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An explicit Hybrid Model Predictive Control Strategy for Intravenous Anaesthesia

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Abstract: The paper describes a strategy for the control of intravenous depth of anaesthesia for the induction and maintenance phase. Based on the anaesthesia model, described by a piece-wise affine system, a hybrid model predictive control problem results, which is solved explicitly via the solution of a novel multi-parametric mixed integer quadratic programming algorithm. The control strategy is successfully tested on a set of 7 patients.

Keywords: intravenous anaesthesia, multi-parametric/explicit model predictive control, multi-parametric mixed-integer quadratic programming, hybrid systems, nonlinearity, inter- and intra- patient variability.

1. INTRODUCTION

The control of anaesthesia is still a challenging task despite the large number of publications on this topic during the last decades. Anaesthesia plays a very important role in surgery and in the intensive care unit. It is a reversible pharmacological state of the patient where hypnosis, analgesia and muscle relaxation are guaranteed and maintained throughout the surgery Bailey & Haddad (2005). The role of the anaesthetist has become complex and indispensable in order to maintain the patients' vital functions before, during and after surgery. The automation of some routine actions of the anaesthetist can reduce the workload and most importantly increase the safety of the patient.

Some of the most important tasks that need to be dealt with in the control of anaesthesia are the presence of nonlinearities, inter- and intra-patient variability, multivariable characteristics, variable time delays, dynamics dependent on the hypnotic agent, model analysis variability, Haddad, Hayakawa & Bailey (2003), Absalom, De Keyser & Struys (2011). A lot of work has been done on the development of PID tuning techniques, model based strategies using predictive Struys et al. (2003),Ionescu et al. (2014), Hodrea, Morar & Nascu (2012), robust Caiado Daniela, Lemos João & Costa Bertinho (2013), adaptive Haddad, Hayakawa & Bailey (2003), Nascu et al. (2012) and multi-parametric MPC Nascu et al. (2014b), Krieger & Pistikopoulos (2014) for the control of both intravenous and volatile anaesthesia.

In the anaesthesia process as well as in most biomedical systems the strong nonlinearities are included in the pharmacodynamic models that are part of the mathematical model. In particular the Hill curve representation is often used as an approximation for the description of such nonlinearities. For the case of infusion of anaesthetic agents, the nonlinear Hill curve approximation has been used in both volatile Krieger et al. (2014) and intravenous Nascu et al. (2012; Nascu et al. (2014a) anaesthesia and it describes the relation between the concentration of the drug and the effect observed on the patient.

One of the main challenges in such systems is in dealing with the nonlinearities. A way of dealing with this is by linearizing the Hill function. Due to the S – shape characteristic of the Hill curve, a piecewise linearization around three points can be performed, resulting in a piece-wise affine formulation. The control of such a system corresponds to a hybrid model predictive control (hMPC) problem Bemporad & Morari (1999) which often requires the solution of a mixed-integer quadratic programming (MIQP) problem formulation.

The online implementation of hMPC involves the online solution of an MIQP problem, which introduces a high computational burden. Thus in this paper, we present a step-by-step procedure for the development of explicit hMPC controllers via a novel multi-parametric MIQP algorithm. This development is part of PAROC, a comprehensive framework and software solution for the general design, operational optimization and control of process systems Pistikopoulos et al. (2014). The framework includes a high-fidelity model of the system which can be approximated using discrete time models in state space form based on model order reduction techniques or system identification. The model is then used to formulate an optimization problem subject to the state space model and constraints. The resulting multi-parametric programming problem is solved with state-of-the-art techniques. In the last step of the framework, the

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solution is validated against the original high fidelity model, thus closing the loop.

The paper is organised as follows: the patient model, the piecewise linearization and the hybrid multi-parametric control strategy is presented in the following section. Section 3 presents the simulation results for the induction and maintenance phase for a set of 7 patients. Finally Section 4 summarizes the main outcome of this paper and future work.

2. THEORETICAL BACKGROUND

2.1 Patient Model

The distribution of drugs in the body is based on a compartmental model composed of pharmacokinetic (PK) and pharmacodynamic (PD) blocks. The pharmacokinetic model represents the relation between the drug administration and drug concentration in the body, whereas the PD 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 considered to be uniform, as perfect and instantaneous mixing is assumed. The structure of the compartmental model is described in Fig. 1 Struys et al. (2004), Schnider et al. (1998) .Nascu et al. (2012; Ionescu, Nascu & Keyser (2011)

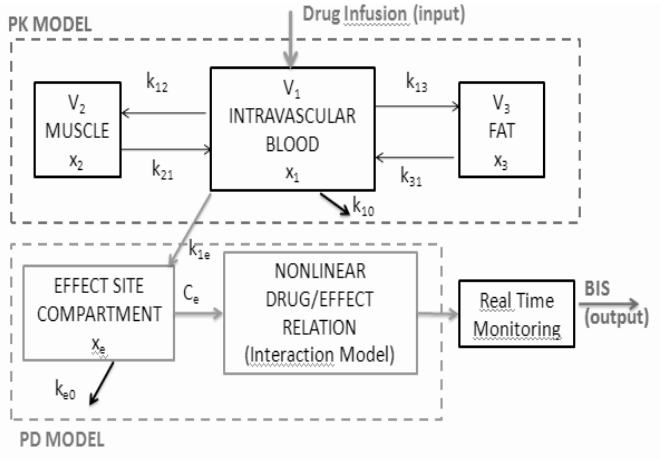

Fig. 1. Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model.

The PK-PD models most commonly used are the 4th order compartmental model described by Schnider Schnider et al. (1998), Schnider et al. (1999) and Minto Minto, Schnider & Shafer (1997), Minto et al. (1997), respectively. These models, developed, tested and validated on a wide range of real patient data are commonly used in literature for the control of anaesthesia. The PK model and the first term of the PD model are considered linear studied on real patient data with the collaboration of anaesthesiologists and validated using blood samples provided by hospitals. Schnider et al. (1998; Schnider et al. (1999; West et al. (2013):

$$\begin{aligned}
\dot{x}_1(t) &= -\left[k_{10}+k_{12}+k_{13}\right]\cdot x_1(t) + k_{21}\cdot x_2(t) \\
&+ k_{31}\cdot x_3(t) + u(t)/V_1 \\
\dot{x}_2(t) &= k_{12}\cdot x_1(t) - k_{21}\cdot x_2(t) \\
\dot{x}_3(t) &= k_{13}\cdot x_1(t) - k_{31}\cdot x_3(t) \\
\dot{x}_e(t) &= -k_{e0}\cdot x_e(t) + k_{1e}\cdot x_1(t)
\end{aligned} \tag{1}$$

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 $i \neq j$, denote the drug transfer frequency from the i^{th} to the j^{th} compartment and $u(t)$ [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:

$$\begin{aligned}
&V_1 = 4.27\,[l],\ \mathrm{V}_2 = 18.9 - 0.391\cdot(age - 53)\,[l],\ \mathrm{V}_3 = 2.38\,[l] \\
&\mathrm{C}_{11} = 1.89 + 0.456(weight - 77) - 0.0681(lbm - 59) + \\
&\quad + 0.264(height - 177)\,[l/\min] \\
&\mathrm{C}_{12} = 1.29 - 0.024(age - 53)\,[l/\min],\ \mathrm{C}_{13} = 0.836\,[l/\min] \\
&\mathrm{k}_{10} = \frac{C_{l1}}{V_1}\,[\min^{-1}],\ \mathrm{k}_{12} = \frac{C_{l2}}{V_1}\,[\min^{-1}],\ \mathrm{k}_{13} = \frac{C_{l3}}{V_1}\,[\min^{-1}], \\
&\mathrm{k}_{21} = \frac{C_{l2}}{V_2}\,[\min^{-1}],\ \mathrm{k}_{31} = \frac{C_{l3}}{V_3}\,[\min^{-1}],\ k_{e0} = 0.456\,[\min^{-1}]
\end{aligned} \tag{2}$$

where C_{l1} is the rate at which the drug is cleared from the body, and C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. The lean body mass (lbm) for men (m) and women (f) are calculated by:

$$\begin{aligned}
lbm_m &= 1.1\cdot weight - 128\frac{weight^2}{height^2} \\
lbm_f &= 1.07\cdot weight - 148\frac{weight^2}{height^2}
\end{aligned} \tag{3}$$

An additional hypothetical effect compartment is added to represent the lag between plasma drug concentration and drug response. The drug concentration in this compartment is represented by x_e, called the *effect-site compartment concentration*. The effect compartment receives drug from the central compartment by a first-order process and it is considered as a virtual additional compartment. Therefore, 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 $k_{e0}=k_{1e}=0.456$ [$\min^{-1}$] Schnider et al. (1998), Schnider et al. (1999), Nunes et al. (2009). When considering the drug effect observed on the patient, the Bispectral Index (BIS) variable can be related to the effect drug concentration C_e by the empirical static nonlinear relationship Struys et al. (2003), Schnider et al. (1998), Schnider et al. (1999), called also the *Hill curve:*