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A linear model for estimating *propofol* individualized dosage

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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 side effects which may be associated with 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 (Schraag, 2001). This work presents statistical models to estimate both the infusion rate and the *bolus* administration. The modeling strategy relies on multivariate linear models for panel data (Wooldridge, 2002), based on patient characteristics such as age, height, weight and gender along with the desired target concentration. A clinical database collected with a RugLoopII device on 84 patients undergoing ultrasonographic endoscopy under sedation-analgesia with *propofol* and *remifentanil*, (Gambús et al., 2011), 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* and infusion rates comparable to those of TCI.

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 to attain a desired effect. Hence, nowadays a computer-assisted target controlled infusion device, TCI, 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 (Absalom and Struys, 2007) in order to obtain a predefined target effect concentration.

Several research groups (Glen, 1998; Gray and Kenny, 1998), have published studies in order to evaluate the accuracy of the TCI system for *propofol* administration in achieving the desired effect concentration. In particular, Swinhoe et al. (1998) and Fechner et al. (1998) evaluated the behavior of TCI for predicting the *propofol* dose infusion rate and both works consider its performance acceptable for clinical purposes. Some studies (Struys et al., 1997; Passot et al., 2002) compare the clinical profile of target-controlled infusions of *propofol* with that of manually-controlled infusions but their comparative effectiveness remains controversial (Leslie et al., 2008).

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 along 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, first 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

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database collected by RugLoopII on patients undergoing ultrasonographic endoscopy under sedation-analgesia with *propofol* and *remifentanil* and rely on patient data (age, weight, height and lean body mass) 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 used in this study is collected with RugLoopII, a target controlled infusion (TCI) and collection software, which controls the syringe pumps for *propofol* (the hypnotic drug) using pharmacokinetic model of Schnider (Schnider et al., 1999), and for *remifentanil* (analgesic drug) using pharmakocinetic model of Minto (Minto et al., 1997)). 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 gender, age, weight, height and lean body mass (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 seconds are available.

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 [1] (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

Several characteristics of the *propofol*/*remifentanil* administration are worth noting. The targeted *propofol* concentrations, CT, are in the range [0.5;4.7] $\mu g\ ml^{-1}$ with an average of 2.2 $\mu g\ ml^{-1}$ and a standard deviation of 0.65 $\mu g\ ml^{-1}$. 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 $\mu g\ ml^{-1}$, 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 minutes with an average of 56 minutes. 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] $ng\ ml^{-1}$.

[1] Hallynck et al. (1981)

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

3. METHODS

In a clinical procedure a *bolus* is administrated in a short period of time, with the purpose of rapidly achieving a 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* $\boldsymbol{Y}$ as a linear (in the parameters) function of the patient characteristics represented by the linear regression equation:

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

where the design matrix $\boldsymbol{X}$ 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 $\boldsymbol{\epsilon}$ is a vector of zero mean random variables with diagonal covariance matrix with entries σ_i^2.

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 seconds. 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 (Fahrmeir and Tutz, 2001) 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, (Wooldridge, 2002). Let y_{it} be the infusion rate of the ith patient at time t and let $\boldsymbol{X}_{it}$ 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

$$y_{it} = \alpha + \boldsymbol{X}_{it}\boldsymbol{\beta} + v_{it} \tag{2}$$

where $v_{it} = \nu_i + \epsilon_{it}$ are the cluster-specific intercepts. For each t, v_{it} is the sum of the unobserved effect, ν_i, with an idiosyncratic error, ϵ_{it}.

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 test set by OLS allowing for heteroscedasticity 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.

Table 3. Estimated coefficients.

Variable	Coefficient	p-value
1	-2.209	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

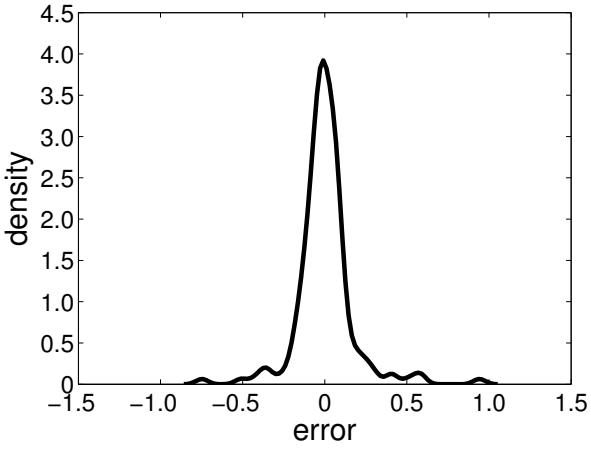

Fig. 1. Estimated density function of the error on *bolus* estimation based on (3).

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 lean body mass and age, respectively, are negative indicating that higher lean body mass as well as older age lead to decreased *bolus*.

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 ml 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.

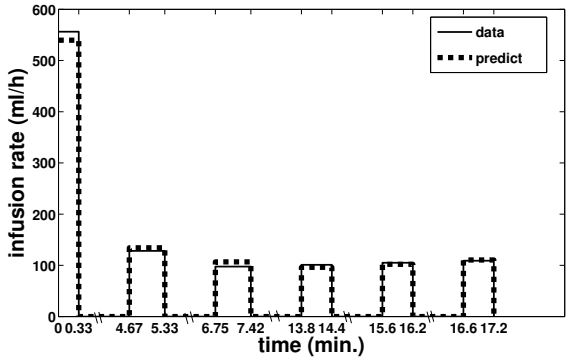

Fig. 2. Mean infusion rate for *propofol bolus* from the test set - case 9.

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 Pooled OLS allowing for heteroscedasticity between clusters which are identified by the target concentration. 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:

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

where IR_t is the infusion rate of *propofol* in $ml\ hr^{-1}$ at time t. Noting that $t_{\Delta CT} = t - k$, where k represents the instant of target concentration CT readjustment and rewritting (4) as (5), it is 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.

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

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

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 lean body mass;
- 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 model, Fig. 3 to Fig. 6 present the predicted and the infused rate for four cases from the test set. Fig. 5 which represents the predicted and the infused rates for case 7 deserves special attention. In fact, although the target *propofol* concentration, CT, 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 ($RMSE = 5.38$, $MAPE = 7\%$).

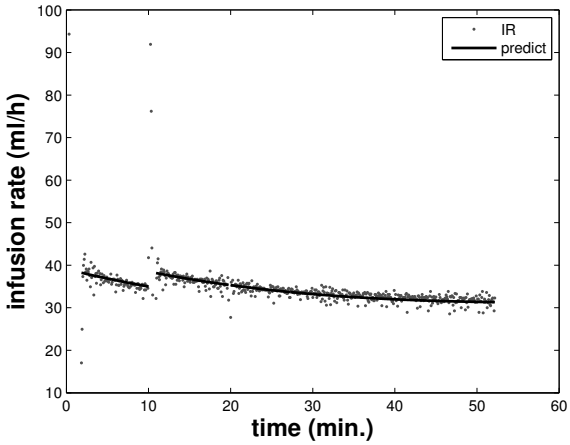

Fig. 3. A case with two values for target *propofol* concentration, CT - case 3.

5. CONCLUSION

Considering that the model 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 it was clearly achieved. Moreover, the performance of the models in a test set with a broad range of characteristics including interventions with/without tar-

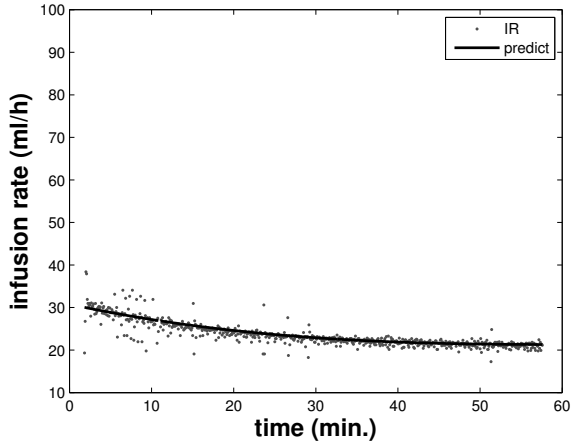

Fig. 4. A case with a single target *propofol* concentration, *CT* - case 4.

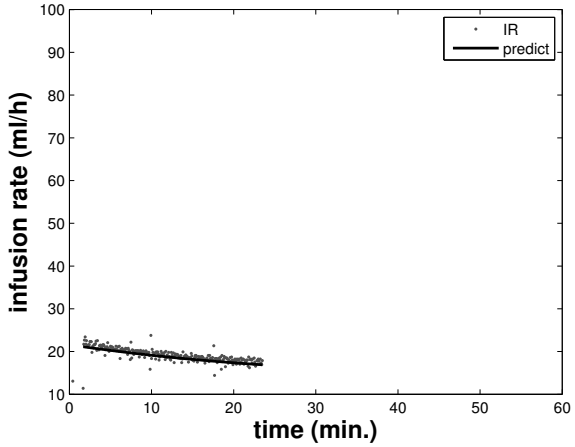

Fig. 5. A case with a single target *propofol* concentration, *CT*, corresponding to a cluster not included in the training set - case 7

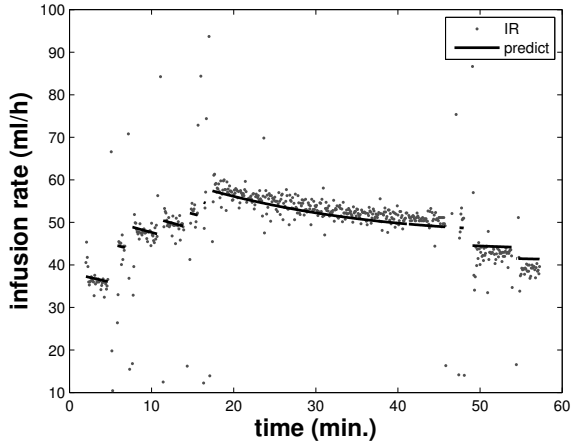

Fig. 6. A case with several readjustments of the target *propofol* concentration, *CT* - case 9 Fig. 2.

get *propofol* concentration readjustments and new target *propofol* concentration was satisfactory.

Also, the effect of weight, height, age, lean body mass and the target *propofol* concentration both on the *bolus*, model (3), and the infusion rate, model (4), is in good agreement with pharmacokinetic theory.

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. Moreover, the structure of these models makes them adequate to be used in a model-based closed loop automatic *propofol* administration system.

As future work the authors have plans to test these models on larger sedation dataset as soon as they become available.

As a final remark, 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.

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