Individualizing propofol dosage: a multivariate linear model approach

Conceição Rocha, Teresa Mendonça & Maria Eduarda Silva

Springer

Springer

ORIGINAL RESEARCH

Individualizing propofol dosage: a multivariate linear model approach

**Conceição Rocha · Teresa Mendonça ·
Maria Eduarda Silva**

Abstract In the last decades *propofol* became established as an intravenous agent for the induction and maintenance of both sedation and general anesthesia procedures. In order to achieve the desired clinical effects appropriate infusion rate strategies must be designed. Moreover, it is important to avoid or minimize associated side effects namely adverse cardiorespiratory effects and delayed recovery. Nowadays, to attain these purposes the continuous *propofol* delivery is usually performed through target-controlled infusion (TCI) systems whose algorithms rely on pharmacokinetic and pharmacodynamic models. This work presents statistical models to estimate both the infusion rate and the *bolus* administration. The modeling strategy relies on multivariate linear models, based on patient characteristics such as age, height, weight and gender along with the desired target concentration. A clinical database collected with a RugLo-opII device on 84 patients undergoing ultrasonographic endoscopy under sedation-analgesia with *propofol* and *remifentanil* is used to estimate the models (training set with 74 cases) and assess their performance (test set with 10 cases). The results obtained in the test set comprising a broad range of characteristics are satisfactory since the models are able to predict *bolus*, infusion rates and the effect-site concentrations comparable to those of TCI. Furthermore, comparisons of the effect-site concentrations for dosages predicted by the proposed Linear model and the Marsh model for the same target concentration is achieved using Schnider model and a factorial design on the factors (patients characteristics). The results indicate that the Linear model predicts a dosage profile that is faster in leading to an effect-site concentration closer to the desired target concentration.

Keywords Model approximation · Estimation parameters · Regression analysis · Error analysis · Linear prediction · Medical applications

1 Introduction

Usually *propofol* infusions are manually-controlled based upon the posology and the clinician experience. Nevertheless, several methods, algorithms and devices have been proposed in order to obtain a reliable prediction of the dose required to attain a desired effect. Hence, nowadays a computer-assisted target controlled infusion (TCI) device is widely used in the continuous administration of *propofol*, in a variety of anesthetic procedures and environments. This device is a delivery pump that administers the *propofol* accordingly to the pharmacokinetic *propofol* model, assuming averaged parameters derived from population samples and infusion control algorithms [1] in order to obtain a predefined target effect concentration.

There are two adult models for *propofol* programmed into commercially available TCI pumps, the Marsh model and the Schnider model. In the first one the pharmacokinetic parameters depend on patient weight and is considered suitable to model the plasma *propofol* concentration. In the Schnider model the pharmacokinetic parameters

C. Rocha (✉) · T. Mendonça
Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal
e-mail: mnrocha@fc.up.pt

C. Rocha · T. Mendonça · M. E. Silva
Center for Research & Development in Mathematics and Applications (CIDMA), Aveiro, Portugal

M. E. Silva
Faculdade de Economia da Universidade do Porto,
Rua Dr. Roberto Frias, 4200-464 Porto, Portugal

depend not only on patient weight but also on his age, height, gender and lean body mass (LBM) [13]. Based in some studies [10], the Schnider model is recommended to be used for TCI and advisory displays [15].

Several research groups [5, 6], have published studies in order to evaluate the accuracy of the TCI system for *propofol* administration in achieving the desired effect concentration. In particular, [17] and [3] evaluated the behavior of TCI for predicting the *propofol* dose infusion rate and both works consider its performance acceptable for clinical purposes. Some studies [12,16] compare the clinical profile of TCI of *propofol* with that of manually-controlled infusions but their comparative effectiveness remains controversial [9].

From clinical experience reported in a large number of published analysis, it turns out that a TCI based system for the administration of *propofol* is highly helpful. Nevertheless, the cost associated with the referred devices alongside with the fact that the delivery algorithm used is not open access, comprise the main restrictions to the wide use of such systems.

Usually the administration of intravenous sedative-hypnotic agents comprehends two steps: an initial *bolus* of drug, *propofol* in this case study, followed by a continuous infusion. However, in many situations the target concentration, *CT*, needs readjustment and when its value must be increased an intermediate bolus of drug is administrated. The purpose of this work is to infer both *boluses* and the subsequent infusion rate from patient characteristics and the desired target concentration using linear models. The models are developed based on a clinical database collected by RugLoopII on patients undergoing ultrasonographic endoscopy under sedation-analgesia with *propofol* and *remifentanil* and rely on patient data (age, height, weight and LBM) and the desired target concentration. The models proposed here present a mean behavior comparable to that of a TCI system and may be considered a step forward to the definition of a simple model for estimating *propofol* individualized dosage based on patient attributes. Moreover, the structure of these models makes them adequate to be used in a model-based closed loop automatic *propofol* administration system.

2 Data

The clinical database [4] used in this study is collected with RugLoopII, a TCI and collection software, which controls the syringe pumps for *propofol* (the hypnotic drug) using pharmacokinetic model of Schnider, and for *remifentanil* (analgesic drug) using pharmakocinetic model of Minto [11]. The data base consists of 84 patients, 56 males and 28 females, undergoing ultrasonographic endoscopy under sedation-analgesia with *propofol* and *remifentanil* and Depth of

Anesthesia, DoA, quantified by BIS (A-2000, v3.31 Covidien, USA). The database comprises, for each patient, characteristics such as age, height, weight, gender and LBM which are summarized in Table 1 (CV(%) = standard deviation/mean × 100). The database also provides recordings of several variables describing the sedation-analgesia process. In particular, total infused volume and targeted concentration for *propofol* and *remifentanil* recorded each 5 sec are available. The infusion *propofol* concentration was 10 mg ml^{-1} for all the 84 cases.

Several characteristics of the *propofol/remifentanil* administration are worth noting. The targeted *propofol* concentrations, *CT*, are in the range [0.5;4.7] μg ml^{-1} with an average of 2.2 μg ml^{-1} and a standard deviation of 0.65 μg ml^{-1}. However, there are only 27 target concentrations to which we will refer as 27 clusters. In 46 of the 84 cases the targeted *propofol* concentrations were readjusted during the clinical procedure up to 11 times, as described in Table 2. This means that these patients were administrated several *boluses*. For the 38 patients who did not experience *CT* readjustment the most frequently targeted *propofol* concentrations were 1.5, 2.0 and 3.0 μg ml^{-1}, respectively 11, 14 and 8 times. Note that the *boluses* range between 0.446 ml and 5.48 ml and are administrated as a series of shots over a time span of several minutes, hereafter denoted by $\Delta t_{bolus} \in [0.17, 1.08]$.The duration of *propofol* administration varies between 16 and 116 min with an average of 56 min. Seven of the eighty four patients did not receive *remifentanil* and for the remaining seventy seven patients, the targeted *remifentanil* concentrations were in the range [0.5;3.5] ng ml^{-1}.

3 Methods

In a clinical procedure a *bolus* is administrated in a short period of time, with the purpose of rapidly achieving a

Table 1 Summary statistics of patient characteristics

Patient data	Group	Min	Max	Mean	CV (%)
Age (years)	Total	19	83	60.6	22.2
	M	35	82	61.2	20.4
	F	19	83	59.5	25.8
Height (cm)	Total	145	192	166.9	5.7
	M	151	192	171.4	4.5
	F	145	165	158.0	3.4
Weight (Kg)	Total	41	119	69.9	20.6
	M	53	119	72.5	19.7
	F	41	90	64.7	20.5
LBM [7] (Kg)	Total	32.7	76.1	51.89	17.1
	M	44.3	76.1	56.21	13.0
	F	32.7	50.4	43.26	9.5

Table 2 Distribution of the number of different targeted *propofol* concentrations (n *CT*) per patient

n *CT*	1	2	3	4	5	6	7	8	9	10	11
n patients	38	9	6	10	8	1	5	0	4	1	2

physiological state. The *bolus of propofol* that each patient receives depends not only on the targeted *propofol* concentration and the patient own characteristics but also on his previous state. For each case or individual there is one measure, the initial *bolus* and there may be more measures for those individuals for whom the target concentration needed readjustment. Although there are repeated measures for some individuals, these are not correlated. Thus, the dataset for the *bolus* may be looked upon as a cross sectional dataset and the objective is to express the *bolus Y* as a linear (in the parameters) function of the patient characteristics represented by the linear regression equation:

$$Y = X\beta + \epsilon \tag{1}$$

where the design matrix X contains:

- information on the patient—the patient age in years, *Age*; the patient weight in kilograms, *Weight*; the patient height in centimeters, *Height*; the lean body mass in kilograms, *LBM*;
- target *propofol* concentration, *CT*;
- information on the previous state of the patient:

  – the required increment on target *propofol* concentration, ΔCT (> 0), at the beginning $\Delta CT = CT$;
  – whether it is the first *bolus*, coded by a dummy variable

$$Dum = \begin{cases} 1, & \text{if is an initial } bolus \\ 0, & \text{otherwise} \end{cases}$$

- interaction terms

and ϵ is a vector of zero mean random variables with diagonal covariance matrix with entries σ_i^2 and represents the unobserved random errors.

Now, concerning the continuous infusion rate, the data structure is quite different: for each patient the infusion rate (computed from the total infused volume) and target concentration for *propofol* are available each 5 sec. Obviously, the infusion rate is correlated over time and thus this data set constitutes a longitudinal dataset. Longitudinal datasets in which the behavior of entities are observed across time [2] have both the cross-sectional and time series dimensions and allow the study of individual dynamics as well as the time ordering of events. There are several models available on the literature for longitudinal data and in this work we consider random effects population models that explicitly contain a time-constant unobserved effect, [18]. Let y_{it} be the infusion

rate of the ith patient at time t and let X_{it} be the design matrix that contains, for each t, not only variables pertaining information on the patient and target *propofol* concentration but also information concerning the time elapsed since the beginning of *propofol* administration, t, in seconds and the time elapsed since the last change in the target concentration CT, $t_{\Delta CT}$ plus interactions. Then

$$y_{it} = \alpha + X_{it}\beta + v_{it} \tag{2}$$

where $v_{it} = v_i + \epsilon_{it}$ are the cluster-specific intercepts. For each t, v_{it} is the sum of the unobserved effect, v_i, with an idiosyncratic error, ϵ_{it}, which describes variations over individuals and time.

To assess the performance of the models the dataset is randomly divided into a training set with 74 cases and a test set with the remaining 10 cases. The models are calibrated using the training set and residual analysis are carried out to study the quality of the fit of the models. To assess the predictive performance of the models root mean squared errors and mean absolute error are computed for the 10 cases in the test set.

4 Results

4.1 Model for the *boluses*

A *propofol bolus* in milliliters, *bolus*, is obtained from the model described by the following equation,
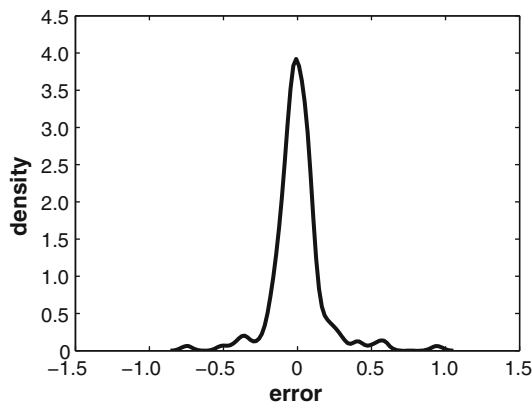
$$\begin{aligned} bolus = &\beta_0 + \beta_1 Weight + \beta_2 Height + \beta_3 LBM + \beta_4 CT \\ &+ \beta_5 \Delta CT + \beta_6 Age \cdot \Delta CT + \beta_7 Dum \cdot CT. \end{aligned} \tag{3}$$

Estimates for the coefficients of the model using the training set by ordinary least squares (OLS) allowing for heteroscedasticity [18] via White estimates of standard errors are given in Table 3. The estimated model presents a coefficient of determination $R^2 = 0.98$, i.e, 98 % of the variation of *propofol bolus* around its mean is explained by the variables. To further assess the quality of the fit the probability density of the error, estimated using a normal kernel density estimation with 100 equally spaced points (MATLAB 7.10.0(R2010a)) is plotted in Fig. 1. The errors are symmetricaly distributed around the value zero. Moreover, there is no correlation between the errors and the *boluses* indicating a valid model.

To interpret the model we start by analyzing the sign of the coefficients associated to the information on the patient: the coefficients β_1 and β_2 associated with weight and height, respectively, are positive indicating that heavier and taller patients need more *bolus*; the coefficients β_3 and β_6 associated with LBM and age, respectively, are negative indicating that higher LBM as well as older age lead to decreased *bolus*.

Table 3 Estimated coefficients

Variable	Coefficient	p value
1	−2.091	0.0010
Weight	0.01936	0.0000
Height	0.01441	0.0052
LBM	−0.03152	0.0000
CT	0.1664	0.0000
ΔCT	2.140	0.0000
$Age \cdot \Delta CT$	−0.005657	0.0000
$Dum \cdot CT$	−0.3407	0.0007

Fig. 2 Mean infusion rate for *propofol bolus* from the test set—case 9

Fig. 1 Estimated density function of the error on *bolus* estimation based on (3)

Analyzing the coefficients β_4, β_5, β_6 and β_7 it is easy to conclude that the *bolus* increases with the target *propofol* concentration, *CT*. Moreover, that increase is larger for younger age patients.

Model (3) is now applied to predict the *bolus* for the test set. In this set there are 10 cases corresponding to 10 initial and 20 intermediate *bolus*. The observed errors range from −0.165 to 0.191 ml with a mean of −0.007 and a standard deviation of 0.088 ml, corresponding to absolute percentage errors between 0.3 and 24 % with a mean of 6 %. The error analysis is consistent with a good performance of the model. To further illustrate this finding, Fig. 2 represents the *bolus* as a mean infusion rate over the observed Δt_{bolus} for case 9 which is particularly interesting since there are multiple target concentration changes.

4.2 Model for the infusion rate of *propofol*

Now, the objective is to model the infusion rate during the continuous drug administration, IR_t.

The training data set constitutes a longitudinal (or panel) data set and the model under consideration is of the form (2). The model is estimated by OLS assuming that neither the temporal nor the individual effects are statistically significant, Pooled OLS, allowing for heteroscedasticity between clusters which are identified by the target concentration [18]. Residual analysis indicates the absence of autocorrelation and an approximately symmetrical distribution around zero supporting an adequate model.

The estimated model is described by the following equation with coefficients given by Table 4:

$$
\begin{aligned}
IR_t =& (\beta_1 + \beta_2 Age + \beta_3 Weight + \beta_4 Weight^2 \\
& + \beta_5 Height \cdot Weight + \beta_6 LBM \cdot Weight) \cdot CT_t \\
& + (\beta_7 Age + \beta_8 Height + \beta_9 CT_t + \beta_{10} CT_t \cdot t \\
& + \beta_{11} CT_t \cdot t^2) \cdot t + (\beta_{12} Age + \beta_{13} CT_t \\
& + \beta_{14} Height \cdot t_{\Delta CT} + \beta_{15} Age \cdot t_{\Delta CT}) \cdot t_{\Delta CT},
\end{aligned}
\tag{4}
$$

where IR_t is the infusion rate of *propofol* in ml hr^{-1} at time t.

Table 4 Estimated coefficients

Variable	Coefficient	p value
CT	19.289	0.000
$Age \cdot CT$	−0.078958	0.000
$Weight \cdot CT$	−0.16257	0.000
$Weight^2 \cdot CT$	0.0021733	0.000
$Height \cdot Weight \cdot CT$	0.0022762	0.000
$LBM \cdot Weight \cdot CT$	−0.0053415	0.000
$Age \cdot t$	0.0000463	0.000
$Height \cdot t$	−0.0000224	0.000
$CT \cdot t$	−0.0038381	0.000
$CT \cdot t^2$	1.01E−06	0.000
$CT \cdot t^3$	−8.28E−11	0.000
$Age \cdot t_{\Delta CT}$	0.0000183	0.000
$CT \cdot t_{\Delta CT}$	−0.0006188	0.000
$Height \cdot t^2_{\Delta CT}$	3.44E−09	0.003
$Age \cdot t^2_{\Delta CT}$	−8.23E−09	0.005

Fig. 3 The predicted and the infused rates (*left*), and the corresponding effect-site concentration (*right*) for a case with a single target *propofol* concentration, *CT*—case 4
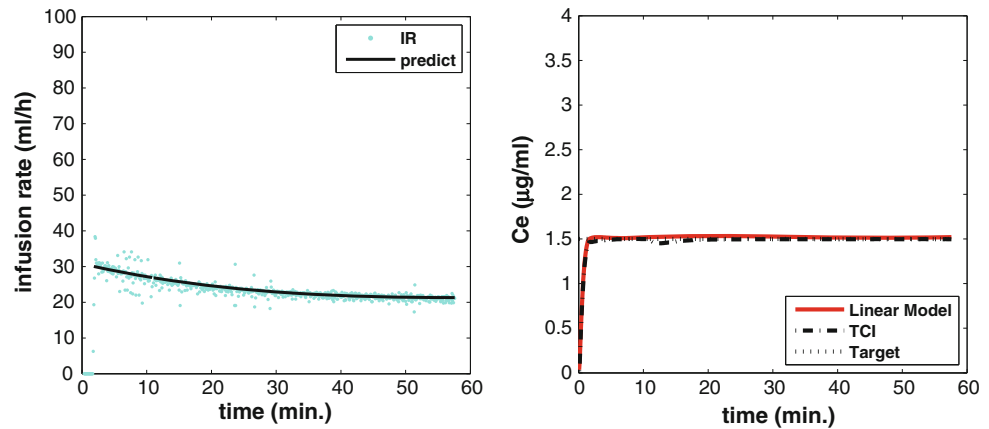
Fig. 4 The predicted and the infused rates (*left*), and the corresponding effect-site concentration (*right*) for a case with two values for target *propofol* concentration, *CT*—case 3
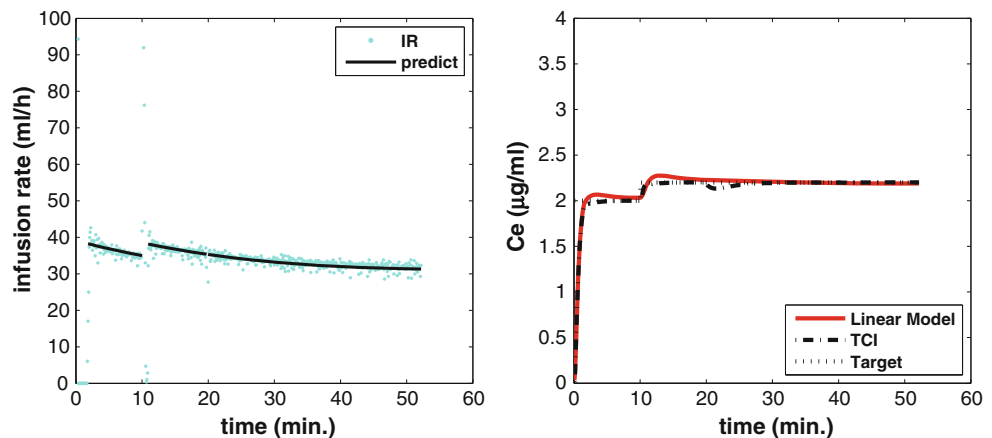
Model (4) may be rewritten as (5) with $t_{\Delta CT} = t - k$, where k represents the instant of target concentration *CT* readjustment.

$$
\begin{aligned}
IR_t = &\left[\left(\beta_1 + \beta_2 Age + \beta_3 Weight + \beta_4 Weight^2\right.\right. \\
&\left.+ \beta_5 Height \cdot Weight + \beta_6 LBM \cdot ..Weight\right) \cdot CT_t\right] \\
&+ \left[(\beta_{14} Height + \beta_{15} Age)k^2 - (\beta_{12} Age + \beta_{13} CT_t)k\right] \\
&+ \left[(\beta_7 Age + \beta_8 Height + \beta_9 CT_t + \beta_{12} Age + \beta_{13} CT_t\right. \\
&- 2k(\beta_{14} Height.. + \beta_{15} Age) + (\beta_{10} CT_t + \beta_{14} Height \\
&\left.+ \beta_{15} Age)t + \beta_{11} CT_t \cdot t^2)t\right].
\end{aligned}
\tag{5}
$$

It is now easy to see three main components of the infusion rate at time t (delimited by [ ]). The first, which may be called the baseline depends on the patient characteristics and the instant target concentration; the second results from a readjustment of target concentration and alters the baseline component; finally the third models a time dependent dynamic component of IR_t.

From the analysis of the coefficients and based on the range of the variables, results the following model interpretation:

– at the beginning and for a null target concentration the infusion rate is zero;
– the baseline increases with the target *propofol* concentration and the increase is larger for heavier, taller and younger patients as well as patients with lower LBM;
– the time dependent dynamic component is nonlinear but exhibits a decreasing trend; however, if the clinical intervention is long and depending on patient characteristics, the infusion rate may present an increasing trend for several minutes, reverting to the decreasing trend afterwards;
– as before, higher target concentration, taller stature and young age contribute to increase the initial velocity of the infusion rate decrease.

To assess its predictive performance model (4) is applied to the test set. The root mean squared error, *RMSE*, and the mean absolute error are computed for the 10 cases. The *RMSE* varies between 1.11 and 6.76 ml hr^{-1} and the absolute percentage error between 3 and 9 %.

To further illustrate the good performance of the models (3) and (4), the effect-site concentrations induced by *propofol* administered by these models and by TCI are computed

Fig. 5 The predicted and the infused rates (*left*), and the corresponding effect-site concentration (*right*) for a case with a single target *propofol* concentration, C_T, corresponding to a cluster not included in the training set—case 7
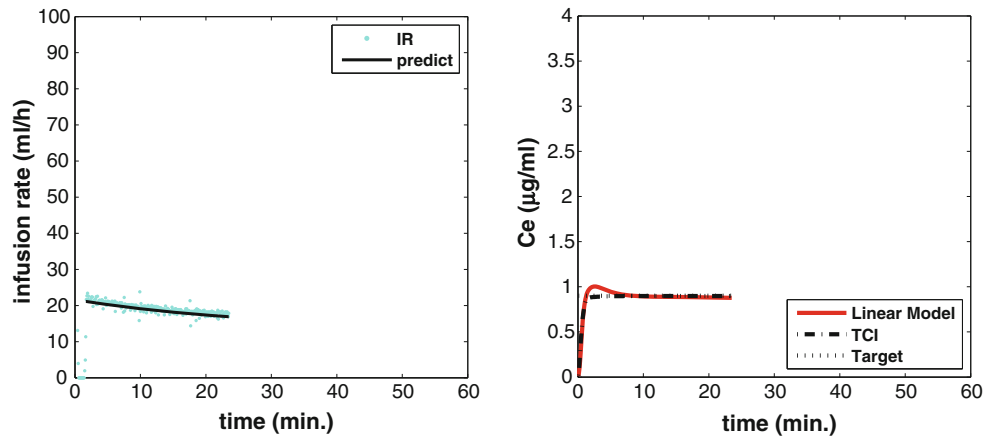
Fig. 6 The predicted and the infused rates (*left*), and the corresponding effect-site concentration (*right*) for a case with several readjustments of the target *propofol* concentration, C_T—case 9 Fig. 2
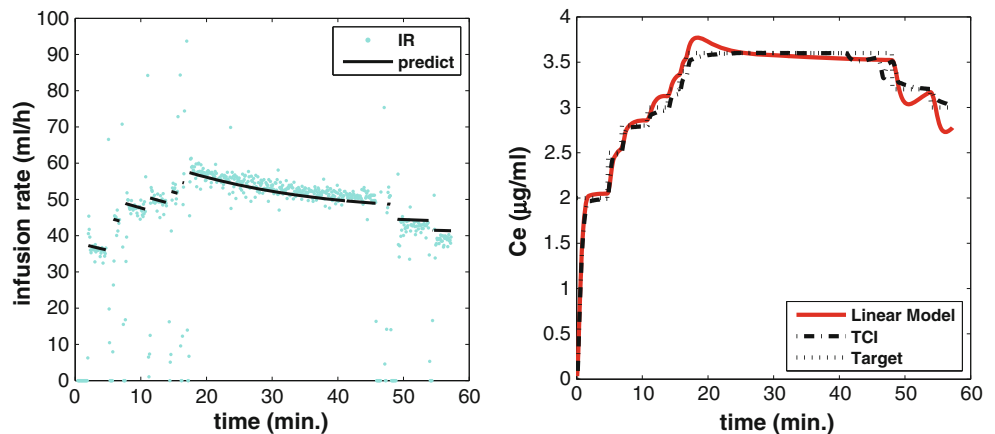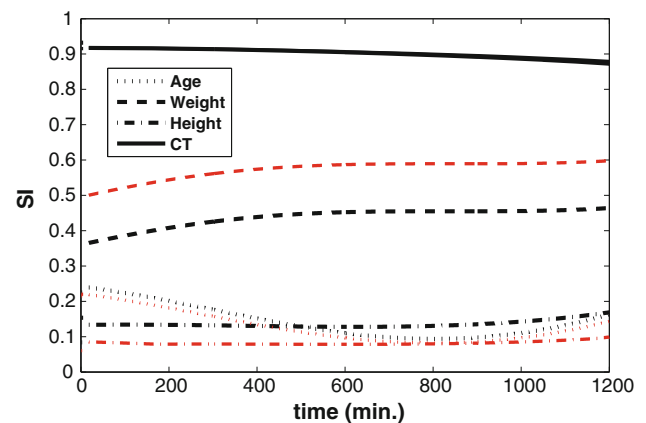

Table 5 Factor range use in the sensitivity analysis

Factor	Min	Max
Age (years)	19	90
Height (cm)	140	195
Weight (Kg)	40	120
CT (μg ml^{-1})	0.5	6.0

Fig. 7 Time evolution of the Sensitivity Index for the Linear model. More dense and *dark line* for male and less *dense line* for female

adopting exactly the same procedure. Figures 4 , 5 , 6 present the predicted and the infused rates (left), and the corresponding effect-site concentrations (right), for four cases from the test set. Figure 5 which represents the predicted and the infused rates (left), and the corresponding effect-site concentration (right) for case 7 deserves special attention. In fact, although the target *propofol* concentration, C_T, for case 7 corresponds to a cluster not included in the training set, the predict performance of the model is comparable with the remaining cases on the test set (*RMSE* = 5.38, *MAPE* = 7 %).

5 Sensitivity analysis

To determine which factors contribute most to output variability, a sensitivity analysis is conducted using the sensitive index which provides an indication of parameter and model variability [8].

The sensitivity index, *SI* is defined as the relative difference in the output when one input parameter is varied from its minimum to its maximum value [8]. Thus, in the case under study here, *SI* is defined as
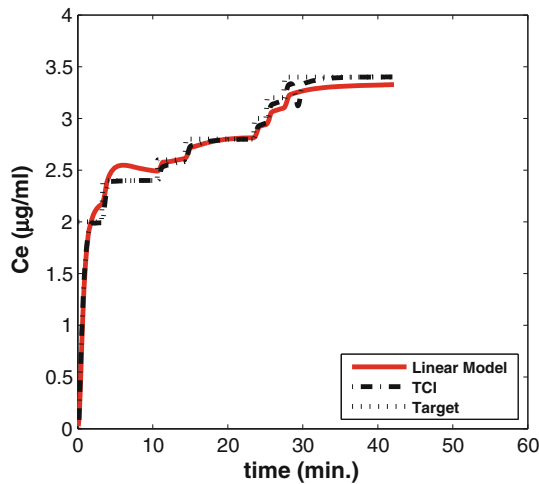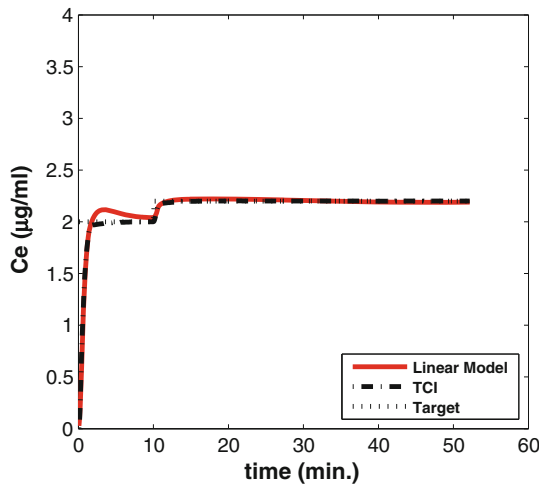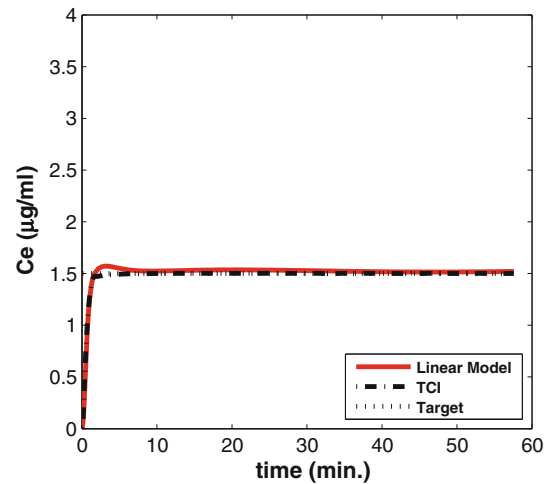
Fig. 8 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a female with 76 years old, weighing 54 kg, 145 cm height and corresponding LBM of 37 kg
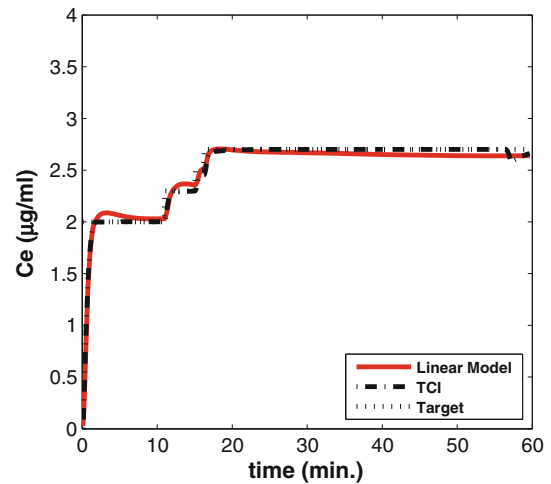
Fig. 10 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 61 years old, weighing 74 kg, 182 cm height and corresponding LBM of 60 kg

Fig. 9 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a female with 69 years old, weighing 59 kg, 156 cm height and corresponding LBM of 42 kg

Fig. 11 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 57 years old, weighing 65 kg, 174 cm height and corresponding LBM of 54 kg

$$SI = \frac{IR_{max} - IR_{min}}{IR_{max}}, \tag{6}$$

where IR_{max} and IR_{min} correspond to, respectively, the maximum and the minimum of the infusion rate resulting from varying the factor over its entire range. The ranges for factors Age, Height and Weight considered in this section and reported in Table 5 result from the ranges observed in the data set and reported in Table 1. The range for CT reported in Table 5 is wider than that reported in Table 1 for the data set but has been observed in recent surgeries and is clinically accepted.

Figure 7 represents the time evolution of *SI* for each factor, age, height, weight and CT by gender. The results indicate that the factor that contributes most to the infusion rate variability is the target *propofol* concentration, CT with a similar *SI* values for men and women. Among the remaining three factors, age, weight and height, weight is the one that presents the highest sensitivity index and also the one which differs most between the genders. It is noteworthy that *SI* for the factor weight is about 10 % larger for women. The results also indicate that *SI* for the factor age decreases in the first hour and for the other factors is approximately constant over time.

Thus, these results indicate that the infusion rate is sensitive essentially to the target concentration, CT and the weight of the patient.

The dosage profile here proposed for the PL model is described by **Algorithm 1**.

Algorithm 1 *Propofol* Linear model- PL model

if $t = 0$ (the beginning of the anesthetic procedure) **then**

$$IR = \begin{cases} 144*\text{bolus from (3)} & \text{, for } 0 \leq t \leq 25 \text{ sec.} \\ 0 & \text{, for } 25 < t \leq 95 \text{ sec.} \\ \text{IR from (4)} & \text{, for } 95 < t \leq t_f^1 \text{ sec.} \end{cases}$$

else

    if a higher CT is need at $t = t_1$ **then**

$$IR = \begin{cases} 720*\text{bolus from (3)}/7 & \text{, for } t_1 \leq t \leq t_1 + 35 \text{ sec.} \\ 0 & \text{, for } t_1 + 35 < t \leq t_1 + 50 \text{ sec.} \\ \text{IR from (4)} & \text{, for } t_1 + 50 < t \leq t_f \text{ sec.} \end{cases}$$

    end if

    if CT needs decrease at $t = t_2$: **then**

$$IR = \begin{cases} 0 & \text{, for } t_2 \leq t \leq t_2 + 5n \text{ sec.} \\ \text{IR from (4)} & \text{, for } t_2 + 5n < t \leq t_f \text{ sec.} \end{cases}$$

    end if

end if

[1] Note that the proposed *propofol* infusion rate model (4) was developed for clinical interventions no longer than 2 hours. For clinical procedures longer than 2 hours, typically surgical procedures with general anesthesia, an extension of this model is under development.

---

6 The *propofol* linear model: PL model

In this section the Linear model for *propofol* dosage is proposed. In order to complete the profile dosage and fully specify the model, a procedure for *propofol* administration both to increase and decrease CT is needed. To increase CT, the rate at which the *boluses* are administrated as well as the moment at which the continuous infusion administration must start are defined based on mean values of the database. Thus,

- an interval of 25 and 35 sec is adopted for the initial and subsequent, respectively, *boluses* administration;
- the continuous infusion administration starts 95 sec after the initialization of *propofol* administration (anesthetic procedure) and 50 sec after an increase in CT.

On the other hand, to decrease CT it is necessary to cease *propofol* administration during a time interval that depends on the previous CT and the new CT. Based on the database information, the number of observations without *propofol* administration, n, may be expressed as a linear function of the logarithm of the ratio between the two target concentrations. Using a simple linear regression the following model is obtained

$$n = [66.219 * \log(\text{previous } CT/\text{new } CT) + 3.479], \quad (7)$$

with [.] denoting the largest whole number contained. This model (7) presents a coefficient of determination $R^2 = 0.94$.

## 7 PL model vs TCI

7.1 PL model vs schnider model

The results obtained so far indicate that the PL model represented by **Algorithm 1**, developed in Sect. 4 is able to predict *bolus* and infusion rates comparable to those of TCI. However, since effect-site concentrations resulting from the dosages are
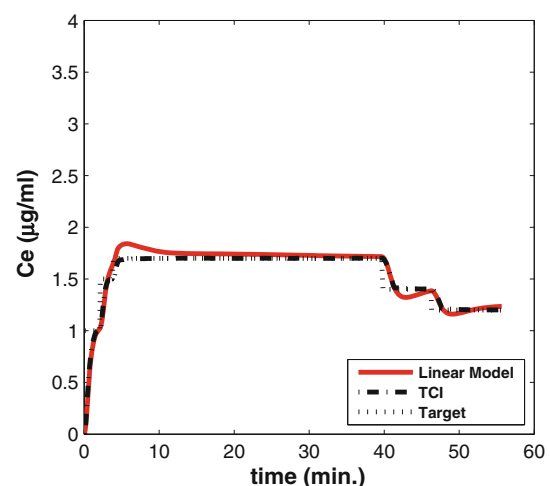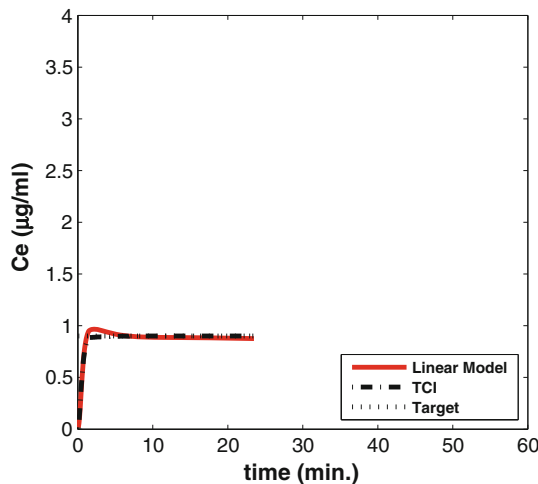
Fig. 12 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 71 years old, weighing 65 kg, 169 cm height and corresponding LBM of 53 kg
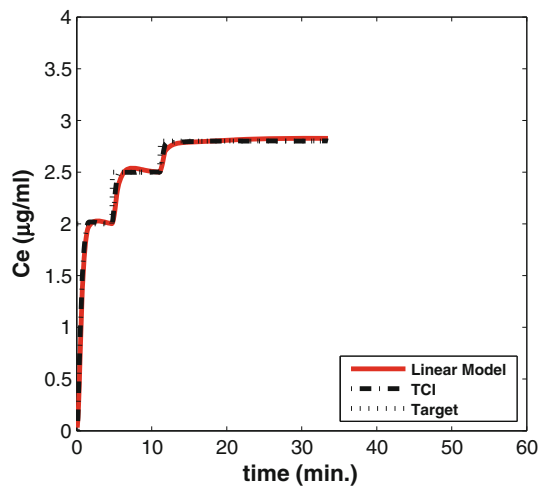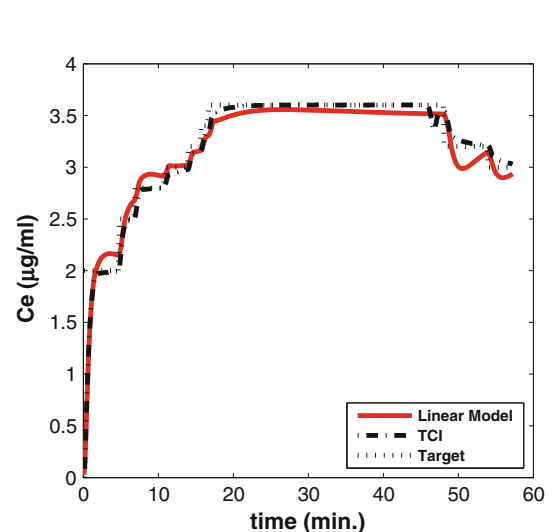
Fig. 13 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 44 years old, weighing 76 kg, 178 cm height and corresponding LBM of 60 kg
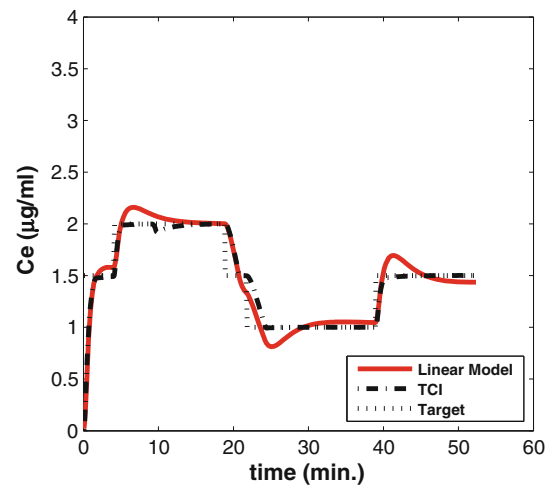
Fig. 15 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 72 years old, weighing 80 kg, 170 cm height and corresponding LBM of 60 kg

Fig. 14 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 56 years old, weighing 102kg, 192 cm height and corresponding LBM of 76 kg

Fig. 16 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 71 years old, weighing 61kg, 172 cm height and corresponding LBM of 51 kg

important, the purpose of this section is to compare the effect-site concentrations resulting from the Linear model and the Schnider model. A design of experiments to perform this comparison cannot be made with the dosage obtained from the Schnider model since the authors do not have access to a TCI device which implements this model. For this reason the comparison between the two models will be conducted on the 10 cases of the test set.

Based on all the ten graphics represented in Figs. 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 of the time evolution of the two effect-site concentrations, corresponding to the dosage profiles of PL model and TCI system, along with the target concentration programmed by the clinician we may say that:

- the PL model has a performance very similar to the performance of the TCI programmed with the Schnider model;
- small differences between the two models are detected for a short time after some target concentration, CT, changes.

7.2 PL model vs marsh model

In this section and to compare the effect-site concentrations resulting from the PL model and the Marsh model, a TCI
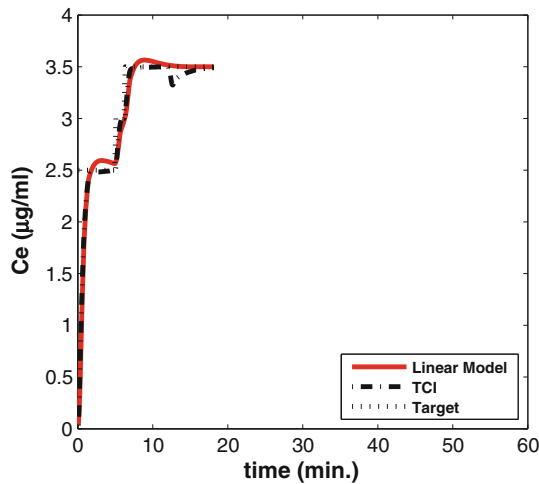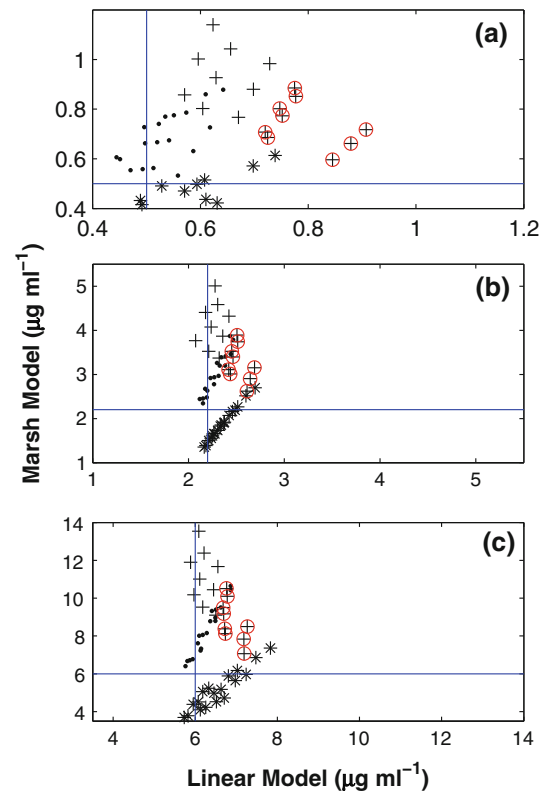
Fig. 17 Time evolution of the two effect-site concentrations corresponding to the dosage profiles of PL model and TCI system along with the target concentration programmed for a male with 60 years old, weighing 76 kg, 169 cm height and corresponding LBM of 58 kg
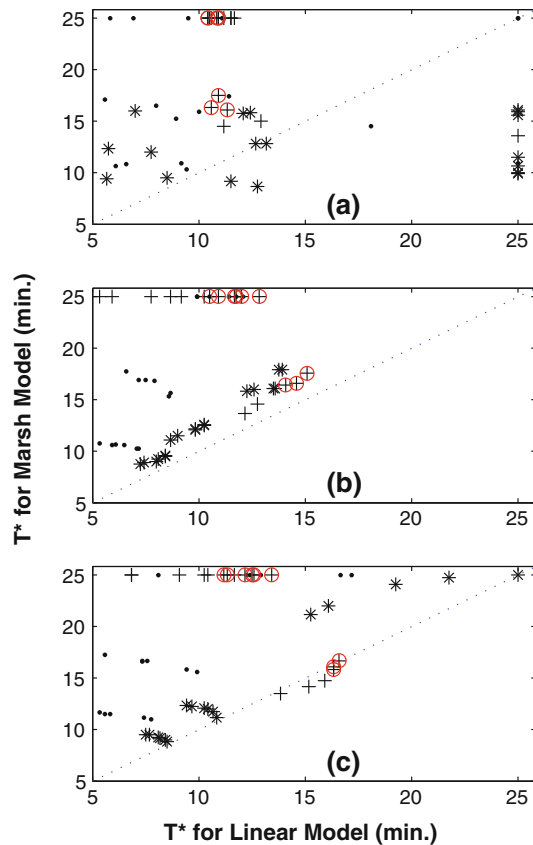
Fig. 18 Elapsed time to attain a stable concentration for different target concentration: 0.5 µg ml^{-1}, (**a**), 2.2 µg ml^{-1}, (**b**), and 6.0 µg ml^{-1}, (**c**). The circle identifies cases with LBM greater than the maximum LBM referred in [1]

Fig. 19 Maximum concentration in the transient phase for a target concentration of 0.5 µg ml^{-1}, (**a**), 2.2 µg ml^{-1}, (**b**), and 6.0 µg ml^{-1}, (**c**). The circle identifies cases with LBM greater than the maximum LBM referred in [1]

device is used to compute the infusion rate for each case comprising a set of CT, age, height, weight and gender, using the Marsh model. Then the model of Schnider is used to compute the effect-site concentration obtained from the dosages indicated by the TCI and the PL model.

To conduct the comparison between the effect-site concentrations resulting from the two models for the same target concentration value, a factorial design is considered: for each gender, the maximum, minimum and mean value referred in Table 5 (see Sect. 2) is assigned to each factor in a total of 162 cases combinations or cases to be analysed.

To perform a more informative comparison between the two models a division in two phases of the effect-site concentration (time evolution) is considered, the induction phase and a stationary phase. In this analysis three variables will be considered, the time taken by the induction phase, Fig. 18, the maximum concentration on the induction phase, Fig. 19 and the mean error between the target concentration and the effect-site concentration in the stationary phase, Fig. 20. As discussed in [1] the models programmed in the TCI are not valid for values of LBM higher than a given value function of the height. So, in each figure, whenever that happens a circle identifies the case.

Figure 18 are scatter plots of the induction phase duration for both dosages, PL model and Marsh model, for each attributes combination and separated by target concentration:
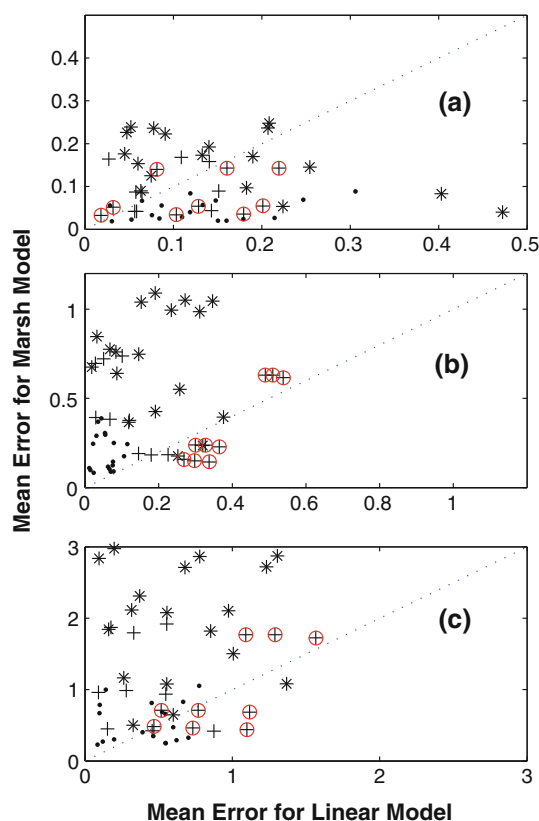
Fig. 20 Mean absolute error in the stationary phase for a target concentration of 0.5 µg ml^{-1}, (**a**), 2.2 µg ml^{-1}, (**b**), and 6.0 µg ml^{-1}, (**c**). The *circle* identifies cases with LBM greater than the maximum LBM referred in [1]

0.5 µg ml^{-1}, (a), 2.2 µg ml^{-1}, (b), and 6.0 µg ml^{-1}, (c). Considering the fact that most points are above the dashed line for all the target concentrations the PL model takes less time to attain the stationary phase. From the analysis of Fig. 19 results the following information:

- for a 40 *kg* weight, in the most cases, the Marsh model does not allow to attain the target concentration;
- for a 120 *kg* weight the Marsh model leads to maximum effect-site concentrations almost twice the target value;
- the PL model leads to maximum effect-site concentrations near its target value for almost all the cases;
- the PL model presents a relatively higher maximum effect-site concentrations for the lower target concentration.

From Fig. 20 results that the PL model presents a mean absolute error inferior to the one given by the Marsh model for both, mean and maximum, target concentrations. Nevertheless for the target concentration of 0.5 µg ml^{-1}, (a), the Marsh model presents results slightly better than the Linear model.

Combining the information of the last three figures the PL model predicts a dosage profile that is faster in leading to an effect-site concentration closer to the target

concentration. Nevertheless, both models lead to undesirable results for low target concentrations.

8 Discussion and conclusions

Considering that the models used in this work for longitudinal data are the simplest available on the literature, the results are promising. In fact, the objective was not to reproduce the behavior of the TCI administration, but to predict *bolus* and infusion rates comparable to those of TCI and these issues were clearly achieved. Moreover, the performance of the models in a test set with a broad range of characteristics including interventions with/without target *propofol* concentration readjustments and new target *propofol* concentration was satisfactory. Also, the effect of age, height, weight, LBM and the target *propofol* concentration both on the *bolus*, model (3), and the infusion rate, model (4), is in agreement with pharmacokinetic principles. The target concentration is the factor that contributes most for the infusion rate variability with a sensitivity index which is similar for both genders. The next factor contributing to the infusion rate variability is the patients weight with a higher sensitivity index for women. The results further indicate that the PL model predicts a dosage profile that leads to an effect-site concentration close to the desired target concentration as fast as TCI's Schnider model. The results obtained so far may be considered a step towards to the definition of a simple model for estimating *propofol* individualized dosage based on the patient attributes. It is noteworthy that this PL model leads to a unique personalized profile dosage.

Several advantages of the PL model, conveyed by its structure and properties may be highlighted. First, it enables easily the inclusion of other clinical parameters in order to obtain a better representation of individualized patient issues and clinical mindset. Furthermore, it allows straightforwardly the use of other measures for DoA, instead of the target effect concentration (*CT*), whenever they can be considered as function of *CT*. Moreover, the PL model is specially suited to be used in a model-based closed loop automatic *propofol* administration system, since there is a wide range of control algorithms for linear systems available which present good stability and robustness properties. Finally, the PL model is a statistical model, thus enabling further inferential procedures, such as confidence intervals and hypothesis testing.

As future work the authors have plans to test this model on larger sedation datasets as soon as they become available.

References

1. Absalom A, Struys M. Overview of target controlled infusions and total intravenous anaesthesia. Academia Press, Gent; 2007.
2. Fahrmeir L, Tutz G. Multivariate statistical modelling based on generalized linear models. Springer, Berlin; 2001.
3. Fechner J, Albrecht S, Ihmsen H, Knoll R, Schwilden H, Schuttler J. Predictability and precision of "target-controlled infusion" (TCI) of propofol with the "Disoprifusor TCI" system. Anaesthesist 1988;47, 663–668.
4. Gambús P, Jensen EW, Jospin M, Borrat X, Martinez Pallí G, Fernández-Candil J, Valencia JF, Barba X, Caminal P, Trocóniz IF. Modeling the effect of propofol and remifentanil combinations for sedation-analgesia in endoscopic procedures using an adaptive neuro fuzzy inference system (ANFIS). Anesthesia and Analgesia 2011;112(2), 331–339.
5. Glen J. The development of 'Diprifusor': a TCI system for propofol. Anaesthesia 1998; 53(Suppl 1), 13–21.
6. Gray J, Kenny G. Development of the technology for 'Diprifusor' TCI systems. Anaesthesia 1998;53(Suppl 1): 22–27.
7. Hallynck T, Soep H, Thomis J, Boelaert J, Daneels R, Dettli L. Should clearance be normalised to body surface or to lean body mass?. Br J Clin Pharmacol. 1981;11(5), 523–26.
8. Hamby DM. A review of techniques for parameter sensitivity analysis of environmental models. Environ Monit Assess 1994;32, 135–154.
9. Leslie K, Clavisi O, Hargrove J. Target-controlled infusion versus manually-controlled infusion of propofol for general anaesthesia or sedation in adults. Cochrane Database of Syst Rev 3 2008; doi:10.1002/14651858.CD006059.pub2.
10. Masui K, Upto RN, Doufas AG, Coetzee J, Kazama T, Mortier EP, Struys MM. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: a comparision using bolus, continuous, and target-controlled infusion data. Anesth Analg 2010;111(2), 368–379.
11. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil: II . model application. Anesthesiology 1997;86, 24–33.
12. Passot S, Servin F, Allary R, Pascal J, Prades J, Auboyer C, Molliex S. Target-Controlled Versus Manually-Controlled Infusion of Propofol for Direct Laryngoscopy and Bronchoscopy. Anesth Analg 2002;94(5), 1212–1216.
13. Schnider TW, Minto CF, Schafer SL, Gambus PL, Andersen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90, 1502–1516.
14. Schraag, S. Theoretical basis of target controlled anaesthesia: history, concept and clinical perspectives. Best Pract Res Clin Anaesthesiol 2001;15(1), 1–17.
15. Struys M, Sahinovic M, Lichtenbelt BJ, Vereecke H, Absalom A. Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. Br J Anaesth 2011;107(1), 38–47. doi:10.1093/bja/aer108.
16. Struys M, Versichelen L, Thas O, Herregods L, Rolly G. Comparison of computer-controlled administration of propofol with two manually controlled infusion techniques. Anaesthesia 1997;52(1), 41–50. doi:10.1111/j.1365-2044.1997.002-az001.x.
17. Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a 'Diprifusor' TCI system. Anaesthesia 1998;53: 61–67. doi:10.1111/j.1365-2044.1998.53s104.x.
18. Wooldridge JM. Econometric analysis of cross section and panel data. MIT Press, Cambridge; 2002.