An optimal control approach to anesthesia administration

Paolo Di Giamberardino [1], Daniela Iacoviello [2]

Abstract— **Drug dosage represents an interesting topic in view of providing guidance to determine efficient and less toxic as possible personalized dosing. In particular, anesthesia effects strongly depends on subject's characteristics, weight, height, age; the bispectral (BIS) index, in the scale** 0-100**, is an index ranging from deep unconsciousness up to the normal brain activity, with the values between** 40 **and** 60 **ideal for general anesthesia conditions. In this paper, an optimal control strategy is proposed to regulate the drug concentration close to a reference value (corresponding to the BIS reference one) by using as less anesthesia as possible. The first results seem interesting showing the influence of specific parameters in the evolution of the drug inside the body, in particular in the site of drug infusion, in the peripheral fast compartment, say the muscles, and the slow dynamic one, say the fat.**

I. Introduction

Drug dosage control has been receiving increasing attention in recent years, to provide guidance for increasingly less toxic, more efficient and more personalized dosing. This is particularly important for dosages related to diseases such as diabetes, which are highly dependent on the patient's age, or chemotherapy, which is extremely toxic to healthy tissue, [1], [2], [3], [4]. Another area in which the dosage of a drug is extremely important concerns anesthesia, [5], [6], [7], [8]; it involves bringing the patient into a state of non-perception of pain, state of sleeping, without running the risk of death. The process of anesthesia is the combination of hypnosis, analgesia and neuromuscolar blockade, [9]. An index used as controlled variable is the bispectral index (BIS) in the scale from 0 to 100, where the lower values represent deep unconsciousness and higher values the normal brain activity, [10], the target range is $40-60$ for general anesthesia. Another index used to monitor brain's electrical activity is the wavelet-based anesthetic value for central nervous system index (WAV_{CNS}), that ranges from the isoelectric EEG, assigned value 0, to fully awake, value 100; also for this index the target range is $40-60$.

The problem of regulating the depth of hypnosis (DoH) by means of propofol in a total intravenous anesthesia modality has been largely addressed, to monitor and control drug delivery, [5], [11]; in [7], the open-loop and closed loop target - controlled infusion systems are discussed. The anesthesiologist experience, based on pharmacokinetics principles, determines the initial drug concentration and, depending on the patient's conditions, monitors and controls the dosage; on the other hand, attempts fo a human-independent closed loop systems, trying to mimic automatic dosage controller, must be a support to the anesthesiologists, thus making the distinction between open-loop and closed-loop not clear. The control strategy starts from a pharmacokinetics/pharmacodynamics model, being important both the steps of infusion-distribution-elimination of the drug in the body and the effect-site drug concentration, that is *how the body modifies the drug* as well as *how the drug modifies the body*. The dynamics of the anesthetic is generally described by means of a compartmental model in which the primary compartment, the blood, is the main compartment, and it is flanked by two other sites, referred to as the fast and the slow compartments, indicating respectively well perfused body tissues (i.e. muscles) and poorly perfused ones (i.e. fat). Generally, the dynamics is described with the same model, referring to the drug quantities in the compartments, as in [5], or to the drug concentrations, as in [6]. It is necessary to stress that in anesthesia the dosage is strictly linked to the sex, age and physical structure of the patient, as height and weight; these biometric values influence the model parameters, thus providing different dynamics depending on the subject. What distinguishes the different approaches in literature is the control strategy for the regulation of propofol administration as anaesthetic. Taking into account the requirements for a save and effective anesthesia, the control approaches more investigated in the last 10 years, as the model predictive approach, [6], and the optimal PID control, as in [5]. In particular, the latter approach seems to be more effective than the former one showing a faster induction time. In [12], it is discussed the possibility of propofol–remifentanil induced general anesthesia with a data driven identification, where the possibility of introducing artificial intelligence for drug infusion rate advisory systems is outlined in [13]. In this paper, an optimal control is proposed, able to induce anesthesia in short time without oscillations in the BIS behaviour and keeping the reference value with as low dosage as possible. The paper is organized as follows: in Section II the mathematical model adopted in this paper is briefly recalled, whereas in Section III the optimal control strategy is introduced. In Section IV, numeral results show the effectiveness of the proposed control, and in Section V conclusions and and future works are outlined.

II. Materials and methods

A. Modeling

The model adopted in this Section is the one described in [5], that follows the classical compartmental structure. Three

[1]Department of Computer, Control and Management Engineering Antonio Ruberti, Sapienza University of Rome
paolo.digiamberardino@uniroma1.it
[2]Department of Computer, Control and Management Engineering Antonio Ruberti, Sapienza University of Rome
daniela.iacoviello@uniroma1.it

main compartments are considered; the first one, whose quantities are identified by the subscript 1, is the primary compartment, site of the drug infusion indicated in the following with u; the second compartment, whose quantities are identified by the subscript 2, is the peripheral fast compartment (including, for example muscles and tendons). The third compartment, whose quantities are identified by the subscript 3, is the slow dynamic compartment (including, for example, fat and bones). In the model, x_i , $i = 1,2,3$, is the drug quantity in the i–th compartment, measured in milligram $[mg]$. It is necessary to introduce also x_4, the effect site concentration; this quantity has the important role of taking into account the lag between the blood plasma concentration and its clinical effects. The dynamical model assumes the form

$$\begin{aligned}\dot{x_1}(t) =& -(k_{10}+k_{12}+k_{13})x_1(t)+k_{12}x_2(t)\\ &+k_{31}x_3(t)+u(t) \quad (1)\\ \dot{x_2}(t) =& k_{12}x_1(t)-k_{21}x_2(t) \quad (2)\\ \dot{x_3}(t) =& k_{13}x_1(t)-k_{31}x_3(t) \quad (3)\\ \dot{x_4}(t) =& -k_{14}x_4(t)+k_{24}\frac{x_1(t)}{V_1} \quad (4)\end{aligned}$$

where V_i is the volume of the i–th compartment, measured in liter $[L]$; from [5], they are usually taken as

$$V_1 = 4.27 \quad V_2 = 18.9-0.391(age-53) \quad V_3 = 2.38 \quad (5)$$

The parameter k_{10} denotes the elimination rate of the drug from compartment 1; k_{14} is the elimination rate in the effect site concentration equation, whereas k_{24} is the effect site rate transfer parameter. The transfer constants k_{12}, k_{13}, k_{21}, k_{31}, are expressed by means of quantities strictly depending on characteristics of patient, like sex, the age, the height, the weight:

$$k_{12}=\frac{C_2}{V_1}, k_{13}=\frac{C_3}{V_1}, k_{21}=\frac{C_2}{V_2}, k_{31}=\frac{C_3}{V_3} \quad (6)$$

where C_i, measured in $[L/min]$, are the clearance of the i–th compartment, [5]:

$$\begin{aligned}C_1 =& 1.89+0.00456(weight-77)-0.0681(lbm-59)\\ &+0.02654(height-177) \quad (7)\\ C_2 =& 1.89+0.024(age-53) \quad (8)\\ C_3 =& 0.0836 \quad (9)\end{aligned}$$

with weight expressed in kilograms $[Kg]$, height in centimeters $[cm]$ and lbm, the *lean body mass*, is usually obtained by the method of James described in [14], distinguishing between male

$$lbm = 1.1weight-128\frac{weight^2}{height^2} \quad (10)$$

and female

$$lbm = 1.07weight-148\frac{weight^2}{height^2} \quad (11)$$

The bispectral index scale (BIS) yields a measure of the brain activity based on the bispectral analysis of the patient EEG signal. The values are normalized between 0, and 100 with:

- $BIS \in [0-20]$: deep unconsciousness, typical of a state of deep general anesthesia;
- $BIS \in [20-40]$: a state of moderate unconsciousness, suitable for surgical procedures requiring a high degree of muscle relaxation and analgesia;
- $BIS \in [40-60]$: optimal state of hypnosis for most surgical procedures, with a good balance between sedation and response to stimuli;
- $BIS \in [60-80]$: a state of light sedation, suitable for less invasive interventions or for procedures that require a certain level of patient cooperation;
- $BIS \in [80-100]$: awake patient, with normal brain activity.

The relation between the plasma drug concentration and clinical effects is governed by a sigmoid–like behaviour:

$$BIS(t) = E_0 - E_{max}\left(\frac{x_4^{\gamma}(t)}{x_4^{\gamma}(t)+C_{e50}^{\gamma}}\right) \quad (12)$$

where E_0 is the baseline value corresponding to the initial infusion free state and C_{e50} is the concentration of drug necessary to obtain the half maximal effect.

Note that formula (12) allows to determine also the range of values acceptable for variable $x_4(t)$ during the anaesthesia process, once the acceptable values of BIS have been substituted. In particular,

$$x_4(t) = \frac{(E_0-BIS(t))^{1/\gamma}C_{e50}}{(BIS(t)-E_0+E_{max})^{1/\gamma}} \quad (13)$$

In the next Section III, an optimal control strategy is determined, aiming at a safe anesthesia with a dosage as low as possible.

III. Optimal anesthesia strategy

The determination of the suitable anesthesia strategy to induce unconsciousness to patient, both to avoid pain and memory of the surgery, is required for a suitable dosage of medication, possibly personalized to avoid over or underdosing. The goal is to determine the strategy that allows to use as less medication as possible, forcing the state x_4 to track the ideal value x_4^{ref} obtained from (13), once $BIS = BIS_{ref}$, that is the value of the bispectral index scale corresponding to the desired unconsciousness condition, typically set between $[40 \quad 60]$.

Problem: Consider the system (1) - (4), with given initial conditions $x_{i0} = x_i(t_i)$, $i = 1,..,4$; find, in the fixed interval $[t_i, t_f]$, a control satisfying the box constraints:

$$q_1(t) = u_{min}-u(t) \le 0 \quad q_2(t) = u(t)-u_{max} \le 0 \quad (14)$$

and minimizing the cost index:

$$J(u) = \int_{t_i}^{t_f}(p(t)(x_4(t)-x_4^{ref})^2+r(t)u^2(t))dt \quad (15)$$

with $p(t) \ge 0$ and $r(t) > 0$.

Note that the system (1)-(4) is linear, the cost index (15) is quadratic; the initial and final time are fixed and the control must satisfy box constraints (14), $u(t) \in [u_{min}, u_{max}]$. Therefore, the problem is convex, thus allowing the application of necessary and sufficient conditions of global optimum. In particular, by applying the calculus of variation and optimal control theory, the following result can be stated.

Theorem Given the system (1)–(4) with fixed initial condition x_{io}, $i = 1,..,4$, and the cost index (15), define the Hamiltonian function:

$$H(x,u,\lambda) = p(t)(x_4(t) - x_4^{ref})^2 + r(t)u^2(t) + \lambda^T(t)\dot{x}(t)$$

where $\lambda^T(t) = \begin{pmatrix}\lambda_1(t) & \lambda_2(t) & \lambda_3(t) & \lambda_4(t)\end{pmatrix}^T$ is the costate function and $x(t) = \begin{pmatrix}x_1(t) & x_2(t) & x_3(t) & x_4(t)\end{pmatrix}^T$ is the state vector. Necessary and sufficient condition for an admissible solution $(x(t),u(t))$ to be optimal is that there exist a costate vector $\lambda \in C^1[t_i,t_f]$ almost everywhere, and $\eta \in C^0[t_i,t_f]$ almost everywhere, such that the following conditions are satisfied:

$$\begin{aligned}
\dot{\lambda_1}(t) =& \lambda_1(t)(k_{10}+k_{12}+k_{13}) - \lambda_2(t)k_{12} \\
& - \lambda_3(t)k_{13} - \lambda_4(t)\frac{k_{24}}{V} \\
\dot{\lambda_2}(t) =& \lambda_1(t)k_{12} + \lambda_2(t)k_{12} \\
\dot{\lambda_3}(t) =& -\lambda_1(t)k_{13} + \lambda_3(t)k_{31} \\
\dot{\lambda_4}(t) =& -p(t)(x_4(t) - x_4^{ref}) + \lambda_4(t)k_{14}
\end{aligned}$$

$$\lambda_i(t_f) = 0, \quad i = 1,...,4 \tag{16}$$

$$\begin{aligned}
2r(t)u(t) - \eta_1(t) + \eta_2(t) + \lambda_1(t) &= 0 \\
\eta_1(t)(u_{min} - u(t)) &= 0 \\
\eta_2(t)(u(t) - u_{max}) &= 0
\end{aligned}$$

$$\eta_i \geq 0, \quad i = 1,2$$

Proof: The theorem is easily shown once, denoting with $q(t) = (q_1(t) \quad q_2(t))^T \leq 0$ the box constraint and $\eta(t) = (\eta_1(t) \quad \eta_2(t))^T$ the multiplier function, the following necessary and sufficient conditions

$$\begin{aligned}
\dot{\lambda}(t) &= -\frac{\partial H}{\partial x}^T - \frac{\partial q}{\partial x}^T \eta \\
0 &= \frac{\partial H}{\partial u}^T + \frac{\partial q}{\partial u}^T \eta \\
\eta_i(t)q_i(t) &= 0, \quad \eta_i(t) \geq 0 \\
\lambda(t_f) &= 0
\end{aligned}$$

are applied to the given system and cost index. ◁

The application of this theorem yields, for the optimal control, the following expression:

$$u^o(t) = \begin{cases} u_{min} & if \quad 2ru_{min} + \lambda_1(t) > 0 \\ u_{max} & if \quad 2ru_{max} + \lambda_1(t) < 0 \\ -\frac{\lambda_1(t)}{2r} & if \quad -\frac{\lambda_1(t)}{2r} \in [u_{min}, u_{max}] \end{cases}$$

IV. Numerical results and discussion

The results stated in the previous Section are now applied for numerical simulations. The model parameters in (1)–(4) are chosen taking into account the considerations in [5]; referring to a female patient of 40 years, with a weight of 54 kilos and a height of 163 centimeters, the formulas in (5), (7) and (8), with (11), yield:

$$V_2 = 23.9830 \quad C_1 = 0.0434 \quad C_2 = 0.0267 \tag{17}$$

once the unit of measures have been transformed from minutes (as adopted in [5]) to seconds. Therefore, the transfer constant k_{ij}, from (6) are:

$$\begin{aligned}
k_{10} = 0.0102 \quad k_{12} = 0.0063 \quad k_{13} &= 3.2631 \cdot 10^{-4} \\
k_{21} = 0.0011 \quad k_{31} &= 5.8543 \cdot 10^{-4}
\end{aligned}$$

Moreover, for the x_4 dynamics the values:

$$k_{14} = k_{24} = 0.0076$$

have been chosen. The fixed quantities in formula (13) are chosen equal to $E_0 = 98.8$, $E_{max} = 94.1$, $C_{e50} = 6.33$ and $\gamma = 2.4$ according to the age-dependent values in Table 1 in [5].

As far as the specific choice of the weight functions $p(t)$ and $r(t)$, the goal is to induce the patient as far as possible to a BIS value in the interval [40 60], keeping this condition up to the final instant t_f; in the cost index this tracking is expressed by means of the term $x_4(t) - x_4^{ref}(t)$ once formula (13) is used. To this aim, it is set $BIS = 50$ as reference value, thus obtaining $x_4^{ref} = 6.5438$. The tracking requirement can be fulfilled by choosing:

$$p(t) = \varepsilon_1 + \varepsilon_2 e^{-\alpha t} \tag{18}$$

with $\varepsilon_i \geq 0$, $i = 1,2$. The exponential term with negative coefficient weighting the tracking error allows an increased value of the weight at the beginning of the time interval to induce a fast and safe sedation, whereas the constant ε_1 guarantees the proximity of x_4 to x_4^{ref} in the entire interval. The chosen numerical values are:

$$\alpha = \frac{1}{60} \cdot 10 \quad \varepsilon_1 = 5 \quad \varepsilon_2 = 1 \tag{19}$$

Their influence will be investigated in the simulations. The value of α is motivated aiming at reducing the weight function $\varepsilon_2 e^{-\alpha t}$ of a factor of e^{-10} every minute; The control u is already constrained by (14) and for the cost index the weight function $r(t)$ has been chosen a constant value $\beta = 0.01$ to allow a suitable control action, without a too hard limit . As far as the constraints $q_i(t)$, $i = 1,2$, the maximum value is chosen considering the dosage suggested in literature, $u_{max} = 5$, keeping equal to 0 the minimum amount of sedation. In fact, maximum infusion rate of about 300 $[mg \cdot min^{-1}]$ (medium value proposed in [5]) corresponds to the present choice of $u_{max} = 5$ $[mg \cdot s^{-1}]$ once considering the different time scale.

As seen, the anesthesia dosage and administration modality is strongly dependent on the characteristics of the patient;

in this section three female patients (P) are considered, different with respect to age, weight (W), height (H) and also with respect to parameters in formula (12) that strongly affects the evolution of the bispectral index scale, C_{e50}, γ, E_0, E_{max}. The numerical values assigned to these parameters are referred in [5] and shown in Table I within. To analyze the amount of drug in each compartment, and the evolution of the control action and of its effect on the BIS evolution, the patient 1 is considered as reference; in Fig. 1 it is shown the state evolution in the chosen time interval of 6 minutes. It can be noted, in particular, that the evolution of x_4 reaches the reference value of $x_4^{ref} = 6.5438$ in less than 2 minutes, corresponding to the time in which the BIS evolution is around the reference value of 50, Fig. 2; this result is obtained by using the control action in Fig. 3 in which a strong action is required up to 30 seconds followed by a maintenance amount of about 0.5. The total quantity of drug used in 6 minutes is 238.3297 $[mg]$. These preliminary results appears interesting also when compared with different approaches, as the ones in [5].

The influence of the patient's characteristics on the control action is studied comparing the evolution of the state components, of the BIS and of the obtained optimal control, for the three subjects of Table I; from the Figures 4–7 it can be noted that the patients 2 and 3, despite significant differences in age and weight, show similar evolution, especially with respect to x_1^o, x_3^o and x_4^o. As far as the BIS profile, it can be noted that, while for the patient 1 the BIS values approaches the reference one, 50, monotonically, for the patients 2 and 3 the BIS function decrease for about 2 minutes and then increases tracking the reference value. The control action requires in the three cases a maximum effort, followed, for the first patient, by an almost constant value around 0.3 with an increase up to 0.55 at about 5 minutes. For the second and the third subjects, after the maximum value, assumed for about 40 seconds, a null value is kept up to 2 minutes; successively, the drug infusion improves, reaching 0.7 and then, starting from the minute 3 up to 5, it reaches the values around 0.65. The total control effort for patient 2 is 279.9552 $[mg]$, whereas for patient 3 it is equal to 327.5982 $[mg]$.

From this data analysis it is confirmed that what really distinguishes the three patients states evolution seems the parameter C_{e50}; to verify this hypothesis, it is studied the effect of possible different values for C_{e50} on the same patient 1. In Fig. 10, it is shown the evolution of BIS as function of normalized $x_4 \in [1, 15]$, once C_{e50} has values between 2.5 and 13; it can be noted that for the same patient the same amount of drug concentration x_4 can yield different BIS behavior. In other words, knowledge of this parameter is essential to determine the correct dosage of anesthesia, as BIS is very sensitive to its variations, requiring, as obvious, higher doses of drug as C_{e50} increases.

A different control approach is to substitute the cost index in (15) with a different one in which the tracking is not with respect to the state variable x_4 and its reference value x_4^{ref}, but aiming at reducing the quadratic difference between BIS and the reference value, set equal to 50. This approach is reasonable, being the BIS function measurable by the physicians. The numerical results are obtained with the same parameters used for the patient 1, with an increase of the weight ε_1 up to $5 \cdot 10^6$ to obtain a satisfactory tracking; this is due to the different order of magnitude of BIS with respect to the x_4. In Fig. 11 the state evolution is depicted; note that $x_4(t)$, after about 50 seconds, correctly tracks the $x_4^{ref} = 6.5438$, whereas it can be noted the oscillatory behavior of $x_1(t)$. The $BIS(t)$ reaches the reference value for the first time after about 65 seconds from the drug administration, showing an oscillatory behavior around $BIS_{ref} = 50$, Fig.12. It is interesting to note the control action, Fig.13, and its difference with respect to the corresponding result obtained with cost index (15), Fig. 3; in this case, after a maximum dose for about 25 seconds, it is suggested to strongly decrease the administration up to 150 seconds and the increase the administration with a sinusoidal law around an average value of 0.5. The total control effort, 237.7098 $[mg]$, is comparable with the one previously obtained.

TABLE I: Characteristics of the female patients considered

P	Age	W(Kg)	H(cm)	C_{e50}	γ	E_0	E_{max}
1	40	54	163	6.33	2.24	98.8	94.1
2	43	59	163	12	2.42	90.2	147
3	28	52	164	8.44	4.10	91.2	80.7

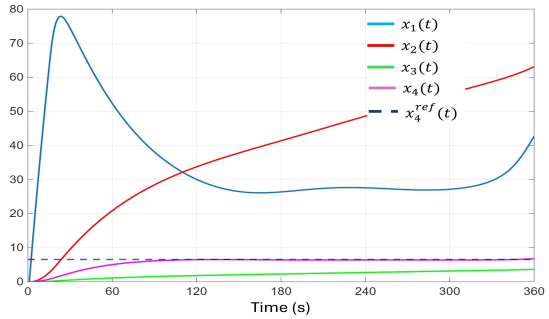

Fig. 1: State evolution for the 40 years old female patient 1 of Table I

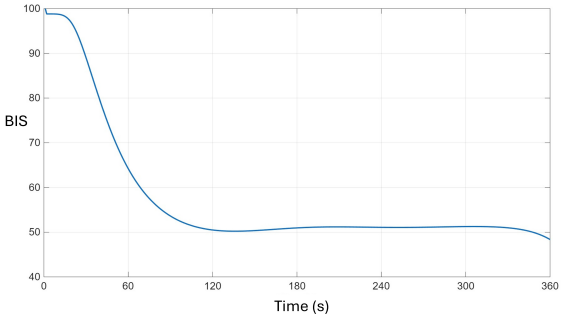

Fig. 2: BIS evolution for an effective and safe anesthesia for the 40 years old female patient 1 of Table I

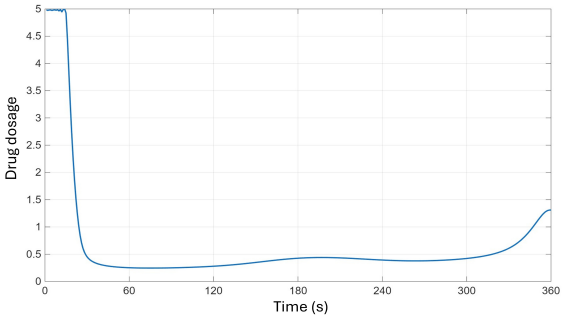

Fig. 3: Drug dosage for an effective and safe anesthesia for the 40 years old female patient 1 of Table I

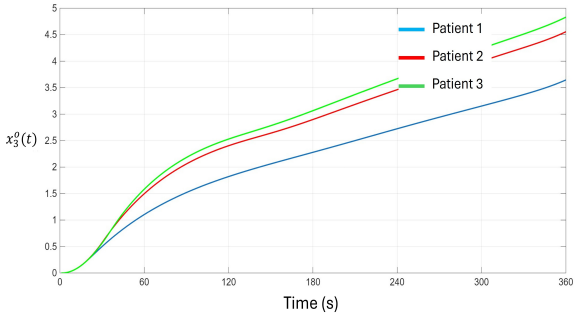

Fig. 6: Comparison of the $x_3^o(t)$ evolutions for the patients of Table I

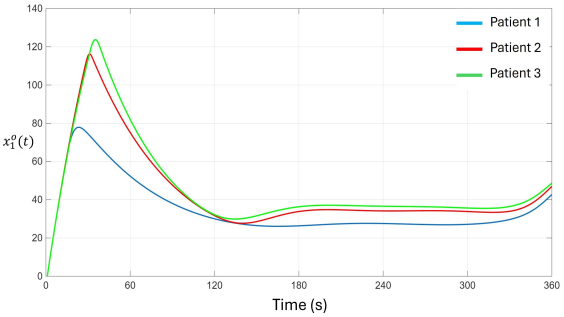

Fig. 4: Comparison of the $x_1^o(t)$ evolutions for the patients of Table I

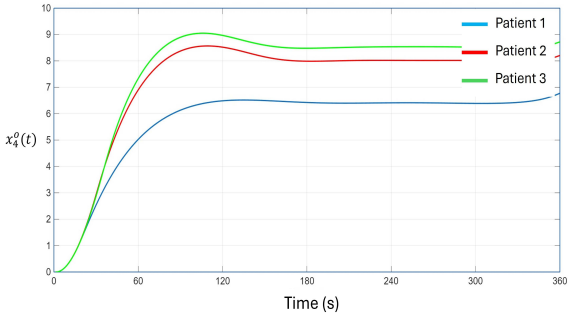

Fig. 7: Comparison of the $x_4^o(t)$ evolutions for the patients of Table I

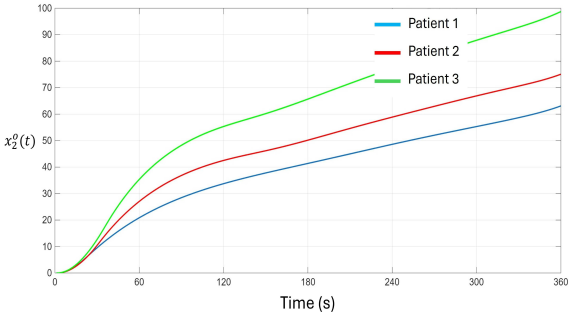

Fig. 5: Comparison of the $x_2^o(t)$ evolutions for the patients of Table I

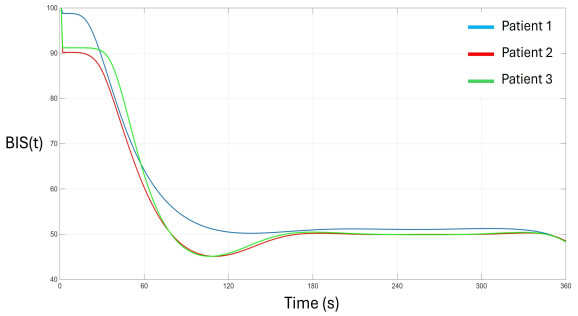

Fig. 8: Comparison of the $BIS(t)$ evolutions for the patients of Table I

V. Conclusions and Future Work

The increasing requirements of drug dosage personalized with respect to the specific patient is particularly important when referring to anesthesia; its peculiarity is in the requirements of reaching, as soon as possible, a controlled state of hypnosis along with a good balance between sedation and response to stimuli, by means of an optimized administration of suitable drug, as the propofol. By using a well consolidated model consisting of three compartments, the infusion, the fast and slow peripheral ones, an optimal control problem is defined determining the optimal dosage, thus allowing to reach a fast and safe unconscious state. An effective indicator is the *BIS*, the bispectral index, that in the desired anesthesia case must be between 40 and 60 in a scale $[0 \quad 100]$. While investigating the role of some model parameters, it has been noted the influence of the C_{e50}, that is the concentration of drug necessary to obtain the half maximal effect; the analysis intra-patient suggests that it can influence the dosage to obtain the reference value for *BIS*. The results are interesting in terms of total amount of drug infusion, also when compared with other approaches. Further investigation will be devoted in the suitable choice of the cost index (in this paper two possibilities are proposed) and in considering the introduction of uncertainties, to deal with intra-patients and inter-patients variability with respect to parameters variations.

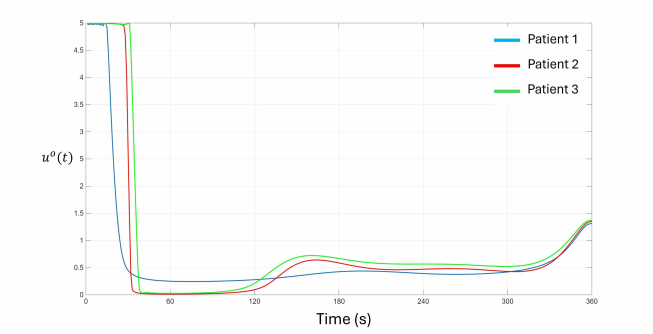

Fig. 9: Comparison of the $u^o(t)$ evolutions for the patients of Table I

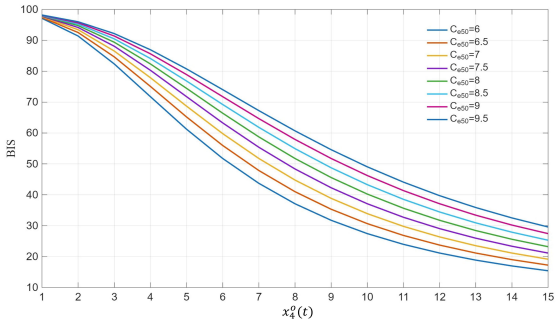

Fig. 10: Analysis of the influence of C_{e50} on the *BIS* evolution, assuming normalized $x_4 = 1, 2, ...15$. The parameters of the *BIS* function are the ones of Patient 1 in Table I

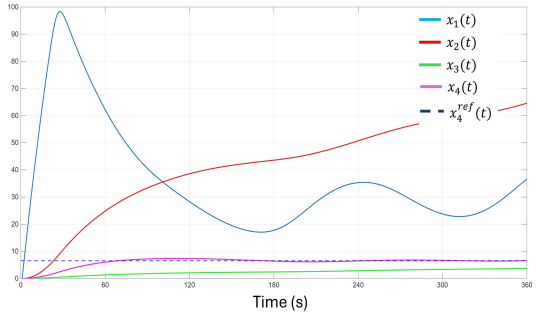

Fig. 11: State evolution for the 40 years old female patient 1 of Table I, when minimizing the tracking error of the $BIS(t)$ function with respect to the reference value 50

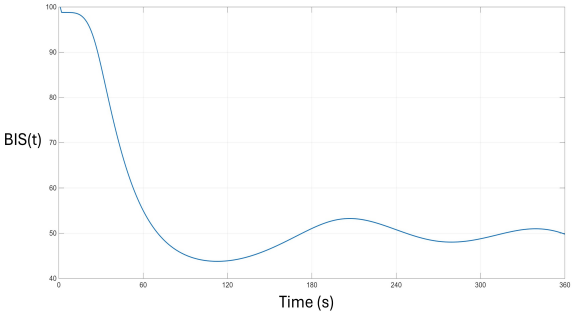

Fig. 12: BIS evolution for an effective and safe anesthesia for the 40 years old female patient 1 of Table I, when minimizing the tracking error of the $BIS(t)$ function with respect to the reference value 50

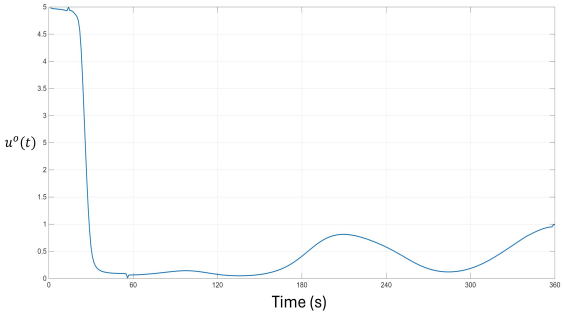

Fig. 13: Drug dosage for an effective and safe anesthesia for the 40 years old female patient 1 of Table I, when minimizing the tracking error of the $BIS(t)$ function with respect to the reference value 50

REFERENCES

[1] I. S. Mughal, L. Patnè, R. Caponneto, " A comprehensive review of modls and nonlinear control strategies for blood glucose regulation in artificial pancreas", Annual Reviews in Control, 57, 2024

[2] P. Lecca, "Control theory and cancer chemotherapy: how they interact", Frontiers Bioengineering Biotechnology, 2021

[3] A.H.Rivera, P.Velarde, A.Z.Cabeza, J. M. Maestre, "Drug dosing for cancer therapy: astochastic model predictive control perspective", Journal of Theoretical Biology, 615, 2025.

[4] H. Moore, "How to mathematically optimize drug regimens using optimal control", J Pharmacokinet Pharmacodyn, 45, 2018.

[5] F. Padula, C. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, G. Vivacqua, "Optimized PID control of depth of hypnosis in anesthesia", Computer Methods and Programs in Biomedicine, 144, pp. 21-35, 2017.

[6] I. Nascu, R. Oberdeck, E. N. Pistikopoulos, "Explicit hybrid model predictive control strategies for intravenous anaesthesia", Computers and Chemical Engineering, 106, 2017.

[7] M. Ghita, M. Neckebroek, C. Muresan, D. Copot, "Closed-Loop Control of Anesthesia: Survey on Actual Trends, Challenges and Perspectives", IEEE Access, 2020.

[8] P. Safrankova, J. Bruthans, "Target-controlled infusion of propofol: a systematic review of recent results", Journal of medical systems, 49, 2025

[9] J.M. Bailey, W.M. Haddad, "Drug dosing control in clinical pharmacology", IEEE Control Syst., 25, 35–31, 2005.

[10] Y. Gu, J. Hao, J. Wang, P. Liang, X. Png, X.Qin, Y.Zhang, D.He, "Effectiveness Assessment of Bispectral Index Monitoring-Compared with Conventional Monitoring in GeneralAnesthesia: A Systematic Review and Meta-Analysis", Wiley Anesthesiology Research and Practice, 2024.

[11] Z.Liang, G.Geng, Q. Song, M. Tang, "A time-synchronized multimodal monitoring system for general anesthesia", Medicine in novel technology and devices, 23, 2024

[12] E.Yumuk, D.Copot, C.Ionescu, M. Neckebroek, "Data-driven identification and comparison of full multivariable models for propofol–remifentanil induced general anesthesia", Journal of Process Control, 139, 2024.

[13] A. Absalom, T. Schnider, "The future of target-controlled infusion and new pharmacokinetic models", Curr Opin Anaesthesiol., 38, 2025.

[14] T.H. Hallynck, H.H. Soep, J.A. Thomis, J. Boelaert, R. Daneels, L. Dettli, "Should clearance be normalised to body surface or to lean body mass?" Br. J. Clin. Phar- macol., 11, 523–526, 1981.