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Paolino, Nicola; Norlund, Frida; Schiavo, Michele; Visioli, Antonio; Soltesz, Kristian

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Adjusting aggressiveness of Depth-of-Hypnosis PID control by MPC-based feedforward

Nicola Paolino[1], Frida Norlund[2], Michele Schiavo[1], Antonio Visioli[1] and Kristian Soltesz[2]

***Abstract*— In this paper we propose a technique to enhance the performance of a Proportional-Integral-Derivative (PID)-based control structure for Depth-of-Hypnosis control in total intravenous anesthesia when set-point changes are required during the maintenance phase. In particular, the PID controller, tuned for disturbance rejection, is integrated with a feedforward action based on Model Predictive Control (MPC). A tuning parameter determines the aggressiveness of the controller, thus allowing the anesthesiologist to select the most appropriate transient response depending on the kind of patient and of surgery. Simulation results show that the method is useful in providing an effective tool for the anesthesiologist to interact with the control system.**

I. INTRODUCTION

In the clinical practice of total intravenous anesthesia (TIVA) one of the main tasks that the anesthesiologist must carry out consists of regulating the administration of the hypnotic drug propofol to establish a suitable Depth-of-Hypnosis (DoH) in the patient. This is of primary importance since too shallow DoH could result in episodes of intraoperative awareness. Conversely, too deep DoH, which is caused by propofol overdose, could provoke drug-induced side-effects. To titrate propofol, the anesthesiologist relies on the Bispectral Index (BIS) [1], a processed electroencephalogram index that quantifies DoH by providing a number ranging from 0 (absence of cortical activity) to 100 (fully awake patient). The anesthesia process is divided into two main phases. The first one is anesthesia induction. Here, the task that the anesthesiologist must accomplish consists of administering propofol to quickly drive the BIS from a value close to 100 to a value close to 50 (usually, from 40 to 60), while avoiding undershoots (BIS values below 30). The second one is anesthesia maintenance. Here, the anesthesiologist must titrate propofol to maintain the BIS as close as possible to the target value despite the presence of disturbances caused by the surgical stimulation. In this phase, the BIS target value is usually fixed to 50, but different values (usually in the range from 40 to 60) could be desired for specific phases of the surgical procedure. Closed-loop control of TIVA has attracted significant research attention over the past two decades [2]. Indeed, DoH regulation is only one part of the anesthesiologist workload, which is quite demanding and thus prone to human errors due to tiredness. In this context, feedback control can enhance treatment accuracy, improve patient safety, and reduce the workload of clinicians [3]. However, it is worth noting that this technology aims to complement, rather than replace, anesthesiologists. So, taking into account the presence of the anesthesiologist-in-the-loop [4] is of primary importance for the design of these systems as they must be easily comprehensible by a clinician while being robust to the presence of a human possibly acting within the loop. Over the years, noteworthy clinical results have been obtained with approaches based on classic Proportional-Integral-Derivative (PID) controllers [5–8] thanks to their simplicity and robustness in clinical applications. Model Predictive Control (MPC) emerges as a promising alternative in order to increase the control system performance thanks to its ability to anticipate the future behavior of the system. Nevertheless, the practical application of MPC in closed-loop anesthesia has been relatively limited. Pioneering studies [9–13] have shown that while MPC holds potential, its performance is hindered by discrepancies between the model and the real response of the patient to drug administration. For this reason, replacing the functioning PID-based control system altogether with an MPC at once can be seen as a risky step from a clinical point of view and the anesthesiologist, who has to interact with the control system, could not accept it. In light of these considerations, in this paper we propose the application of a novel control approach, originally proposed in [14], that combines the strengths of both PID and MPC controllers. In particular, the PID controller, tuned for disturbance rejection, is enhanced with a feedforward action based on the MPC when set-point changes are required during the maintenance phase of anesthesia. This way, thanks to the MPC, it will be possible to personalize the control system behavior, according to the patient's needs and the phase of surgery, without performing a new PID tuning. To this end, a tuning parameter allows the anesthesiologist to adjust the aggressiveness of the control system. This method provides a flexible and adaptive approach to DoH control, enhancing both the performance and safety of closed-loop anesthesia systems.

II. MATERIALS AND METHODS

We consider the case when, during the maintenance phase, the set-point value of the BIS has to be decreased as required by the surgical procedure. Since the increment of the BIS level can be easily achieved by stopping the propofol infusion for a given time interval, we did not considered this situation in the paper. The proposed control structure is shown in Fig. 1, where the propofol flow rate is the control variable

[1]Nicola Paolino, Michele Schiavo and Antonio Visioli are with the Department of Mechanical and Industrial Engineering, University of Brescia, Brescia, Italy name.surname@unibs.it

[2]Frida Norlund and Kristian Soltesz are with the Department of Automatic Control, Lund University, Lund, Sweden name.surname@control.lth.se

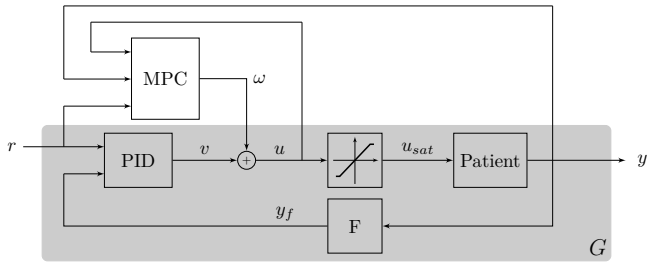


Fig. 1. Block diagram of the control scheme. The gray area is an already available closed-loop system G, which is integrated with the MPC block.

$u(t)$ obtained by adding the MPC-based feedforward term $\omega(t)$ to the PID action $v(t)$, thus $u(t) = v(t) + \omega(t)$. The process variable $y(t)$ is the patient's current BIS value and since it is noisy, it is filtered with a second order filter F. Thus, the control error $e(t)$ is calculated as

$$e(t) = r(t) - y_f(t) \tag{1}$$

where $r(t)$ is the BIS set-point value. The control variable $u(t)$ is subject to saturation due to mechanical limitation of the surgical infusion pumps. Indeed, by taking into account commercially available pump (e.g. Graseby 3400, Smiths Medical, London, UK) that can operate at a minimum and maximum infusion rate of 0 $\mathrm{mL\,h^{-1}}$ and 1200 $\mathrm{mL\,h^{-1}}$, respectively, and by considering a standard propofol concentration of 20 $\mathrm{mg\,mL^{-1}}$, the propofol infusion rate $u_{sat}(t)$ can range from 0 $\mathrm{mg\,s^{-1}}$ to 6.67 $\mathrm{mg\,s^{-1}}$.

A. Patient model

The MPC block exploits a pharmacokinetic-pharmacodynamic (PK-PD) model of the patient dynamics [15, 16]. In particular, a compartmental model is used and it is expressed in state-space form as

$$\dot{\boldsymbol{x}}(t) = A\boldsymbol{x}(t) + Bu(t), \tag{2a}$$
$$C_e(t) = C\boldsymbol{x}(t), \tag{2b}$$

where

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \dfrac{k_{1e}}{V1} & 0 & 0 & -k_{e0} \end{bmatrix}, \tag{3a}$$

$$B = \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}^\top, \tag{3b}$$

$$C = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix}. \tag{3c}$$

The first state component, $x_1(t)$ [mg], represents the mass of propofol in the blood plasma, while the last, $x_4(t) = C_e(t)$ $[\mathrm{mg\,L^{-1}}]$, models the effect-site concentration, which, for DoH, is located in the cortex of the brain. The other state components, $x_2(t)$ and $x_3(t)$, models drug distribution across fast (muscles) and slow (fat) tissue, respectively. The parameters k_{10}, k_{12}, k_{13}, k_{21}, k_{31}, k_{e0}, and k_{1e}, in units of $\mathrm{s^{-1}}$, are exchange rate constants, and V_1 [L] represents the plasma volume.

The relationship between the effect-site drug concentration and the hypnotic effect is modeled using a sigmoid nonlinear function, namely the Hill function

$$y(C_e) = E_0 - E_{\max}\left(\frac{C_e^\gamma}{C_e^\gamma + C_{e50}^\gamma}\right). \tag{4}$$

The baseline DoH level in absence of drug is $E_0 \lessapprox 100$ BIS, and the maximum achievable hypnotic depth is $E_{\max} \lessapprox 100$ BIS. The effect-site concentration C_{e50} $[\mathrm{mg\,L^{-1}}]$ is the concentration that produces an hypnotic level which is exactly half of the maximum achievable effect defined by $E_{\max}$ (that is, $E_0 - E_{\max}/2$). The third parameter of Eq. (4), γ, is a unitless shape parameter that defines the slope of the curve. For the sake of simplicity, a linear MPC algorithm is used and therefore the Hill function (Eq. (4)), has been linearized around the BIS value of 50. The corresponding gain is calculated as

$$K_{hill} = -E_{\max}\left[\frac{\gamma\, C_{e_{ref}}^{\gamma-1}\, C_{e50}^\gamma}{\left(C_{e_{ref}}^\gamma + C_{e50}^\gamma\right)^2}\right], \tag{5}$$

where $C_{e_{ref}}$ is the patient's effect-site drug concentration value that produces a BIS equal to 50, and it is computed by inverting Eq. (4):

$$C_{e_{ref}} = C_{e50}\left(\frac{E_{\max}}{E_0 - 50} - 1\right)^{-1/\gamma}. \tag{6}$$

The values of the parameters of the linear part of the model can be determined from the demographics of each patient (gender, height, weight, age). On the other hand, the values of the parameter of the Hill function are unknown and the "average" values reported in [17] have to be used, thus introducing a significant uncertainty in the model employed in the controller.

B. PID Controller

The PID controller is implemented in standard ideal form [18]. Therefore, by considering the state vector

$$\boldsymbol{x_c}(t) = \left[\int_0^t (r(\tau - y_f(\tau)))d\tau \quad y_f(t) \quad \dot{y}_f(t)\right]^\top \tag{7}$$

the controller state-space formulation is

$$\dot{\boldsymbol{x}}_c(t) = A_c\boldsymbol{x_c}(t) + B_{cr}r(t) + B_{cy}y(t), \tag{8a}$$
$$v(t) = C_c\boldsymbol{x_c}(t) + D_{cr}r(t) + D_{cy}y(t), \tag{8b}$$

where

$$A_c = \begin{bmatrix} 0 & -1 & 0 \\ 0 & 0 & 1 \\ 0 & -\dfrac{1}{T_f^2} & -\dfrac{2}{T_f} \end{bmatrix}, \tag{9a}$$

$$B_{cr} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}^\top, \tag{9b}$$

$$B_{cy} = \begin{bmatrix} 0 & 0 & \dfrac{1}{T_f^2} \end{bmatrix}^\top, \tag{9c}$$

$$C_c = \begin{bmatrix} -\frac{K_p}{T_i} & K_p & K_pT_d \end{bmatrix}, \tag{9d}$$

$$D_{cr} = -K_p, \tag{9e}$$

$$D_{cy} = 0. \tag{9f}$$

K_p [mg/BIS/s]	T_i [s]	T_d [s]	T_f [s]
0.4446	1250.7326	20.3660	0.7204

TABLE I

PID PARAMETERS TAKEN FROM [20]

Here, K_p is the proportional gain while T_i, T_d and T_f are the integral, derivative and filter time constants, respectively. As already mentioned, the tuning parameters (shown in Table I) have been selected in order to minimize the worst-case integrated absolute error (IAE) for a set of patients that are representative of a wide population [19].

C. MPC Controller

A linear MPC has been designed, using the Matlab MPC toolbox, to provide a control action $\omega(t)$ that is added to the control signal $v(t)$ produced by the PID controller. To achieve this, the MPC has been designed for the closed-loop system G, highlighted with a gray box in Fig. 1. Note that G has been designed in order to have two inputs ($r(t)$ and $\omega(t)$) and two outputs ($u(t)$ and $y(t)$).

To derive the linear formulation of the closed-loop system G, it is necessary to write the linear model of the patient in state-space form. Thus, by rearranging Eq. (3) together with Eq. (5), the patient's linear state-space model can be written as

$$\dot{\boldsymbol{x}}_p(t) = A_p \boldsymbol{x}_p(t) + B_p u(t), \tag{10a}$$
$$y(t) = C_p \boldsymbol{x}_p(t) + D_p u(t), \tag{10b}$$

where

$$A_p = A, \qquad B_p = B, \tag{11a}$$
$$C_p = K_{hill} C, \qquad D_p = 0. \tag{11b}$$

Therefore, by considering the state vector

$$\boldsymbol{x}_G = \begin{bmatrix} \boldsymbol{x}_p & \boldsymbol{x}_c \end{bmatrix}^\top \tag{12}$$

the linear system G can be written in state-space form as

$$G := \begin{cases} \dot{\boldsymbol{x}}_G(t) = A_G \boldsymbol{x}_G(t) + B_{Gr} r(t) + B_{Gw} \omega(t) \\ y(t) = C_{G_1} \boldsymbol{x}_G(t) + D_{Gr_1} r(t) + D_{Gw_1} \omega(t) \\ u(t) = C_{G_2} \boldsymbol{x}_G(t) + D_{Gr_2} r(t) + D_{Gw_2} \omega(t) \end{cases} \tag{13}$$

where

$$A_G = \begin{bmatrix} A_p + B_p E_p D_{cy} C_p & B_p E_p C_c \\ B_{cy} E_c C_p & A_c + B_{cy} E_c D_p C_c \end{bmatrix}, \tag{14a}$$
$$B_{Gr} = \begin{bmatrix} B_p E_p D_{cr} & B_{cr} + B_{cy} E_c D_p D_{cr} \end{bmatrix}^\top, \tag{14b}$$
$$B_{Gw} = \begin{bmatrix} B_p (I + E_p D_{cy} D_p) & B_{cy} E_c D_p \end{bmatrix}^\top, \tag{14c}$$
$$C_G = \begin{bmatrix} C_{G_1} \\ C_{G_2} \end{bmatrix} = \begin{bmatrix} E_c C_p & E_c D_p C_c \\ E_p D_{cy} C_p & E_p C_c \end{bmatrix}, \tag{14d}$$
$$D_{Gr} = \begin{bmatrix} D_{Gr_1} \\ D_{Gr_2} \end{bmatrix} = \begin{bmatrix} E_c D_p D_{cr} \\ E_p D_{cr} \end{bmatrix}, \tag{14e}$$
$$D_{Gw} = \begin{bmatrix} D_{Gw_1} \\ D_{Gw_2} \end{bmatrix} = \begin{bmatrix} E_c D_p \\ I + E_p D_{cy} D_p \end{bmatrix}. \tag{14f}$$

With this formulation the MPC solves a quadratic programming optimization problem to determine the control moves over a prediction horizon h of 150 s. The control horizon as been set to 50 s and the model discretisation has been performed by using the zero-order hold and a sampling time of 1 s. Moreover, the MPC uses a built-in Kalman filter to estimate the model states. Precisely, the cost function to be minimized is:

$$J(\alpha) = \int_0^h (1-\alpha)(r(t+\tau) - y(t+\tau))^2 + \alpha \omega(t+\tau)^2 \, d\tau \tag{15}$$

with $0 \leq \tau \leq h$. In the latter, by adjusting the tuning parameter $\alpha \in [0, 1]$, it is possible to regulate the trade-off between penalizing the control error or the MPC action.

Furthermore, the optimization problem is subject to system dynamics and constraints on the value of the resulting $u(t)$. Thus the MPC output $\omega(t)$ is determined by solving the following optimization problem

$$\min_w \; J(\alpha), \tag{16}$$

subject to

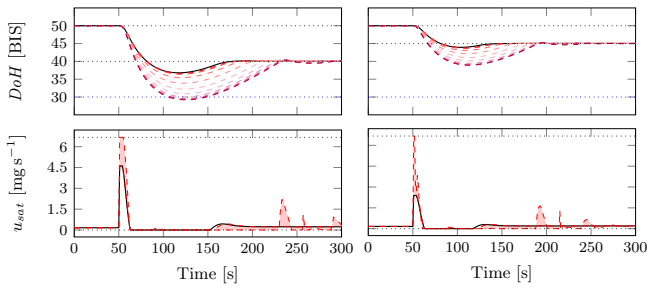
$$\begin{aligned} &G, \\ &0 \leq u(t) \leq 6.67. \end{aligned} \tag{17}$$

The posed optimization problem implies that a value of α equal to 1 produces a control signal that is the one derived from the nominal PID-based closed-loop scenario. On the contrary, a value of α equal to 0 overrides the PID by providing a control action primarily based on the MPC. In other words, it is possible to smoothly add the MPC to the PID, where the performance of the PID is fixed while the MPC can boost the control signal when required. Therefore, the anesthesiologist, by selecting the desired value of α can smoothly adapt the controller aggressiveness when reference changes are requested by the surgical procedure.

III. RESULTS

To test the effectiveness of the proposed solution, several simulations have been performed, where the patient has been represented by using the nonlinear model described in Eqs. (3) and (4). The thirteen patients of the dataset employed in [19] (where the thirteenth patient is created by calculating the average values of the parameters of the other twelve ones) have been considered since they are representative of a wide population, and the tuning parameter α has been varied from 1 to 0 in steps of 0.1, thus simulating eleven scenarios for each patient. Additionally, two reference changes have been considered, namely $r_1 = 45$ BIS and $r_2 = 40$ BIS. As already mentioned, positive reference steps have not been considered as they would simply cause the controller to switch the control action off due to the speed transient being constrained by the lower pump's saturation limit.

As a first illustrative result we consider the thirteen patient and the set-point step responses are shown in Fig. 2, where each dashed line is related to a different value of α. The use of the MPC-based feedforward action is compared with the use of the feedback PID controller only. As expected, the control system has a monotonic behaviour, that is, by



a) P13: reference changed to 40 b) P13: reference changed to 45

Fig. 2. Results obtained for patient 13. Top: DoH level. Black solid line: DoH level obtained by PID only (α=1). Red dashed lines: DoH level obtained by PID and MPC with $\alpha \in [0.9, 0]$ with a step of 0.1. Black dotted lines: Bis reference of 50, 45, and 40. Blue dotted line: safety limit of BIS = 30. Bottom: propofol infusion rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

decreasing α the aggressiveness is increased. In the most aggressive scenario, represented by the lower red dashed line, the response reaches the safety limit of BIS $= 30$. However, this undershoot episode does not pose any harm to the patient since this low level is maintained for only a brief period.

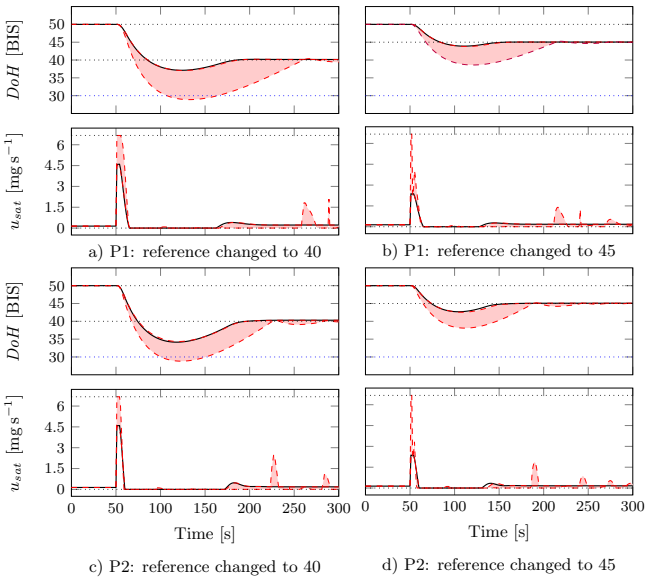
The results related to the other twelve patients are shown, two-by-two, in Fig. 3-Fig. 8. They confirm that the presence of the feedforward action provides the required flexibility to the anesthesiologist, as indicated by the shaded red area. Indeed, by adjusting the value of α, it is possible to increase the speed of response in attaining the new set-point when the reference value of BIS $= 50$ is not the most appropriate.

It is worth stressing that the system also guarantees the required robustness, as the uncertainty in the Hill function parameters has been considered and the linearization employed for the MPC controller around the BIS value of 50 does not cause any significant decrement in the performance.

The parameter α has a clear physical meaning, thus allowing the anesthesiologist to easily adapt the controller to the different requirements that can be present in the different surgeries and also in different situations in a single surgery.

IV. CONCLUSIONS

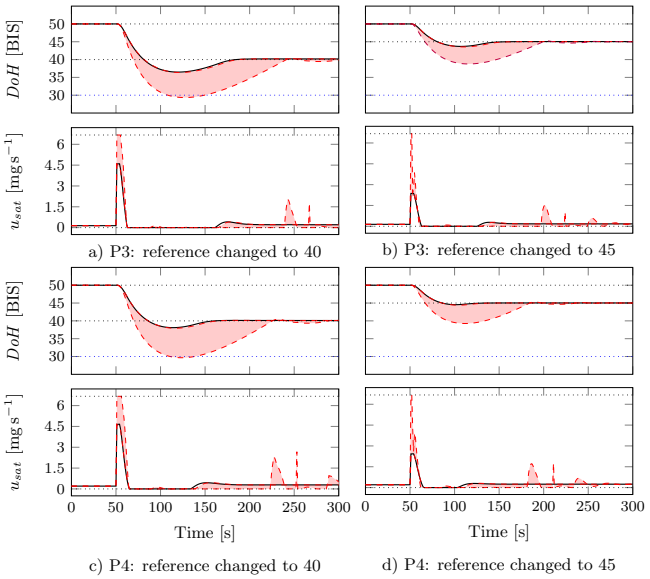
In this paper we have proposed a new approach to improve DoH control during total intravenous anesthesia. Set-point changes during the maintenance phase (in particular, those where the BIS value has to be lowered) are handled through the integration of an MPC controller with a pre-existing PID-based control system. The rationale of the method is to keep in place a satisfactory PID controller and to add the MPC controller to allow the anesthesiologist to select the required set-point step speed of response. A single parameter with a clear physical meaning can be adjusted for this purpose. Simulation results have demonstrated that the method is robust, allowing the system to be employed with different patients and for different requirements without the need of any retuning, thus being a very good candidate to be used in



a) P1: reference changed to 40 b) P1: reference changed to 45

c) P2: reference changed to 40 d) P2: reference changed to 45

Fig. 3. Results related to patients 1 (top) and 2 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.



a) P3: reference changed to 40 b) P3: reference changed to 45

c) P4: reference changed to 40 d) P4: reference changed to 45

Fig. 4. Results related to patients 3 (top) and 4 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

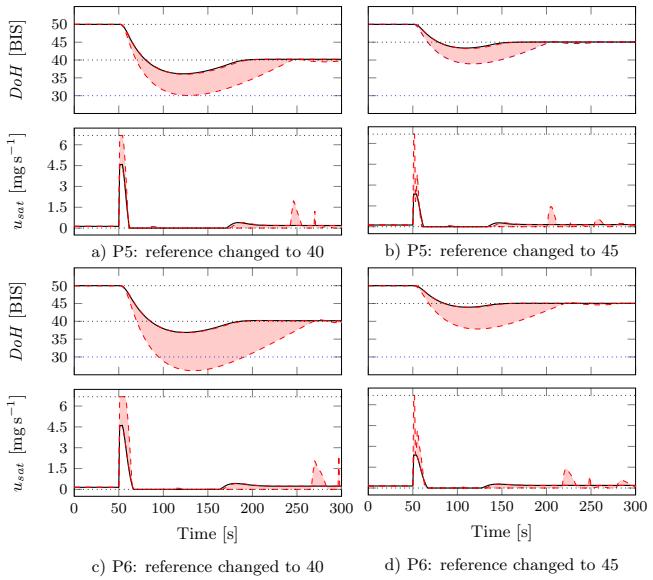


Fig. 5. Results related to patients 5 (top) and 6 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

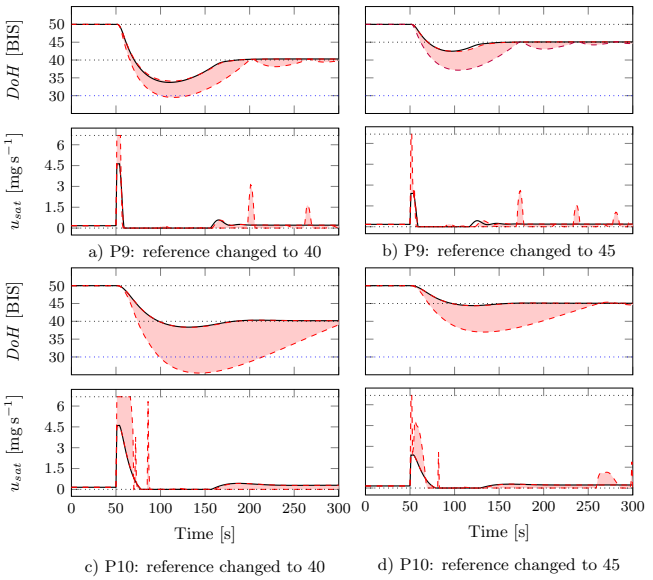


Fig. 7. Results related to patients 9 (top) and 10 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

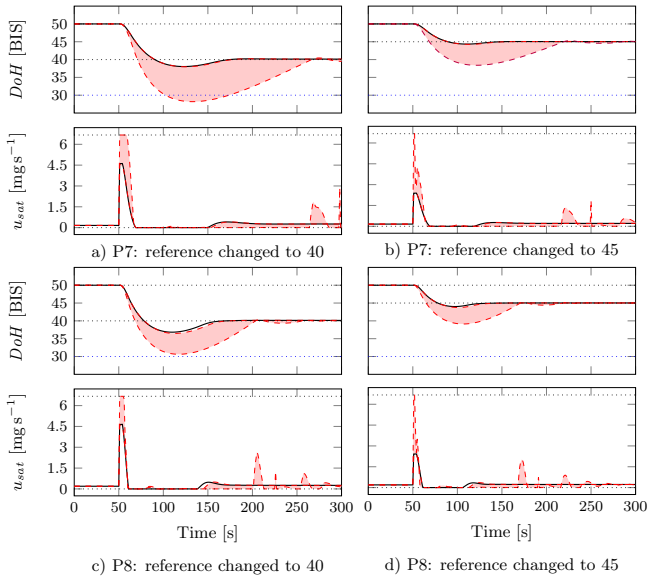


Fig. 6. Results related to patients 7 (top) and 8 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

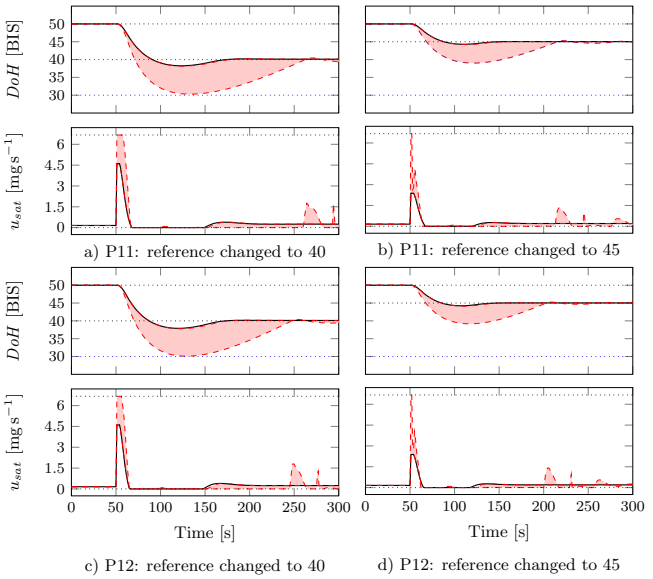


Fig. 8. Results related to patients 11 (top) and 12 (bottom). Top subplot: DoH level. Black solid line: PID only (α=1). Upper red dashed line: PID and MPC with $\alpha = 0.9$. Lower red dashed line: PID and MPC with $\alpha = 0$. Red dashed area: space of operation by changing α. Black dotted lines BIS reference of 50, 45, and 40 BIS. Blue dotted line: safety limit of BIS=30. Bottom subplot: propofol flow rate. Black solid line: PID only. Upper red dashed line: PID and MPC with $\alpha = 0$. Lower red dashed line: PID and MPC with $\alpha = 0.9$. Red shaded area: space of operation by changing α. Left: reference change from 50 to 40. Right: reference change from 50 to 45.

clinical practice, where the interaction of the control system with the anesthesiologist is of great concern.

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