MODEL DEVELOPMENT FOR PROPOFOL AND REMIFENTANIL MANAGEMENT DURING ICU ANESTHESIA

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Abstract: This paper presents the development of a MISO (multiple-input single-output) patient model for sedation and analgesia components used in ICU. The two inputs are Propofol and Remifentanil and the output is the Bispectral Index. The MISO model consists of two well-known PK-PD models for Propofol and Remifentanil, and an interaction model which describes the synergistic effect of these two drugs on the Bispectral Index. The interaction model parameters were identified using a nonlinear least squares method. Data collected during clinical trials in ICU at Ghent University Hospital have been used for model development. The final purpose is to use this model for prediction in a model based predictive control strategy.

1 INTRODUCTION

General anesthesia plays an important role in surgery and Intensive Care Unit (ICU) and requires critical assessment of induced quantities of drugs into the patient. There are three major interactive parts in anesthesia: sedation, analgesia and neuromuscular blockade.

Usually, anesthesiologists control the drug dosing during anesthesia by monitoring hemodynamic signals. This open-loop technique reaches the target level of sedation fast, but it may result in minimal values (undershoot) which are not safe for the patient. On the other hand, if the drug delivery regulation is done automatically, anesthesiologists will have more time to concentrate on critical issues that may threaten the safety of the patient. Control of anesthesia poses a manifold of challenges: multivariable characteristics, variable time delays, inter- and intra-patient variability, dynamics dependent on anesthetic substances and stability issues (Haddad, Hayakawa & Bailey, 2003; Struys *et al.,* 2003).

Numerous PID controllers have been designed during decades, but since these controllers cannot anticipate the response of the patient and do not have any prior knowledge of the drug metabolism, the performances were sub-optimal. Therefore, model based strategies using fuzzy (Curatolo *et al*., 1996), adaptive (Haddad, Hayakawa & Bailey, 2003) and predictive (Nunes *et al.,* 2007; Ionescu *et al.,* 2008) control algorithms have been developed and applied in clinical trials.

For many control techniques, compartmental models are used to represent the drug distribution in the body for patients undergoing anesthesia. SISO patient models for control of most anesthetic drugs already exist in the literature (O'Hara, Bogen & Noordergraaf, 1992). General anesthesia consists of loss of consciousness through the action of anesthetics, but also inhibition of pain through the action of analgesics. Therefore a MISO model is required for improved control performances. The anesthetic drug used in this study is Propofol, while the analgesic drug is Remifentanil. These two drugs are the inputs of the model, and the output is the Bispectral Index (BIS), a measure for brain activity.

The clinical data used for model development are presented in the next section. The structure of the MISO model is given in section 3 and the identification results are discussed in section 4. The conclusions of this study are summarized in a final section and some future steps are suggested.

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2 CLINICAL DATA

The Propofol and Remifentanil dynamics with respect to the Bispectral Index are taken from real-life clinical tests in patients during ICU at Ghent University Hospital. For model development and validation, data from 9 patients in open loop control are used. The drugs are administered in open loop using a TCI (Target-Controlled Infusion) device called Rugloop (Struys, De Smet & Versichelen, 2003). Briefly, the anesthesiologist sets the desired target concentration . The system, based on a mathematical model, calculates the infusion rates required to achieve and maintain this target concentration and applies the drug accordingly.

The biometric values of the patients used for this study were: 63±9 years, 172±14 cm, 91±23 kg, all male. All patients have undergone cardiac surgery prior to ICU.

3 MODEL DEVELOPMENT

The block diagram of the MISO model is depicted in Fig.1. It consists of two individual pharmacokinetic and pharmacodynamic models: for Propofol (Schnider *et al.,* 1998; Minto *et al*., 1997) and Remifentanil (Minto *et al*., 1997), respectively, and a nonlinear interaction model describing the drugs synergistic effect on BIS.

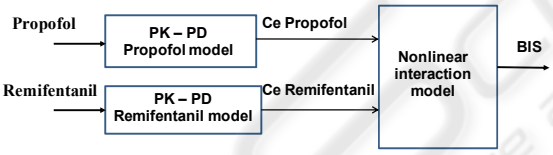

Figure 1: Block diagram of the MISO model.

The two individual PK-PD models are commonly used in the TCI devices and have the same structure: three compartments for pharmacokinetics and one effect-site compartment for pharmacodynamics. A non-linear relation between the Bispectral index and the effect of the two drugs is used (Minto *et al*., 2000).

3.1 Propofol and Remifentanil PK-PD Models

The individual PK-PD models for Propofol (Schnider *et al*., 1998) and Remifentanil (Minto *et al.* 1997) are depicted in Fig. 2.

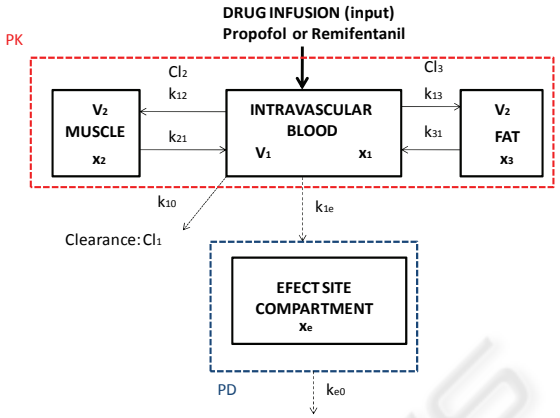

Figure 2: Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model.

The PK model predicts the blood concentration profile of the drug after infusion. The PD model describes the relation between the blood concentration and the corresponding clinical effect. The Propofol and Remifentanil PK-PD mathematical models, the rates of drug metabolism or elimination, the rates of drug transfer between different compartments, and volumes of distribution are taken from (Schnider *et al*., 1998; Minto *et al.* 1997).

The PK models are expressed by the following equations:

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

where x_1 [mg] denotes the amount of drug in the central compartment (blood). 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 remainder of the drug in the body is assumed to reside in two peripheral compartments: one identified as muscle tissue and the other one identified as fat mass. The masses of drug in these compartments are denoted by x_2 and x_3, respectively. The constants k_{ji} for j≠i, denote the transfer rate of drug from the j^{th} to the i^{th} compartment. The constant k_{10} is the rate constant for the processes that irreversibly remove drug from the central and peripheral compartments, and $u(t)$ [mg/s] is the infusion rate of the anesthetic drug

(Propofol or Remifentanil) into the central compartment (blood).

An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The effect compartment receives drug from the central compartment by a first-order process. The input to the effect site compartment is expressed by a first-order rate constant, k_{1e}. The output is also expressed by a first-order rate constant, k_{e0}. This effect site compartment is represented by the following equation:

$$\dot{x}_e(t) = -k_{e0} \cdot x_e(t) + k_{1e} \cdot C_p(t) \quad (2)$$

where $k_{e0} = 0.456[\min^{-1}], k_{1e} = 0.456[\min^{-1}]$ and x_e is the amount of drug in the *effect compartment.*

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:

$$\dot{C}_e(t) = k_{e0} \cdot (C_p(t) - C_e(t)) \quad (3)$$

with *Ce* called the *effect-site compartment concentration*.

3.2 Nonlinear Interaction Model

The interaction model which relates BIS to the effect concentrations of Propofol and Remifentanil was developed based on the response-surface methodology. The latter is a statistical methodology for estimating and interpreting the response of a variable dependent on multiple inputs (Schnider *et al.* 1998).

The combination of two drugs can be either additive, either synergistic (or supra-additive), either infra-additive (greater amounts of both drugs are needed to produce the drug effect when administered together). Propofol and Remifentanil have a supra-additive interaction.

The effects of individual drugs are modeled by relating BIS to drug effect concentration C_e using a Sigmoid model:

$$BIS(t) = E_0 - E_{\max} \cdot \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + C_{50}^{\gamma}} \quad (4)$$

To obtain the interaction model, the concentrations were normalized to their respective potencies $C_{50,\mathrm{Pr}op}$ (Propofol effect concentration at half of the maximum effect) and $C_{50,\mathrm{Re}m}$ (Remifentanil effect concentration at half of the maximum effect).

$$U_{\mathrm{Pr}op}(t) = \frac{C_{e\mathrm{Pr}op}(t)}{C_{50,\mathrm{Pr}op}}; \; U_{\mathrm{Re}m}(t) = \frac{C_{e\mathrm{Re}m}(t)}{C_{50,\mathrm{Re}m}} \quad (5)$$

The ratio of the interacting drugs can be expressed by:

$$\theta(t) = \frac{U_{\mathrm{Pr}op}(t)}{U_{\mathrm{Re}m}(t) + U_{\mathrm{Pr}op}(t)} \quad (6)$$

where: θ is the concentration ratio of the new combined drug and ranges from 0 (Remifentanil only) to 1 (Propofol only). The concentration-response relation of the two drugs can be described as:

$$BIS(t) = E_0 - E_{\max}(\theta) \cdot \frac{\left(\frac{U_{\mathrm{Pr}op}(t) + U_{\mathrm{Re}m}(t)}{U_{50}(\theta)}\right)^{\gamma(\theta)}}{1 + \left(\frac{U_{\mathrm{Pr}op}(t) + U_{\mathrm{Re}m}(t)}{U_{50}(\theta)}\right)^{\gamma(\theta)}} \quad (7)$$

where: $U_{\mathrm{Pr}op}(t) + U_{\mathrm{Re}m}(t)$ is the new 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.

According to (Minto *et al.*, 2009), $E_{max}(\theta)$ is constant and $U_{50}(\theta)$ can be expressed by a quadratic polynomial:

$$U_{50}(\theta) = 1 - \beta \cdot \theta + \beta \cdot \theta^2 \quad (8)$$

The unknown coefficient β can be estimated from the data. Since the interaction between the two drugs is supra-additive, 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.

4 PARAMETER IDENTIFICATION

The models are fitted to the data collected from the 9 patients during the maintenance phase of anesthesia. The interaction model parameters ($\beta, \gamma, C_{50,\mathrm{Pr}op}, C_{50,\mathrm{Re}m}$) are estimated for each patient, using the nonlinear least squares method, based on a large-scale algorithm. Before being used

in the identification procedure, the BIS signal is pre-filtered with a 3rd order low-pass Butterworth filter.

For some patients, BIS is strongly affected by disturbances, such as leg movement or coughing. For example, these disturbances appear for patient 1 as depicted in Fig. 3. Several peaks can be observed in the BIS signal, which had to be removed (their effect is not related to Propofol or Remifentanil variations).

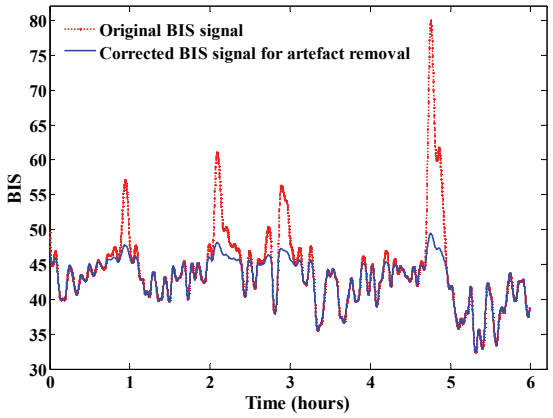

Figure 3: BIS signal for patient 1; original (--) and filtered signal (-).

By eliminating the artefacts due to coughing or leg movement, the optimisation procedure converged to the global optimum. However, the patient model is varying during ICU (intra-patient variability). Therefore, the total measurement (6 hours) of the input-output data has been divided in windows (w) with various lengths. The identification was performed on data from each window. Three cases were considered:

1. Identification with 8 windows ($w = 8$)
2. Identification with 25 windows ($w = 25$)
3. Identification with 50 windows ($w = 50$).

For model validation, the mean absolute error (MAE) was evaluated as follows:

$$MAE = \frac{1}{n}\sum_{k=1}^{n}|(Bis_{Est} - Bis_{\mathrm{Re}al})| \quad (9)$$

Table 1 presents the MAE obtained for each patient, considering the three cases. It can be observed that the best model prediction is obtained in case of patient 9, while the worst case scenario corresponds to patient 4. Propofol and Remifentanil signals used for identification and the results obtained for these two patients are presented in Fig. 4. and Fig. 5, respectively.

Table 1: Mean absolute error (MAE) for each patient.

Patient \ MAE	w=8	w=25	w=50
1	2.06	1.41	1.18
2	3.13	2.12	1.93
3	2.68	1.78	1.46
4	4.31	2.80	2.17
5	2.01	1.62	1.23
6	1.99	1.83	1.51
7	3.28	2.11	1.61
8	1.86	1.23	0.88
9	1.56	1.08	0.80

The results confirmed the assumption that by using multiple windows in the identification method, the performance is increased. However, using 50 windows means that the parameters are estimated every 8 minutes and this is not realistic, because the time constant of the patient is bigger. A trade-off between the prediction model performance and the number of windows should be considered. In this study, the time elapsed during the identification procedure to converge to the optimal results is about 1.57 seconds. It is then applicable in an on-line estimation procedure, since the sample time is 10 seconds.

Although the highest MAE was obtained in case of patient 4, one can observe that the estimated BIS follows the real BIS signal. Therefore, the model performance is acceptable.

The interaction model parameters (7) estimated with the nonlinear least squares algorithm for the best and the worst case scenario are presented in Table 2. Values higher than zero were obtained for β in case of each patient, which means that $U_{50}(\theta)$ is lower than 1 for any value of θ. Therefore, the effect of the two drugs combined is higher than the sum of their separate effect at the same doses (10), so the Propofol and Remifentanil supra-additive interaction was confirmed.

$$\frac{U_{\mathrm{Pr}op} + U_{\mathrm{Re}m}}{U_{50}(\theta)} > U_{\mathrm{Pr}op} + U_{\mathrm{Re}m} \quad (10)$$

Each patient has a different sensitivity to the drug, therefore different values of $C_{50,\mathrm{Pr}op}$ and $C_{50,\mathrm{Re}m}$ were obtained (inter-patient variability).

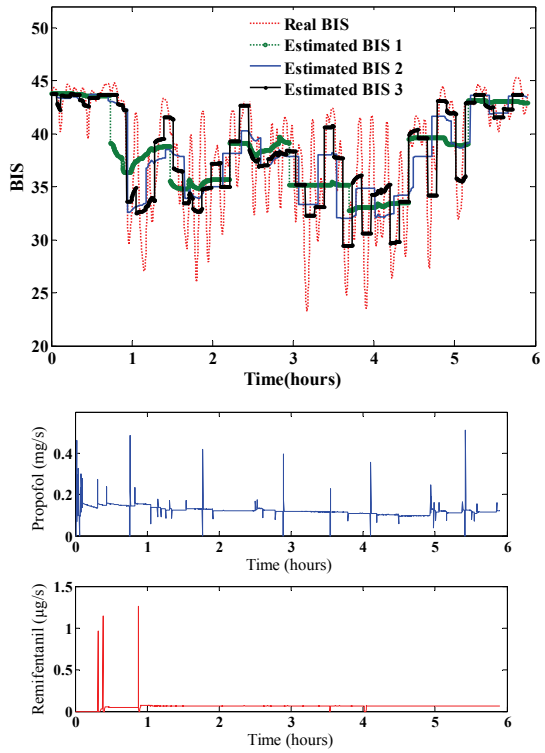

Figure 4: The worst case scenario (Patient 4) - Real BIS versus modeled BIS, case 1 for *w*=8, case 2 for *w*=25 and case 3 for *w*=50 (top); Propofol and Remifentanil signals used for identification (bottom).

Table 2: Estimated parameters for the best and the worst case scenario.

Parameter / Patient	Case	γ	β	$C_{50,Prop}$ (µg/ml)	$C_{50,Rem}$ (ng/ml)
4	1	4.5 ± 0.5	0.6 ± 0.3	8.1 ± 1.9	44.7 ± 4.7
	2	4.3 ± 0.5	0.5 ± 0.3	7.7 ± 2.2	45.2 ± 5.3
	3	4.5 ± 0.5	0.5 ± 0.3	7.5 ± 2.5	45.1 ± 5.0
9	1	4.3 ± 0.4	0.4 ± 0.2	4.6 ± 0.3	44.9 ± 4.9
	2	3.9 ± 0.5	0.4 ± 0.2	6.9 ± 2.8	44.9 ± 4.8
	3	4.1 ± 0.4	0.4 ± 0.3	5.9 ± 1.9	45.1 ± 4.9

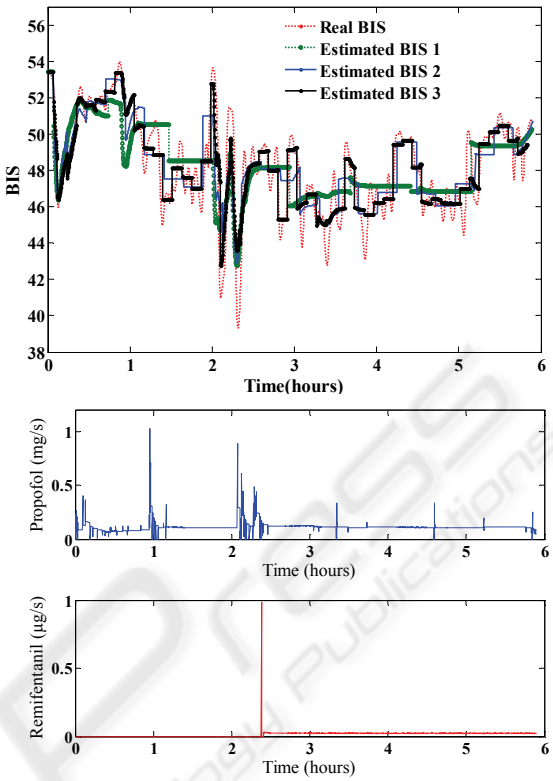

Figure 5: The best case scenario (Patient 9) - Real BIS versus modeled BIS, case 1 for *w*=8, case 2 for *w*=25, case 3 for *w*=50 (top); Propofol and Remifentanil signals used for identification (bottom).

5 CONCLUSIONS

In this paper, a MISO patient model has been developed for Propofol and Remifentanil management during ICU anesthesia. The interaction model parameters were identified using a nonlinear least squares method. The total measurement of the input-output data has been divided in several windows (*w*) and the identification was performed on each window, considering three cases: *w=8*, *w=25* and *w=50*. A trade-off between the prediction model performance and the number of windows has been considered. Therefore, an identification procedure with *w=25* proved to be a reasonable choice.

The results obtained are well correlated with the data from the patients, providing reliable prediction for Bispectral Index evolution as a result of manipulated variables Propofol and Remifentanil. The final purpose is to use the synergistic effects of these two drugs in a model-based predictive control

of anesthesia during ICU, administering both Propofol and Remifentanil.

Even though the presented model has a good accuracy, an online identification needs to be performed and several investigations must be carried out before applying it in real-life. It will be possible to exploit afterwards the benefits of multi-drug anesthesia in an automatic control algorithm.

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