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# VALIDATION OF THE MATHEMATICAL MODEL FOR PATIENTS USED IN GENERAL ANESTHESIA

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**ABSTRACT**

In this work the validity of patient model used for prediction in a model-based controller during the clinical trials is examined. The time constant of the pharmacodynamic model and the time delay introduced by the BIS monitor are varied in order to determine which one of these parameters has a greater influence on the output of simulated BIS. First the time constant is changed and no time delay is considered in order to observe its effect on the simulated BIS signal, then the time constant is considered fixed and the time delay value is changed. The results show that the time delay has a greater influence on the simulated BIS than the time constant. Therefore, in the prediction model used by the model-based controller is very important to have a good estimation of the time delay because if time delay is sub-estimated, the control action is useless.

**Keywords:** anesthesia control, pharmacodynamic model, pharmacokinetic model, time constant, time delay.

## 1. INTRODUCTION

Adequate anesthesia can be defined as a reversible pharmacological state where the patient's muscle relaxation, analgesia and hypnosis are guaranteed. Anesthesiologists administer drugs and adjust several medical devices to achieve such goals and to compensate for the effect of surgical manipulation while maintaining the vital functions of the patient.

One of the devices used by clinicians to assess the depth of anesthesia is the Bispectral Index (BIS) monitor, which uses electroencephalographic (EEG) signals (closely related to the level of consciousness of the patient) in order to derive a monotonous measure of depth of anesthesia in a range from 0 to 100 (see Figure-1).

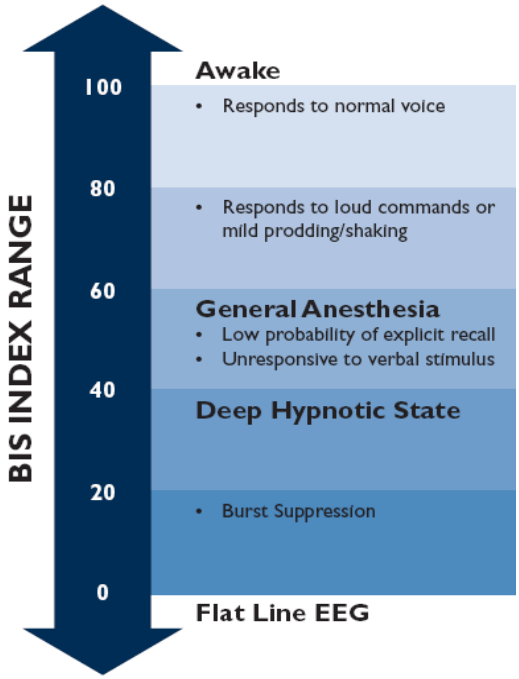


**Figure-1.** BIS Index range guidelines.

BIS equals to 0 means that the patient does not have cerebral activity and BIS equals to 100 denotes that the patient is awake and conscious. When the patient is in Intensive Care Unit (ICU), the desired BIS target is 50 and must remain between 40 and 60.

In order to develop a model-based controller for the drug administration during anesthesia in ICU, a patient model is necessary. If a model-based controller is projected for a precise administration of drugs, the model used in prediction becomes of vital importance for simulation and control. The model used for prediction should not be too complex, in order not to take too much computational time. On the other hand, it must represent the dynamics of the patient as good as possible, in response to the specific drug considered (in this case Propofol).

## 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.

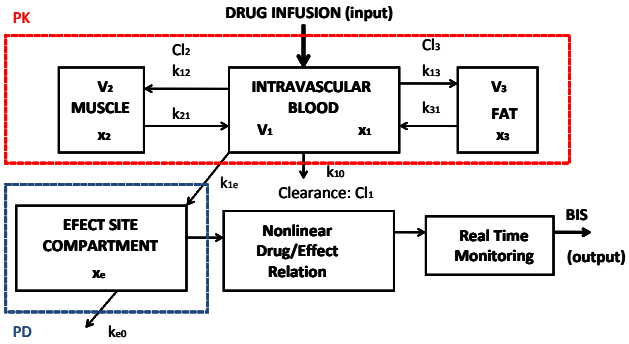


**Figure-2.** Multi-compartmental model.

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-2) 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:

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

with $lbm$ (lean body mass):

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

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-2), 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:

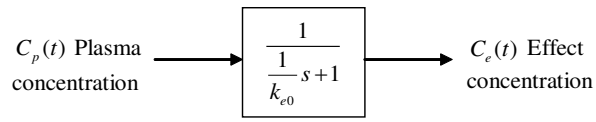


**Figure-3.** Effect-site compartment model.

In this model, $1/k_{e0}$ represents the time constant of the system ($\tau$) 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 $\gamma$ 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.

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.

Regarding the PD model, the value of $k_{e0}$ is also known, but not the parameters of the *Sigmoid Hill Curve*. Since these parameters are unknown for each patient some nominal values have been used for the simulations. The nominal value for $C_{50}$ is 2.5µg/ml and for $\gamma$ is 3.01. The other two parameters of the Hill curve, $E_{max}$and $E_0$ are considered equal to the value of 100.

## 3. RESULTS AND DISCUSSIONS

The purpose of this section is to examine the validity of patient model used for prediction in a model-based controller during the clinical trials. The time constant of the PD model and the time delay introduced by the BIS monitor were varied in order to determine which one of these parameters has a greater influence on the output of simulated BIS. In order to achieve this, the recorded signals in the clinical trials were used as input of a simulator. First the time constant is changed and no time delay is considered in order to observe its effect on the simulated BIS signal, then the time constant is considered fixed and the time delay value is changed.

The simulator developed uses the Propofol infusion rate $u(t)$ as input signal to the PK model, which uses the biometric values of each patient to produce the Propofol plasma concentration $C_{pProp}$; this signal goes to PD model, which has the time constant of the system ($\tau = 131.58$ seconds for all of the patients), and the result is the Propofol effect site concentration $C_{eProp}$; this signal is applied to the Sigmoid Hill model, which uses nominal values to produce the BIS signal. Sometimes the signal quality of measured BIS is not very good and a time delay between the signal displayed by the BIS monitor and the real BIS of the patient appears. This time delay ($\tau_d$) is included in the simulator. In this way, the used model in the simulator of the patient can be represented by the block diagram in Figure-4.

Data of patient 10 were used in this case. In order to appreciate in a better way and to compare the real and the simulated BIS signals, the real BIS signal was filtered using a 3rd order low pass filter and a cutoff frequency of 2.5 mHz to eliminate the noise. Propofol and filtered BIS signals during a certain time interval are presented in Figure-5. In this case, it can be observed that when the Propofol level increases the BIS level starts to decrease, indicating an inverse proportionality between these signals.

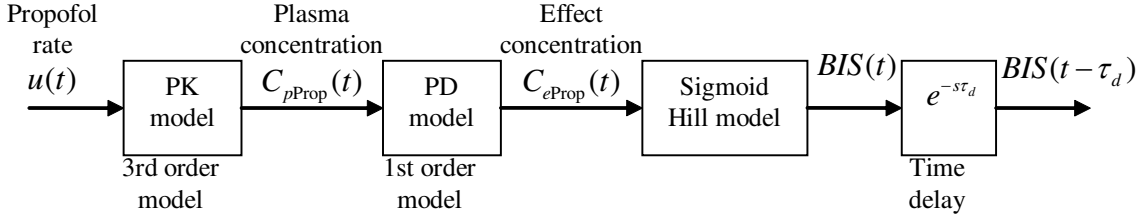


**Figure-4.** Simulator block diagram.

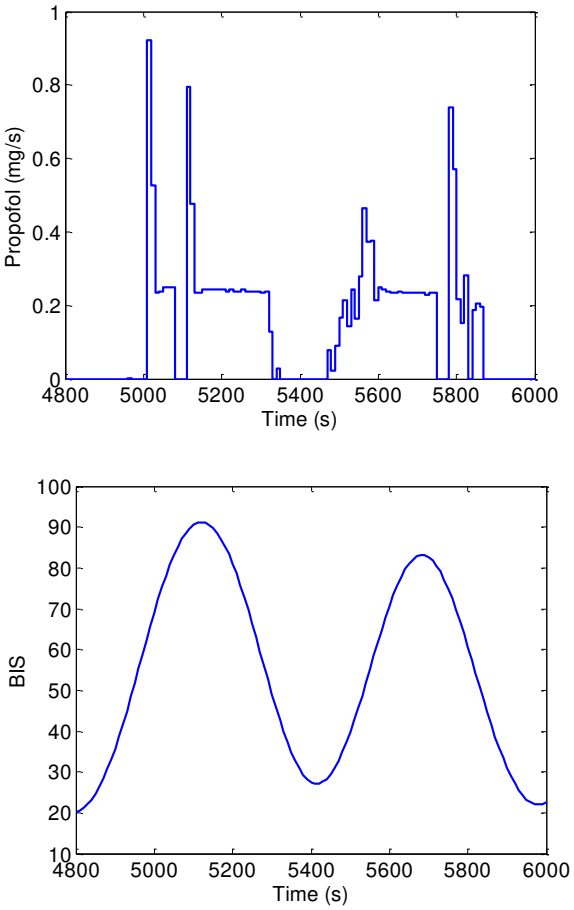


**Figure-5.** Propofol (left) and filtered BIS (right) signals-Patient 10.

### 3.1 Changes in the time constant

Initially, Propofol signal is applied to the PK-PD model of the simulator getting as output the effect site concentration, $C_{eProp}$ signal.

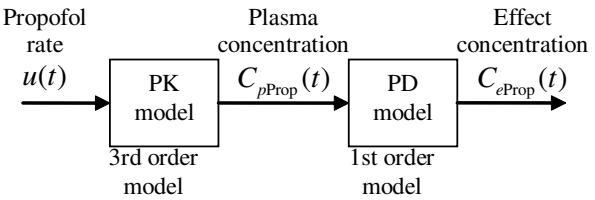


**Figure-6.** PK-PD models.

The time constant of the nominal PD model is $\tau = 131.58$ seconds. The value of this constant is increased by 20%, 50% and 80%, this is 26.32 s, 65.79 s and 105.26 s respectively; getting the $C_{eProp}$ values shown as follows.

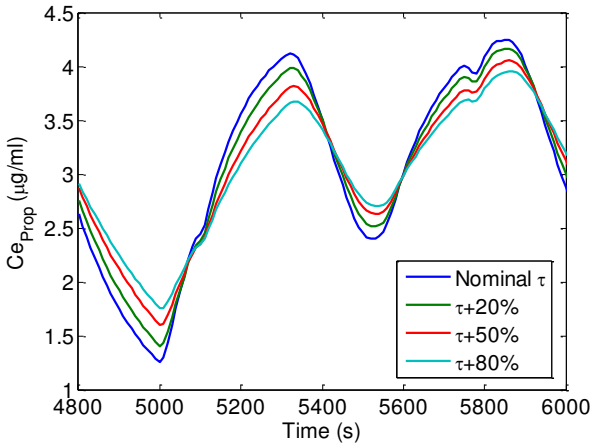


**Figure-7.** $C_{eProp}$ when $\tau$ is increased.

It can be observed that when the value of the time constant is increased the response speed of the system is reduced. When the value of the time constant is increased by 80% the time peak of the response shows a delay of 10 seconds compared to the nominal system response.

Subsequently, the value of the time constant is decreased by 20%, 50% and 80% and the $C_{eProp}$ values presented bellow are obtained.

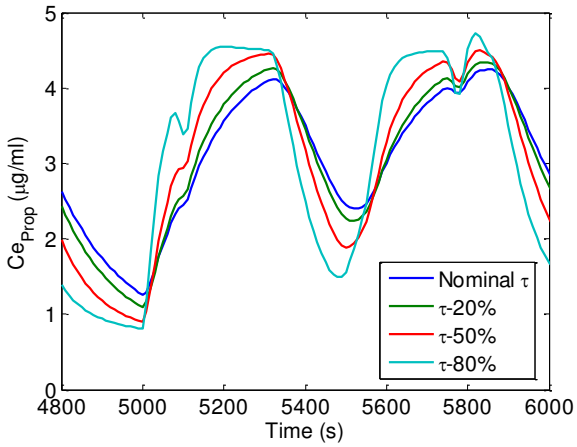


**Figure-8.** $C_{eProp}$ when $\tau$ is decreased.

When the value of the time constant is decreased, the response speed of the system increases. If the value of the time constant is decreased by 80% the time peak of the response is 10 seconds smaller than of the nominal system. Secondly, Propofol signal was used as input of the simulator without taking into account any time delay (Figure-9). The time constant of the nominal PD model is increased and decreased by 20%, 50% and 80% obtaining the BIS values shown in Figure-10.

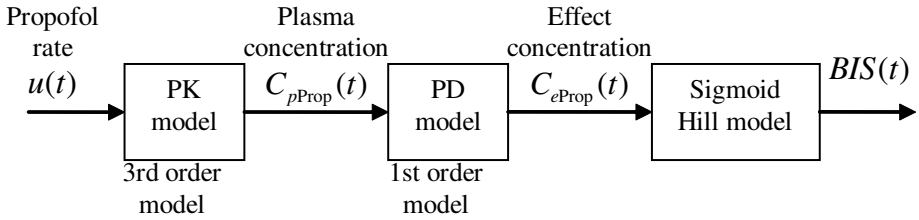


**Figure-9.** Simulator without time delay.

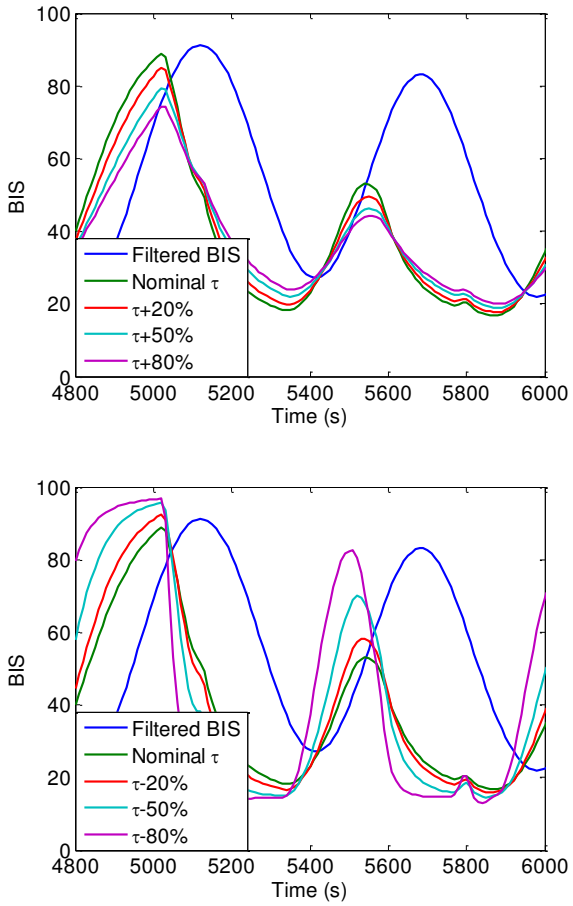


**Figure-10.** BIS when $\tau$ is increased (left) and decreased (right).

The increase or decrease of the time constant only influences the speed of system response. When the time constant is increased or decreased by 80%, the time peak of the response shows a shift of only 10 seconds compared to the nominal system response. Furthermore, the rise and fall slope of the nominal case (with $\tau = 131.58$ seconds) is closer to the real BIS than the slope in the cases when the time constant was varied.

Furthermore, it can be seen that when the Propofol signal presents peak values from zero to values higher than 0.5 mg/s (Figure-11 - left), the BIS level falls rapidly (Figure-11 - right), and the rise slope of the BIS signal is different that the fall slope.This occurs because the system never reaches the steady state and the rise or fall speed depends of the conditions in which the simulated system is when a high value of Propofol is applied. To verify this, a Propofol test signal (Figure-12 - left) was used in the simulator as input. The output of the PK-PD model is presented in Figure-12 (right). The static characteristic response (Figure-13) shows an apparent hysteresis because the system never reaches the steady state. However, when positive steps are applied (Figure-14 - left) the dynamic response of the PK-PD model is very similar to the case when negative steps are applied (Figure-14 - right). It can be observed that the apparent hysteresis occurs because the system never reaches the steady state and the rise or fall speed depends on the conditions in which the simulated system is when a high value of Propofol is applied.

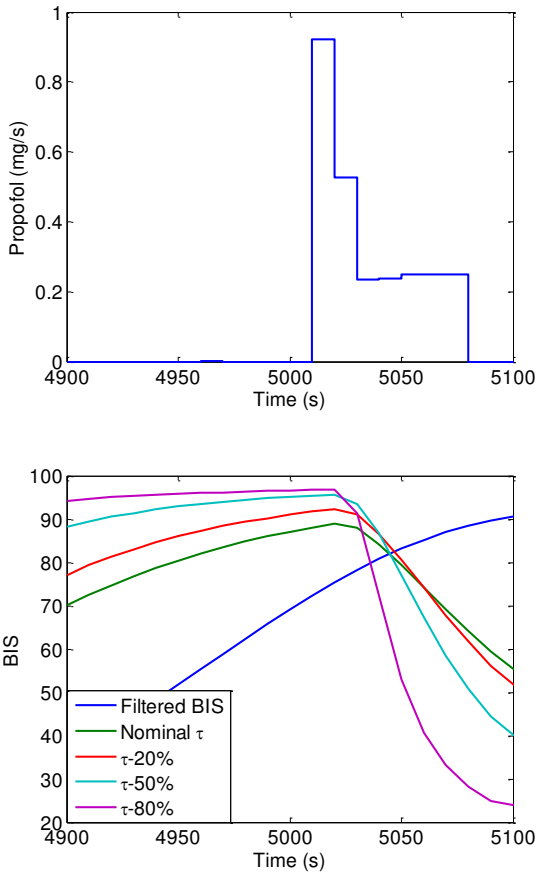


**Figure-11.** Peak of Propofol (left) and reduction of BIS (right).

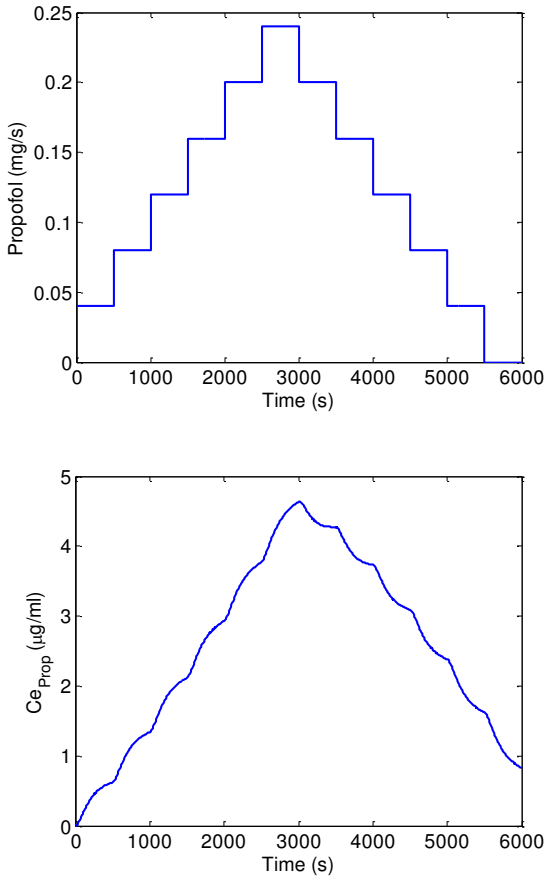


**Figure-12.** Propofol test signal (left) and $C_{ePrassociated}$ response (right).

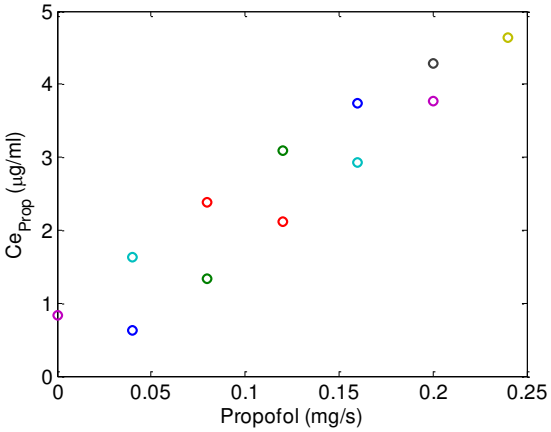


**Figure-13.** Static response for test signal.

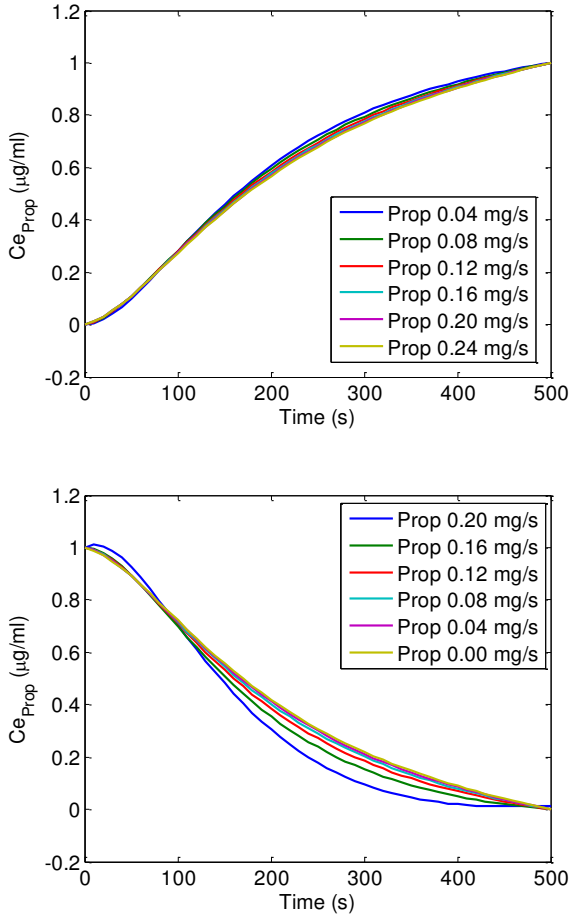


**Figure-14.** PK-PD model's dynamic response for positive (left) and negative (right) steps.

### 3.2 Changes in the time delay

The increase or decrease the time constant influences the speed of system response. However, a shift between the real and simulated BIS signals can be clearly observed. In this section, the time constant of the system is considered fixed ($\tau = 131.58$seconds) and the time delay value is changed.

Initially, a time delay of 8 samples (80 seconds) is used in the simulator (Figure-15). The comparison between the filtered real BIS signal and BIS signal from the simulator is presented in Figure-16. The slope of the simulated BIS signal is the same as that of the real BIS, but the delay of 8 samples is not sufficient yet to ensure that the peaks of the signals occur in the same moments of time. Subsequently, a time delay of 15 samples (150 seconds) is used in the simulator. The two BIS signals (real and simulated) are presented in Figure-17.

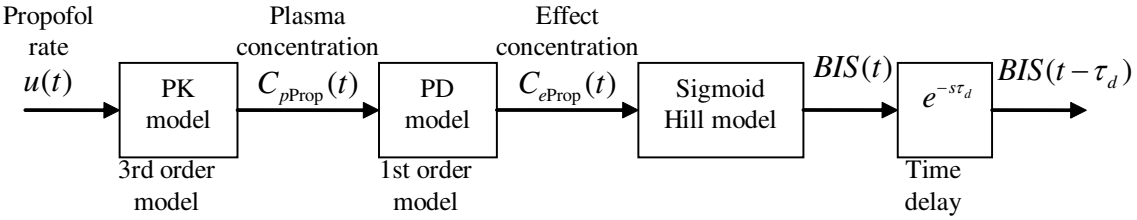


**Figure-15.** Simulator with time delay.

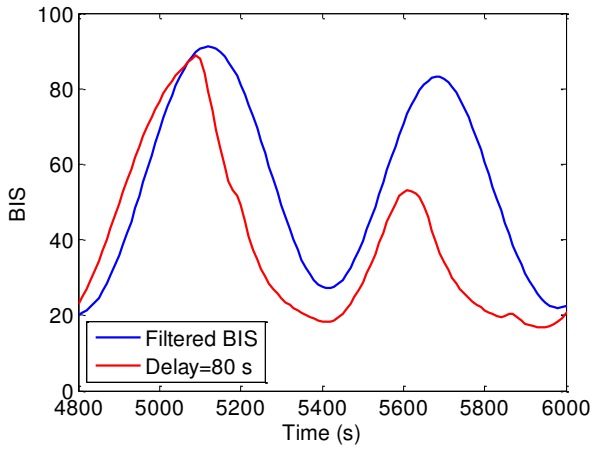


**Figure-16.** Comparison between real and simulated BIS (delay 80 s).

When a time delay of 15 samples is used, the response of the simulated BIS is very close to the actual patient response. In this manner, the changes in time delay, when the time constant of the system remains fixed in $\tau = 131.58$ seconds, allows obtaining a response of the simulator very close to the actual patient response. The best approximation is obtained for $\tau_d = 15$ samples.

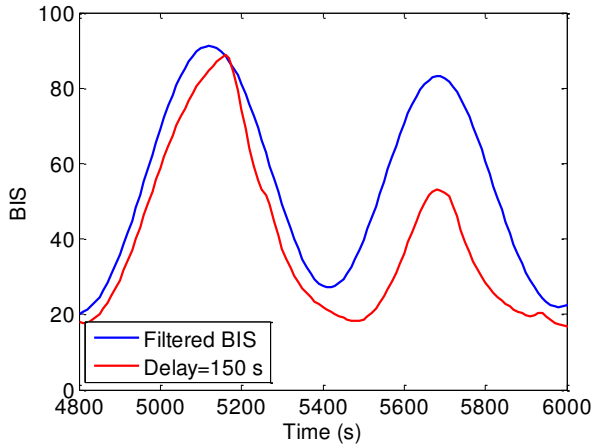


**Figure-17.** Comparison between real and simulated BIS (delay 150 s).

The time delay has a greater influence on the simulated BIS than the time constant. Therefore, in the prediction model used by the model-based controller is very important to have a good estimation of the time delay because if time delay is sub-estimated, the control action is useless. The 4th order model can be used in prediction if a correct time delay is estimated. The estimation procedure of time delay will be presented in a future work.

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