PATIENT VARIABILITY AND UNCERTAINTY QUANTIFICATION IN ANESTHESIA: PART I - PKPD MODELING AND IDENTIFICATION

Stéphane Bibian * **Guy A. Dumont** **
Mihai Huzmezan *** **Craig R. Ries** ****

* *Cleveland Medical Devices, NeuroWave Division, Cleveland, OH, USA*
** *University of British Columbia, Department of Electrical and Computer Engineering, Vancouver, BC, Canada*
*** *United Technologies Research Center, East Hartford, CT, USA*
**** *University of British Columbia, Department of Anesthesiology, Vancouver, BC, Canada*

Abstract: The outcome of any surgery is particularly dependent on the adequate delivery of anesthetic drugs. Not surprisingly, clinical researchers have been trying to automatize their delivery in order to provide anesthesiologists with titration tools that can target the exact needs of each individual patient. As compared to today's population-normed drug delivery strategy, closed-loop drug delivery systems would provide patients with customized pharmacological action, thereby improving surgery outcome. While some anesthesia closed-loop designs have already shown promising results within controlled clinical protocols, the pharmacological variability that exists between patients needs to be addressed within a mathematical framework to prove the stability of the control laws, and gain faster and wider acceptance of these systems by the clinical community and regulatory committees. This paper is the first of a series of 2 papers addressing the issue of pharmacological variability, and how this variability translates into quantifiable system uncertainty. In this work, we focus essentially on deriving patient-specific models to assess inter-patient variability. These models will serve as basis for illustrating the uncertainty quantification approach proposed in the accompanying paper.

Keywords: Anesthesia closed-loop control, Pharmacokinetic modeling, Pharmacodynamic modeling, Uncertainty, Propofol.

1. INTRODUCTION

Surgical acts are usually accompanied by the activation of both Central and Autonomic Nervous Systems (CNS and ANS). This CNS/ANS activation usually results in hypertension, tachycardia, arousal, hormonal discharge, *etc.* Clinical anesthesia consists of limiting this activation through the administration of CNS/ANS depressant drugs (*i.e.*, anesthetics). One of the anesthesiologist's role is to constantly adjust the drug titration in order to maintain an adequate activation *vs.* depression balance throughout the surgery, such that to avoid both under- and over-dosing. The driving idea in anesthesia closed-loop control is the automatic delivery of anesthetic drugs based on a

quantitative feedback measure of the CNS/ANS activity.

Automation in clinical anesthesia has been suggested since the early 1950s (Bickford, 1950). While many attempts have been documented over the last 60 years, automated anesthesia has not yet found its way into mainstream practice, even though the clinical utility of such systems has been demonstrated (Liu *et al.*, 2005; Locher *et al.*, 2004).

One argument brought forth by detractors of automated anesthesia delivery is the potential for titration errors due to the pharmacological variability that exists between patients with respect to drug effect *vs.* drug administration. This variability introduces significant system uncertainty, which can yield instable dynamic behaviors. Some prior attempts at closed-loop anesthesia have indeed shown instability even in a limited healthy adult patient population (Absalom *et al.*, 2002). The consequence of system uncertainty onto the behavior of the closed-loop system is therefore an issue that needs to be addressed in order to gain acceptance and regulatory approval of such systems.

This paper and the accompanying article (Bibian *et al.*, 2006) focus on expressing patient variability into quantified system uncertainty. This quantification can then be readily used in the control design to prove the stability of the closed-loop system for a given population of patients.

In order to illustrate our approach, we first derive patient-specific pharmacokinetic-pharmacodynamic (PKPD) models that express the dynamic behavior of the anesthetic drug effect with respect to the infusion rate. In particular, this paper focuses on the modeling of propofol, a widely used anesthetic for the depression of cortical activity. A total of 44 propofol PKPD models are derived from adult patients undergoing elective surgery. These models are fully disclosed in this paper.

Our PKPD modeling approach is described in Section II. The identification procedure and the resulting models are the subject of Section III. These models are further used to illustrate inter-patient variability.

2. PROPOFOL PKPD MODEL

Combined pharmacokinetic-pharmacodynamic models (PKPD) are used to express the dynamic behavior of the drug effect with respect to the infusion rate. To model the effect of propofol – a CNS depressant drug – we use the PKPD model structure summarized in the block diagram of Fig. 1.a. This model has three distinct parts detailed in the following paragraphs.

2.1 Propofol Pharmacokinetics

The pharmacokinetic model describes the evolution of the drug concentration in the blood following the administration of the drug:

$$PK(s) = \frac{C_p(s)}{I(s)}, \tag{1}$$

where $PK(s)$ is the pharmacokinetic model, $C_p(s)$ is the drug plasma concentration and $I(s)$ is the administered dose. For most anesthetic drugs, the mathematical model $PK(s)$ governing drug pharmacokinetics can be expressed as a third order transfer function:

$$PK(s) = \frac{1}{V_1} \cdot \frac{(s+k_{21}) \cdot (s+k_{31})}{(s+\pi) \cdot (s+\alpha) \cdot (s+\beta)}, \tag{2}$$

where V_1 is the central compartment volume and π, α, β, k_{21}, and k_{31} are the pharmacokinetic distribution time constants. These PK parameters have been found to be mostly dependent on the patient's age, weight, lean body mass, *etc.*, as well as the method of drug administration. Drugs delivered through boluses (large doses over very short amount of time) have different kinetics as compared to the same drugs delivered with a slower infusion rate.

Note that the notation used in (2) has the advantage of clearly expressing each one of the system dynamic modes, hence allowing a trained observer to readily identify the frequency response of the system. However, pharmacologists usually prefer the use of clearances and compartmental volumes rather than that of poles and zeros. Some simple mathematical manipulations are therefore needed in order to express the PK sets published in the literature into the notation of (2).

2.2 Propofol Pharmacodynamics

The pharmacodynamic model expresses the relationship between the blood plasma concentration of a given drug, and its corresponding clinical effect. This model usually comprises of a Linear Time Invariant (LTI) element $PD(s)$, followed by a non-linear element.

The LTI element is typically given by the following generic relationship:

$$PD(s) = \mathrm{e}^{-T_d \cdot s} \cdot \frac{\sum_{k=1}^{m} b_k \cdot s^k + b_0}{s^n + \sum_{k=0}^{n-1} a_k \cdot s^k} \cdot \frac{1}{2EC_{50}}, \tag{3}$$

where $m \leq n$, T_d is the time delay corresponding to the arm-to-brain travel time of the drug, and EC_{50} is the concentration of drug which yields 50% of the maximal effect. Note that no *a priori* decision should be made as to the structure of $PD(s)$. The exact order of $PD(s)$ must be determined based on the analysis of the identification