PATIENT VARIABILITY AND UNCERTAINTY QUANTIFICATION IN ANESTHESIA: PART II - PKPD UNCERTAINTY

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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, close loop drug delivery systems would provide patients with customized pharmacological action, thereby improving surgery outcome. While some anesthesia close 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 second of a series of 2 papers addressing the issue of pharmacological variability and PKPD uncertainty. In the first paper, we presented our own drug modeling approach, which we applied towards the identification of 44 adult patient models for propofol, a central nervous system depressant drug. The individual patient models have shown a large inter-patient variability. In this paper, we further expand on our previous result in order to derive an uncertainty metrics that can be used in the control design to ensure stability and assess performances. *Copyright ©2006 IFAC*

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1. INTRODUCTION

In our accompanying paper (Bibian *et al.*, 2006), we derived PKPD propofol models for 44 patients undergoing elective surgery. These models were obtained using a modified PKPD approach, and

our WAV$_{CNS}$ sensor designed for quantifying cortical activity. In this paper, we use the information obtained during the identification procedure in order to quantify the pharmacological variability into system uncertainty. This is achieved by considering the uncertainty of the PKPD model in

the frequency domain, and using a unstructured multiplicative uncertainty framework to translate the frequency response uncertainty into a mathematical expression suitable for control design.

In Section 2, we discuss the origin of pharmacological variability in terms of inter- and intra-patient variability. In Section 3, we present our uncertainty characterization approach. In Section 4, we apply our methodology to the PKPD models derived in the accompanying paper. In particular, we show that system uncertainty can be particularly large and may be difficult to manage in the controller design. However, we show how the uncertainty can be reduced satisfactorily by simply limiting the operating range of the controller.

2. ORIGIN OF PKPD UNCERTAINTY

Before characterizing PKPD uncertainty into a quantitative metrics, it is useful to first consider the origin and mechanism of pharmacological variability.

It is customary to distinguish between two different types of uncertainty: the uncertainty caused by inter-patient variability (*i.e.*, the variability observed between different individuals), and the uncertainty originating from intra-patient variability (*i.e.*, the variability observed within one particular individual).

2.1 Inter-patient Variability

Inter-patient variability affects both the pharmacokinetics and pharmacodynamics of any given drug. For instance, it has been shown that age as well as weight, lean body mass, ethnicity, *etc.*, are all factors of PKPD variability in humans. Co-existing illnesses involving either the liver and/or kidneys may also significantly alter the way drugs are metabolized and eliminated from the body. In general, 2 patients with similar physiological characteristics (age, weight, lean body mass, *etc.*) may have largely different PKPD parameters. For instance, patient #15 (female, 21 yrs old, 53 kg, 157 cm) in Table 1 (from (Bibian *et al.*, 2006)), and patient #53 (female, 21 yrs old, 67 kg, 163 cm) have significantly different time delay (45 sec *vs.* 4 sec), EC$_{50}$ parameter (3.8 μg/ml *vs.* 2.3 μg/ml), and saturation characteristics (Hill steepness of 1.2 *vs.* 2.5).

Inter-patient variability can be easily characterized by considering the differences between PKPD models obtained over a large population of patients. In particular, our previous study on 44 adult patients spanning the 18-60 yrs age groups provides a good representative sample of an adult population.

2.2 Intra-patient Variability

Intra-patient variability expresses the variability observed in the drug response within one particular subject. This variability originates from different factors.

Drug administration. It is a well-documented fact that the pharmacokinetics of intravenous agents differ depending on the method of administration of the drug. Even though bolus and infusion PK models have the same steady state gain, the initial peak plasma concentration following a bolus administration is significantly over-predicted by the corresponding infusion model.

During steady state (and for small setpoint changes and/or disturbances), it is likely that the controller will administer propofol at an infusion rate inferior to 0.5 mg·min^{-1}·kg^{-1}. In this range, it is expected that the propofol pharmacokinetics will be accurately described by the infusion model. However, during large transients, the controller may have to output large infusion rates (>1 mg·min^{-1}·kg^{-1}), in which case the propofol uptake and distribution may follow the behavior observed for bolus regimen. Therefore, the controller design must account for the difference in dynamics between the bolus and infusion PK models. This difference in models can be expressed as system uncertainty by associating to each case presented in Table 1 (from (Bibian *et al.*, 2006)) the 2 possible PK frequency responses.

Controller Setpoint. The Hill saturation can be viewed as a gain dependent on the operating point of the system. In terms of the closed-loop application, it is desired to maintain control over a wide range of WAV$_{\text{CNS}}$ values (*e.g.*, from 80 to 20). As a result, for each PKPD model, we can linearize the Hill equation as a gain K bounded between two values $K_{\max}$ and $K_{\min}$, and defined as:

$$\begin{cases} K_{\max} = \max\{K_{\overline{x}}, \quad \overline{x}_{\min} \leq \overline{x} \leq \overline{x}_{\max}\} \\ K_{\min} = \min\{K_{\overline{x}}, \quad \overline{x}_{\min} \leq \overline{x} \leq \overline{x}_{\max}\}, \end{cases} \quad (1)$$

where:

$$\overline{x}_{\min} = \frac{1}{2} \cdot \sqrt[\gamma]{\frac{E_{\min}}{1 - E_{\min}}} \quad (2)$$

and where $E_{\min} = 0.2$ corresponds to the smallest desired effect (shallow sedation: WAV$_{\text{CNS}}$=80). $\overline{x}_{\max}$ is obtained in a similar fashion with $E_{\max} = 0.8$, corresponding to the strongest desired control setpoint (very deep anesthetic sleep where WAV$_{\text{CNS}}$=20).

The Hill saturation being simplified as a bounded gain $K \in [K_{\min}; K_{\max}]$, we can associate for each case in Table 1 (from (Bibian *et al.*, 2006)) 2 frequency responses corresponding to the minimum and maximum Hill gains.