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Anesthesiologist in the Loop and Predictive Algorithm to Maintain Hypnosis While Mimicking Surgical Disturbance

Clara M. Ionescu * **Dana Copot** * **Robin De Keyser** *

* *Ghent University, Research Group on Dynamical Systems and Control, Technologiepark 914, 9052 Ghent-Zwijnaarde, Belgium (e-mail: claramihaela.ionescu@ ugent.be).*

Abstract: Many regulatory loops in drug delivery systems for depth of anesthesia optimization problem consider only the effect of the controller output on the patient pharmacokinetic and pharmacodynamic response. In reality, these drug assist devices are over-ruled by the anesthesiologist for setpoint changes, bolus intake and additional disturbances from the surgical team. Additionally, inter-patient variability imposes variations in the dynamic response and often intra-patient variability is also present. This paper introduces for the first time in literature a study on the effect of both controller and anesthesiologist in the loop for hypnosis regulation. Among the many control loops, model based predictive control is closest to mimic the anticipatory action of the anesthesiologist in real life and can actively deal with issues as time lags, delays, constraints, etc. This control algorithm is here combined with the action of the anesthesiologist. A disturbance signal to mimic surgical excitation has been introduced and a database of 25 patients has been derived from clinical insight. The results given in this paper reveal the antagonist effect in closed loop of the intervention from the anaesthesiologist when additional bolus intake is present. This observation explains induced dynamics in the closed loop observed in clinical trials and may be used as a starting point for next step in developing tools for improved assistance in clinical care.

Keywords: regulatory loops, predictive control, patient variability, anaesthesia, drug dosing control, antagonist effect, feedforward action, disturbance rejection

1. INTRODUCTION

Many regulatory loops address drug dosing problems, with applications varying among diabetes (Kovacs, 2017), anaesthesia (Copot and Ionescu, 2014), immunodeficiency (Popovic et al., 2015) and hormonal treatment (Churilov et al., 2009). Drug intake, uptake and clearance have been characterized using either compartmental models, either input-output filters by means of linear transfer functions. Compartmental models for drug kinetics are available in the literature from population data and are based on Gaussian normalized distributions (Pereira, 2010). Additional dynamic response in drug effect is added as a pharmacodynamic (PD) additional compartment, usually nonlinear. The pharmacokinetic (PK) and PD models then combined deliver the response to a drug input administered either oral or intravenous, of an average patient (Holford and Sheiner, 1999).

These average patient models are no longer valid in the framework of individualised treatment paradigm, irrespective of the medical application. It is therefore important to deliver models which are sufficiently accurate yet simple in structure such that adaptation may be obtained (Nino et al., 2009). To circumvent the complexity of compartmental models, input output models driven from online data have been proposed as transfer functions with poles and zeros identified for each patient (Soltesz et al., 2013; Dumont et al., 2009). Their time constants may be related to various residence times from different tissue properties and volumetric elements.

The complete regulatory paradigm is however much more complex that anything literature addresses from control engineering point of view. The computer based drug dosing optimisation is always limited in the information it receives from the system (i.e. vital signals from the patient). In general anaesthesia, the anesthesiologist must provide a cocktail of optimal dosages of various drugs to induce and maintain this complex physiological state in the patient, while avoiding under- and over-dosing, and coping with great patient variability (Ionescu et al., 2014; Copot and Ionescu, 2014). As such, anaesthesia is much of an art rather than a numerical problem. The expertise of the team of doctors and the unique patient response may play at times a role delimiting the fine line between life and death-threatening situations.

Rather than delivering control algorithms based on individualised patient models and optimal dosing protocols, in an effort to mimic the operation theater with the actors playing a role, fuzzy control seemed to be a good tool at hand for multiple variable control (Shieh et al., 2005). The fact that the controller was using a patient model

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based on neural network modelling with manifold of inputs to extract via nonlinear functions the response to specific drug input was clearly a step towards reality. However, the necessity to ensure stability and maintain constraints for patient well-being and safety required a control law which can provide an analytical solution. Furthermore, feedback based control loops have a drawback in their looking backward policy, whereas true anticipatory reactions of the anaesthesiologist require predictive control techniques, i.e. looking in the future policies (Ionescu et al., 2014).

In this paper, we revisit our previous predictive control algorithms for hypnosis regulation to include and analyse the effect of anaesthesiologist in the loop (Ionescu et al., 2008, 2014, 2015; Nascu et al., 2015). Since these are merely assist devices, the clinical expert will always have a supervisory role and intervene whenever necessary. From a control engineering viewpoint, the action of anaesthesiologist is based on information which is not available to the controller. For instance, the controller sees only the hypnotic state of the patient, past values and past drug dosing samples, makes a prediction for optimizing the best suitable dosing scenario to reach/maintain the desired level of hypnosis. The anaesthesiologist, however, has a broader view of information, from the various sensing devices monitoring vital signs of the patient, e.g. heart rate, respiratory rate, distal oxygenation, and can anticipate effects in the hypnotic state from the information cocktail. Additional drugs to stabilise various other vital signs alter the information and the controller does not know this, i.e. in heart surgery patients medication alters heart rate and indication of elevated hypnosis may not be directly observable in the feedback signal (Ionescu et al., 2014).

The paper is organized as follows. Next section presents the materials and methods used, i.e. the PK-PD model used to simulate the patients. The surgical stimulation profile acting as a disturbance is also presented in the same section. Third section presents the control algorithm and the additional bolus intake protocol. The results and discussion thereof are given in the fourth section, and a conclusion section summarizes the main outcome of this work and points to further use.

2. PATIENT MODEL FOR HYPNOSIS

As an important part of the anaesthesia paradigm, hypnosis is characterized by unconsciousness, i.e. inability of the patient to recall intra-operatory events. In order to control the depth of anesthesia by means of model-based control strategies, a suitably defined model which captures the dynamics of the relation between drug uptake, drug effect and the patient is required (Nascu et al., 2015; Ionescu et al., 2015).

The selection of the model input and output variables is crucial for achieving optimal control (Dumont et al., 2009; Ionescu et al., 2014). The PK-PD model most commonly used for Propofol is the 4th order compartmental model described in (Schnider et al., 1998, 1999). A generic schematic representation of a PK-PD compartmental model is presented in Fig. 1.

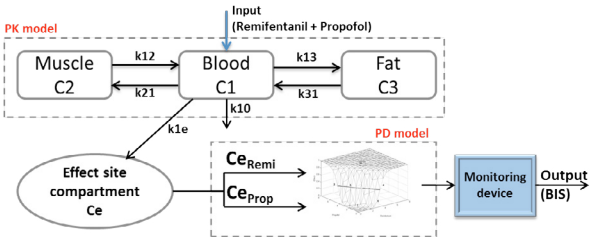

Fig. 1. A schematic representation of a compartmental model for PK and PD with two inputs and one output. For the purpose of this paper, only one input (Propofol) has been considered active and the second one (Remifentanil) is zero.

The ODEs characterizing the Propofol uptake as the PK model are given by the relations to the variation of concentrations x_i with $i = 1..3$ the respective compartments (i.e. blood, muscle, fat):

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

with $u(t)$ the input infusion rate of drug (Propofol, Remifentanil, or a combination of both).

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

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

with the parameters k_{ji} for ij, denoting the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ $[mg/s]$ the infusion rate of the anaesthetic drug into the central compartment.

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

An additional hypothetical effect compartment represents the lag between drug plasma concentration and drug response. The amount of drug in this compartment is represented by x_e. The parameters of the PK models depend on age, weight, height and gender (Schnider et al., 1998, 1999) and can be calculated for Propofol as follows :

$$\begin{aligned}&V_1 = 4.27[l] \quad V_3 = 2.38[l] \\ &V_2 = 18.9 - 0.391 \cdot (age - 53)[l]\end{aligned} \tag{5}$$

The volumes V_1, V_2 and V_3 represent the compartmental volume, i.e. blood, muscle and fat.

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

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

$$C_{l3} = 0.836[l/min] \tag{8}$$

$$\begin{aligned}&k_{10} = \frac{C_{l1}}{V_1}[min^{-1}]; k_{12} = \frac{C_{l2}}{V_1}[min^{-1}] \\ &k_{13} = \frac{C_{l3}}{V_1}[min^{-1}]\end{aligned} \tag{9}$$

$$\begin{aligned}&k_{21} = \frac{C_{l2}}{V_2}[min^{-1}]; k_{31} = \frac{C_{l3}}{V_3}[min^{-1}] \\ &k_{e0} = 0.456[min^{-1}]\end{aligned} \tag{10}$$

where lbm represent the lean body mass, C_{l1} is the rate (called also clearance rate) at which the drug is cleared