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A model-based control scheme for depth of hypnosis in anesthesia

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ABSTRACT

In this paper we propose a model-based scheme to control the depth of hypnosis in anesthesia that uses the BIS signal as controlled variable. In particular, the control scheme exploits the propofol pharmacokinetics/pharmacodynamics model of the patient so that the estimated effect-site concentration is used as a feedback signal for a standard PID controller, which compensates for the model uncertainties. The tuning of the parameters is performed off-line using genetic algorithms to minimize a performance index over a given data set of patients.

The effectiveness of the proposed method is verified by means of a Monte Carlo method that takes into account both the intra-patient and inter-patient variability. In general, we obtain a fast induction phase with limited overshoot and a good disturbance rejection during maintenance of anesthesia.

1. Introduction

The development of feedback control strategies for general anesthesia has been a research topic for many years [1].

General anesthesia provides a suitable level of depth of hypnosis (DoH), analgesia, and neuromuscolar blockade to the patients under surgery. Each of these effects is regulated by using a specific drug, which is administered by considering different vital signs and its clinical effects.

In the clinical practice of total intravenous anesthesia (TIVA), the DoH is manually controlled by the anesthesiologist that regulates the infusion of the hypnotic agent propofol to ensure a suitable consciousness suppression. The desired level of hypnosis is decided relying on experience, on recommended doses, and on the trends of specific vital signs of the patient, such as blood pressure, heart rate, diaphoresis, spontaneous breathing, and facial grimacing. The bispectral index (BIS, Aspect Medical Systems, Norwood, USA) is widely employed to measure the level of hypnosis of the patient during anesthesia. It provides an estimation of DoH based on the bispectral analysis of the electroencephalogram (EEG) resulting in a dimensionless number between 0, equivalent to EEG silence, to 100, equivalent to the patient fully awake [2]. A target range between 40 and 60 is suggested to prevent awareness and to reduce the dose of anesthetic agent that is needed to maintain optimal anesthesia level. In the clinical practice an initial intravenous propofol bolus of propofol is used in order to obtain a fast consciousness suppression. This phase, called anesthesia induction phase, may cause severe arterial hypotension and is associated with low BIS levels [3]. During maintenance of anesthesia, various stimuli may induce variations in BIS levels which need continuous clinical monitoring of the patient's conditions and adjustment of propofol infusion

Abbreviations: AEP, auditory evoked potential; BIS, bispectral index; BIS-NADIR, lowest value of the bispectral index; DoH, depth of hypnosis; EEG, electroencephalogram; IAE, integrated absolute error; PID, proportional-integral-derivative; PD, pharmacodynamics; PK, pharmacokinetics; PSD, power spectral density; ST10, 10% settling time; ST20, 20% settling time; TCI, target controlled infusion; TIVA, total intravenous anesthesia; TT, time to target; TV, total variation; US, undershoot.

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rate. Finally, by stopping the infusion of hypnotic drugs, the patient recovers from the anesthesia.

A closed-loop control system for the automatic regulation of propofol during TIVA might provide significant benefits. In fact, the workload of the anesthesiologist decreases and, consequently, the problems due to distraction or fatigue are reduced. A closed-loop system may improve the patient's safety thanks to continuous monitoring of the DoH and possibly reduces the dose of anesthetic drug administered. This in turn may have beneficial effects on patient's health with faster recovery from anesthesia and reduced occurrence of post-operative complications.

In the last decades, several control technologies have been introduced in clinical practice [4], most notably, the mathematical models of the human body response to drugs administration. Indeed, these models are useful for the design of an automatic control system that replicates and improves the clinical procedure. In order to describe the human body response to propofol, a Wiener model is typically employed. This model structure consists of a linear dynamic system and a static nonlinear function. The linear part describes the relationship between propofol infusion and its clinical effect by means of a mammillary compartmental model. In particular, the linear part comprises the pharmacokinetics model (PK), which describes the infusion, the distribution and the elimination of the drugs in the body, and the pharmacodynamics model (PD) [5], which describes the relationship between the blood concentration of the drug and its clinical effect by means of a fictitious compartment, called effect-side compartment. The static nonlinear function of the propofol Wiener model is called Hill function and expresses the relation between the effect-site drug concentration and the BIS level.

In the clinical practice, a system called target controlled infusion (TCI) integrates the linear part of propofol Wiener model to improve the infusion procedure by considering a personalized drug dosage. This device, however, is an *open-loop* controller that automatically calculates an appropriate drug infusion based on the partial inversion of the propofol Wiener model, without actual measurement of drug concentration in the blood or the target organ. The anesthesiologist selects the expected blood concentration or the effect site target concentration and the patient data (age, gender, height, weight) to define the patient model. However, TCI usually requires the manual regulation of the reference during the infusion procedure due to modeling uncertainties and inter-patient variability. In other words, the anesthesiologist closes the loop to provide the control system robustness. Indeed, robustness to the variability of patient responses is a fundamental feature in the control of anesthesia. The control problem also consists in achieving a fast set-point tracking, with almost no undershoot in the induction phase, and a fast disturbance rejection in the maintenance phase. These competing objectives must be achieved in a context where the model nonlinearity and the parameters uncertainty introduce further difficulties.

Despite these obstacles, different approaches have been proposed in literature for *closed-loop* automatic control of anesthesia. Many applications have been developed based on a simple proportional-integral-derivative (PID) controller considering the BIS signal as feedback. The intra-patient and inter-patient variability have been also considered in the PID controller tuning. For example, in [6] the controller has been tuned based on a standard dataset of patient models and the simulations results show that the clinical specifications are fulfilled on the entire dataset by using a robust tuning. Another approach consists in the identification of the patient model during an initial manual infusion phase, then used to tune appropriately the controller online for each specific patient [7]. In [8], a gain scheduling strategy has been implemented on a standard PID controller where an optimal tuning is provided separately for the induction phase and the maintenance phase, in order to improve the performance of anesthesia. An event-based control strategy has been proposed in [9] to mimic the conduct of anesthesia in daily practice by changing the infusion rate only if it is really necessary, i.e., when an event occurs. The BIS noise issue has been also addressed by implementing on the feedback signal a new event generator that exhibits strong filtering capabilities. Other solutions exploit the use of different feedback signals, for example the WAV_{CNS} [10,11] and the auditory evoked potential [12]. In general, clinical studies have proven that PID controllers can improve the performance provided by TCI or manual infusion [13–15].

Other approaches implement different controllers, e.g. fractional control [6,16], μ-synthesis [10], fuzzy control [17,18], neural network based control [19], and positive control [20].

In general, as the nominal PK/PD model of the patient is available, it seems meaningful to explicitly exploit this information in the control system in order to provide an individualized drug administration, which is always desirable for the patient and appreciated by the anesthesiologists. This idea has been already exploited in the Model Predictive Control approaches [21–25] as well as in the inversion-based technique [26], which have been developed in the last years.

In this paper, we propose a new control scheme for automatic regulation of propofol infusion during TIVA that incorporates the model of the patient and the nonlinear Hill function inversion. In particular, the feedback of the control scheme becomes the effect site concentration estimated with the linear part of the Wiener model. To this end, an innovation signal is fed back to compensate for model uncertainties. From a technical point of view, this control scheme facilitates the controller development thanks to the automatic compensation of the nonlinear component of the model. Indeed, the dynamics that are observable from the feedback signal are, at least in the nominal case, those of the linear PK/PD model. In this context, a standard PID controller, which is tuned by applying an optimization procedure based on genetic algorithm and a standard dataset of patient representative of a wide population [8,21,23,27], has been applied. The PID parameters are therefore suitable to robustly address the inter-patient variability. The intra-patient variability has then been analyzed by applying a Monte Carlo method that considers the model parameters uncertainties for each patient and shows that the proposed approach is also robust to intra-patient variability.

The paper is organized as follows. In Section 2 the pharmacokinetic and pharmacodynamic models of propofol are briefly reviewed and the benchmark set of patients is reported for the reader's convenience. The control architecture and the tuning methodology are presented in Section 3. Simulation results are presented and discussed in Section 4. Finally, conclusions are drawn in Section 5.

2. Pharmacokinetic-pharmacodynamic modeling of propofol

The depth of hypnosis induced by propofol administration is usually modeled by means of a Wiener model, where a linear system is in series with a static nonlinear function. The linear part is composed by a PK/PD model. The pharmacokinetics characterizes the relation between the drug infusion and its plasmatic concentration by modeling distribution and elimination of propofol in the body. The pharmacodynamics describes the relation between the plasmatic concentration of the drug and its effect site concentration. For propofol, the series of the PK/PD models consists of a fourth-order system with two zeros whose parameters depend on the total body weight, height and gender of the patient (see [28,29] for details). A mammillary three-compartmental model is adopted