

Modelling of Blood Loss Influence on Propofol Concentrations and Anesthetic States in Critical Responses*

Mihaela Ghita^{1,2}, Dana Copot^{1,2}, Isabela Birs^{1,2,3}, Cristina Muresan³, Martine Neckebroek⁴ and Clara Ionescu^{1,2}

Abstract—This work studies the classical pharmacokinetic-pharmacodynamic (PK-PD) model of Propofol for total intravenous anesthesia in response to intraoperative blood loss. Anesthetic and hemodynamic stability are impaired in the setting of trauma surgeries or major procedures with high hemorrhage risk. Blood loss has immediate effects on the cardiovascular system, but also affects the plasma concentration of the perioperatively infused drugs. During perioperative transition periods, when fast blood losses occur, the PK models on which the target-controlled infusion (TCI) is based should be updated. Then, the population-based parameters move towards an individualized strategy that accounts also for the actual blood volume in the patient. This paper evaluates the influence of changing blood volume on the PK model of Propofol, hence on the anesthesia state of the patient. The simulations also account for the hemodynamic responses due to the conflicting interactions of both hemorrhage and anesthetic drug infusion. This model has great potential for inclusion in multiple-closed loop control strategies of anesthesia-hemodynamic states, as it is simple and adapted from well-known PK models, for which control strategies are already mature.

I. INTRODUCTION

Excessive blood loss consistently occurs during trauma surgery and certain other major operations, causing hemodynamic and anesthetic instability [1]. There are several orthopedic procedures that can result in large volumes of blood loss, while hemorrhage is the leading cause of preventable death in trauma patients [2]. Clinical recommendations exist for managing fluid losses in anesthesia practice,

*M. Ghita is holder of FWO doctoral fellowship 1184220N; I. Birs of BOF post-doctoral grant BOF22/PDO/008; D. Copot of FWO postdoctoral grant 12X6823N. This work was partially supported by the grants of the Romanian Ministry of Education and Research, CNCS-UEFISCDI, PN-III-P1-1.1-PD-2021-0204 and of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022-I9, 760018/27.01.2023. Disclaimer: This work has received funding from the European Research Council (ERC) Consolidator Grant AMICAS 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 EU or the European Research Council Executive Agency. Neither the EU nor the granting authority can be held responsible for them.

^{1,2} These authors are affiliated with with the Research Group of Dynamical Systems and Control, Depart. of Electromechanical, Systems and Metal Engineering, Ghent University, and with the Flanders Make Core Lab MIRO: Machineries, Intelligence, Robots and Electromechanical Systems, 9052 Ghent, Belgium mihaela.ghita, dana.copot, isabelaroxana.birs, claramihaela.ionescu@ugent.be

³ C. Muresan and I. Birs are with the Department of Automation, Technical University of Cluj-Napoca, 400114 Cluj-Napoca, Romania. cristina.muresan@aut.utcluj.ro

⁴ MD M. Neckebroek is with Ghent University Hospital, Department of Anesthesiology, 9000 Gent, Belgium. martine.neckebroek@ugent.be

either based on conventional perceptions or advanced kinetic analysis of body fluid dynamics [1], [3]. However, critical responses during hemorrhage in anesthetized patients need to be accounted for not only by anesthesiologists, but also by the computer-controlled strategies excessively developed for anesthesia maintenance [4], [5].

Closed-loop controllers have emerged in medicine to facilitate medical automation and clinician support, proving to outperform manual control [6]. However, several limitations hamper their mature implementation in clinical practice, such as the insufficient account for the multi-faceted patient physiology, the limited collective safety-assuring management of multiple devices and loops, and the premature assessment methodology of the physiological closed-loop systems [7]. This rising challenge exists not because of a lack of technology, as several models and control strategies have been tested in simulations and clinical trials [8], but because the vital functions compound a complex system to be controlled. As a multivariable, interconnected system, the body raises control challenges in terms of system stability and robustness against inter- and intra-variability. Even more, models of human dynamics have been extensively developed, yet the internal body regulations make it harder to find a universally valid model to account for the concurrent dynamics that determine the holistic physiological state of a patient. However, from the control viewpoint, simple models are needed to predict the multiple dynamics, not necessarily the over-complicated physiological-based models. Another key requirement for the proper function of the controller is reliable feedback data from the patient being controlled. Here, the medicine uses surrogates as sensing and therapeutic endpoints (i.e., controlled variables) due to their non-invasiveness of measurement, being easy to be monitored in real-time. Hence, the limited available measurements of the optimal physiological parameters applicable to therapeutic monitoring empower the use of prediction models. The burden of predicting the patient's state trajectory stems from the large uncertainty in unmodelled patient responses.

This paper proposes a PK model adaptation to blood loss of the anesthetic drug Propofol in order to evaluate the influence of volume changes in critical responses on the hemodynamic and anesthesia states. The accuracy of Propofol PK may be impaired when the drug distribution volume is significantly changed. The need for such a model appears in the context of TCI-guided Propofol infusion, which uses a population-based PK model for the calculation

of the drug infusion rates based on the plasma concentrations optimized by the anesthesiologist. Propofol TCI cannot take this into account, as it has been proven that they tend to overestimate Propofol plasma concentrations at the end of surgeries with intraoperative blood loss [9]. However, measuring the Propofol plasma levels by laboratory methods is impossible during anesthesia and no techniques exist yet for real-time monitoring of patient blood Propofol concentration. Thereby, the PK-PD models are a powerful non-clinical tool for drug infusion guidance, which requires adaptation during critical intraoperative periods. Given the complexities associated with the multiple responses of the patient compared to conventional engineering systems, it is important to include possible interactions and conflicts in such a variable system.

Concluding, there is a significant opportunity to add the cross-communication between anesthesia, hemodynamic states and hemorrhage, especially during fast periods of hemodynamic instability.

II. MODELLING HEMORRHAGE-DRUG-EFFECTS

A. Existing models

In patients to undergo operations with expected blood loss, (i) the hemorrhage decreases the filling pressure of the cardiovascular (CV) system and influences other internal hemodynamics, while (ii) TCI intends to titrate Propofol to maintain a safe depth of hypnosis, taking into account the (iii) dose-dependent PD of Propofol on the CV system (i.e., inhibiting baroreflex responses). However, the distribution volume of the titrated Propofol decreases during blood loss, so both the PK and PD of Propofol are exposed to changes.

Much of the current literature on mathematical models pays particular attention to either CV responses to blood or fluid perturbation, or Propofol's influence on hemodynamics during anesthesia. However, blood loss during Propofol-based anesthesia is strongly correlated to several complex physiologic dynamics such as volume kinetics, CV autoregulation, drug sensitivity and cerebral function. The models that could account for these dynamics are reviewed in Fig. 1. A real-life mimicking framework that accounts for blood loss should include the influence of blood loss on the CV auto-regulation model, the hemorrhage resuscitation or hemodynamic stabilization treatments (i.e., fluid and/or vasopressor infusion), the PK-PD of intravenous Propofol, and the drug interactions with the cardiac physiology. Therefore, in realistic scenarios during total intravenous anesthesia (TIVA), the outputs of the system are changed both by the inputs (i.e., Propofol or other treatments, surgical manipulations) and the disturbing events (i.e., varying distribution volumes or functions due to blood loss). Both input types, the manipulated variables and the disturbances act on the patient and may change the hemodynamic stability, fluid management, respiratory rates, or other unknown dynamics.

Starting with the Propofol input, its sedation effect represented by the Bispectral index (BIS) is predicted using the PK-PD model (different compartmental models previously published by *Schnider et al.* [10], *Eleveld et al.* [11]

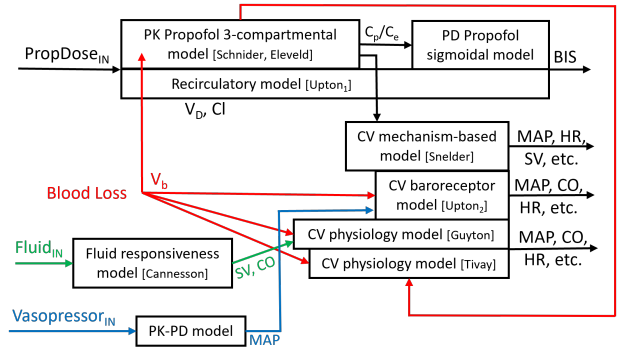


Fig. 1. Models for relationships between Propofol dose-dependent outputs of cerebral-cardiovascular dynamics in patients undergoing Propofol-induced anesthesia during blood loss episodes.

connected with a Hill curve [12], [13], [14] by an effect-site compartment) or the physiologically-based recirculatory model proposed by *Upton et al.* [15]. The influence of Propofol on the CV system was modelled by *Su et al.* [16] using a mechanism-based PD model for Propofol derived from *Snelder et al.* [17] and the PK by *Eleveld et al.* [11]. A fractal PK model for Propofol was also proposed by *Copot et al.* [18] to predict drug trapping in long-term infusions.

Continuing with the physiological effects of blood loss on the CV systems, several models exist. One is the model by *Rinehart et al.* [19], implementing the link between blood loss and the CV system through the constrained Frank-Starling baroreceptor mechanism-based model [20], derived from the CV physiology from *Guyton et al.* [21]. The benefit of this model is that it produces physiologically plausible hemodynamic curves, and the outputs (i.e., mean arterial pressure – MAP, heart rate – HR, cardiac stroke volume – SV, cardiac output – CO, etc.) have already been compared with and validated against published physiology [19]. However, the model describes the Frank-Starling mechanism, hence the adjustments of the CV system to changes in loads of inflowing blood. The model has been implemented in the context of intra-operative fluid therapy for closed-loop fluid resuscitation testing [19], and also linked to vasopressor drug responses [22]. Moreover, for simulated hemorrhage scenarios, *Rinehart et al.* [23] used the relationships between hemodynamics described by *Guyton et al.* [21] to obtain dynamic predictors of fluid responsiveness, based on the responsiveness changes during volume expansion [24].

The complex physiological model to predict the CV and BIS responses to combined hemorrhage resuscitation and intravenous Propofol sedation therapy was proposed by *Yin et al.* [25]. The work combines a CV physiology model based on the behavior known in the literature from *Guyton et al.* [21] and the Propofol 3-compartment PK model [11], the effect-site delay model and a sigmoidal PD associated with BIS. The CV model accounts for the volume kinetics in the vessels and autonomic-cardiac regulation [3], which was linked to the Propofol PK-PD models through extensions to replicate the interactions between hemorrhage resuscitation and sedation treatments.

B. Population PK-PD modelling for Propofol

The *Schnider* model for Propofol [10] was derived from population biometrics, but it was developed in the absence of surgery or major blood loss. A generic schema of the PK-PD model is presented in Fig. 2, where the blood loss has not yet been considered to occur in the total blood volume V_b .

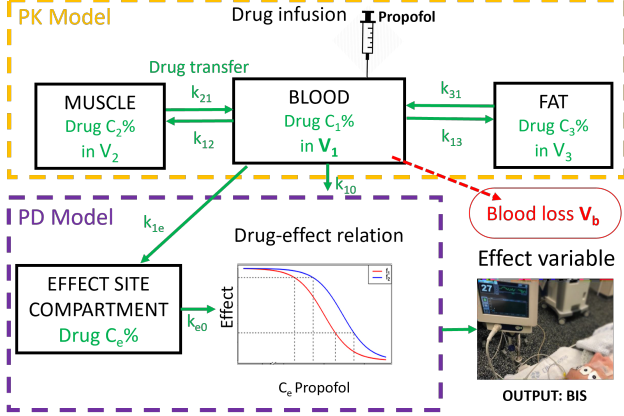


Fig. 2. Three-compartment PK model used to describe the concentration-time profiles and the PD model of the drug-effect relation. The input (Propofol) is administered and absorbed into the blood compartment, from where it is distributed to the peripheral compartments with drug transfer rates k_{ij} . The BIS effect variable is measured from the effect-site compartment in real-time. Blood loss is proposed to be considered.

Blood losses may readily participate in the dynamic fluid exchanges at the microcirculatory level, being proportional to the degree of injury and surgical manipulation. Assuming that the fluid loss during a surgical procedure may be estimated, even if inexactly, from the suction canisters and subtracting whatever volume has been used for irrigation, its effects are further studied.

This paper proposes the adaptation of the PK-PD three-compartmental model for Propofol from Fig. 2, where the blood loss from the blood volume V_b is further incorporated in the classical PK-PD model by changing the nominal distribution volume V_1 [l] of the drug in the blood compartment. Considering the system composed of the three-compartmental PK model and the plasma/effect-site equilibrium relationship, the state-space representation is as follows:

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

where $u(t)$ is the mass flow of infused Propofol into the central compartment expressed in [mg/s], $C_e(t)$ [$\mu\text{g/ml}$] is Propofol concentration in the effect-site compartment, and k_{ji} [1/s] for $i \neq j$ the drug transfer rate constants from the j^{th} to the i^{th} compartment. The PK model is given by differential equations in terms of the variation of

Propofol masses x_i [mg] within the blood ($i=1$), muscle ($i=2$) and fat ($i=3$) compartments. An additional hypothetical effect compartment represents the lag between drug plasma concentration and drug response, where $C_p(t) = x_1(t)/V_1(t)$ corresponds to Propofol plasma concentration [26].

The PK model's parameters depend on age, weight, height and gender and can be calculated for Propofol as follows:

$$V_1 = 4.27; V_2 = 18.9 - 0.391(\text{age} - 53); V_3 = 238; \quad (2)$$

where the volumes V_1, V_2, V_3 [l] represent the compartmental volumes for blood, muscle and fat.

$$Cl_1 = 1.89 + 0.0456(W - 77) - 0.0681(LBM - 59) + 0.0264(H - 177) \quad (3)$$

$$Cl_2 = 1.29 - 0.024(\text{age} - 53); \quad Cl_3 = 0.836$$

$$\begin{aligned} k_{10} &= \frac{Cl_1}{V_1}; \quad k_{12} = \frac{Cl_2}{V_1}; \quad k_{13} = \frac{Cl_3}{V_1}; \\ k_{21} &= \frac{Cl_2}{V_2}; \quad k_{31} = \frac{Cl_3}{V_3}; \quad k_{e0} = k_{1e} = 0.456; \end{aligned} \quad (4)$$

with LBM the lean body mass, W weight, H height, and Cl_{1-3} [l/min] the clearance rates at which the drug is distributed between the compartments. For this work, the rates k_{ji} are transformed to [1/s]. The lbm in (3) is calculated for male and female by:

$$\begin{aligned} LBM_m &= 1.1 \cdot W - 128 \cdot W^2/H^2 \\ LBM_f &= 1.07 \cdot W - 148 \cdot W^2/H^2 \end{aligned} \quad (5)$$

The relation between the effect site concentration and the measured effect in the brain (BIS) is modelled as a nonlinear sigmoid Hill curve scaled between 0%-100% (awake):

$$BIS(t) = E_0 - E_{max} \frac{c_e^\gamma(t)}{c_e^\gamma(t) + c_{50}^\gamma} \quad (6)$$

where E_0 is the BIS value in awake state; E_{max} is the maximum effect that can be achieved by Propofol; c_{50} is the Propofol concentration at half of the maximum effect, that together with γ determines the patient sensitivity to the drug [14], [27].

C. Blood loss simulations

In order to evaluate the PK-PD dynamics during hemorrhage, a set of patients' characteristic variables [28] has been used, as provided in Table I. The simulations include the blood loss by modifying the central compartment volume V_1 , hence the blood volume distribution of Propofol, in the PK-PD model from (1) at 1000 s. The decrease in V_1 should also influence the relationships in (3), causing slower clearances and faster intercompartmental transfer from the blood compartment. The blood volume $V_b=V_1$ was decreased from the nominal value of 4.27 [l] to a constant value of 4, 3.75 and 3, respectively, until the end of the simulation time (2000 s). The blood loss was assumed a step change, but this may be the case only for small blood volume changes in real scenarios during trauma surgeries, as real-life large blood loss would be better simulated as an exponential decay.

The dynamics of Propofol concentrations, BIS and cardiovascular variables during blood loss were simulated for one patient, to show the changes in the responses at each

volume variation. For these simulations, the nominal PD values were chosen ($\gamma = 2$; $C_{50} = 4.16$; $E_0 = E_{max} = 100$), to illustrate the changes in the BIS effect that were influenced by the blood loss but unaffected by the patient's sensitivity to Propofol.

The variability between all the patients in Table I was also studied in the context of blood loss starting at 1000 s, while Propofol was infused at a constant rate u after a bolus. The infusion rate was selected for each patient in order to obtain the optimal BIS value (~ 50) at the end of simulation time (2000 s) for the nominal state ($V_b = 4.27$ l) of each patient, and was kept constant during all blood loss scenarios.

The hemodynamic changes of Propofol were also simulated using the following relationships from [29]:

$$MAP = \frac{1}{k_{1MAP} * C_e + k_{0MAP}}; CO = \frac{1}{k_{1CO} * C_e + k_{0CO}} \quad (7)$$

$$E_{MAP} = E_0 - E_{max} \frac{MAP^\beta}{MAP^\beta + C_{50MAP}^\beta} \quad (8)$$

$$E_{CO} = E_0 - E_{max} \frac{CO^\beta}{CO^\beta + C_{50CO}^\beta}$$

with E_0 and E_{max} the minimum and maximum effects that Propofol has on hemodynamics, $E_0=0$, C_{50} the Propofol concentration at half of the maximum effect and β with C_{50} for the patient sensitivity to Propofol.

TABLE I

PK-PD MODEL PARAMETERS FOR THE CONSIDERED POPULATION

Id	Age	H[cm]	W[kg]	Gen	c_{50}	γ	E_0	E_{max}
1	40	163	54	F	6.33	2.24	98.8	94.1
2	36	163	50	F	6.76	4.29	98.6	86.0
3	28	164	52	F	8.44	4.10	91.2	80.7
4	50	163	83	F	6.44	2.18	95.9	102
5	28	164	60	M	4.93	2.46	94.7	85.3
6	43	163	59	F	12.0	2.42	90.2	147
7	37	187	75	M	8.02	2.10	92.0	104
8	38	174	80	F	6.56	4.12	95.5	76.4
9	41	170	70	F	6.15	6.89	89.2	63.8
10	37	167	58	F	13.7	1.65	83.1	151
11	42	179	78	M	4.82	1.85	91.8	77.9
12	34	172	58	F	4.95	1.84	96.2	90.8
13	38	169	65	F	7.42	3.00	93.1	96.58

III. PRELIMINARY RESULTS AND DISCUSSION

The effects on the patient's response to the blood loss variation for a constant Propofol infusion rate are shown in Figs. 3 and 4, using one patient as an example (id 1). Figure 3 illustrates the increase of Propofol plasma concentrations C_p peaks at the moment of the simulated reduction in the blood volume at time=1000 s (dashed lines), followed by the C_p return to the nominal trend when no blood loss occurred (continuous lines), even if the loss in volume remains constant. The results follow the literature, as studies on swine have shown plasma Propofol concentration increases during continuous Propofol infusion and hemorrhagic shock [30], [31]. The PK-PD alteration caused by the blood loss may

be caused by changes in intercompartmental clearances (i.e., slower Cl_{1-3}) and the increase in the potency of Propofol (i.e., lower C_e required to achieve half of the maximal effect) [31]. However, the PK model used for simulations here [10] implies clearances not dependent on volume, as calculated from (30), hence no influence of blood volume could be observed. Nevertheless, the simulations demonstrated higher drug transfer rates k_{1i} from the central compartment (blood) to the peripheral ones when varying V_b , with a smaller drug amount x_1 remaining in the blood. As the plasma concentration is dependent on x_1 and V_1 , which are both assumed to decrease during hemorrhage, but x_1 more than V_1 , then the higher peaks appear in C_p .

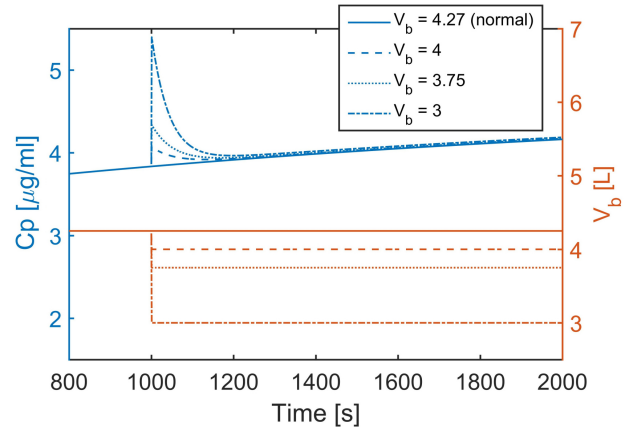


Fig. 3. Plasma concentrations of Propofol for step-like varying blood volume V_b at time=1000 s, after which the blood volume is constant until the simulation ends. The blood loss is assumed a step change to study the PK dynamics in extreme situations, but the simulations started from a nominal blood volume. The Propofol infusion rate u is constant, simulated for the PK characteristics of Patient 1.

The variation in the Propofol effect-site concentrations and BIS values determined by changes in the lost blood volume is depicted in Fig. 4, showing an inversely dependent relationship ($C_e \uparrow$ when $V_b \downarrow$ at 1000 s). Moreover, nonlinear changes in BIS are observed during 1000–1400 s for the volume losses (dashed lines) of 5.8% ($V_b = 4$ l), 11.7% ($V_b = 3.75$ l) and 29.4% ($V_b = 3$ l) from the nominal volume ($V_b = 4.27$ l, continuous line). Afterwards, for every blood loss scenario, BIS returns to its nominal value (~ 50), for which a constant Propofol infusion rate was a priori used. The methodology is not similar to the TCI, which targets a constant C_e or C_p . However, when closed-loop control is implied to maintain an optimal anesthetic state, the changes observed in the time constants of the patient's response during hemorrhage may impose challenges on the controller's stability during the first minutes of fast blood loss.

The Propofol effects on the hemodynamics are shown in Fig. 5 for the decrease in the MAP and CO variables, which is in line with the findings in previous studies in swine during stepwise increasing hemorrhage with constant Propofol infusion [30]. The reduction in blood volume during acute blood loss causes a fall in central venous pressure

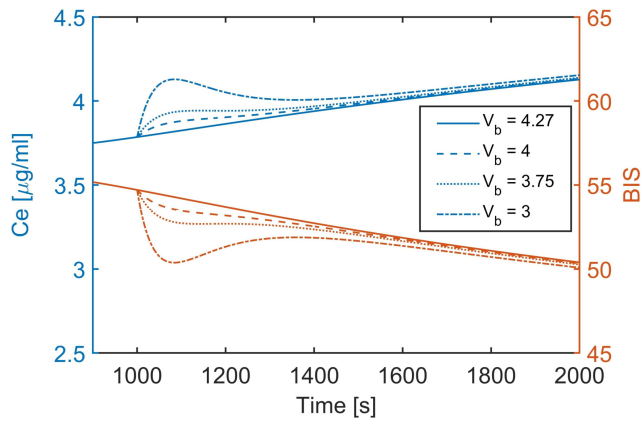


Fig. 4. Effect-site concentrations and the corresponding BIS for step-like varying blood volume V_b at time = 1000 s, after which the blood volume is constant until the simulation ends. The Propofol infusion rate u is constant, simulated for the PK characteristics of Patient 1.

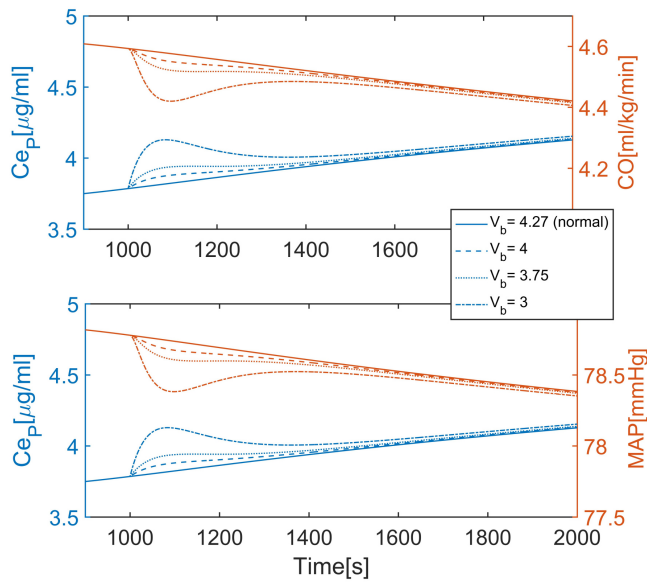


Fig. 5. Mean arterial pressure and cardiac output influenced by Propofol for step-like varying blood volume V_b at time = 1000 s, after which the blood volume is constant until the simulation ends. The Propofol infusion rate u is constant, simulated for the PK characteristics of Patient 1.

and cardiac filling. This leads to reduced CO (less blood pumped by the heart) and MAP (less blood in circulation). In literature, Propofol is known to have extensive effects on the cardiovascular system, with the most prominent effect being MAP reduction [32]. However, the changes in CO are still under discussion as the increase in Propofol may not cause any variation in CO, due to internal compensation [33].

The simulations for all patients with different PK-PD characteristics are depicted in Fig. 6, in the absence of blood loss ($V_b = 4.27$ l, continuous blue lines) and during maximum simulated blood loss in this paper ($V_b = 3$ l, dashed red lines). In all patients, it is observed an increase in C_p at the moment of blood volume reduction, followed by its return

to the nominal values, corresponding to the normal volume, even if the disturbance in the blood is constant until the end of the simulation. The consequence of the larger C_p is the decrease in BIS starting when the blood loss is initiated, and its restoration back to its former state, obtaining BIS ~ 50 .

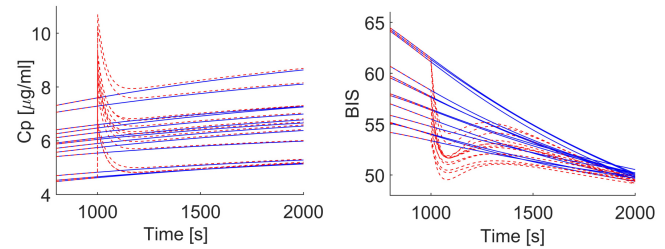


Fig. 6. Inter-patient variability and trends of plasma concentrations and BIS in all patients for nominal blood volume ($V_b = 4.27$ l, continuous blue lines) and maximum simulated blood loss at time = 1000 s ($V_b = 3$ l, dashed red lines) with constant Propofol infusion rate u for each PK-PD patient's characteristics. The simulations started with a nominal blood volume. The infusion rate was selected to obtain a BIS ~ 50 at time = 2000 s.

The difference between the patients' responses to blood loss was studied in Fig. 7 regarding the peaks occurring for each patient in the first 200 s after blood loss was initiated, causing changes in the time constants of critical responses. The peaks in C_p occurring immediately after blood loss are shown to non-linearly increase for each simulated volume loss for all patients. The values of Propofol concentration are different between patients, as they were calculated based on the PK characteristics of each patient, but they have similar trends. However, increases in C_p up to 3 $\mu\text{g/ml}$ will potentially cause important changes in measured effect-BIS. Hence, in the context of closed-loop infusion of Propofol, the control strategies should take into consideration the V_b that enters the used models. Using an observer developed on a volume kinetics model for plant dynamics, hemorrhage can be non-invasively detected based on readily-available blood hemoglobin measurements [34]. The BIS variability in all patients is also depicted in Fig. 7, showing different pharmacodynamics when blood loss increases compared to the patient's nominal state.

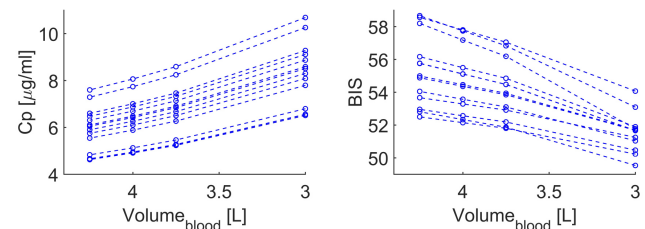


Fig. 7. Intra-patient variability of plasma concentrations and BIS in all patients for varying blood volumes. The circles correspond to the C_p /BIS peaks occurring for each patient in the first 200 s after hemorrhage initiation. The simulations started from a nominal blood volume.

This paper is limited in terms of the blood loss effects on CV autoregulation because no CV model was included in the simulation to study the hemodynamics as a consequence of volume loss kinetics. However, the study in

[23] showed increased HR, decreased CO and MAP in hemorrhage scenarios, even with fluid given. The blood loss decreases the filling pressure of the circulation and, as a consequence, decreases venous return, resulting in the fall of CO. These effects cause powerful sympathetic reflexes, stimulating vasoconstriction so that HR increases. Therefore, the influence of internal changes within the CV system needs to be further investigated in relation to the PK-PD of Propofol during varying blood volumes, and integrated into existing anesthesia-hemodynamic patient simulators [29].

Subsequent plasma loss compromises cardiac performance, which may lead to end-organ hypoperfusion, ischemia, etc. The common practice when a significant fluid loss occurs is the intravenous infusion of fluids to maintain the volume kinetics in the body, hence the plasma concentrations of the infused drugs. However, in critical responses, when fast unexpected bleeding occurs and the added fluid by the anesthesiologist is slower absorbed, the total circulating volume (blood loss and fluid gain) may be hard to stay balanced. In this regard, closed-loop systems optimizing the drug doses required for maintaining the safe depth of anesthesia need to account for the fast changes in the PK of the patient during blood loss. For example, gain scheduling or event-based control systems may be good candidates to obtain effectiveness and robustness in critical responses before the volumes are equilibrated with fluid administration, reducing the risks associated with CV instability. As changes in the time constants and gains in patients' responses have been observed in this work, a sensitivity analysis is opportune to be further performed to explore in depth the quantitative changes caused by several trends of blood loss, even in exponential decay.

In conclusion, predictive models are of utmost importance in accounting for disturbing events during anesthesia, such as blood loss. Because the simulations have shown changes in Propofol concentration during hemorrhage, the PK-PD model used may be further incorporated into the closed-loop control strategies for anesthesia-hemodynamic management.

REFERENCES

- [1] H.C. Hemmings, Jr., T.D. Egan (ed.), *Pharmacology and physiology for anesthesia: foundations and clinical application*, second ed. Philadelphia, PA: Elsevier, Inc., 2019.
- [2] C.S. Scher, A.D. Kaye, H. Liu, S. Perelman, S. Leavitt (ed), *Essentials of blood product management in anesthesia practice*. Cham, CH: Springer, 2021.
- [3] A. Tivay, G.C. Kramer, J.-O. Hahn, *Collective variational inference for personalized and generative physiological modeling: A case study on hemorrhage resuscitation*, *IEEE Trans. Biomed. Eng.*, 69(2), 666–677, 2022.
- [4] M. Schiavo *et al.*, *A modified PID-based control scheme for depth-of-hypnosis control: Design and experimental results*, *Comput. Methods Programs Biomed.*, 219, 106760, 2022.
- [5] C.M. Ionescu *et al.*, *Anesthesiologist in the loop and predictive algorithm to maintain hypnosis while mimicking surgical disturbance*, *IFAC papers Online*, 50(1), 15080–15085, 2017.
- [6] M. Neckebroek *et al.*, *A comparison of Propofol-to-BIS post-operative intensive care sedation by means of target controlled infusion, Bayesian-based and predictive control methods: an observational, open-label pilot study*, *J. Clin. Mon. Comp.*, 33(4), 75–686, 2019.
- [7] J.-O. Hahn, O. T. Inan, *Physiological closed-loop control in critical care: opportunities for innovations*, *Prog. Biom. Eng.*, 4, 033001, 2022.
- [8] M. Ghita *et al.*, *Closed-loop control of anesthesia: survey on actual trends, challenges and perspectives*, *IEEE Access*, 8, 206264–79, 2020.
- [9] T. Mohler *et al.*, *Measuring the accuracy of Propofol target-controlled infusion (TCI) before and after surgery with major blood loss*, *J. Clin. Monit. Comput.*, 34(1), 97–103, 2020.
- [10] T.W. Schnider *et al.*, *The influence of method of administration and covariates on the pharmacokinetics of Propofol in adult volunteers*, *Anesthesiology*, 88, 1170–1182, 1998.
- [11] D.J. Eleveld *et al.*, *Pharmacokinetic-pharmacodynamic model for Propofol for broad application in anaesthesia and sedation*, *Br. J. Anaesth.*, 120(5), 942–959, 2018.
- [12] T.W. Schnider *et al.*, *The influence of age on Propofol pharmacodynamics*, *Anesthesiology*, 90, 1502–1516, 1999.
- [13] C.M. Ionescu, *A computationally efficient Hill curve adaptation strategy during continuous monitoring of dose-effect relation in anaesthesia*, *Nonlinear Dyn.*, 92(3), 843–852, 2018.
- [14] R. De Keyser *et al.*, *Estimation of patient sensitivity to drug effect during Propofol hypnosis*, 2015 IEEE SMC Conf., Hong Kong, 2015.
- [15] R. Upton, G. Ludbrook, *A physiologically based, recirculatory model of the kinetics and dynamics of Propofol in man*, *Anesthesiology*, 103, 344–352, 2005.
- [16] H. Su *et al.*, *Mechanism-based pharmacodynamic model for Propofol haemodynamic effects in healthy volunteers*, *Br. J. Anaesth.*, 128(5), 806–816, 2022.
- [17] N. Snelder *et al.*, *Drug effects on the CVS in conscious rats: separating cardiac output into heart rate and stroke volume using PKPD modelling*, *Br. J. Pharmacol.*, 171, 5076e92, 2014.
- [18] D. Copot, C. Ionescu, *Tailored pharmacokinetic model to predict drug trapping in long-term anesthesia*, *J. Adv. Res.*, 32, 27–36, 2021.
- [19] J. Rinehart *et al.*, *Closed-loop fluid resuscitation: robustness against weight an cardiac contractility variations*, *Anesth. Analg.*, 117(5), 1110–1118, 2013.
- [20] R.N. Upton, G.L. Ludbrook, *Pharmacokinetic-pharmacodynamic modelling of the cardiovascular effects of drugs: method development and application to magnesium in sheep*, *BMC Pharma.*, 5(5), 2005.
- [21] A.C. Guyton, J.E. Hall (ed.), *Cardiovascular physiology IV*. Baltimore: University Park Press, 1982.
- [22] J. Rinehart *et al.*, *Closed-loop vasopressor control: in-silico study of robustness against pharmacodynamic variability*, *J. Clin. Monit. Comput.*, 33, 795–802, 2019.
- [23] J. Rinehart *et al.*, *Evaluation of a novel administration system based on dynamic predictors of fluid responsiveness: an in silico simulation study*, *Crit. Care*, 15, R278, 2011.
- [24] M. Cannesson *et al.*, *Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: A "gray zone" approach*, *Anesthesiology*, 115(2), 231–241, 2011.
- [25] W. Yin *et al.*, *Conflicting interactions in multiple closed-loop controlled critical care treatments: a hemorrhage resuscitation-intravenous propofol sedation case study*, *Biomed. Signal Process Control*, 71, 103268, 2022.
- [26] M. Schiavo *et al.*, *Optimized feedforward control of propofol for induction of hypnosis in general anesthesia*, *Biomed. Signal. Process Control*, 66, 102476, 2021.
- [27] C.M. Ionescu *et al.*, *Nonlinear dynamics of the patient's response to drug effect during general anesthesia*, *Commun. Nonlinear. Sci. Numer. Simul.*, 20(3), 914–926, 2015.
- [28] L. Merigo *et al.*, *Event-based control of depth of hypnosis in anesthesia*, *Comput. Methods Programs Biomed.*, 147, 63–83, 2017.
- [29] C.M. Ionescu *et al.*, *An open source patient simulator for design and evaluation of computer based multiple drug dosing control for anesthetic and hemodynamic variables*, *IEEE Access*, 9, 8680–94, 2021.
- [30] T. Kazama *et al.*, *Influence of hemorrhage on Propofol pseudo-steady state concentration*, *Anesthesiology*, 97, 1156–1161, 2002.
- [31] K.B. Johnson *et al.*, *The influence of hemorrhagic shock on Propofol: A pharmacokinetic and pharmacodynamic analysis*, *Anesthesiology*, 99, 409–420, 2003.
- [32] M.M. Sahinovic, M.M.R.F. Struys, A.R. Absalom, *Clinical pharmacokinetics and pharmacodynamics of Propofol*, *Clin. Pharmacokinet.*, 57(12), 1539–1558, 2018.
- [33] F. de Wit *et al.*, *The effect of Propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances*, *Br. J. Anesth.*, 116(6), 784–789, 2016.
- [34] X. Jin *et al.*, *Observer design and analysis for non-invasive hemorrhage detection*, *IFAC PapersOnLine*, 54-20, 310–315, 2021.