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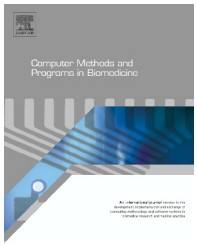

Robust model predictive control for optimal continuous drug administration

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ABSTRACT

In this paper the model predictive control (MPC) technology is used for tackling the optimal drug administration problem. The important advantage of MPC compared to other control technologies is that it explicitly takes into account the constraints of the system. In particular, for drug treatments of living organisms, MPC can guarantee satisfaction of the minimum toxic concentration (MTC) constraints. A whole-body physiologically-based pharmacokinetic (PBPK) model serves as the dynamic prediction model of the system after it is formulated as a discrete-time state-space model. Only plasma measurements are assumed to be measured on-line. The rest of the states (drug concentrations in other organs and tissues) are estimated in real time by designing an artificial observer. The complete system (observer and MPC controller) is able to drive the drug concentration to the desired levels at the organs of interest, while satisfying the imposed constraints, even in the presence of modelling errors, disturbances and noise.

A case study on a PBPK model with 7 compartments, constraints on 5 tissues and a variable drug concentration set-point illustrates the efficiency of the methodology in drug dosing control applications. The proposed methodology is also tested in an uncertain setting and proves successful in presence of modelling errors and inaccurate measurements.

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1. Introduction

Determining the best dose for a patient is a key question in medicine and is of equal importance to drug discovery in the narrower sense of finding a chemical compound with the desired therapeutic properties [1].

Traditionally, drug administration scheduling is designed using average population pharmacokinetic and/or pharmacodynamic profiles [2,3]. This common practice yields suboptimal therapies and does not consider the distinct attributes of the patients treating them as a bulk. Outliers of the general distribution are likely to exhibit adverse effects due to violation of toxicity constraints or may fail to retain the therapeutic levels. The lack of any feedback that comes with the assumption of zero disturbances contributes even more to the probability of adverse effects. Nowadays, the grounds have shifted and the need for accuracy and efficiency calls for closed-loop practices thus introducing control theory into the field of drug administration. Drug dosing controllers should not only lead to a stable closed-loop system but also need to take into account the state and actuator constraints

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which in some cases are patient-specific [4]. Such constraints result from safety considerations against adverse effects and are qualified by means of the tissue-specific minimum toxic concentration (MTC) values. Upper bounds are also imposed on the influx rate when the administration is intravenous. Computer-aided drug administration can provide an optimal solution to the problem, with the guarantee that all safety requirements are fulfilled.

The study of the disposition of the administered drug inside the body is the first step towards designing an administration policy. Physiologically-based pharmacokinetic (PBPK) models use knowledge of the physiology and the anatomy of the studied species to accurately describe plasma, tissue, and, in some cases, tumour concentrations, following drug delivery [5,6]. These models have found extensive use in toxicology studies, delivery of anaesthetics [7], treating diabetes [8], and, more recently, in describing chemotherapeutic distribution [9]. PBPK models rely on fundamental principles such as mass balance equations and reaction kinetics and mathematically are materialised as systems of ordinary differential equations (ODEs) [10]. The main reason why they have gained their remarkable popularity is that they provide a mechanistic explanation to the drug pharmacokinetics [11]. The distribution of a drug following intravenous administration is carried out by two main mechanisms that take place in parallel: perfusion over the capillary bed and diffusion within the organs [12]. Diffusion-driven pharmacokinetics – which appear primarily as molecule size increases – is well described by the model of capillary membranes that separate the tissue from the blood circulation. For that reason, all compartments are represented as pairs of their tissue and plasma counterparts and pairs of mass balance equations are formulated. Therein, permeability coefficients appear which characterise the diffusion-driven mass flow.

From a systems theory point of view, PBPK models are single-input multiple-output (SIMO) dynamical systems where the input is the influx rate of the administered drug and the state consists of the concentration of the drug at each compartment that participates in the model. The applicability of the PBPK modelling approach can be extended to account for drug–drug interactions thus resulting to multiple-input multiple-output (MIMO) systems. Therefore, it is straightforward to use PBPK models in a feedback control setting.

Model predictive control (MPC) originated mainly from the process industry and has become famous for its stability and inherent robustness properties and for the fact that it can take systematically into account the constraints imposed on the state and input variables of the system [13,14]. Recently, it has made its presence felt in medicine as well: Gaweda et al. [15] employed MPC to design a feedback controller for administration of recombinant human erythropoietin to patients with end-stage renal disease. The authors of the present paper employed a black-box modelling approach using Finite-Impulse Response (FIR) models to cast the drug dosing control problem as an MPC problem [16]. A nonlinear MPC scheme was employed by Day et al. [17] for the control of inflammation in critically ill patients however without taking into account any safety constraints. MPC was also identified by Parker [18] as a control methodology with many implications for drug concentration regulation.

The MPC has also been adopted to tackle the drug dosing problem. For example, Dua et al. [19] combined multiparametric programming and MPC to derive an explicit expression of the feedback control law for the regulation of blood glucose levels in patients with Type-I diabetes. MPC control strategies for glucose control have also been proposed by Magni et al. [20] and Hovorka et al. [21]. MPC has also been used as a feedback control method in anaesthesia by Ting et al. [22], Ionescu et al. [23], Cardoso and Lemos [24], Caruso and Morari [25], and Ingole et al. [26]. In most of the above studies, there is a prevailing requirement which is not always possible to be met: at each instant the drug concentrations in the organs or tissues of interest should be measured and their values should be provided to the controller [27]. This, being true for simple settings such as the control of arterial pressure [28], is hardly the case for drugs that aim at the liver or the brain as any installation of sensors is fiercely pervasive. For that reason, it is requisite to design a state observer; a dynamical system which asymptotically reconstructs the concentrations that cannot be measured and feeds them to the controller. The overall system comprising of the PPBK model, the controller and the observer should provide closed-loop stability and satisfaction of the safety constraints.

In this paper, it is shown that PBPK models perfectly fit a recently proposed advanced offset-free MPC method which requires a state-space representation of the PBPK model and the design of a state observer. A hypothetical PBPK model with 7 compartments (and overall 14 sub-compartments) is constructed using data available in the literature and is utilised as a case study to illustrate the advantages of the MPC methodology. A unified framework for controlling the intravenous administration of drugs is proposed based on a realistic administration scenario. The suggested offset-free setting allows the treating physician to modify the set-point concentration of the drug in the target organ so as to readjust the course of the therapy and achieve the expected effect. We apply the proposed MPC controller to a set of 200 patients considering the intra-patient variability that is present in practice and we demonstrate that the proposed methodology is resilient to measurement noise and modelling errors. Preliminary results of this work appeared in Sopasakis et al. [29].

2. Theoretical section

Generally speaking a PBPK model comprises four fundamental groups of compartments: Non-metabolising, metabolising and excretory, the lungs and the blood compartment. Each compartment is further subdivided in two sub-compartments; one aiming at describing the perfusion through the corresponding organ or tissue and the other describing the diffusion. Hereinafter we use the notation $C_v^i[\mu g\ L^{-1}]$ for the venous concentration of the drug through the flow-limiting sub-compartment of compartment i. $V^i[L]$ and $V_{bl}^i[L]$ denotes the volume of tissue and the volume of blood in organ i while $C^i[\mu g/L]$ is reserved for the concentration in the corresponding diffusion-limited sub-compartment. By $Q_i[L\ h^{-1}]$ we denote the volumetric flow rate of blood through i. Finally, $C_{art}[\mu g/L]$ is the arterial concentration of the drug, $Q_c[L\ h^{-1}]$ denotes the

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