Human-Imitating Control of Depth of Hypnosis Combining MPC and Event-Based PID Strategies

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***Abstract*—In this letter we propose a human-imitating control methodology for the Depth-of-Hypnosys (DoH) in total intravenous anesthesia (TIVA) where the bispectral index (BIS) is used as process variable. The method suitably combines a move-blocking model predictive controller (MPC) that minimizes the time-to-target when the BIS value is not in the required range and an event-based Proportional-Integral-Derivative (PID) controller that provides a strong filtering action when the DoH is satisfactory. A fast induction is achieved and awareness episodes are avoided with a control action that is piecewise constant so that it mimics the behavior of the anesthesiologist and is more likely to be accepted in the clinical practice.**

***Index Terms*—Anesthesia control, MPC, PID control.**

I. INTRODUCTION

AUTOMATIC control of anesthesia has multiple advantages compared to human control for both patients and anesthesiologists [4]. Indeed, an efficient control system can enhance patient safety by averting drugs underdosing and overdosing, which could lead to adverse consequences such as delirium, post-operative nausea and vomiting in cases of overdosing, and traumatic awareness episodes in cases of underdosing. In total intravenous anesthesia (TIVA) the anesthesiologist's task includes managing Depth-of-Hypnosis (DoH), analgesia, and neuromuscular blockade through the appropriate administration of specific drugs. Hypnosis is usually induced by means of propofol. A feedback control system can be implemented thanks to the use of a DoH sensor. In particular, the bispectral index (BIS) is a processed electroencephalogram signal that ranges from 0 to 100, with 100 representing a fully awake patient and 0 signifying a flat electroencephalogram. The optimal BIS value during operation is generally 50, with a permissible range from 60 to 40, which represents the actual target for the control task. In fact, the anesthesia process consists of two phases: induction and maintenance. During the (initial) induction phase, the required patient's DoH level needs to be attained quickly, namely, in less than 5 minutes, starting from its initial value. It is therefore a set-point following task where the transient time has to be minimized while preventing severe undershoots, which could lead to potentially dangerous episodes of hypotension. When the induction phase is completed, the maintenance phase starts. This is a load disturbance rejection task where the aim is to keep the BIS value within the range from 40 to 60 notwithstanding the occurrence of noxious stimuli from surgical procedures. In this scenario, it is of utmost importance to prevent awareness episodes. Indeed, avoiding the BIS from exceeding 70 for a prolonged period is crucial to prevent stress to the patient. In the clinical practice, when there is a risk of such episodes the anesthesiologist administers a bolus of propofol. Similarly, a bolus is typically administered during the induction phase to speed up the BIS decrease and prevent patient discomfort.

Many different control methodologies have been proposed in the literature in order to tackle the design difficulties given by the nonlinear pharmacokinetic/pharmacodynamic (PK/PD) model of propofol, by the presence of a measurement noise and by the need of ensuring an adequate robustness, that is, of satisfying the tight control requirements for all the patients. Proportional-Integral-Derivative (PID) based controllers have been demonstrated to be effective, especially when a gain scheduling technique is used to comply with the different control tasks in the induction and maintenance phase [12], [17], [21], [23]. Model Predictive Control (MPC) has also been suggested as a valid alternative capable of handling the system constraints. Generally, the system's nominal static nonlinearity is inverted to implement a linear MPC technique [3], [10],

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[13], [15], [16]. However, achieving a high performance with MPC alone would necessitate having a very accurate patient PK/PD model available, which is extremely difficult in practice. With the aim of providing a fast induction and of preventing awareness episodes as much as possible during maintenance, a method that combines MPC and PID control has been proposed in [7]. A PID controller is utilized when the BIS value is in the range of 60 to 40, indicating that the DoH is at an acceptable level. When the BIS is above 60 and there is a risk of awareness, an MPC technique is used to minimize the time it takes for the BIS to drop below 60 (naturally providing a bolus). The MPC is also used when the BIS is below 40, thus avoiding burst suppression episodes. In addition to the advantages provided for the patient, such a control system has the benefit of replicating the anti-awareness anesthesiologists' manual control actions. Actually, having a human-imitating automatic control system that mimics the anesthesiologist's behavior is really important because the anesthesiologist always has to supervise the control system and, therefore, understanding its behavior plays a key role in the acceptance of such a device in the clinical practice. Pursuing this strategy, in this letter we propose to improve the combined MPC-PID method by employing an event-based PID control strategy [8] and a move-blocking MPC [2] in such a way that the noise is effectively filtered and the control action is generally piecewise constant so that it can be easily understood and validated by the anesthesiologist.

II. PROBLEM FORMULATION

During induction, the goal is to drive the BIS level to the reference value of 50 as fast as possible (no more than 5 minutes), by avoiding an undershoot of less than 30 to prevent burst suppression [1], which has been linked to postoperative delirium [20]. Then, in the maintenance phase, it is required to keep the BIS value around 50, namely in the range from 40 to 60, despite surgical stimuli. In particular, the primary goal is to avoid patient awareness, which might occur if the BIS value is too high. Thus, if this situation occurs, it is necessary to bring back the BIS in the safe range of [40, 60] as quickly as possible.

A. Patient Model

The depth of hypnosis induced by propofol administration is usually modeled through a PK/PD model with a Wiener structure, which is a linear part in series with a static nonlinearity [18], [19]. By defining the state vector as $x(t) = [q_1(t), q_2(t), q_3(t), C_e(t)]^T \in \mathbb{R}^4$, where q_i, $i = 1, 2, 3$, is the quantity of drug in the ith compartment and C_e is the drug effect-site concentration, the linear part, which consists of a fourth-order system, can be written in state-space form as:

$$\dot{x}(t) = A\,x(t) + B\,u(t),$$

where the system matrix A and the input matrix B are:

$$A = \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{1e}/V_1 & 0 & 0 & -k_{e0} \end{bmatrix}, B = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{1}$$

Some parameters of the A matrix elements depend on the patient's demographic data, such as $k_{10} = g(\text{weight, height, gender})$, $k_{12} = g(\text{age})$ and $k_{21} = g(\text{age})$, while others are constant: $V_1 = 4.27\,\text{l}$, $k_{1e} = k_{e0} = 0.456\,\text{s}^{-1}$. On the other hand, the static nonlinear function is defined as:

$$\text{BIS}(t) = f(x(t)) = h(C_e(t)) \tag{2}$$

where $h : \mathbb{R} \to \mathbb{R}$, is called Hill function and correlates the effect-site compartment and the DoH assessed via the BIS:

$$h(C_e(t)) = E_0 - E_{\max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right) \tag{3}$$

and $f : \mathbb{R}^4 \to \mathbb{R}$ is an output function such that $f([q_1(t), q_2(t), q_3(t), C_e(t)]^T) = h(C_e(t))$. In (3), γ is the maximum steepness of the function h while $C_{e_{50}}$ is the concentration in the effect-site compartment required to reach half of the maximum effect.

III. CONTROL SYSTEM STRUCTURE

The proposed control structure is shown in Figure 1 where the BIS reference signal is denoted as BIS^R, the disturbance signal is denoted as d and n is the measurement noise. It comprises a Selector, an MPC with a move-blocking mechanism, a Kalman filter, and an event-based PID controller. The MPC relies on a personalized PK/PD model specific for each patient, based on their gender, height, age, and weight, while the nonlinearity is compensated by inverting the Hill function.

A. Controller Selector

The primary responsibility of the controller selector is to discern between employing either the MPC control action u_{MPC} or the PID one u_{PID}. A discrete-time MPC and event-based PID are employed, which implies that the control action remains constant during the interval between sampling times. By selecting the sampling period T_s equal to 1 s, a continuous-time control signal $u : \mathbb{R} \to \mathbb{R}$ is obtained by applying a zero-order hold filter (ZOH) to a discrete-time input $u^* : \mathbb{Z} \to \mathbb{R}$, that is

$$u(t) = u^*(k), \quad t \in [kT_s, (k+1)T_s] \tag{4}$$

The MPC is used to drive the patient within a safe operational range from 40 to 60, while the PID controller is employed within this interval:

$$u^*(k) = \begin{cases} u^*_{PID}(k) & \text{if } BIS(k) \in [40, 60] \\ u^*_{MPC}(k) & \text{otherwise} \end{cases} \tag{5}$$

This choice is motivated by the capability of the MPC to more accurately emulate the anesthesiologist's behavior by providing a bolus-like control action. A bumpless switching between the two control actions is employed. This is achieved by putting the PID controller in tracking mode when it is not used. Similarly, the Kalman filter always tracks the output to provide the predicted four components of the state to the MPC when the selector sets it to operate.

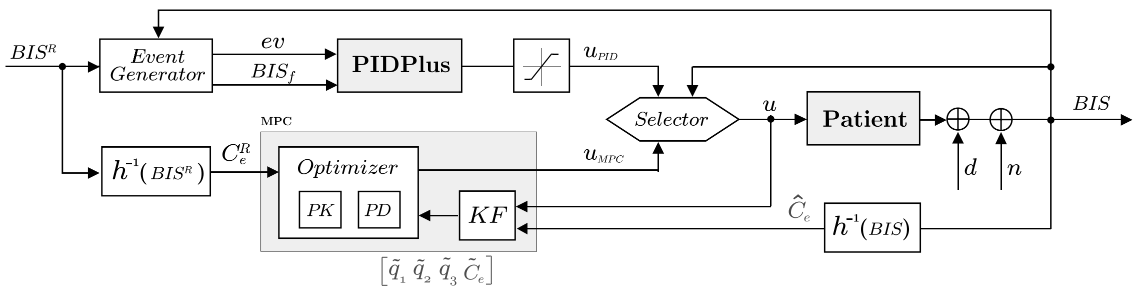

Fig. 1. Closed loop control scheme for DoH.

B. Model Predictive Controller

In order to apply a linear MPC algorithm, the nonlinear function (3) is inverted. We calculate the effect site concentration $\widehat{C}_e$ from the measured BIS, to be used by the Kalman filter (see Section III-C), and the equivalent reference effect site concentration C_e^R as

$$\widehat{C}_e = h^{-1}(BIS), \qquad C_e^R = h^{-1}(BIS^R) \tag{6}$$

Although the nominal values of parameters used in (6) might differ from the actual value of the process, the BIS will coincide with its target value when the controlled variable reaches its target value BIS^R because the Hill function and its inverse are one-to-one mappings. Note that BIS^R is set to 50 as the target level to reach, which is a common practice in general anesthesia. As mentioned before, the linear parameters of the model are known based on patient demographics, while the parameters of the Hill function are unknown a priori. Therefore, for the induction phase, we utilize the average parameter values reported in [24], which are $\gamma = 2.69$, and $C_{e_{50}} = 4.92$. Conversely, during the maintenance phase, a more aggressive control strategy is employed to mitigate the risk of consciousness. Consequently, the parameters of the Hill function are selected as $\gamma = 1.65$ and $C_{e_{50}} = 7.42$. For both the considered Hill functions we set $E_0 = E_{\max} = 100$, to span the entire operational range of the BIS.

Moreover, since a discrete MPC is employed, functions x^*, BIS^* have to satisfy the difference equation

$$\begin{cases} x^*(k+1) = A_D x^*(k) + B_D u^*_{MPC}(k) \\ BIS^*(k) = f(x^*(k)), \end{cases} \tag{7}$$

where $A_D = e^{AT_s}$ and $B_D = \int_0^{T_s} e^{A\tau} B \, \mathrm{d}\tau$. At each sampling time $\tilde{k}$, the optimal control action $u^*_{MPC}(\tilde{k})$ is calculated as the one that solves the following (minimum-time) optimization problem, in which N_P is the prediction horizon:

$$\min_{0 \le \bar{k} \le N_P} \quad \bar{k} \tag{8}$$

s.t.

$$0 \le u^*_{MPC}(k) \le u_{sat} \qquad k = 0, \dots, N_C \tag{9a}$$
$$u^*_{MPC}(i+1) = u^*_{MPC}(i) \quad {}^{i=M_B k, \dots, M_B(k+1)-1}_{\wedge\, k=0,\dots,(N_C/M_B)-1} \tag{9b}$$
$$u^*_{MPC}(k) - u^*_{MPC}(k-1) \le SR \qquad k = 1, \dots, N_C \tag{9c}$$
$$u^*_{MPC}(0) - u^*_{MPC}(\tilde{k}-1) \le SR \tag{9d}$$
$$x^*(k+1) = A_D x^*(k) + B_D u^*(k) \qquad k = 0, \dots, N_P \tag{9e}$$
$$x_4^*(k) \le h^{-1}(BIS_{\min}) \qquad k = 0, \dots, N_P \tag{9f}$$
$$x_4^*(k) \ge h^{-1}(BIS_{\max}) \qquad k = \bar{k}, \dots, N_P \tag{9g}$$
$$x_4^*(k) \ge h^{-1}\big(BIS^R\big) \qquad sk = \bar{k}, \dots, N_P \tag{9h}$$
$$x^*(0) = x^*_{KF}(\tilde{k}-1) \tag{9i}$$

The set of constraints (9a)–(9d) refer to the manipulated variable throughout the control horizon, N_C:

- (9a) represents input limitations. The Graseby 3400 (Smiths Medical, London, U.K.) pump is considered, with a saturation limit of $u_{sat} = 6.67$ mg/s;
- (9b) serves to enforce the move-blocking strategy and ensure a piecewise constant human-imitating control action. $M_B = 5$ represents the duration of each move block. Without loss of generality, we assume that N_C is a multiple of M_B;
- (9c)–(9d) are the constraints on the slew rate of the drug dosage adjusted based on the anesthesia phase ($SR = 0.1$ for the induction phase and $SR = 0.4$ for the maintenance one). In particular, only positive changes in dosage are limited, which allow the MPC to immediately set the propofol infusion to zero. Moreover, if an abrupt disturbance occurs that would drive the BIS to a value above 60, then the maximum slew rate SR is set equal to $u_{sat} = 6.67$ mg/s for one instant so that a bolus with the maximum amplitude can be applied.

Then, (9e)–(9i) set the constraints on the process variable and the patient dynamics along the prediction horizon N_P:

- (9e) denotes the patient's dynamics, which correspond to the MPC model (see (1);
- (9f) guarantees that the calculated BIS^* signal never falls below $BIS_{\min} = 40$ along the prediction horizon;
- (9g) states that the calculated BIS^* signal must be below $BIS_{\max} = 60$ at all samples greater than or equal to $\bar{k}$;
- (9h) expresses that the effect-site concentration must be above the target effect-site concentration C_e^R at all samples in the prediction horizon greater than or equal to $\bar{k}$;
- (9i) is a condition that imposes the initial condition $x^*(0)$ to be equal to the predicted state resulting from the Kalman filter at the previous iteration $x^*_{KF}(\tilde{k}-1)$.

In a single iteration, a bisection procedure is applied in order to determine the optimal $\bar{k}$, that is the minimum $\bar{k}$ that makes Problem (9)–(9i) feasible, starting from $\bar{k} = N_P$. The objective function (8) makes the problem a minimum Time-to-Target, which is the time needed for the BIS level to reach for the first time the BIS value of 60. Finally, a receding horizon strategy, with a move-blocking concept, is applied so that only the first M_B calculated values of $u^*_{MPC}(k)$ are applied

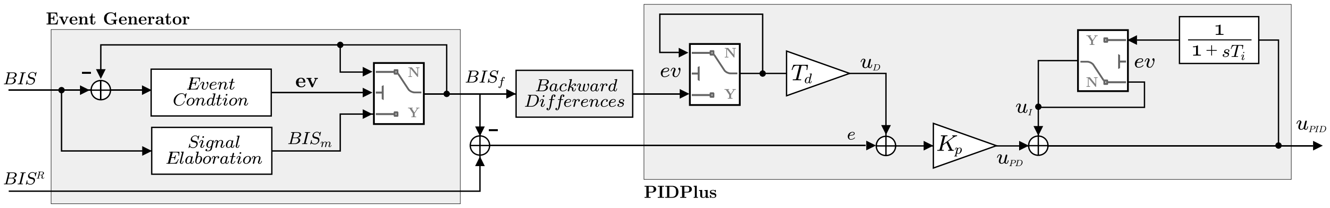

Fig. 2. The considered event generator and PIDPlus structure derived from automatic reset form of standard PID.

and then the optimization problem is solved again after M_B sampling periods. The prediction horizon N_P and control horizon N_C have both been set to 80. Setting both to the same value has been made to achieve a more aggressive control action while the value 80 was based on the observed time-to-peak effect after a propofol bolus injection, as reported in [19].

C. Kalman Filter

The Kalman filter determines an estimation of the four component of the state, denoted by $x_{KF}(\tilde{k}) = [\tilde{q}_1, \tilde{q}_2, \tilde{q}_3, \tilde{C}_e]^T$, at each sampling instant $\tilde{k}$, so that constraint (9i) can be satisfied when the MPC starts operating every M_B time steps. The parameters R, Q and P of the Kalman filter are set according to [11].

D. Event-Based PID Controller

Figure 2 illustrates a block diagram representing the event-based control system, comprising an event generator and a PIDPlus controller. The event generator consists of two components: the event condition block and the signal elaboration block. The former follows the event condition generation (10) while the latter calculates the average value BIS_m according to (11).

$$\left| \int_{t_{\text{last}}}^{t} \left[BIS(t) - BIS_f(t_{\text{last}}) \right] dt \right| > \Delta_i \quad \vee \quad t_w > t_{\max} \quad (10)$$

$$BIS_m(t) = \frac{\int_{t_{\text{last}}}^{t} BIS(t)dt}{t - t_{\text{last}}} \quad (11)$$

In particular, $BIS(t)$ is the process variable, $BIS_f(t_{\text{last}})$ denotes the last sample transmitted to the controller, t_{last} denotes the time of the previous event, t denotes the current time, t_w is the waiting time which represents the time elapsed since the previous event. Note that BIS_f equals BIS_m when an event occurs. The design parameters of the event generator Δ_i and $t_{\max}$ have been set to 9.45 and 20, respectively, using the tuning methodology proposed in [9] for the same problem. The second part of the event condition is a safety measure to ensure event triggering under all circumstances. This feature is valuable during maintenance with periodic events and small infusion level changes to keep the BIS level required. This behavior mimics the manual infusion regulation performed by anesthesiologists during surgery.

The PIDPlus controller implemented is shown in Figure 2. Here, K_p represents the proportional gain, T_d denotes the derivative time constant, e indicates the control error, and u_{PID} denotes the control variable. The operational procedure of the PIDPlus controller can be delineated as in Algorithm 1. Note that signal $u(k-1)$ denotes the controller output from the previous iteration, which can be either from the MPC or the PID controller, depending on the selector choice (refer to (5). The PID parameters have been set equal to $K_p = 0.0353$ mg/s $T_i = 198.86$ s and $T_d = 25.60$ s [8].

Algorithm 1 PIDPlus Control Action Calculation

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$t_w(k) \leftarrow T_s + t_w(k-1)$                              ▷ Update waiting time

if ev$(k) = 1$ then                                              ▷ Event occurrence
    $u_D(k) \leftarrow T_d \cdot (BIS_f(k) - BIS_{\text{last}})/t_w(k)$
    $e(k) \leftarrow BIS_f(k) - BIS^R$                           ▷ Update control error
    $u_I(k) \leftarrow u_I(k-1) + (u(k-1) - u_I(k-1)) \cdot (1 - e^{-t_w(k)/T_i})$

    $t_w(k-1) \leftarrow 0$                                      ▷ Reset waiting time
    $BIS_{\text{last}} \leftarrow BIS_f(k)$    $e_{\text{last}} \leftarrow e(k)$
    $u_{D\ \text{last}} \leftarrow u_D(k)$    $u_{I\ \text{last}} \leftarrow u_I(k)$
end if

$u_{PID}(k) \leftarrow K_p \cdot (e_{\text{last}} + u_{D\ \text{last}}) + u_{I\ \text{last}}$
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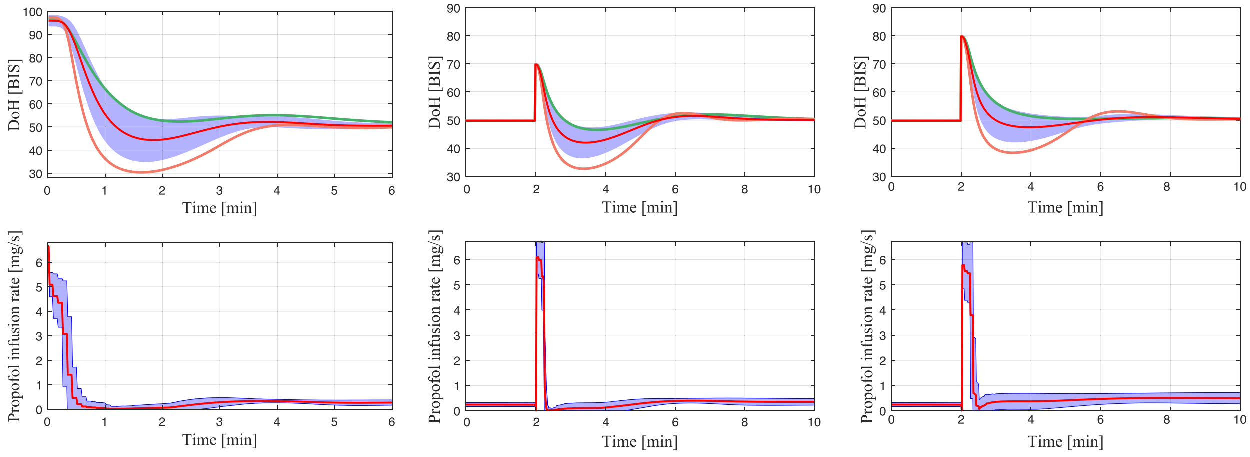
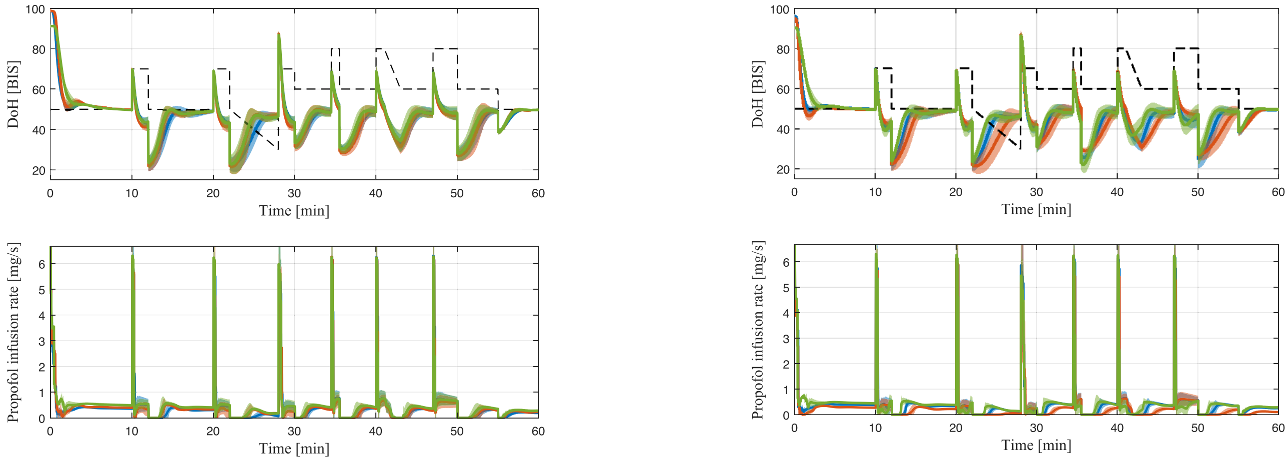
IV. SIMULATION RESULTS

Simulations have been performed using MATLAB 2023b on a 64-bit PC platform with an Intel i7 2.20 GHz processor and 16 GB RAM, running Microsoft Windows 11. The optimization Problem (9)–(9i) has been solved online using the standard linear programming solver GUROBI [5]. On average, the control signal calculation process took approximately 1.52 s, which means that the proposed approach is capable of solving the optimization problem below the cycle time of 5 seconds, being $M_B = 5$. The proposed method involved generating 500 patient models using a Monte Carlo Method (MCM). To do this, we randomly selected the gender, the age in a range from 18 to 70 years and the height in a range from 150 to 190 cm. Each patient's weight was then calculated based on their height and a random BMI in the range 18.5 kg m^{-2} to 29.9 kg m^{-2}, thus ensuring that sensible height and weight combinations were considered. Then, the same number of different Hill functions have been randomly generated from the normal distribution of the parameters E_0, $E_{\max}$, γ and C_{e50} with their mean μ and standard deviation σ values taken from [18] and [24]. Results are shown in Figures, 3(a), 3(b) and 3(c). As illustrated in the figures, the proposed control structure is able to meet the clinical requirements for both anesthesia phases in all the 500 patients, and the control action is piecewise constant with short time interval boluses when required. In the previous tests, it was assumed that there was a perfect knowledge of the linear part of the patient model. In order to evaluate the controller's ability to handle mismatches in the linear part of the model, the dataset of 12 patients proposed in [6] is considered. Then for each patient,

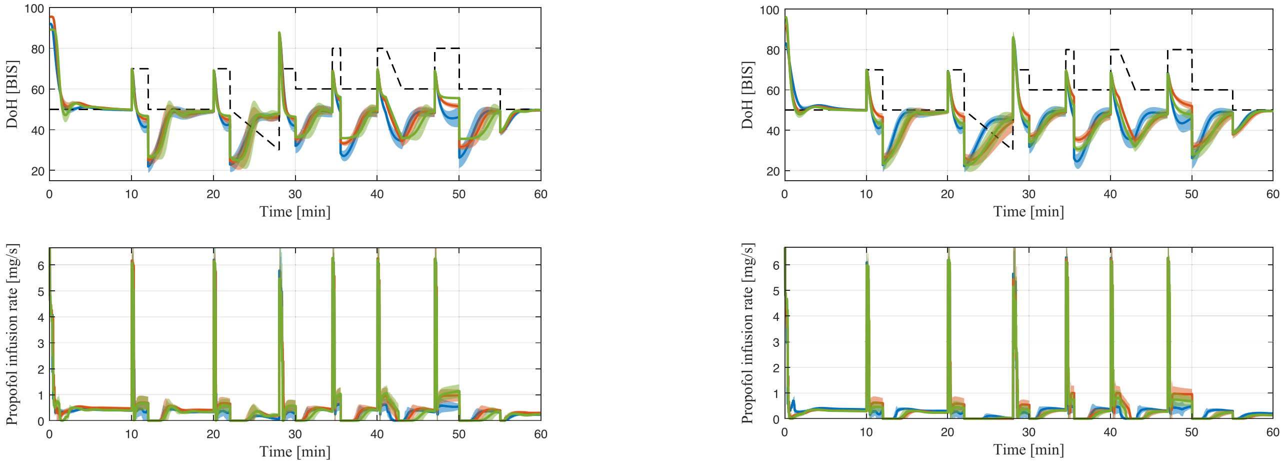


(a) Induction Phase (b) Maintenance phase 20 (c) Maintenance phase 30

Fig. 3. Responses for induction and maintenance phase with a step disturbance with amplitude 20 and 30 obtained for 500 patients. The mean value μ — and shaded region ▨ representing $\pm 2\sigma$. Additionally, the response for the worst-case patient is highlighted in terms of Time-to-Target — and lowest *BIS* reached —.



(a) Patient 1 —, Patient 2 — and Patient 3 — (b) Patient 4 —, Patient 5 — and Patient 6 —



(c) Patient 7 —, Patient 8 — and Patient 9 — (d) Patient 10 —, Patient 11 — and Patient 12 —

Fig. 4. Responses obtained for the dataset from [6] with the application of MCM on the linear component. The dashed line - - - denotes the disturbance profile *d*, while each solid line represents the mean value μ with the corresponding shaded region representing $\pm 2\sigma$ of the 500 patients.

a set of 500 models has been generated by applying another MCM on the parameters of the linear part using statistical distribution [18].

Both phases of anesthesia have been evaluated by first considering the induction phase and then, after 10 minutes, by applying, in the maintenance phase, the disturbance profile

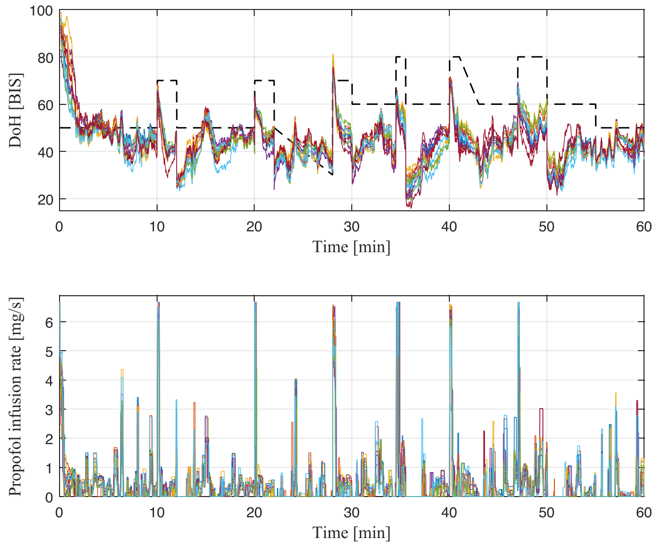


Fig. 5. Simulation results for the 12 patients taken from [6] obtained with noise addition n.

proposed in [22], which is very challenging as it naturally yields to very high and low BIS levels. Results are shown in Figure 4. As it can be seen, the clinical requirements are also fulfilled in this case. Finally, in order to simulate the proposed control structure in a real environment, a typical noise associated with the BIS sensor measurement signal has been applied [14]. The purpose is to test and evaluate how the process noise affects the performance of the control system in terms of process variable and control action. Results related to the previous dataset of the 12 patients are shown in Figure 5, where again the induction phase is followed by the disturbance profile proposed in [22]. The clinical requirements are met and the automatic control action closely mimics the typical manual control even with noise. This is made possible by the event generator and by the Kalman filter in the MPC, which ensure that the control structure is not affected by the noise.

V. CONCLUSION

In this letter we have proposed a combined approach with a minimum time-to-target MPC and an event-based PID controller used to control the DoH measured by the BIS signal. The main feature is that the control action is similar to the typical one applied by an anesthesiologist so that the supervision of the overall system is much simplified. Both inter- and intra-patient robustness have been evaluated in simulation and the effectiveness of the methodology is demonstrated.

REFERENCES

[1] J. Bruhn, T. W. Bouillon, and S. L. Shafer, “Bispectral index (BIS) and burst suppression: Revealing a part of the BIS algorithm,” *J. Clin. Monit. Comput.*, vol. 16, no. 8, pp. 593–596, 2000.

[2] R. Cagienard, P. Grieder, E. C. Kerrigan, and M. Morari, “Move blocking strategies in receding horizon control,” *J. Process Control*, vol. 17, no. 6, pp. 563–570, 2007.

[3] H. Chang, A. Krieger, A. Astolfi, and E. N. Pistikopoulos, “Robust multi-parametric model predictive control for LPV systems with application to anaesthesia,” *J. Process. Control*, vol. 44, no. 10, pp. 1538–1547, 2014.

[4] M. Ghita, M. Neckebroek, C. Muresan, and D. Copot, “Closed-loop control of anesthesia: Survey on actual trends, challenges and perspectives,” *IEEE Access*, vol. 8, pp. 206264–206279, 2020.

[5] *Gurobi Optimizer Reference Manual, Version 9.5*, Gurobi LLC, Beaverton, OR, USA, 2023.

[6] C. M. Ionescu, R. De Keyser, B. C. Torrico, T. De Smet, M. M. R. F. Struys, and J. E. Normey-Rico, “Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia,” *IEEE Trans. Biomed. Eng.*, vol. 55, no. 9, pp. 2161–2170, Sep. 2008.

[7] M. Milanesi, L. Consolini, G. Di Credico, M. Laurini, M. Schiavo, and A. Visioli, “A minimum time-to-target MPC approach for depth of hypnosis in total intravenous anesthesia,” in *Proc. 12th IFAC Symp. Biol. Med. Syst.*, 2024.

[8] L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, and A. Visioli, “Event-based control of depth of hypnosis in anesthesia,” *Comput. Methods Programs Biomed.*, vol. 147, pp. 63–83, Aug. 2017.

[9] L. Merigo, F. Padula, N. Latronico, M. Paltenghi, and A. Visioli, “Event-based control tuning of propofol and remifentanil coadministration for general anaesthesia,” *Inst. Eng. Technol. Control Theory Appl.*, vol. 14, no. 19, pp. 2995–3008, 2020.

[10] I. Nascu and E. N. Pistikopoulos, “Modeling, estimation and control of the anaesthesia process,” *Comput. Chem. Eng.*, vol. 107, pp. 318–332, Dec. 2017.

[11] S. Ntouskas and H. Sarimveis, “A robust model predictive control framework for the regulation of anesthesia process with propofol,” *Optimal Control Appl. Methods*, vol. 42, no. 4, pp. 965–986, 2021.

[12] F. Padula, C. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, and G. Vivacqua, “Optimized PID control of depth of hypnosis in anesthesia,” *Comput. Methods Programs Biomed.*, vol. 144, pp. 21–35, Jun. 2017.

[13] A. Pawlowski, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, “Linear MPC for anesthesia process with external predictor,” *Comput. Chem. Eng.*, vol. 161, May 2022, Art. no. 107747.

[14] A. Pawlowski, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, “MPC for propofol anesthesia: The noise issue,” in *Proc. IEEE Conf. Control Technol. Appl.*, 2022, pp. 1087–1092.

[15] A. Pawlowski, M. Schiavo, N. Latronico, M. Paltenghi, and A. Visioli, “Event-based MPC for propofol administration in anesthesia,” *Comput. Methods Programs Biomed.*, vol. 229, Feb. 2023, Art. no. 107289.

[16] Y. Sawaguchi, E. Furutani, G. Shirakami, M. Araki, and K. Fukuda, “A model-predictive hypnosis control system under total intravenous anesthesia,” *IEEE Trans. Biomed. Eng.*, vol. 55, no. 3, pp. 874–887, Mar. 2008.

[17] M. Schiavo, F. Padula, N. Latronico, M. Paltenghi, and A. Visioli, “Individualized PID tuning for maintenance of general anesthesia with propofol and remifentanil coadministration,” *J. Process Control*, vol. 109, pp. 74–82, 2022.

[18] T. W. Schnider et al., “The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers,” *Anesthesiology*, vol. 88, no. 5, pp. 1170–1182, 1998.

[19] T. W. Schnider et al., “The influence of age on propofol pharmacodynamics,” *Anesthesiology*, vol. 90, no. 6, pp. 1502–1516, 1999.

[20] M. Soehle, A. Dittmann, R. K. Ellerkmann, G. Baumgarten, C. Putensen, and U. Guenther, “Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: A prospective, observational study,” *BMC Anesthesiol.*, vol. 15, no. 1, p. 61, 2015.

[21] K. Soltesz, J. Hahn, T. Hägglund, G. A. Dumont, and J. M. Ansermino, “Individualized closed-loop control of propofol anesthesia: A preliminary study,” *Biomed. Signal Process. Control*, vol. 8, no. 6, pp. 500–508, 2013.

[22] M. M. R. F. Struys, T. De Smet, S. Greenwald, A. R. Absalom, S. Bingé, and E. P. Mortier, “Performance evaluation of two published closed-loop control systems using bispectral index monitoring: A simulation study,” *Anesthesiology*, vol. 100, no. 3, pp. 640–647, 2004.

[23] K. van Heusden et al., “Optimizing robust PID control of propofol anesthesia for children: Design and clinical evaluation,” *IEEE Trans. Biomed. Eng.*, vol. 66, no. 10, pp. 2918–2923, Oct. 2019.

[24] A. L. G. Vanluchene, H. Vereecke, O. Thas, E. P. Mortier, S. L. Shafer, and M. M. R. F. Struys, “Spectral entropy as an electroencephalographic measure of anesthetic drug effect: A comparison with bispectral index and processed midlatency auditory evoked response,” *J. Am. Soc. Anesthesiol.*, vol. 101, no. 1, pp. 34–42, 2004.

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