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Evaluation of a Propofol and Remifentanil Interaction Model for Predictive Control of Anesthesia Induction

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Abstract— **This paper introduces a simplified linear interaction model between two drugs, namely Propofol and Remifentanil, which will be used in a model based predictive control algorithm for (nonlinear) automatic induction and regulation of DOA. Depth of anesthesia (DOA) is evaluated by means of the Bispectral index (BIS). The simulation tests are performed on a set of 24 virtually generated realistic patient models. The results are promising and the performance of the controller shows a high-efficiency, optimal dosage of the two drugs in order to achieve the desired BIS reference.**

I. Introduction

THE problem of finding suitable variables for optimal simultaneous control of the two components of depth of anesthesia (DOA), being hypnosis and analgesia, during closed-loop control is nowadays intensively investigated and many research groups worldwide are striving to find a clinically accurate solution. For measuring the hypnotic component of anesthesia, various indexes are present, mostly computerized from the spontaneous or evoked electroencephalogram (EEG) [1]. The bispectral index (BIS) is a single composite measure derived from the spontaneous EEG and has been proven to have a high sensitivity and specificity to measure anesthetic drug effect [2]. BIS is now recognized as one of the reference measures of DOA for closed loop control purposes [3],[4]. In contrast to cerebral drug effect produced by hypnotics, an accurate measure for analgesia is still lacking. However, when BIS is known, a suitable interaction model between hypnotics and analgesics might be helpful to simultaneously control both components of DOA.

Various interaction models between intravenous hypnotics and analgesics have been described [5]. Pharmacodynamic response surface models are three- (or more) dimensional structures which have been developed to quantitatively describe the relationship between two (or more) drug concentrations with their corresponding combined clinical drug effect. Response surface models are powerful sources of information on drug interactions as they combine information about any isobole and the concentration response curve of any combination of the drugs involved. Using the mathematically described response surface, one can predict the corresponding drug effect for any two (or more) drug concentrations of the interacting drugs [5]. Until now, these interaction models have not been used in closed-loop control of DOA.

Among all control algorithms, a recent trend has been observed to apply model based predictive control (MPC) strategies [4],[6],[7]. Their intrinsic ability to deal with inter- and intra- patient variability, variable time delays and nonlinear dynamics have made them a suitable tool for achieving optimal performance. The inherent capability of MPC to outperform other control strategies has been shown in [8] by means of a simulation study evaluating both performance and robustness of the closed loop. However, the drawback of the MPC is that it requires the apriori knowledge of the model of the patient, relating the input and output variables of interest. The availability of the models depends strongly on the complexity of the interaction between the manipulated drugs and the output variable quantifying the DOA.

In this paper we present a simplified linear multiple input – single output interaction model relating Propofol and Remifentanil to BIS. This model is then used for predicting the patient's DOA and calculate the optimal infusion rates of the two manipulated drugs. The closed loop performance is then evaluated using the nonlinear interaction model for the same two drugs for the induction phase of DOA.

The paper is organized as follows: the description of the model and its identified parameters are given in the second section. The third section presents briefly the MPC algorithm with its tuning parameters and the results for induction on the 24 virtual realistically generated patients are given in the fourth section. A conclusion section summarizes the main outcome of this paper and its perspectives.

II. Patient Modelling

A. The pharmacokinetic-pharmacodynamic models

Propofol is a hypnotic agent, for which the pharmacologic properties have been well described and studied in different kind of patients [9], [10], [11], [12]. Given its beneficial pharmacological profile, Propofol is used as one of the drugs of choice for both induction and maintenance of the hypnotic component of anesthesia and intensive care sedation .

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Remifentanil is an opioid with a unique pharmacologic profile, best characterized by its high metabolic clearance, independent of the most common metabolic pathways which are usually known to metabolize anesthetic drugs [13], [14]. When administered together, these two drugs interact synergistically on both hypnotic and analgesic components of sedation. These two drugs are the inputs of the model and the output is the Bispectral Index (BIS), a signal derived from the electroencephalogram (EEG). Using EEG, several derived, computerised parameters like the BIS have been tested and validated as a promising measure of the hypnotic component of anesthesia [15]. BIS combines several features extracted from EEG including higher order spectra of the signal which can reveal phase coupling of single waveforms. Multivariate statistics were used to combine the different features into a single indicator value [2], [9]. BIS values lie in the range of 0-100; whereas 90-100 range represents fully awake patients; 60-70 range and 40-60 range indicate light and moderate hypnotic state, respectively. For the induction phase of DOA, a BIS value of 50 is considered suitable.

The general block diagram of the MISO patient model is depicted Figure 1.

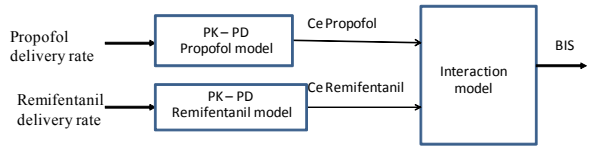

Fig. 1: Schematic representation of the MISO system

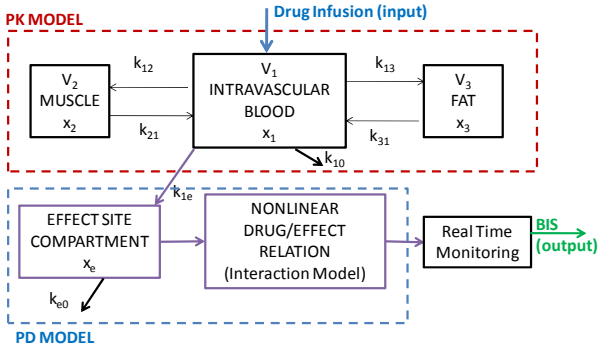

Fig. 2: Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model.

In Figure 1 the pharmacokinetic (PK) – pharmacodynamic (PD) blocks denote compartmental models. Compartmental models are used to represent the distribution of drugs in the body, i.e. mass balance. They rely on a conservation principle applied to the exchange of chemicals among coupled macroscopic systems called compartments (central compartment, fast (muscle) and slow (fat) equilibrating peripheral compartments). In each compartment the drug concentration is assumed to be uniform, as in a perfect and instantaneous mixing. The transport rate that leaves the compartment is assumed to be proportional to the drug concentration. The PK-PD models most commonly used for Propofol and Remifentanil are the 4th order compartmental model described by Schnider [10], [11] and Minto [13], [14], respectively. These models have the same structure, as that depicted in Figure 2.

The PK-PD models are represented by the following equations:

$$\begin{aligned}\dot{x}_1(t) &= -\left[k_{10}+k_{12}+k_{13}\right]\cdot x_1(t)+k_{21}\cdot x_2(t)\\ &\quad +k_{31}\cdot x_3(t)+u(t)\\ \dot{x}_2(t) &= k_{12}\cdot x_1(t)-k_{21}\cdot x_2(t)\\ \dot{x}_3(t) &= k_{13}\cdot x_1(t)-k_{31}\cdot x_3(t)\\ \dot{x}_e(t) &= -k_{e0}\cdot x_e(t)+k_{1e}\cdot x_1(t)\end{aligned} \quad (1)$$

where x_1 [mg] denotes the amount of drug in the central compartment. The blood concentration is expressed by x_1/V_1. The peripheral compartments 2 and 3 model the drug exchange of the blood with well and poorly diffused body tissues. The masses of drug in fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3, respectively. The parameters k_{ji}, for $i \neq j$, denote the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ [mg/s] is the infusion rate of the anesthetic drug into the central compartment. The parameters k_{ij} of the PK models depend on age, weight, height and gender and can be calculated for Propofol:

$$V_1 = 4.27\ [l]$$

$$V_2 = 18.9 - 0.391\cdot(age-53)\ [l]$$

$$V_3 = 2.38\ [l]$$

$$C_{l1} = 1.89 + 0.0456(weight-77) - 0.0681(lbm-59) + 0.0264(height-177)\ [l/\min]$$

$$C_{l2} = 1.29 - 0.024(age-53)\ [l/\min]$$

$$C_{l3} = 0.836\ [l/\min]$$

$$k_{10} = \frac{C_{l1}}{V_1}\left[\min^{-1}\right], k_{12} = \frac{C_{l2}}{V_1}\left[\min^{-1}\right], k_{13} = \frac{C_{l3}}{V_1}\left[\min^{-1}\right],$$

$$k_{21} = \frac{C_{l2}}{V_2}\left[\min^{-1}\right], k_{31} = \frac{C_{l3}}{V_3}\left[\min^{-1}\right]$$

where C_{l1} is the rate at which the drug is cleared from the body, and C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. Similarly, for Remifentanil:

$$V_1 = 5.1 - 0.0201(age-40) + 0.072(lbm-55)\ [l]$$

$$V_2 = 9.82 - 0.0811(age-40) + 0.108(lbm-55)\ [l], V_3 = 5.42\ [l]$$

$$C_{l1} = 2.6 - 0.0162(age-40) + 0.0191(lbm-55)\ [l/\min]$$

$$C_{l2} = 2.05 - 0.0301(age-40)\ [l/\min]$$

$$C_{l3} = 0.076 - 0.00113(age-40)\ [l/\min]$$

$$k_{e0} = 0.595 - 0.007(age-40)\ \left[\min^{-1}\right]$$

$$k_{10} = \frac{C_{l1}}{V_1}\left[\min^{-1}\right], k_{12} = \frac{C_{l2}}{V_1}\left[\min^{-1}\right], k_{13} = \frac{C_{l3}}{V_1}\left[\min^{-1}\right]$$

$$k_{21} = \frac{C_{l2}}{V_2}\left[\min^{-1}\right], k_{31} = \frac{C_{l3}}{V_3}\left[\min^{-1}\right].$$ The lean body mass (lbm) for men and women have the following expressions:

$1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2}$ and $1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2}$, respectively.

An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The concentration of drug in this compartment is represented by x_e. The effect compartment receives drug from the central compartment by a first-order process and it is regarded as a virtual additional compartment. Therefore, the drug transfer frequency from the central compartment to the effect site-compartment is equal to the frequency of drug removal from the effect-site compartment: $k_{e0} = k_{1e} = 0.456$ [min^{-1}]. Knowing k_{e0}, the apparent concentration in the effect compartment can be calculated since k_{e0} will precisely characterize the temporal effects of equilibration between the plasma concentration and the corresponding drug effect. Consequently, the equation is often used as:

$$\dot{C}_e(t) = k_{e0} \cdot (C_e(t) - C_p(t)) \tag{2}$$

with C_e called the *effect-site compartment concentration*. The BIS variable can be related to the drug effect concentration C_e by the empirical static but time varying nonlinear relationship [4], called also the *Hill curve:*

$$BIS(t) = E_0 - E_{\max} \cdot \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + C_{50}^{\gamma}} \tag{3}$$

where E_0 denotes the baseline (awake state—without drug) value, which, by convention, is typically assigned a value of 100, $E_{\max}$ denotes the maximum effect achieved by the drug infusion, C_{50} is the drug concentration at half maximal effect and represents the patient sensitivity to the drug, and γ determines the steepness of the curve.

B. The Nonlinear Interaction PD model

When considering the effect of two drugs, the Hill curve from (3) becomes a plane, whose parameters represent the synergistic effect of both Propofol and Remifentanil effect site compartment concentrations. The concentration-response relation of the two drugs can be described by a normalized relation:

$$BIS(t) = E_0 - E_{\max}(\theta) \cdot \frac{\left(\frac{U_{\text{Prop}}(t) + U_{\text{Rem}}(t)}{U_{50}(\theta)} \right)^{\gamma(\theta)}}{1 + \left(\frac{U_{\text{Prop}}(t) + U_{\text{Rem}}(t)}{U_{50}(\theta)} \right)^{\gamma(\theta)}} \tag{4}$$

where: $U_{\text{Prop}}(t) + U_{\text{Rem}}(t)$ is the combined drug concentration; $\gamma(\theta)$ is the steepness of the concentration-response relation at ratio θ; $U_{50}(\theta)$ is the number of units (U) associated with 50% of maximum effect at ratio θ; $E_{max}(\theta)$ is the maximum possible drug effect at ratio θ [13], with the effect-site concentrations $C_{e\text{Prop}}(t)$ and $C_{e\text{Rem}}(t)$ normalized to their respective potencies $C_{50,\text{Prop}}$ and $C_{50,\text{Rem}}$ described by:

$$U_{\text{Prop}}(t) = \frac{C_{e\text{Prop}}(t)}{C_{50,\text{Prop}}};\ U_{\text{Rem}}(t) = \frac{C_{e\text{Rem}}(t)}{C_{50,\text{Rem}}} \tag{5}$$

and the ratio of the interacting drugs expressed by:

$$\theta(t) = \frac{U_{\text{Prop}}(t)}{U_{\text{Rem}}(t) + U_{\text{Prop}}(t)} \tag{6}$$

In this formulation, θ represents the concentration ratio of the new combined drug and ranges from 0 (remifentanil only) to 1 (Propofol only). According to [14], $E_{max}(\theta)$ and E_0 are set to 100 and $U_{50}(\theta)$ can be expressed by a quadratic polynomial:

$$U_{50}(\theta) = 1 - \beta \cdot \theta + \beta \cdot \theta^2 \tag{7}$$

The unknown coefficient β can be estimated from the patient data. Since the interaction between the two drugs is supra-additive (the effect of the two drugs combined is higher than the sum of each separate effect), β should be a positive number. This means that $U_{50}(\theta)$ is lower than 1 for any value of θ between 0 and 1. To simulate the combined effect of Propofol and Remifentanil using the nonlinear expression from (4), the following values have been assigned [15]:

$$\beta = 0.22;\ \gamma(\theta) = 0.9;\ C_{50,Prop} = 3.1;\ C_{50,Rem} = 34 \tag{8}$$

C. The Linear Approximation for the Interaction PD Model

During the monitoring of the patient's DOA in the intensive care unit, it was observed that the BIS values are oscillating within a limited interval, i.e. the 40-60 BIS interval. In this interval of BIS values, the Hill curve for one drug (3) is linear. For a two-drug interaction model surface, this reduces to a plane. Thus, instead of identifying the unknown parameters of the nonlinear relation from (4), we can use instead its simplified linear approximation:

$$BIS(t) = m_1 \cdot Ce_{\text{Prop}}(t - T_d) + m_2 \cdot Ce_{\text{Rem}}(t - T_d) + c \tag{9}$$

with m_1 and m_2 the slopes of the two axis plane, c a constant and T_d the time delay introduced by the signal processing of the BIS monitor. The advantage of this linear approximation is that the number of parameters is much reduced, so an adaptation of these parameters in real-time would not pose the same mathematical complexity as that of adapting parameters in (4). The unknown parameters of the Hill curve linear approximation (9) were identified using the least-squares method. The parameter t_i represents the moment when the artifact appears. A procedure based on cross-

correlation analysis [16] was implemented to estimate online the time delay.

The patient dynamics may vary during ICU anesthesia, therefore the total length of the measurements was divided in several windows and a least squares algorithm has been employed in each window. Briefly, the algorithm can be described as follows [16]: the identification is initially performed on a window of 20 samples and then the window is increased with 10 samples. In case the parameters m_1 and m_2 did not reach the upper limit of -0.1 (since both parameters should have negative values), the algorithm checks if the variation of the parameters is large enough (higher than 0.5) and if the condition $|m_1| > |m_2|$ is fulfilled. If both these conditions are fulfilled, the values of the parameters are recorded, and the whole procedure is repeated on a new window of 20 samples. In case the parameters have reached the limits, the previous values of the parameters are used and the window is enlarged with 10 samples. Based on randomly selected patient characteristics and disturbance analysis, a set of values for the interaction model have been derived:

$$m_1 = -12.83; m_2 = -7.73; c = 100 \qquad (10)$$

III. Model Based Predictive Control

In the general MPC scheme represented in figure 3, the patient model is used to predict the current value of the output variable (BIS). The difference between the measured BIS from the patient and the model output (residual), serves as feedback signal in the prediction block. With this residual and the input *u*, the prediction block predicts the future values of the output BIS. On the basis of these predicted BIS values, the controller calculates the future optimal infusion rates over a number of samples in the future, called the prediction horizon. However, only the first calculated sample is applied to the process (i.e. principle of receding horizon).

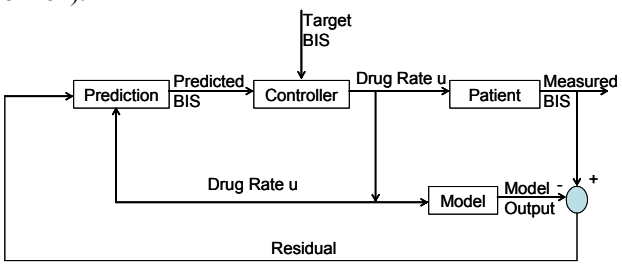

Fig. 3: MPC scheme for closed loop BIS regulation

In this paper, we apply the EPSAC (Extended Prediction Self-Adaptive Control) strategy described in detail in [17]. The EPSAC-MPC is based on a generic process model:

$$y(t) = x(t) + n(t) \qquad (11)$$

The disturbance $n(t)$ includes the effects in the measured output $y(t)$ which do not come from the model input $u(t)$ via the available model. These non-measurable disturbances have a stochastic character with non-zero average value, which can be modelled by a colored noise process:

$$n(t) = \left[C(q^{-1}) / D(q^{-1}) \right] \cdot e(t) \qquad (12)$$

with: $e(t)$ - uncorrelated (white) noise with zero mean value; $C(q^{-1})$ and $D(q^{-1})$ - monic polynomials in the backward shift operator q^{-1} of orders n_c and n_d. The disturbance filter $C(q^{-1}) / D(q^{-1})$ is defined as a pure integrator, to ensure zero steady state error.

The relationship between $u(t)$ and $x(t)$ is given by the generic dynamic system model:

$$x(t) = f\left[x(t-1), x(t-2), \cdots, u(t-1), u(t-2), \cdots \right] \qquad (13)$$

In our case the input applied to the patient, $u(t)$, is a vector containing the Propofol and Remifentanil delivery rates. The model output is then represented by:

$$x(t) = m_1 \cdot C_{e\Pr op}(t - T_d) + m_2 \cdot C_{e\mathrm{Re}m}(t - T_d) \qquad (14)$$

The process output is predicted at time instant t over the prediction horizon N_2, based on the measurements available at that moment and the future outputs of the control signal. The predicted values of the output are:

$$y(t+k/t) = x(t+k/t) + n(t+k/t) \qquad (15)$$

Prediction of $x(t+k|t)$ and of $n(t+k|t)$ can be done respectively by recursion of the process model and by using filtering techniques on the noise model (12) [17].

In EPSAC for linear models, the future response is considered as being the cumulative result of two effects:

$$y(t+k/t) = y_{base}(t+k/t) + y_{opt}(t+k/t) \qquad (16)$$

where $y_{base}(t+k/t)$ represents:

- effect of past control $\{u(t\text{-}1),\ u(t\text{-}2),\ \ldots\}$ (initial conditions at time t);
- effect of a *base* future control scenario, called $u_{\text{base}}(t+k\,|\,t),\ k \geq 0$, which is defined *a priori*; for linear systems the choice is irrelevant, a simple choice being $\{u_{\text{base}}(t+k\,|\,t) \equiv 0,\ k \geq 0\}$;
- effect of future (predicted) disturbances $n(t+k|t)$.

and $y_{opt}(t+k/t)$ represents:

- effect of the *optimizing* future control actions $\{\delta u(t\,|\,t),\ \delta u(t+1\,|\,t),\ \ldots\ \delta u(t+N_u-1\,|\,t)\}$ with $\delta u(t+k\,|\,t) = u(t+k\,|\,t) - u_{\text{base}}(t+k\,|\,t)$. The *design* parameter N_u, called the *control horizon* (a well-known concept in MPC-literature), is considered in this paper equal to 1.

The controller output is obtained by minimizing:

$$J(\mathbf{U}) = \sum_{k=N_1}^{N_2} \left[r(t+k/t) - y(t+k/t) \right]^2 \qquad (17)$$

where *r(t+k/t)* is the desired *reference trajectory*. The controller output is obtained by minimizing a cost function. The cost function (17) is a quadratic form in **U,** having the following structure:

$$J(\mathbf{U}) = (\mathbf{R} - \bar{\mathbf{Y}} - \mathbf{G}\cdot\mathbf{U})^T \cdot (\mathbf{R} - \bar{\mathbf{Y}} - \mathbf{G}\mathbf{U}) \qquad (18)$$

which leads after minimization w.r.t. **U** to the optimal solution:

$$\mathbf{U}^* = \left[\mathbf{G}^T \cdot \mathbf{G}\right]^{-1} \mathbf{G}^T \cdot (\mathbf{R} - \bar{\mathbf{Y}}) \qquad (19)$$

with **R** the reference trajectory, $\overline{\mathbf{Y}}$ and **U** defined as:

$$\overline{\mathbf{Y}} = \left[Y_{base}(t + N_1 / t).....Y_{base}(t + N_2 / t)\right]^T \qquad (20)$$

$$\mathbf{U} = \left[\delta u(t/t).....\delta u(t + N_u - 1/t)\right]^T \qquad (21)$$

The **G** matrix is represented by:

$$\mathbf{G} = \begin{bmatrix} m_1 \cdot g\mathrm{Prop}_{N_1} & m_2 \cdot g\mathrm{Rem}_{N_1} \\ ... & ... \\ m_1 \cdot g\mathrm{Prop}_{N_2} & m_2 \cdot g\mathrm{Rem}_{N_2} \end{bmatrix} \qquad (22)$$

where $g\mathrm{Prop}_{N_1}$ …. $g\mathrm{Prop}_{N_2}$ and $g\mathrm{Rem}_{N_1}$ … $g\mathrm{Rem}_{N_2}$ are the coefficients of the unit step response of the PK-PD Propofol model and PK-PD Remifentanil model, respectively.

Since we have two inputs and one output, the default cost function from (17) becomes an ill-posed optimization problem with an infinite number of solutions. Hence, the cost function can be extended in order to penalize the control movements and in this way the search region is restricted, allowing unique solutions:

$$J(\mathbf{U}) = (\mathbf{R} - \mathbf{Y})^T \cdot (\mathbf{R} - \mathbf{Y}) + \lambda \cdot \mathbf{U}^T \cdot \mathbf{U}$$
$$\text{with} \quad \mathbf{Y} = \bar{\mathbf{Y}} + \mathbf{G} \cdot \mathbf{U} \qquad (23)$$

Since we are in the linear case, and the control horizon is selected to 1, we have that the control input is calculated by

$$\mathbf{U}^* = (\mathbf{G}^T\mathbf{G} + \lambda\mathbf{I})^{-1} \cdot \mathbf{G}^T \cdot (\mathbf{R} - \bar{\mathbf{Y}}) \qquad (24)$$

and this represents the control signal which will be applied to the patient.

IV. Results

The patient model presented in section 2.A was used in combination with the linear approximation described in section 2.C to predict the future BIS values in the EPSAC MPC algorithm. A recommended sample time of 10 seconds is applied. The following constraints were used for Propofol and Remifentanil: 0-3.3 mg/s and 0-3.3 µg/s, respectively. The weighting factor was chosen empirically as $\lambda = 100$. In practice, the variable time delay is estimated online using a procedure based on correlation analysis [16]. The time delay has been taken into account in this paper with a nominal value of 40 seconds (4 samples). The tuning of the EPSAC parameters was considered optimal for the following values: $N_1 = T_d = 4$, $N_u = 1$, $N_2 = N_1 + 10$. In order to simulate the real patient, the model from section 2.A has been used together with the nonlinear interaction model from section 2.B, introducing in this way significant modelling errors between the patient BIS output and the predicted BIS output.

Each patient reacts different to the same amount of infused drug, therefore the controller was applied to different patients in order to test the robustness of the controller to the inter-patient variability (patient's sensitivity to the drug). For the PK-PD patient model, the parameters were calculated based on the virtual biometric values presented in Table 1, using realistically ad random generated values.

Table 1. Biometric values of the virtual patients, generated ad random, and used to calculate the PK-PD model.

Patient	Age (years)	Length (cm)	Weight (Kg)	Gender
1	74	164	88	M
2	67	161	69	M
3	75	176	101	M
4	69	173	97	M
5	45	171	64	M
6	57	182	80	M
7	74	155	55	F
8	71	172	78	M
9	65	176	77	M
10	72	192	73	M
11	69	168	84	F
12	60	190	92	M
13	61	177	81	M
14	54	173	86	M
15	71	172	83	M
16	53	186	114	M
17	72	162	87	M
18	61	181	93	F
19	70	167	77	M
20	69	168	82	M
21	69	158	81	M
22	60	165	85	F
23	70	173	69	M
24	56	186	99	M
Mean	**66.4**	**172.8**	**83.1**	**-**
Std	**7.3**	**9.8**	**12.7**	**-**

Figure 4 depicts the BIS values during the induction phase. Notice the time delay in the beginning, corresponding to 40 seconds. The inter-patient variability can be observed by the variation in the patient's response, i.e. the sensitivity to the drug. Figure 5 depicts the performance of the controller for the induction phase, by means of the BIS index within the acceptable {55,45} interval, and the corresponding Propofol and Remifentanil infusion rates, respectively.

The advantage of the current MISO controller over the single-input single output EPSAC-MPC formulation [4] is that the limits on the Propofol are never reached, allowing a smooth convergence to the targeted BIS value. The averaged time-to-target, defined as the required time to reach for the first time the targeted BIS value (here BIS target has been set to 50), is of 145.8 seconds with a standard deviation of 46.8 seconds. The lowest BIS value during the induction phase is 44.49, with a standard deviation of 1.88, showing

that the controller reduces significantly the undershoot (i.e. no over-sedation). The averaged settling time, defined as the time when BIS enters the {55,45} interval and remains within it, has been of 224.4 seconds, with a standard deviation of 60 seconds. Finally, the undershoot, defined as the BIS values below the 45 lower limit is on the average 1.21, with a standard deviation of 1.28; thus negligible.

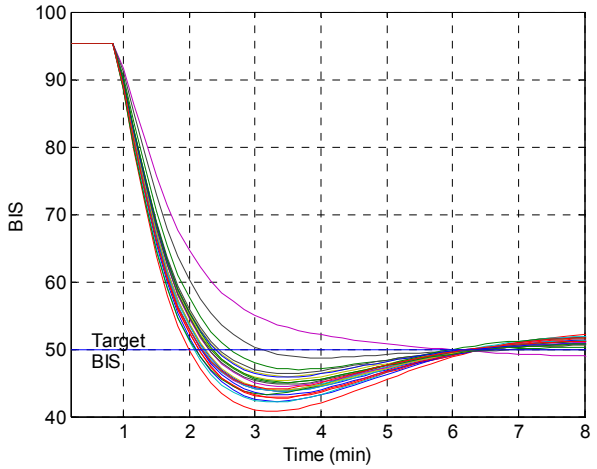

Fig. 4: The simulated BIS signal during the closed loop control of anesthesia induction

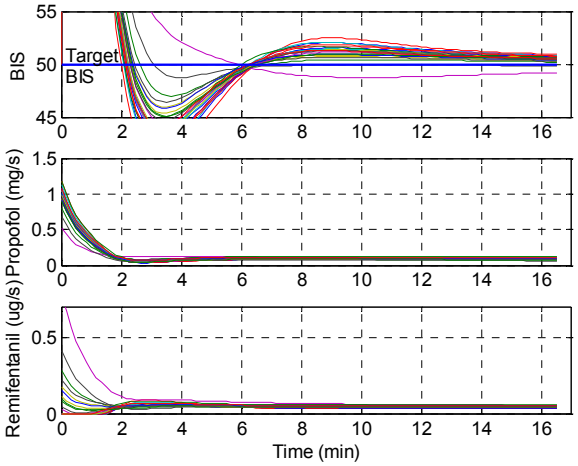

Fig. 5: A detailed view on the BIS signal in the {55;45} interval and the corresponding calculated inputs for all 24 patients.

V. Conclusion

This paper introduces a simplified linear interaction model based on the synergistic effect of Propofol and Remifentanil on the Bispectral index for inducing anesthesia. The paper presents a linear alternative formulation of the complex nonlinear model based on the Hill curve, by taking into account the fact that during the main time interval of surgery and intensive care, the BIS values are within the linear zone. Identification has led to a set of averaged values for this linear formulation and the simulation tests for induction purposes show a good ability of the patient model to predict useful information in a model based predictive control scheme. The model based predictive control algorithm has been tested on a patient database where the nonlinear interaction model has been used to obtain the Bispectral index values. Despite significant modelling errors (nonlinear vs linear approximation of the Hill curve), the controller was able to successfully induce all patients into anesthesia with smooth control effort (drug infusion rates). This robust controller is currently implemented for performing clinical trials.

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