2024 European Control Conference (ECC)
June 25-28, 2024. Stockholm, Sweden

A Decoupled Fractional Order Control Strategy to Increase Patient Safety During Anesthesia-Hemodynamic Interactions

Erwin Hegedus[1], Marcian D. Mihai[1], Isabela R. Birs[1,2], Hamed Farbakhsh[2], Erhan Yumuk[2,3]
Dana Copot[1,2], Robain De Keyser[2], Clara M. Ionescu[1,2], Cristina I. Muresan[1]

Abstract— **Monitoring and control of general anesthesia, involving cardiac output or mean arterial pressure are critical to ensure patient safety during surgery. Several computer control solutions have been developed for each of the anesthesia components and hemodynamic processes. However, most do not tackle the synergistic and antagonistic effects of the anesthetic and hemodynamic drugs. Hitherto, only a handful of preliminary results and ideas regarding multivariable control have been reported so far, usually considering a simplified decentralized approach. A decoupled control strategy is proposed here to reduce the interaction between the hemodynamic and anesthesia sub-systems, hence increasing the robustness and stability of the overall control loop. Due to their intrinsic robustness to uncertainty and process model variability, fractional order controllers are designed to ensure that more specific performance criteria are addressed, compared to the traditional PIDs. The decoupled control strategy is compared to the decentralized approach to validate the minimization of the interactions. A robustness analysis is performed using a benchmark patient model and data from 24 patients.**

I. Introduction

As recent pandemic events have demonstrated, human error is always a possibility in manual control of drug delivery systems, particularly when practitioners are overworked. Thus, computer control is desirable in biomedicine, and it has been proposed as a viable solution in anesthesia [1]. Without the assistance of an anesthesiologist, recent research has demonstrated that computer-controlled systems in anesthesia can predict appropriate medication combinations more accurately [2], [3].

Many medical procedures require general anesthesia, which entails the best possible control of hypnosis, analgesia, and neuromuscular blocking [4]. Other hemodynamic indicators, such as cardiac output (CO) and mean arterial pressure (MAP), are crucial, nevertheless, particularly for individuals with heart conditions [5]. Electroencephalogram (EEG) data are traditionally used to assess hypnosis. These signals are then processed into the Bispectral index (BIS) and manually adjusted by administering a certain dose of Propofol. Analgesia is measured with the Ramsay Agitation Score (RASS), and neuromuscular blockade (NMB) is estimated using the electromyogram. Typically, Remifentanil and Atracurium are used as equivalent medications. Sodium Nitroprusside (SNP) and Dopamine (DOP) are typically used to maintain CO and MAP levels.

Most research regarding automatic control of anesthesia is focused on regulating BIS levels or the neuromuscular blockade in single input single output approaches [4]. Some tackle the idea of using two drugs to control BIS levels [6],[7]. A fractional order Smith Predictor with a multivariable fault tolerance module was designed for maintaining smooth BIS and MAP signals despite the delay, BIS sensor fault, and surgical disturbances [8]. Fractional order control strategies have been developed for controlling CO and MAP and to reduce the interactions between the two drugs [9].

A multivariable approach in anesthesia and hemodynamics is the subject of very few research investigations and control schemes. Even less attention is paid to how the patient is affected by the interactions between the anesthetic and hemodynamic medications [10], [11]. Preliminary results exist, including predictive control and decentralized fractional order control [12], [13], [14].

In this paper, the interactions between the anesthesia and hemodynamic subsystems are addressed in an improved control scheme compared to the decentralized approach. A steady state decoupled method is used to minimize drug interactions. Such an approach has yet to be considered. Once the decoupling is achieved, fractional order PID (FO-PID) controller are designed. A benchmark patient model [10] is used to test and validate the proposed approach. Comparison with a decentralized approach [14] is performed. A robustness analysis is performed considering data for 24 patients and a surgical stimulus acting as a disturbance. The closed loop simulations results show that the decoupled approach can effectively minimize the antagonistic and synergic effects of the drugs upon both anesthesia and hemodynamic variables.

The paper is organized as follows. Section II details the performance specifications and the tuning methodology for the FO-PIDs. The interactions between the anesthesia and

[1]Department of Automation, Technical University of Cluj-Napoca, Memorandumului Street, no. 28, 400114 Cluj-Napoca, Romania, (E-mail: Erwin.Hegedus@aut.utcluj.ro, Marcian.Mihai@aut.utcluj.ro, Isabela.Birs@aut.utcluj.ro, Cristina.Muresan@aut.utcluj.ro)
[2]Ghent University, Department of Electromechanics, Systems and Metal Engineering, Research Group on Dynamical Systems and Control, Tech Lane Science Park 125, Zwijnaarde 9052, Belgium (E-mail: Hamed.Farbakhsh@ugent.be, Erhan.Yumuk@ugent.be, Dana.Copot@ugent.be, Robain.DeKeyser@ugent.be, ClaraMihaela.Ionescu@ugent.be)
[3]Istanbul Technical University, Department of Control and Automation Engineering, Istanbul, Turkey (E-mail: yumuk@itu.edu.tr

hemodynamic subsystems, as well as the decoupling strategy are presented in Section III. The comparisons between the decentralized and decoupled approaches are detailed in Section IV, while the robustness of the proposed method is analysed in Section V. The concluding remarks are included in the final part, Section VI.

II. From Performance Criteria to FO-PID Parameters

The generalized transfer function for a fractional order PID controller is given as:

$$C(s)=k_p\left(1+\frac{k_i}{s^{\lambda}}+k_d s^{\mu}\right) \quad (1)$$

The controller in (1) has five tuning parameters: the proportional gain k_p, the derivative and integral gains k_d and k_i, and the two fractional orders of integration and differentiation $\lambda, \mu \in [0,2]$. To estimate the controller parameters 5 performance criteria are specified.

For the hemodynamic system, an ideal overshoot of less than 10% is sought and a settling time of less than 750 seconds [15], [16]. The CO should be kept within 4-8 l/min, while the MAP admissible range is 65-110 mmHg. On the anesthesia part, the NMB and RASS signals should settle within 300 seconds and with a maximum undershoot of 5% [13], [14]. Safe intervals for variation are –2.6 to -2.4 for RASS and 10-13% for NMB. During maintenance phase, the BIS signal should be kept within 40-60, with a fast rejection of output or input disturbances (surgical stimuli or anesthesiologist boluses). The main challenge here is the strong synergistic and antagonistic effects between the drugs that cause large variations in the BIS signal whenever hemodynamic variables are disturbed and vice-versa [10]. Specific performance indicators refer to:

- The time required for the controller to bring the BIS signal back into [45 ÷ 55] interval after a disturbance has occurred (TTd)
- The smallest and largest amplitudes of the BIS signal as a result of a disturbance (BIS-NADIRs and BIS-NADIRl).

The drug rates should also be kept within a minimum and maximum value. For example, DP ranges between 4 to 7 μg/kg/min and SNP should not exceed a rate of 10 μg/kg/min [17]. The Propofol and Remifentanil progression rates, during maintenance phase, should fall between a minimum and maximum of 0.1-2 mg/kg/min for Propofol and 0.1-3 μg/kg/min for Remifentanil [7], [14].

All these performance criteria are translated into mathematical equations. One of the most important and frequently used performance criteria is related to the stability of the closed loop and has a direct effect on the expected over/undershoot is the phase margin (PM). It is usually selected to be large, which implies a smaller overshoot. The mathematical equation that tackles the overshoot requirement can be written as follows:

$$\angle H_{OL}(j\omega_c) = -\pi + PM \quad (2)$$

where $H_{OL}(s)=C(s)P(s)$ is simply the open loop transfer function and ω_c is the gain crossover frequency. Here P(s) represents the simplified transfer function that links the drug rate to the corresponding measured output signal, such as BIS, MAP, CO, etc.

Time requirements are addressed via the gain crossover frequency. Large values for ω_c lead to smaller settling times. The magnitude equation is used to indirectly specify the requirement for a fast settling time:

$$|H_{OL}|(j\omega_c)=1 \quad (3)$$

To handle possible gain uncertainties resulting from patient variability, a robustness criterion is attached to the previous two tuning equations:

$$\left.\frac{d\angle H_{OL}(j\omega)}{d\omega}\right|_{\omega=\omega_c} = 0 \quad (4)$$

To handle noise and surgical stimuli that largely affect the BIS signal, a performance specification related to the complementary sensitivity function, T(s), is also used:

$$\left|T(j\omega)=\frac{H_{OL}(j\omega)}{1+H_{OL}(j\omega)}\right|_{dB} \le A_{dB} \quad (5)$$

where A is the imposed noise attenuation for frequencies $\omega \ge \omega_t$, with $|T(j\omega_t)|_{dB} = A_{dB}$.

Input disturbances also occur frequently due to interference from the anesthesiologist that can supply boluses of Propofol, for example. These boluses should be treated by the control strategy in terms of the sensitivity function, S(s):

$$\left|S(j\omega)=\frac{1}{1+H_{OL}(j\omega)}\right|_{dB} \le B_{dB} \quad (6)$$

where B is the imposed value of the S(jω) function for frequencies $\omega \le \omega_s$, with $|S(j\omega_s)|_{dB} = B_{dB}$.

During the maintenance phase, all patient signals to be controlled must be kept within a safe operating range. This is addressed via a minimum of the integral of absolute error (IAE):

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

where e(t)=r(t)-y(t) with r(t) the reference value and y(t) the measured patient signal.

III. A Steady-State Decoupling Strategy to Reduce Anesthesia-Hemodynamic Interactions

In this manuscript, the patient simulator is the one previously reported in [10], which includes interactions between the hemodynamic and anesthetic variables. The reader is referred to [10] for a detailed model of the anesthesia-hemodynamic system. As mentioned in the introductory section, previous decentralized approaches have been considered for this patient simulator. In this paper, a steady-state decoupling strategy is designed to minimize the interactions between the anesthesia and hemodynamic systems. As numerous research studies have shown that the NMB is already decoupled from the remaining system [10],

[14], the same FO-PI controller is used here as well to control the NMB via variations in the infused Atracurium. The FO-PI controller is:

$$C_{NMB}(s) = 0.08\left(1 + \frac{0.0227}{s^{1.05}}\right) \quad (8)$$

which has been tuned to meet $\omega_c = 0.01$ rad/s, PM = 85° and the iso-damping property in (4).

A block diagram of the remaining anaesthesia and hemodynamic signals to be controlled and the interactions between the drugs is detailed in Fig. 1, where u_1 stands for the Propofol, u_2 is the Remifentanil, u_3 and u_4 are the Dopamine and Sodium Nitroprusside drug rates. The outputs to be controlled are denoted as y_1=BIS, y_2=RASS, y_3=Co and finally y_4=MAP.

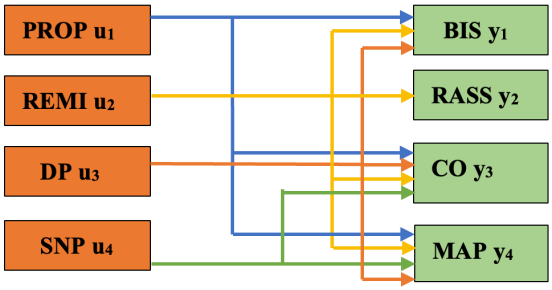


Fig. 1. Block diagram of the anaesthesia-hemodynamic system and interactions

The proposed decoupled control strategy is given in Fig. 2, where the reference setpoints for the BIS, RASS, CO and MAP signals are denoted as r_1, r_2, r_3 and r_4. The error signals to be minimised are denoted as e_1, e_2, e_3 and e_4. Notice the presence of the steady-state decoupler between the controllers and the anaesthesia-hemodynamic system.

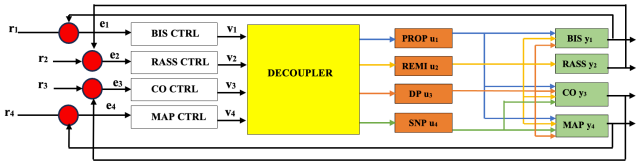


Fig. 2. Proposed decoupling control strategy for the anaesthesia-hemodynamic system

Based on Fig. 2, the following equations hold:

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{pmatrix} = \begin{pmatrix} G_{11}(s) & G_{12}(s) & G_{13}(s) & 0 \\ 0 & G_{22}(s) & 0 & 0 \\ G_{31}(s) & G_{32}(s) & G_{33}(s) & G_{34}(s) \\ G_{41}(s) & G_{42}(s) & G_{43}(s) & G_{44}(s) \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} \quad (9)$$

or in matrix form $\boldsymbol{Y} = \boldsymbol{G} \times \boldsymbol{U}$ and

$$\begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} = \begin{pmatrix} D_{11} & D_{12} & D_{13} & D_{14} \\ 0 & D_{22} & 0 & 0 \\ D_{31} & D_{32} & D_{33} & D_{34} \\ D_{41} & D_{42} & D_{43} & D_{44} \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \boldsymbol{D} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} \quad (10)$$

where $G_{ij}(s)$ are the transfer functions that described the dynamics of the output signals with respect to the administered drugs and D_{ij} are scalars used to decouple the anaesthesia-hemodynamic system. A steady state decoupling between the fictive control signals v_1-v_4 and the measured outputs y_1-y_4, implies that the following equation holds:

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{pmatrix} = \boldsymbol{G}(0) \times \boldsymbol{D} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \boldsymbol{I} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} \quad (11)$$

where $\boldsymbol{I}$ is the identity matrix and $\boldsymbol{G}(0)$ is the steady state matrix G(s). The decoupling scalars D_{ij} are computed using (11), such that $\boldsymbol{G}(0) \times \boldsymbol{D} = \boldsymbol{I}$. Once the decoupling scalars are determined, the elements on the main diagonal of $\boldsymbol{G}(s) \times \boldsymbol{D}$ are computed. For the nominal patient model, with parameters specified in [10], the following transfer functions are obtained:

$$\frac{y_1(s)}{v_1(s)} = \frac{-16.64(s+0.024)}{(s+0.18)(s+0.021)} e^{-20s} \quad (12)$$

$$\frac{y_2(s)}{v_2(s)} = \frac{0.0127}{(s+0.22)(s+0.057)} \quad (13)$$

$$\frac{y_3(s)}{v_3(s)} = \frac{0.02936}{(s+0.004)} e^{-47s} \quad (14)$$

$$\frac{y_4(s)}{v_4(s)} = \frac{-0.493}{(s+0.022)} e^{-50s} \quad (15)$$

The decoupled patient mathematical models in (12)-(15) are used to tune the 4 controllers that meet the performance specifications mentioned in Section II for BIS, RASS, CO and MAP signals.

To maintain the BIS level within safe ranges from 40 to 60, despite surgical stimuli and possible Propofol boluses administered by the anesthesiologist, a FO-PI controller is tuned to minimize (7), with constraints on (5) and (6). To estimate the parameters of the FO-PI ($k_d = 0$ in (1)), the Matlab "fmincon" optimization routine was used resulting in:

$$C_{BIS}(s) = 0.0053\left(1 + \frac{0.0532}{s^{1.04}}\right) \quad (16)$$

For the RASS signal, a FO-PID controller is designed, with the following performance specifications: $\omega_c = 0.035$ rad/sec, PM= 80° and the iso-damping property. To determine the parameters of the controller, the system of nonlinear equations (2)-(4) is solved using Matlab optimization routines that yield the final transfer function of the controller:

$$C_{RASS}(s) = 0.6324\left(1 + \frac{0.0511}{s^{1.05}} + 0.9544s^{0.56}\right) \quad (17)$$

To control the CO signal, a FO-PID is tuned to meet the following specifications: PM=85°, $\omega_c = 0.035$rad/s, robustness condition in (4) and minimization of the IAE as defined in (7). The result of the Matlab optimization routine yields the following FO-PID transfer function:

$$C_{CO}(s) = 0.1639\left(1 + \frac{0.0026}{s^{1.06}} + 2.99s^{0.52}\right) \quad (18)$$

For the MAP output, the performance criteria that have been used to tune the FO-PID controller are the following:

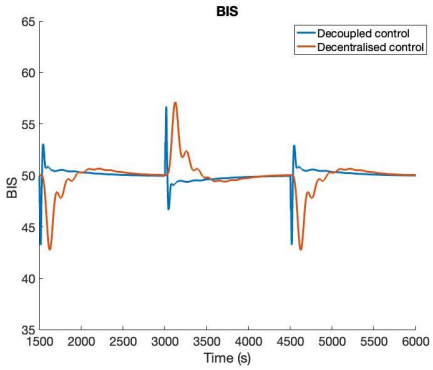
PM=80º, ω_c = 0.0056rad/s, robustness to gain variations and minimization of the error signal as indicated in (7). The FO-PID controller that meets all design specifications is computed as:

$$C_{MAP}(s) = 0.0207\left(1 + \frac{0.0078}{s^{1.08}} + 1.012s^{0.45}\right) \quad (19)$$

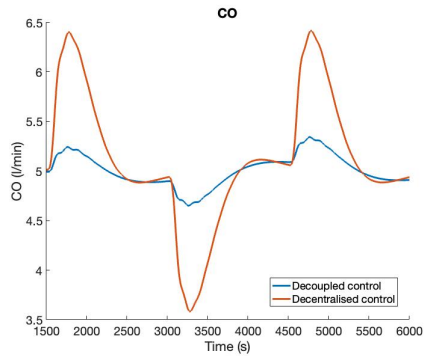
To implement the FO-PID controllers, the Oustaloup Recursive Approximation method has been used, with the low and high frequency ranges taken two decades before and after the corresponding gain crossover frequency and with the order of approximation N=5.

IV. Decoupled Vs Decentralized FO-PID Control

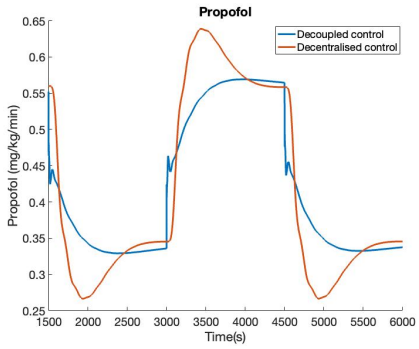
To validate the decoupling FO-PID control strategy, a comparison with the decentralized control [14] is presented first. Two case scenarios are considered to analyse the ability of the proposed control solution to reduce interactions between the anaesthesia and hemodynamic variables and administered drugs. The first case scenario implies variations in the MAP signal as follows: 85mmHg->80mmHg->85mmHg->80mmHg occurring at 1500, 3000 and 4500 seconds. According to Fig. 1, interaction is expected on the CO and BIS signals. The variations of these two signals are given in Fig. 3a) and b). The corresponding drug rates are indicated in Fig. 3c) and d). Notice the significant reduction in interaction, with a faster time to target for both BIS and CO when using the proposed decoupled control strategy. Notice also the reduced drug rates, both in terms of Propofol and Dopamine, compared to the decentralised case.



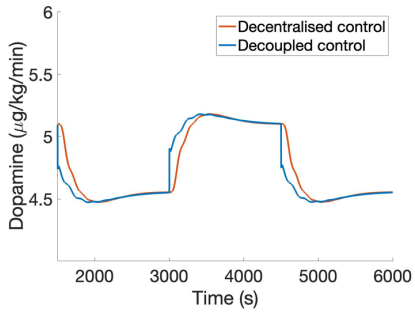
a)



b)



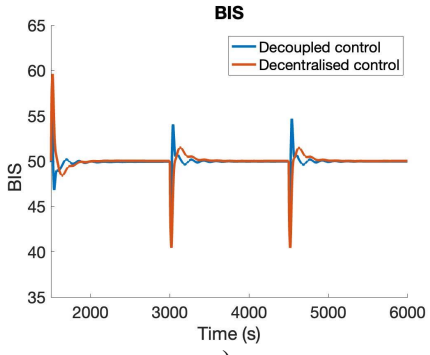
c)



d)

Fig. 3. Interaction on BIS and CO due to MAP variations a) BIS variation b) CO variation c) Propofol d) Dopamine

A second case scenario is considered to evaluate the interaction using the proposed decoupled control strategy, compared to the decentralized approach where the CO signal changes from 5l/min->5.5l/min->5lmin->4.5l/min at 1500, 3000 and 4500 seconds. The resulting changes in the BIS and MAP signals are indicated in Fig. 4a) and b), with the corresponding Propofol and Sodium Nitroprusside drug rates given in Fig. 4c) and d). Variations in the CO setpoint trigger variations in the MAP signal (due to the interaction between the hemodynamic drugs), visible in Fig. 4b). Notice that the BIS signal varies due to the interactions between the hemodynamic and anesthetic drugs (Fig. 4a)). However, the amplitude of the signal is maintained closely to the 50 setpoint when using the proposed decoupled control strategy, compared to the decentralized one. A faster rejection of interactions is achieved with the decoupled control strategy, as well. Drug rates are kept within admissible ranges (Fig. 4c) and d)).



a)

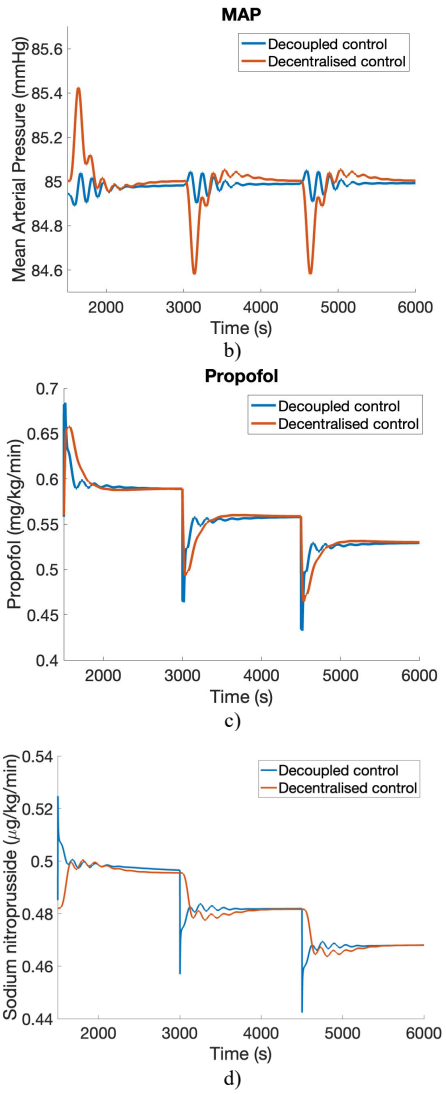


Fig. 4. Interaction on BIS and MAP due to CO variations a) BIS variation b) MAP variation c) Propofol d) Sodium Nitroprusside

V. Robustness Analysis For 24 Patients

The comparison between decentralized and decoupled approaches in Section IV has been done considering only the nominal patient. In this section, the controllers designed for the nominal patient are used in the robustness analysis for a set of 24 patients. A surgical stimulus is considered [10] that directly affects the BIS signal. Fig. 5 shows the variation of the BIS signal for all 24 patients. The quantitative performance of the decoupled control strategy is detailed in Table I. The TTd has been rounded to the nearest integer value and at the same time, the maximum TTd for each patient is included in Table I. Notice there is a fast TTd, due to fast attenuation of the disturbance. The maximum amplitude of the BIS signal is close to the upper limit of 55, whereas the minimum value is around 42. In all of the 24 patients, the designed controllers manage to maintain the BIS signal within the safety range of 40 to 60.

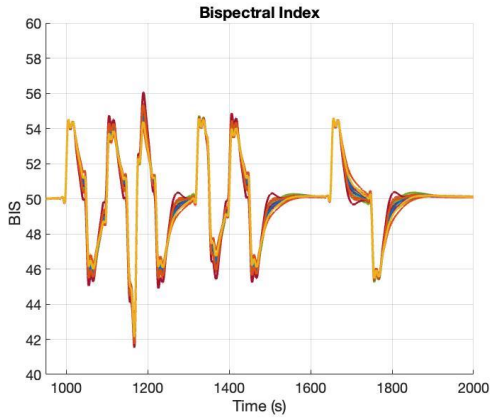
TABLE I
Performance measures for the decoupled FO-PID control strategy

Patient no	TTd	BIS-NADIRl	BIS-NADIRs
1	15.00	55.00	41.97
2	16.00	55.44	41.65
3	14.00	54.70	42.13
4	15.00	54.69	42.08
5	16.00	54.75	41.79
6	15.00	54.63	41.99
7	17.00	56.07	41.52
8	16.00	55.23	41.81
9	16.00	54.98	41.86
10	16.00	55.04	41.92
11	15.00	54.96	41.93
12	14.00	54.60	42.07
13	15.00	54.79	41.92
14	15.00	54.65	41.98
15	16.00	55.10	41.88
16	10.00	54.62	42.34
17	15.00	54.98	41.95
18	15.00	54.60	42.05
19	16.00	55.26	41.79
20	16.00	55.07	41.87
21	16.00	55.03	41.89
22	15.00	54.77	41.92
23	16.00	55.36	41.74
24	14.00	54.61	42.12

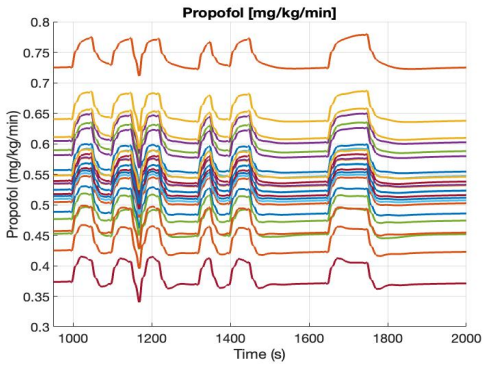
VI. Conclusion

Dynamic interactions and variability of vital signals during general anesthesia are critical in determining the safety of the patient and enhance clinical outcome and fast rehabilitation after surgery. In order to minimize the interactions between the anesthesia and hemodynamic subsystems, a steady-state decoupled control technique is presented here and compared to a previously reported decentralized approach. The fractional order controllers are tuned to reduce the effect of surgical stimulus during the maintenance phase. The simulation results show that the proposed decoupled control strategy manages to significantly reduce hemodynamic and anesthetic interactions. The analysis using real parameters from 24 patients has shown that the designed FO-PIDs are also robust to surgical stimulus.

Further research includes a combined design based on a decentralized approach during induction, followed by a steady state decoupling strategy during maintenance.



a)



b)

Fig. 5. Closed loop results using the decoupled FO-PID control strategy a) BIS as a result of surgical stimulus b) Propofol

ACKNOWLEDGMENT

This work was supported in part by a grant of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022 – I9, grant number 760018/27.01.2023 and PNRR-III- C9-2022 – I8, grant number 760068/23.05.2023. Isabela R. Birs is financed by a grant of the Ministry of Research, Innovation and Digitization, CNCS - UEFISCDI, project number PN-III-P1-1.1-PD-2021-0204, within PNCDI III.

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. I. R. Birs acknowledges the support of Flanders Research Foundation, Postdoc grant 1203224N, 2023-2026. D. Copot acknowledges the support of Flanders Research Foundation, Postdoc grant 12X6823N, 2023-2026.

REFERENCES

[1] D. Copot, *Automated Drug Delivery in Anesthesia*. Amsterdam: Elsevier, 2020.

[2] A. Joosten, J. Rinehart, A. Bardaji, P. Van der Linden, V. Jame, L. Van Obbergh, B. Alexander, M. Cannesson, S. Vacas, N. Liu, H. Slama, L. Barvais, "Anesthetic Management Using Multiple Closed- loop Systems and Delayed Neurocognitive Recovery: A Randomized Controlled Trial", *Anesthesiology*, vol. 132, pp. 253–266, 2020.

[3] C. Zaouter, A. Joosten, S. Rinehart, S. Michel, T. Hemmerling, "Autonomous Systems in Anesthesia Where Do We Stand in 2020? A Narrative Review", *Anesthesia and Analgesia*, vol. 130, pp. 1120-1132, 2020

[4] M. Ghita, M. Neckebroek, C. Muresan, D. Copot, "Closed-Loop Control of Anesthesia: Survey on Actual Trends, Challenges and Perspectives", *IEEE Access*, vol. 8, pp. 206264-206279, 2020.

[5] J.L. Fellahi, E. Futier, C. Vaisse, O. Collange, O. Huet, J. Loriau, E. Gayat, B. Tavernier, M. Biais, K. Asehnoune, B. Cholley, D. Longrois, "Perioperative hemodynamic optimization: from guidelines to implementation—an experts' opinion paper", *Ann. Intensive Care 11*, vol. 11, article number 11, 2021.

[6] Y. He, S. Peng, M. Chen, Z. Yang and Y. Chen, "A Transformer-Based Prediction Method for Depth of Anesthesia During Target-Controlled Infusion of Propofol and Remifentanil," in *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 31, pp. 3363-3374, 2023, doi: 10.1109/TNSRE.2023.3305363.

[7] A. Pawłowski, M. Schiavo, N. Latronico, M. Paltenghi, A.Visioli, "Model predictive control using MISO approach for drug co-administration in anesthesia, *Journal of Process Control*, vol. 117, pp. 98-111, 2022.

[8] Patel B, Patel H, Shah D, Sarvaia A. Control strategy with multivariable fault tolerance module for automatic intravenous anesthesia. Biomed Eng Lett. 2020 Aug 16;10(4):555-578. doi: 10.1007/s13534-020-00169-2. PMID: 33194248; PMCID: PMC7655894.

[9] D. Copot, C. Muresan, I. Birs, L. Kovacs, "Robust Hemodynamic Control Under General Anesthesia Conditions", *IFAC-PapersOnLine,* vol. 53, pp. 16179-16184, 2020.

[10] C. Ionescu, M. Neckebroek, M. Ghita, D. Copot, "An Open Source Patient Simulator for Design and Evaluation of Computer Based Multiple Drug Dosing Control for Anesthetic and Hemodynamic Variables", *IEEE Access*, vol. 9, pp. 8680-8694, 2021

[11] A. Savoca, K. van Heusden, D. Manca, J.M. Ansermino, G.A. Dumont, "The effect of cardiac output on the pharmacokinetics and pharmacodynamics of propofol during closed-loop induction of anesthesia", *Comput Methods Programs Biomed*, vol. 192, article 105406, 2020.

[12] A. Maxim, D. Copot, "Closed-loop control of anesthesia and hemodynamic system: a Model Predictive Control approach", *IFAC-PapersOnLine*, vol. 54, pp. 37-42, 2021.

[13] E.T. Hegedus, I.R. Birs, M. Ghita, C.I. Muresan, "Fractional-Order Control Strategy for Anesthesia–Hemodynamic Stabilization in Patients Undergoing Surgical Procedures", *Fractal Fract,* vol. 6, article 614, 2022.

[14] E. Hegedus, M. Ghita, I. R. Birs, D. Copot and C. I. Muresan, "Robustness analysis of a fractional order control system for the hemodynamic variables in anesthetized patients," *2023 European Control Conference (ECC)*, Bucharest, Romania, 2023, pp. 1-6, doi: 10.23919/ECC57647.2023.10178146.

[15] A. Bhattacharjee and A. Sutradhar, "Online Identification and Internal Model Control for Regulating Hemodynamic Variables in Congestive Heart Failure Patient", *Int J Pharm Med Biol Sci*, vol.4, pp. 85-89, 2015.

[16] R. R. Rao, B. Aufderheide and B. W. Bequette, "Multiple model predictive control of hemodynamic variables: an experimental study," *Proceedings of the 1999 American Control Conference,* San Diego, CA, USA, 1999, vol. 2, pp. 1253-1257, DOI:10.1109/ACC.1999.783568.

[17] C.C. Palerm, B.W. Bequette, "Hemodynamic Control using Direct Model Reference Adaptive Control – Experimental Results". *European Journal of Control,* vol. 11, pp. 558–571, 2005.