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Drug Interaction Between Propofol and Remifentanil in Individualised Drug Delivery Systems

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Abstract: Optimal and safe control of drug delivery systems with continuous infusion protocol is of key importance to avoid over-dosing or under-dosing of the patient. Advanced model based control techniques are able to predict and regulate the amount of drugs given to the patient but they rely heavily on patient model. This paper discusses and investigates the effects of synergistic drug interaction between Propofol (hypnotic) and Remifentanil (opioid) and its requirements on the robustness and stability of the closed loop system.

Keywords: drug delivery systems, interaction modeling, personalized healthcare

1. INTRODUCTION

Individualised drug delivery systems during general anesthesia represent an important step forward in clinical practice. The anesthesiologist has to provide specific care during surgery or maintenance for the three main components of general anesthesia (i.e. neuromuscular blockade, hypnosis and analgesia) (Absalom et al. (2011); Struys et al. (2003); Bailey and Haddad (2005)). In order to achieve adequate levels of anesthesia the anesthesiologists must adjust several parameters. An overview of the inputs and the outputs of the anesthesia paradigm is depicted in figure 1.

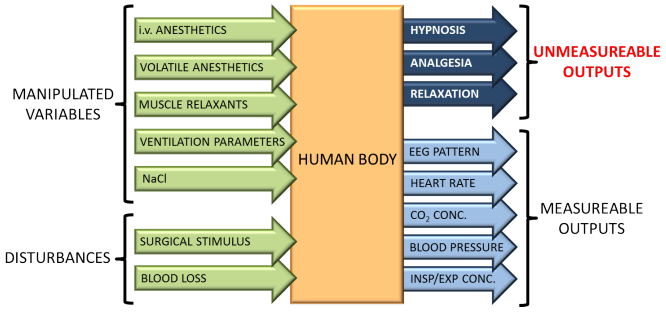

Fig. 1. Oversimplified overview of the anesthesia paradigm.

Nowadays, in clinical practice, open-loop systems such as target controlled infusion systems are used. The open-loop control strategies rise inaccuracies in drug delivery due to the fact that they are based on generic population models which obviously diverge from the real patient response. The role of the anesthesiologist is to tackle this difference by adequately changing the drug infusion rates. To ease the burden of this crucial role, a solution may be given by introducing model based closed-loop control techniques. These strategies are based on the availability of a patient model and then the role of the anesthetist will be freed of some regular tasks so that he can focus more on the state of the patient. From the patient-individualized control point of view, pharmacodynamics models capture the inter- and intra-patient variability and pose most challenges for control (i.e. highly nonlinear characteristic) (Schnider et al. (1998, 1999)). This is mainly due to the nonlinearity introduced by the multiple drug interaction model and significant unmeasurable disturbances present in the system (noxious stimuli). A solution for optimal control strategy of general anesthesia has not yet been found. Closed-loop control strategies for depth of anesthesia (DOA) regulatory systems are nowadays investigated by several research groups worldwide, and a brief overview is given below, within the physical limits of this paper.

Neuromuscular blockade (NMB) level is measured from the electromyography signal obtained by electrical stimulation. Control of NMB is done my means of continuous infusion of a muscle relaxant. During the last two decades several automatic control strategies for NMB have been developed (Teixeira et al. (2014)).

Quantification of the hypnotic agent can be done by means of availability of various indexes which are derived from signals such as electroencephalogram (EEG). For instance, bispectral (BIS) index is derived form EEG and it has been shown to have a high sensitivity and specificity to measure the drug effect (Struys et al. (2003)). Currently, BIS signal is used as a reference for closed loop purposes (Ionescu et al. (2008)).

The third component, i.e. analgesia, is still to be demystified (Ionescu et al. (2014)). An accurate and objective measurement of the patient's response to analgesic drug is still lacking. However, when BIS is known, a suitable

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interaction model between hypnotics and analgesics might be helpful to simultaneously control both components of depth of anesthesia.

Various interaction models between intravenous hypnotics and analgesics have been described (Bouillon et al. (2004)). Pharmacodynamic (PD) response surface models have been developed to quantitatively describe the relationship between two (or more) drug concentrations with their corresponding combined clinical drug effect. Until now, these interaction models have not been effectively used in closed-loop control of depth of anesthesia.

The role of this paper is to illustrate the degree of nonlinearity present in case of inter- or intra- patient variability and how it affects the performance of the closed loop system. For this purpose, we make use of the PD model for synergy between Propofol (hypnotic drug) and Remifentanil (opioid drug) and simulate various situations. Closed loop control elements are enumerated and motivated.

The structure of the paper is the following: *Section 2* describes the hypnotic and opioid agents. In this section the pharmacokinetic and pharmacodynamics of the two drugs are presented. This is followed by *Section 3* where the interaction between the hypnotic and opioid agents is analyzed. In this section some simulation results are presented and discussed. *Section 4* focuses on the control problem in general anesthesia. In this section an overview of the state of the art is presented and the importance of drug interaction in developing an optimal control strategy for general anesthesia is tackled.

2. HYPNOTIC AND OPIOID AGENTS

Before discussing the PD properties of the hypnotic and opioid drug a schematic representation of a three compartmental model is presented in figure 2.

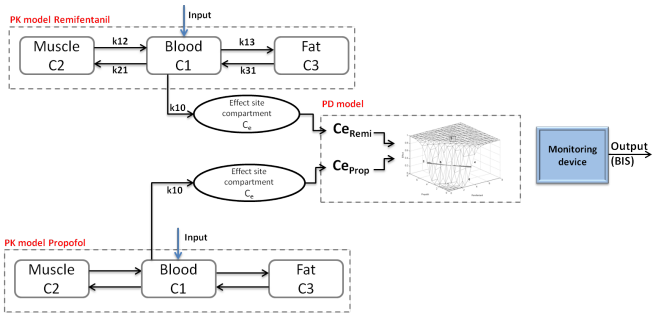

Fig. 2. A schematic representation of a three compartmental PK-PD model of the patient.

In this figure $k12$, $k21$, $k13$, $k31$, $k1e$ represent the intercompartmental rate constants, $k10$ represents the clearance rate from compartment 1. Concentrations in each compartment are denoted by C_1 - compartment 1, C_2 - compartment 2, C_3 - compartment 3, C_e - effect site compartment.

During general anesthesia the patient receives a hypnotic drug (eg. Propofol) to ensure loss of consciousness and absence of post-operative recall of events occurred during surgery. Additionally, the patient receives a dose of opioid drug (eg Remifentanil) to ensure the absence of pain. Some reasons why Remifentanil is increasingly used in combination with Propofol in todays clinical practice are listed below:
i) recently released sophisticated drug delivery systems such as target-controlled infusion (Egan and Shafer (2003)) allow for precise titration and safe administration in patients with very narrow therapeutic margin;
ii) some new clinical applications are currently growing, such as Remifentanils use as the sole agent for sedation during painful procedures in patients breathing spontaneously, or as the analgesic component in intensive care sedation;
iii) simultaneously, Remifentanil has permitted important scientific research, leading to better understanding of postoperative hyperalgesia and acute tolerance to the analgesic action of opioids.

Remifentanil equilibration half-time between plasma and the effect compartment has been modelled using continuous EEG and is fast (0.1-1.5 min) (Glass et al. (1994)). Transfer to central nervous system competes with distribution processes and time to peak effect should be considered instead. During intravenous administration, the PK properties of Propofol are characterized by an initial distribution half-life of 2 - 8 min, with the slow distribution half-life ranging from 30 - 70 min. This depends on several factors such as: method of administration (i.e. bolus or infusion dosing) age, disease, body weight, gender, etc. (Gepts et al. (1988); Shafer and Varvel (1991); Schnider et al. (1998, 1999); Kirkpatrick et al. (1988)). These properties make these two drugs ideal candidates for continuous infusion DOA regulatory systems.

Propofol concentration for loss of consciousness is reduced by 25% in the presence of Remifentanil (i.e. 6 ng/ml) (Nieuwenhuijs et al. (2003); Manyam et al. (2006); Albertin et al. (2006); Bouillon et al. (2004); Kern et al. (2004); Drover et al. (2004); Mertens et al. (2003); Fechner et al. (2003)). Hence, a synergistic interaction with hypnotics is present in the reaction of Remifentanil. The minimal hypnotic concentration required to control noxious stimuli is markedly reduced (50-60%) when a lower concentration of opioid is added (Manyam et al. (2006)). Intermediate opioid concentrations allow a further reduction in hypnotic requirement of 15-20%. The combination which allows the quickest recovery is shifted towards high Remifentanil, low hypnotic concentrations. Typically, Remifentanil concentrations must be above 8 ng/ml for laryngoscopy or incision. This synergistic interaction is also observed for the hypnotic effect, but is of a lower magnitude. Without opioid, the hypnotic concentration required for loss of consciousness is lower than the one to prevent response to noxio us stimuli.

3. DRUG-INTERACTION ANALYSIS

In clinical practice the anesthesiologist takes advantage of the synergy between drugs. One such advantage is given by the fact that the therapeutic goals of the anesthetic drugs can be achieved faster and with less toxicity. Another advantage is that when combination of drugs is used, also a faster recovery is achieved in comparison to the case when individual drugs in higher doses are administered (**?**). The

synergistic interaction between hypnotics and opioids is characterized using response surface methodology (Minto et al. (2000); Bouillon et al. (2004); Kern et al. (2004); Manyam et al. (2006)). The response-surface approach creates a three dimensional plot of the sedative and opioid concentrations versus drug effect, quantitatively describing the PD interaction of the two drugs.

The response-surface method serves as a scientific basis to perform the analysis of the inter- and intra-patient variability. Combined with PK knowledge, the opioid-hypnotic response surfaces may be used to establish the target concentrations of the two drugs. In this way, an adequate anesthesia level may be achieved and the recovery process may be optimized (Minto and Schnider (2008)).

Clinical application of these drug interaction models through the use of computer simulations constitutes a revolutionary advance in understanding of anesthetic drug clinical behavior. Clinical display systems incorporating these response-surface drug interaction models are being tested for real time use in the operating room as an approach to drug dosage optimization (Struys et al. (2003); Johnson et al. (2008)).

Nowadays, response-surface models represents a strong framework to guide the formulation of rational dosing strategies. The response surface is navigated in the sense that various points on the surface map are targeted at different times during the anesthetic to achieve the goals of the anesthetic. Response surface method has enabled an in depth and clinically relevant understanding of the marvelous synergy of sedatives and opioids when they are administered together. It is this knowledge that can be used now by the control engineers to exploit its benefits for individualized drug dosing strategies (Ionescu et al. (2014)).

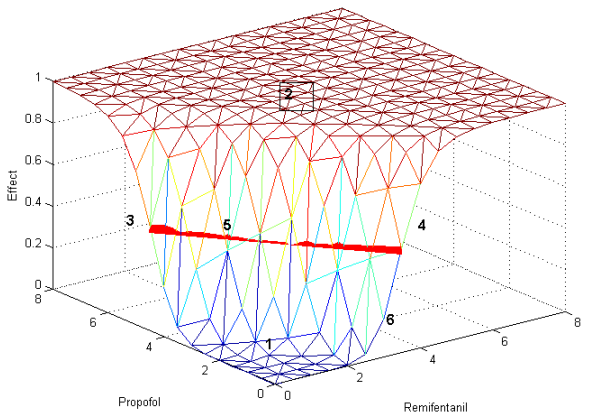

Fig. 3. The relationship between opioid and hypnotic drug concentrations and the probability of non-responsiveness.

In presence of synergic drug interaction, a response surface as in figure 3 is obtained. The X- and Y- axes of figure 3 are the normalized concentrations of opioid and hypnotic, respectively. The Z axis of figure 3 is probability of non-responsiveness. This surface has fundamental properties of the opioid-hypnotic relationship. In this figure #1 represent no chance of non-responsiveness (this can be because the patient is wide awake) while #2 represent no chance of response. #3 shows the relationship between the hypnotic drug and response when no opioid is given to the patient, #4 shows the relationship between the hypnotic drug and response when large doses of opioid are given to the patient and #5 represent the maximum synergy between the two drugs. The cross X denotes the mean population values at 50% effect for Propofol concentration C_{50P} and for Remifentanil concentration C_{50R}, respectively.

A general interaction model for Remifentanil and Propofol can be represented by the following equation (Kern et al. (2004)):

$$E = E_{max} \frac{\left(\frac{C_P}{C_{50P}} + \frac{C_R}{C_{50R}} + \sigma * \frac{C_P}{C_{50P}} * \frac{C_R}{C_{50R}}\right)^{\gamma}}{1 + \left(\frac{C_P}{C_{50P}} + \frac{C_R}{C_{50R}} + \sigma + \frac{C_P}{C_{50P}} + \frac{C_R}{C_{50R}}\right)^{\gamma}} \quad (1)$$

where: E_{max} represent the maximum effect of both drugs, C_P and C_R are the Propofol and Remifentanil concentration in the effect compartment, C_{50P} and C_{50R} represent the drug concentration for 50% of the maximum effect, γ denotes patient's sensitivity to the drugs and σ characterizes the nature of the interaction between the two drugs.

In figures 4 and 5 the surface response of Propofol and Remifentanil interaction but also the probability of non-responsiveness are shown. Each patient has an individualized response to drugs. Therefore, for each patient a different concentration of Propofol and respectively Remifentanil is requested. Moreover, other important parameters in characterizing interaction between two drugs are σ and γ (ref. (1)).

In the remainder of this section, we illustrate the changes in surface response when varying σ (figure 4) and γ (figure 5). In figure 4 the response surface when varying σ is presented. In general, we have that the interaction:

$$\begin{array}{l} \text{for } \sigma = 0, \text{ is additive} \\ \text{for } \sigma < 0, \text{ is antagonistic and} \\ \text{for } \sigma > 0, \text{ is synergic.} \end{array} \quad (2)$$

In figure 5 the influence of γ on patient's sensitivity to the drug effect is presented for synergistic case, the one valid for combinations of Propofol and Remifetanil.

4. CLOSED-LOOP CONTROL OF ANESTHESIA

In the last decade, automated drug delivery systems have become popular among researchers, due to enhanced need for individualised drug delivery protocols and the enabling role of control methodologies. The main functions of the automation systems in anesthesia are monitoring and controlling of the main variables (hypnosis, analgesia and muscle relaxation). In the past, monitoring of the patient during general anesthesia was performed by looking at several signs such as: sweat, head lifting, movement, etc. Nowadays, monitoring of general anesthesia has been considerably improved. From the point of view of controlling the main variables many efforts have been made in order to provide the anesthetist with trustworthy techniques for monitoring.

Current state of use in terms of target controlled infusion combined with feedback control in drug delivery systems is still based on averaged population models. In

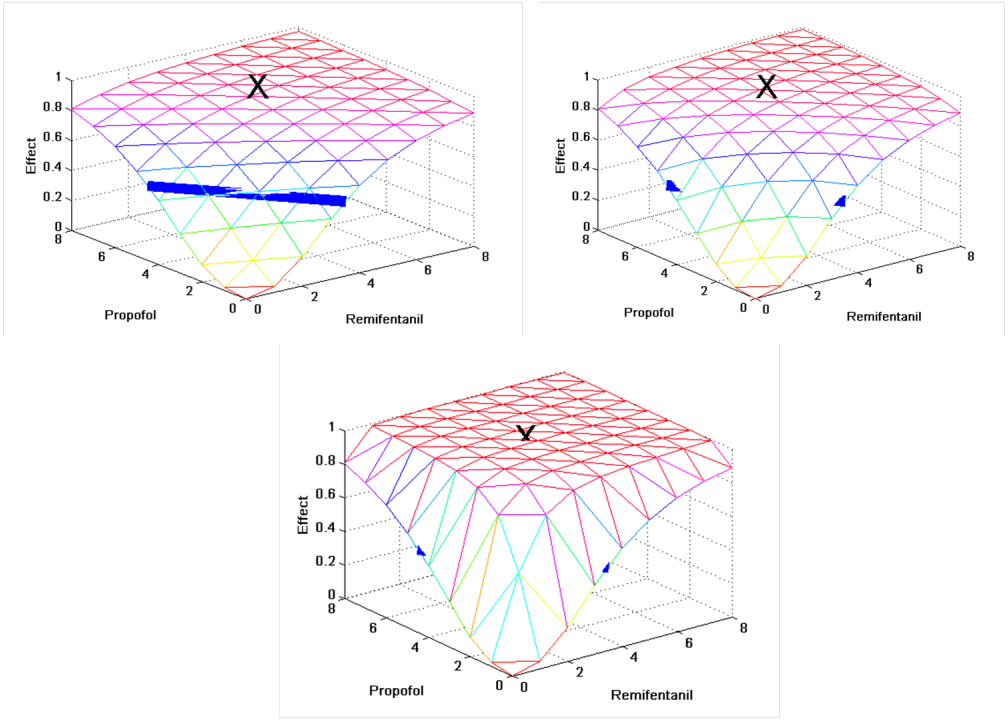

Fig. 4. Surface showing the interaction between hypnotic and opioid drug and the probability of non-responsiveness for changes in σ. The values of σ used to show the changes in surface response are: σ=0.04 (top left), σ=0.5 (top right) and σ=8 (bottom) and γ was fixed to 2.5.

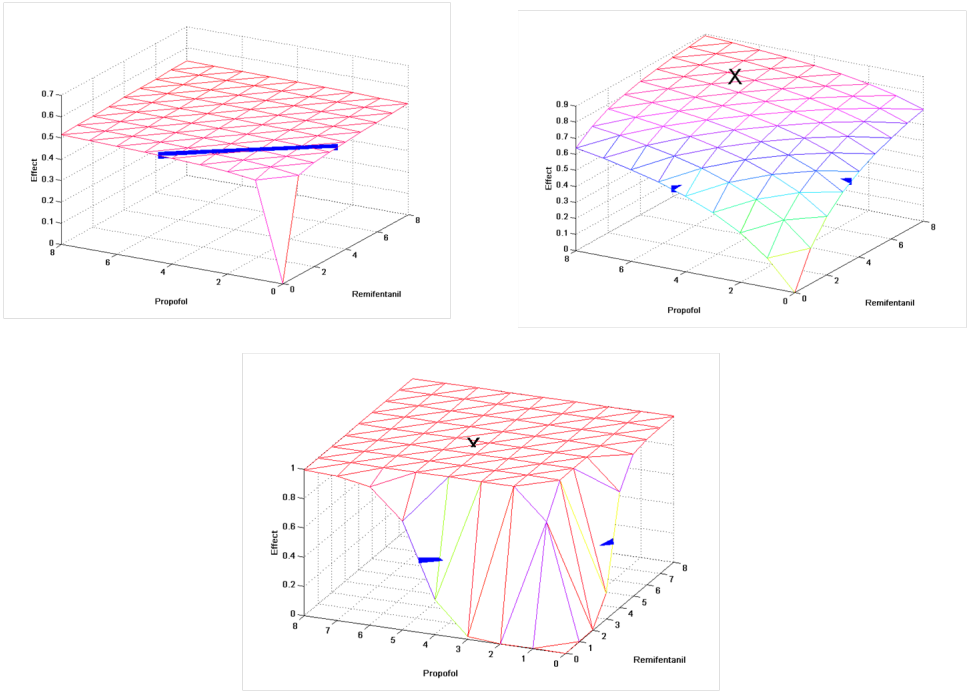

Fig. 5. Surface showing the interaction between hypnotic and opioid drug and the probability of non-responsiveness for changes in γ (γ=0.1 (top left), γ=1 (top right) and γ=10 (bottom) and σ was fixed at 0.2).

anesthesia, several studies including classic and advanced control strategies have been reported successfully (Dumont (2014); Ionescu et al. (2011); Dumont et al. (2009); Rocha et al. (2014); Ionescu et al. (2008); Krieger and Pistikopoulos (2014); Ionescu et al. (2015)).

We will discuss here the model based adaptive closed loop control principle, for this is the precursor of model based predictive control drug delivery systems (see figure 6).

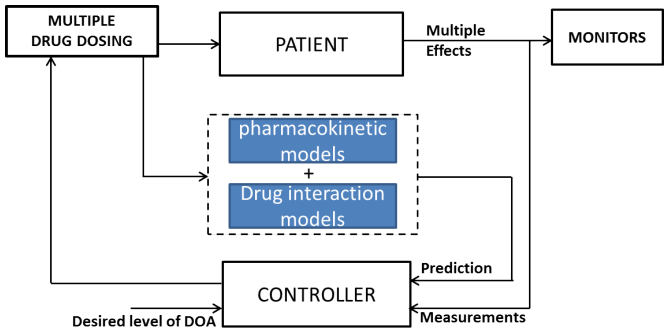

Fig. 6. Block diagram of a model-based adaptive closed-loop system for automatic drug delivery.

The control system consists of four parts (figure 6):
1) the patient as the system to be controlled;
2) the response, which is considered as a measurable representation of the process to be controlled;
3) a model of the input-output relationship
4) a controller.
To achieve adequate anesthesia anesthesiologists regularly adjust the settings of several drug infusion devices as well as the parameters of the breathing system to modify the manipulated variables shown in figure 1. Several authors have recognized the advantages associated with the use of automatic controllers in anesthesia (Ionescu et al. (2008); Absalom et al. (2011); Dumont et al. (2009); Dumont (2014); Ionescu et al. (2011)) and they are briefly reviewed below.

First, if the routine tasks are taken over by automatic controllers, anesthesiologists are able to concentrate on critical issues which may threaten the patient's safety. Second, by exploiting both accurate infusion devices and newly developed monitoring techniques, automatic controllers would be able to provide drug administration profiles which may avoid over-dosing and under-dosing. Moreover, they may take advantage of the drug synergies, for which now a proper modeling framework was developed (Minto et al. (2000)). The ultimate advantage would be a reduction in costs due to the reduced drug consumption and the shorter time spent by the patient in the post anesthesia care unit. Third, if enhanced with adaptation possibilties, initial versions of automated depth of anesthesia regulation systems could provide individualised protocols if PD models were to be adjusted to the actual patient instead of a population based generic model parameters. Finally, if tuned properly, automatic controllers may be able to compensate and tailor the drug administration profile to the particular stimulation intensity of each surgical procedure (Dumont (2014); Absalom et al. (2011); Ionescu et al. (2015); Rocha et al. (2014)).

As observed from the variations in the σ and the γ parameter values, no unique controller will be able to cope with all possible inter- and intra-patient variability situations. Therefore, some sort of adaptation mechanism of the PD model is of utmost necessity to achieve optimal drug dosing profiles in an individualised DOA regulatory system.

5. CONCLUSIONS

The interaction between analgesics and hypnotic is fundamental to understanding and defining the current anesthetic depth. If individualised DOA regulatory systems are envisaged, one needs to take into account the effects of inter- and intra-patient variability into account. This can be done solely by introducing adaptation mechanisms into the closed loop control strategy.

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