Biomedical Signal Processing and Control 40 (2018) 443–453

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Multi-model robust control of depth of hypnosis

Nasser Sadati[a,*], Mehdi Hosseinzadeh[b], Guy A. Dumont[c]

[a] Department of Electrical Engineering, Sharif University of Technology, Tehran 113659363, Iran
[b] School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran 14395515, Iran
[c] Department of Electrical and Computer Engineering, The University of British Columbia, Vancouver, BC V6T 1Z4, Canada

ARTICLE INFO

Article history:
Received 24 January 2017
Received in revised form 7 August 2017
Accepted 7 October 2017

Keywords:
Automated drug delivery
Anesthesia
Pharmacokinetic–pharmacodynamic modeling
Depth of hypnosis
Multi-model robust control scheme

ABSTRACT

This paper presents a multi-model robust control scheme to control the depth of hypnosis during intravenous administration of propofol. The objective of the proposed control scheme is to provide an adequate drug administration regime for propofol to avoid overdosing and underdosing of patients. The proposed scheme is designed to withstand the patient's inherent drug response variability, to achieve good output disturbance and sensor noise rejection, and to attain a good set point response. A comprehensive simulation study of 44 patients is presented to assess the performance of the proposed control scheme.

1. Introduction

During general anesthesia, anesthesiologists adjust the level of hypnosis based on dose regimes given by drug manufacturers and their own observation of inadequate anesthesia. Thus, their actions are comparable to those of a manual feedback controller. Although a wide variety of applications use control technology, the lack of knowledge of the underlying mechanisms of anesthesia and its large intra- and inter-patient variability for a long time prevented development of any appropriate conventional control framework that could perform satisfactorily in a clinical setting. However, recent advances in sensing devices, along with robust control theory, have generated new hopes of finally bridging the gap between manual and automated control of anesthesia, at least at the regulatory level.

In this paper, we will concentrate our efforts mainly on developing a multi-model robust control scheme for consideration as a new paradigm for closed-loop control of anesthesia. The structure of this paper is as follows. Section 2 provides preliminaries and an overview of the anesthesia. Section 2.1 briefly introduces the measurement index that represents the effects of anesthetics on the brain in terms of depth of hypnosis. Section 2.2 presents the application of closed-loop systems to control of the hypnosis depth. Section 2.3 presents the relationship between dose and pharmacological effect of the intravenously administered drugs, along with drug-response relationship of propofol. Section 3 presents the proposed control scheme. Section 3.1 presents the nominal model used to design a robust controller. Section 3.2 presents the design procedure for a mixed H_2/H_∞ controller. Section 3.3 investigates the effect of the nonlinear saturation function presence on the stability of the closed-loop system. Sections 3.4 and 3.5 investigate the design of a multi-model robust controller strategy and its stability, respectively. Section 4 presents the simulation results for 44 patients, obtained with the proposed control scheme. Finally, Section 5 presents concluding remarks.

2. Anesthesia

Anesthesia is a temporary reversible state consisting of unconsciousness, loss of recall, lack of pain perception, and sometimes muscle relaxation. It means lack of ability to sense or a state of being unable to feel anything [1]. In general, anesthesia consists of three components: hypnosis, analgesia, and neuromuscular blockade. This paper will deal mainly with the control of depth of hypnosis by intravenously administration of the hypnotic drug propofol. Hypnosis describes a state of anesthesia related to unconsciousness of patients and inability in patients to recall (amnesia). The last issue is particularly important because an awakening patient might feel pain and be aware of the surgical procedure but be unable to communicate this with clinical staff; intra-operative awareness can be

* Corresponding author.
E-mail addresses: sadati@ece.ubc.ca (N. Sadati), mehdi.hosseinzadeh@ieee.org (M. Hosseinzadeh), guyd@ece.ubc.ca (G.A. Dumont).

https://doi.org/10.1016/j.bspc.2017.10.003
1746-8094/

Nomenclature

(A, B, C, D)	system matrices
α	sector of the nonlinear element
Δ_j^i	uncertainty transfer function of the ith patient in the jth group
η_j	weighting factor for the jth controller
γ	hill parameter
$\hat{E}_q^j$	predicted output by the jth KF
$\mathrm{WAV_{CNS}}$	wavelet-based anesthetic value for central nervous system
ψ	nonlinear element
C_i	drug concentration of compartment i in the three-compartment model
E_q	quantified effect
E_r	effect site concentration
E_{obs}	observed effect
EC_{50}	steady-state concentration to obtain 50% of the effect
G_o^j	nominal model for the jth group
G_p^i	PKPD model for the ith patient
I	drug infusion rate
I_j	output of the jth controller
K	controller transfer function
k_d	rate of propofol distribution between the plasma and the effect compartments
k_{ij}	rate constants (flow $i \to j$)
KF	Kalman filter
Q_j	set of patients in jth group
T_2	transfer function from measurement noise to tracking error
T_∞	transfer function from input disturbance to tracking error
T_d	arm-to-brain travel time
V	Lyapunov function
V_i	volume of compartment i in the three-compartment model
W_Δ	uncertainty weighting function
W_{error}	error weighting function
x_p	state variable of the system (PKPD model)
x_{c_j}	state variable of jth controller
x_{cl_j}	state variable of the closed-loop system when the jth controller is applied
EEG	electroencephalogram
LMI	linear matrix inequality
PD	pharmacodynamic
PK	pharmacokinetic
PKPD	pharmacokinetic–pharmacodynamic

a traumatic experience, much feared by both the patient and the anesthetist.

Propofol hypnosis can be divided into three temporal phases [2]. The aim of induction phase is to bring the patient to a reference depth of hypnosis. Once a stable depth of hypnosis close to the reference is achieved, the maintenance phase begins, during which surgery takes place. The surgical stimuli can be viewed as output disturbances that reduce the depth of hypnosis. Hence, the challenge during the maintenance phase is to administer propofol to counteract the disturbances without over- or underdosing. Once surgery is completed, the emergence phase, during which administration of propofol is terminated, occurs.

2.1. Measurement index

Since the early 1940s, when the effect of anesthetic drugs on the EEG first became known, a number of techniques have been used to extract univariate features of EEG that quantify the hypnotic component of anesthesia. Bispectral analysis is one of the most-used techniques for closed-loop control of depth of hypnosis [3]. The resulting index, referred to as bispectral index or BIS, is a dimensionless number scaled from 100-0, with 100 representing an awake state and zero representing the maximum level of hypnosis. It is worth noting that the BIS generates a time-variable delay ranging from 15 to 55 seconds, which severely limits the performance of closed-loop feedback control and may lead to limit cycles and oscillations [4].

In [5], it has been shown that the wavelet coefficients derived from the EEG signals can be used to derive a univariate descriptor for the depth of hypnosis. Two clinical studies [6] and [7] have successfully validated the resulting index, referred to as $\mathrm{WAV_{CNS}}$. Like BIS, $\mathrm{WAV_{CNS}}$ uses a 100-0 scale to represent the patient depth of hypnosis. Special care was taken in the $\mathrm{WAV_{CNS}}$ algorithm to avoid non-linearity and non-minimum phase elements usage, which makes it virtually delay-free. It has been shown that the $\mathrm{WAV_{CNS}}$ compares well with the BIS index during steady-state intervals, while offering a reduced computational complexity and an improved dynamic behavior during transient intervals [8] and [9]. The $\mathrm{WAV_{CNS}}$ technology has been integrated into the NeuroSENSE® NS-701 Monitor as a real-time dual-channel high sampling rate EEG monitor designed specifically for use in operating rooms, intensive care units, and emergency rooms [10].

2.2. Control of depth of hypnosis

For automatic control of hypnosis (see Fig. 1), a large number of controllers are available. In [11], an ON/OFF controller is presented, where mean arterial blood pressure and a measure of EEG frequency were chosen as controlled variables. [12,13] propose fuzzy rule-based closed-loop systems to control the inhalation concentration of isoflurane and the infusion profile of propofol, respectively. [14,15] present a cascaded internal model control technique to control hypnosis using bispectral analysis of EEG signals. In this approach, the master controller provides end-tidal concentration references to the slave controller. These references depend on the difference between the measured and the set point values the master controller provides. The proposed controller has demonstrated good overall performance. Suggested future work includes simultaneously considering the measurements of mean arterial pressure. In [16], an adaptive model-based controller is developed to administer the amount of hypnotic drugs. The proposed controller has been tested on ten patients undergoing surgery and has demonstrated the ability to induce sedation with a minimum amount of drugs. A PID controller for the intravenous administration of propofol has been proposed in [17]. Of the ten patients on whom the closed-loop system has been tested, three showed severe oscillation around the targeted set point. This instability could be easily attributed to poor tuning of the controller. In [18], a cascade feedback control structure for controlling the bispectral index (BIS) is presented. In [19], a robust PID controller and robust controller based on fractional calculus have been developed to regulate the hypnotic state of anesthesia with the intravenous administration of propofol. The performance of both controllers was assessed by simulating 44 patients, showing that with the use of robust control, safe, reliable, and hopefully certifiable automatic drug delivery system can be achieved. In [20], an H_∞ controller to control the maintenance phase is presented and its clinical results are reported. [21,22] present a robust controller based on μ synthesis. In [23], a robust individualized approach is presented for