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Modeling and control of pharmacodynamics

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ABSTRACT

Modeling and control of drug dosing regimes are particularly well-suited for applications of control design and analysis techniques. These problems frequently incorporate the use of mathematical models, lending themselves to a large range of model-based control methods. There has been ongoing research aimed at the development of closed-loop drug dosing and delivery regimens in a number of specific medical domains for more than five decades. In this paper, we discuss the development of modeling and control methods aimed at closed-loop delivery of pharmaceutical agents. We focus most of this discussion on the problem of controlling sedation levels during surgical procedures; results from the application of linear parameter varying and robust $\mathcal{L}_1$−adaptive modeling and control approaches are presented in some detail.

1. Introduction

Engineering and technology have played a major role in medical advancements and improvements throughout the past century. Notable recent innovations include robotic surgery, controlled prosthetics, bio-materials and advanced imaging technologies. More specifically, over the past 50 years, contributions to medicine founded in control methods have ranged from the invention of the pacemaker in 1950 and ventricular assist devices in the 1980s, to more recent advances incorporating robotic and image-guided surgery, and the ongoing development of the artificial pancreas. Modeling and control of drug dosing regimes are particularly well-suited for applications of control design and analysis techniques; these problems typically incorporate extensive use of mathematical models lending themselves to a large range of model-based control methods. As it turns out, there has been ongoing research aimed at the development of closed-loop drug dosing and delivery regimens in a number of specific medical domains for decades. For example, delivery of insulin for control of diabetes has been considered for over 50 years [39], with a variety of closed-loop methods considered including on–off control, control-to-range algorithms, proportional-integral-derivative (PID) designs, model-predictive control (MPC) approaches, and fuzzy-logic methods [78,22,9,81,8,10,34]; in particular, see [8,34] for surveys of control-relevant issues and design approaches for diabetes treatment. Chemotherapy dosing and timing control methods for treatment of various cancers and HIV have been investigated for close to 40 years, with optimal control methods being most commonly used, and recent efforts including game-theoretic approaches, piecewise-linear and positive systems methods, and MPC approaches [80,53,88,59,37,36]. And, control of anesthetic dosing during surgery to optimally control sedation level and manage hemodynamic functions has been a research interest for over 50 years, with early applications including on–off and PID control designs, and more recent methods including MPC, robust and adaptive control designs [12,2,27,28,50,5,62,41].

In this paper, we focus on the development of modeling and control methods aimed at closed loop (or semi-closed loop) control of pharmacodynamics. We first overview the classic modeling approaches considered for the purpose of analysis and control in Section 2, and note some challenges associated with these approaches. We then discuss a few recent alternative approaches, from which we proceed with a brief review of results on the more specific problem of modeling and control of anesthetic pharmacodynamics in Section 3. We focus a longer discussion on our results for modeling the response to anesthesia using piecewise-linear and linear parameter varying (LPV) models, and compare these to results using the standard modeling approaches on the same data sets. In Section 4, we provide a discussion and some simulation results from applications of recent feedback control approaches for anesthesia delivery. A short summary is given in Section 5. We begin with a discussion of the standard modeling paradigm used in pharmacodynamics, that of compartment models, which captures the basic dose–effect relationships and transport delays expected in administration of pharmaceutical agents, but does not capture drug synergy effects or the response to disturbances.

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2. Pharmacodynamics models

The traditional modeling paradigm used to describe the relationships between drug inputs, for example anesthetic agents or insulin, and patient outputs or *effects*, for example, blood pressure, sedation level or blood glucose concentration, is that of *compartment models*. These models combine *pharmacokinetic* and *pharmacodynamic* properties, offering a continuous profile of a drug's concentration versus time in the patient, which further may be related to the time course of the drug's effect by incorporating an *effect compartment*. We begin with an overview of compartment models, and then note some alternative model structures used in anesthesia and insulin pharmacodynamic modeling.

2.1. Compartment models

Pharmacokinetic (PK) compartment models are used to model and/or predict the disposition of drug in the body, by modeling the simultaneous diffusion of drug through body tissues and the flow of drug in the blood. The common quote used to describe the purpose of PK models is that they capture "*what the body does to the drug*". These models are meant to account for mass balances of the drug distribution, relying on an anatomical notion of the relation of tissues to circulating blood for the derivation of models. That is, a series of conceptual compartments, intended to represent the body's tissues and organs grouped roughly in order of decreasing blood flow, is used to describe the interchange of drug within the body. At each compartment, drug flows into the compartment from external inputs, or via transfer from other compartments, or both. Drug flows out of the compartment by transfer to other compartments and/or by elimination via metabolic clearance.

As an example, a three compartment model, shown in Fig. 1(a), would be represented mathematically by the state

$$\begin{aligned}\frac{dx_1}{dt} &= I + x_2k_{21} + x_3k_{31} - x_1k_{10} - x_1k_{12} - x_1k_{13}\\ \frac{dx_2}{dt} &= x_1k_{12} - x_2k_{21}\\ \frac{dx_3}{dt} &= x_1k_{13} - x_3k_{31}\end{aligned} \tag{1}$$

where x_i is the amount of drug in the ith compartment, k_{ij} is the distribution transfer rate from the ith compartment to the jth compartment, k_{10} is the clearance transfer rate out of the central compartment, and I represents the anesthetic infusion rate into the central compartment. Note that it is naturally assumed that the constraints $x_i(t) \geq 0$, for all $t \geq 0$ and all i, hold.

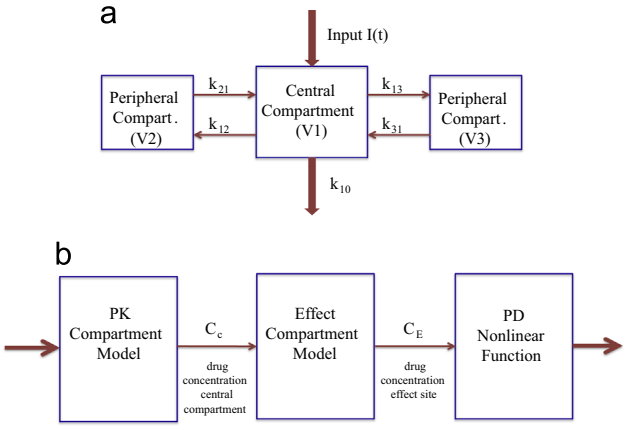

Fig. 1. (a) A three-compartment pharmacokinetic model. (b) The block diagram of a combined pharmacokinetic–pharmacodynamic (PK–PD) model.

The drug is administered to and distributed from the central compartment, which represents the highly perfused tissues, for example the lungs for inhaled anesthetics. The peripheral compartment with volume V_2 represents a *vessel rich* grouping of tissues and organs (e.g., brain and liver), which is assumed to reach steady-state equilibrium quickly. The peripheral compartment with volume V_3 may then correspond to fatty tissues and other *vessel poor* tissues and organs which equilibrate slowly (e.g., bones). It is assumed that the infused drug will mix immediately in the volume space of the central compartment (e.g., the heart for intravenous injections and the lungs for inhaled anesthetics). The drug concentration in the central compartment then decreases due to metabolic clearance and distribution to other compartments. The associated transfer rate constants, k_{ij}, are determined empirically. For drugs administered by bolus, single compartment models are used most commonly.

Pharmacodynamic (PD) compartment models are used to describe the relationship between drug concentration and the observed clinical effect; effect signals may be any number of patient vital signs, electroencephalogram (EEG) signals, or blood glucose levels, as examples. In this case it is frequently said that PD models address "*what the drug does to the body*". These models are typically given by static nonlinear functions, which are used to describe the equilibrium relationship between the drug concentration, C, and drug effect, E. A commonly used pharmacodynamic model structure is given by the well-known Hill equation:

$$E = \frac{E_{max}C^{\alpha}}{EC_{50}^{\alpha} + C^{\alpha}} \tag{2}$$

where E is the predicted effect of the drug, for example the mean arterial pressure (MAP) of the patient, E_{max} is the maximum possible effect, C is the drug concentration at time t, EC_{50} is the drug concentration for which 50% of the maximum effect is seen, and α is the *Hill coefficient of sigmoidicity* (a short discussion of the use of the Hill equation for PK–PD modeling follows). Frequently a non-zero baseline effect E_0 is included (i.e., effect at drug concentration 0), giving

$$E = E_0 + \frac{E_{max}C^{\alpha}}{EC_{50}^{\alpha} + C^{\alpha}}. \tag{3}$$

As well the effect modeled can be either positive or negative. Note that the effect being modeled can be static or dynamic; if the drug concentration changes with time the effect may change also.

Measurements of specific effects and either measured or predicted values of concentrations are used to derive the models, in accordance with the desired model structure. Concentrations at the actual effect site are required to construct accurate PD models. However, effect site concentrations are typically not available, or not easily accessed without resorting to invasive measurement techniques. Thus, *predicted concentrations* in the blood, derived from the PK models, are frequently used in order to capture the response from the input drug source to the gross effect output. In this case, an additional *effect compartment* is cascaded with the central compartment of the PK model to capture the transport time to the effect site; see Fig. 1(b).

It is assumed that the amount of drug in the effect compartment itself is extremely small and has no impact on the pharmacokinetic steady-state condition. To model the time to equilibration of drug concentration at the effect site from the central compartment, an additional first order linear differential equation is used, given by

$$\frac{dC_e}{dt} = K_{e0}(C_c - C_e), \tag{4}$$