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Controlling the depth of anesthesia by a novel positive control strategy☆

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ABSTRACT

In this paper a positive control law is designed for multi-input positive systems that ensures asymptotic tracking of a desired output reference value. This control law can be viewed as a generalization of another one proposed in the literature for the control of the total mass in SISO compartmental systems, but is suitable for a wider class of positive systems. The controller proposed here is applied to the control of the depth of anesthesia (DoA), by means of the administration of *propofol* and *remifentanil*, when using a parameter parsimonious Wiener model recently introduced in the literature. Its performance is illustrated by realistic simulations.

1. Introduction

The goal of automatically controlled drug administration is to determine the dosage to be administered to achieve and keep a certain effect of a drug in the patient. In this work, the primary goal is to track the level of the depth of anesthesia, here measured by the bispectral index (BIS), which is transformed into a problem of tracking the effect concentration by inverting the generalized Hill equation. This problem can be modeled as an output reference tracking problem. More specifically, after modeling the phenomenon in question by a control system in which the control input is the dosage of drug to be administered and the output is the corresponding effect, one seeks a control law that forces the system output to converge to the desired reference value.

Since the quantities involved in this process are all nonnegative, this problem falls within the realm of positive systems. These systems have gained increasing attention in the control literature during the last decades. See for example Farina and Rinaldi [1], Haddad et al. [2], Roszak and Davison [3], Roszak and Davison [4], Kaczorek [5], Willems [6], Soltesz et al. [7]. In this latter reference, a controller by integral action together with a positivity constraint was proposed, showing that the

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input is positive provided that the integral gain $\epsilon > 0$ is chosen sufficiently small. This controller does not presuppose a full knowledge of the model, however it does need the a priori knowledge of the steady-state gain matrix, in order to obtain a suitable value for the integral gain ϵ. This may take a long time to obtain in case the process poles are not fast enough. This constitutes a disadvantage for its use in our application. The controller presented in this paper ensures reference tracking independently from the positive value of the design parameter, without requiring the knowledge of the steady-state gain matrix. Nevertheless, it does require information about the model parameters and the corresponding state. However, these parameters can be identified in a short preliminary stage, and a state observer can be included in order to estimate the state online. The control law, developed in this work, is considered to be nonlinear, not due to use of nonlinear design methods, but rather because of the imposition of positivity constraint on the control variable, which makes it a nonlinear function of the state of the system.

In this paper we consider single output positive systems with multiple inputs and design a nonlinear positive control law that ensures asymptotic tracking of a desired output reference value. This control law can be viewed as a generalization of the one proposed in Bastin and Provost [8] for the control of the total mass in SISO compartmental systems. However, whereas the control law in Bastin and Provost [8] is only designed for compartmental systems, our control law is suitable for a wider class of positive systems as is sustained by the new theoretical results presented in the paper (Section 2).

Our results prove to be useful for the control of the depth of anesthesia, a problem that has lately deserved much attention. For instance, the work developed in Soltesz et al. [7] presents two controllers in parallel for the DoA of a patient based on a PID controller for the administration of *propofol* and a proportional controller for the input of *remifentanil*. Here, we present one single multi-output feedback controller for both drugs. A good overview of the underlying problem may be found in Dumont [9] and in the references therein.

The proposed controller is applied to the control of the depth of anesthesia by means of *propofol* and *remifentanil* using the recently proposed parameter parsimonious Wiener model (see Silva et al. [10]). The performance of the controller is analyzed by means of several simulations along with realistic simulations relying on identified real patients data collected in the surgery room during general anesthesia.

The present paper is structured as follows. In Section 2 a control law is designed for output reference tracking in MISO positive systems. The application of the corresponding controller in general anesthesia is presented in Section 3. In Section 4 the performance of the proposed controller is illustrated by means of several simulations, and the results of its application in realistic simulated patients are presented in Section 5. Conclusions follow in Section 6.

2. Output reference tracking for MISO positive systems

In this section the general problem of reference tracking for multi-input/single-output (MISO) positive systems is presented. The application to the control of anesthesia will be presented in Section 3.

2.1. Problem description

Consider a positive system with m inputs and a single output described by the state-space model

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ y(t) = Cx(t), \end{cases} \tag{1}$$

where A is a $n \times n$ Meztler matrix, i.e., a matrix in which all the off-diagonal components are nonnegative, and B and C are matrices with nonnegative entries (see Godfrey [11]) of dimension $n \times m$ and $1 \times m$, respectively. Here, for short, in the sequel (1) is denoted by (A, B, C). Moreover, for a vector v, the notations $v \geq 0$ ($v > 0$) and $v \leq 0$ ($v < 0$) mean that all its entries are respectively positive (strictly positive) and negative (strictly negative). The same applies to matrices.

Given a desired constant reference value y^* for the output, a control law $u = Kx + L$ is sought such that the closed-loop system

$$\begin{cases} \dot{x}(t) = (A + BK)x(t) + BL \\ y(t) = Cx(t), \end{cases} \tag{2}$$

has bounded trajectories and tracks the reference, i.e., such that its output verifies $\lim_{t\to\infty} y(t) = y^*$.

2.2. Controller design

Here we solve the problem of output reference tracking, by regarding it as a problem of controlling the system to a level set $\Omega_{y^*} = \{x \in \mathbb{R}^n_+ : Cx = y^*\}$ in the state space, where $\mathbb{R}^n_+ = \{x \in \mathbb{R}^n : x \geq 0\}$.

For this purpose, we first design an auxiliary control law, $\tilde{u}$, and then impose positivity to $\tilde{u}$ in order to obtain a positive control input u. We also make the following assumptions: (A1) A is stable, (A2) CB is a nonzero row matrix and (A3) $CA < 0$.

Let

$$\tilde{u}(t) = -ECAx(t) + E\lambda(y^* - y(t)), \tag{3}$$

where $\lambda > 0$ is a design parameter, and E is a column matrix with nonnegative entries such that $CBE = 1$. Note that such a matrix always exists since CB has nonnegative entries, at least one of each is strictly positive. The application of this control input leads to the closed-loop dynamics

$$\dot{x}(t) = Ax(t) + B(E\lambda(y^* - y(t)) - ECAx(t)) \tag{4}$$

which implies that

$$\dot{y}(t) = C\dot{x}(t) = CAx(t) + \lambda(y^* - y(t)) - CAx(t) \tag{5}$$

$$= -\lambda(y(t) - y^*) \tag{6}$$

and therefore

$$\dot{\overline{y(t) - y*}} = -\lambda(y(t) - y*). \tag{7}$$