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Adaptive control for nonlinear compartmental dynamical systems with applications to clinical pharmacology ☆

Wassim M. Haddad[a,*], Tomohisa Hayakawa[b], James M. Bailey[c]

[a] *School of Aerospace Engineering, Georgia Institute of Technology, Atlanta, GA 30332-0150, United States*
[b] *CREST, Japan Science and Technology Agency, Saitama 332-0012, Japan*
[c] *Department of Anesthesiology, Northeast Georgia Medical Center, Gainsville, GA 30503, United States*

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Abstract

There are significant potential clinical applications of adaptive control for pharmacology in general, and anesthesia and critical care unit medicine in particular. Specifically, monitoring and controlling the levels of consciousness in surgery are of particular importance. Nonnegative and compartmental models provide a broad framework for biological and physiological systems, including clinical pharmacology, and are well suited for developing models for closed-loop control of drug administration. In this paper, we develop a direct adaptive control framework for nonlinear uncertain nonnegative and compartmental systems with nonnegative control inputs. The proposed framework is Lyapunov-based and guarantees partial asymptotic set-point regulation, that is, asymptotic set-point regulation 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 nonnegative orthant of the state space. Finally, a numerical example involving the infusion of the anesthetic drug propofol for maintaining a desired constant level of consciousness for noncardiac surgery is provided to demonstrate implementation of the proposed approach.

Keywords: Adaptive control; Nonlinear compartmental systems; Nonnegative control; Set-point regulation; Automated anesthesia; Electroencephalography; Bispectral index

1. Introduction

Nonnegative and compartmental models provide a broad framework for biological and physiological systems, including clinical pharmacology, and are well suited for the problem of closed-loop control of drug administration. Specifically, nonnegative and compartmental dynamical systems [15] are composed of homogeneous interconnected subsystems (or compartments) which exchange variable nonnegative quantities of material with conservation laws describing transfer, accumulation, and elimination between the compartments and the environment. It thus follows from physical considerations that the state trajectory of such systems remains in the nonnegative orthant of the state space for nonnegative initial conditions [10]. Using nonnegative 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. Furthermore, the remainder of the state associated with the adaptive controller gains is shown to be Lyapunov stable. In addition, the adaptive controllers are constructed *without* requiring knowledge of

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* Corresponding author. Tel.: +1 404 894 1078; fax: +1 404 894 2760.
E-mail addresses: wm.haddad@aerospace.gatech.edu (W.M. Haddad), tomohisa_hayakawa@ipc.i.u-tokyo.ac.jp (T. Hayakawa), james.bailey@nghs.com (J.M. Bailey).

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the system dynamics while providing a nonnegative control (source) input for robust stabilization with respect to the nonnegative orthant.

Administration of drugs to produce general anesthesia has traditionally been guided by clinical evaluation. However, the clinical measures of depth of anesthesia are imperfect, primarily since the most reliable, purposeful movement in response to noxious stimulus is masked by the concomitant administration of paralytic agents, given to improve operating conditions for the surgeon. There has been a long-standing interest in the use of the electroencephalogram (EEG) as an objective, quantitative measure of consciousness that can be used as a performance variable for closed-loop control of anesthesia. Closed-loop control in clinical pharmacology may improve the quality of drug administration, lessening the dependence of patient outcome on the skills of the clinician [2].

Previous efforts to develop closed-loop control of general intravenous anesthesia have used a proportional-integral-derivative control algorithm and linear adaptive control algorithms based on pharmacokinetic/pharmacodynamic models [1,23,26,29]. Intravenous anesthesia has also been delivered by a closed-loop controller that uses auditory-evoked responses and cardiovascular responses as the control variables with a fuzzy-logic control algorithm [21]. Adaptive algorithms are promising since the relationships between drug dose and blood concentration (pharmacokinetics) and between blood concentration and physiological effect (pharmacodynamics) vary widely among individual subjects [2]. Previous model-based algorithms have assumed either a fixed pharmacokinetic model or a fixed pharmacodynamic model [26,29].

In this paper, we present a less restrictive direct adaptive control framework that accounts for interpatient and intrapatient pharmacokinetic and pharmacodynamic variability. In particular, building on the adaptive control framework for *linear* compartmental models presented in [12], we develop a direct adaptive control framework for adaptive set-point regulation of *nonlinear* uncertain nonnegative and compartmental systems. We illustrate the implementation of the adaptive controller with an example of closed-loop control of an intravenous anesthetic, propofol, that is characterized by a new nonlinear pharmacokinetic and pharmacodynamic model. A related but different adaptive control framework is given in [11]. Specifically, unlike the results of the present paper which exclusively deal with the specific problem of clinical pharmacology, wherein the adaptive control algorithm is tailored to compartmental systems of a certain structure, the results in [11] address unstable nonnegative dynamical systems. An additional crucial difference between the present framework and [11] is that the proposed adaptive controller guarantees that the control signal remains nonnegative, which is critical for addressing active control of drug dosing. These key differences result in disjoint controller architectures in the sense that neither result can be obtained as a special case of the other. Finally, it is important to note that even though adaptive control for nonnegative systems has received little attention in the literature, nonadaptive control for nonnegative dynamical systems has been addressed in the literature. Notable contributions include [3,4,7,14].

2. Mathematical preliminaries

In this section we introduce notation, several definitions, and some key results concerning nonlinear nonnegative dynamical systems [5,10] that are necessary for developing the main results of this paper. Specifically, for $x \in \mathbb{R}^n$ we write $x \geqslant \geqslant 0$ (resp., $x \gg 0$) to indicate that every component of x is nonnegative (resp., positive). In this case, we state that x is *nonnegative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n\times m}$ is *nonnegative* or *positive* if every entry of A is nonnegative or positive, respectively, which is written as $A \geqslant \geqslant 0$ or $A \gg 0$, respectively. 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 $x \geqslant \geqslant 0$ and $x \gg 0$. Finally, we state that a real function $u : [0, T] \to \mathbb{R}^m$ is a *nonnegative* (resp., *positive*) *function* if $u(t) \geqslant \geqslant 0$ (resp., $u(t) \gg 0$) on the interval $[0, T]$.

In this paper we consider controlled nonlinear dynamical systems of the form

$$\dot{x}(t) = f(x(t)) + G(x(t))u(t), \quad x(0) = x_0, \quad t \geqslant 0, \tag{1}$$

where $x(t) \in \mathbb{R}^n$, $t \geqslant 0$, $u(t) \in \mathbb{R}^m$, $t \geqslant 0$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is Lipschitz continuous and satisfies $f(0) = 0$, $G : \mathbb{R}^n \to \mathbb{R}^{n\times m}$ is continuous, and $u : [0, \infty) \to \mathbb{R}^m$ is measurable and locally bounded.

The following definitions and proposition are needed for the main result of the paper.

Definition 2.1 (*Haddad and Chellaboina [10]*). Let $f = [f_1, \ldots, f_n]^{\mathrm{T}} : \mathscr{D} \to \mathbb{R}^n$, where $\mathscr{D}$ is an open subset of $\mathbb{R}^n$ that contains $\overline{\mathbb{R}}^n_+$. Then, f is *essentially nonnegative* if $f_i(x) \geqslant 0$, for all $i = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}^n_+$ such that $x_i = 0$, where x_i denotes the ith element of x.

Definition 2.2. The nonlinear dynamical system given by (1) is *nonnegative* if for every $x(0) \in \overline{\mathbb{R}}^n_+$ and $u(t) \geqslant \geqslant 0$, $t \geqslant 0$, the solution $x(t)$, $t \geqslant 0$, to (1) is nonnegative.

Proposition 2.1 (*Haddad and Chellaboina [10]*). *The nonlinear dynamical system given by* (1) *is nonnegative if* $f : \mathbb{R}^n \to \mathbb{R}^n$ *is essentially nonnegative and* $G(x) \geqslant \geqslant 0$, $x \in \overline{\mathbb{R}}^n_+$.

It follows from Proposition 2.1 that a nonnegative input signal $G(x(t))u(t)$, $t \geqslant 0$, is sufficient to guarantee the nonnegativity of the state of (1).

3. Adaptive control for nonlinear nonnegative uncertain dynamical systems

In this section, we consider the problem of characterizing adaptive feedback control laws for nonlinear nonnegative and compartmental uncertain dynamical systems to achieve *set-point* regulation in the nonnegative orthant. Specifically, we consider the controlled nonlinear uncertain system $\mathscr{G}$ given by (1), where $x(t) \in \mathbb{R}^n$, $t \geqslant 0$, is the state vector, $u(t) \in \mathbb{R}^m$, $t \geqslant 0$, is the control input, $f : \mathbb{R}^n \to \mathbb{R}^n$ is an *unknown* essentially nonnegative function and satisfies $f(0) = 0$, and $G : \mathbb{R}^n \to \mathbb{R}^{n\times m}$ is an *unknown* nonnegative input matrix function. The control input $u(\cdot)$ in (1) is restricted to the class of *admissible controls* consisting of measurable and locally bounded functions such that $u(t) \in \mathbb{R}^m$, $t \geqslant 0$. Furthermore, for the nonlinear system $\mathscr{G}$ we assume that the properties required for the existence and uniqueness of solutions are satisfied, that is, $f(\cdot)$, $G(\cdot)$, and $u(\cdot)$ satisfy sufficient regularity conditions such that (1) has a unique solution forward in time.

As discussed in the Introduction, control (source) inputs of drug delivery systems for physiological processes are usually constrained to be nonnegative as are the system states. Hence, in this paper we develop adaptive control laws for nonnegative systems with nonnegative control inputs. Specifically, for a given desired set point $x_{\mathrm{e}} \in \overline{\mathbb{R}}^n_+$, our aim is to design a control input $u(t)$, $t \geqslant 0$, such that $\lim_{t\to\infty}\|x(t) - x_{\mathrm{e}}\| = 0$. We assume that control inputs are injected directly into m separate compartments and the input matrix function is given by

$$G(x) = \begin{bmatrix} B_{\mathrm{u}} G_{\mathrm{n}}(x) \\ 0_{(n-m)\times m} \end{bmatrix}, \tag{2}$$

where $B_{\mathrm{u}} = \mathrm{diag}[b_1, \ldots, b_m]$ is an *unknown* nonnegative diagonal matrix and $G_{\mathrm{n}} = \mathrm{diag}[g_{\mathrm{n}_1}(x), \ldots, g_{\mathrm{n}_m}(x)]$, where $g_{\mathrm{n}i} : \overline{\mathbb{R}}^n_+ \to \mathbb{R}_+$, $i = 1, \ldots, m$, is a known nonnegative diagonal matrix function. For compartmental systems this assumption is not restrictive since control inputs correspond to control inflows to each individual compartment. For the statement of the next result we assume that for a given $x_{\mathrm{e}} \in \overline{\mathbb{R}}^n_+$, there exists a nonnegative vector $u_{\mathrm{e}} \in \overline{\mathbb{R}}^m_+$ such that

$$0 = f(x_{\mathrm{e}}) + \hat{B} u_{\mathrm{e}}, \tag{3}$$

where $\hat{B} = [B_{\mathrm{u}}, 0_{m\times(n-m)}]^{\mathrm{T}}$, and the equilibrium point x_{e} of (1) is globally asymptotically stable for all $x_0 \in \overline{\mathbb{R}}^n_+$ with $G_{\mathrm{n}}(x(t))u(t) \equiv u_{\mathrm{e}}$.

Theorem 3.1. *Consider the nonlinear uncertain system $\mathscr{G}$ given by* (1) *where $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative and $G : \mathbb{R}^n \to \mathbb{R}^{n\times m}$ is nonnegative and is given by* (2). *Assume that there exist continuously differentiable functions $V_{s_i} : \mathbb{R} \to \mathbb{R}$, $i = 1, \ldots, m$, and $\hat{V}_{\mathrm{s}} : \mathbb{R}^{n-m} \to \mathbb{R}$, Lipschitz continuous functions $F_i : \mathbb{R}^n \to \mathbb{R}^{s_i}$, $i = 1, \ldots, m$, and a continuous function $\ell : \mathbb{R}^n \to \mathbb{R}^p$ such that $V_{\mathrm{s}}(\cdot)$ is positive definite, radially unbounded, $V_{\mathrm{s}}(0) = 0$, $\ell(0) = 0$, $F_i(0) = 0$, $i = 1, \ldots, m$, and, for all $e \in \mathbb{R}^n$,*

$$V_{\mathrm{s}i}'(e_i) F_i(e) \geqslant\geqslant 0, \quad i = 1, \ldots, m, \tag{4}$$

$$0 = V_{\mathrm{s}}'(e) f_{\mathrm{e}}(e) + \ell^{\mathrm{T}}(e)\ell(e), \tag{5}$$

where $V_{\mathrm{s}}(e) = V_{s_1}(e_1) + \cdots + V_{s_m}(e_m) + \hat{V}_{\mathrm{s}}(e_{m+1}, \ldots, e_n)$ and $f_{\mathrm{e}}(e) \triangleq f(e + x_{\mathrm{e}}) - f(x_{\mathrm{e}})$. Furthermore, let q_i and $\hat{q}_i$, $i = 1, \ldots, m$, be positive constants. Then the adaptive feedback control law

$$u_i(t) = \max\{0, \hat{u}_i(t)\}, \quad i = 1, \ldots, m, \tag{6}$$

where

$$\hat{u}_i(t) = g_{\mathrm{n}_i}^{-1}(x(t)) k_i^{\mathrm{T}}(t) F_i(x(t) - x_{\mathrm{e}}) + g_{\mathrm{n}_i}^{-1}(x(t))\phi_i(t), \quad i = 1, \ldots, m, \tag{7}$$

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

$$\dot{k}_i^{\mathrm{T}}(t) = \begin{cases} 0 & \text{if } \hat{u}_i(t) < 0, \\ -\frac{q_i}{2} V_{\mathrm{s}i}'(x_i(t) - x_{e_i}) & \\ \quad \times F_i^{\mathrm{T}}(x(t) - x_{\mathrm{e}}) & \text{otherwise}, \end{cases} \qquad k_i(0) \leqslant\leqslant 0, \ i = 1, \ldots, m, \tag{8}$$

$$\dot{\phi}_i(t) = \begin{cases} 0 & \text{if } \phi_i(t) = 0 \\ & \text{and } V_{\mathrm{s}i}'(x_i(t) - x_{e_i}) \geqslant 0, \\ & \text{or if } \hat{u}_i(t) \leqslant 0, \\ -\frac{\hat{q}_i}{2} V_{\mathrm{s}i}' & \\ \quad \times (x_i(t) - x_{e_i}), & \text{otherwise}, \end{cases} \qquad \phi_i(0) = 0, \ i = 1, \ldots, m, \tag{9}$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, K_g, u_{\mathrm{e}})$, where $K(t) \triangleq \text{block-diag}[k_1^{\mathrm{T}}(t), \ldots, k_m^{\mathrm{T}}(t)]$ and $K_g \triangleq \text{block-diag}[k_{g_1}^{\mathrm{T}}, \ldots, k_{g_m}^{\mathrm{T}}] \leqslant\leqslant 0$, of the closed-loop system given by (1), (6), (8), *and* (9) *is Lyapunov stable. If, in addition, $\ell^{\mathrm{T}}(e)\ell(e) > 0$, $e \in \mathbb{R}^n$, $e \neq 0$, then $x(t) \to x_{\mathrm{e}}$ as $t \to \infty$ for all $x_0 \in \overline{\mathbb{R}}^n_+$. Furthermore, $u(t) \geqslant\geqslant 0$, $t \geqslant 0$, and $x(t) \geqslant\geqslant 0$, $t \geqslant 0$, for all $x_0 \in \overline{\mathbb{R}}^n_+$.*

Proof. First, define $e(t) \triangleq x(t) - x_e$, $F(e) \triangleq [F_1^T(e), \ldots, F_m^T(e)]^T$, $K_u(t) \triangleq$ block-diag $[k_{u_1}^T(t), \ldots, k_{u_m}^T(t)]$, and $\phi_u(t) \triangleq [\phi_{u_1}(t), \ldots, \phi_{u_m}(t)]^T$, where

$$k_{u_i}(t) = \begin{cases} 0 & \text{if } \hat{u}_i(t) \leqslant 0, \\ k_i(t) & \text{otherwise,} \end{cases} \quad i = 1, \ldots, m, \tag{10}$$

$$\phi_{u_i}(t) = \begin{cases} 0 & \text{if } \hat{u}_i(t) \leqslant 0, \\ \phi_i(t) & \text{otherwise,} \end{cases} \quad i = 1, \ldots, m. \tag{11}$$

Now, note that with $u(t)$, $t \geqslant 0$, given by (6) it follows from (1) that

$$\dot{x}(t) = f(x(t)) + \hat{B}K_u(t)F(x(t) - x_e) + \hat{B}\phi_u(t), \quad x(0) = x_0, \quad t \geqslant 0 \tag{12}$$

or, equivalently, using (3),

$$\dot{e}(t) = f_e(e(t)) + \hat{B}K_u(t)F(x(t) - x_e) + \hat{B}(\phi_u(t) - u_e), \quad e(0) = x_0 - x_e, \ t \geqslant 0. \tag{13}$$

To show Lyapunov stability of the closed-loop system (8), (9), and (13) consider the Lyapunov function candidate

$$V(e, K, \phi) = V_s(e) + \operatorname{tr}(K - K_g)^T Q^{-1}(K - K_g) + (\phi - u_e)^T \hat{Q}^{-1}(\phi - u_e) \tag{14}$$

or, equivalently,

$$V(e, K, \phi) = V_s(e) + \sum_{i=1}^{m} \frac{b_i}{q_i}(k_i - k_{g_i})^T(k_i - k_{g_i}) + \sum_{i=1}^{m} \frac{b_i}{\hat{q}_i}(\phi_i - u_{e_i})^2, \tag{15}$$

where

$$Q = \left[\frac{q_1}{b_1}, \ldots, \frac{q_m}{b_m}\right],$$
$$\hat{Q} = \operatorname{diag}\left[\frac{\hat{q}_1}{b_1}, \ldots, \frac{\hat{q}_m}{b_m}\right].$$

Note that $V(0, K_g, u_e)=0$ and, since $V_s(\cdot)$, Q, and $\hat{Q}$ are positive definite, $V(e, K, \phi) > 0$ for all $(e, K, \phi) \neq (0, K_g, u_e)$. Furthermore, $V(e, K, \phi)$ is radially unbounded. Now, letting $e(t)$, $t \geqslant 0$, denote the solution to (13) and using (8) and (9), it follows that the Lyapunov derivative along the closed-loop system trajectories is given by

$$\begin{aligned}
\dot{V}(e(t), K(t), \phi(t)) &= V_s'(e(t))[f_e(e(t)) + \hat{B}K_u(t)F(x(t) - x_e) + \hat{B}(\phi_u(t) - u_e)] \\
&\quad + 2\operatorname{tr}(K(t) - K_g)^T Q^{-1}\dot{K}(t) \\
&\quad + 2(\phi(t) - u_e)^T \hat{Q}^{-1}\dot{\phi}(t) \\
&= -\ell^T(e(t))\ell(e(t)) \\
&\quad + \sum_{i=1}^{m} V_{s_i}'(e_i(t))b_i k_{u_i}^T(t)F_i(e(t)) \\
&\quad + \sum_{i=1}^{m} b_i V_{s_i}'(e_i(t))(\phi_{u_i}(t) - u_{e_i}) \\
&\quad + \sum_{i=1}^{m} \frac{2b_i}{q_i}\dot{k}_i^T(t)(k_i(t) - k_{g_i}) \\
&\quad + \sum_{i=1}^{m} \frac{2b_i}{\hat{q}_i}(\phi_i(t) - u_{e_i})\dot{\phi}_i(t) \\
&= -\ell^T(e(t))\ell(e(t)) \\
&\quad + \sum_{i=1}^{m} b_i \left[V_{s_i}'(e_i(t))k_{u_i}^T(t)F_i(e(t)) + \frac{2}{q_i}\dot{k}_i^T(t)(k_i(t) - k_{g_i})\right] \\
&\quad + \sum_{i=1}^{m} b_i \left[V_{s_i}'(e_i(t))(\phi_{u_i}(t) - u_{e_i}) + \frac{2}{\hat{q}_i}(\phi_i(t) - u_{e_i})\dot{\phi}_i(t)\right].
\end{aligned} \tag{16}$$

For each $i \in \{1, \ldots, m\}$ and for the two cases given in (8) and (9), the last two terms on the right-hand side of (16) give the following:

(i) If $\hat{u}_i(t) \leqslant 0$, then $k_{u_i}(t) = 0$, $\phi_{u_i}(t) = 0$, $\dot{k}_i(t) = 0$ and $\dot{\phi}_i(t) = 0$. Furthermore, since $\phi_i(t) \geqslant 0$ and $k_i(t) \leqslant \leqslant 0$ for all $t \geqslant 0$, it follows from (7) that $\hat{u}_i(t) \leqslant 0$ only if $F_i(x(t) - x_e) \geqslant \geqslant 0$ which implies $V_{s_i}'(e_i(t)) \geqslant 0$ by (4), and hence,

$$V_{s_i}'(e_i(t))k_{u_i}^T(t)F_i(e(t)) + \frac{2}{q_i}\dot{k}_i^T(t)(k_i(t) - k_{g_i}) = 0,$$

$$V_{s_i}'(e_i(t))(\phi_{u_i}(t) - u_{e_i}) + \frac{2}{\hat{q}_i}(\phi_i(t) - u_{e_i}) \times \dot{\phi}_i(t) = -V_{s_i}'(e_i(t))u_{e_i} \leqslant 0.$$

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

$$V_{s_i}'(e_i(t))k_{u_i}^{\mathrm{T}}(t)F_i(e(t))+\frac{2}{q_i}\dot{k}_i^{\mathrm{T}}(t)(k_i(t)-k_{g_i})$$
$$=V_{s_i}'(e_i(t))k_{g_i}^{\mathrm{T}}(t)F_i(e(t))\leqslant 0,$$
$$V_{s_i}'(e_i(t))(\phi_{u_i}(t)-u_{e_i})+\frac{2}{\hat{q}_i}(\phi_i(t)-u_{e_i})\dot{\phi}_i(t)$$
$$=\begin{cases}-V_{s_i}'(e_i(t)) & \\ \quad\times u_{e_i}\leqslant 0 & \text{if } \phi_i(t)=0 \text{ and}\\ & V_{s_i}'(x_i(t)-x_{e_i})\geqslant 0,\\ 0 & \text{otherwise.}\end{cases}$$

Hence, it follows that in either case

$$\dot{V}(e(t),K(t),\phi(t))\leqslant -\ell^{\mathrm{T}}(e(t))\ell(e(t))\leqslant 0,\quad t\geqslant 0, \tag{17}$$

which proves that the solution $(e(t),K(t),\phi(t))\equiv(0,K_g,u_{\mathrm{e}})$ to (8), (9), and (13) is Lyapunov stable. Thus, the solutions of the closed-loop system (8), (9), and (13) are bounded in $\mathbb{R}^n\times\mathbb{R}^{m\times s}\times\mathbb{R}^m$, and hence, since $V_{s_i}(\cdot)$ is continuously differentiable and $F_i(\cdot)$ is Lipschitz continuous for $i=1,\ldots,m$, it follows from Theorem 2.4 of Khalil [20] that there exists a unique solution to (8), (9), and (13) that is defined for all $t\geqslant 0$. Furthermore, it follows from Theorem 4.4 of Khalil [20] that $\ell(e(t))\to 0$ as $t\to\infty$. If, in addition, $\ell^{\mathrm{T}}(e)\ell(e)>0$, $e\in\mathbb{R}^n$, $e\neq 0$, then $x(t)\to x_{\mathrm{e}}$ as $t\to\infty$ for all $x_0\in\overline{\mathbb{R}}_+^n$. Finally, $u(t)\geqslant\geqslant 0$, $t\geqslant 0$, is a restatement of (6). Now, since $f:\mathbb{R}^n\to\mathbb{R}^n$is essentially nonnegative, $G(x)\geqslant\geqslant 0$, $x\in\overline{\mathbb{R}}_+^n$, and $u(t)\geqslant\geqslant 0$, $t\geqslant 0$, it follows from Proposition 2.1 that $x(t)\geqslant\geqslant 0$, $t\geqslant 0$, for all $x_0\in\overline{\mathbb{R}}_+^n$. □

In Theorem 3.1 the control input $u(t)$, $t\geqslant 0$, is always nonnegative regardless of the values of $x_i(t)$, $k_i(t)$, and $\phi_i(t)$, $t\geqslant 0$, $i=1,\ldots,m$, which ensures that the closed-loop plant states remain nonnegative by Proposition 2.1 for nonnegative and compartmental dynamical systems. Furthermore, note that in Theorem 3.1 we assumed that the equilibrium point x_{e} of (1) is globally asymptotically stable with $G_{\mathrm{n}}(x(t))u(t)\equiv u_{\mathrm{e}}$. In general, however, unlike linear nonnegative systems with asymptotically stable plant dynamics, a given set point $x_{\mathrm{e}}\in\overline{\mathbb{R}}_+^n$ for the nonlinear nonnegative dynamical system (1) may not be asymptotically stabilizable with a constant control $G_{\mathrm{n}}(x(t))u(t)\equiv u_{\mathrm{e}}\in\overline{\mathbb{R}}_+^m$. However, if $f(x)$ is homogeneous, cooperative, that is, the Jacobian matrix $\frac{\partial f(x)}{\partial x}$ is essentially nonnegative for all $x\in\overline{\mathbb{R}}_+^n$ [28], the Jacobian matrix $\frac{\partial f(x)}{\partial x}$ is irreducible for all $x\in\overline{\mathbb{R}}_+^n$ [28], and the zero solution $x(t)\equiv 0$ of the undisturbed ($u(t)\equiv 0$) system (1) is globally asymptotically stable, then the set point $x_{\mathrm{e}}\in\mathbb{R}_+^n$ satisfying (3) is a unique equilibrium point with $G_{\mathrm{n}}(x(t))u(t)\equiv u_{\mathrm{e}}\in\mathbb{R}_+^m$ and is also asymptotically stable for all $x_0\in\overline{\mathbb{R}}_+^n$ [6]. This implies that the solution $x(t)\equiv x_{\mathrm{e}}$ to (1) with $G_{\mathrm{n}}(x(t))u(t)\equiv u_{\mathrm{e}}$ is asymptotically stable. Finally, we note that if the equilibrium point x_{e} of (1) is locally asymptotically stable for all $x_0\in\mathscr{D}\subset\overline{\mathbb{R}}_+^n$ with $G_{\mathrm{n}}(x(t))u(t)\equiv u_{\mathrm{e}}$, then Theorem 3.1 guarantees local asymptotic stability.

It is important to note that the adaptive control law (6), (8), and (9) does *not* require the explicit knowledge of the nonnegative vector u_{e}; all that is required is the existence of the nonnegative constant vector u_{e} and a partially component decoupled Lyapunov function $V_{\mathrm{s}}(e)$ such that (4) and (5) are satisfied and the equilibrium condition (3) holds. Furthermore, note that in the case where $F(e)$ is only a function of $\hat{e}\triangleq[e_1,\ldots,e_m]^{\mathrm{T}}$, the adaptive feedback controller given in Theorem 3.1 can be viewed as an adaptive *output* feedback controller with outputs $y=Cx$, where $C\triangleq[I_m,0_{m\times(n-m)}]$. In this case, it follows from (6) that the explicit knowledge of $x_{\mathrm{u}}\triangleq[x_{m+1},\ldots,x_n]^{\mathrm{T}}$ and $x_{\mathrm{eu}}=[x_{\mathrm{e}m+1},\ldots,x_{\mathrm{e}n}]^{\mathrm{T}}$ as well as $u_{\mathrm{e}}\in\mathbb{R}^m$ is not required. In addition, if $f(\cdot)$ in (1) is given by a linear function, that is, $f(x)=Ax$, where $A\in\mathbb{R}^{n\times n}$ is essentially nonnegative and asymptotically stable, then $f_{\mathrm{e}}(\cdot)$ is given by $f_{\mathrm{e}}(e)=Ae$. In this case, it follows from Theorem 3.3 of Haddad and Chellaboina [10] that there exist a positive *diagonal* matrix $P\in\mathbb{R}^{n\times n}$ and a positive-definite matrix $R\in\mathbb{R}^{n\times n}$ such that

$$0=A^{\mathrm{T}}P+PA+R \tag{18}$$

and hence, we can always construct a component decoupled function $V_{\mathrm{s}}(e)=e^{\mathrm{T}}Pe$ which satisfies (5). Furthermore, in this case, we can always construct functions $F_i(\cdot)$, $i=1,\ldots,m$, such that (4) holds.

Unlike linear asymptotically stable nonnegative systems, the existence of a component decoupled Lyapunov function is not necessarily guaranteed for nonlinear asymptotically stable nonnegative systems. Even though the existence of diagonal-type Lyapunov functions for asymptotically stable nonlinear nonnegative systems is not assured, there do exist classes of nonnegative dynamical systems that do admit component decoupled Lyapunov functions. For details, see [17].

4. Nonlinear adaptive control for general anesthesia

To numerically illustrate the efficacy of our adaptive control framework we consider a nonlinear pharmacokinetic model for the intravenous anesthetic propofol. The pharmacokinetics of propofol are described by the three-compartment model [2,22] shown in Fig. 1. As discussed in [2], this model is remarkably effective in describing the drug distribution for the intravenous anesthetic propofol. The mass of the drug in the intravascular blood volume (blood within arteries or veins) as well as the highly perfused organs (organs with high ratios of perfusion to weight) such as the heart, brain, kidney, and liver is denoted by x_1. The remainder of the drug in the body is assumed to reside in two peripheral compartments, comprised of muscle and fat, and the masses in these compartments are denoted by x_2 and x_3.

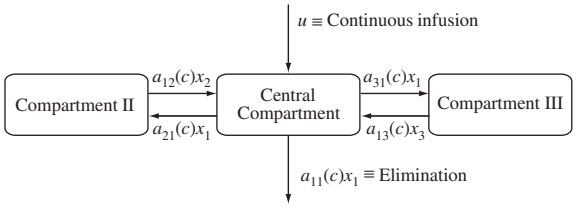

Fig. 1. Pharmacokinetic model for drug distribution during anesthesia.

A mass balance of the three-state compartmental model yields

$$\begin{aligned}\dot{x}_1(t) = & -[a_{11}(c(t)) + a_{21}(c(t)) + a_{31}(c(t))]x_1(t) \\ & + a_{12}(c(t))x_2(t) + a_{13}(c(t))x_3(t) + u(t), \\ & x_1(0) = x_{10}, \quad t \geqslant 0, \end{aligned} \tag{19}$$

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

$$\dot{x}_3(t) = a_{31}(c(t))x_1(t) - a_{13}(c(t))x_3(t), \ \ x_3(0) = x_{30}, \tag{21}$$

where $c(t) = x_1(t)/V_c$, V_c is the volume of the central compartment, $a_{ij}(c)$, $i \neq j$, is the rate of transfer of drug from the jth compartment to the ith compartment, $a_{11}(c)$ is the rate of drug metabolism and elimination (metabolism typically occurs in the liver), and $u(t)$, $t \geqslant 0$, is the infusion rate of the anesthetic drug propofol into the central compartment. The transfer coefficients are assumed to be functions of the drug concentration c since it is well known that the pharmacokinetics of propofol are influenced by cardiac output [30] and, in turn, cardiac output is influenced by propofol plasma concentrations, both due to venodilation (pooling of blood in dilated veins) and myocardial depression (decrease in cardiac output) [24].

Experimental data indicate that the transfer coefficients should be nonincreasing functions of the propofol concentration [24]. By far, the most widely used empirical models for pharmacodynamic concentration–effect relationships are modifications of the Hill equation [13]. Applying this almost ubiquitous empirical model to the relationship between transfer coefficients implies that

$$\begin{aligned} a_{ij}(c) &= A_{ij} Q_{ij}(c), \\ Q_{ij}(c) &= Q_0 C_{50,ij}^{\alpha_{ij}} / (C_{50,ij}^{\alpha_{ij}} + c^{\alpha_{ij}}), \end{aligned} \tag{22}$$

where for $i, j \in \{1, 2, 3\}$, $i \neq j$, $C_{50,ij}$ is the drug concentration associated with a 50% decrease in the transfer coefficient, α_{ij} is a parameter that determines the steepness of the concentration–effect relationship, and A_{ij} are positive constants. Note that both pharmacokinetic parameters are functions of i and j, that is, there are distinct Hill equations for each transfer coefficient. Furthermore, since for many drugs the rate of metabolism $a_{11}(c)$ is proportional to the rate of transport of drug to the liver we assume that $a_{11}(c)$ is also proportional to cardiac output so that $a_{11}(c) = A_{11} Q_{11}(c)$.

For simplicity of exposition and to provide a nonlinear model to illustrate implementation of our adaptive controller, we will assume that C_{50} and α are independent of i and j. Also, since decreases in cardiac output are observed at clinically utilized propofol concentrations we will arbitrarily assign C_{50} a value of 4 μg/ml since this value is in the midrange of clinically utilized values. We will also arbitrarily assign α a value of 3 [19]. This value is within the typical range of those observed for ligand–receptor binding (see the discussion in [8]). Note that these assumptions on C_{50} and α (both the independence from i and j and the assumed values) are made to provide a numerical framework for simulation. Even if these assumptions are incorrect, the basic Hill equations relating the transfer coefficients to propofol concentration are consistent with standard pharmacodynamic modeling. Even though the transfer and loss coefficients A_{12}, A_{21}, A_{13}, A_{31}, and A_{11} are positive, and $\alpha > 1$, $C_{50} > 0$, and $Q_0 > 0$, these parameters can be uncertain due to patient gender, weight, pre-existing disease, age, and concomitant medication. Hence, the need for adaptive control to regulate intravenous anesthetics during surgery is essential.

For set-point regulation define $e(t) \triangleq x(t) - x_e$, where $x_e \in \mathbb{R}^3$ is the set point satisfying the equilibrium condition for (19)–(21) with $x_1(t) \equiv x_{e1}$, $x_2(t) \equiv x_{e2}$, $x_3(t) \equiv x_{e3}$, and $u(t) \equiv u_e$, so that $f_e(e) = [f_{e1}(e), f_{e2}(e), f_{e3}(e)]^T$ is given by

$$\begin{aligned} f_{e1}(e) = & -[a_e(c) + a_{21}(c) + a_{31}(c)](e_1 + x_{e1}) \\ & + a_{12}(c)(e_2 + x_{e2}) + a_{13}(c)(e_3 + x_{e3}) \\ & - [a_e(c_e) + a_{21}(c_e) + a_{31}(c_e)]x_{e1} \\ & + a_{12}(c_e)x_{e2} + a_{13}(c_e)x_{e3}, \end{aligned} \tag{23}$$

$$\begin{aligned} f_{e2}(e) = & a_{21}(c)(e_1 + x_{e1}) - a_{12}(c)(e_2 + x_{e2}) \\ & - [a_{21}(c_e)x_{e1} - a_{12}(c_e)x_{e2}], \end{aligned} \tag{24}$$

$$\begin{aligned} f_{e3}(e) = & a_{31}(c)(e_1 + x_{e1}) - a_{13}(c)(e_3 + x_{e3}) \\ & - [a_{31}(c_e)x_{e1} - a_{13}(c_e)x_{e3}], \end{aligned} \tag{25}$$

where $c_e \triangleq x_{e1}/V_c$. The existence of this equilibrium point follows from the fact that the Jacobian matrix of (19)–(21) is essentially nonnegative and every solution of (19)–(21) is bounded. See Theorem 9 of Jacquez and Simon [16] for details. Furthermore, let $F(e) = e_1$ and $V_s(e) = e_1^2 + p_2 e_2^2 + p_3 e_3^2$, where $p_2, p_3 > 0$, so that $V_{s_1}'(e)F(e) = 2e_1^2 \geqslant 0$. Next, linearizing $f_e(e)$ about 0 and computing the eigenvalues of the resulting Jacobian matrix, it can be shown that x_e is asymptotically stable. Since we establish local asymptotic stability of x_e, our results guarantee local asymptotic stabilizability.

Even though propofol concentrations in the blood are known to be correlated with lack of purposeful responsiveness (and presumably consciousness) [18], 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 [9,23,27]. 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.

The bispectral index (BIS), an EEG indicator, has been proposed as a measure of anesthetic effect [23]. This index quantifies the nonlinear relationships between the component frequencies in the EEG, as well as analyzes their phase and amplitude. The BIS signal is related to drug concentration by the empirical relationship

$$\mathrm{BIS}(c_{\mathrm{eff}}) = \mathrm{BIS}_0 \left(1 - \frac{c_{\mathrm{eff}}^{\gamma}}{c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma}}\right), \tag{26}$$

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 μg/ml in the effect-site compartment (brain), EC_{50} is the concentration at half-maximal effect and represents the patient's sensitivity to the drug, and γ determines the degree of nonlinearity in (26). Here, the effect-site compartment is introduced to account for finite equilibration time between the central compartment concentration and the central nervous system concentration [25]. During actual surgery the BIS signal is obtained directly from the EEG and not (26).

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

$$\dot{c}_{\mathrm{eff}}(t) = a_{\mathrm{eff}}(c(t) - c_{\mathrm{eff}}(t)), \quad c_{\mathrm{eff}}(0) = c(0), \quad t \geqslant 0, \tag{27}$$

where a_{eff} in min^{-1} is a positive time constant. In reality, the effect-site compartment equilibrates with the central compartment in a matter of a few minutes. The parameters a_{eff}, EC_{50}, and γ are determined by data fitting and vary from patient to patient. BIS index values of 0 and 100 correspond, respectively, to an isoelectric EEG signal (no cerebral electrical activity) and an EEG signal of a fully conscious patient. The range between 40 and 60 indicates a moderate hypnotic state [27].

In the following numerical simulation we set $\mathrm{EC}_{50} = 5.6\,\mu\mathrm{g/m}\ell$, $\gamma = 2.39$, and $\mathrm{BIS}_0 = 100$, so that the BIS signal is shown in Fig. 2. The target (desired) BIS value, $\mathrm{BIS}_{\mathrm{target}}$, is set at 50. In this case, the linearized BIS function about the target BIS value is given by

$$\begin{aligned}\mathrm{BIS}(c_{\mathrm{eff}}) &\simeq \mathrm{BIS}(\mathrm{EC}_{50}) - \mathrm{BIS}_0 \cdot \mathrm{EC}_{50}^{\gamma} \\ &\quad \times \left.\frac{\gamma c_{\mathrm{eff}}^{\gamma-1}}{(c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma})^2}\right|_{c_{\mathrm{eff}}=\mathrm{EC}_{50}} \\ &\quad \times (c_{\mathrm{eff}} - \mathrm{EC}_{50}) \\ &= 109.75 - 10.67 c_{\mathrm{eff}}. \end{aligned} \tag{28}$$

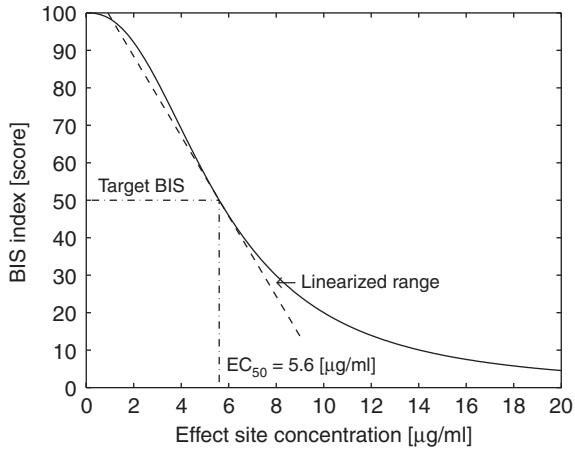

Fig. 2. BIS index versus effect-site concentration.

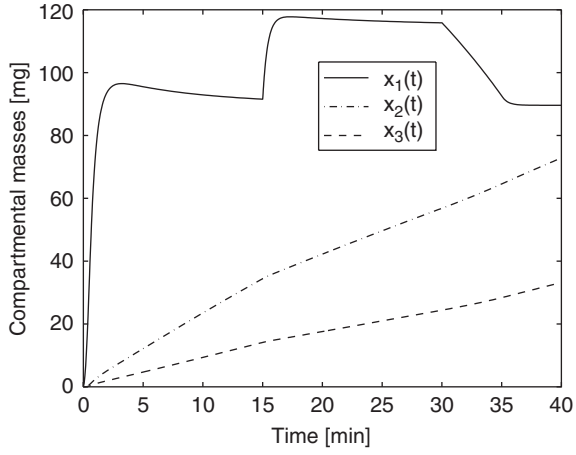

Fig. 3. Compartmental masses versus time.

Furthermore, for simplicity of exposition, we assume that the effect-site compartment equilibrates instantaneously with the central compartment, that is, we assume that $c_{\mathrm{eff}}(t) = c(t)$ for all $t \geqslant 0$. Now, using the adaptive feedback controller (6) with $i = 1$, $F_1(x(t) - x_{\mathrm{e}}) = \mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}$, $q_1 = q_{\mathrm{BIS}}$, and $\hat{q}_1 = \hat{q}_{\mathrm{BIS}}$, where q_{BIS_1} and $\hat{q}_{\mathrm{BIS}_1}$ are positive constants, it follows from Theorem 3.1 that $\mathrm{BIS}(t) \to \mathrm{BIS}_{\mathrm{target}}$ as $t \to \infty$ for all (uncertain) nonnegative values of the pharmacokinetic transfer and loss coefficients (A_{12}, A_{21}, A_{13}, A_{31}, A_{11}) as well as all (uncertain) nonnegative coefficients α, C_{50}, and Q_0 in the range of c_{eff} where the linearized BIS (28) is valid.

Since our adaptive controller only requires the error signal $\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}$ over the linearized range of (26), we do not require knowledge of the slope of the linearized (28), nor do we require knowledge of the pharmacodynamic parameters γ and EC_{50}. For our simulation we assume $V_{\mathrm{c}} = (0.228\,\ell/\mathrm{kg})(M\,\mathrm{kg})$, where $M = 70\,\mathrm{kg}$ is the mass of the patient, $A_{21}Q_0 = 0.112\,\mathrm{min}^{-1}$, $A_{12}Q_0 = 0.055\,\mathrm{min}^{-1}$, $A_{31}Q_0 = 0.0419\,\mathrm{min}^{-1}$, $A_{13}Q_0 = 0.0033\,\mathrm{min}^{-1}$,

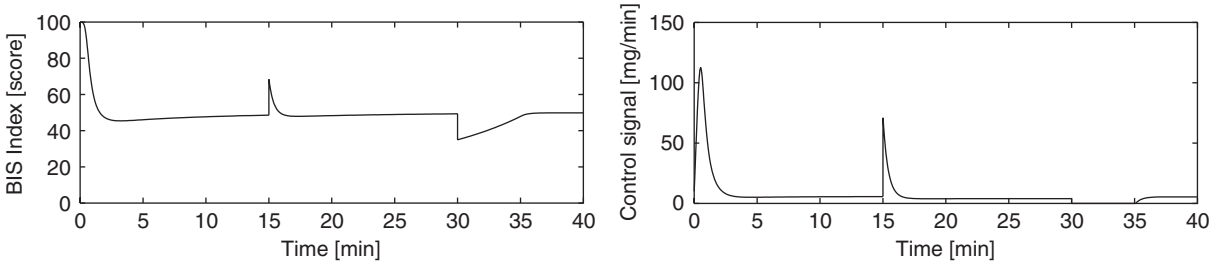

Fig. 4. BIS index versus time and control signal (infusion rate) versus time.

$A_{11}Q_0 = 0.119\,\mathrm{min}^{-1}$, $\alpha = 3$, and $C_{50} = 4\,\mu\mathrm{g/m}\ell$ [19,22]. Note that the parameter values for α and C_{50} probably exaggerate the effect of propofol on cardiac output. They have been selected to accentuate nonlinearity but they are not biologically unrealistic. Furthermore, to illustrate the efficacy of the proposed adaptive controller we switch the pharmacodynamic parameters EC_{50} and γ, respectively, from $5.6\,\mu\mathrm{g/m}\ell$ and 2.39 to $7.2\,\mu\mathrm{g/m}\ell$ and 3.39 at $t = 15$ min and back to $5.6\,\mu\mathrm{g/m}\ell$ and 2.39 at $t = 30$ min. With $q_{\mathrm{BIS}_1} = 2 \times 10^{-6}\,\mathrm{g/min}^2$, $\hat{q}_{\mathrm{BIS}_1} = 3 \times 10^{-4}\,\mathrm{g/min}^2$, and initial conditions $x(0) = [0,\ 0,\ 0]^{\mathrm{T}}\,\mathrm{g}$, $k_1(0) = 0\,\mathrm{g/min}$, and $\phi_1(0) = 0.01\,\mathrm{g/min}$, Fig. 3 shows the masses of propofol in the three compartments versus time. Finally, Fig. 4 shows the BIS index and the control signal (propofol infusion rate) versus time.

Unlike previous algorithms for closed-loop control of anesthesia [26,29], the adaptive controller (6)–(9) does not require knowledge of the pharmacokinetic and pharmacodynamic parameters. However, the adaptive controller (6)–(9) does not account for time delays due to equilibration between the control circulation and the effect-site compartment or due to the proprietary signal-averaging algorithms within the BIS monitor. Nevertheless, initial clinical testing has shown very promising results of this adaptive controller [2].

5. Conclusion

Nonnegative and compartmental models are remarkably effective in describing the dynamical behavior of biological and physiological systems. While compartmental systems have wide applicability in biology and medicine, their use in the specific field of pharmacology is indispensable for developing models for active control of drug administration. In this paper, we developed an adaptive control framework for adaptive set-point regulation of nonlinear nonnegative 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 nonnegativity of the closed-loop system states associated with the plant dynamics along with the nonnegativity of the control signal. Finally, using a nonlinear three-compartment patient model for the disposition of anesthetic drug propofol, the proposed adaptive control framework was illustrated by the control of a desired constant level of consciousness for noncardiac 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. While some of the noise is due to signals emanating from muscle rather than the central nervous system (and hence minimized by muscle paralysis), much of it is stochastic in nature.

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