VOL. 12, NO. 9, MAY 2017 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

IDENTIFICATION OF PARAMETERS FOR HILL CURVE USED IN GENERAL ANESTHESIA

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ABSTRACT

In this contribution the data collected from clinical trials in open-loop are used to identify the parameters of the nonlinear and linear Hill Curve models. Initially, the parameters are found when only the Propofol signal is considered as an input and the BIS signal is an output - SISO case. Later, Propofol and Remifentanil signals are considered inputs and the BIS signal is an output - MISO case. The algorithms used to find the unknown parameters of the model as well as the results are presented.

Keywords: anesthesia control, hill curve identification, intensive care unit, pharmacodynamic model, pharmacokinetic model.

1. INTRODUCTION

The modeling from one system's behavior and/or from physical laws aims to establish the structure of the equations which rule this system's behavior and to establish a priori value of its parameters (lengths, masses, inertia, capacities, resistance, friction and so on). But it's rarely possible to obtain a priori an accurate knowledge of all the parameters of the model. In order to sharpen and complete this knowledge, it is therefore necessary to make an identification of the system: from its reactions to given and well-known promptings, if the system can be observed, we can identify still unknown parameters.

The identification, although it represents a big chapter in the automatics, can not anymore be considered as only an integral part of this discipline, with only as aim leading or diagnostic strategies. Its use in the engineering science, sometimes with a different terminology, shows it is a full discipline from the experimental sciences linked to the modeling.

In automatics, two approaches for the systems identification can be distinguished: Offline and Online.

In an offline mode (or batch mode), an experiment is carried out and afterwards all the data are processed simultaneously. The methods employed for offline system identification are thus based on information from the plant which has been obtained previously.

In an online mode (or recursive mode), the data are used as soon as they are available. The parameters can thus be continuously estimated during the experiment. It is employed not only with control algorithms, but also for many filtering problems and signal processing.

The offline mode is described in this work. The data collected from clinical trials in open-loop will be used to identify the Single Input-Single Output (SISO) and the Multiple Inputs-Single Output (MISO) Hill curve models. The algorithms used to identify the unknown parameters of the model as well as the results will be presented.

2. MATERIALS AND METHODS

The relationship between the Propofol infusion rate and its effect can be described by pharmacokinetic (PK) and pharmacodynamic (PD) models. PK model describes the distribution of Propofol in the patient body and PD model describes the relationship between Propofol blood concentration and its clinical effect.

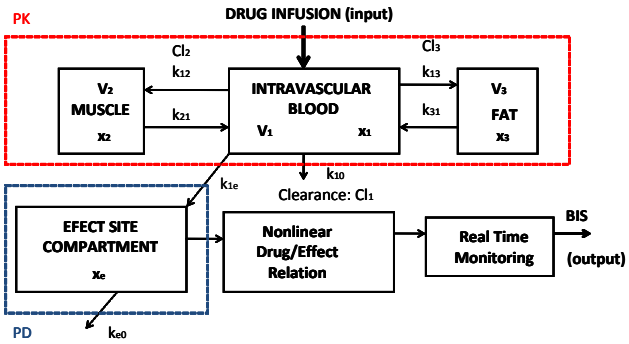

Figure-1. Multi-compartmental model.

In the past, different patient models have been developed for Propofol, however one popular model is the Propofol three-compartmental Schnider model (Schnider *et al.*, 1998). This PK model can be described by a three-compartmental model (see upper part Figure-1) and it is represented in space states by the following equations:

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{bmatrix} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & -k_{31} & 0 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u(t)$$

$$y(t) = C_p(t) = \begin{bmatrix} \frac{1}{V_1} & 0 & 0 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix}$$

where x_1 denotes the amount of drug in the central compartment (blood) and its units are milligrams (mg). The peripheral compartments model the drug exchange between the blood and the others body tissues. The amount of drug in these compartments is denoted by x_2 (muscle tissue) and x_3 (fat mass), respectively. The constants, k_{ji} for $i \neq j$, denote the drug transfer rate from the j^{th} tothe i^{th} compartment. The constant k_{10} is the constant rate for the process that irreversibly removes Propofol from the central and peripheral compartments; its

units are min^{-1}. Finally, $u(t)$ is the Propofol infusion rate in the central compartment (blood) and represents the input of the system, its units are milligrams per second (mg/s) and it is limited to 3.33 mg/s by the pump.

The output of the PK model is the plasma concentration of Propofol (C_p), which is calculated dividing x_1 by V_1, the central compartment volume. Similarly, the concentrations in the other compartments are obtained dividing x_2 and x_3 by V_2 and V_3, respectively (Ionescu *et al*., 2008). In this case, the units for the compartment volume are liters (l) and these values are given by:

$$V_1 = 4.27$$
$$V_2 = 18.9 - 0.391(age - 53)$$
$$V_3 = 238$$

The k_{ji} constants are obtained as follows:

$$k_{10} = C_{l1}/V_1$$
$$k_{12} = C_{l2}/V_1$$
$$k_{13} = C_{l3}/V_1$$
$$k_{21} = C_{l2}/V_2$$
$$k_{31} = C_{l3}/V_3$$

where C_l (clearance) is the rate at which a substance is removed from the body by the kidneys and its units are liters per minute (l/min). These values are obtained as follows:

$$\mathrm{C_{l1}} = 1.89 + 0.0456(\mathrm{weight} - 77) - 0.0681(\mathrm{lbm} - 59) + 0.064(\mathrm{height} - 177)$$
$$C_{l2} = 1.29 + 0.024(age - 53)$$
$$C_{l3} = 0.836$$

with lbm (lean body mass):

$$lbm_{MALE} = 1.1weight - 128\frac{weight^2}{height^2}$$
$$lbm_{FEMALE} = 1.07weight - 148\frac{weight^2}{height^2}$$

As can be observed in the above equations, some of the values depend on the mass (in kilogram), height (in centimeter), age (in years), and gender of the patients.

Regarding the PD model (see lower part Figure-1), an additional hypothetical effect compartment was proposed in order to represent the lag between the plasma concentration of Propofol and the patient response to the drug. The effect site compartment receives Propofol from the central compartment by a first-order model:

$$\dot{x_e}(t) = -k_{e0}x_e(t) + k_{1e}\dot{x_1}(t)$$

where k_{e0} and k_{1e} are constants and x_e is the amount of Propofol in the effect compartment. If the effect compartment is supposed very small compared to the other compartments, then k_{1e} will be a very small fraction of k_{e0} (Shafer *et al.*, 1998). The apparent concentration of Propofol in the effect site compartment can be calculated once k_{e0} is known, because this will characterize the temporal effects of equilibration between the plasma concentration of Propofol and its corresponding effect. Thus, the equation is often used as:

$$\dot{C_e}(t) = k_{e0}\left[C_p(t) - C_e(t)\right]$$

where C_e is the effect site compartment concentration of Propofol and the value of k_{e0} is 0.456 min^{-1}. Therefore, the effect site compartment model can be represented as follows:

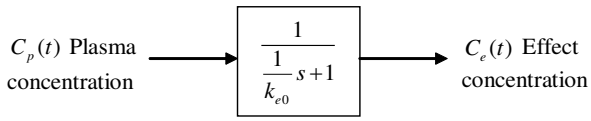

Figure-2. Effect-site compartment model.

In this model, $1/k_{e0}$ represents the time constant of the system (τ) and its value is $\tau = 131.58$ seconds for all of the patients.

The measured BIS can be related to the effect-site concentration C_e by the empirical static but time-varying nonlinear relationship (Bailey and Haddad, 2005), called also the *Sigmoid Hill Curve*:

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

E_0 is the BIS value when the patient is awake, by convention, a value of 100 is typically assigned; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half maximum effect and represents the patient sensitivity to the drug; and γ determines the degree of nonlinearity (steepness of the curve) (Haddad *et al*., 2003). Thus, the combination of the PK and PD models allows a complete modelling of the patient. The parameters involved in the PK model are known because they depend of the biometric values for each patient.Regarding the PD model, the value of k_{e0} is also known, but not the parameters of the *Sigmoid Hill Curve*.

The group of interest corresponds to 10 patients to whom the Propofol infusion rate was administrated by the nurse. The detailed biometric values of the patients in this group are shown in Table-1.

Table-1. Biometric values of the patients.

Patient	**Age** (years)	**Length** (cm)	**Weight** (kg)	**Gender**
1	71	172	83	M
2	53	186	114	M
3	72	162	87	F
4	61	182	93	M
5	70	167	77	M
6	69	168	82	M
7	69	158	81	F
8	60	165	85	M
9	70	173	69	M
10	56	186	99	M

The average age of the group is 65.10 years with a standard deviation of ± 6.94 years. The average length of the patients is 171.90 cm with a standard deviation of 9.88 cm. The average weight of the patients is 87.00 Kg with a standard deviation of 12.53 Kg.

3. RESULTS AND DISCUSSIONS

3.1Hill curve model for SISOCase

In the previous section, it was established that a patient could be modeled through a multi compartmental system. This system includes pharmacodynamic and pharmacokinetic models as well as a nonlinear interaction model which describes the relationship between C_e and the Bispectral Index. It is also known that the BIS monitor introduces some time delay on the BIS signal. In order to represent this situation the Sigmoid Hill Curve can be written as follows:

$$BIS(t) = E_0 - E_{max}\frac{C_e^{\gamma}(t-\tau_d)}{C_e^{\gamma}(t-\tau_d) - C_{50}^{\gamma}}$$

Data of patient 10 were used in this case. In order to appreciate in a better way and to compare the real BIS signal, it was filtered using a 3rd order low pass filter and a cutoff frequency of 2.5 mHz to eliminate the noise. C_e from Propofol and filtered BIS signals are presented below.

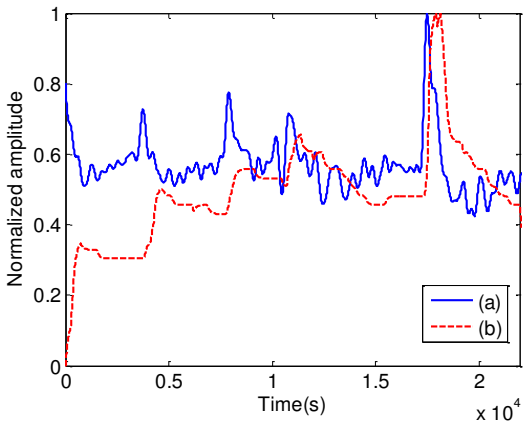

Figure-3. Normalized (a) Filtered BIS and (b)C_{eProp} signals.

If one looks at the filtered BIS signal, several peaks can be observed, which correspond to leg movement and coughing. Since these peaks are the effect of disturbances, and not the effect of Propofol. Taking into account this, the relationship between C_e and the Bispectral Index can be re-written as follows.

$$BIS(t) = E_0 - E_{max}\frac{C_e^{\gamma}(t-\tau_d)}{C_e^{\gamma}(t-\tau_d) - C_{50}^{\gamma}} + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}}u(t-t_1)$$

Where the last part represents the disturbance model and it is a filtered positive unit step; this step occurs at time t_1.

3.1.1. Nonlinear Hill curve

In order to estimate the different parameters of the previous BIS equation, a small part of the signals is taken. It can be observed that the difference in time between BIS and C_{eProp} signals is around 100 seconds, i.e. the time delay in this case is 10 samples ($\tau_d = 10$ samples).

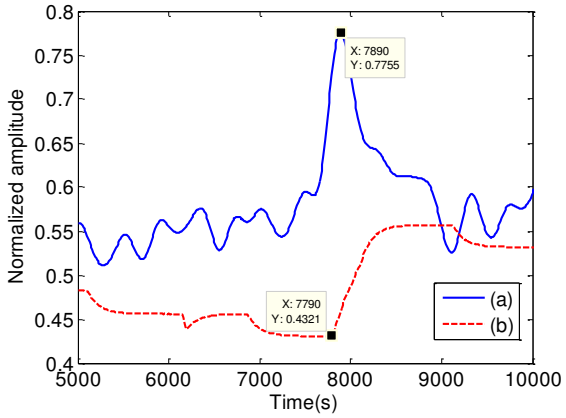

Figure-4. Small part of (a) filtered BIS and (b) C_{eProp} signals taken for identification

The parameters are estimated using the MATLAB® functionlsqnonlin. The results are given below.

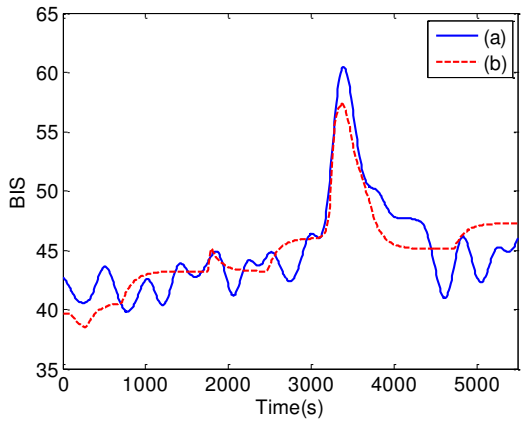

Figure-5. (a) Filtered and (b) estimated BIS for nonlinear SISO case.

Because the number of parameters is higher than the number of equations used for estimation, the lsqnonlin function finds a local solution for this problem. The parameter values in this case are:

$E_0 = 98.2$
$E_{max} = 102.0$
$C_{50} = 1.7$ [µg/ml]
$\gamma = 1.9$
$a_1 = -0.7$

The algorithm needs around 3.8 seconds to estimate all the parameters.

3.1.2. Linear Hill curve

Because in the Intensive Care Unit the Bispectral Index is generally between 40 and 60, the previous BIS equation is linearized around C_{50Prop}.

$$BIS(t) = E_0 - \frac{E_{max}}{2} + \frac{\gamma E_{max}}{4} - \frac{\gamma E_{max}}{4C_{50}} C_e(t-\tau_d) + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}} u(t-t_1)$$

The same small part of the signals is taken and the result of the estimation is shown in Figure-6.

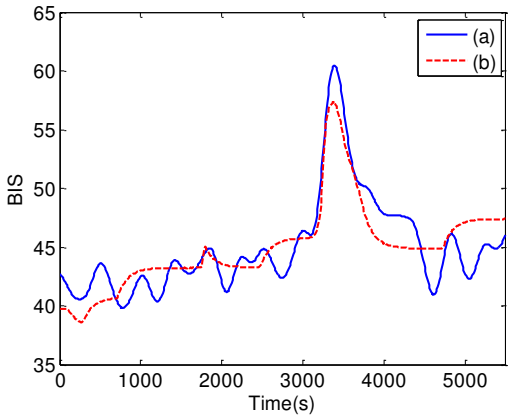

Figure-6. (a) Filtered and (b) estimated BIS for linear SISO case.

In this case the number of parameters is also higher than the number of equations used for estimation. In this way, the `lsqnonlin`function finds a local solution for this problem. The parameter values found in this case are:

$E_0 = 100$
$E_{max} = 99.9$
$C_{50} = 1.5$ [µg/ml]
$\gamma = 1.5$
$b_1 = 0.8$
$a_1 = -0.8$

In this case, the algorithm calculates all of the parameters in 1.9 seconds.

3.1.3. Simplified linear Hill curve

The linearized Hill curve model can be simplified in order to reduce the number of parameter to be estimated.

$$BIS(t) = b - mC_e(t-\tau_d) + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}} u(t-t_1)$$

The same small part of the signals is taken and the result of the estimation is shown below.

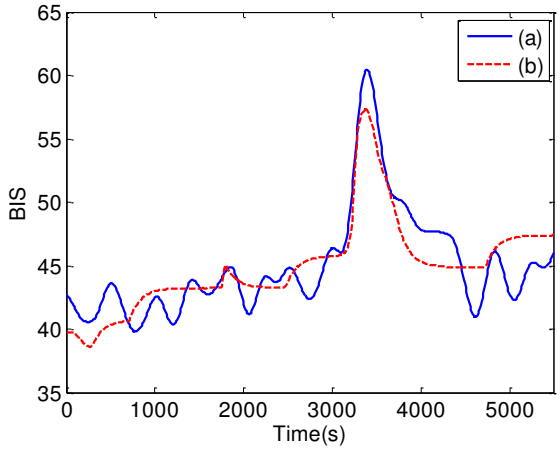

Figure-7. (a) Filtered and (b) estimated BIS for simplified linear SISO case.

In this case the number of parameters to be estimated is decreased but it is still higher than the number of equations used for estimation. In this way, the lsqnonlin function finds also a local solution for this problem. The parameter values found in this case are:

$m = 25.3$
$b = 88.7$
$b_1 = 0.8$
$a_1 = -0.8$

Because the number of parameters is lower, the algorithm needs 1.1 seconds to find them.

For all of the three models the result is good, but it can be improved if the Hill curve model takes into account the Remifentanil signal like a second input.

3.2 Hill curve model for MISOCase

Pharmacodynamic drug interaction is usually described by mathematical models. The combination of Propofol and Remifentanil can be represented by a point on the graph. If the graph is straight, then the interaction is additive. If the graph bows toward the origin, the interaction is synergistic (or supra-additive), which means that the effect of the two drugs taken together is greater than the sum of their separate effect at the same doses. If the graph bows away from the origin, the interaction is infra-additive (greater amounts of both drugs are needed to produce the drug effect when administered together).

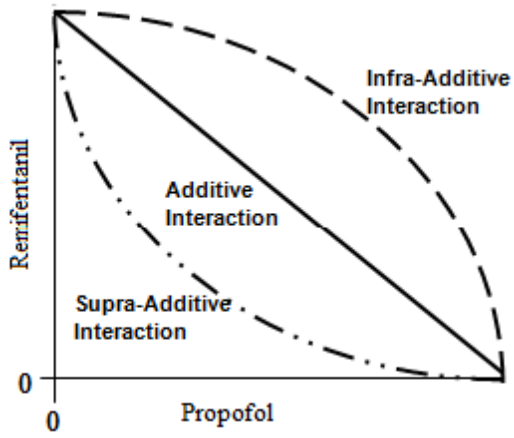

Figure-8. Intravenous anesthetic synergy.

Propofol and Remifentanil have a supra-additive interaction. To obtain the interaction model (BIS depending on the C_{eProp} and $\boldsymbol{C_{eRem}}$), first the concentrations were normalized to their respective potencies C_{50Prop} (Propofol effect concentration at half of the maximum effect) and C_{50Rem} (Remifentanil effect concentration at half of the maximum effect).

$$U_{Prop}(t) = \frac{C_{eProp}(t)}{C_{50Prop}} \frac{[\mu g/ml]}{[\mu g/ml]}$$

$$U_{Rem}(t) = \frac{C_{eRem}(t)}{C_{50Rem}} \frac{[ng/ml]}{[ng/ml]}$$

Remifentanil effect concentration at half of the maximum effect is calculated with the following formula (Ionescu *et al.*, 2008):

$$C_{50Rem} = 13.1 - 0.148(age - 40)[ng/ml]$$

The ratio of the interacting drugs (regardless of the interaction type) can be expressed by:

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

θ is the concentration ratio of the new drug and ranges from 0 (Remifentanil only) to 1 (Propofol only). The new combined drug has its own sigmoid concentration-response relation, as depicted in the Figure-9 (general case).

The concentration-response relation of the two drugs can be described as:

$$\mathrm{BIS(t)} = \mathrm{E_0} - \mathrm{E_{max}}(\theta) \frac{[\mathrm{U_{Prop}(t)} + \mathrm{U_{Rem}(t)}]^{\gamma(\theta)}}{[\mathrm{U_{Prop}(t)} + \mathrm{U_{Rem}(t)}]^{\gamma(\theta)} + [\mathrm{U_{50}}(\theta)]^{\gamma(\theta)}}$$

where θ is the concentration ratio of the two drugs; $U_{Prop}(t) + U_{Rem}(t)$ is the new drug concentration; $\gamma(\theta)$

is the steepness of the concentration-response relation at ratio θ; $U_{50}(\theta)$ is the number of units (U) associated with 50% of maximum effect at ratio θ; $E_{max}(\theta)$ is the maximum possible drug effect at ratio θ. According to (Price *et al.*, 1960), $U_{50}(\theta)$ can be expressed by the following quadratic polynomial:

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

where β is a parameter which ranges between 0 and 1. Table-2 presents the possible values of β for the three drug interaction types. When β is equal to zero, the interaction is additive, whereas, if β is positive or negative, supra- and infra-additive respectively, interaction is obtained.

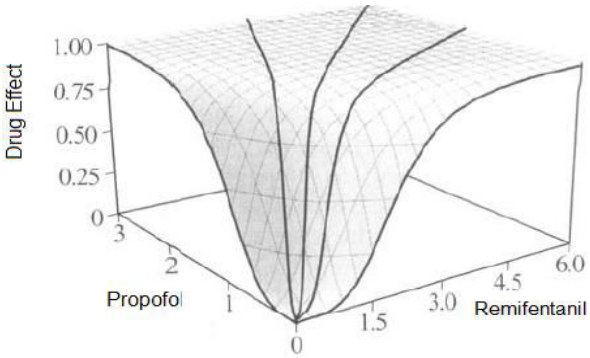

Figure-9. Sigmoid concentration-response relation for Propofol and Remifentanil.

Table-2. Interaction depending of β.

Interaction	β	$U_{50}(\theta)$
Additive	0	1
Supra-additive	>0	<1
Infra-additive	<0	>1

3.2.1. Nonlinear Hill curve

In order to estimate the different parameters of the concentration-response relation of the two drugs, a small part of the signals is taken.

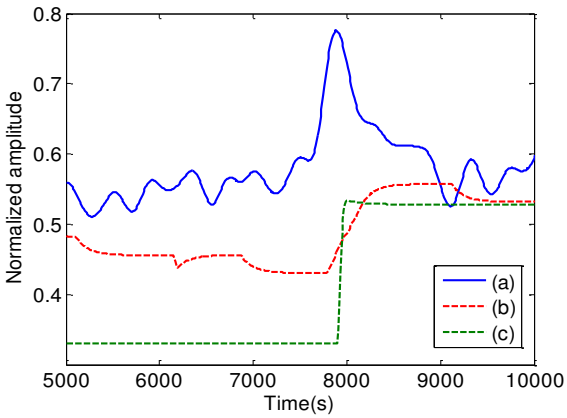

Figure-10. Small part of (a) Filtered BIS, (b) C_{eProp} and (c) C_{eRem} signals taken for identification.

In this case, the difference in time between BIS and C_{eProp} signals is also around 100 seconds, i.e. the time delay is 10 samples ($\tau_d = 10$ samples).

The BIS equation due to the two drugs is re-written as:

$$\mathrm{BIS(t)} = \mathrm{E_0} - \mathrm{E_{max}}\frac{\left[\mathrm{U_{Prop}(t)} + \mathrm{U_{Rem}(t)}\right]^{\gamma}}{\left[\mathrm{U_{Prop}(t)} + \mathrm{U_{Rem}(t)}\right]^{\gamma} + [1 - \beta\theta + \beta\theta^2]^{\gamma}} + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}}\mathrm{u(t - t_1)}$$

And the parameters are estimated using the MATLAB® lsqnonlin function. The results are given below.

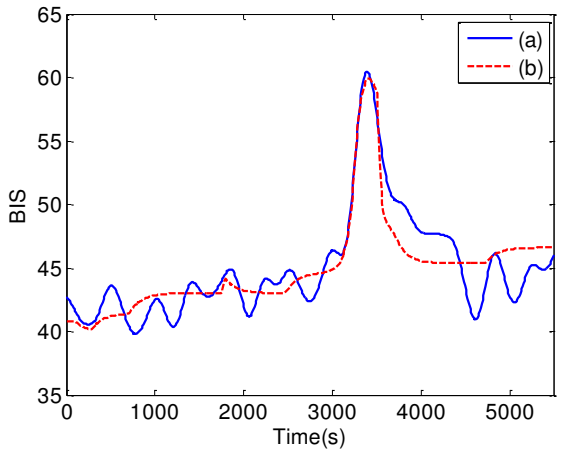

Figure-11. (a) Filtered and (b) estimated BIS for nonlinear MISO case.

Because the number of parameters is higher than the number of equations used for estimation, the lsqnonlin function finds a local solution for this problem. The parameter values in this case are:

$E_0 = 88.9$
$E_{max} = 110.4$
$C_{50Prop} = 3.6$ [µg/ml]
$C_{50Rem} = 2.7$ [ng/ml]
$\beta = 0.9$
$\gamma = 1.7$
$b_1 = 0.5$
$a_1 = -0.9$

The algorithm needs around 5.6 seconds to estimate all of the parameters.

3.2.2. Linear Hill curve

Because in the Intensive Care Unit the Bispectral Index is generally between 40 and 60, the previous equation is linearized around C_{50Prop} and C_{50Rem}.

$$BIS(t) = E_0 - \frac{2^{\gamma}E_{max}}{2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}} + \frac{2^{\gamma}\gamma E_{max}}{2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}} - \frac{2^{\gamma}\gamma E_{max}}{\left[2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}\right]^2}$$
$$+ \left(\frac{2^{2\gamma}\gamma E_{max}}{2\left[2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}\right]^2 C_{50Prop}} - \frac{2^{2\gamma}\gamma E_{max}}{2\left[2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}\right] C_{50Prop}} \right) C_{ePROP}(t - \tau_d)$$
$$+ \left(\frac{2^{2\gamma}\gamma E_{max}}{2\left[2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}\right]^2 C_{50Rem}} - \frac{2^{2\gamma}\gamma E_{max}}{2\left[2^{\gamma} + \left(1 - \frac{1}{4}\beta\right)^{\gamma}\right] C_{50Rem}} \right) C_{eREM}(t - \tau_d) + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}} u(t - t_1)$$

The same small part of the signals is taken and the result of the estimation is shown below.

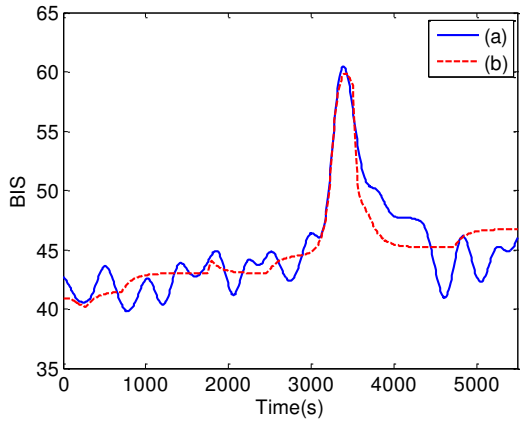

Figure-12. (a) Filtered and (b) estimated BIS for linear MISO case.

In this case the number of parameters is also higher than the number of equations used for estimation. In this way, the lsqnonlin function finds a local solution for this problem. The parameter values found in this case are:

$E_0 = 100.1$
$E_{max} = 99.9$
$C_{50Prop} = 1.7$ [µg/ml]
$C_{50Rem} = 1.0$ [ng/ml]
$\beta = -1.8$
$\gamma = 2.5$
$b_1 = 0.5$
$a_1 = -0.9$

In this case, the algorithm calculates all of the parameters in 0.4 seconds.

3.2.3. Simplified linear Hill curve

The linearized Hill curve model can be simplified in order to reduce the number of parameter to be estimated.

$$BIS(t) = b + m_1 C_{ePROP}(t - \tau_d) + m_2 C_{eREM}(t - \tau_d) + \frac{b_1 q^{-1}}{1 + a_1 q^{-1}} u(t - t_1)$$

The same small part of the signals is taken and the result of the estimation is shown below.

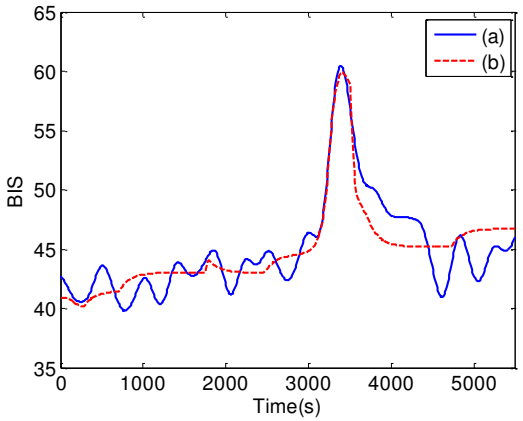

Figure-13. (a) Filtered and (b) estimated BIS for simplified linear MISO case.

In this case the number of parameters to be estimated is decreased but it is still higher than the number of equations used for estimation. In this way, the lsqnonlin function finds also a local solution for this problem. The parameter values found in this case are:

$m_1 = -15.4$
$m_2 = -27.4$
$b = 84.3$
$b_1 = 0.5$
$a_1 = -0.9$

Because the number of parameters is lower, the algorithm needs 0.4 seconds to find them.

For all of the three models the result is better than when only Propofol is used, however the identification was made using a small part of the signal and only for one patient. Thus, in the future, a reliable MISO model should be identified in order to be used in the controller. The identification procedure implemented in this contribution

is offline, but for future works an online procedure should be implemented.

Before applying the Hill curve model identified using MISO case in real-life, several investigations must be carried out. Indeed, to handle the inter- and intra-patient variation of the hypnotic state, the model-based controller with adaptation on prediction model is a suitable solution. In order to apply adaptive control algorithms, it is advisable that the number of model parameters to be adapted is as low as possible. Since the initial patient model is complex, the first step is to obtain a reduced model, such as to have a minimal number of parameters. Further on, the reduced model could be used effectively in a closed-loop predictive-adaptive control strategy for Propofol and Remifentanil delivery during anesthesia. It will be thus possible to exploit the benefits of multi-drug anesthesia in an automatic control.

ACKNOWLEDGEMENT

This work has been funded by IWT TBM project number 060776 supported by the Flemish Institute for Innovation through Science and Technology.

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