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Data-based Extended Moving Horizon Estimation for MISO Anesthesia Dynamics*

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Abstract— **This paper presents an extended moving horizon observer to estimate both the states and the pharmacodynamic (PD) parameters of an anesthesia model, based on real data. The inputs of this model are the injection rates of Propofol and Remifentanil. The states represent the concentration of the anesthetic agents in different compartments of the human body (muscles, fat, blood) and in the effect site. The considered output is the Bispectral index (BIS) which is derived from the electroencephalogram (EEG). The observer is designed such that the parameters are estimated during the anesthesia induction phase, and then almost frozen for the rest of the surgery. The estimator is validated on real data that were extracted from the VitalDB database (Lee et al., 2022).**

I. Introduction

During surgery, the anesthesiologists use different types of anesthetic agents in order to induce and maintain the depth of unconsciousness (hypnosis), the absence of movement (areflexia), and the absence of pain (analgesia) [10].

The level of hypnosis is measured by monitoring the electroencephalogram (EEG) signals and combining several extracted features to determine the depth of anesthesia, usually via processed variables such as the Bispectral Index (BIS) which takes values in the interval $[0, 100]$. The range $[40, 60]$ characterizes a moderate hypnosis state and the value 50 is generally considered as suitable for surgery.

Compartmental modeling of the drugs distribution has been widely used in the literature, it relies on the conservation principle applied to the exchange of chemicals between different coupled macroscopic systems (compartments) [9]. The anesthetic agent concentrations are assumed to be uniform within a given compartment and the transport rate leaving a compartment is assumed to be proportional to its corresponding concentration.

The 4^{th} order Pharmacokinetic-Pharmacodynamic (PK-PD) model has been commonly considered in the literature. This model considers four compartments, the central one (blood), the fast equilibrating one (muscles), the slow equilibrating one (fat), and the effect site. In [10] a similar structure has been considered using the Schnider model for Propofol pharmacokinetic [16] and the Minto model for Remifentanil phamacokinetic [13].

Estimating the internal states and the parameters of a dynamical model is important to achieve robust performances when using state feedback schemes. For linear unconstrained systems, it is well established that the Kalman filter is the optimal state estimator, when the states and the inputs are subject to normally distributed noises [8]. In the presence of hard constraints, such as non-negative drug concentrations, Kalman filtering is not directly applicable. In the case of nonlinear constrained systems, Moving-Horizon-Estimation (MHE) has proven to be a powerful tool for state estimation [15]. Furthermore, with the advances of optimization solvers, MHE suits well the context of online estimation based on a window of available past measurements.

The automation of therapy injections has the potential to decrease the clinical workload while maintaining the same care quality [18]. Therefore, many closed-loop strategies have been proposed for anesthesia dynamics, for example, [17] where the authors proposed a Model Predictive Control (MPC) and an MHE for a Single Input Single Output (SISO) model describing the dynamic interactions between the inhaled anesthetic Sevolufrane and the BIS signal. In [5], an extended Kalman filter has been proposed for a minimally parametrized Multiple-Input-Single-Output (MISO) model describing the dynamics between the Propofol and Remifentanil injection rates (inputs) and the BIS as an output, in order to estimate the states and some PK-PD parameters. However, the results rely on approximations and the presented observer is aggressive in the sense that it allows to fit the output with the noise, which means that the parameters change even during the maintenance phase.

Contrary to PK parameters, the PD parameters do not have standard expressions in terms of patient information. According to [11], the uncertainty introduced by the PD parameters shows a more significant influence on the measurable outputs than the one introduced by the PK parameters. Therefore, in this paper, we propose an extended MHE allowing us to estimate both the states and the PD parameters for the complete MISO system with a nonlinear output equation. Furthermore, the cost function is designed such that the penalty on parameters is activated during the maintenance phase in order to avoid having noisy parameters due to the presence of noise on the data, which means that the parameters are identified only during the anesthesia induction

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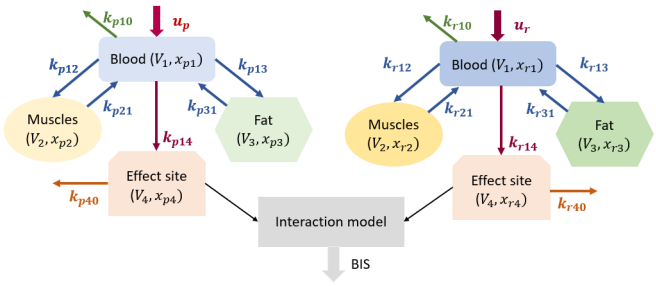

Fig. 1. Compartmental scheme of the pharmacokinetic and the pharmacodynamic model of Propofol and Remifentanil

phase.

The states being complex to measure practically for the case of anesthesia, the observer is first validated on simulated data, for which the state profiles and the parameter values are available. Then, the observer is applied to different real clinical cases from the VitalDB database [12]. We show that an online estimation of both the states and the parameters is practically feasible since the average needed time for one iteration varies between 12 and 19ms for a sampling time of 2s. Furthermore, we show that the distributions of the parameters, that were estimated based on real data, closely correspond to practically validated distributions that have been presented in [4].

This paper is structured as follows: Section II presents the dynamical model that is used for the estimation problem, in Section III the Moving Horizon Estimation technique is recalled and its use for state and parameter estimation is explained. In Section IV we present an observer validation framework. In Section V we present the estimation results for different cases from the VitalDB database and we carry out a statistical analysis on the different estimated parameters. Finally, in Section VI, we present a summary of the results and suggest future perspectives.

II. Dynamical Model

Compartmental modeling has been widely used for anesthesia dynamics [10]. The latter consists, firstly, in considering different compartments of the human body, such as the blood, the muscles and the fat, each of them being characterized by its own volume. Then, the concentrations of the anesthetic agents within each compartment are modeled using a set of coupled ordinary differential equations (ODEs).

Pharmacokinetic (PK) allows to characterize the evolution of the injected anesthetic agents in the human body through the absorption phenomenon. Whereas pharmacodynamic (PD) allows to characterize the effect of the drug on the organism, through the BIS in the case of hypnosis study for example.

In the real clinical world, patients usually receive different types of anesthetic agents [18]. Therefore, it is important to model the interaction between treatments whether it is synergistic or antagonistic, in order to have a reliable hypnosis indicator, in the case of the BIS for example.

The PK-PD models that are commonly considered for Propofol and Remifentanil are of order 4 (as depicted in Fig.1) The interaction between both drugs is modeled through the relation between the BIS and the effect site concentration of Propofol (x_{p4}) and Remifentanil (x_{r4}). We describe in the sequel the different parts of the model that has been considered in this paper.

A. Propofol PK-PD modeling

Propofol is a hypnotic agent that is used to induce and maintain the hypnosis of the patient during surgery. The PK-PD linear model linking the Propofol infusion rate u_p to the Propofol concentration in the effect site x_{p4} is the following:

$$\begin{pmatrix} \dot{x}_{p1} \\ \dot{x}_{p2} \\ \dot{x}_{p3} \\ \dot{x}_{p4} \end{pmatrix} = \begin{pmatrix} -a_{11p} & a_{12p} & a_{13p} & 0 \\ a_{21p} & -a_{21p} & 0 & 0 \\ a_{31p} & 0 & -a_{31p} & 0 \\ a_{41p} & 0 & 0 & -a_{41p} \end{pmatrix} \begin{pmatrix} x_{p1} \\ x_{p2} \\ x_{p3} \\ x_{p4} \end{pmatrix} + \begin{pmatrix} \frac{1}{V_{1p}} \\ 0 \\ 0 \\ 0 \end{pmatrix} u_p \tag{1}$$

where $x_p = (x_{p1}, x_{p2}, x_{p3}, x_{p4})^T \in \mathbb{R}^4_+$ stands for the vector of Propofol concentrations in the different considered compartments and $u_p \in \mathbb{R}_+$ stands for the Propofol infusion rate. By considering that A_p is the state matrix and $B_p = (\frac{1}{V_{1p}}, 0, 0, 0)^T$, Model (2) can be condensed in the following equation:

$$\dot{x}_p = A_p x_p + B_p u_p \tag{2}$$

The matrices A_p and B_p are considered as in equation (2) since the standard model for pharmacokinetic describes the direct effect that the intravenous input u_p has on the blood concentration. Furthermore, it models the inter-compartmental clearances between the blood compartment, the fat and muscles compartments, as well as the elimination clearance of the drug from the blood compartment. Moreover, the effect compartment is connected to the central compartment (blood) by a first-order rate constant in order to model the delay between a variation in the blood concentration and the beginning of its corresponding effect.

B. Remifentanil PK-PD modeling

Remifentanil is an opioid with a high metabolic clearance, when administered with Propofol, both drugs interact in a synergistic way on hypnosis and analgesia. The PK-PD model of Remifentanil has a similar form as the Propofol one, with different parameter values. Therefore, it can also be described by the following equation:

$$\dot{x}_r = A_r x_r + B_r u_r \tag{3}$$

where $x_r = (x_{r1}, x_{r2}, x_{r3}, x_{r4})^T \in \mathbb{R}^4_+$ stands for the vector of Remifentanil concentrations in the different considered compartments and $u_r \in \mathbb{R}_+$ stands for the Remifentanil infusion rate.

Since both Propofol and Remifentanil interact separately on the different compartments, the total PK-PD model can be characterized by the following decoupled system:

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

where $0^{l\times k}$ stands for a zero elements matrix of dimension $l \times k$. By considering that $x = (x_p, x_r)^T \in \mathbb{R}^8$ and $u = (u_p, u_r)^T \in \mathbb{R}^2$, we can rewrite model (4) as:

$$\dot{x} = A_T x + B_T u \tag{5}$$

With $A_T \in \mathbb{R}^{8\times 8}$ and $B_T \in \mathbb{R}^{8\times 2}$ being respectively the state and the input matrices.

The parameters of A_T and B_T are related to the patient information (age, height, weight and gender). Several expressions have been proposed in the literature, for example, Schnider model in [16] for the Propofol PK parameters (in A_p and B_p), Minto model in [13] for the Remifentanil PK parameters (in A_r and B_r) as well as Eleveld model for both Propofol and Remifentanil PK [6], [7].

C. Propofol & Remifentanil synergy modeling

The interaction model linking x_{p4} and x_{r4} (as depicted in Fig.1) determines the output equation that characterizes the BIS. The latter is defined as a Hill function depending on an interaction term U as follows:

$$y = BIS = E_0 - E_{max}\frac{U^\gamma}{1+U^\gamma} \tag{6}$$

where E_0, E_{max} and γ are static parameters representing, respectively, the initial BIS value, the maximal drug effect on the BIS and the slope of the Hill function. The drug interaction term U is defined as follows:

$$U = \frac{U_p + U_r}{1 - \beta\theta + \beta\theta^2} \tag{7}$$

with:

$$U_p = \frac{x_{p4}}{c_{50p}} \quad U_r = \frac{x_{r4}}{c_{50r}} \quad \theta = \frac{U_p}{U_p + U_r} \tag{8}$$

where c_{50p}, c_{50r} and β are also static parameters, standing respectively for the Propofol half-effect concentration, the Remifentanil half-effect concentration and the interaction coefficient.

The PD parameters E_{max}, c_{50p}, c_{50r}, γ and β are patient dependent and have to be identified based on the BIS (output) signal. Several works in the literature proposed to simplify this model by considering E_{max}=E_0 and $\beta = 0$, for example in [4]. In order to carry out a consistent comparison with respect to the clinically validated parameters distributions, we consider the same simplification and estimate only the three parameters c_{50p}, c_{50r} and γ, we denote by $\eta = \left(c_{50p}, c_{50r}, \gamma\right)^T \in \mathbb{R}^3$ the vector of PD parameters to be estimated. Finally, the global system is defined by linear dynamics and a nonlinear output equation as follows:

$$\begin{cases} \dot{x} = A_T x + B_T u \\ y = h(x, \eta) \end{cases} \tag{9}$$

III. Extended Moving Horizon Estimation

Extended observers have been presented in the literature [3] and used to estimate exogenous disturbances or the model parameters, in addition to the states. It consists in considering the disturbances (or the parameters) as part of the state vector, with a given dynamical model or invariant dynamics in the case of static parameters.

Since the objective of this paper is to estimate both the states and the PD parameters, the state dynamics can be extended by adding $\dot{\eta} = 0$ to the dynamics by considering $\bar{x} = (x, \eta)^T$ as follows:

$$\begin{cases} \dot{\bar{x}} = \bar{A}_T \bar{x} + \bar{B}_T u \\ y = h(\bar{x}) \end{cases} \tag{10}$$

Discretizing model (10) with a sampling period T_e, by using the forward Euler method, results in the following extended discrete time system:

$$\begin{cases} \bar{x}_{k+1} = A\bar{x}_k + Bu_k = \Phi(\bar{x}_k, u_k) \\ y_k = h(\bar{x}_k) \end{cases} \tag{11}$$

where $A = I + T_e\bar{A}_T$ and $B = T_e\bar{B}_T$, other discretization methods can also be considered. However, since the PK system is relatively slow and in order to induce lower computation time, the Euler method with the associated sampling period of 1 or 2 sec is found appropriate.

Moving Horizon Estimation (MHE) is a widely used observation technique [1], allowing to recover the states of a given dynamical system, based on the input and the output measurements. In MHE, the current state is estimated by minimizing a cost over a fixed number of past measurements called the estimation horizon and denoted by N_{MHE}. The decision variables being the states over the measurement window, the cost to minimize represents a trade-off between minimizing the output error and ensuring the compatibility of the estimated states with respect to the model and the previous estimated state.

The main advantage of MHE is the explicit handling of the constraints, especially in the context of anesthesia dynamics estimation where the states represent drug concentrations and have to be non-negative. Moreover, the PD parameters that we aim at estimating have also to be non-negative.

The cost function to be minimized at each time step k can be written as follows:

$$\begin{aligned} J_{N_{MHE}}(\bar{\mathbf{x}}_k \mid \hat{\bar{\mathbf{x}}}_{k-1}, \mathbf{y}^m, \mathbf{u}^m) = &\sum_{i=k-N_{MHE}}^{k} \|y_i^m - h(\bar{x}_i)\|_Q \\ &+ \sum_{i=k-N_{MHE}+1}^{k} \|\bar{x}_i - \Phi(\hat{\bar{x}}_{i-1}, u_{i-1}^m)\|_{R(k)} \end{aligned} \tag{12}$$

where $\bar{\mathbf{x}}_k$ and $\hat{\bar{\mathbf{x}}}_{k-1}$ represent, respectively, the state over the estimation horizon (decision variable) and the previous estimated state up to time $k-1$. The remaining arguments, namely $\mathbf{y}^m$ and $\mathbf{u}^m$ represent the output and the input measurements profiles over the estimation horizon, Q and R

represent the penalty matrices. Note that the first summation in the cost allows to ensure the fitting with the output while the second one allows to ensure the compatibility of the estimated state with respect to the evolution of the previous estimated one by the dynamical model.

The compatibility cost is penalized with a time dependent weighting diagonal matrix $R(k)$, following a sigmoid function. This allows to identify the parameters during the anesthesia induction phase and to maintain them for the rest of the surgery through a proper penalization. The diagonal elements of $R(k)$ have the following parameterized form:

$$r_{jj}(k) = \theta_1 + \theta_2 e^{-\theta_3 e^{-\theta_4 k}} \tag{13}$$

where $j = 1, \ldots, 13$. This function allows to have a bounded weight $(\theta_1 + \theta_2)$ for high values of time k, provided that $\theta_3, \theta_4 > 0$. θ_1 is used to penalize the states representing the drugs concentrations within the compartments, whereas θ_2 is used to penalize the parameters during the maintenance phase. For some parameters, a use of θ_1 is required during the induction phase in order to avoid a high variation.

The optimization problem to be solved at each time step k is the following:

$$\begin{aligned} \min_{\bar{\mathbf{x}}_k} \quad & J_{N_{MHE}}(\bar{\mathbf{x}}_k \mid \hat{\bar{\mathbf{x}}}_{k-1}, \mathbf{y}^m, \mathbf{u}^m) \\ \text{s.t.} \quad & \bar{x}_{i+1} = \Phi(\bar{x}_i, u_i^m), \forall i = k - N_{MHE}, \cdots, k \\ & \bar{x}_i \in \mathscr{X}, \forall i = k - N_{MHE}, \cdots, k \end{aligned} \tag{14}$$

Solving (14) at each time step k allows to estimate the states (and the parameters) in a receding horizon way, by sliding the measurements window of length N_{MHE} at each time step k. The dynamical constraints have been implemented with the multiple shooting technique allowing to improve the convergence and the sparsity of the optimization problem by lifting it to a higher dimension.

The set $\mathscr{X} \in \mathbb{R}^{13}$ allows to define box constraints on the states and the parameters. Regarding the initial guess of the decision variables, a warm start has been implemented, allowing to initialize the states over the estimation horizon by the previous estimated states. At the first time step $k = 0$, since no estimation is available, the states x (representing the concentrations) are initialized at 0, since $u = 0$ at the beginning of the surgery, while the parameters η are initialized at an arbitrary pre-tuned PD model.

Since the tuning of the penalty matrices Q and R has a high impact on the estimation quality, in particular in the the context of real data that are corrupted with noise, these matrices are firstly tuned on noisy simulated data, for which we know the real states and parameters, in order to fit them to a realistic scenario and then they are fine-tuned based on real data. The fine-tuning is done in such a way to ensure a smooth BIS profile that do not catch the noise on the output.

IV. Observer validation

The observability of the non-extended anesthesia system (without parameters) has already been proved in the literature, for example in [14]. However, when extending the system with the parameters dynamics, proving theoretically the observability becomes complex. Therefore, we propose in this section to assess the observability of the extended system based on simulated data for which we know the real states and parameters.

We will consider in the sequel a population of 100 simulated patients, for whom the PD parameters are drawn using the distributions clinically measured in [4] and presented in Table I, the maximal and minimal bounds are hypothetical values allowing to truncate the normal distribution in order to avoid unrealistic values in the simulations. The PK parameters of Propofol and Remifentanil are computed using Schnider and Minto models [16], [13]. .

Parameter	c_{50p}	c_{50r}	γ
Min*	2	6	1
Max*	9	25	5
Mean	4.47	19.3	1.43
Standard deviation	1.34	5.79	0.73

TABLE I

THE PD PARAMETERS STATISTICS CONSIDERED FOR THE OPTIMIZATION PROBLEM [4], * STANDS FOR HYPOTHETICAL VALUES

Problem (14) has been successively solved, for the 100 simulated cases, by considering $N_{MHE} = 20$, $T_e = 1s$ and using CasADi [2]. The state constraints can be set based on the solution of (2) and (3), given the measured inputs u_p and u_r. Furthermore, several tests on the estimation errors showed that there is no noticeable improvement for estimation horizons that are higher than 20. The computation time for one optimization step is 26 ms, which is reasonable for an online implementation.

The results presented in Figs. 2-3 correspond to one patient and show that in the absence of noise, the output is well fitted and the parameters are well estimated.

Fig. 4 presents the histograms of the mean relative absolute error of the BIS and the states, when no noise affects the BIS, when the BIS is affected with a white noise of variance 1 and when the penalty term $R(k)$ is constant with no noise on the BIS. We can see that in the noise-free case, the estimation errors are centered around 0 and present a low dispersion, which is almost similar for the case where the BIS is corrupted with a white noise, except for the error of x_2 which presents a higher mean error. In the case where $R(k)$ is considered to be constant, we can see that the errors present a higher dispersion even though no noise has been added to the BIS.

Moreover, Fig. 4 shows that the parameters estimation errors are centered around zero and present a low dispersion in the noise-free case, their means remain close to 0 in the noisy case, with a higher dispersion. We can also see that when using a constant penalization $R(k)$, and without any noise, the parameters errors present higher dispersions than in the noisy case.

To summarize, using a simulated based data framework, it is shown that an insight on the observability of the extended system can be gained and the underlying statistics of the estimation errors seems encouraging. The relevance of considering a time-dependent cost in order to freeze the PD parameters, lowering thereby their dispersion is highlighted.

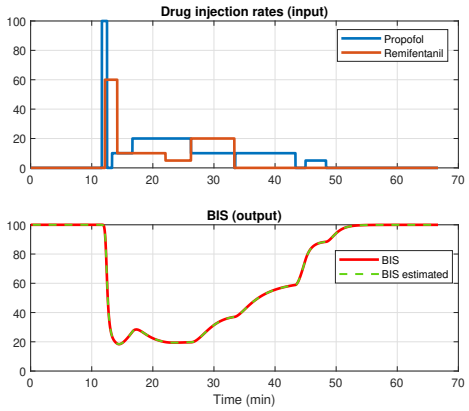

Fig. 2. The drug injection rate profiles, the measured and the estimated BIS for $N_{MHE} = 20$

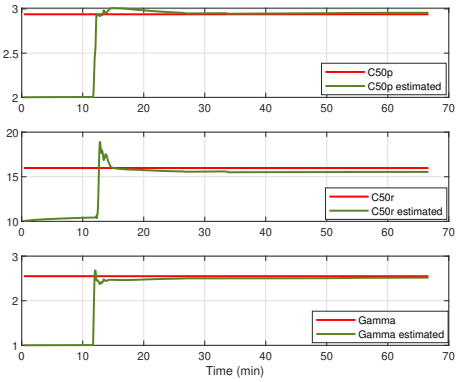

Fig. 3. The real and estimated PD parameters for $N_{MHE} = 20$

V. Data-based numerical results

A. Presentation of clinical data

The clinical data used in this paper have been imported from VitaldB [12]. The latter is an open-source database that was created to facilitate the analysis and the monitoring of vital signs during surgery. This database gives access to high-resolution multi-parameter data from 6388 cases with several indicator signals.

We considered a population of 50 cases from the database, this population has a median age of 55, a median height of 64, a median weight of 166 and a 32% proportion of women. They have been selected based on two criteria, the first one is the use of both Propofol and Remifentanil and the second one is the BIS stability. Indeed, the database contains some cases with an unstable BIS during the maintenance phase, which is due to different possible exogenous disturbances. Therefore, in order to avoid skewing the estimation of the parameters with exogenous signals, we consider only the cases with a stable BIS during the maintenance phase. Furthermore, the data have been processed in order to remove the NaNs.

B. MHE implementation on Real-data

The MHE optimization problem has been solved using CasADi [2] with $N_{MHE} = 20$ and $T_e = 2s$. The initial guesses were set to the nominal values. The PK parameters have been considered according to the Eleveld Model [7], [6], since it showed a better fitting of clinically measured PD parameters distributions presented in [4]. E_0 has been identified from the first samples of the BIS, since it represents the BIS value before the induction phase. Figs. 5-6 show the results of the extended MHE for the case ID 167, we can see that the parameters are quasi static during the maintenance phase and the estimated BIS fits the measured one even though the latter presents a relatively high variance noise. We can also see that the BIS that was calculated for nominal PD parameters presents a high fitting error, which highlights the importance of estimating the PD parameters.

Fig. 7 shows the distribution of the estimated parameters with the practically validated ones, we can see that the distribution of c_{50p} presents a good fitting, while the distributions of c_{50r} and γ are slightly shifted. This can be explained by the difference of the population that have been considered for the study in [4], since the median age presents a considerable difference.

VI. Conclusion

We presented in this paper a data-based extended moving horizon estimator for anesthesia dynamics, the latter allows to estimate both the state and the parameters. It is important to highlight the fact that the work presented in this paper is preliminary and can be extended to a larger data set in order to better approximate the parameters distributions. The estimated variables can be used in a state feedback scheme in order to stabilize the BIS in the interval $[40, 60]$. Moreover, a global statistical analysis can be carried out based on the estimated parameters in order to study the correlation between the different variables. Furthermore, fault detection based observers can be considered in order to detect the presence of external disturbances on the BIS signal.

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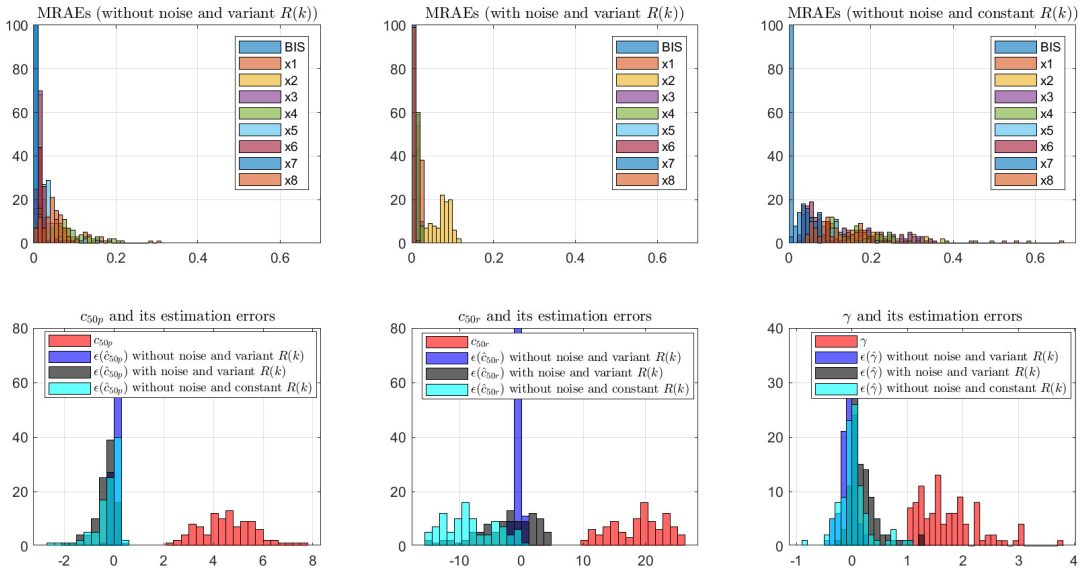

Fig. 4. Histograms of the Mean Relative Absolute Errors (MRAEs) of the BIS and the states (top) and histograms of the true parameters and their corresponding estimation errors $\varepsilon(\hat{c}_{50p})$, $\varepsilon(\hat{c}_{50r})$ and $\varepsilon(\hat{\gamma})$ (bottom).

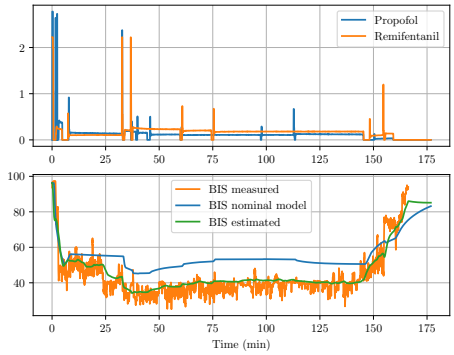

Fig. 5. Case ID 167: the drug injection rates (top), the measured and the estimated BIS (bottom)

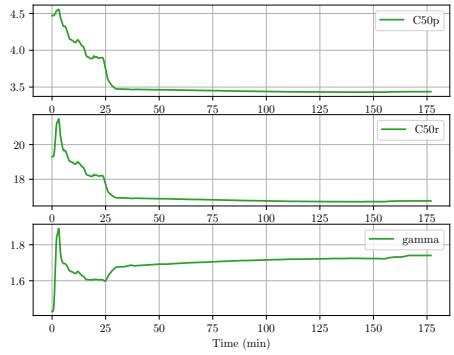

Fig. 6. Case ID 167: the estimated parameters

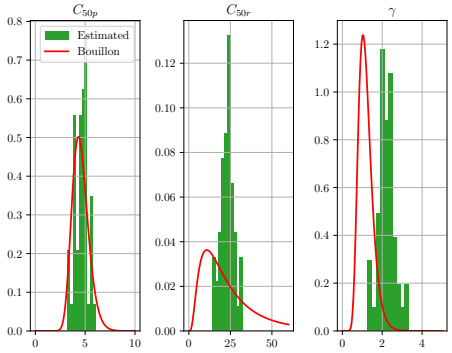

Fig. 7. Histograms of the estimated parameters with the practically validated distributions in [4]

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