Direct Adaptive Control of Nonnegative and Compartmental Dynamical Systems with Time Delay

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***Abstract*— In this paper, we develop a direct adaptive control framework for uncertain linear nonnegative and compartmental dynamical systems with unknown time delay. 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 delay. The framework additionally guarantees nonnegativity of the control signal. Finally, we demonstrate the framework on a drug delivery model for general anesthesia involving system time delays.**

I. Introduction

Nonnegative and compartmental models play a key role in the understanding of many processes in biological and medical sciences [1–9]. Compartmental systems are modeled by interconnected subsystems (or compartments) which exchange variable nonnegative quantities of material with conservation laws describing transfer, accumulation, and elimination between compartments and the environment. In many compartmental pharmacokinetic 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. For example, if a bolus of drug is injected into the circulation and we seek its concentration level in the extracellular and intercellular space of some organ, there exists a time lag before it is detected in that organ [6], [10], [11]. In this case, assuming instantaneous mass transfer between compartments will yield erroneous models. Hence, to accurately describe the distribution of pharmacological agents in the human body, it is necessary to include in any mathematical compartmental pharmacokinetic model some 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 [12–15].

In a recent paper [16], the authors present a direct adaptive control framework for set-point regulation of linear nonnegative and compartmental systems with applications to clinical pharmacology. In this paper, we extend the results of [16] to the case of nonnegative and compartmental dynamical systems with unknown system time delay. Specifically, we develop a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation for linear uncertain nonnegative and compartmental dynamical systems with unknown time delay. The specific focus of the paper is on pharmacokinetic models and their applications to drug delivery systems. In particular, we develop direct adaptive controllers with nonnegative control inputs as well as adaptive controllers with the absence of such a restriction. Finally, we demonstrate the framework on a drug delivery model for general anesthesia that involves system time delays.

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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 delay [17], [18] that are necessary 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*[1] 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 ([19]): Let $A \in \mathbb{R}^{n\times n}$. A is *essentially nonnegative* if $A_{(i,j)} \geq 0$, $i, j = 1, \cdots, n$, $i \neq j$.

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

$$\begin{aligned}\dot{x}(t) &= Ax(t) + A_{\mathrm{d}}x(t-\tau) + Bu(t), \quad x(\theta) = \eta(\theta),\\ &\qquad -\tau \leq \theta \leq 0, \quad t \geq 0,\end{aligned} \tag{1}$$

[1]In this paper it is important to distinguish between a square nonnegative (resp., positive) matrix and a nonnegative-definite (resp., positive-definite) matrix.

where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $A \in \mathbb{R}^{n\times n}$, $A_{\rm d} \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$, $\tau \geq 0$, $\eta(\cdot) \in \mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R}^n)$ is a continuous vector valued function specifying the initial state of the system, and $\mathcal{C}([-\tau, 0], \mathbb{R}^n)$ denotes a Banach space of continuous functions mapping the interval $[-\tau, 0]$ 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 $t - \tau$ and t, or, equivalently, the *element* x_t in the space of continuous functions defined on the interval $[-\tau, 0]$ and taking values in $\mathbb{R}^n$; that is, $x_t \in \mathcal{C}([-\tau, 0], \mathbb{R}^n)$, where $x_t(\theta) \triangleq x(t + \theta)$, $\theta \in [-\tau, 0]$. Furthermore, since for a given time t the piece of the trajectories x_t is defined on $[-\tau, 0]$, the uniform norm $\|\!|x_t|\!\| = \sup_{\theta\in[-\tau,0]} \|x(t + \theta)\|$, 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 [12], [13]. Finally, note that since $\eta(\cdot)$ is continuous it follows from Theorem 2.1 of [13, p. 14] that there exists a unique solution $x(\eta)$ defined on $[-\tau, \infty)$ that coincides with η on $[-\tau, 0]$ and satisfies (1) for all $t \geq 0$.

The following theorem gives necessary and sufficient conditions for asymptotic stability of a linear time-delay nonnegative dynamical system $\mathcal{G}$ given by (1) in the case where $u(t) \equiv 0$. For this result, 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 $\mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C} : \psi(\theta) \geq\geq 0, \theta \in [-\tau, 0]\}$, the solution $x(t)$, $t \geq 0$, to (1) is nonnegative.

Theorem 2.1 ([17], [18]): Consider the linear nonnegative dynamical system $\mathcal{G}$ given by (1) where $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\rm d} \in \mathbb{R}^{n\times n}$ is nonnegative, and $u(t) \equiv 0$. Then, $\mathcal{G}$ is asymptotically stable for all $\tau \in [0, \infty)$ if and only if there exist $p, r \in \mathbb{R}^n$ such that $p >> 0$ and $r >> 0$ satisfy $0 = (A + A_{\rm d})^{\rm T} p + r$.

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 [6].

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

Definition 2.5 ([17], [18]): The linear time-delay dynamical system (1) is called a *compartmental dynamical system* if A and $A_{\rm d}$ are given by

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

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

Note that if (1) is a compartmental system, then $A + A_{\rm d}$ is a compartmental matrix. In pharmacokinetic applications, an important subclass of compartmental systems are *mammillary* systems [6]. 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 $A_{\rm d}$ given by

$$A = {\rm diag}[-\sum_{j=1}^{n} a_{j1}, -a_{12}, \cdots, -a_{1n}], \quad (2)$$

$$A_{{\rm d}(i,j)} = \begin{cases} 0, & i = j, \\ 0, & i \neq 1 \text{ and } j \neq 1, \\ a_{ij}, & \text{otherwise}, \end{cases} \quad (3)$$

where the transfer coefficients a_{ij}, $i, j = 1, \cdots, n$, and the loss coefficient a_{11} are positive.

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

Proposition 2.1: Consider a linear time-delay mammillary system given by (1) where A and $A_{\rm d}$ are given by (2) and (3), respectively. Then there exist a positive-definite matrix $Q \in \mathbb{R}^{n\times n}$ and a positive diagonal matrix $P \in \mathbb{R}^{n\times n}$ such that

$$0 > A^{\rm T} P + PA + Q + PA_{\rm d} Q^{-1} A_{\rm d}^{\rm T} P. \quad (4)$$

III. Adaptive Control for Linear Nonnegative Uncertain Dynamical Systems with Time Delay

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

$$\dot{x}(t) = Ax(t) + A_{\rm d} x(t - \tau) + Bu(t), \quad x(\theta) = \eta(\theta), \quad -\tau \leq \theta \leq 0, \quad t \geq 0, \quad (5)$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, is the state of the system, $u(t) \in \mathbb{R}^m$, $t \geq 0$, is the control input, $A \in \mathbb{R}^{n\times n}$ is an *unknown* essentially nonnegative matrix, $A_{\rm d} \in \mathbb{R}^{n\times n}$ and $B \in \mathbb{R}^{n\times m}$ are *unknown* nonnegative matrices, $\eta(\cdot) \in \{\psi(\cdot) \in \mathcal{C}_+([-\tau, 0], \mathbb{R}^n) : \psi(\theta) \geq\geq 0, \theta \in [-\tau, 0]\}$, and $\tau \geq 0$ is an *unknown* system delay amount. The control input $u(\cdot)$ in (5) is restricted to the class of admissible controls consisting of measurable functions such that $u(t) \in \mathbb{R}^m$, $t \geq 0$.

Even though active control of drug delivery systems for physiological applications requires control (source) inputs to be nonnegative, in many applications of nonnegative systems such as biological systems, population dynamics, and ecological systems, the positivity constraint on the control input is not natural. Hence, in this section we do not place any restriction on the sign of the control signal and design an adaptive controller that guarantees that the system states remain in the nonnegative orthant and converge to a desired equilibrium state. Specifically, for a given desired set point $x_{\rm e} \in \overline{\mathbb{R}}_+^n$, our aim is to design a control input $u(t)$, $t \geq 0$, such that $\lim_{t\to\infty} \|x(t) - x_{\rm e}\| = 0$. 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 $\lim_{t\to\infty} x_i(t) = x_{{\rm d}i} \geq 0$ for $i = 1, \cdots, m \leq n$, where $x_{{\rm d}i}$ 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

$$B = \begin{bmatrix} B_u \\ 0_{(n-m)\times m} \end{bmatrix}, \quad (6)$$

where $B_u \triangleq {\rm diag}[b_1, \cdots, b_m]$ and $b_i \in \mathbb{R}_+$, $i = 1, \cdots, m$. For compartmental systems this assumption is not restrictive

since control inputs correspond to control inflows to each individual compartment. Here, we assume that for $i \in \{1, \cdots, m\}$, b_i is *unknown*. 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 $x_{\mathrm{d}} \triangleq [x_{\mathrm{d}1}, \cdots, x_{\mathrm{d}m}]^{\mathrm{T}}$ and $x_{\mathrm{u}} \triangleq [x_{\mathrm{u}1}, \cdots, x_{\mathrm{u}(n-m)}]^{\mathrm{T}}$.

Theorem 3.1: Consider the linear uncertain time-delay dynamical system $\mathcal{G}$ given by (5) where A is essentially nonnegative, A_{d} is nonnegative, and B is nonnegative and given by (6). Assume there exist nonnegative vectors $x_{\mathrm{u}} \in \overline{\mathbb{R}}_+^{n-m}$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}_+^{m}$ such that

$$0 = (A + A_{\mathrm{d}})x_{\mathrm{e}} + Bu_{\mathrm{e}}. \tag{7}$$

Furthermore, assume there exist a diagonal matrix $K_{\mathrm{g}} = \mathrm{diag}[k_{\mathrm{g}1}, \cdots, k_{\mathrm{g}m}]$, positive diagonal matrix $P \triangleq \mathrm{diag}[p_1, \cdots, p_n]$, and positive-definite matrices $\tilde{Q}$, $R \in \mathbb{R}^{n \times n}$ such that

$$0 = A_{\mathrm{s}}^{\mathrm{T}}P + PA_{\mathrm{s}} + \tilde{Q} + PA_{\mathrm{d}}\tilde{Q}^{-1}A_{\mathrm{d}}^{\mathrm{T}}P + R, \tag{8}$$

where $A_{\mathrm{s}} \triangleq A + B\tilde{K}_{\mathrm{g}}$ and $\tilde{K}_{\mathrm{g}} \triangleq [K_{\mathrm{g}}\ 0_{m\times(n-m)}]$. Finally, let q_i and $\hat{q}_i$, $i = 1, \cdots, m$, be positive constants. Then the adaptive feedback control law

$$u(t) = K(t)(\hat{x}(t) - x_{\mathrm{d}}) + \phi(t), \tag{9}$$

where $K(t) = \mathrm{diag}[k_1(t), \cdots, k_m(t)]$, $\hat{x}(t) = [x_1(t), \cdots, x_m(t)]^{\mathrm{T}}$, and $\phi(t) \in \mathbb{R}^m$, $t \geq 0$, or, equivalently,

$$u_i(t) = k_i(t)(x_i(t) - x_{\mathrm{d}i}) + \phi_i(t), \quad i = 1, \cdots, m, \tag{10}$$

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

$$\begin{aligned} \dot{k}_i(t) &= -q_i(x_i(t) - x_{\mathrm{d}i})^2, \\ &\quad k_i(0) \leq 0, \quad i = 1, \cdots, m, \end{aligned} \tag{11}$$

$$\begin{aligned} \dot{\phi}_i(t) &= \begin{cases} 0, \text{ if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{\mathrm{d}i}, \\ -\hat{q}_i(x_i(t) - x_{\mathrm{d}i}), \text{ otherwise}, \end{cases} \\ &\quad \phi_i(0) \geq 0, \quad i = 1, \cdots, m, \end{aligned} \tag{12}$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, K_{\mathrm{g}}, u_{\mathrm{e}})$ of the closed-loop system given by (5), (9), (11), (12) is Lyapunov stable and $x_i(t) \to x_{\mathrm{d}i}$, $i = 1, \cdots, m$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. Furthermore, $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$.

Remark 3.1: Note that the conditions in Theorem 3.1 imply that $x(t) \to x_{\mathrm{e}}$ as $t \to \infty$ and hence it follows from (11) and (12) that $(x_t, K(t), \phi(t)) \to \mathcal{M} \triangleq \{(x_t, K, \phi) \in \mathcal{C}_+ \times \mathbb{R}^{m\times m} \times \mathbb{R}^m : x_t \equiv x_{\mathrm{e}},\ \dot{K} = 0,\ \dot{\phi} = 0\}$ as $t \to \infty$.

Remark 3.2: The results presented in Theorem 3.1 can be easily extended to systems with multiple delays.

It is important to note that the adaptive control law (9), (11), and (12) does not require the explicit knowledge of the system matrices A, A_{d}, and B, the gain matrix K_{g}, and the nonnegative constant vector u_{e}; even though Theorem 3.1 requires the existence of K_{g} and nonnegative vectors x_{u} and u_{e} such that the conditions (7) and (8) hold. Furthermore, in the case where $A + A_{\mathrm{d}}$ is semistable and minimum phase with respect to the output $y = \hat{x}$, or $A + A_{\mathrm{d}}$ is asymptotically stable, then there always exists a diagonal matrix $K_{\mathrm{g}} \in \mathbb{R}^{m\times m}$ such that $A_{\mathrm{s}} + A_{\mathrm{d}}$ is asymptotically stable. In addition, note that for $i = 1, \cdots, m$, the control input signal $u_i(t)$, $t \geq 0$, can be negative depending on the values of $x_i(t)$, $k_i(t)$, and $\phi_i(t)$, $t \geq 0$. However, as is required in nonnegative and compartmental dynamical systems the closed-loop plant states remain nonnegative. Finally, in the case where (5) is a mammillary system, A_{s} is diagonal and hence it follows from Proposition 2.1 that there exists a positive diagonal matrix $P \in \mathbb{R}^{n\times n}$ such that (8) holds. Similar remark is also true for Theorem 4.1.

In the case where our objective is zero set-point regulation, that is, $\psi_{\mathrm{e}}(\theta) = x_{\mathrm{e}} = 0$, $\theta \in [-\tau, 0]$, the adaptive controller given in Theorem 3.1 can be considerably simplified. Specifically, since in this case $x(t) \geq\geq x_{\mathrm{e}} = 0$, $t \geq 0$, and condition (7) is trivially satisfied with $u_{\mathrm{e}} = 0$, we can set $\phi(t) \equiv 0$ so that update law (12) is superfluous. Furthermore, since (7) is trivially satisfied, A can possess eigenvalues in the open right-half plane. Alternatively, exploiting a *linear* Lyapunov-Krasovskii functional construction for the plant dynamics, an even simpler adaptive controller can be derived. This result is given in the following theorem.

Theorem 3.2: Consider the linear uncertain time-delay system $\mathcal{G}$ given by (5) where B is nonnegative and given by (6). Assume there exists a diagonal matrix $K_{\mathrm{g}} = \mathrm{diag}[k_{\mathrm{g}1}, \cdots, k_{\mathrm{g}m}]$ such that $A_{\mathrm{s}} + A_{\mathrm{d}}$ is asymptotically stable, where $A_{\mathrm{s}} = A + B\tilde{K}_{\mathrm{g}}$ and $\tilde{K}_{\mathrm{g}} = [K_{\mathrm{g}}, 0_{m\times(n-m)}]$. Furthermore, let q_i, $i = 1, \cdots, m$, be positive constants. Then the adaptive feedback control law

$$u(t) = K(t)\hat{x}(t), \tag{13}$$

where $K(t) = \mathrm{diag}[k_1(t), \cdots, k_m(t)]$ and $\hat{x}(t) = [x_1(t), \cdots, x_m(t)]^{\mathrm{T}}$, or, equivalently,

$$u_i(t) = k_i(t)x_i(t), \quad i = 1, \cdots, m, \tag{14}$$

where $k_i(t) \in \mathbb{R}$, $i = 1, \cdots, m$, with update law

$$\dot{K}(t) = -\mathrm{diag}[q_1x_1(t), \cdots, q_mx_m(t)], \quad K(0) \leq\leq 0, \tag{15}$$

guarantees that the solution $(x(t), K(t)) \equiv (0, K_{\mathrm{g}})$ of the closed-loop system given by (5), (13), (15) is Lyapunov stable and $x(t) \to 0$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$.

IV. Adaptive Control for Linear Nonnegative Dynamical Systems with Nonnegative Control and Time Delay

In drug delivery systems for physiological processes, control (source) inputs are usually constrained to be nonnegative as are the system states. Hence, in this section we develop adaptive control laws for nonnegative retarded systems with nonnegative control inputs. However, since condition (7) 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 [20] that there does not exist a continuous stabilizing *nonnegative* feedback if $0 \in \mathrm{spec}(A + A_{\mathrm{d}})$ and $x_{\mathrm{e}} \in \mathbb{R}_+^n$ (see [16] for further details). Hence, in this section we assume that $A + A_{\mathrm{d}}$ 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 $\lim_{t\to\infty} x_i(t) = x_{\mathrm{d}i} \geq 0$ for $i = 1, \cdots, m \leq n$, where $x_{\mathrm{d}i}$ is a desired set point for the ith compartmental state while guaranteeing a nonnegative control input.

Theorem 4.1: Consider the linear uncertain time-delay system $\mathcal{G}$ given by (5), where A is essentially nonnegative, A_{d} is nonnegative, $A + A_{\mathrm{d}}$ is asymptotically stable, and B is nonnegative and given by (6). For a given $x_{\mathrm{d}} \in \mathbb{R}^m$, assume there exist vectors $x_{\mathrm{u}} \in \mathbb{R}_+^{n-m}$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}_+^m$ such that (7) holds. In addition, assume that there exist a positive

diagonal matrix $P \triangleq \mathrm{diag}[p_1, \cdots, p_n]$, and positive-definite matrices $\tilde{Q}$, $R \in \mathbb{R}^{n\times n}$ such that

$$0 = A^{\mathrm{T}}P + PA + \tilde{Q} + PA_{\mathrm{d}}\tilde{Q}^{-1}A_{\mathrm{d}}^{\mathrm{T}}P + R. \qquad (16)$$

Furthermore, let q_i and $\hat{q}_i$, $i = 1, \cdots, m$, be positive constants. Then, the adaptive feedback control law

$$u_i(t) = \max\{0, \hat{u}_i(t)\}, \quad i = 1, \cdots, m, \qquad (17)$$

where

$$\hat{u}_i(t) = k_i(t)(x_i(t) - x_{\mathrm{d}i}) + \phi_i(t), \quad i = 1, \cdots, m, \quad (18)$$

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

$$\dot{k}_i(t) = \begin{cases} 0, \text{ if } \hat{u}_i(t) < 0, \\ -q_i(x_i(t) - x_{\mathrm{d}i})^2, \text{otherwise}, \end{cases} \quad k_i(0) \leq 0, \quad i = 1, \cdots, m, \qquad (19)$$

$$\dot{\phi}_i(t) = \begin{cases} 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) > x_{\mathrm{d}i}, \\ & \text{or if } \hat{u}_i(t) \leq 0, \qquad \phi_i(0) \geq 0, \\ -\hat{q}_i(x_i(t) - x_{\mathrm{d}i}), \text{otherwise}, \end{cases} \quad i = 1, \cdots, m, \qquad (20)$$

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 (5), (17), (19), (20) is Lyapunov stable and $x_i(t) \to x_{\mathrm{d}i}$, $i = 1, \cdots, m$, as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. Furthermore, $u(t) \geq\geq 0$, $t \geq 0$, and $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$.

V. Adaptive Control for General Anesthesia

In this section, we illustrate the adaptive control framework developed in this paper on a model for the disposition of the intravenous anesthetic propofol [16], [21], [22] for induction and maintenance of general anesthesia. This model is discussed in [16] and is based on the three-compartment mammillary model shown in Figure 1 with the first compartment acting as the central compartment and the remaining two compartments exchanging with the central compartment. The three-compartment mammillary system with all transfer times between compartments given by $\tau > 0$ provides a pharmacokinetic model for a patient describing the distribution of propofol into the central compartment (identified with the intravascular blood volume as well as highly perfused organs) and other various tissue groups of the body. A mass balance for the whole compartmental system yields

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

$$\dot{x}_2(t) = -a_{12}x_2(t) + a_{21}x_1(t - \tau), \quad x_2(\theta) = \eta_2(\theta), \quad -\tau \leq \theta \leq 0, \qquad (22)$$

$$\dot{x}_3(t) = -a_{13}x_3(t) + a_{31}x_1(t - \tau), \quad x_3(\theta) = \eta_3(\theta), \quad -\tau \leq \theta \leq 0, \qquad (23)$$

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 (propofol) into the central compartment, $a_{ij} > 0$, $i \neq j$, $i, j = 1, 2, 3$, are the rate constants in min^{-1} for drug transfer between compartments, and $a_{11} > 0$ is the rate constant in min^{-1} for elimination from the central compartment. Even though these transfer and loss coefficients are positive, they can be 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 control.

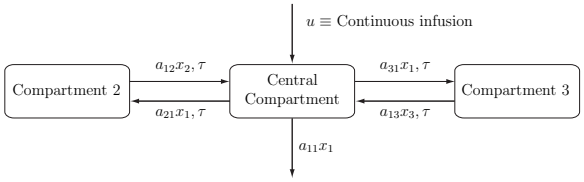

Fig. 1. Three-compartment mammillary model for disposition of propofol

It has been reported in [23] 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 [22], V_{c} can be approximately calculated by $V_{\mathrm{c}} = (0.159\,\ell/\mathrm{kg})(M\,\mathrm{kg})$, where M is the weight (mass) in kilograms of the patient.

Next, note that (21)–(23) can be written in the state space form (5) with $x = [x_1,\ x_2,\ x_3]^{\mathrm{T}}$, $A = \mathrm{diag}[-(a_{11} + a_{21} + a_{31}),\ -a_{12},\ -a_{13}]$

$$A_{\mathrm{d}} = \begin{bmatrix} 0 & a_{12} & a_{13} \\ a_{21} & 0 & 0 \\ a_{31} & 0 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}. \qquad (24)$$

Now, it can be shown that for $x_{\mathrm{d}1}/V_{\mathrm{c}} = 3.4$ μg/mℓ, all the conditions of Theorem 4.1 are satisfied. Even though propofol concentration levels in the blood plasma are a good indication of the 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 [24]. 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), a new EEG indicator, as a measure of anesthetic effect [25]. 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 a nonlinear monotonically decreasing function of the level of consciousness and is given by

$$\mathrm{BIS}(c_{\mathrm{eff}}) = \mathrm{BIS}_0 \left(1 - \frac{c_{\mathrm{eff}}^{\gamma}}{c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma}}\right), \qquad (25)$$

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

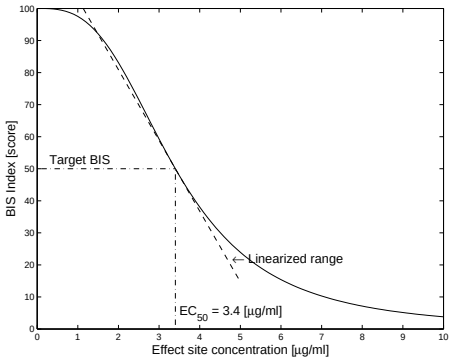

Fig. 2. BIS index versus effect site concentration

drug, and γ determines the degree of nonlinearity in (25). Here, the effect site compartment is introduced as a correlate between the central compartment concentration and the central nervous system concentration [26]. The effect site compartment concentration is related to the concentration in the central compartment by the first-order delay model

$$\dot{c}_{\rm eff}(t) = a_{\rm eff}(x_1(t)/V_{\rm c} - c_{\rm eff}(t)),\ c_{\rm eff}(0) = x_1(0),\ t \geq 0, \tag{26}$$

where $a_{\rm eff}$ in $\rm min^{-1}$ 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 $a_{\rm eff}$, $\rm EC_{50}$, 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 and an EEG signal of a fully conscious patient; while the range between 40 and 60 indicates a moderate hypnotic state [27].

In the following numerical simulation we set $\rm EC_{50} = 3.4$ μg/mℓ, $\gamma = 3$, and $\rm BIS_0 = 100$, so that the BIS signal is shown in Figure 2. The target (desired) BIS value, $\rm BIS_{target}$, is set at 50. In this case, the linearized BIS function about the target BIS value is given by

$$\begin{aligned} \rm BIS(c_{eff}) \quad &\simeq \quad BIS(EC_{50}) - BIS_0 \cdot EC_{50}^{\gamma} \\ &\cdot \frac{\gamma c_{\rm eff}^{\gamma-1}}{(c_{\rm eff}^{\gamma} + \rm EC_{50}^{\gamma})^2}\bigg|_{c_{\rm eff}=\rm EC_{50}} \cdot c_{\rm eff} = 125 - 22.06 c_{\rm eff}. \end{aligned} \tag{27}$$

Furthermore, for simplicity of exposition, we assume that the effect site compartment equilibrates instantaneously with the central compartment; that is, we assume that $a_{\rm eff} \to \infty$ and hence $c_{\rm eff}(t) = x_1(t)/V_{\rm c}$, $t \geq 0$. Now, using the adaptive feedback controller

$$u_1(t) = \max\{0, \hat{u}_1(t)\}, \tag{28}$$

where

$$\hat{u}_1(t) = -k_1(t)(\rm BIS(t) - BIS_{target}) + \phi_1(t), \tag{29}$$

$k_1(t) \in \mathbb{R}$, $t \geq 0$, and $\phi_1(t) \in \mathbb{R}$, $t \geq 0$, with update laws

$$\begin{aligned} \dot{k}_1(t) \quad &= \quad \begin{cases} 0, \text{ if } \hat{u}_1(t) < 0, \\ -q_{\rm BIS_1}(\rm BIS(t) - BIS_{target})^2, \text{otherwise}, \end{cases} \\ &\qquad k_1(0) \leq 0, \end{aligned} \tag{30}$$

$$\begin{aligned} \dot{\phi}_1(t) \quad &= \quad \begin{cases} 0, & \text{if } \phi_1(t) = 0 \text{ and } \rm BIS(t) > BIS_{target}, \\ & \text{or if } \hat{u}_1(t) \leq 0, \qquad \phi_1(0) \geq 0, \\ \hat{q}_{\rm BIS_1}(\rm BIS(t) - BIS_{target}), \text{otherwise}, \end{cases} \end{aligned} \tag{31}$$

Set	a_{11}	a_{21}	a_{12}	a_{31}	a_{13}
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 [28]

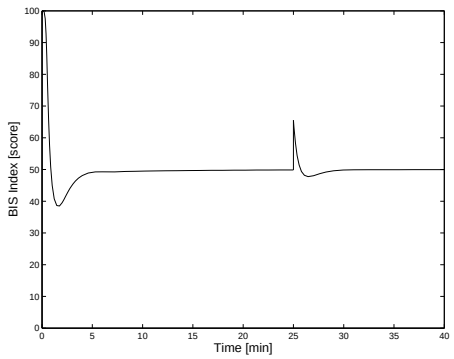

Fig. 3. BIS Index versus time

where $q_{\rm BIS_1}$ and $\hat{q}_{\rm BIS_1}$ are arbitrary positive constants, it follows from Theorem 4.1 that the control input (anesthetic infusion rate) $u(t) \geq 0$ for all $t \geq 0$ and $\rm BIS(t) \to BIS_{target}$ as $t \to \infty$ for any (uncertain) positive values of the transfer and loss coefficients in the range of $c_{\rm eff}$ where the linearized BIS equation (27) 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 (25). Furthermore, since our adaptive controller only requires the error signal $\rm BIS(t) - BIS_{target}$ over the linearized range of (25), we do not require knowledge of the slope of the linearized equation (27), nor do we require knowledge of the parameters γ and $\rm EC_{50}$. To illustrate the robustness properties of the proposed adaptive control law, we use the average set of pharmacokinetic parameters given in [28] for 29 patients requiring general anesthesia for noncardiac surgery. For our design we assume $M = 70$ kg and we switch from Set A to Set B given in Table I at $t = 25$ min. Furthermore, we assume that at $t = 25$ min the pharmacodynamic parameters $\rm EC_{50}$ and γ are switched from 3.4 μg/mℓ and 3 to 4.0 μg/mℓ and 4, respectively. Here we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $q_{\rm BIS_1} = 1 \times 10^{-6}$ g/min^2, $\hat{q}_{\rm BIS_1} = 1 \times 10^{-3}$ g/min^2, and initial conditions $x(0) = [0,\ 0,\ 0]^{\rm T}$ g, $k_1(0) = 0\ \rm min^{-1}$, and $\phi_1(0) = 0.01$ g/min^{-1}. Figure 3 shows the BIS index versus time and figure 4 shows the propofol concentration in the central compartment versus time.

VI. CONCLUSION

In this paper, we developed a direct adaptive control framework for linear uncertain nonnegative and compartmental dynamical systems with unknown time delay. In particular, a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation for nonnegative and compartmental time-delay systems with specific applications to mammillary pharmacokinetic models was developed. Finally, we demonstrated the framework on a drug delivery pharmacokinetic/pharmacodynamic model with time delay. Extensions of the proposed adaptive control framework to nonlinear nonnegative systems as well as to systems with exogenous disturbances will be addressed in a future paper.

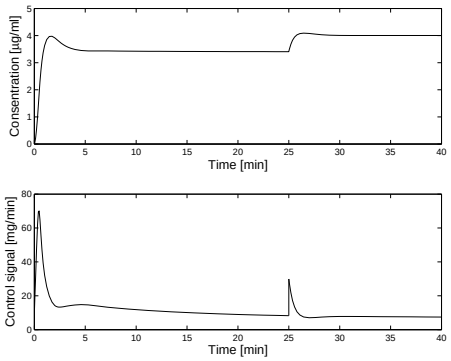

Fig. 4. Drug concentration in the central compartment and control signal (infusion rate) versus time

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