Estimation of patient sensitivity to drug effect during Propofol hypnosis

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***Abstract*—In this paper we introduce a methodology for adapting a population model to the actual patient dynamics, i.e. an individualization of target controlled infusion (TCI) based infusion. The solution proposed in this paper is to use the effect site concentration (Ce) of the drug into the patient as a feedback signal and to adapt the parameters of the Hill curve (relating the BIS and Ce) during the induction phase, resulting in a patient-individualized closed loop control of anesthesia. This allows moving from conventional generic patient models for drug infusion regulatory loops to personalized medicine.**

***Index Terms*—model-based control, anesthesia modeling, drug delivery systems, personalized healthcare.**

I. Introduction

Drug delivery systems play a crucial role in clinical practice. Therefore, control strategies applied to drug delivery systems will lead to a longer and healthier life of patients worldwide. An optimal control strategy should ensure the following:

- on-line and fast calculation of the optimal drug dose;
- model adaptation according to the patient state (personalized healthcare);
- patients safety;
- side effect reduction by means of drug infusion rate optimization.

First and the most important challenge is patient safety followed by issues such as: acceptance of the medical staff to what the engineering community is offering, communication between physicians and engineers due to different terminology. Besides, all these social challenges, difficulties from the modeling point of view have to be tackled (e.g. inter- and intra-patient variability, time and dose constrains, etc.). Despite all these difficulties, control of biomedical applications hold a tremendous promise.

In clinical practice target controlled infusion (TCI) systems are used for drug infusion [1]. Target controlled infusion principle is the following: the anesthesiologist decides the necessary concentration to achieve the desired effect as fast as possible without overdosing. Concentration is calculated using a pharmacokinetic model that takes into account the patient biometric parameters (e.g. age, weight, height, etc). TCI system is based on open-loop control strategy entitled to adjust drug concentration in the blood. Drug regulation is done by giving an initial bolus and followed by infusion.

Control of biomedical applications requires the same elements as any other process control application. These components are: a system to be controlled (the patient), a controlled variable that measures the relevant drug effect, a setpoint for this variable, and actuator, which could be the infusion pump driving the administration of drug and last but not least a controller to manipulate the actuator. In model-based control strategies the availability of a model is necessary.

The standard modeling strategy which has been commonly used to describe the relationships between drug inputs and patient output indicators (or effects) is that of compartment models [1]. Pharmacokinetic (PK) compartment models are widely used as means of predicting the distribution of drug in the body by modeling the simultaneous diffusion of drug through body tissues and the blood flow [2]. Most drugs are characterized by models containing a central compartment, which typically is represented by blood, and peripheral compartments that represent groupings of internal organs and fatty tissues of the body. A virtual effect compartment may be included, typically consisting of a nonlinear pharmacodynamic (PD) model plus a first order linear time invariant system that is used to reflect the time-lag in the patient response to anesthesia (see [3], [4], [5] for details).

In this paper we introduce a methodology for adapting a population model for Propofol induced hypnosis to the actual patient dynamics, i.e. an individualization of TCI based infusion. This allows moving from conventional generic patient models for drug infusion regulatory loops to personalized medicine. The structure of this paper is as follows: In Section II the model of Propofol hypnotic is given. In this section an updated overview of the model used nowadays in clinical practice is presented. Section III describes the current status of control strategies applied to anesthesia, missing pieces and challenges to tackle with towards a fully automated drug delivery system. This is followed by Section IV, results are presented and discussed. Conclusions are presented in the last section of the article.

II. Propofol hypnosis

For a large number of surgeries (e.g. heart surgery, brain surgery, orthopedy, etc.) the patient has to be fully anesthetized. The anesthesia paradigm is defined as a combination of three main components: (1) hypnosis, (2) neuromuscular blockade and (3) analgesia. Hypnosis is characterized by unconsciousness, inability of the patient to recall intra-operatory events.

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Neuromuscular blockade is preventing unwanted movement or muscle tone and causes paralysis during surgical procedures. Analgesia is characterized by absence of pain perception. In order to control the depth of anesthesia by means of model-based control strategies, a model which captures the dynamics of the patient is required [6], [7].

The selection of the model input and output variables is crucial for achieving optimal control [8], [9]. Pharmacokinetic and pharmacodynamic blocks denote compartmental models [2]. The Pharmacokinetic/pharmacodynamics models most commonly used for propofol and remifentanil are the 4th order compartmental model described in [10], [11], [12] Pharmacokinetic/pharmacodynamics models represents an important step in the process of drug development and this modeling tool also brought a significant contribution to anesthesia. Pharmacokinetic/pharmacodynamics models are a set of mathematical equations used to predict the drug effect in time. A schematic representation of a three compartmental model is presented in Figure 1. In this figure V_1, V_2 and V_3 represents the volume for the corresponding compartment.

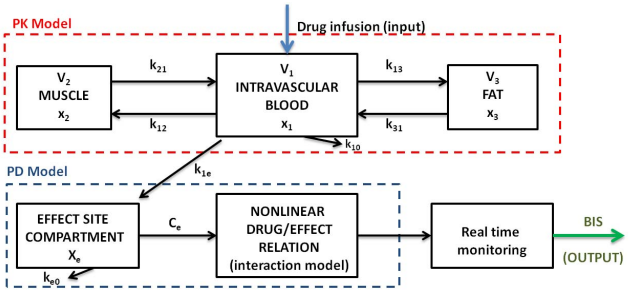

Fig. 1. A schematic representation of a three compartmental model.

Compartmental analysis is based on mathematical models, i.e. systems of ordinary differential equations (see equations 1-4) which are widely used to characterize the uptake, distribution and elimination of a drug into the human body.

$$\dot{x}_1(t) = k_{12}x_1(t) - k_{13}x_1(t) - k_{10}x_1(t) - k1_e x_1(t) \\ -k_{21}x_2(t) + k_{31}x_3(t) + u(t)/V_1 \quad (1)$$

$$\dot{x}_2(t) = k_{21}x_1(t) - k_{12}x_2(t) \quad (2)$$

$$\dot{x}_3(t) = k_{13}x_1(t) - k_{31}x_3(t) \quad (3)$$

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \quad (4)$$

The peripheral compartments two and three model the drug exchange of the blood with well and poorly diffused body tissues. The amount of drug in fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3, respectively. The parameters k_{ji} for ij, denote the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ $[mg/s]$ is the infusion rate of the anesthetic drug into the central compartment. An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The amount of drug in this compartment is represented by x_e. The effect compartment receives drug from the central compartment by a first-order process and it is regarded as a volume-less additional compartment. Therefore, the drug transfer frequency from the central compartment to the effect site-compartment is equal to the frequency of drug removal from the effect-site compartment.

The parameters of the pharmacokinetic models depend on age, weight, height and gender [10], [11], [12] and can be calculated for Propofol as follows :

$$V_1 = 4.27[l] \quad V_3 = 2.38[l] \\ V_2 = 18.9 - 0.391 \cdot (age - 53)[l] \quad (5)$$

$$C_{l1} = 1.89 + 0.0456(weight - 77) - \\ 0.0681(lbm - 59) + +0.0264(height - 177)[l/min] \quad (6)$$

$$C_{l2} = 1.29 - 0.024(age - 53)[l/min] \quad (7)$$

$$C_{l3} = 0.836[l/min] \quad (8)$$

$$k_{10} = \frac{C_{l1}}{V_1}[min^{-1}]; k_{12} = \frac{C_{l2}}{V_1}[min^{-1}] \\ k_{13} = \frac{C_{l3}}{V_1}[min^{-1}] \quad (9)$$

$$k_{21} = \frac{C_{l2}}{V_2}[min^{-1}]; k_{31} = \frac{C_{l3}}{V_3}[min^{-1}] \\ k_{e0} = 0.456[min^{-1}] \quad (10)$$

where lbm represent the lean body mass, C_{l1} is the rate (called also clearance rate) at which the drug is cleared from the body, C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution.

The lbm for man and women is calculated using the following expressions:

$$lbm_m = 1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2} \quad (11)$$

$$lbm_f = 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2} \quad (12)$$

The relation between the effect site concentration and the Bispectral Index (BIS) is given by a nonlinear sigmoid Hill curve:

$$BIS(t) = E_0 - E_{max}\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_{50}^{\gamma}} \quad (13)$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the C_{50} determines the patient sensitivity to the drug. E_0 and E_{max} are considered equal to the value of 100.

A. Adaptation of the Hill curve parameters for patient-individualized anesthesia control

Since the most important challenge for control is the inter- and intra-patient variability [6], [7], [9], it makes sense to adapt the parameters of the Hill curve to fit the actual Hill curve of the patient instead of a nominal one. The main disadvantage, with nominal Hill curve parameters is that of under- or over-dose. The available measured BIS values and the calculated $\widehat{C_e}$

from the 4th order pharmacokinetic-pharmacodynamic model are related by the linear approximation and the time delay [13]:

$$BIS(t) = K * \widehat{C_e}(t-\tau) + d \tag{14}$$

where the time delay τ is fixed and K and d are estimated at every sample time for every preselected time delay value. Notice that in steady-state, the time delay is not necessary since

$$BIS_{ss} = \widehat{K} C_e^* + \widehat{d} \tag{15}$$

which allows to extract and hence to adapt the desired C_e^* for a desired BIS value at every sample time. In the context of TCI, adapting C_e^* will provide a more accurate drug dosing. In fact, for a desired BIS_{ss} of 50, this is nothing else than the estimation of the C_{50} of the patient. The estimation is based on a classic linear least squares algorithm and the error is calculated using the following expression:

$$\sigma^2 = \frac{1}{N} \sum_{i=1}^{N} \varepsilon^2(i) \tag{16}$$

with N the number of samples (if a sliding time interval is used) and ε the error between the real and estimated values.

Notice that in case of $C_e = \widehat{C_e}$ then the pharmacokinetic-pharmacodynamic model is accurately describing the patient. However, the adaptation of K and d parameters imply that the pharmacokinetic-pharmacodynamic model does not necessarily need to be perfectly known. Any error in its gain will be corrected intrinsically by correcting the error in the Hill curve.

B. Analysis of the Hill curve parameters

Consider again the form of the sigmoid Hill curve from (13). Introducing $X = \frac{C_e}{C_{50}}$ we have:

$$X^\gamma = \frac{E_0 - E}{E_{max} - E_0 + E} \tag{17}$$

with E the effect of the drug (i.e. BIS). The derivative, i.e. the slope of the nonlinear curve, is given by:

$$\begin{gathered} \frac{dE}{dX} = -E_{max}[\frac{\gamma X^{\gamma-1}}{1+X^\gamma} - \frac{X^\gamma \gamma X^{\gamma-1}}{(1+X^\gamma)}] = \\ -E_{max}\gamma \frac{X^{\gamma-1}}{(1+X^\gamma)^2} \end{gathered} \tag{18}$$

using

$$\frac{X^\gamma}{1+X^\gamma} = \frac{E_0 - E}{E_{max}} \tag{19}$$

it follows that the derivative with respect to C_e can be written as:

$$\frac{dE}{dC_e} = \frac{dE}{dX}\frac{dX}{dC_e} = \frac{-E_{max}\gamma}{C_{50}} \frac{1}{X^{\gamma-1}[\frac{X^\gamma}{1+X^\gamma}]^2} \tag{20}$$

and using $X = \frac{C_e}{C_{50}}$ we obtain:

$$\frac{dE}{dC_e} = \frac{-\gamma}{C_{50}} \frac{(-E_{max} - E_0 + E)(E_0 - E)}{E_{max}} \tag{21}$$

which suggests that the slope of the Hill curve depends not only on the γ values, but also on the ratio $(-\gamma)/C_{50}$. For the case that $E_{max} = E_0 = 100$ it follows that:

$$\frac{dE}{dC_e} = \frac{-\gamma}{C_{50}} \frac{E(100 - E)}{100} \tag{22}$$

and for the case $E = 50$ we have that:

$$\frac{dE}{dC_e} = -25 \frac{\gamma}{C_{50}} \tag{23}$$

The latter relation can be then used to obtain the slope of the patient and determine the actual sensitivity to the drug effect, which changes in time during clinical interventions.

III. Model based control strategy for anesthesia

In this section the challenges from the control point of view are presented. From the perspective of control system, three levels of complexity can be distinguished. The basic procedure is the open-loop practice in which the anaesthetist, according to the parameters of the patient (age, weight, sex, ASA) directly uses predefined infusion rates of hypnotic drugs. According to the response observed through patient vital signs the drug rates can be modified (the anesthetist is then the controller).

Fully automated drug delivery systems for anesthesia will be an important step forward in clinical practice. It contributes to patient safety and reduces the workload of the anesthesiologist while providing him more flexibility to focus on critical issues. Moreover, a cost reduction and a faster return of the patient to daily duties will be achieved [1]. There is significant research in the area of individualized patient models and closed loop control strategies for anesthesia [8], [14], [15].

In Figure 2 a schematic representation of a feedback control strategy from the drug delivery point of view in anesthesia is presented. Note that all these control strategies require the availability of a patient model. Obviously, the more accurate the model, the better the performance of the closed loop, i.e. lesser chance for over- and under-dosing.

The closed loop control scheme consists of:

- the syringe pump, as the actuator;
- the patient, as the system to be controlled;
- the monitoring device, which can be considered as the measurable representation of the system to be controlled;
- the controller, which is represented by the anesthesiologist (when no feedback control is implemented) and by the computer (when feedback control is implemented) and in this case the role of the anesthesiologist is that of a supervisor.

The work of [16], [17] showed that PID controllers can ensure intraoperative hemodynamic stability and a faster recovery of the patient can be achieved. Moreover, the work of Absalom [18], [19], [20] presents the improved performance of the closed loop control over manual operation. In the last years, massive research focused on advanced control of anesthesia has been done. Several approaches on the control structure, controlled variables and model prediction have been investigated. In [21], [22], [23] the use of drug concetration in the brain has been used as a controlled variable. From the control structure point of view, model based predictive control technique has been also investigated [14], [15], [6], [9].

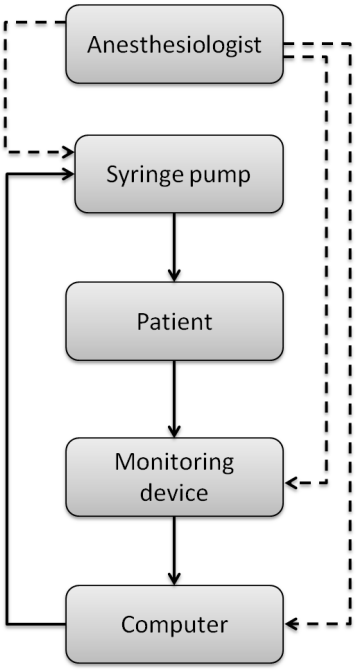

Fig. 2. Schematic representation of a feedback control strategy for drug delivery in anesthesia.

IV. Results and Discussions

For the purpose of illustrating the efficacy of the proposed strategy for model adaptation, Table 1 presents the changes occurring in the Hill curve. We assume the patient changes its drug effect (pharmacodynamics) dynamics from a sensitive case to a resistant case (this is also the case in practice). Take for example a dry sponge put in the water for the first time. The amount of water in this case will be much lager then if the sponge would be apriori wet. During anesthesia, the reaction at molecular levels of the GABA receptors is dependent on previous state [1].

The nominal setpoint $C_e^* = 5mg/ml$ will be used during the target controlled infusion strategy. After ΔBIS, ideally, one should apply closed loop (feedback based) control, e.g. PID control. However, the setpoint needs to be specified. The adaptation strategy adapts the setpoint and thus converges to the true C_{50} value at all times.

The intra-patient variability in the Hill curves is shown in Figure 3 using values from Table 1 and (13). It can be observed that at first the patient is the most sensitive to drug effect. The estimated sensitivity (gain) and the corresponding C_{50} values are given in Figure 4 below. It can be observed that the gain at the beginning is an order of the magnitude higher than at the end of scenario. Without an adaptation from the nominal values, any control strategy will be sub-optimal (possibly unstable) when facing such high variations in the gain in the closed loop.

One can note from Figure 4 that there are also significant changes in the C_{50} values. Any target controlled infusion

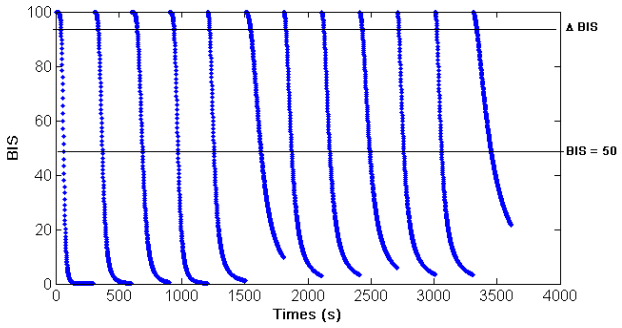

Fig. 3. Changes in the Hill curve in time for our hypothetic patient as given in Table 1

C_{50}	γ
6.15	6.89
6.76	4.29
8.44	4.10
6.56	4.12
4.93	2.46
12.00	2.42
6.33	2.24
6.44	2.18
8.02	2.10
4.95	1.84
4.82	1.85
13.70	1.65
7.42	3.00

TABLE I
Patient parameters as in (13) used for estimation of the new setpoint

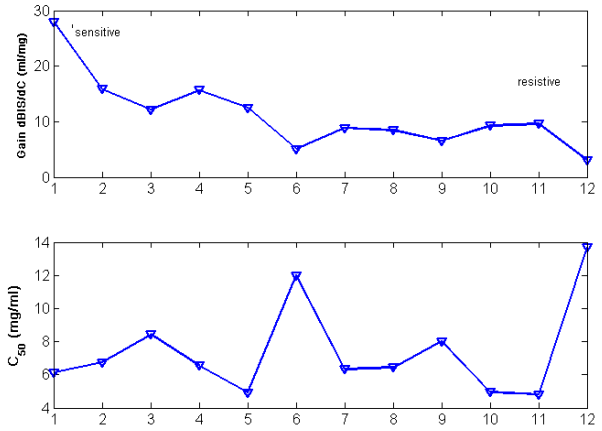

Fig. 4. Sensitivity (gain) and C50 values from Table 1.

system based on specifying C_e to achieve the nominal C_{50} will face significant modeling uncertainty. The result of our adaption algorithm is given in Figure 5. Notice that in this case the estimation was reinitialized at a fixed time interval (600 seconds) at the nominal value for C_{50}. This approach has some advantage that at certain times (2400, 5400 seconds, etc.) the steady state value is closer to this nominal value

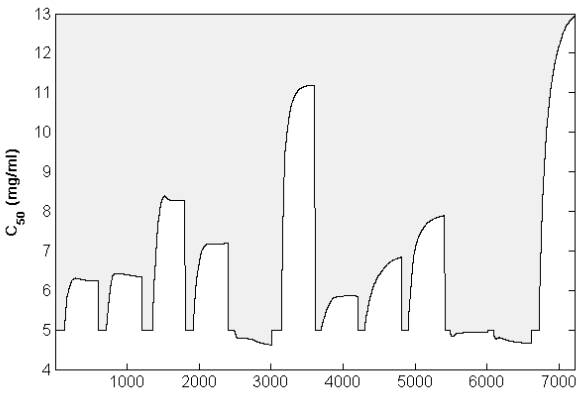

Fig. 5. Estimation of the C_{50} values.

than to the previously estimated value. However it also has some disadvantages, since in most of the cases the true C_{50} value lies quite far from the nominal one. This drawback is a counteracted by the relatively fast convergences of the least square estimation algorithm due to the simplicity of the approach (i.e. (15) represents a line).

The particular approach of estimating a line is based on the fact that after the hypnosis induction phase, the BIS value will remain in the 40-60 interval in the condition of target controlled infusion regulation or PID control. In this paper, however, the identified C_{50} can be used to derive the corresponding γ values and use these in (13) for obtaining the Hill curve of the patient at all times.

V. Conclusions

This paper proposes a simple yet effective methodology to estimate the patient sensitivity to drug effect during Propofol hypnosis. Hypothetic case of intra-patient variability was used to demonstrate the effectiveness of the proposed strategy. The result of this work can be further explored by introducing model-based closed loop feedback control such as PID or advanced control strategies.

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