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Adaptive Control of Mammillary Drug Delivery Systems with Actuator Amplitude Constraints and System Time Delays

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Abstract— **In this paper, we develop a direct adaptive control framework for uncertain linear compartmental dynamical systems with actuator amplitude constraints and system time delays. The specific focus of the paper is on compartmental pharmacokinetic models and their applications to drug delivery systems. In particular, we develop a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation of the closed-loop system in the nonnegative orthant in the presence of unknown system time delays and control amplitude constraints. The framework additionally guarantees nonnegativity of the control signal. Finally, a numerical example, involving the infusion of the anesthetic drug propofol for maintaining a desired constant level of depth of anesthesia for noncardiac surgery, is provided to demonstrate the framework on a drug delivery mammillary model for general anesthesia involving system time delays and control infusion rate constraints.**

I. Introduction

Compartmental models play a key role in the understanding of many processes in biological and medical sciences [1], [2]. Compartmental dynamical systems involve interconnected subsystems (or compartments) that exchange variable nonnegative quantities of material with conservation laws describing transfer, accumulation, and elimination between compartments and the environment. In many compartmental system models, transfers between compartments are assumed to be instantaneous, that is, the model does not account for material in transit. Even though this is a valid assumption for certain biological and physiological systems, it is not true in general, especially in pharmacokinetic and pharmacodynamic models [1]. For example, if a bolus (impulsive) dose of drug is injected and we seek its concentration level in the extracellular and intercellular space of some organ, a time lag exists before it is detected in that organ [1]. In this case, assuming instantaneous mass transfer between compartments will yield erroneous models. Although mixing times can be modeled by including additional compartments in series, even this model assumes instantaneous mixing in the initial compartment. To accurately describe the distribution of pharmacological agents in the human body, it is necessary to include in any mathematical compartmental pharmacokinetic model information of the past system states. In this case, the state of the system at any given time involves a *piece of trajectories* in the space of continuous functions defined on an interval in the nonnegative orthant. This of course leads to (infinite-dimensional) delay dynamical systems [3].

Since compartmental models provide a broad framework for biological and physiological systems, including clinical pharmacology, they are well suited for developing models for closed-loop control of drug administration. However, given the significant magnitude of intrapatient and interpatient variability, and the fact that an individual patient's drug sensitivity varies with time, adaptive control for active drug administration is clearly essential. In a recent paper [4], we developed an adaptive control algorithm using the electroencephalogram (EEG) as an objective, quantitative measure of consciousness for closed-loop control of anesthesia. An implicit assumption inherent in [4] is that the control law is implemented without any regard to actuator amplitude and rate saturation constraints. Of course, any electromechanical control actuation device (syringe pump) is subject to amplitude and/or rate constraints leading to saturation nonlinearities enforcing limitations on control amplitude and control rates. More importantly, in pharmacological applications, drug infusion rates can vary from patient to patient, and, to avoid overdosing, it is vital that the infusion rate does not exceed the patient-specific threshold values. As a consequence, control constraints, that is, infusion pump rate constraints, need to be accounted for in drug delivery systems.

In this paper, we extend the results of [4] to the case of compartmental dynamical systems with unknown system time delays and control amplitude constraints. Specifically, we develop a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation for linear uncertain compartmental dynamical systems with unknown time delay and control amplitude constraints. The specific focus of the paper is on pharmacokinetic models and their applications to drug delivery systems. Since the most common pharmacokinetic models are linear and *mammillary* [1], that is, models comprised of a *central compartment* from which there is outflow from the system and which exchanges material reversibly with one or more *peripheral compartments*, we develop direct adaptive controllers for mammillary systems. Finally, we numerically demonstrate the framework on a drug delivery model for general anesthesia that involves system time delays as well as control infusion rate constraints.

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II. Mathematical Preliminaries

In this section we introduce notation, several definitions, and some key results concerning linear nonnegative dynamical systems with time delays [5], [6] that are needed for developing the main results of this paper. Specifically, for $x \in \mathbb{R}^n$ we write $x \geq\geq 0$ (resp., $x >> 0$) to indicate that every component of x is nonnegative (resp., positive). In this case we say that x is *nonnegative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n\times m}$ is *nonnegative* or *positive* if every entry of A is nonnegative or positive, respectively, which is written as $A \geq\geq 0$ or $A >> 0$, respectively. Furthermore, for $A \in \mathbb{R}^{n\times n}$ we write $A \geq 0$ (resp., $A > 0$) to indicate that A is a nonnegative-definite (resp., positive-definite) matrix. Let $\overline{\mathbb{R}}^n_+$ and $\mathbb{R}^n_+$ denote the nonnegative and positive orthants of $\mathbb{R}^n$, that is, if $x \in \mathbb{R}^n$, then $x \in \overline{\mathbb{R}}^n_+$ and $x \in \mathbb{R}^n_+$ are equivalent, respectively, to $x \geq\geq 0$ and $x >> 0$. The following definition introduces the notion of a nonnegative (resp., positive) function.

Definition 2.1: Let $T > 0$. A real function $u : [0, T] \to \mathbb{R}^m$ is a *nonnegative* (resp., *positive*) *function* if $u(t) \geq\geq 0$ (resp., $u(t) >> 0$) on the interval $[0, T]$.

The next definition introduces the notion of essentially nonnegative matrices.

Definition 2.2: Let $A \in \mathbb{R}^{n\times n}$. A is *essentially nonnegative* if $A_{(i,j)} \geq 0$, $i, j = 1, \ldots, n$, $i \neq j$, where $A_{(i,j)}$ denotes the (i, j)th entry of A.

In this paper, we consider a controlled linear time-delay dynamical system $\mathcal{G}$ of the form

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(t - \tau_i) + Bu(t),$$
$$x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \quad (1)$$

where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $A \in \mathbb{R}^{n\times n}$, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, $B \in \mathbb{R}^{n\times m}$, $\bar{\tau} = \max_{i\in\{1,\ldots,n_{\mathrm{d}}\}} \tau_i$, $\tau_i \geq 0$, $i = 1, \ldots, n_{\mathrm{d}}$, $\eta(\cdot) \in \mathcal{C} = \mathcal{C}([-\bar{\tau}, 0], \mathbb{R}^n)$ is a continuous vector valued function specifying the initial state of the system, and $\mathcal{C}([-\bar{\tau}, 0], \mathbb{R}^n)$ denotes a Banach space of continuous functions mapping the interval $[-\bar{\tau}, 0]$ into $\mathbb{R}^n$ with the topology of uniform convergence. Note that the state of (1) at time t is the *piece of trajectories* x between $t - \bar{\tau}$ and t, or, equivalently, the *element* x_t in the space of continuous functions defined on the interval $[-\bar{\tau}, 0]$ and taking values in $\mathbb{R}^n$; that is, $x_t \in \mathcal{C}([-\bar{\tau}, 0], \mathbb{R}^n)$, where $x_t(\theta) \triangleq x(t + \theta)$, $\theta \in [-\bar{\tau}, 0]$. Furthermore, since for a given time t the piece of the trajectories x_t is defined on $[-\bar{\tau}, 0]$, the uniform norm $\|\!|x_t|\!\| = \sup_{\theta\in[-\bar{\tau},0]} \|x(t + \theta)\|$, where $\|\cdot\|$ denotes the Euclidean vector norm, is used for the definitions of Lyapunov and asymptotic stability of (1) with $u(t) \equiv 0$. For further details see [3]. Finally, note that since $\eta(\cdot)$ is continuous it follows from Theorem 2.1 of [3, p. 14] that there exists a unique solution $x(\eta)$ defined on $[-\bar{\tau}, \infty)$ that coincides with η on $[-\bar{\tau}, 0]$ and satisfies (1) for all $t \geq 0$. The following definition is needed.

Definition 2.3: The linear time-delay dynamical system given by (1) is *nonnegative* if for every $\eta(\cdot) \in \mathcal{C}_+$, and $u(t) \geq\geq 0$, $t \geq 0$, where $\mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C} : \psi(\theta) \geq\geq 0, \theta \in [-\bar{\tau}, 0]\}$, the solution $x(t)$, $t \geq 0$, to (1) is nonnegative.

Next, we consider a subclass of nonnegative systems, namely, compartmental systems. As noted in the Introduction, linear compartmental dynamical systems are of major importance in biological and physiological systems. For example, almost the entire field of distribution of tracer labelled materials in steady state systems can be captured by linear compartmental dynamical systems [1].

Definition 2.4: Let $A \in \mathbb{R}^{n\times n}$. A is a *compartmental matrix* if A is essentially nonnegative and $\sum_{i=1}^n A_{(i,j)} \leq 0$, $j = 1, \ldots, n$.

Definition 2.5: The linear time-delay dynamical system (1) is called a *compartmental dynamical system* if A and $A_{\mathrm{d}} \triangleq \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$, $n_{\mathrm{d}} = n^2 - n$, are given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^n a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \quad (2)$$

$$A_{\mathrm{d}(i,j)} = \begin{cases} 0, & i = j, \\ a_{ij}, & i \neq j, \end{cases} \quad (3)$$

where $a_{ii} \geq 0$, $i \in \{1, \ldots, n\}$, denote the loss coefficients of the ith compartment and $a_{ij} \geq 0$, $i \neq j$, $i, j \in \{1, \ldots, n\}$, denote the transfer coefficients from the jth compartment to the ith compartment.

Note that if (1) is a compartmental system, then $A + A_{\mathrm{d}}$ is a compartmental matrix. Furthermore, note that if A and $A_{\mathrm{d}l}$, $l = 1, \ldots, n^2 - n$, are given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^n a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \quad (4)$$

$$A_{\mathrm{d}l(i,j)} = \begin{cases} a_{ij}, & i = \lfloor \frac{l-1}{n-1} \rfloor + 1, \\ & j = (l-1)(\mathrm{mod}\, n-1) + 1, \\ & \text{if } (l-1)(\mathrm{mod}\, n-1) < \lfloor \frac{l-1}{n-1} \rfloor, \\ a_{ij}, & i = \lfloor \frac{l-1}{n-1} \rfloor + 1, \\ & j = (l-1)(\mathrm{mod}\, n-1) + 2, \\ & \text{if } (l-1)(\mathrm{mod}\, n-1) \geq \lfloor \frac{l-1}{n-1} \rfloor, \\ 0, & \text{otherwise}, \end{cases} \quad (5)$$

where $\lfloor\cdot\rfloor$ denotes the greatest integer function (i.e., $\lfloor n \rfloor$ gives the largest integer less than or equal to n) and $q \bmod n$ denotes the common residue operation giving one of the integers $0, \ldots, n-1$ and defining modular arithmetic modulo n, then this system is a compartmental dynamical system.

In pharmacokinetic applications, an important subclass of compartmental systems are *mammillary* systems [1]. As noted in the Introduction, mammillary systems are comprised of a central compartment from which there is outflow and which exchanges material reversibly with one or more peripheral compartments. An *inflow-closed* (i.e., $u(t) \equiv 0$) time-delay mammillary system is given by (1) with A and $A_{\mathrm{d}l}$, $l = 1, \ldots, n-1$, given by

$$A = \mathrm{diag}[-\sum_{j=1}^n a_{j1}, -a_{12}, \ldots, -a_{1n}], \quad (6)$$

$$A_{\mathrm{d}l(i,j)} = \begin{cases} a_{ij}, & i = 1, j = (l-1)(\mathrm{mod}\, n-1) + 2, \\ a_{ij}, & i = (l-1)(\mathrm{mod}\, n-1) + 2, j = 1, \\ 0, & \text{otherwise}, \end{cases} \quad (7)$$

where $1 \leq l \leq n-1$, and the transfer coefficients a_{ij}, $i, j = 1, \ldots, n$, and the loss coefficient a_{11} are nonnegative. In this case,

$$A + \sum_{i=1}^{n-1} A_{\mathrm{d}i} = \begin{bmatrix} -\sum_{j=1}^n a_{j1} & a_{12} & \ldots & a_{1n} \\ a_{21} & -a_{12} & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & 0 & \ldots & -a_{1n} \end{bmatrix}. \quad (8)$$

The following proposition is needed for the main results of the paper.

Proposition 2.1 ([5], [6]): The linear time-delay dynamical system $\mathcal{G}$ given by (1) is *nonnegative* if and only if $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$, is nonnegative, and $B \in \mathbb{R}^{n\times m}$ is nonnegative.

Since stabilization of nonnegative systems naturally deals with equilibrium states in the interior of the nonnegative orthant $\overline{\mathbb{R}}^n_+$, the following proposition provides necessary conditions for the existence of an interior equilibrium state $x(\theta) = x_{\mathrm{e}} \in \mathbb{R}^n_+$, $\theta \in [-\bar{\tau}, 0]$, of (1) in terms of the stability properties of the system matrices A and $A_{\mathrm{d}i}$, $i = 1,\ldots,n_{\mathrm{d}}$. For this result, recall that a matrix $M \in \mathbb{R}^{n\times n}$ is *semistable* if and only if $\lim_{t\to\infty} e^{Mt}$ exists.

Proposition 2.2: Consider the nonnegative time-delay dynamical system (1) and assume there exist $x_{\mathrm{e}} \in \mathbb{R}^n_+$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}^m_+$ such that

$$0 = (A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})x_{\mathrm{e}} + Bu_{\mathrm{e}}. \tag{9}$$

Then, $A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is semistable.

It follows from Proposition 2.2 that the existence of an equilibrium state $x(\theta) = x_{\mathrm{e}} \in \mathbb{R}^n_+$, $\theta \in [-\bar{\tau}, 0]$, for (1) implies that the matrix $A+\sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is semistable. Hence, if (9) holds for $x_{\mathrm{e}} \in \mathbb{R}^n_+$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}^m_+$, then $A+\sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is asymptotically stable or $0 \in \mathrm{spec}(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})$ is a simple eigenvalue of $A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$, where $\mathrm{spec}(X)$ denotes the spectrum of the square matrix X, and all other eigenvalues of $A+\sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ have negative real parts since $-(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})$ is an M-matrix [2].

Finally, the following proposition is needed for the main result of this paper.

Proposition 2.3: Consider the linear time-delay mammillary system given by (1) where A and $A_{\mathrm{d}i}$, $i = 1,\ldots,n-1$, are given by (6) and (7), respectively. Then there exist positive diagonal matrices $P \in \mathbb{R}^{n\times n}$ and $Q_i \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n-1$, such that

$$0 > A^{\mathrm{T}}P + PA + \sum_{i=1}^{n-1} Q_i + \sum_{i=1}^{n-1} PA_{\mathrm{d}i}Q_i^{-1}A_{\mathrm{d}i}^{\mathrm{T}}P. \tag{10}$$

III. Adaptive Control for Compartmental Dynamical Systems with Control Constraints and Time Delay

In this section we consider the problem of characterizing adaptive feedback control laws for uncertain compartmental dynamical systems with actuator amplitude constraints and system time delays to achieve *set-point* regulation in the nonnegative orthant. Specifically, consider the following controlled linear uncertain time-delay dynamical system $\mathcal{G}$ given by

$$\begin{aligned}\dot{x}(t) &= Ax(t) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(t-\tau_i) + Bu(t),\\ x(\theta) &= \eta(\theta), \quad -\bar{\tau} \le \theta \le 0, \quad t \ge 0,\end{aligned} \tag{11}$$

where $x(t) \in \mathbb{R}^n$, $t \ge 0$, is the state of the system, $u(t) \in \mathbb{R}^m$, $t \ge 0$, is the control input, $A \in \mathbb{R}^{n\times n}$ is an *unknown* essentially nonnegative matrix, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$, and $B \in \mathbb{R}^{n\times m}$ are *unknown* nonnegative matrices, $\eta(\cdot) \in \{\psi(\cdot) \in \mathcal{C}_+([-\bar{\tau}, 0], \mathbb{R}^n) : \psi(\theta) \ge\ge 0,\ \theta \in [-\bar{\tau}, 0]\}$, and $\bar{\tau} = \max_{i\in\{1,\ldots,n_{\mathrm{d}}\}} \tau_i$, where $\tau_i \ge 0$, $i = 1,\ldots,n_{\mathrm{d}}$, are *unknown* system delays. The control input $u(\cdot)$ in (11) is restricted to the class of admissible controls consisting of measurable functions such that $u(t) \in \mathcal{U} \subset \overline{\mathbb{R}}^m_+$, where $\mathcal{U} \triangleq \{u(t) \in \mathbb{R}^m\colon\ 0 \le u_i(t) \le u_{\max,i},\ i = 1,\ldots,m,\ t \ge 0\}$, and $u_{\max,i} > 0$, $i = 1,\ldots,m$, are given.

The assumption that $u(t) \in \mathcal{U} \subset \overline{\mathbb{R}}^m_+$ is motivated by the fact that control (source) inputs for drug delivery systems of physiological processes are usually constrained to be nonnegative as are the system states. Since A is essentially nonnegative and $A_{\mathrm{d}i}$, $i = 1,\ldots,n_{\mathrm{d}}$, and B are nonnegative, it follows from Proposition 2.1 that the state trajectories of (11) remain in the nonnegative orthant of the state space for nonnegative initial conditions and nonnegative inputs. For a given desired set point $x_{\mathrm{e}} \in \overline{\mathbb{R}}^n_+$, our aim is to design a nonnegative control input $u(t)$, $t \ge 0$, such that $\lim_{t\to\infty} \|x(t) - x_{\mathrm{e}}\| = 0$. However, since in many applications of nonnegative systems and in particular, compartmental systems, it is often necessary to regulate a subset of the nonnegative state variables which usually include a central compartment, here we require that $\lim_{t\to\infty} x_i(t) = x_{\mathrm{d}i} \ge 0$ for $i = 1,\ldots,m \le n$, where $x_{\mathrm{d}i}$ is a desired set point for the ith state $x_i(t)$. Furthermore, we assume that control inputs are injected directly into m separate compartments such that the input matrix is given by

$$B = \begin{bmatrix} B_{\mathrm{u}}^{\mathrm{T}} & 0_{m\times(n-m)} \end{bmatrix}^{\mathrm{T}} \tag{12}$$

where $B_u \triangleq \mathrm{diag}[b_1,\ldots,b_m]$ and $b_i \in \mathbb{R}_+$, $i = 1,\ldots,m$. For compartmental systems this assumption is not restrictive since control inputs correspond to control inflows to each individual compartments. Here, we assume that for $i \in \{1,\ldots,m\}$, b_i is *unknown*.

It is important to note that, since condition (9) is required to be satisfied for $x_{\mathrm{e}} \in \overline{\mathbb{R}}^n_+$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}^m_+$, it follows from Brockett's necessary condition for asymptotic stabilizability [7] that there does not exist a continuous stabilizing *nonnegative* feedback if $0 \in \mathrm{spec}(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})$ and $x_{\mathrm{e}} \in \mathbb{R}^n_+$ (see [4] for further details). Hence, we assume that $A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is an asymptotically stable compartmental matrix. Thus, we proceed with the aforementioned assumptions to design adaptive controllers for uncertain time-delay compartmental systems that guarantee that $\lim_{t\to\infty} x_i(t) = x_{\mathrm{d}i} \ge 0$ for $i = 1,\ldots,m \le n$, where $x_{\mathrm{d}i}$ is a desired set point for the ith compartmental state while guaranteeing a nonnegative control input with $u(t) \in \mathcal{U}$, $t \ge 0$. For the statement of our main result define $x_{\mathrm{e}} \triangleq [x_{\mathrm{d}}^{\mathrm{T}}, x_{\mathrm{u}}^{\mathrm{T}}]^{\mathrm{T}}$, where $x_{\mathrm{d}} \triangleq [x_{\mathrm{d}1},\ldots,x_{\mathrm{d}m}]^{\mathrm{T}}$ and $x_{\mathrm{u}} \triangleq [x_{\mathrm{u}1},\ldots,x_{\mathrm{u}(n-m)}]^{\mathrm{T}}$.

Theorem 3.1: Consider the linear uncertain time-delay mammillary system $\mathcal{G}$ given by (11), where A and $A_{\mathrm{d}i}$, $i = 1,\ldots,n-1 = n_{\mathrm{d}}$, are given by (6) and (7), respectively, $A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is asymptotically stable, and B is nonnegative and given by (12). For a given $x_{\mathrm{d}} \in \mathbb{R}^m_+$, assume there exist vectors $x_{\mathrm{u}} \in \mathbb{R}^{n-m}_+$ and $u_{\mathrm{e}} \in \mathcal{U}$ such that (9) holds. Furthermore, let q_i and $\hat{q}_i$, $i = 1,\ldots,m$, be positive constants. Then, the adaptive feedback control law

$$\begin{aligned}u_i(t) &= \frac{1}{4}\Big(\hat{u}_i(t) + |\hat{u}_i(t)| + 2u_{\max,i}\\ &\quad - \Big|\hat{u}_i(t) + |\hat{u}_i(t)| - 2u_{\max,i}\Big|\Big),\ i = 1,\ldots,m,\end{aligned} \tag{13}$$

where

$$\hat{u}_i(t) = k_i(t)(x_i(t) - x_{\mathrm{d}i}) + \phi_i(t), \quad i = 1, \ldots, m, \quad (14)$$

$k_i(t) \in \mathbb{R}$, $t \geq 0$, and $\phi_i(t) \in \mathbb{R}$, $t \geq 0$, $i = 1, \ldots, m$, with update laws

$$\dot{k}_i(t) = \begin{cases} 0, & \text{if } \hat{u}_i(t) < 0 \text{ or } \hat{u}_i(t) > u_{\max,i}, \\ -q_i(x_i(t) - x_{\mathrm{d}i})^2, & \text{otherwise} \end{cases}$$

$$k_i(0) \leq 0, \quad i = 1, \ldots, m, \quad (15)$$

$$\dot{\phi}_i(t) = \begin{cases} 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) > x_{\mathrm{d}i}, \\ 0, & \text{if } \phi_i(t) = u_{\max,i} \text{ and } x_i(t) < x_{\mathrm{d}i}, \\ 0, & \text{if } \hat{u}_i(t) < 0 \text{ or } \hat{u}_i(t) > u_{\max,i}, \\ -\hat{q}_i(x_i(t) - x_{\mathrm{d}i}), & \text{otherwise}, \end{cases}$$

$$0 \leq \phi_i(0) \leq u_{\max,i}, \quad i = 1, \ldots, m, \quad (16)$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, 0, u_{\mathrm{e}})$ of the closed-loop system given by (11), (13), (15), (16) is Lyapunov stable and $x_i(t) \to x_{\mathrm{d}i}$, $i = 1, \ldots, m$, as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. Furthermore, $u(t) \in \mathcal{U} \subset \overline{\mathbb{R}}_+^m$, $t \geq 0$, and $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$.

It is important to note that the adaptive control law (13), (15), and (16) does not require the explicit knowledge of the system matrices A, $A_{\mathrm{d}i}$, $i = 1, \ldots, n_{\mathrm{d}}$, and B, and the nonnegative constant vector u_{e}. All that is required is the existence of nonnegative vectors x_{u} and u_{e} such that condition (9) holds. Furthermore, note that Theorem 3.1 also holds for nonnegative time-delay dynamical systems as long as there exists a positive diagonal matrix $P \in \mathbb{R}^{n \times n}$ such that

$$0 = A^{\mathrm{T}}P + PA + \sum_{i=1}^{n_{\mathrm{d}}} \tilde{Q}_i + \sum_{i=1}^{n_{\mathrm{d}}} PA_{\mathrm{d}i}\tilde{Q}_i^{-1}A_{\mathrm{d}i}^{\mathrm{T}}P + R. \quad (17)$$

holds. As noted in Proposition 2.3, if (11) is a mammillary system the existence of a positive diagonal matrix $P \in \mathbb{R}^{n \times n}$ satisfying (17) is automatically guaranteed.

IV. Adaptive Control for General Anesthesia

Almost all anesthetics are *myocardial* depressants, that is, they decrease the strength of the contraction of the heart and lower *cardiac output* (i.e., the volume of blood pumped by the heart per unit time). As a consequence, decreased cardiac output slows down the transfer of blood from the central compartments comprising the heart, brain, kidney, and liver to the peripheral compartments of muscle and fat. In addition, decreased cardiac output can increase drug concentrations in the central compartments, compounding side effects. This instability can lead to overdosing which, at the very least, can delay recovery from anesthesia and, in the worst case, can result in respiratory and cardiovascular collapse. Alternatively, underdosing can cause psychological trauma from awareness and pain during surgery.

Control of drug effect is clinically important since overdosing or underdosing incur risk for the patient. To illustrate the adaptive control framework developed in this paper for general anesthesia we consider a hypothetical model for the intravenous anesthetic propofol. The pharmacokinetics of propofol are described by the three-compartment model [4] shown in Figure 1, where x_1 denotes the mass of drug in the central compartment, which is the site for drug administration and includes the *intravascular blood* (blood within arteries or veins) volume as well as *highly perfused* organs, that is, organs with high ratios of blood flow to weight such as the heart, brain, kidney, and liver, which receive a large fraction of the cardiac output. The remainder of the drug in the body is assumed to reside in two peripheral compartments, one identified with muscle and one with fat; the masses in these compartments are denoted by x_2 and x_3, respectively. These compartments receive less than 20% of the cardiac output. Finally, the transfer time between the central compartment and peripheral compartment 2 (muscle) is given by $\tau_1 > 0$, and transfer time between the central compartment and peripheral compartment 3 (fat) is given by $\tau_2 > 0$.

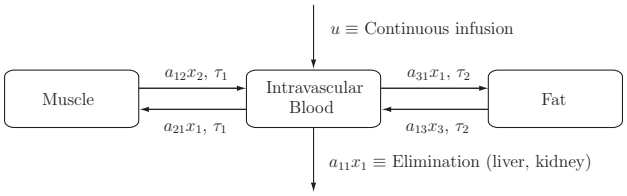

Fig. 1. Three-compartment mammillary model for disposition of propofol

A mass balance for the three-state compartmental model yields

$$\dot{x}_1(t) = -(a_{11} + a_{21} + a_{31})x_1(t) + a_{12}x_2(t - \tau_1) + a_{13}x_3(t - \tau_2) + u(t), \quad x_1(\theta) = \eta_1(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \quad (18)$$

$$\dot{x}_2(t) = -a_{12}x_2(t) + a_{21}x_1(t - \tau_1), \quad x_2(\theta) = \eta_2(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad (19)$$

$$\dot{x}_3(t) = -a_{13}x_3(t) + a_{31}x_1(t - \tau_2), \quad x_3(\theta) = \eta_3(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad (20)$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$, $t \geq 0$, are the masses in grams of propofol in the central compartment and compartments 2 and 3, respectively, $u(t)$, $t \geq 0$, is the infusion rate in grams/min of the anesthetic drug propofol into the central compartment, $\bar{\tau} = \max\{\tau_1, \tau_2\}$, $a_{ij} > 0$, $i \neq j$, $i, j = 1, 2, 3$, are the rate constants in min^{-1} for drug transfer between compartments, and $a_{11} > 0$ is the rate constant in min^{-1} of drug metabolism and elimination (metabolism typically occurs in the liver) from the central compartment. Even though the transfer and loss coefficients are positive, they are uncertain due to patient gender, weight, pre-existing disease, age, and concomitant medication. Hence, adaptive control for propofol set-point regulation can significantly improve the outcome for drug administration over manual (open-loop) control.

It has been reported in [8] that a 2.5–6 μg/ml blood concentration level of propofol is required during the maintenance stage in general anesthesia depending on patient fitness and extent of surgical stimulation. Hence, continuous infusion control is required for maintaining this desired level of anesthesia. Here we assume that the transfer and loss coefficients a_{11}, a_{12}, a_{21}, a_{13}, and a_{31} are unknown and our objective is to regulate the propofol concentration level of the central compartment to the desired level of 3.4 μg/ml in the face of system uncertainty. Furthermore, since propofol mass in the blood plasma cannot be measured directly, we measure the concentration of propofol in the central compartment, that is, x_1/V_{c}, where V_{c} is the volume in liters of the central compartment. As noted in [9], V_{c} can be approximately calculated by $V_{\mathrm{c}} = (0.159\,\mathrm{l/kg})(M\,\mathrm{kg})$, where M is the mass in kilograms of the patient.

Next, note that (18)–(20) can be written in the state space

form (1) with state vector $x = [x_1,\, x_2,\, x_3]^{\mathrm{T}}$,

$$A = \begin{bmatrix} -(a_{11}+a_{21}+a_{31}) & 0 & 0 \\ 0 & -a_{12} & 0 \\ 0 & 0 & -a_{13} \end{bmatrix},$$
$$B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad A_{\mathrm{d}_1} = \begin{bmatrix} 0 & a_{12} & 0 \\ a_{21} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$
$$A_{\mathrm{d}_2} = \begin{bmatrix} 0 & 0 & a_{13} \\ 0 & 0 & 0 \\ a_{31} & 0 & 0 \end{bmatrix}. \tag{21}$$

Now, it can be shown that for $x_{\mathrm{d}1}/V_{\mathrm{c}} = 3.4$ μg/ml, all the conditions of Theorem 3.1 are satisfied. Even though propofol concentration levels in the blood plasma will lead to the desired depth of anesthesia, they cannot be measured in *real-time* during surgery. Furthermore, we are more interested in drug *effect* (depth of hypnosis) rather than drug *concentration*. Hence, we consider a more realistic model involving pharmacokinetics (drug concentration as a function of time) and pharmacodynamics (drug effect as a function of concentration) for control of anesthesia. Specifically, we use an electroencephalogram (EEG) signal as a measure of drug effect of anesthetic compounds on the brain [10]. Since electroencephalography provides real-time monitoring of the central nervous system activity, it can be used to quantify levels of consciousness and hence is amenable for feedback (closed-loop) control in general anesthesia. Furthermore, we use the Bispectral Index (BIS), an EEG indicator, as a measure of anesthetic effect [11]. This index quantifies the nonlinear relationships between the component frequencies in the electroencephalogram, as well as analyzing their phase and amplitude.

The BIS signal is related to drug concentration by the empirical relationship

$$\mathrm{BIS}(c_{\mathrm{eff}}) = \mathrm{BIS}_0 \left(1 - \frac{c_{\mathrm{eff}}^{\gamma}}{c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma}}\right), \tag{22}$$

where BIS_0 denotes the base line (awake state) value and, by convention, is typically assigned a value of 100, c_{eff} is the propofol concentration in grams/liter in the effect site compartment (brain), EC_{50} is the concentration at half maximal effect and represents the patient's sensitivity to the drug, and γ determines the degree of nonlinearity in (22). Here, the effect-site compartment is introduced to account for finite equilibration time between the central compartment concentration and the central nervous system concentration [12].

The effect-site compartment concentration is related to the concentration in the central compartment by the first-order model

$$\dot{c}_{\mathrm{eff}}(t) = a_{\mathrm{eff}}(x_1(t)/V_{\mathrm{c}} - c_{\mathrm{eff}}(t)), \quad c_{\mathrm{eff}}(0) = x_1(0), \quad t \geq 0, \tag{23}$$

where a_{eff} in min^{-1} is an unknown positive time constant. In reality, the effect-site compartment equilibrates with the central compartment in a matter of a few minutes. The parameters a_{eff}, EC_{50} , and γ are determined by data fitting and vary from patient to patient. BIS index values of 0 and 100 correspond, respectively, to an *isoelectric* EEG signal (no cerebral electrical activity) and an EEG signal of a fully conscious patient; the range between 40 and 60 indicates a moderate hypnotic state [13].

In the following numerical simulation we set $\mathrm{EC}_{50} = 3.4$ μg/ml, $\gamma = 3$, and $\mathrm{BIS}_0 = 100$, so that the BIS signal is shown in Figure 2. The values for the pharmacodynamic parameters (EC_{50}, γ) are within the typical range of those observed for ligand-receptor binding [14], [15]. The target (desired) BIS value, $\mathrm{BIS}_{\mathrm{target}}$, is set at 50. In this case, the linearized BIS function about the target BIS value is given by

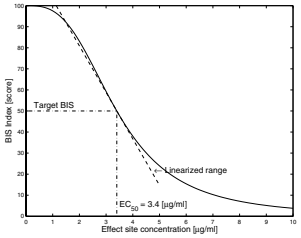

Fig. 2. BIS index versus effect site concentration

$$\begin{aligned} \mathrm{BIS}(c_{\mathrm{eff}}) &\simeq \mathrm{BIS}(\mathrm{EC}_{50}) - \mathrm{BIS}_0 \cdot \mathrm{EC}_{50}^{\gamma} \\ &\quad \cdot \frac{\gamma c_{\mathrm{eff}}^{\gamma-1}}{(c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma})^2}\bigg|_{c_{\mathrm{eff}}=\mathrm{EC}_{50}} \cdot c_{\mathrm{eff}} \\ &= 125 - 22.06 c_{\mathrm{eff}}. \end{aligned} \tag{24}$$

Furthermore, for simplicity of exposition, we assume that the effect-site compartment equilibrates instantaneously with the central compartment, that is, we assume that $c_{\mathrm{eff}}(t) = x_1(t)/V_{\mathrm{c}}$ for all $t \geq 0$.

Now, using the adaptive feedback controller

$$\begin{aligned} u_1(t) &= \frac{1}{4}\Big(\hat{u}_1(t) + |\hat{u}_1(t)| + 2u_{\max,1} \\ &\quad - \Big|\hat{u}_1(t) + |\hat{u}_1(t)| - 2u_{\max,1}\Big|\Big), \end{aligned} \tag{25}$$

where

$$\hat{u}_1(t) = -k_1(t)(\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}) + \phi_1(t), \tag{26}$$

and $k_1(t)$ and $\phi_1(t)$ are scalars for $t \geq 0$, with update laws

$$\dot{k}_1(t) = \begin{cases} 0, & \text{if } \hat{u}_1(t) < 0 \text{ or } \hat{u}_1(t) > u_{\max,1}, \\ -q_{\mathrm{BIS}_1}(\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}})^2, & \text{otherwise}, \end{cases} \quad k_1(0) \leq 0, \tag{27}$$

$$\dot{\phi}_1(t) = \begin{cases} 0, & \text{if } \phi_1(t) = 0 \text{ and } \mathrm{BIS}(t) > \mathrm{BIS}_{\mathrm{target}}, \\ 0, & \text{if } \phi_1(t) = u_{\max,1} \text{ and } \mathrm{BIS}(t) < \mathrm{BIS}_{\mathrm{target}}, \\ 0, & \text{if } \hat{u}_1(t) > u_{\max,1} \text{ or } \hat{u}_1(t) < 0, \\ -\hat{q}_{\mathrm{BIS}_1}(\mathrm{BIS}(t)) - \mathrm{BIS}_{\mathrm{target}}), & \text{otherwise}, \end{cases} \quad 0 \leq \phi_1(0) \leq u_{\max,1}, \tag{28}$$

where q_{BIS_1} and $\hat{q}_{\mathrm{BIS}_1}$ are positive constants, it follows from Theorem 3.1 that the control input (anesthetic infusion rate) satisfies $0 \leq u_1(t) \leq u_{\max,1}$ for all $t \geq 0$ and $\mathrm{BIS}(t) \to \mathrm{BIS}_{\mathrm{target}}$ as $t \to \infty$ for all nonnegative values of the transfer and loss coefficients in the range of c_{eff} where the linearized BIS equation (24) is valid. It is important to note that during actual surgery or intensive care unit sedation, the BIS signal is obtained directly from the EEG and not (22). Furthermore, since our adaptive controller only requires the error signal $\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}$ over the linearized range of (22), we do not require knowledge of the slope of the linearized equation (24), nor do we require knowledge of the parameters γ and EC_{50}.

Set	a_{11} (min^{-1})	a_{21} (min^{-1})	a_{12} (min^{-1})	a_{31} (min^{-1})	a_{13} (min^{-1})
A	0.152	0.207	0.092	0.040	0.0048
B	0.119	0.114	0.055	0.041	0.0033

TABLE I

PHARMACOKINETIC PARAMETERS [16]

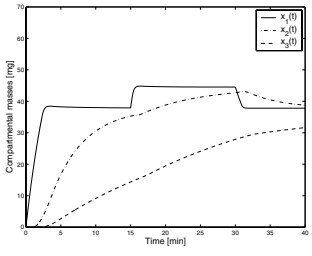

Fig. 3. Compartmental masses versus time

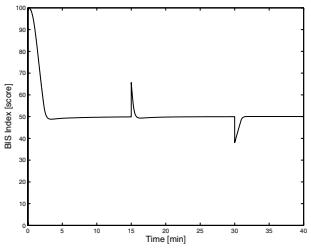

Fig. 4. BIS index versus time

To numerically illustrate the efficacy of the proposed adaptive control law, we use the average set of pharmacokinetic parameters given in [16] for 29 patients requiring general anesthesia for noncardiac surgery. For our design we assume $M = 70$ kg, $\tau_1 = 1$ min, $\tau_2 = 2$ min, and use the data given in Table I. Furthermore, to illustrate the adaptive controller we switch the pharmacodynamic parameters (EC_{50}, γ) and the pharmacokinetic parameters (the entries of the system matrices A, A_{d_1}, and A_{d_2}) from 3.4 μg/ml, 3, and Set A to 4.0 μg/ml, 4, and Set B at $t = 15$ min, and back to 3.4 μg/ml, 3, and Set A at $t = 30$ min. Here we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $q_{\mathrm{BIS}_1} = 1 \times 10^{-4}$ g/min^2, $\hat{q}_{\mathrm{BIS}_1} = 1 \times 10^{-3}$ g/min^2, $u_{\max,1} = 20$ g/min, and initial conditions $x(0) = [0,\, 0,\, 0]^{\mathrm{T}}$ g, $k_1(0) = 0$ min^{-1}, and $\phi_1(0) = 0.01$ g/min^{-1}, Figure 3 shows the masses of propofol in all three compartments versus time. Figure 4 shows the BIS index versus time. Figure 5 shows the propofol concentration in the central compartment and the control signal (propofol infusion rate) versus time. Finally, Figure 6 shows the adaptive gain history versus time.

The adaptive controller (25)–(28) does not require knowledge of the pharmacokinetic and pharmacodynamic parameters, in contrast to previous algorithms for closed-loop control of anesthesia [17]. However, the adaptive controller (25)–(28) does not account for time delays due to equilibration between the central circulation and the effect-site compartment, as well as due to the proprietary signal-averaging algorithm within the BIS monitor. The adaptive controller also ignores measurement noise. Extensive clinical testing is needed to access the significance of these assumptions and approximations.

V. CONCLUSION

In this paper, we developed a direct adaptive control framework for linear uncertain compartmental dynamical systems with control input constraints and system time delays. In particular, a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation for compartmental time-delay systems with specific applications to mammillary pharmacokinetic models was developed. Finally, we numerically demonstrated the framework on a drug delivery pharmacokinetic/pharmacodynamic model with time delays and control infusion rate constraints.

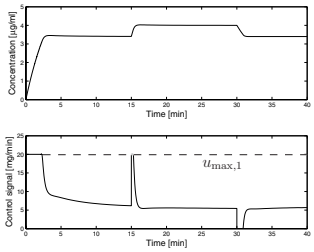

Fig. 5. Drug concentration in the central compartment and control signal (infusion rate) versus time

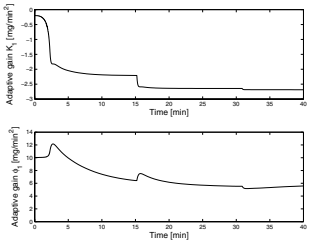

Fig. 6. Adaptive gain history versus time

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