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Data-driven modeling of pharmacological systems using endpoint information fusion

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ABSTRACT

This study investigated the feasibility of deriving data-driven model of a class of pharmacological systems using the information fusion of endpoint responses. For a class of pharmacological systems subsuming conventional steady-state dose-response models, compartmental pharmacokinetic–pharmacodynamic models and indirect response models, a relation between multiple endpoint responses was formalized and analyzed to elucidate if this class of systems is identifiable, i.e., if the data-driven model of this class of systems can be derived from the endpoint responses alone. It was shown that this class of systems is fully identifiable in case all the responses involve effect compartments. However, it was also observed that persistently exciting dose profiles may be required in accurately deriving reliable data-driven model with low variance. The findings from the identifiability analysis were demonstrated using benchmark pharmacological system examples.

1. Introduction

It has been suggested that high-fidelity model of pharmacological systems may contribute to improved healthcare through low-cost and expedited simulation of new therapeutic regimens, accurate prediction of patient response to medication therapy, and design of automated systems for medication infusion. For example, pharmacological models have been used to design and evaluate dose schedules in topotecan therapy for pediatric neuroblastoma [1], cancer chemotherapy [2] and diabetes mellitus [3]. These models have also been used in predicting the clinical responses of patients to anesthesia [4] and vasoactive [5] drugs. Besides, design of automated systems for medication infusion based on the pharmacological models has been studied in the field of anesthesia [6–9] and diabetes mellitus [10,11].

Conventional methods to derive data-driven pharmacological models necessitate the measurements of medication dose, plasma concentration of medication and the resulting endpoint(s) (Fig. 1(a)). In research settings, the PK model is derived using medication dose and plasma concentration of medication as input and output, respectively, while the PD model is derived using plasma concentration of medication and endpoint as input and output, respectively. However, this modeling framework cannot be used in real clinical settings in which plasma concentration of medication is not measured. To cope with this problem, the population PK model was often used to yield model-based prediction of plasma concentration of medication from dose data [8,12–15]. However, this approach is susceptible to large errors due to drastic inter-individual variability in the PK profile (see, e.g., [16]). More recently, efforts to derive subject-specific PKPD model were made via low-order modeling. In Silva et al. [17], PK and effect compartment models for anesthesia medications were merged into a low-order rational transfer function incorporating both population-averaged and subject-specific parameters. Hahn et al. [16] proposed a low-order model directly relating medication dose to an endpoint, which could be fully adapted to dose-endpoint data on an individual basis. These models showed promise in accurately predicting subject-specific endpoint responses to medication doses. However, they failed to retain the compartmental model structure, thereby compromising the physiologic transparency. To date, attempts to derive data-driven model of pharmacological systems in the absence of plasma concentration of medication appear to be very rare.

This study investigates the feasibility of deriving data-driven model of a class of pharmacological systems using dose and endpoint responses alone. The key idea is to exploit the fact that all endpoints originate from the same plasma concentration of medication via distinct PD mechanisms (Fig. 1(b)). In this way, a relation between multiple endpoints is derived that can be solved using the endpoint data alone to yield data-driven PD models. Then, plasma concentration of medication can be de-convolved from the endpoint data using the PD model. Finally, PK model can be derived using (measured) medication dose and (model-predicted) plasma concentration of medication (Fig. 1(b)).

This paper is organized as follows: Section 2 formalizes the proposed data-driven modeling method and presents the theoretical

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0010-4825/

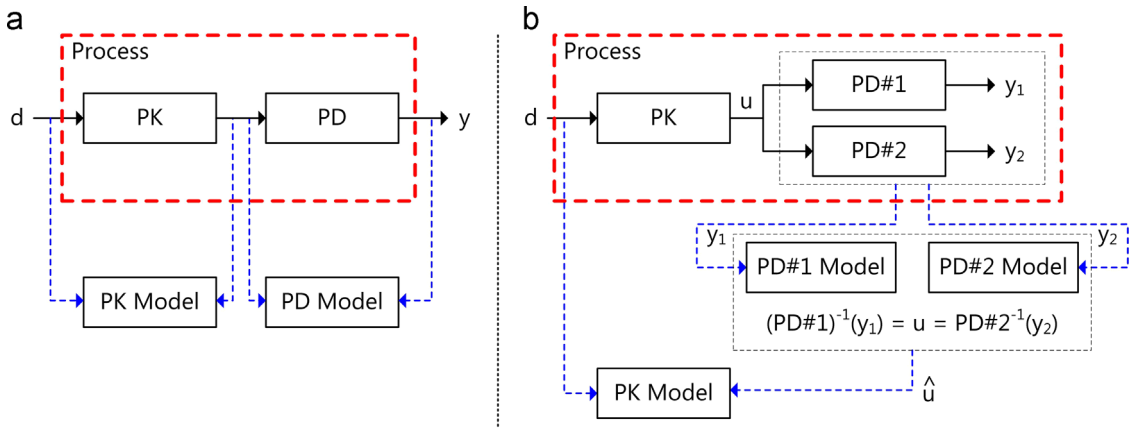

Fig. 1. Conventional versus proposed data-driven modeling of pharmacological systems.

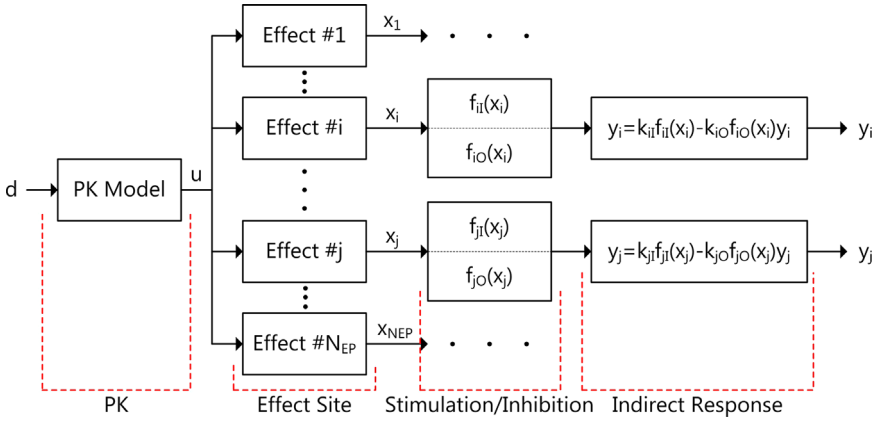

Fig. 2. A class of pharmacological systems considered in this study.

analysis conducted in this study. Section 3 outlines the application of the method to benchmark examples on data-driven pharmacological systems modeling problems. Section 4 shows and discusses the results. The paper is concluded in Section 5.

2. Theoretical analysis

2.1. A class of pharmacological systems

The class of pharmacological systems considered in this study is shown in Fig. 2. The system consists of a compartmental PK model followed by multiple PD models, each of which includes an effect compartment and an indirect response model. The PK model is given by an ordinary differential equation

$$u^{(n)}+\alpha_{n-1}u^{(n-1)}+\cdots+\alpha_0 u=\beta_{m-1}d^{(m-1)}+\cdots+\beta_0 d \tag{1}$$

where d is the medication dose, u is the plasma concentration of medication, and α_j, $j=1,\cdots n-1$ and β_k, $k=1,\cdots m-1$ are constant coefficients. The superscript (i) denotes i-th order time derivative. The effect compartment models are given by:

$$\tau_j\dot{x}_j+x_j=u \tag{2}$$

where x_j is the effect site concentration of medication associated with the j-th endpoint ($j=1,\cdots,N_{EP}$ where N_{EP} is the number of endpoints), and τ_j is the corresponding equilibration time constant. These x_j's affect the endpoints y_j ($j=1,\cdots,N_{EP}$) by stimulating/inhibiting its production or dissipation via nonlinear functions $f_{jI}(x_j)$ and $f_{jO}(x_j)$, $j=1,\cdots,N_{EP}$:

$$\dot{y}_j=k_{jI}f_{jI}(x_j)-k_{jO}f_{jO}(x_j)y_j \tag{3}$$

where k_{jI} and k_{jO} are the zeroth-order production and first-order dissipation constants associated with y_j, and $f_{jI}(x_j)$ and $f_{jO}(x_j)$ are given by

$$f_{jI}(x_j)=1\pm\frac{b_{jI}x_j}{a_{jI}+x_j},\quad f_{jO}(x_j)=1\pm\frac{b_{jO}x_j}{a_{jO}+x_j} \tag{4}$$

where $0<b_{jI}\le 1$ and $0<b_{jO}\le 1$ denote the maximum stimulation/inhibition effect, while a_{jI} and a_{jO} are the effect site concentrations of medication at which 50% of maximum stimulation/inhibition effect occurs. It is assumed that x_j exerts effect on either f_{jI} or f_{jO}, but not both [18]. Note that plus and minus signs in (4) denote, respectively, stimulation and inhibition. Note also that k_{jI} and k_{jO} are related to each other by $k_{jI}=k_{jO}y_{j0}$ where y_{j0} is the baseline value of the j-th endpoint [18]. Indeed, in the steady state ($\dot{y}_j=0$) under zero medication dose ($x_j=0$ and thus $f_{jI}(x_j)=f_{jO}(x_j)=1$), (3) reduces to $k_{jI}=k_{jO}y_{j0}$.

It must be emphasized that the class of pharmacological systems shown in Fig. 2 subsumes a wide range of conventional pharmacological models, including steady-state dose-response models (e.g., [19]), direct effect models (e.g., [1,6–9,20]) and indirect response models (e.g., [18,21,22]). Indeed, it is obvious that (1) steady-state dose-response model yields by removing the PK model then setting $\dot{x}_j=\dot{y}_j=0$ and $a_{jO}=b_{jO}=0$, (2) direct effect model yields by setting $\dot{y}_j=0$ and $a_{jO}=b_{jO}=0$, and (3) indirect response model yields by setting $\dot{x}_j=0$. Thus, findings from this study are applicable to a broad range of pharmacological systems being widely used in today's pharmacology.