MPC for Propofol Anesthesia: the Noise Issue

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Abstract: The design of automatic control systems for general anesthesia is a challenging task due to the severe safety requirements and process constraints. This is even more complex when model-based control techniques are used due to the significant variability of the process model. Additionally, issues like noisy measurements and interference also influence the control system overall performance. In this context, adequate filtering and control system sampling period selection should be analyzed to test their influence on the controller. In this paper, an MPC system for the depth of hypnosis, where the BIS signal is used as a controlled variable, is analyzed. The main purpose is to test and evaluate how the process noise affects the performance of the control system. The analysis is performed in a simulation study using a dataset of virtual patients representative of a wide population. Results show that a satisfactory performance is obtained when the noise is explicitly taken into account in the controller tuning procedure for a specific sampling period.

1. Introduction

Control systems for the anaesthesia process need to face many challenging problems, which are mainly related to the presence of a human being in the control loop. Among others, the most critical issues are related with the robustness due to the inter- and intra-patient variability. In the context of control systems that exploits a Model Predictive Control (MPC) approach, these issues are even more critical since the model uncertainty affects the predictions and, as a consequence, they can be detrimental for the correct determination of the control action [1].

The application of MPC techniques to the control of depth of hypnosis (DoH) in the anaesthesia process using propofol has been analyzed in several works, e.g. [2–9]. This interest is motivated mainly by the possibility of predicting the patient response to drug administration [4, 7]. In particular, the methods described in [2, 3] are focused on inter-/intra-patient variability, targeting the most vulnerable aspect in MPC approaches, namely, model uncertainties. These approaches usually results in a complex control system with heavy computational requirements and re-tuning or adaptation is not trivial [9]. For example the MPC based control system proposed in [2] exploits state observers, which provide the drug concentration estimation in body compartments. These estimations are used for predicting the effect of the drug in the control signal computation. The estimator uses a Kalman filter technique, which handles model uncertainties at the expense of a large settling time of the BIS in the induction phase.

Another example can be found in [3], where authors propose a piece-wise linearization of the Hill function to eliminate the nonlinear component from the control loop, thus simplifying the model that represents the patient. The resulting control scheme uses a hybrid multi-parametric-MPC (mp-MPC) approach, which is successfully evaluated considering the induction as well as the maintenance phases for a set of 12 virtual patients. A similar approach has been presented in [5, 6], where the piece-wise linearization of the Hill function is combined with a hybrid MPC.

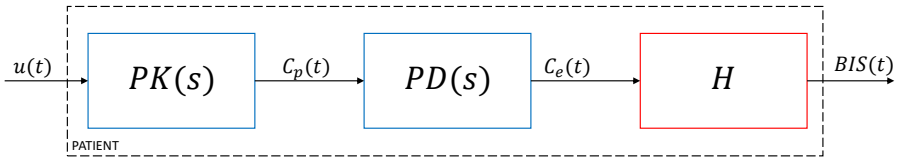

Fig. 1: Schematic representation on the patient PK-PD model for propofol dosage response.

A control system exploiting the pharmacokinetic/pharmacodynamic (PK/PD) model and its application to the linear MPC has been devised in [7]. In particular, the Hill function compensation is introduced in the feedback loop and the EPSAC algorithm is used as the feedback controller. The control system proposed in [8] also uses the inverse of the nonlinear part of the pharmacodynamic model to provide the linearization of the system. The authors provide a different approach for the propofol chemo-dynamics, considering a time delay. The main analyzed issue is related to the mismatch in time delays between the used model and the patient. Results from a clinical trial prove that MPC based system can be effective in DoH control in general anaesthesia.

From the analyzed works, it appears that MPC-based control systems are able to provide a satisfactory performance, that is, to meet the clinical requirements. However, the BIS signal used as a feedback measure is characterized by a high signal-to-noise ratio that needs to be considered in the control algorithm [12, 13]. Despite this, the noise handling issue in the anaesthesia process is frequently treated as a secondary problem or even neglected during the control system design, even if it is well known that, if the process noise is not handled properly in the control system, it can result in a severe performance degradation or even controller instability.

Bearing in mind the previously mentioned aspects, this work is devoted to analyze the performance of a DoH MPC control system for intravenous anaesthesia affected by the process noise. The DoH level is represented by the BIS and propofol dosage is used as control variable. The main goal of this study is to provide a quantitative measure that reflects the performance degradation due to the noise presence when compared to noise-free case. The considered MPC control architecture has been previously introduced in [11] and it exploits a realistic nonlinear patient model. The original structure is extended here with a suitably designed additional low-pass filter that attenuates the process noise. We have tested the system by using both white noise and real process noise that reflects not only the noise related with signal acquisition process but also other unmeasurable interferences and disturbances. Furthermore, the use of different sampling periods for the feedback controller has been analyzed. The evaluation is made in simulation using widely accepted performance indexes.

The paper is organized as follows: Section II reviews the PK/PD model of propofol used in the control scheme. Section III describes the proposed control architecture for the DoH, the GPC algorithm, the noise characteristics and the tuning procedure. Section IV presents the simulations results for the set of virtual patients and performance evaluation. Finally, conclusions are given in Section V.

2. Patient Model

The PK/PD model used to describe the patient response to the propofol administration is well known from the literature [14, 17, 18]. In particular, regarding the PK, a three compartment mammillary system can be modelled. A state space model can be derived, where the states are the quantity of drug in each compartment, the input is the drug dosage and the output is the plasmatic concentration, which is proportional to the concentration of the drug in the central blood compartment. The conversion of this model in a transfer function form yields a linear third-order PK term:

$$PK(s) = \frac{C_p(s)}{U(s)} = \frac{1}{V_1} \frac{(s+k_{21})(s+k_{31})}{(s+p_1)(s+p_2)(s+p_3)} \tag{1}$$

where C_p is the plasmatic concentration, U is the propofol infusion rate and p_1, p_2, p_3 are parameters that depend on the demographics of the patient (age, weight, height, gender) [15].
The PK term is connected in series with the PD part, which consists of a first-order linear system in series with a static nonlinearity (Hill function). The linear part of the PD has the plasmatic concentration as input and the effect site concentration C_e as output and it can be modelled by means of this transfer function:

$$PD(s) = \frac{C_e(s)}{C_p(s)} = \frac{k_{e0}}{s+k_{e0}} \tag{2}$$

where $k_{e0} = 0.456\ [min^{-1}]$.
Finally, the Hill function expresses the relationship between the effect-site concentration and the BIS value. Its

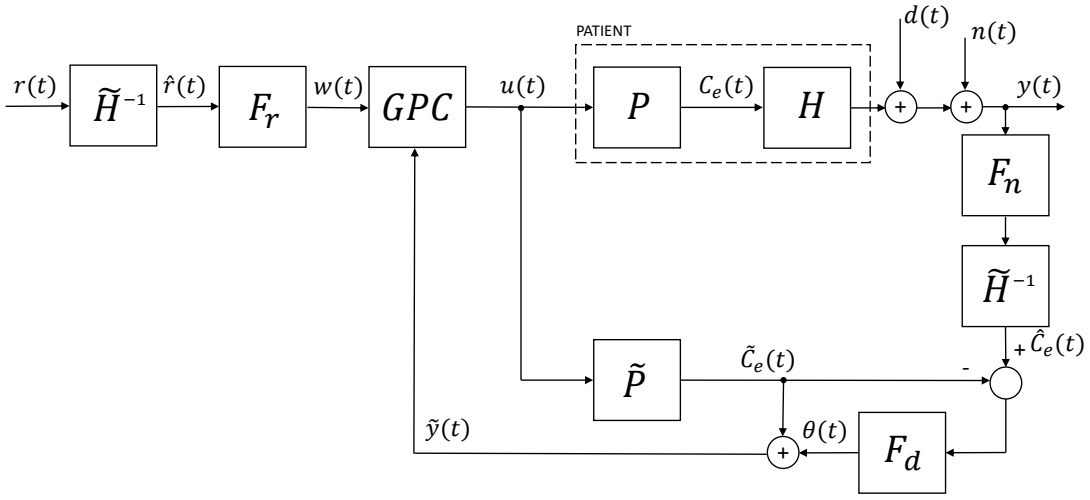

Fig. 2: The GPC-based control scheme proposed in [11] with the additional filter F_n, for a noise attenuation.

expression is [7, 10, 16]:

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

where E_0 is the patient's measured value of the BIS before the beginning of the anesthesia procedure, E_{max} is the maximum effect that can be reached by the drug administration, γ is the steepness of the function (in other words, it means the sensitivity of the patient to the propofol), and $C_{e_{50}}$ is the drug concentration that is needed in order to achieve half of the maximal effect. Figure 1 shows the block diagram of the complete propofol response model. It appears that the PK/PD model is actually a Wiener model and this can be exploited in the design of the (MPC) controller.

2.1. Virtual Patients Dataset

The inter-patient variability is taken into account by considering a set of patients, which has been already proved to be representative for a very wide range of adult population [5, 7]. The values of the model parameters for thirteen individuals can be found in [18]. In this context, it is worth noting that the parameters of the last patient are obtained by calculating the average values of the parameters of the other twelve patients. Thus, it is sensible to consider this thirteenth patient as the nominal case for the tuning of the controller (see Section 3.4).

3. Anaesthesia control system

In this section the evaluation scenario is briefly introduced. The analysis is performed using the MPC-based architecture proposed in [11]. In the approach presented here the original control scheme has been extended with an additional filter in order to reduce the impact of noise on the controller. The feedback MPC controller is implemented using the GPC algorithm, which is also reviewed. Moreover, we provide description of the noise characteristics in the BIS signal used to measure the DoH, including the information from the real signal analysis. Finally, the resulting control system tuning is described. Indeed, a proper tuning is necessary, due to the presence of the additional noise filter in the control loop that affects the performance of the controller.

3.1. Control Scheme

The control structure is shown in Figure 2, where it can be observed that the patient is represented by the nonlinear model previously introduced. However, in practice, exact values of the model components are unknown and need to be calculated using an inaccurate PK/PD model. For this reason, in the compensator structure we refer to these elements as $\tilde{P}$ and $\tilde{H}$ for the linear and the nonlinear part, respectively, in order to clearly distinguish it from real ones. As already mentioned, $\tilde{P}$ can be obtained for each individual patient based on their physiological data. Instead, since $\tilde{H}$ cannot be obtained for each individual patient, its value is computed by considering the average values of the parameters reported in literature [14–16]. The $\tilde{P}$ block input signal $u(t)$ represents the propofol dosage rate and its output is the estimated effect site concentration $C_e(t)$ of the patient. To compensate the nonlinear behaviour present in the PK/PD model, the inverse of average Hill function $\tilde{H}^{-1}$ is computed [11].

In the resulting control scheme, $w(t)$ is the filtered value of $\hat{r}(t)$, which is the effect site concentration reference value that reflects the desired BIS reference $r(t)$. The $\hat{r}(t)$ value is computed using $\tilde{H}^{-1}$ that relates the BIS and the estimated effect site concentration $C_e(t)$ of the patient. In the nominal case, we have therefore that $\hat{C}_e(t) = \tilde{C}_e(t)$ and the resulting feedback signal is equal to $\tilde{C}_e(t)$. This situation changes only when the controlled process output is affected by the disturbances $d(t)$. In practice, model uncertainties are unavoidable, and for this reason, the $\theta(t)$ signal will be used to compensate differences related to modelling uncertainties and for the disturbances induced by surgical intervention. The value of $\theta(t)$ signal depends on the mismatch between the effect site concentration $\hat{C}_e(t)$ and estimated effect site concentration $C_e(t)$ computed using the BIS signal through the inversion of average Hill function. Thus, the $w(t)$ signal is used as the reference for the GPC controller, while the controlled variable is $\tilde{y}(t)$, containing information regarding patient model mismatch and disturbances (the feedback signal). The resulting contribution of the $\theta(t)$ signal is attenuated by the F_d filter, placed in the feedback loop, which reduces the effect of uncertainties and disturbances on the GPC controller, simultaneously guaranteeing a zero steady-state tracking error.

Moreover, the original scheme has been extended with the F_n filter that is used to reduce the noise component $n(t)$ in the BIS feedback signal. F_n is selected as a first-order low-pass filter:

$$F_n(s) = \frac{1}{T_n s + 1} \tag{4}$$

where T_n represents its time constant. As can be observed, F_n affects the control loop dynamics and for this reason, T_n needs to be adjusted among other design variables during a control system tuning procedure (explained in Section 3.4).

3.2. *Generalized Predictive Controller*

As it is well known [21], the GPC algorithm uses a vector of control signals that minimizes a multi-segment cost function of the following form:

$$J = \sum_{j=N_1}^{N} [\hat{y}(t+j|t) - w(t+j)]^2 + \sum_{j=1}^{N_u} \lambda [\Delta u(t+j-1)]^2 \tag{5}$$

where $\hat{y}(k+j|t)$ refers to the optimal prediction of the process output obtained with known information up to the time instant t, $\Delta u(t+j-1)$ is a future set of control signal values obtained from the cost function optimization, $\Delta = (1-z^{-1})$ is a differentiation term, N_1 and N define the prediction horizons, N_u is the length of the control horizon expressed in discrete time samples, and λ weights the future control efforts (with respect to the tracking errors) along the control horizon. The desired performance of the GPC algorithm is obtained by adjusting the weighting factor in addition to the prediction and control horizons. The reference trajectory along the prediction horizon is denoted as $w(k+j)$ [21]. In (5), the j-set future prediction of process output with information up to discrete time instance t, $\hat{y}(k+j|t)$, is obtained using the linear discrete time CARIMA model characterizing the controlled system [21]. The prediction equation in vectorial form can be written in the following form:

$$\widehat{\mathbf{y}} = \mathbf{G}\mathbf{u} + \mathbf{f}; \tag{6}$$

where $\widehat{\mathbf{y}}$ are the future process outputs, $\mathbf{G}$ is the dynamics matrix, $\mathbf{u}$ are the control signal values (decision variable) and $\mathbf{f}$ are the values of the free response of the process (see [21] for more details).

Additionally, the constraints of the process, like saturation limits or actuator slew rates, can be handled in the optimization procedure. In general, they are expressed as a set of inequalities in vectorial form, $\mathbf{R}\Delta\mathbf{u} \leqslant \mathbf{c}$, which are considered during the optimization procedure [21]. Finally, the quadratic optimization problem (QP) can be formulated as:

$$J(\mathbf{u}) = \frac{1}{2}\mathbf{u}^T\mathbf{H}\mathbf{u} + \mathbf{b}^T\mathbf{u} + \mathbf{f}_0$$

subject to:

$$\mathbf{R}\Delta\mathbf{u} \leqslant \mathbf{c}$$

where $\mathbf{H} = 2(\mathbf{G}^T\mathbf{G} + \lambda\mathbf{I})$, $\mathbf{b}^T = 2(\mathbf{f}-\mathbf{w})^T\mathbf{G}$, $\mathbf{f}_0 = (\mathbf{f}-\mathbf{w})^T(\mathbf{f}-\mathbf{w})$ and $\mathbf{w}$ is the vector of reference signals [21].

3.3. *Noise in Depth of Hypnosis*

The BIS is an empirically derived scale, where a proprietary algorithm transforms the EEG and computes a measure between 100 and 0 that indicates the patient's anesthetic state in real time. In most cases, the BIS monitor provides a new value every second. Its value has a significant noise component, which can be modeled as a white

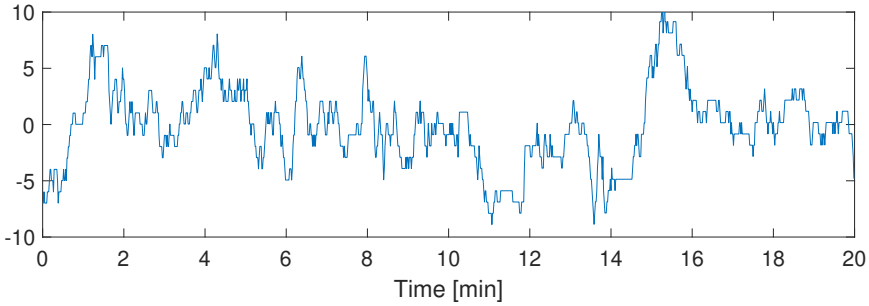

Fig. 3: Real noise from the experimental test.

Gaussian additive noise [18]. Analyzing the real BIS signals obtained from clinical data provided by Department of Anesthesiology, Critical Care and Emergency of the Spedali Civili di Brescia Hospital, Brescia (Italy) it was obtained that its power spectral density (PSD) has the average value of 39.3392 [18]. An example of the BIS signal from the real clinical data is shown in Figure 3.

From the signal processing point of view, this high measurement noise can be attenuated through a filter added *a posteriori*, which is designed to reduce the noise dominant frequencies and pass others in interesting bandwidth. However, in the control architecture introduced previously, this approach will affect the overall accuracy of the control system. For example, it might result in a sluggish response or there can be the robustness issue due to the changes in the control loop dynamics. In the approach presented here, the noise filter F_n is taken into account during control system tuning procedure, where all parameters are set to obtained the desired control system performance.

3.4. System Tuning for Noise Handling

The control architecture, shown in Section 3, requires the tuning of the GPC controller parameters [22], that is, N, N_u and λ, as well as of the proposed filters parameters, T_r, T_d and T_n. Following the tuning procedure for a noise-free case from [11,19], the tuning is performed to meet the desired performance characterized by the clinical specifications.

During the induction phase, the controller have to reach the desired DoH level, defined as the BIS value equal to 50, in around 5 minutes avoiding a significant undershoot. For the maintenance phase, the controller needs to minimize the effect of unmeasurable disturbances due to surgical stimuli. For the presented approach we follow the same methodology used in [18], where unmeasurable disturbances were represented as a two consecutive steps in the BIS level signal. They are of amplitude 10 and -10 within time interval of 10 minutes. During this phase, the BIS signal value should be kept in the BIS range from 40 to 60 to reduce the probability of health issues for the patient.

In the analyzed system, the performance in the induction phase is mainly limited by the F_r filter time constant T_r and for comparison purposes we use the value $T_r = 22.4$ proposed in [11], which is fixed for all the tested configurations. In this way, we assure that the resulting changes in the control system performance are directly linked to the effect of the noise.

The remaining tuning parameters are obtained using an optimization procedure based on genetic algorithms [23]. The objective function to minimize is the worst-case Integral Absolute Error (IAE) of the process output by considering the average patient. The IAE performance index is defined as $\int_0^\infty |r(t) - y(t)|dt$. The optimization is performed for the average patient (see Section 2.1) considering additive white Gaussian noise with the determined PSD and a noise amplitude of ± 2.5. Additionally, the optimization is repeated for different sampling periods to test how this factor influences the control system performance in the presence of noise. In this way, the noise issue can be handled by the whole control system and not only by the specific filter. As a result, we obtain tuning parameters values that are summarized in Table 1. The determined set has been compared to the optimal tuning for analyzed control architecture for the noise-free configuration with a sampling period of 1 second (shown as 1_{nf}).

4. Simulation Study

In this section, simulations using a set of patients models are evaluated. Moreover, for the analyzed scenario, the saturation constraints are handled with the GPC controller. For this the control signal $u(t)$, representing the propofol infusion rate [mg/s], was limited between a minimum value of 0 and a maximum dosage of 6.67 [mg/s].

Table 1: Control system tuning parameters obtained for different sampling periods T_m.

T_m	N	N_u	λ	T_d	T_r	T_n
1_{nf}	27	7	1.60	22.7	22.4	–
1	24	2	14.43	47.33	22.4	24.64
2	15	19	10.27	54.36	22.4	16.63
5	15	18	100.80	32.59	22.4	57.66
10	13	5	94.66	63.37	22.4	86.99

These limits were obtained using a standard concentration for Propofol 20 [mg/ml] [18].

4.1. Performance Indexes

The proposed approach has been evaluated on the data set of virtual patients (see Section 2.1). For the performance evaluation, we consider a set of indexes, proposed in [7]. During the induction phase (set-point following) following verification measures have been selected: TT, BIS-NADIR, ST10, ST20, US45 were computed following the procedures detailed in [7, 23]. The performance in the maintenance phase was measured using only two selected meaningful indices, the TT and BIS-NADIR. Both were computed individually for the negative and the positive step (changes in the disturbance signal), represented respectively by $_n$ and $_p$ subindexes.

4.2. Tests on patients database

The obtained tuning parameters for different sampling periods have been evaluated for a set of the 13 virtual patients. However, it needs to be highlighted that during the tuning optimization procedure only the average patient has been used. Due to this, the performed simulations shows how the analyzed control scheme responds to the inter-patient variability simultaneously considering noise issues. The simulation scenario consists of a step change in the BIS reference from 100 to 50 at time 0, representing the induction phase. This should end in approximately 5 minutes, following the clinical specifications. Once the induction phase target is achieved, the maintenance phase starts. In this phase we evaluate the response of the system to disturbances (e.g. surgical stimuli) represented as a step signal of amplitude 10 in the BIS level, introduced at minute 11 of simulation time, followed by another step of amplitude -10 after 5 minutes. During the simulation, we use additive white Gaussian noise to replicate the actual measurement noise (see Section 3.3).

As an example, the result obtained for $T_m = 1$ is shown in Figure 4. It can be observed that, for this configuration, the control system provides a satisfactory performance for both the induction and maintenance phases, despite presence of the noise. Moreover, the control architecture handles adequately the inter-patient variability providing the necessary robustness due to the model uncertainties. Additionally, to show the influence of the sampling period, we perform the same simulation for $T_m = 5$ and the obtained results are shown in Figure 5. For this case, the control system needs slightly more time to reach the desired BIS zone for the induction phase. Regarding the maintenance phase, it can be observed that disturbance compensation is similar to the previous case where $T_m = 1$ was used. The performance evaluation for the induction phase, using the previously defined indexes, is summarized in Table 2, where the average values for all 13 patients are considered for all the tested sampling periods. For comparison purposes, the performance obtained for a noise-free case using the same control architecture with $T_m = 1$ is also included and marked as 1_{nf}. The obtained values indicate that sampling periods between 1 and 5 seconds are acceptable from the performance point of view. Moreover, the performance evaluation for the maintenance phase is shown in Table 3. A performance degradation is also visible for this phase, obtaining the lowest performance for the configuration with $T_m = 10$. From the obtained results, it can be determined that the noise issue can be handled properly in the analyzed control scheme. However, the performance degradation is visible and grows when the sampling period increases.

The response of the analyzed control system to real noise signal (see Figure 3) is shown in Figure 6, where the simulations considers also the step disturbances in the maintenance phase. As in the previous case, the obtained performance meets the requirements. It appears that the process noise can be properly handled by the control system if it is explicitly taken into account during the design stage. This property is especially important in the MPC-based control scheme, due to known sensibility to process noise that frequently results in a poor robustness of the controller. However, in the analyzed case, the increased robustness to the noisy BIS signal comes at the expense of the performance degradation.

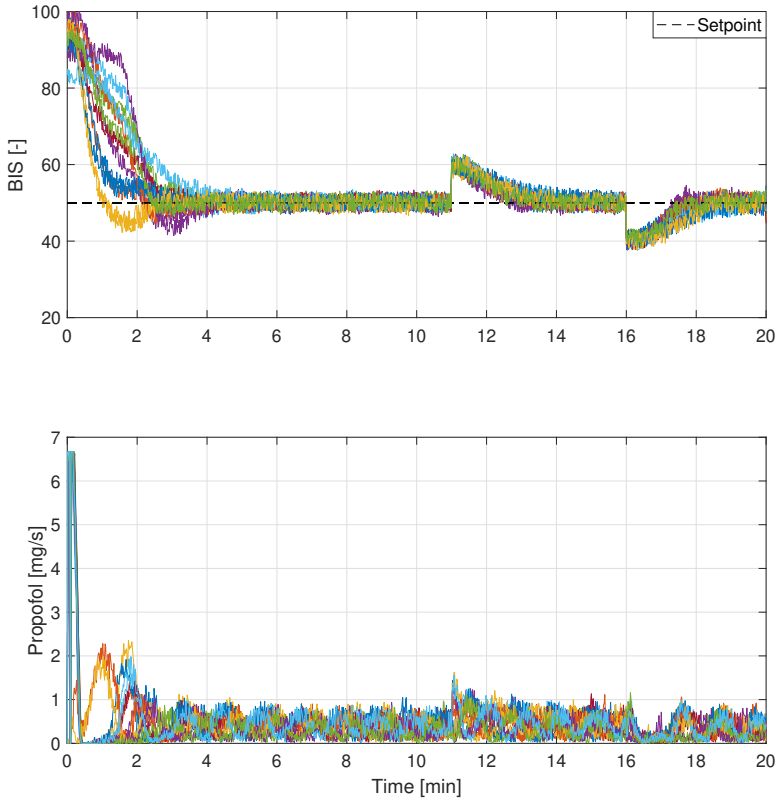

Fig. 4: Control system performance for the 13 patients with white noise and sampling period $T_m = 1$ second.

5. Conclusions

In this paper, the performance degradation due to the noise presence in the control loop for the DoH in intravenous anesthesia has been analyzed. As a test-bed we have considered an MPC-based control scheme where the BIS signal is used to represent the DoH level and propofol infusion is used as a controlled variable. To assure the proper noise handling, an additional filter in the feedback loop has been included. However, its presence requires the retuning of the overall control system. A simulation study, considering a representative set of virtual patients has been used to test different noise characteristics and sampling periods. Moreover, for the evaluation of the control system, a widely accepted set of performance indexes was used. The obtained results confirmed that clinical requirements can be satisfied if the noise issue is explicitly considered during the design stage.

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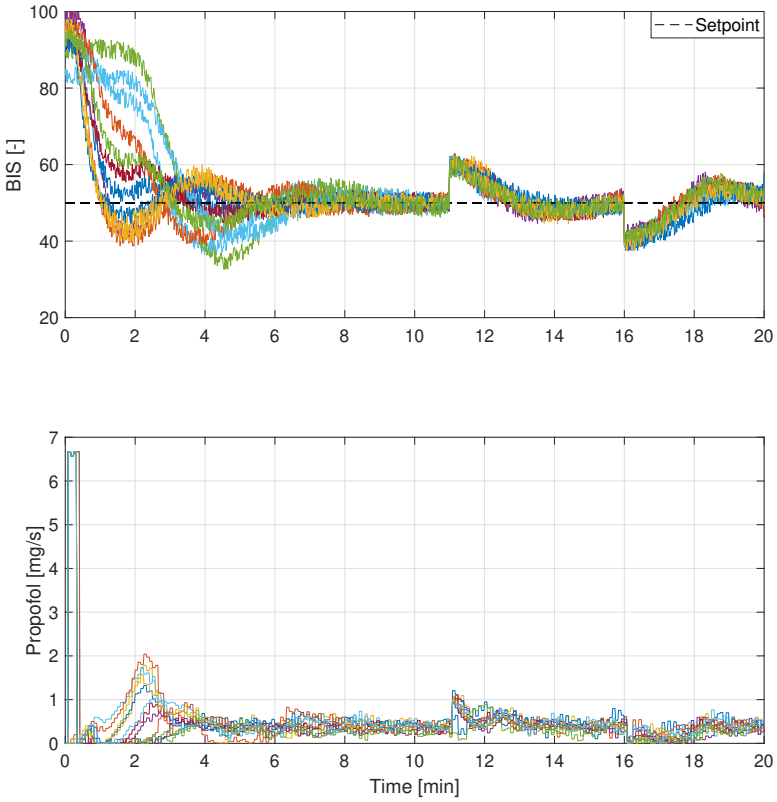

Fig. 5: Control system performance for the 13 patients with white noise and sampling period $T_m = 5$ second.

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Table 2: Average performance indexes values for the induction phase for the patients dataset.

T_m	**TT [min]**	**BIS-NADIR**	**ST20 [min]**	**ST10 [min]**	**US**
1_{nf}	1.41	48.22	1.16	1.66	0.58
1	1.78	45.05	1.65	2.60	1.02
2	1.37	41.34	2.02	3.17	4.18
5	1.78	38.28	3.15	5.85	6.85
10	1.28	20.58	7.34	9.70	24.42

Table 3: Average performance indexes values for the maintenance phase for the patients dataset.

T_m	**TTp [min]**	**BIS-NADIRp**	**TTn [min]**	**BIS-NADIRn**
1_{nf}	0.38	49.98	0.89	50.05
1	0.72	47.19	1.30	52.34
2	0.88	47.07	1.14	51.98
5	1.22	45.01	1.29	56.85
10	0.95	43.68	1.36	53.44

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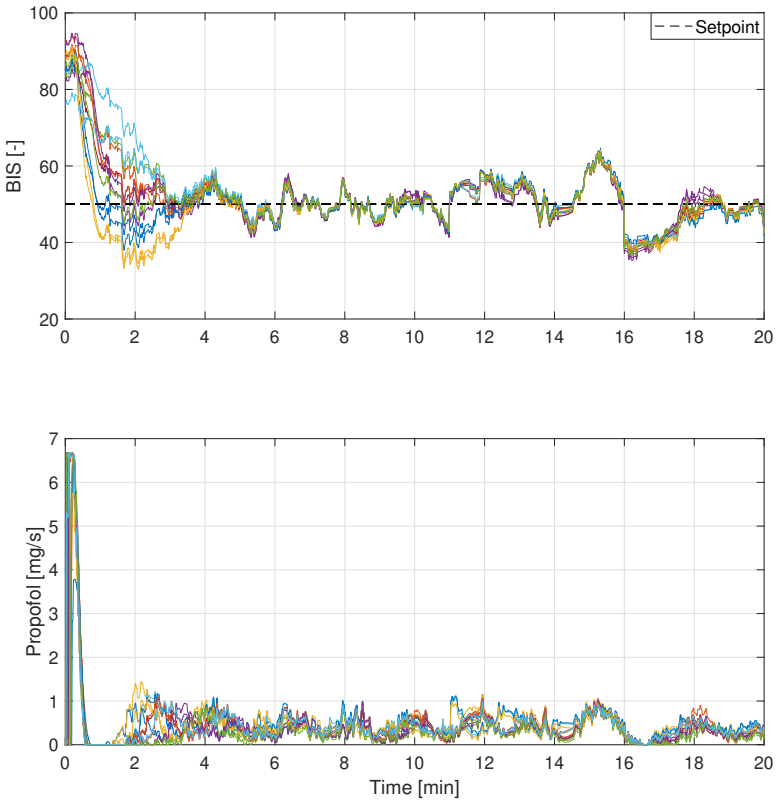

Fig. 6: Control system performance for real noise form the process and sampling time, $T_m = 2$ seconds.