PID control of hypnotic induction in anaesthesia employing multiobjective optimization design procedures

Ricardo Massao Kagami* Renan Muniz Franco**
Gilberto Reynoso-Meza* Roberto Zanetti Freire*

**Industrial and Systems Engineering Graduate Program (PPGEPS), Pontifícia Universidade Católica do Paraná (PUCPR), Brazil, (e-mails: ricardo.zanotto@pucpr.br, g.reynosomeza@pucpr.br, roberto.freire@pucpr.br).*

***Department of Chemistry – Apucarana's Campus, Universidade Tecnológica Federal do Paraná (UTFPR), Brazil, (e-mail: rfranco@alunos.utfpr.edu.br)*

Abstract: General anaesthesia is a clinical procedure that involves the continuous monitoring of several parameters for the correct application of anaesthetics and associated drugs. Focusing on the automatic control in anaesthesia, this work presents a multiobjective optimization design of controllers based on the Non-dominated Sorting Genetic Algorithm II (NSGA-II) to solve the problem of drug delivery for induction of anaesthesia. Five Proportional-Integral-Derivative (PID) controllers in a decentralized scheme were tuned for one specific patient and tested in a total of 24 simulated patients. Acting over the infusions of Propofol, Remifentanil, Atracurium, Dobutamine, and Sodium Nitroprusside the proposed controllers could maintain the controlled variables in a safe range for surgical procedures.

Keywords: Anaesthesia, controller tuning, multiobjective problem, multivariable control, PID controller.

1. INTRODUCTION

For essential surgery procedures, access to safe anaesthesia is considered by the World Health Organization (WHO), a basic human right (Gelb et al., 2018). To conduct anaesthesia, adequate quantities of anaesthetic, analgesics, and other auxiliary drugs should be available and the WHO recommends the monitoring of several parameters such as blood pressure, neuromuscular functions, depth of anaesthesia, among others.

The monitoring of anaesthetic and hemodynamic variables, ensure the safety of the patient's life, being a critical task for operations since different information needs to be constantly monitored, and regulated. So that deviations from the ideal operating condition may result in severe trauma and eventually death of the patient (Butterworth et al., 2018).

The regulation of drugs applications in anaesthesia is mainly conducted manually by anesthesiologists, and in some cases, the drugs delivery is computer-controlled, done by open-loop target-controlled infusion systems, not existing closed-loop solutions implemented in clinical care (Ghita et al., 2020). Otherwise, studies were conducted to explore diverse possibilities of closed-loop control solutions to the drug delivery problem for anaesthesia.

In the work proposed by Ionescu et al. (2008), a model-based predictive controller with extended prediction self-adaptive control (MPC-EPSAC) was employed to control the bispectral index through the manipulation of Propofol infusion dosing during anaesthesia procedures and is simulated for 12 patient models. In another work, was employed an MPC-EPSAC strategy, where a wavelet time-frequency analysis is used to extract information from the bispectral index (BIS) to manipulate the applications of Propofol and Remifentanil infusions, to control depth of sedation (Ionescu et al., 2015).

To regulate the depth of hypnosis in anaesthesia Padula et al. (2017) proposed a Proportional-Integral-Derivative (PID) controller, with the propofol administration as the manipulated variable and the BIS as a controlled variable. The PID was optimized through genetic algorithms, with the integral of absolute error (IAE) as the minimization objective function, testing the solution in 12 patient models.

Other recent works have explored the use of PID controllers in the coadministration of propofol and remifentanil in general anaesthesia procedures, as presented by Merigo et al. (2019), with a fixed ratio of the drugs infusions and the possibility of an anesthesiologist to control the hypnotic state during surgery, and Schiavo et al. (2021), where two sets of tuning parameters allowed the control during the induction and maintenance phase of surgery, both works used BIS as feedback signal.

Two different control strategies, a predictive controller and a Bayesian rule-based optimized control, were evaluated by Neckebroek et al. (2019) to regulate BIS through the application of propofol, additionally, supplementary analgesia Remifentanil was considered, and the results were compared with manually-adapted human control. Nevertheless, such a problem remains as an open control problem, due to its complexity and multiple requirements to fulfil.

In this work, we proposed a PID controller with static gains, tuned using multiobjective optimization design procedures (Reynoso-Meza et al., 2013), to regulate the application of five drugs and control the safe induction of the patient to a hypnotic

$$\begin{bmatrix} BIS(s) \\ RASS(s) \\ NMB(s) \\ CO(s) \\ MAP(s) \end{bmatrix} = \begin{bmatrix} G_{BIS,PR}(s) & G_{BIS,RE}(s) & 0 & 0 & 0 \\ 0 & G_{RASS,RE}(s) & 0 & 0 & 0 \\ 0 & G_{NMB,RE}(s) & G_{NMB,AT}(s) & 0 & 0 \\ G_{CO,PR}(s) & G_{CO,RE}(s) & 0 & G_{CO,DB}(s) & G_{CO,SNP}(s) \\ G_{MAP,PR}(s) & G_{MAP,RE}(s) & 0 & G_{MAP,DB}(s) & G_{MAP,SNP}(s) \end{bmatrix} \begin{bmatrix} PR \\ RE \\ AT \\ DB \\ SNP \end{bmatrix} \quad (1)$$

state. Aiming also to control the perception of pain, neuromuscular block, cardiac output, and the mean arterial pressure to levels where surgical procedures can be initiated.

The next section of the presented paper shows the drug dosing control problem for anaesthetic and hemodynamic variables in patients in a simulation environment. Section 3 presents the stated multiobjective approach for the described problem, assuming the control strategy adopted in this work. Section 4 discusses the results obtained in this research, followed by the conclusion and future works that were described in section 5.

2. THE DRUG DELIVERY PROBLEM

To simulate the biological behaviour of patients submitted to the hypnosis induction, with multiple variables and control objectives, the work presented in (Ionescu et al., 2021) proposed an open-source model for multiple drug dosing control, where anaesthetic and hemodynamic variables can be monitored and considered in the control strategy. The proposed benchmark includes a representative database of 24 patients with different information, e.g., age with median value 69 years and varying between [45; 75] years, height with median 172.5 cm, interval [155; 192] cm, weight 82.5 kg of median value, [55; 114] kg, and lean body mass (LBM) with median 60% and interval [77; 44]%, causing the behaviour and reactions to the drugs to occur differently for each of the simulated patients.

The related system was modelled based on the control of the application of five different drugs, i.e., Propofol infusion (PR), Remifentanil infusion (RE), Atracurium infusion (AT), Dobutamine infusion (DB), and Sodium Nitroprusside (SNP), to control five output indicators, the Bispectral Index (BIS), Ramsey Agitation and Sedation Score ($RASS$), Neuromuscular Blockade (NMB), Cardiac Output (CO) and Mean Arterial Pressure (MAP). The description of the manipulated and output variables, their operation ranges, and initial conditions are presented in Table 1.

3. PROCEDURES FOR CONTROL TUNING

In this section, we discuss the multiobjective optimization procedures, which was proposed by Reynoso-Meza et al. (2013), that is composed of three main steps: the formulation of the multiobjective problem where the parametric model is obtained and the cost functions established; the multiobjective optimization with the selection and employment of a multiobjective optimization algorithm to obtain the Pareto Front; and, in the final step, the decision making where some selection criteria are applied to obtain a single feasible solution for the problem.

3.1 Multiobjective Problem Formulation

To identify the transfer functions of the multiple inputs multiple outputs (MIMO) system, open-loop tests were performed considering patient 1. The criteria for simulation of the drugs stimulation, i.e., the application of the drugs to the open-loop system, was based on the standards of the Brazilian therapeutic national formulary (Ministry of Health et al., 2010), where the Propofol is indicated to induce the patient to the ideal hypnosis state; Remifentanil as adjuvant analgesia; Atracurium a neuromuscular blocker, used for muscle relaxation; Dobutamine to increase the strength of cardiac muscle contraction; and Sodium Nitroprusside acts as a vasodilator to reduce heart pressure.

To obtain the parametric model, used in the multiobjective optimization step, the drugs profiles described previously were considered, being applied directly into patient 1, with 74 years, height 164 cm, weight 88 kg and LBM 60%, of the simulation model provided in (Ionescu et al., 2021) in an open-loop structure, with the application of one drug at a time.

The open-loop structure, constituting a MIMO model, characterising the relationships between the five controlled variables BIS, $RASS$, NMB, MAP, and CO through the five manipulated variables PR, RE, AT, DB and SNP are presented in (1).

Table 1. Manipulated variables, disturbances, and output variables

Description	Symbol	Operation Range	Initial Value	Unit
Manipulated Variables (MV)				
Propofol infusion	PR	[0, 5]	0	$mg(kg\ min)^{-1}$
Remifentanil infusion	RE	[0, 2.5]	0	$\mu g(kg\ min)^{-1}$
Atracurium infusion	AT	[0, 15]	0	$\mu g\ (kg\ min)^{-1}$
Dobutamine infusion	DB	[0, 10]	0	$\mu g(kg\ min)^{-1}$
Sodium Nitroprusside infusion	SNP	[0, 10]	0	$\mu g(kg\ min)^{-1}$
Output Variables (OV)				
Bispectral Index	BIS	[40, 60]	100	%
Ramsay Agitation and Sedation Score	$RASS$	[-5, 4]	0	-
Neuromuscular Blockade	NMB	[0, 100]	100	%
Cardiac Output	CO	[4, 7]	5	$L\ min^{-1}$
Mean Arterial Pressure	MAP	[65, 110]	80	$mmHg$

The transfer functions of the MIMO model, are presented in (2-14), the transport delay was obtained through the average time of onset of drugs action (Ministry of Health et al., 2010), and as the Atracurium was described as a drug with a quick onset of action, however, to simulate the time from the drug setting and the desirable effect response, a delay of 10 s was considered.

$$G_{BIS,PR}(s) = -\frac{26.8}{215.1s+1}e^{-30s} \quad (2)$$

$$G_{BIS,RE}(s) - \frac{2.95}{11.4s+1}e^{-60s} \quad (3)$$

$$G_{RASS,RE}(s) = -\frac{2.32}{18.5s+1}e^{-60s} \quad (4)$$

$$G_{NMB,RE}(s) = -\frac{0.55}{6.07s+1}e^{-60s} \quad (5)$$

$$G_{NMB,AT}(s) = -\frac{6.55}{7.8s+1}e^{-10s} \quad (6)$$

$$G_{MAP,PR}(s) = -\frac{3.6}{718.6s+1}e^{-30s} \quad (7)$$

$$G_{MAP,RE}(s) = -\frac{4.15}{26.7s+1}e^{-60s} \quad (8)$$

$$G_{MAP,DB}(s) = \frac{-10.96s+3.00}{35.55e3s^3+1.18e3s^2+69.66s+1}e^{-60s} \quad (9)$$

$$G_{MAP,SNP}(s) = \frac{62.21s-15.02}{21.24e3s^3+8.26e2s^2+61.82+1}e^{-45s} \quad (10)$$

$$G_{CO,PR}(s) = -\frac{0.48}{509.8s+1}e^{-30s} \quad (11)$$

$$G_{CO,RE}(s) = \frac{0.466}{17.1s+1}e^{-60s} \quad (12)$$

$$G_{CO,DB}(s) = \frac{-61s+5}{5.639e3s^2+317.3s+1}e^{-60s} \quad (13)$$

$$G_{CO,SNP}(s) = \frac{-94.8s+1}{2.025e3s^2+161.5s+1}e^{-45s} \quad (14)$$

Related to the parametric model, characterised by a closed-loop control structure (Fig. 1), with reference $R_.(s)$ based on the intervals for surgeries, its main objective is to present a set of PID controllers with static gains and structure:

$$C(s) = K_p + \frac{K_i}{s} + K_d\frac{Ns}{s+N}, \quad (15)$$

in a decentralized control scheme, where the application of one specific drug aims to regulate one specific controlled variable.

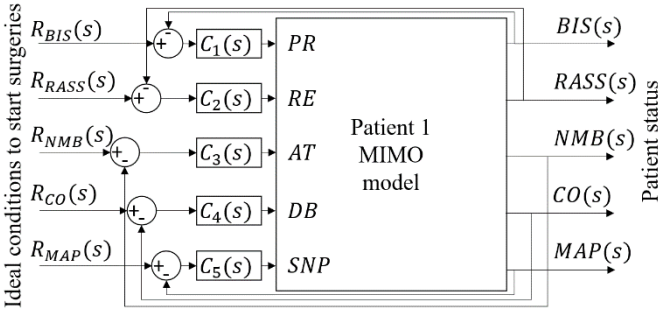

Figure 1. Parametric model.

To evaluate possible solutions of controllers, two performance metrics were considered (16-17), the integral of absolute error $J_{IAE}(\boldsymbol{\theta})$, representing the difference between the reference and the output of the controlled variables, and the total variation of the control signal $J_{TV}(\boldsymbol{\theta})$, a robustness measure related to the output signal of the controller $C(s)$, i.e., time variations in the application of the drug/manipulated variable.

$$J_{IAE}(\boldsymbol{\theta}) = \int |e_i(t)|dt\,, \qquad J_{TV}(\boldsymbol{\theta}) = \int \left|\frac{dU_i(t)}{dt}\right| dt \quad (16)$$

Thus, the multiobjective function is defined as:

$$\min_{\boldsymbol{\theta}} J_m(\boldsymbol{\theta}) = \left[J_{k(IAE)}(\boldsymbol{\theta}),\ J_{k(TV)}(\boldsymbol{\theta})\right]^T, k = [1, \ldots, 5], \quad (17)$$

where $\boldsymbol{\theta} = \left[K_{p1}, K_{i1}, K_{d1}, N_1, \ldots, K_{p5}, K_{i5}, K_{d5}, N_5\right]^T$ is the decision vector, associated with the proportional gains (K_{pk}), integral gains (K_{ik}), derivative gains (K_{dk}) and derivative filters (N_k) of the PID controller equation, the relationship between the 10 cost functions, the 5 PID controllers, and manipulated and controlled variables are presented in Table 2.

Table 2. Relationship controllers/cost functions/variables

Cost Functions	Controller	Manipulated Variable	Controlled Variable
$J_{1(IAE)}$, $J_{1(TV)}$	$C_1(s)$	PR	BIS
$J_{2(IAE)}$, $J_{2(TV)}$	$C_2(s)$	RE	$RASS$
$J_{3(IAE)}$, $J_{3(TV)}$	$C_3(s)$	AT	NMB
$J_{4(IAE)}$, $J_{4(TV)}$	$C_4(s)$	DB	CO
$J_{5(IAE)}$, $J_{5(TV)}$	$C_5(s)$	SNP	MAP

The constraints of the multiobjective optimization problem are defined as the critical stabilization limits for the PID gains of the decision vector and are presented in Table 3.

Table 3. Restrictions of the multiobjective problem

	K_p	K_i	K_d	N
$C_1(s)$	[-6e-2, 0]	[-6.2e-4, 0]	[-5e-2, 0]	[0, 100]
$C_2(s)$	[-0.4, 0]	[-3.7e-2, 0]	[-0.35, 0]	[0, 100]
$C_3(s)$	[-5.3e-2, 0]	[-5.7e-3, 0]	[-0.05, 0]	[0, 100]
$C_4(s)$	[0, 0.19]	[0, 1.3e-3]	[0, 0.17]	[0, 100]
$C_5(s)$	[-7.5e-3, 0]	[-3.3e-4, 0]	[-6e-3, 0]	[0, 100]

3.2 Multiobjective optimization and Controller Selection

The multiobjective optimization step consists of the application of an algorithm to obtain a Pareto Front, we selected the Non-dominated Sorting Genetic Algorithm II (NSGA-II) (Deb et al., 2002), since diverse works were presented for control tuning with good results in different areas of study (Deng et al., 2019; Kagami et al., 2020).

The NSGA-II was applied considering a population of 50 individuals and 100 generations, with default values for the genetic operators. Figure 2 presents the Pareto Front with cost functions of the solutions standardised with mean 0 and standard deviation [-1, 1], the chosen solution is highlighted, and the selection criteria are described below.

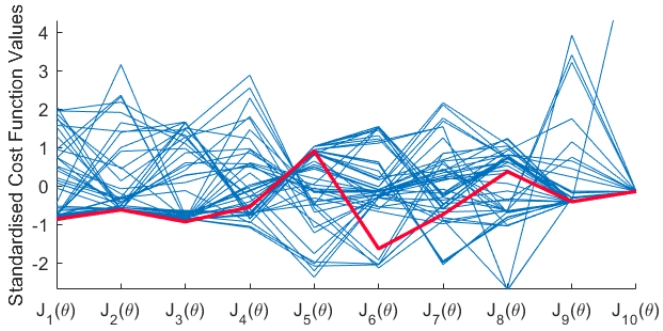

Figure 2. Standardised Pareto Front.

To select a single solution for the problem, different strategies can be employed, such as the use of multi-criteria decision-making methods (MCDM), the trade-offs exploration presented in the Pareto Front, or even the application of successive filtering aims to remove undesirable behaviours from the set of solutions (Reynoso-Meza et al., 2017).

Due to the difficulty of conducting a trade-off analysis in the obtained Pareto Front, mainly caused by the objectives dimensionality, the MCDM Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) (Hwang & Yoon, 1981; Lai et al., 1994) was applied. The concept of TOPSIS orders the Pareto Front solutions based on proximity to the Positive Ideal Solution (PIS) and the remoteness of the Negative Ideal Solution (NIS), i.e., calculate de Euclidian distance of PIS ($d\{\text{PIS}\}$) and NIS ($d\{\text{NIS}\}$) for each solution and select the best solution, according to (18), the concept to a 2-dimensional problem is represented in Fig. 3.

$$\text{best solution} = \arg\min\left\{\frac{d\{NIS\} - d\{PIS\}}{d\{NIS\}}\right\} \qquad (18)$$

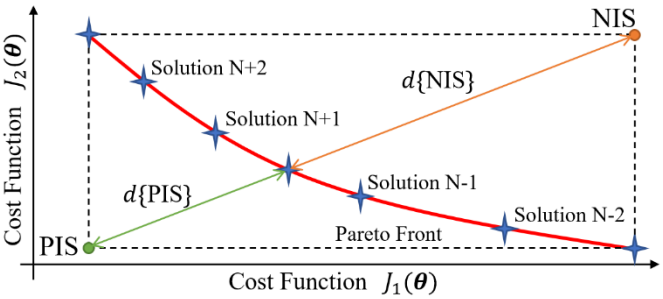

Figure 3. 2-dimensional TOPSIS concept.

4. RESULTS AND ANALYSIS

The PID controller solution, obtained as described in the previous section is presented in Table 4.

Table 4. Gains of the PID controllers

	K_p	K_i	K_d	N
$C_1(s)$	-3.98e-3	-2.15e-4	-1.42e-2	74.18
$C_2(s)$	-3.46e-1	-2.36e-2	-2.70e-1	76.39
$C_3(s)$	-3.67e-2	-5.60e-3	-1.60e-2	57.18
$C_4(s)$	1.06e-1	5.57e-4	2.62e-2	35.95
$C_5(s)$	-3.21e-3	-1.78e-4	-6.00e-3	33.14

The parametric model used for controller tuning considered only patient 1 (age 74 years, height 164 cm, weight 88 kg and LBM 60%). Nonetheless, further control tests consider the full set of patients are evaluated in the benchmark (Ionescu et al., 2021). The tests aimed to verify the feasibility of the PID controllers with static gains, in the induction to the hypnotic, pain suppressed and muscular relaxation state, making it possible to start surgical operations.

Related to the BIS, the interval [40, 60]%, provides patient's health safety, and reduced risk of postoperative cognitive dysfunction. Conducting operations outside this range should also be avoided, as having $BIS > 60\%$ can cause sudden regaining of consciousness, and $BIS < 40\%$ refers to the deep hypnotic state, presenting cortical silence and increasing burst suppression pattern (Butterworth et al., 2018). Exposure to $BIS < 40\%$ for a time longer than 5 minutes is also associated with postoperative problems (Nunes et al., 2015).

The BIS of the proposed solution, tested in all 24 patients, is presented in Fig. 4, in all cases, there were no occurrences in which the upper limit was exceeded after entering the operation zone. Concerning overshooting the lower limit, there were occurrences in only two patients, the first one reaching 39.45% and remaining outside the interval for 4 seconds, and the second one, reaching 36.10% and remaining outside the interval for 12 seconds, significantly shorter than the time limit of 5 minutes. The time to reach the interval varied between 39 and 48 seconds, with a mean of 41.5 seconds.

Related to sedation level, the $RASS$ with a value of -5 indicates an unarousable state, with no response to voice or physical stimulation that endangers the patient's life and should be avoided (Hobaika et al., 2007; Rasheed et al., 2018), therefore close to -4 the desired indicator. It is possible to visualise, in Fig. 5, the transitions between the different sedation scales in the 24 patient cases, with the time-varying between 43 and 68 seconds, with 53.5 seconds of mean time.

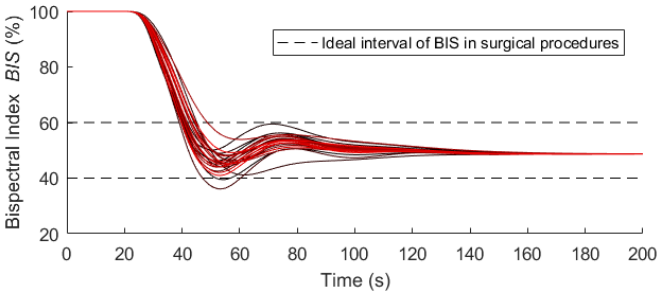

Figure 4. Controlled BIS response.

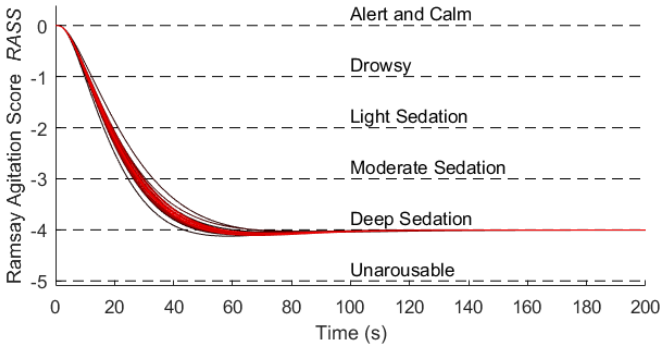

Figure 5. Controlled $RASS$ response.

The NMB considered to work in the interval [0, 5]% indicates that the muscles will be sufficiently flaccid so that the patient does not have contractions and spasms and facilitates the intubation procedure (Cardoso et al., 2016), this interval was reached in a time between 48 and 49 seconds, Fig. 6.

The safety intervals considered for CO and MAP, [4, 7] $L\,min^{-1}$ and [65, 110] mmHg respectively, were not exceeded. CO presented a variation of 5 to 5.4 $L\,min^{-1}$ and MAP 80 to 68.7 $mmHg$ during all the transition time to the hypnotic state, the haemodynamics are shown in Fig. 7.

The control signal of manipulated variables, i.e., the profiles of drug applications, are presented in Fig. 8 for PR (with an application peak of 5 $mg(kg\,min)^{-1}$ at the initial instant and quick stabilisation), RE and AT. In the case of DB and SNP, the first one acts to increase the CO, but it did not show any reduction during the conduction to the hypnotic state; the same happened with SNP with acts reducing the MAP, no being necessary to use both.

Since the PID controllers were designed to work with the induction of the patients to the operating state, their performance during the surgical stages does not present good maintenance performance relative to the ideal interval of these procedures, as presented in Fig. 9, thus other control strategies should be adopted.

5. CONCLUSIONS

This work presented the use of a multiobjective optimization framework aiming to control drug applications using simple PID controllers in a decentralized scheme to the safe induction of the patient to a hypnotic state. Having also considered pain perception, neuromuscular blockade, cardiac output and mean arterial pressure as control objectives.

In the adopted strategy, hill nonlinear behaviours were approximated by linear functions, so that the tunned controllers for the model identified in the response of patient 1, could act in a generalist way toward the behaviours of the other patients. Thus, the considered approach was able to conduct all the 24 simulated patients to the hypnotic state, and safety regions for surgical procedures.

The proposed controllers reached the BIS interval in a time-varying from 39 to 48 seconds, providing overshoots with duration and exposure time sufficiently small, so that would not endanger the health of patients under real-life circumstances. The transition between the $RASS$ index from 0 to -4 was conducted smoothly by the controller, not coming closer to the -5 value (a life-threatening coma), with a mean time of 53.5 seconds.

The presented strategy showed that the PID controllers with static gains, when correctly tunned, based on multiobjective optimization procedures, can perform satisfactory results despite its simplicity, even so, further studies are necessary to ensure safety, before clinical trials are carried out.

The next steps of this research will consider the control for disturbance rejection of surgical interventions with the improvement of strategies for interval reference tracking.

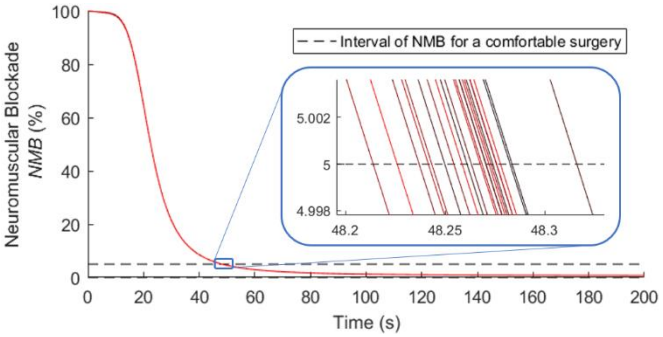

Figure 6. Controlled NMB response.

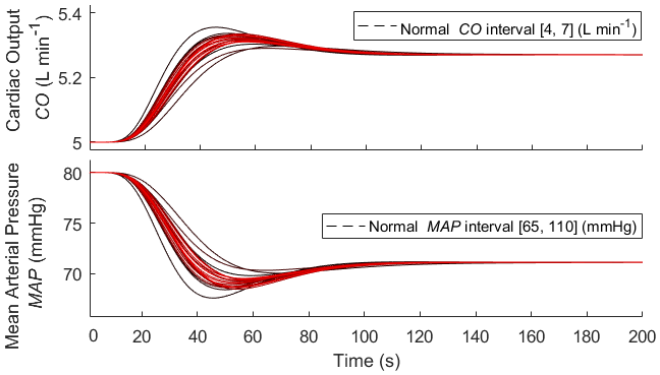

Figure 7. Controlled CO and MAP responses.

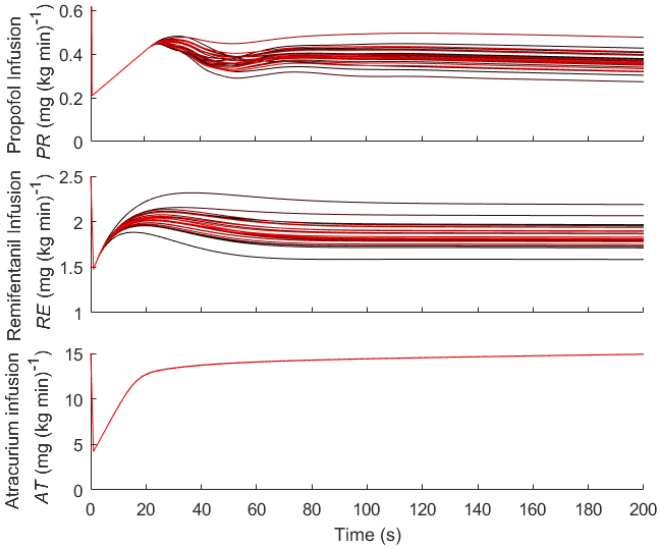

Figure 8. Manipulated PR, RE and AT infusions.

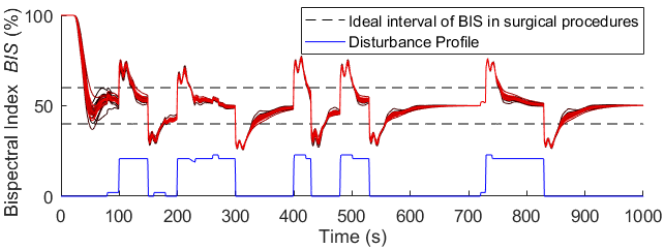

Figure 9. BIS response with the presence of disturbances.

ACKNOWLEDGMENT

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The Conselho Nacional de

Desenvolvimento de Científico e Tecnológico (CNPq), and the Fundação Araucária (FAPPR) – Brazil – Finance Codes: 310079/2019-5-PQ2, 437105/2018-0-Univ, 51432/2018-PPP, 016-20/FA-PPP and PRONEX-042/2018.

REFERENCES

Butterworth, J. F., Mackey, D. C., & Wasnick, J. D. (2018). *Morgan and Mikhail's Clinical Anesthesiology* (6th ed.). McGraw-Hill Education / Medical.

Cardoso, M. V. P., Andrade, M. A. V., Melo, J. A. V. de, Rocha, W. C., Resende, F. A., & Amorim, A. V. C. (2016). Bases of neuromuscular monitoring. *Rev Med Minas Gerais*, *26*(Supl 1), 34–38.

Deb, K., Pratap, A., Agarwal, S., & Meyarivan, T. (2002). A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans on Evolutionary Comp*, *6*(2), 182–197.

Deng, T., Lin, C., Luo, J., & Chen, B. (2019). NSGA-II multi-objectives optimization algorithm for energy management control of hybrid electric vehicle. *Proceedings of the Institution of Mechanical Engineers, Part D: Jour of Automobile Eng*, *233*(4), 1023–1034.

Gelb, A. W., Morriss, W. W., Johnson, W., & Merry, A. F. (2018). World Health Organization-World Federation of Societies of Anaesthesiologists (WHO-WFSA) International Standards for a Safe Practice of Anesthesia. *Canadian Jour of Anesthesia/Jour Canadien d'anesthésie*, *65*(6), 698–708.

Ghita, M., Neckebroek, M., Muresan, C., & Copot, D. (2020). Closed-loop control of anesthesia: Survey on actual trends, challenges and perspectives. *IEEE Access*, *8*, 206264–206279.

Hobaika, A. B. S., Fantini, C. N. C., Figueiredo, C. L., Santos, P. R., & Alves, N. G. (2007). Consciousness level monitorization in anesthesia. *Rev. Med. Minas Gerais*, *17*, 54–59.

Hwang, C.-L., & Yoon, K. (1981). Methods for Multiple Attribute Decision Making. In *Lecture Notes in Economics and Math Systems* (pp. 58–191). Springer.

Ionescu, C. M., Keyser, R. De, Torrico, B. C., Smet, T. De, Struys, M. M. R. F., & Normey-Rico, J. E. (2008). Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia. *IEEE Trans on Biom Eng*, *55*(9), 2161–2170.

Ionescu, C. M., Neckebroek, M., Ghita, M., & Copot, D. (2021). An Open Source Patient Simulator for Design and Evaluation of Computer Based Multiple Drug Dosing Control for Anesthetic and Hemodynamic Variables. *IEEE Access*, *9*, 1–1.

Ionescu, C., Machado, J., De Keyser, R., Decruyenaere, J., & Struys, M. M. R. F. (2015). Nonlinear dynamics of the patient's response to drug effect during general anesthesia. *Communications in Nonlinear Science and Numerical Simulation*, *20*(3), 914–926.

Kagami, R. M., Kovalski, G., Uhlmann, T. S., Mendes, L. A., & Freire, R. Z. (2020). A Generic WebLab Control Tuning Experience Using the Ball and Beam Process and Multiobjective Optimization Approach. *Information*, *11*(3), 132.

Lai, Y.-J., Liu, T.-Y., & Hwang, C.-L. (1994). Theory and Methodology TOPSIS for MODM. *European Journal of Operational Research*, *76*, 486–500.

Merigo, L., Padula, F., Latronico, N., Paltenghi, M., & Visioli, A. (2019). Optimized PID control of propofol and remifentanil coadministration for general anesthesia. *Communications in Nonlinear Science and Numerical Simulation*, *72*, 194–212.

Ministry of Health, B., Secretariat for Science, Technology and Strategic Supplies, ., & Department of Pharmaceutical Assistance and Strategic Supplies, . (2010). *Formulário Terapêutico Nacional 2010: RENAME 2010 (Therapeutic National Formulary)* (2nd ed.). Editora MS (Brazilian Ministry of Health).

Neckebroek, M., Ionescu, C. M., van Amsterdam, K., De Smet, T., De Baets, P., Decruyenaere, J., De Keyser, R., & Struys, M. M. R. F. (2019). 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. *Journal of Clinical Monitoring and Computing*, *33*(4), 675–686.

Nunes, R. R., Fonseca, N. M., Simões, C. M., Rosa, D. M., Silva, E. D., Cavalcante, S. L., Lopes, C. G., & Stefani, L. C. (2015). Brazilian consensus on anesthetic depth monitoring. *Brazilian Jour of Anesthes*, *65*(6), 427–436.

Padula, F., Ionescu, C., Latronico, N., Paltenghi, M., Visioli, A., & Vivacqua, G. (2017). Optimized PID control of depth of hypnosis in anesthesia. *Computer Methods and Programs in Biomedicine*, *144*, 21–35.

Rasheed, A., Amirah, M., Abdallah, M., PJ, P., Issa, M., & Alharthy, A. (2018). RAMSAY Sedation Scale and Richmond Agitation Sedation Scale (RASS): A Cross Sectional Study. *Health Science Jour*, *12*(6), 1–5.

Reynoso-Meza, G., Blasco Ferragud, X., Sanchis Saez, J., & Herrero Durá, J. M. (2017). *Controller Tuning with Evolutionary Multiobjective Optimization* (J. Mukherjee (ed.); Vol. 85). Springer International Publishing.

Reynoso-Meza, G., Garcia-Nieto, S., Sanchis, J., & Blasco, F. X. (2013). Controller Tuning by Means of Multi-Objective Optimization Algorithms: A Global Tuning Framework. *IEEE Trans on Control Systems Technology*, *21*(2), 445–458.

Schiavo, M., Padula, F., Latronico, N., Merigo, L., Paltenghi, M., & Visioli, A. (2021). Performance evaluation of an optimized PID controller for propofol and remifentanil coadministration in general anesthesia. *IFAC Jour of Systems and Control*, *15*, 100121.