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Explicit hybrid model predictive control strategies for intravenous anaesthesia

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ABSTRACT

In this work, we first present a piece-wise affine model for intravenous anaesthesia, based on which a hybrid explicit/multiparametric model predictive control strategy is developed. To deal with the inter- and intra-patient variability, an estimation strategy, the multiparametric moving horizon estimator, and different robust algorithms such as Offset Correction, State-Output Correction and Prediction Output Correction are further designed and implemented simultaneously with the hybrid multiparametric model predictive control. Simulation results for a set of 12 virtually generated patients for the regulation of the depth of anaesthesia by means of the Bispectral Index with Propofol as the anaesthetic, demonstrate the validity and usefulness of the proposed advanced control and estimation strategies.

1. Introduction

Control of drug delivery systems, such as diabetes, leukaemia, perioperative hemodynamic control and anaesthesia, have been receiving considerable attention over the last decades. (Fuentes-Garí et al., 2015; Hodrea et al., 2014; Krieger et al., 2014; Krieger and Pistikopoulos, 2014; Padula et al., 2016; Pefani et al., 2014; Zavitsanou et al., 2014, 2011). Nevertheless, there has been little impact on routine clinical practice and there are still a large number of challenges that need to be tackled. Some of the main issues in controlling such systems are: reliable sensors, inter- and intra-patient variability and the presence of strong nonlinearities (Absalom et al., 2011; Haddad et al., 2003). These nonlinearities are typically present in the pharmacodynamic model of the system and are described by the Hill curve representing the relation between the concentration of the drug and the effect observed on the patient.

Anaesthesia in particular plays a very important role in surgery and the intensive care unit. It is defined as a reversible pharmacological state of the patient where hypnosis, analgesia and muscle relaxation are guaranteed (Bailey and Haddad, 2005). Analgesics block the sensation of pain; hypnotics produce unconsciousness, while muscle relaxants prevent unwanted movement of muscle tone.

In this work we focus on different ways in dealing with two important challenges in controlling the depth of anaesthesia (DOA): nonlinearity and inter- and intra-patient variability. Advanced control strategies using either hybrid and robust multiparametric model predictive control or simultaneous hybrid multiparametric model predictive control and state estimation techniques are developed and tested. Here we first generate a piece-wise linearization of the Hill curve. The main advantage of this procedure is that the parameter space is linearized and that the uncertainty in some key parameters of the Hill curve is compensated for. As a result of the linearization, the anaesthesia model is described by a piece-wise affine system. This leads to a hybrid model predictive control problem (Bemporad and Morari, 1999b) which is solved explicitly offline via the solution of a state-of-the-art multi-parametric mixed integer quadratic programming problem (mp-MIQP) (Dua et al., 2002; Oberdieck and Pistikopoulos, 2015) in the POP toolbox (Oberdieck et al., 2016).

The second challenge addressed here is the high inter- and intra-patient variability, which introduces a high degree of uncertainty in the system. A number of robust control strategies and a state estimation technique are developed and presented simultaneously with the hybrid multiparametric model predictive control (mp-hMPC). State estimation is used for the unavailable states as well as in order to overcome issues that arise from noisy outputs. In particular, moving horizon estimators (MHE), implemented in a multi-parametric fashion (Darby and Nikolaou, 2007; Nascu et al., 2014b; Voelker et al., 2013) is used simultaneously with

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the mp-hMPC control. The control strategies are tested on a set of 12 patients for the induction and maintenance phase of general anaesthesia.

The paper is organized as follows: the pharmacokinetic and pharmacodynamic patient model, the formulation of the hybrid patient model, design of the hybrid multiparametric model predictive controller along with the robust control strategies and the moving horizon estimation strategy are presented in Section 2. The simulation results of the designed controllers using the presented robust and estimation strategies for the induction and maintenance phases are presented in Section 3 followed by discussions in Section 4. Finally, Section 5 summarize the main outcome of this paper.

Table 1
Intravenous anaesthesia mathematical model.

Intravenous Anaesthesia		
PK model	$\dot{x}_1(t) = -[k_{10} + k_{12} + k_{13}] \cdot x_1(t) + k_{21} \cdot x_2(t) + k_{31} \cdot x_3(t) + u(t)/V_1$ $\dot{x}_2(t) = k_{12} \cdot x_1(t) - k_{21} \cdot x_2(t)$ $\dot{x}_3(t) = k_{13} \cdot x_1(t) - k_{31} \cdot x_3(t)$	(1)
Effect site compartment	$\dot{C}_e(t) = k_{e0} \cdot (C_e(t) - x_1(t))$	(2)
PD model (Hill curve)	$BIS(t) = E_0 - E_{\max} \cdot \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + EC_{50}^{\gamma}}$	(3)

2. Theoretical background

2.1. Anaesthesia fundamentals

General anaesthesia ensures that patients are unconscious, feel no pain, have no memory of the surgery, remain still during the operation and have adequate autonomic nervous system, respiratory and cardiac responses to keep them alive. Achieving this is possible by using a variety of drugs (anaesthetics).

The practice of modern clinical anaesthesia is based on the concepts of the anaesthesia triad and balanced anaesthesia. Anaesthesiologists administer a combination of drugs and adjust several infusion devices to achieve an adequate balance between hypnosis, analgesia and muscle relaxation of the patient.

Hypnosis describes a state of anaesthesia related to patient drug induced unconsciousness where the patient neither perceives nor recalls (amnesia) noxious stimuli, i.e. stimuli associated with transmission of pain during events that occurred during surgery. Analgesia describes a special state of anaesthesia related to the disability of the patient to perceive pain. Skeletal muscles relaxation or neuromuscular blockade is a standard practice during general anaesthesia to facilitate the access to internal organs and to depress movement responses to surgical stimulations.

The hypnosis profile is divided in three phases: induction, maintenance and emergence. The induction phase of anaesthesia, is the period between the administration of induction agents and loss of consciousness. During this phase the patient is transferred from a fully awake state to a stable level of hypnosis, usually taking up to 15 min. Although this phase is short it is also very critical. The surgical procedure takes place during the maintenance phase of anaesthesia. Here is important to maintain an adequate DOA and to blunt nociceptive reactions. Once the procedure is completed, drug administration is discontinued and the emergence phase of anaesthesia begins. During this phase, the patient emerges from the anesthetized state to the fully awake state.

2.2. Anaesthesia patient model

2.2.1. Patient model

The patient model for the administration of intravenous anaesthesia is composed of the pharmacokinetic (PK) and pharmacodynamic (PD) models, representing the distribution of drugs in the body, i.e. the mass balance. The pharmacokinetic model represents the relation between the drug administration and the drug concentration in the body, whereas the pharmacodynamic model represents the relation between the concentration of the drug in the central compartment and the effect observed on the patient. In each compartment the drug concentration is assumed to be uniform, as perfect and instantaneous mixing is assumed.

A common anaesthetic drug used in intravenous anaesthesia for the induction and maintenance phases is Propofol which has both fast redistribution and metabolism and does not accumulate in tissues as some of the other drugs (Ionescu et al., 2015). For measuring the hypnotic effect, the Bispectral Index (BIS), derived from the electroencephalogram (EEG), is used. A BIS value of 0 equals EEG silence, while a BIS value of 100 is the expected value of a fully awake and conscious adult, 60–70 and 40–60 range represents light and moderate hypnotic condition, respectively (Bailey and Haddad, 2005).

The PK-PD models most commonly used for Propofol are the 4th order compartmental model described by Schnider (Schnider et al., 1998, 1999) and Minto (Minto et al., 1997a,b), respectively. In (Schnider et al., 1998) measures of goodness of fit of the pharmacokinetic model were analysed on a set of 24 volunteers. The observed concentrations in plasma were described reasonably accurately by the model (83% accuracy). In (Schnider et al., 1999) the pharmacokinetic model was validated on the clinical data obtained from the 24 volunteers. The predictive accuracy of the pharmacokinetic model was validated in (Schüttler and Ihmsen, 2000). The authors analysed 4112 samples of 270 individuals (150 men, 120 women, aged 2–88 years, weighing 12–100 kg).

Table 1 presents the resulting mathematical model: note that (1) and (2) are linear, the parameters describing the PK model can be found in (Naşcu et al., 2015), whereas (3) is nonlinear.

where x_1 represents the drug concentration in the central compartment [mg/l]. The peripheral compartments 2 (muscle) and 3 (fat) model the drug exchange of the blood with well and poorly diffused body tissues. The concentrations of drug in the fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3 respectively. The parameters k_{ij} for i = 1:3, $i \neq j$, denote the drug transfer frequency from the i^{th} to the j^{th} compartment, k_{10} the frequency of drug removal from the central compartment. $u(t)$ [mg/min] is the infusion rate of the anaesthetic or analgesic drug into the central compartment. The parameters k_{ij} of the PK models depend on age, weight, height and gender and can be calculated for Propofol as presented in Table 3. A more detailed description of the patient model can be found in (Naşcu et al., 2015).

The additional hypothetical effect compartment is added to represent the lag between plasma drug concentration and drug response. Its corresponding drug concentration is represented by the *effect-site compartment concentration* C_e. The drug transfer frequency for Propofol from the central compartment to the effect site-compartment is considered in clinical practice to be equal to the frequency of drug removal from the effect-site compartment $k_{e0} = k_{1e} = 0.456$ [min^{-1}](Nunes et al., 2009; Schnider et al., 1998, 1999).

The *Hill curve (3), corresponds to the second part of the PD model.* E_0 denotes the baseline value (awake state – without drug), which by convention is typically assigned a value of 100, $E_{\max}$ denotes the maximum effect achieved by the drug infusion, EC_{50} is the drug concentration at 50% of the maximal effect and represents the patient sensitivity to the drug, and γ determines the steepness of the curve.