

Adaptive control for non-negative and compartmental dynamical systems with applications to general anesthesia

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SUMMARY

Non-negative and compartmental dynamical system models are composed of homogeneous interconnected subsystems or compartments which exchange variable non-negative quantities of material with conservation laws describing transfer, accumulation, and elimination between the compartments and the environment. These models are widespread in biological and physiological sciences and play a key role in understanding these processes. In this paper, we develop a direct adaptive control framework for linear uncertain non-negative and compartmental systems. The proposed framework is Lyapunov-based and guarantees partial asymptotic set-point regulation; that is, asymptotic set-point stability with respect to part of the closed-loop system states associated with the plant. In addition, the adaptive controller guarantees that the physical system states remain in the non-negative orthant of the state space. Finally, a numerical example involving the infusion of the anesthetic drug propofol for maintaining a desired constant level of depth of anesthesia for non-cardiac surgery is provided to demonstrate the efficacy of the proposed approach. Copyright © 2003 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Even though advanced robust and adaptive control methodologies have been (and are being) extensively developed for highly complex engineering systems, modern active control technology has received far less consideration in medical systems. The main reason for this state of affairs is

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the steep barriers to communication between mathematics/control engineering and medicine. However, this is slowly changing and there is no doubt that control-system technology has a great deal to offer medicine. For example, critical care patients, whether undergoing surgery or recovering in intensive care units, require drug administration to regulate key physiological (state) variables (e.g. blood pressure, cardiac output, heart rate, glucose, etc.) within desired levels. The rate of infusion of each administered drug is *critical*, requiring constant monitoring and frequent adjustments. Open-loop control (manual control) by clinical personnel can be very tedious, imprecise, time consuming, and often of poor quality. Hence, the need for active control (closed-loop control) in medical systems is severe; with the potential in improving the quality of medical care as well as curtailing the increasing cost of health care.

The complex highly uncertain and hostile environment of surgery places stringent performance requirements for closed-loop set-point regulation of physiological variables. For example, during cardiac surgery, blood pressure control is vital and is subject to numerous highly uncertain exogenous disturbances. Vasoactive and cardioactive drugs are administered resulting in large disturbance oscillations to the system (patient). The arterial line may be flushed and blood may be drawn, corrupting sensor blood pressure measurements. Low anesthetic levels may cause the patient to react to painful stimuli, thereby changing system response characteristics. The flow rate of vasodilator drug infusion may fluctuate causing transient changes in the infusion delay time. Hemorrhage, patient position changes, cooling and warming of the patient, and changes in anesthesia levels will also effect system response characteristics.

In light of the complex and highly uncertain nature of system response characteristics under surgery requiring controls, it is not surprising that reliable system models for many high performance drug delivery systems are unavailable. In the face of such high levels of system uncertainty, robust controllers may unnecessarily sacrifice system performance whereas adaptive controllers can tolerate far greater system uncertainty levels to improve system performance [1–4]. In contrast to fixed-gain robust controllers, which maintain specified constants within the feedback control law to *sustain* robust performance, adaptive controllers directly or indirectly adjust feedback gains to maintain closed-loop stability and *improve* performance in the face of system uncertainties. Specifically, indirect adaptive controllers utilize parameter update laws to identify unknown system parameters and adjust feedback gains to account for system variation, while direct adaptive controllers directly adjust the controller gains in response to system variations (drug administration).

In this paper we develop a direct adaptive control framework for adaptive set-point regulation of linear uncertain non-negative and compartmental systems. Non-negative and compartmental dynamical systems [5–18] are composed of homogeneous interconnected subsystems (or compartments) which exchange variable non-negative quantities of material with conservation laws describing transfer, accumulation, and elimination between the compartments and the environment. It follows from physical considerations that the state trajectory of such systems remains in the non-negative orthant of the state space for non-negative initial conditions. Non-negative and compartmental models thus play a key role in understanding many processes in biological and medical sciences. Using non-negative and compartmental model structures, a Lyapunov-based direct adaptive control framework is developed that guarantees partial asymptotic set-point stability of the closed-loop system; that is, asymptotic set-point stability with respect to part of the closed-loop system states associated with the physiological state variables. In particular, adaptive controllers are constructed *without* requiring knowledge of the system dynamics while providing a non-negative control (source)

input for robust stabilization with respect to the non-negative orthant. Furthermore, in certain applications of non-negative and compartmental systems such as biological systems, population dynamics, and ecological systems involving positive and negative inflows, the non-negativity constraint on the control input is not natural. In this case, we also develop adaptive controllers that do not place any restriction on the sign of the control signal while guaranteeing that the physical system states remain in the non-negative orthant of the state space.

Even though the proposed adaptive control framework is applicable to general linear non-negative and compartmental dynamical systems, in this paper our application objective is in clinical pharmacology. In particular, we develop adaptive controllers for drug administration for general anesthesia. Adaptive control algorithms in pharmacology are vital since the relationships between drug dose and blood concentration (pharmacokinetics) and between blood concentrations and physiological effect (pharmacodynamics) vary widely among individual patients. Active control for the administration of general anesthesia is not new to this paper and has been considered in the literature. Specifically, building on pioneering work of Bickford [19] several groups have developed and clinically tested closed-loop controllers for the delivery of intravenous anesthesia using an electroencephalogram (EEG) signal for the performance and measurement variable. Two model-based control algorithms have been developed using a pharmacokinetic model relating drug concentration to drug dose and a pharmacodynamic model relating drug effect to drug concentration. Unfortunately, biological systems have significant pharmacokinetic and pharmacodynamic variability among individual subjects and using population mean values of pharmacokinetic and pharmacodynamic model parameters may result in very pronounced bias for any specific individual. To simplify one could assume that pharmacodynamics (the relationship between drug concentration and effect) do not vary among individuals and any difference between individual responses is due to pharmacokinetic variability. Alternatively, one could assume that the pharmacokinetic parameters are always correct and all variability is pharmacodynamic. Schwilden *et al.* [20, 21] developed an algorithm which used the former strategy and developed an adaptive control algorithm which progressively refined estimates of individual pharmacokinetic parameters by minimizing the difference between the observed and predicted EEG signal. This algorithm was implemented for the intravenous anesthetic agents methohexital and propofol but did not appear to offer great advantage over standard manual control. This may have been due to the approximations of the algorithm or due to the deficiencies of the median EEG frequency (the EEG signal utilized by the investigators) as a measure of the depth of anesthesia. In the alternative approach, Struys *et al.* [22] have described a closed-loop controller of the delivery of the intravenous anesthetic propofol using a model-based adaptive control algorithm with the Bispectral Index (BIS), a derivative of the EEG signal, as the performance and measurement variable that assumes that all variability is pharmacodynamic. More specifically, with induction of anesthesia they calculated a predicted concentration using the pharmacokinetic model and then constructed a BIS-concentration relationship using the observed BIS during induction and the predicted propofol concentration. With each time epoch, the difference between the target BIS signal and the observed BIS signal is used to update the pharmacodynamic parameters relating concentration and BIS signal for the individual patient. Using this algorithm, Struys *et al.* [22] demonstrated excellent performance as measured by the difference between the target and observed BIS signals. However, as pointed out by Glass and Rampil [23], the excellent performance of the system may have been because the system was not fully stressed. In their study, Struys *et al.* [22] administered a relatively high fixed dose of the opioid remifentanyl, in

conjunction with propofol. This blunted the patient response to surgical stimuli and meant that the propofol was needed only to produce unconsciousness in patients who were profoundly analgesic. The result was that only small adjustments in propofol concentrations were necessary. Whether the system would have been robust in the absence of deep narcotization is an open question.

In contrast, to the above adaptive control algorithms, Absalom *et al.* [24] have described and implemented a proportional-integral-derivative control algorithm that is independent of pharmacokinetic and pharmacodynamic models. While overall precision and bias of this controller was good, the clinical performance was not acceptable due to oscillations observed in 3 of the 10 patients investigated. In this paper, we present a less restrictive direct adaptive control framework as compared to the existing algorithms discussed above that accounts for interpatient pharmacokinetic and pharmacodynamic variability.

2. MATHEMATICAL PRELIMINARIES

In this section we introduce notation, several definitions, and some key results concerning linear non-negative dynamical systems [15,16,18,25] 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., $x \geq 0$) to indicate that every component of x is non-negative (resp., positive). In this case we say that x is *non-negative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n \times m}$ is *non-negative*¹ or *positive* if every entry of A is non-negative or positive, respectively, which is written as $A \geq \geq 0$ or $A \geq 0$, respectively. Let $\bar{\mathbb{R}}_+^n$ and \mathbb{R}_+^n denote the non-negative and positive orthants of \mathbb{R}^n ; that is, if $x \in \mathbb{R}^n$, then $x \in \bar{\mathbb{R}}_+^n$ and $x \in \mathbb{R}_+^n$ are equivalent, respectively, to $x \geq \geq 0$ and $x \geq 0$. The following definition introduces the notion of a non-negative function.

Definition 2.1

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

The next definition introduces the notion of essentially non-negative matrices.

Definition 2.2

Bernstein and Hyland [16] and Haddad *et al.* [18]. Let $A \in \mathbb{R}^{n \times m}$. A is *essentially non-negative* if $A_{(i,j)} \geq 0$, $i, j = 1, \dots, n$, $i \neq j$.

Next, consider the linear non-negative dynamical system

$$\dot{x}(t) = Ax(t), \quad x(0) = x_0, \quad t \geq 0 \quad (1)$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, and $A \in \mathbb{R}^{n \times n}$ is essentially non-negative. The solution to (1) is standard and is given by $x(t) = e^{At}x(0)$, $t \geq 0$. The following lemma proven in Reference [16] (see also Reference [18]) shows that A is essentially non-negative if and only if the state transition matrix e^{At} is non-negative on $[0, \infty]$.

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

Proposition 2.1

Let $A \in \mathbb{R}^{n \times n}$. Then A is essentially non-negative if and only if e^{At} is non-negative for all $t \geq 0$. Hence, if A is essentially non-negative and $x_0 \geq 0$, then $x(t) \geq 0$, $t \geq 0$, where $x(t)$, $t \geq 0$, denotes the solution to (1).

The following result shows that, for non-negative initial conditions, the states of a *time-varying* linear dynamical system \mathcal{G} of the form

$$\dot{x}(t) = A(t)x(t), \quad x(t_0) = x_0, \quad t \geq t_0 \quad (2)$$

where $t_0 \in [0, \infty)$ and $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is continuous and essentially non-negative pointwise-in-time, remain non-negative.

Proposition 2.2

Consider the time-varying dynamical system (2) where $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is continuous. Then \mathbb{R}_+^n is an invariant set with respect to (2) if and only if $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is essentially non-negative pointwise-in-time.

Proof

The result is a direct consequence of Proposition 6.1 of Reference [18] (see also Reference [26]) by equivalently representing the time-varying system (2) as an autonomous non-linear system by appending another state to represent time. Specifically, defining $y(t - t_0) \triangleq x(t)$ and $y_{n+1}(t - t_0) \triangleq t$, it follows that the solution $x(t)$, $t \geq t_0$, to (2) can be equivalently characterized by the solution $y(\tau)$, $\tau \geq 0$, where $\tau \triangleq t - t_0$, to the non-linear autonomous system

$$\dot{y}(\tau) = A(y_{n+1}(\tau))y(\tau), \quad y(0) = y_0, \quad \tau \geq 0 \quad (3)$$

$$\dot{y}_{n+1}(\tau) = 1, \quad y_{n+1}(0) = t_0 \quad (4)$$

where $\dot{y}(\cdot)$ and $\dot{y}_{n+1}(\cdot)$ denote differentiation with respect to τ . Now, since $\dot{y}_i(\tau) \geq 0$, $\tau \geq 0$, for $i = 1, \dots, n+1$, whenever $y_i(\tau) = 0$, the result is a direct consequence of Proposition 6.1 of Reference [18]. \square

The following theorems give necessary and sufficient conditions for asymptotic stability of a linear non-negative dynamical system using *linear* and *quadratic* Lyapunov functions, respectively. For the statement of the first theorem recall that (1) is *semistable* if and only if $\lim_{t \rightarrow \infty} e^{At}$ exists [16, 18, 27].

Theorem 2.1

Haddad *et al.* [18]. Consider the linear dynamical system \mathcal{G} given by (1) where $A \in \mathbb{R}^{n \times n}$ is essentially non-negative. Then the following statements hold:

- (i) \mathcal{G} is Lyapunov stable if and only if \mathcal{G} is semistable.
- (ii) If there exist vectors $p, r \in \mathbb{R}^n$ such that $p \geq 0$ and $r \geq 0$ satisfy

$$0 = A^T p + r \quad (5)$$

then \mathcal{G} is semistable (and hence Lyapunov stable).

- (iii) If \mathcal{G} is semistable, then there exist vectors $p, r \in \mathbb{R}^n$ such that $p \geq 0$, $p \neq 0$, and $r \geq 0$ satisfy (5).
- (iv) If there exist vectors $p, r \in \mathbb{R}^n$ such that $p \geq 0$, $p \neq 0$, and $r \geq 0$ satisfy (5) and (A, r^T) is observable, then $p \geq 0$ and \mathcal{G} is asymptotically stable.

Furthermore, the following statements are equivalent:

- (v) \mathcal{G} is asymptotically stable.
- (vi) There exist vectors $p, r \in \mathbb{R}^n$ such that $p \geq 0$ and $r \geq 0$ satisfy (5).

Theorem 2.2

Haddad *et al.* [18]. Consider the linear dynamical system \mathcal{G} given by (1) where $A \in \mathbb{R}^{n \times n}$ is essentially non-negative. Then \mathcal{G} is asymptotically stable if and only if there exist a positive diagonal matrix $P \in \mathbb{R}^{n \times n}$ and an $n \times n$ positive-definite matrix R such that

$$0 = A^T P + P A + R \quad (6)$$

Next, we consider a subclass of non-negative systems; namely, compartmental systems. As discussed 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 [14].

Definition 2.3

Let $A \in \mathbb{R}^{n \times n}$. A is a *compartmental matrix* if A is essentially non-negative and $\sum_{i=1}^n A_{(i,j)} \leq 0, j = 1, \dots, n$.

If A is a compartmental matrix, then the non-negative system (1) is called an *inflow-closed compartmental system* [14,17,18]. As shown in References [16,18], if A is a compartmental matrix, then the entries in A are given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^n a_{kj}, & i = j \\ a_{ij}, & i \neq j \end{cases} \quad (7)$$

where $a_{ii} \geq 0, i \in \{1, \dots, n\}$, denotes the loss coefficient of the i th compartment and $a_{ij} \geq 0, i \neq j, i, j \in \{1, \dots, n\}$, denotes the transfer coefficient from the j th compartment to the i th compartment. Note that it follows from (7) that $\sum_{i=1}^n A_{(i,j)} \leq 0, j = 1, \dots, n$. Recall that an inflow-closed compartmental system possesses a dissipation property and hence is Lyapunov stable since the total mass in the system given by the sum of all components of the state $x(t), t \geq 0$, is nonincreasing along the forward trajectories of (1). In particular, with $V(x) = e^T x$, where $e = [1, 1, \dots, 1]^T$, it follows that $\dot{V}(x) = e^T A x = \sum_{j=1}^n [\sum_{i=1}^n A_{(i,j)}] x_j \leq 0, x \in \mathbb{R}_+^n$. Furthermore, since $\text{ind}(A) \leq 1$ (see References [16,18]), where $\text{ind}(A)$ denotes the index of A , it follows that A is semistable. Hence, all solutions of inflow-closed linear compartmental systems are convergent. Of course, if $\det A \neq 0$, where $\det A$ denotes the determinant of A , then A is asymptotically stable. Alternatively, semistability and asymptotic stability can be deduced from Theorem 2.1. In particular, with $p = e \geq 0$ and $r = -A^T e = [-a_{11}, -a_{22}, \dots, -a_{nn}] \geq 0$, (5) is satisfied which implies, by Theorem 3.2 of Reference [18], that an inflow-closed compartmental

system is semistable if A is singular and asymptotically stable if A is nonsingular. For details of the above facts see References [16, 18].

Next, we show that every asymptotically stable linear non-negative system is equivalent, modulo a similarity transformation, to a compartmental system.

Proposition 2.3

Haddad *et al.* [18]. Let $A \in \mathbb{R}^{n \times n}$ be asymptotically stable. Then A is essentially non-negative if and only if there exists an invertible diagonal matrix $S \in \mathbb{R}^{n \times n}$ such that SAS^{-1} is a compartmental matrix.

Finally, in this paper we consider controlled dynamical systems of the form

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0, \quad (8)$$

where $x(t) \in \mathbb{R}^n, t \geq 0, u(t) \in \mathbb{R}^m, t \geq 0, A \in \mathbb{R}^{n \times n}$, and $B \in \mathbb{R}^{n \times m}$. The following definition and proposition are needed for the main results of the paper.

Definition 2.4

The linear dynamical system given by (8) is *non-negative* if for every $x(0) \in \bar{\mathbb{R}}_+^n$ and $u(t) \geq 0, t \geq 0$, the solution $x(t), t \geq 0$, to (8) is non-negative.

Proposition 2.4

Haddad *et al.* [18]. The linear dynamical system given by (8) is non-negative if and only if $A \in \mathbb{R}^{n \times n}$ is essentially non-negative and $B \in \mathbb{R}^{n \times m}$ is non-negative.

It follows from Proposition 2.4 that the control input signal $Bu(t), t \geq 0$, needs to be non-negative to guarantee the non-negativity of the state of (8). This is due to the fact that when the initial state of (8) belongs to the boundary of the non-negative orthant, a negative input can destroy the non-negativity of the state of (8). Alternatively, however, if the initial state is in the interior of the non-negative orthant, then it follows from continuity of solutions with respect to the system initial conditions that, over a small interval of time, non-negativity of the state of (8) is guaranteed *irrespective* of the sign of each element of the control input $Bu(t)$ over this time interval. However, unlike open-loop control wherein lack of coordination between the input and the state necessitates non-negativity of the control input, a *feedback* control signal predicated on the system state variables allows for the anticipation of loss of non-negativity of the state. Hence, state feedback control signals can take negative values while assuring non-negativity of the system states. For further discussion of the above fact see Reference [28].

Next, we present a time-varying extension to Proposition 2.4 needed for the main theorems of this paper. Specifically, we consider the time-varying system

$$\dot{x}(t) = A(t)x(t) + Bu(t), \quad x(t_0) = x_0, \quad t \geq t_0 \quad (9)$$

where $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is continuous. For the following result the definition of non-negativity holds with (8) replaced by (9).

Proposition 2.5

Consider the time-varying dynamical system (9) where $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is continuous. If $A : [0, \infty) \rightarrow \mathbb{R}^{n \times n}$ is essentially non-negative pointwise-in-time and $B \in \mathbb{R}^{n \times m}$ is non-negative, then the solution $x(t)$, $t \geq t_0$, to (9) is non-negative.

Proof

The proof is similar to the proof of Proposition 2.2 using Proposition 7.1 of Reference [18] and hence is omitted. \square

Since stabilization of non-negative systems naturally deals with equilibrium points in the interior of the non-negative orthant $\bar{\mathbb{R}}_+^n$, the following proposition provides necessary conditions for the existence of an interior equilibrium point $x_e \in \mathbb{R}_+^n$ of (8) in terms of the stability properties of the system dynamics matrix A .

Proposition 2.6

Consider the non-negative dynamical system (8) and assume there exists $x_e \in \mathbb{R}_+^n$ and $u_e \in \bar{\mathbb{R}}_+^m$ such that

$$0 = Ax_e + Bu_e \quad (10)$$

Then, A is semistable.

Proof

The proof is a direct consequence of (ii) of Theorem 2.1 with A replaced by A^T , $p = x_e$, and $r = Bu_e$. \square

It follows from Proposition 2.6 that the existence of an equilibrium point $x_e \in \mathbb{R}_+^n$ for (8) implies that the system matrix A is semistable. Hence, if (10) holds for $x_e \in \mathbb{R}_+^n$ and $u_e \in \bar{\mathbb{R}}_+^m$, A is asymptotically stable or $0 \in \text{spec}(A)$, where $\text{spec}(A)$ denotes the spectrum of A , is a simple eigenvalue of A and all other eigenvalues of A have negative real parts since $-A$ is an M -matrix [25]. In light of the above constraints, it was shown in Reference [28] using Brockett's necessary condition for asymptotic stabilizability [29] that if $0 \in \text{spec}(A)$, then there does *not* exist a *continuous* stabilizing *non-negative* feedback for set-point regulation in \mathbb{R}_+^n for a non-negative system. However, that is not to say that asymptotic feedback regulation using *discontinuous* feedback is not possible.

3. ADAPTIVE CONTROL FOR LINEAR NON-NEGATIVE UNCERTAIN DYNAMICAL SYSTEMS

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

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0 \quad (11)$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, is the state vector, $u(t) \in \mathbb{R}^m$, $t \geq 0$ is the control input, $A \in \mathbb{R}^{n \times n}$ is an *unknown* essentially non-negative matrix, and $B \in \mathbb{R}^{n \times m}$ is an *unknown* non-negative input matrix. The control input $u(\cdot)$ in (11) is restricted to the class of *admissible controls* consisting of measurable functions such that $u(t) \in \mathbb{R}^m$, $t \geq 0$.

As discussed in the Introduction, it follows from physical considerations that the state trajectories of non-negative and compartmental dynamical systems remain in the non-negative orthant of the state space for non-negative initial conditions. However, even though active control of drug delivery systems for physiological applications additionally require control (source) inputs to be non-negative, in many applications of non-negative 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 non-negative orthant and converge to a desired equilibrium state.

Specifically, for a given desired set point $x_e \in \bar{\mathbb{R}}_+^n$, our aim is to design a control input $u(t)$, $t \geq 0$, so that $\lim_{t \rightarrow \infty} \|x(t) - x_e\| = 0$. However, since in many applications of non-negative systems and in particular, compartmental systems, it is often necessary to regulate a subset of the non-negative state variables which usually include a central compartment, here we require that $\lim_{t \rightarrow \infty} x_i(t) = x_{di} \geq 0$ for $i = 1, \dots, m \leq n$, where x_{di} is a desired set point for the i th state $x_i(t)$. Furthermore, we assume that control inputs are injected directly into m separate compartments so that the input matrix is given by

$$B = \begin{bmatrix} B_u \\ 0_{(n-m) \times m} \end{bmatrix} \quad (12)$$

where $B_u \triangleq \text{diag}[b_1, \dots, b_m]$ and $b_i \in \mathbb{R}_+$, $i = 1, \dots, m$. Here, we assume that for $i \in \{1, \dots, m\}$, b_i is *unknown*. For the statement of our main result define $x_e \triangleq [x_d^T, x_u^T]^T$, where $x_e \triangleq [x_{d1}, \dots, x_{dm}]^T$ and $x_u \triangleq [x_{u1}, \dots, x_{u(n-m)}]^T$.

Theorem 3.1

Consider the linear uncertain dynamical system \mathcal{G} given by (11) where A is essentially non-negative and B is non-negative and given by (12). For a given x_d assume there exist non-negative vectors $x_u \in \bar{\mathbb{R}}_+^{n-m}$ and $u_e \in \bar{\mathbb{R}}_+^m$ such that

$$0 = Ax_e + Bu_e \quad (13)$$

Furthermore, assume there exists a diagonal matrix $K_g = \text{diag}[k_{g1}, \dots, k_{gm}] \in \mathbb{R}^{m \times m}$ such that $A_s \triangleq A + B\tilde{K}_g$ is asymptotically stable, where $\tilde{K}_g \triangleq [K_g, 0_{m \times (n-m)}]$. Finally, let q_i and \hat{q}_i , $i = 1, \dots, m$, be positive constants. Then the adaptive feedback control law

$$u(t) = K(t)(\hat{x}(t) - x_d) + \phi(t) \quad (14)$$

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

$$u_i(t) = k_i(t)(x_i(t) - x_{di}) + \phi_i(t), \quad i = 1, \dots, m \quad (15)$$

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

$$\dot{k}_i(t) = -q_i(x_i(t) - x_{di})^2, \quad k_i(0) \leq 0, \quad t \geq 0, \quad i = 1, \dots, m \quad (16)$$

$$\phi_i(t) = \begin{cases} 0 & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{di} \\ -\hat{q}_i(x_i(t) - x_{di}) & \text{otherwise} \end{cases} \quad \phi_i(0) \geq 0, \quad i = 1, \dots, m \quad (17)$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_e, K_g, u_e)$ of the closed-loop system given by (11), (14), (16), (17) is Lyapunov stable and $x_i(t) \rightarrow x_{di}, i = 1, \dots, m$, as $t \rightarrow \infty$ for all $x_0 \in \bar{\mathbb{R}}_+^n$. Furthermore, $x(t) \geq 0, t \geq 0$, for all $x_0 \in \bar{\mathbb{R}}_+^n$.

Proof

Note that with $u(t), t \geq 0$, given by (14) it follows from (11) that

$$\dot{x}(t) = Ax(t) + BK(t)(\hat{x}(t) - x_d) + B\phi(t), \quad x(0) = x_0, \quad t \geq 0, \quad (18)$$

or, equivalently, using (13) and $A_s = A + B\tilde{K}_g$,

$$\dot{x}(t) = A_s(x(t) - x_e) + B(K(t) - K_g)(\hat{x}(t) - x_d) + B(\phi(t) - u_e), \quad x(0) = x_0, \quad t \geq 0. \quad (19)$$

Furthermore, since A_s is essentially non-negative and asymptotically stable, it follows from Theorem 2.2 that there exists a positive diagonal matrix $P \triangleq \text{diag}[p_1, \dots, p_n]$ and a positive definite matrix $R \in \mathbb{R}^{n \times n}$ such that

$$0 = A_s^T P + P A_s + R \quad (20)$$

To show Lyapunov stability of the closed-loop system (16), (17), and (19) consider the Lyapunov function candidate

$$V(x, K, \phi) = (x - x_e)^T P (x - x_e) + \text{tr}(K - K_g)^T Q^{-1} (K - K_g) + (\phi - u_e)^T \hat{Q}^{-1} (\phi - u_e) \quad (21)$$

or, equivalently,

$$V(x, K, \phi) = \sum_{i=1}^n p_i (x_i - x_{ei})^2 + \sum_{i=1}^m \frac{p_i b_i}{q_i} (k_i - k_{gi})^2 + \sum_{i=1}^m \frac{p_i b_i}{\hat{q}_i} (\phi_i - u_{ei})^2$$

where

$$Q = \text{diag} \left[\frac{q_1}{p_1 b_1}, \dots, \frac{q_m}{p_m b_m} \right]$$

and

$$\hat{Q} = \text{diag} \left[\frac{\hat{q}_1}{p_1 b_1}, \dots, \frac{\hat{q}_m}{p_m b_m} \right].$$

Note that $V(x_e, K_g, u_e) = 0$ and, since P, Q , and \hat{Q} are positive definite, $V(x, K, \phi) > 0$ for all $(x, K, \phi) \neq (x_e, K_g, u_e)$. Furthermore, $V(x, K, \phi)$ is radially unbounded. Now, letting $x(t), t \geq 0$, denote the solution to (19) and using (16) and (17), it follows that the Lyapunov derivative along the closed-loop system trajectories is given by

$$\begin{aligned} \dot{V}(x(t), K(t), \phi(t)) &= 2(x(t) - x_e)^T P [A_s(x(t) - x_e) + B(K(t) - K_g)(\hat{x}(t) - x_d) \\ &\quad + B(\phi(t) - u_e)] + 2\text{tr}(K(t) - K_g)^T Q^{-1} \dot{K}(t) + 2(\phi(t) - u_e)^T \hat{Q}^{-1} \dot{\phi}(t) \\ &= -(x(t) - x_e)^T R (x(t) - x_e) + 2 \sum_{i=1}^m p_i b_i (k_i(t) - k_{gi})(x_i(t) - x_{di})^2 \end{aligned}$$

$$\begin{aligned}
 &+ 2 \sum_{i=1}^m p_i b_i (x_i(t) - x_{di})(\phi_i(t) - u_{ei}) + 2 \sum_{i=1}^m \frac{p_i b_i}{\hat{q}_i} (k_i(t) - k_{gi}) \dot{k}_i(t) \\
 &+ 2 \sum_{i=1}^m \frac{p_i b_i}{\hat{q}_i} (\phi_i(t) - u_{ei}) \dot{\phi}_i(t) \\
 &= -(x(t) - x_e)^T R (x(t) - x_e) \\
 &+ 2 \sum_{i=1}^m p_i b_i (\phi_i(t) - u_{ei}) \left[(x_i(t) - x_{di}) + \frac{1}{\hat{q}_i} \dot{\phi}_i(t) \right]. \tag{22}
 \end{aligned}$$

Now, for each $i \in \{1, \dots, m\}$ and for the two cases given in (17), the last term on the right-hand side of (22) gives: (i) If $\phi_i(t) = 0$ and $x_i(t) \geq x_{di}$, then $\dot{\phi}_i(t) = 0$ and hence

$$p_i b_i (\phi_i(t) - u_{ei}) \left[(x_i(t) - x_{di}) + \frac{1}{\hat{q}_i} \dot{\phi}_i(t) \right] = -p_i b_i u_{ei} (x_i(t) - x_{di}) \leq 0 \tag{ii}$$

(ii) Otherwise, $\dot{\phi}_i(t) = -\hat{q}_i(x_i(t) - x_{di})$ and hence

$$p_i b_i (\phi_i(t) - u_{ei}) \left[(x_i(t) - x_{di}) + \frac{1}{\hat{q}_i} \dot{\phi}_i(t) \right] = 0$$

Hence, it follows that in either case

$$\begin{aligned}
 \dot{V}(x(t), K(t), \phi(t)) &\leq -(x(t) - x_e)^T R (x(t) - x_e) \\
 &\leq 0, \quad t \geq 0, \tag{23}
 \end{aligned}$$

which proves that the solution $(x(t), K(t), \phi(t)) \equiv (x_e, K_g, u_e)$ to (16), (17), and (19) is Lyapunov stable. Furthermore, since $R > 0$ it follows from Theorem 2.2 of Reference [30] that $x(t) \rightarrow x_e$ as $t \rightarrow \infty$ for all $x_0 \in \bar{\mathbb{R}}_+^n$.

Finally to show that $x(t) \geq 0, t \geq 0$, for all $x_0 \in \bar{\mathbb{R}}_+^n$, note that the closed-loop system(11), (14), (16), and (17) is given by

$$\begin{aligned}
 \dot{x}(t) &= Ax(t) + BK(t)(x(t) - x_d) + B\phi(t) \\
 &= (A + B[K(t), 0_{m \times (n-m)}])x(t) - BK(t)x_d + B\phi(t) \\
 &= \tilde{A}(t)x(t) + v(t) + w(t) \tag{24}
 \end{aligned}$$

where

$$\tilde{A}(t) \triangleq \begin{bmatrix} a_{11} + b_1 k_1(t) & a_{12} & \cdots & a_{1m} & a_{1m+1} & \cdots & a_{1n} \\ a_{21} & a_{22} + b_2 k_2(t) & \ddots & \vdots & \vdots & \ddots & a_{2n} \\ \vdots & & \ddots & \vdots & \vdots & & \vdots \\ a_{m1} & \cdots & & a_{mm} + b_m k_m(t) & a_{mm+1} & \cdots & a_{mn} \\ a_{m+11} & \cdots & & a_{m+1m} & a_{m+1m+1} & \cdots & a_{m+1n} \\ \vdots & \ddots & & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & \cdots & & a_{nm} & a_{nm+1} & \cdots & a_{nn} \end{bmatrix} \tag{25}$$

$$v(t) \triangleq - \begin{bmatrix} b_1 k_1(t) x_{d1} \\ \vdots \\ b_m k_m(t) x_{dm} \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \quad w(t) \triangleq \begin{bmatrix} b_1 \phi_1(t) \\ \vdots \\ b_m \phi_m(t) \\ 0 \\ \vdots \\ 0 \end{bmatrix} \quad (26)$$

Now, since, by (16) and (17), $k_i(t) \leq 0, t \geq 0, i = 1, \dots, m$, and $\phi_i(t) \geq 0, t \geq 0, i = 1, \dots, m$, it follows that $v(t) \geq 0, t \geq 0$, and $w(t) \geq 0, t \geq 0$. Hence, since $\tilde{A}(t), t \geq 0$, is essentially non-negative pointwise-in-time, it follows from Proposition 2.5 that $x(t) \geq 0, t \geq 0$, for all $x_0 \in \mathbb{R}_+^n$. \square

Remark 3.1

Note that the conditions in Theorem 3.1 imply that $x(t) \rightarrow x_e$ as $t \rightarrow \infty$ and hence it follows from (16) and (17) that $(x(t), K(t), \phi(t)) \rightarrow \mathcal{M} \triangleq \{(x, K, \phi) \in \mathbb{R}^n \times \mathbb{R}^{m \times m} \times \mathbb{R}^m : x = x_e, \dot{K} = 0, \dot{\phi} = 0\}$ as $t \rightarrow \infty$.

It is important to note that the adaptive control law (14), (16), and (17) does *not* require the explicit knowledge of the gain matrix K_g and the non-negative constant vector u_e ; even though Theorem 3.1 requires the existence of K_g and non-negative vectors x_u and u_e such that A_s is essentially non-negative and asymptotically stable and condition (13) holds. Furthermore, in the case where A is semistable and minimum phase with respect to the output $y = \hat{x}$, or A is asymptotically stable, then there always exists a diagonal matrix $\tilde{K}_g \in \mathbb{R}^{m \times n}$ such that A_s is asymptotically stable. Necessary and sufficient conditions for set-point stabilization of the pair (A, B) , where A is singular and compartmental are given in [28,31]. Finally, note that for $i = 1, \dots, m$, 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 non-negative and compartmental dynamical systems the closed-loop plant states remain non-negative.

In the case where our objective is zero set-point regulation, that is, $x_e = 0$, the adaptive controller given in Theorem 3.1 can be considerably simplified. Specifically, since in this case $x(t) \geq x_e = 0, t \geq 0$, and condition (13) is trivially satisfied with $u_e = 0$, we can set $\phi(t) \equiv 0$ so that update law (17) is superfluous. Furthermore, since (13) is trivially satisfied, A can possess eigenvalues in the right-half plane. Alternatively, exploiting a *linear* Lyapunov function 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 dynamical system \mathcal{G} given by (11) where A is essentially non-negative and B is non-negative and given by (12). Assume there exists a diagonal matrix $K_g = \text{diag}[k_{g1}, \dots, k_{gm}] \in \mathbb{R}^{m \times m}$ such that $A_s \triangleq A + BK_g$ is asymptotically stable, where $\tilde{K}_g \triangleq [K_g, 0_{m \times (n-m)}]$. Furthermore, let $q_i, i = 1, \dots, m$, be positive constants. Then the adaptive

feedback control law

$$u(t) = K(t)\hat{x}(t) \quad (27)$$

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

$$u_i(t) = k_i(t)x_i(t), \quad i = 1, \dots, m \quad (28)$$

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

$$\dot{K}(t) = -\text{diag}[q_1x_1(t), \dots, q_mx_m(t)] \quad (29)$$

guarantees that the solution $(x(t), K(t)) \equiv (0, K_g)$ of the closed-loop system given by (11), (27), (29) is Lyapunov stable and $x(t) \rightarrow 0$ as $t \rightarrow \infty$ for all $x_0 \in \mathbb{R}_+^n$. Furthermore, $x(t) \geq 0, t \geq 0$, for all $x_0 \in \mathbb{R}_+^n$.

Proof

Note that with $u(t)$, $t \geq 0$, given by (27) it follows from (11) that

$$\begin{aligned} \dot{x}(t) &= Ax(t) + BK(t)\hat{x}(t), \quad x(0) = x_0, \quad t \geq 0, \\ &= (A + B[K(t), 0_{m \times (n-m)}])x(t) \\ &= \tilde{A}(t)x(t) \end{aligned} \quad (30)$$

where $\tilde{A}(t)$, $t \geq 0$, is given by (25). Now, since $\tilde{A}(t)$, $t \geq 0$, is essentially non-negative pointwise-in-time, it follows from Proposition 2.2 that $x(t) \geq 0, t \geq 0$, for all $x_0 \in \mathbb{R}_+^n$. Next, using $A_s = A + B\tilde{K}_g$, note that (30) can be equivalently written as

$$\dot{x}(t) = A_sx(t) + B(K(t) - K_g)\hat{x}(t), \quad x(0) = x_0, \quad t \geq 0 \quad (31)$$

Furthermore, since A_s is essentially non-negative and asymptotically stable, it follows from Theorem 2.1 that there exist $p, r \in \mathbb{R}^n$ such that $p \geq 0$ and $r \geq 0$ satisfy

$$0 = A_s^T p + r \quad (32)$$

To show the Lyapunov stability of the closed-loop system (29) and (31) consider the Lyapunov function candidate

$$V(x, K) = p^T x + \frac{1}{2} \text{tr}(K - K_g)^T Q^{-1}(K - K_g) \quad (33)$$

or, equivalently,

$$V(x, K) = p^T x + \frac{1}{2} \sum_{i=1}^m \frac{p_i b_i}{q_i} (k_i - k_{gi})^2 \quad (34)$$

where

$$Q = \text{diag} \left[\frac{q_1}{p_1 b_1}, \dots, \frac{q_m}{p_m b_m} \right]$$

Note that $V(0, K_g) = 0$ and, since $p \geq 0$ and $Q > 0$, $V(x, K) > 0$ for all $(x, K) \neq (0, K_g)$. Furthermore, $V(x, K)$ is radially unbounded with respect to the non-negative orthant. Now, letting $x(t)$, $t \geq 0$, denote the solution to (31) and using (29), it follows that the Lyapunov

derivative along the closed-loop system trajectories is given by

$$\begin{aligned} \dot{V}(x(t), K(t)) &= p^T[A_s x(t) + B(K(t) - K_g)\dot{x}(t)] + \text{tr}(K(t) - K_g)^T Q^{-1} \dot{K}(t) \\ &= -r^T x(t) + \sum_{i=1}^m p_i b_i (k_i(t) - k_{gi}) x_i(t) + \sum_{i=1}^m \frac{p_i b_i}{q_i} (k_i(t) - k_{gi}) \dot{k}_i(t) \\ &= -r^T x(t) \\ &\leq 0, \quad t \geq 0, \end{aligned}$$

which proves that the solution $(x(t), K(t)) \equiv (0, K_g)$ to (29) and (31) is Lyapunov stable. Furthermore, since $r \geq 0$ it follows from Theorem 2.2 of Reference [30] that $x(t) \rightarrow 0$ as $t \rightarrow \infty$ for all $x_0 \in \mathbb{R}_+^n$. \square

Finally, we generalize Theorem 3.1 to the case where the input matrix is not necessarily non-negative. For the statement of the following result define $\text{sgn } b_i \triangleq b_i/|b_i|$.

Theorem 3.3

Consider the linear uncertain dynamical system \mathcal{G} given by (11) where A is essentially non-negative and B is given by (12) where $b_i, i = 1, \dots, m$, is an *unknown* constant, but $\text{sgn } b_i$ is known. For a given x_d assume there exist a non-negative vector $x_u \in \mathbb{R}_+^{n-m}$ and a vector $u_e \in \mathbb{R}^m$ such that (13) holds with $Ax_e \leq 0$. Furthermore, assume there exists a diagonal matrix $K_g = \text{diag}[k_{g1}, \dots, k_{gm}] \in \mathbb{R}^{m \times m}$ such that $A_s \triangleq A + B\tilde{K}_g$ is asymptotically stable, where $\tilde{K}_g \triangleq [K_g, 0_{m \times (n-m)}]$. Finally, let q_i and $\hat{q}_i, i = 1, \dots, m$, be positive constants. Then the adaptive feedback control law (14) with update laws

$$\dot{k}_i(t) = -(\text{sgn } b_i) q_i (x_i(t) - x_{di})^2, \quad i = 1, \dots, m \tag{35}$$

$$\dot{\phi}_i(t) = \begin{cases} 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{di}, \\ -(\text{sgn } b_i) \hat{q}_i (x_i(t) - x_{di}) & \text{otherwise} \end{cases} \quad i = 1, \dots, m \tag{36}$$

where $k_i(0)$ and $\phi_i(0)$ are such that $(\text{sgn } b_i) k_i(0) \leq 0$ and $(\text{sgn } b_i) \phi_i(0) \geq 0$, respectively, guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_e, K_g, u_e)$ of the closed-loop system given by (11), (14), (35), (36) is Lyapunov stable and $x_i(t) \rightarrow x_{di}, i = 1, \dots, m$, as $t \rightarrow \infty$ for all $x_0 \in \mathbb{R}_+^n$. Furthermore, $x(t) \geq 0, t \geq 0$, for all $x_0 \in \mathbb{R}_+^n$.

Proof

The proof is similar to that of Theorem 3.1 with Q and \hat{Q} replaced by

$$Q = \text{diag} \left[\frac{q_1}{p_1 |b_1|}, \dots, \frac{q_m}{p_m |b_m|} \right]$$

and

$$\hat{Q} = \text{diag} \left[\frac{\hat{q}_1}{p_1 |b_1|}, \dots, \frac{\hat{q}_m}{p_m |b_m|} \right]$$

respectively. \square

Note that the adaptive controller given in Theorem 3.3 does not destroy non-negativity with respect to the plant states. In particular, the closed-loop system dynamics are given by (24). Now, it can be seen that if b_i is negative, then $k_i(t) \geq 0, t \geq 0$, and $\phi_i(t) \leq 0, t \geq 0$, and hence $v(t) \geq 0, t \geq 0$, and $w(t) \geq 0, t \geq 0$. Hence, by Proposition 2.5, $x(t) \geq 0, t \geq 0$.

4. ADAPTIVE CONTROL FOR LINEAR NON-NEGATIVE DYNAMICAL SYSTEMS WITH NON-NEGATIVE CONTROL

As discussed in the Introduction, control (source) inputs of drug delivery systems for physiological processes are usually constrained to be non-negative as are the system states. Hence, in this section we develop adaptive control laws for essentially non-negative systems with non-negative control inputs. However, as noted in Section 2, since condition (10) is required to be satisfied for $x_e \in \mathbb{R}_+^n$ and $u_e \in \mathbb{R}_+^m$, it follows from Brockett’s necessary condition for asymptotic stabilizability [28] that there does not exist a continuous stabilizing *non-negative* feedback if $0 \in \text{spec}(A)$ and $x_e \in \mathbb{R}_+^n$. Hence, in this section we assume that A is asymptotically stable and hence, without loss of generality, by Proposition 2.3 we further assume that A is an asymptotically stable compartmental matrix. Thus, we proceed with the aforementioned assumptions to design adaptive controllers for uncertain compartmental systems that guarantee that $\lim_{t \rightarrow \infty} x_i(t) = x_{di} \geq 0$ for $i = 1, \dots, m \leq n$, where x_{di} is a desired set point for the i th compartmental state while guaranteeing a non-negative control input.

Theorem 4.1

Consider the linear uncertain dynamical system \mathcal{G} given by (11), where A is an asymptotically stable compartmental matrix, and B is non-negative and given by (12). For a given $x_d \in \mathbb{R}_+^m$ assume there exist vectors $x_u \in \mathbb{R}_+^{n-m}$ and $u_e \in \mathbb{R}_+^m$ such that (13) holds. Furthermore, let q_i and $\hat{q}_i, i = 1, \dots, m$, be positive constants. Then the adaptive feedback control law

$$u_i(t) = \max\{0, \hat{u}_i(t)\}, \quad i = 1, \dots, m, \tag{37}$$

where

$$\hat{u}_i(t) = k_i(t)(x_i(t) - x_{di}) + \phi_i(t), \quad i = 1, \dots, m \tag{38}$$

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

$$\dot{k}_i(t) = \begin{cases} 0 & \text{if } u_i(t) < 0, \\ k_i(0) \leq 0, & i = 1, \dots, m \\ -q_i(x_i(t) - x_{di})^2 & \text{otherwise,} \end{cases} \tag{39}$$

$$\dot{\phi}_i(t) = \begin{cases} 0 & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{di}, \text{ or if } \hat{u}_i(t) \leq 0, \\ -\hat{q}_i(x_i(t) - x_{di}) & \text{otherwise,} \end{cases} \quad \phi_i(0) \geq 0, \quad i = 1, \dots, m, \tag{40}$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_e, K_g, u_e)$, where $K_g = \text{diag}[k_{g1}, \dots, k_{gm}] \leq 0$, of the closed-loop system given by (11), (37), (39), (40) is Lyapunov stable and $x_i(t) \rightarrow x_{di}, i = 1, \dots, m$, as $t \rightarrow \infty$ for all $x_0 \in \mathbb{R}_+^n$. Furthermore, $u(t) \geq 0, t \geq 0$, and $x(t) \geq 0, t \geq 0$, for all $x_0 \in \mathbb{R}_+^n$.

Proof

First, define $K_u \triangleq \text{diag}[k_{u1}(t), \dots, k_{um}(t)]$ and $\phi_u(t) \triangleq [\phi_{u1}(t), \dots, \phi_{um}(t)]^T$, where

$$k_{ui}(t) = \begin{cases} 0 & \text{if } \hat{u}_i(t) < 0, \\ k_i(t) & \text{otherwise,} \end{cases} \quad i = 1, \dots, m \quad (41)$$

$$\phi_{ui}(t) = \begin{cases} 0 & \text{if } \hat{u}_i(t) < 0, \\ \phi_i(t) & \text{otherwise,} \end{cases} \quad i = 1, \dots, m \quad (42)$$

Now, note that with $u(t), t \geq 0$, given by (37) it follows from (11) that

$$\dot{x}(t) = Ax(t) + BK_u(t)(\hat{x}(t) - x_d) + B\phi_u(t), \quad x(0) = x_0, \quad t \geq 0 \quad (43)$$

or, equivalently, using (13),

$$\dot{x}(t) = A(x(t) - x_e) + BK_u(t)(\hat{x}(t) - x_d) + B(\phi_u(t) - u_e), \quad x(0) = x_0, \quad t \geq 0 \quad (44)$$

Furthermore, note that since A is essentially non-negative and asymptotically stable, it follows from Theorem 2.2 that there exists a positive diagonal matrix $P \triangleq \text{diag}[p_1, \dots, p_n]$ and a positive-definite matrix $R \in \mathbb{R}^{n \times n}$ such that

$$0 = A^T P + PA + R \quad (45)$$

To show Lyapunov stability of the closed-loop system (39), (40), and (44) consider the Lyapunov function candidate

$$V(x, K, \phi) = (x - x_e)^T P(x - x_e) + \text{tr}(K - K_g)^T Q^{-1}(K - K_g) + (\phi - u_e)^T \hat{Q}^{-1}(\phi - u_e) \quad (46)$$

or, equivalently,

$$V(x, K, \phi) = \sum_{i=1}^n p_i (x_i - x_{ei})^2 + \sum_{i=1}^m \frac{p_i b_i}{q_i} (k_i - k_{gi})^2 + \sum_{i=1}^m \frac{p_i b_i}{\hat{q}_i} (\phi_i - u_{ei})^2,$$

where

$$Q = \text{diag} \left[\frac{q_1}{p_1 b_1}, \dots, \frac{q_m}{p_m b_m} \right]$$

and

$$\hat{Q} = \text{diag} \left[\frac{\hat{q}_1}{p_1 b_1}, \dots, \frac{\hat{q}_m}{p_m b_m} \right]$$

Note that $V(x_e, K_g, u_e) = 0$ and, since P , Q , and \hat{Q} are positive definite, $V(x, K, \phi) > 0$ for all $(x, K, \phi) \neq (x_e, K_g, u_e)$. Furthermore, $V(x, K, \phi)$ is radially unbounded. Now, letting $x(t), t \geq 0$, denote the solution to (44) and using (39) and (40), it follows that the Lyapunov derivative along the closed-loop system trajectories is given by

$$\begin{aligned} \dot{V}(x(t), K(t), \phi(t)) &= 2(x(t) - x_e)^T P[A(x(t) - x_e) + BK_u(t)(\hat{x}(t) - x_d) + B(\phi_u(t) - u_e)] \\ &\quad + 2\text{tr}(K(t) - K_g)^T Q^{-1} \dot{K}(t) + 2(\phi(t) - u_e)^T \hat{Q}^{-1} \dot{\phi}(t) \\ &= -(x(t) - x_e)^T R(x(t) - x_e) + 2 \sum_{i=1}^m p_i b_i k_{ui}(t) (x_i(t) - x_{di})^2 \end{aligned}$$

$$\begin{aligned}
 &+ 2 \sum_{i=1}^m p_i b_i (x_i(t) - x_{di})(\phi_{ui}(t) - u_{ei}) + 2 \sum_{i=1}^m \frac{p_i b_i}{q_i} (k_i(t) - k_{gi}) \dot{k}_i(t) \\
 &+ 2 \sum_{i=1}^m \frac{p_i b_i}{\hat{q}_i} (\phi_i(t) - u_{ei}) \dot{\phi}_i(t) \\
 &= -(x(t) - x_e)^T R (x(t) - x_e) \\
 &+ 2 \sum_{i=1}^m p_i b_i \left[k_{ui}(t) (x_i(t) - x_{di})^2 + \frac{1}{q_i} (k_i(t) - k_{gi}) \dot{k}_i(t) \right] \\
 &+ 2 \sum_{i=1}^m p_i b_i \left[(x_i(t) - x_{di})(\phi_{ui}(t) - u_{ei}) + \frac{1}{\hat{q}_i} (\phi_i(t) - u_{ei}) \dot{\phi}_i(t) \right]. \tag{47}
 \end{aligned}$$

Now, for each $i \in \{1, \dots, m\}$ and for the two cases given in (39) and (40), the last two terms on the right-hand side of (47) give:

(i) If $\hat{u}_i(t) < 0$, then $k_{ui}(t) = 0, \phi_{ui}(t) = 0, \dot{k}_i(t) = 0$ and $\dot{\phi}_i(t) = 0$. Furthermore, since $\phi_i(t) \geq 0$ and $k_i(t) \leq 0$ for all $t \geq 0$, it follows from (38) that $\hat{u}_i(t) < 0$ only if $x_i(t) > x_{di}$ and hence

$$k_{ui}(t)(x_i(t) - x_{di})^2 + \frac{1}{q_i}(k_i(t) - k_{gi})\dot{k}_i(t) = 0$$

$$(x_i(t) - x_{di})(\phi_{ui}(t) - u_{ei}) + \frac{1}{\hat{q}_i}(\phi_i(t) - u_{ei})\dot{\phi}_i(t) = -(x_i(t) - x_{di})u_{ei} \leq 0$$

(ii) Otherwise, $k_{ui}(t) = k_i(t)$ and $\phi_{ui}(t) = \phi_i(t)$, and hence

$$k_{ui}(t)(x_i(t) - x_{di})^2 + \frac{1}{q_i}(k_i(t) - k_{gi})\dot{k}_i(t) = k_{gi}(x_i(t) - x_{di})^2 \leq 0$$

$$\begin{aligned}
 &(x_i(t) - x_{di})(\phi_{ui}(t) - u_{ei}) + \frac{1}{\hat{q}_i}(\phi_i(t) - u_{ei})\dot{\phi}_i(t) \\
 &= \begin{cases} -(x_i(t) - x_{di})u_{ei} \leq 0 & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{di} \\ 0 & \text{otherwise} \end{cases}
 \end{aligned}$$

Hence, it follows that in either case

$$\begin{aligned}
 \dot{V}(x(t), K(t), \phi(t)) &\leq -(x(t) - x_e)^T R (x(t) - x_e) \\
 &\leq 0, \quad t \geq 0, \tag{48}
 \end{aligned}$$

which proves that the solution $(x(t), K(t), \phi(t)) \equiv (x_e, K_g, u_e)$ to (39), (40), and (44) is Lyapunov stable. Furthermore, since $R > 0$ it follows from Theorem 2.2 of Reference [30] that $x(t) \rightarrow x_e$ as $t \rightarrow \infty$ for all $x \in \bar{\mathbb{R}}_+^n$.

Finally, $u(t) \geq 0, t \geq 0$, is a restatement of (37). Now, since $B \geq 0$ and $u(t) \geq 0, t \geq 0$, it follows from Proposition 2.4 that $x(t) \geq 0, t \geq 0$, for all $x_0 \in \bar{\mathbb{R}}_+^n$. \square

Remark 4.1

As in the case of Theorem 3.1, the conditions in Theorem 4.1 imply that $x(t) \rightarrow x_e$ as $t \rightarrow \infty$ and hence it follows from (39) and (40) that $(x(t), K(t), \phi(t)) \rightarrow \mathcal{M} \triangleq \{(x, K, \phi) \in \mathbb{R}^n \times \mathbb{R}^{m \times m} \times \mathbb{R}^m : x = x_e, \dot{K} = 0, \dot{\phi} = 0\}$ as $t \rightarrow \infty$.

It is important to note that the adaptive control law (37), (39), and (40) does *not* require the explicit knowledge of the constant vector u_e , even though Theorem 4.1 requires the existence of $x_u \in \mathbb{R}_+^{n-m}$ and $u_e \in \mathbb{R}_+^m$ such that condition (13) holds. Furthermore, the control input $u_i(t)$, $t \geq 0$, is always non-negative regardless of the values of $x_i(t)$, $k_i(t)$, and $\phi_i(t)$, $t \geq 0$, $i = 1, \dots, m$, which ensures that the closed-loop plant states remain non-negative by Proposition 2.4. Finally, it should be noted that since A is asymptotically stable, the adaptive gains $k_i(t)$, $t \geq 0$, $i = 1, \dots, m$, only change the performance of the closed-loop system and do not destroy stability even when we set $k_i(t) = 0, t \geq 0$, with $k_i(0) \leq 0, i = 1, \dots, m$.

5. ADAPTIVE CONTROL FOR GENERAL ANESTHESIA

The potential clinical applications of adaptive control for pharmacology in general, and anesthesia and critical care medicine in particular, are clearly apparent. Specifically, monitoring and controlling the depth of anesthesia in surgery is of particular importance. Propofol is an intravenous anesthetic that has been used for both induction and maintenance of general anesthesia [32]. A simple yet effective patient model for the disposition of propofol 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 [33, 34]. The three-compartment mammillary system 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 the other various tissue groups of the body. A mass balance for the whole compartmental system yields

$$\dot{x}_1(t) = -(a_{11} + a_{21} + a_{31})x_1(t) + a_{12}x_2(t) + a_{13}x_3(t) + u(t), \quad x_1(0) = x_{10}, \quad t \geq 0 \quad (49)$$

$$\dot{x}_2(t) = a_{21}x_1(t) - a_{12}x_2(t), \quad x_2(0) = x_{20} \quad (50)$$

$$\dot{x}_3(t) = a_{31}x_1(t) - a_{13}x_3(t), \quad x_3(0) = x_{30} \quad (51)$$

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, $a_{ij} \geq 0, i \neq j, i, j = 1, 2, 3$, are the rate constants in

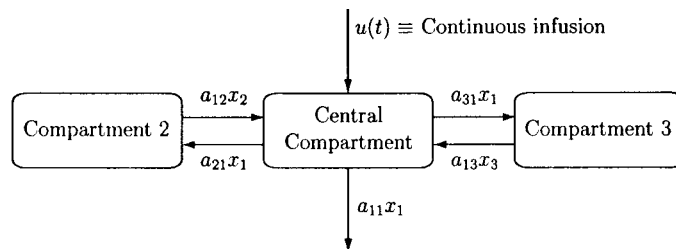


Figure 1. Three-compartment mammillary model for disposition of propofol.

min^{-1} for drug transfer between compartments, and $a_{11} \geq 0$ in min^{-1} is the rate constant for elimination from the central compartment. Even though these transfer and loss coefficients are non-negative, they can be uncertain due to patient gender, weight, pre-existing disease, age, and concomitant medication. Hence, adaptive control for propofol regulation during surgery can significantly improve the outcomes for drug administration over manual control.

It has been reported in Reference [35] that a $2.5\text{--}6\ \mu\text{g}/\text{m}\ell$ 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 $4\ \mu\text{g}/\text{m}\ell$ 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 [34], V_c can be approximately calculated by $V_c = (0.159\ \ell/\text{kg})(M\ \text{kg})$, where M is the weight (mass) in kilograms of the patient. In our control design we assume $M = 70\ \text{kg}$ so that the desired level of propofol mass in the central component is given by $x_{d1} = (4\ \mu\text{g}/\text{m}\ell)(0.159\ \ell/\text{kg})(70\ \text{kg}) = 44.52\ \text{mg}$.

Next, note that (49)–(51) can be written in state space form (11) with $x = [x_1, x_2, x_3]^T$,

$$A = \begin{bmatrix} -(a_{11} + a_{21} + a_{31}) & a_{12} & a_{13} \\ a_{21} & -a_{12} & 0 \\ a_{31} & 0 & -a_{13} \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \quad (52)$$

Now, it can be shown that for $x_{d1}/V_c = 4\ \mu\text{g}/\text{m}\ell$, all the conditions of Theorem 4.1 are satisfied. Hence, it follows from Theorem 4.1 that the adaptive dynamic feedback controller (37) with update laws (39), (40) guarantees that $x_1(t) \rightarrow x_{d1}$ as $t \rightarrow \infty$ for any (uncertain) non-negative values of the transfer and loss coefficients. To illustrate the robustness properties of the proposed adaptive control law, we use the average set of pharmacokinetic parameters given in Reference [33] for 29 patients requiring general anesthesia for non-cardiac surgery. For our design we switch from Set A to Set B given in Table I at $t = 25\ \text{min}$. With $q_1 = 1000\ \text{g}^{-2}\ \text{min}^{-2}$, $\hat{q}_1 = 0.5\ \text{min}^{-2}$, and initial conditions $x(0) = [0, 0, 0]^T\ \text{g}$, $k_f(0) = 0\ \text{min}^{-1}$, and $\phi_1(0) = 0.01\ \text{g}/\text{min}^{-1}$, Figure 2 shows the masses of propofol in all three compartments versus time. Figure 3 shows the propofol concentration in the central compartment and the control signal (propofol infusion rate) versus time. Finally, Figure 4 shows the adaptive gain history versus time.

In the above simulations, the adaptive controller was designed using a pharmacokinetic model (a model describing drug concentrations as a function of time and dose) for the disposition of propofol. 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

Table I. Pharmacokinetic parameters [33].

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

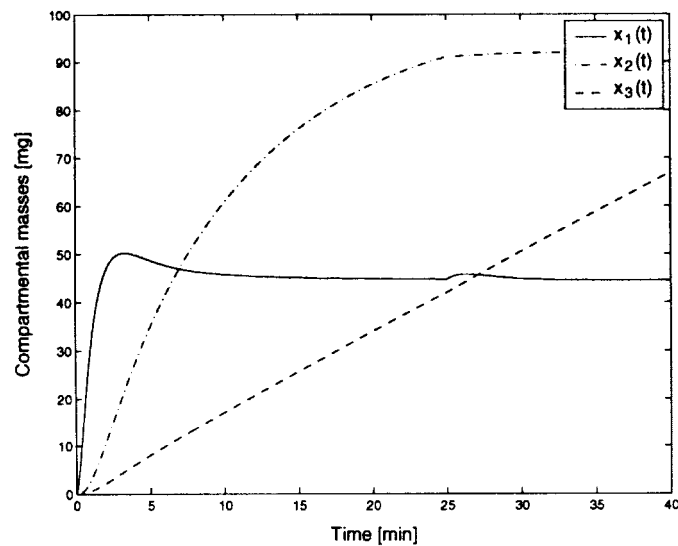


Figure 2. Compartmental masses versus time.

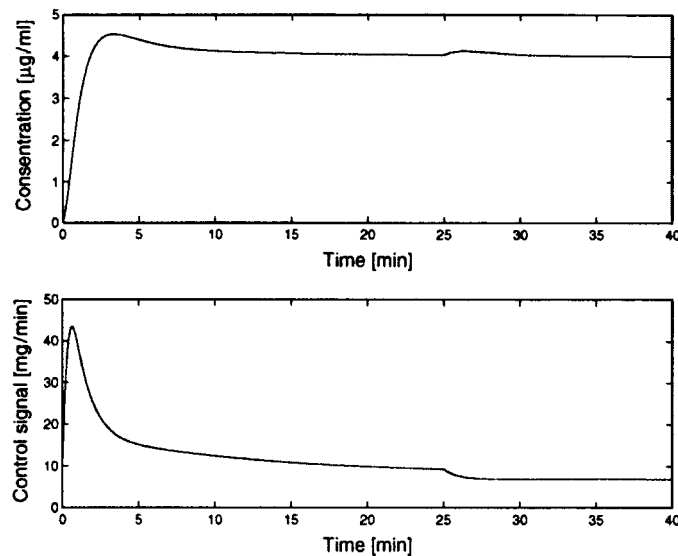


Figure 3. Drug concentration in the central compartment and control signal (infusion rate) versus time.

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 [36]. Since electroencephalography provides real-time monitoring of the central nervous system activity,

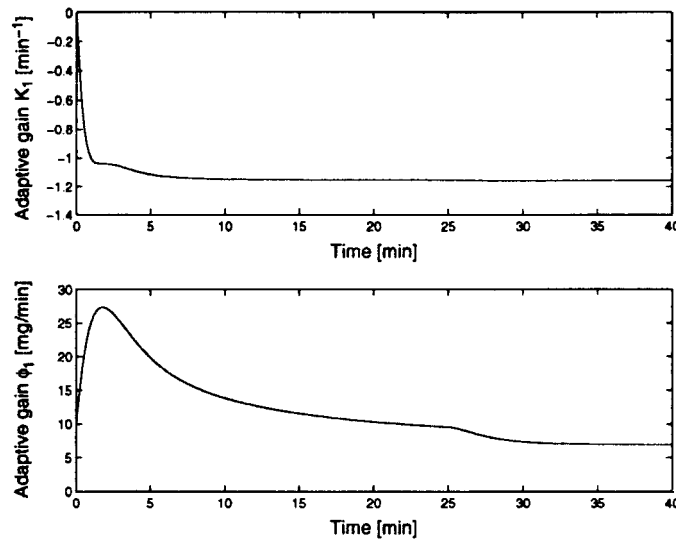


Figure 4. Adaptive gain history versus time.

it can be used to quantify levels of consciousness and hence is amenable for feedback (closed-loop) control in general anesthesia. Recently, a new EEG indicator, the Bispectral Index (BIS), has been proposed as a measure of anesthetic effect [37]. This index quantifies the non-linear relationships between the component frequencies in the electroencephalogram, as well as analyzing their phase and amplitude. The BIS signal is a non-linear monotonically decreasing function of the depth of anesthesia and is given by

$$BIS(c_{eff}(t)) = BIS_0 \left(1 - \frac{c_{eff}^\gamma(t)}{c_{eff}^\gamma(t) + EC_{50}^\gamma} \right) \quad (53)$$

where BIS_0 denotes the baseline (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 non-linearity in (53). Here, the effect site compartment is introduced as a correlate between the central compartment concentration and the central nervous system concentration [38]. The effect site compartment concentration is related to the concentration in the central compartment by the first-order model

$$\dot{c}_{eff}(t) = a_{eff}(x_1(t)/V_c - c_{eff}(t)), \quad c_{eff}(0) = x_1(0), \quad t \geq 0, \quad (54)$$

where a_{eff} in min^{-1} is a positive time constant. Assuming $x_1(0) = 0$, it follows that

$$c_{eff}(t) = \int_0^t e^{-a_{eff}(t-s)} a_{eff} x_1(s) / V_c ds \quad (55)$$

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

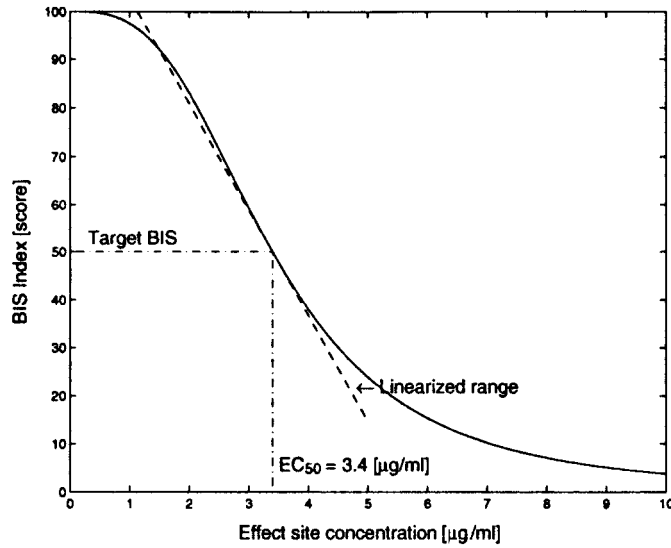


Figure 5. BIS Index versus effect site concentration.

signal and an EEG signal of a fully conscious patient; while the range between 40 and 60 indicates a moderate hypnotic state [39].

In the following numerical simulation we set $EC_{50} = 3.4 \mu g/ml$, $\gamma = 3$, and $BIS_0 = 100$, so that the BIS signal is shown in Figure 5. The target (desired) BIS value, BIS_{target} , is set at 50. In this case, the linearized BIS function about the target BIS value is given by

$$\begin{aligned}
 BIS(c_{eff}(t)) &\simeq BIS(EC_{50}) - BIS_0 \cdot EC_{50}^\gamma \cdot \left. \frac{\gamma c_{eff}^{\gamma-1}}{(c_{eff}^\gamma + EC_{50}^\gamma)^2} \right|_{c_{eff}=EC_{50}} \cdot (c_{eff}(t) - EC_{50}) \\
 &= 125 - 22.06c_{eff}(t)
 \end{aligned} \tag{56}$$

Furthermore, for simplicity of exposition, we assume that the effect site compartment equilibrates instantaneously with the central compartment; that is, we assume that $a_{eff} \rightarrow \infty$, so that (55) reduces to $c_{eff}(t) = x_1(t)/V_c, t \geq 0$. Now, using the adaptive feedback controller

$$u_1(t) = \max\{0, \hat{u}_1(t)\} \tag{57}$$

where

$$\hat{u}_1(t) = -k_1(t)(BIS(c_{eff}(t)) - BIS_{target}) + \phi_1(t) \tag{58}$$

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

$$\dot{k}_1(t) = \begin{cases} 0 & \text{if } \hat{u}_1(t) < 0 \\ -q_{BIS_1}(BIS(c_{eff}(t)) - BIS_{target})^2 & \text{otherwise} \end{cases} \quad k_1(0) \leq 0, \tag{59}$$

$$\dot{\phi}_1(t) = \begin{cases} 0 & \text{if } \phi_1(t) = 0 \text{ and } BIS(c_{eff}(t)) > BIS_{\text{target}} \\ \hat{q}_{BIS_1} BIS(c_{eff}(t)) - BIS_{\text{target}} & \text{otherwise} \end{cases} \quad \phi_1(0) \geq 0, \quad (60)$$

where q_{BIS_1} and \hat{q}_{BIS_1} are arbitrary positive constants, it follows from Theorem 4.1 that $BIS(c_{eff}(t)) \rightarrow BIS_{\text{target}}$ as $t \rightarrow \infty$ for any (uncertain) non-negative values of the transfer and loss coefficients in the range of c_{eff} where the linearized BIS equation (56) is valid. It is important to note that during actual surgery the BIS signal is obtained directly from the EEG and not (53). Furthermore, since our adaptive controller only requires the error signal $BIS(c_{eff}(t)) - BIS_{\text{target}}$ over the linearized range of (53), we do not require knowledge of the slope of the linearized equation (56), nor do we require knowledge of the parameters γ and EC_{50} . Once again, 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 EC_{50} and γ are switched from $3.4 \mu\text{g/ml}$ and 3 to $4.0 \mu\text{g/ml}$ and 2 , respectively. Here we consider non-cardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $q_{BIS_1} = 1 \times 10^{-6} \text{ g/min}^2$, $q_{BIS_2} = 1 \times 10^{-3} \text{ g/min}^2$, and initial conditions $x(0) = [0, 0, 0]^T \text{ g}$, $k_1(0) = 0 \text{ g/min}$, and $\phi_1 = 0.01 \text{ g/min}$, Figure 6 shows the masses of propofol in all three compartments versus time. Figure 7 shows the BIS Index versus time. Figure 8 shows the propofol concentration in the central compartment and the control signal (propofol infusion rate) versus time. Finally, Figure 9 shows the adaptive gain history versus time.

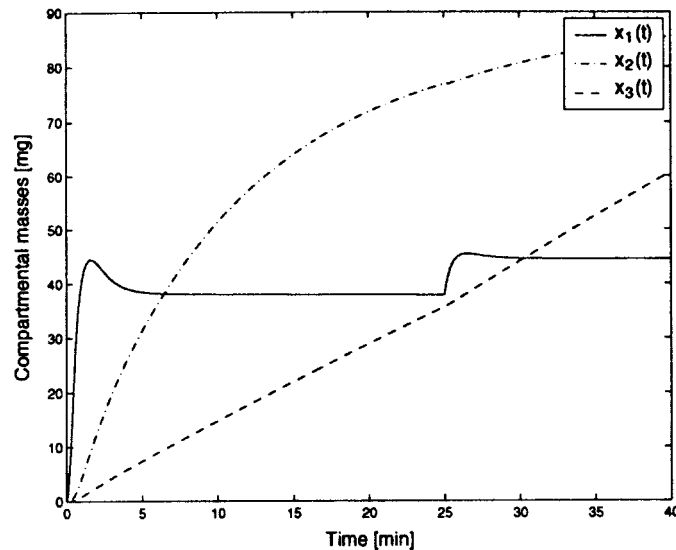


Figure 6. Compartmental masses versus time.

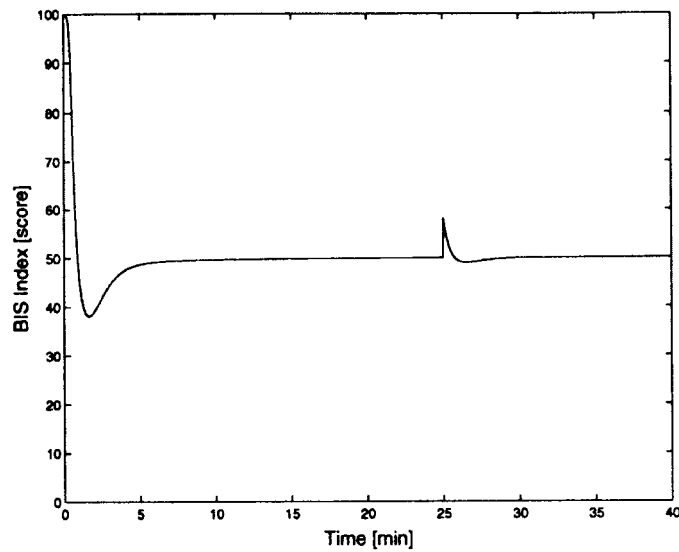


Figure 7. BIS Index versus time.

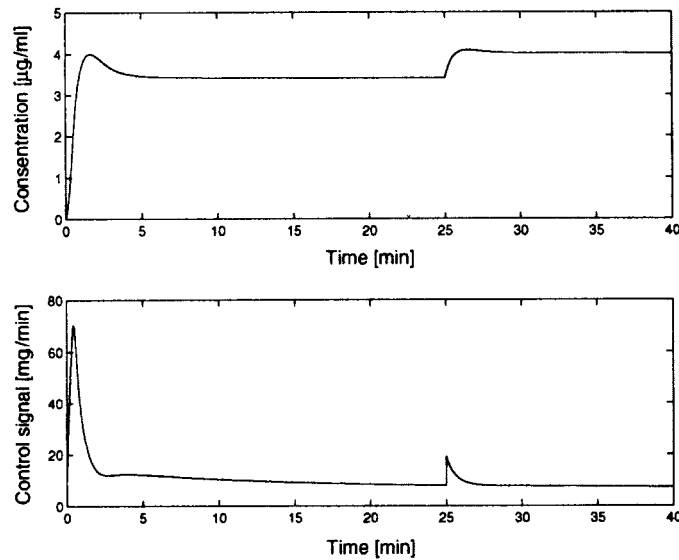


Figure 8. Drug concentration in the central compartment and control signal (infusion time rate) versus time.

6. CONCLUSION

Non-negative and compartmental systems are widely used to capture system dynamics involving the interchange of mass and energy between homogeneous subsystems or compartments. Thus,

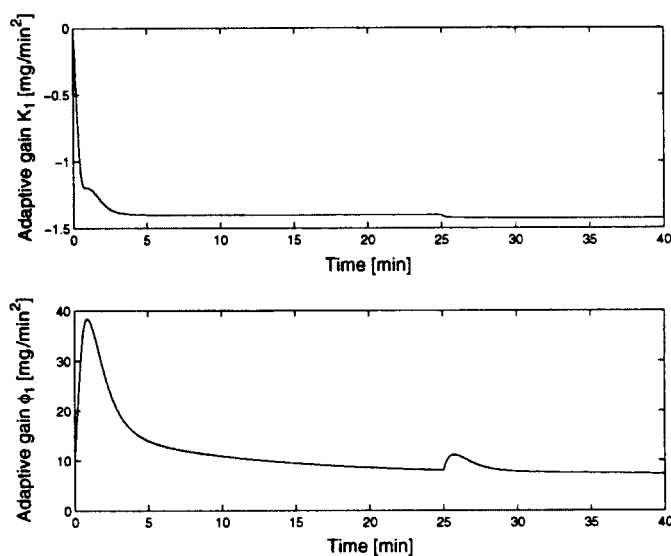


Figure 9. Adaptive gain history versus time.

it is not surprising that non-negative and compartmental models are remarkably effective in describing the dynamical behavior of biological and physiological systems. In this paper, we developed an adaptive control framework for adaptive set-point regulation of linear uncertain non-negative and compartmental systems. Using Lyapunov methods the proposed framework was shown to guarantee partial asymptotic set-point stability of the closed-loop system while additionally guaranteeing the non-negativity of the closed-loop system states associated with the plant dynamics. Finally, using a three-compartment mammillary patient model for the disposition of propofol, the proposed adaptive control framework was used to monitor and control a desired constant level of depth of anesthesia for non cardiac surgery. Even though measurement noise was not addressed in our framework, it should be noted that EEG signals may have as much as 10% variation due to noise. In particular, the BIS signal may be corrupted by electromyographic noise; that is, signals emanating from muscle rather than the central nervous system. Clinical implementation of the proposed algorithm would thus have to include muscle paralysis to minimize the effects of electromyographic noise. Extensions of the proposed adaptive control framework that directly address robustness to noise disturbances in the spirit of [40] will be addressed in a future paper.

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