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PID and Model Predictive Control Approach for Drug Dosage in Anesthesia During Induction: a Comparative Study ⋆

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Abstract: In this paper, a PID controller is compared to an extended moving horizon estimator coupled with a model predictive control approach for the problem of dosing propofol and remifentanil during the induction of anesthesia. For the PID controller, taken from the literature, a fixed ratio is considered between propofol and remifentanil flow rates and an anti-windup strategy is used to prevent integration wind-up. The optimal control approach uses an MHE to estimate both the states and the pharmacodynamic parameters of the system, followed by a non-linear model predictive controller to compute the optimal drug rates according to the model. Both controllers are tuned using the same criterion, and are compared by simulating 500 uncertain patient models for the induction phase.

Keywords: Anesthesia, Drug Control, PID, Model Predictive Control.

1. INTRODUCTION

General anesthesia assumes a critical role in creating optimal conditions for surgical interventions, facilitating surgeon proficiency while mitigating patient discomfort and postoperative issues. Within the medical domain, anesthesia involves the meticulous manual control of areflexia (absence of movement), analgesia (absence of pain), and hypnosis (loss of consciousness) in the patient. Employing physiological signals such as the Bispectral index (BIS), the mean arterial pressure or the cardiac frequency, the anesthesiologist dynamically adjusts the infusion rates of diverse pharmacological agents to attain and sustain precise anesthesia levels. Beyond sedation management, the anesthesiologist has to monitor the hemodynamic and respiratory state, assessed by metrics like mean arterial pressure, cardiac output and oxygen blood saturation. This vigilance is crucial, given the intricate interplay between the cardiovascular system and the multifaceted process of administering multiple drugs for anesthesia.

The complexity of the anesthesia process, coupled with the need for precise control, has motivated the development of several automated control strategies (Copot (2020)). The majority of the strategies that have been clinically tested are based on the use of a proportional-integral-derivative (PID) controller (Brogi et al. (2017)), which is a simple and robust controller that is widely used in industrial applications. Despite its simplicity in implementation and tuning, as well as resilience to noise and disturbances, it does not exploit the patient model information, is sub-optimal for constrained systems, and does not explicitly consider uncertainties. Hence, in this paper a moving horizon estimator (MHE) coupled with model predictive control (MPC) is investigated as an alternative solution for the control of drug during anesthesia.

While most of the research efforts have predominantly focused on regulating the Bispectral index (BIS) considering only propofol as an input (Single-Input Single-Output, SISO system), recent studies have endeavored to address the control of both propofol and remifentanil for regulating the BIS value (Multiple-Input Single-Output, MISO system), representing a significant step toward the ultimate goal of a full multi-input multi-output (MIMO) control system. In this paper, the comparison is made on the MISO problem, using Merigo et al. (2019) as the baseline for PID controller. In addition to addressing the aforementioned limitations, the MHE-MPC framework is readily adaptable to a MIMO problem. Indeed, tackling a MIMO problem appears inevitable for fully automating the anesthesia process, given the synergistic effects of most drugs on various variables (Ionescu et al. (2021)).

Note that comparisons of PID and more advanced methods have been already performed in Gonzalez-Cava et al. (2021), Merigo et al. (2020), Yelneedi et al. (2009) and Chakravarty et al. (2020) on the SISO system. These studies concord on concluding that more complex controllers yield only marginal gains over PID. The primary source of error in the control process is identified as the intra and inter-patient uncertainties associated with the patient model. To address this challenge, Wahlquist et al. (2020)

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proposes an individualized tuning of the PID controller using a patient partitioning, and Schiavo et al. (2022) presents a tuning method tailored on the specific anesthesia patient model. In this paper, an extended MHE, proposed in Moussa et al. (2023), is used with an MPC to estimate both the system parameters and states, offering a comprehensive approach to handle uncertainties in the anesthesia control system.

MPC methods have also been proposed in several papers, in Ionescu et al. (2008), and Nascu et al. (2011) for the SISO system and in Eskandari et al. (2020), and Pawłowski et al. (2022) for the MISO system for instance. In Eskandari et al. (2020) the authors put forward a mid-range controller strategy that leverages the use of remifentanil for short-term and small-scale modulation of the Bispectral index (BIS), while relying on propofol for longer-term regulation. In Pawłowski et al. (2022) a constant ratio is used between the two drugs in the MPC, and the controller is then tested using Monte-Carlo simulations. The main novelty proposed in this paper is to use the estimation of the system parameters as a way to handle patient uncertainties. The effectiveness of the parameter estimation using MHE has been already demonstrated in Moussa et al. (2023). In this preliminary work, the interest of the method coupled with MPC is demonstrated by comparing this approach to a PID on the induction phase of anesthesia.

The paper is organized as follows. In Section 2, the models of the patient and the drugs are recalled. In Section 3, the PID and MHE-MPC control approaches are presented. Then, in Section 4, the tuning of the controllers and the results of the simulations are presented and discussed. Finally, in Section 5, the conclusion and possible extensions of the work are discussed.

2. STANDARD MODELS

Anesthesia models typically consist of two parts: Pharmacokinetic (PK) and Pharmacodynamic (PD). PK describes drug concentration dynamics in the body, while PD links drug concentrations to physiological effects.

2.1 Compartments Pharmacokinetic Model

For pharmacokinetic (PK) models of both drugs, propofol and remifentanil, a common approach is to use a four-compartments model. This model divides the body into three physical compartments: blood, muscles, and fat; and a virtual effect-site, as illustrated in Fig. 1. The compartment model results in a linear system represented by the following equations:

$$\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{x}_4\end{pmatrix} = \begin{pmatrix}-(k_{10}+k_{12}+k_{13}) & k_{12} & k_{13} & 0\\ k_{21} & -k_{21} & 0 & 0\\ k_{31} & 0 & -k_{31} & 0\\ k_e & 0 & 0 & -k_e\end{pmatrix}\begin{pmatrix}x_1\\ x_2\\ x_3\\ x_4\end{pmatrix} + \begin{pmatrix}\frac{1}{V_1}\\ 0\\ 0\\ 0\end{pmatrix} u \tag{1}$$

where x_1, x_2, x_3, and x_4 respectively represent the drug concentrations in blood, muscle, fat, and effect-site. The coefficients can be determined from Eq. (2) below, except for k_e which is not related to a physical meaning:

$$k_{10} = \frac{Cl_1}{V_1}, \quad k_{12} = \frac{Cl_2}{V_1}, \quad k_{13} = \frac{Cl_3}{V_1}, \quad k_{21} = \frac{Cl_2}{V_2}, \quad k_{31} = \frac{Cl_3}{V_3} \tag{2}$$

with V_i and Cl_i $(i = 1, 2, 3)$ respectively the volume and the clearance rates of each compartment. The input u is the drug infusion rate. In this paper, the maximum infusion rate of propofol is $6.67mg/s$ and that of remifentanil is $16.67\mu g/s$. Next, the notation x_p and x_r for the states of the compartment model for propofol and remifentanil is used. Also, A_p, B_p, A_r, and B_r are the transition matrices of both drugs. Finally, both compartment models can be described by the decoupled system:

$$\begin{pmatrix}\dot{x}_p\\ \dot{x}_r\end{pmatrix} = \begin{pmatrix}A_p & 0_{4\times4}\\ 0_{4\times4} & A_r\end{pmatrix}\begin{pmatrix}x_p\\ x_r\end{pmatrix} + \begin{pmatrix}B_p & 0_{4\times1}\\ 0_{4\times1} & B_r\end{pmatrix}\begin{pmatrix}u_p\\ u_r\end{pmatrix}. \tag{3}$$

2.2 Pharmacodynamic Model

The impact of a drug concentration on the BIS is typically modeled by a Hill function. Due to the synergetic effect between propofol and remifentanil, the effect can be modeled as a response surface model (Minto et al. (2000)):

$$BIS(t) = E_0\left(1 - \frac{I(t)^\gamma}{1 + I(t)^\gamma}\right) \tag{4}$$

with E_0 the initial BIS, γ the slope coefficient of the surface and $I(t)$ the interaction term defined by:

$$I(t) = \frac{x_{p4}(t)}{C_{50p}} + \frac{x_{r4}(t)}{C_{50r}}. \tag{5}$$

In these equations, x_{p4} and x_{r4} are the propofol and remifentanil effect-site concentrations, C_{50p} and C_{50r} are the propofol and remifentanil half-effect concentrations for BIS (*i.e.* the concentrations to obtain half of the effect of the drugs). Finally, the fully discretized model subject to noise can be summarized by the following structure:

$$\begin{cases} x(k+1) &= Ax(k) + Bu(k)\\ BIS(k) &= h(x(k)) + w(k)\end{cases} \tag{6}$$

where h is the non-linear output function from Eq. (4)-(5) and w models both the measurement noise and the eventual output disturbances.

In the simulation, the parameters of Eleveld et al. (2018) and Eleveld et al. (2017) are used respectively for propofol and remifentanil PK model. For the PD model, the parameters from Bouillon et al. (2004) are implemented.

To make simulations as close to the reality as possible, uncertainties are added to the parameters. Particularly, each parameter uncertainty follows a log-normal distribution (the parameters of this distribution are specified in the previously cited papers) and a realization of the

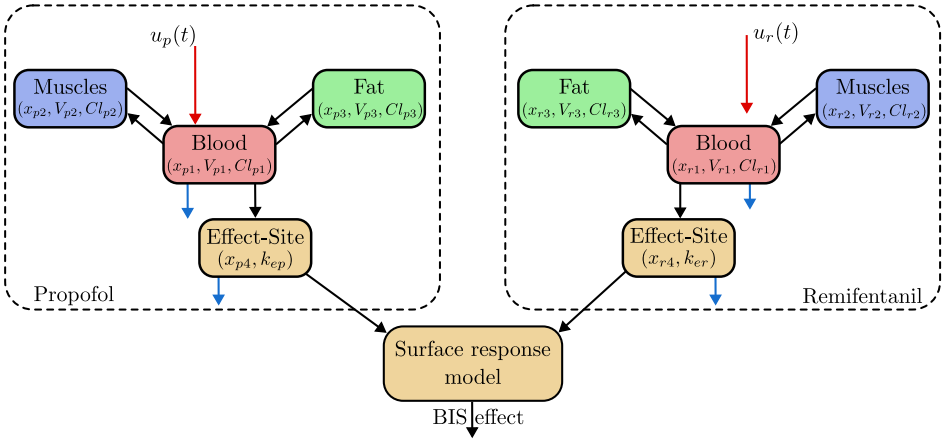

Fig. 1. Schemes of the PK-PD compartments model

distribution is used for each patient. The simulations are done using the Python Anesthesia Simulator (Aubouin-Pairault et al. (2023)).

3. METHOD

3.1 PID Control

The PID controller used in this paper is the one presented in Merigo et al. (2019). In this controller, the propofol flow rate is first computed as in Eq.(7), and the remifentanil flow rate is computed from a fixed ratio r of the propofol flow rate ($u_r = ru_p$). Additionally, an anti-windup strategy is used to prevent integration wind-up.

$$u_p(t) = K_p \left(e(t) + \frac{1}{T_i} \int_0^t e(\tau) d\tau + T_d \frac{de(t)}{dt} \right), \qquad (7)$$

where $e(t)$ is the regulation error defined by $e(t) = BIS_{ref} - BIS(t)$. Before applying the control input to the patient, the outputs of the controller are saturated to satisfy the constraint of the system.

3.2 MHE-MPC Control

In this subsection, the MHE-MPC approach used in this paper is presented. The MHE is used to estimate both the state of the system and the unknown parameters of the PD system $\theta = (C_{50p}, C_{50r}, \gamma)$. Then, a non-linear model predictive controller is used to compute the optimal drug rates according to the model and the estimated states and parameters. The MPC approach is presented in Fig. 2. To improve the disturbance rejection capability of the MPC approach, a disturbance with constant dynamics is considered as a state of the system, in addition to the PD parameters. The extended system dynamics, whose state is $\bar{x} = \begin{pmatrix} x \\ \theta \\ d \end{pmatrix}$, is given by:

$$\begin{cases} \bar{x}(k+1) &= \bar{A}\bar{x} + \bar{B}u(k) \\ BIS(k) &= \bar{h}(\bar{x}) = h(x(k), \theta) + d(k) \end{cases} \qquad (8)$$

with $\bar{A} = \begin{pmatrix} A & 0_{8\times4} \\ 0_{4\times8} & I_{4\times4} \end{pmatrix}$ and $\bar{B} = \begin{pmatrix} B \\ 0_{4\times2} \end{pmatrix}$.

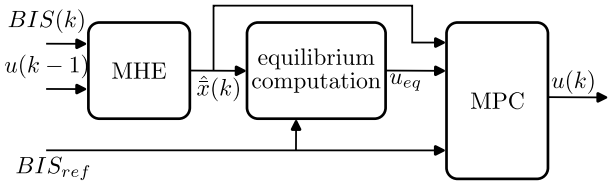

Fig. 2. Scheme of the MHE-MPC controller.

Moving Horizon Estimator The MHE used in this paper is the one presented in Moussa et al. (2023), the analysis of the performances have been done on this paper and are not elaborated here. The cost of the MHE is given by:

$$J_{MHE}(\bar{x}(k)) = \sum_{i=0}^{N_{MHE}} \|BIS(k-i) - \bar{h}(\bar{\mathbf{x}}(k-i))\|_Q + \sum_{i=1}^{N_{MHE}} \|\bar{x}(k-i+1) - \bar{A}\hat{\bar{x}}(k-i) - \bar{B}u(k-i)\|_{R_{MHE}(k)}$$

where $\bar{x}$ and $\hat{\bar{x}}$ represent, respectively, the state over the estimation horizon (decision variable) and the previous estimated state up to time $k-1$. The remaining arguments, namely y and u, represent the output and the input measurements profiles over the estimation horizon, Q and R_{MHE} represent the penalty matrices, and N_{MHE} is the length of the estimation window. Note that, as in the cited paper, the time-varying penalty matrix R_{MHE} has been tuned for modulating in time the priorities of either the PD parameters or the disturbance estimations, to overcome potential observability issues. The final MHE optimization problem is given by:

$$\begin{aligned} \hat{\bar{x}}(k_{|k}) = \arg\min_{\bar{x}} \quad & J_{MHE}(\bar{x}(k)) \\ \text{subject to} \quad & \bar{x}(k+i+1) = \bar{A}\bar{x}(k+i) + \bar{B}u(k+i) \\ & \text{for } i \in [0, N_{MHE} - 1] \end{aligned} \qquad (9)$$

The MHE is used to estimate the state of the system, the unknown parameters of the PD system and the constant disturbance. The estimated extended state is then used in the MPC to compute the control input.

Model Predictive Control Model Predictive Control is an advanced control method based on solving online an

optimization problem to obtain the optimal control input in presence of constraints on the state and the control input (Rawlings et al. (2009)). The cost of the optimization problem is given by:

$$J_{MPC}(\bar{x}, u) = \sum_{i=1}^{N_{MPC}} \|BIS_{ref} - \bar{h}(\bar{x}(k+i))\| + \|u(k+i) - u_{eq}\|_{R_{MPC}} \quad (10)$$

where BIS_{ref} is the final BIS target (50 in our simulation), $R_{MPC} = diag(R_1, R_2)$ is the cost matrix for the control input, N_{MPC} is the prediction horizon. The equilibrium control input u_{eq} is computed at each step, solving the following optimization problem (denoted as equilibrium computation in Fig. 2):

$$\begin{aligned} u_{eq} = \arg\min_{u} \quad & (BIS_{ref} - \bar{h}(\bar{x}(k)))^2 \\ & + \left(u_p\sqrt{R_1} - u_r\sqrt{R_2}\right)^2 \\ \text{subject to} \quad & \bar{x} = \bar{A}\bar{x} + \bar{B}u \\ & u \in \mathbb{U}, \end{aligned}$$

where u_p, and u_r are the element of the vector u, and $\mathbb{U}$ is the set of feasible control inputs, as specified in Section 2. Thus, u_{eq} is the control input which stabilizes the system at BIS_{ref} according to the estimated PD parameters. In this equation R_1 and R_2 are chosen to set the ratio between u_p and u_r at the equilibrium. They are similar to the role of r in the PID, in fact, $r = \sqrt{R_2/R_1}$. The final optimization problem of the MPC is given by:

$$\begin{aligned} u(k) = \arg\min_{u} \quad & J_{MPC}(\bar{x}, u) \\ \text{subject to} \quad & \bar{x}(k+i+1) = \bar{A}\bar{x}(k+i) + \bar{B}u(k+i) \\ & \quad \text{for } i \in [0, N_{MPC} - 1] \\ & u(k+i) \in \mathbb{U} \quad \text{for } i \in [0, N_{MPC}] \\ & \bar{x}(k) = \hat{\bar{x}}(k). \end{aligned} \quad (11)$$

4. NUMERICAL SIMULATION

4.1 Controller Tuning

The induction phase is the part of the anesthesia process where the patient falls asleep. The goal of the controller is to reach the target BIS interval [45, 55] in a time interval between 2 and 3 minutes without too much undershoot.

In order to tune the controllers, the same criterion is used for both controllers. The criterion evaluates the regulation error over the simulation time, and is defined as:

$$J = \max_{i=1,\dots,N_{tun}} \left(\sum_{k=1}^{N_{sim}} f_{cost}(BIS_i(k) - BIS_{ref}) \right) \quad (12)$$

with:

$$f_{cost}(x) = \begin{cases} x^3 & \text{if } x > 0 \\ x^4 & \text{otherwise} \end{cases} \quad (13)$$

where N_{tun} is the number of simulations on which the tuning is performed and N_{sim} the simulations length.

This particular cost, inspired by the integral of the absolute error from Merigo et al. (2019), is used to penalize more the BIS undershoot than the overshoot. In fact, a BIS value below 40 must be avoided as it is associated with post-operative morbidity Leslie et al. (2010).

Applying this criterion to a subset of $N_{tun} = 16$ patients, both controllers are tuned with a tree-structured parzen estimator algorithm Akiba et al. (2019) for optimization. For the PID controller, the ratio is set at two, and the parameters to tune include the proportional gain K_p, integral time constant T_i, and derivative time constant T_d. For the MHE-MPC controller, the parameters of the MHE are the same as in the original paper Moussa et al. (2023), the prediction horizon is set to $N_{MPC} = 30$, and only the the scalar r such that $R_{MPC} = r \times diag([4, 1])$ is tuned. For both methods the sampling time is set to two seconds with a total duration time of ten minutes ($N_{sim} = 300$) for the simulation.

4.2 Simulation Setup

To assess the performances of the controllers, simulations are done with 500 different patients using random uniform sampling to obtain age, sex, height, and weight. Then uncertainties are added to both the PK and PD models with log-normal distributions as described in Eleveld et al. (2018), Eleveld et al. (2017), and Bouillon et al. (2004). A noise has been added to the output as a white noise (standard deviation of 3) filtered by a second order low-pass filter with a cut-off frequency of 0.03 Hz.

The performance criteria are those proposed in Ionescu et al. (2008):

- *Time to target* (TT): time to reach the target BIS interval [45, 55].
- *BIS NADIR*: minimum BIS value reached during the induction phase.
- *Settling time 10* (ST10), respectively (ST20): time to reach the interval target ±10%, respectively 20%, and stay within this range.

In addition, the integral absolute error (IAE) is also computed:

$$IAE = \int_0^{t_{max}} |BIS(t) - BIS_{target}(t)|dt \quad (14)$$

The involved optimization problems are solved using CASADI software (Andersson et al. (2019)) with IPOPT solver. The maximum computation time of the proposed solution for one step is 0.14s, which makes it a plausible solution. The whole code to perform the simulations presented in the paper is written in Python and available at `https://github.com/BobAubouin/TIVA_Drug_Control` and uses Aubouin-Pairault et al. (2023) to perform all the simulations. It has been shared in view of more easily reproducible results in the future.

4.3 Results

The simulation results over 500 patients are presented in Table. 1 and Fig. 3. Moreover, the BIS trajectories of the

Controller	IAE	TT (min)		BIS_NADIR		ST10 (min)		ST20 (min)	
	mean ± std	mean ± std	max	mean ± std	min	mean ± std	max	mean ± std	max
PID	4258.0±1647.0	2.12±1.27	8.1	42.89±4.14	23.51	7.96±1.86	9.93	2.68±2.09	9.9
MHE-NMPC	4098.0±2001.0	2.26±1.75	9.3	43.4±5.98	18.09	7.83±1.94	9.93	2.88±2.18	9.9

Table 1. Performance criteria for the two controllers in the induction phase

case with the worst undershoot for each controller are shown in Fig. 4.

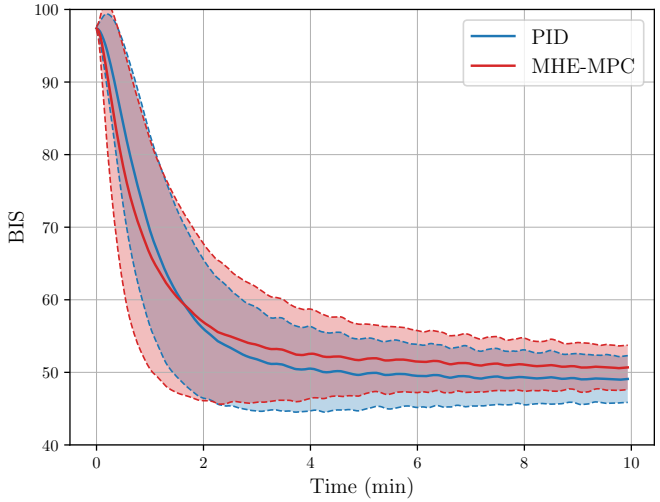

Fig. 3. Mean BIS over the 500 patients for the two controllers. The plot is the mean value ± standard deviation.

The results show that the MHE-MPC controller outperforms the PID controller in terms of IAE value which demonstrates the benefit of the proposed method. Especially, the mean undershoot value is reduced for almost the same mean time to target. The settling times (ST20 and ST10) are similar between both solutions. However, the standard deviations associated to those mean values are higher for the proposed solution which demonstrate that the goal of reducing the impact of patient model uncertainties is not achieved.

Looking at Fig. 4, it can be seen that the MHE-MPC controller produces the worst undershoot but with a different behaviour than the PID. In fact, despite using the same cost for the tuning process, the PID converges to a slower solution than the MHE-MPC solution. However for those worst cases, if the value of the undershoot is worst for the MHE-MPC solution, the controller reacts quickly to converge to the target. The PID controller has a different behaviour and presents an important steady-state error at the end of the simulation.

Nevertheless, the conclusion can be mitigated considering that the PID used for the comparison has been optimized on a patient table while in the more recent paper Schiavo et al. (2022) the authors proposed to optimize the PID for each patient characteristics, and thus for each PK model. Since this controller was longer to implement and to test, though, the one from Merigo et al. (2019) has been used.

In addition, the complexity introduced by the MHE-MPC (three non-linear optimization per step) might not fully justify the improvement amount on the time response.

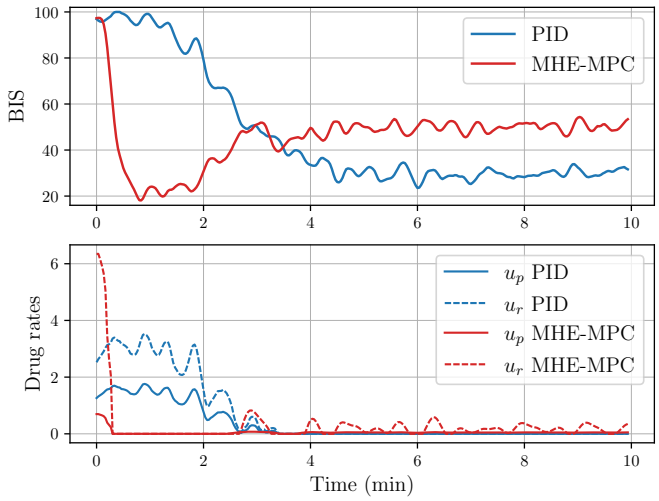

Fig. 4. BIS values for the worst case of each controller (in terms of undershoot) for the two controllers.

5. CONCLUSION

In this paper, a standard PID and an extended MHE-MPC approach have been compared. Results on a large set of uncertain patients demonstrate that the MHE-MPC approach is able to reach the target BIS with an average undershoot smaller than the PID controller with the same time to target, improving the trade-off between time response and undershoot. Nevertheless, this minor improvement might be questionable, in particular considering the complexity introduced by the MHE-MPC approach. From a practical point of view, the use of a PID seems a reasonable choice for this drug control problem. New metrics about patient safety and controller complexity could be considered in the future to be able to do an informed choice.

On the other hand, this first investigation only considers the induction phase of anesthesia. There is work in progress on the extension of this work to the maintenance phase of anesthesia and an improvement of the estimation method.

Moreover, the MHE-MPC should still be studied in the future as it could be an interesting solution to deal with more complex drug control problems. In fact, the propofol-remifentanil to BIS problem is only a small part of the anesthesia paradigm and the MHE-MPC could be a good candidate to handle multi-output problems for instance.

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