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Individualized closed-loop control of propofol anesthesia: A preliminary study

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ABSTRACT

This paper proposes an individualized approach to closed-loop control of depth of hypnosis during propofol anesthesia. The novelty of the paper lies in the individualization of the controller at the end of the induction phase of anesthesia, based on a patient model identified from the dose–response relationship during induction of anesthesia. The proposed approach is shown to be superior to administration of propofol based on population-based infusion schemes tailored to individual patients. This approach has the potential to outperform fully adaptive approaches in regards to controller robustness against measurement variability due to surgical stimulation. To streamline controller synthesis, two output filters were introduced (inverting the Hill dose–response model and the linear time-invariant sensor model), which yield a close-to-linear representation of the system dynamics when used with a compartmental patient model. These filters are especially useful during the induction phase of anesthesia in which a nonlinear dose–response relationship complicates the design of an appropriate controller. The proposed approach was evaluated in simulation on pharmacokinetic and pharmacodynamic models of 44 patients identified from real clinical data. A model of the NeuroSense, a hypnotic depth monitor based on wavelet analysis of EEG, was also included. This monitor is similar to the well-known BIS, but has linear time-invariant dynamics and does not introduce a delay. The proposed scheme was compared with a population-based controller, i.e. a controller only utilizing models based on demographic covariates for its tuning. On average, the proposed approach offered 25% improvement in disturbance attenuation, measured as the integrated absolute error following a step disturbance. The corresponding standard deviation from the reference was also decreased by 25%. Results are discussed and possible directions of future work are proposed.

1. Introduction

The purpose of administering anesthetic drugs during surgical procedures is to prevent unintended intra-operative awareness and to preserve stable suppression of noxious stimulation on the circulatory and hormonal systems, and on occasion to provide muscle relaxation [1]. Accordingly, anesthetic drugs are categorized into hypnotics, analgesics and neuromuscular blocking drugs. The fulfillment of the above-mentioned objectives is complicated by highly patient-specific and uncertain dose–response dynamics [2], unpredictable disturbances introduced by surgical stimulation [3] and synergetic effects between drugs (e.g. hypnotic–opioid synergy) [4]. Additional constraints are imposed by the fact that some anesthetic drugs have undesirable side effects (e.g. cardiovascular depression, cognitive impairment, nausea, vomiting and respiratory depression). Thus, the drugs must be restrictively administered during surgical procedures [5].

The hypnosis profile is divided into three temporal phases. During the induction phase of anesthesia, the patient is transferred from a fully awake state to a stable level of hypnosis. The surgical procedure takes place during the maintenance phase of anesthesia. Once the procedure is completed, drug administration

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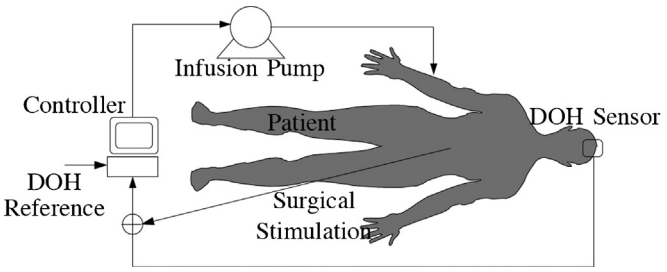

Fig. 1. Closed-loop DOH control system.

is discontinued to yield the emergence phase of anesthesia. During this phase, the patient emerges from the anesthetized state to the fully awake state.

Classically, an anesthesiologist manually controls administration of anesthetic drugs in the operating room. Doses are determined based on measured and/or predicted patient response. The predictions are based on clinical experience complemented by anticipated response to surgical stimulation and synergetic effects between drugs. Expert knowledge and experience play an important role, because the process exhibits a high degree of uncertainty.

A computer application can be used for a priori computation of an adequate hypnotic dose profile. This is exploited in the Target Controlled Infusion (TCI) paradigm [6,7]. TCI uses pharmacokinetic (PK) and pharmacodynamic (PD) models to regulate the predicted plasma or effect site (brain) drug concentration to a desired level set by the anesthesiologist. Considering that these concentrations are calculated rather than measured, TCI is regarded as an open-loop scheme. Thus, the performance of any TCI system relies heavily on the accuracy of the patient model. Furthermore, it is highly susceptible to disturbances caused by surgical stimulation and hypnotic–opioid synergy. Consequently, the TCI profile needs to be manually adjusted to counteract such disturbances.

An important step toward automated anesthesia drug delivery is to allow a computer application to make adjustments based on appropriate sensor measurements. In this scenario the anesthesiologist provides reference profiles for the measured quantity and the computer administers drugs to track the reference. This paradigm, known as closed-loop control, has been enabled with the introduction of clinical sensors for depth of hypnosis such as the Bispectral Index (BIS) [8], Entropy monitor [9] and the wavelet-based NeuroSense monitor [10]. In this paper a model of the commercially available NeuroSense monitor (NeuroWave Systems, Cleveland Heights, USA) is used. It provides the WAV_{CNS} index, presented in Section 2.3, as a measure of clinical effect. It is shown that the WAV_{CNS} correlates well with the BIS in steady state [10], and in addition, it boasts improved time-invariant dynamic response. Fig. 1 outlines the components of a closed-loop controlled anesthesia system.

The minimum requirement for any controller is that the closed-loop system is robust against measurement noise, disturbances (e.g. surgical stimulation) and model uncertainties. Improving robustness usually results in compromised controller performance and an appropriate trade-off between robustness and control performance is required. This compromise explains the existence of a multitude of control schemes and corresponding tuning procedures that have been evaluated for drug delivery in anesthesia. These schemes have included internal model control (IMC) [11], modeling error compensation (MEC) [12], model predictive control (MPC) [13], neural-fuzzy control [14], proportional integral derivative control (PID) [15] and robust control [15,16]. An intensive list of previous work on closed-loop control of anesthesia can be found in a historic review [17] and more recently in [18] as well as in [3]. It was

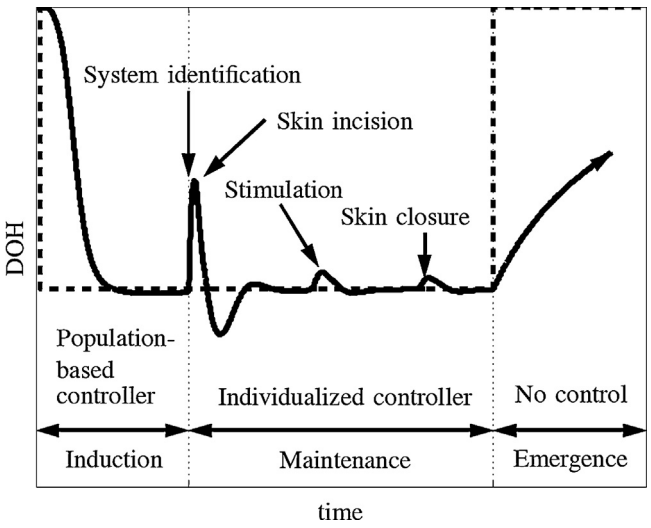

Fig. 2. Temporal layout of proposed control schema.

concluded in [19,20] that closed-loop strategies might outperform manual infusion dosing. In particular, closed-loop administration of propofol is expected to lead to a mean decrease in drug dose, while providing adequately deep anesthesia.

The output (WAV_{CNS} index provided by the NeuroSense monitor) and its corresponding input (dose) history can be used to adapt the control scheme to improve titration of drugs to the need of an individual patient. However, such adaptive approaches can fail if the behavior of the clinical front end is not fully explained by the dose, or if the output does not adequately excite the process to be controlled. In control of anesthesia, unknown surgical stimulations affect the clinical front end. With current technology, it is not possible to separate this effect from that of the drug. Hence, the clinical front end measurement is not fully explained by the dose during intubation or after incision, thereby posing a challenge for any adaptive scheme. This challenge is exacerbated by the fact that measurement noise is of comparable magnitude to output variability during the maintenance phase of anesthesia [3].

This paper proposes an individualized approach to closed-loop control of depth of hypnosis during propofol anesthesia. Its novelty lies in the individualization of the controller at the end of the induction phase of anesthesia, based on a patient model identified from dose–response relationship during induction of anesthesia. The proposed approach is superior to population-based drug administration in titrating drug to the need of each individual patient. This novel approach also has potential to outperform fully adaptive approaches in regards to controller robustness against measurement variability due to surgical stimulation. An overview of the proposed approach is given in Fig. 2.

To streamline controller synthesis, two output filters are introduced, which yield close-to-linear representation of the system dynamics when used with a compartmental patient model (the Hill dose–response model and the linear time-invariant sensor model). This synthesis is useful during the induction phase of anesthesia in which nonlinear dose–response relationship complicates the design of an appropriate controller.

This paper is organized as follows: Section 2 describes the model of hypnosis used in this paper. Section 3 elaborates on the control design procedure employed once a plant model is given, whereas the system identification procedure to obtain the plant model is discussed in Section 4. Sections 5 and 6 describe the simulation setup and performance evaluation measures. Section 7 presents and discusses the results and Section 8 outlines the limitations of the study. Section 9 provides the conclusions.