

Comparative Analysis of Pharmacokinetic-Pharmacodynamic Models for Propofol and Remifentanil Using Model Predictive Control

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Abstract—This study aims to compare the effectiveness of different Pharmacokinetic-Pharmacodynamic (PK-PD) models for administering Propofol and Remifentanil, two critical agents in anesthesia. Initially, different PK models were introduced: one for Propofol based on the Schnider model and another for Remifentanil using the Minto model. Alternatively, both drugs were modeled using the Eleveld models. The PK-PD models were integrated into a closed-loop control system using model predictive control (MPC) with disturbances to control the Bispectral index (BIS) and the Richmond Agitation Sedation Scale (RASS). The methodology involved simulating the anesthetic agents in the open-source patient simulator (2 inputs, 2 outputs) with 12 patient datasets in a controlled environment to simulate the patient response variability, allowing for a detailed analysis of the model's performance in maintaining optimal drug concentrations. The primary focus was on the system's ability to adapt to surgical disturbances, a key challenge in anesthesia management, and whether a different modeling of drugs can have an impact on their effects. The results indicated significant differences in the performance of the two models configurations. The Eleveld model for Propofol showed less usage of drugs to maintain the desired BIS value. Concluding that this comparative analysis offers a valuable reference for selecting appropriate modeling approaches in the development of advanced control strategies in anesthesia.

Index Terms—MPC control; depth of hypnosis; intensive care, PK-PD model; closed-loop control of anesthesia .

This work was funded in part by the European Research Council (ERC) Consolidator Grant AMICAS, grant agreement No. 101043225. Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

Cristina I. Muresan is financed by a grant of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022 – 19, grant number 760018/27.01.2023. This work was in part supported by a grant of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022 – 18, grant number 760068/23.05.2023. I.R. Birs acknowledges the support of Flanders Research Foundation, Postdoc grant 1203224N and by a grant of the Romanian Ministry of Research, Innovation and Digitization, PN-III-P1-1.1-PD-2021-0204, within PNC DI III. D. Copot acknowledges the support of Flanders Research Foundation, Postdoc grant 12X6819N.

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I. INTRODUCTION

General anesthesia is a clinically induced state characterized by three main components: analgesia, hypnosis, and neuromuscular blockade. Optimal dosing of anesthetic drugs is critical for ensuring patient safety and optimizing surgical outcomes. Inadequate doses may lead to the undesirable occurrence of intraoperative awareness and patient distress, while excessive doses can result in life-threatening complications. The pharmacokinetic - pharmacodynamic (PK-PD) models play a vital role in this process, helping to predict how drugs are metabolized and exert their effects within the body. These models have led to advancements in understanding drug interactions and dose optimization to balance desired and undesired effects.

PK-PD models represent a cornerstone of closed-loop anesthesia control. These models describe how drugs are absorbed, distributed, metabolized, and eliminated within the human body and how these processes influence the drug's effect [1]. Various PK models have been developed for Propofol and Remifentanil precise dosing during anesthesia [2]. F. Linassi et al. [3] investigated the performance of the Schnider and Eleveld models for Propofol Target-Controlled Infusion anesthesia. Their study aimed to compare the effect of these models on the predicted effect-site concentrations at the loss of responsiveness during anesthesia maintenance and at the return of responsiveness. In their conclusion, the authors highlighted that the Schnider and Eleveld models had varying impacts on effect-site concentrations. D. J. Eleveld [4] performed simulations of Remifentanil Target-Controlled Infusion using three different PK models, Minto, Eleveld, and Kim [5]. Their research aimed to identify suitable target concentrations for Remifentanil administration across various patient groups. These studies showed that a good choice of patient's model could lead to a better estimation of the drug effect site concentration, which may lead to less drug infusion.

In addressing the challenge of precise anesthesia management [6], closed-loop control has emerged as a valuable tool. Indeed, its integration in this field marks a significant leap in the personalization of drug delivery, enhancing the precision of drug administration and allowing for real-time adjustments to maintain the desired anesthetic depth with the minimization of associated risks. The significance of closed-loop control in anesthesia lies in its ability to continuously monitor patient responses and dynamically adjust drug administration to maintain the desired depth of anesthesia. This

real-time feedback mechanism can significantly improve the quality of patient care, reduce the risk of adverse events, and enhance overall surgical outcomes [7]. Closed-loop anesthesia has exhibited superior performance compared to manually administered drug infusions concerning the duration of maintaining appropriate anesthesia levels [8], and has demonstrated the capacity to reduce post-anesthesia recovery times [9]. Clinical trials have extensively assessed closed-loop intravenous anesthesia in hundreds of cases [10], [11], [12]. Various approaches have been proposed to enhance robustness and safety analysis, including the application of methods such as fuzzy PID [13], adaptive model predictive control (MPC) [14], robust predictive control [15], and adaptive predictive control [16].

This study aims to compare two different approaches of PK models on the regulation of Propofol and Remifentanyl to maintain depth of unconsciousness and the absence of nociception. The first approach under investigation is traditional and based on clinical practice, which is the Schnider and Minto PK models for Propofol and Remifentanyl, respectively. The second is more recent and versatile which is the Eleveld PK model for both drugs. These models will then be integrated into a closed-loop control using the MPC. This comparative analysis underlines the importance of carefully dosing the drugs to achieve the desired anesthetic depth while monitoring parameters like the Bispectral Index (BIS) and the Richmond Agitation Sedation Scale (RASS) for optimal patient safety, underscoring the critical role of model selection in the precision and safety of anesthesia drug delivery systems.

This paper is organized as follows: Section 2 introduces the PK-PD models used for this study with an overview of the three different PK models used. Section 3 explains the Extended Predictive Self-Adaptive Control (EPSAC) that will be used to regulate the administration of Propofol and Remifentanyl, which induce hypnosis and analgesia respectively. We explore the application of this control approach on two distinct two-by-two patient simulators. Section 4 presents the simulation, results, and discussion, along with the limitations of the study. A conclusion section summarizes the results of the paper and proposes further developments.

II. MATERIALS AND METHODS

Pharmacokinetics is the movement of drugs through the body, whereas pharmacodynamics is the body's biological response to drugs. In this study, two states are discussed: Hypnosis (depth of unconsciousness) and analgesia (absence of nociception) [7]. The PK model for Propofol and Remifentanyl, the drugs that induce the previous states, can be represented by a general three-compartment model as follows: blood, muscles, and fat, as represented in Fig 1. In many cases, simply modeling the response based on systemic concentrations in the PK model is insufficient. This issue arises particularly when there is a delay between the peak effect and the peak concentration [17]. To manage this numerically, it is effective to incorporate an additional compartment in the model that represents the tissue near the

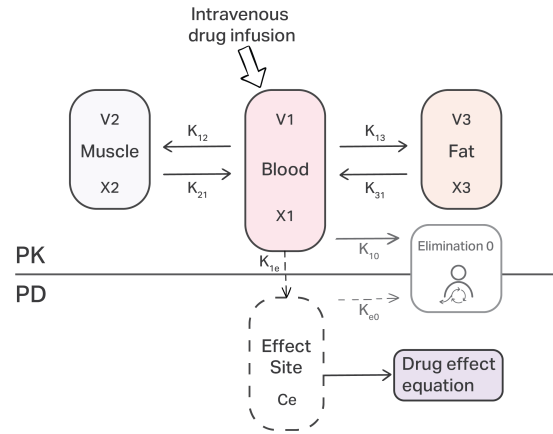


Fig. 1. Three-compartmental scheme of the pharmacokinetic model

cell, known as the effect site compartment C_e , which is the linear part of the PD model.

In general, the linear part of PK-PD model is represented by the state-space representation (1):

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

where states x_i , $i = (1, 2, 3, t)$, represent the concentration in the volume of compartments. The input $u(t)$, in $[mg/s]$ for Propofol and $[\mu g/s]$ for Remifentanyl, denotes the drug infusion rate. The output $y(t) = C_e(t)$, in $[mg/s]$ for Propofol and $[\mu g/s]$ for Remifentanyl, is the effect-site concentration and $k_{ij}[1/s]$, $i \neq j$, are the constants that represent the drug transfer rate from the i^{th} compartment to the j^{th} compartment.

In the first study case, the drug transfer rate coefficients k_{ij} are calculated using the Schnider model [18] for Propofol, and the Minto model [19] for Remifentanyl. In the second investigation, the Eleveld model is more complex and has a comprehensive structure. It incorporates compartments model for pharmacokinetics, which represents the absorption, distribution, metabolism, and excretion of these drugs within the body. The equations used to calculate the PK-PD model for Propofol are found in [1], and for Remifentanyl in [4]. The effect site concentration, which is the output of the PK-PD model is used as an input to calculate the nonlinear part of the PD model, which represents the drug effect measured using indexes: RASS for analgesia and BIS for hypnotics. The concentration site of Remifentanyl has a direct and independent relation to RASS and is calculated with:

$$RASS = \frac{1}{k_1 C_{er} + k_0} \cdot \frac{-2}{s + 2} \quad (2)$$

with $k_1 = k_0 = 0.81$ and C_{er} is the effect site concentration of Remifentanil.

Remifentanil in combination with Propofol have a synergic effect on the BIS. It is represented by the surface model which is a static nonlinear surface [20]:

$$BIS = E_0 - E_{max} \cdot \left(\frac{\left(\frac{C_{er}}{C_{50r}} + \frac{C_{ep}}{C_{50p}} + \sigma \frac{C_{er}C_{ep}}{C_{50r}C_{50p}} \right)^\gamma}{1 + \left(\frac{C_{er}}{C_{50r}} + \frac{C_{ep}}{C_{50p}} + \sigma \frac{C_{er}C_{ep}}{C_{50r}C_{50p}} \right)^\gamma} \right) \quad (3)$$

where E_0 is baseline effect, E_{max} is maximum possible effect, C_{r50} and C_{p50} are the concentration at half effect (50%), C_{er} and C_{ep} are the effect site concentration of Remifentanil and Propofol respectively, γ describes the steepness of the dose-response curve, and σ is the degree of synergy between the drugs.

In order to investigate the interpatient variability, Table I [21], which gives the biometric and drug effect values for a set of representative dataset of patients, is used.

III. CONTROL STRATEGY

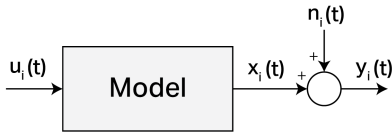


Fig. 2. Simple representation of the process model

This section briefly summarizes the extension of the EPSAC predictive control. The analysis of the method is described considering the case of a 2 inputs and 2 outputs process in Fig 2:

$$y_i(t) = x_i(t) + n_i(t), \quad i = 1, 2 \quad (4)$$

where $y_i(t)$ is (measured) process outputs, $u_j(t)$ is process inputs, $x_i(t)$ is PK-PD model outputs, and $n_i(t)$ is the unmodelled dynamics, noise and disturbance.

The prediction of the process outputs are calculated with:

$$y_i(t+k|t) = x_i(t+k|t) + n_i(t+k|t), \quad i = 1, 2 \quad (5)$$

for $k = N_{1i}, \dots, N_{2i}$ where N_{1i} and N_{2i} are the minimum and the maximum prediction horizons for each i -output of the process. Our problem resides now on finding $x_i(t+k|t)$ and $n_i(t+k|t)$. The first multi-step prediction problem is solved by recursion of the process models, while the second is solved using filtering techniques on the noise model. A detailed description is given in [22]. The future response of the process is considered to be the result of two effects:

$$y_i(t+k|t) = y_{ibase}(t+k|t) + y_{iopt}(t+k|t), \quad i = 1, 2 \quad (6)$$

where $y_{ibase}(t+k|t)$ is the effect of past controls and the basic future control scenario, called $u_{jbase}(t+k|t)$, for $k = 0, \dots, N_{uj} - 1$ (N_u being the control horizon), and for $j = 1, 2$. $y_{iopt}(t+k|t)$ is the effect of the optimizing future

control actions: $\delta u_j(t+k|t) = u_j(t+k|t) - u_{jbase}(t+k|t)$, $k = 0 \dots N_{uj} - 1$, where $u_j(t+k|t)$ are the desired optimal control actions. The optimizing control actions δu_j can be considered as a series of impulses h^j and a final step g^j of input j to output i . The EPSAC-MPC equations for the MIMO two input-two output case can be expressed in matrix notation:

$$Y_i = Y_{ibase} + Y_{iopt} = \bar{Y}_i + \sum_{j=1}^{n_u=2} G_{ij} U_j \quad (7)$$

where for $i = 1, 2$, and $j = 1, 2$:

$$\mathbf{Y}_i = [y_i(t + N_{1i}|t) \dots y_i(t + N_{2i}|t)]^T$$

$$\bar{\mathbf{Y}}_i = [y_{ibase}(t + N_{1i}|t) \dots y_{ibase}(t + N_{2i}|t)]^T$$

$$\mathbf{U}_j = [\delta u_j(t|t) \dots \delta u_j(t + N_{uj} - 1|t)]^T$$

$$\mathbf{G}_{ij} = \begin{bmatrix} h_{N_{1i}}^{ij} & h_{N_{1i}-1}^{ij} & \dots & h_{N_{1i}-N_{uj}+2}^{ij} & g_{N_{1i}-N_{uj}+1}^{ij} \\ h_{N_{1i}+1}^{ij} & h_{N_{1i}}^{ij} & \dots & & \\ \vdots & & \ddots & & \vdots \\ h_{N_{2i}}^{ij} & h_{N_{2i}-1}^{ij} & \dots & h_{N_{2i}-N_{uj}+2}^{ij} & g_{N_{2i}-N_{uj}+1}^{ij} \end{bmatrix}$$

In our study, the objective is to find the optimal control vectors \mathbf{U}_1^* and \mathbf{U}_2^* which minimize the cost function:

$$J(\mathbf{U}_1) = \sum_{k=N_{11}}^{N_{21}} [r_1(t+k|t) - y_1(t+k|t)]^2 \quad (8)$$

$$J(\mathbf{U}_2) = \sum_{k=N_{12}}^{N_{22}} [r_2(t+k|t) - y_2(t+k|t)]^2$$

In (8), $r_i(t)$ $i \in \{1, 2\}$ represents a reference trajectory. The control law used in the real process is specified in (9).

$$\begin{aligned} \mathbf{U}_1^*(t) &= (\mathbf{G}_{11}^T \mathbf{G}_{11})^{-1} \mathbf{G}_{11}^T (\mathbf{R}_1 - \bar{\mathbf{Y}}_1 - \mathbf{G}_{12} \mathbf{U}_2) \\ \mathbf{U}_2^*(t) &= (\mathbf{G}_{22}^T \mathbf{G}_{22})^{-1} \mathbf{G}_{22}^T (\mathbf{R}_2 - \bar{\mathbf{Y}}_2 - \mathbf{G}_{21} \mathbf{U}_1) \end{aligned} \quad (9)$$

IV. SIMULATIONS AND RESULTS

In this section, the implementation of the EPSAC control scheme was evaluated by examining the simulation results with a sampling time of 1 second. To accomplish this goal, the controller was integrated into a 2-inputs 2-outputs MIMO open-source patient simulator. The simulator takes Propofol and Remifentanil as input variables and provides BIS and RASS as output variables. To examine the robustness of the controller, two disturbance profiles were added in the different approaches as shown in Fig 3. The simulations involved 12 patients, and the average value, patient 13, as shown in Table I. The prediction horizon was set to 70 samples in this study to ensure adequate system performance during closed-loop operations [23]. Additionally, saturation was placed on the infusion rates of the administered medications based on the clinical trials: from 0 to 6.6mg/s for Propofol and from 0 to 16.67μg/s for Remifentanil. The simulations were conducted while considering two types of

TABLE I

12 PATIENT DATABASE FOR THE COMBINED INFUSION MODELS OF PROPOFOL-REMIFENTANIL. PATIENT 13 IS THE AVERAGE PATIENT

Id	Age	Gender	Height[cm]	Weight[kg]	C_{50p}	C_{50r}	γ	σ	E_0	E_{max}
1	40	F	163	54	6.33	12.5	2.24	7.13	98.8	94.10
2	36	F	163	50	6.76	12.7	4.29	3.60	98.6	86.00
3	28	F	164	52	8.44	7.1	4.10	1.56	91.2	80.70
4	50	F	163	83	6.44	11.1	2.18	3.04	95.9	102.00
5	28	M	164	60	4.93	12.5	2.46	2.32	94.7	85.30
6	43	F	163	59	12.00	12.7	2.42	3.83	90.2	147.00
7	37	M	187	75	8.02	10.5	2.10	1.48	92.0	104.00
8	38	F	174	80	6.56	9.9	4.12	1.61	95.5	76.40
9	41	F	170	70	6.15	11.6	6.89	4.70	89.2	63.80
10	37	F	167	58	13.70	16.7	3.65	8.80	83.1	151.00
11	42	M	179	78	4.82	14.0	1.85	2.13	91.8	77.90
12	34	F	172	58	4.95	8.8	1.84	1.44	96.2	90.80
13	38	F	169	64.75	7.42	11.67	3.17	3.47	93.1	96.58

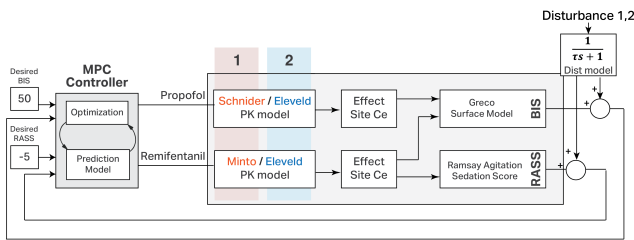


Fig. 3. The EPSAC control scheme for Propofol and Remifentaniil with the use of distinct PK-PD models in two separate simulations: the first simulation uses Shneider and Minto models (1), while the second simulation employs Eleved Models (2).

disturbance profiles illustrated in Fig. 4. These disturbances are made from real surgical procedures, namely laparoscopy and hysterectomy, and are adjusted based on the BIS and RASS output variables. Each disturbance profile corresponds to a specific surgical scenario, and they persist for 6000 and 3000 seconds for disturbances 1 and 2, respectively. Furthermore, the disturbance profile passes through a disturbance model filter denoted as $F_d = \frac{1}{\tau s + 1}$ to mitigate their impact, where τ is a time constant set to 50. The simulations involved 13 patients, and the results are displayed in Fig. 5. The upper part of the figure illustrates the application of the Eleved model for Propofol and Remifentaniil. In contrast, the lower part shows the outcomes of using the Schnider model for Propofol and the Minto model for Remifentaniil. In Fig. 5, even in the presence of disturbances and variations between patients, the BIS index was targeted at 50, and it was possible to attain a satisfactory level of safety within clinical intervals. Additionally, the RASS value serves as an indicator of nociception and demonstrates favorable tracking results, ranging from -1 (indicating low sedation) to -5 (representing deep sedation). The comparative study was carried out, and the results of control efforts were depicted through boxplot representation in Fig. 6 and Fig. 7. This presentation shows the infusion of Propofol in different PK-PD models during the maintenance phase when the BIS index attains the desired value of 50: from the 200-second mark after the start of

surgery until its completion. Fig. 6 illustrates the results of the Propofol control effort in two models under the influence of disturbance 1. It is evident that the Eleved model requires a lower infusion rate of Propofol input compared to the Schnider model. This suggests that less medication is needed to achieve the desired BIS index value of 50, ensuring a satisfactory level of sedation. In Fig. 7, the results of the Propofol control effort under the influence of disturbance 2 are displayed. During the maintenance phase, it is evident that the Eleved model requires a smaller amount of Propofol input compared to its control effort in the Schnider PK-PD model. This indicates a more efficient utilization of Propofol in the Eleved model under these conditions.

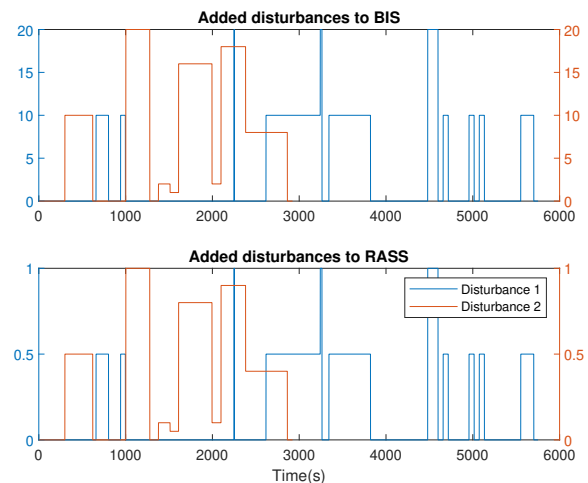


Fig. 4. Added disturbance profiles to output variables BIS and RASS on top and below, respectively. Disturbance Profile 1 indicates a specific surgery profile that takes time for 6000 seconds, and disturbance Profile 2 illustrates a surgery that lasts for 3000 seconds. Both profiles are scaled regarding the output variables.

V. DISCUSSION

In this study, the comparative analysis of two distinct approaches of PK models, namely Schnider for Propofol and Minto for Remifentaniil for the first one versus Eleved for

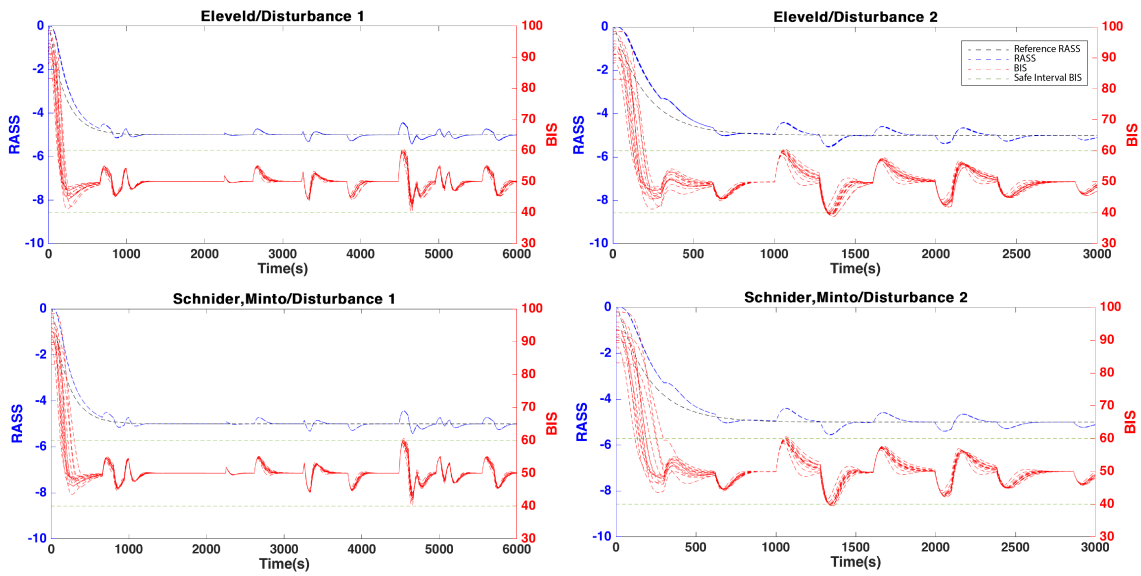


Fig. 5. The inter-patient variability of closed-loop representation of 2×2 inputs-outputs anesthesia variables for 12 patients during general anesthesia for BIS and RASS output variables. The top two figures represent the results of using the Eleveld model for Propofol and Remifentanyl. The two figures in beneath illustrate the application of Schnider model for Propofol and Minto for Remifentanyl. The desired value for BIS is 50 and for RASS is -5 depicted as (- -) while the clinical safe interval is between 40-60 for BIS and highlighted with (- -).

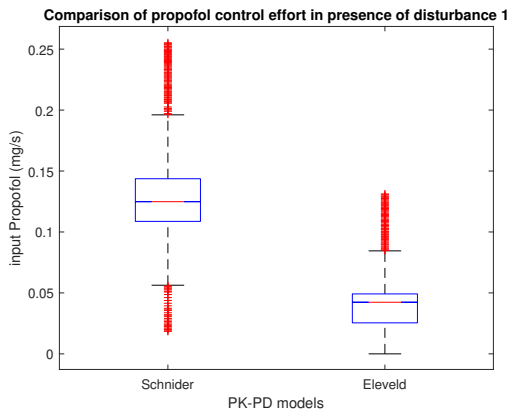


Fig. 6. The comparison of Propofol control effort for different PK-PD models in the presence of disturbance 1. The boxplot comparison indicates the results of input Propofol from the moment of 200 seconds until the end of surgery (maintenance phase) with Schnider and Eleveld models. The findings were obtained using data from the 13th patient in the database.

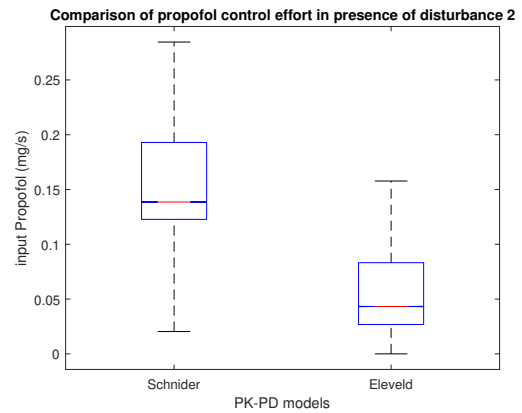


Fig. 7. The comparison of Propofol control effort for different PK-PD models in the presence of disturbance 2. The boxplot comparison indicates the results of input Propofol from the moment of 200 seconds until the end of surgery (maintenance phase) with Schnider and Eleveld models. The findings were obtained using data from the 13th patient in the database.

both of the drugs in the second one, for medical administration during general anesthesia, revealed substantial variations in drug concentration profiles and patient responses. The results of our simulations indicate that the controller demonstrated a more efficient control input (Propofol) in the Eleveld model (second simulation) compared to the Schnider model (first simulation). This finding suggests that the Eleveld PK model might offer improved precision in maintaining the desired sedation level while requiring a lower proportion of Propofol input for the same patient's profile. The novelty of these findings lies in providing concrete evidence of the impacts of choosing more reliable PK models on anesthetic drug management. The ability of the controller, applied to

the Eleveld model, to achieve the desired sedation level with reduced drug input signifies its potential for enhancing patient safety and minimizing the risk of complications associated with excessive drug administration. Indeed, in [3], the clinical comparison between the two models revealed that the Eleveld model exhibits a lower C'_{ep} compared to the Schnider model due to differences in their PK-PD profiles. The Schnider model uses fixed values for volumes V_1 , V_3 ; adjusts the volume of distribution in V_2 ; and uses height, weight, and sex as covariates of metabolic clearance. In contrast, the Eleveld model does not fix values for volumes and incorporates demographic variables more extensively as covariates, aiming for improved prediction performance: A

smaller volume of distribution in the central compartment (V1) or decreased clearance in a PK-PD model generally leads to a quicker reach of the targeted Propofol concentration in a patient. Additionally, a higher k_{e0} , as in the Schnider model, leads to faster equilibration and thus a higher C_{ep} at loss of response compared to a model with a lower k_{e0} , like the Eleveld model. Since we are using the same patients to compare two different approaches to modelling their PK-PD model, we can conclude that the higher C_{ep} is directly linked to increasing the drug input.

The findings of this study emphasize the importance of selecting appropriate PK models in closed-loop anesthesia control. The comparison of PK models provides insights into improving the precision of drug administration, maintaining desired anesthetic depths, and minimizing associated risks for patients undergoing surgical procedures. While this study focused on Propofol and Remifentanyl, exploring the comparative effectiveness of PK models for other anesthetic agents could provide a more comprehensive understanding of their impact on anesthesia management. Additionally, considering the diverse patient population, including various demographics and medical conditions, in further investigations would offer insights into the model's adaptability and effectiveness.

VI. CONCLUSIONS

In conclusion, this hypothesis analysis underscores the significance of choosing a more accurate model (in our case PK model) in anesthesia control, with the Eleveld model showing promise in reducing drug doses while maintaining effective sedation levels. Through this research, we contribute to the ongoing efforts to enhance the quality of anesthesia care and minimize the associated risks for patients undergoing surgical procedures. Further research and real-world validation of these findings could significantly advance the field of anesthesia care and improving patient safety.

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