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Modelling and indentification for the action of propofol and remifentanil on the BIS level ⋆

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Abstract: In this paper a model for the action of propofol and remifentanil on the BIS level suitably modified in order to provide the online identification of its parameters is proposed. Besides a novel identification method, which is compatible the usual clinical procedures, is also proposed. This method provides the identification of the 4 parameters of the model around the time of instant T_{50}, when BIS is equal to half of its maximum value.
The new model design and identification method are validated by means of simulations, using a database of real cases in the framework of Galeno project, via a TCI (target-controled-infusion) scheme.

Keywords: Identification method, bispectral index, depth of anesthesia.

1. INTRODUCTION

Automation in anesthesia has deserved the attention of numerous researchers in the last years (Ionescu et al. (2008), Neckebroek et al. (2019), Sawaguchi et al. (2008), Dumont (2012) and Nogueira et al. (2015)). Particular emphasis has been given to the design and implementation of automatic schemes to determine the dosing of the different anesthetics based on individual patient characteristics rather than on population criteria (Almeida et al. (2016), Merigo et al. (2018), Silva et al. (2019a), Silva et al. (2019b) and Nogueira et al. (2019)).

Essential to this aim are the development of simple models for the drugs effects, and efficient on-line identification methods to estimate the patient dependent parameters present in such models.

In this paper we focus on modelling and parameter identification for the action of the hypnotic propofol and the analgesic remifentanil on the depth of anesthesia (DoA). This component of anesthesia is usually evaluated using measurements of the Bispectral Index (BIS), which in turn can be obtained from an EEG (Absolom and Kenny (2003), Absolom et al. (2002), Liu et al. (2011), Struys et al. (2004) and Ionescu et al. (2014)).

As is well-known, the combined effect of two drugs can be mathematically descibed by means of two dynamical models that relate the dose of each of the drugs with the corresponding effect concentration, together with a static nonlinearity that takes the interaction of the two drugs into account in order to yield the final effect.

The "traditional" description of the relation between the drug dose and the corresponding effect cencentration is done via pharmacokinetic/pharmacodynamic (PK/PD) models. Although these models have a clear physiological meaning, they present many parameters, which is incovenient for parameter identification procedures.

To overcome this drawback, here we consider the parameter parsimonious models introduced in Silva et al. (2010) to describe the relation between the dose of propofol/remifentanil and the corresponding effect concentration. Each of these models only involves one patient dependent parameter.

In order to model the combined effect of propofol and remifentanil, we follow Minto et al. (2000) to obtain a static nonlinear relation that yields the BIS level as a

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function of the effect concentration of each drug. This static nonlinearity is a generalization of Hill's equation and involves, in turn, two patient dependent parameters.

Our model is similar to the one proposed in (Silva et al., 2010), Almeida et al. (2016) and Nogueira et al. (2019) but here the roles of propofol and remifentanil are switched with respect to that model. As we shall later see, this facilitates the use of identification procedures that are in line with the usual clinical practice.

Our goal is thus, to design and implement a simple on-line procedure in order to estimate the four patient dependent parameters involved in the total model. To this purpose, we take advantage of drug administration patterns that are compatible with the clinical practice. This allows a fast identification of the parameters and their subsequent use either on manual or automatic individualized drug dosing during the remaining anesthetic and surgical procedure.

The organization of this paper is as follows. The model for the effect of propofol and remifentanil on the BIS level is presented on Section 2. Section 3 is devoted to the theoretical foundations of the proposed parameter estimation procedure. Simulation results are presented in Section 4 and, finally, some concluding remarks are made in Section 5.

2. MODEL FOR THE ACTION OF PROPOFOL AND REMIFENTANIL ON THE BIS LEVEL

The effect of propofol and remifentanil on the BIS level consists of two parts: one part with linear dynamics which relates the drug dosages u_p and u_r, to the effect concentrations C_e^p and C_e^r and another part consisting of a static non linearity relating the effect concentrations C_e^p and C_e^r with the BIS level, as shown in Figure 1.

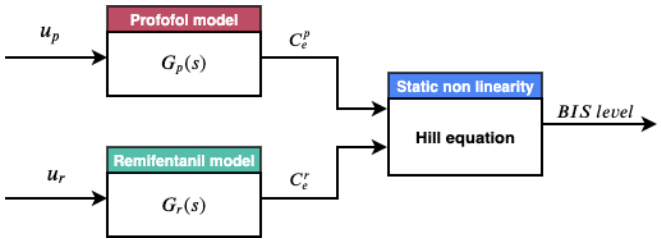

Fig. 1. General scheme for the effect of propofol and remifentanil on the BIS level.

The models intoduced in Silva et al. (2010) for the effect concentrations of propofol and remifentanil are given by the following transfer functions

$$\frac{C_e^p(s)}{U^p(s)} = \frac{90\alpha^3}{(s+\alpha)(s+9\alpha)(s+10\alpha)} \tag{1}$$

and

$$\frac{C_e^r(s)}{U^r(s)} = \frac{6\eta^3}{(s+\eta)(s+2\eta)(s+3\eta)} \tag{2}$$

where $C_e^p(s)$ and $C_e^r(s)$ are the Laplace transforms of the propofol and the remifentanil effect concentrations, $U^p(s)$ and $U^r(s)$ are the Laplace transforms of the propofol and the remifentanil drug doses, and α and η are patient dependent parameters. The coefficients that affect the parameters (1, 9 and 10 for propofol, and 1, 2 and 3 for remifentanil) were determined by optimized fitting using the information of a large database of real cases collected during surgeries.

According to Minto et al. (2000), the combined effect E of two drugs A and B is given by the generalized Hill equation:

$$E(t) = \frac{E_0}{1 + (\mathcal{U}_A(t) + m\mathcal{U}_B(t))^\gamma}, \tag{3}$$

where E_0 corresponds to the case where no drugs are administered; $\mathcal{U}_A$ and $\mathcal{U}_B$ stand for the potency of A and B, respectively, and are given by:

$$\mathcal{U}_A(t) = \frac{C_e^A(t)}{EC_{50}^A}; \quad \mathcal{U}_B(t) = \frac{C_e^B(t)}{EC_{50}^B}, \tag{4}$$

where EC_{50}^A and EC_{50}^B are the effect concentrations of A and B, respectively, associated with 50 % drug effect. Finally, m and γ are patient dependent parameters.

In Silva et al. (2010), remifentanil was taken as drug A, whereas propofol was taken as drug B, yielding the following expression for the combined effect of the two drugs on the BIS level, here denoted by $z(t)$, is given by the generalized Hill equation

$$z(t) = \frac{97.7}{1 + (m\mathcal{U}_p(t) + \mathcal{U}_r(t))^\gamma}, \tag{5}$$

where $\mathcal{U}_p$ and $\mathcal{U}_r$ stand for the potency of propofol and remifentanil, respectively, and are given by

$$\mathcal{U}_p(t) = \frac{C_e^p(t)}{EC_{50}^p}; \quad \mathcal{U}_r(t) = \frac{C_e^r(t)}{EC_{50}^r}, \tag{6}$$

where EC_{50}^p and EC_{50}^r are the effect concentrations of propofol, respectively, remifentanil that correspond to half of the maximum drug effect. These values were determined in Silva et al. (2010) from the aforementioned database of real cases as:

$$EC_{50}^p = 10 \text{ and } EC_{50}^r = 0.01. \tag{7}$$

Finally, m and γ are patient dependent parameters. Thus, in total, the model comprises four patient dependent parameters to be identified, namely: α, η, γ and m.

This model allows a simple parameter estimation procedure for the parameters γ and m (taking mean values for α and η), based on the patient BIS response to the administration of a constant dose of remifentanil followed by a constant dose of propofol, Almeida et al. (2016).

However this drug administration pattern is not in line with the common anesthetic procedures, where propofol is administered before remifentanil.

In order to overcome this drawback, we switch the roles of propofol and remifentanil in equation 4, i.e., we take

propofol as being drug A and remifentanil as being drug B, yielding:

$$z(t) = \frac{97.7}{1 + (\mathcal{U}_p(t) + m\mathcal{U}_r(t))^{\gamma}}, \tag{8}$$

where $\mathcal{U}_p$ and $\mathcal{U}_r$ are still given by 6.

The new model also possesses four patient dependent parameters. For simplicity, they are still denoted by α, η, γ and m, but, obviously, for a given patient, their values will not coincide with the ones of the model proposed in Silva et al. (2010).

The estimation of our model parameters will be achieved according to the on-line estimation procedure proposed in the next section.

3. ON-LINE PARAMETER ESTIMATION FOR THE BIS MODEL

The estimation procedure proposed here consists of two main steps. First the parameters α and γ are estimated based on the patient's response to a bolus of $600\mu g/kg$ of propofol. After these parameters are estimated, a constant dose of $3\mu g/kg/min$ of propofol together with a constant dose of $0.002\mu g/kg/min$ of remifentanil is administered. This allows to estimate the parameters m and η as explained in the sequel.

3.1 Estimation of α and γ

According to (1), the administration of a bolus of $600\mu g/kg$ of propofol produces a frequency domain response:

$$C_e^p(s) = \frac{90\alpha^3}{(s+\alpha)(s+90\alpha)(s+10\alpha)}\ 600 \tag{9}$$

Corresponding to the following time domain response:

$$\begin{aligned} C_e^p(t) = 750\alpha e^{-\alpha t} - 6750\alpha e^{-9\alpha t} + \\ +6000\alpha e^{-10\alpha t}, \qquad t \geq 0 \end{aligned} \tag{10}$$

By (8), and taking into account that no remifentanil has been administered, this produces a BIS level response:

$$z^p(t) = \frac{97.7}{1 + \left(\frac{C_e^p(t)}{10}\right)^{\gamma}} \tag{11}$$

Thus, when $z^p(t)$ is equal to half its maximum value, i.e., at the time instant $t = T_{50}^p$ when

$$z^p(t) = \frac{97.7}{2} = 48.85, \tag{12}$$

the value of $C_e^p(T_{50}^p)$ satisfies:

$$C_e^p(T_{50}^p) = 10. \tag{13}$$

Now, since the value of T_{50}^p can be obtained by inspection of the BIS level response (recall that $z_{50}^p = 48.85$), it is enough to solve (13) for α (with $C_e^P(T_{50}^p)$ given by (11)), i.e.:

$$\begin{aligned} C_e^p(t) = 750\alpha e^{-\alpha T_{50}^p} - 6750\alpha e^{-9\alpha T_{50}^p} + \\ +6000\alpha e^{-10\alpha T_{50}^p} = 10 \end{aligned} \tag{14}$$

in order to obtain an estimate $\hat{\alpha}$ for this patameter. The order to estimation of γ can be performed by analyzing the BIS level $z(T^*)$ response at a time intant $T^* \geq T_{50}^p$. At this time instant, an estimate

$$\begin{aligned} \hat{C_e^{p*}} = C_e^p(T^*) = 750\hat{\alpha} e^{-\hat{\alpha} T^*} - 6750\hat{\alpha} e^{-9\hat{\alpha} T^*} + \\ +6000\hat{\alpha} e^{-10\hat{\alpha} T^*} \end{aligned} \tag{15}$$

of $\hat{C}_e^p(T^*)$ is available and the estimate $\hat{\gamma}$ for γ can be computed by solving for γ equation:

$$z(T^*) = \frac{97.7}{1 + \left(\frac{\hat{C}_e^p(T^*)}{10}\right)^{\gamma}} \tag{16}$$

which yields

$$\hat{\gamma} = \frac{\log(\frac{97.7}{z^p(T^*)} - 1)}{\log(\frac{\hat{C}_e^{p*}}{10})}. \tag{17}$$

3.2 Estimation of η and m

In order to obtain estimates for the parameters η and m, a constant dose of $0.002\mu g/kg/min$ of remifentanil is administered from the time instant T^* on. The corresponding frequency domain response for the effect concentration of remifentanil is then, according to (2), given by:

$$C_e^r(s) = \frac{6\eta}{(s+\eta)(s+2\eta)(s+3\eta)}\ \frac{0.002}{s} e^{-sT^*}, \tag{18}$$

which corresponds to the time domain response, where $\Delta t = t - T^*$

$$C_e^r(t) = \begin{cases} 0, & t < T^* \\ \dfrac{(-3e^{-\eta(\Delta t)} + 3e^{-2\eta(\Delta t)} - e^{-\eta(\Delta t)} + 1)}{500}, & t \geq T^* \end{cases} \tag{19}$$

Together with the constant dose of remifentanil, a constant dose of $3\mu g/kg/min$ of propofol is administered (according to clinical practice). The corresponding frequency domain response for the effect concentration of propofol is given by:

$$\tilde{C}_e^p(s) = \frac{90\alpha^3}{(s+\alpha)(s+9\alpha)(s+10\alpha)}\ \frac{3}{s} e^{-sT^*} \tag{20}$$

This is to be added to the effect concentration of propofol induced by the bolus, in order to obtain the joint response:

$$C_e^p(s) = \frac{90\alpha^3}{(s+\alpha)(s+9\alpha)(s+10\alpha)}\,(600 + \frac{3}{s}e^{-sT^*}) \quad (21)$$

or, in time domain:

$$C_e^p(t) = \mathcal{L}^{-1}[C_e^p(s)] \quad (22)$$

Thus, it follows from (8) that the produced BIS level response is given by:

$$z(t) = \begin{cases} z^p(t), & t < T^* \\ \dfrac{97.7}{1 + \left(\frac{C_e^p(t)}{10} + m\frac{C_e^p(t)}{0.01}\right)^\gamma}, & t \geq T^* \end{cases}$$

Now, reading out the values $z(t')$ and $z(t'')$ of the BIS level response for two time instants t' and $t'' \geq T^*$ we get:

$$z(t') \approx \frac{97.7}{1 + \left(\frac{\hat{C}_e^p(t')}{10} + m\frac{C_e^r(t')}{0.01}\right)^{\hat{\gamma}}} \quad (23)$$

and

$$z(t'') \approx \frac{97.7}{1 + \left(\frac{\hat{C}_e^p(t'')}{10} + m\frac{C_e^r(t'')}{0.01}\right)^{\hat{\gamma}}} \quad (24)$$

where $\hat{C}_e^p(t')$ and $\hat{C}_e^p(t'')$ are the estimates for the effect concentration of propofol obtained from (4) by replacing the parameter α by its estimate $\hat{\alpha}$.

Equations (23) and (24) allow to compute approximate values for $mC_e^r(t')$ and $mC_e^r(t'')$, based on which estimates $\hat{m}$ for m and $\hat{\eta}$ for η can be obtained. Indeed, after some computations, one has:

$$mC_e^r(t') \approx 0.01\Big[\Big(\frac{97.7}{z(t')} - 1\Big)^{\frac{1}{\hat{\gamma}}} - \frac{\hat{C}_e^p(t')}{10}\Big] := a \quad (25)$$

and

$$mC_e^r(t'') \approx 0.01\Big[\Big(\frac{97.7}{z(t'')} - 1\Big)^{\frac{1}{\hat{\gamma}}} - \frac{\hat{C}_e^p(t'')}{10}\Big] := b \quad (26)$$

(where, for implicity the values of right-hand sides of equations (25) and (26) have been designated by a and b, respectively)

Now, it follows from (25) and (26) that

$$\frac{C_e^r(t')}{C_e^r(t'')} \approx \frac{a}{b}, \quad (27)$$

where the expressions for $C_e^r(t')$ and $C_e^r(t'')$ can be computed from (19). Thus, solving the equation

$$\frac{-3e^{-\eta(t'-T^*)} + 3e^{-2\eta(t'-T^*)} + e^{-3\eta(t'-T^*)} + 1}{-3e^{-\eta(t''-T^*)} + 3e^{-2\eta(t''-T^*)} + e^{-3\eta(t''-T^*)} + 1} = \quad (28)$$

$$= \frac{a}{b}$$

for η yields an estimate $\hat{\eta}$ for this parameter.

In order to simplify the solution of equation (29), one may take t'' in such a way that $t'' - T^* = 2\theta$, where $\theta := (t' - T^*)$.

Defining $r = e^{-\eta\theta}$, equation (29) becomes

$$-3r + 3r^2 + r^3 + 1 = \frac{a}{b}(-3r^2 + 3r^4 + r^6 + 1) \quad (29)$$

or equivalentely:

$$\frac{a}{b}r^6 + 3\frac{a}{b}r^4 - r^3 - (3\frac{a}{b} + 3)r^2 + 3r(\frac{a}{b} - 1) = 0 \quad (30)$$

Solving (30) for the real root r^* such that $0 < r^* < 1$, we obtain

$$\hat{\eta} = \frac{log(r^*)}{-\theta} \quad (31)$$

Finally, using (for instance) (25), one obtains the estimate:

$$\hat{m} = \frac{a}{\hat{C}_e^r(t')}, \quad (32)$$

where $\hat{C}_e^r(t')$ is given by (19) with $\eta = \hat{\eta}$ and $t = t'$

4. SIMULATION RESULTS

In order to validate the proposed model and parameter estimation procedures, the following strategy is used. We consider the model proposed in Silva et al. (2010), for which a table of parameters, identified from a database of real cases in the framework of Galeno project, is avaliable. This serves as basis for creating simulated patients, considered to be the "real" patients, to which our modelling and identification procedure is applied.

The parameters of the model proposed in Silva et al. (2010) and the identified parameters of our model, for four randomly chosen cases are displayed in Tables 1 and 2, respectively.

Table 1. Parameter values for the model of Silva et al. (2010), taken from Almeida et al. (2016)

Patient	α	γ	η	m
Case 1	0.0667	1.7695	0.3989	2.1502
Case 2	0.0489	1.5627	0.1269	1.4171
Case 3	0.0737	0.7812	0.2793	0.8986
Case 4	0.0860	0.9780	0.0212	1.4203

Table 2. Estimated parameters values for the new proposed model

Patient	$\hat{\alpha}$	$\hat{\gamma}$	$\hat{\eta}$	$\hat{m}$
Case 1	0.0902	1.9807	1.9831	1.6110
Case 2	0.0568	1.6965	2.1614	0.2145
Case 3	0.0704	0.7627	7.3080	0.1080
Case 4	0.0988	1.0331	1.6423	1.0684

As expected, the parameters of the two models do not coincide, due to the different structure of these models.

In order to evaluate the performance of our procedure, we compare the responses of the simulated patients and of our identified patients to the administration of propofol and remifentanil via a TCI scheme where the dosages are computed from the data of the identified patient as explained next.

Assume that a BIS level of $z^* = 50$ is to be tracked (as is usual in the clinical practice). This can be achieved by the administration of constant doses u^{p*} and u^{r*} of propofol and remifentanil, respectively. Here we consider that the dose of remifentanil to be delivered is given by:

$$u_e^{r*} = \rho u^{p*}, \tag{33}$$

where ρ is a constant to be chosen according to clinical criteria, and the steady-state dose u^{p*} is to be determined. Note that such dosages correspond to the following steady-state values of the effect concentrations of C^{p*} and $C_e^{r*} = \rho C^{p*}$ of propofol and remifentanil, respectively:

$$C_e^{p*} = u^{p*} \tag{34}$$

$$C_e^{r*} = u^{r*} = \rho u^{p*}, \tag{35}$$

since the steady state gains of the transfer functions (1) and (2) are both equal to 1.

Now, from equations (8),(6) and (7), it follows that, for the estimated patient:

$$50 = z^* = \frac{97.7}{1 + \left(\frac{u^{p*}}{10} + \hat{m}\rho\frac{u^{p*}}{0.01}\right)^{\hat{\gamma}}}, \tag{36}$$

yielding the propofol steady-state dose:

$$u^{p*} = \left(\frac{1}{0.1 + 100\rho\hat{m}}\right)\left(\frac{97.7 - 50}{50}\right)^{1/\hat{\gamma}}; \tag{37}$$

the steady-state dose of remifentanil is:

$$u^{r*} = \rho u^{p*}. \tag{38}$$

The results of the simulations are displayed in the figures below. In all cases ρ was taken to be $\rho = 10^{-4}$ (which is compatible with the clinical practice). The drug doses were computed based on the estimated parameters and applied to the "real" patients. For control purposes, the estimated doses were also applied to the estimated patients. As one also can see, the steady-state BIS level of the real patients is close to the desired refrence level.

5. CONCLUSIONS

A new model for the action of the hypnotic propofol and the analgesic remifentanil on the DoA, measured by the BIS level, was proposed. This model is similar to the one presented in Silva et al. (2010), but the roles of the two drugs are switched. This makes it more suitable for on-line parameter identification in practical cases, as it is compatible with usual clinical anesthetic procedures and profiles of clinical drug administration. Taking advantage of the model structure, we proposed a simple parameter identification method and evaluated its performance via simulations. The obtained results look promising, encouraging the application of the new method in a clinical environment.

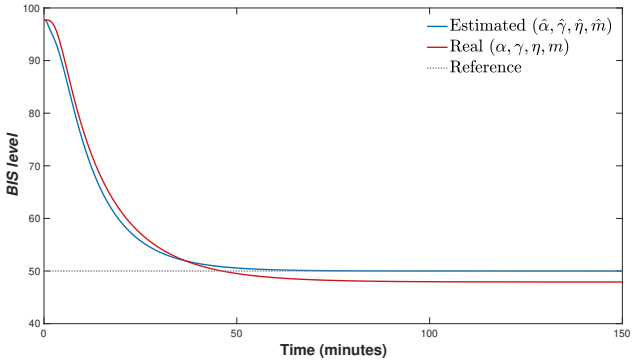

Fig. 2. BIS responses for "real" and estimated patients of Case 1. The administrated constant drug doses are $u^{p*} = 8.4101 \mu g/kg/min$, $u^{r*} = 10^{-4} u^{p*} = 8.4101 \times 10^{-4} \mu g/kg/min$, for a desired BIS reference level of 50. The achieved steady-state BIS level for the "real" patient is 47.92.

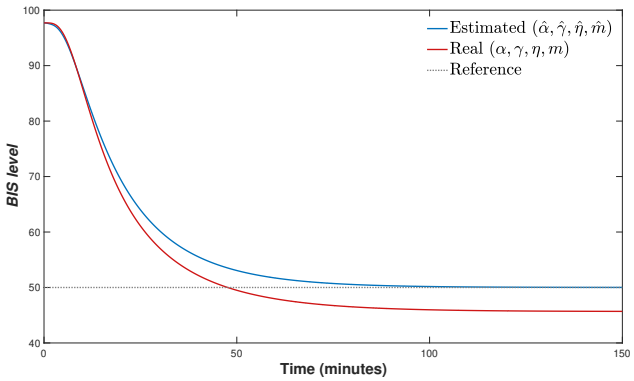

Fig. 3. BIS responses for "real" and estimated patients of Case 2. The administrated constant drug doses are $u^{p*} = 9.5220 \mu g/kg/min$, $u^{r*} = 10^{-4} u^{p*} = 9.5220 \times 10^{-4} \mu g/kg/min$, for a desired BIS reference level of 50. The achieved steady-state BIS level for the "real" patient is 45.69.

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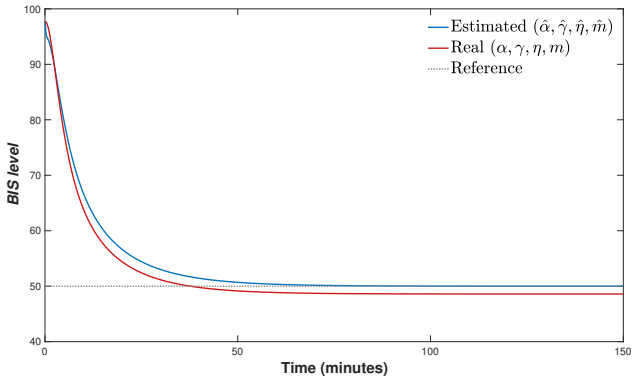

Fig. 4. BIS responses for "real" and estimated patients of Case 3. The administrated constant drug doses are $u^{p*} = 9.3008 \mu g/kg/min$, $u^{r*} = 10^{-4} u^{p*} = 9.3008 \times 10^{-4} \mu g/kg/min$, for a desired BIS reference level of 50. The achieved steady-state BIS level for the "real" patient is 48.59.

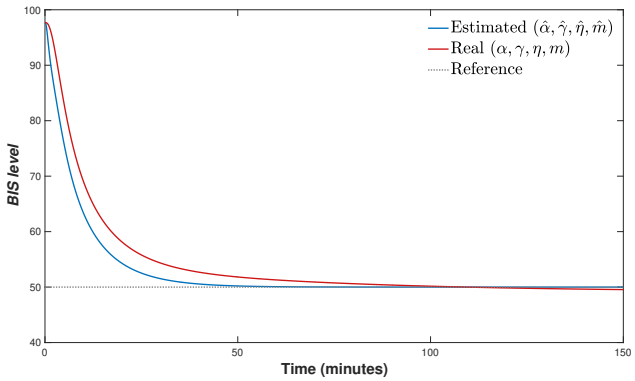

Fig. 5. BIS responses for "real" and estimated patients of Case 4. The administrated constant drug doses are $u^{p*} = 8.6321 \mu g/kg/min$, $u^{r*} = 10^{-4} u^{p*} = 8.6321 \times 10^{-4} \mu g/kg/min$, for a desired BIS reference level of 50. The achieved steady-state BIS level for the "real" patient is 49.55.

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