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On the Identification of the Propofol PK/PD Model Using BIS Measurements

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Abstract: In this paper we analyse the use of different models to describe the effects of propofol in the induction of hypnosis on a patient during surgery. In particular, we consider the standard three-compartmental pharmacokinetics/pharmacodynamics Wiener model and a suitable reduction of it. The estimation of the parameters is based on real bispectral index scale surgical data and it is performed by using genetic algorithms. The results obtained for different patients show that the standard model fits the data better than the reduced model, but it is overparameterized and its structure is much more complex to be used for the control design. Conversely, the simplification of the identification procedure obtained with the reduced model, which has only three parameters, is paid by only a slight decrement of the performance.

Keywords: Total intravenous anesthesia, Depth-of-Hypnosis, PK/PD model, Model reduction, Genetic Algorithms.

1. INTRODUCTION

In surgery it is essential to provide an adequate level of anesthesia to the patient. The aim of general anesthesia is to temporarily induce the consciousness suppression (hypnosis), the pain inhibition (analgesia), and the muscle contraction inhibition (or relaxation) with specific drugs. In this paper we focus on the use of propofol as anesthetic in total intravenous anesthesia (TIVA) and in particular on the mathematical model that describes the human body response to this drug and on the estimation of its parameters. Propofol is typically used in the induction and maintenance of a desired depth of hypnosis (DoH) in surgery or in the sedation of patients during invasive medical exams such as endoscopy (Byrne et al., 2008).
In order to measure the brain activity and therefore the DoH, the bispectral index scale (BIS) is often employed. This index is based on a bispectral analysis of the electroencephalogram (EEG) and consists on a dimensionless number which ranges from 0, equivalent to EEG silence, to 100, equivalent to a fully awake state. In the standard clinical practice the anesthesiologist manually regulates the propofol infusion based on this index, on recommended doses and on his/her experience. In order to improve the efficacy of the treatment and the safety of the patient, automatic and semi-automatic drug infusion systems have been developed in the last decades. In particular, the so-called target controlled infusion (TCI) (Ehrenfeld and eds., 2014) has been introduced in order to calculate the appropriate drug administration, given the demographics data of the patient. This is actually an open-loop control system, thus subject to robustness issues. Thus, on another side, many studies have also dealt with closed-loop control systems that exploit the BIS level as a feedback variable to automatically regulate the propofol infusion and improve the control of DoH. Example of these control systems are presented in (Ionescu et al., 2008; Nascu et al., 2012). In any case, it is clear that a suitable model for the human

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body drug response is essential to develop an effective automatic infusion system that replicates and improves this clinical procedure. In fact, in TCI-based systems the model of the patient is implemented to calculate the infusion profile, while in closed-loop control systems the model is necessary for a correct design of the controller.
The patient model describes the relationship between the propofol infusion rate and the drug effect measured by the BIS. The effect of propofol is traditionally modelled as a Wiener model, i.e., a model composed by a linear part in series with a static nonlinearity. The linear part consists of a pharmacokinetics (PK) model that describes the infusion, distribution and elimination of the drugs in the body and a pharmacodynamics (PD) part that represents the relationship between the plasma concentration and the effect site concentration. The three compartmental PK/PD model proposed by Schnider (Schnider et al., 1998, 1999) is typically adopted for propofol. The nonlinearity, represented as a Hill function, expresses the relation between the effect site concentration and the clinical effect, measured as the BIS level. The parameters of the nominal model that have to be estimated are the compartment volumes, the micro-constant rates for mass transfers between compartments, the drug clearances in the human body and the parameters of the Hill function. Such parameters should be estimated on-line, during the clinical procedure. However, the PK/PD model has a high number of parameters, which implies that a suitably exciting input, usually not compatible with the standard administration protocols, should be given to the patient in order to estimate their values. In fact, the clinical practice usually consists of the initial administration of a bolus of propofol in the induction phase, followed by a constant infusion rate with a low-variance profile. Moreover, clinical devices have in general a limited sampling rate that reduces the number of available data.
For this reason, a significant research effort has been provided in order to develop reduced models that describe the propofol body response with a smaller number of parameters. For example in (Sartori et al., 2005; Bibian et al., 2006; Coppens et al., 2011) some parameters of PK/PD model are fixed during the identification, in (Hahn et al., 2012) a first-order model has been developed and in (Lin et al., 2004) multivariable piecewise linear models are used.
A reduced-order model that considers also the analgesic drug has been presented in (da Silva et al., 2010) and validated in (da Silva et al., 2013). In this paper we propose a modification of this reduced model to describe the relevant case of the body response to propofol only. The goal is to investigate the effectiveness of this reduced model and to compare its performance with the one of Schnider's model, by using real surgical data. Indeed, by considering also the presence of the analgesic drug, a comparison between the two models has already been performed in (Mendonça et al., 2012). Therein, a prediction error method (PEM) has been used to estimate the parameters of the reduced model while a hybrid method presented in (Alonso et al., 2008) has been used for the full model. However, as mentioned also in (Mendonça et al., 2012), PEM requires a proper tuning and presents convergence issues depending on the initial parameters choice. The hybrid method does not have this problem, but it is developed only for the identification of the nonlinear function parameters of PK/PD model, considering parameters of the linear part as known constants. For this reason, in this paper we use genetic algorithms (GAs) (Mitchell, 1998) to estimate the parameters of both models. GAs are capable to determine a global optimum of an optimization problem in a stochastic sense independently from the number of parameters. In this context we also consider the PK/PD Schnider model with and without fixed parameters in order to evaluate their role in the overall identification procedure.

2. MODELS DESCRIPTION

2.1 PK/PD full model

The DoH induced by the propofol administration is usually modelled by means of Wiener model, where a linear model is in series with a static nonlinear function (Marsh et al., 1991; Schnider et al., 1998, 1999; Vanluchene et al., 2004). A mamillary three-compartmental model is adopted to describe the (linear) PK model. This representation was developed and validated on real patients by using blood samples during anesthesia (Schnider et al., 1998, 1999). The compartments are interconnected by a mass flux exchange, so that the following system results:

$$\begin{aligned} \dot{q}_1(t) &= -(k_{10}+k_{12}+k_{13})q_1(t) + k_{21}q_2(t) + \\ &\quad +k_{31}q_3(t) + u(t) \\ \dot{q}_2(t) &= k_{12}q_1(t) - k_{21}q_2(t) \\ \dot{q}_3(t) &= k_{13}q_1(t) - k_{31}q_3(t) \end{aligned} \tag{1}$$

where $q(t)$ [mg] is the quantity of the drug over the time for each compartment. In particular, $q_1(t)$ refers to primary blood compartment, $q_2(t)$ refers to the peripheral fast compartment that includes well perfused body tissues like muscles, and $q_3(t)$ refers to slow dynamics compartment that includes poor perfused body tissues like fat. The input of the model is $u(t)$ [mg/min] and represents the infusion rate of the drug. The parameters k_{ij} for $i \neq j$ denote the drug transfer frequency from the ith to the jth compartment. They depend on age, weight, height and gender of the patient by means of the following parametric relations:

$$\begin{aligned} &V_1 = t_1, \quad V_2 = t_2 - t_7(age-53), \quad V_3 = t_3 \\ &C_{l1} = t_4 + t_8(weight-77) - t_9(lbm-59) \\ &\qquad +t_{10}(height-177), \\ &C_{l2} = t_5 - t_{11}(age-53), \quad C_{l3} = t_6 \\ &k_{12} = \frac{C_{l2}}{V_1}, \quad k_{13} = \frac{C_{l3}}{V_1}, \quad k_{21} = \frac{C_{l2}}{V_2}, \quad k_{31} = \frac{C_{l3}}{V_3} \end{aligned} \tag{2}$$

where V_i [L] and C_{li} [L/min] are, respectively, the volume and the clearance of the ith compartment and *lbm* is the lean body mass which can be obtained as (Hallynck et al., 1981):

$$\begin{aligned} lbm &= 1.1\,weight - 128\frac{weight^2}{height^2} \quad \text{for Male} \\ lbm &= 1.07\,weight - 148\frac{weight^2}{height^2} \quad \text{for Female} \end{aligned} \tag{3}$$

where *weight* is expressed in kilograms [kg] and *height* in centimeters [cm]. The nominal values and the standard errors of the parameters t_i, $i = 1, \ldots, 11$ used in the PK model are shown in Table 1 (Schnider et al., 1998). The

Table 1. Parameters for the PK model.

Parameter	Value	SE
t_1	4.27	0.278
t_2	18.9	2.330
t_3	238	34.900
t_4	1.89	0.059
t_5	1.29	0.112
t_6	0.836	0.044
t_7	-0.391	0.070
t_8	0.0456	0.009
t_9	-0.0681	0.017
t_{10}	0.0264	0.009
t_{11}	-0.024	0.005

output of the model is the plasmatic concentration of the drug, calculated as $C_p(t) = q_1(t)/V_1$ and it is also the input of the PD part of the model. In the pharmacodynamics model, a fictitious compartment called effect-site compartment is added to represent the lag between the plasma concentration and the corresponding drug effect. The drug concentration in the effect-site compartment is denoted as C_e. The relation between the primary and the effect-site compartment is represented by a first-order delay-free function:

$$\dot{C}_e(t) = k_{1e}C_p(t) - k_{e0}C_e(t) \tag{4}$$

According to Schnider et al. (1999), the propofol transfer frequency k_{1e} can be considered constant and equal to the frequency of drug removal from the effect-site compartment k_{e0}:

$$k_{1e} = k_{e0} = 0.456 \ \ [\text{min}^{-1}] \tag{5}$$

Finally, a static nonlinear function, known as Hill function, correlates the effect-site drug concentration and clinical effect, represented by the BIS (Struys et al., 2003; Vanluchene et al., 2004; Ionescu et al., 2008). This sigmoid function can be written as

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e50}^\gamma}\right), \tag{6}$$

where E_0 is the baseline value representing the BIS level of the patient in the initial state before the infusion, $E_0 - E_{max}$ is the maximum reachable effect achieved by the infusion, γ denotes the steepness of the curve that represents the receptiveness of the patient to the drug and C_{e50} is the necessary concentration of the drug to reach the half maximal effect. Eventually the parameters to be estimated for the full PK/PD model are:

$$\begin{aligned}\theta = (&t_1 \quad t_2 \quad t_3 \quad t_4 \quad t_5 \quad t_6 \quad t_7 \quad t_8 \quad t_9 \quad t_{10} \quad t_{11} \\ &E_0 \quad E_{max} \quad C_{e50} \quad \gamma)\end{aligned} \tag{7}$$

In many works the nominal values of the t_i parameters are assumed in order to reduce the complexity of the identification procedure, but this issue will be fully investigated in the following sections.

2.2 Minimally parameterized model

A new Wiener model has been proposed in (da Silva et al., 2010) to describe the response of the human body to both propofol and remifentanil. The latter is a typical analgesic drug given with propofol during general anesthesia. In this paper that model is suitably adapted in order to represent only the propofol response. The model reduction is based on the model structure presented in (da Silva et al., 2012), where a new single-input single-output (SISO) Wiener model is developed for the human response to atracurium, a neuromuscular blockade drug. In (da Silva et al., 2010) the linear dynamics of the propofol model is described by a third-order continuous-time model. We maintain that structure also to describe the response of propofol only, thus obtaining:

$$\hat{X}_e^{prop}(s,\alpha) = \frac{k_1k_2k_3\alpha^3}{(s+k_1\alpha)(s+k_2\alpha)(s+k_3\alpha)}R^{prop}(s) \tag{8}$$

where $\hat{X}_e^{prop}(s,\alpha)$ is the Laplace transform of the output of the linear part of the model, that is, the effect-site concentration, and $R^{prop}(s)$ is the Laplace transform of the input, that is, the propofol infusion rate in [mg/min]. The transfer function (8) has a single parameter α to be estimated, which depends on the patient. The parameters k_i, $i = 1, ..., 3$ have been determined by using a batch identification procedure over a large database of patients (da Silva et al., 2010). These parameters are fixed at the values $k_1 = 10$, $k_2 = 9$, $k_3 = 1$. As for the full Schnider model, a nonlinear function describes the relation between the effect-site concentration and the clinical effect of propofol, measured by the BIS index. By applying the approximation proposed in (da Silva et al., 2010), a reduction of the Hill equation (6) is performed by fixing the baseline value E_0 to the maximum reachable effect $E_{max} = y_0$, where $y_0 = 97.7$ is the commercial BIS monitor saturation value. Nevertheless, on the contrary of what has been done in (da Silva et al., 2010), where the value of $C_{e_{50}}$ for both propofol and remifentanil is fixed to the average patients value, here the value of $C_{e_{50}}$ is a parameter to be estimated, yielding:

$$BIS(t) = \frac{y_0}{1 + \left(\frac{C_e(t)}{C_{e_{50}}}\right)^\gamma} \tag{9}$$

The rationale behind this choice is to obtain a better estimation of the gain of the system.
The parameters to be estimated for this new reduced model are therefore:

$$\theta = (\alpha \quad \gamma \quad C_{e_{50}}) \tag{10}$$

3. CLINICAL DATA

The data used in this paper for the model identification purpose have been collected during plastic surgeries in the Department of Anesthesia, Critical Care Medicine and Emergency of the Brescia University Hospital (Italy). The patients were subject to total intravenous anesthesia using, along the whole surgery, both propofol and remifentanil. Induction and maintenance of anesthesia was based on standard clinical practice, and was not modified for the purpose of this study. In particular, the drug administration protocol has been established in such a way that, in the initial induction phase, only propofol was used and no external stimuli were provided to the patients. Remifentanil was added only after obtaining a steady-state BIS level, that is, about after 5 [min] from the bolus injection. The induction phase can be therefore used for the parameter identification of the model that describes the human body response to propofol.
The induction phase consists of a drug bolus followed by a constant infusion rate in order to achieve the desired BIS value in a range between 40 and 60. The time interval for the bolus administration and the amount of

Table 2. Patients data.

Patient	Gender	Weight [Kg]	Age	Height [cm]
1	F	90	83	160
2	F	63	68	160
3	F	81	68	158
4	F	60	51	158
5	M	120	27	160
6	F	60	13	170
7	M	70	68	168
8	F	54	56	160

Table 3. Results obtained by estimating only the Hill function parameters of the full model.

Patient	E_{max}	$C_{e_{50}}$	γ	Var.
1	144.2614	6.1211	2.1479	171.41
2	70.4017	3.8238	15.8079	38.1629
3	105.4477	4.0905	1.9497	233.9927
4	158.5657	8.9067	1.2018	255.9543
5	147.0424	5.8686	2.8697	92.6355
6	156.0934	6.5781	1.5291	151.8139
7	126.4284	10.3198	1.0286	225.2469
8	52.4876	4.0654	43.4104	44.7005

administered drug were decided by the anesthesiologist based on recommended doses and on his/her own clinical experience. The anesthesiologist manually controlled the infusion rate by using an *Orchestra module DPS* pump and checked the BIS level of the patient on a *Draeger Infinity Delta* monitor. Through this instrumentation, by means of appropriate protocols, it is possible to collect the propofol infusion rate and the BIS value with a standard PC with a sampling period of one second. The data of eight patients (whose characteristics are shown in Table 2) have been used for the purpose of this paper.

4. IDENTIFICATION OF THE FULL MODEL

4.1 Estimation of the Hill function parameters only

The first approach that has been considered for the identification of the full PK/PD model is based on the estimation of the parameters of the nonlinear part only, that is, the Hill function parameters, as suggested in (Alonso et al., 2008). In particular, the parameters to estimate are E_{max}, $C_{e_{50}}$ and γ, while the average (nominal) values of the parameters t_i, $i = 1, \ldots, 11$, reported in Table 1 are considered for the linear part. As in (Alonso et al., 2008; da Silva et al., 2010), the parameter E_0 of the nonlinear function is fixed at the saturation value y_0 of the BIS monitor.

As mentioned in the introduction, GAs have been used to find the values of the parameters that minimize the variance between the measured BIS and the model output obtained by using the employed propofol infusion profile as input. It is worth noting that, with respect to other optimization approaches, GAs do not require a starting point: it is only necessary to define the search space, which can be easily provided by considering the physical meaning of the parameters.

The results obtained for the considered set of patients are shown in Table 3. As an illustrative example, the comparison between the measured BIS signal and the model output for the patient 1 is presented in Figure 1 with blue line. Similar results are found for the other patients

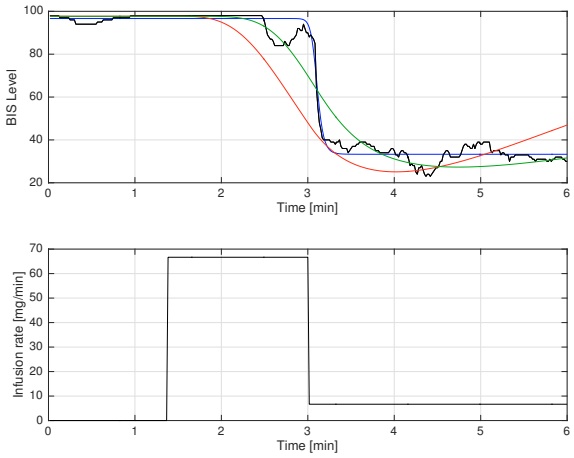

Fig. 1. Results obtained for patient 1. Top plot: measured BIS signal (black line) and model outputs. Bottom plot: propofol infusion rate.

but they are not shown for the sake of brevity. It can be seen that, although the general trend is captured by the model, the result is not very satisfactory. For this reason it is necessary to investigate the improvement that can be achieved by including the parameters of the linear part in the overall estimation procedure.

4.2 Estimation of all the parameters

The second approach consists in estimating, again by using GAs, all the parameters appearing in (7). Of course, the procedure is much complex than the one performed in the previous section because the parameters to estimate are 14 instead of 3. However, the fact that the parameters of the linear part are no longer fixed, allows to address the inter-patient variability and therefore an improvement of the model. Note that, again, the value of E_0 is set to 97.7 as in the previous approach. The search space for the t_i parameters can be easily determined by considering their nominal values and their standard errors reported in Table 1.

The results obtained in this case are shown in Table 4. It appears that the obtained variances (to be minimized by the GA) are significantly smaller compared to the ones obtained in the previous case. The improvement of the accuracy of the model is confirmed by considering again patient 1 as illustrative example. The comparison between the measured BIS and the model output is plotted in Figure 1 with red line.

Despite the performance improvement achieved by estimating all the parameters (note also that GAs are able to handle an incremented number of parameters at the expense of an increase of computational complexity), it has to be noted that this approach presents a significant problem. In fact, the genetic algorithms can find different solutions with almost the same cost function. This means that there are local minima in the cost function with almost the same degree of optimality, that is, the model is actually overparameterized. An example is shown in Table 5, where two different results related to the application of the genetic algorithm to patient 1 are reported. It can

Table 4. Results obtained by estimating all the parameters of the full model.

Patient	E_{max}	$C_{e_{50}}$	γ	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}	Var.
1	63.3403	4.9209	32.2025	5.4495	11.8436	144.2989	1.7821	1.1130	0.8504	-0.3606	0.0374	0.0063	0.0649	-0.0140	16.9236
2	77.9273	5.1806	3.6700	4.7059	27.4241	387.7539	2.1026	0.9036	0.7245	-0.2721	0.0762	0.0026	0.0490	-0.0361	5.9077
3	69.4207	5.2024	4.0516	5.6405	10.2382	256.0284	1.6528	1.3817	0.6198	-0.6428	0.0151	0.0067	0.0615	-0.0420	16.7245
4	66.1865	5.3831	6.9119	5.4904	7.3125	247.8711	1.6394	1.8371	0.6926	-0.0865	0.0839	-0.0324	0.0039	-0.0262	39.5793
5	67.3865	4.9293	14.4104	3.8203	11.0654	396.9805	1.8452	1.6023	0.9549	-0.4712	0.0239	-0.1126	0.0504	-0.0486	16.4827
6	77.2297	4.8383	6.7710	4.1405	10.6118	222.2261	1.7141	1.8486	0.7252	-0.0584	0.0692	-0.0817	0.0619	-0.0355	11.2708
7	64.0798	8.5981	6.3765	5.6203	9.0954	301.8072	1.6107	1.1771	0.8277	-0.5649	0.0753	-0.0001	0.0370	-0.0422	38.6729
8	69.9069	5.9314	2.0097	4.0717	7.4595	105.8133	1.7394	1.7908	0.7772	-0.5431	0.0696	-0.0054	0.0705	-0.0107	18.7593

be noted that, despite the important differences in the parameter, the obtained variances are very similar.

5. IDENTIFICATION OF THE REDUCED MODEL

As mentioned in Section 2.2, a reduced model has been devised by removing the effects of the remifentanil from the model presented in (da Silva et al., 2010). In this case the three parameters to estimate are α, γ and $C_{e_{50}}$. It is worth noting that the number of parameters is the same as in case of the full model where only the nonlinear part is considered, but here the parameter α allows the modification of the linear part. This is an important difference because this parameter can modify the dynamic response significantly. By using again a GA-based approach, the results shown in Table 6 are obtained (the corresponding results for patient 1 are plotted in Figure 1 with green line.
It can be seen that in general the performance is only slightly worse than the one obtained by using the full model and the reduced model can be considered to be in any case effective in representing the propofol effect in the induction phase.

6. DISCUSSION

The variances obtained for the different patients with the considered approaches are summarized in Figure 2. As it has been already pointed out, it appears that the use of the full model with the estimation of all the parameters provides the best performance in matching the real BIS signal. However, it also presents severe problems because of the overparameterization of the model. Furthermore, the number of parameters to estimate is very high and for this reason the model is unsuitable to be used in an online estimation context. It is worth noting that in this paper GAs have been used in order to provide a fair comparison between the different techniques, as they provide a global optimum of the optimization problem, but the use of this tool is very computationally demanding.
The solution to fix the linear part of the model based just on the demographics of the patient and to consider only the nonlinear part in the estimation procedure greatly simplifies the estimation procedure, but it does not provide satisfactory results. In fact, the main disadvantage in this case is that the time constants of the linear part are fixed and this prevents the model to address the intra-patient variability and therefore to capture the whole dynamics of the system. On the contrary, the minimally parameterized reduced model (8) allows the selection of the time constants through the parameter α (without affecting the gain that is normalized to one) and eventually it guarantees a very good compromise between the obtained accuracy and

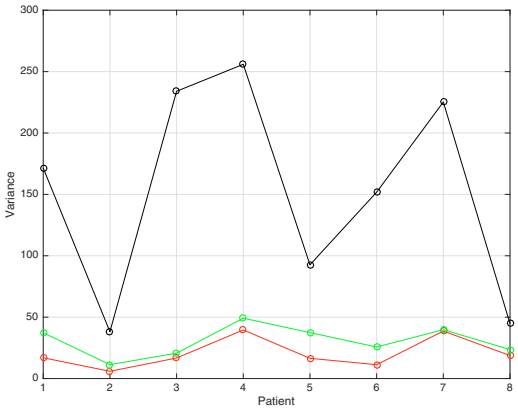

Fig. 2. Comparison between the variances obtained with the considered approaches for the different patients. Black line: full model with the estimation of the Hill function parameters only. Red line: full model with the estimation of all the parameters. Green line: reduced model.

the simplicity of implementation, although the physical meaning of the parameters is partially lost.

7. CONCLUSIONS

In this paper the identification of the human body response to propofol has been analyzed. In particular, three different approaches have been compared by using genetic algorithms. The first two methods consider the full Schnider model. In the first case the linear part is fixed for a given patient and only the Hill function parameters are estimated, while in the second case all the parameters are determined in the identification procedure. In the third approach a reduced model has been implemented. The results obtained by considering a set of patients show that the reduced model is capable to capture quite well the dynamics of the system and does not present the drawbacks of the full model, in particular, the overparameterization of the model.

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Table 5. Results of two applications of the GA for the estimation of all the parameters of the full model of patient 1.

Patient	E_{max}	$C_{e_{50}}$	γ	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}	Var.
1_A	63.3403	4.9209	32.2025	5.4495	11.8436	144.2989	1.7821	1.1130	0.8504	-0.3606	0.0374	0.0063	0.0649	-0.0140	16.9236
1_B	63.3580	4.6511	33.3519	5.5149	24.7021	287.8014	1.6158	1.3723	0.8618	-0.3138	0.0182	-0.0216	0.0701	-0.0029	16.9150

Table 6. Results obtained by estimating the reduced model.

Patient	α	γ	$C_{e_{50}}$	Var.
1	0.1994	2.7775	11.2619	37.3219
2	0.1670	1.8590	6.4880	11.3181
3	0.1596	2.0515	8.2996	20.6812
4	0.1791	2.4993	11.7378	49.1722
5	0.3020	4.1053	22.6953	37.4264
6	0.2305	2.7957	14.1694	25.6980
7	0.1534	3.0209	14.1305	39.7877
8	0.1171	0.8362	4.4035	23.6276

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