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Semi-adaptive switching control for infusion of two interacting medications

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ABSTRACT

In this paper, a semi-adaptive switching control approach to the infusion of two interacting medications was investigated. A two-mode switching control technique was developed based on two-input two-output dose-response models associated with two distinct operating regimes, where the dose-response model associated with each mode was obtained by linearizing a nonlinear two-input two-output dose-response model near an operating point in the neighborhood of which one medication is used as primary therapy while the other is used as secondary therapy. The controller associated with each mode was designed based on a semi-adaptive control technique, where a subset of high-sensitivity model parameters are adapted in real time while the remaining low-sensitivity parameters are fixed at relevant nominal values. In this way, the controller can account for the therapeutic regime-dependent influence of medications and inter-medication synergy on clinical responses, while making use of dose-response measurements for online adaptation of dose-response models. The proposed approach was applied to an example scenario in which cardiac output and respiratory rate are regulated via the infusion of propofol and remifentanil in an in-silico simulation setting. The results illustrated that the semi-adaptive switching control approach could provide benefits in terms of reference tracking performance and parameter estimation accuracy.

1. Introduction

During the care of critically ill patients receiving surgical and intensive treatments, multiple medications are often administered to achieve a multitude of therapeutic goals. For example, anesthesia involves the infusion of hypnotics, opioid, and neuromuscular blockade to achieve hypnosis, analgesia, and paralysis [1–3], while circulatory resuscitation requires the infusion of fluids and vasoactive medications to achieve desired cardiac and vascular performances (e.g., [4–6]). Currently, medication infusion task is performed by human caregivers. Noting that a caregiver monitors patient's response to medications and adjusts infusion rates to achieve therapeutic goals, medication infusion process is essentially a manually operated feedback control system that may ultimately be automated by computer control. In fact, recent reports indicate that there are promising opportunities associated with the introduction of autonomy to the medication infusion arena via closed-loop control to improve therapeutic efficacy while reducing clinical workload [7–11], although numerous stringent safety requirements must be met before autonomy can be deployed to assist clinicians in real-world patient care.

However, the control design problem for infusion of multiple medications present unique challenges due to the nonlinearities in the process dynamics and interactions among medications (i.e., inter-medication synergy [12,13]). First, the dose-response relationship associated with each medication usually exhibits stiff nonlinearity that cannot be linearly parameterized (e.g., the Hill equation [14]). Second, the inter-medication synergy introduces added complexity to the dose-response relationship due to the input-output coupling (e.g., the response surface models [15–17]). In the presence of these challenges, linearization of dose-response relationship in the vicinity of an operating point has been the mainstay of model-based control design for the infusion of a single medication (e.g., [18,19]). Given, however, that the coupling effect between multiple medications frequently exhibits complex behaviors (e.g., bi-phasic [15–17]) due to the regime-dependent inter-medication synergy, the use of a dose-response relationship linearized in the neighborhood of a single operating

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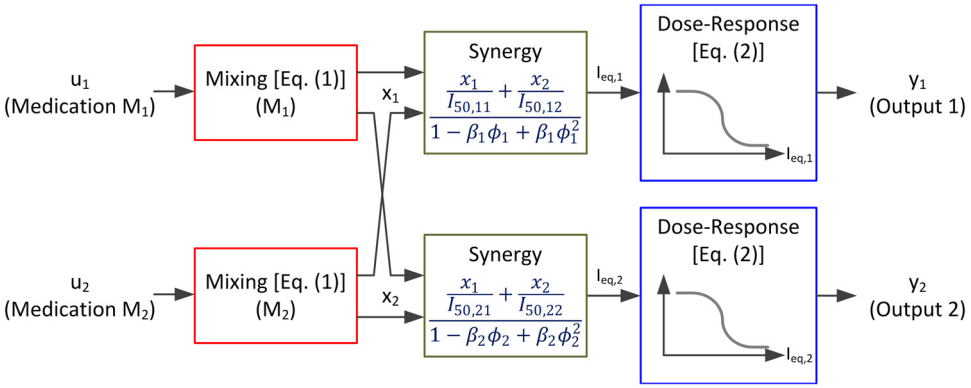

Fig. 1. Dose-response model for two interacting medications, consisting of a low-order mixing model and a response surface model.

regime may not suffice for trustworthy design and analysis of closed-loop controllers for the infusion of multiple interacting medications. In addition to the challenges originating from the nonlinear dose-response relationship, the dose-response relationship exhibits a large degree of inter-individual variability and uncertainty. To cope with the variability, adaptive patient-specific rather than population-averaged control approach may be preferred.

Despite these outstanding challenges, there is not a large body of prior work related to closed-loop control for the infusion of interacting medications compared with closed-loop control for a single medication (e.g., propofol [20,21], remifentanil [22,23], isoflurane [24–26], and fluids [27–29] to list a few recent reports). Existing reports include model-free control (e.g., self-organizing fuzzy logic [30,31]) and model-based control using a dose-response model linearized in the neighborhood of an operating regime [32]. The limited body of state-of-the-art and the projected potential of advanced model-based control in the automation of medication infusion (e.g., [33]) naturally motivate rigorous study of closed-loop control design problem for the infusion of multiple interacting medications. In particular, there are opportunities to address the aforementioned challenges by leveraging the key ideas from the state-of-the-art switching control [34,35] as well as direct (in which the controller parameters are adapted) and indirect (in which the plant parameters are adapted, based on which controller is updated) adaptive control [36,37] theories.

In our initial attempt to address the aforementioned challenges, we investigated a semi-adaptive switching control approach to the infusion of two interacting medications. A two-mode switching control technique was developed based on two-input two-output dose-response models associated with two distinct operating regimes, where the dose-response model associated with each mode was obtained by linearizing a nonlinear two-input two-output dose-response model near an operating point in the neighborhood of which one medication is used as primary therapy while the other is used as secondary therapy. The controller associated with each mode was designed based on a semi-adaptive control technique developed in our prior work [22], where a subset of high-sensitivity model parameters are adapted in real time while the remaining low-sensitivity parameters are fixed at relevant nominal values. In this way, the controller can account for the therapeutic regime-dependent influence of medications and inter-medication synergy on clinical responses, while making use of dose-response measurements for online adaptation of dose-response models. Compared with the existing model-free approach [30,31] whose stability can only be analyzed by massive in-silico and in-vivo trials, the proposed approach boasts stability and performance guarantee via rigorous mathematical analysis. Compared with the existing model-based approach based on a single operating regime [32], it has potential to achieve superior performance characteristics. The proposed approach was applied to an example scenario in which cardiac output and respiratory rate are regulated via the infusion of propofol and remifentanil in an in-silico simulation setting.

This paper is organized as follows. Section 2 presents a global nonlinear dose-response model applicable to two interacting medications and locally linearized control-oriented dose-response models derived from the global model. Section 3 describes in detail the semi-adaptive switching control approach to two-input two-output medication infusion problems. Section 4 presents and discusses the results obtained from in-silico testing of the semi-adaptive switching control. Section 5 concludes the paper with potential future directions.

2. Dose-response modeling

2.1. Global nonlinear dose-response model for two interacting medications

We developed a two-input two-output nonlinear dose-response model for two interacting medications by adopting and combining a low-order mixing model developed in our previous work [22,38] and a response surface model originally developed by Minto et al. [15] (Fig. 1). The low-order mixing model represents the relationship between the intravenous infusion rate of a medication and its hypothetical infusion rate at the site of action [22,38]:

$$\begin{aligned}\dot{x}_1 &= -k_{e1}x_1 + k_{e1}u_1\\ \dot{x}_2 &= -k_{e2}x_2 + k_{e2}u_2\end{aligned} \tag{1}$$

where u_1 and u_2 are the intravenous infusion rates associated with the two medications M_1 and M_2, x_1 and x_2 the hypothetical infusion rates at the sites of action, and k_{e1} and k_{e2} the equilibration constants. The response surface model developed by Minto et al. is a multi-