Clinical evaluation of closed-loop controlled propofol infusion in children

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Design and clinical evaluation of robust PID control of propofol anesthesia in children

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***Abstract*— This paper describes the design of a robust PID controller for propofol infusion in children and presents the results of clinical evaluation of this closed-loop system during endoscopic investigations in children age 6y-17y. The controller design is based on a set of models that describes the inter-patient variability in the response to propofol infusion in the study population. The PID controller is tuned to achieve sufficient robustness margins for the identified uncertainty. 108 children were enrolled in the study, anesthesia was closed-loop controlled in 102 of these cases. Clinical evaluation of the system shows that closed-loop control of both induction and maintenance of anesthesia in children based on the WAV_{CNS} index as a measure of clinical effect is feasible. A robustly tuned PID controller can accommodate the inter-patient variability in children and spontaneous breathing can be maintained in most subjects.**

***Index Terms*— Anesthesia, robust control, clinical trials, PID control**

I. Introduction

Propofol is an intravenously administered anesthetic drug that is commonly used for induction and maintenance of anesthesia. In general anesthesia in the operating room, propofol is often used in combination with fast acting opioids like remifentanil [2]. Individual responses to propofol and remifentanil infusion vary largely in adults and even more in children [3]. When administered together, propofol and remifentanil have a synergistic effect. Underdosing of anesthetic drugs may lead to awareness or insufficient analgesia. Overdosing may cause the patient to stop breathing and could provoke cardiovascular collapse. The anesthesiologist therefore continuously monitors the patient state and adjusts drug dosing accordingly to balance the anesthetic state, autonomic function and response to noxious stimuli (see [4] for an introduction to clinical anesthesia).

Drug infusion rates in intravenous anesthesia are traditionally manually controlled by the anesthesiologist. Computer aided open-loop delivery systems known as target controlled infusion (TCI) systems are commercially available. TCI systems use population-based pharmacokinetic[1] (PK) and pharmacodynamic[2] (PD) models to calculate an adequate infusion profile to achieve the drug concentration defined by the anesthesiologist [2]. To accommodate the inter-patient variability, this target concentration needs to be adjusted by the anesthesiologist. Closed-loop control of drug infusion has the potential to reduce the effect of inter-patient variability and improve control of the general anesthetic state [4]. Feasibility of closed-loop control of propofol infusion based on continuous measurement of the depth of hypnosis (DOH) has been shown in several clinical studies in adults (e.g. [5], [6], [7], [8], [9], [10], [11], [12], [13], [14]). Such studies have had little impact on clinical practice due to concerns about the safety of these systems and the reliability of the sensors. Furthermore, demonstration of improved patient outcome is required to convince clinicians of the benefits of closed-loop controlled systems.

The large inter-patient variability in individual responses to propofol infusion is an important cause for concern in the safety of closed-loop systems. Oscillatory behaviour was observed in some clinical trials, for example in the evaluation of a PID controller [15] and a neuro-adaptive controller [16]. For wide acceptance of a closed-loop system by clinicians and regulatory authorities, guarantees of robust stability and performance are required. It has been shown in simulation that it is possible to design a closed-loop drug delivery system for control of DOH that is robust in the presence of significant inter-patient variability [17]. Using a combination of robust control techniques and models that describe the inter-patient variability [18], stability and performance of the closed-loop can be achieved despite large variability.

This study aims to 1) verify the feasibility of robust PID control of propofol infusion in children, using the WAV_{CNS} index (NeuroSENSE monitor, NeuroWave Systems Inc., Cleveland Heights, USA) as a measure of the clinical effect, 2) demonstrate that a robustly tuned PID controller can accommodate the large inter-patient variability observed in this patient group and 3) assess the performance that can be achieved with robust PID control. This paper describes the controller design process and provides technical details of this study. The presentation of the results from the clinical study focusses on evaluation of the achieved control performance, identification of limitations of the proposed design and directions for future research and improvements from a control

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Part of the data reported in this paper has been published in [1] and presented at STA2012, CAS2012 SPA2012 and WCA2012.

[1] Pharmacokinetics describe the transport and metabolism of a drug.

[2] Pharmacodynamics relate plasma drug concentration to clinical effect.

engineering perspective. A clinical perspective on this study is presented in [19].

This paper is organized as follows: Section II gives an overview of closed-loop control in anesthesia and describes the system requirements as well as the hardware used in this study. The controller design, including quantification of the uncertainty, is detailed in Section III. The clinical study and clinical results are described in Section IV. The achieved performance and limitations are discussed in Section V. Conclusions are given in Section VI.

II. Closed-loop control in anesthesia

A. Review of control in anesthesia

The state of general clinical anesthesia is a combination of hypnosis (also referred to as anesthesia), analgesia (suppression of nociception[3]) and muscle relaxation. From these three components of clinical anesthesia, control of depth of hypnosis has attracted the most attention in automation research [7], [8], [9], [10], [11], [13], [16]. Recently developed DOH monitors like the Bispectral Index (BIS) monitor and the NeuroSENSE monitor provide measures of DOH suitable for control[4]. Equivalent monitors for nociception have not been studied for closed-loop control. Most clinical studies have therefore been limited to control of DOH, and use manual control or TCI schemes for opioid infusion. Feasibility of control of both DOH and analgesia through propofol and remifentanil infusion based on feedback of the measured DOH has been shown recently [5], [6]. Control of muscle relaxation can be separated from control of DOH and nociception because neuromuscular blockade has no explicit interaction with anesthetic drugs and opioids and is not addressed in this study.

Closed-loop control systems that have been evaluated clinically vary widely in control strategy and experimental setup. In several studies, maintenance of anesthesia was closed-loop controlled, while induction of anesthesia was open-loop controlled using a TCI [10], [13] or manually controlled [20], [11]. Induction of anesthesia was closed-loop controlled in [8]. Several systems use TCI as a basis for the closed-loop system, where the closed-loop controller adjusts the setpoint of the target concentration based on feedback from the measure of the clinical effect [10], [8], [9], [13].

Randomized clinical trials, comparing closed-loop controlled anesthesia to open-loop strategies show the potential of closed-loop controlled anesthesia [6], [9], [13]. Stability issues observed in clinical trials using heuristically tuned controllers and controllers lacking robustness with respect to the inter-patient variability have also raised awareness for the need of robustness [20], [16], [15]. This study aims to show that a simple PID controller can provide robust control of DOH in children, if the controller tuning is based on robust control principles that take the inter-patient variability explicitly into account. Quantification of inter-patient variability is essential for this robust approach.

[3]Stress response caused by noxious stimuli such as surgery or the insertion of a large bore endoscope that can be perceived as pain.

[4]Measures of the DOH range from 0-100, where the awake state corresponds to 90-100, an isoelectric EEG corresponds to 0. The typical range for general anesthesia is 40-60.

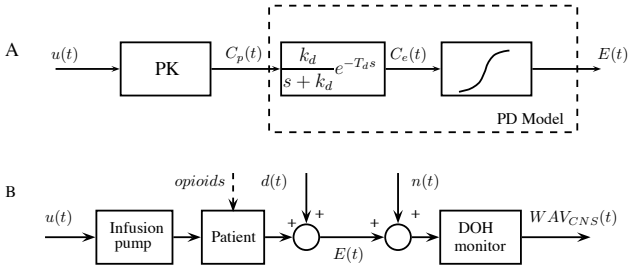

Fig. 1. A: PKPD model structure. The PK model is followed by the PD model consisting of a linear first-order transfer function and the nonlinear Hill function. Fig. B: Block diagram representing propofol anesthesia in open-loop. $u(t)$ is the infusion rate set by the anesthesiologist. The infusion pump delivers propofol to the patient. In this study, the opioid remifentanil was administered in addition to propofol, indicated by the dashed line. The DOH monitor provides a measure of the clinical effect ($WAV_{CNS}(t)$). Both stimulation from the procedure ($d(t)$) and measurement noise ($n(t)$) affect the measured WAV_{CNS}.

B. Characteristics of propofol anesthesia

The effect of propofol on the DOH is traditionally modeled using compartmental pharmacokinetic-pharmacodynamic (PKPD) models. The PK model relates the propofol infusion rates to the plasma concentrations $C_p(t)$. The PD model relates $C_p(t)$ to the clinical effect. An LTI model describes the relation between $C_p(t)$ and the effect site concentrations $C_e(t)$, the relation between $C_e(t)$ and the clinical effect $E(t)$ is described by a nonlinear Hill function, as shown in Fig. 1A.

A block diagram representing propofol anesthesia in open-loop is shown in Fig. 1B. The dynamics of the infusion pump are assumed to be negligible. The patient response is nonlinear (see Fig. 1A). In this study, the opioid remifentanil is administered in addition to propofol. When administered together, propofol and remifentanil have a synergistic effect. The clinical effect of anesthetic and analgesic agents is affected by nociceptive stimulation caused by the procedure, $d(t)$. Nociception decreases the clinical effect and can therefore not be assumed zero mean. The response to such disturbances depends on the level of analgesia. The characteristics of the measurement noise are affected by the NeuroSENSE filter settings and are therefore represented by $n(t)$ entering the system before the DOH monitor.

C. Design criteria

The controller designed for this study was required to provide safe and adequate anesthesia for children aged 6-17y, ASA I–II[5]. The design was required to accommodate the inter-patient variability observed in this patient group.

The controller was evaluated during upper and lower gastrointestinal endoscopic investigations, during which the surgical stimulation is limited. Anesthesiologists attempt to maintain the patient breathing spontaneously throughout such cases. Since deep anesthesia is associated with apnea, it was particularly important in this study to limit the DOH overshoot

[5]American Society of Anesthesiologists physical status classification system. ASA I: normal healthy patient, ASA II: patient with mild systemic disease.