left( \frac{WGT}{WGT_{ref}} \right)^{-0.25} \cdot e^{\eta_2}, & \text{venous samples} \end{cases}$$

$$BIS_{baseline} = \theta_3$$

$$\gamma = \begin{cases} \theta_9, & C_e \leq C_{50} \\ \theta_4, & C_e > C_{50} \end{cases}$$

$$BIS_{delay} [\text{s}] = 15 + e^{(\theta_6 \cdot AGE)}$$

$$BIS = BIS_{baseline} \cdot \left( 1 - \frac{C_e^\gamma}{C_{50}^\gamma + C_e^\gamma} \right)$$

Like for the PK model, the symbols  $\theta$  represent the estimated model parameters while  $\eta$  are random variables representing inter-individual variability. They are shown in Table 2.4. In the end, the rate transfer constants  $k_{ij}$  are calculated by using Eq. (2.3).

## 2.3 Anesthesia Control

The administration of anesthetic agents can be organized according to the degree of automation and feedback involved in the control process. Traditional approaches, often referred to as open-loop systems, rely on predefined infusion profiles or clinician-driven adjustments based on clinical judgment and intermittent observations. These methods

offer simplicity and transparency but require constant supervision to ensure adequate anesthesia depth. In contrast, closed-loop systems introduce automation by continuously monitoring physiological variables and dynamically adjusting drug infusion in response to patient-specific feedback. By integrating sensing, modeling, and control, closed-loop anesthesia aims to enhance precision, reduce clinician workload, and improve patient safety through individualized drug delivery.

### 2.3.1 Open-Loop Control

Besides manual control, target-controlled infusion (TCI) (Struys et al., 2016; Absalom et al., 2011) represents one of the most established methods to automatically administer anesthesia. With TCI, the anesthesiologist can impose a desired effect-site concentration. The system then exploits a patient-specific PKPD model to compute an optimal dosing trajectory that reaches the target concentration while minimizing transient time and avoiding under- or overshoot.

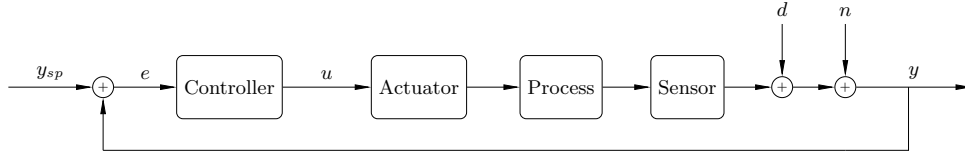
Although TCI has proven to be safe and effective, it presents several limitations. Specifically, TCI is a model-based system; therefore, if the patient is not well described by the pharmacological model, its performance degrades. Moreover, the system does not use feedback from measurements. As a result, model inaccuracies may lead to under- or overdosing, which can seriously harm the patient. The only correction the anesthesiologist can perform consists in adjusting the desired effect-site concentration to compensate for inadequate patient response to drug administration, but it can be difficult for the clinician since direct measurements of the drug concentration in blood are not available.

Consequently, while TCI remains a valuable tool in clinical anesthesia, its dependence on fixed pharmacological models and absence of feedback highlight the need for more adaptive and patient-specific control strategies.

### 2.3.2 Closed-Loop Control

In recent years, closed-loop control has attracted increasing attention (Ghita et al., 2020; Copot and Ionescu, 2014), as these systems have demonstrated superior performance compared to traditional open-loop approaches. In a personalized closed-loop drug delivery system, the control architecture integrates several key technologies, such as sensors, infusion pumps, and real-time processing units. As previously discussed, the main feedback variable for monitoring the hypnotic component of anesthesia is the BIS, which quantifies brain activity on a scale from 0 (no brain activity) to 100 (fully awake patient). Alternative feedback signals include the  $WAV_{CNS}$  (Hahn et al., 2012) and the auditory evoked potential (AEP) (Plourde, 2006).

The design of an effective closed-loop anesthesia system relies heavily on the choice of the control algorithm, which determines how drug infusion is adjusted in response to feedback signals. Among the most widely used strategies in both industrial and biomedical applications is the PID controller (Schiavo et al., 2023, 2020, 2021). However, inter- and



**Figure 2.4:** Example of a closed-loop control scheme.

intra-patient variability pose a major challenge to closed-loop drug delivery, as a single set of control parameters may not ensure optimal performance across all patients. Possible solutions include robust PID tuning based on population data (Paolino et al., 2024) or the use of adaptive and online control algorithms capable of continuously updating their parameters in real time.

Beyond classical approaches, advanced methods such as FOPID (Paolino et al., 2023b, 2025b), Model Predictive Control (MPC) (Pawłowski et al., 2023, 2022; Pawłowski et al., 2023; Paolino et al., 2025a), high-order controller (Milanesi et al., 2024b,a), neural networks (Ortolani et al., 2002), and Kalman filter based control (Wahlquist et al., 2025) have gained popularity for their ability to handle nonlinearities and patient-specific dynamics. Meanwhile, accurate sensing of analgesia remains an open challenge. Recent studies have introduced two promising indices, qCON and qNOX (Jensen et al., 2014), where the former reflects the hypnotic effect and the latter estimates nociceptive responses. The integration of such multimodal monitoring technologies opens the way toward Multiple-Input Multiple-Output (MIMO) control systems, enabling simultaneous and more precise regulation of different anesthetic components.

## 2.4 Fundamentals of Control Theory

Control theory provides the mathematical and conceptual framework for designing systems capable of autonomously regulating their behavior to achieve a desired objective. In engineering and biomedical applications alike, the purpose of a control system is to ensure that one or more variables of interest such as temperature, pressure, flow rate, or, in anesthesia, the Depth-of-Hypnosis, remain within prescribed limits despite external disturbances, parameter variations, or measurement noise.

The defining characteristic of a modern control system is the presence of feedback. Feedback enables the system to continuously compare its actual behavior with the desired one and to adjust its actions accordingly, thus achieving robustness and adaptability in the presence of uncertainty. Therefore, in a closed-loop control algorithm the system continuously measures the output, compares it with the desired reference, and uses the resulting error signal to adjust the input. This closed information path allows the controller to correct deviations and maintain the controlled variable close to its target value, even in the presence of perturbations or parameter drift. A schematic representation of a feedback control loop is shown in Fig. 2.4. The goal of feedback control can be expressed in terms of four fundamental objectives:

- *reference tracking*; the system output  $y(t)$  should follow the desired set-point  $y_{sp}$  as accurately as possible;
- *disturbance rejection*; the control system must reject the effect of external disturbances  $d$  acting on the the process;
- *robustness*; the closed-loop performance should remain satisfactory despite modeling uncertainties or process variations;
- *control effort minimization*; the control action  $u$  should be effective but not excessive, minimizing actuator wear, or energy consumption.

Achieving these goals simultaneously requires a trade-off between responsiveness, stability, and robustness, that is one of the central challenges in control design. Moreover, when designing a control algorithm, it is essential to remember that the best control system is the simplest one that meets the requirements.

### 2.4.1 PID Control

Proportional–Integral–Derivative controllers represent the most widespread feedback control strategy in industrial applications. Their success derives from a favorable balance between performance, simplicity, and robustness. The continuous-time control law of a PID controller can be expressed as:

$$u(t) = K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(\tau) d\tau + T_d \frac{de(t)}{dt} \right). \quad (2.6)$$

The PID controller computes its control action  $u(t)$ , in this case the anesthetic infusion rate, as a function of the control error  $e(t)$ . The control error represents the instantaneous deviation between the desired target output  $y_{sp}$  (the set-point) and the actual measured output of the system  $y(t)$ . Formally:

$$e(t) = y_{sp}(t) - y(t). \quad (2.7)$$

The set-point, or reference, is the trajectory that the system output should follow. As stated before, in anesthesia,  $y_{sp}$  typically corresponds to the target value of Depth-of-Hypnosis, namely a BIS of 50.  $y(t)$  is the measured output, that is the real-time feedback signal obtained from sensors. In this context, it is the measured BIS value, which reflects the patient's current hypnotic state as estimated from EEG signals. Therefore, The objective of the controller is to drive the control error to zero ( $e(t) \rightarrow 0$ ), ensuring that the system output tracks the set-point accurately despite process delays, pharmacological variability, and external disturbances. Despite its conceptual simplicity, the PID controller integrates proportional, integral, and derivative actions that jointly determine transient and steady-state performance. Precisely:

| Increment of | Speed Response | Stability |
|--------------|----------------|-----------|
| $K_p$        | Increase       | Decrease  |
| $T_i$        | Decrease       | Increase  |
| $T_d$        | Decrease       | Increase  |

**Table 2.5:** PID parameters tuning

- *proportional action*: it provides an output directly proportional to the instantaneous error, improving speed response but introducing a steady-state offset;
- *integral action*: it eliminates steady-state error by integrating the past error, acting as an automatic bias adjustment;
- *derivative action*: it predicts future error trends, enhancing damping and reducing overshoot by anticipating the system's response.

In practical implementations, the derivative action is never applied to the raw measurement but to a filtered version of the error signal. This filtered derivative implementation improves robustness to BIS noise and prevents excessive control activity, which is particularly important in drug infusion systems where actuator saturation and safety constraints must be respected. Therefore, the filtered transfer function, in the Laplace domain, results to be:

$$PID(s) = K_p \left( 1 + \frac{1}{T_i s} + \frac{T_d s}{1 + s \frac{T_d}{N}} \right). \quad (2.8)$$

The parameter  $N$  defines the ratio between the derivative time constant and the derivative filter time constant, thereby setting the cutoff frequency of the low-pass filter and regulating the trade-off between noise attenuation and preservation of the anticipatory action of the derivative term. Typically,  $N$  can assume values between 5 (strong noise filtering) and 20 (aggressive derivative action).

By tuning the PID parameters is possible to change the overall control performance. Table 2.5 shows how each parameters affect the PID behavior. The combined effect of the three terms allows the controller to improve speed, accuracy, and stability, but tuning must balance robustness and performance.

### 2.4.2 FOPID Control

Fractional-order control represents a generalization of classical PID control theory in which integrals and derivatives are extended from integer order to arbitrary real orders. The fractional-order PID controller, commonly denoted as FOPID, enhances the conventional PID structure by introducing two additional design parameters, namely the fractional integral order  $\lambda$  and the fractional derivative order  $\mu$ . This extension provides greater flexibility in shaping the closed-loop dynamics, enabling more precise tuning of phase and

gain characteristics.

The continuous-time control law of a fractional-order PID controller is given by:

$$u(t) = K_p \left( e(t) + \frac{1}{T_i} D^{-\lambda} e(t) + T_d D^\mu \right), \quad (2.9)$$

where  $D^x$  denotes the fractional-order derivative or integral operator of order  $x$ . Here,  $\lambda$  and  $\mu$  can assume positive values greater than zero. Note that, when  $\lambda = 1$  and  $\mu = 1$ , the classical integer-order PID controller is recovered. Thus, the fractional-order structure can be interpreted as a natural extension of PID, offering a continuum of intermediate behaviors between pure proportional, integral, and derivative actions. The operators  $\lambda$  and  $\mu$  allow fine-grained adjustment of both magnitude and phase, enabling improved shaping of the open-loop response. Moreover, they provide additional degrees of freedom to increase phase margin, reduce overshoot, and improve robustness without excessively altering closed-loop bandwidth. Such flexibility is particularly beneficial in systems with significant modeling uncertainty or with slow, delayed dynamics.

Also in this case, practical implementation requires to apply a low-pass filter to the derivative term. Thus, the Laplace domain transfer function results to be:

$$FOPID(s) = K_p \left( 1 + \frac{1}{T_i s^\lambda} + \frac{T_d s^\mu}{1 + s^\mu \frac{T_d}{N^\mu}} \right). \quad (2.10)$$

Moreover, fractional-order operators cannot be implemented directly as finite-order differential equations. For this reason, practical realization of FOPID controllers relies on approximations such as continued-fraction expansions (Vinagre et al., 2000), or CRONE approximations (Oustaloup et al., 2006). These methods approximate the non-integer terms over a selected frequency band allowing fractional behavior to be implemented using higher-order linear filters.

### 2.4.3 PIDA Control

The PIDA controller extends the classical PID structure by introducing an additional acceleration term A, corresponding to the second derivative of the error. In contrast to conventional PID controllers, whose derivative action provides only first-order predictive behavior, a PIDA controller offers second-order prediction, enabling more accurate anticipation of the system's future evolution. The continuous-time control law of a PIDA controller is given by:

$$u(t) = K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(\tau) d\tau + T_d \frac{de(t)}{dt} + T_a \frac{d^2 e(t)}{dt^2} \right), \quad (2.11)$$

where  $T_a$  is the acceleration time constant. The acceleration term significantly modifies the controller's phase lead, often enabling stabilization of processes that are difficult to

regulate with PID alone. Because the acceleration term involves the second derivative of the error, PIDA controllers are particularly sensitive to measurement noise. Therefore, practical implementations require explicit filtering of derivative and acceleration signals, typically through cascaded low-pass filters or by embedding the PIDA structure within a filtered PID framework. Proper filter tuning is essential to balance noise attenuation and predictive performance. Therefore, the filtered Laplace domain transfer function is:

$$PIDA(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{T_d s}{1 + \frac{T_d}{N_1} s} + \frac{T_a s^2}{\left(1 + \frac{T_a}{N_2} s\right)^2} \right). \quad (2.12)$$

#### 2.4.4 PIDD<sup>2α</sup> Control

The fractional-order PIDD<sup>2α</sup> controller represents a generalization of the PIDA family, introducing a fractional double-derivative term that enhances the predictive capability of the controller. The idea behind this extension is to provide additional degrees of freedom for shaping phase lead, damping, and transient performance, particularly in systems characterized by long delays, slow responses, or higher-order dynamics. The continuous-time control law of a PIDD<sup>2α</sup> controller can be expressed as:

$$u(t) = K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(\tau) d\tau + T_d \frac{de(t)}{dt} + T_a \frac{d^{2\alpha} e(t)}{dt^{2\alpha}} \right). \quad (2.13)$$

Tuning  $\alpha$  ( $0 < \alpha \leq 1$ ) allows to fine-grained adjustment of the controller's anticipatory behavior, resulting in an increased phase margin, improved damping of oscillations, reduced overshoot during rapid transients and, enhances robustness against modelling uncertainty. Again, similar filtering considerations apply to the PIDD<sup>2α</sup> controller, where the fractional second-derivative term provides enhanced predictive capability but also increases sensitivity to high-frequency noise. In this case, fractional differentiation is implemented through band-limited approximations, which naturally introduce smoothing effects. Therefore, the Laplace domain transfer function results to be:

$$PIDD^{2\alpha}(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{T_d s}{1 + \frac{T_d}{N_1} s} + \frac{T_a s^{2\alpha}}{\left(1 + \frac{T_a}{N_2} s\right)^2} \right). \quad (2.14)$$

#### 2.4.5 Model Predictive Control

Model Predictive Control represents a family of advanced control strategies characterized by the explicit use of a process model to predict and optimize the future evolution of the controlled variable. Unlike conventional feedback controllers, such as PID, MPC determines the current control action by solving an optimization problem at each sampling instant, subject to system dynamics and operating constraints. The key idea behind MPC is to

react in the present based on predictions of future behavior. By anticipating how the system will evolve, MPC can proactively avoid constraint violations, reject disturbances, and achieve smoother transitions, which is particularly relevant in biomedical applications, where safety and constraint handling are essential.

Practically, at each control step  $t$ , the MPC employs a model of the process to predict the future outputs  $\hat{y}(t+k)$  over a finite prediction horizon  $N_p$ . The prediction is based on the current state or past input-output data and a sequence of future control moves. The predicted outputs are compared against a desired reference trajectory and the control sequence is chosen to minimize a cost function  $J$ . The optimization yields an optimal sequence of control inputs, but only the first element is applied to the process. At the next sampling instant  $t+1$ , the horizon is receded forward and the entire optimization is solved again.

Although MPC provides powerful predictive capabilities, its performance depends critically on the accuracy of the underlying process model. A mismatch between the model and the real system can degrade control quality or compromise robustness. The need to solve an optimization problem at every sampling instant also introduces a computational burden that may limit its use in fast or resource-constrained systems. Moreover, ensuring guaranteed closed-loop stability typically requires additional design considerations, and the tuning of horizons and weighting factors must be carried out with care. Nevertheless, when appropriately implemented, MPC delivers excellent performance, particularly in systems affected by delays, constraints, and multivariable interactions.

#### 2.4.6 Kalman Filter

State estimation is a central component of modern control systems, particularly when the variables required for effective feedback are not directly measurable or are corrupted by noise. Practical systems often rely on sensors that provide only indirect and inherently noisy information about the underlying state of the process (Kalman, 1960). This limitation makes it necessary to combine sensor data with a mathematical model of system dynamics in order to reconstruct the quantities of interest. The Kalman filter provides an elegant and rigorous solution to this problem by formulating state estimation as a recursive probabilistic inference task.

The foundation of the Kalman filter lies in the representation of the system through a linear state-space model, which describes how the state evolves and how it gives rise to measurable outputs. Even in simple physical systems, making prediction is challenging because both the system dynamics and the measurements are affected by uncertainty. The filter therefore propagates forward an estimate of the current state using the model, while simultaneously tracking the uncertainty associated with this estimate. This predictive capability ensures that the filter maintains a coherent estimate of the state even when no new measurements are available.

When a new measurement does arrive, the filter updates its prediction by weighing the new

information against what it already believes. This process is governed by the Kalman gain, which determines the relative contribution of the prediction and the measurement. The gain is chosen in a way that minimizes the variance of the estimation error, thus making the Kalman filter an optimal estimator for linear systems in the presence of Gaussian noise. If the measurements are noisy, the filter relies more heavily on the model; if the model is uncertain, the filter leans more on the data. In this way, the Kalman gain acts as a dynamic weight that continuously adapts to the level of uncertainty. These operations, prediction followed by correction, form the two recursive stages that define the Kalman filter and allow the filter to update both the state estimate and its uncertainty in a mathematically consistent manner and with minimal computational effort. Because each update depends only on the previous estimate and the newest measurement, the algorithm is well suited for real-time control applications.

Although the classical Kalman filter assumes a linear model, many real processes exhibit nonlinear behavior, which requires approximate filtering strategies. Extensions such as the Extended Kalman Filter (Corporation, 1974; Simon, 2006) and the Unscented Kalman Filter (Julier and Uhlmann, 2004) address this challenge by linearizing the model analytically or statistically. While these techniques are no longer strictly optimal, they maintain the recursive structure of the original filter and are widely adopted across disciplines, including robotics, navigation, and biomedical engineering.

In summary, the Kalman filter offers a computationally efficient framework for estimating hidden states in noisy environments. By integrating model-based predictions with incoming measurements, it produces accurate and reliable state estimates that are essential for advanced feedback control. Its ability to manage uncertainty, update estimates recursively, and operate in real time explains its pervasive use in engineering applications. These properties make it particularly valuable in biomedical systems, where signals are often noisy, states are not directly observable, and robust estimation is necessary for safe and effective control.

## Chapter 3

# Thesis Contribution

This chapter summarizes the main scientific contributions of the papers included in this thesis, which collectively address the design, analysis, and validation of advanced control strategies for closed-loop anesthesia. The work spans the full methodological pipeline, from pharmacokinetic–pharmacodynamic modeling and controller tuning to robustness analysis under patient variability, signal degradation, and clinical disturbances, as well as initial in vivo validation.

Across the papers, particular emphasis is placed on clinically oriented control design: the use of physiologically grounded population models (with special attention to age-related effects), the comparison between classical, fractional-order, and higher-order predictive control structures, the integration of model-based estimation to handle unreliable measurements, and the development of clinician-in-the-loop architectures that preserve interpretability and safety. Together, these contributions aim to improve depth-of-hypnosis regulation while explicitly accounting for hemodynamic impact, inter-patient variability, and real-world operating constraints.

### 3.1 Included Papers

#### Paper I

N. Paolino, M. Schiavo, C. Ionesu, N. Latronico, M. Paltenghi, A. Visioli. (2023). **Event-based PID Control for Anesthesia Administration: Effect on Hemodynamic Variables**. In Proceedings of: *21st European Control Conference (ECC23)*. ECC57647.2023.10178185.

#### Key findings

- An event-based PID controller for co-administration of propofol and remifentanyl was evaluated in silico using an open source patient simulator (Ionescu et al., 2021) that includes both anesthetic (BIS for DoH, RASS as an analgesia surrogate) and hemodynamics (e.g., mean arterial pressure (MAP), cardiac output (CO)) variables;

- With a fixed opioid–hypnotic ratio, BIS regulation meets requirements, but MAP and RASS often drift below desired thresholds (hypotension / excessive opioid effect) in many patients; allowing the anesthesiologist to change the ratio during the case improves MAP and RASS while keeping BIS acceptable;
- The event generator provides a noise-filtering effect, reducing control effort and avoiding actuator “chasing” of noisy BIS fluctuations, while preserving BIS performance comparable to standard PID;
- Conclusion: the architecture can maintain DoH while supporting clinician-in-the-loop adjustment of opioid–hypnotic balance to better manage hemodynamics and potentially reduce perioperative side effects.

## Paper II

N. Paolino, M. Schiavo, N. Latronico, M. Paltenghi, A. Visioli. (2023). **On the use of the Eleveld PK/PD model for the design of PID Control of Anesthesia.** In Proceedings of: *22nd World Congress of the International Federation of Automatic Control (IFAC23)*. 10.1016/j.ifacol.2023.10.1428.

### Key findings

- A PID controller tuned using the adult-focused Schnider model was stress-tested in simulation on patients represented by the more general Eleveld model (children–adults–elderly), to assess cross-model robustness;
- Results indicate clinically acceptable performance for children and adults ( $< 60$  years) regardless of whether Schnider or Eleveld is used to represent patients;
- For elderly patients, the Eleveld representation introduces a large age-dependent dead time, and the same controller can exhibit large undershoot/settling issues and oscillatory disturbance rejection—performance that was not seen when elderly are represented with Schnider;
- Conclusion: model choice materially affects controller behavior in the elderly; the suitability of Eleveld for controller tuning in older patients needs further investigation, especially given limited elderly representation in model development.

## Paper III

N. Paolino, M. Schiavo, N. Latronico, F. Padula, M. Paltenghi, A. Visioli. (2023). **On the use of FOPID Controllers for Maintenance Phase of General Anesthesia.** *Applied Sciences*. 10.3390/app13137381.

**Key findings**

- Fractional-order PID control for propofol-based DoH maintenance (BIS) was tuned using two strategies: (i) genetic algorithms minimizing worst-case IAE; (ii) an isodamping/max-sensitivity approach (phase-margin invariance) not available to standard PID;
- Across Monte Carlo simulations capturing inter- and intra-patient variability, all controllers (PID and FOPID variants) meet clinical requirements and show adequate robustness;
- FOPID tuned by IAE minimization can be slightly better than isodamping-tuned FOPID, but overall gains vs a well-tuned standard PID are marginal;
- Conclusion: FOPID is viable and robust for DoH control, but the performance/complexity trade-off still favors classic PID in this setting.

**Paper IV**

N. Paolino, M. Schiavo, N. Latronico, M. Paltenghi, A. Visioli. (2024). **PK/PD model based design of PID Control for Closed-loop Anesthesia.** *IFAC Journal of Systems and Control*. 10.1016/j.ifacsc.2024.100247.

**Key findings**

- Using the Eleveld propofol PK/PD model, the paper compares population-based PID tuning to individualized tuning (per-patient optimization using demographics) for both induction and maintenance;
- In large simulation cohorts, individualized tuning improves performance indices and reduces dispersion, with particularly strong benefits in elderly patients, where population-based tuning can be too aggressive (undershoot/failure to settle in induction; oscillations in maintenance) due to pronounced age-dependent delay;
- The individualized approach yields clinically sensible trends: controller bandwidth increases with weight and decreases with age, aligning with clinical dosing intuition;
- Conclusion: individualized PID tuning leveraging Eleveld covariates is a reliable route to robust personalization, but overall performance depends on model fidelity (notably, limitations for elderly dynamics).

**Paper V**

M. Milanesi, N. Paolino, M. Schiavo, F. Padula, A. Visioli. (2024). **PIDA Control of Depth-of-Hypnosis in Total Intravenous Anesthesia.** In *Proceedings of: 4th IFAC Conference on Advances in Proportional-Integral-Derivative Control (PID24)*. 10.1016/j.ifacol.2024.08.033.

**Key findings**

- A proportional–integral–derivative–acceleration (PIDA) controller was designed and tuned for Depth-of-Hypnosis regulation, extending classical PID with a second-order predictive term to better handle delayed anesthetic dynamics;
- A systematic tuning methodology was developed and evaluated on a population of simulated patients described by PK/PD models, with performance assessed in terms of tracking accuracy, robustness, and control effort;
- Results show that PIDA control can achieve improved transient performance and disturbance rejection compared to standard PID, while maintaining a comparable level of robustness across patient variability;
- Conclusion: PIDA represents a viable intermediate solution between classical PID and more complex control strategies, offering enhanced predictive capability with limited additional complexity.

**Paper VI**

M. Milanesi, N. Paolino, M. Schiavo, F. Padula, A. Visioli. (2024). **Analysis of the Performance Achievable with a PIDD2 Controller for Depth-of-Hypnosis in Total Intravenous Anesthesia.** In *Proceedings of: 12th IFAC Symposium on Biological and Medical Systems (BMS24)*. 10.1016/j.ifacol.2024.11.084.

**Key findings**

- A fractional-order PIDD2 <sup>$\alpha$</sup>  controller was investigated to assess the maximum achievable performance obtainable by extending PIDA with a fractional second-derivative term;
- The additional degree of freedom provided by the fractional order  $\alpha$  was shown to improve noise filtering and phase shaping, particularly in the presence of measurement degradation and inter-patient variability;
- Extensive simulation studies indicate that PIDD2 <sup>$\alpha$</sup>  can outperform both PID and PIDA in specific scenarios, albeit at the cost of increased tuning and implementation complexity;
- Conclusion: while offering superior theoretical performance, PIDD2 <sup>$\alpha$</sup>  controllers highlight a clear trade-off between achievable robustness and practical deployability in clinical anesthesia systems.

## Paper VII

Y. Whalquist, N. Paolino, M. Schiavo, A. Visioli, K. Soltesz. (2025). **Kalman filter soft sensor to handle signal quality loss in closed-loop controlled anesthesia.** *Biomedical Signal Processing and Control*. 10.1016/j.bspc.2025.107506.

### Key findings

- A soft-sensor architecture that fuses a patient model with DoH measurements using a Kalman filter is proposed, adapting measurement reliance online via BIS signal quality (SQI) by mapping SQI to an effective measurement-noise variance range;
- In realistic simulation scenarios with model uncertainty, surgical disturbances, and measurement corruption, the soft sensor markedly improves DoH regulation compared with using the monitor output directly as feedback;
- Reported distributions show near-complete retention of BIS within the clinically desired range when moving from monitor feedback to soft-sensor feedback;
- Conclusion: combining model-based prediction and data-driven measurement with SQI-aware weighting yields robust control benefits, motivating clinical evaluation within an existing closed-loop research platform.

## Paper VIII

N. Paolino, M. Schiavo, F. Padula, N. Latronico, M. Paltenghi, A. Visioli. (2025). **In vivo performance evaluation of a FOPID controller for closed-loop anesthesia.** *IEEE Transactions on Control Systems Technology*. 10.1109/TCST.2025.3577975.

### Key findings

- A FOPID controller is evaluated in vivo in 10 plastic-surgery patients, regulating BIS by adjusting propofol (with remifentanyl coadministration), including practical safety logic for signal loss/low SQI (fallback to baseline infusions and bumpless resumption);
- In 7/10 patients the controller performed “flawlessly”; in cases with signal loss, safety behavior prevented harm and recovery to safe BIS occurred rapidly once feedback returned;
- Hemodynamics remained stable: heart rate (HR) and MAP stayed within recommended bounds throughout, supporting the claim that clinically relevant overdosing episodes were avoided;
- Conclusion: the FOPID-based solution achieved tight DoH control and robust disturbance handling clinically; despite BIS often sitting slightly below 40, clinicians

did not need to interrupt automatic control, and awakening times were consistent with total intravenous anesthesia practice.

## Paper IX

N. Paolino, F. Norlund, M. Schiavo, A. Visioli, K. Sotesz (2025). **Adjusting aggressiveness of Depth-of-Hypnosis control by means of an MPC feedforward action.** In Proceedings of: *The 2025 American Control Conference (ACC25)*. ACC63710.2025.11108074.

## Key findings

- Introduces a hybrid scheme where an already tuned PID (optimized for disturbance rejection) is augmented by an MPC-based feedforward term specifically for set-point decreases during maintenance (e.g., moving BIS target from 50 toward 45 or 40);
- A single tuning parameter ( $\alpha$ ) modulates aggressiveness: decreasing  $\alpha$  increases speed of reaching the new set-point, expanding the “space of operation” available to the anesthesiologist without retuning the PID;
- Simulations indicate the approach preserves robustness even with uncertainty in Hill-function parameters and despite MPC linearization around  $\text{BIS} = 50$ , while giving the clinician an interpretable knob to match surgical/patient needs;
- Conclusion: MPC feedforward is a practical clinician-in-the-loop enhancement to PID for controlled set-point transitions during maintenance.

## Chapter 4

# Conclusions

This chapter discusses the main implications of the results presented in the articles included in this thesis, with particular emphasis on their relevance to the field of closed-loop anesthesia. Rather than reiterating individual results, the discussion aims to synthesize the findings across papers, highlight methodological and clinical implications, and identify common themes, limitations, and future perspectives emerging from the work.

### 4.1 Implications and Relevance to the Field

The articles collected in this thesis address several open challenges in closed-loop control of general anesthesia, namely robustness to patient variability, integration of clinically meaningful models, management of unreliable measurements, and preservation of clinician authority within automated systems. Together, they support the feasibility of safe, interpretable, and adaptable automation in anesthesia delivery.

A first major implication concerns the role of PKPD modeling in controller design. In (Paolino et al., 2023c) and (Paolino et al., 2024), it is shown that the choice of patient model is not neutral from a control perspective. While population-based models enable wide applicability, age-dependent dynamics—particularly in elderly patients—introduce delays and sensitivity characteristics that directly affect closed-loop performance. These findings emphasize that controller robustness cannot be assessed independently of the underlying model structure and that personalization based on demographic covariates is not merely a refinement but a necessary step toward reliable automation in heterogeneous populations.

The comparison between classical PID and fractional-order PID controllers, addressed in (Paolino et al., 2023b) and extended clinically in (Paolino et al., 2025b), has important methodological implications. While fractional-order controllers offer additional tuning degrees of freedom and theoretically enhanced robustness, the results indicate that their practical advantage over well-tuned classical PID controllers is limited in the depth-of-hypnosis regulation problem. This reinforces the relevance of simplicity, transparency, and ease of tuning in safety-critical medical applications, where marginal performance gains

may not justify increased implementation complexity unless accompanied by clear clinical benefits.

Another key contribution of this thesis is the explicit consideration of measurement quality and signal reliability. In (Wahlquist et al., 2025), the integration of signal quality indices into a model-based estimation framework demonstrates that control performance can be preserved even under severe measurement degradation. This result is highly relevant for real-world deployment, as it addresses one of the main practical barriers to closed-loop anesthesia: the intermittent unreliability of commercial depth-of-hypnosis monitors. The proposed soft-sensor architecture represents a concrete step toward fault-tolerant anesthesia automation.

The importance of maintaining a clinician-in-the-loop paradigm is highlighted in multiple contributions. (Paolino et al., 2023a) shows that allowing clinicians to adjust the hypnotic–opioid balance within an automated framework improves hemodynamic outcomes without compromising depth-of-hypnosis control. Similarly, (Paolino et al., 2025a) introduces a mechanism to modulate controller aggressiveness without retuning or sacrificing robustness. These approaches align with current clinical expectations, positioning automation as an aid and workload-reduction tool rather than a fully autonomous replacement of the anesthesiologist.

From a broader perspective, the thesis contributes to bridging the gap between control-theoretic design and clinical applicability. Across all articles, simulation studies are deliberately structured to reflect realistic disturbances, inter- and intra-patient variability, and clinical constraints, while selected approaches are validated in vivo. This methodological continuity strengthens the translational relevance of the results and supports their integration into future clinical research platforms.

The collective results of this thesis highlight the importance of balancing performance, robustness, interpretability, and implementation complexity when designing closed-loop anesthesia systems. Classical PID control remains a strong baseline solution, offering reliable and clinically acceptable performance across a wide range of patients when appropriately tuned and combined with personalization strategies.

The analysis of fractional-order and higher-order predictive controllers provides additional insight into the limits of achievable performance. Fractional-order PID controllers offer greater tuning flexibility but only marginal improvements over well-tuned PID in most scenarios. In contrast, PIDA (Milanesi et al., 2024b) and fractional PIDD2 <sup>$\alpha$</sup>  (Milanesi et al., 2024a) controllers demonstrate that explicitly increasing the predictive order of the controller can improve transient response, disturbance rejection, and noise attenuation, particularly in challenging conditions characterized by long delays or degraded measurements.

However, these benefits come at the cost of increased tuning effort and implementation complexity. The results suggest that while advanced controller structures can provide performance gains, their clinical adoption must carefully consider robustness, transparency, and ease of integration within existing anesthesia workflows.

The work presented in this thesis demonstrates that closed-loop control of general anesthesia can be designed to be robust, interpretable, and clinically meaningful when control strategies are tightly coupled with appropriate patient models, estimation techniques, and clinician interaction mechanisms.

The main conclusions can be summarized as follows. First, classical PID control remains a strong baseline solution for depth-of-hypnosis regulation, provided that model choice and tuning strategies account for patient-specific dynamics, particularly in elderly populations. Second, fractional-order control is feasible and safe in both simulation and clinical settings, but its added value over classical approaches is context-dependent and does not automatically translate into superior clinical performance. Third, model-based estimation combined with signal-quality awareness is an effective strategy to mitigate measurement unreliability, a critical issue for real-world deployment. Finally, automation strategies that preserve clinician authority—by enabling adjustment of drug balance or control aggressiveness—are better aligned with clinical practice and may facilitate acceptance of closed-loop systems. Overall, this thesis supports a pragmatic and clinically grounded approach to closed-loop anesthesia. The work clarifies how different control architectures, from PID to fractional and higher-order predictive structures, perform under realistic conditions and patient variability. By combining physiological modeling, robust control design, state estimation, and clinician-in-the-loop interaction, the proposed solutions contribute toward the safe, interpretable, and personalized automation of anesthesia delivery.

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# Paper I

## Event-based PID Control for Anesthesia Administration: Effect on Hemodynamic Variables

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### Abstract

This paper aims to investigate the effects of an event-based Proportional-Integral-Derivative control system for propofol and remifentanyl coadministration on hemodynamics variables in general anesthesia. The validity of the considered control system with respect the anesthetic variables has already been proven in previous works. Here hemodynamic variables are also analyzed by using a specifically devised simulator. In general anesthesia, the balance between propofol and remifentanyl is a key factor to optimize the automatic infusion of anesthesia during long and invasive surgical procedures. Indeed, the possibility given by the control system to change the ratio between the infusion rates of the two drugs during the surgery allows the anesthesiologist to handle the patient's hemodynamics in each situation, thus, providing an improved healthcare. Results obtained from simulations suggest that the devised control solution can provide a suitable depth of hypnosis of the patients by always keeping the hemodynamic variables inside their recommended values.

Originally published in Proceedings of 2023 European Control Conference. The original version is available at [ECC57647.2023.10178185](https://doi.org/10.1109/ECC57647.2023.10178185).

## 2 Introduction

General anesthesia allows patients to undergo long and invasive surgeries thanks to its three main effects that are: suppression of consciousness (hypnosis), suppression of pain (analgesia) and muscle relaxation (mioresolution). Hypnosis is associated with loss of consciousness and prevents intra-operative awareness and memorization (Mashour and Pryor, 2020). Analgesia prevents the patients from experiencing pain by suppressing the physiological response to noxious stimuli. In total intravenous anesthesia (TIVA) an adequate state of unconsciousness and of pain suppression is attained by administrating two different drugs, namely, propofol and remifentanil. The anesthesiologist establishes the infusion rate and the drugs dosage by analyzing some indicators and on the basis of recommended patterns. Thus, it is clear that his/her experience is crucial in the success of the whole surgical procedure. Besides anesthetic activities, the anesthesiologist has to perform several challenging tasks that can lead to errors that could be harmful for the patient. For these reasons, nowadays, the development of feedback control systems for the infusion of anesthesia is increasing rapidly. In this context, the depth of hypnosis (DoH) is the feedback variable and this is measured through the analysis of the patient's electroencephalogram. The most widespread monitor used to sense the electrical activity of the brain is the bispectral index scale (BIS). In particular, the BIS allows the estimation of the DoH by means of a number in the range from 0 (EEG silence) to 100 (fully awake patient). Thanks to its ease of use, many control system strategies for the infusion of propofol have been proposed based on the BIS monitor, such as Proportional-Integral-Derivative (PID) control (Padula et al., 2017), adaptive control (Soltesz et al., 2013), model predictive control (MPC) (Pawlowski et al., 2022), fuzzy logic control (Meier et al., 1992), neural network (Gu et al., 2019) and reinforcement learning (Moore et al., 2014). However, the BIS monitor is able to estimate only the DoH but also analgesia plays a key role. Unfortunately, measuring analgesia is still challenging and there are not available pain sensors to be used in the clinical practice. For this reason, multiple-input-single-output (MISO) control solutions have been investigated, where the inputs are the infusion rates of propofol and remifentanil and the BIS is the only output. This implies that the interaction between the two drugs has to be considered during the controller design (Bouillon, 2008). Moreover, it is well known in the literature that coadministration of drugs could increase or decrease the effect of each single drug and therefore it is necessary to verify possible side effects of the control strategy on other hemodynamic variables, as it has been done in (Schiavo et al., 2021b) for the PID-based control strategy described in (Merigo et al., 2019a; Schiavo et al., 2021a).

In this paper we analyze the event-based PID control architecture proposed in (Merigo et al., 2020), where the anesthesiologist can choose the desired value of the ratio between the propofol and remifentanil infusion rates, with the aim to provide the most appropriate opioid-hypnotic balance. In particular, the effectiveness of the event-based control system and the effect of the ratio on various hemodynamics variables are evaluated in simulation

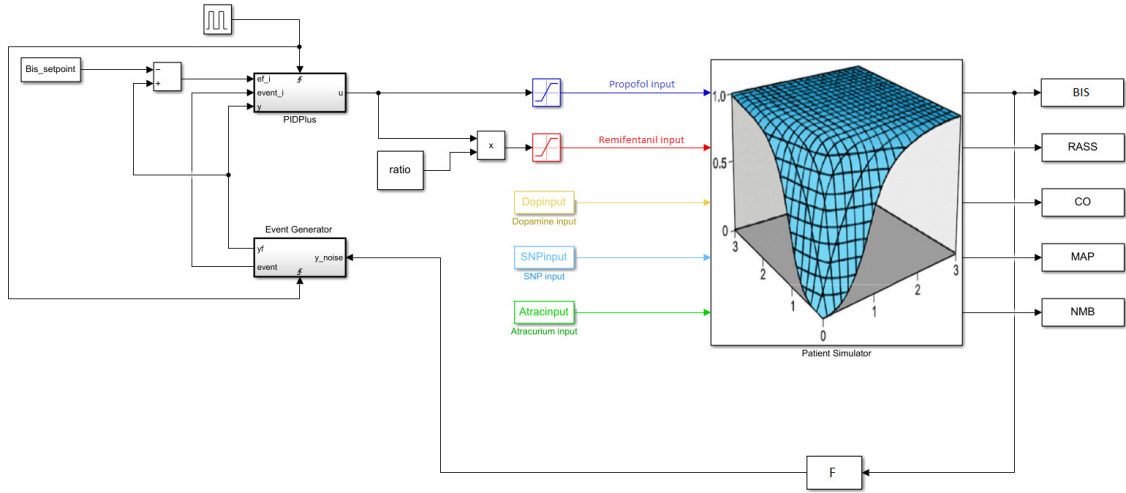
by employing the patient simulator that has been presented in (Ionescu et al., 2021). The content of the paper is as follows. In Section 3 an overview of the simulator is presented. In Section 4 the control algorithm is reviewed. In Section 5 simulation results are shown, and they are then discussed and analyzed in Section 6. Conclusions are in Section 7.

### 3 Patient Simulator

As previously said in Section 2, the open source patient simulator proposed in (Ionescu et al., 2021) has been exploited to assess the performance of the control system presented in (Merigo et al., 2020). This tool has been designed through a multidisciplinary approach involving medicine and engineering and it allows the user to have a well-rounded view of the anesthetic and hemodynamic variables by considering their complex synergetic and antagonistic interaction. Precisely, concerning the anesthetic system, the simulator provides the BIS as a measure of the hypnotic state and the Ramsay Agitation Sedation Score (RASS) as an indicator of analgesia. In this scenario, the RASS variable has been used to measure the analgesia since, as previously said, more specific measurements are not available yet. Concerning the hemodynamic system, the tool provides the measure of the mean arterial pressure (MAP) and of the cardiac output (CO). The simulator has some more additional features, such as the possibility to consider additional bolus administrations of dopamine, sodium nitroprussiate and atracurium as inputs. However, in this paper, the attention is only paid to the changes of BIS, RASS, MAP and CO variables due to the administration of propofol and remifentanil. Exploiting the fact that the simulator can be modified, the measurement units of the propofol and remifentanil infusion rates have been changed to  $mg/s$  and  $\mu g/s$ , respectively, in order to meet the specifications of the devised control system. Moreover, it has been chosen to use, as disturbance profile, the one proposed in (Soltész, 2013). In this way it is easier to assess the controller performance. Then, a noise signal extracted from real data has been added to the simulator in order to make the simulation more realistic and to better evaluate the filtering action of the event-based controller (Pawlowski et al., 2022). Finally, a change has been performed also in the nonlinear part of the model used to describe the interaction between propofol and remifentanil. In particular, the one proposed in (Bouillon et al., 2004) has been exploited so that the BIS value is expressed as:

$$BIS(t) = E_0 - E_{max} \left( \frac{\left( \frac{U_p(t) + U_r(t)}{U_{50}(\phi)} \right)^\gamma}{1 + \left( \frac{U_p(t) + U_r(t)}{U_{50}(\phi)} \right)^\gamma} \right), \quad (1)$$

where  $E_0$  is the BIS value of the patient before starting the infusions,  $E_0 - E_{max}$  is the maximum reachable clinical effect, and  $\gamma$  is the steepness of the concentration-effect surface. Moreover,  $U_p$  and  $U_r$  represent, respectively, the propofol and remifentanil concentrations ( $C_{e,p}(t)$  and  $C_{e,r}(t)$ ) normalized with respect to their concentrations necessary to reach



**Figure 1:** Schematic view of the event-based PID controller and patient simulator. This figure has been tailored from (Ionescu et al., 2021).

50% of the maximal drug effect ( $C_{e50,p}$  and  $C_{e50,r}$ ):

$$U_p(t) = \frac{C_{e,p}(t)}{C_{e50,p}}, \quad U_r(t) = \frac{C_{e,r}(t)}{C_{e50,r}}. \quad (2)$$

Then,  $U_{50}(\phi)$  is used to normalize the drugs combined effect:

$$U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2, \quad (3)$$

where  $\beta$  is an interaction term that expresses the synergetic effect of propofol and remifentanyl, and  $\phi$  is a dimensionless parameter that gives the combination power of the two drugs:

$$\phi = \frac{U_p(t)}{U_p(t) + U_r(t)}. \quad (4)$$

## 4 Control System

The control algorithm analyzed in this paper has been exhaustively described in (Merigo et al., 2020). Some of its main aspects are summarized hereafter. The whole control architecture is shown in Fig. 1. The control system exploits an event-based strategy to regulate the depth of hypnosis by propofol and remifentanyl coadministration and by considering the BIS as a controlled variable. This control scheme mimics the real anesthesiologists behavior since, in clinical practice, the drug dosage is updated basing on the events that occur during the surgical procedure. The control structure is characterized by the presence of a PIDPlus controller (Blevins et al., 2015) and of an event generator block which sends an output only when a certain logical condition (event occurrence) becomes true. A PIDPlus controller is a suitably modified standard PID controller that is able to deal with non periodic sampling instants. The event generation condition that has

been adopted is the one proposed in (Merigo et al., 2018), defined as:

$$\left| \int_{t_{last}}^t BIS(t) - BIS_f(t_{last}) dt \right| > \Delta_i \text{ OR } t_w > t_{max}, \quad (5)$$

where  $t$  is the current time instant,  $BIS(t)$  is the current BIS value,  $BIS_f(t_{last})$  is the last BIS sample sent to the controller,  $t_{last}$  is the time instant when the previous event has been triggered,  $t_w$  is the elapsed time interval from the previous event, and  $\Delta_i$  and  $t_{max}$  are the design parameters of the event generator. In particular,  $\Delta_i$  is the event generator threshold, which handles the trade-off between the control performance and the number of events, and  $t_{max}$  is the maximum time after which an occurrence of an event is forced in any case, for safety reasons. Looking at the scheme in Fig. 1, a second-order low-pass filter  $F$  with time constant  $T_f$  is also employed at the input of the event generator block in order to filter high noise peaks on the BIS signal. Moreover, it is important to note that the ratio block plays a key role in the control scheme since it allows the anesthesiologist to select the opioid-hypnotic ratio based on his/her experience, according to the patient's state and to the surgical procedure. From a control system design viewpoint, the ratio represents a degree of freedom that results from having a system with two inputs and one output. It is calculated as the ratio between the remifentanyl and the propofol infusion rates. As described in (Merigo et al., 2019b), the ratio value can be chosen in the range from 0.5 to 15. Since the same BIS value can be attained with different concentrations of propofol and remifentanyl, the ratio enables the desired BIS value to be reached with a higher propofol concentration and a lower remifentanyl concentration or vice versa. This tuning knob allows the anesthesiologist to select the optimal drugs balance in every moment of the surgical procedure, thus obtaining an improved quality of care and a reduction of side effects.

#### 4.1 Event Generator Tuning

The tuning procedure of the parameters  $\Delta_i$  and  $t_{max}$  has been thoroughly described in (Merigo et al., 2020). The maximum time interval after which a new sample of the BIS is sent to the controller is denoted as  $t_{max}$ . Basing on the clinical practice, the value of  $t_{max}$  has been fixed to 20 seconds. This value is selected for safety reasons by taking into account that the time constant of the system is a few minutes. Concerning the tuning procedure of  $\Delta_i$ , this parameter has been chosen so that a relevant variation of the BIS value is detected. This procedure allows the control system to filter possible noise affecting the feedback line. Moreover, different tunings have been considered for the induction and maintenance phases. Thus, from the tuning procedure the value of  $\Delta_i$  has turned out to be equal to 9.4505 and 20.5683 for the induction and maintenance phase, respectively.

#### 4.2 PIDPlus Controller Tuning

The tuning parameters of a PIDPlus are the classic ones of a standard PID controller, precisely  $K_p$ ,  $T_i$  and  $T_d$ . The same considerations about induction and maintenance,

| Parameter | Induction                               | Maintenance                             |
|-----------|-----------------------------------------|-----------------------------------------|
| $K_p$     | $0.0139 \cdot (ratio)^{-0.44} - 0.0015$ | $0.0136 \cdot (ratio)^{-0.43} - 0.0018$ |
| $T_i$     | 197.47                                  | 287.62                                  |
| $T_d$     | 29.18                                   | 6.25                                    |

**Table 1:** Tuning rules for each phase of anesthesia: induction and maintenance. Tailored from (Merigo et al., 2020).

| Id | Age | Hgt [cm] | Wgt [kg] | Gender | $C_{e50,p}$ | $C_{e50,r}$ | $\gamma$ | $\beta$ | $E_0$ | $E_{max}$ |
|----|-----|----------|----------|--------|-------------|-------------|----------|---------|-------|-----------|
| 1  | 40  | 163      | 54       | F      | 6.33        | 12.5        | 2.24     | 2.00    | 98.8  | 94.10     |
| 2  | 36  | 163      | 50       | F      | 6.76        | 12.7        | 4.29     | 1.50    | 98.6  | 86.00     |
| 3  | 28  | 164      | 52       | F      | 8.44        | 7.1         | 4.10     | 1.00    | 91.2  | 80.70     |
| 4  | 50  | 163      | 83       | F      | 6.44        | 11.1        | 2.18     | 1.30    | 95.9  | 102.00    |
| 5  | 28  | 164      | 60       | M      | 4.93        | 12.5        | 2.46     | 1.20    | 94.7  | 85.30     |
| 6  | 43  | 163      | 59       | F      | 12.00       | 12.7        | 2.42     | 1.30    | 90.2  | 147.00    |
| 7  | 37  | 187      | 75       | M      | 8.02        | 10.5        | 2.10     | 0.80    | 92.0  | 104.00    |
| 8  | 38  | 174      | 80       | F      | 6.56        | 9.9         | 4.12     | 1.00    | 95.5  | 76.40     |
| 9  | 41  | 170      | 70       | F      | 6.15        | 11.6        | 6.89     | 1.70    | 89.2  | 63.80     |
| 10 | 37  | 167      | 58       | F      | 13.70       | 16.7        | 3.65     | 1.90    | 83.1  | 151.00    |
| 11 | 42  | 179      | 78       | M      | 4.82        | 14.0        | 1.85     | 1.20    | 91.8  | 77.90     |
| 12 | 34  | 172      | 58       | F      | 4.95        | 8.8         | 1.84     | 0.90    | 96.2  | 90.80     |
| 13 | 38  | 169      | 65       | F      | 7.42        | 10.5        | 3.00     | 1.00    | 93.1  | 96.58     |

**Table 2:** Demographic values and model parameters for all the patients (Hgt: height, Wgt: weight) taken from (Merigo et al., 2019a).

presented in Section 4.1, could be applied also in this case. Thus, the tuning for the two phases should be different. This means that a gain scheduling strategy is employed. Moreover, the PIDPlus parameters have been determined for each propofol-remifentanyl ratio between the range of 0.5-15 (spaced of 0.5). Accordingly, for every set of parameters, the optimal values are determined by solving an optimization problem considering as a cost function the integrated absolute error (IAE), defined as:

$$IAE = \int |e(t)| dt. \quad (6)$$

A particle swarm optimization (PSO) algorithm has been exploited to solve each posed optimization problem. Then, the obtained parameters have been fitted with a suitable function to determine a tuning rule. The function obtained relates the  $K_p$  gain of the PIDPlus to the current ratio value. The tuning rules for both anesthesia phases are in Table 1.

## 5 Simulation Results

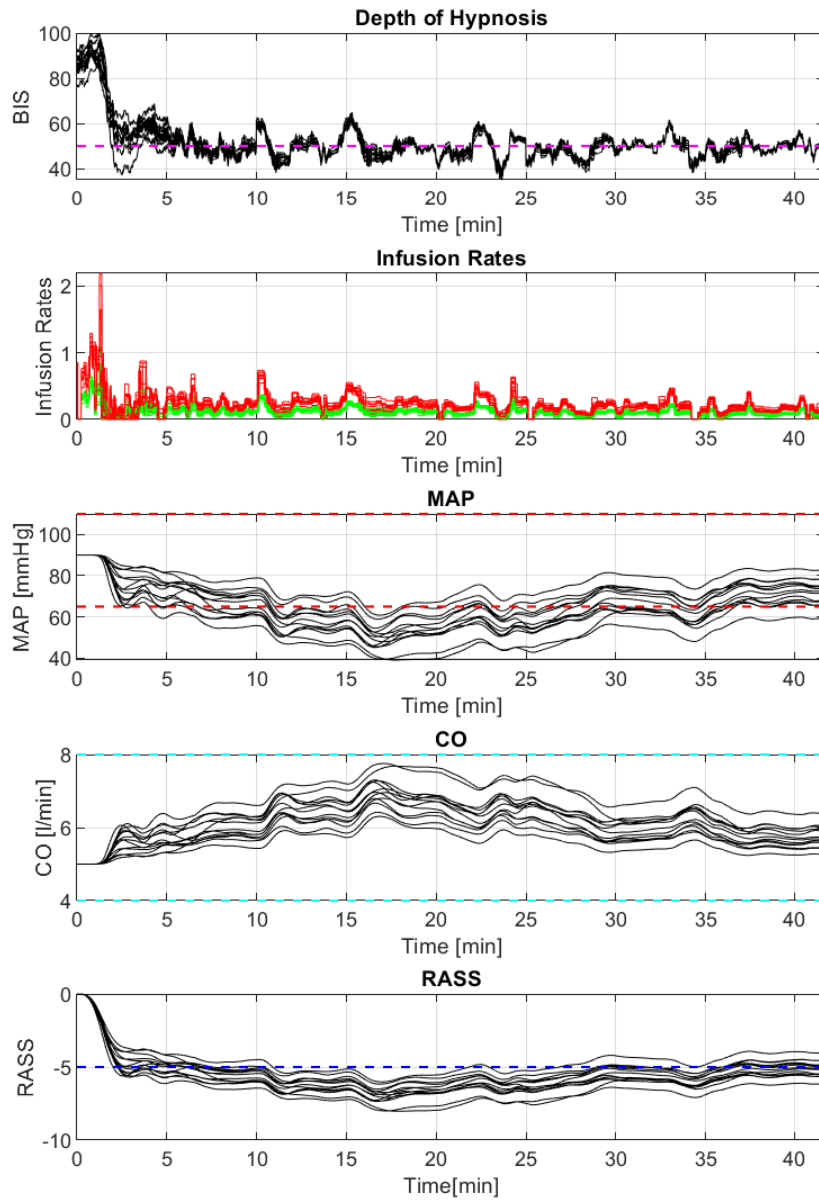
A simulation of 13 patients has been carried out in order to evaluate the performance of the control system presented in Section 4. The parameters of the patients are taken from (Merigo et al., 2020) and are shown in Table 2 for convenience. The simulations have

been performed by choosing 50 as BIS target since, in clinical practice, it is suggested to maintain the BIS in the range from 40 to 60 (Rosow and Manberg, 2001). Concerning the hemodynamic variables, the baseline value for the mean arterial pressure has been fixed to 90 *mmHg*, while that of cardiac output has been fixed to 5 *l/min*. Typically, during a surgical procedure, it is advisable to keep the MAP inside the range from 65 to 110 *mmHg* and the CO inside the range from 4 to 8 *l/min*. Instead, a recommended value for RASS is -5. In particular, if the level of RASS is above the -5 threshold, it means that the patient's anesthetic level is insufficient. On the contrary, if the level is under the -5 threshold, the anesthetic level is correct, but the anesthesiologist is using more drugs than needed.

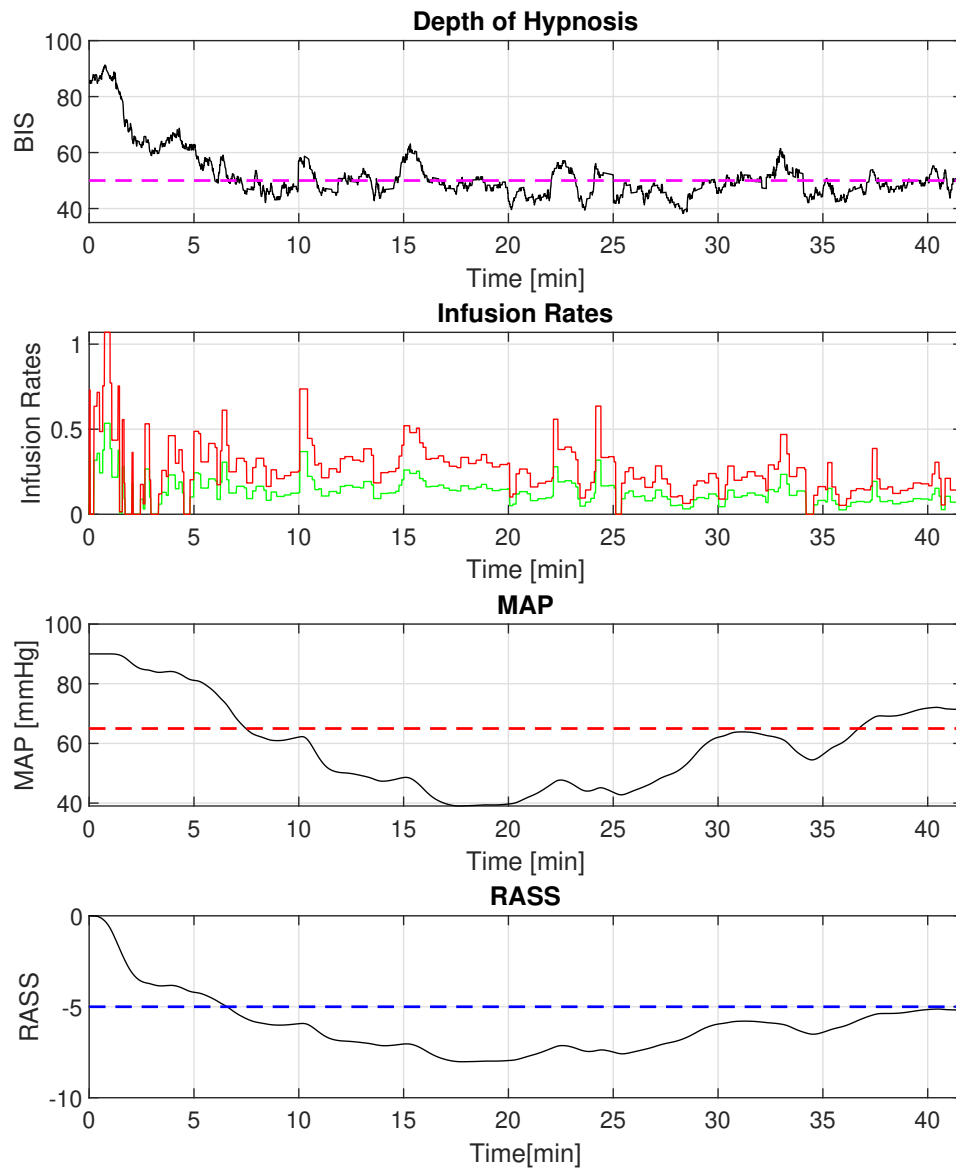
Simulation results performed with a fixed opioid-hypnotic ratio equal to 2 are shown in Fig. 2. The simulation is structured as follows for all the patients. It has been chosen to perform a simulation of 42 minutes. At the beginning the induction tuning rule is applied to force the BIS from its baseline value to the desired target of 50. At minute 5 the induction phase is considered to be finished, thus the anesthesiologist performs the gain scheduling procedure so that the maintenance tuning rule is applied (until the end). At minute 10 a surgical disturbance is applied to the BIS signal. In particular, the disturbance is a positive step of amplitude 10. This disturbance lasts till minute 25, where it is stopped, that is, a negative step of amplitude -10 is applied to the BIS signal.

The control system is able to rapidly drive the BIS to the reference value of 50 without causing relevant undershoot episodes for every considered patient. Concerning the hemodynamic variables, the CO is kept inside the recommended values in every patient. For this reason, this variable will be omitted in further considerations. In 11 out of 13 patients the MAP values drops below the safety value of 65 *mmHg* for most of the time of the simulation. As regards the RASS, for every patient it varies between -5 and -8. This behavior indicates that the dosage of remifentanyl is slightly higher than required. These potentially dangerous MAP and RASS behaviors must be handled by the control system. The proposed solution consists of manually modifying the ratio value in order to always infuse an adequate propofol-remifentanyl balance. To further analyze this strategy, we consider patient 11 as a single example.

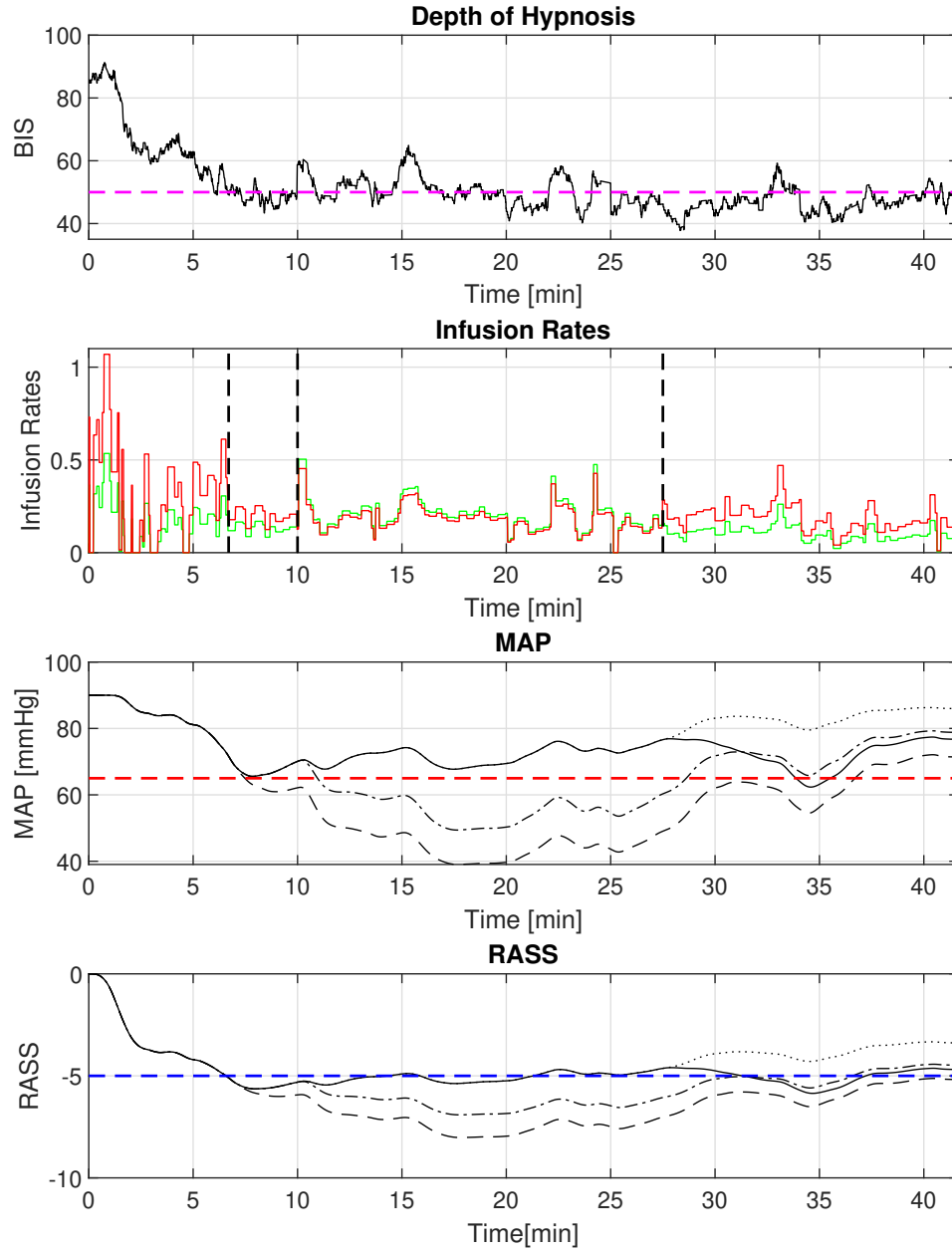
In Fig. 3, it is possible to see the response of this patient. Despite the BIS signal is always inside the appropriate interval from 40 to 60, the patient seems to be sensitive to remifentanyl since it has the RASS and MAP values below the target. As said before, this means that the amount of administered remifentanyl is too high. Thus, it is sensible to decrease the ratio in order to reduce the remifentanyl effect. In Fig. 4, the simulation response of patient 11, obtained by switching the ratio, is presented. At the beginning, the anesthesia is induced with a ratio equal to 2. After performing the gain scheduling, at minutes 7, the anesthesiologist decreases the ratio to 1.5 since the RASS trend is decreasing. In fact, the presence of a surgical disturbance applied to the BIS signal tends to decrease the MAP and RASS, so that the anesthesiologist decides to change the ratio to 0.9 in order to maintain an adequate level of sedation. This value is maintained until the 27th minutes, where an increment of the hemodynamic variables can be noticed since the disturbance



**Figure 2:** Results for all patients with a constant ratio equal to 2. Green solid line: propofol infusion rate [ $mg/kg/min$ ]. Red solid line: remifentanyl infusion rate [ $\mu g/kg/min$ ]. Magenta dashed line: BIS target. Red dashed lines: MAP safety limits. Cyan dashed lines: CO safety limits. Blue dashed line: RASS target.



**Figure 3:** Results for patient 11 with a constant ratio equal to 2. Green solid line: propofol infusion rate [ $mg/kg/min$ ]. Red solid line: remifentanyl infusion rate [ $\mu g/kg/min$ ]. Magenta dashed line: BIS target. Red dashed line: MAP safety limit. Blue dashed line: RASS target.



**Figure 4:** Results for patient 11 with ratio changing during the simulation. Green solid line: propofol infusion rate [ $mg/kg/min$ ]. Red solid line: remifentanyl infusion rate [ $\mu g/kg/min$ ]. Magenta dashed line: BIS target. Black vertical dashed lines: time instant when ratio changing occurs. Red dashed line: MAP safety limit. Blue dashed line: RASS target. For MAP and RASS the black solid line represents the response obtained by switching the ratio. Black dashed line: ratio = 2. Black dash-dotted line: ratio = 1.5. Black dotted line: ratio = 0.9.

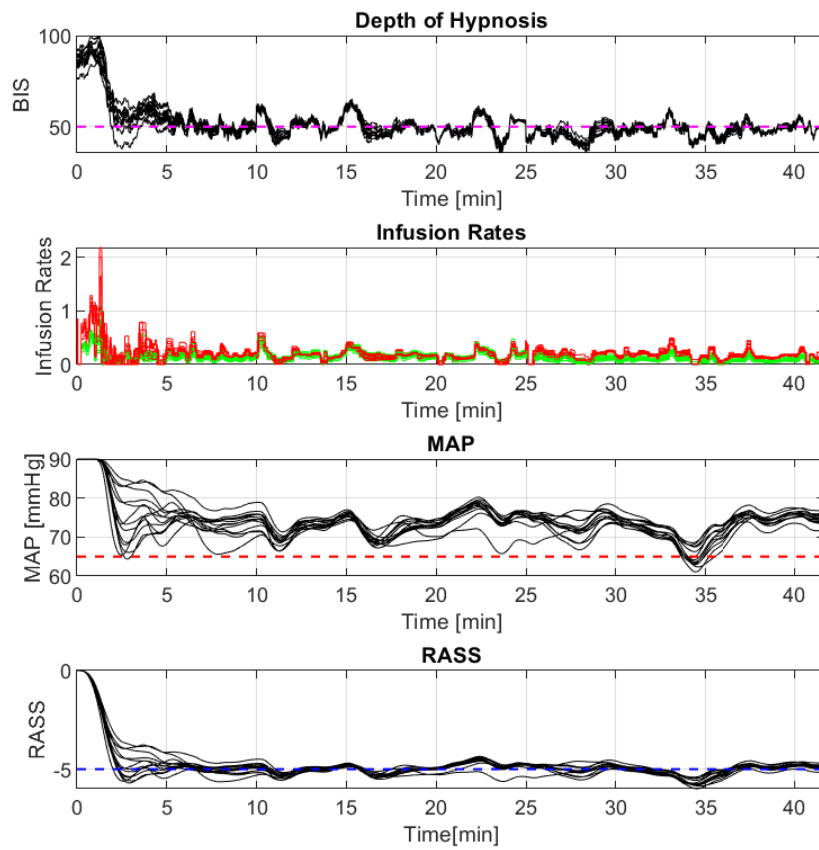
| 1st Change |            |       | 2nd Change |       | 3rd Change |       | 4th Change |       |
|------------|------------|-------|------------|-------|------------|-------|------------|-------|
| Id         | Time [min] | Value | Time [min] | Value | Time [min] | Value | Time [min] | Value |
| 1          | 10         | 1.6   | 25         | 3     |            |       |            |       |
| 2          | 2          | 1     | 5          | 1.5   | 10         | 1     | 25         | 2     |
| 3          | 4          | 1.6   | 10.5       | 1.2   | 25         | 2     |            |       |
| 4          | 2.5        | 1.3   | 11         | 1     | 17         | 1.5   |            |       |
| 5          | 10         | 1.2   | 25         | 2.5   |            |       |            |       |
| 6          | 6          | 1.5   | 10         | 1.2   | 25         | 2.2   |            |       |
| 7          | 6          | 1.5   | 10         | 1     | 25         | 2     |            |       |
| 8          | 2.5        | 1     | 11         | 0.8   | 25         | 1.3   |            |       |
| 9          | 10         | 1.4   | 25         | 2.2   |            |       |            |       |
| 10         | 2.5        | 1.2   | 11         | 1     | 25         | 1.6   |            |       |
| 11         | 7          | 1.5   | 10         | 0.9   | 27.5       | 1.8   |            |       |
| 12         | 10         | 1.1   | 25         | 2.5   |            |       |            |       |
| 13         | 2.5        | 1.2   | 11         | 1     | 25         | 1.6   |            |       |

**Table 3:** Timeline of the ratio changing for all patients. The baseline value of the ratio is 2 for all patients. Note that blank cells denote that no further changing have been done.

expired some minutes before. Accordingly, the anesthesiologist performs a last ratio change to 1.8, to keep the variables at their recommended values. Note that, every time the ratio is changed, the PIDplus proportional gain changes accordingly to the tuning rule of Table 1. Looking at the infusion rates of Fig. 3 and Fig. 4, it is possible to notice the effect of the ratio switching. In particular, in the third zone, the gap between the green and red solid lines is much reduced. In conclusion, it is sensible to underline that, despite the ratio changing, the BIS signal of the two cases is about the same. For the sake of completeness, in Fig. 5, the simulation results obtained for every patient by switching the ratio are presented. Moreover, in Table 3, it is possible to see, for all patients, at which time the ratio has been changed and its new value. It is worth stressing that every anesthetic and hemodynamic variable is inside its recommended value.

## 6 Discussion

The robustness and effectiveness of the control solution presented in Section 4 has been thoroughly analyzed for the DoH in (Merigo et al., 2020). In this paper, thanks to the open source patient simulator described in (Ionescu et al., 2021), it has been possible to study the effects of the control system on the patients hemodynamics. From the simulation performed for each of the 13 patients, with a fixed opioid-hypnotic ratio equal to 2, the control system meets the requirements concerning the BIS signal. On the other hand, in the majority of the cases, the MAP and RASS fall below the desired thresholds resulting in hypotension and excessive infusion of remifentanyl. However, the simulations carried out on the same patients, by modifying the ratio value, have shown encouraging results since both MAP and RASS achieve their recommended values. Moreover, the option to change the opioid-hypnotic balance according to the state of each patient is the added value of the

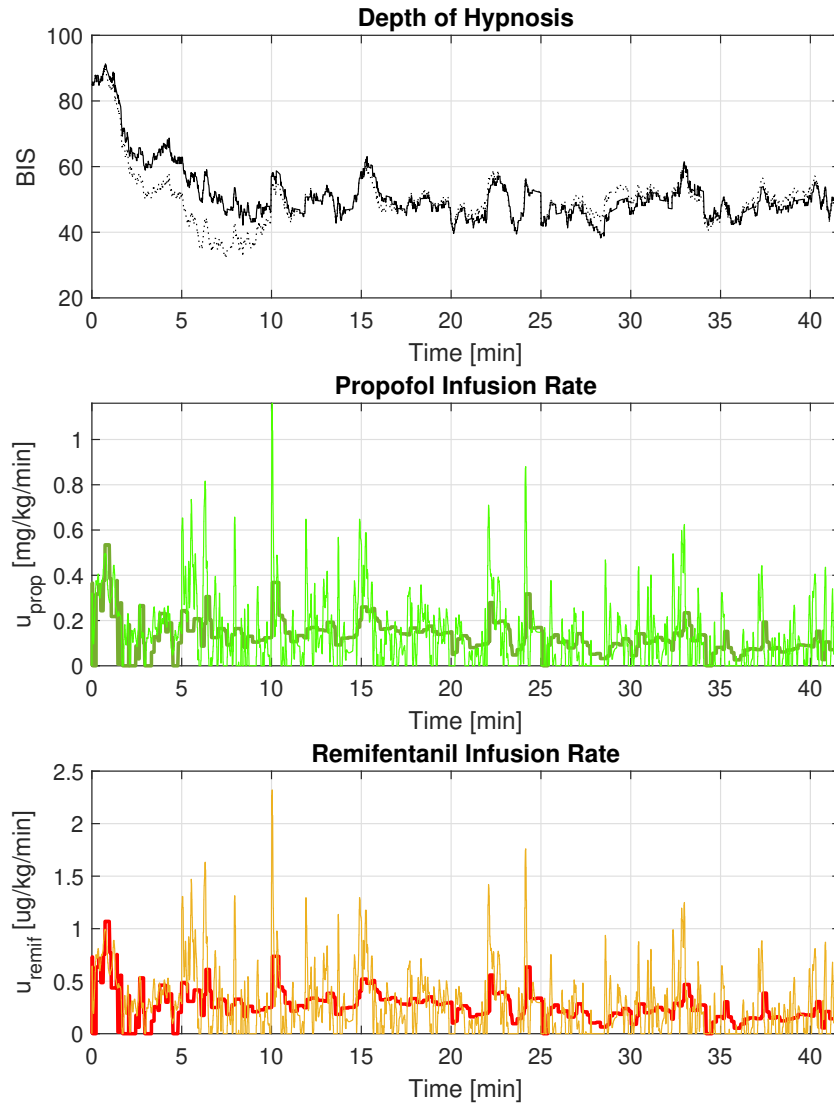


**Figure 5:** Results for all patients with a ratio changing during the surgical procedure. Green solid line: propofol infusion rate [ $mg/kg/min$ ]. Red solid line: remifentanyl infusion rate [ $\mu g/kg/min$ ]. Magenta dashed line: BIS target. Red dashed line: MAP safety limit. Blue dashed line: RASS target.

described control solution and could bring further advantages to the anesthesia practice. It is important to underline that the simulations performed are simple compared to the situations that can occur during a surgical procedure. In fact, there are other aspects that should be considered for the regulation of the propofol-remifentanil balance. Concerning the filtering action of the event-based controller, in Fig. 6 it is possible to see how the event generator filters the noise reducing the control effort. This allows the excitement of the actuators to be reduced so that they do not follow detrimental variations of the BIS signal due to the presence of noise. Moreover, it can be recalled that there are not significant differences between an event-based controller and a standard PID controller in terms of BIS performance since the two signals present a very similar trend (Merigo et al., 2020).

## 7 Conclusions

An event-based PID controller for the coadministration of propofol and remifentanil has been assessed by using an in-silico approach that allows the investigation of the effects of this system on the hemodynamic variables of patients. The event-based controller confirms its satisfactory behavior in both infusing anesthesia and filtering the noise that affects the BIS signal. In the proposed solution, during the surgical procedure, the propofol-remifentanil balance can be manually regulated by the anesthesiologist in order to deal with the patients characteristics and their response to drugs infusion. Therefore, the option to modify the opioid-hypnotic ratio can help the anesthesiologist to suitably handle DoH, analgesia and hemodynamics at the same time, resulting in a reduction of intra-operative and post-operative side effects.



**Figure 6:** Simulation responses for patient 11 with ratio changing. The solid black line represent the BIS trend obtained with the event-based controller. The dotted black line represents the BIS obtained with a standard PID controller. Infusion rates represented with a dark green and red solid lines result from the event-based controller, whereas, the green and orange solid lines represent the infusion rates that result from the standard PID controller.

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# Paper II

## On the use of the Eleveld PKPD Model for the Design of PID Control of Anesthesia

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### Abstract

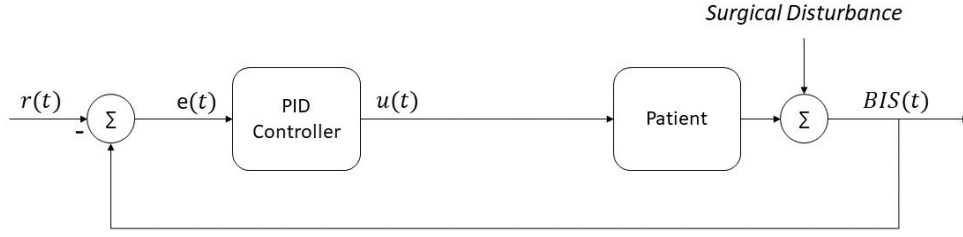
This paper investigates the use of different pharmacokinetic/pharmacodynamic models for the design of a PID-based control structure for total intravenous anesthesia. In particular, a PID controller tuned by exploiting the Schnider model for propofol administration (which has been developed for adults) in order to ensure the required robustness and performance is evaluated by considering patients modelled by using the recently developed Eleveld model. The latter is more general and, in principle, takes into account children, adults and elderly people. Simulation results show that clinically acceptable performance are obtained, disregarding the adopted model, for children and adults. On the contrary, the use of the Eleveld model to tune the controller for elderly people, for which a significant delay emerges, requires further investigation.

Originally published in Proceedings of 22nd IFAC World Congress. The original version is available at [10.1016/j.ifacol.2023.10.1428](https://doi.org/10.1016/j.ifacol.2023.10.1428).

## 1 Introduction

Total intravenous anesthesia (TIVA) has enabled surgeons to perform long and invasive surgeries without making patients feel pain. In particular, this is possible thanks to the anesthesia three main effects that are hypnosis, analgesia and muscular paralysis. Hypnosis forces the patient into an unconscious state by preventing intra-operative awareness and memorization (Mashour and Pryor, 2020). Analgesia inhibits the patient's pain sensation by suppressing the physiological response to nociceptive stimulation. Finally, muscular paralysis prevents involuntary muscle contractions that could occur during the surgical procedure. In clinical practice, an adequate anesthetized level is reached by the infusion of two different drugs, namely propofol and remifentanyl, whereas curare causes paralysis. In the operating room, the anesthesiologist usually decides the amount of drugs to administer basing on recommended infusion patterns, on his/her experience and analyzing the patient's response to external stimuli. Therefore, it is clear that the clinical environment is both complex and dynamic for the anesthesiologist. This, combined with the inherent risks of surgery and anesthesia, makes crises frequent and challenging to deal with (Oberfrank et al., 2020). For this reason, an automatic closed-loop control system for anesthesia infusion could increase patient safety by reducing side effects and recovery time, thus resulting in an improved healthcare.

In this paper, only aspects related to the propofol infusion are treated. A crucial and fundamental role in a closed-loop system is played by the controller and by the feedback sensor. In anesthesia, the bispectral index scale (BIS) is the most widespread estimator of the depth of hypnosis (DoH). This sensing device allows the electrical activity of the brain to be mapped into a dimensionless scale that ranges from 0 (EEG silence) to 100 (full brain activity). Concerning the controller, many control solutions have been developed based on a popular and largely widespread industrial controller, namely, the proportional-integral-derivative (PID) controller (Liu et al., 2006; Puri et al., 2007; Soltesz et al., 2013; Padula et al., 2017; Merigo et al., 2017; Schiavo et al., 2021, 2022). During the design and tuning phase of the controller, a key role is played by the pharmacological model used to describe the relationship between the drug dosage and its clinical effect on the patient. In fact, the robustness of the controller is a major issue to be considered in its design and, as it is typical in process control engineering, the availability of an accurate model has a major impact on the control system performance. There have been many pharmacokinetic/pharmacodynamics (PK/PD) models for propofol proposed in the literature (Marsh et al., 1991; Kataria et al., 1994; Cortinez et al., 2010; Sepulveda et al., 2011; Amutike et al., 2001), each one with its own targets (e.g., children) and constraints (Vandemoortele et al., 2022). In fact, the choice of the most appropriate PK/PD model for the PID tuning is not trivial. Up to now, the most employed model for the purpose of designing a control system is the Schnider one (Schnider et al., 1998, 1999), which has been experimentally derived by analyzing a sample of only adult patients. Based on this, a PID controller has been tuned by minimizing the worst-case integrated absolute error for a



**Figure 1:** The closed-loop control scheme.

dataset of thirteen patients that are supposed to be representative of a wide population. The patients database can be found in (Ionescu et al., 2008; Padula et al., 2017). The controller has then been tested in simulation on many other adult patients generated again with the Schnider model and its robustness in this context has been demonstrated. Recently, a new PK/PD model for propofol, denoted for brevity as the Eleveld model, has been proposed (Eleveld et al., 2018). It has the clear advantage to be general, that is, it includes children, adults and also elderly people (although it has to be pointed out that only three individuals older than 67 years have been analyzed in the development of the model). It is therefore interesting to investigate the use of such a model in the design of a feedback controller. Therefore, the aim of this paper is to evaluate the application of a PID controller designed on the Schnider model to a set of patients generated by using the Eleveld model. This will allow, on the one hand to test further the robustness of the controller by including patients that are not involved in the study population used to derive the Schnider model (in particular, children) and, on the other hand, to evaluate the suitability of the Eleveld model for the design of a control system.

## 2 Control System Description

As previously said, the control system under consideration is based on a PID controller that regulates the DoH by propofol administration and exploiting the BIS signal as a controlled variable. The control scheme is shown in Fig. 1. The PID controller has been implemented in ideal form with filtered derivative action and its transfer function is:

$$C(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{sT_d}{1 + s\frac{T_d}{N}} \right), \quad (1)$$

where  $K_p$  is the proportional gain,  $T_i$  is the integral time constant,  $T_d$  is the derivative time constant and  $N = 5$  is the parameter of the derivative action first-order filter. Moreover, the control structure implements an anti-windup strategy (conditional integration) in order to handle actuator saturation. The controller tuning has been performed by applying genetic algorithm (GA) in order to minimize the worst-case integrated absolute error,

| Parameter | Schnider Model  |                   | Eleveled Model  |                   |
|-----------|-----------------|-------------------|-----------------|-------------------|
|           | Induction Phase | Maintenance Phase | Induction Phase | Maintenance Phase |
| $K_p$     | 0.0540          | 0.2013            | 0.0764          | 0.1194            |
| $T_i$     | 314.8759        | 385.8701          | 900.8022        | 336.5807          |
| $T_d$     | 31.6219         | 13.7577           | 77.5484         | 34.8369           |

**Table 1:** PID tuning parameters for both induction and maintenance phase.

defined as:

$$IAE = \int |e(t)| dt, \quad (2)$$

where  $e(t)$  is the control error, calculated as the difference between the BIS value and the desired target value  $r(t)$  of the DoH that is fixed to 50. Firstly, for the optimization procedure, the thirteen patients, previously mentioned, have been modelled by means of the Schnider PK/PD model (Schnider et al., 1998, 1999), which describes the relationship between the propofol dose and its plasmatic concentration (i.e., pharmacokinetics) by means of three compartments. The pharmacodynamics is described by another compartment that is used to relate the plasmatic concentration to the clinical effect; this is in series with a nonlinear static function known as the Hill function (Ionescu, 2018). Summarizing, starting from the demographic variables of a patient, this fourth-compartmental model combined with the nonlinear function, is able to estimate the patient's BIS value over time. It is worth noting that separate optimizations have been performed for the induction and the maintenance phase, thus implementing a gain scheduling strategy as previously done in (Padula et al., 2017). Secondly, a PID controller has been designed based on the Eleveled model. Thus, the patients previously modelled with the Schnider model have been represented by the Eleveled one. Also in this case, a genetic algorithm has been exploited to minimize the worst-case IAE. The PID parameters obtained from the tuning procedure are listed in Table 1.

### 3 Eleveled Model Description

As previously said in Section 1, the Schnider model has been developed studying a population sample made of only adults. Thus, in principle, with this model it is not possible to describe the propofol effects on pediatric patients and, in general, this limitation could affect the controller performance. For this reason it is worth considering the recently developed Eleveled model (Eleveled et al., 2018), which is able to represent a broad population such as children, adults and elderly people, for the design of a PID controller. The model has been developed by taking into account data coming from 1033 patients and volunteers present in the open TCI (target-controlled infusion) database. The model is a three compartmental mammillary model that explores several covariates such as weight, age, post-menstrual age (PMA), height, gender, body mass index (BMI) and

presence/absence of opioids in order to improve the model prediction reliability. For the model development, a reference individual (a 35 *yr* male of 70 *kg* and 170 *cm*) is considered and allometric scaling has been exploited to scale model parameters, such as volumes of distribution and clearances, for each patient.

Summarising, the model aims to write the PK/PD model parameters with an allometric scaling approach to take into account intra- and inter-patient variability and to minimize prediction errors on patients with characteristics that stand outside the originally population involved in the study. Besides the allometric scaling, the Eleveld model exploits also a maturation model based on the PMA and introduces age dependent effect-site constants. This technique allows to scale some patient's model parameters depending on their maturation and age. In particular, the PD model is characterized by the presence of a delay function that is strictly related to the patient's age. In fact, the higher is the age, the higher is the dead time. Moreover, some changes are performed when drugs coadministration occurs or depending on the blood sample used to derive drug concentration. All these expedients make the Eleveld model suitable to a broad population since it is able to take into account several patients covariates. For the sake of brevity, model equations have been omitted in this paper.

## 4 Simulation Results

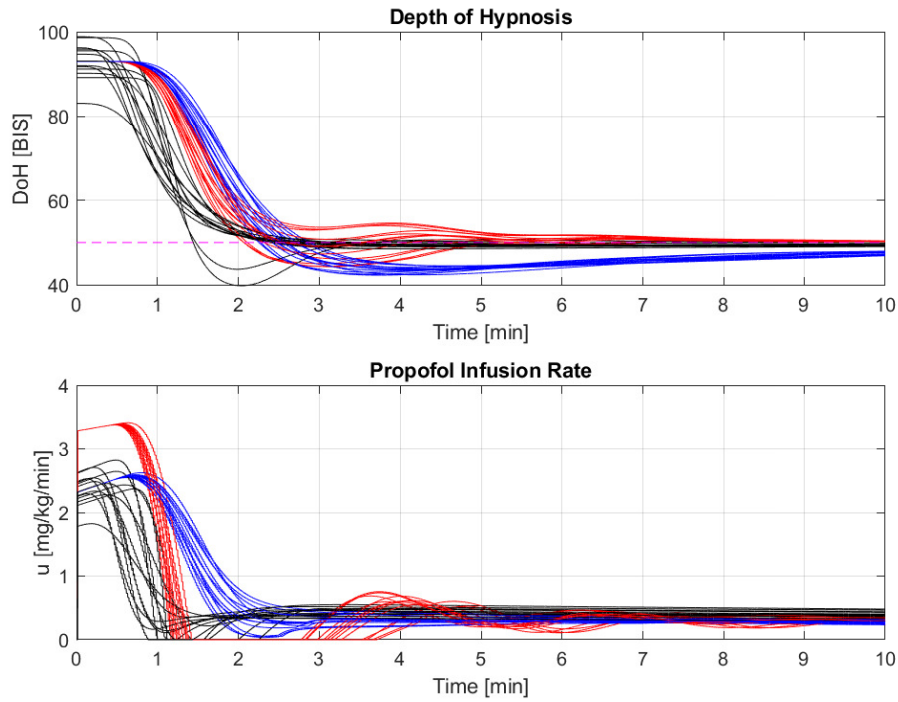
In order to prove the robustness of the control system tuned on the Schnider model and presented in Section 2, two different situations have been considered, one related to the induction phase and the other one to the maintenance phase. First, the dataset of the thirteen adults patients used for the tuning of the controller has been exploited. Then, these parameters have been suitably modified in order to meet the Eleveld model requirements and these are shown in Table 2. Hence, simulations have been performed by first considering the patients modelled with the Schnider model and then the patients modelled with the Eleveld one. Concerning the controller tuned on the Eleveld model, the simulation has been only done on its tuning database.

### 4.1 Induction Phase

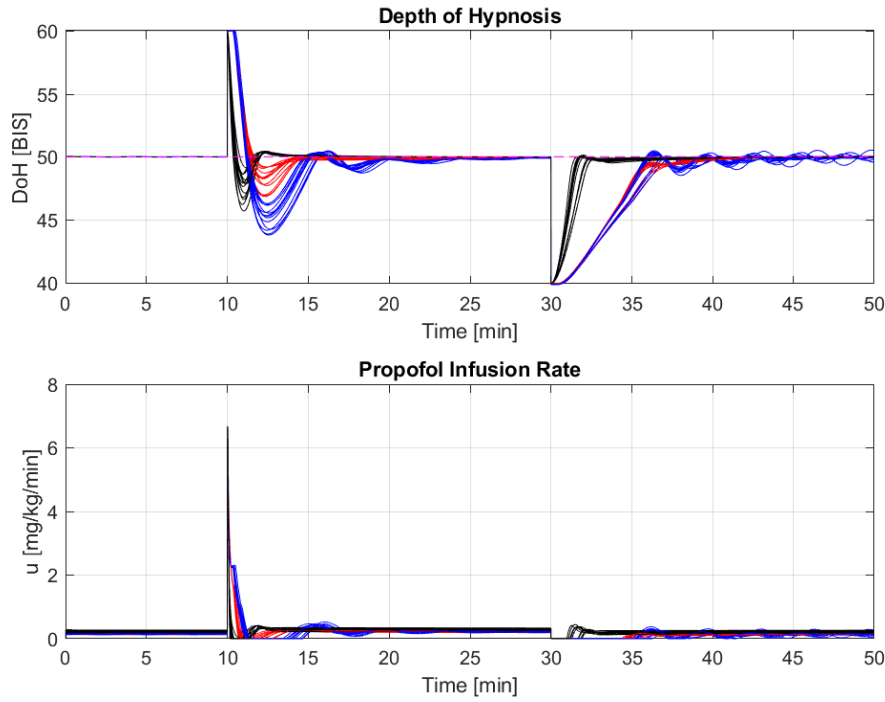
The induction phase has been simulated in a time interval of 10 minutes by applying a step reference signal from the initial BIS value to 50. Simulation results obtained from both controllers are shown in Fig. 2. From the figure it is possible to see that when the patients are modelled with the Schnider model the controller is able to complete the induction in more or less 3 minutes without causing substantial undershoot episodes. Instead, when patients are modelled with the Eleveld model, the controller tuned on Schnider model needs more time to complete the induction despite no relevant undershoots episodes are present. In any case, the difference between the two cases is very small, so that it could be said that the controller meets the clinical requirements regardless of the model used to

| Id | Age [yr] | PMA [weeks] | Hgt [cm] | Wgt [kg] | Gender | Blood Sample | Opiates |
|----|----------|-------------|----------|----------|--------|--------------|---------|
| 1  | 40       | 2120        | 163      | 54       | F      | arterial     | absent  |
| 2  | 36       | 1912        | 163      | 50       | F      | arterial     | absent  |
| 3  | 28       | 1496        | 164      | 52       | F      | arterial     | absent  |
| 4  | 50       | 2640        | 163      | 83       | F      | arterial     | absent  |
| 5  | 28       | 1496        | 164      | 60       | M      | arterial     | absent  |
| 6  | 43       | 2276        | 163      | 59       | F      | arterial     | absent  |
| 7  | 37       | 1964        | 187      | 75       | M      | arterial     | absent  |
| 8  | 38       | 2016        | 174      | 80       | F      | arterial     | absent  |
| 9  | 41       | 2172        | 170      | 70       | F      | arterial     | absent  |
| 10 | 37       | 1964        | 167      | 58       | F      | arterial     | absent  |
| 11 | 42       | 2224        | 179      | 78       | M      | arterial     | absent  |
| 12 | 34       | 1808        | 172      | 58       | F      | arterial     | absent  |
| 13 | 38       | 2016        | 169      | 65       | F      | arterial     | absent  |

**Table 2:** The dataset of adults patients with the Eleveld model parameters. The PMA has been computed as:  $age \cdot 52 + 40$ .



**Figure 2:** Induction phase simulation results for the thirteen patients. Black line: Schnider controller and patients. Blue line: Schnider controller and Eleveld patients. Red line: Eleveld controller and patients. Magenta line: BIS target.

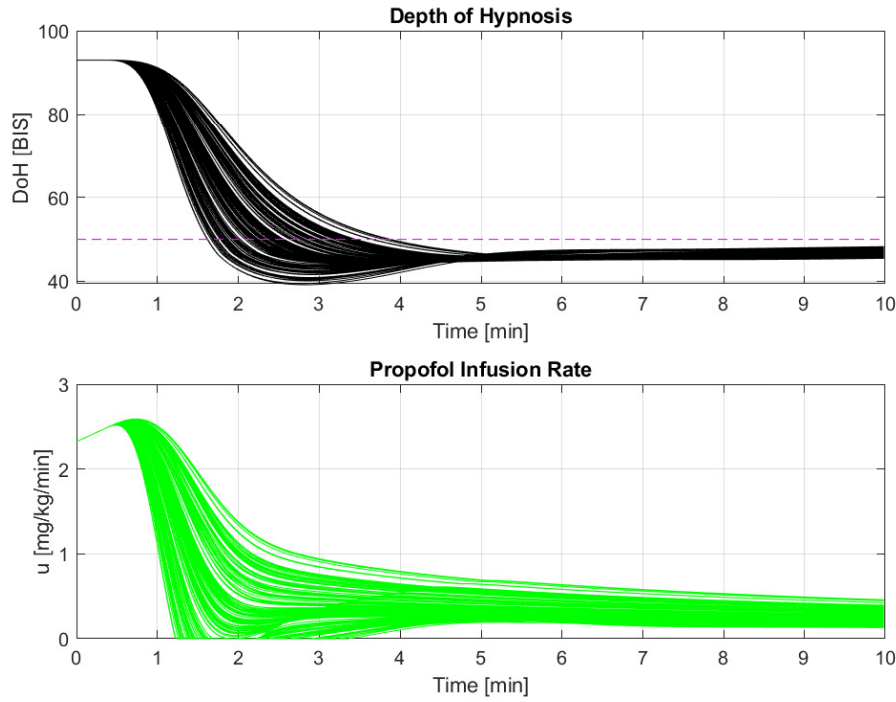


**Figure 3:** Maintenance phase simulation results for the thirteen patients. Black line: Schnider controller and patients. Blue line: Schnider controller and Eleveld patients. Red line: Eleveld controller and patients. Magenta line: BIS target.

represent the patients. The specific tuning for the Eleveld model seems to decrease the undershoot but it also shows a slow transient.

## 4.2 Maintenance Phase

The maintenance phase starts immediately after the induction phase. Since the effect of the induction dose is short, it is necessary to continuously administer propofol to maintain an adequate DoH to avoid patient intra-operative awareness. Thereby, the control task consist in maintaining the BIS level in the 40-60 range. The external stimuli coming from the surgery are seen by the control system as disturbances. These alterations are modelled like an additive signal that acts directly on the BIS. This approach has been widely proposed and studied in the literature. Thus, in this work, the double step profile proposed in (Soltesz, 2013) has been used. Moreover, the length of the simulation has been fixed to fifty minutes in which the positive step disturbance is applied at the tenth minute and the negative one at the thirtieth minute. A reasoning similar to the one followed for the induction phase has been applied also in this case. Therefore, the simulation results obtained for both controllers are shown in Fig. 3. From the figure it is possible to see that for each scenario the controller is able to maintain the BIS inside the desired range of 40-60 without causing relevant episodes of overshoot or undershoot. When patients are modelled with the Eleveld model the responses are characterized by oscillations. Anyway, these

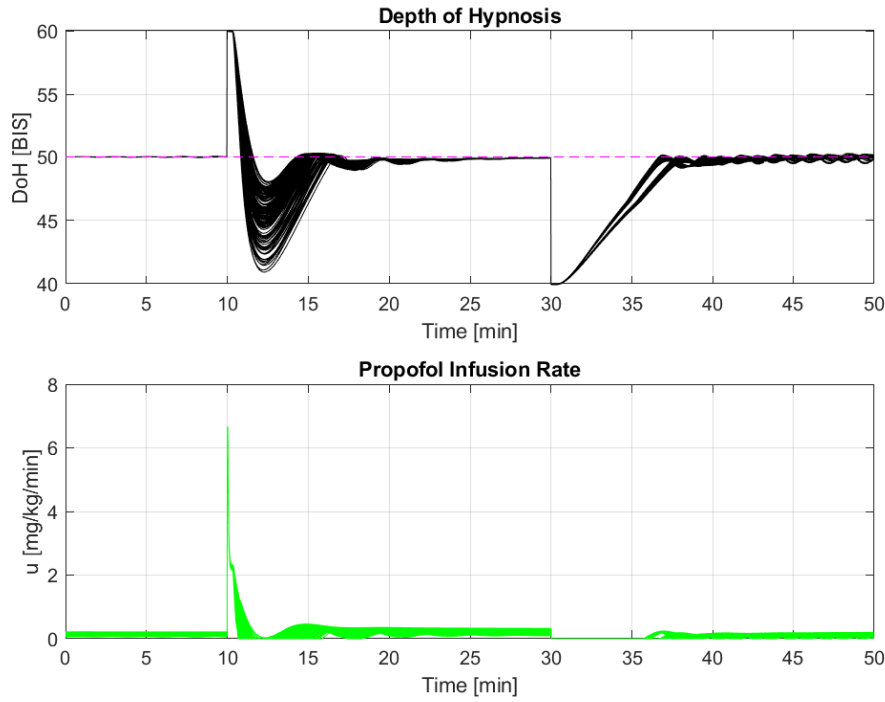


**Figure 4:** Induction phase simulation results for the 150 children modelled with the Eleveld model. The magenta line is the BIS target.

oscillations are not dangerous for patients since they have a limited and small amplitude. The specific tuning for the Eleveld model decreases the oscillations but it also provides much slower transients. In every scenario described before, the controller designed on the Schnider model seems to outperform the one tuned on the Eleveld model even if both controllers are used to infuse the drug in patients that are described with the same model used for the controller tuning.

### 4.3 Other Datasets

To further investigate the robustness of the control system, it has been chosen to create three datasets of 150 fictitious patients each, for different ranges of age. In particular, children are considered from 6 *yr* to 17 *yr*, then adults are from 18 to 60 *yr* and, finally, elderly people from 60 to 90. In all cases, patients have been derived by randomly selecting the age and the gender and then by randomly selecting the height and the body mass index in the suitable range for that age and gender. Simulations for these patients have been carried out similarly as before. The simulations results obtained for the 150 children modelled with the Eleveld model are shown in Figs. 4 and 5 for the induction and maintenance phases, respectively (note that the Schnider model does not describe the PK/PD of children and therefore this case has not been considered). It appears that the clinical specifications are met as the induction time is below 5 minutes and the rejection of disturbances is without significant oscillations.



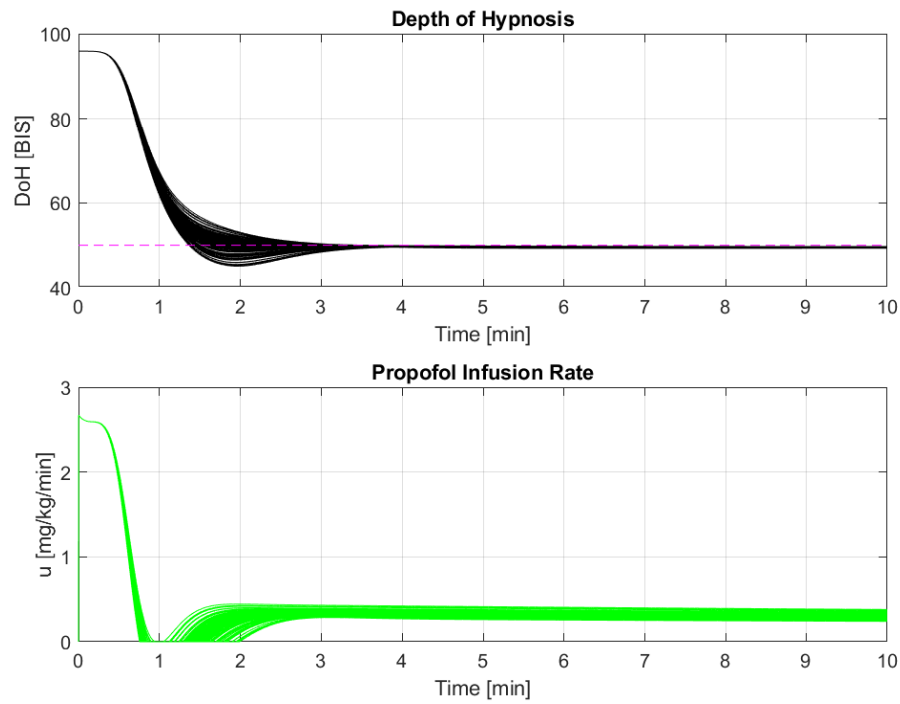
**Figure 5:** Maintenance phase simulation results for the 150 children modelled with the Eleveld model. The magenta line is the BIS target.

Figs. 6 to 9 shows the simulations results for adults with the Schnider and Eleveld models, respectively. Concerning the induction phase, the responses obtained with the Eleveld model present a slower transient and a higher undershoot, despite the BIS is always above the safety limit of 30. Consequently, it can be said that the controller is able to complete the induction but slowly. It spends about 8 minutes to reach a steady state value. This is more than the 3-5 minutes requested by the clinical practice. Regarding the maintenance phase with the Eleveld model, it appears that the oscillations that have been previously noticed in the 13 patients occur here in a more pronounced way, even if their amplitude is still acceptable.

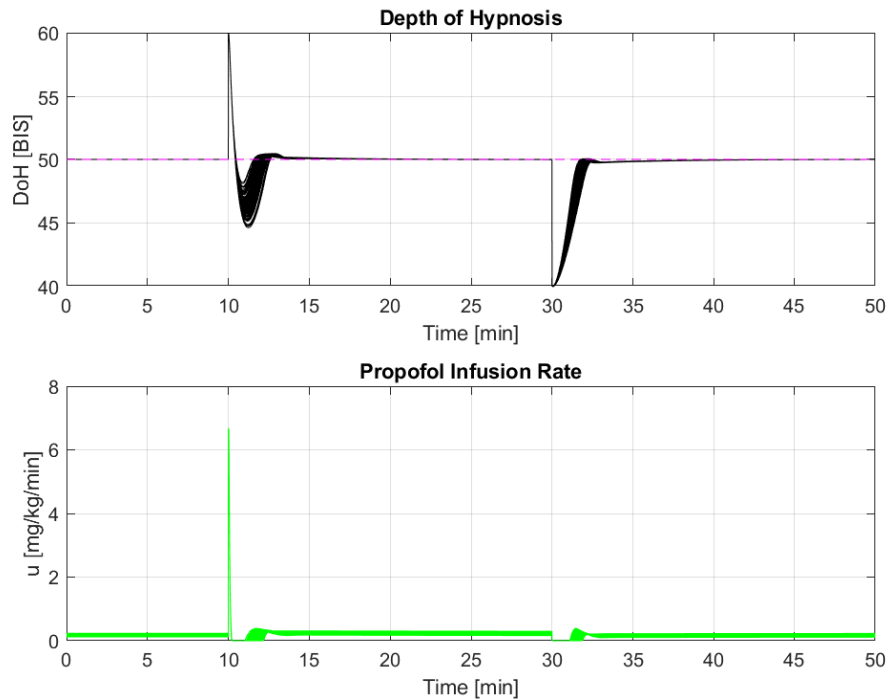
Finally, the results obtained with the elderly people are shown in Figs. 10 to 13. In this case it can be seen that, while the performance obtained with the Schnider model is acceptable, the responses obtained with the Eleveld model are not satisfactory, as the induction phase presents a large undershoot and a large settling time and there are large oscillations in the rejection of disturbances.

## 5 Discussion

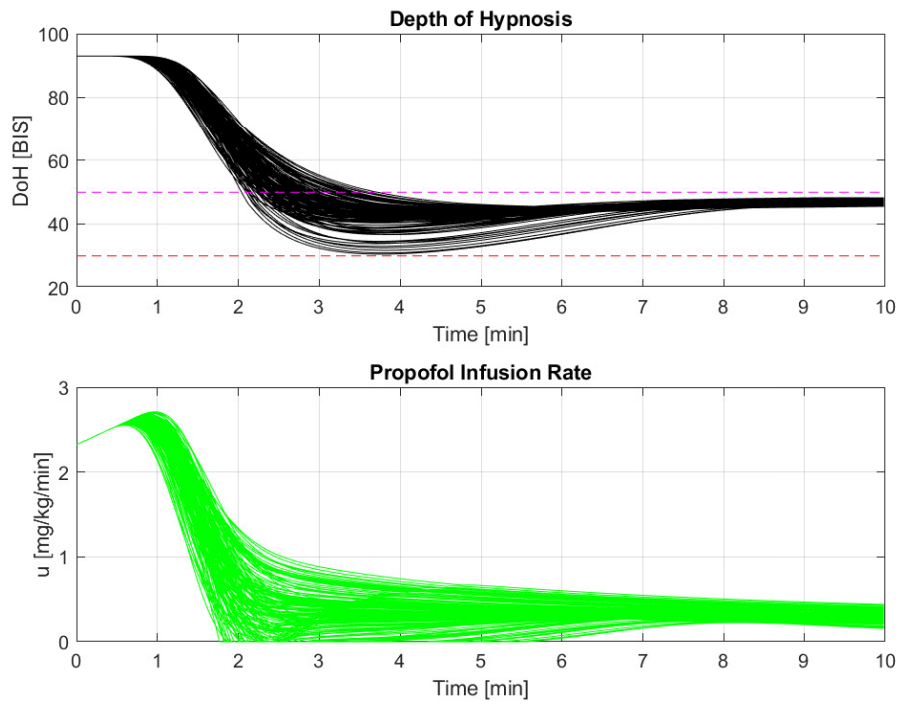
The simulation results obtained with the dataset of 13 patients used to tune the controller are satisfactory with both the Schnider and Eleveld models. If the Schnider model is then employed, the 13 patients are demonstrated to be representative of a wide



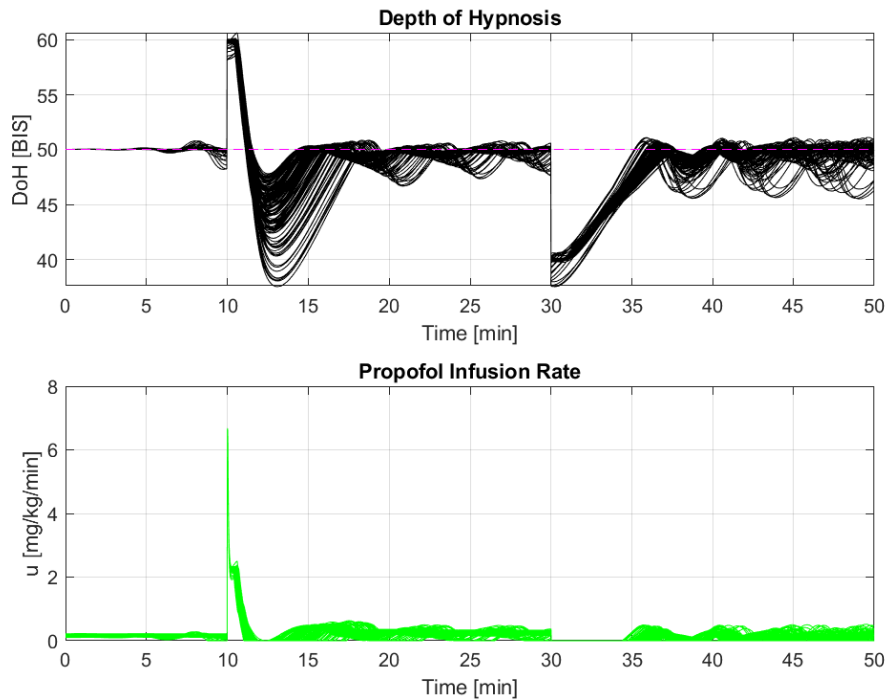
**Figure 6:** Induction phase simulation results for the 150 adults modelled with the Schnider model. The magenta line is the BIS target.



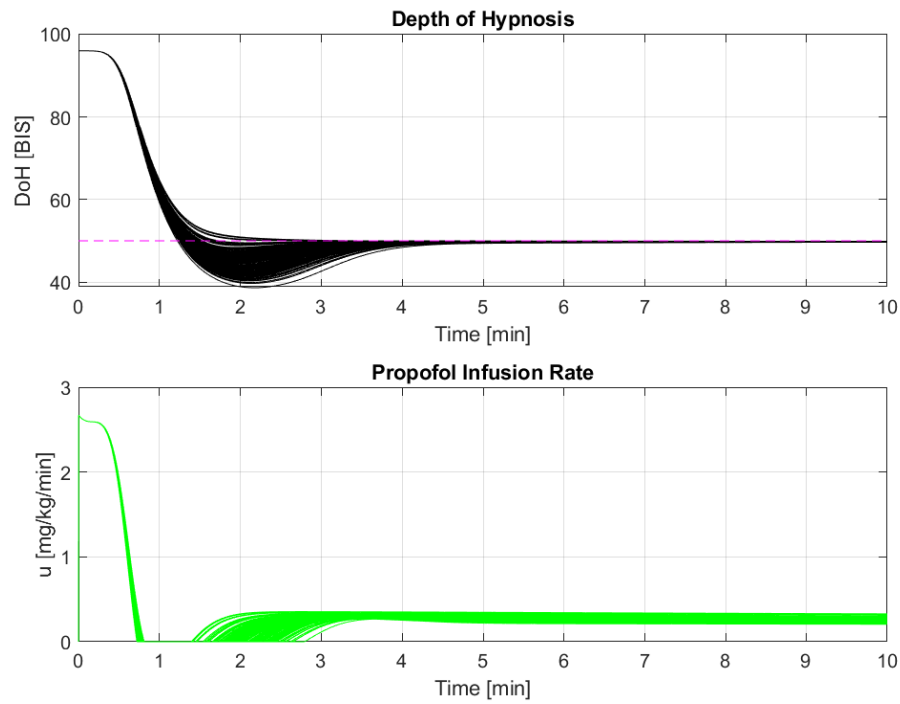
**Figure 7:** Maintenance phase simulation results for the 150 adults modelled with the Schnider model. The magenta line is the BIS target.



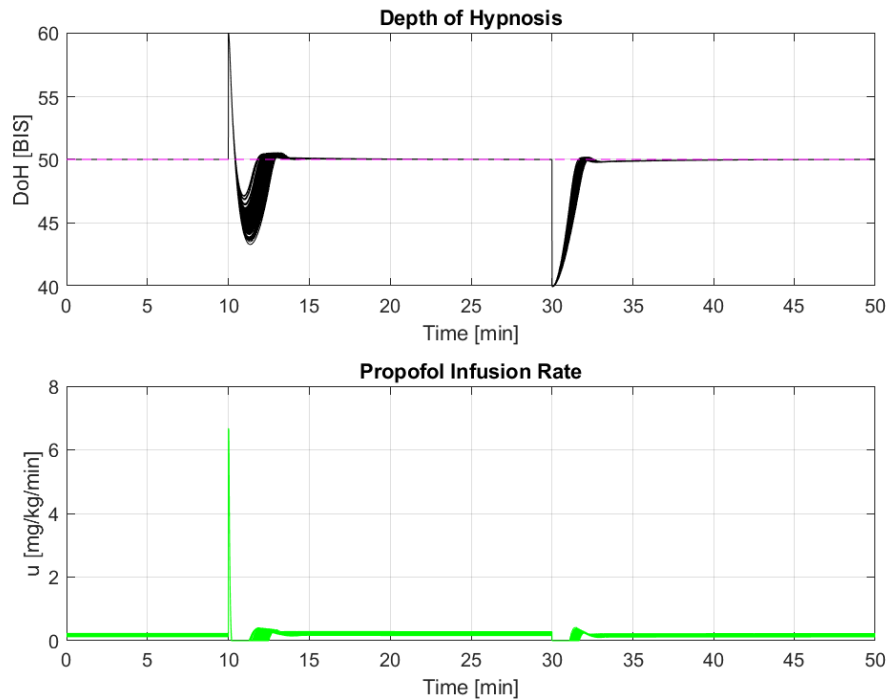
**Figure 8:** Induction phase simulation results for the 150 adults modelled with the Eleveld model. The magenta line is the BIS target. The red line is the BIS safety limit.



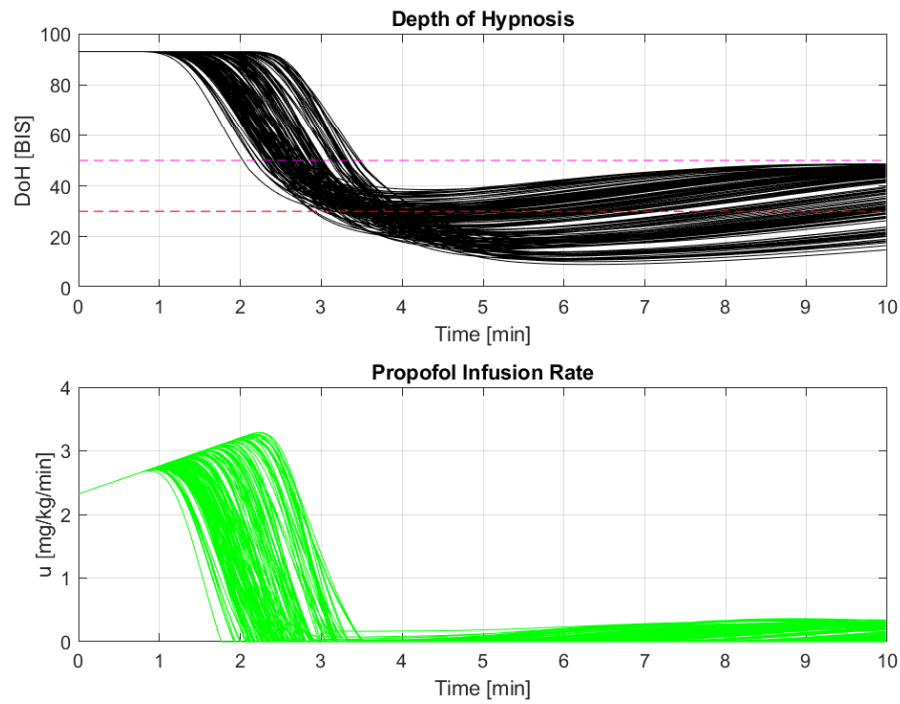
**Figure 9:** Maintenance phase simulation results for the 150 adults modelled with the Eleveld model. The magenta line is the BIS target.



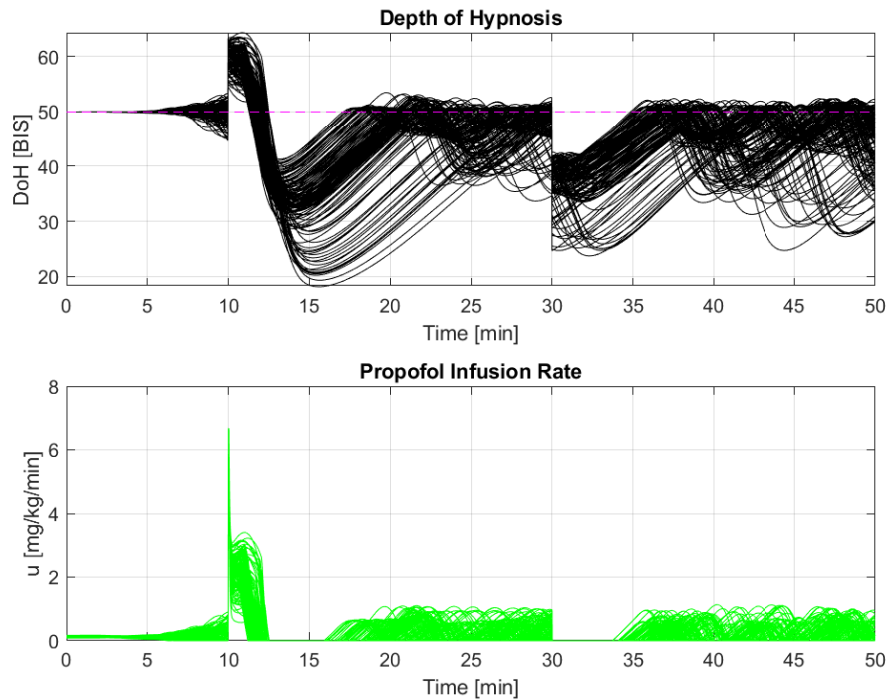
**Figure 10:** Induction phase simulation results for the 150 elderly people with the Schnider model. The magenta line is the BIS target.



**Figure 11:** Maintenance phase simulation results for the 150 elderly people modelled with the Schnider model. The magenta line is the BIS target.



**Figure 12:** Induction phase simulation results for the 150 elderly people modelled with the Eleveld model. The magenta line is the BIS target. The red line is the BIS safety limit.



**Figure 13:** Maintenance phase simulation results for the 150 elderly people modelled with the Eleveld model. The magenta line is the BIS target.

population as the clinical requirements are met for children, adults and elderly people. On the other side, if the Eleveld model is used, the PID controller meets the clinical requirements for children and adults, but fails to provide a satisfactory performance for elderly people. This can be due to the presence of a significant dead time that depends on the age of the patient. It has to be taken into account that, as already mentioned in the introduction, only three individuals older than 67 years have been taken into account in developing the model. This means that the Eleveld model could not be suitable to be employed for the design of a controller for elderly people and, in any case, the dataset of 13 patients is not representative of a wide population. Thus, the issue of which model has to be used for the controller tuning needs to be further investigated.

## 6 Conclusions

In this paper a PID-based controller for propofol administration has been tested through simulations. The general purpose Eleveld PK/PD model has been employed in order to understand if the proposed control solution, tuned basing on the Schnider model, is sensible and suitable for patients with different demographic characteristics. From the presented simulation results, it appears that the PID controller meets the clinical requirements for both models when the patient is less than 60 years old. On the other side, results are not coherent for elderly people, since patients described by the Schnider model gives satisfactory results, while those described by the Eleveld model do not, because of the presence of a large dead time that causes large oscillations. Further, the controller tuned on the Eleveld model provides slower responses in general. This imply that additional investigations are needed to evaluate the most suitable model for controller design purposes.

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# Paper III

## On the use of FOPID Controllers for Maintenance Phase of General Anesthesia

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### Abstract

This paper investigates the performance achievable with a fractional-order PID regulator controlling the Depth-of-Hypnosis (measured via the Bispectral Index Scale) through the administration of propofol during the maintenance phase of total intravenous anesthesia. In particular, two different methodologies have been applied to tune the controller: in the first case genetic algorithms (GA) have been used to minimize the integrated absolute error, while in the second case the isodamping approach –a method that targets phase margin invariance with respect to the process dc-gain– has been employed. In both cases performance has been extensively analyzed and compared with that of a standard PID controller by simulating multiple patients through a Monte Carlo method. Results demonstrate that a fractional-order PID controller can be effectively used in controlling Depth-of-Hypnosis, but the improvement with respect to a standard PID controller is marginal.

Originally published in Applied Sciences. The original version is available at [10.3390/app13137381](https://doi.org/10.3390/app13137381).

## 1 Introduction

Many closed-loop control algorithms for total intravenous anesthesia (TIVA) have been developed in the last years (Copot and Ionescu, 2014; M. Ghita and Copot, 2020) because of the benefits that an automatic control system can provide in this context. In fact, an effective control system can be a valuable tool for the anesthesiologist, who supervises the overall system, because it has the potential to limit errors caused by distraction and to reduce possible drug overdosing and underdosing, thereby increasing the safety of the patient.

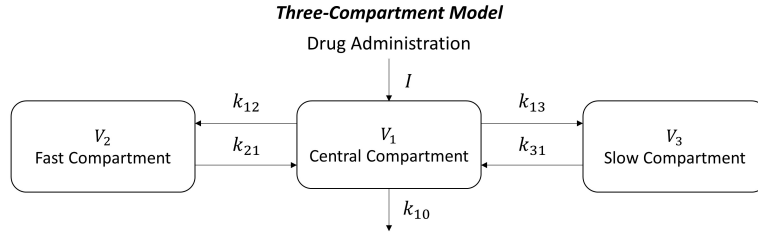
Although in TIVA also analgesia and neuromuscular blockade should be provided, the main task generally requires to control Depth-of-Hypnosis (DoH) through the hypnotic drug propofol. A feedback control system can be implemented by measuring the DoH by means of a processed electroencephalogram (pEEG) mechanism. Among these techniques, the most common one is the Bispectral Index Scale (BIS), which provides a measures of the DoH ranging from 100 (fully awake patient) to 0 (flat EEG). The overall anesthesia process consists of three phases. At the beginning there is the induction phase where the BIS has to be driven to the set-point value of 50 in a time interval of less than 5 minutes and without an excessive undershoot that might cause problems to the patient. Usually, this is achieved through the administration of a bolus of propofol, where the amount of drug depends on the physical characteristics of the patient (thus, by applying a feedforward action from a control system point of view). Once the BIS has settled to the set-point value, the maintenance phase starts. During maintenance, the control task is to keep the BIS in the range from 40 to 60 despite the surgical activity and the presence of noxious stimuli (excessively low values can result in dangerous hypotension or burst suppression episodes, while excessively high values can result in traumatic patient awareness). Finally, in the emergence phase the drug administration is stopped and the patient wakes up. The maintenance phase can last for hours and is critical in anesthesia, which implies that a control system should be designed by mainly considering the disturbance rejection task. Further, the controller should also be robust to intra- and inter-patient variability, since satisfactory clinical outcomes should be guaranteed for all the patients.

The nonlinearity of the pharmacokinetic/pharmacodynamic (PK/PD) model (Padula et al., 2017) makes the control design challenging and for this reason many approaches have been proposed in the literature. Proportional-Integral-Derivative (PID) controllers have been widely investigated as they are the most widespread controllers in industry and, indeed, they have been proven to be very effective also in anesthesia (Padula et al., 2017; Liu et al., 2006; Puri et al., 2007; Soltész et al., 2013; Merigo et al., 2017; Schiavo et al., 2021b, 2022). Some variations of the standard PID algorithm have also been devised, including the event-based PID controller, which has been shown to be able to better mimic the behavior of the anesthesiologist (Merigo et al., 2017). In the context of PID control, a great interest is in the use of fractional-order PID (FOPID) controllers as they provide additional flexibility in the controller design which, in principle, should result in a better performance.

Indeed, a FOPID controller has five parameters to tune: in addition to the classic three parameters (proportional gain, integral time constant and derivative time constant), also the integral and derivative orders can be freely chosen as real numbers and this implies, for example, that a loop shaping design can be improved. The use of fractional control in anesthesia has already been considered. In particular, a CRONE controller has been firstly applied in (Dumont et al., 2009) for the DoH control where the  $WAV_{CNS}$  system is used instead of the BIS, resulting in a high-order controller. The CRONE approach has also been used in (B. Patel and Sarvaia, 2020) for the design of a fault-tolerant control system consisting of a PID controller with a fractional-order filter. A fractional adaptive high-gain controller has been proposed in (Alavi and Tabatabaei, 2019), where the assessment of the controller performance is made by considering four patients. A fractional-order closed-loop model reference adaptive control has been presented in (Navarro-Guerrero and Tang, 2017, 2018) with the main aim to increase the robustness of the system.

Regarding FOPID controllers specifically, they have been employed for the DoH control in (Copot et al., 2017), where the isodamping approach (Chen and Moore, 2005) has been used to tune a FOPI controller and the methodology has been evaluated by considering 24 patients. A more general framework, involving also hemodynamic variables, has been considered in (E. Hegedus and Muresan, 2021; E. T. Hegedus and Muresan, 2022) and also in this case the FOPID controllers have been tested on the same 24 patients. Finally, a multivariable approach targeted to the control of cardiac output and mean arterial pressure has been presented in (Sahoo et al., 2020; Birs et al., 2019; D. Copot and Kovacs, 2020). Despite some pioneering studies on the use of fractional control in anesthesia, it appears that a thorough analysis of the performance achievable with a FOPID controller and a rigorous comparison with PID controllers are still missing. Indeed, a FOPID controller is more complex than a PID controller and therefore it should provide clear advantages with respect to its integer-order counterpart to justify its adoption. In this paper we provide such an analysis. In particular, we tune both a PID controller and a FOPID controller by using genetic algorithms to minimize the worst-case integrated absolute error (IAE) over a dataset of 13 patients that is representative of a wide population. Note that this approach has already been proven to be effective for PID controllers (Padula et al., 2017) and has also been confirmed by clinical results (Schiavo et al., 2021a). The obtained controllers are then tested on many virtual patients, generated with Monte Carlo method, in order to consider both inter- and intra-patient variability. In addition, a FOPID controller is designed by also applying the isodamping approach (M. Beschi, 2017) and tested on the same set of patients generated by the Monte Carlo method. In this way, the two typical options for the design of the FOPID controller are both considered.

XXX The paper is organized as follows. The patient model, the control architectures and the design of the controllers are explained in Section 2. The extensive simulation results are presented in Section 3 and discussed in Section 4. Finally, conclusions are drawn in Section 5 XXX.



**Figure 1:** Schematic of the pharmacokinetics compartmental model.

## 2 Materials and Methods

The aim of the paper is to compare the performance achieved by a FOPID and PID controllers. To this end, it is essential to design the controllers optimizing the same functional, so that the comparison is fair, which in turn requires the PK/PD model of the patient.

### 2.1 Patient Model

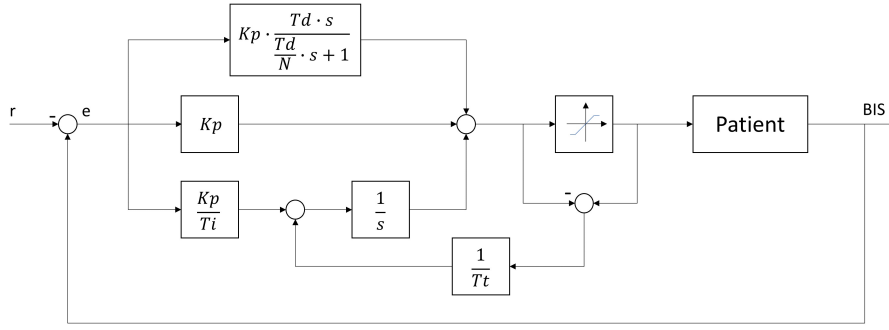
In the design of the controller, a key role is played by the model used to represent the patient during the propofol administration. The well-known Schnider PK/PD model (Schnider et al., 1998, 1999) has been employed in this study. Pharmacokinetics describes the relationship between the administered drug and its plasmatic concentration, whilst pharmacodynamics describes the relationship between the plasmatic concentration and the clinical effect on the human body. A mammillary three-compartmental model is used for pharmacokinetics of propofol. In this model structure there are two peripheral compartments and a central compartment, see Figure 1. Each compartment describes cumulative volumes that have the same drug concentration. These compartments interact with each other by transferring drug, according to the following mass flow equations that describe this exchange:

$$\begin{aligned}
 \dot{q}_1(t) &= -(k_{10} + k_{12} + k_{13})q_1(t) + k_{21}q_2(t) + k_{31}q_3(t) + u(t) \\
 \dot{q}_2(t) &= k_{12}q_1(t) - k_{21}q_2(t) \\
 \dot{q}_3(t) &= k_{13}q_1(t) - k_{31}q_3(t)
 \end{aligned} \tag{1}$$

where  $u(t)$  [mg/min] is the drug infusion rate,  $q_i(t)$  [mg] is the quantity of drug in each compartment and  $k_{ij}$  (for  $i \neq j$ ) [ $\text{min}^{-1}$ ] represents the drug transfer frequency from the  $i$ th to the  $j$ th compartment. The output of this model is the plasmatic concentration of propofol, that is:

$$C_p(t) = \frac{q_1(t)}{V_1}, \quad \left[ \frac{\text{mg}}{\text{L}} \right] \tag{2}$$

where  $V_1$  represents the volume of the primary compartment. The output  $C_p(t)$  of the PK model is the input of the PD model, which describes that relation between the plasmatic concentration and the BIS value. A linear dynamic part relates the plasmatic



**Figure 2:** PID-based control structure.

concentration of propofol in the central compartment to the drug concentration in the effect-site compartment. From the metabolism of the cerebral cortex it is possible to write:

$$\dot{C}_e(t) = k_{e0}(C_p(t) - C_e(t)), \quad (3)$$

where  $k_{e0}$  quantifies the lag time and its estimated value is:

$$k_{e0} = 0.0495. \quad [min^{-1}] \quad (4)$$

The last part of the PD model is an algebraic nonlinearity which describes the relationship between the effect-site concentration and the BIS value (the clinical effect of the drug). It is represented by a sigmoid curve referred to as Hill function:

$$BIS(t) = E_0 - E_{max} \left( \frac{C_e(t)^\gamma}{C_{e50}^\gamma + C_e(t)^\gamma} \right), \quad (5)$$

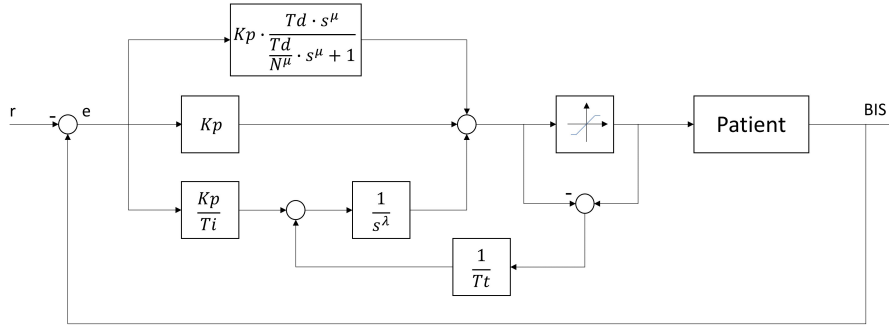
where  $E_0$  is the baseline effect that represents the initial drug-free state of the patient,  $E_0 - E_{max}$  is the maximum reachable clinical effect,  $C_e$  is the value of the drug concentration inside the effect-site,  $\gamma$  represents the slope of the sigmoidal curve and  $C_{e50}$  is the drug concentration that is necessary to reach 50% of the maximal effect.

## 2.2 PID controller

The (standard) PID control scheme that has been considered in this paper is shown in Figure 2. The PID controller is in ideal form, that is, its transfer function is

$$C(s) = K_p \left( 1 + \frac{1}{T_i s} + \frac{T_d s}{\frac{T_d}{N} s + 1} \right), \quad (6)$$

where  $K_p$  is the proportional gain,  $T_i$  is the integral time constant and  $T_d$  is the derivative action time constant. The derivative action is filtered using of a first-order system with  $N = 5$  (Visioli, 2006). Further, an anti-windup back calculation strategy (where  $T_t = \sqrt{T_i T_d}$  is the tracking time constant) is employed (Visioli, 2006). The presence of the anti-windup



**Figure 3:** FOPID-based control structure.

is necessary to handle the actuator saturation. It is easily understandable that this clinical syringe pumps can not have a negative infusion rate, thus the lower saturation limit is set to 0. The upper saturation limit depends on which type of infusion pump is used since the rate is related to the syringe size. In this work, the specifications of a Graseby™ 3500 pump have been used to model the surgical equipment available in a typical surgery room. Accordingly, the maximum flow rate of 1200 [ml/h] has been set, resulting in a maximum infusion rate of 6.67 [mg/sec] by considering a propofol concentration of 20 [mg/ml].

The controller has been tuned by minimizing the worst-case integrated absolute error (IAE) for a specific set of 13 patients representative of a wide population, see (Ionescu et al., 2008; Padula et al., 2017) for the details of the patients demographics. The IAE is defined as

$$IAE = \int_0^{\infty} |BIS(t) - r(t)| dt, \quad (7)$$

where  $BIS(t)$  is the value of the BIS signal of the patient at time  $t$  and  $r(t) = 50$  is its reference value. The optimization problem has been solved in MATLAB by using genetic algorithms with a population size of 100. A Gaussian mutation has been used to add a random number taken from a Gaussian distribution with mean 0 to each entry of the parent vector, thus resulting in a random perturbation of the individuals which will belong to the future generation. Furthermore, a scattered crossover has also been employed to create a random binary vector. The genetic algorithm selects hereditary genes from the first parent when the random vector element is a 1, and the genes from the second parent where the vector has a 0. Then, the selected genes are combined to form the child. The resulting optimal values of  $K_p$ ,  $T_i$ ,  $T_d$  and  $T_t$  are shown in Table 1.

### 2.3 FOPID controller

The transfer function of the FOPID controller is

$$C(s) = K_p \left( 1 + \frac{1}{T_i s^\lambda} + \frac{T_d s^\mu}{T_d^\mu s^\mu + 1} \right), \quad (8)$$

where  $\lambda$  and  $\mu$  are the fractional order terms of the integral and derivative action, respectively. These new parameters introduce, compared to the PID controller, additional design flexibility, which can be exploited to improve the robustness/performance trade-off. Looking at the control scheme, shown in Figure 3, it is possible to see that, also in this case, a back-calculation anti-windup technique has been implemented (F. Padula and Pagnoni, 2012). The advantage of the back-calculation approach is that it relies on the integrator own dynamics, thereby making it suitable for PID and FOPID alike.

To implement a fractional-order controller it is necessary to approximate the non-integer order part with a transfer function that consists of a series of zeros and poles of integer order. In this context, the CRONE approximation (Oustaloup et al., 2006) has been used with 8 pairs of poles and zeros and within a range of frequencies that goes from  $10^{-4}$  to  $10$  [rad/s].

Two different methods have been employed to tune the FOPID controller. In the first case, the FOPID controller has been tuned by applying the same methodology employed for the PID controller, namely, by minimizing the worst-case IAE for the set of 13 patients. The second method exploits the isodamping property. This approach consists in flattening the phase at the gain crossover frequency to guarantee zero phase margin variations with respect to the changes in the process dc-gain (M. Beschi and Visioli, 2017). In this context, a nominal process model is needed to design the controller. The demographics values of the thirteenth patient of the previously mentioned database has been used as reference. Moreover, the model nonlinearity, i.e., the Hill function, has been linearized around the BIS value of 50. Thus, the process can be written as:

$$P(s) = K \frac{\left(\frac{s}{z_1} + 1\right) \left(\frac{s}{z_2} + 1\right)}{\left(\frac{s}{p_1} + 1\right) \left(\frac{s}{p_2} + 1\right) \left(\frac{s}{p_3} + 1\right) \left(\frac{s}{p_4} + 1\right)}, \quad (9)$$

where  $z_1$ ,  $z_2$  and  $p_1$ ,  $p_2$ ,  $p_3$  are the zeroes and poles that come from the PK model,  $p_4$  is the pole deriving from the PD model and  $K$  is the product of the dc-gains of the PK model, the PD model and the slope of the Hill function at  $BIS = 50$ . More precisely, the linearized Hill function is

$$K_{Hill} = E_{max} \left[ \frac{\gamma C e_{ref}^{\gamma-1} C e_{50}^{\gamma}}{\left(C e_{ref}^{\gamma} + C e_{50}^{\gamma}\right)^2} \right], \quad (10)$$

where  $C e_{ref}$  is the drug concentration value in the patient that produces a BIS equal to 50, and it is calculated as follows:

$$C e_{ref} = \left[ \frac{C e_{50}^{\gamma} (E_0 - 50)}{E_{max} + 50 - E_0} \right]^{1/\gamma}. \quad (11)$$

The values of  $E_0$ ,  $E_{max}$ ,  $C e_{50}$  and  $\gamma$  have been taken from (Vanluchene et al., 2004). The optimal controller parameters have then been determined by solving an optimization

problem which minimizes the maximum sensitivity  $M_s$ , defined as,

$$M_s := \max_{\omega} |S(j\omega)| = \max_{\omega} \left| \frac{1}{1 + C(j\omega)P(j\omega)} \right|. \quad (12)$$

subject to the following frequency constraints:

- $\omega_c = \bar{\omega}_c$  (desired gain crossover frequency);
- $\phi_m = \bar{\phi}_m$  (desired phase margin);
- $\frac{d\phi_m}{dx} = 0$  (isodamping condition).

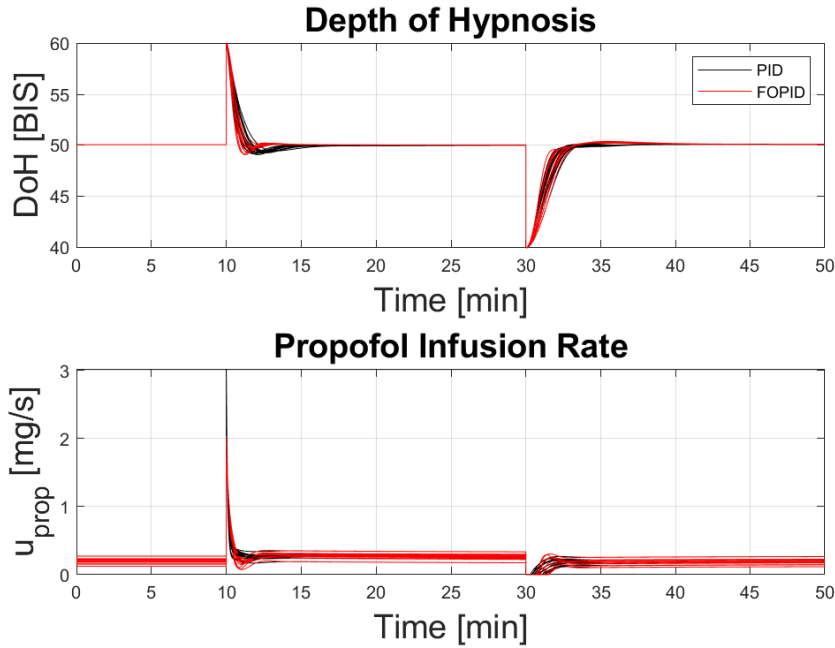
Two sets of values of  $\bar{\omega}_c$  and  $\bar{\phi}_m$  have been selected (thus obtaining two sets of optimal FOPID parameters). These sets have been determined by considering the frequency response of the loop transfer function  $L(s) = C(s)P(s)$ , where each one of the linearized models of the 13 patients is in series with either the PID controller tuned with the optimization method described in Section 2.2 or the PID controller presented in (Schiavo et al., 2021b), where an individualized approach has been employed. In particular, for each one of the 13 patients, the values of the gain crossover frequency and of the phase margin have been determined and the resulting average values have been used as constraints in the isodamping optimization problem. The first case (from PID controller of Section 2.2), is denoted as ISO1, and has  $\bar{\omega}_c = 0.08$  [rad/s] and  $\bar{\phi}_m = 57.5^\circ$ . The second case (from PID controller designed in (Schiavo et al., 2021b)) is denoted as ISO2 and consists of  $\bar{\omega}_c = 0.03$  [rad/s] and  $\bar{\phi}_m = 65^\circ$ . Note that the second set should provide a slower and more robust controller. In fact, from the first set a worst-case maximum sensitivity of 1.204 has been obtained, while using the second set of constraints yields  $M_s = 1.053$ . Indeed, two different design options have been considered in order to thoroughly evaluate the effectiveness of the isodamping approach in different contexts. Genetic algorithms have been exploited also in this case to solve the optimization problem. However, in this scenario, the problem is subject to some equality constraints, which causes the genetic algorithms to solve many subproblems at each iteration. For this purpose, the default mutation function 'mutationadaptfeasible' for constrained GA problems has been used. This function randomly generates directions that are adaptive with respect to the last successful or unsuccessful generation. The mutation chooses a direction and step length that satisfies bounds and linear constraints. A constraints tolerance equals to  $1 \times 10^{-4}$  have been used. The resulting optimal values of the controller parameters are shown in Table 1. Note that  $N$  has been fixed to 5 for all controllers and all design procedures.

### 3 Results

In this section the simulation results are presented. It has been chosen to simulate a maintenance phase of 50 minutes. During this time interval the control task is to maintain the BIS level at the desired set-point value. The double step signal proposed in

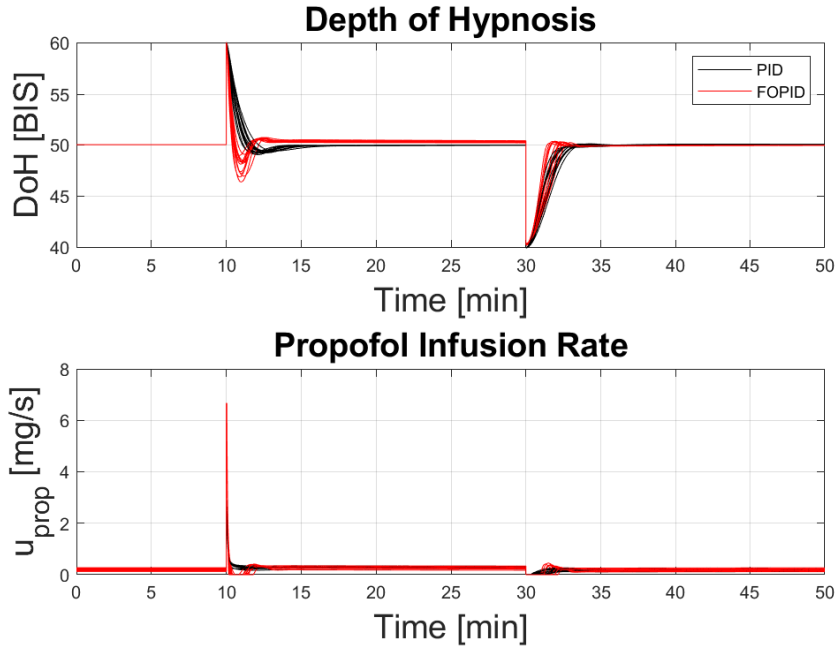
| Controller | $K_p$  | $T_i$ | $T_d$ | $T_t$ | $\lambda$ | $\mu$  | IAE    |
|------------|--------|-------|-------|-------|-----------|--------|--------|
| PID        | 0.0458 | 156.4 | 22.34 | 84.44 | -         | -      | 1685.2 |
| FOPID IAE  | 0.0393 | 59.56 | 22.94 | 89.96 | 0.8467    | 0.7978 | 1531.3 |
| FOPID ISO1 | 0.2053 | 207.1 | 13.01 | 51.90 | 0.1136    | 1.005  | 1695.9 |
| FOPID ISO2 | 0.0552 | 373.9 | 30.34 | 106.5 | 0.9994    | 1.2084 | 2354.1 |

**Table 1:** Tuning parameters for each controller. Note that for the isodamping scenarios (ISO) the value of  $T_t$  has been computed as  $\sqrt{T_i T_d}$ . The worst case IAE achieved on the 13 patients is shown in the IAE column.



**Figure 4:** Simulation responses obtained with the 13 patients of the tuning procedure. Black solid line: PID controller. Red solid line: FOPID controller.

(Soltesz, 2013) has been exploited to model the external stimuli coming from the surgery. In particular, a positive step signal (at the tenth minute) with amplitude 10 is followed, after 20 minutes, by a negative step of the same amplitude. Initially, the 13 patients of the design database have been analyzed. Figure 4 shows the responses obtained by the PID and the FOPID controllers both tuned by minimizing the IAE. In this scenario, the two controllers perform in a similar way in rejecting both the positive and the negative steps. A marginal difference can be found in the positive step rejection, with the FOPID controller being slightly faster compared to the PID controller, whilst the two behave virtually in the same way with the negative step. Figure 5 presents the results obtained with the FOPID tuned with the isodamping approach where the maximum sensitivity is minimized subject to a gain crossover frequency of 0.08 [rad/s] and a desired phase margin of  $57.5^\circ$  (ISO1). The performance of the PID and FOPID controllers is different,

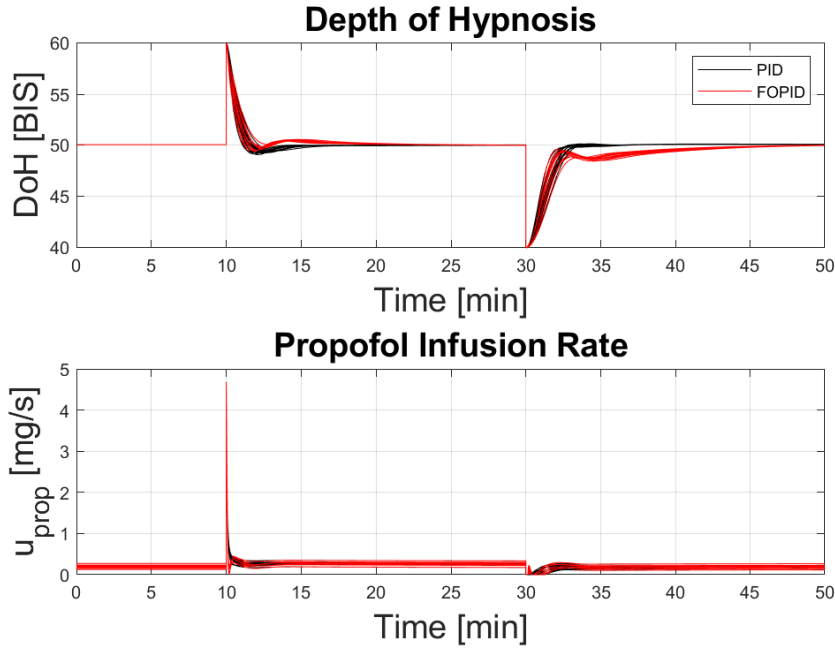


**Figure 5:** Simulation responses obtained with the 13 patients of the tuning procedure. Black solid line: PID controller. Red solid line: FOPID ISO1 controller.

with the FOPID providing a faster transient response but also with a more pronounced undershoot. This is mainly due to the larger value of the proportional gain  $K_p$ , see Table 1. This behavior is also noticeable in the rejection of the negative step. Here, however, the FOPID is again faster but the overshoot is minimal, leading to an overall much better transient response. Figure 6 shows the responses obtained with the FOPID tuned by applying the isodamping approach subject to a gain crossover frequency of 0.03 [rad/s] and a phase margin of  $65^\circ$  (ISO2) (again, in comparison with the PID controller). The PID and the FOPID provide more or less the same performance in rejecting the positive step. Conversely, the controllers have a different behavior in rejecting the negative disturbance. Here, the FOPID presents a slower and a more damped transient response with respect to the PID, causing a delay in reaching the steady-state value. All these considerations are confirmed from the performance indices proposed in (Ionescu et al., 2008), i.e.,

- Time-to-Target (TT): the time interval required to the BIS value to enter for the first time in the range of  $50 \pm 10\%$ ;
- BIS-NADIR: the lowest or highest reached BIS value during the whole control interval for a positive or negative step, respectively.

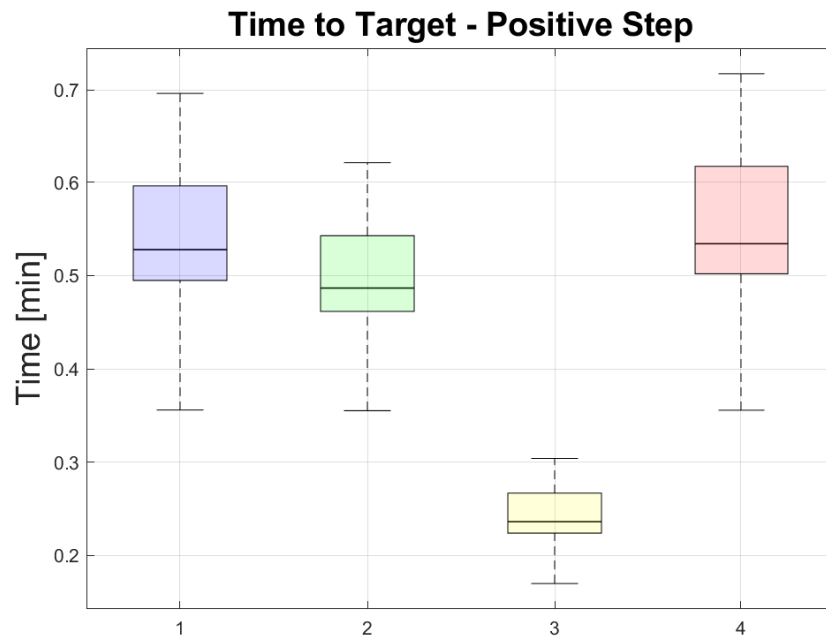
Figures 7 and 8 show the Time-to-Target boxplot for each controller. The FOPID ISO1 (yellow box), since it is more aggressive, is faster compared to the others in rejecting disturbances. However, looking at Figure 9 and 10, this controller presents more pronounced undershoots and overshoots. The performance provided by the other three controllers is



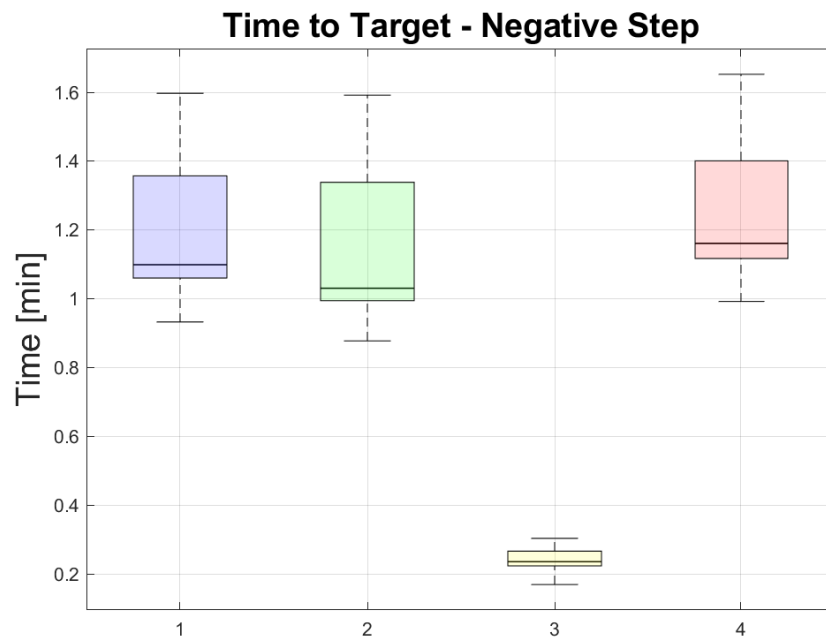
**Figure 6:** Simulation responses obtained with the 13 patients of the tuning procedure. Black solid line: PID controller. Red solid line: FOPID ISO2 controller.

very similar when rejecting both the positive and the negative steps. Overall, it can be concluded that all the controllers satisfy the clinical requirements and there are no major differences between them. In order to provide a more rigorous comparison, the controllers have been tested on a much larger population of patients than the 13 individual set used for the designing. New patients have been generated through the Monte Carlo method presented in (Schiavo et al., 2021b) and both inter-patient and intra-patient variabilities have been considered. In particular, a set of 500 patients with different demographic data has been created to study inter-patient variability. Further, 500 patients with different model parameters have been generated from each of the 13 patients in the original database to investigate intra-patient variability. Hence, a diverse set totaling 6500 patients has been used to analyze the performance of the controllers.

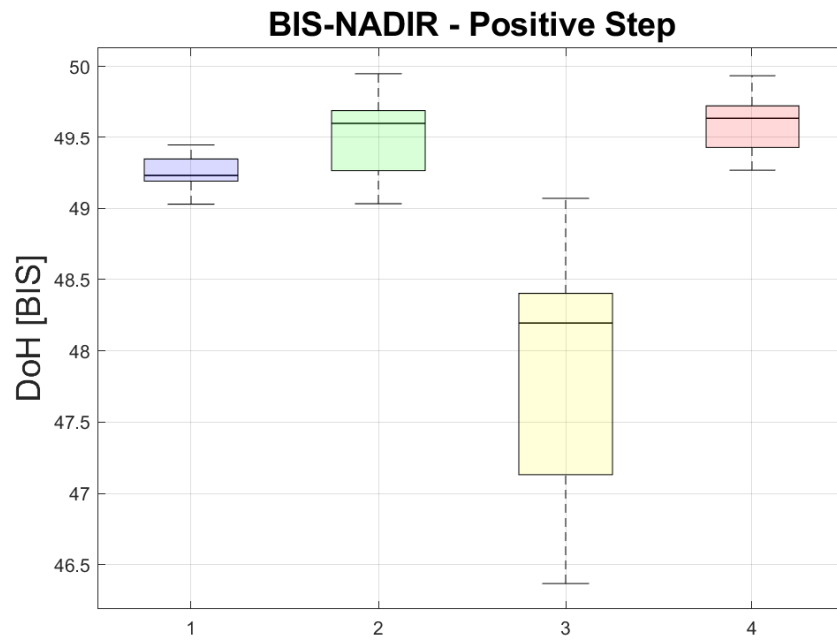
Figure 11 shows the comparison between the PID and the FOPID, both tuned by minimizing the IAE. The FOPID controller presents a slightly larger undershoot in the positive step rejection. As expected, the performance is virtually the same in rejecting the negative step. The results obtained with the FOPID ISO1 are shown in Figure 12. Also in this scenario, results confirm that the controller is more aggressive and a larger undershoot occurs. In fact, this controller is less robust than the others. Figure 13 shows the results obtained with the FOPID ISO2. Here, the issues in the rejection of the negative step are present again. It is important to underline that the proposed control solution meets the control system requirements for each of the 500 patients. On average, all the designed controllers demonstrated a satisfactory robustness to inter-patient variability, as clinical requirements



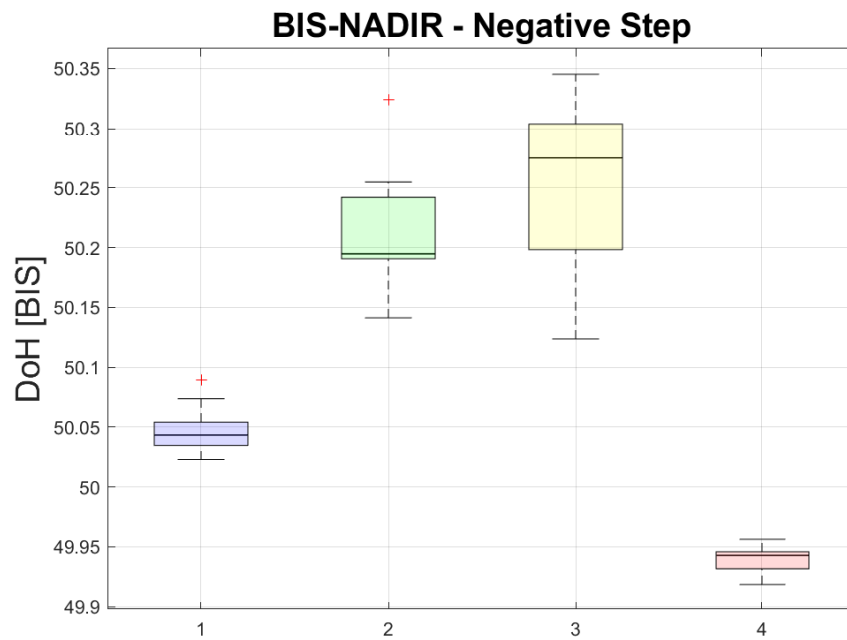
**Figure 7:** Time-to-Target indices for each controller with a positive step. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



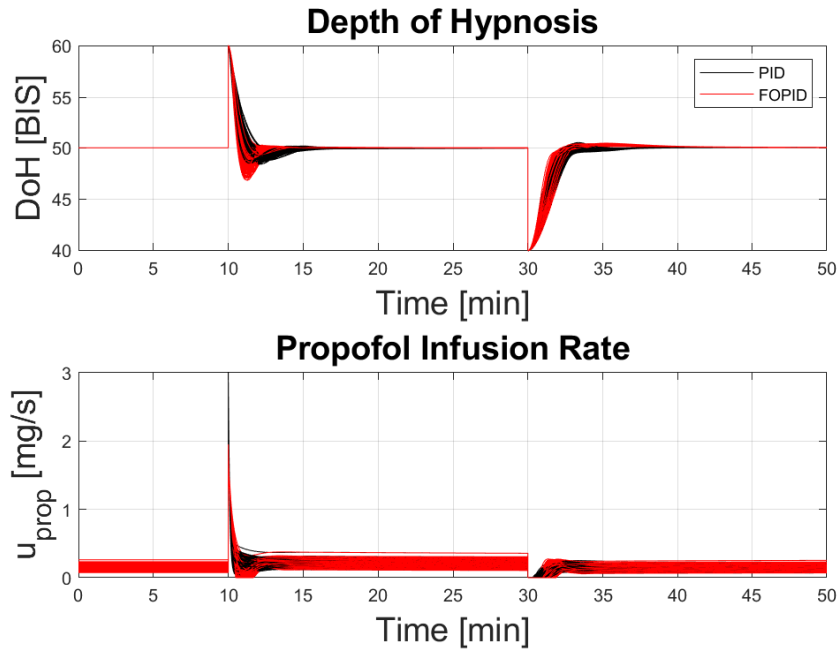
**Figure 8:** Time-to-Target indices for each controller with a negative step. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



**Figure 9:** BIS-NADIR indices for each controller with a positive step. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.

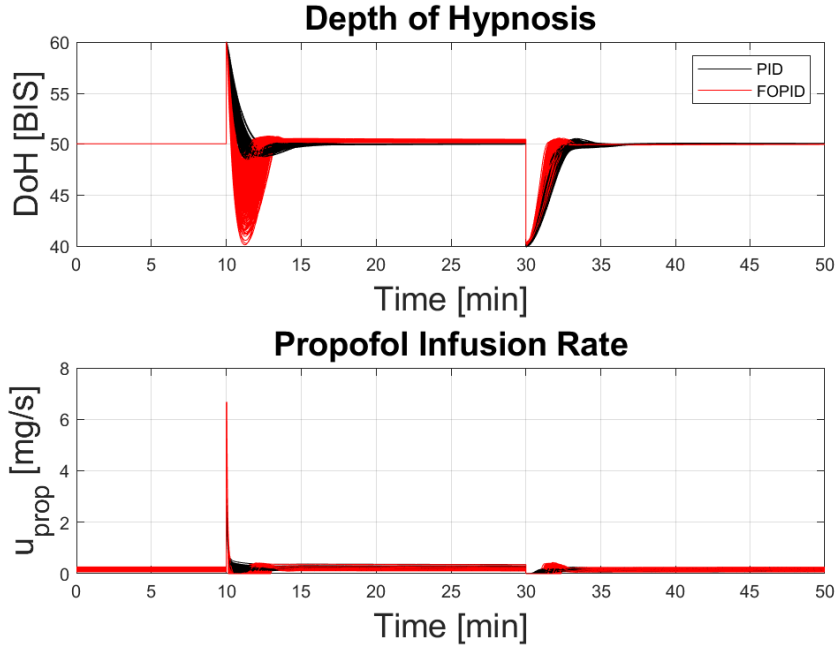


**Figure 10:** BIS-NADIR indices for each controller with a negative step. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.

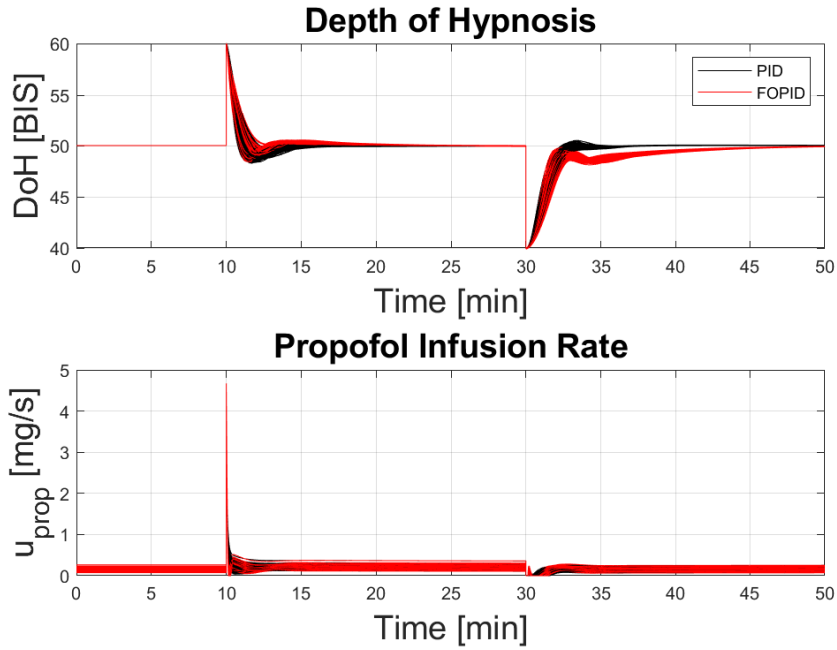


**Figure 11:** Simulation responses obtained on the 500 patients to study inter-patients variability. Black solid line: PID controller. Red solid line: FOPID IAE controller.

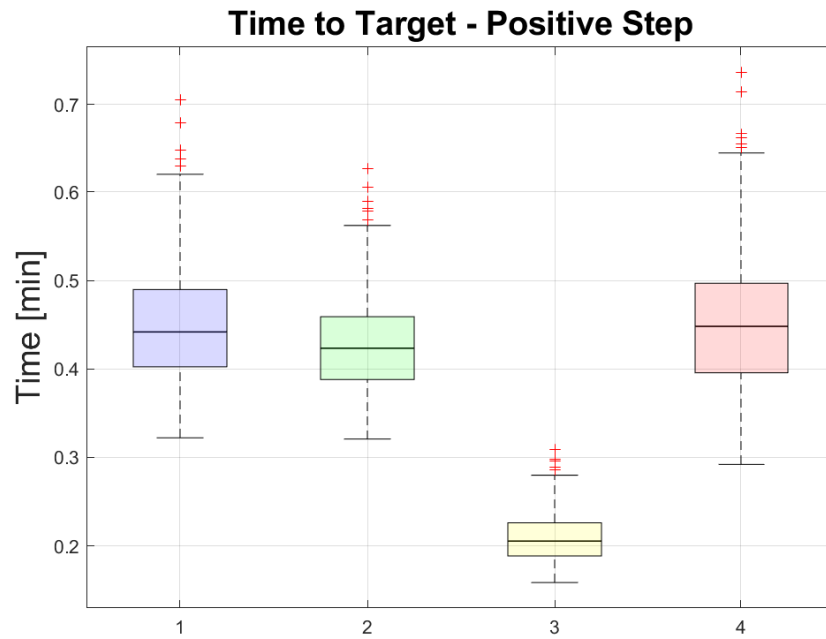
are always met. This is confirmed by the performance indices shown in Figures 14, 15, 16 and 17. Finally, the performance indices related to intra-patient variability are shown (for each patient) in Figures 18-69. Plots of the disturbance responses are omitted for brevity. The same considerations of the inter-patient variability apply to intra-patient variability. The consistency between inter- and intra-patient variability analysis and the results obtained with the design set of 13 individuals also confirm that the set used in the design phase is indeed a representative sample of a diverse population.



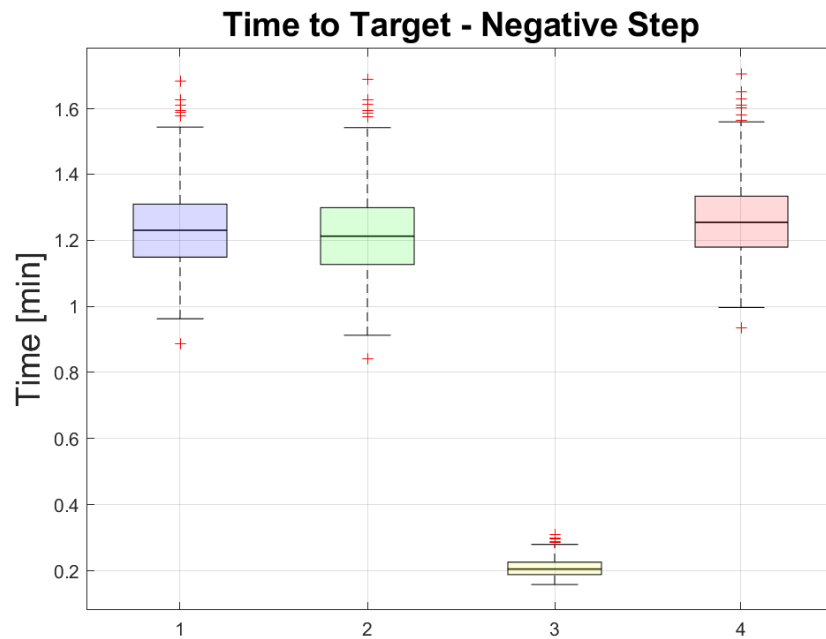
**Figure 12:** Simulation responses obtained on the 500 patients to study inter-patients variability. Black solid line: PID controller. Red solid line: FOPID ISO1 controller.



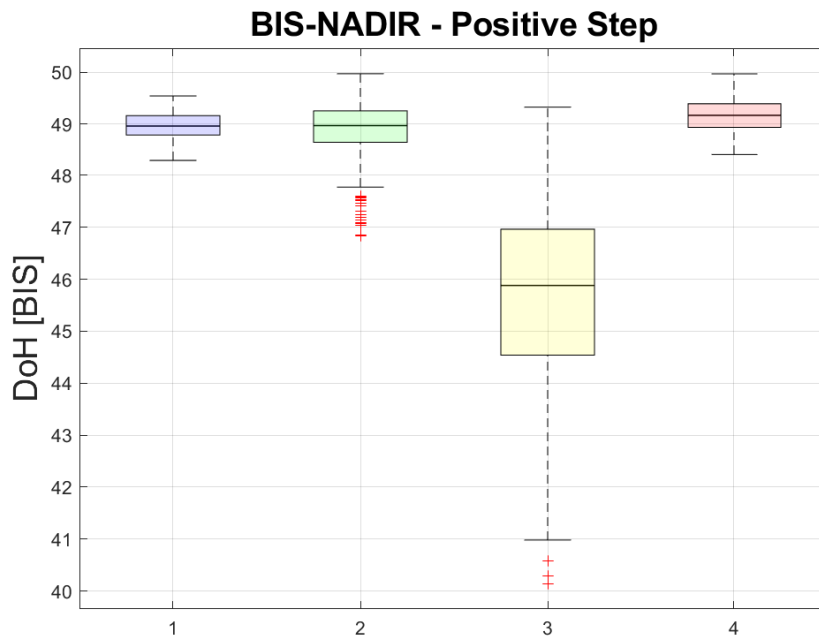
**Figure 13:** Simulation responses obtained on the 500 patients to study inter-patients variability. Black solid line: PID controller. Red solid line: FOPID ISO2 controller.



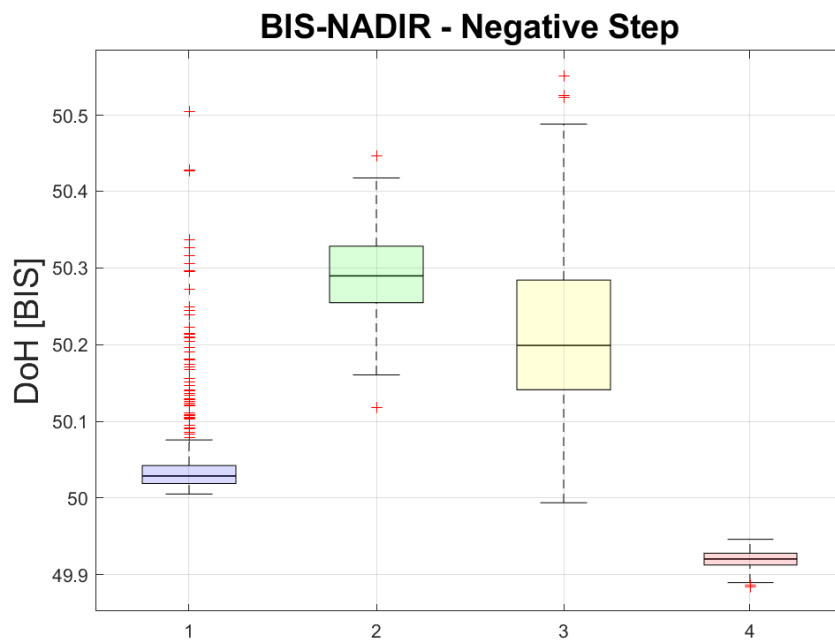
**Figure 14:** Time-to-Target indices for each controller when a positive step occurs. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



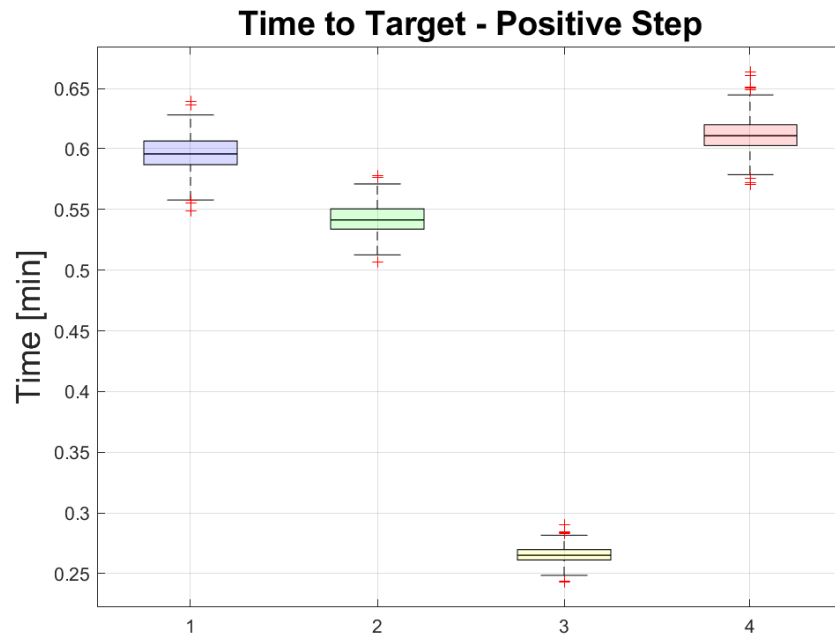
**Figure 15:** Time-to-Target indices for each controller when a negative step occurs. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



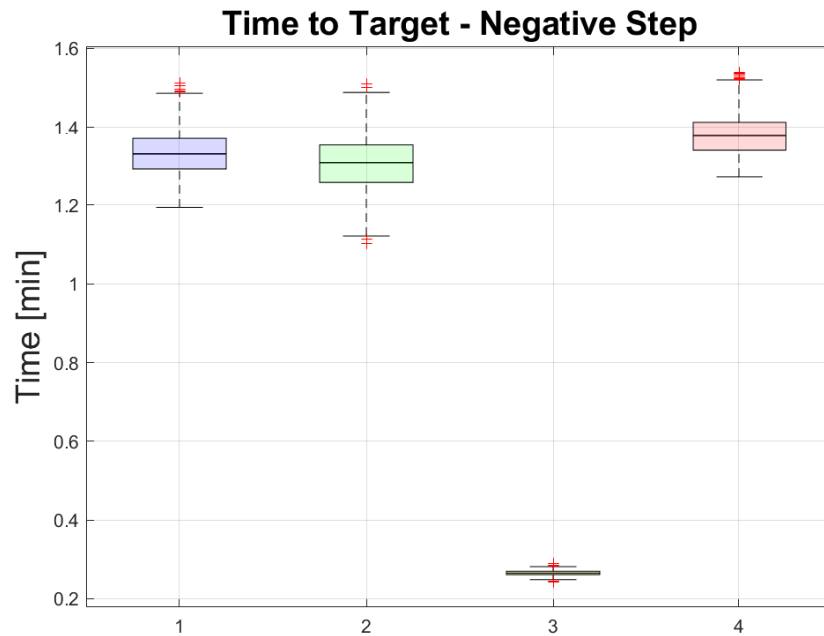
**Figure 16:** BIS-NADIR indices for each controller when a positive step occurs. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



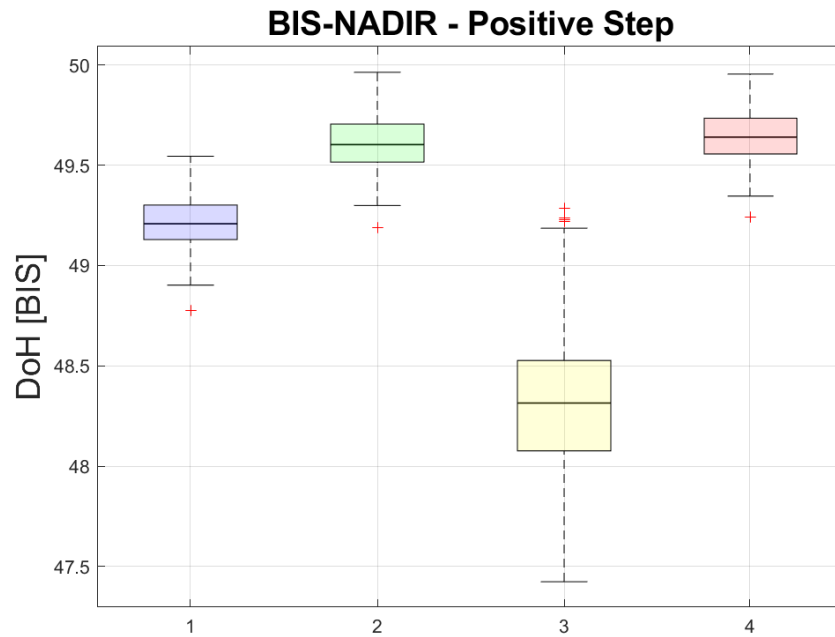
**Figure 17:** BIS-NADIR indices for each controller when a negative step occurs. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



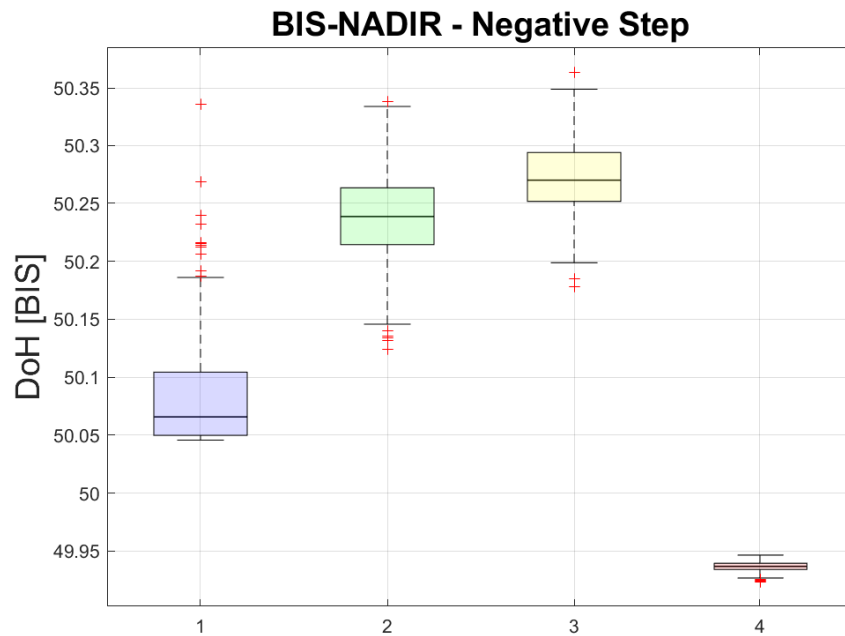
**Figure 18:** Intra-patient robustness of patient 1. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



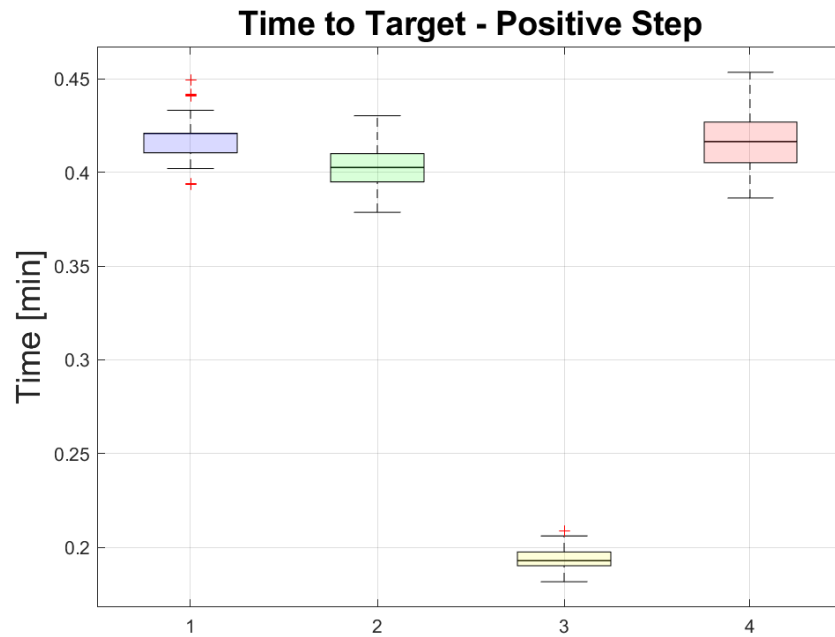
**Figure 19:** Intra-patient robustness of patient 1. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



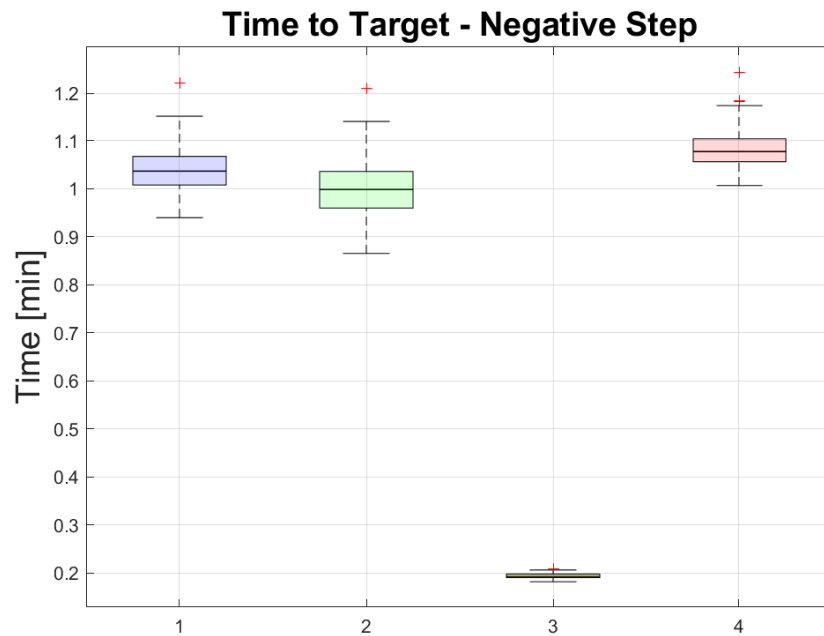
**Figure 20:** Intra-patient robustness of patient 1. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



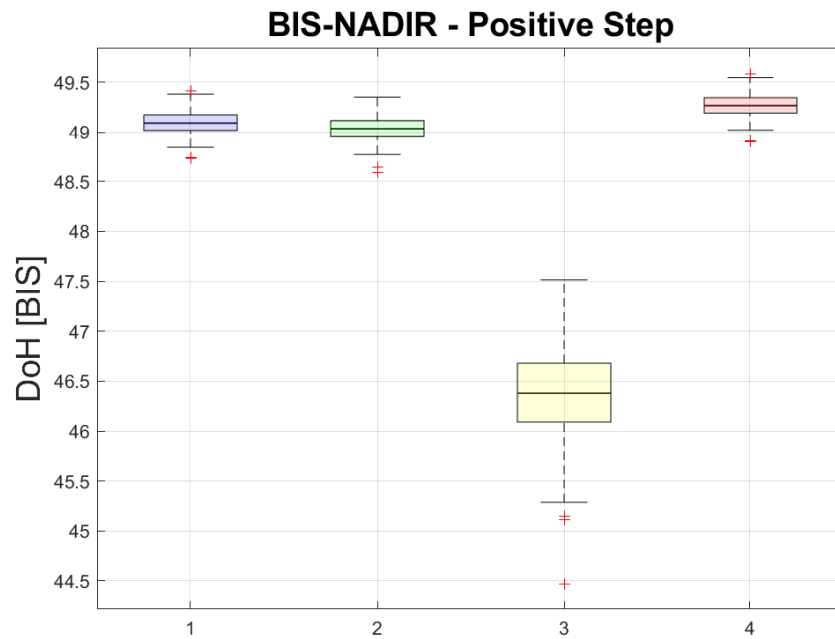
**Figure 21:** Intra-patient robustness of patient 1. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



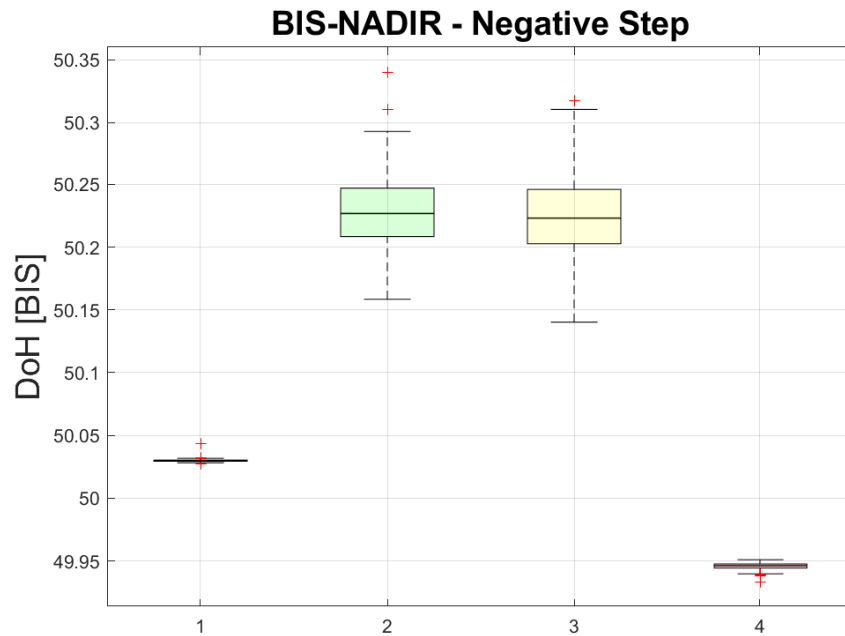
**Figure 22:** Intra-patient robustness of patient 2. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



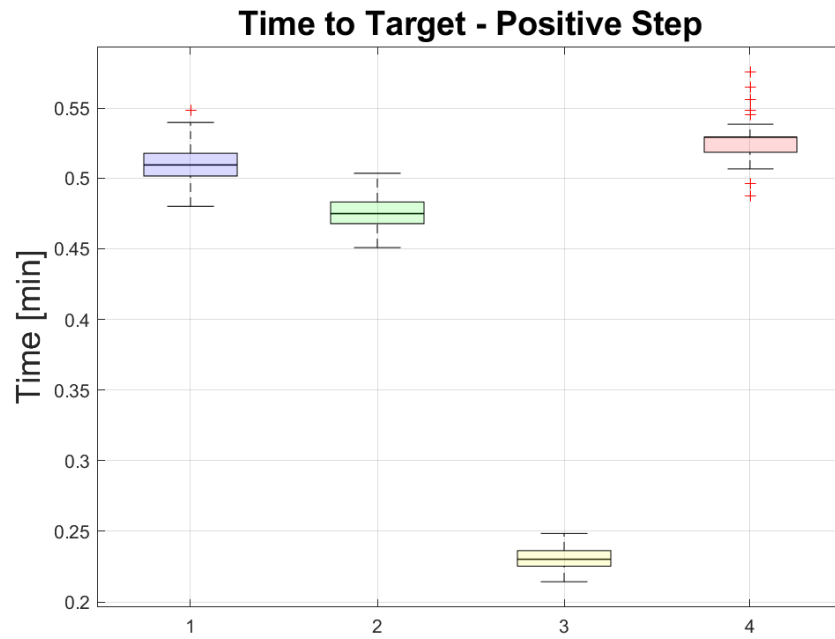
**Figure 23:** Intra-patient robustness of patient 2. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



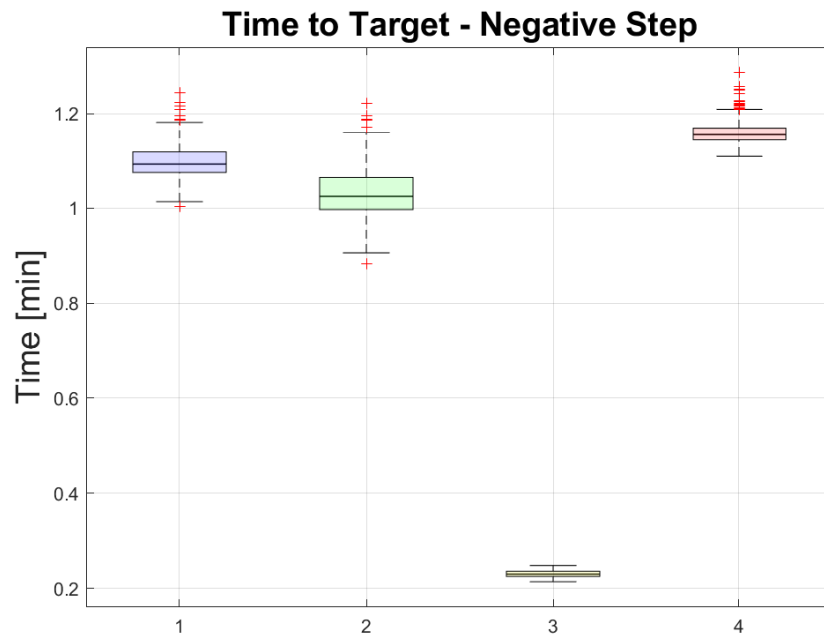
**Figure 24:** Intra-patient robustness of patient 2. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



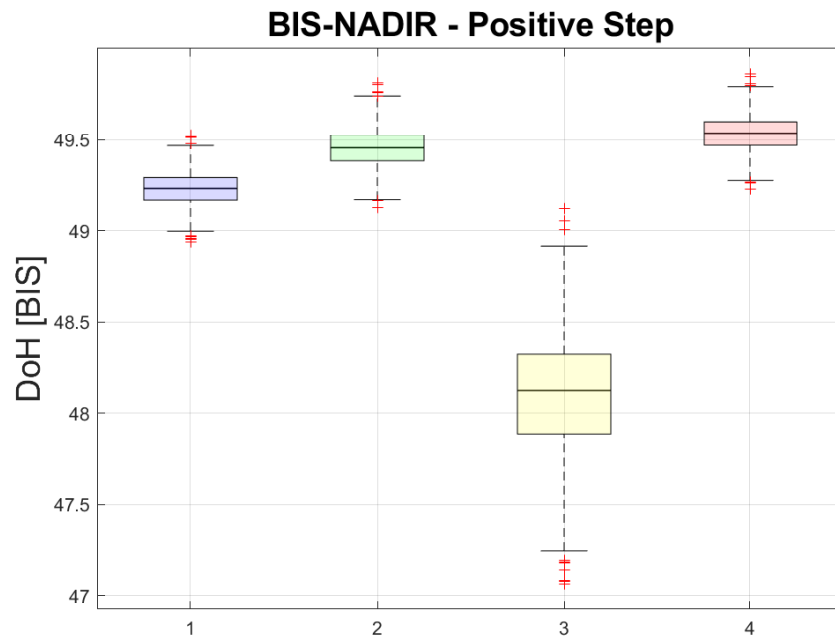
**Figure 25:** Intra-patient robustness of patient 2. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



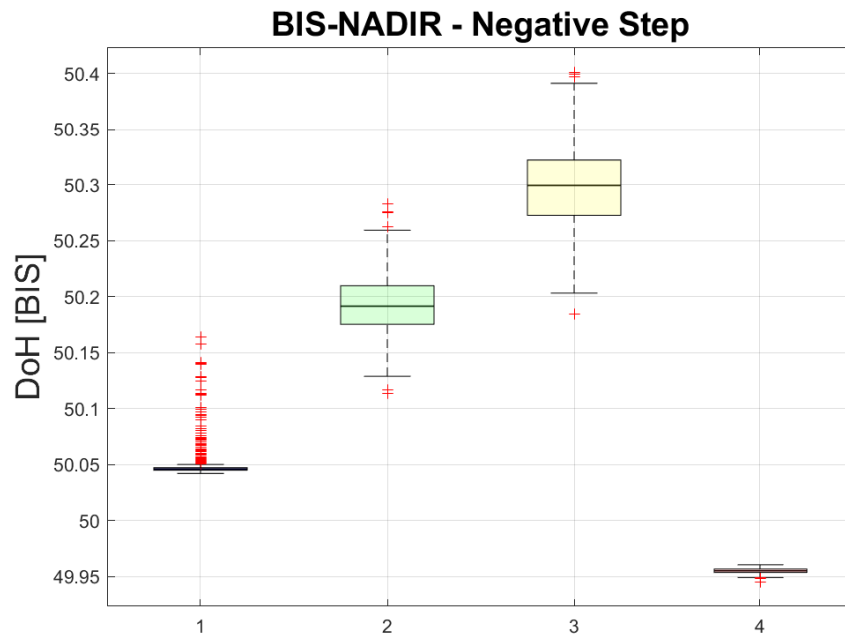
**Figure 26:** Intra-patient robustness of patient 3. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



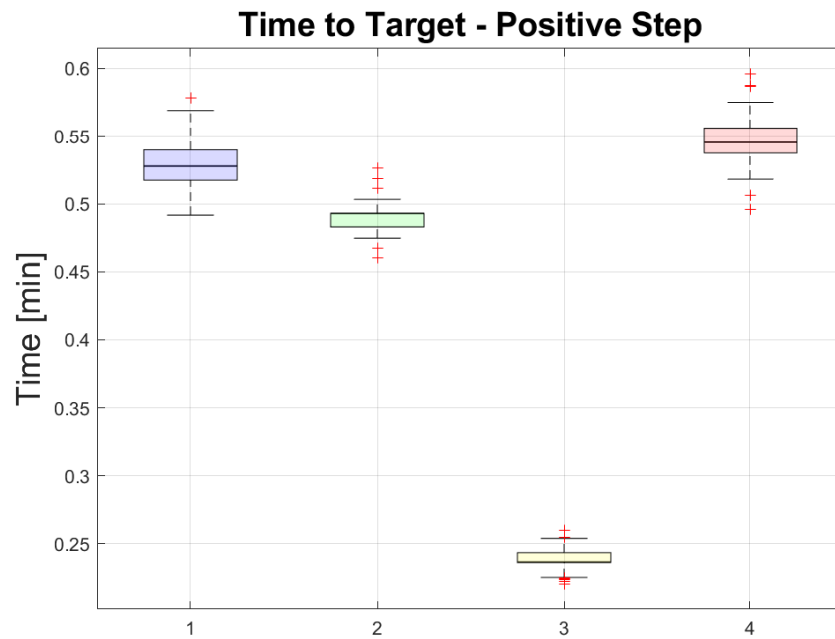
**Figure 27:** Intra-patient robustness of patient 3. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



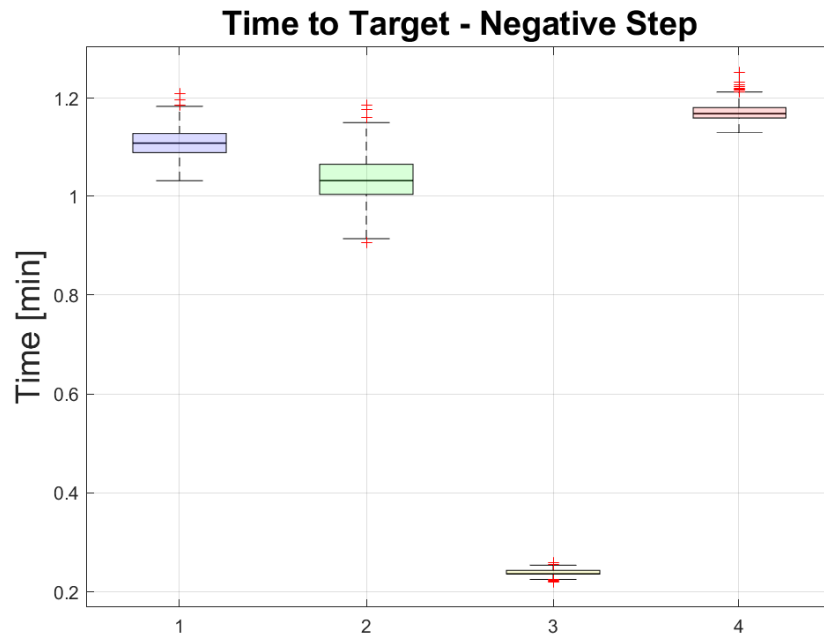
**Figure 28:** Intra-patient robustness of patient 3. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



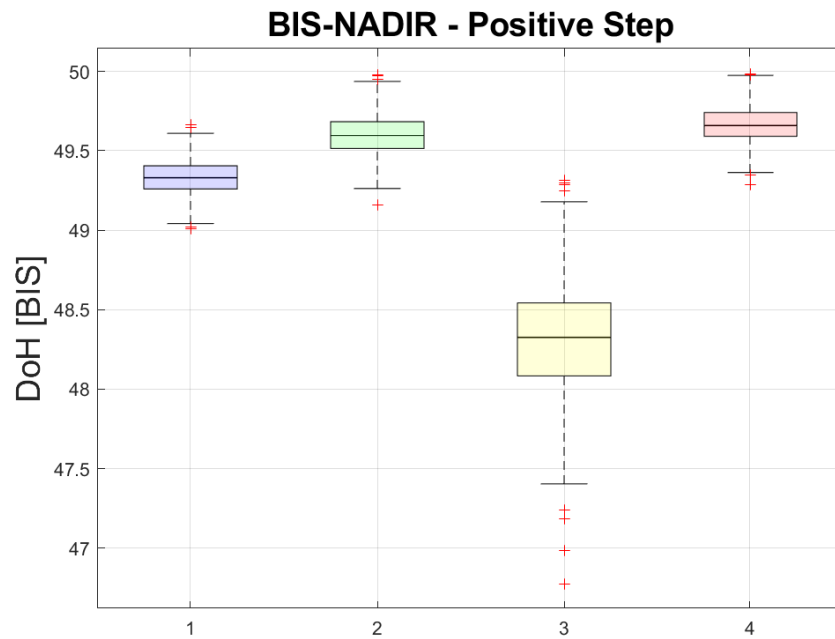
**Figure 29:** Intra-patient robustness of patient 3. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



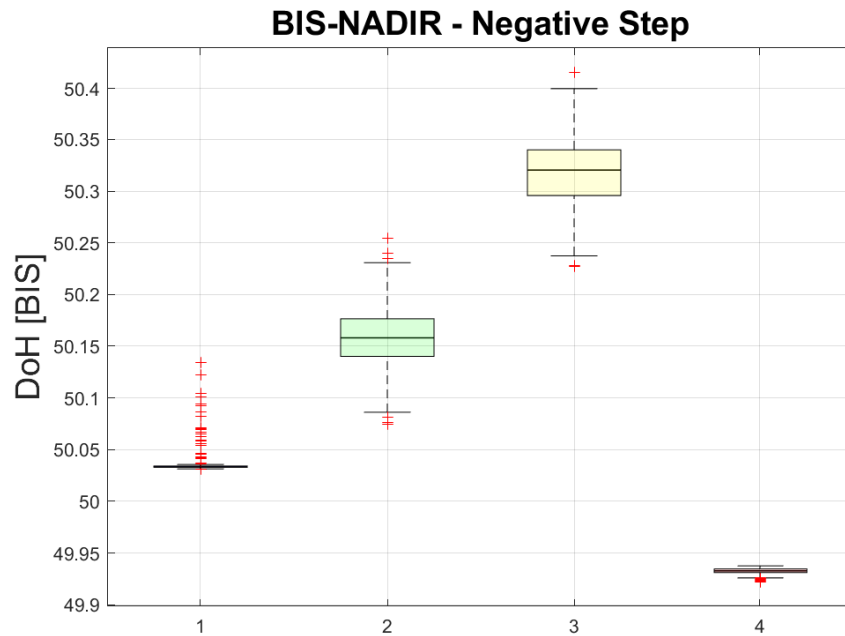
**Figure 30:** Intra-patient robustness of patient 4. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



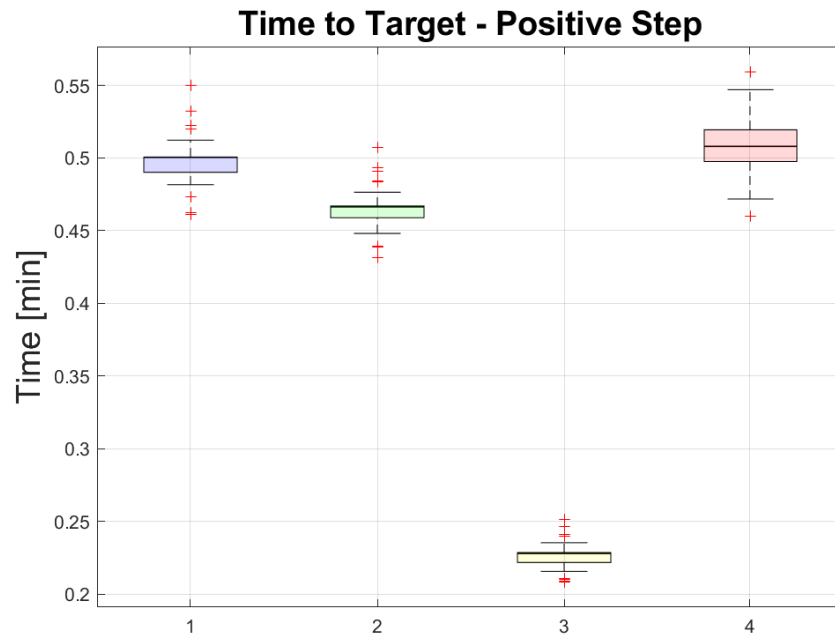
**Figure 31:** Intra-patient robustness of patient 4. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



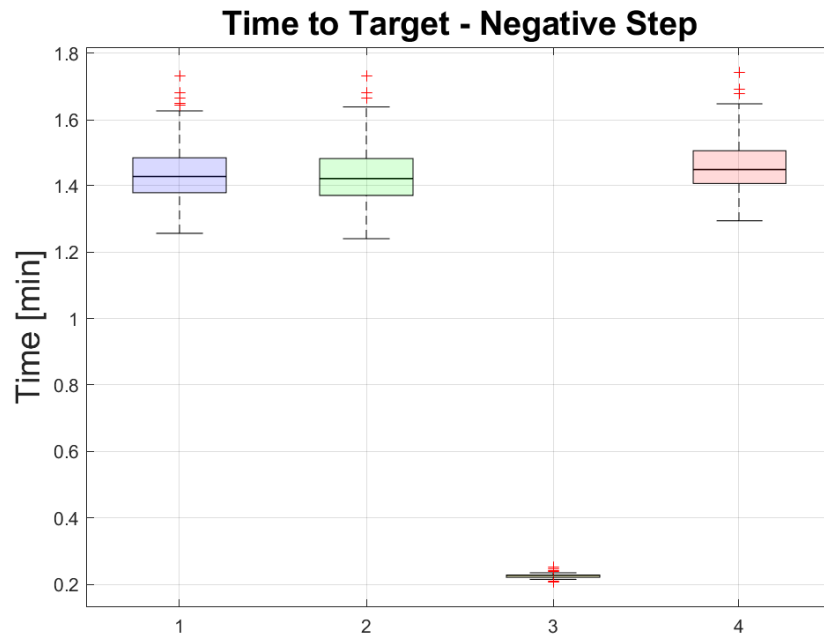
**Figure 32:** Intra-patient robustness of patient 4. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



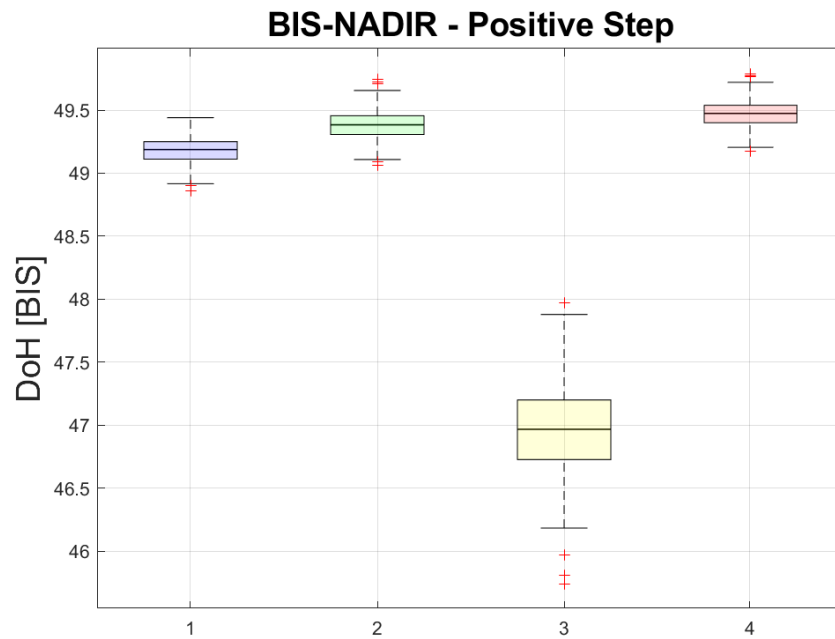
**Figure 33:** Intra-patient robustness of patient 4. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



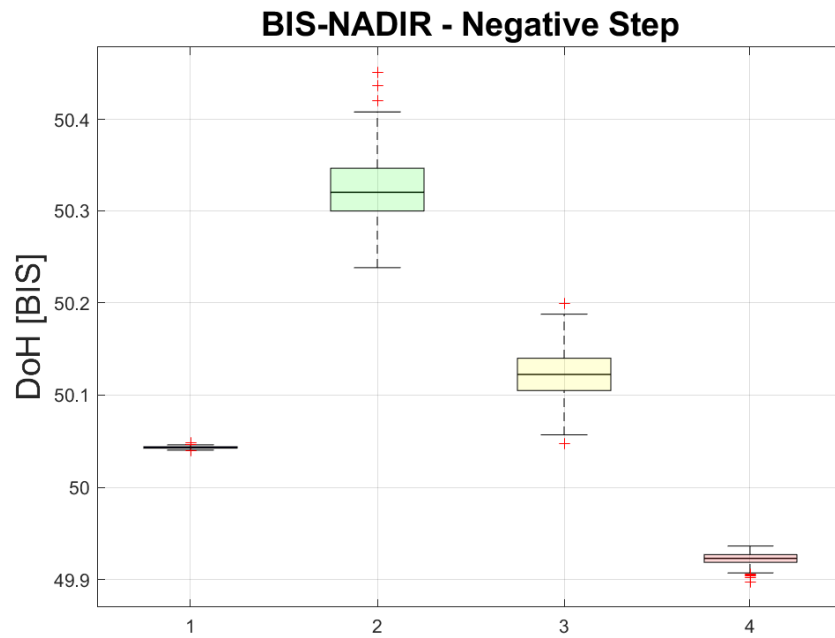
**Figure 34:** Intra-patient robustness of patient 5. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



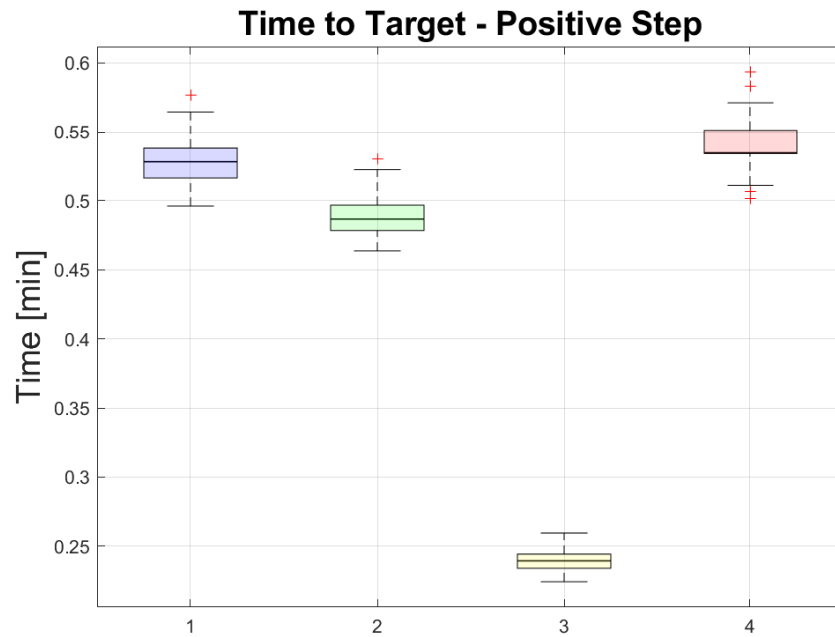
**Figure 35:** Intra-patient robustness of patient 5. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



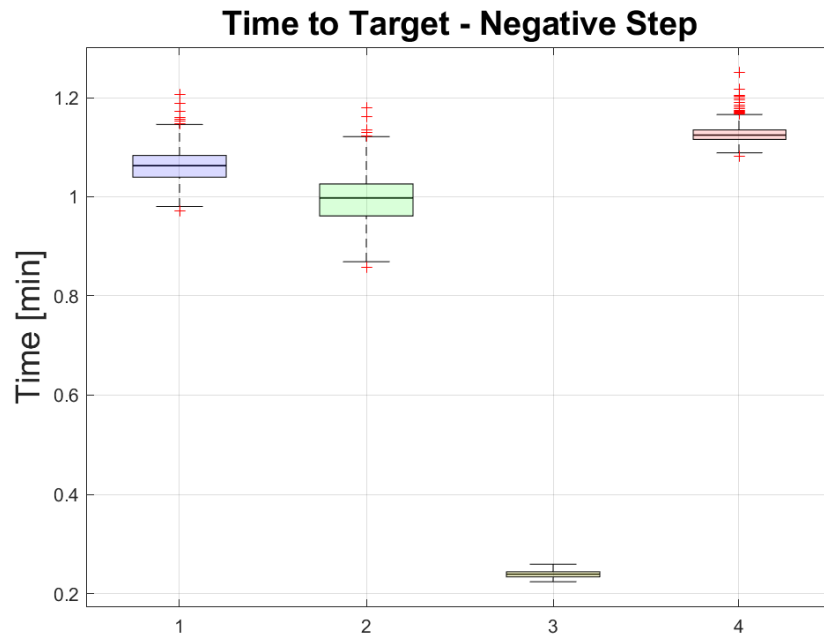
**Figure 36:** Intra-patient robustness of patient 5. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



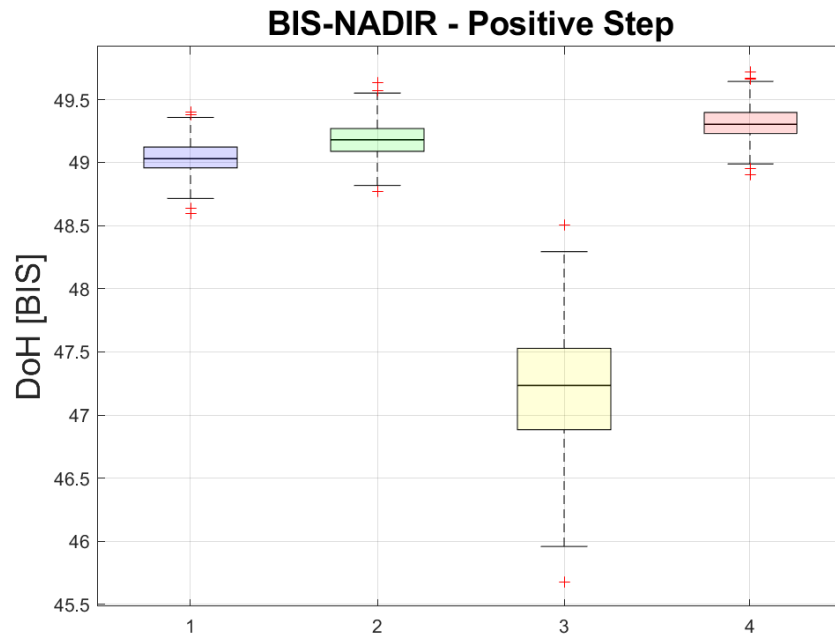
**Figure 37:** Intra-patient robustness of patient 5. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



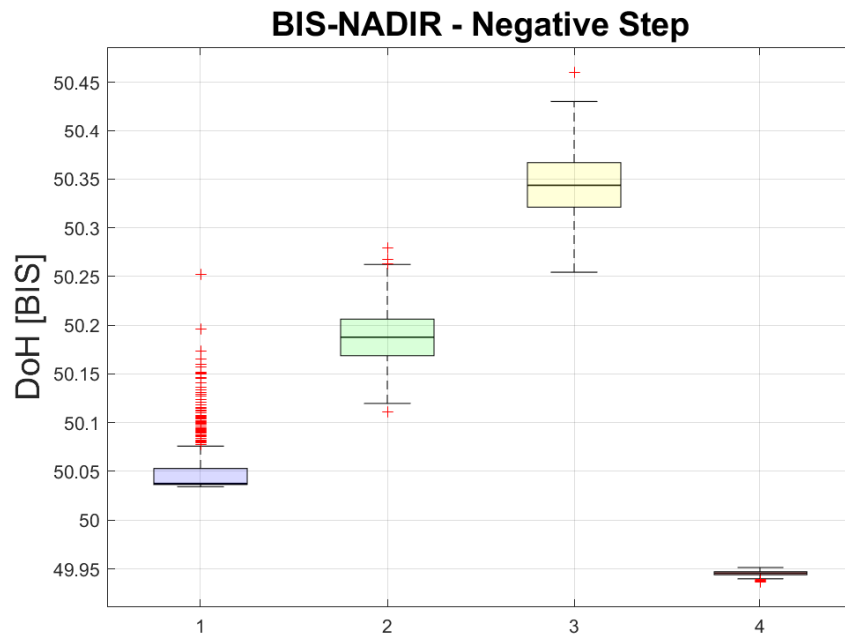
**Figure 38:** Intra-patient robustness of patient 6. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



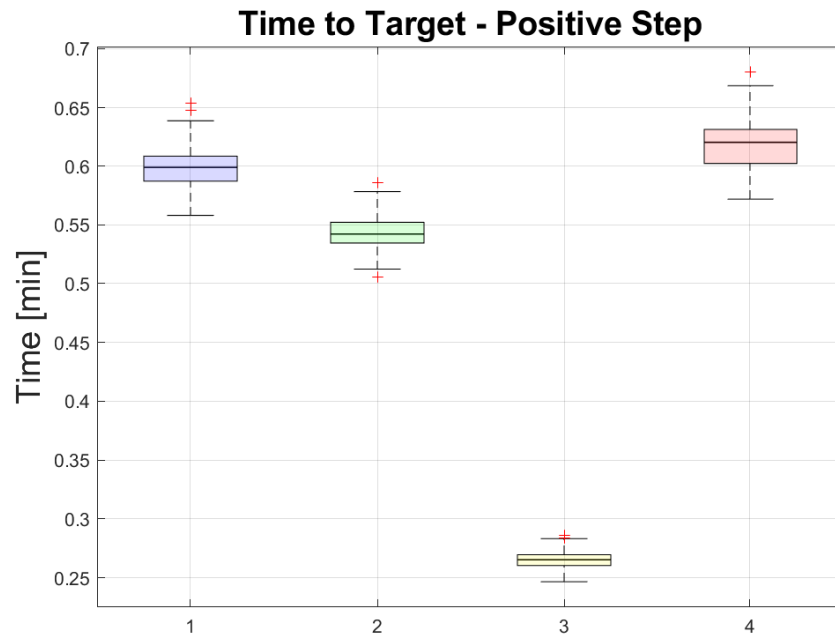
**Figure 39:** Intra-patient robustness of patient 6. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



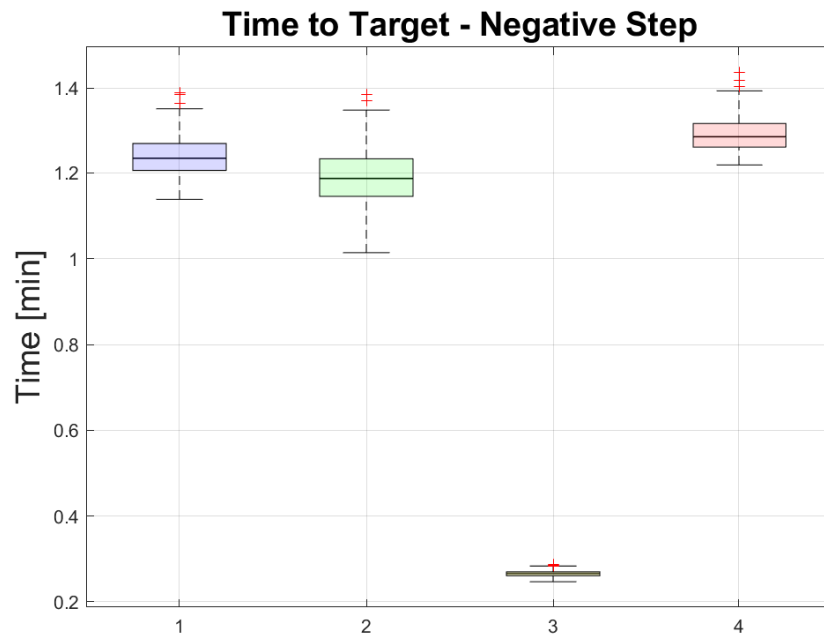
**Figure 40:** Intra-patient robustness of patient 6. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



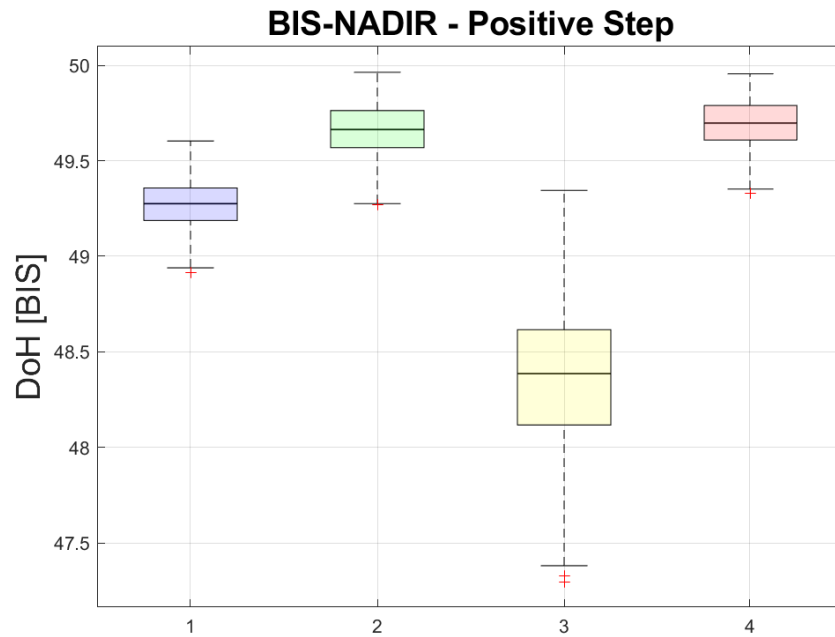
**Figure 41:** Intra-patient robustness of patient 6. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



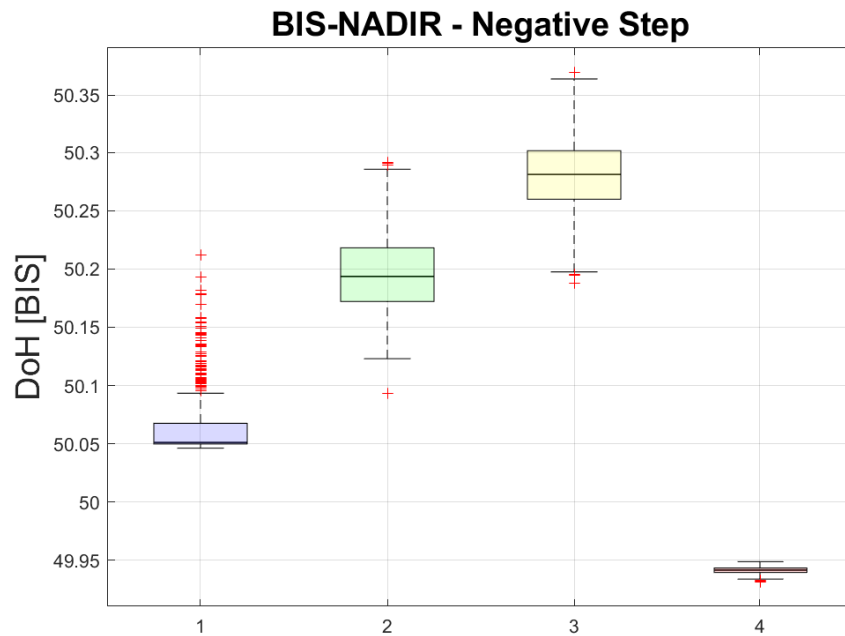
**Figure 42:** Intra-patient robustness of patient 7. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



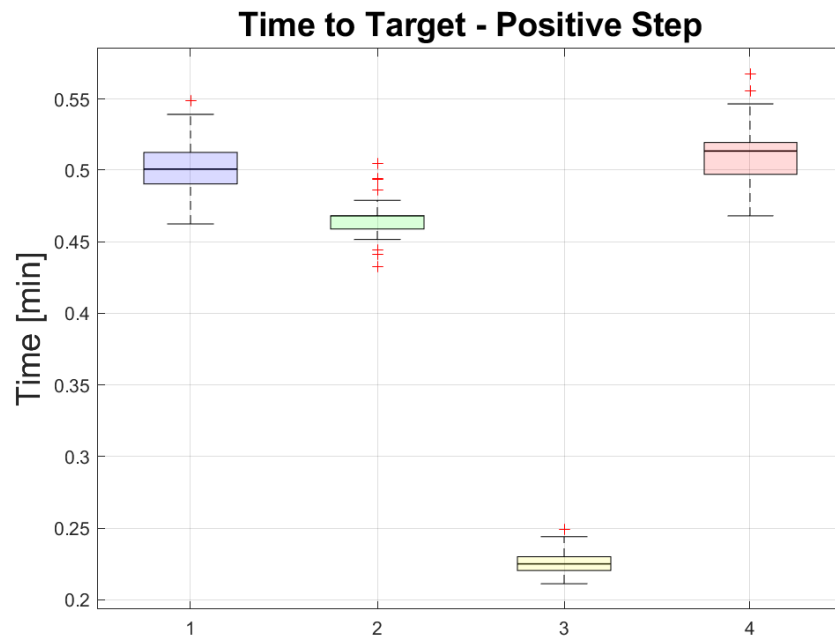
**Figure 43:** Intra-patient robustness of patient 7. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



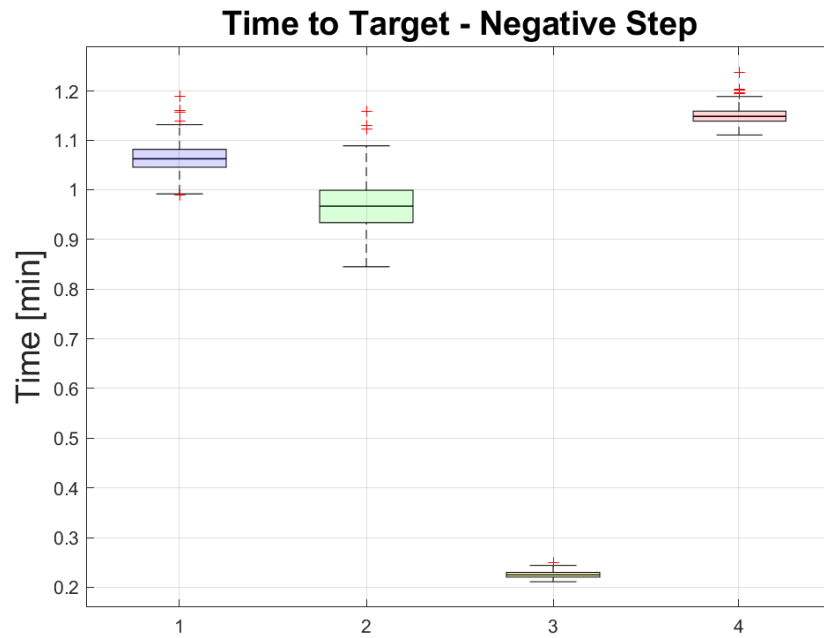
**Figure 44:** Intra-patient robustness of patient 7. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



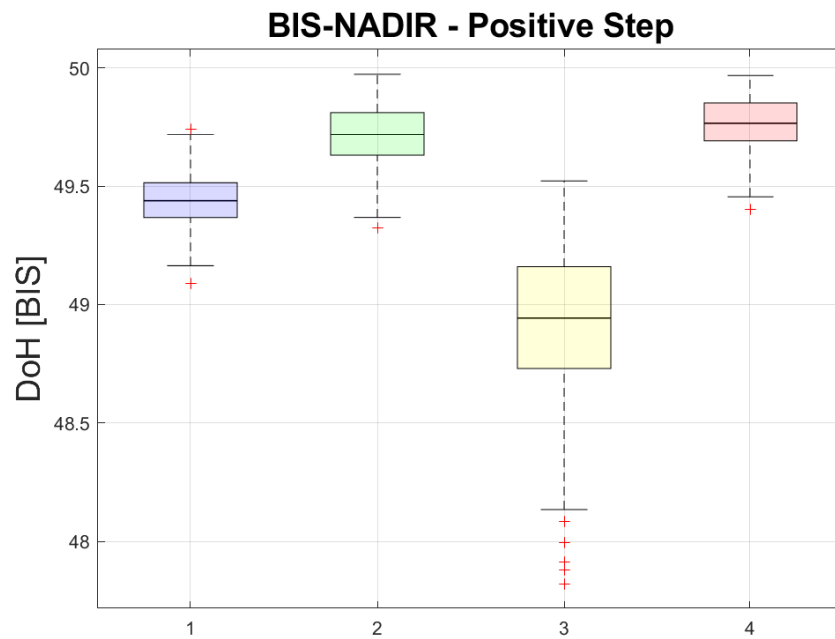
**Figure 45:** Intra-patient robustness of patient 7. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



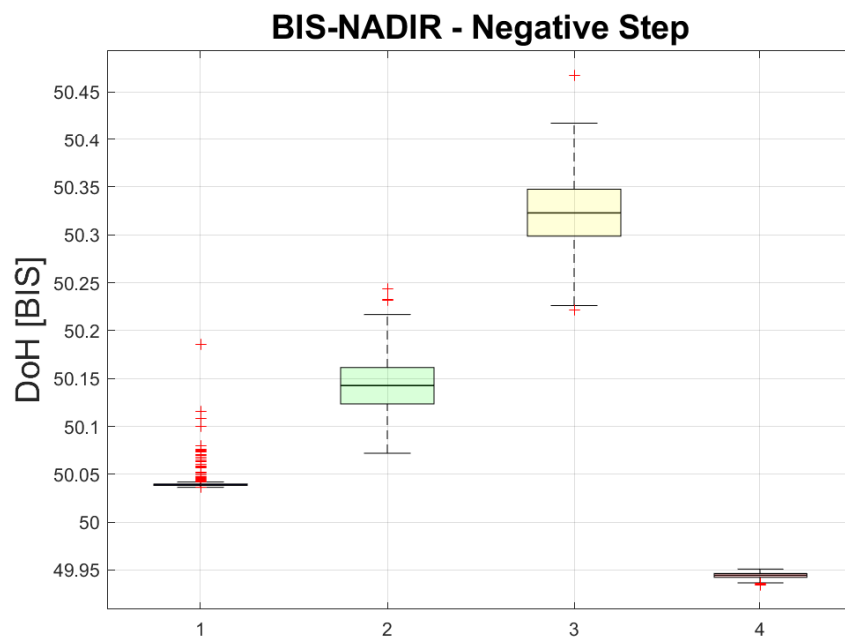
**Figure 46:** Intra-patient robustness of patient 8. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



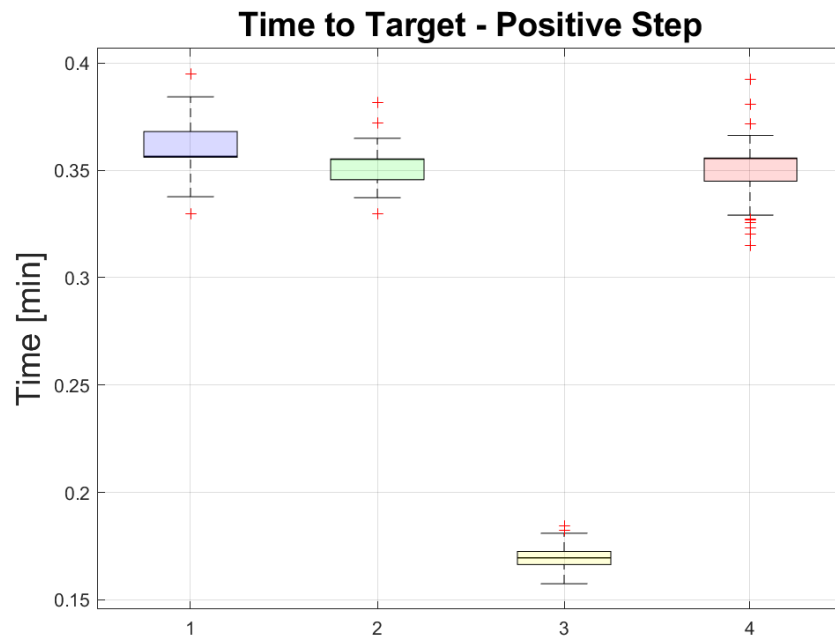
**Figure 47:** Intra-patient robustness of patient 8. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



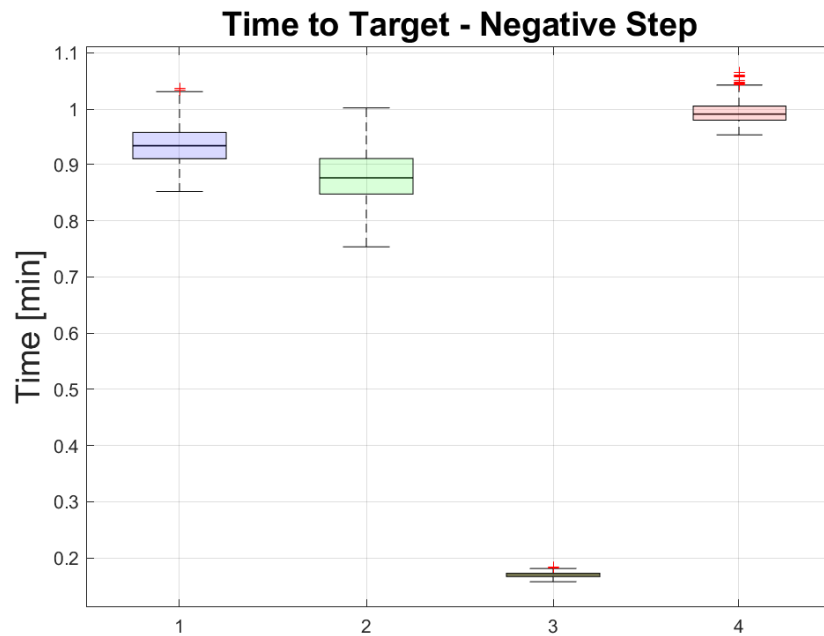
**Figure 48:** Intra-patient robustness of patient 8. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



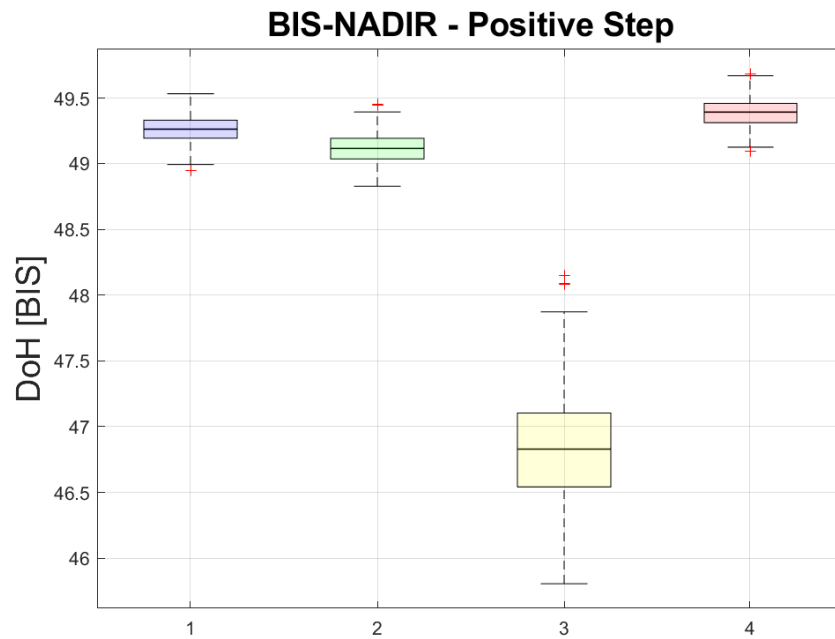
**Figure 49:** Intra-patient robustness of patient 8. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



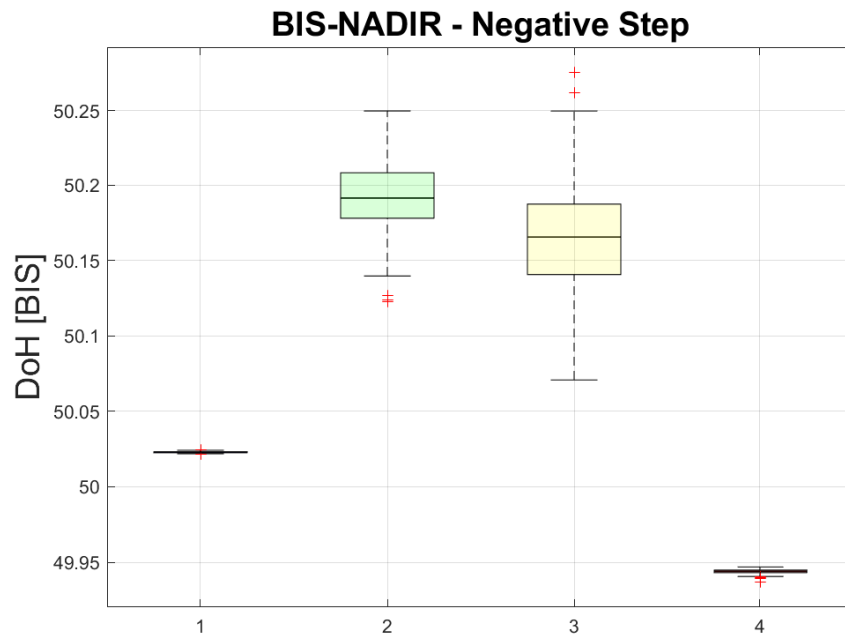
**Figure 50:** Intra-patient robustness of patient 9. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



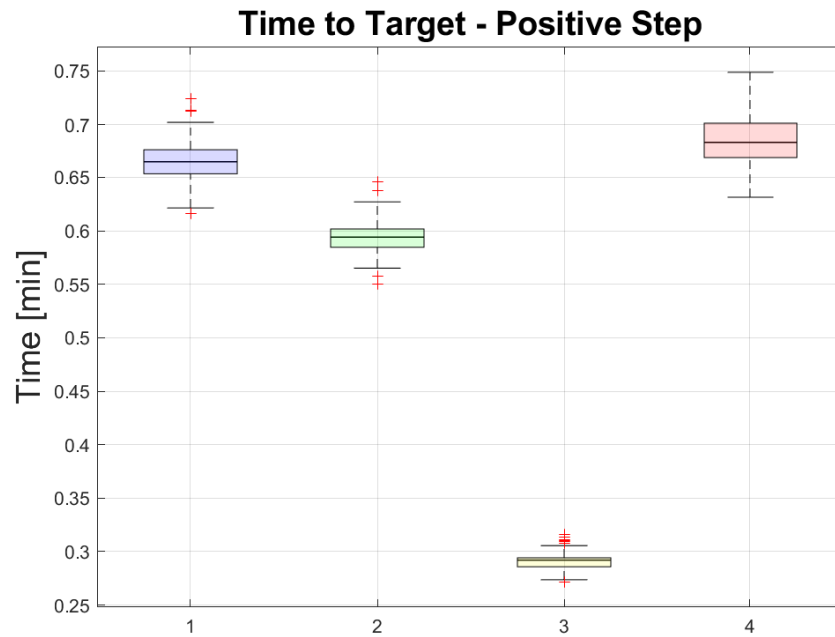
**Figure 51:** Intra-patient robustness of patient 9. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



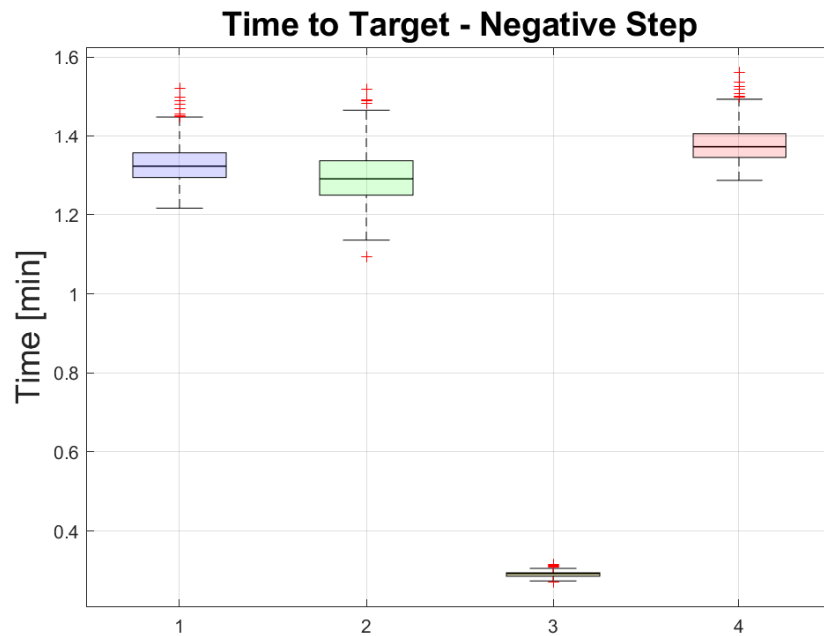
**Figure 52:** Intra-patient robustness of patient 9. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



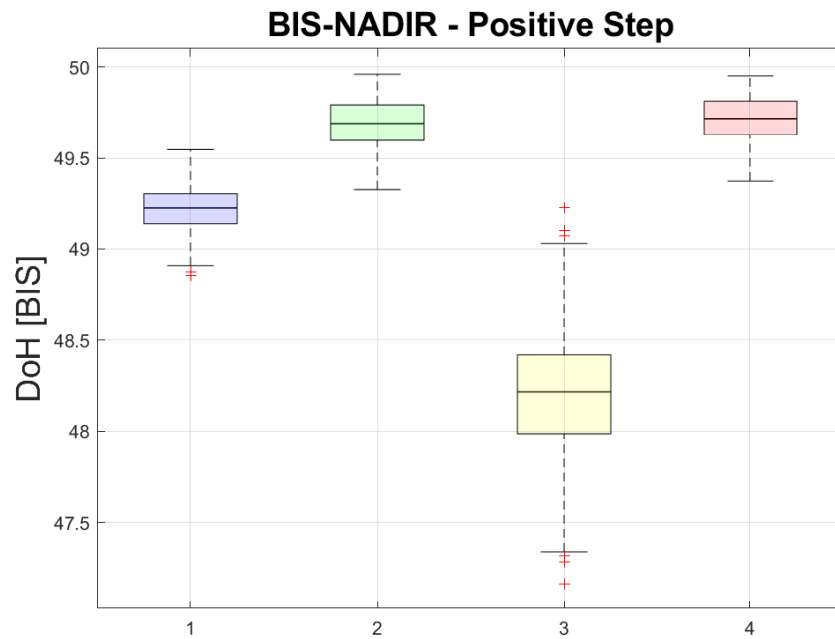
**Figure 53:** Intra-patient robustness of patient 9. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



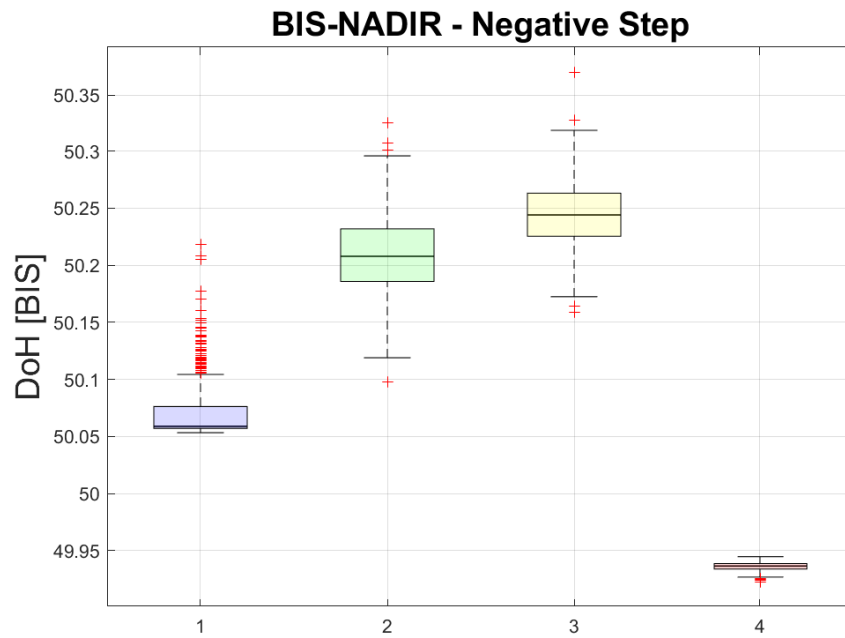
**Figure 54:** Intra-patient robustness of patient 10. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



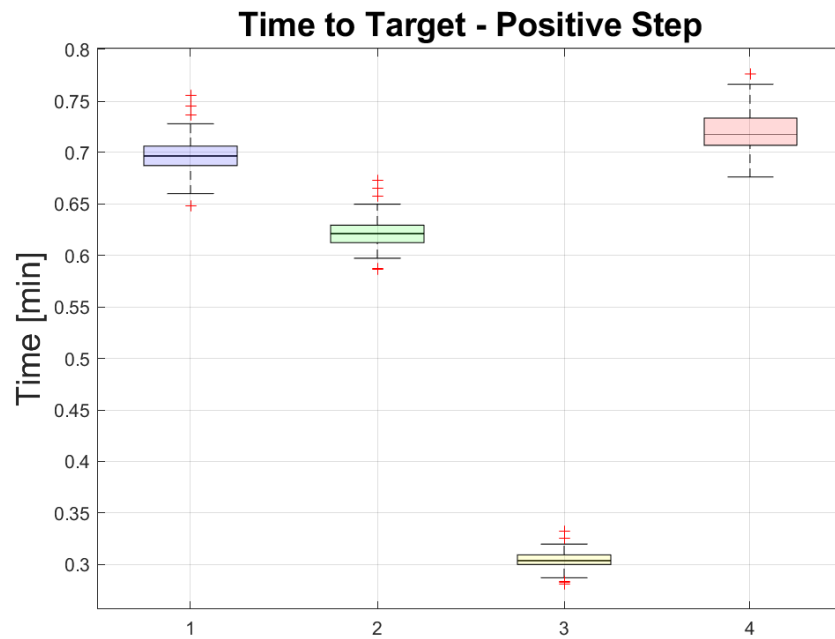
**Figure 55:** Intra-patient robustness of patient 10. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



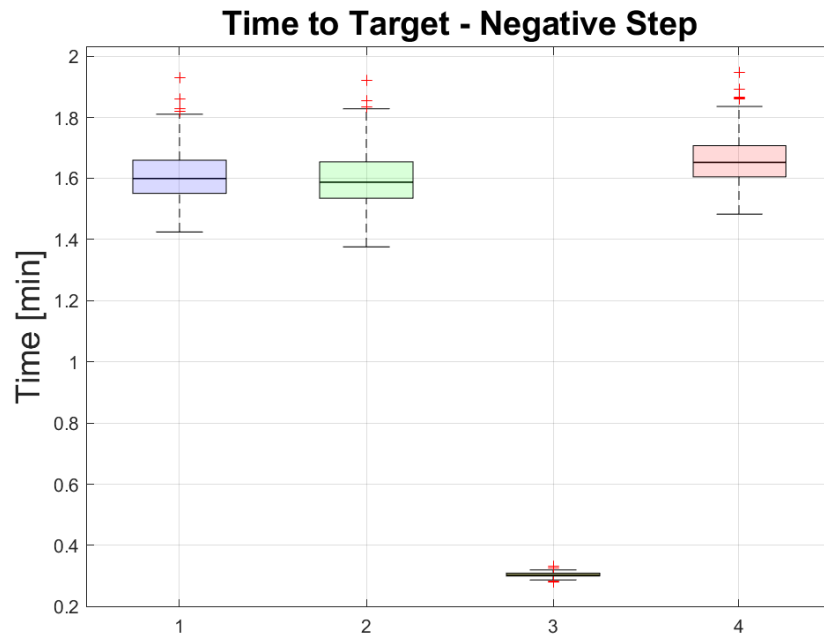
**Figure 56:** Intra-patient robustness of patient 10. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



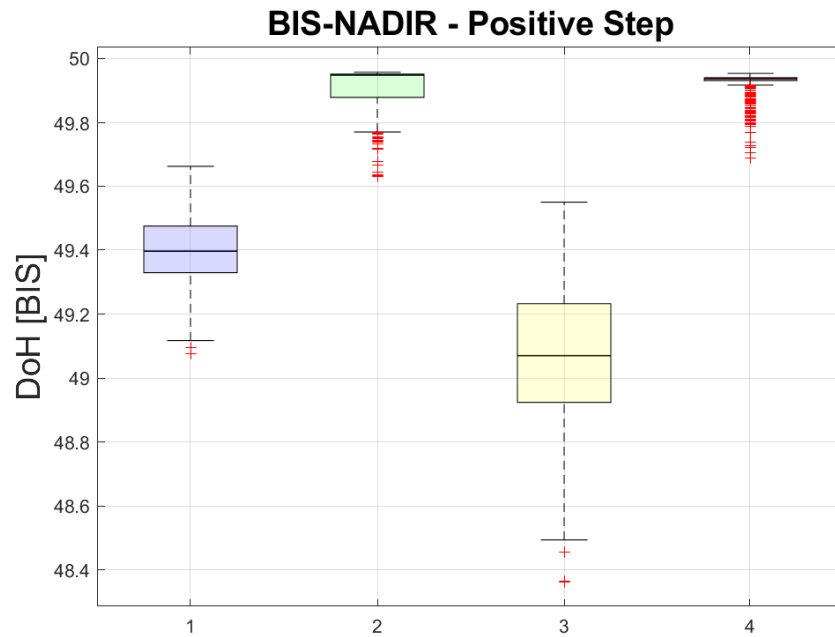
**Figure 57:** Intra-patient robustness of patient 10. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



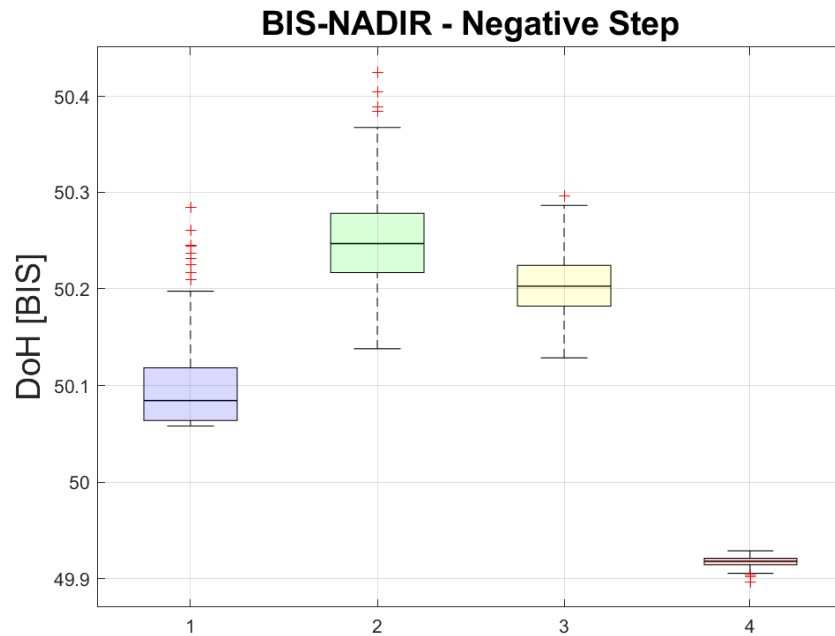
**Figure 58:** Intra-patient robustness of patient 11. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



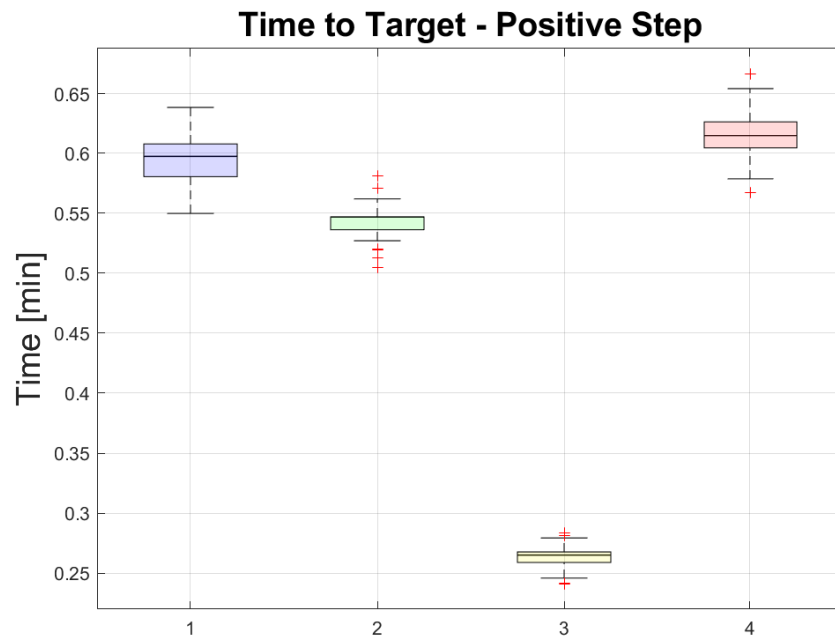
**Figure 59:** Intra-patient robustness of patient 11. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



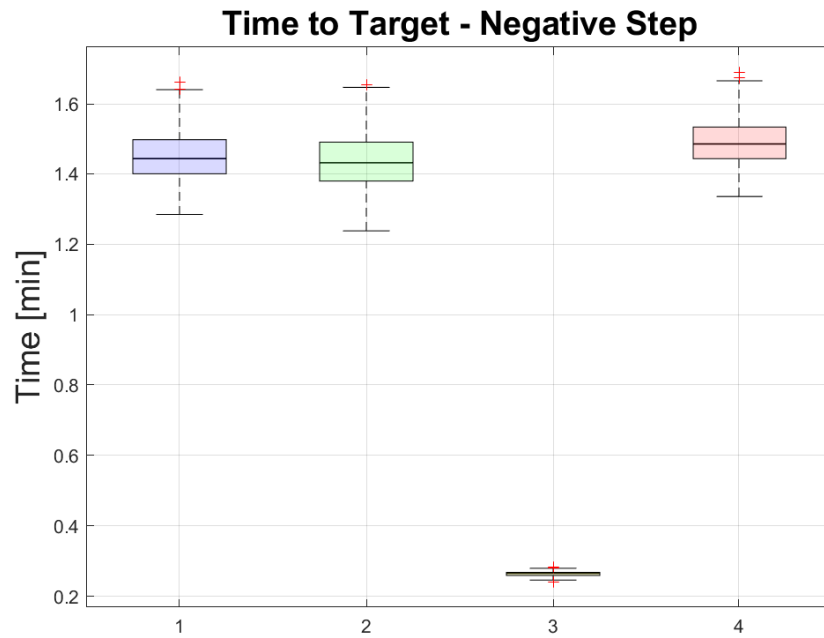
**Figure 60:** Intra-patient robustness of patient 11. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



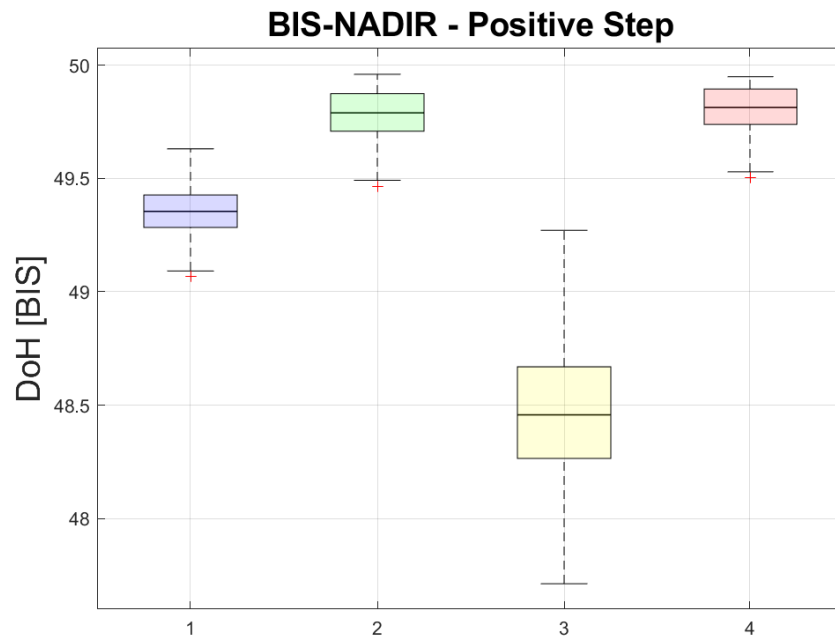
**Figure 61:** Intra-patient robustness of patient 11. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



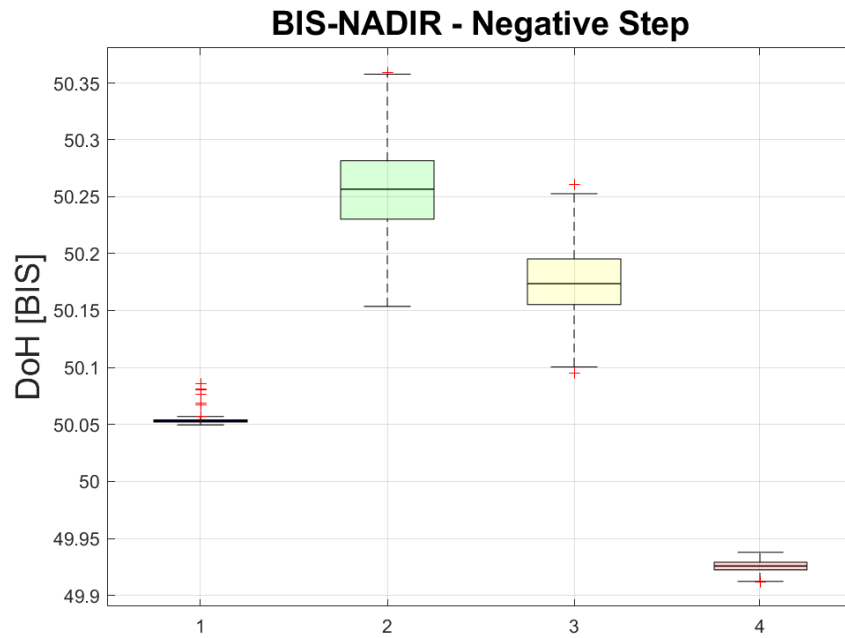
**Figure 62:** Intra-patient robustness of patient 12. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



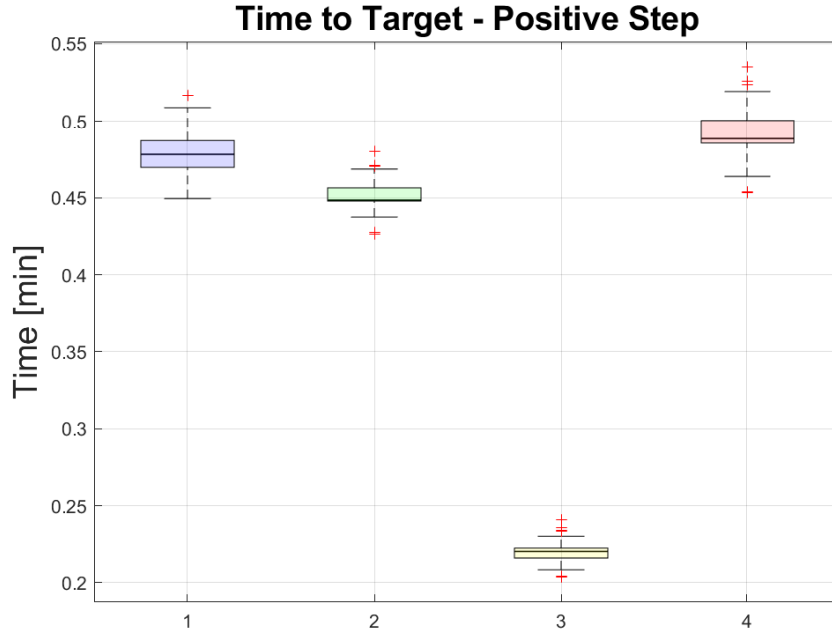
**Figure 63:** Intra-patient robustness of patient 12. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



**Figure 64:** Intra-patient robustness of patient 12. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



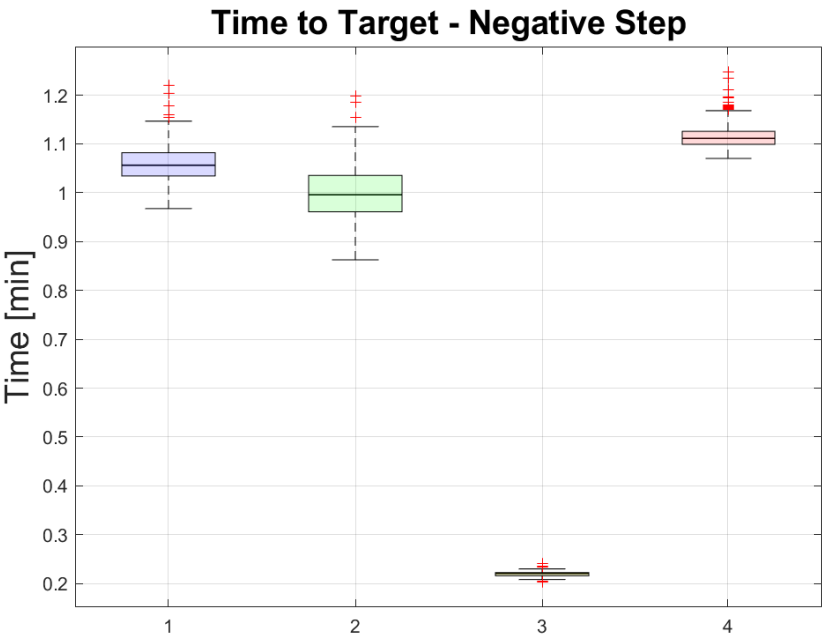
**Figure 65:** Intra-patient robustness of patient 12. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



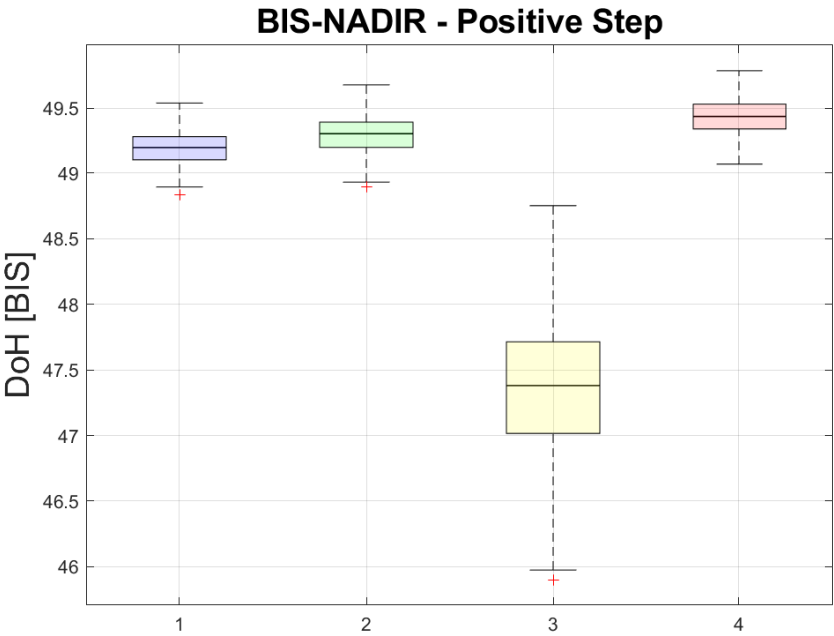
**Figure 66:** Intra-patient robustness of patient 13. Positive step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.

## 4 Discussion

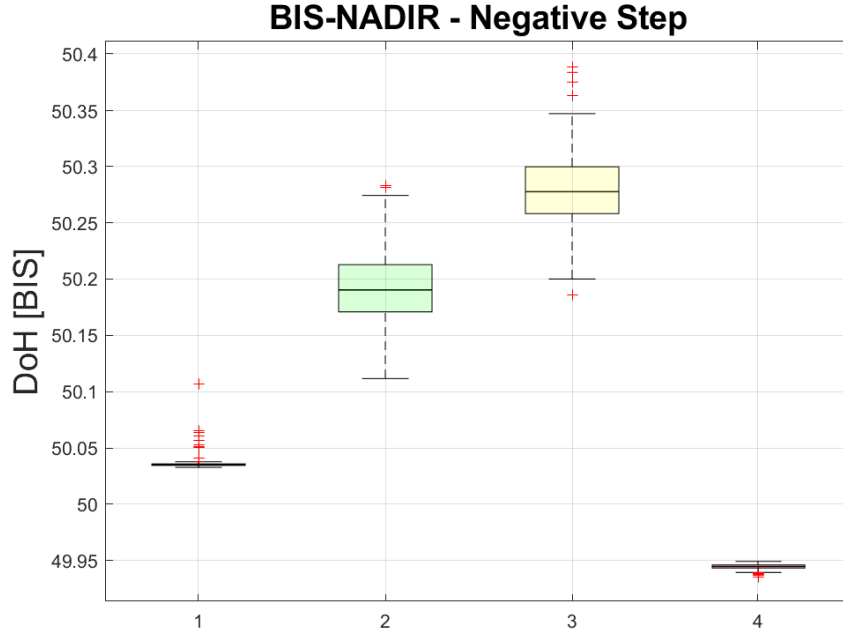
The results presented in Section 3 show that with a fractional-order PID controller is possible to achieve a satisfactory performance (all the clinical requirements are met) in the maintenance phase of anesthesia during surgical procedures. From the presented results, it appears that tuning a FOPID controller by minimizing the IAE provides a slightly better performance compared to the one obtained when the isodamping condition is imposed. All the analyzed controllers are able to handle both inter- and intra-patient variabilities, providing adequate robustness. From the performed simulations, it appears in any case that the performance obtained with a FOPID controller is very similar to the one obtained with a PID controller. Therefore, it can be concluded that a FOPID closed-loop control system can be used to titrate propofol to achieve the required Depth-of-Hypnosis, but a traditional PID controller seems to be still the best option in terms of the trade-off between performance and complexity of implementation. Thanks to the encouraging results obtained from this simulation study, it would be interesting to test the FOPID-based control structure in a real clinical scenario. Since the Oustaloup approximation (Oustaloup et al., 2006) has been exploited during the design phase of the fractional-order controller, the controller transfer function turns out to be of high order. Anyway, it is still possible to perform a controller discretization in order to implement it in the control software that has been used for the clinical investigation (Schiavo et al., 2022, 2023). Moreover, since the proposed control solution does not take into account the analgesic drug infusion,



**Figure 67:** Intra-patient robustness of patient 13. Negative step Time-to-Target indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



**Figure 68:** Intra-patient robustness of patient 13. Positive step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.



**Figure 69:** Intra-patient robustness of patient 13. Negative step BIS-NADIR indices for each controller. 1) Blue box: PID controller. 2) Green box: FOPID IAE. 3) Yellow box: FOPID ISO1. 4) Red box: FOPID ISO2.

this variable will be manually regulated by the anesthesiologist and it will be seen as a disturbance from the controller. In future works, a fractional-order PID controller will be designed for both components of anesthesia (i.e. hypnosis and analgesia) by exploiting a MISO system that considers both the propofol and remifentanyl flow rates as control actions and the BIS as the only process variable.

## 5 Conclusions

In this paper a thorough comparison between PID and FOPID-controllers for the DoH control through propofol administration in general anesthesia has been presented. Two different tuning methods have been applied to FOPID controllers, namely, the minimization of the IAE and the minimization of the maximum sensitivity by applying an isodamping approach (which cannot be used with PID controllers). From the presented simulation results it appears that a FOPID is an effective solution, as it allows the clinical requirements to be met in terms of performance and robustness. However, the FOPID controller does not significantly improve on the performance achieved with the PID controller tuned by minimizing the IAE.

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# Paper IV

## PKPD Model-based Design of PID Control for Closed-loop Anesthesia

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### Abstract

This paper investigates the use of pharmacokinetic/pharmacodynamic models for the design of a Proportional-Integral-Derivative controller for total intravenous anesthesia. In particular, we consider the administration of propofol as manipulated variable and the BIS signal as the process variable, and we evaluate the use of both a population-based and a personalized approach to tune the controller by using the Eleveld model. Simulation results show that the personalized controller outperforms the population-based one, which fails to provide the required clinical performance for elderly people.

Thus, the development of a pharmacokinetic/pharmacodynamic model specifically devised for control design purposes would be beneficial to provide a truly personalized control law and to increase the overall performance.

Originally published in IFAC Journal of Systems and Control. The original version is available at [10.1016/j.ifacsc.2024.100247](https://doi.org/10.1016/j.ifacsc.2024.100247).

## 1 Introduction

Several research efforts have been made for years to meet the demand for increasingly safe and reliable healthcare. In particular, control engineering has contributed to develop solutions to assist the anesthesiologist to increase the patient safety during surgeries by suitably dosing of the hypnotic drug propofol, as hypnosis (Vuyk et al., 2015), together with analgesia (Schumacher and Fukuda, 2020) and neuromuscular blockade (Brull et al., 2020), is one of the main components in total intravenous anesthesia (TIVA) (Brown et al., 2010).

Nowadays, Target Controlled Infusion (TCI) devices (Absalom et al., 2016) are the most widespread computer-based systems employed to titrate propofol in operating rooms in order to achieve the required Depth-of-Hypnosis (DoH). By exploiting pharmacological models, these systems estimate the drug infusion rate needed to reach a specific drug concentration in the patient. In fact, the anesthesiologist selects the desired concentration level according to clinical considerations and the TCI device sets the drug infusion rate to reach it. A drawback of this technology is that it works in open loop. Hence, the anesthesiologist is directly involved in closing the control loop.

In the literature, it is well known that closed-loop systems outperform open-loop ones, if properly designed. For this reason, recently, the research has focused on finding solutions based on closed-loop control architectures (Mendez et al., 2016, 2018; Hosseinzadeh et al., 2020; Ionescu et al., 2021). This is possible because of the availability of processed electroencephalograms (pEEG) such as the bispectral index (BIS) signal (Vuyk and Mertens, 2003), a quantitative DoH indicator that is suitable to be used as controlled variable. Many of these control solutions exploit standard Proportional-Integral-Derivative (PID) feedback controllers. Indeed, PID controllers are the most common controllers in the industrial field since they are simple and easy to use and they have turned out to be a reliable solution even when employed in the anesthesia context (Puri et al., 2007; Dumont et al., 2009; Reboso et al., 2012; Soltesz et al., 2013; Padula et al., 2017; van Heusden et al., 2019; Gonzalez-Cava et al., 2021; Schiavo et al., 2022). Other control strategies aim to expand this basic architecture, by using for example the event-based (Merigo et al., 2017, 2020) and fractional order (Copot et al., 2017; Paolino et al., 2023) PID controllers.

In many of these approaches the controller is tuned through simulations in which the patient is simulated by using a pharmacokinetics/pharmacodynamics (PK/PD) model that describes the dose-effect relationship (Kim et al., 2015) and plays, therefore, a key role in the controller design.

Pharmacokinetics studies the relationship between the drug dose and the plasmatic drug concentration. This relationship has a linear behavior and is represented with compartmental models. As regards propofol, three compartments corresponding to fictitious volumes exhibiting homogeneous properties are considered. They are the central compartment (i.e., site of drug administration), the fast compartment (i.e., muscle tissues) and the slow compartment (i.e., fat tissues).

Pharmacodynamics is divided into two parts. The first one relates the plasmatic concentration inside the central compartment to the concentration inside the effect site and it is modelled with an additional compartment. The second one relates the effect site concentration to the therapeutic effect. For the propofol-BIS relationship, this is described with a nonlinear Hill function (Ionescu et al., 2015; Ionescu, 2018).

Many PK/PD models have been proposed in the last decades (Minto and Schnider, 2008), each one of them with its own characteristics and drawbacks (Vandemoortele et al., 2022). The Schnider model (Schnider et al., 1998, 1999) has been successfully used to tune PID controllers with a population-based method (Padula et al., 2017), and the effectiveness of this approach has been indeed confirmed by clinical results (Schiavo et al., 2021a, 2022b). In a previous work (Paolino et al., 2023b), the use of the recently developed Eleveld model (Eleveld et al., 2018) has been also considered for PID controllers tuning. This choice has been fostered by the fact that, in principle, this new model is more general and takes into account children, adults and elderly people, while the Schnider model focuses only on adults. The obtained results show that, disregarding the model used for the population-based tuning, the PID controller meets the clinical requirements when the patient is less than 60 years old. On the contrary, for elderly people, when the controller is tuned basing on the Schnider model but the patient is represented by the Eleveld model, the achieved results are not satisfactory. This is due to the presence of an age-dependent delay in the Eleveld model that significantly degrades the controller performance.

In this paper we propose a novel approach to patient-individualized PID tuning by using the Eleveld model. This approach is built upon a previously proposed method based on the Schnider model (Schiavo et al., 2021). The rationale is to enhance the existing approach by exploiting the Eleveld model's more detailed representation of how PK/PD model parameters correlate with patient's physical characteristics. Unlike the Schnider model, which links only the PK model parameters to patient demographics, the Eleveld model establishes relationships between both PK and PD model parameters and the patient's demographic information.

This extension allows the personalized approach to be applied not only to the maintenance phase (when the BIS value has to be kept to its set-point value during the surgery despite the presence of disturbances such as noxious stimuli) but also to the induction phase (when the desired BIS value has to be attained at the beginning of the surgery from its initial condition). In fact, by using the Schnider model, the personalized tuning failed to yield satisfactory results during the induction phase due to the predominance of the nonlinear behavior of the Hill function, whose parameters are not related to the patient's demographic data and therefore only average values can be employed, introducing a significant modelling uncertainty in the system.

The paper is organized as follows. Section 2 presents the model employed in the study. Moreover, a brief description of the control structure and the tuning procedure is proposed. The extensive simulation results are presented in Section 3 and discussed in Section 4. Finally, conclusions are drawn in Section 5.

## 2 Materials and Methods

### 2.1 Eleveld Model

Hereafter a brief description of the Eleveld model is presented. As already mentioned in Section 1, pharmacological models may play a key role in everyday anesthesia practice. In particular, PK/PD models are a reliable resource when applied to patients with similar characteristics to those involved in the study performed for model realization but their accuracy might significantly degrade when they are employed to describe patients with characteristics that deviate from those of the modelling cohort.

To cope with this issue, a model with the aim to be more accurate in estimating covariates across a broad population with different ages, heights, weights, and gender has been proposed in (Eleveld et al., 2018). Therefore, this should increase the model performance in predicting the time course of drug concentration in plasma and the relationship between propofol concentration and its clinical effect.

The model has been developed by taking into account data coming from 1033 patients and volunteers present in the open-TCI database (opentci.org). For the model development, a reference individual (a 35 yr male of 70 kg and 170 cm) is considered and allometric scaling (White and Seymour, 2005) has been exploited to scale model parameters, such as volumes of distribution and clearances, for each patient. A compartmental structure has been used to design the model. Therefore, the drug transfer dynamics between each compartment can be written as a system of differential equations, namely:

$$\begin{cases} \dot{q}_1(t) &= -(k_{10} + k_{12} + k_{13}) \cdot q_1(t) + k_{21} \cdot q_2(t) + k_{31} \cdot q_3(t) + u(t) \\ \dot{q}_2(t) &= k_{12} \cdot q_1(t) - k_{21} \cdot q_2(t) \\ \dot{q}_3(t) &= k_{13} \cdot q_1(t) - k_{31} \cdot q_3(t) \\ \dot{C}_e(t) &= k_{1e} \cdot \left( \frac{q_1(t)}{V_1} \right) - k_{e0} \cdot C_e(t) \end{cases} \quad (1)$$

where  $u(t)$  is the propofol mass flow, expressed in mg/s,  $q_1(t)$ ,  $q_2(t)$  and  $q_3(t)$  are the drug masses, in mg, in the primary, fast and slow compartment, respectively. Then,  $k_{12}$ ,  $k_{13}$ ,  $k_{21}$ ,  $k_{31}$  and  $k_{1e}$  are the drug transfer rates between every compartments, expressed in  $s^{-1}$ ,  $C_e(t)$  is the drug concentration in the effect-site compartment expressed in mg/L,  $k_{10}$  and  $k_{e0}$  are the drug elimination rates, expressed in  $s^{-1}$ , from the primary compartment and from the effect-site compartment, respectively, and  $V_1$  is the volume of the primary compartment expressed in L. These magnitudes have been devised starting from patient demographic information to improve the model prediction reliability. In particular,  $k_{10}$ ,  $k_{12}$ , and  $k_{21}$  are function of patient's age and weight, while  $k_{13}$ , and  $k_{31}$  are function of patient's age, weight, height and gender, and  $k_{e0}$  is function of patient's weight.

The major novelty lies in the pharmacodynamic part. Compared to other pharmacological models proposed in the literature, the Eleveld's one relates the BIS nonlinearity to the patient's demographic information. As said before, the nonlinearity is modeled with the

Hill function. It is a sigmoid curve whose mathematical expression is:

$$\overline{\text{BIS}}(t) = E_0 - E_{max} \left( \frac{C_e(t)^\gamma}{C_{e50}^\gamma + C_e(t)^\gamma} \right), \quad (2)$$

where  $E_0$  is the baseline BIS value that represents the initial drug-free state of the patient,  $E_0 - E_{max}$  is the maximum reachable clinical effect,  $C_e$  is the value of the drug concentration inside the effect-site,  $\gamma$  represents the slope of the sigmoidal curve, and  $C_{e50}$ , which depends on the patient's age, is the drug concentration that is necessary to reach 50% of the maximal effect.

Note that the Hill function slope  $\gamma$  assumes known constant values depending on the current  $C_e(t)$  value. Moreover, the PD model presents a time delay that is function of the patient's age (Elefeld et al., 2018):

$$\text{BIS}_{delay} = 15 + e^{(0.0517 \cdot age)} \text{ [s]}. \quad (3)$$

So that the process variable  $\text{BIS}(t)$  results to be:

$$\text{BIS}(t) = \overline{\text{BIS}}(t - \text{BIS}_{delay}). \quad (4)$$

It appears that, for elderly patients, this delay assumes considerable values. For example, for a ninety years old patient the delay is equal to 120 s. This can be challenging for controllers which may struggle to handle such a remarkable dead time.

In conclusion, the Elefeld model, starting from the patient's demographic information allows the estimation of the pharmacokinetics, of the pharmacodynamics, and of the relationship between the effect-site concentration and the clinical effect. In principle, it is therefore a very good candidate to be used to design a personalized control law.

## 2.2 Control Structure

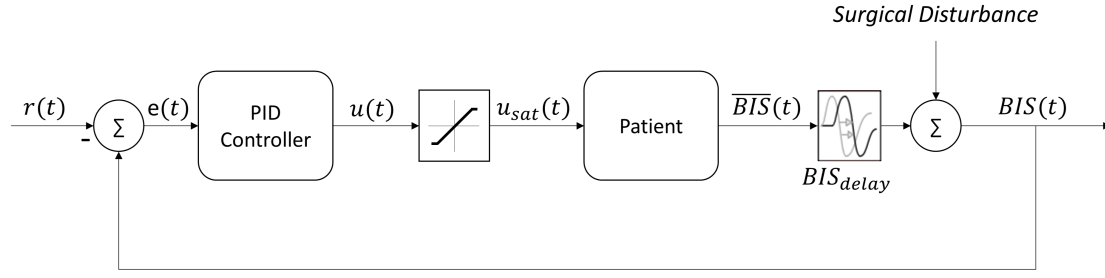
The closed-loop control scheme considered in this paper is based on a standard PID controller and is shown in Fig. 1, where the control variable  $u(t)$  is the propofol infusion rate, the process variable  $\text{BIS}(t)$  is the patient's current BIS value, the reference signal  $r(t)$  is the desired BIS value and the control error  $e(t)$  is calculated as:

$$e(t) = \text{BIS}(t) - r(t). \quad (5)$$

The effect of disturbances due to the surgical stimulation is modeled as a signal that is added directly to the process variable.

The transfer function of the PID controller, which is implemented in standard ideal form with filtered derivative term, is:

$$\text{PID}(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{sT_d}{1 + s\frac{T_d}{N}} \right), \quad (6)$$



**Figure 1:** Schematic representation of the considered PID-based closed-loop control structure.

where  $K_p$  is the proportional gain,  $T_i$  and  $T_d$  are the integral and derivative time constants, respectively,  $N$  is equal to 5 and determines the time constant of the low-pass filter of the derivative action.

The control variable  $u(t)$  is subjected to saturation. Indeed, by considering a standard propofol concentration of 20 mg/mL, the propofol infusion rate  $u_{sat}(t)$  can range from 0 mg/s to 6.67 mg/s. These values are obtained by considering commercially available infusion pumps (Graseby 3400, Smiths Medical, London, UK) that can operate at a minimum and maximum infusion rate of 0 mL/h and 1200 mL/h, respectively. The conditional integration anti-windup strategy (Visioli, 2006) has been used to handle actuator saturation.

The PID controller handles both the induction and the maintenance phases of anesthesia. During the induction phase, the patient is forced to be driven from an alert to an unconscious state. From a process control viewpoint, this phase can be seen as a set-point following task where the BIS has to be lowered from its baseline value, which is close to 100, to the desired target value of 50, since this is the target for DoH that is commonly used in the clinical practice. Typically, this transient phase should not be longer than 5 minutes.

As regards the maintenance phase, propofol must be continuously administered to avoid intra-operative awareness, but, at the same time, it is crucial to prevent overdose and underdose episodes. The surgery is performed during this time interval and the BIS level should be maintained as much as possible inside the 40-60 range despite surgical stimuli acting on the patient (Rosow and Manberg, 2001). Thus, the maintenance phase can be seen as a disturbance rejection control task where the effect of the surgical stimulation on the BIS must be compensated as quickly as possible.

### 2.3 Tuning Procedure

In this paper two different tuning methodologies are employed and their performance is compared. In both of them an optimization problem is solved to tune the controller. In particular, we determine the optimal values of  $K_p$ ,  $T_i$  and  $T_d$  that minimize the integrated absolute error (IAE), defined as:

$$IAE = \int_0^{\infty} |e(t)| dt, \quad (7)$$

where  $r(t)$  has been set constant and equal to the set-point value of 50. The IAE is obtained by performing a numerical simulation of the response to propofol infusion considering the closed-loop scheme shown in Fig. 1 and the Eleveld model to simulate the patient's dynamics. Both methodologies are applied separately for the induction and for the maintenance phases. This implies that two different simulation scenarios have been considered.

The induction phase is simulated by applying a negative step reference signal to  $r(t)$  from the baseline BIS value of the patient to the target value of 50. As regards the maintenance phase, to simulate the effect of the surgical activity, the double-step disturbance profile proposed in (Soltesz, 2013) is added to the process variable  $BIS(t)$ . Therefore, a positive step of amplitude 10 is applied followed by a negative one of the same amplitude after 20 minutes.

The first employed tuning methodology is the population-based tuning approach proposed in (Padula et al., 2017). In particular, the optimization problem consists of minimizing the worst-case IAE obtained on a dataset of thirteen patients (Ionescu et al., 2008) that has been proven, also by means of clinical experiments, to be representative of a wide population if the Schnider model is employed (Padula et al., 2017; Schiavo et al., 2021a, 2022b). This can be formalized as:

$$\{K_p, T_i, T_d\} = \arg \min \max_{k \in \{1, \dots, 13\}} \text{IAE}_k, \quad (8)$$

where the index  $k$  represents each patient of the considered dataset. The values of the tuning parameters obtained with this approach are shown in Table 1.

The second employed tuning methodology is the individualized tuning approach proposed in (Schiavo et al., 2021). Here, the optimization problem consists of minimizing the IAE for each specific patient separately and it can be formalized as:

$$\{K_{p_k}, T_{i_k}, T_{d_k}\} = \arg \min \text{IAE}_k, \quad (9)$$

In particular, once the patient's age, weight, height and gender are known, the PK/PD model of that specific patient is constructed and it is used to simulate the response to propofol administration, thus obtaining the IAE. As an example, the PID tuning parameters obtained with this approach on the dataset of the thirteen patients are shown in Table 2. It is worth stressing that, in this case, an optimization problem has been solved for each patient, thus thirteen individualized combinations of optimal PID tuning parameters have been obtained. With this methodology, the potentiality of the Eleveld model in estimating covariates across a broad population of patients can be better exploited, thus determining an optimal controller tuned ad-hoc for each patient, which can improve the performance obtainable with the population-based tuning approach. It is worth stressing that the individualized tuning can be effectively implemented in everyday anesthesia practice since, once the patient's demographic data are known, the tuning procedure needs few seconds to be completed.

|       | Induction phase | Maintenance phase |
|-------|-----------------|-------------------|
| $K_p$ | 0.0764          | 0.1194            |
| $T_i$ | 900.8           | 336.6             |
| $T_d$ | 77.55           | 34.84             |

**Table 1:** PID parameters obtained for the induction and maintenance phases by applying the population-based tuning methodology. The values of the proportional gain  $K_p$  are expressed in mg/s, while the time constants  $T_i$  and  $T_d$  are expressed in s.

Both optimization problem have been solved in MATLAB by using genetic algorithms with a population size equal to 150, while Gaussian mutation and scattered crossover have been exploited to generate the child of the current generation. The Gaussian mutation consist in picking a random number, from a Gaussian distribution with mean 0, to perturb individuals that will belong to the next generation. The scattering crossover builds a random vector of zeros and ones. Then, each child is generated by picking random genes from parent 1 if the scatter vector element is a 0 or from parent 2 if the vector element is a 1.

It is worth highlighting that, when the individualized tuning approach was first proposed in (Schiavo et al., 2021) by using the Schnider model, its application was limited to the maintenance phase of anesthesia. Indeed, when applied to the induction phase, this method failed in providing an improved performance with respect to the population-based tuning. This is due to the fact that, in the Schnider model, only the parameters of the linear PK depends on patient’s demographic data, while those of the Hill function are fixed at average values. However, the contribution of this latter is predominant in the induction phase since it shows a strong nonlinear behavior at low propofol effect-site concentrations. Thus, in this phase, the effect that covariates have on the linear part of the model is shadowed by the presence of the Hill function. Consequently, the benefits of the individualized tuning become marginal.

### 3 Simulation Results

An extensive simulation study has been performed to compare and analyze the performance obtained with the population-based tuning and with the individualized tuning. Both the induction and the maintenance phases have been considered and the same simulation scenarios used for the tuning procedure have been used. The evaluation is first performed on the thirteen patients of the tuning dataset. Then, to test the robustness and the general validity of the obtained results, a wider population is considered.

#### 3.1 Performance Evaluation

The performance indices proposed in (Ionescu et al., 2008) have been used to objectively evaluate the performance of the proposed tuning methodologies. Concerning the induction

| k  | Induction phase |       |       | Maintenance phase |       |       |
|----|-----------------|-------|-------|-------------------|-------|-------|
|    | $K_p$           | $T_i$ | $T_d$ | $K_p$             | $T_i$ | $T_d$ |
| 1  | 0.0627          | 778.5 | 82.36 | 0.0759            | 345.7 | 50.16 |
| 2  | 0.0620          | 710.1 | 74.42 | 0.0802            | 363.1 | 45.46 |
| 3  | 0.0762          | 762.9 | 78.20 | 0.1058            | 327.8 | 37.51 |
| 4  | 0.0670          | 772.0 | 76.40 | 0.0857            | 382.4 | 53.45 |
| 5  | 0.0872          | 778.7 | 78.79 | 0.1196            | 352.7 | 37.20 |
| 6  | 0.0647          | 874.4 | 90.69 | 0.0821            | 342.5 | 47.83 |
| 7  | 0.0889          | 766.4 | 76.92 | 0.1146            | 328.6 | 43.13 |
| 8  | 0.0892          | 775.4 | 76.66 | 0.1179            | 331.7 | 45.54 |
| 9  | 0.0781          | 836.2 | 83.21 | 0.0941            | 359.6 | 47.97 |
| 10 | 0.0668          | 739.4 | 70.75 | 0.0820            | 431.2 | 48.42 |
| 11 | 0.0808          | 769.6 | 76.71 | 0.0983            | 346.7 | 48.96 |
| 12 | 0.0751          | 762.3 | 78.27 | 0.0962            | 340.7 | 44.31 |
| 13 | 0.0741          | 763.6 | 77.53 | 0.0880            | 339.7 | 50.53 |

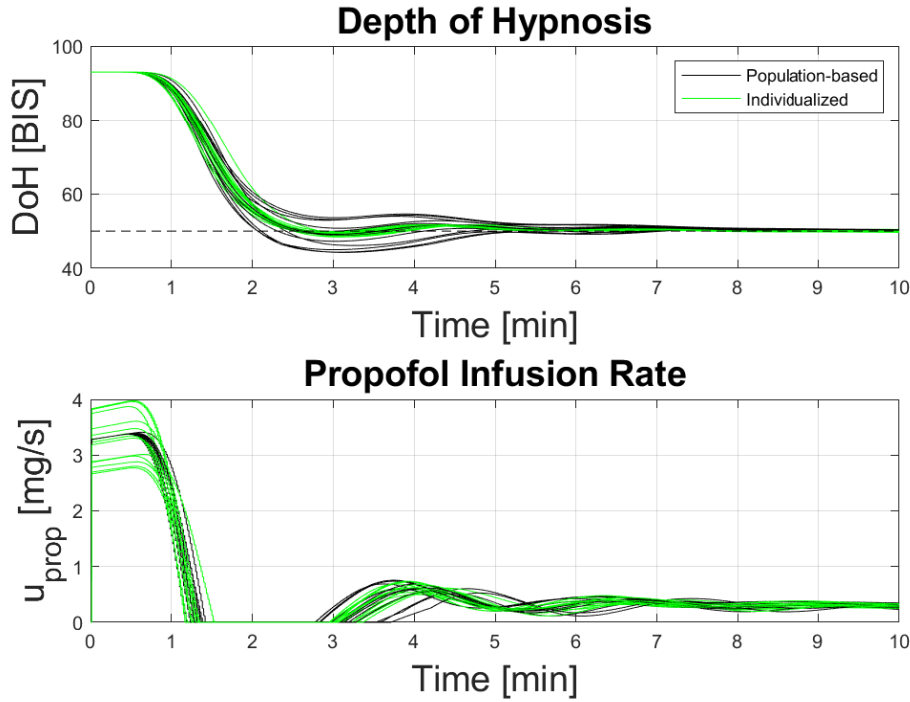
**Table 2:** PID parameters obtained for the induction and maintenance phases for each patient of the dataset by applying the individualized tuning methodology. The values of the proportional gain  $K_p$  are expressed in mg/s, while the time constants  $T_i$  and  $T_d$  are expressed in s.

phase they are:

- *Time-to-Target (TT)*: it represents the time required to the BIS signal to enter for the first time in the target value of  $50 \pm 10\%$ , indeed inside the BIS interval of 45-55;
- *BIS-NADIR*: it is the lowest reached BIS value during the whole induction phase;
- *Settling Time at 10% (ST10)*: it represents the time span necessary to the BIS to reach and steady inside the the target range of  $50 \pm 10\%$  (45-55 interval);
- *Settling Time at 20% (ST20)*: defined as the time interval required to the BIS to reach and steady inside the the target range of  $50 \pm 20\%$  (40-60 interval).

Since the maintenance control task is different from the induction one, the performance indices just presented have been slightly modified. They are:

- *Time-to-Target (TT)*: it represents the time required to the BIS signal to enter for the first time in the target value of  $50 \pm 10\%$  after the disturbance occurs. It is calculated separately for the positive and for the negative step, namely  $TT_{pos}$  and  $TT_{neg}$ , respectively;
- *BIS-NADIR<sub>pos</sub>*: it is the lowest reached BIS value during the positive step rejection (undershoot);
- *BIS-NADIR<sub>neg</sub>*: it is the highest reached BIS value during the negative step rejection (overshoot).



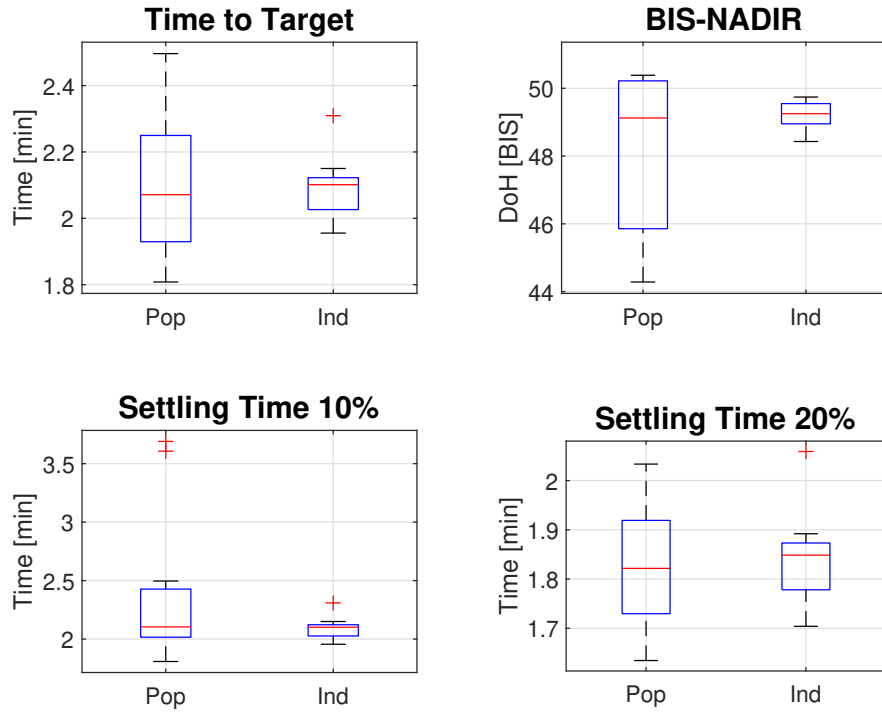
**Figure 2:** Induction phase simulation results for the thirteen patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

### 3.2 Simulations on the Thirteen Patients

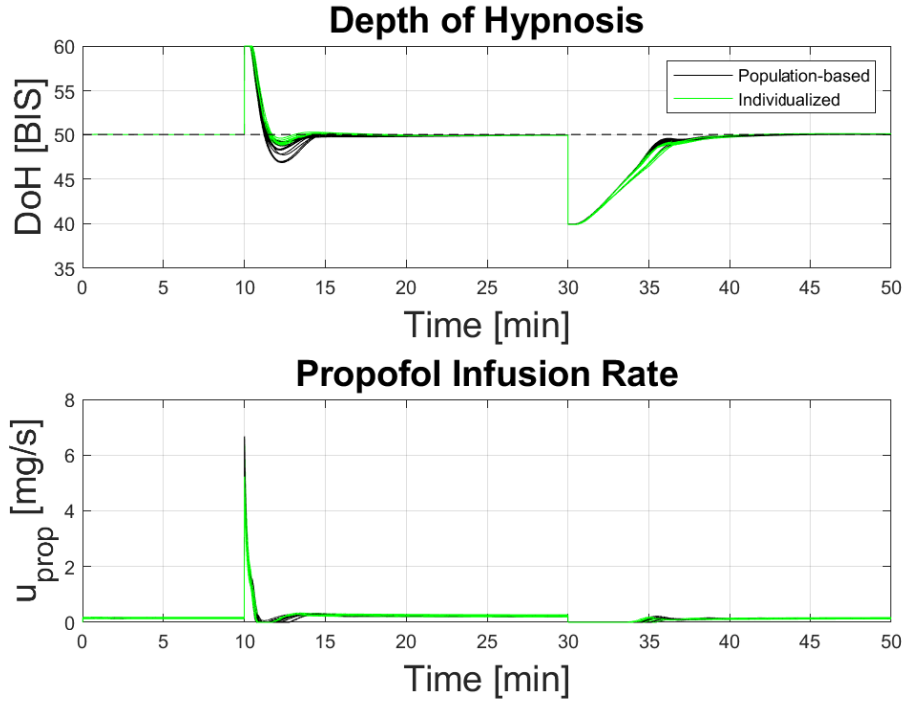
Fig. 2 shows the results obtained during the induction phase with the population-based tuning (black line) and with the individualized tuning (green line) on the thirteen patients. Looking at the responses, some differences are present between the two controllers, although both meet the clinical requirements. The individualized tuning approach yields an oscillation-free transient and, in general terms, achieves a faster response. Moreover, by fully exploiting the PK/PD model information, the initial infusion rate is modulated according to the patient's dynamics.

These results are also confirmed by the performance indices. From Fig. 3, it is possible to see that with an individualized tuning it is possible to achieve a better performance in terms of speed of response and stability. It is worth noting that the individualized tuning is able to reduce the variability of the performance indices, as witnessed by the amplitude of the boxes and whiskers shown in Fig. 3. Both control solutions have satisfactory performance and meet the clinical requirements but the individualized tuning reduces the effect of inter-patient variability on the controller performance.

Concerning the maintenance phase simulation, results are shown in Fig. 4. Here the two controllers have a similar performance in rejecting the negative step. On the contrary, differences are present in the positive step rejection. In particular, the individualized controller provides a response without relevant episodes of undershoot. Moreover, the population-based controller administers a larger drug quantity, reaching the actuator satu-



**Figure 3:** Boxplots of the induction performance indices for the thirteen patients. Pop: population-based controller tuning. Ind: individualized controller tuning. The red line represents the median value, the lower and upper blue box limit are the 25th and 75th percentile respectively, black whiskers represents the upper and lower adjacent, and red crosses are the population outlier.



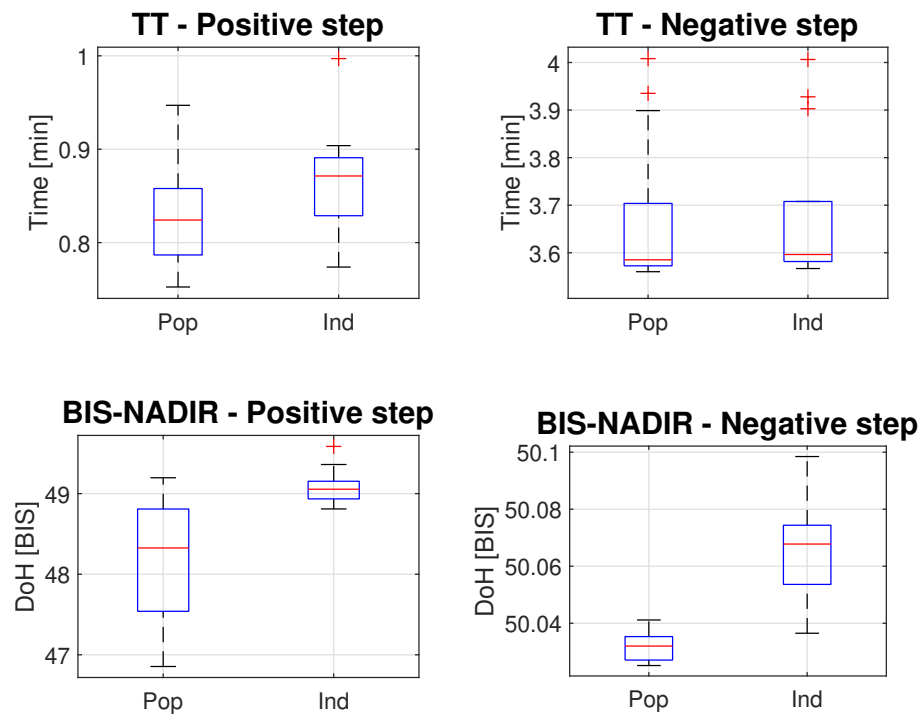
**Figure 4:** Maintenance phase simulation results for the thirteen patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

ration limit. This results in a more pronounced undershoot. Once again, the performance indices analysis confirms this. Boxplots are shown in Fig. 5, where it is possible to notice that the individualized tuning results in a slightly longer  $TT_{pos}$  but it significantly reduces the  $BIS-NADIR_{pos}$  and its variability. However, also for the maintenance phase, both controllers fulfil the clinical requirements.

### 3.3 Simulation on a Wide Population

Simulations on a broad population have been performed to test the robustness of the proposed solution. The new patient set is composed of 150 adults and 150 elderly people, each one with different demographic parameters. The approach is sensible since the database used to tune the population-based controller is supposed to be representative of a large population (which is the case with the Schnider model). The new patients have been derived by randomly selecting the age and the gender from a uniformly distributed population and, then, by randomly choosing the height and the body mass index inside the suitable range for the decided set of age and gender. The available range of parameters has been determined starting from average population values. In particular, height boundary values are 165-190 cm for males and 153-174 cm for females, whereas BMI ranges between 17.5 and 32 for both genders. Moreover, the adult population age is from 20 to 60, while for the elderly people is from 60 to 90.

Also in this scenario the induction and the maintenance phase have been addressed



**Figure 5:** Boxplots of the maintenance performance indices for the thirteen patients. Pop: population-based controller tuning. Ind: individualized controller tuning. The red line represents the median value, the lower and upper blue box limit are the 25th and 75th percentile respectively, black whiskers represents the upper and lower adjacent, and red crosses are the population outlier.

separately. Fig. 6 shows the results obtained during the induction phase for adults. Here, the differences between the population-based controller and the individualized solution are more pronounced. Again, the personalized PID controller provides a better performance. By observing the propofol infusion rate plot, it is worth noting the large variability in the administered dose of propofol provided by the individualized controller. Indeed, in some cases, the controller infuses a large quantity of propofol, even reaching saturation. However, this does not cause overdoses since large undershoots are not observed. Thus, this means that the personalized PID parameters vary in a sensible manner with respect to the patients characteristics. This is shown in Fig. 7, where surfaces have been determined by generating a sample population, and for each individual, by tuning the optimal PID parameters. The population covariates are in the following ranges:  $age \in [20, 90]$  in steps of 10 years,  $height \in [150, 190]$  cm in steps of 5 cm and  $weight \in [50, 90]$  kg in steps of 5 kg, and for each combination of the above, there are both a female and a male individual. It appears that there is a strict correlation between the  $K_p$  value and the demographic information of the patient. Indeed,  $K_p$  varies according to the patient's age, height and weight, showing a clear increasing trend. This is not true for  $T_i$  and  $T_d$ , which do not show a clear correlation with the patient characteristics. Moreover, by calculating the coefficient of variation (CV), defined as:

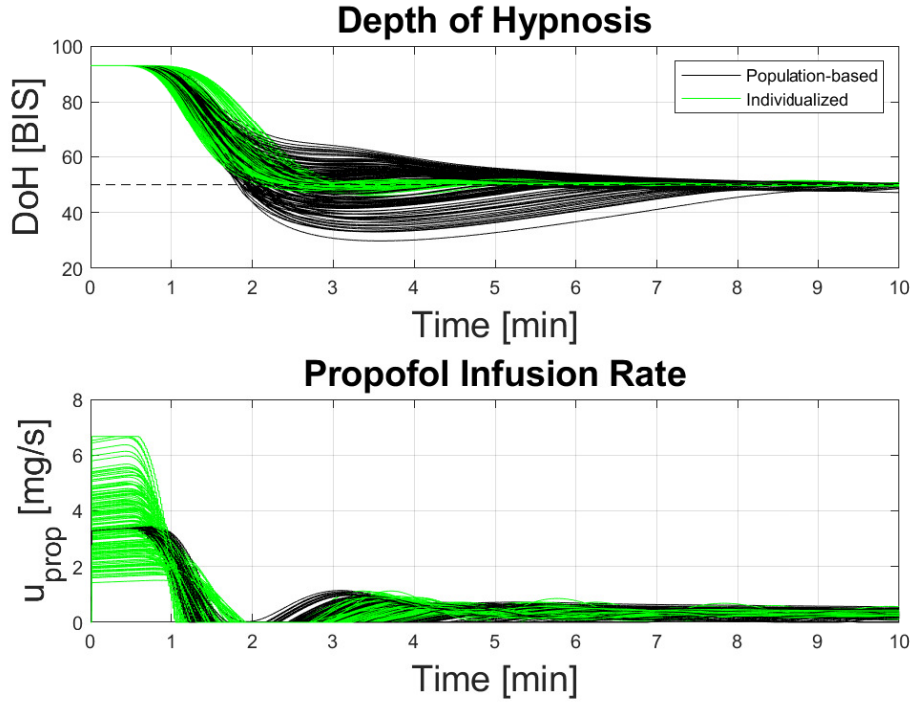
$$CV = \frac{\sigma}{|\mu|} \cdot 100[\%], \quad (10)$$

where  $\sigma$  is the standard deviation and  $\mu$  is the average, for the proportional gain, it results to be equal to 56.44% for males and for 58.11% females. Thus, the variation is very relevant and justifies the design choice of developing an individualized PID controller.

The results are also confirmed by looking at the performance indices. From the boxplots shown in Fig. 8 it is possible to see that the individualized tuning improves all the performance indices with respect to the population-based tuning by also shrinking their dispersion.

Fig. 9 shows the induction phase results for the elderly people. It immediately appears that the population-based tuning is too aggressive, and for this reason, it causes relevant episodes of undershoot. Indeed, this solution fails to complete the induction phase in 10 minutes since the BIS never reaches the steady state. For this reason, performance indices have been omitted for this scenario. Thus, the thirteen patients used during the tuning procedure do not describe a broad population when represented with the Eleveld model. Concerning the individualized controller, in some cases, it produces a very slow transient. This is because of the low values of proportional gain that result from the optimization, as shown in Fig. 10, and because, according to the Eleveld model, the dead time is strictly correlated to the patient's age. Thus, the older the patient is, the higher the delay is. However, the individualized PID controller meets all the clinical requirements by providing satisfactory performance despite the delay.

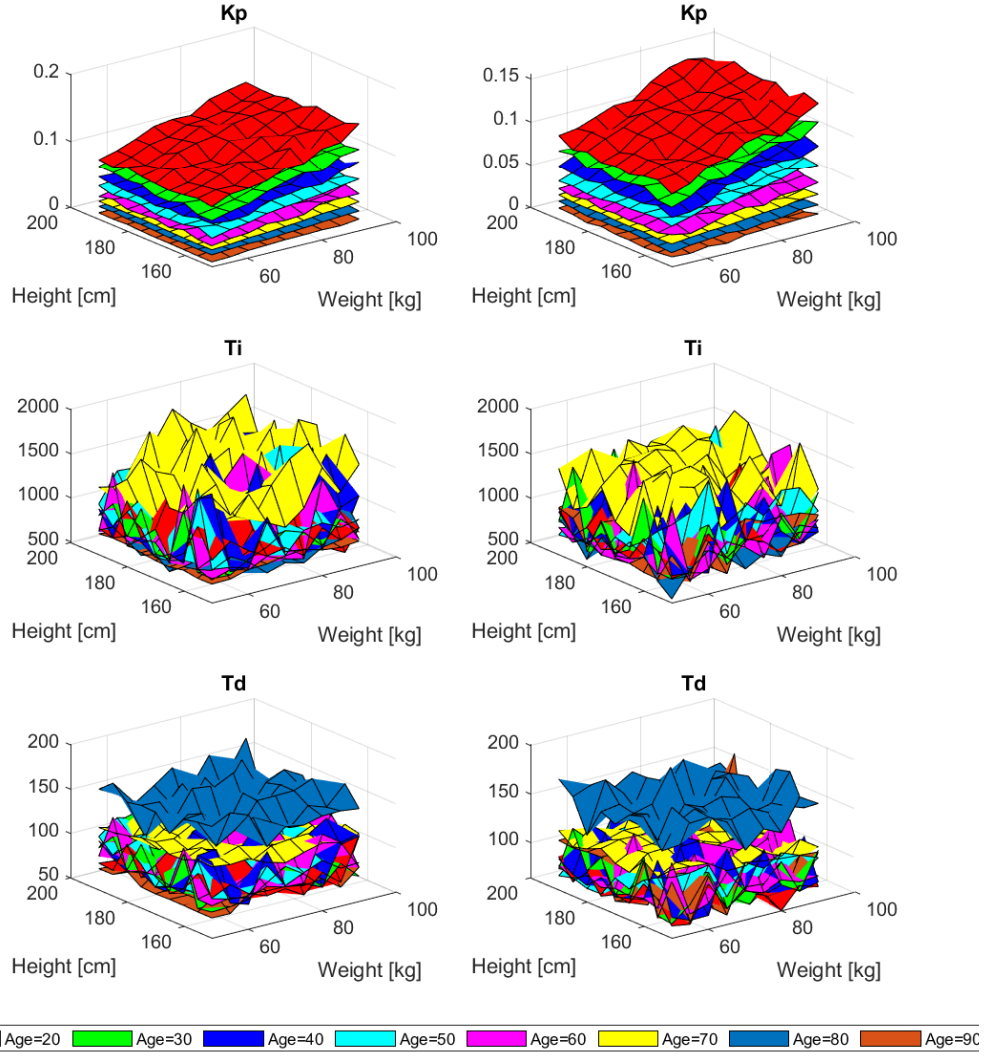
Concerning the maintenance phase, Fig. 11 shows results related to adults. The population-based controller provides responses characterized by the presence of large undershoots,



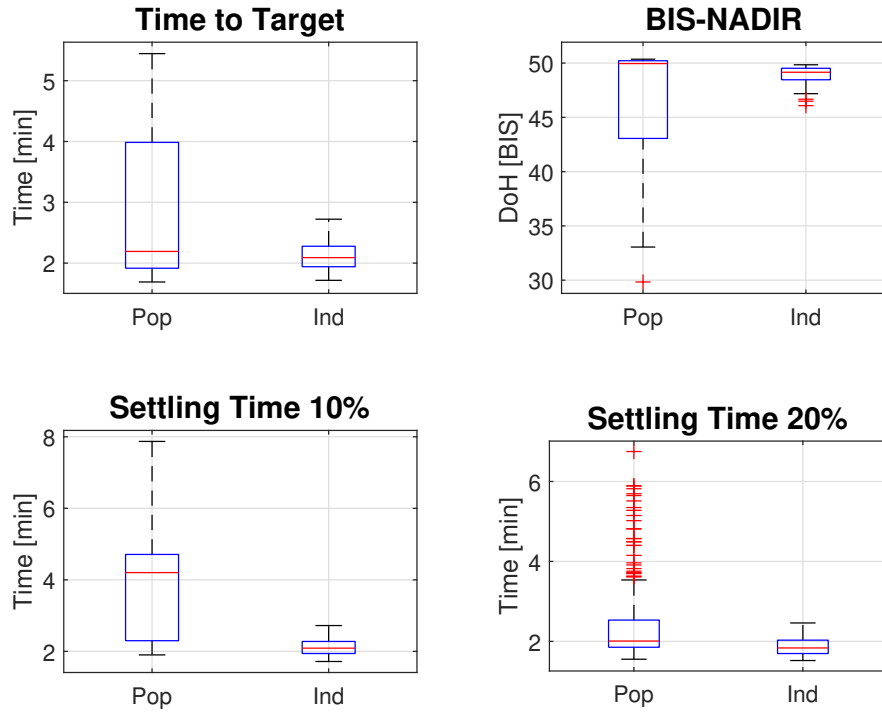
**Figure 6:** Induction phase simulation results for the 150 adults patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

whereas the individualized controllers have a more stable response. The two solutions perform similarly in rejecting the negative step. The only difference is the presence of oscillations at the steady state when using the population-based PID.

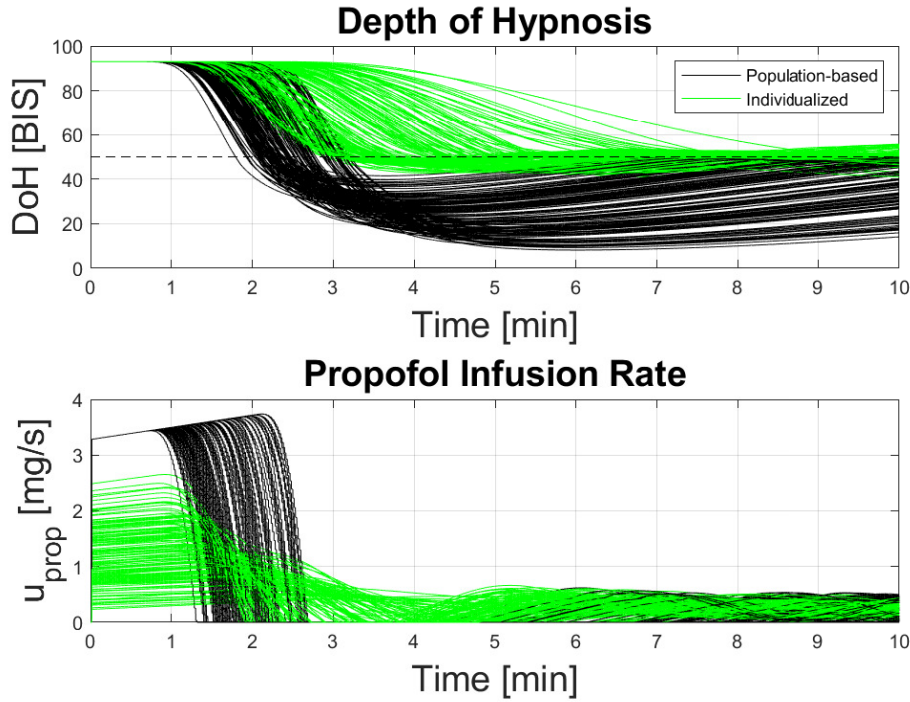
From the boxplots of the performance indices shown in Fig. 12, it is possible to observe that the individualized tuning is able to significantly reduce the  $BIS-NADIR_{pos}$  without causing an excessive increase of  $TT_{pos}$ . It is also possible to see that the two controllers perform similarly in rejecting the negative step disturbance. Maintenance phase simulation results for the elderly people are shown in Fig. 13. Here, the individualized controller outperforms the population-based one, confirming that the latter is not suitable for this case. Indeed, the PID tuned with the population-based approach struggles to complete the infusion, due to the presence of wide oscillations, and provides an unsatisfactory performance. On the contrary, the individualized PID is not affected by oscillations and delivers a satisfactory performance despite it is possible to notice that the age dependant delay also affects the disturbance rejection task. Once again, results are confirmed by the performance indices shown in Fig. 14. In particular, in this case both the performance with respect to the positive disturbance and to the negative disturbance rejection is improved by the individualized PID tuning. Undershoot, overshoot and the variability of the  $TT_{neg}$  are significantly reduced. The  $TT_{pos}$  is slightly incremented, however it remains bounded within values that are in accordance with the clinical practice.



**Figure 7:** PID parameters values for the population involved in the controller tuning for the induction phase. The parameters for females are shown in the left column while the parameters for males are shown in the right column.



**Figure 8:** Boxplots of the induction performance indices for the 150 adults patients. Pop: population-based controller tuning. Ind: individualized controller tuning. The red line represents the median value, the lower and upper blue box limit are the 25th and 75th percentile respectively, black whiskers represents the upper and lower adjacent, and red crosses are the population outliers.



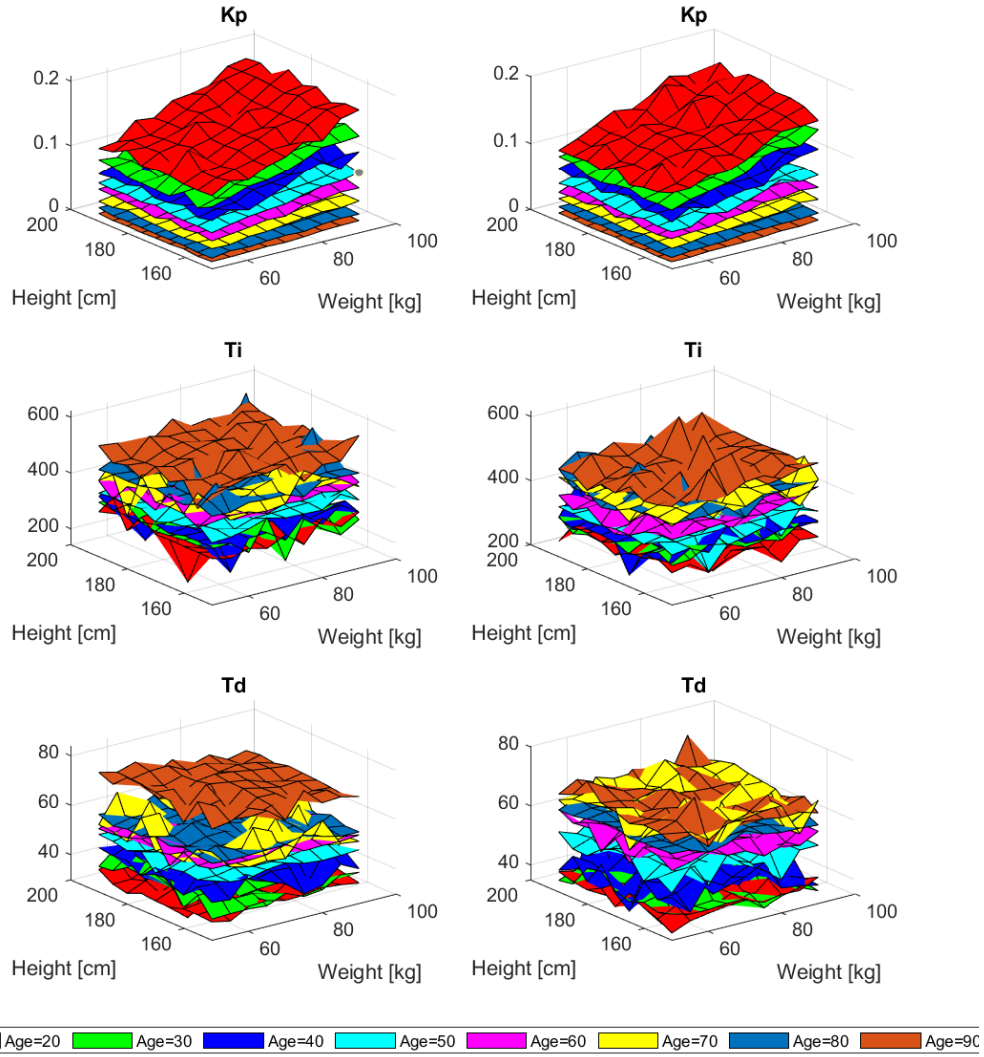
**Figure 9:** Induction phase simulation results for the 150 elderly patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

## 4 Discussion

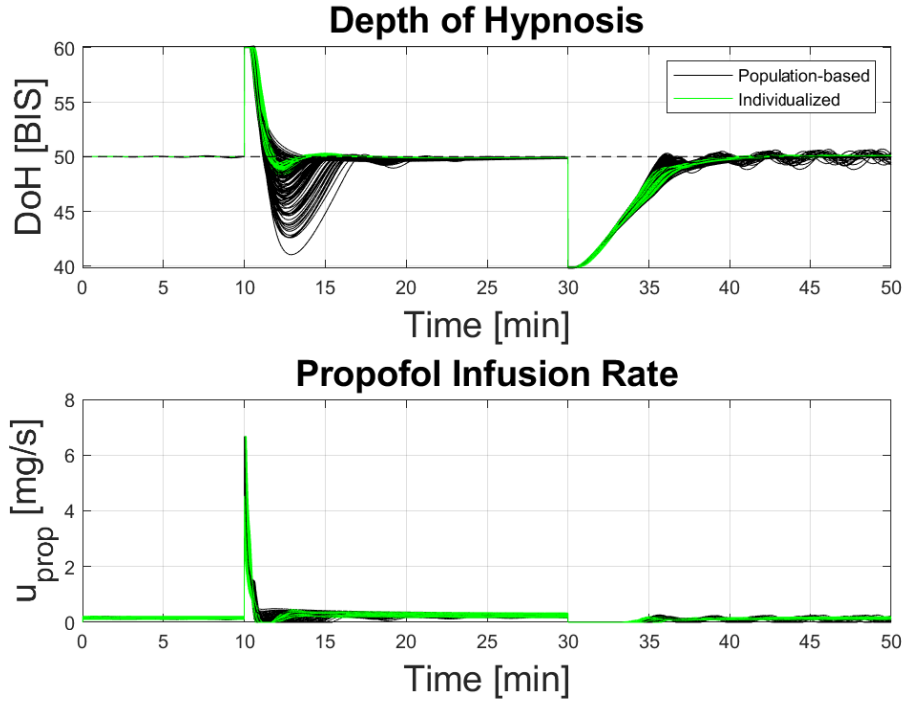
The simulation results obtained with the dataset of thirteen patients used to tune the controller are satisfactory with both the population-based and the individualized tuning. However, the latter shows a reduced effect of inter-patient variability on control performance. This advantage is more evident when a population of 150 adults patients is considered. In this case, the individualized tuning shows an improvement in control performance with respect to the population-based tuning, both in the induction phase and in the maintenance phase.

However, when a population of 150 elderly patients is considered, the advantages of the individualized tuning are really remarkable. Indeed, in this case the population-based tuning is not able to deliver a satisfactory performance, as in the induction phase an excessive undershoot is observed and in the maintenance phase oscillations are present. This is due to the age-dependent delay described in the Eleveld model that assumes relevant values (around 2 minutes) in the elderly population. The advantage of the individualized tuning consists in the fact that it can take into account this aspect, thus providing a tuning that is optimized according to the characteristics of each patient.

The relevance of this aspect is witnessed by the trends of the tuning parameters shown in Figs. 7 and 10, and by the CV values reported in Section 3. However, not only the age of the patient plays a role in the determination of the optimal tuning. Indeed, for  $K_p$  also the weight is relevant. In particular, with the individualized tuning the controller bandwidth is

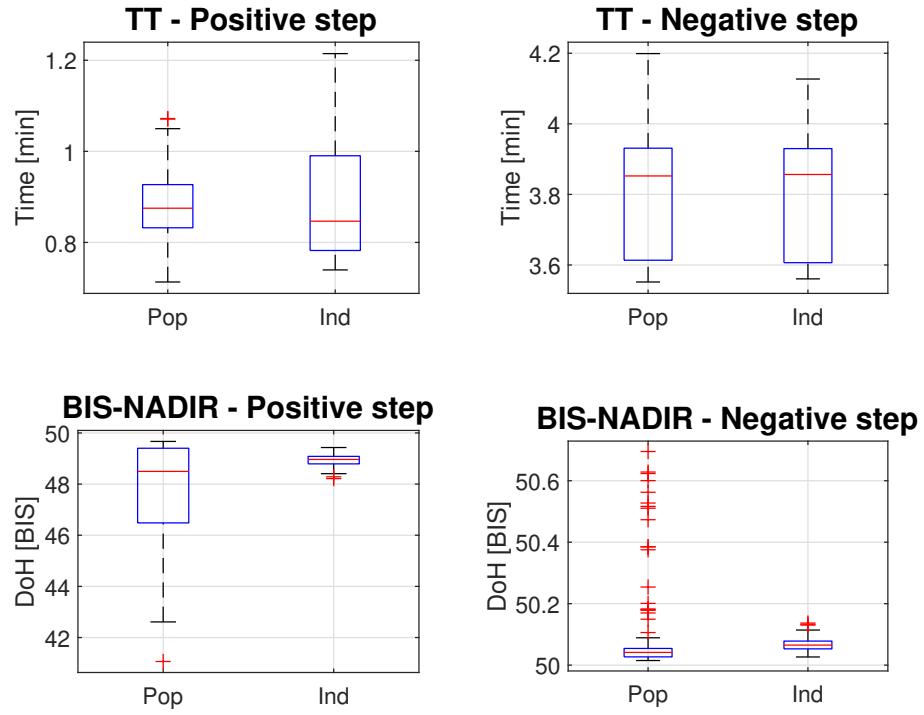


**Figure 10:** PID parameters values for the population involved in the controller tuning for the maintenance phase. The parameters for females are shown in the left column while the parameters for males are shown in the right column.

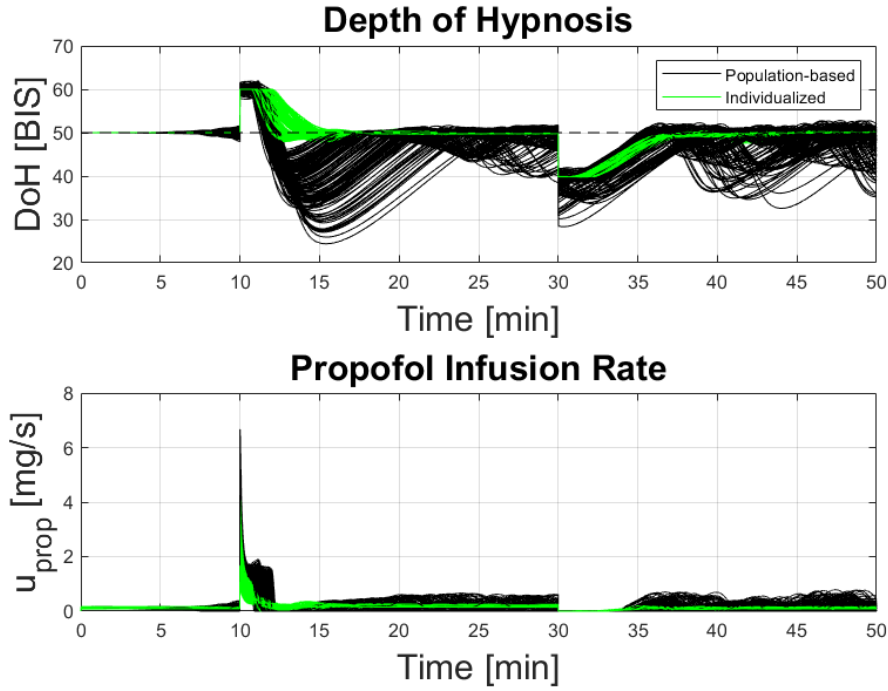


**Figure 11:** Maintenance phase simulation results for the 150 adults patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

directly proportional to the weight and inversely proportional to the age. It is worth noting that this behavior is sensible and it is in accordance with the clinical practice. Indeed, the anesthesiologists tend to give more propofol to patients with a higher weight and less propofol to the elderly patients since they are more prone to the onset of drug-related side effects such as bradycardia, hypotension and post-operative delirium (Fritz et al., 2016). Concerning the comparison with the results obtained in previous works, in which an individualized PID has been tuned by exploiting the Schnider model (Schiavo et al., 2021) and two population-based PID controllers have been devised by comparing the Schnider and the Eleveld model (Paolino et al., 2023), the controllers provide satisfactory performance when carrying out individualized tuning. Conversely, this does not happen when a population-based approach is followed. Precisely, with the Eleveld model, it is hard to develop a generalized controller since, for some patients, the presence of the delay is very pronounced. For this reason, the Schnider model reaches better performance in this context. However, the Schnider model has been developed starting from a limited patient group and does not relate every PK/PD model parameter to the patient demographic characteristics. This is why, with the Schnider model, individualized tuning can be exploited only for the maintenance phase of anesthesia. Instead, since the Eleveld model allows the control design to take advantage of patient information, its use to tune a highly personalized controller is promising. From the proposed simulation results, the individualized controller based on the Eleveld model provides a satisfactory performance in administering propofol to



**Figure 12:** Boxplots of the maintenance performance indices for the 150 adults patients. Pop: population-based controller tuning. Ind: individualized controller tuning. The red line represents the median value, the lower and upper blue box limit are the 25th and 75th percentile respectively, black whiskers represents the upper and lower adjacent, and red crosses are the population outliers.



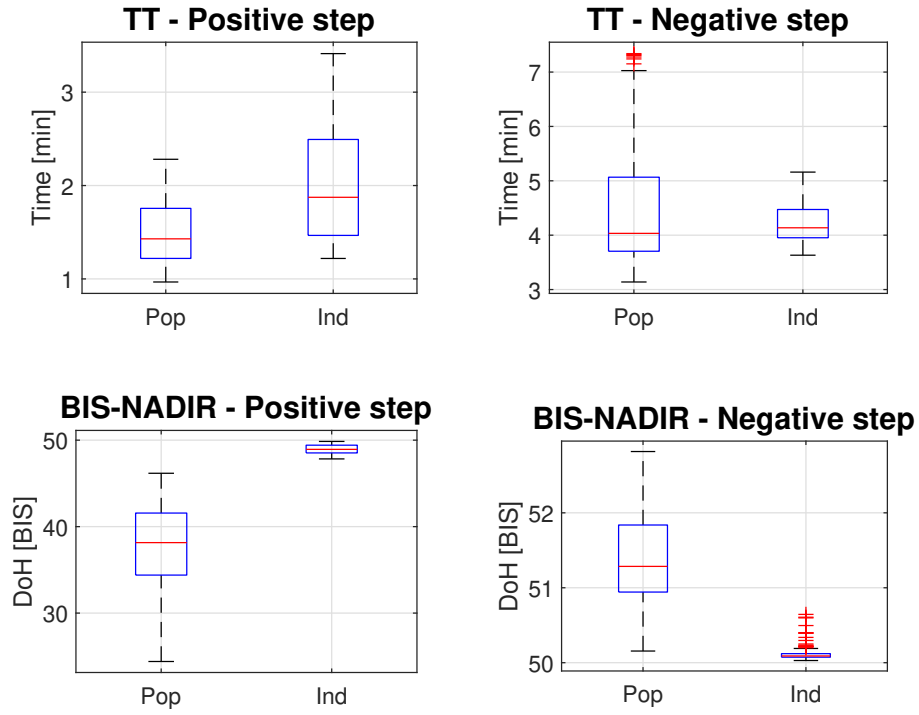
**Figure 13:** Maintenance phase simulation results for the 150 elderly patients. Black line: population-based controller tuning. Green line: individualized controller tuning.

every patient. Moreover, the Eleveld model can be used to represent children, giving the possibility to extend anesthesia control to young patients. Despite the obtained promising results, it must be pointed out that the Eleveld model might have some limitation in describing the dynamics of the elderly people as only three individuals older than 67 years have been taken into account in developing the model (Eleveld et al., 2018). Thus, the individualized tuning will be as good as the model employed to perform it. Thus the development of even more accurate models can lead to a significant improvement in performance when individualized PID tuning methodologies are employed.

## 5 Conclusions

In this paper, we have investigated the use of the Eleveld PK/PD model for propofol to tune a PID controller for closed-loop anesthesia control. In particular, we have evaluated the use of both a population-based and an individualized tuning approach. Then, we performed a thorough simulation study to compare the performance of the two methodologies. The obtained results show that the individualized PID controller achieves a better performance compared to the population-based one. This confirmed the results obtained in a previous work, where the population-based PID tuning showed unsatisfactory results with elderly patients.

Conversely, the individualized PID controller achieves a satisfactory performance in administering propofol in every simulated scenario and for each kind of patients, regardless to



**Figure 14:** Boxplots of the maintenance performance indices for the 150 elderly patients. Pop: population-based controller tuning. Ind: individualized controller tuning. The red line represents the median value, the lower and upper blue box limit are the 25th and 75th percentile respectively, black whiskers represents the upper and lower adjacent, and red crosses are the population outliers.

their characteristics. Thus, the individualized tuning seems to be a reliable solution. This can be explained by the fact that this approach is strongly related to the PK/PD model involved during the tuning phase and the Eleveld model is highly dependent on patient demographic information. Thus, exploiting all the model information during the tuning phase could lead to the development of a more robust controller.

However, it should be pointed out that the Eleveld model has not been developed for control purposes and it is affected by some limitations, especially in describing the dynamics of elderly patients. Therefore, the development of a pharmacological model specifically devised for control purposes could be very beneficial to further optimize the performance of closed-loop anesthesia administration. In any case, exploiting the Eleveld model to design a high personalized PID controller seems to be a reliable solution and a good starting point to move forward the development of fully personalized control solutions.

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# Paper V

## PIDA Control of Depth-of-Hypnosis in Total Intravenous Anesthesia

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### Abstract

In this paper we discuss the use of a Proportional-Integral-Derivative-Acceleration (PIDA) controller for the Depth-of-Hypnosis (DoH) control in total intravenous anesthesia (TIVA). In particular, the infusion rate of the hypnotic drug propofol is the control variable and the bispectral index (BIS) is the controlled variable. The PIDA controller is tuned by using a population-based approach and its robustness is evaluated with a Monte Carlo method. The noise amplification is reduced by means of suitably designed low-pass filters. A comparison with a PID controller is performed, showing that the addition of the acceleration action allows us to design a more aggressive controller, thus reducing the risk of awareness of the patient in the maintenance phase.

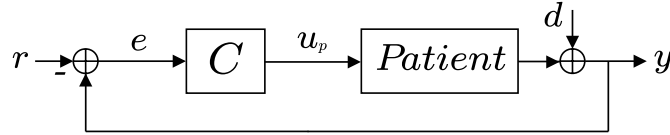
Originally published in Proceedings of the 4th IFAC Conference on Advances in Proportional-Integral-Derivate Control (PID 2024). The original version is available at [10.1016/j.ifacol.2024.08.033](https://doi.org/10.1016/j.ifacol.2024.08.033).

## 1 Introduction

Closed-loop control of anesthesia has emerged as an interesting research topic because of the advantages it can provide for both the patients and the anesthesiologists (Ghita et al., 2020). In fact, if properly designed, control systems can improve the effectiveness of anesthesia as they help to avoid under- and over-dosing episodes (Brogi et al., 2017). Moreover, they decrease the workload of the anesthesiologist, so that he/she can focus on other tasks and the possibility of human errors is reduced.

In this context, total intravenous anesthesia (TIVA) is usually considered, where drugs are administered in order to obtain the required level of hypnosis, analgesia and paralysis, in addition to controlling hemodynamic variables (Ionescu et al., 2021). In particular, the automatic control of the Depth-of-Hypnosis (DoH) can be implemented by measuring the bispectral index (BIS), which is a processed electroencephalogram (pEEG) sensor (Rampil, 1998), and by using the infusion rate of the hypnotic drug propofol as control variable. Different solutions have been proposed in this scenario. Proportional-Integral-Derivative (PID) control has been extensively studied (Soltesz et al., 2013; Padula et al., 2017; van Heusden et al., 2019; Schiavo et al., 2021), since it is the standard option in process control, and also more advanced techniques, such as fuzzy control (Mendez et al., 2016, 2018), fractional control (Dumont et al., 2009; Copot et al., 2017; Paolino et al., 2023), event-based control (Merigo et al., 2017) have been considered. It is worth mentioning that also Model Predictive Control (MPC) techniques have been applied as they have the advantage of explicitly taking into account the system constraints (Ionescu et al., 2008; Naşcu et al., 2017; Pawlowski et al., 2022). However, MPC needs an accurate Pharmacokinetic/Pharmacodynamic (PK/PD) model, which might not be available. It is therefore relevant to investigate new advanced techniques that retain the same relative simplicity of PID control (that is, they are not model-based) but they are able to improve the performance. Recently, Proportional-Integral-Derivative-Acceleration (PIDA) controllers, also called Proportional-Integral-Double-Derivative controllers (PIDD or PIDD2), have been proposed as a valid alternative to PID controllers when the process dynamics are of integral type or of high-order (Huba et al., 2021; Visioli and Sanchez-Moreno, 2024). The addition of a control action that is proportional to the double derivative of the control error increases the order of the controller and allows the designer to increase the bandwidth while keeping the robustness at a reasonable level (Milanesi et al., 2022). It has been shown that possible problems associated to the amplification of the measurement noise and to the occurrence of kicks in the control action can be solved by suitably designed low-pass filters (Ferrari and Visioli, 2022). In this paper we investigate the application of a PIDA algorithm to the control of DoH in both the induction and maintenance phases of TIVA. In the induction phase, the BIS value has to be lowered as fast as possible to the required set-point value without a significant undershoot. In the maintenance phase, the BIS value has to be kept at the required set-point value despite the presence of noxious stimuli, and awareness episodes have to be avoided. The tuning of the controller has been performed by applying

a procedure that has already been shown to be successful in process control. In particular, a genetic algorithm has been employed to minimize the worst-case integrated absolute error for a set of patients that are representative of a wide population. The robustness of the approach against inter- and intra-patient variability has then been tested by applying a Monte Carlo method. The paper is organized as follows. The problem is formulated in Section 2 and the design of the controller is described in Section 3. Simulation results are presented and discussed in Section 4 and, finally, conclusions are given in Section 5.



**Figure 1:** The DoH control scheme.

## 2 Problem formulation

We consider the standard unity-feedback control scheme of Figure 1, where the set-point and load disturbance signals are denoted as  $r$  and  $d$  respectively, the propofol infusion rate is denoted as  $u_p$  [mg/s], the BIS value is denoted as  $y$  and the control error is calculated as  $e = y - r$ . The patient can be modelled with a typical mamillary three-compartmental PK/PD model, that results in a fourth-order dynamic linear part in series with a static nonlinear Hill function. In particular, the parameters of the linear part depend, with a given uncertainty, on the demographics of the patient (weight, height, age and gender), while the parameter of the nonlinear Hill function are not known a priori. All the details about the model can be found in (Schnider et al., 1998; Ionescu et al., 2008, 2015; Padula et al., 2017). The controller  $C$  is of PIDA type with transfer function

$$C(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{T_d s}{1 + \frac{T_d}{N_1} s} + \frac{T_a s^2}{\left(1 + \frac{T_a}{N_2} s\right)^2} \right) \quad (1)$$

where  $K_p$  is the proportional gain,  $T_i$  is the integral time constant,  $T_d$  is the derivative time constant,  $N_1$  is the coefficient of the first-order low-pass filter applied to the derivative action,  $T_a$  is the double derivative (acceleration) time constant (with a slight abuse of notation, since its units is  $s^2$ ) and  $N_2$  is the parameter of the second-order low-pass filter applied to the acceleration action. Note that if  $T_a = 0$ , then we have a standard PID controller. A conditional integration technique has also been employed to avoid integrator windup (Visioli, 2006).

Two specific control tasks have to be considered in the anesthesia process. In the induction phase, the BIS level should be brought from the initial level (when the patient is awake) to the required value of 50 in a short time (less than 5 minutes) without an excessive

undershoot (the BIS should not go below the indicative value of 30) to avoid possibly dangerous hypotension. This is indeed a set-point following task from the process control point of view. During the maintenance phase, the BIS value should be kept as much as possible in the range between 40 and 60 despite the presence of noxious stimuli, modelled as step disturbances on the process output (Soltesz, 2013). From a process control point of view, this is a disturbance rejection task. In general, underdosing and overdosing should be avoided as much as possible. The former might yield awareness during the surgery, which can be very traumatic for the patient, while the latter can yield delirium and/or post-operative nausea and vomiting after the surgery, which leads to a serious discomfort for the patient and a prolonged recovery time.

### 3 Tuning Methodology

Following the same approach as in (Padula et al., 2017), the tuning of the controller is performed with a genetic algorithm that minimizes the worst-case Integrated Absolute Error (IAE) for the individuals in a dataset of 13 patients that have been proven to be representative of a wide population (Ionescu et al., 2008). The choice of the IAE, defined as

$$IAE = \int_0^{\infty} |r(t) - y(t)| dt, \quad (2)$$

is justified as fast transients without excessive under and overshoots are required. Formally, the following optimization problem has been solved:

$$\min_{K_p, T_i, T_d, T_a} \max_{k \in \{1, \dots, 13\}} IAE_k(K_p, T_i, T_d, T_a), \quad (3)$$

where  $k$  ranges over the patients in the dataset.

The optimization problem has been solved separately for the set-point following and for the disturbance rejection task. This allows us to investigate the best performance achievable by the PIDA controller in the two phases of anesthesia separately. For the calculation of the IAE, a step has been applied to the set-point signal  $r$  from the initial BIS value to the target BIS value of 50 for the induction phase and a step of amplitude 10 followed by another one of amplitude -10 after 4 min have been applied to the disturbance signal  $d$  for the maintenance phase. In order to take into account actuator saturation constraints, in each control task the lower saturation limit has been set to zero, whereas the upper limit has been set to 6.67 mg/s. These specifications have been derived from the Graseby™ 3500 pump, a common surgical device that is found in operating rooms.

The genetic algorithm has been used to tune the controller parameters in a noise-free setting. However, to ensure a suitable filtering,  $N_1$  and  $N_2$  have been set to 5. In fact, given the high noise level of the real BIS signal, this choice helps preventing significant fluctuations in the pump infusion rates.

For the sake of comparison, the same tuning procedure has also been applied to a PID

controller (again with  $N_1 = 5$ ), so that the improvement achievable with the addition of the acceleration action can be clearly assessed.

## 4 Simulation Results

The control system evaluation is performed for the induction and maintenance phases focusing on the medical specifications. Moreover, the robustness analysis concerning the inter- and intra-patient variability is shown, by comparing the results using specific performance indexes.

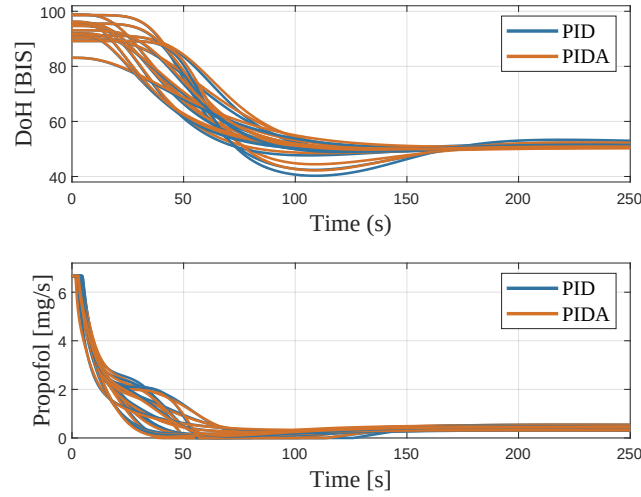
### 4.1 Tuning dataset

The controller performance is first analyzed by considering the response of the PIDA control scheme to the set-point change from the initial BIS value to the desired BIS level of 50 (induction phase). The results of the GA optimization are shown in Table 1, together with those obtained for PID control. It appears that they are similar and the performance improvement achieved by the PIDA controller is only of 3.1% in terms of the worst-case IAE. The inability of the PIDA controller to significantly improve the performance compared to the PID controller is confirmed by analyzing the responses obtained for the 13 patients of the tuning dataset shown in Figure 2.

Results regarding the maintenance phase are shown in Table 2. In this case, the determined optimal parameters yield a PIDA controller that is more aggressive than the PID controller (with an improved worst-case IAE). In particular, we notice that thanks to the stabilizing effect of the double derivative action, the optimizer can achieve optimal disturbance rejection by substantially increasing the proportional gain (to respond to disturbances promptly through a larger closed-loop bandwidth) and the integral time constant (to avoid excessive overshoots) compared to the optimal PID controller which relies primarily integral action. The PIDA controller achieves a faster positive-step rejection than the PID controller, while both controllers show similar performances in the negative step (see Figure 3). As already mentioned, this type of behaviour is desirable in anesthesia, despite the small undershoot that occurs, as it minimizes the risk of awareness episodes for the patient. This is achieved thanks to the double derivative action, which provides a larger control action and mimics the manual control action of an anesthesiologist in such a scenario (who generally provides an additional bolus of propofol if awareness is expected). On the contrary, when a negative step occurs, the performance of the two controllers is comparable since it is limited by the lower saturation of the actuator yielding almost the same results in terms of overshoot and settling time.

**Table 1:** Tuning parameters in the setpoint following task.

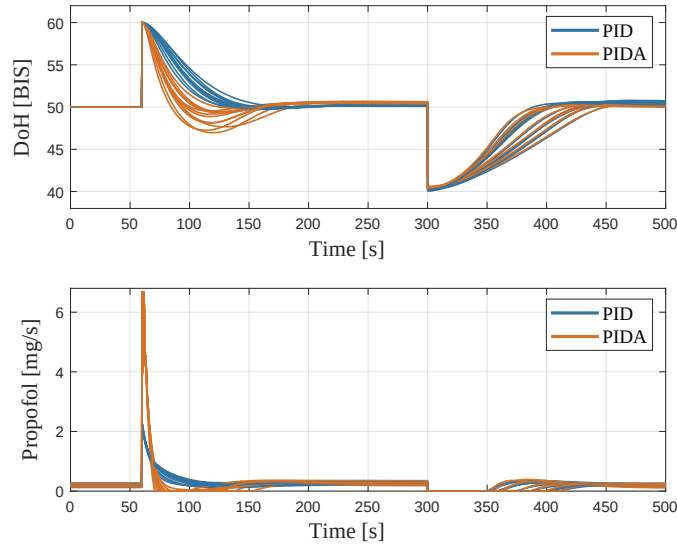
| Controller | $K_p$ | $T_i$   | $T_d$ | $T_a$ | worst-case IAE |
|------------|-------|---------|-------|-------|----------------|
| PID        | 0.049 | 303.077 | 23.25 | -     | 3063.17        |
| PIDA       | 0.045 | 270.58  | 26.90 | 6.70  | 2968.52        |



**Figure 2:** Simulation responses obtained with the 13 patients used in the tuning procedure for the set-point following task.

**Table 2:** Tuning parameters in the load disturbance rejection task.

| Controller | $K_p$  | $T_i$   | $T_d$ | $T_a$  | worst-case $IAE$ |
|------------|--------|---------|-------|--------|------------------|
| PID        | 0.0989 | 631.53  | 18.72 | -      | 1284.60          |
| PIDA       | 0.14   | 3103.65 | 18.35 | 0.3839 | 1108.70          |



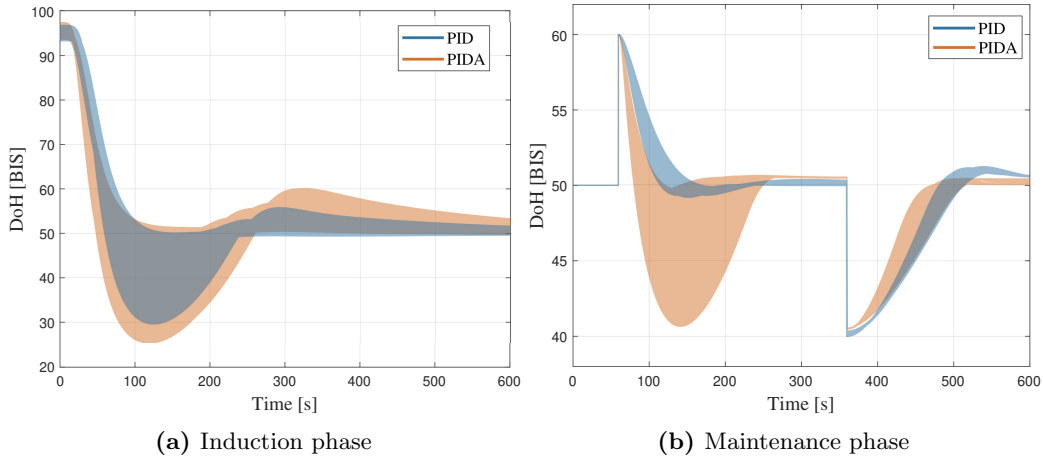
**Figure 3:** Simulation responses obtained with the 13 patients used in the tuning procedure for the load disturbance rejection task.

## 4.2 Robustness evaluation

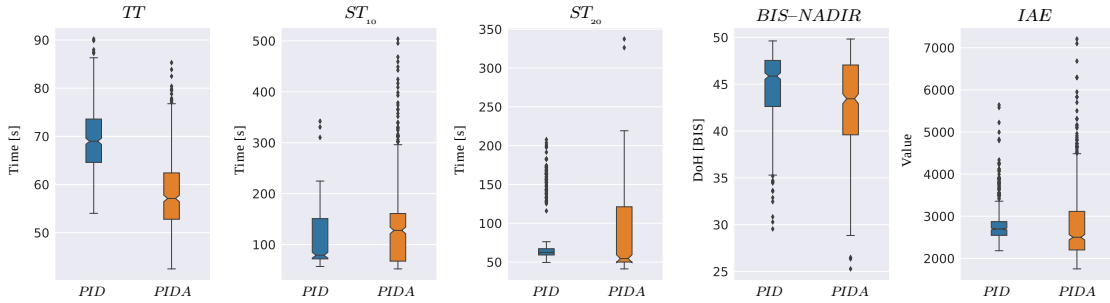
To test the robustness of the controller, a much more extensive group of patients has been considered. In particular, as already done in (Schiavo et al., 2021), to evaluate the performance against inter-patient variability, a Monte Carlo approach has been implemented

to generate a set of 500 patients with different demographics. Further, in order to address the intra-patient variability, using a similar approach, additional 500 patients have been created from each one of the 13 patients in the original dataset (thus, overall, 6500 patients have been simulated to test intra-patient robustness).

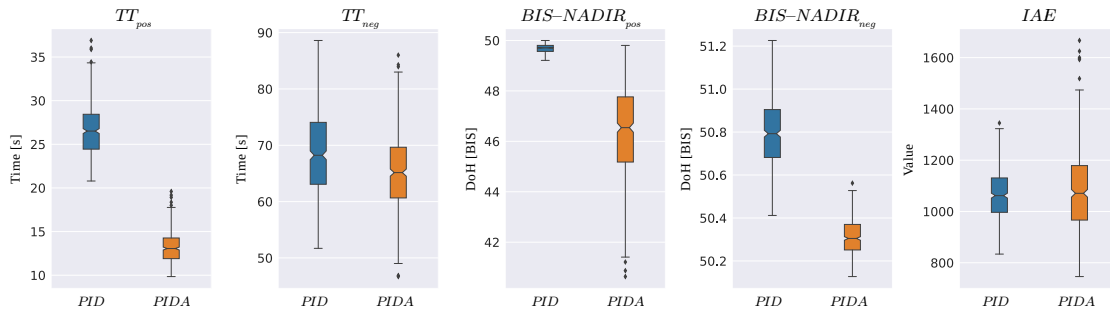
In order to provide a rigorous assessment, the performance indexes proposed in Ionescu et al. (2008) have been evaluated. For the induction phase they are:



**Figure 4:** Responses obtained with the 500 patients used to test robustness to inter-patient variability.



**Figure 5:** Performance indexes for inter-patient variability (induction phase).



**Figure 6:** Performance indexes for inter-patient variability (maintenance phase).

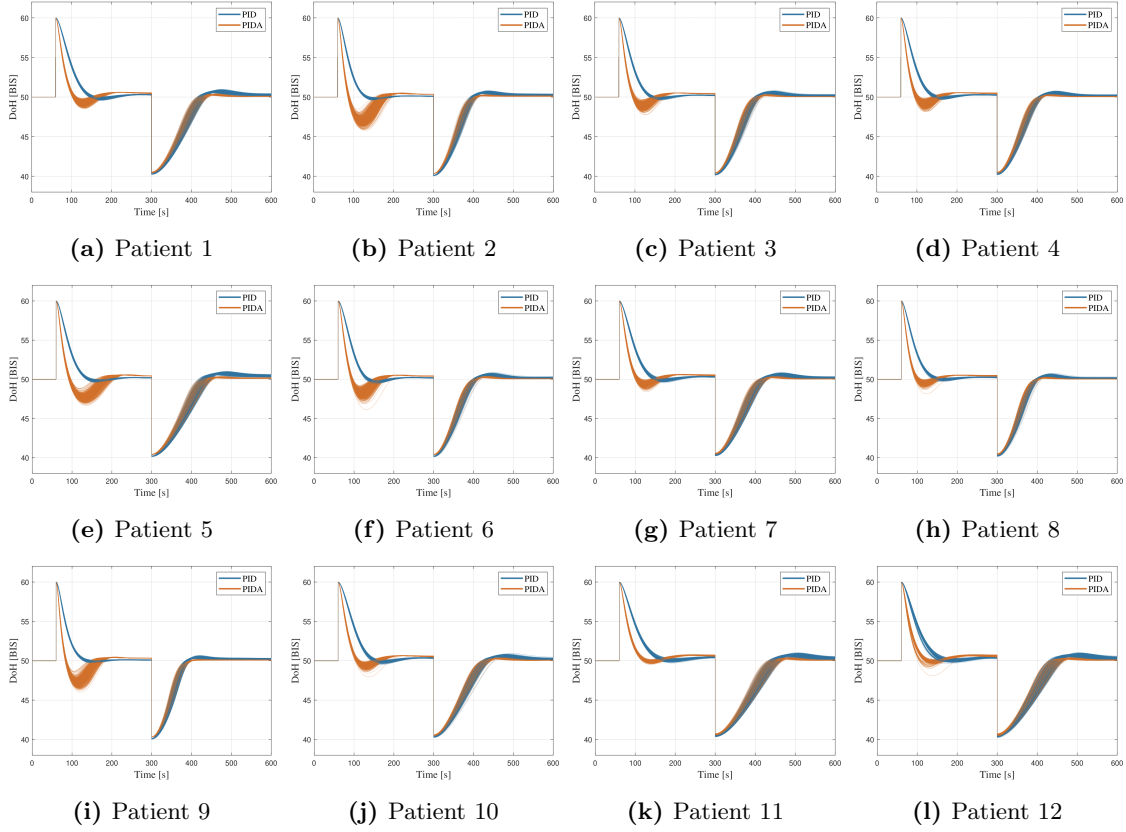
- $TT$ : observed time-to-target required for reaching the first time the target interval of  $[45 \div 55]$  BIS values;
- $BIS - NADIR$ : the lowest observed BIS value;
- $ST_{10}$ : settling time at 10%, representing the time interval for BIS to settle within the  $50 \pm 5\%$  range.
- $ST_{20}$ : settling time at 20%, which means taking into account a BIS range between 40 and 60.

For the maintenance phase, the only meaningful indexes are  $TT$  and  $BIS - NADIR$  and they are calculated separately for the positive and for the negative step, represented as  $pos$  and  $neg$  subscripts, respectively.

The responses obtained for the induction phase are shown in Figure 4 and they clearly show that there is no point in using the acceleration action for this case as the slight decrement of the  $TT$  value is paid for by an increment of the undershoot. This is also confirmed by the performance indexes shown in Figure 5 where it appears that PIDA controllers provide a lower  $TT$ , but the values of  $ST_{10}$  and  $ST_{20}$  are comparable for PIDA and PID control schemes (in all cases the clinical requirements are met). However, by looking at the  $BIS - NADIR$  value, it appears that even if the interquartile range is kept in the range  $40 \div 30$  for both controllers, PIDA controllers tend to fall below the minimum level of 30, with some outliers going even lower. For this reason, intra-patient variability is not further considered for the setpoint following case.

On the contrary, results related to the maintenance phase show the advantage of using the acceleration action in providing a faster compensation of the disturbance, as it can be observed in Figure 4 related to inter-patient variability, where, despite the large variability, the undershoot is kept inside the required range. By considering the performance indexes in Figure 6, we note that, in terms of time-to-target indexes, PIDA controllers have an advantage over PID controllers. This difference is more significant for the positive step, where the performance is not limited by the lower saturation. In particular, in all 500 patients tested, the time-to-target in the positive step ( $TT_{pos}$ ) is always less with PIDA controllers than with PID controllers. Although the PIDA controller is more aggressive than the PID and larger undershoots occur (see the  $BIS - NADIR_{pos}$ ), these remain within clinically acceptable bounds. In general, results show that the control system is robust to the inter-patient variability and the clinical specifications are always met.

Similar considerations apply to intra-patient variability (see Figures 8 and 7). The PIDA controller has a lower  $TT_{pos}$  for all the 13 patients, while the difference in the  $TT_{neg}$  is smaller, but still the PIDA controller shows better performance. By examining the  $BIS - NADIR$  indices, it can be observed that in the case of the positive index, there is a greater variability for the PIDA controllers, whereas for the negative index, the variability is reduced. However, for all 13 patients, the BIS level is always kept within the required range from 40 to 50.



**Figure 7:** Load disturbance responses for intra-patient variability (patient 13 is omitted for brevity).

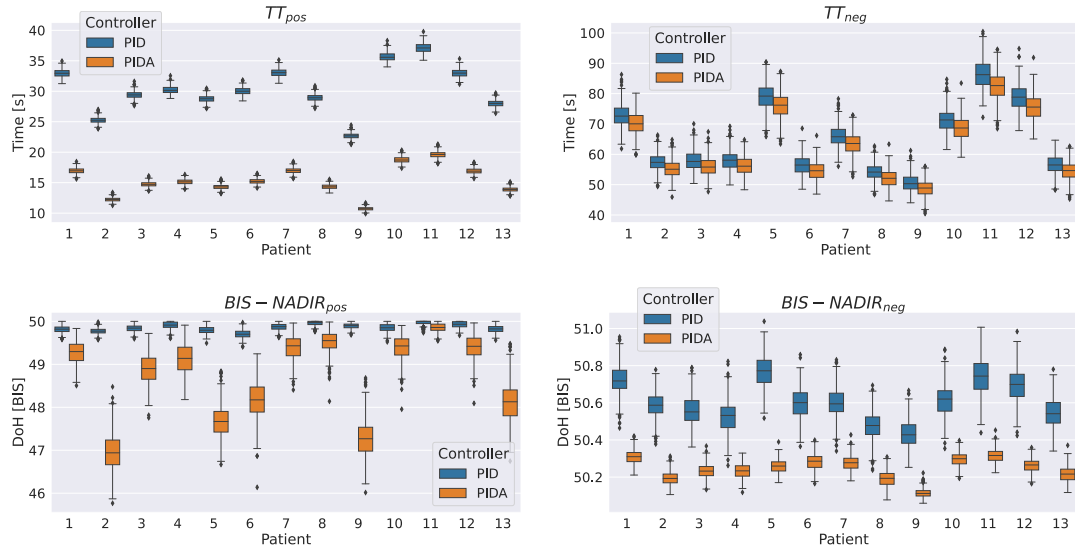
## 5 Conclusions

In this paper we have proposed the use of PIDA controllers for the control of DoH in TIVA. The tuning of the controller has been done by applying a population-based approach, that is, by minimizing the worst-case integrated absolute error in a dataset of 13 patients that are able to represent a wide population. A comparison with PID control has shown that the improvement in the induction phase is marginal, while the more aggressive control action in the maintenance phase reduces the risk of awareness for the patient. Further, the additional acceleration action does not impair the robustness of the system to inter- and intra-patient variability and the proper use of low-pass filters avoids a detrimental amplification of the measurement noise.

Thus, PIDA controllers are good candidates to be employed in closed-loop control of anesthesia and future work will involve clinical trials to confirm these conclusions.

## Acknowledgements

This work was partially supported by the European Union NextGeneration EU (PIANO NAZIONALE DI RIPRESA E RESILIENZA (PNRR) - MISSIONE 4 COMPONENTE 2, INVESTIMENTO 3.3—Decreto del Ministero dell’Università e della Ricerca n.352 del



**Figure 8:** Performance indexes for the load disturbance rejection task with the Monte Carlo method for intra-patient variability.

09/04/2022). The grant of Nicola Paolino has been partially funded by CSMT Innovative Contamination Hub.

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# Paper VI

## Analysis of the Performance Achievable with a PIDD<sup>2 $\alpha$</sup> Controller for Depth-of-Hypnosis in Total Intravenous Anesthesia

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### Abstract

In this paper we use a population-based approach to design a fractional-order Proportional-Integral-Double-Derivative (PIDD<sup>2 $\alpha$</sup> ) controller for Depth-of-Hypnosis (DoH) in general anesthesia. In particular, we consider the control problem of achieving and keeping the bispectral index (BIS) at the required value by manipulating the infusion rate of the propofol drug. The performance of the controller is then analyzed and compared with that achieved with a Proportional-Integral-Derivative (PID) and a Proportional-Integral-Derivative-Acceleration (PIDA) controller. Results show that, with the considered design methodology, the improvement obtained by using a fractional-order double-derivative action is marginal and does not justify the increment of the complexity in the controller implementation.

Originally published in Proceedings of the 4th IFAC Conference on Advances in Proportional-Integral-Derivate Control (PID 2024). The original version is available at [10.1016/j.ifacol.2024.11.084](https://doi.org/10.1016/j.ifacol.2024.11.084).

## 1 Introduction

The automatic control of the anesthesia process has been recognized to provide many advantages with respect to manual control, both from the patient and from the anesthesiologist point of view (Ghita et al., 2020; Zaouter et al., 2020). Indeed, if properly designed, the automatic control system can increase patient safety by avoiding underdosing and overdosing, with a consequent reduction of side effects (for example, traumatic awareness episodes in case of underdosing and post-operative nausea, vomiting and delirium in case of overdosing). In addition, the anesthesiologists workload is reduced so that the risk of possible errors due to distraction or fatigue decreases and he/she can focus on other tasks, thus improving the overall quality of the procedure.

In general, in Total IntraVenous Anesthesia (TIVA) the main task of the anesthesiologist is to ensure the correct level of Depth-of-Hypnosis (DoH) (Vuyk et al., 2015), analgesia (Schumacher and Fukuda, 2020) and neuromuscular blockade (Brull et al., 2020) administering specific drugs. Focusing on hypnosis, which is obviously of primary concern, it is usually achieved through propofol administration. The design of a feedback controller can be done thanks to the availability of a DoH sensor. The most employed one is the bispectral index (BIS), which is a processed electroencephalogram signal that gives a number from 100, corresponding to the fully awake patient, to 0, corresponding to a flat electroencephalogram. During surgery the desired BIS value is usually 50, but values in the range 60 to 40 are perfectly acceptable, also by taking into account that the signal is very noisy. The anesthesia process consists of two phases: in the first one (induction) the BIS value has to be driven from the initial value to 50 in a short time (less than 5 minutes) in order to reduce the discomfort for the patient and the overall surgery time. From the control system design perspective this is a set-point following task where the settling time has to be minimized while preventing large undershoots, as this can cause possibly dangerous hypotension episodes. The second phase (maintenance) starts when induction is completed and consists of keeping the BIS value as close as possible to 50 despite the occurrence of disturbances given by the surgical activity (noxious stimuli). From the control system design perspective, this is a disturbance rejection problem. In this context, the relationship between the propofol infusion rate and the BIS value can be modelled as a Wiener system with a linear dynamics in series with a static nonlinearity. Further, there is a significant uncertainty in the model and robustness against inter- and intra-patient variability must be ensured by the controller.

It appears that the design of a control system is a challenging problem, but Proportional-Integral-Derivative (PID) controllers have been proven to be effective despite their relative simplicity (Schiavo et al., 2022; Dumont et al., 2009; Reboso et al., 2012; Soltesz et al., 2013; Padula et al., 2017; van Heusden et al., 2019; Gonzalez-Cava et al., 2021). With the aim to improve the performance, the basic control algorithm has been expanded by using, for example, event-based sampling (Merigo et al., 2020). Further, the use of fractional-order PID (FOPID) controllers has also been proposed, in order to exploit their

additional parameters that yield an increased flexibility in the design (Dumont et al., 2009; Copot et al., 2017). However, FOPID controllers only deliver a marginal performance improvement when considering population-based tuning (Paolino et al., 2023).

With the same rationale, it has been also proposed to use Proportional-Integral-Derivative-Acceleration (PIDA) controllers where the double derivative action is added to a standard PID controller (Milanesi et al., 2024a). Such a kind of controllers are also called Proportional-Integral-Double-Derivative (PIDD or, alternatively, PIDD<sup>2</sup>) controllers. From the presented analysis, again with a population-based tuning, it results that the use of the double derivative action yields a more aggressive controller that can be used to better prevent awareness episodes. Recently, the use of PIDD controllers where a fractional-order double derivative action is implemented –referred to as PIDD<sup>2α</sup> controllers– has been proposed for general process control applications (Fawwaz et al., 2023; Milanesi et al., 2024b). It is therefore sensible to investigate their use in the anesthesia process and evaluate whether they are able to improve the performance with respect to PIDD controllers.

Thus, in this paper, we perform such a kind of analysis by tuning the PIDD<sup>2α</sup> controllers using a population-based approach and by evaluating their performance in both the induction and maintenance phases.

The paper is organized as follows. The control architecture and the control problem are described in Section 2, while the tuning methodology is explained in Section 3. Simulation results are shown and discussed in Section 4, while conclusions are given in Section 5.

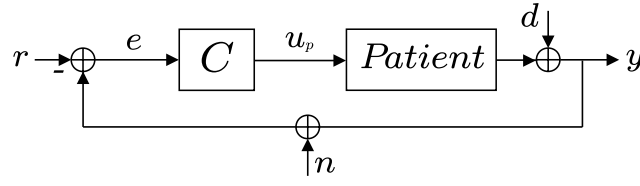
## 2 Control scheme and control problem

The control architecture is shown in Figure 1, where the BIS reference signal is denoted as  $r$ , the disturbance signal is denoted as  $d$ ,  $y$  is the BIS signal,  $n$  is the measurement noise,  $u_p$  [mg/s] is the propofol infusion rate and the control error is calculated as  $e = y - r$ . As it is standard practice, the patient is described by means of a pharmacokinetic/pharmacodynamic (PK/PD) model, where pharmacokinetics describes the dynamics of drug concentration in the human body and pharmacodynamics describes the relationship between the drug concentration and the clinical effect (that is, the BIS value). In this paper we use the well-known Schnider PK/PD model that consists of a fourth-order dynamic linear part in series with a static nonlinear Hill function (Schnider et al., 1998; Ionescu et al., 2008, 2015; Padula et al., 2017).

The controller  $C$  is a PIDD<sup>2α</sup> controller with transfer function

$$C(s) = K_p \left( 1 + \frac{1}{sT_i} + \frac{T_d s}{1 + \frac{T_d}{N_1} s} + \frac{T_a s^{2\alpha}}{\left(1 + \frac{T_a}{N_2} s\right)^2} \right) \quad (1)$$

where  $K_p$  is the proportional gain,  $T_i$  is the integral time constant,  $T_d$  is the derivative time constant,  $T_a$  is the double-derivative (acceleration) time constant,  $\alpha$  is the fractional order of the double derivative action, and  $N_1$  and  $N_2$  are the parameters of the first-order and



**Figure 1:** The DoH control scheme.

second-order low-pass filters applied to the derivative and acceleration actions, respectively. As the BIS signal is very noisy, these parameters have been selected as  $N_1 = N_2 = 5$  in order to achieve a strong filtering effect without introducing an excessive phase lag in the system dynamics. The conditional integration technique has also been implemented to prevent integrator windup. Note that, if  $T_a = 0$ , then we have a standard PID controller and if  $\alpha = 1$ , then we have a standard PIDD<sup>2</sup> controller.

Due to the infinite-dimensional nature of fractional operators, fractional-order controllers cannot be implemented with a standard technology, and an integer-order approximation has been employed. Indeed, the fractional term has been approximated with a fifth-order integer transfer function by using the classic Oustaloup approximation (Oustaloup et al., 2000).

The actuator consists of an infusion pump that is subject to saturation constraints that have to be taken into account in the design of the controller. In particular, according to a standard device (Graseby 3500 pump), the lower saturation limit is zero and the upper saturation limit is 6.67 mg/s.

As already mentioned in the introduction, the control problem involves an initial set-point following task (induction phase) where the BIS signal has to be brought as fast as possible (in any case, in less than 5 minutes) in the range from 60 to 40 and without dropping below 30, in order to avoid side effects related to overdosing. Next, during the maintenance phase, the controller should reject noxious disturbances, which are modelled as a sequence of positive and negative step disturbances on the process output. In this phase it is essential that awareness (that is, excessively high values of the BIS) is avoided as this is very traumatic for the patient. However, also overdosing yielding excessively low values of the BIS has to be avoided because this implies a longer post-operative recovery time.

### 3 Controller tuning

In order to tune the PIDD<sup>2α</sup> controller and fairly assess its performance in comparison with other controllers, we have employed a population-based approach, as we have already done for PID and PIDD<sup>2</sup> controllers (Padula et al., 2017; Milanese et al., 2024a). In particular, we have considered a dataset of 13 patients that have been demonstrated to represent a wide population of adults (Ionescu et al., 2008). Then, we have used a genetic algorithm to determine the optimal controller parameters that minimize the worst-case

Integrated Absolute Error (IAE), defined as

$$IAE = \int_0^{\infty} |r(t) - y(t)| dt,$$

for the considered patients. More formally, the optimization problem can be stated as

$$\min_{K_p, T_i, T_d, T_a, \alpha} \max_{k \in \{1, \dots, 13\}} IAE_k(K_p, T_i, T_d, T_a, \alpha),$$

where  $k = 1, \dots, 13$  is the number of the patient in the dataset.

The employed genetic algorithm had an initial population size of 30, and the algorithm iterates as long as the average relative change in the best fitness function is  $10^{-3}$ . During each iteration, the population of 30 individuals is evaluated based on the worst-case IAE derived from the 13 patient simulations. Individuals are then selected to serve as parents for producing the next generation, with selection favouring those with lower worst-case IAE scores. A new generation is created using Gaussian mutation and scattered crossover. Gaussian mutation involves adding a random number from a Gaussian distribution to individuals in the next generation. Scattered crossover creates a random vector of zeros and ones. Each child is generated by selecting genes from parent 1 if the corresponding element in the scatter vector was 0, and from parent 2 if it is 1.

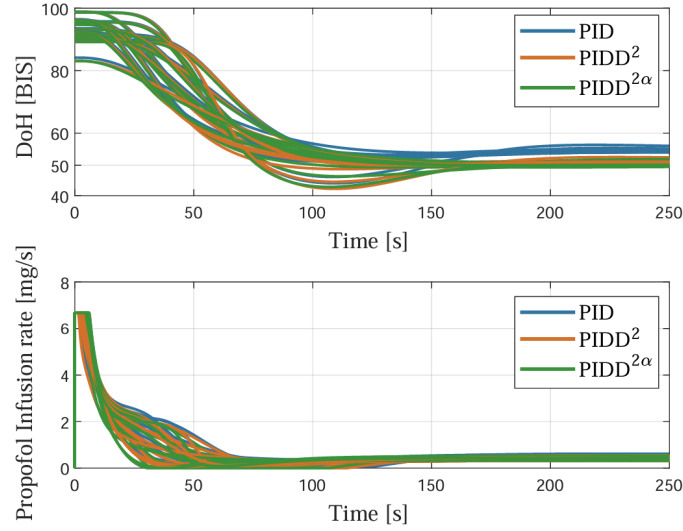
The tuning procedure has been performed separately for the set-point following and for the disturbance rejection tasks, so that a gain scheduling approach can eventually be applied. For the induction phase, a constant set-point step signal with a value of 50 has been applied, while for the maintenance phase, the IAE has been calculated in the response of a step disturbance of amplitude 10 followed by another one of amplitude  $-10$  after 4 min. The resulting controller parameters are shown in Tables 1 and 2, where the parameters obtained by applying the same approach to a PID and a PIDD<sup>2</sup> are also shown for the sake of comparison. We notice that, thanks to the stabilizing effect of the double (possibly fractional) derivative action, the optimizer finds proportional gains the integral time constants of the PIDD and PIDD<sup>2α</sup> much larger than those of the PID controller. In other words, the phase increase induced by the double derivative action allows the optimizer to achieve optimal disturbance rejection by substantially increasing the bandwidth through the proportional gain (for a prompt reaction to disturbances) and the integral time constant (to avoid excessive overshoots induced by the integrator). In comparison, the classical PID controller relies primarily integral action for rejecting disturbances.

**Table 1:** Controller parameters for the induction phase.

| C                  | $K_p$ | $T_i$   | $T_d$ | $T_a$ | $\alpha$ | IAE     |
|--------------------|-------|---------|-------|-------|----------|---------|
| PID                | 0.049 | 303.077 | 23.25 | -     | -        | 3063.17 |
| PIDD <sup>2</sup>  | 0.045 | 270.58  | 26.90 | 6.70  | 1        | 2968.52 |
| PIDD <sup>2α</sup> | 0.047 | 257.82  | 26.48 | 11.13 | 0.60     | 2912.67 |

**Table 2:** Controller parameters for the maintenance phase.

| C                                    | $K_p$  | $T_i$   | $T_d$ | $T_a$  | $\alpha$ | IAE     |
|--------------------------------------|--------|---------|-------|--------|----------|---------|
| PID                                  | 0.0989 | 631.53  | 18.72 | -      | -        | 1284.60 |
| PIDD <sup>2</sup>                    | 0.14   | 3103.65 | 18.35 | 0.3839 | 1        | 1108.70 |
| PIDD <sup>2<math>\alpha</math></sup> | 0.20   | 3102.74 | 16.41 | 4.96   | 0.67     | 1097.60 |

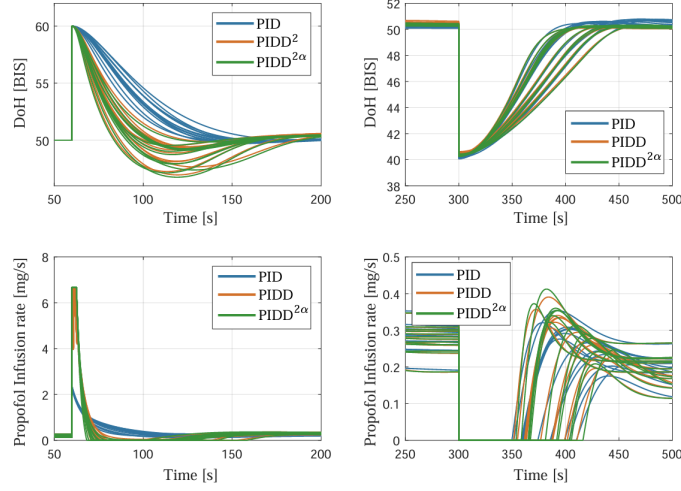
**Figure 2:** Simulation responses obtained in the induction phase for the tuning dataset of 13 patients.

## 4 Simulation Results

Both the induction and the maintenance phases have been analyzed and a comparison with the PID and PIDD<sup>2</sup> controllers tuned with the same approach has been carried out. The evaluation of the control system performance has been done by first considering the dataset of the 13 patients employed in the tuning of the controller and then by assessing the controller robustness against inter- and intra-patient variability. The controller robustness is assessed by considering new large sets of patients generated using a Monte Carlo method. In this context, in order to provide a quantitative robustness evaluation, well-known performance indices have been used (Ionescu et al., 2008). For the induction phase they are:

- $TT$  (time-to-target): the time required for the BIS to enter for the first time the interval of  $[45 \div 55]$ ;
- $BIS - NADIR$ : the lowest attained BIS value;
- $ST_{10}$  (10% settling time): the time required for BIS to settle within the  $50 \pm 10\%$  range.
- $ST_{20}$  (20% settling time): the time required for BIS to settle within the  $50 \pm 20\%$  range.

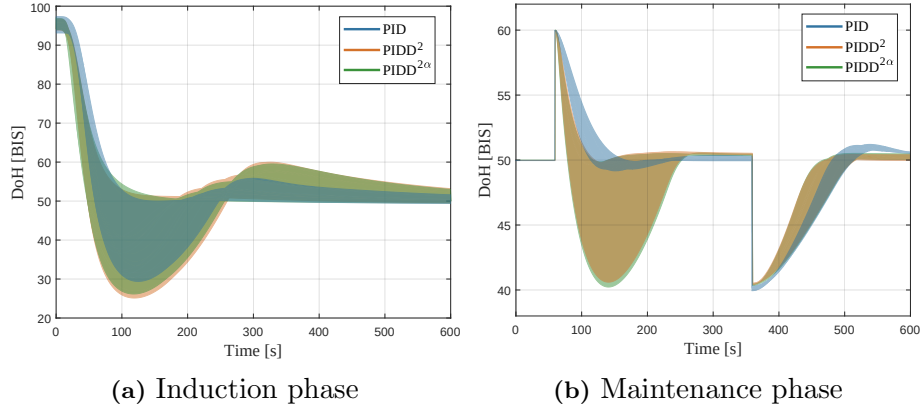
The only significant indices for the maintenance phase are  $TT$  and  $BIS - NADIR$ , which are computed independently for the positive and negative steps and denoted by the subscripts  $pos$  and  $neg$ , respectively.



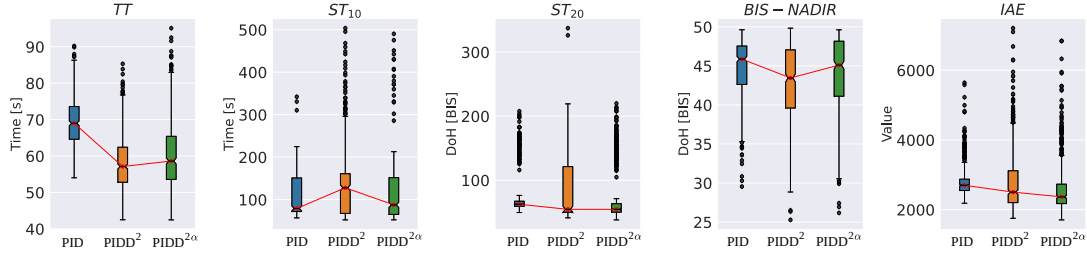
**Figure 3:** Simulation responses obtained in the maintenance phase for the tuning dataset of 13 patients.

#### 4.1 Tuning dataset

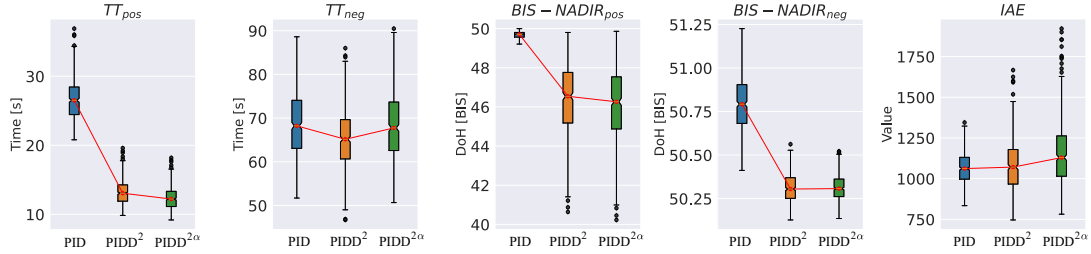
The simulation responses with the 13 patients of the tuning dataset are shown in Fig. 2 and 3 for the induction and maintenance phases, respectively. It appears that, in the induction phase, all the controllers satisfy the clinical requirements but they perform very similarly, although  $PIDD^2$  and  $PIDD^{2\alpha}$  provide a slightly smaller time-to-target and a slightly larger undershoot. The use of a fractional-order double-derivative action does not give a significant performance improvement, despite the marginal decrement of the IAE value obtained (see Table 1). Regarding the maintenance phase, we can observe that, also in this case, the fractional-order double-derivative action does not give a clear advantage in terms of disturbance rejection. In fact,  $PIDD^2$  and  $PIDD^{2\alpha}$  perform very similarly. Compared to PID control, they both ensure an aggressive response that better avoids possible awareness episodes without any dangerous oscillation.



**Figure 4:** Responses obtained with the 500 patients used to test robustness to inter-patient variability.



**Figure 5:** Performance indexes for inter-patient variability (induction phase).



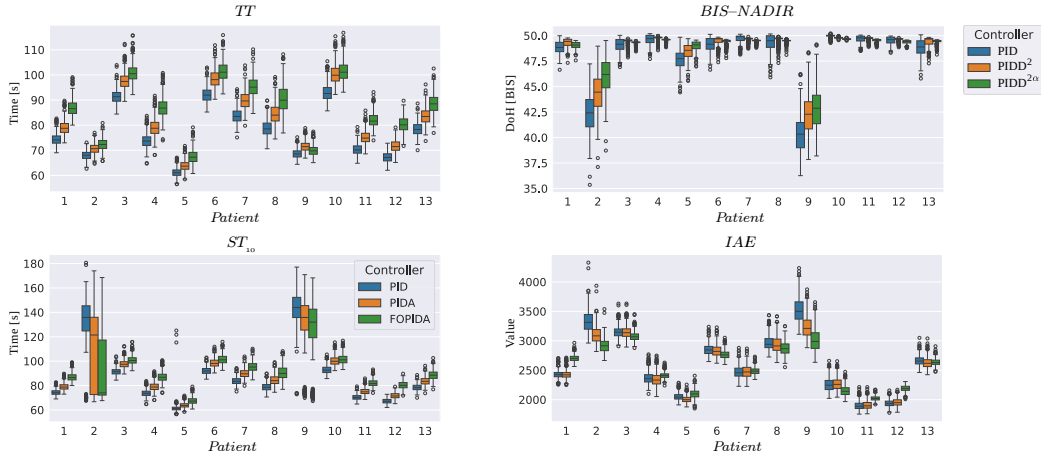
**Figure 6:** Performance indexes for inter-patient variability (maintenance phase).

## 4.2 Robustness evaluation

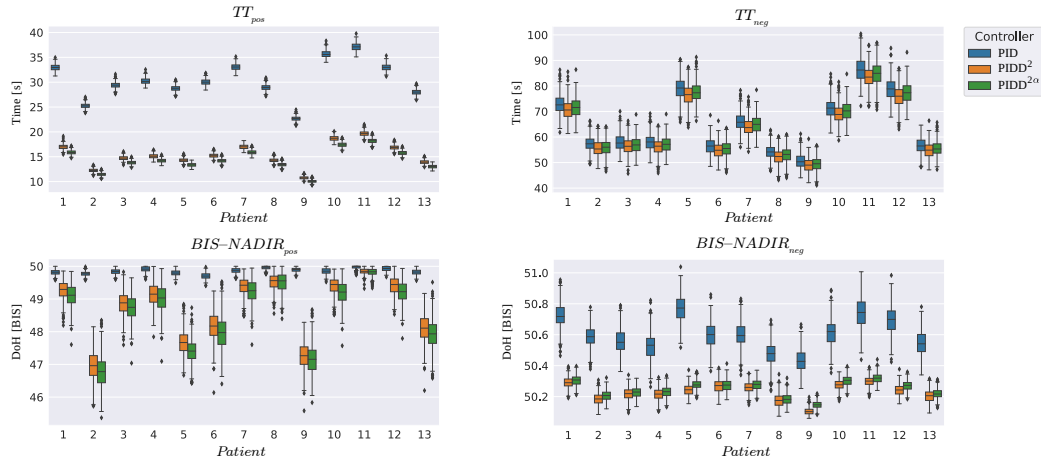
Robustness against inter-patient variability has been initially evaluated with a set of 500 patients with different demographics generated by means of a Monte Carlo method (Schiavo et al., 2021). The responses obtained for the induction phase are shown in Figure 4a. It can be observed that the use of the fractional-order double derivative action yields a reduction of the undershoot, but this is not significant and the three controllers provide virtually the same performance. This is confirmed by the performance indices shown in Figure 5, where the median values are those connected between them with segments, the lower and upper limits of the boxes are the 25<sup>th</sup> and 75<sup>th</sup> percentile, respectively, whiskers represent the upper and lower adjacents, and crosses are the population outliers.

Then, results related to the maintenance phase, shown in Figure 4b, highlight again that the capability of the  $PIDD^2$  controller of better preventing awareness is not significantly modified if a fractional-order double derivative action is employed. This also appears from the performance indices shown in Figure 6. In fact, with respect to PID control, the time to target is reduced without a significant increment of the BIS-NADIR value, but, in general, there is a strong similarity in the performance of  $PIDD^2$  and  $PIDD^{2\alpha}$  controllers.

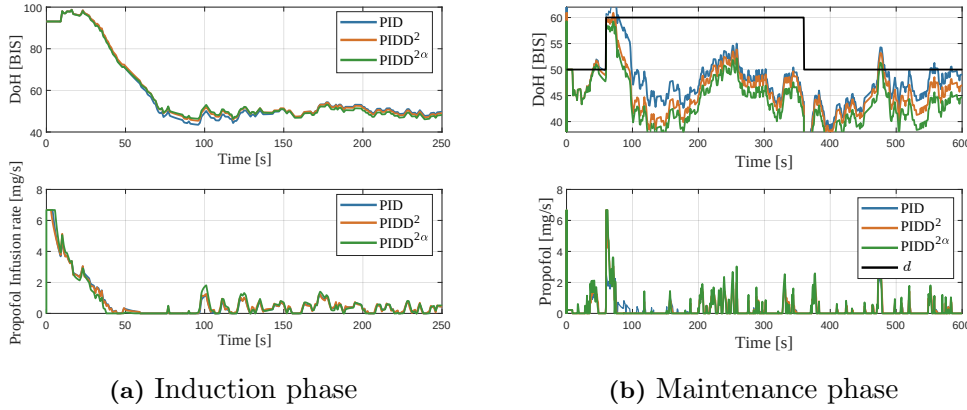
In order to assess the intra-patient robustness, 500 patients have been created from each one of the 13 patients in the tuning dataset (overall, 6500 patients have been therefore considered). Based on the results summarized in Figures 7 and 8, we can draw the same conclusions as before, that is, there is not a clear advantage in using a double derivative of fractional order as the performance improvement is marginal with respect to a  $PIDD^2$  controller.



**Figure 7:** Performance indexes for the induction phase with the Monte Carlo method for intra-patient variability.



**Figure 8:** Performance indexes for the maintenance phase with the Monte Carlo method for intra-patient variability.



**Figure 9:** Simulation results with noise for the average patient 13 in the tuning dataset.

### 4.3 Noise filtering

As the use of a (fractional-order) double derivative action can be critical for noise amplification, it is worth testing the  $PIDD^{2\alpha}$  controller in the presence of a typical noise associated with the BIS sensor. For this purpose, we have simulated both the induction and maintenance phases with the addition of a noise signal taken from a real BIS signal (Pawlowski et al., 2022b). Results are shown in Figures 9a and 9b where, again, a comparison with PID and  $PIDD^2$  control has been made. It can be observed that the employed low-pass filters ensure that the control action signal is acceptable and that noise amplification due to the use of the fractional-order double derivative action is not detrimental for the actuator.

## 5 Conclusions

In this paper we have investigated the performance achievable by a  $PIDD^{2\alpha}$  controller in the control of Depth-of-Hypnosis in total intravenous anesthesia. Using a population-based optimal tuning, we have compared the results in both the induction and maintenance phases with those obtained using a PID and a  $PIDD^2$  controller. A thorough analysis has shown that the use of a fractional-order double derivative action does not yield a significant performance improvement with respect to an integer-order one. Thus, in the given scenario, increasing the complexity of the controller does not seem to be justified.

In any case, it is worth highlighting that the use of a fractional-order double derivative action could be useful in other design contexts (for example, when a robust design is pursued) that need further investigation.

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# Paper VII

## Kalman Filter Soft Sensor to Handle Signal Quality Loss in Closed-loop Controlled Anesthesia

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### Abstract

**Background and objective:** This study aims to enhance the performance of a closed-loop anesthetic depth control system by fusing noise-corrupted clinical measurements with a non-perfect pharmacological model.

**Methods:** We implement a Kalman filter to constitute a trade-off between model prediction and measurement signal dependence for depth of hypnosis (*DoH*) control using a previously evaluated PID controller. This trade-off is adjusted online, based on signal quality index (*SQI*) feedback, provided by the clinical *DoH* monitor, in this case assumed to be the bispectral index (BIS) monitor.

**Results:** Our simulations show that the proposed solution leads to fundamental performance improvements over the traditional monitor feedback case, which fails to provide the required clinical performance when the *SQI* drops due to signal inference. In particular, the soft sensor approach increases the time of *DoH* within the recommended clinical range of 40–60 BIS from 71% to 99%, compared to simple feedback of the noisy monitor output.

**Conclusion:** Our Kalman filter soft-sensor approach succeeds in importantly increasing system robustness to measurement signal disturbances by combining sensor measurements and model predictions.

Originally published in Biomedical Signal Processing and Control. The original version is available at [10.1016/j.bspc.2025.107506](https://doi.org/10.1016/j.bspc.2025.107506).

## 1 Introduction

A key challenge in general anesthesia is to adequately control the depth of hypnosis (*DoH*) in the patient (Blayney, 2012). In this paper, we consider *DoH* control using the intravenously infused drug propofol. The control is challenging, since *DoH* cannot be measured directly, but is only observed indirectly through correlated signals and patient signs. In addition to manual titration, two computer-controlled dosing regimens have gained ground.

Of these, target-controlled infusion (TCI) (Absalom et al., 2016) has received the broadest clinical acceptance to date. TCI is a model-based feed-forward strategy, that optimizes an infusion trajectory offline, based on a user-provided reference. As such, it is vulnerable both to model errors and external disturbances, since the infusion is not based on actual measurements of the patient state. However, if the anesthesiologist suspects model errors or disturbances based on patient observations, they can update the setpoint concentration. The other computer-controlled dosing strategy that has to date been employed in several research studies is closed-loop control. It relies on feedback from a *DoH* estimate, provided by a non-invasive processed electroencephalogram (pEEG) monitor (Rampil, 1998). Such monitors report *DoH* on the bispectral index (BIS) scale, where 100 is the maximum achievable cortical activity (being awake corresponds to a value near 100), and 0 represents an iso-electric EEG (corresponding to the maximally achievable *DoH*) (Vuyk and Mertens, 2003).

Closed-loop systems are well known to outperform open-loop ones when suitably designed and tuned. That is why several research efforts have been made to design closed-loop architectures, as demonstrated by (Ghita et al., 2020; Hosseinzadeh et al., 2020; Agarwal et al., 2009). The closed-loop control algorithm could be a simple proportional-integrative-derivative (PID) (Visioli, 2006) controller as in (Dumont et al., 2009; Gonzalez-Cava et al., 2021; Padula et al., 2017; Puri et al., 2007; Soltesz et al., 2013), or some more advanced one as in e.g., (Merigo et al., 2017, 2020; Pawlowski et al., 2022a; Copot et al., 2017; Paolino et al., 2023; Mendez et al., 2016, 2018).

We have previously shown that the control performance of these systems is mainly limited by the modeling uncertainties such as those coming from inter- and intra-patient variability, rather than by the choice of control algorithm (Gonzalez-Cava et al., 2021; Soltesz et al., 2019). Hence, we base our example on a PID-controlled system, although the methodology we introduce is equally applicable to other types of controllers. While closed-loop systems provide some means to attenuate external disturbances and cope with model errors, they are vulnerable to corruption of the measurement that constitutes the feedback signal.

Alongside a *DoH* estimate, clinical *DoH* monitors provide a signal quality index (*SQI*) ranging from 0–100 (low–high signal quality). This index, which is updated and displayed on the monitor, provides the anesthesiologist with an estimate of the current BIS measurement reliability. In clinical practice, a *DoH* measure associated with an  $SQI \leq 50$  is considered unreliable (BIS, 2013). Signal quality loss directly affects the anesthesiologist’s working

procedure since they cannot rely on the *DoH* monitor while adjusting the drug infusion rate. Low *SQI* values are common during general surgery (Dahaba, 2005; Chan et al., 2012). This can, for example, be due to forehead motion, improper sensor placement, or electrical inference from the use of an electro-scalpel (Gjika et al., 2016).

We consider a scenario where the monitor *DoH* estimate is corrupted by inference. By introducing a novel soft-sensor approach to closed-loop controlled anesthesia, we can maintain patient safety despite loss of signal quality. This is achieved by a Kalman filter, a classic methodology that has been only recently exploited in biomedical and biomechanical engineering (Oikonomou et al., 2009; Misgeld et al., 2017). In particular, the usage of a Kalman filter in the anesthesia field has been proposed in, for example, (Aubouin-Pairault et al., 2024) to estimate both the state and parameters of the system to predict the future trajectory.

Here, a linear Kalman filter is used to shift the balance from measurement to model reliance (i.e., from ordinary closed-loop towards TCI), when *SQI* is decreased. When signal quality is good (*SQI* closer to 100), feedback will essentially be based on the monitor output, as in conventional closed-loop controlled anesthesia. In contrast, when signal quality is poor (*SQI* closer to 0), the feedback will be based mainly on the model prediction, and effectively behave like TCI.

In this work, we introduce a novel Kalman-filter-based soft-sensor concept for anesthesia control. To demonstrate this methodology, we use a patient simulator that explicitly models both patient variability (model uncertainty), measurement disturbances that our model-based soft-sensor is purposed to attenuate, and measurement noise.

The novelty of our approach thus lies in using the Kalman filter as a tuning knob to shift between model and measurement reliance, rather than as the minimum-variance estimator where its tuning parameters are optimized to minimize estimation error, assuming some Gaussian state and measurement noise processes.

## 2 System architecture

Our proposed closed-loop control architecture is shown in Fig. 1. It consists of four main components: the patient dynamics (Section 2.1), the Kalman-filter-based soft sensor (Section 2.2), the clinical *DoH* monitor (Section 2.3), and the drug-dosing closed-loop controller (Section 2.4).

### 2.1 Patient

Kalman filtering is a model-based approach, and in our case, patient dynamics are modeled by a conventional four-compartment linear pharmacological model (Soltesz et al., 2019; Schnider et al., 1998; Åström and Murray, 2008). These linear models are the gold standard to represent propofol pharmacokinetics and they have been employed in



sigmoid output nonlinearity (Goutelle et al., 2008)

$$DoH(t) = h(C_e(t); \gamma, C_{e50}, E_0, E_{\max}) = E_0 - E_{\max} \frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e50}^\gamma}. \quad (3)$$

The  $DoH$  level in the absence of a drug is  $E_0 \lesssim 100$  BIS, and the maximum deviation from this level is  $E_{\max} \lesssim 100$  BIS. The effect-site concentration  $C_{e50}$  [mg L<sup>-1</sup>] is the concentration at which the hypnotic depth is halfway between the limits defined through  $E_0$  and  $E_{\max}$ ,  $DoH = E_0 - E_{\max}/2$ . The third parameter of Eq. (3),  $\gamma$ , is a unitless shape parameter that defines the steepness of the sigmoid, such that the limit  $\gamma \rightarrow \infty$  defines a  $DoH$  step between  $E_0$  and  $E_0 - E_{\max}$  at  $C_e = C_{e50}$ . Together, Eqs. (2c) and (3) constitutes a so-called pharmacokinetic–pharmacodynamic (PKPD) model, as thoroughly introduced and explained in (Soltesz et al., 2019).

Since we will use our model in a closed-loop interconnection with a periodically sampled controller, we will use the approximation-error-free zero-order-hold discretization of Eq. (2c). Denoting the sampling period  $T_s = 1$  s, we index the samples so that if  $\mathbf{x}(t) = \mathbf{x}_k$ , then  $\mathbf{x}(t + T_s) = \mathbf{x}_{k+1}$ . This results in the discrete state space representation

$$\mathbf{x}_{k+1} = F\mathbf{x}_k + Gu_k, \quad (4a)$$

$$(C_e)_k = H\mathbf{x}_k, \quad (4b)$$

with constant matrices  $F = \exp(AT_s)$ ,  $G = \int_0^{T_s} \exp(As) ds B$ , and  $H = C$ , as derived and explained in (Åström and Wittenmark, 2013). The input at sample  $k$  is denoted  $u_k$ . The drug response dynamics vary between patients and are commonly modeled with fixed and random effects. The fixed effects model the variability that can be explained by covariates such as age, height, and weight. The random effects model the remaining variability that is not explained by covariates (Soltesz et al., 2019). This is a well-established methodology for modeling dynamic uncertainty in the drug response.

For a particular model parameter  $\theta$  with fixed effect (nominal) value  $\theta_0$ , the parameter is assumed to be drawn from the log-normal distribution

$$\theta = \theta_0 \exp(\eta_p), \quad (5)$$

where the random effect  $\eta_p$  is a normal stochastic variable with zero mean and variance  $\sigma_p^2$  (Vanluchene et al., 2004).

To reflect this, we use the Schnider population model (Schnider et al., 1998), which expresses the model parameters mentioned in the individual patient covariates age, height, weight, and gender. The Schnider model incorporates intra-patient variability (i.e., random effects) through coefficients of variation (CV). The variances  $\sigma_\theta^2$  of the PK parameter  $\theta$  relates to the corresponding  $CV_\theta$  through (Canchola et al., 2017)

$$\sigma_\theta^2 = \log \left( \left( \frac{CV_\theta}{100} \right)^2 + 1 \right). \quad (6)$$

Surgical stimulation typically increases the level of awareness in the patient, thus affecting  $DoH$ . It is customary (Melia et al., 2017; Soltesz et al., 2019) to model the effect of such stimulation as an additive disturbance  $d$ , acting on  $DoH$ , as shown in Fig. 1.

## 2.2 Soft sensor

The Kalman filter is an optimal state estimator, in the sense that it provides the state estimate that minimizes error variance, given that the system dynamics are linear and the noise is Gaussian (Welch and Bishop, 1995).

While the Hill function Eq. (3) is non-linear, it is invertible. Particularly, if we equate the right-hand-side of Eq. (3) its inverse is

$$C_e(t) = h^{-1}(DoH(t); \gamma, C_{e50}, E_0, E_{\max}) = C_{e50} \left( \frac{E_{\max}}{E_0 - DoH(t)} - 1 \right)^{-1/\gamma}. \quad (7)$$

Since the parameters are not known with certainty, we will use estimates  $\hat{\gamma}$ ,  $\hat{C}_{e50}$ ,  $\hat{E}_0$ ,  $\hat{E}_{\max}$ , as explained further in Section 3.2. The blocks  $\hat{h}$  and  $\hat{h}^{-1}$  in Fig. 1 are thus obtained analogs of Eq. (3) and Eq. (7). In particular,  $\hat{h}^{-1}$  constitutes a linearizing transform, providing a purely measurement-based plasma concentration estimate  $\tilde{C}_e$ , used to drive the Kalman filter.

The Kalman filter utilizes the model Eq. (2c) together with a sequence of sampled input–output data  $u, \tilde{C}_e$  to provide an online estimate  $\hat{\mathbf{x}}$  of the system state  $\mathbf{x}$ .

Internally, the filter stores its estimate, alongside an error covariance matrix estimate  $P$ , which it updates dynamically and uses to compute a gain vector  $L$  that is used to drive the estimated state towards the actual one based on model input–output data.

In the following, we present the equations defining the standard Kalman filter. We use  $\hat{\mathbf{x}}_{k,k-1}$  to denote the estimate of  $\mathbf{x}_k$ , based on data up to and including  $k-1$ ;  $\hat{\mathbf{x}}_{k,k}$  is the updated estimate incorporating the data sample  $k$ . The same double-index notation is used for the covariance estimate  $P$ . The update equations for the gain  $L$ , covariance  $P$  and state estimate  $\hat{\mathbf{x}}$  are given by

$$L_k = P_{k,k-1} H^\top (H P_{k,k-1} H^\top + R_k)^{-1}, \quad (8a)$$

$$P_{k,k} = (I - L_k H) P_{k,k-1} (I - L_k H)^\top + L_k R_k L_k^\top, \quad (8b)$$

$$\hat{\mathbf{x}}_{k,k} = \hat{\mathbf{x}}_{k,k-1} + L_k ((\tilde{C}_e)_k - H \hat{\mathbf{x}}_{k,k-1}), \quad (8c)$$

$$(\hat{C}_e)_k = H \hat{\mathbf{x}}_{k,k}, \quad (8d)$$

while the prediction step is defined by

$$\hat{\mathbf{x}}_{k+1,k} = F \hat{\mathbf{x}}_{k,k} + G u_k, \quad (9a)$$

$$P_{k+1,k} = F P_{k,k} F^\top + Q_k, \quad (9b)$$

where  $F, G, H$  define the model dynamics according to Eq. (4b). The measurement equation is given by Eq. (8d). The matrices  $Q$  and  $R$  are the assumed covariances of the additive Gaussian noise, which corrupts the true state  $\mathbf{x}$  and the output  $C_e$ , respectively. Since we only have one measurement signal,  $R$  is scalar in our case. Further details, including a derivation of Eqs. (8d) to (9b) being optimal in the minimum-variance sense, can be found in (Becker, 2023).

In essence, the Kalman filter combines its prior state estimate with the current measurement to reduce the uncertainty associated with its current state estimate. When the measurement covariance  $R$  is large, the Kalman gain is low. Then, the Kalman filter therefore relies more on the model than the measurement for its state estimate update.

The main novelty of our approach is to relate the measurement covariance  $R$  to the  $SQI$ , to establish a trade-off between measurement and model reliance. We do this by asserting the simple affine relationship

$$R(SQI) = R_{\min} + (R_{\max} - R_{\min}) \left( 1 - \frac{SQI}{100} \right), \quad (10)$$

where the tuning parameters  $R_{\min}$  and  $R_{\max}$  define the values of  $R$  attained at  $SQI = 100$  and  $SQI = 0$ , respectively. This means that if  $SQI = 100$  and the signal quality is perfect, a small value of  $R$ ,  $R_{\min}$ , is used. Adversely, if the signal quality is poor with  $SQI = 0$ ,  $R$  becomes  $R_{\max}$ . As the algorithms used to calculate the  $SQI$  are proprietary, it is not straightforward to tailor the mapping model from  $SQI$  to  $R$ . As a first approach, we have opted for a simple linear model to constitute the mapping between  $SQI$  and  $R$ .

Since our setting lacks process noise as modeled by Kalman covariance  $Q$ , we use  $Q$  as a constant parameter. For simplicity, we assert a diagonal structure of  $Q$ , corresponding to the independent noise added to individual states being mutually independent Gaussians. We therefore consider the four diagonal elements of  $Q$ , together with  $R_{\min}$  and  $R_{\max}$  to be parameters of our filter, where  $R$  varies with  $SQI$  according to Eq. (10).

In our application, we do not have support for the assumption that the process noise is Gaussian. Instead, we consider  $R$  and  $Q$  as free design parameters of the filter, that are tuned using a population-based approach (that is, using the same values for all the patients) to enable shifting between model and measurement reliance. Therefore, the Kalman filter will not be optimal even though the performance may still be satisfactory. If the noise characteristics at some point will be known to be better described by some other (spectral) noise model, this can be incorporated into the observer design.

The parameters values were optimized offline to minimize the mean square error (MSE) between the simulated patient  $DoH$  and the corresponding Kalman filter estimate  $\widehat{DoH}$ , which is the norm  $\mathcal{L}_2$  of  $\widehat{DoH} - DoH$ . MSE values for each patient were summed, which means that they all contributed equally. The choice of patient population and simulation scenario used in this optimization are those described below in Section 3.2 and Section 3.1, respectively.

In summary, our design choices are to:

- Optimize  $R_{\min}$ ,  $R_{\max}$  and diagonal fixed (time-independent)  $Q$  offline to minimize estimation error across a set of simulations (see Section 4);
- Update  $R$  online, based on the current  $SQI$ , according to Eq. (10).

### 2.3 Monitor

The  $DoH$  estimate  $y$ , emerging from a clinical monitor, is noisy, even when  $SQI = 100$ . To reflect this, we use an additive noise model  $n$ , as shown in Fig. 1. We will consider both an idealized noise-free case,  $n = 0$ , and a clinically realistic case, where  $n$  is a random cycled noise sequence, recorded by a BIS monitor under stable anesthetic conditions, as explained in (Pawlowski et al., 2022b).

As schematically illustrated in Fig. 1, the (not directly measurable) electro-scalpel inference signal  $m$  enters the monitor, where its effect (through an uncharacterized function  $f$ ) is mapped to  $SQI$ . Here, we model this inference with a delay  $\tau$  that is computed starting from the  $SQI$  as

$$\tau = \tau_{\max} \left( 1 - \frac{SQI}{100} \right). \quad (11)$$

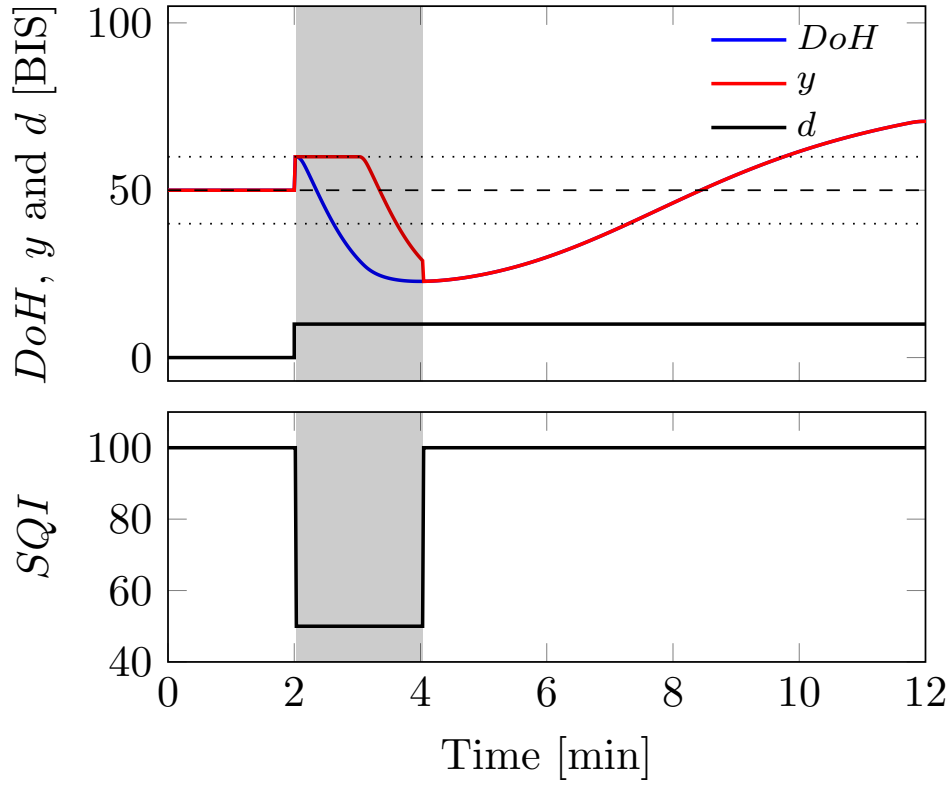
That is, the inference  $m$  affects the  $SQI$  and results in the monitor output being delayed from  $y(t)$  to  $y(t - \tau)$ , whenever  $SQI < 100$ . The delay ranges linearly between  $\tau = 0$  s and  $\tau = \tau_{\max} = 120$  s, based on  $SQI$ . This delay model is consistent with observations of our clinical collaborators and is supported by behavior observed in previous studies, e.g., (Chan et al., 2012).

In this formulation, the delay of the BIS monitor is not taken into account. We have focused on providing a delay model that describes the degradation of the  $SQI$ . Modeling the monitor delay poses a challenge, as the manufacturer has not disclosed the exact response and filtering dynamics of the BIS monitor. Neglecting modeling of the BIS delay has been shown to work in practice, as several clinical studies have been successfully carried out without considering the BIS delay (Liu et al., 2006; Struys et al., 2001).

A simulated example of the monitor model is shown in Fig. 2, to illustrate how inference by the electro-scalpel is assumed to affect the monitor and the true  $DoH$ , respectively. The blue and red curves in Fig. 2 show the actual  $DoH$ , and monitor output  $y$ , respectively. The discrepancy is due to the delay model Eq. (11) and constitutes the measurement corruption that our soft-sensor approach aims to mitigate the effect. For visual clarity, Fig. 2 shows a scenario with  $n = 0$ , i.e., in the absence of measurement noise.

### 2.4 Controller

We use a filtered PID controller (Visioli, 2006), which has previously been evaluated in (Schiavo et al., 2021c). Its underlying continuous-time transfer function from error  $e$  to



**Figure 2:**  $DoH$  (top, blue) and monitor output  $y$  (top, red). An  $SQI$  (bottom, black) drop from 100 to 50 is introduced at  $t = 2$  min, and after that, an additive step disturbance  $d = 10$  BIS (top, black) occurs. The signal degradation remains during 2 min (shaded area). The associated inference-induced corruption of the monitor output (top, discrepancy between blue and red) is defined in Section 2.3. The dashed black line indicates the  $DoH$  reference, and the dotted lines delimit the range between  $DoH = 40$  BIS and  $DoH = 60$  BIS.

unsaturated infusion rate  $\tilde{u}$  is

$$\frac{\tilde{U}(s)}{E(s)} = K_p \left( 1 + \frac{1}{sT_i} + \frac{sT_d}{1 + sT_d/N} \right), \quad (12)$$

with proportional gain  $K_p = 0.2$  mg/BIS/s, integral time  $T_i = 386$  s, derivative time  $T_d = 13.8$  s, and filtering factor  $N = 5$ . The PID controller values have been obtained by minimizing the integral absolute error (IAE) over a simulation example with additive disturbances, see (Schiavo et al., 2021c) for details.

The actual infusion rate  $u$  is then saturated to within the range  $0\text{--}1200$  mL h<sup>−1</sup>, representative of several clinical infusion pumps. For the concentration of standard propofol solutions of  $20$  mg mL<sup>−1</sup>, this corresponds to  $u$  within the range  $0\text{--}6.67$  mg s<sup>−1</sup>.

### 3 Comparative simulation study

This section defines the details of our comparative study.

### 3.1 Surgical scenario

The performance of the proposed control structure was evaluated by repeated simulation of a maintenance phase of fifty minutes of anesthesia. We compare a nominal case, “monitor feedback”, with our novel architecture, “soft-sensor feedback”. In the monitor feedback case, the soft-sensor block of Fig. 1 was replaced with the moving average filter that was clinically evaluated in connection with the controller of Section 2.4, as described in (Schiavo et al., 2021b). This filter averages the eight most recent samples and was used to smooth out the signal.

We study a disturbance scenario to evaluate and compare performance: electro-scalpel activity causes a drop in  $SQI$  from 100 to 50, immediately followed by a step disturbance  $d = 10$  BIS to reflect a lowered hypnotic depth in the patient resulting from the stimulation. After 2 min, surgical stimulation stops and  $SQI$  returns to 100. However, the disturbance  $d = 10$  BIS remains, reflecting a lasting nociceptive response. As the actual  $SQI$  dynamics are unknown, we have modeled the  $SQI$  drop with a double-step since it represents the “worst-case” nature in being abrupt. Moreover, steps are arguably the most common disturbance models considered in the context of closed-loop control systems.

Both the 2 min duration of electro-scalpel stimulation and the associated drop to  $SQI = 50$  were derived from data collected during several surgeries. To also investigate the effect of a negative output disturbance step, a second inference episode is initiated with the return from  $d = 10$  BIS to  $d = 0$  BIS.

The Kalman filter was initialized in the state that corresponds to a  $DoH$  of 50 in stationarity, i.e.,  $x_0 = -F^{-1}Bu_{\text{ref}}$ , where  $u_{\text{ref}}$  is the control signal corresponding to a  $DoH$  of 50 in stationarity.

The transients that arise during the initial convergence of the moving average and the Kalman filter, respectively, were truncated from the comparative evaluation. This is realistic, as in clinical use, the filter would typically be activated and allowed to converge before the system is switched from manual to closed-loop drug delivery.

### 3.2 Patient model population

We have taken both inter- and intra-patient variability into account. This has been achieved by simulating the procedure, detailed in Section 3.1, for 13 distinct individuals with covariates (age, height, weight, sex) and parameter values ( $E_0$ ,  $E_{\text{max}}$ ,  $C_{e50}$ ,  $\gamma$ ) disclosed in (Padula et al., 2017), who have already proven to be representative of a broad population. The covariate values were used to obtain a nominal patient model Eq. (2c) using the Schnider model (Schnider et al., 1998).

For each nominal model, 10 perturbations were obtained by drawing from the associated random effect distributions Eq. (5) to reflect model uncertainty caused by variability. Here, it can be noted that different draws were used in the optimization of the Kalman filter, as described in Section 2.2, and the subsequent evaluation simulations.

The Kalman filter incorporates the fixed-effects model only, which introduces a model error

between the true patient and the Kalman filter model. The soft-sensor design was also performed without knowledge of  $E_0$ ,  $E_{\max}$ ,  $C_{e50}$ , and  $\gamma$  for each patient in the data set of (Padula et al., 2017). Instead, the  $\hat{h}^{-1}$  and  $\hat{h}$  blocks of the soft sensor (see Fig. 1) were designed on previously published assumed typical values  $E_0 = 95.9$  BIS,  $E_{\max} = 87.5$  BIS,  $C_{e50} = 4.92$  mg L<sup>-1</sup>, and  $\gamma = 2.69$  according to (Vanluchene et al., 2004).

### 3.3 Performance evaluation

To evaluate the performance of the proposed control structure, we compared the *DoH* resulting from a closed loop between the soft-sensor and monitor feedback cases, with and without measurement noise. This comparison was conducted across a population of simulated patients, detailed in Section 3.2.

To evaluate disturbance rejection from the proposed control structure, we used two performance indices, introduced in (Ionescu et al., 2008):

- NADIR: the lowest or highest *DoH* reached after a positive or negative step disturbance, respectively (indicated by NADIR pos and NADIR neg).
- Time-to-target (TT): the time from step disturbance to first entering the range of 45–55 BIS.

From a clinical point of view, it is interesting to see how well the controller manages to maintain *DoH* within the 40–60 BIS range, as mentioned, e.g., (Soltész, 2013), which was also investigated.

## 4 Results

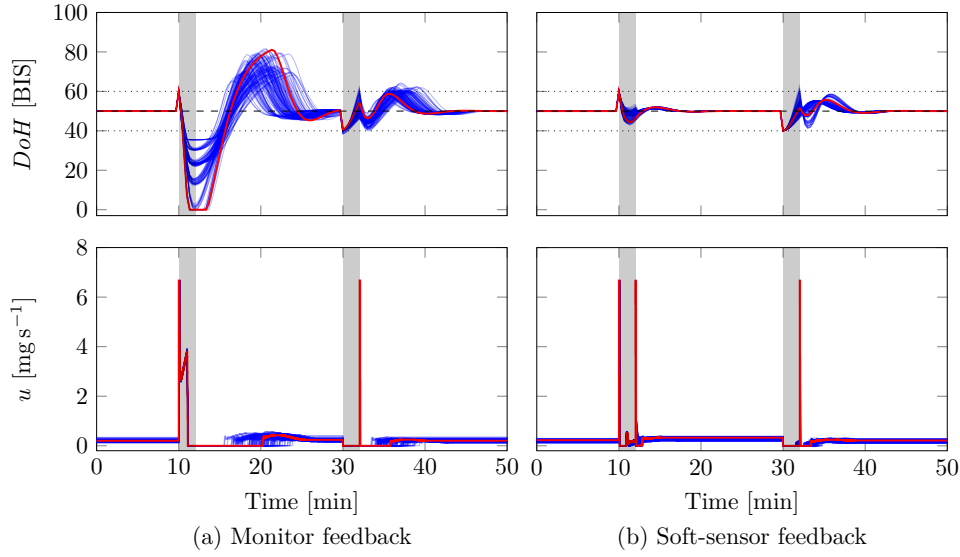
Fig. 3 shows *DoH* resulting from simulating the scenario of Section 3.1 for each of the 130 perturbed patient models according to Section 3.2. The figure corresponds to the noise-free case  $n = 0$ . Fig. 3(a) shows the results using the conventional monitor feedback approach; Fig. 3(b) shows the results resulting from our novel soft-sensor architecture. The median patient, in terms of *DoH* reference deviation MSE, is highlighted in red. The Kalman filter parameters used for the simulations in Fig. 3(b) from the optimization described in Section 2.2 are

$$R_{\min} = 5.07 \cdot 10^{-6}, \quad (13a)$$

$$R_{\max} = 0.250, \quad (13b)$$

$$Q = \text{diag} (4.79 \cdot 10^{-3}, 0, 1.52 \cdot 10^{-1}, 2.77 \cdot 10^{-4}). \quad (13c)$$

Results shown in Fig. 4 are related to simulations performed with the introduction of measurement noise  $n$  according to Section 2.3. The Kalman filter parameters, obtained



**Figure 3:** Blue solid lines represent  $DoH$  (upper) and propofol infusion rates (lower) for 10 perturbations of each of 13 nominal patient PKPD model, as explained in Section 3.2. The red solid line represents the mean response obtained for the entire set. According to Section 3.1, a positive step disturbance enters at  $t = 10$  min, followed by a negative one at  $t = 30$  min. The  $SQI$  drops to 50 immediately following each disturbance, before it returns to 100 after 2 min, as indicated by the shaded areas. The dashed black line indicates the  $DoH$  reference  $r = 50$  BIS, and the dotted lines illustrate the limits of the clinically recommended range between  $DoH = 40$  BIS and  $DoH = 60$  BIS. Fig. 3(a) corresponds to the nominal case, where feedback is established directly from the monitor measurement; Fig. 3(b) employs feedback from the proposed soft sensor. A representative patient simulation is shown in red for each case.

with noise present during the offline optimization phase, were

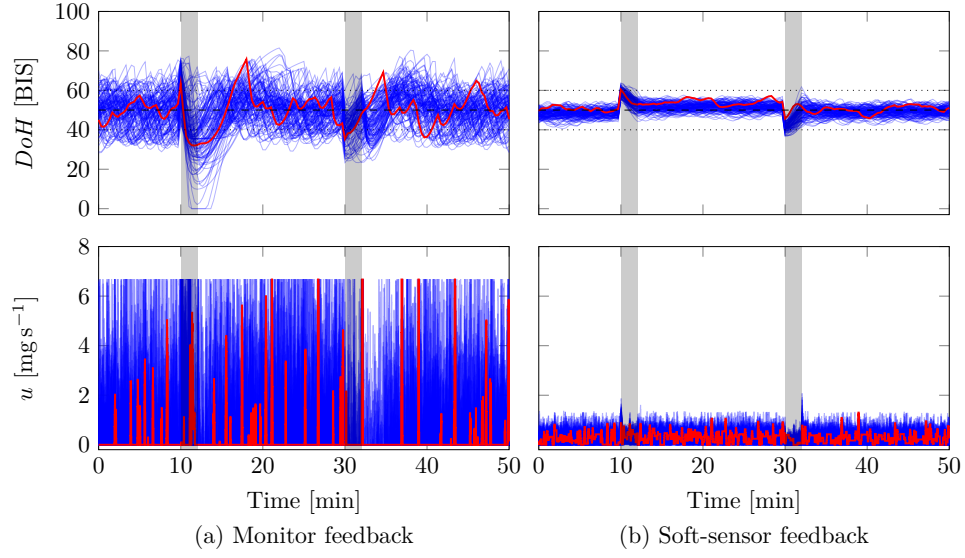
$$R_{\min} = 0.771, \quad (14a)$$

$$R_{\max} = 1.79, \quad (14b)$$

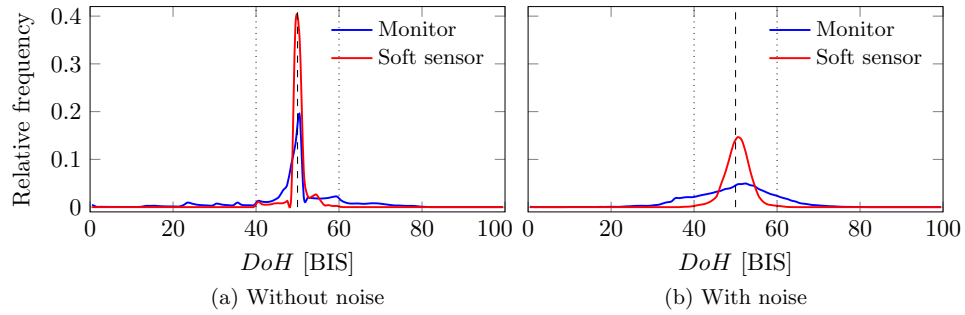
$$Q = \text{diag} (5.79 \cdot 10^{-2}, 1.83 \cdot 10^{-2}, 2.70 \cdot 10^{-2}, 2.12 \cdot 10^{-4}). \quad (14c)$$

Fig. 5 shows histograms of the  $DoH$  values in Fig. 3 and Fig. 4. The percentage of  $DoH$  values within the clinically desired 40–60 BIS range in Fig. 5 is 76% for monitor feedback and 100% for soft-sensor feedback without noise. The corresponding values are 71% and 99%, respectively, for the case with noise. Performance measures introduced in Section 3.3 are reported in Table 1.

To evaluate the proposed soft sensor on a wider range of individuals and to show that the tuning of the parameters is effective in general, we study the same simulation scenario as in Fig. 3 over a larger data set of 500 individuals, introduced in (Schiavo et al., 2021a). This is shown in Fig. 6.



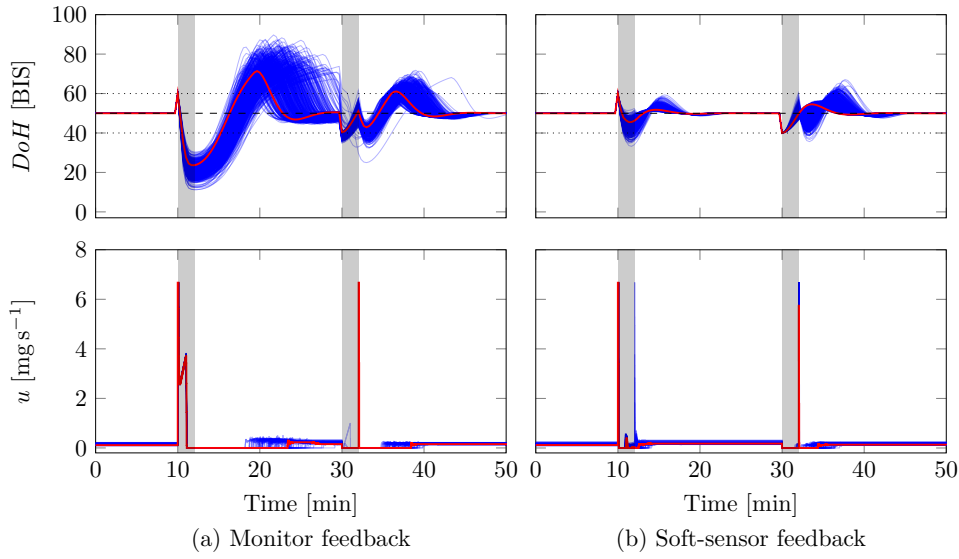
**Figure 4:** Simulated  $DoH$  (upper) and propofol infusion rate (lower) for 130 perturbed patient PKPD models, in the presence of measurement noise. Figure and color content correspond to that of Fig. 3.



**Figure 5:** Distribution of  $DoH$  values from Figs. 3 to 4, without and with Kalman filter soft sensor in the control loop.

| Feedback    | Noise | NADIR pos<br>[BIS] | NADIR neg<br>[BIS] | TT pos<br>[s] | TT neg<br>[s] |
|-------------|-------|--------------------|--------------------|---------------|---------------|
| Monitor     | No    | 0–35 (23)          | 57–64 (60)         | 9–15 (12)     | 50–106 (65)   |
| Soft sensor | No    | 43–50 (48)         | 54–63 (55)         | 10–21 (14)    | 49–104 (66)   |
| Monitor     | Yes   | 0–45 (34)          | 57–81 (65)         | 0–269 (15)    | 0–350 (55)    |
| Soft sensor | Yes   | 44–52 (48)         | 50–62 (53)         | 0–264 (70)    | 0–313 (59)    |

**Table 1:** Spread of performance measures presented as min–max (median) for the simulations in Figs. 3 to 4.



**Figure 6:** Simulated  $DoH$  (upper) and propofol infusion rate (lower) for 500 patient PKPD models to evaluate how the soft sensor handles inter-patient variability on a larger data set from (Schiavo et al., 2021a). Figure and color content correspond to that of Fig. 3.

## 5 Discussion

We have conducted a comparison between closed-loop  $DoH$  control using conventional low-pass filtered monitor output as a feedback signal and a novel soft-sensor architecture that integrates the patient model and the knowledge of signal quality.

The performance improvement of our novel architecture over that of the conventional one is perhaps best visualized in the histograms of Fig. 5. They show that the distribution of  $DoH$  values is more closely centered around the  $DoH$  maintenance reference  $r = 50$  BIS. This is also reflected in the performance indices reported of Table 1. While the difference in time-to-target (TT) between the compared architectures is marginal, the under- and overshoots associated with reaching the target, as well as  $DoH$  oscillations, differ substantially, as seen in Figs. 3 to 6.

An in-depth effort has been made to ensure realistic simulation circumstances. Instead of assuming perfect model knowledge, which is common in simulation works studying closed-loop control anesthesia, we have adopted a stochastic uncertainty in model param-

eters, grounded in clinical data (Schnider et al., 1998). Specifically, we have repeatedly sampled (10 perturbations) from this uncertainty for each of 13 nominal patients defined through population covariate values from a published dataset (Padula et al., 2017), with the pharmacodynamic parameters of Eq. (3). The design of the soft sensor is based solely on assumed knowledge of the nominal model, as described in Section 3.2. Along the same lines, we have used previously published models of surgical disturbance  $d$  (Soltesz et al., 2019), and measurement noise  $n$  (Pawlowski et al., 2022b).

For relating electro-scalpel inference  $m$  to  $SQI$ , as well as corruption of monitor measurement  $y$ , we have formulated our own model Eq. (11), as introduced in Section 2.3. This has been done based on communication with our senior anesthesiologist collaborator, who has observed a delay in monitoring reporting following such inference. We believe that the fidelity of this simple model could be improved upon. However, its sole purpose in the current context is to provide a substantial corruption of the monitor output  $y$ , which is reflected in  $SQI$ . The fact that the inference signal  $m$  in our simple model is directly mapped to  $SQI = m$  is just a matter of convenience for notation. Neither this nor the knowledge about how  $SQI$  therefore relates to the delay  $\tau$  through Eq. (11) has been exploited in the soft-sensor design. Instead, the soft sensor assumes only that the measurement uncertainty—in terms of variance  $R$  of an additive Gaussian measurement noise—is an affine function of  $SQI$ , according to Eq. (10), mapping the 100–0  $SQI$  range to an  $R_{\min}$ – $R_{\max}$  range. Thus, the soft sensor is agnostic of the monitor dynamics mapping inference  $m$  to corruption on  $y$ , which is later reported by the  $SQI$ . Although the monitor dynamics are not taken into account in the proposed architecture, the performance is satisfactory. Doing so would be unrealistic, even if the performance could be slightly improved.

Another implication is that our methodology can be expected to work satisfactorily not only with the BIS monitor but also other clinical monitors, such as the WAV<sub>CNS</sub> (Hahn et al., 2012) or CONOX (Jensen et al., 2014), that output both a  $DoH$  estimate  $y$  and associated  $SQI$ .

On a similar note, our Kalman filter assumes signal corruption by Gaussian noise added to the signal  $\tilde{C}_e$  in Fig. 1. At least for the noise contribution of  $n$  to this signal, a more accurate model could be incorporated. Also, here, satisfactory performance in the absence of such a model is positive, since it demonstrates that a low-fidelity noise model is sufficient for our architecture to outperform the nominal one with simple monitor feedback. While more advanced sensor fusion methods like the extended or unscented Kalman filters could be considered in scenarios where the model is not linear like in Eq. (1b), the simple linear Kalman filter already provides significant performance improvements. Its simplicity and interpretability make it an attractive choice for real-world implementation unless there is a strong motivation for more complex alternatives.

Some of the residual error arising from model mismatch is accounted for by the process noise model  $Q$ . Like with  $R$ , the underlying assumed noise structure does not match exactly that of the considered system. However, optimizing  $R$  and (an assumed diagonal)

$Q$  according to Section 2.2 yields satisfactory performance. To implement this soft-sensor in practice,  $R_{\min}$ ,  $R_{\max}$  and  $Q$  would be optimized offline, with  $R$  then adjusted online based on Eq. (10).

## 6 Conclusions

A realistic closed-loop controlled anesthesia scenario is considered, in which model uncertainties and external disturbances are present. In this setting, our comparative simulation study clearly illustrates robust performance benefits from merging a model-based and data-driven approach through a Kalman filter soft sensor. In particular, it enables online balance between model and measurement reliance, based on an estimation of measurement quality.

Based on the results presented, we are confident to take the next steps toward the clinical evaluation of the proposed soft-sensor architecture within an existing clinical closed-loop anesthesia research platform, which to date has seen extensive clinical use (Schiavo et al., 2021b, 2022).

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# Paper VIII

## In Vivo Performance Evaluation of an FOPID Controller for Closed-loop Anesthesia

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### Abstract

In this paper we design and evaluate a fractional-order proportional-integral-derivative (FOPID) controller for the regulation of total intravenous anesthesia (TIVA). In particular, the FOPID controller has been designed to regulate patient's depth of hypnosis (DoH), measured via the bispectral index (BIS) monitor, by coadministering both the hypnotic and analgesic drugs used in TIVA. Separate tunings are obtained for the induction phase and for the maintenance phase. For the former, a methodology based on the minimization of the integrated absolute error (IAE) has been employed, while for the latter, the isodamping design approach has been applied. Experiments carried out on ten patients undergoing plastic surgery show that the FOPID controller meets the clinical requirements for each one of the ten patients without requiring any manual intervention of the anesthesiologist. Notably, the controller provided a fast rejection of disturbances without provoking harmful overdosing episodes.

Originally published in IEEE Transactions on Control Systems Technology. The original version is available at 10.1109/TCST.2025.3577975.

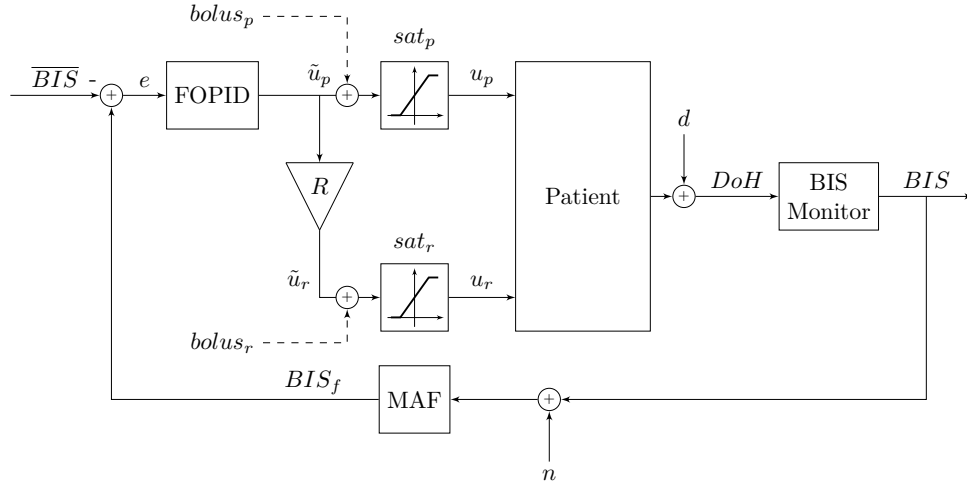
## 1 Introduction

Total Intravenous Anesthesia (TIVA) achieves unconsciousness and pain relief by administering a mixture of drugs. Typically, this blend includes hypnotic (Vuyk et al., 2020) and analgesic (Schumacher and Fukuda, 2020) agents. During anesthesia, it is important to make reasonable adjustments to the drugs and their dosing to ensure a successful surgical outcome. In particular, managing drugs dosing and interaction could be critical and requires specific care since they can alter and amplify each other effect on the patient (Bouillon, 2008). Determining the right balance is not straightforward because the patient's level of analgesia can only be partially assessed using indirect measures and signals. As such, the quality of care is highly reliant on the anesthesiologist's experience. For these reasons, several automated drug infusion systems have been designed to date to assist anesthesiologists in adjusting the drugs infusion rate, always prioritizing patient safety (Copot and Ionescu, 2014).

In clinical practice, Target Controlled Infusion (TCI) (Absalom et al., 2016) is the most widespread commercially available computer-based system and it is used to adjust the infusion pattern to reach a desired concentration in the effect site. However, TCI works in feed forward and relies entirely on a mathematical model of the patient, which is not always accurate. To overcome these limitation, several closed-loop control schemes have been designed to enhance anesthesia reliability and performance (Ghita et al., 2020).

Closed-loop controllers need a quantitative measure to close the control loop. In anesthesia, information retrieved from processed electroencephalograms (pEEG) is commonly used as feedback signal (Rampil, 1998; Nguyen-Ky et al., 2021; Liu et al., 2024). The Bispectral Index (BIS) (Avidan M. S. et al., 2008) monitor is, to date, considered the gold standard to measure the patient's Depth of Hypnosis (DoH). Hence, several closed-loop control solutions exploit it as feedback signal. The BIS maps the brain's electrical activity into a scale that ranges from 0 (flat EEG) to 100 (highest cortical activity). During anesthesia, the target is to maintain the BIS as close as possible to 50 for the entire duration of the surgery, but, in the clinical practice, values between 40 and 60 are considered satisfactory (Rosow and Manberg, 2001).

Unlike hypnosis, a clinically accepted measure of analgesia is not yet available (Ghita et al., 2023). However, the concentration of the analgesic drug exhibits an interaction with the measured DoH. For this reason, several control schemes are based on a Multiple-Input-Single-Output (MISO) system. Many of these solutions take advantage of Proportional-Integrative-Derivative (PID) controllers (Visioli, 2006) to adequately regulate drug infusion rates. PID controllers, which are typically used in industry, have also shown to be a promising solution when applied to anesthesia (Yousefi et al., 2019). Various PID-based control structures proved to be an effective resource during clinical experiments (Schiavo et al., 2023, 2020, 2021). In addition to PID controllers, other control algorithms have been developed to improve control performance, such as event-based control (Schiavo et al., 2023) and model predictive control (MPC) (Sawaguchi et al., 2008; Pawlowski et al., 2023).



**Figure 1:** Block scheme of the experimental set-up. The reference  $\overline{BIS}$  has been set to 50. The signal  $d$  represents the surgical stimuli acting on the patient, while  $n$  is the noise acting on the monitoring equipment. The dashed arrows are the feedforward actions that are used to administer drugs boluses.

A generalization of the PID algorithm which has attracted a great deal of attention in the last few years is the fractional-order PID (FOPID) controller. The FOPID controller exploits fractional calculus to extend the integral and derivative actions of the classical PID controller to any real order.

In this paper, we propose a FOPID-based coadministration control structure to manipulate the flow rate of propofol and remifentanyl by measuring the patient's DoH via the BIS. FOPID controllers have already been applied to anesthesia (Copot et al., 2017; Hegedus et al., 2022; Paolino et al., 2023) but they have never been tested on real patients. Moreover, the proposed solution is the first coadministration application of a FOPID controller. The main difference between FOPID and PID controllers lies in the fact that FOPID controllers have five tuning parameters, whereas PID controllers only have three. The additional degrees of freedom are represented by the integral and derivative orders, which can be freely chosen as real numbers. This added flexibility, if properly exploited during the design phase, should result in a higher-performing controller.

The paper is organized as follows. A general overview of the experimental setup, together with a detailed description of the tuning procedure, is presented in Section 2. Section 3 presents and discusses the results obtained with the ten enrolled patients. Conclusions are drawn in Section 4.

## 2 Methods

The block scheme in Fig. 1 shows a schematic representation of the clinical set-up used to carry out the experiments. The control software has been implemented in MATLAB<sup>®</sup> and runs on a commercially available laptop (Hewlett-Packard 15-da1000nl, HP Inc., Palo Alto, California, USA). The controller receives the control error  $e = BIS_f - \overline{BIS}$  as input

and provides the command to set the pumps' infusion rate as output. Importantly, the remifentanyl flow rate  $\tilde{u}_r$  (expressed in  $\mu\text{g s}^{-1}$ ) is adjusted proportionally to the propofol flow rate  $\tilde{u}_p$  (expressed in  $\text{mg s}^{-1}$ ). In particular, the ratio  $R$  between the two drugs' infusion rates, based on clinical expertise, has been fixed to 2 (Schiavo et al., 2021). To speed up the induction phase, the controller administers boluses of propofol and remifentanyl by a feedforward action. Moreover, the drugs flow rates are subjected to saturation to meet the limitations of the surgical syringe pumps available in the surgery room. In Fig. 1, the saturation elements are represented by two blocks called  $sat_p$  and  $sat_r$ , respectively.

The specifications of an Graseby™ 3500 pump have been used, yielding a maximum flow rate of  $1200 \text{ mL h}^{-1}$  for both actuators. Concerning the feedback signal, a Moving Average Filter (MAF) of eight samples has been added to smooth the noise ( $n$ ) affecting the BIS signal (Schiavo et al., 2021). Moreover, the controller exploits the conditional integration anti-windup strategy to avoid problems due to the concurrent presence of the integral action and the actuators saturation limits. Another important feature consists of administering a baseline infusion during the maintenance phase whenever the predicted effect-site concentration falls below a safety threshold and at the same time the BIS values remains inside the safety range. This scenario may occur during low surgical stimulation phases that last over long time intervals. This practice mirrors modern clinical protocols where drug infusions are never reduced to zero during maintenance. However, the baseline infusion might be stopped if the BIS value drops below the desired BIS set-point.

## 2.1 Pharmacological Model

The controller has been tuned through repeated simulations, where the patient-drugs interaction was described using a suitable pharmacological model. Specifically, the Schnider and Minto models (Schnider et al., 1998, 1999; Minto et al., 1997) have been utilized to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of propofol and remifentanyl, respectively. A three-compartment model is commonly used for PK, while PD is modeled via a fictitious compartment referred to as the effect-site compartment.

Drugs interaction and the relationship between drug concentration and clinical effect are mathematically described by the Hill function, which is defined as

$$DoH = E_0 - E_{\max} \left( \frac{\left( \frac{U_p + U_r}{U_{50}(\phi)} \right)^\gamma}{1 + \left( \frac{U_p + U_r}{U_{50}(\phi)} \right)^\gamma} \right), \quad (1)$$

where  $E_0$  is the baseline BIS value before drugs administration and  $E_0 - E_{\max}$  represents the maximal achievable effect. The parameter  $\gamma$  is the slope of the surface and represents the patient's responsiveness to the drug, whereas  $U_{50}(\phi)$  is computed as follows

$$U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2, \quad (2)$$

and  $\phi$  is defined as

$$\phi = \frac{U_p}{U_p + U_r}. \quad (3)$$

$U_p$  and  $U_r$  are obtained by normalizing the effect-site concentration of propofol ( $C_{e,p}$ ) and remifentanyl ( $C_{e,r}$ ) by the concentration that produces 50% of the maximal DoH effect, namely  $C_{e50,p}$  and  $C_{e50,r}$ . Finally,  $\beta$  represents the synergistic effect of the two drugs.

## 2.2 Controller Design

The FOPID controller transfer function is

$$C(s) = K_p \left( 1 + \frac{1}{T_i s^\lambda} + \frac{T_d s^\mu}{\frac{T_d}{N^\mu} s^\mu + 1} \right), \quad (4)$$

where  $\lambda$  and  $\mu$  are the two additional tuning parameters mentioned in the introduction. In a standard PID controller,  $\lambda$  and  $\mu$  are constrained to be 1, therefore, the controller behavior depends exclusively on the proportional gain  $K_p$  and on the integral and derivative time constants,  $T_i$  and  $T_d$  respectively. Conversely, in a fractional-order controller,  $\lambda$  and  $\mu$  can assume every value between 0 and 2. The two additional degrees of freedom should allow the robustness/performance trade-off to be better handled. Note that, by taking into account that the BIS signal is very noisy,  $N$  has been set to 5 because this is a typical value that provides high noise filtering without affecting significantly the controller's dynamics.

Two different sets of FOPID tuning parameters have been obtained, one for the induction phase and one for the maintenance phase. The two problems have been addressed separately (see Section 2.2 and Section 2.2, respectively), since each phase requires different control specifications. In particular, the induction problem is a set-point following task in which the DoH level must track a BIS level of 50 starting from its baseline value. Induction should last less than 5 minutes and undershoot episodes must be bounded. Instead, during the maintenance phase, it is essential to reject disturbances to keep the BIS as close as possible to 50 (practically, in the range from 40 to 60), to avoid intra-operative awareness or overdosing.

The implementation of a FOPID controller can be challenging because of the infinite dimensional nature of the integral and derivative terms. To overcome this problem, the CRONE approximation proposed in (Oustaloup et al., 2006) has been used. This procedure produces a high-order real-rational (integer) approximation of the non-integer transfer function which is valid in a predefined frequency range. In this study, we use 8 pairs of zeros and poles to achieve an approximation in the frequency range that goes from  $10^{-6}$  to  $10^2$   $\text{rad s}^{-1}$ . Finally, the Tustin method has been exploited to obtain the discrete-time approximation of the controller.

**Table 1:** Controller's optimal parameters and optimization bounds for the induction phase.

| Parameter | Lower Bound | Upper Bound | Final Value |
|-----------|-------------|-------------|-------------|
| $K_p$     | 0.0005      | 0.05        | 0.0143      |
| $T_i$     | 50          | 500         | 229.9577    |
| $T_d$     | 0.1         | 100         | 30.4362     |
| $\lambda$ | 0           | 2           | 0.9215      |
| $\mu$     | 0           | 2           | 1.0049      |
| IAE       |             |             | 3683.95     |

### Induction Phase Tuning

A genetic algorithm (Kramer, 2017) has been used to solve an optimization problem to tune the FOPID parameters  $K_p$ ,  $T_i$ ,  $T_d$ ,  $\lambda$ , and  $\mu$ , by minimizing the integrated absolute error (IAE) over the set of 13 patients, presented in (Padula et al., 2017). The IAE is defined as

$$IAE = \int_0^{T_{sim}} |BIS(t) - \overline{BIS}(t)| dt. \quad (5)$$

In particular, to compute the IAE, an induction phase of  $T_{sim} = 10$  minutes has been simulated. For the simulations, the patients have been modeled using the PKPD model presented in Section 2.1. The optimization has been performed using MATLAB<sup>®</sup> global optimization toolbox's `ga` with a population size of 100 and subject to the parameters bounds shown in Table 1. Genetic algorithms has been selected because the computational effort is not of concern, as optimization is performed offline, and because they provide a global minimum in a stochastic sense. Concurrently, the use of IAE is justified by its ability to achieve a fast transient response with minimal undershoot. Moreover, during the induction phase, the response is primarily influenced by the nonlinear component, thereby making methods based on linearization unsuitable. The optimization has been stopped when the variation of the value of the fitness function between two consecutive iterations was less than  $10^{-3}$ . By observing Table 1, it can be noticed that the values of  $\mu$  and  $\lambda$  are close to 1. This means that, in the induction phase, the performance obtained with a FOPID controller is virtually the same as the one obtained with a PID controller.

### Maintenance Phase Tuning

Concerning maintenance, the FOPID controller has been designed by imposing the isodamping condition, as in (Paolino et al., 2023), where only the propofol infusion has been considered. The isodamping approach involves flattening the phase at the gain crossover frequency to ensure that the phase margin remains constant despite changes in the process DC gain, which, in the context of this paper, is represented by the gain variability among different patients (from 448.73 [BIS s/mg] to 1519 [BIS s/mg] in the case of the thirteen patients). A constant phase margin implies that robustness is invariant with respect to gain variations. In particular, having the same phase margin for different gains

yields the same relative overshoot. Thus, achieving the isodamping condition allows the designer to increase the closed-loop bandwidth without losing stability under uncertainty, or maintain the bandwidth while improving on robustness, which implies faster transients, faster disturbance rejection and ultimately a better prevention of intra-operative awareness. To this end, although it is theoretically possible to use a FOPI controller to achieve the isodamping, we decided to exploit a FOPID in order to take advantage of the full controller capabilities to reduce the maximum sensitivity  $M_s$ .

The transfer function of a nominal process, denoted as  $P$ , is required during the controller design to perform the isodamping tuning method. The demographic data of only the thirteenth patient, from the aforementioned database, served as reference to compute the nominal process. The following steps will clarify step-by-step the design procedure presenting in details all equations involved. With a straightforward substitution, Eq. (1) can be rewritten as

$$DoH = E_0 - E_{\max} \left( \frac{\star^\gamma}{1 + \star^\gamma} \right), \quad (6)$$

where (see Eqs. (2) and (3))

$$\star = \frac{S^3}{S^2 - \beta U_p S + \beta U_p^2} \quad (7)$$

and  $S = U_p + U_r$ . In the sequel, we define the numerator and denominator of Eq. (7) as

$$A := S^3, \quad B := S^2 - \beta U_p S + \beta U_p^2, \quad (8)$$

respectively. Here,  $S$  is computed using  $U_p = C_{ref,p}/C_{e50,p}$  and  $U_r = C_{ref,r}/C_{e50,r}$ . Then, we linearize the model's nonlinearity (Hill function) around the equilibrium point defined by the propofol and remifentanil effect-site concentrations,  $C_{ref,p}$  and  $C_{ref,r}$ , that produce  $BIS = 50$ . Note that, due to the ratio between drugs' infusion rates imposed by the controller, the equilibrium is unique and  $C_{ref,r} = C_{ref,p}/r$ , with  $r$  computed as

$$r = \frac{K_1}{RK_2}, \quad (9)$$

where  $K_1$  and  $K_2$  are the product of the DC gains of the PK model and the PD model for propofol and remifentanil respectively. By inverting Eq. (6) we obtain

$$C_{ref,p} = \frac{E}{D} \left( \frac{E_0 - 50}{50 - E_0 + E_{\max}} \right)^{1/\gamma}, \quad (10)$$

where

$$D = \frac{rC_{e50,r} + C_{e50,p}}{rC_{e50,r}C_{e50,p}}, \quad (11a)$$

$$E = (rC_{e50,r} + C_{e50,p})^2 - \beta(rC_{e50,r} + C_{e50,p})(rC_{e50,r}) + \beta \frac{(rC_{e50,r})^2}{(rC_{e50,r} + C_{e50,p})^2}. \quad (11b)$$

By differentiating Eq. (6) with respect to propofol and remifentanil effect-site concentrations

we obtain

$$\left. \frac{\partial DoH}{\partial C_{e,p}} \right|_{C_{e,p}=C_{ref,p}} = E_{\max} \left[ \frac{\gamma \star^{\gamma-1} H}{(1 + \star^\gamma)^2} \right], \quad (12a)$$

$$\left. \frac{\partial DoH}{\partial C_{e,r}} \right|_{C_{e,r}=C_{ref,r}} = E_{\max} \left[ \frac{\gamma \star^{\gamma-1} G}{(1 + \star^\gamma)^2} \right], \quad (12b)$$

where

$$H = \frac{3S^2}{B} \frac{1}{C_{e50,p}} - \frac{A}{B^2} \left( 2S \frac{1}{C_{e50,p}} - \beta S \frac{1}{C_{e50,p}} + 2\beta C_{ref,p} \frac{1}{C_{e50,p}^2} \right), \quad (13a)$$

$$G = \frac{3S^2}{B} \frac{1}{C_{e50,r}} - \frac{A}{B^2} \left( 2S \frac{1}{C_{e50,r}} - \beta \frac{C_{ref,p}}{C_{e50,p}} \frac{1}{C_{e50,r}} \right). \quad (13b)$$

The nominal loop transfer function, which relates variations of the controller output (i.e. variations of the propofol infusion rate) to the variations of the therapeutic effect, can be computed as

$$P(s) = \frac{\Delta DoH(s)}{\Delta U_p(s)} = \begin{bmatrix} \left. \frac{\partial DoH}{\partial C_{e,p}} \right|_{C_{e,p}=C_{ref,p}} & \left. \frac{\partial DoH}{\partial C_{e,r}} \right|_{C_{e,r}=C_{ref,r}} \end{bmatrix} \begin{bmatrix} P_p & 0 \\ 0 & P_r \end{bmatrix} \begin{bmatrix} 1 \\ R \end{bmatrix}, \quad (14)$$

where  $P_p$  and  $P_r$  are defined as

$$P_p(s) = \frac{K_1 \left( \frac{s}{z_{1,p}} + 1 \right) \left( \frac{s}{z_{2,p}} + 1 \right)}{\left( \frac{s}{p_{1,p}} + 1 \right) \left( \frac{s}{p_{2,p}} + 1 \right) \left( \frac{s}{p_{3,p}} + 1 \right) \left( \frac{s}{p_{4,p}} + 1 \right)}, \quad (15a)$$

$$P_r(s) = \frac{K_2 \left( \frac{s}{z_{1,r}} + 1 \right) \left( \frac{s}{z_{2,r}} + 1 \right)}{\left( \frac{s}{p_{1,r}} + 1 \right) \left( \frac{s}{p_{2,r}} + 1 \right) \left( \frac{s}{p_{3,r}} + 1 \right) \left( \frac{s}{p_{4,r}} + 1 \right)}, \quad (15b)$$

and  $z_{1,p}$ ,  $z_{1,r}$ ,  $z_{2,p}$ ,  $z_{2,r}$ , and  $p_{1,p}$ ,  $p_{1,r}$ ,  $p_{2,p}$ ,  $p_{2,r}$ ,  $p_{3,p}$ ,  $p_{3,r}$  are the zeros and poles of the PK propofol and remifentanil models, while  $p_{4,p}$  and  $p_{4,r}$  are the poles of the PD propofol and remifentanil models, respectively.

Once the nominal model of the system has been obtained, the controller is designed by maximizing robustness subject to constraint of the closed-loop bandwidth, gain margin and isodamping property. This is achieved by finding a set of controller parameters that minimizes the maximum sensitivity  $M_s$  (thus maximizing robustness), which is defined as

$$M_s := \max_{\omega} |S(j\omega)| = \max_{\omega} \left| \frac{1}{1 + C(j\omega)P(j\omega)} \right|. \quad (16)$$

More formally, the following optimization problem has been solved exploiting a genetic algorithm:

$$\min_{(K_p, T_i, T_d, \lambda, \mu)} M_s \quad (17)$$

subject to:

**Table 2:** Controller's optimal parameters and optimization bounds for the maintenance phase.

| Parameter | Lower Bound | Upper Bound | Final Value |
|-----------|-------------|-------------|-------------|
| $K_p$     | 0.0005      | 0.05        | 0.0462      |
| $T_i$     | 50          | 1000        | 905.70      |
| $T_d$     | 0.1         | 100         | 19.712      |
| $\lambda$ |             |             | 1           |
| $\mu$     | 0           | 2           | 1.1409      |
| $M_s$     |             |             | 1.088       |

1.  $\omega_c = 0.0467 \text{ rad s}^{-1}$  (desired gain crossover frequency);
2.  $\phi_m = 63.5^\circ$  (desired phase margin);
3.  $\left. \frac{d\phi_m}{d\omega} \right|_{\omega=\omega_c} = 0$  (isodamping condition).

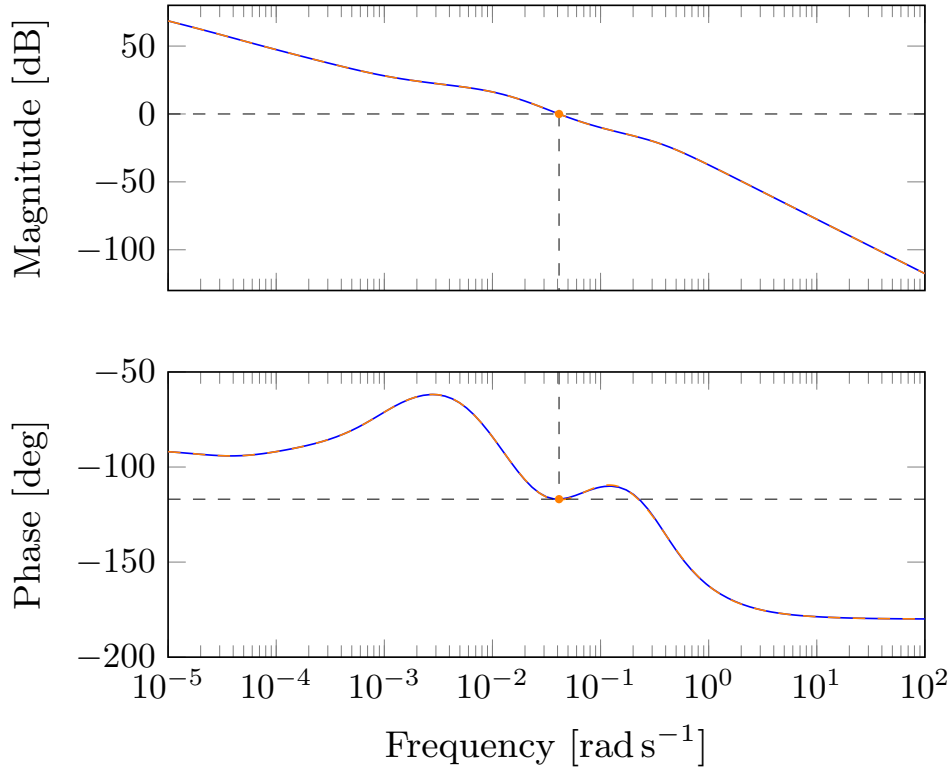
The values of the constraints have been computed by analyzing the frequency response of the loop transfer function  $L(s) = C(s)P(s)$  of the linearized models of the 13 patients in series with the PID controller previously presented in (Schiavo et al., 2021). Then, the values of the gain crossover frequency and of the phase margin have been determined for each system. The resulting average values have been used to assign  $\omega_c$  and  $\phi_m$  in the isodamping problem. The isodamping condition sets the derivative of the phase margin at the gain crossover frequency equal to zero to impose the flatness of the phase at  $\omega_c$ . This implies that the different cases will show almost the same overshoot.

Note that, while it is beneficial to use a fractional derivative, the optimal integrator is of integer order. The results of the optimization found integrator time constants that would place the (fractional) zero of the fractional integrator outside the approximation bandwidth, which therefore behaves as a normal integer integrator. Specifically, the optimal values found were  $T_i = 935.15$  and  $\lambda = 0.3625$ , where the value  $\lambda$  of the fractional order becomes irrelevant, and this indicates that a standard integer integrator can be selected. For this reason, we have constrained  $\lambda$  to be equal to 1 with the additional benefit of reducing the dimensionality of the optimization problem. The resulting optimal parameters are listed in Table 2.

Since the design strategy operates in the frequency domain, it is interesting to evaluate the Bode diagram of the loop transfer function to check if the isodamping property is achieved and maintained also when the fractional term is approximated. This is shown in Fig. 2.

### 3 Experimental Results

The performance of the proposed control solution has been experimentally evaluated in ten patients undergoing plastic surgery requiring TIVA. The study has been approved by the Ethics Committee of Brescia (number of the study: NP12861). The patients' clinical



**Figure 2:** Frequency response of the loop transfer function (series between the nominal process  $P$  and the controller). Blue solid line: CRONE approximation. Orange dashed line: FOPID controller.

information and the type of surgery are detailed in Table 3. During induction phase, the controller has to rapidly drive the patient's DoH from its baseline value ( $\approx 100$  BIS) to 50 BIS. The induction must be fast, typically within 3 and 5 minutes. During maintenance, the FOPID has to keep the BIS within the 40-60 range providing a fast disturbance rejection. The transition between the parameters sets is automatically performed by the control algorithm when the DoH falls below 60 BIS and settles there for 30 consecutive seconds. A bumpless switching logic has been exploited to guarantee a smooth transition between the two controllers. As detailed in (Pawlowski et al., 2023), as a safety measure, the feedback controller is automatically switched off when, for at least 5 seconds, the BIS signal is not available or the related Signal Quality Index (SQI) is lower than 40. In this situation, constant drug rates, referred to as baseline infusions and computed on the basis of the patient's weight, are infused. Once, for at least 5 seconds, the BIS signal is continuously available again and the SQI returns above 40 the feedback control is automatically resumed by applying a bumpless strategy. At any moment, manual mode can be activated whenever the anesthesiologist requires it.

The controller's performance can be evaluated from the results in Fig. 3, Fig. 4, Fig. 5, Fig. 6, and Fig. 7. From top to bottom, the figures illustrate the patient's BIS (blue solid line) for the entire duration of the surgery, the BIS target (black dashed line), the recommended BIS range 40-60 (black dotted lines), and the lower BIS limit of 35 (black dash-dotted line). The next plot shows the propofol (blue) and remifentanil (red) infusion

**Table 3:** Patients demographic information and surgery procedures. In the heading, H stands for height, W stands for weight, and G stands for gender.

| Patient | Age | H [cm] | W [kg] | G | Surgery             |
|---------|-----|--------|--------|---|---------------------|
| 1       | 74  | 170    | 57     | F | Ulceration Removal  |
| 2       | 60  | 160    | 58     | F | Electrochemotherapy |
| 3       | 41  | 170    | 66     | F | Mastectomy          |
| 4       | 43  | 160    | 60     | F | Mastectomy          |
| 5       | 84  | 160    | 68     | F | Melanoma Excision   |
| 6       | 75  | 163    | 68     | F | Breast Dermal Flap  |
| 7       | 62  | 164    | 100    | F | Mastectomy          |
| 8       | 47  | 165    | 67     | F | Mastectomy          |
| 9       | 54  | 170    | 62     | F | Mastectomy          |
| 10      | 47  | 165    | 110    | F | Mastectomy          |

rates in  $\text{mL h}^{-1}$ . In the third, the heart rate in bpm (blue solid line), is shown together with safety upper and lower bounds [100-50] (black dotted line). The bottom plot shows the mean arterial pressure in mgHg (blue solid line) with safety upper and lower bounds [110-65] (black dotted line). For every figure, the y-axis of the infusion rates has been intentionally cut to show the full scale with enough detail. Note that in Fig. 3, for patient 1 and 2, the controller administers the baseline drug infusion for almost the whole duration of the maintenance phase. In some patients, vertical lines and missing values in BIS and HR plots are due to sensor misreading. In every scenario, the figures illustrate the administration of propofol and remifentanyl boluses at the beginning of the surgical procedure. These boluses are automatically administered by the controller as a feedforward action.

Based on the plots, it is evident that the controller performed very satisfactorily in managing drug administration for patients 1, 3, 4, 6, 7, 8, and 10. In fact, for seven out of the ten patients, the FOPID controller worked flawlessly. Patient 2 (Fig. 3) experienced signal loss, which is visible at the start of the infusion. During this period, the controller administered two boluses to accelerate the induction phase, but since the BIS signal was no longer available, the controller entered in safety mode and therefore continued infusing at the baseline infusion. Once the signal was restored, the accumulated drug caused the BIS to drop to around 20. However, the controller quickly responded, and the DoH level returned to the safe interval within approximately 3 minutes, thus without any clinical consequence for the patient. Note that the baseline infusion is computed based on the patient's weight, which is in line with the clinical practice of manually controlled anesthesia. The low BIS achieved suggests that patient 2 is particularly sensitive, i.e., the patient exhibits a high gain. In the absence of the BIS signal, the anesthesiologist and the controller alike do not have feedback from the brain on the actual state of the patient. The anesthesiologist would have had to rely on other non-measurable (e.g., lacrimation, sweating) and measurable (e.g., heart rate, blood pressure, respiratory rate, oxygen saturation, body temperature, etc.) vital signs to assess the state of the patient.

For patient 5 (Fig. 5), during the induction phase, the BIS value reached nearly 35

**Table 4:** Results for the induction phase.

| Patient | Time<br>[min] | Lowest DoH<br>[BIS] | Propofol<br>[mg kg <sup>-1</sup> ] | Remifentanil<br>[μg kg <sup>-1</sup> ] |
|---------|---------------|---------------------|------------------------------------|----------------------------------------|
| 1       | 1.52          | 39                  | 2.18                               | 2.42                                   |
| 2       | 1.10          | 40                  | 2.42                               | 1.44                                   |
| 3       | 2.50          | 54                  | 3.11                               | 2.05                                   |
| 4       | 1.15          | 41                  | 2.26                               | 1.62                                   |
| 5       | 0.967         | 37                  | 1.96                               | 1.53                                   |
| 6       | 2.02          | 25                  | 1.60                               | 1.51                                   |
| 7       | 0.950         | 23                  | 1.85                               | 1.32                                   |
| 8       | 1.08          | 36                  | 2.00                               | 1.99                                   |
| 9       | 1.60          | 33                  | 2.12                               | 2.65                                   |
| 10      | 1.45          | 28                  | 1.69                               | 1.01                                   |
| Average | 1.43          | 35.6                | 2.12                               | 1.75                                   |

but remained at this level for less than 7 minutes. Additionally, the heart rate remained consistently within the recommended range. At minute 70, a sharp rise in BIS can be observed, which may be due to painful stimuli, such as suturing. Nevertheless, the controller rapidly adjusted the infusion, bringing the DoH back into the 40-60 range without causing oscillations during the transition.

Regarding patient 9 (Fig. 7), a series of spikes can be observed in the BIS data. Also in this case, the controller quickly counteracted the rise in BIS, preventing any potential episodes of intra-operative awareness. Generally, the controller never required manual intervention from the anesthesiologist. Therefore, it can be concluded that the controller effectively kept the patients in an acceptable unconscious state and the hemodynamic variables suggest adequate management of the pain level.

Table 4 shows the results related to the induction phase. According to (West et al., 2018; Liu et al., 2006), the induction duration is calculated as the time elapsed between the start of infusion and the instant when the DoH remains under 60 BIS for at least 30 seconds. The lowest DoH is the smallest BIS value observed within 60 seconds following the induction time.

On average, the induction process takes almost one and a half minutes, meeting the clinical requirement to last no longer than five minutes. The fast induction causes the DoH to drop below 40 BIS, but the undershoots were limited and did not lead to any harmful episodes in the patients.

As previously stated, by looking at Figs. 3 to 5, patients 2, 3, and 6 encountered issues with the BIS monitor during the induction phase. However, the durations of the sensor faults were brief, and they were properly managed by the safety mechanism implemented in the controller. Thus, the lack of information did not cause any harm or discomfort to the patient during the anesthesia procedure. Moreover, none of the patients experienced burst suppression, which is caused by excessively deep levels of DoH (Besch et al., 2011).

The performance achieved in the maintenance phase are summarized in Table 5. Looking at the data, it is possible to see that the FOPID controller tended to keep the BIS a little below the 40-60 range. This behavior is due to the presence of the non integer derivative term  $\mu$ , which, being greater than 1, could amplify noise which, in combination with the lower saturation limit, causes the controller to infuse doses slightly biased towards higher values. However, analyzing the 35-55 interval, it is clear that the DoH level were always inside safety boundary limits. Data are shown in Table 6. This information, together with the performance indices listed in Table 7, highlights that the patients' DoH assumed acceptable values even if slightly below the recommended lower BIS limit of 40.

Concerning performance indices, MDPE shows whether the measured BIS is mainly above or below the reference value. MDAPE quantifies the controller ability to accurately track the reference, while WOBBLE estimates the effect of intra-patient variability on performance errors. Despite a negative average MDPE, indicating as expected that the DoHs were slightly below the BIS reference, the BIS dispersions were bound within safety limits. This shows that the automatic system provided tight control. Moreover, the WOBBLE analysis points to the fact that intra-patient variability marginally impacted the performance.

Another important aspect to consider are the hemodynamic variables, namely heart rate (HR) and mean arterial pressure (MAP). The hemodynamics provides a general overview of the patient's anesthetic state. Indeed, analgesic underdose would result in a sudden rise in blood pressure and heart rate after surgical stimuli. Instead, a remifentanyl overdose would result in hypotension and bradycardia. For every patient, the level of the HR and the MAP were inside the recommended bounds at all times, indicating satisfactory anesthesia procedures.

In summary, the proposed FOPID-based control solution achieved satisfactory performance and is a promising avenue. The isodamping condition combined with the strong derivative action allows robustness to be achieved without compromising on disturbance rejection performance. This becomes apparent from the experimental results by noting that the controller behaves similarly for every patient, rapidly counteracting DoH rising episodes. Moreover, even though the resulting BIS level sits slightly below the 40 BIS threshold most of the time, by globally looking at the patient's variables and vital signs, the anesthesiologist never decided to interrupt the automatic control. The quality of the delivered anesthesia is also confirmed by the awaking time, reported in Table 5. On average, patients took 10 minutes to wake up after the drug infusion was stopped, which is consistent with the clinical practice of TIVA and does not indicate overdosing.

## 4 Conclusions

In this study, we evaluated the in vivo performance of a fractional-order PID controller for closed-loop anesthesia in ten patients undergoing plastic surgery. The controller was designed to regulate the depth of hypnosis using the BIS monitor by adjusting the

**Table 5:** Maintenance phase statistics. The BIS % is computed over the whole maintenance phase duration.

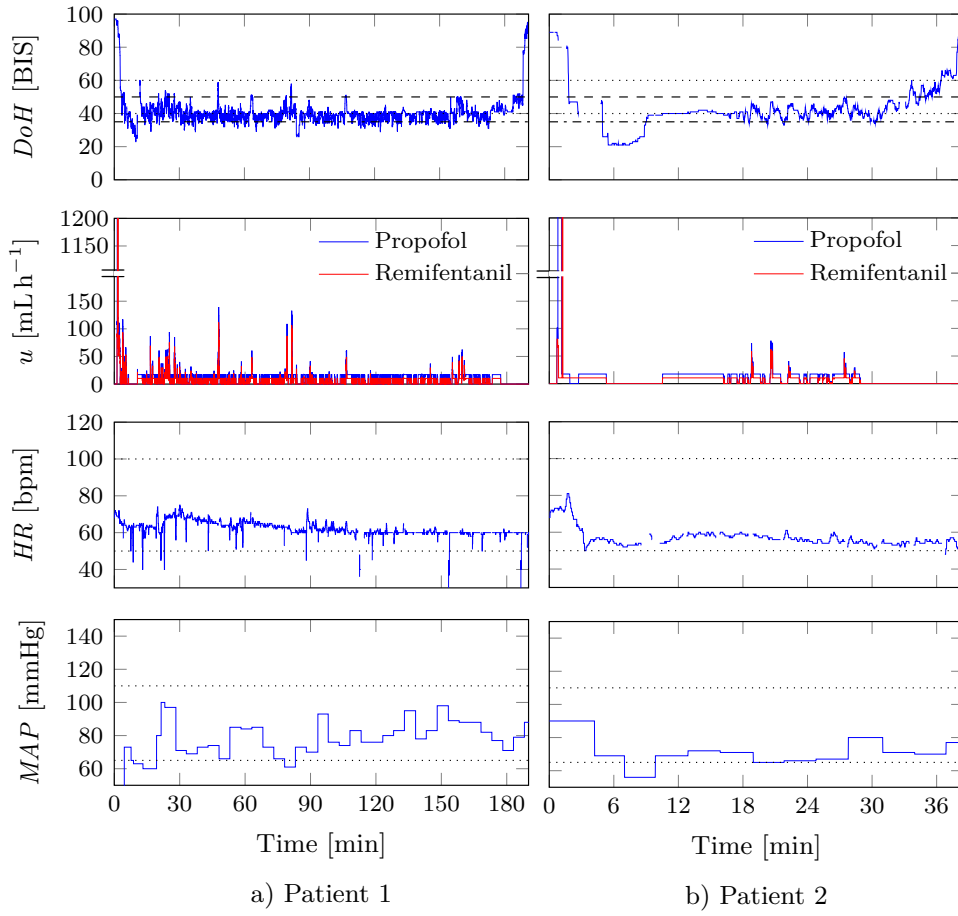
| Patient | Time<br>[min] | BIS 40–60<br>[%] | BIS < 40<br>[%] | BIS > 60<br>[%] | Propofol<br>[mg kg <sup>-1</sup> h <sup>-1</sup> ] | Remifentanyl<br>[μg kg <sup>-1</sup> min <sup>-1</sup> ] | Awakening<br>[min] |
|---------|---------------|------------------|-----------------|-----------------|----------------------------------------------------|----------------------------------------------------------|--------------------|
| 1       | 174.45        | 52.44            | 47.56           | 0               | 3.80                                               | 0.10                                                     | 12.01              |
| 2       | 27.12         | 60.03            | 39.97           | 0               | 4.06                                               | 0.11                                                     | 9.55               |
| 3       | 146.02        | 81.99            | 17.33           | 0.68            | 6.54                                               | 0.19                                                     | 10.58              |
| 4       | 239.58        | 55.73            | 44.05           | 0.22            | 5.71                                               | 0.17                                                     | 8.83               |
| 5       | 68.55         | 59.36            | 39.73           | 0.91            | 5.36                                               | 0.15                                                     | 17.80              |
| 6       | 111.75        | 55.71            | 43.96           | 0.33            | 5.27                                               | 0.14                                                     | 10.38              |
| 7       | 272.15        | 74.88            | 24.81           | 0.32            | 5.03                                               | 0.12                                                     | 5.33               |
| 8       | 235.55        | 51.31            | 48.69           | 0               | 4.28                                               | 0.12                                                     | 12.37              |
| 9       | 228.28        | 42.63            | 54.04           | 3.34            | 4.88                                               | 0.14                                                     | 6.85               |
| 10      | 146.97        | 72.55            | 26.89           | 0.57            | 4.93                                               | 0.12                                                     | 8.97               |
| Average | 165.04        | 60.66            | 44.10           | 0.64            | 4.99                                               | 0.14                                                     | 10.27              |

**Table 6:** Maintenance phase statistics with different BIS range and thresholds. The BIS % is computed over the whole maintenance phase duration.

| Patient | BIS 35–55 [%] | BIS < 35 [%] | BIS > 55 [%] |
|---------|---------------|--------------|--------------|
| 1       | 89.96         | 9.71         | 0.33         |
| 2       | 82.63         | 17.37        | 0            |
| 3       | 91.07         | 4.74         | 4.19         |
| 4       | 82.70         | 15.17        | 2.13         |
| 5       | 73.67         | 24.49        | 1.84         |
| 6       | 81.89         | 14.80        | 3.31         |
| 7       | 92.99         | 5.37         | 1.63         |
| 8       | 83.64         | 16.11        | 0.25         |
| 9       | 81.60         | 14.50        | 3.89         |
| 10      | 91.36         | 7.30         | 1.34         |
| Average | 85.15         | 12.96        | 1.89         |

**Table 7:** Performance indices related to the maintenance phase. First column: median performance error (MDPE). Second column: median absolute performance error (MDAPE). Third column: WOBBLE. Computation method can be found in (Schiavo et al., 2021).

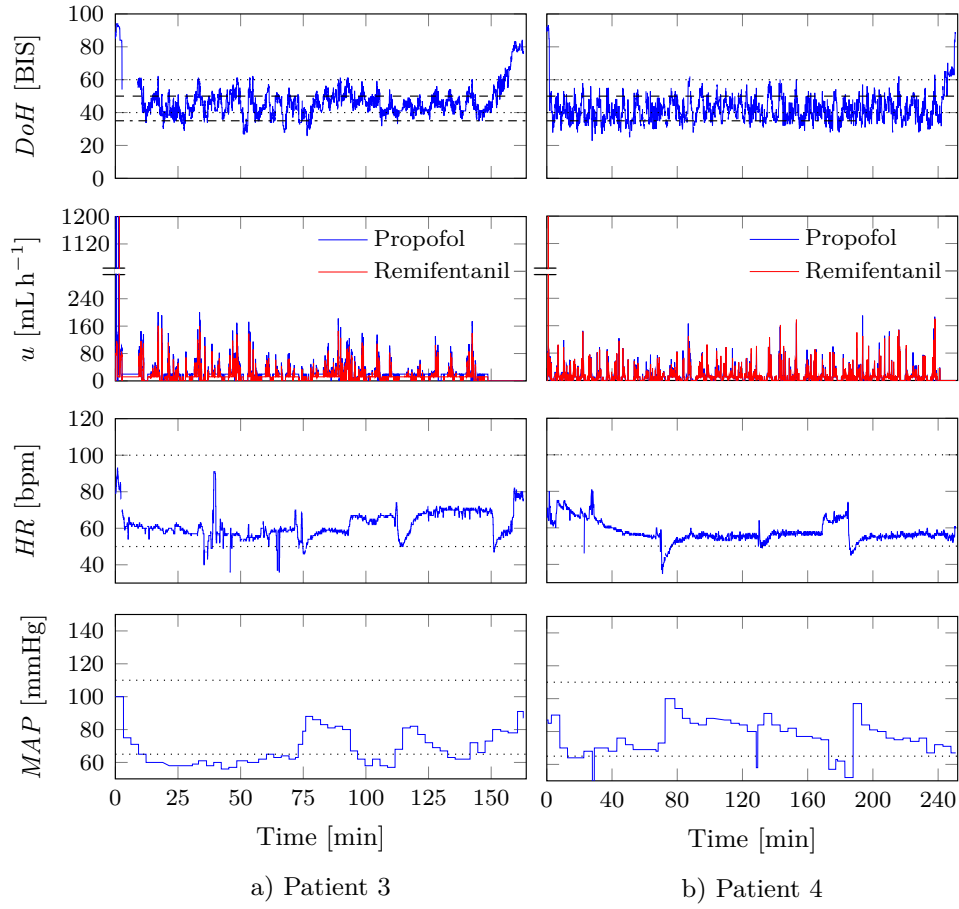
| Patient | MDPE [%] | MDAPE [%] | WOBBLE [%] |
|---------|----------|-----------|------------|
| 1       | -20      | 20        | 4          |
| 2       | -20      | 20        | 4          |
| 3       | -10      | 12        | 8          |
| 4       | -18      | 18        | 10         |
| 5       | -18      | 18        | 10         |
| 6       | -20      | 20        | 8          |
| 7       | -16      | 16        | 6          |
| 8       | -20      | 20        | 8          |
| 9       | -22      | 22        | 4          |
| 10      | -18      | 18        | 6          |
| Average | -18.2    | 18.4      | 6.8        |



**Figure 3:** Clinical results of patient 1 and 2.

coadministration of propofol and remifentanyl. For each patient the FOPID controller successfully maintained the target DoH levels within a clinically acceptable range throughout the surgical procedure. Furthermore, the FOPID demonstrated the ability to manage both the induction and maintenance phases without the need for anesthesiologists to intervene, although the BIS level was slightly below the 40 BIS lower threshold for extended periods.

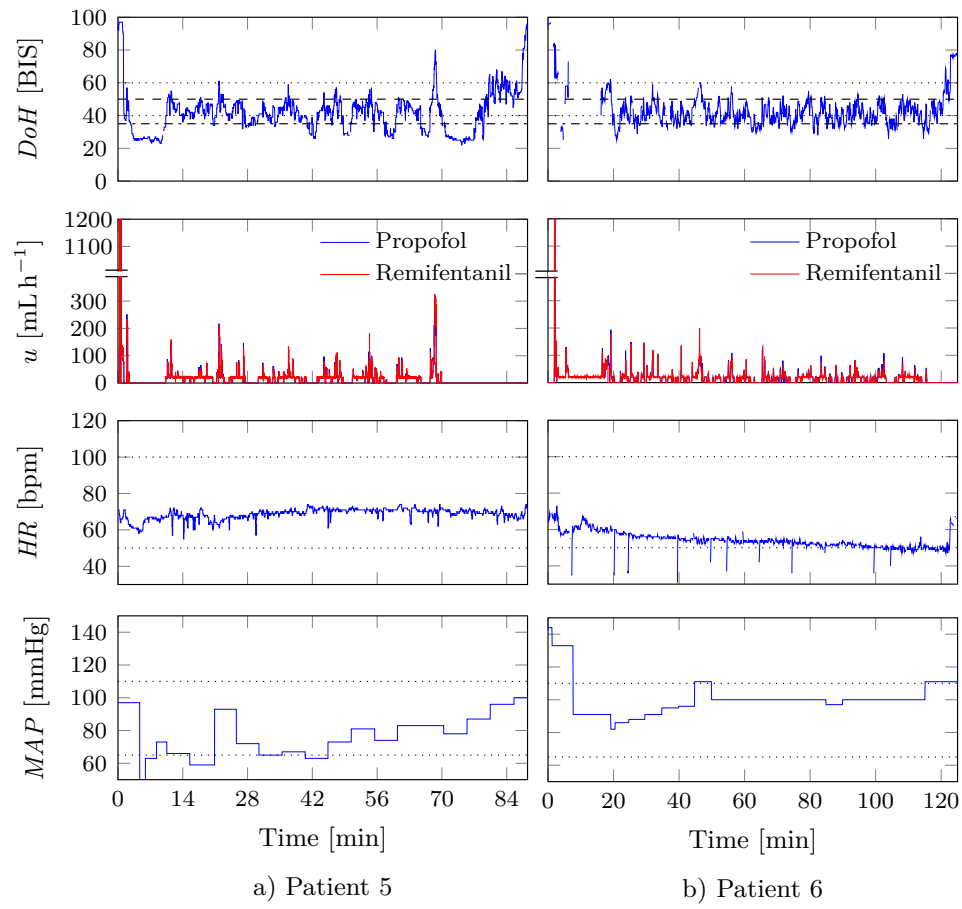
The controller also provided satisfactory hemodynamic stability, with heart rate and mean arterial pressure remaining within the recommended limits for all patients, thus suggesting that overdosing episodes did not occur. The successful application of the FOPID controller in a clinical setting shows that fractional-order controllers is a viable alternative to PID controllers when flexibility and robustness are needed. The designing flexibility that FOPID regulators offer allows the designer to set tighter specifications, thereby increasing robustness, thus preventing the occurrence of excessive undershoot episodes, without affecting closed-loop bandwidth. Moreover, the non-integer derivative term ensures the prevention of light-anesthesia episodes by rapidly and aggressively reacting to BIS rising. Compared with PID-based solutions previously proposed in the literature (Schiavo et al., 2023, 2020), the FOPID controller is more aggressive, as, during the maintenance phase, it reacts more quickly to BIS rising, avoiding intra-operative awareness. Indeed, the fractional



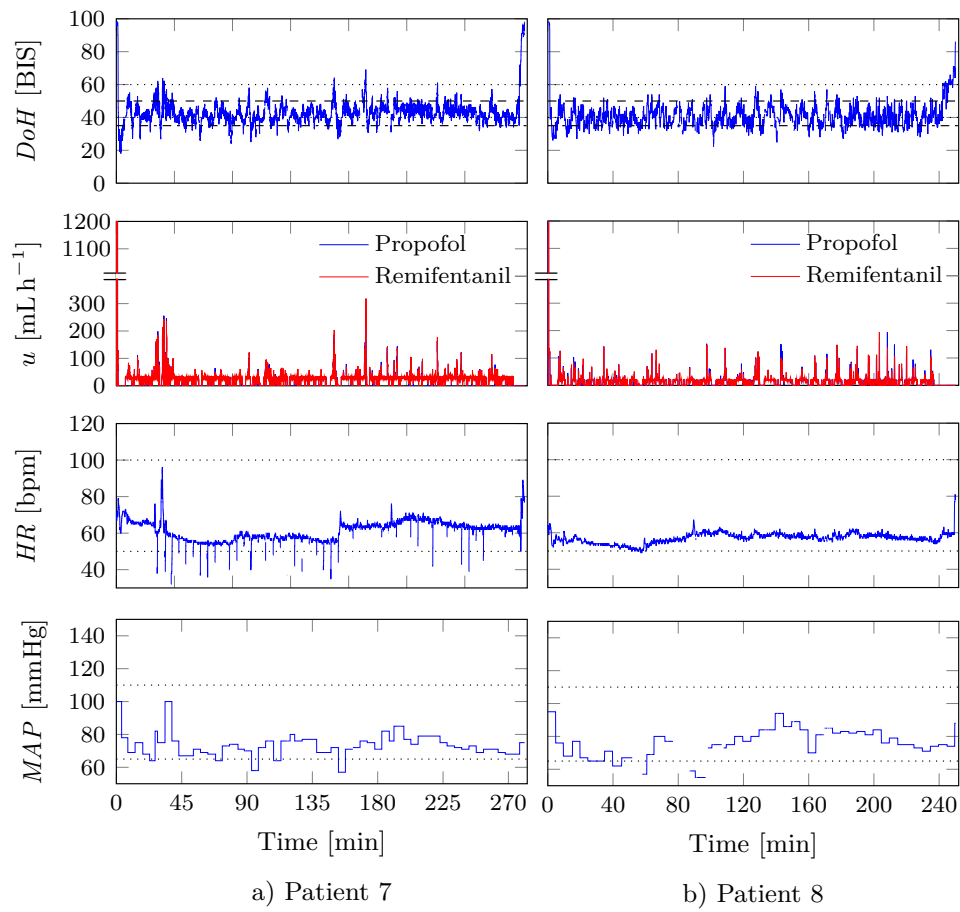
**Figure 4:** Clinical results of patient 3 and 4.

controller reduces the time intervals when the BIS is greater than 60 from about 2% to 0.64%, although it also keeps the BIS in the range 40-60 for about 60% of the time, while the corresponding value with the previously developed PID-based solutions is close to 75%.

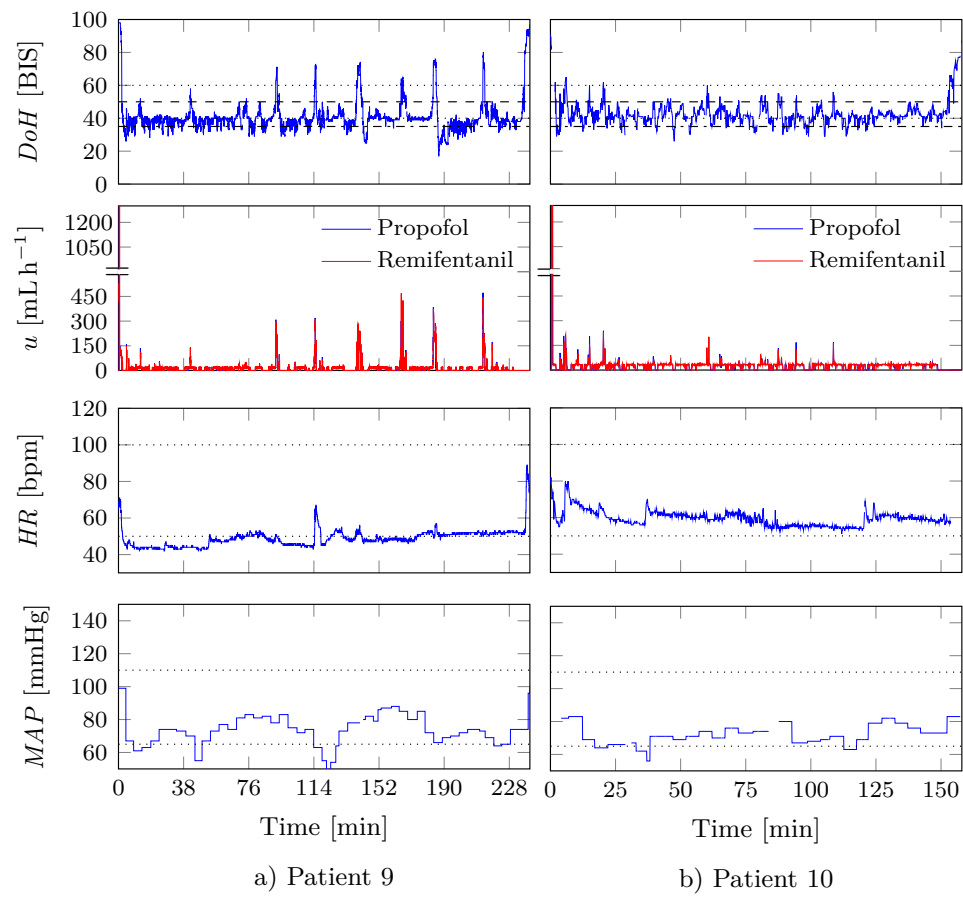
In summary, the study demonstrates that a FOPID-based closed-loop anesthesia system could be a promising and effective tool for controlling the depth of hypnosis and maintaining hemodynamic stability during surgical procedures, strongly preventing intra-operative awareness during the maintenance phase of anesthesia. Future research will explore the application of this control method in a broader range of surgical contexts and with larger cohort of patient to further validate its efficacy and reliability.



**Figure 5:** Clinical results of patient 5 and 6.



**Figure 6:** Clinical results of patient 7 and 8.



**Figure 7:** Clinical results of patient 9 and 10.

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# Paper IX

## Adjusting Aggressiveness of Depth-of-Hypnosis PID Control by MPC-based Feedforward

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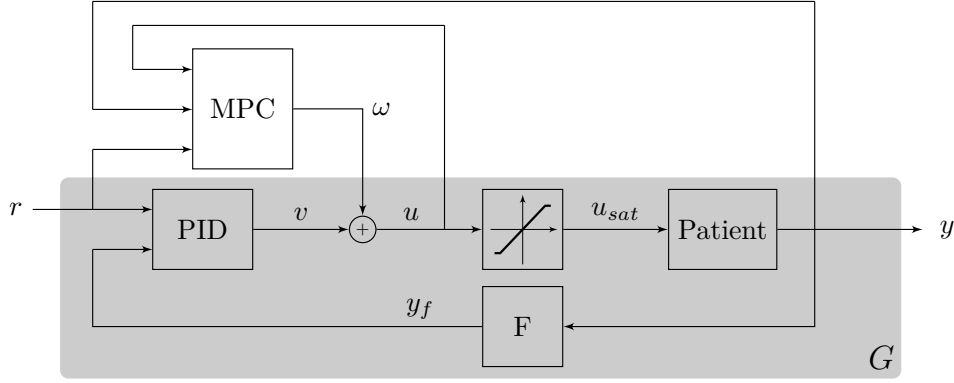
### Abstract

In this paper we propose a technique to enhance the performance of a Proportional-Integral-Derivative (PID)-based control structure for Depth-of-Hypnosis control in total intravenous anesthesia when set-point changes are required during the maintenance phase. In particular, the PID controller, tuned for disturbance rejection, is integrated with a feedforward action based on Model Predictive Control (MPC). A tuning parameter determines the aggressiveness of the controller, thus allowing the anesthesiologist to select the most appropriate transient response depending on the kind of patient and of surgery. Simulation results show that the method is useful in providing an effective tool for the anesthesiologist to interact with the control system.

Originally published in Proceedings of American Control Conference 2025. The original version is available at ACC63710.2025.11108074.

## 1 Introduction

In the clinical practice of total intravenous anesthesia (TIVA) one of the main tasks that the anesthesiologist must carry out consists of regulating the administration of the hypnotic drug propofol to establish a suitable Depth-of-Hypnosis (DoH) in the patient. This is of primary importance since too shallow DoH could result in episodes of intraoperative awareness. Conversely, too deep DoH, which is caused by propofol overdose, could provoke drug-induced side-effects. To titrate propofol, the anesthesiologist relies on the Bispectral Index (BIS) (Rampil, 1998), a processed electroencephalogram index that quantifies DoH by providing a number ranging from 0 (absence of cortical activity) to 100 (fully awake patient). The anesthesia process is divided into two main phases. The first one is anesthesia induction. Here, the task that the anesthesiologist must accomplish consists of administering propofol to quickly drive the BIS from a value close to 100 to a value close to 50 (usually, from 40 to 60), while avoiding undershoots (BIS values below 30). The second one is anesthesia maintenance. Here, the anesthesiologist must titrate propofol to maintain the BIS as close as possible to the target value despite the presence of disturbances caused by the surgical stimulation. In this phase, the BIS target value is usually fixed to 50, but different values (usually in the range from 40 to 60) could be desired for specific phases of the surgical procedure. Closed-loop control of TIVA has attracted significant research attention over the past two decades (Ghita et al., 2020). Indeed, DoH regulation is only one part of the anesthesiologist workload, which is quite demanding and thus prone to human errors due to tiredness. In this context, feedback control can enhance treatment accuracy, improve patient safety, and reduce the workload of clinicians (Zaouter et al., 2020). However, it is worth noting that this technology aims to complement, rather than replace, anesthesiologists. So, taking into account the presence of the anesthesiologist-in-the-loop (Ionescu et al., 2017) is of primary importance for the design of these systems as they must be easily comprehensible by a clinician while being robust to the presence of a human possibly acting within the loop. Over the years, noteworthy clinical results have been obtained with approaches based on classic Proportional-Integral-Derivative (PID) controllers (Liu et al., 2006; Puri et al., 2007; van Heusden et al., 2019; Schiavo et al., 2021) thanks to their simplicity and robustness in clinical applications. Model Predictive Control (MPC) emerges as a promising alternative in order to increase the control system performance thanks to its ability to anticipate the future behavior of the system. Nevertheless, the practical application of MPC in closed-loop anesthesia has been relatively limited. Pioneering studies (Sawaguchi et al., 2008; Neckebroek et al., 2019; Pawlowski et al., 2023; Hosseinzadeh et al., 2020; Aubouin-Pairault et al., 2024) have shown that while MPC holds potential, its performance is hindered by discrepancies between the model and the real response of the patient to drug administration. For this reason, replacing the functioning PID-based control system altogether with an MPC at once can be seen as a risky step from a clinical point of view and the anesthesiologist, who has to interact with the control system, could not accept it. In light of these considerations, in this paper we propose the application



**Figure 1:** Block diagram of the control scheme. The gray area is an already available closed-loop system  $G$ , which is integrated with the MPC block.

of a novel control approach, originally proposed in (Norlund et al., 2024), that combines the strengths of both PID and MPC controllers. In particular, the PID controller, tuned for disturbance rejection, is enhanced with a feedforward action based on the MPC when set-point changes are required during the maintenance phase of anesthesia. This way, thanks to the MPC, it will be possible to personalize the control system behavior, according to the patient's needs and the phase of surgery, without performing a new PID tuning. To this end, a tuning parameter allows the anesthesiologist to adjust the aggressiveness of the control system. This method provides a flexible and adaptive approach to DoH control, enhancing both the performance and safety of closed-loop anesthesia systems.

## 2 Materials and Methods

We consider the case when, during the maintenance phase, the set-point value of the BIS has to be decreased as required by the surgical procedure. Since the increment of the BIS level can be easily achieved by stopping the propofol infusion for a given time interval, we did not consider this situation in the paper. The proposed control structure is shown in Fig. 1, where the propofol flow rate is the control variable  $u(t)$  obtained by adding the MPC-based feedforward term  $\omega(t)$  to the PID action  $v(t)$ , thus  $u(t) = v(t) + \omega(t)$ . The process variable  $y(t)$  is the patient's current BIS value and since it is noisy, it is filtered with a second order filter  $F$ . Thus, the control error  $e(t)$  is calculated as

$$e(t) = r(t) - y_f(t) \quad (1)$$

where  $r(t)$  is the BIS set-point value. The control variable  $u(t)$  is subject to saturation due to mechanical limitation of the surgical infusion pumps. Indeed, by taking into account commercially available pump (e.g. Graseby 3400, Smiths Medical, London, UK) that can operate at a minimum and maximum infusion rate of  $0 \text{ mL h}^{-1}$  and  $1200 \text{ mL h}^{-1}$ , respectively, and by considering a standard propofol concentration of  $20 \text{ mg mL}^{-1}$ , the propofol infusion rate  $u_{sat}(t)$  can range from  $0 \text{ mg s}^{-1}$  to  $6.67 \text{ mg s}^{-1}$ .

## 2.1 Patient model

The MPC block exploits a pharmacokinetic-pharmacodynamic (PK-PD) model of the patient dynamics (Schnider et al., 1998, 1999). In particular, a compartmental model is used and it is expressed in state-space form as

$$\dot{\mathbf{x}}(t) = A\mathbf{x}(t) + Bu(t), \quad (2a)$$

$$C_e(t) = C\mathbf{x}(t), \quad (2b)$$

where

$$A = \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \frac{k_{1e}}{V_1} & 0 & 0 & -k_{e0} \end{bmatrix}, \quad (3a)$$

$$B = \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}^\top, \quad (3b)$$

$$C = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix}. \quad (3c)$$

The first state component,  $x_1(t)$  [mg], represents the mass of propofol in the blood plasma, while the last,  $x_4(t) = C_e(t)$  [mg L<sup>-1</sup>], models the effect-site concentration, which, for DoH, is located in the cortex of the brain. The other state components,  $x_2(t)$  and  $x_3(t)$ , models drug distribution across fast (muscles) and slow (fat) tissue, respectively. The parameters  $k_{10}$ ,  $k_{12}$ ,  $k_{13}$ ,  $k_{21}$ ,  $k_{31}$ ,  $k_{e0}$ , and  $k_{1e}$ , in units of s<sup>-1</sup>, are exchange rate constants, and  $V_1$  [L] represents the plasma volume.

The relationship between the effect-site drug concentration and the hypnotic effect is modeled using a sigmoid nonlinear function, namely the Hill function

$$y(C_e) = E_0 - E_{\max} \left( \frac{C_e^\gamma}{C_e^\gamma + C_{e50}^\gamma} \right). \quad (4)$$

The baseline *DoH* level in absence of drug is  $E_0 \lesssim 100$  BIS, and the maximum achievable hypnotic depth is  $E_{\max} \lesssim 100$  BIS. The effect-site concentration  $C_{e50}$  [mg L<sup>-1</sup>] is the concentration that produces an hypnotic level which is exactly half of the maximum achievable effect defined by  $E_{\max}$  (that is,  $E_0 - E_{\max}/2$ ). The third parameter of Eq. (4),  $\gamma$ , is a unitless shape parameter that defines the slope of the curve. For the sake of simplicity, a linear MPC algorithm is used and therefore the Hill function (Eq. (4)), has been linearized around the BIS value of 50. The corresponding gain is calculated as

$$K_{hill} = -E_{\max} \left[ \frac{\gamma C_{eref}^{\gamma-1} C_{e50}^\gamma}{(C_{eref}^\gamma + C_{e50}^\gamma)^2} \right], \quad (5)$$

where  $C_{eref}$  is the patient's effect-site drug concentration value that produces a BIS equal to 50, and it is computed by inverting Eq. (4):

$$C_{eref} = C_{e50} \left( \frac{E_{\max}}{E_0 - 50} - 1 \right)^{-1/\gamma}. \quad (6)$$

The values of the parameters of the linear part of the model can be determined from the demographics of each patient (gender, height, weight, age). On the other hand, the values of the parameter of the Hill function are unknown and the ‘‘average’’ values reported in (Vanluchene et al., 2004) have to be used, thus introducing a significant uncertainty in the model employed in the controller.

## 2.2 PID Controller

The PID controller is implemented in standard ideal form (Visioli, 2006). Therefore, by considering the state vector

$$\mathbf{x}_c(t) = \left[ \int_0^t (r(\tau) - y_f(\tau)) d\tau \quad y_f(t) \quad \dot{y}_f(t) \right]^\top \quad (7)$$

the controller state-space formulation is

$$\dot{\mathbf{x}}_c(t) = A_c \mathbf{x}_c(t) + B_{cr} r(t) + B_{cy} y(t), \quad (8a)$$

$$v(t) = C_c \mathbf{x}_c(t) + D_{cr} r(t) + D_{cy} y(t), \quad (8b)$$

where

$$A_c = \begin{bmatrix} 0 & -1 & 0 \\ 0 & 0 & 1 \\ 0 & -\frac{1}{T_f^2} & -\frac{2}{T_f} \end{bmatrix}, \quad (9a)$$

$$B_{cr} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}^\top, \quad (9b)$$

$$B_{cy} = \begin{bmatrix} 0 & 0 & \frac{1}{T_f^2} \end{bmatrix}^\top, \quad (9c)$$

$$C_c = \begin{bmatrix} -\frac{K_p}{T_i} & K_p & K_p T_d \end{bmatrix}, \quad (9d)$$

$$D_{cr} = -K_p, \quad (9e)$$

$$D_{cy} = 0. \quad (9f)$$

Here,  $K_p$  is the proportional gain while  $T_i$ ,  $T_d$  and  $T_f$  are the integral, derivative and filter time constants, respectively. As already mentioned, the tuning parameters (shown in Table 1) have been selected in order to minimize the worst-case integrated absolute error (IAE) for a set of patients that are representative of a wide population (Ionescu et al.,

| $K_p$ [mg/BIS/s] | $T_i$ [s] | $T_d$ [s] | $T_f$ [s] |
|------------------|-----------|-----------|-----------|
| 0.4446           | 1250.7326 | 20.3660   | 0.7204    |

**Table 1:** PID parameters taken from (Padula et al., 2017)

2008).

### 2.3 MPC Controller

A linear MPC has been designed, using the Matlab MPC toolbox, to provide a control action  $\omega(t)$  that is added to the control signal  $v(t)$  produced by the PID controller. To achieve this, the MPC has been designed for the closed-loop system  $G$ , highlighted with a gray box in Fig. 1. Note that  $G$  has been designed in order to have two inputs ( $r(t)$  and  $\omega(t)$ ) and two outputs ( $u(t)$  and  $y(t)$ ).

To derive the linear formulation of the closed-loop system  $G$ , it is necessary to write the linear model of the patient in state-space form. Thus, by rearranging Eq. (3c) together with Eq. (5), the patient's linear state-space model can be written as

$$\dot{\mathbf{x}}_p(t) = A_p \mathbf{x}_p(t) + B_p u(t), \quad (10a)$$

$$y(t) = C_p \mathbf{x}_p(t) + D_p u(t), \quad (10b)$$

where

$$A_p = A, \quad B_p = B, \quad (11a)$$

$$C_p = K_{hill} C, \quad D_p = 0. \quad (11b)$$

Therefore, by considering the state vector

$$\mathbf{x}_G = \begin{bmatrix} \mathbf{x}_p & \mathbf{x}_c \end{bmatrix}^\top \quad (12)$$

the linear system  $G$  can be written in state-space form as

$$G := \begin{cases} \dot{\mathbf{x}}_G(t) = A_G \mathbf{x}_G(t) + B_{Gr} r(t) + B_{Gw} \omega(t) \\ y(t) = C_{G1} \mathbf{x}_G(t) + D_{Gr1} r(t) + D_{Gw1} \omega(t) \\ u(t) = C_{G2} \mathbf{x}_G(t) + D_{Gr2} r(t) + D_{Gw2} \omega(t) \end{cases} \quad (13)$$

where

$$A_G = \begin{bmatrix} A_p + B_p E_p D_{cy} C_p & B_p E_p C_c \\ B_{cy} E_c C_p & A_c + B_{cy} E_c D_p C_c \end{bmatrix}, \quad (14a)$$

$$B_{Gr} = \begin{bmatrix} B_p E_p D_{cr} & B_{cr} + B_{cy} E_c D_p D_{cr} \end{bmatrix}^\top, \quad (14b)$$

$$B_{Gw} = \begin{bmatrix} B_p(I + E_p D_{cy} D_p) & B_{cy} E_c D_p \end{bmatrix}^\top, \quad (14c)$$

$$C_G = \begin{bmatrix} C_{G1} \\ C_{G2} \end{bmatrix} = \begin{bmatrix} E_c C_p & E_c D_p C_c \\ E_p D_{cy} C_p & E_p C_c \end{bmatrix}, \quad (14d)$$

$$D_{Gr} = \begin{bmatrix} D_{Gr1} \\ D_{Gr2} \end{bmatrix} = \begin{bmatrix} E_c D_p D_{cr} \\ E_p D_{cr} \end{bmatrix}, \quad (14e)$$

$$D_{Gw} = \begin{bmatrix} D_{Gw1} \\ D_{Gw2} \end{bmatrix} = \begin{bmatrix} E_c D_p \\ I + E_p D_{cy} D_p \end{bmatrix}. \quad (14f)$$

With this formulation the MPC solves a quadratic programming optimization problem to determine the control moves over a prediction horizon  $h$  of 150 s. The control horizon has been set to 50 s and the model discretisation has been performed by using the zero-order hold and a sampling time of 1 s. Moreover, the MPC uses a built-in Kalman filter to estimate the model states. Precisely, the cost function to be minimized is:

$$J(\alpha) = \int_0^h (1 - \alpha)(r(t + \tau) - y(t + \tau))^2 + \alpha \omega(t + \tau)^2 d\tau \quad (15)$$

with  $0 \leq \tau \leq h$ . In the latter, by adjusting the tuning parameter  $\alpha \in [0, 1]$ , it is possible to regulate the trade-off between penalizing the control error or the MPC action.

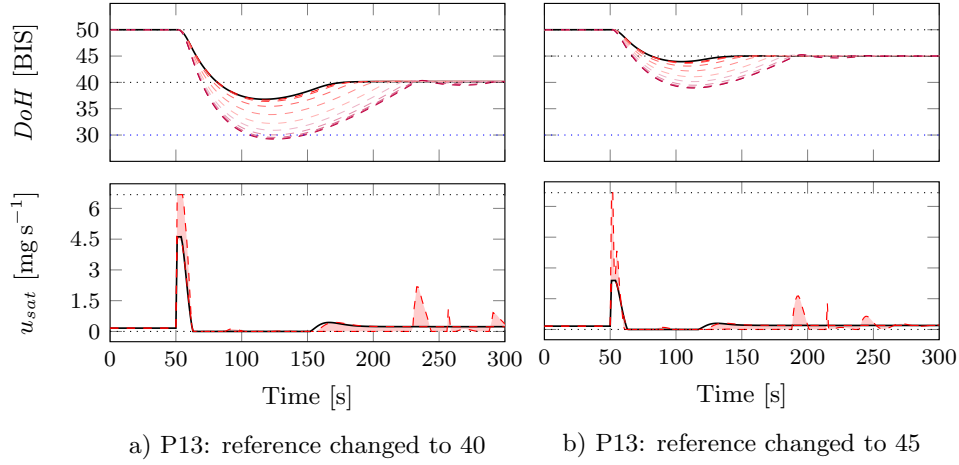
Furthermore, the optimization problem is subject to system dynamics and constraints on the value of the resulting  $u(t)$ . Thus the MPC output  $\omega(t)$  is determined by solving the following optimization problem

$$\min_w J(\alpha), \quad (16)$$

subject to

$$\begin{aligned} & G, \\ & 0 \leq u(t) \leq 6.67. \end{aligned} \quad (17)$$

The posed optimization problem implies that a value of  $\alpha$  equal to 1 produces a control signal that is the one derived from the nominal PID-based closed-loop scenario. On the contrary, a value of  $\alpha$  equal to 0 overrides the PID by providing a control action primarily based on the MPC. In other words, it is possible to smoothly add the MPC to the PID, where the performance of the PID is fixed while the MPC can boost the control signal when required. Therefore, the anesthesiologist, by selecting the desired value of  $\alpha$  can smoothly adapt the controller aggressiveness when reference changes are requested by the surgical procedure.



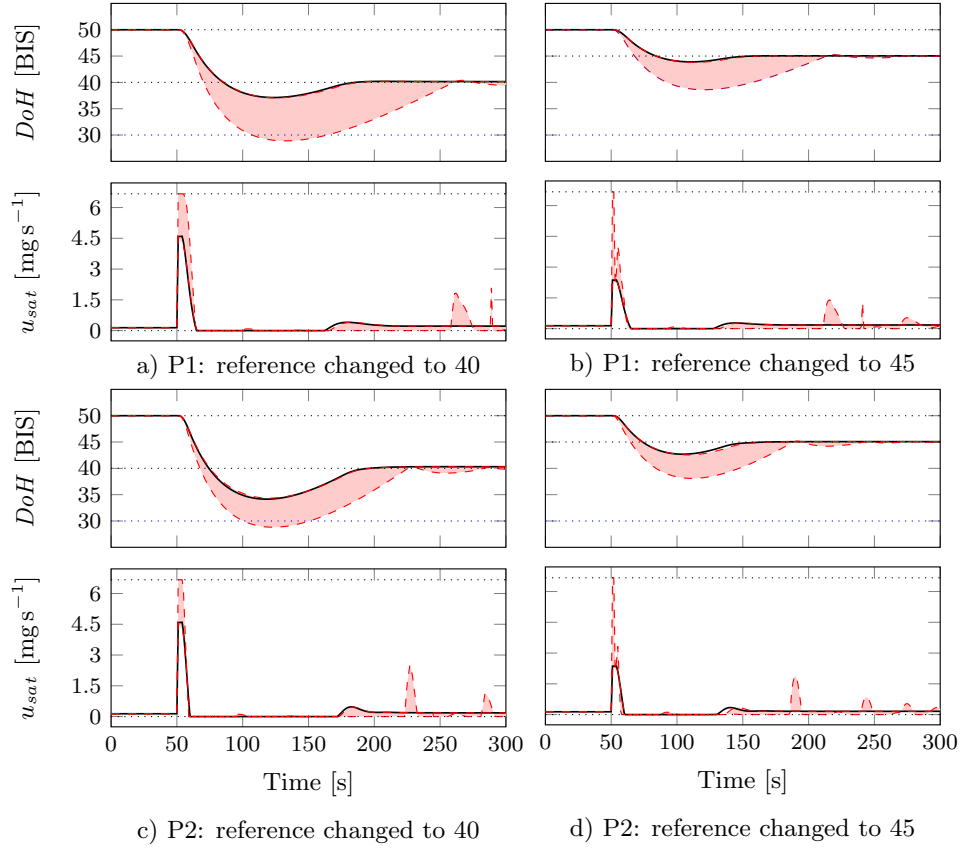
**Figure 2:** Results obtained for patient 13. Top: DoH level. Black solid line: DoH level obtained by PID only ( $\alpha=1$ ). Red dashed lines: DoH level obtained by PID and MPC with  $\alpha \in [0.9, 0]$  with a step of 0.1. Black dotted lines: Bis reference of 50, 45, and 40. Blue dotted line: safety limit of BIS = 30. Bottom: propofol infusion rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.

### 3 Results

To test the effectiveness of the proposed solution, several simulations have been performed, where the patient has been represented by using the nonlinear model described in Eqs. (3c) and (4). The thirteen patients of the dataset employed in (Ionescu et al., 2008) (where the thirteenth patient is created by calculating the average values of the parameters of the other twelve ones) have been considered since they are representative of a wide population, and the tuning parameter  $\alpha$  has been varied from 1 to 0 in steps of 0.1, thus simulating eleven scenarios for each patient. Additionally, two reference changes have been considered, namely  $r_1 = 45$  BIS and  $r_2 = 40$  BIS. As already mentioned, positive reference steps have not been considered as they would simply cause the controller to switch the control action off due to the speed transient being constrained by the lower pump's saturation limit.

As a first illustrative result we consider the thirteen patient and the set-point step responses are shown in Fig. 2, where each dashed line is related to a different value of  $\alpha$ . The use of the MPC-based feedforward action is compared with the use of the feedback PID controller only. As expected, the control system has a monotonic behaviour, that is, by decreasing  $\alpha$  the aggressiveness is increased. In the most aggressive scenario, represented by the lower red dashed line, the response reaches the safety limit of BIS = 30. However, this undershoot episode does not pose any harm to the patient since this low level is maintained for only a brief period.

The results related to the other twelve patients are shown, two-by-two, in Fig. 3-Fig. 8. They confirm that the presence of the feedforward action provides the required flexibility to the anesthesiologist, as indicated by the shaded red area. Indeed, by adjusting the value



**Figure 3:** Results related to patients 1 (top) and 2 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.

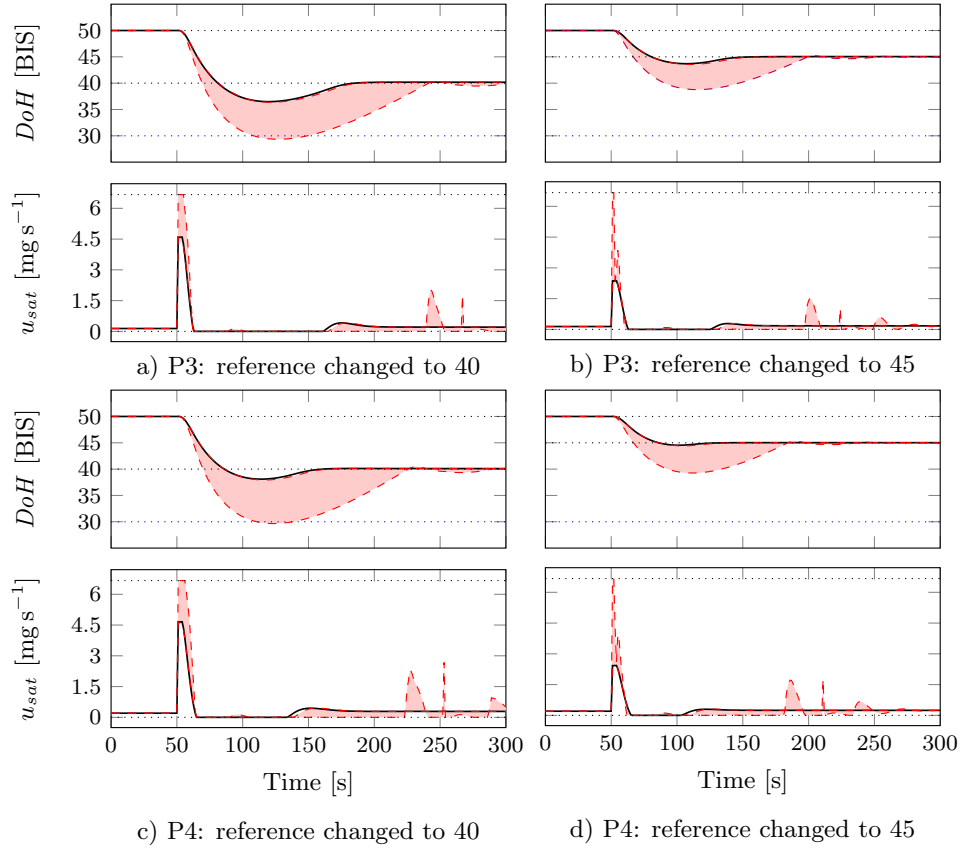
of  $\alpha$ , it is possible to increase the speed of response in attaining the new set-point when the reference value of BIS = 50 is not the most appropriate.

It is worth stressing that the system also guarantees the required robustness, as the uncertainty in the Hill function parameters has been considered and the linearization employed for the MPC controller around the BIS value of 50 does not cause any significant decrement in the performance.

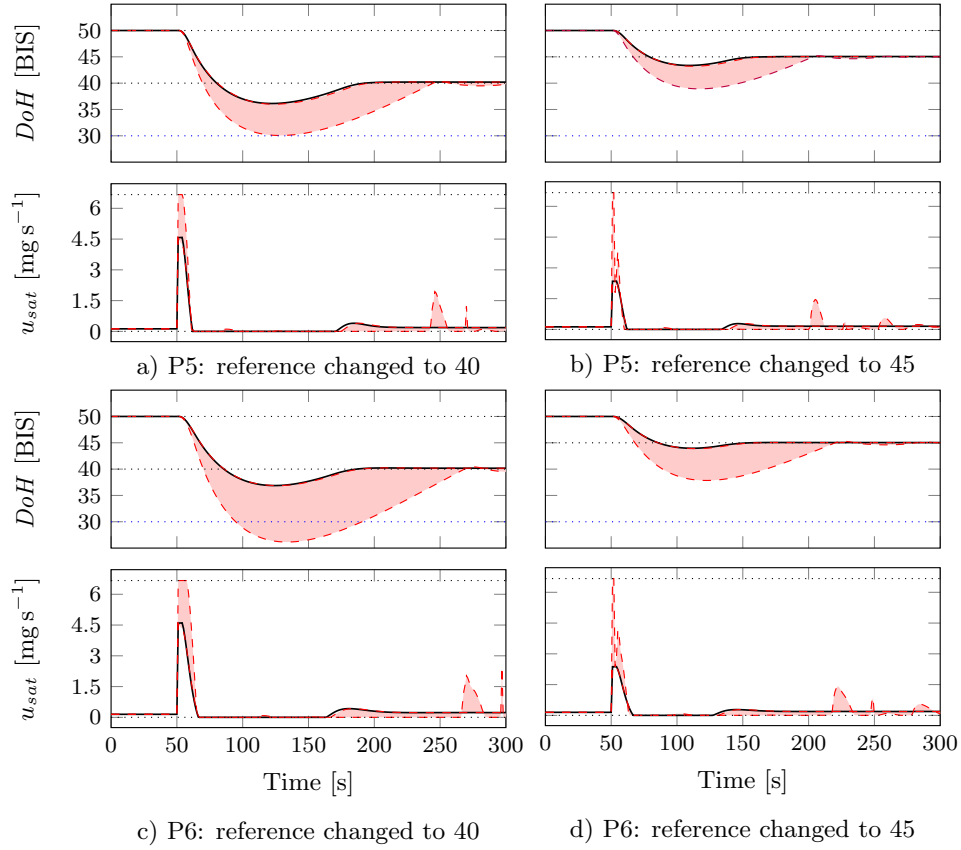
The parameter  $\alpha$  has a clear physical meaning, thus allowing the anesthesiologist to easily adapt the controller to the different requirements that can be present in the different surgeries and also in different situations in a single surgery.

## 4 Conclusions

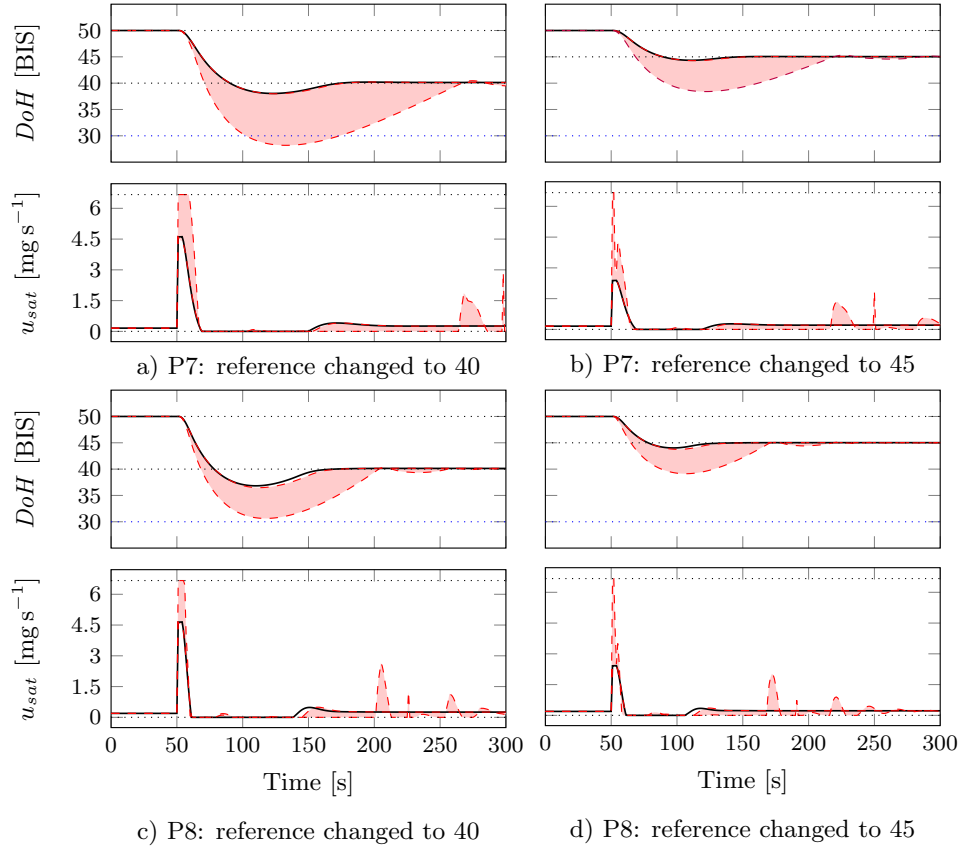
In this paper we have proposed a new approach to improve DoH control during total intravenous anesthesia. Set-point changes during the maintenance phase (in particular,



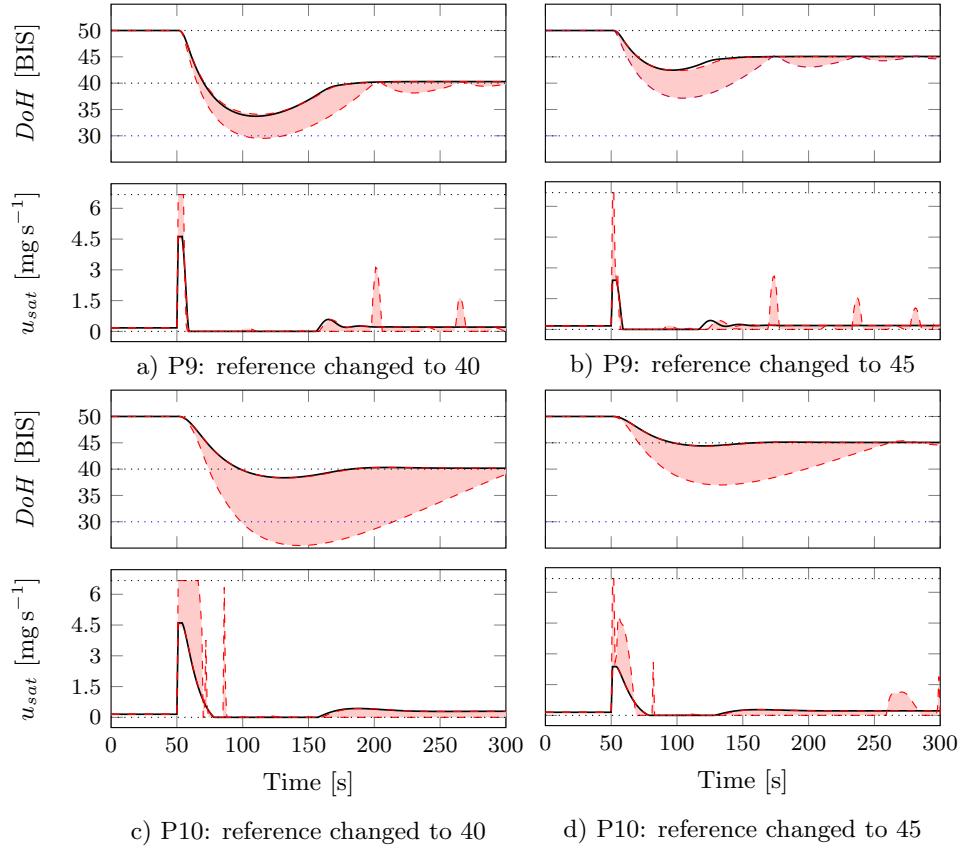
**Figure 4:** Results related to patients 3 (top) and 4 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0$ . Lower red dashed line: PID and MPC with  $\alpha = 0.9$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.



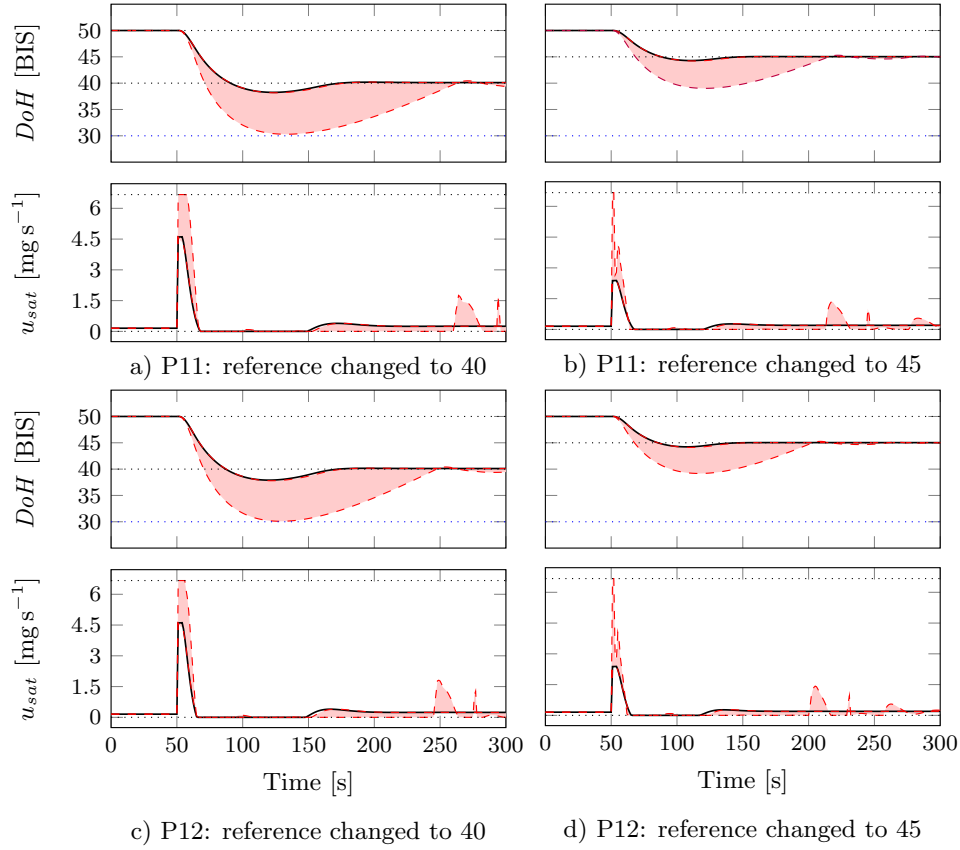
**Figure 5:** Results related to patients 5 (top) and 6 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0$ . Lower red dashed line: PID and MPC with  $\alpha = 0.9$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.



**Figure 6:** Results related to patients 7 (top) and 8 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0$ . Lower red dashed line: PID and MPC with  $\alpha = 0.9$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.



**Figure 7:** Results related to patients 9 (top) and 10 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0$ . Lower red dashed line: PID and MPC with  $\alpha = 0.9$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.



**Figure 8:** Results related to patients 11 (top) and 12 (bottom). Top subplot: DoH level. Black solid line: PID only ( $\alpha=1$ ). Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red dashed area: space of operation by changing  $\alpha$ . Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with  $\alpha = 0.9$ . Lower red dashed line: PID and MPC with  $\alpha = 0$ . Red shaded area: space of operation by changing  $\alpha$ . Left: reference change from 50 to 40. Right: reference change from 50 to 45.

those where the BIS value has to be lowered) are handled through the integration of an MPC controller with a pre-existing PID-based control system. The rationale of the method is to keep in place a satisfactory PID controller and to add the MPC controller to allow the anesthesiologist to select the required set-point step speed of response. A single parameter with a clear physical meaning can be adjusted for this purpose. Simulation results have demonstrated that the method is robust, allowing the system to be employed with different patients and for different requirements without the need of any retuning, thus being a very good candidate to be used in clinical practice, where the interaction of the control system with the anesthesiologist is of great concern.

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