Passivity-Based Neural Network Adaptive Output Feedback Control for Nonlinear Nonnegative Dynamical Systems

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***Abstract*—The potential clinical applications of adaptive neural network control for pharmacology in general, and anesthesia and critical care unit medicine in particular, are clearly apparent. Specifically, monitoring and controlling the depth of anesthesia in surgery is 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 neural adaptive *output feedback* control framework for adaptive set-point regulation of nonlinear uncertain nonnegative and compartmental systems. The proposed framework is Lyapunov-based and guarantees ultimate boundedness of the error signals corresponding to the physical system states and the neural network weighting gains. The approach is applicable to nonlinear nonnegative systems with unmodeled dynamics of unknown dimension and guarantees that the physical system states remain in the nonnegative orthant of the state–space for nonnegative initial conditions. Finally, a numerical example involving the infusion of the anesthetic drug midazolam for maintaining a desired constant level of depth of anesthesia for noncardiac surgery is provided to demonstrate the efficacy of the proposed approach.**

***Index Terms*—Adaptive control, automated anesthesia, bispectral index (BIS), electroencephalography, exponential passivity, neural networks, nonlinear nonnegative systems, nonnegative control, output feedback.**

I. Introduction

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. Recent work has demonstrated that a derivative of the EEG signal, the bispectral index (BIS), correlates with changes in consciousness [1]–[3]. The BIS is a scalar measure ranging from 0 to 100, with the upper value of 100 corresponding to the awake state and the lower limit of 0 corresponding to an isoelectrical EEG signal. The ease of BIS monitoring and its ready availability for use in the operating room, opens the possibility of closed-loop control of anesthetic drug administration, using the BIS as the performance and measurement variable. Current standard practice, open-loop control (manual control) by clinical personnel, can be tedious, imprecise, time-consuming, and sometimes of poor quality, depending on the skills and judgment of the clinician. Underdosing can result in patients psychologically traumatized by pain and awareness during surgery, while overdosing, at the very least, may result in delayed recovery from anesthesia and, in the worst case, may result in respiratory and cardiovascular collapse. Closed-loop control may improve the quality of drug administration, lessening the dependence of patient outcome on the skills of the clinician.

There has been a great deal of interest in the development of algorithms for closed-loop control of intravenous anesthesia. Algorithms for closed-loop control of inhalation anesthesia, using anesthetic concentration as the performance variable, have been developed. However, since it is not possible with current sensor technology to rapidly measure the plasma concentration of intravenously-administered drugs (in contrast to inhalation agents), these algorithms are not useful for intravenous agents. Furthermore, drug concentration, even if it could be measured rapidly, is not the best measurement variable. We are far more interested in drug effect than concentration. More relevant are recently described algorithms for the control of intravenous anesthesia using a processed electroencephalograph as the control variable. Building on pioneering work by Bickford [4], Absalom *et al.* [5] developed a proportional-integral-derivative controller using the BIS, a processed EEG signal, as the performance variable to control the infusion of the hypnotic, propofol. While the median performance of the system was good, in three out of ten patients oscillations of the BIS signal around the set point were observed and anesthesia was deemed clinically inadequate in one out of the ten patients. This would not be acceptable for clinical practice.

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Alternative algorithms have been devised by both Schwilden *et al.* [6], [7] and Struys *et al.* [8]. Both groups have developed and clinically tested closed-loop, model-based adaptive controllers for the delivery of intravenous anesthesia using a processed EEG signal as the measurement variable. The algorithms are based on a pharmacokinetic model predicting the drug concentration as a function of infusion rate and time and a pharmacodynamic model relating the processed EEG signal to concentration. The pharmacokinetic and pharmacodynamic models are characterized by specific parameters. The two algorithms are similar in assuming that certain model parameters are equal to the mean values from previous pharmacokinetic/pharmacodynamic studies while varying a few select parameters of the models to minimize the difference between the desired and observed processed EEG signal. The primary difference between the two algorithms is in the parameters which are fixed to the mean values from previous studies and the parameters that are chosen for variation. Schwilden *et al.* [6], [7] assumed that the pharmacodynamic parameters may be fixed to mean values taken from the literature and vary pharmacokinetic parameters to minimize bias from the target signal.

In contrast, Struys *et al.* [8] assumed that the pharmacokinetic parameters are always correct and that any variability in individual patient response is due to pharmacodynamic variability. Thus, they vary pharmacodynamic parameters to minimize the difference between the observed and target processed EEG signal. Both algorithms have been implemented in the operating room with clinically acceptable performance in small numbers of patients. However, as pointed out by Glass and Rampil [9] in an analysis of the algorithm of Struys *et al.* [8], the systems may not have been fully stressed. For example, in their study, Struys *et al.* [8] administered a relatively high fixed dose of the opioid remifentanil, in conjunction with closed-loop control of the hypnotic, 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 either system would have been robust in less controlled situations is an open question. And it should be noted that both algorithms are model dependent and only partially adaptive, in the sense that only select pharmacokinetic/pharmacodynamic parameters are varied to minimize the signal bias from the target.

Given the uncertainties in both pharmacokinetic and pharmacodynamic models, and the magnitude of interpatient variability, in this paper we present a neural network adaptive control framework that accounts for combined interpatient pharmacokinetic and pharmacodynamic variability. In particular, we develop a neural adaptive *output feedback* control framework for adaptive set-point regulation of nonlinear uncertain nonnegative and compartmental systems. Neural network adaptive controllers are ideal for controlling nonlinear uncertain dynamical systems due to their ability to approximate a large class of continuous nonlinear functions [10]–[16]. However, with the notable exception of [17], neuro adaptive controllers for nonlinear uncertain nonnegative and compartmental systems have not been developed in the literature. 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 [18]–[24] 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. Using nonnegative and compartmental model structures, a Lyapunov-based neural adaptive control framework is developed that guarantees ultimate boundedness of the error signals corresponding to the physical system states as well as the neural network weighting gains.

The neuro adaptive controllers are constructed *without* requiring knowledge of the system dynamics while guaranteeing that the physical system states remain in the nonnegative orthant of the state–space. Furthermore, since in pharmacological applications involving active drug administration control (source) inputs as well as the system states need to be nonnegative, the proposed neuro adaptive controller also guarantees that the control signal remains nonnegative. We emphasize that even though neuro adaptive *full-state feedback* controllers for nonnegative systems have been recently addressed in [17], our present formulation addresses adaptive *output feedback* controllers for nonlinear systems with *unmodeled dynamics* of *unknown dimension* using the exponential passivity, feedback equivalence, and stabilizability of exponentially minimum phase notions developed in [25] and [26]. The framework developed in [17] is limited to full-state feedback controllers and does not address the problem of unmodeled dynamics of unknown dimension. Output feedback controllers are crucial in clinical pharmacology since key physiological (state) variables cannot be measured in practice. Furthermore, the results in [17] are based on the new notions of partial boundedness and partial ultimate boundedness as opposed to the approach of this paper which imposes passivity and positive real requirements on the system dynamics. Thus, the approach of the present paper is related to the neuro adaptive control methods developed in [27] and [28].

II. Mathematical Preliminaries

In this section, we introduce notation, several definitions, and some key results concerning nonlinear nonnegative dynamical systems [24], [29] and exponentially passive systems [25], [26] 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., $x \gg 0$) to indicate that every component of x is nonnegative (resp., positive). In this case, we say that x is *nonnegative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n\times m}$ is *nonnegative*[1] or *positive* if every entry of A is nonnegative or positive, respectively, which

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

is written as $A \geq\geq 0$ 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 $x \geq\geq 0$ and $x \gg 0$. Finally, we write $(\,)^{\mathrm{T}}$ to denote transpose, $\mathrm{tr}(\cdot)$ for the trace operator, $\|\cdot\|$ for the Euclidean vector norm, $\|\cdot\|_{\mathrm{F}}$ for the Frobenius matrix norm, $\mathring{\mathcal{S}}$ for the interior of the set $\mathcal{S}$, and $V'(x)$ for the Fréchet derivative of V at x. The following definition introduces the notion of a nonnegative (resp., positive) function.

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

The following definition introduces the notion of essentially nonnegative vector fields [24], [30].

Definition 2.2: Let $f = [f_1, \ldots, f_n]^{\mathrm{T}} : \mathcal{D} \to \mathbb{R}^n$, where $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ that contains $\overline{\mathbb{R}}_+^n$. Then f is *essentially nonnegative with respect to* $\hat{x} \triangleq [x_1, \ldots, x_m]^{\mathrm{T}}$, $m \leq n$, if $f_i(x) \geq 0$ for all $i = 1, \ldots, m$, and $x \in \overline{\mathbb{R}}_+^n$ such that $x_i = 0$, $i = 1, \ldots, m$, where x_i denotes the ith element of x. f is *essentially nonnegative* if $f_i(x) \geq 0$ for all $i = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}_+^n$ such that $x_i = 0$.

In this paper, we consider controlled nonlinear dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = f(x(t)) + G(x(t))u(t), \quad x(0) = x_0 \quad t \geq 0 \tag{1}$$
$$y(t) = h(x(t)) \tag{2}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $y(t) \in \mathbb{R}^m$, $t \geq 0$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is locally Lipschitz continuous and satisfies $f(0) = 0$, $G : \mathbb{R}^n \to \mathbb{R}^{n \times m}$ is continuous, and $h : \mathbb{R}^n \to \mathbb{R}^m$ is continuous. We assume that $f(\cdot)$ has at least one equilibrium so that, without loss of generality, $f(0) = 0$ and $h(0) = 0$. Furthermore, for the nonlinear dynamical system $\mathcal{G}$ we assume that the required properties for the existence and uniqueness of solutions are satisfied; that is, $f(\cdot)$, $G(\cdot)$, and $u(\cdot)$ satisfy sufficient regularity conditions such that the system (1) has a unique solution forward in time. The following definition and proposition are needed for the main results of the paper.

Definition 2.3: The nonlinear dynamical system given by (1) is *nonnegative* if for every $x(0) \in \overline{\mathbb{R}}_+^n$ and $u(t) \geq\geq 0$, $t \geq 0$, the solution $x(t)$, $t \geq 0$, to (1) is nonnegative.

Proposition 2.1 ([24]): The nonlinear dynamical system given by (1) is nonnegative if $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative and $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$.

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

Next, we introduce the notion of exponential passivity.

Definition 2.4 ([26]): A nonlinear dynamical system $\mathcal{G}$ of the form (1), (2) is *exponentially passive* if there exists a constant $\rho > 0$ such that the *dissipation inequality*

$$0 \leq \int_{t_0}^{t} e^{\rho s} u^{\mathrm{T}}(s) y(s) \mathrm{d}s \tag{3}$$

is satisfied for all $t \geq t_0$ with $x(t_0) = 0$. A nonlinear dynamical system of the form (1), (2) is *passive* if the dissipation inequality (3) is satisfied with $\rho = 0$.

For the statement of the following result, recall the definitions of zero-state observability and complete reachability given in [31].

Theorem 2.1 ([26]): Let $\mathcal{G}$ be zero-state observable and completely reachable. $\mathcal{G}$ is exponentially passive if and only if there exist functions $V_{\mathrm{s}} : \mathbb{R}^n \to \mathbb{R}$ and $\ell : \mathbb{R}^n \to \mathbb{R}^p$, and a scalar $\rho > 0$ such that $V_{\mathrm{s}}(\cdot)$ is continuously differentiable, positive–definite, $V_{\mathrm{s}}(0) = 0$, $\ell(\cdot)$ is continuous, $\ell(0) = 0$, and, for all $x \in \mathbb{R}^n$

$$0 = V_{\mathrm{s}}'(x) f(x) + \rho V_{\mathrm{s}}(x) + \ell^{\mathrm{T}}(x)\ell(x) \tag{4}$$
$$0 = \frac{1}{2} V_{\mathrm{s}}'(x) G(x) - h^{\mathrm{T}}(x). \tag{5}$$

As shown in [26], an equivalent statement for exponential passivity of $\mathcal{G}$ using (4), (5) is given by

$$\dot{V}_{\mathrm{s}}(x) = -\rho V_{\mathrm{s}}(x) + u^{\mathrm{T}} y - \ell^{\mathrm{T}}(x)\ell(x) \quad x \in \mathbb{R}^n. \tag{6}$$

Hence, if $\mathcal{G}$ is exponentially passive (resp., passive), then the undisturbed ($u(t) \equiv 0$) nonlinear dynamical system (1) is asymptotically (resp., Lyapunov) stable. If, in addition, there exist scalars $\alpha, \beta > 0$ and $p \geq 1$ such that $\alpha\|x\|^p \leq V_{\mathrm{s}}(x) \leq \beta\|x\|^p$, $x \in \mathbb{R}^n$, then the undisturbed ($u(t) \equiv 0$) nonlinear dynamical system (1) is *exponentially stable*. This leads to the following stronger notion of exponential passivity [25].

Definition 2.5: A nonlinear dynamical system $\mathcal{G}$ of the form (1), (2) is *strongly exponentially passive* if $\mathcal{G}$ is exponentially passive and there exist a continuously differentiable function $V_{\mathrm{s}} : \mathbb{R}^n \to \mathbb{R}$ and positive scalars $\alpha, \beta > 0$ such that

$$\alpha\|x\|^2 \leq V_{\mathrm{s}}(x) \leq \beta\|x\|^2 \quad x \in \mathbb{R}^n. \tag{7}$$

Since, in this paper, we consider nonlinear dynamical systems in *normal form*, for the remainder of this section we restate some of the key results of [25] in a concise and unified format that supports the developments in Section III. Specifically, we consider the normal form characterization of (1), (2) given by

$$\dot{x}(t) = f_x(x(t), z(t)) + G(x(t), z(t))u(t)$$
$$x(0) = x_0 \quad t \geq 0 \tag{8}$$
$$\dot{z}(t) = f_z(x(t), z(t)), \quad z(0) = z_0 \tag{9}$$
$$y(t) = x(t) \tag{10}$$

where $x(t) \in \mathbb{R}^m$, $t \geq 0$, and $z(t) \in \mathbb{R}^{n-m}$, $t \geq 0$, are the state vectors, $u(t) \in \mathbb{R}^m$, $t \geq 0$, is the control input, $y(t) \in \mathbb{R}^m$, $t \geq 0$, is the system output, $f_x : \mathbb{R}^m \times \mathbb{R}^{n-m} \to \mathbb{R}^m$ and satisfies $f_x(0, z) = 0$, $z \in \mathbb{R}^{n-m}$, $f_z : \mathbb{R}^m \times \mathbb{R}^{n-m} \to \mathbb{R}^{n-m}$ and satisfies $f_z(x, 0) = 0$, $x \in \mathbb{R}^m$, and $G : \mathbb{R}^m \times \mathbb{R}^{n-m} \to \mathbb{R}^{m \times m}$ with $\det G(x, z) \neq 0$, $(x, z) \in \mathbb{R}^m \times \mathbb{R}^{n-m}$. The following definition introduces the notion of exponentially minimum phase.

Definition 2.6: A nonlinear dynamical system $\mathcal{G}$ of the form (8)–(10) is *exponentially minimum phase* if there exist a continuously differentiable function $V_z : \mathbb{R}^{n-m} \to \mathbb{R}$ and positive constants α, β, γ, and δ such that

$$\alpha\|z\|^2 \leq V_z(z) \leq \beta\|z\|^2 \tag{11}$$
$$V_z'(z) f_z(0, z) \leq -\gamma\|z\|^2 \tag{12}$$
$$\|V_z'(z)\| \leq \delta\|z\|. \tag{13}$$

It follows from converse Lyapunov theory that if the zero solution $z(t) \equiv 0$ to $\dot{z}(t) = f_z(0, z(t))$, $z(0) = z_0$, $t \geq 0$, is exponentially stable and $f_z(0, \cdot)$ is continuously differentiable, then there exists a continuously differentiable function $V_z : \mathbb{R}^{n-m} \to \mathbb{R}$ such that (11)–(13) hold. Finally, the following definition and theorem are needed for the main results of this paper. For the statement of this definition let $\tilde{x} \triangleq [x^{\mathrm{T}}, z^{\mathrm{T}}]^{\mathrm{T}}$, $\tilde{f}(\tilde{x}) \triangleq [f_x^{\mathrm{T}}(x,z), f_z^{\mathrm{T}}(x,z)]^{\mathrm{T}}$, and $\tilde{G}(\tilde{x}) \triangleq [G^{\mathrm{T}}(\tilde{x}), 0_{m\times(n-m)}]^{\mathrm{T}}$.

Definition 2.7 ([25]): A nonlinear dynamical system $\mathcal{G}$ of the form (8)–(10) is *semiglobally output feedback exponentially passive* if, for any compact set $\mathcal{D}_{\mathrm{c}} \subset \mathbb{R}^n$, there exists a continuous feedback $u : \mathbb{R}^m \times \mathbb{R}^m \to \mathbb{R}^m$ of the form

$$u = \alpha_{\mathcal{D}_{\mathrm{c}}}(y) + \beta_{\mathcal{D}_{\mathrm{c}}}(y)v \tag{14}$$

where $\det \beta_{\mathcal{D}_{\mathrm{c}}}(y) \neq 0$, $y \in \mathbb{R}^m$, such that the closed-loop system given by (8)–(10) and (14), or, equivalently

$$\dot{\tilde{x}}(t) = \tilde{f}_{\mathcal{D}_{\mathrm{c}}}(\tilde{x}(t)) + \tilde{G}_{\mathcal{D}_{\mathrm{c}}}(\tilde{x}(t))v(t), \;\; \tilde{x}(0) \in \mathcal{D}_{\mathrm{c}}, \;\; t \geq 0 \tag{15}$$

$$y(t) = x(t) \tag{16}$$

where $\tilde{f}_{\mathcal{D}_{\mathrm{c}}}(\tilde{x}) = \tilde{f}(\tilde{x}) + \tilde{G}(\tilde{x})\alpha_{\mathcal{D}_{\mathrm{c}}}(y)$ and $\tilde{G}_{\mathcal{D}_{\mathrm{c}}}(\tilde{x}) = \tilde{G}(\tilde{x})\beta_{\mathcal{D}_{\mathrm{c}}}(y)$, is strongly exponentially passive from v to y for all $\tilde{x} \in \mathcal{D}_{\mathrm{c}}$.

Theorem 2.2 ([25]): Consider the nonlinear dynamical system $\mathcal{G}$ given by (8)–(10). Assume that the input matrix function $G(x,z)$, $(x,z) \in \mathbb{R}^m \times \mathbb{R}^{n-m}$, can be factored as

$$G(x,z) = G_{\mathrm{u}}(z)G_{\mathrm{n}}(x) \tag{17}$$

where $G_{\mathrm{u}} : \mathbb{R}^{n-m} \to \mathbb{R}^{m\times m}$ and $G_{\mathrm{n}} : \mathbb{R}^m \to \mathbb{R}^{m\times m}$ are continuously differentiable matrix functions such that $G_{\mathrm{u}}(z) = G_{\mathrm{u}}^{\mathrm{T}}(z) > 0$, $z \in \mathbb{R}^{n-m}$, and $\det G_{\mathrm{n}}(x) \neq 0$, $x \in \mathbb{R}^m$. Then $\mathcal{G}$ is semiglobally output feedback exponentially passive if and only if $\mathcal{G}$ is exponentially minimum phase.

Remark 2.1: As noted in [25], if $f_z(\cdot,\cdot)$ is globally Lipschitz continuous in $\mathbb{R}^m \times \mathbb{R}^{n-m}$, $G_{\mathrm{u}}(\cdot)$ is uniformly positive–definite; that is, there exists $\mu > 0$ such that $G_{\mathrm{u}}(z) = G_{\mathrm{u}}^{\mathrm{T}}(z) \geq \mu I_m$, $z \in \mathbb{R}^{n-m}$, and the zero solution $z(t) \equiv 0$ to $\dot{z}(t) = f_z(0, z(t))$, $z(0) = z_0$, $t \geq 0$, is globally exponentially stable, then the previous result holds globally.

Remark 2.2: It is important to note that if the conditions in Theorem 2.2 are satisfied, then there exists an *output feedback* control law of the form (14) which renders the closed-loop system exponentially passive from v to y. Specifically, as shown in [25], the output feedback controller achieving exponential passivity is given by

$$u = -G_{\mathrm{n}}^{-1}(y)[G_{\mathrm{u}}^{-1}(0)f_x(0,y) + \chi y] + G_{\mathrm{n}}^{-1}(y)v \tag{18}$$

where $\chi \in \mathbb{R}$ is a positive constant. Finally, it is important to note that in the case where $G_{\mathrm{u}}(z) \equiv I_m$, $\beta_{\mathcal{D}_{\mathrm{c}}}(\cdot)$ in (14) takes the form

$$\beta_{\mathcal{D}_{\mathrm{c}}}(y) = G_{\mathrm{n}}^{-1}(y) = G^{-1}(y). \tag{19}$$

This fact will be used for our main result presented in the following section.

III. Neural Output Feedback Adaptive Control for Nonlinear Nonnegative Uncertain Systems

In this section, we consider the problem of characterizing neural adaptive output feedback control laws for nonlinear nonnegative and compartmental uncertain dynamical systems to achieve *set-point* regulation in the nonnegative orthant. Specifically, consider the controlled nonlinear uncertain dynamical system $\mathcal{G}$ given by (8)–(10) where $f_x : \mathbb{R}^m \times \mathbb{R}^{n-m} \to \mathbb{R}^m$ is essentially nonnegative with respect to x but otherwise unknown and satisfies $f_x(0,z) = 0$, $z \in \mathbb{R}^{n-m}$, $f_z : \mathbb{R}^m \times \mathbb{R}^{n-m} \to \mathbb{R}^{n-m}$ is essentially nonnegative with respect to z but otherwise unknown and satisfies $f_z(x,0) = 0$, $x \in \mathbb{R}^m$, and $G : \mathbb{R}^m \to \mathbb{R}^{m\times m}$ is an unknown nonnegative input matrix function. Furthermore, the system dimension n need not be known. The control input $u(\cdot)$ in (8) 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, control (source) inputs of drug delivery systems for physiological and pharmacological processes are usually constrained to be nonnegative as are the system states. Hence, in this paper we develop neuro adaptive output feedback control laws for nonnegative systems with nonnegative control inputs. Specifically, for a given desired set point $(y_{\mathrm{d}}, z_{\mathrm{e}}) \in \mathbb{R}_+^m \times \mathbb{R}_+^{n-m}$ and for given $\epsilon_1, \epsilon_2 > 0$, our aim is to design a nonnegative control input $u(t)$, $t \geq 0$, such that $\|y(t) - y_{\mathrm{d}}\| < \epsilon_1$ and $\|z(t) - z_{\mathrm{e}}\| < \epsilon_2$ for all $t \geq T$, where $T \in [0, \infty)$, and $x(t) \geq\geq 0$ and $z(t) \geq\geq 0$, $t \geq 0$, for all $(x_0, z_0) \in \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m}$. However, since in many applications of nonnegative systems and in particular, compartmental systems, it is often necessary to regulate a subset of the nonnegative state variables which usually include a central compartment, here we only require that $\|y(t) - y_{\mathrm{d}}\| < \epsilon_1$, $t \geq T$. Furthermore, we assume that we have m *independent* control inputs so that the input matrix function is given by $G(x) = \mathrm{diag}[g_1(x), \ldots, g_m(x)]$, where $g_i : \mathbb{R}^m \to \mathbb{R}_+$, $i = 1, \ldots, m$. For compartmental systems, this assumption is not restrictive since control inputs correspond to control inflows to each individual compartment.

In this paper, we assume that for a given set point $y_{\mathrm{d}} \in \mathbb{R}_+^m$ there exist $z_{\mathrm{e}} \in \mathbb{R}_+^{n-m}$ and $u_{\mathrm{e}} \in \mathbb{R}_+^m$ such that

$$0 = f_x(y_{\mathrm{d}}, z_{\mathrm{e}}) + G(y_{\mathrm{d}})u_{\mathrm{e}} \tag{20}$$

$$0 = f_z(y_{\mathrm{d}}, z_{\mathrm{e}}) \tag{21}$$

and the solution $z(t) \equiv z_{\mathrm{e}}$ to (9) with $x(t) \equiv y_{\mathrm{d}}$ is globally exponentially stable so that $\mathcal{G}$ given by (8)–(10) is exponentially minimum phase at $(y_{\mathrm{d}}, z_{\mathrm{e}})$ with constant control input u_{e}. Note that $(y_{\mathrm{d}}, z_{\mathrm{e}}) \in \mathbb{R}^m \times \mathbb{R}^{n-m}$ is an equilibrium point of (8), (9) if and only if there exists $u_{\mathrm{e}} \in \mathbb{R}_+^m$ such that (20), (21) hold. Next, defining $e_x(t) \triangleq x(t) - y_{\mathrm{d}}$, $e_z(t) \triangleq z(t) - z_{\mathrm{e}}$, and $\hat{G}(e_x) \triangleq G(e_x + y_{\mathrm{d}})$, and using (20), (21), it follows that:

$$\begin{aligned}
\dot{e}_x(t) &= f_x(e_x(t) + y_{\mathrm{d}}, e_z(t) + z_{\mathrm{e}}) \\
&\quad - (f_x(y_{\mathrm{d}}, z_{\mathrm{e}}) + G(y_{\mathrm{d}})u_{\mathrm{e}}) + G(x(t))u(t) \\
&= \tilde{f}_x(e_x(t), e_z(t)) - G(y_{\mathrm{d}})u_{\mathrm{e}} + \hat{G}(e_x(t))u(t) \\
e_x(0) &= x_0 - y_{\mathrm{d}}, \quad t \geq 0
\end{aligned} \tag{22}$$

and

$$\dot{e}_z(t) = \tilde{f}_z(e_x(t), e_z(t)), \quad e_z(0) = z_0 - z_{\rm e} \tag{23}$$

where $\tilde{f}_x(e_x, e_z) \triangleq f_x(e_x + y_{\rm d}, e_z + z_{\rm e}) - f_x(y_{\rm d}, z_{\rm e})$ and $\tilde{f}_z(e_x, e_z) \triangleq f_z(e_x + y_{\rm d}, e_z + z_{\rm e}) - f_z(y_{\rm d}, z_{\rm e})$. Since, by assumption, the solution $z(t) \equiv z_{\rm e}$ to (9) with $x(t) \equiv y_{\rm d}$ is globally exponentially stable, it follows from Definition 2.6 and converse Lyapunov theory that $\mathcal{G}$ is exponentially minimum phase and, hence, it further follows from Theorem 2.2 and Remark 2.2 that for any compact set $\tilde{\mathcal{D}}_{\rm c} \triangleq \tilde{\mathcal{D}}_{cx} \times \tilde{\mathcal{D}}_{cz}$, where $\tilde{\mathcal{D}}_{cx} \subset \mathbb{R}^m$ and $\tilde{\mathcal{D}}_{cz} \subset \mathbb{R}^{n-m}$, and for all $\tilde{e} \triangleq [e_x^{\rm T}, e_z^{\rm T}]^{\rm T} \in \tilde{\mathcal{D}}_{\rm c}$, there exist continuous functions $\alpha_{\tilde{\mathcal{D}}_{\rm c}} : \mathbb{R}^m \to \mathbb{R}^m$ and $\beta_{\tilde{\mathcal{D}}_{\rm c}} : \mathbb{R}^m \to \mathbb{R}^{m\times m}$ with $\beta_{\tilde{\mathcal{D}}_{\rm c}}(e_x) = \hat{G}^{-1}(e_x)$, $e_x \in \mathbb{R}^m$, such that, with $u = \alpha_{\tilde{\mathcal{D}}_{\rm c}}(\tilde{y}) + \beta_{\tilde{\mathcal{D}}_{\rm c}}(\tilde{y})v$, (22), (23) is strongly exponentially passive from v to $\tilde{y} \triangleq x - y_{\rm d} = e_x$. Next, adding and subtracting $\hat{G}(e_x)\alpha_{\tilde{\mathcal{D}}_{\rm c}}(e_x)$ to and from (22), it follows that (22) can be rewritten as:

$$\begin{aligned}\dot{e}_x(t) = {} & [\tilde{f}_x(e_x(t), e_z(t)) + \hat{G}(e_x(t))\alpha_{\tilde{\mathcal{D}}_{\rm c}}(e_x(t))] \\ & + \hat{G}(e_x(t))[u(t) - \alpha_{\tilde{\mathcal{D}}_{\rm c}}(x(t) - y_{\rm d}) - G^{-1}(x(t))G(y_{\rm d})u_{\rm e}] \\ & e_x(0) = x_0 - y_{\rm d}, \quad t \geq 0. \end{aligned} \tag{24}$$

Now, we assume that for a given $\varepsilon_i^* > 0$, the ith component of the vector function $\alpha_{\tilde{\mathcal{D}}_{\rm c}}(x - y_{\rm d}) + G^{-1}(x)G(y_{\rm d})u_{\rm e}$ can be approximated over a compact set $\mathcal{D}_{cx} \triangleq \{x \in \mathbb{R}^m : x - y_{\rm d} \in \tilde{\mathcal{D}}_{cx}\}$ by a linear in parameters neural network up to a desired accuracy so that for $i = 1, \ldots, m$, there exists $\varepsilon_i(\cdot)$ such that $|\varepsilon_i(x)| < \varepsilon_i^*$, $x \in \mathcal{D}_{\rm cx}$, and

$$\alpha_{\tilde{\mathcal{D}}_{\rm c}i}(x - y_{\rm d}) + g_i^{-1}(x)g_i(y_{\rm d})u_{{\rm e}i} = W_i^{\rm T}\sigma_i(x) + \varepsilon_i(x), x \in \mathcal{D}_{\rm cx} \tag{25}$$

where $W_i \in \mathbb{R}^{s_i}$, $i = 1, \ldots, m$, are optimal *unknown* (constant) weights that minimize the approximation error over $\mathcal{D}_{\rm cx}$, $\sigma_i : \mathbb{R}^m \to \mathbb{R}^{s_i}$, $i = 1, \ldots, m$, are a set of basis functions such that each component of $\sigma_i(\cdot)$ takes values between 0 and 1, $\varepsilon_i : \mathcal{D}_{\rm cx} \to \mathbb{R}$, $i = 1, \ldots, m$, are the modeling errors, and $\|W_i\| \leq w_i^*$, where w_i^*, $i = 1, \ldots, m$, are bounds for the optimal weights W_i, $i = 1, \ldots, m$. Since $\alpha_{\tilde{\mathcal{D}}_{\rm c}}(\cdot)$ and $G(\cdot)$ are continuous functions, we can choose $\sigma_i(\cdot)$, $i = 1, \ldots, m$, from a linear space $\mathcal{X}$ of continuous functions that forms an algebra and separates points in $\mathcal{D}_{\rm cx}$. In this case, it follows from the Stone–Weierstrass theorem [32, p. 212] that $\mathcal{X}$ is a dense subset of the set of continuous functions on $\mathcal{D}_{\rm cx}$. Hence, as is the case in the standard neuro adaptive control literature [13], we can construct the signal $u_{{\rm ad}i} = \hat{W}_i^{\rm T}\sigma_i(x)$ involving the estimates of the optimal weights as our adaptive control signal. For the following theorem let $s \triangleq s_1 + \cdots + s_m$ denote the total number of basis functions or, equivalently, the number of nodes of the neural network.

Theorem 3.1: Consider the nonlinear uncertain system $\mathcal{G}$ given by (8)–(10) where $f_x(\cdot, \cdot)$ is essentially nonnegative with respect to x, $f_z(\cdot, \cdot)$ is essentially nonnegative with respect to z, and $G : \mathbb{R}^m \to \mathbb{R}^{m\times m}$ is nonnegative and given by $G(x) = {\rm diag}[g_1(x), \ldots, g_m(x)]$. For a given $y_{\rm d} \in \mathbb{R}_+^m$, assume there exist positive vectors $z_{\rm e} \in \mathbb{R}_+^{n-m}$ and $u_{\rm e} \in \mathbb{R}_+^m$ such that (20) and (21) hold and the equilibrium point $(y_{\rm d}, z_{\rm e})$ of (8), (9) is globally asymptotically stable with $u(t) \equiv u_{\rm e}$. In addition, assume that $\mathcal{G}$ is exponentially minimum phase at $(y_{\rm d}, z_{\rm e})$. Finally, let q_i and γ_i, $i = 1, \ldots, m$, be positive constants. Then the neural adaptive output feedback control law

$$u_i(t) = \max\{0, \hat{u}_i(t)\}, \quad i = 1, \ldots, m \tag{26}$$

where

$$\hat{u}_i(t) = \hat{W}_i^{\rm T}(t)\sigma_i(y(t)), \quad i = 1, \ldots, m \tag{27}$$

and $\hat{W}_i(t) \in \mathbb{R}^{s_i}$, $t \geq 0$, $i = 1, \ldots, m$, with update law

$$\begin{aligned}\dot{\hat{W}}_i(t) = {} & -\frac{q_i}{2}\left[(y_i(t) - y_{{\rm d}i})\sigma_i(y(t)) + \gamma_i|y_i(t) - y_{{\rm d}i}|\hat{W}_i(t)\right] \\ & \hat{W}_i(0) = \hat{W}_{i0}, \quad i = 1, \ldots, m \end{aligned} \tag{28}$$

guarantees that there exists a compact positively invariant set $\mathcal{D}_\alpha \subset \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m} \times \mathbb{R}^{s\times m}$ such that $(y_{\rm d}, z_{\rm e}, W) \in \mathcal{D}_\alpha$, where $W \in \mathbb{R}^{s\times m}$, and the solution $(x(t), z(t), \hat{W}(t))$, $t \geq 0$, of the closed-loop system given by (8), (9), (26), and (28) is ultimately bounded for all $(x(0), z(0), \hat{W}(0)) \in \mathcal{D}_\alpha$ with ultimate bound $\|y(t) - y_{\rm d}\|^2 < \epsilon_1$, $t \geq T = T(x_0, z_0, \hat{W}_0, \epsilon_1)$, where

$$\begin{aligned}\epsilon_1 > {} & \frac{1}{\alpha}\left[\beta\left(\frac{\nu}{\rho\alpha}\right)^2 + q_{\min}\left(\sqrt{\sum_{i=1}^m\left(\frac{\sqrt{s_i} + \gamma_i w_i^*}{2\gamma_i}\right)^2}\right.\right. \\ & \left.\left. + \sqrt{\frac{\nu}{\gamma_{\min}}}\right)^2\right] \end{aligned} \tag{29}$$

$$\nu \triangleq \sum_{i=1}^m(\sqrt{s_i}w_i^* + \varepsilon_i^*)\mu + \sum_{i=1}^m\frac{(\sqrt{s_i} + \gamma_i w_i^*)^2}{4\gamma_i} \tag{30}$$

$$\hat{W}(t) \triangleq {\rm block\text{-}diag}\big[\hat{W}_1(t), \ldots, \hat{W}_m(t)\big] \tag{31}$$

$\gamma_{\min} \triangleq \min_{i\in\{1,\ldots,m\}}\{\gamma_i\}$, $q_{\min} \triangleq \min_{i\in\{1,\ldots,m\}}\{q_i\}$,

$$\mu \triangleq \max_{x\in\mathcal{D}_{\rm cx}}\lambda_{\max}(G(x)) = \max_{i=\{1,\ldots,m\}}\max_{x\in\mathcal{D}_{\rm cx}}\{g_i(x)\} > 0,$$

and α, β are positive constants. Furthermore, $u(t) \geq\geq 0$, $x(t) \geq\geq 0$, and $z(t) \geq\geq 0$ for all $t \geq 0$ and $(x_0, z_0) \in \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m}$.

Proof: First, since, by assumption, (8), (9) is exponentially minimum phase at $(y_{\rm d}, z_{\rm e})$, it follows from Theorem 2.2 and Remark 2.2 that for any compact set $\tilde{\mathcal{D}}_{\rm c}$ and for all $\tilde{e} \triangleq [e_x^{\rm T}, e_z^{\rm T}]^{\rm T} \in \tilde{\mathcal{D}}_{\rm c}$, there exist continuous functions $\alpha_{\tilde{\mathcal{D}}_{\rm c}} : \mathbb{R}^m \to \mathbb{R}^m$ and $\beta_{\tilde{\mathcal{D}}_{\rm c}} : \mathbb{R}^m \to \mathbb{R}^{m\times m}$ with $\beta_{\tilde{\mathcal{D}}_{\rm c}}(e_x) = \hat{G}^{-1}(e_x)$, $e_x \in \mathbb{R}^m$, such that, with $u = \alpha_{\tilde{\mathcal{D}}_{\rm c}}(\tilde{y}) + \beta_{\tilde{\mathcal{D}}_{\rm c}}(\tilde{y})v$, (22), (23) is strongly exponentially passive from v to $\tilde{y} = e_x$. Hence, it follows from Theorem 2.1 that there exist a continuously differentiable function $V_{\rm s} : \mathbb{R}^n \to \mathbb{R}$, a continuous function $\ell : \mathbb{R}^n \to \mathbb{R}^p$, and positive constants ρ, α, β such that $V_{\rm s}(\cdot)$ is positive–definite, $V_{\rm s}(0) = 0$, $\ell(0) = 0$, and, for all $\tilde{e} \in \mathbb{R}^n$,

$$0 = V_{\rm s}'(\tilde{e})[\tilde{f}(\tilde{e}) + \tilde{G}(\tilde{e})\alpha_{\tilde{\mathcal{D}}_{\rm c}}(e_x)] + \rho V_{\rm s}(\tilde{e}) + \ell^{\rm T}(\tilde{e})\ell(\tilde{e}) \tag{32}$$

$$0 = \frac{1}{2}V_{\rm s}'(\tilde{e})\tilde{G}(\tilde{e})\beta_{\tilde{\mathcal{D}}_{\rm c}}(e_x) - \tilde{y} \tag{33}$$

and (7) hold, where $\tilde{f}(\tilde{e}) \triangleq [\tilde{f}_x^{\rm T}(e_x, e_z), \tilde{f}_z^{\rm T}(e_x, e_z)]^{\rm T}$ and $\tilde{G}(\tilde{e}) \triangleq [\hat{G}(e_x), 0]^{\rm T}$.

Next, define

$$\hat{W}_{\rm u}(t) \triangleq {\rm block\text{-}diag}\big[\hat{W}_{\rm u1}(t), \ldots, \hat{W}_{\rm um}(t)\big] \tag{34}$$

where

$$\hat{W}_{\mathrm{u}i}(t)=\begin{cases}0, & \text{if } \hat{u}_i(t)<0\\ \hat{W}_i(t), & \text{otherwise}\end{cases}\qquad i=1,\ldots,m \tag{35}$$

and note that with $u(t)$, $t\geq 0$, given by (26) it follows that (23) and (24) become:

$$\begin{aligned}\dot{e}_x(t)=&[\tilde{f}_x(e_x(t),e_z(t))+\hat{G}(e_x(t))\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\\&+[\hat{G}(e_x(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\beta^{-1}_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))[\hat{W}^{\mathrm{T}}(t)\sigma(y(t))\\&-\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(x(t)-y_{\mathrm{d}})-G^{-1}(x(t))G(y_{\mathrm{d}})u_{\mathrm{e}}]\\&+[\hat{G}(e_x(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\beta^{-1}_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))\\&\cdot(\hat{W}_{\mathrm{u}}(t)-\hat{W}(t))^{\mathrm{T}}\sigma(y(t))\\&e_x(0)=x_0-y_{\mathrm{d}},\quad t\geq 0\end{aligned} \tag{36}$$

and

$$\dot{e}_z(t)=\tilde{f}_z(e_x(t),e_z(t)),\quad e_z(0)=z_0-z_{\mathrm{e}} \tag{37}$$

or, equivalently

$$\begin{aligned}\dot{\tilde{e}}(t)=&[\tilde{f}(\tilde{e}(t))+\tilde{G}(\tilde{e}(t))\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\\&+[\tilde{G}(\tilde{e}(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\beta^{-1}_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))[\hat{W}^{\mathrm{T}}(t)\sigma(y(t))\\&-\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(x(t)-y_{\mathrm{d}})-G^{-1}(x(t))G(y_{\mathrm{d}})u_{\mathrm{e}}]\\&+[\tilde{G}(\tilde{e}(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\beta^{-1}_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))\\&\cdot(\hat{W}_{\mathrm{u}}(t)-\hat{W}(t))^{\mathrm{T}}\sigma(y(t))\\&e_x(0)=x_0-y_{\mathrm{d}},\quad t\geq 0.\end{aligned} \tag{38}$$

To show ultimate boundedness of the closed-loop system (28) and (38), consider the Lyapunov-like function

$$V(\tilde{e},\tilde{W})=V_{\mathrm{s}}(\tilde{e})+\operatorname{tr}\tilde{W}Q^{-1}\tilde{W}^{\mathrm{T}} \tag{39}$$

where $\tilde{W}(t)\triangleq\hat{W}(t)-W$, $W\triangleq\text{block-diag}[W_1,\ldots,W_m]^{\mathrm{T}}$, and $Q\triangleq\operatorname{diag}[q_1,\ldots,q_m]$. Note that $V(0,0)=0$ and, since $V_{\mathrm{s}}(\cdot)$ and Q are positive–definite, $V(\tilde{e},\tilde{W})>0$ for all $(\tilde{e},\tilde{W})\neq(0,0)$. Next, letting $\tilde{e}(t)$, $t\geq 0$, denote the solutions to (38) and using (25), (28), (32) and (33), it follows that the time derivative of $V(\tilde{e},\tilde{W})$ along the closed-loop system trajectories is given by (40), shown at the bottom of the page. Now, for each $i\in\{1,\ldots,m\}$ and for the two cases given in (35), the last term on the right-hand side of (40), gives the following.

1) If $\hat{u}_i(t)<0$, then $\hat{W}_{\mathrm{u}i}(t)=0$ and, hence

$$\begin{aligned}&\tilde{y}_i(t)g_i(x(t))(\hat{W}_{\mathrm{u}i}(t)-W_i)^{\mathrm{T}}\sigma_i(y(t))\\&\quad-\tilde{y}_i(t)\tilde{W}_i^{\mathrm{T}}(t)\sigma_i(y(t))-\gamma_i|\tilde{y}_i(t)|\tilde{W}_i^{\mathrm{T}}(t)\hat{W}_i(t)\\&=-\tilde{y}_i(t)g_i(x(t))W_i^{\mathrm{T}}\sigma_i(y(t))-\tilde{y}_i(t)\tilde{W}_i^{\mathrm{T}}(t)\sigma_i(y(t))\\&\quad-\gamma_i|\tilde{y}_i(t)|\tilde{W}_i^{\mathrm{T}}(t)(\tilde{W}_i(t)+W_i)\\&\leq|\tilde{y}_i(t)|\Big[\sqrt{s_i}\mu w_i^*+(\sqrt{s_i}+\gamma_i w_i^*)\|\tilde{W}_i(t)\|-\gamma_i\|\tilde{W}_i(t)\|^2\Big].\end{aligned}$$

2) Otherwise, $\hat{W}_{\mathrm{u}i}(t)=\hat{W}_i(t)$ and, hence

$$\begin{aligned}&\tilde{y}_i(t)g_i(x(t))(\hat{W}_{\mathrm{u}i}(t)-W_i)^{\mathrm{T}}\sigma_i(y(t))\\&\quad-\tilde{y}_i(t)\tilde{W}_i^{\mathrm{T}}(t)\sigma_i(y(t))-\gamma_i|\tilde{y}_i(t)|\tilde{W}_i^{\mathrm{T}}(t)\hat{W}_i(t)\\&=-\tilde{y}_i(t)\tilde{W}_i^{\mathrm{T}}(t)\sigma_i(y(t))-\gamma_i|\tilde{y}_i(t)|\tilde{W}_i^{\mathrm{T}}(t)(\tilde{W}_i(t)+W_i)\\&\leq\sqrt{s_i}\mu w_i^*|\tilde{y}_i(t)|+\sqrt{s_i}|\tilde{y}_i(t)|\|\tilde{W}_i(t)\|\\&\quad-\gamma_i|\tilde{y}_i(t)|\|\tilde{W}_i(t)\|^2+\gamma_i w_i^*|\tilde{y}_i(t)|\|\tilde{W}_i(t)\|\\&\leq|\tilde{y}_i(t)|\Big[\sqrt{s_i}\mu w_i^*+(\sqrt{s_i}+\gamma_i w_i^*)\|\tilde{W}_i(t)\|-\gamma_i\|\tilde{W}_i(t)\|^2\Big].\end{aligned}$$

Hence, it follows from (40) that in either case:

$$\begin{aligned}&\dot{V}(\tilde{e}(t),\tilde{W}(t))\\&\leq-\rho V_{\mathrm{s}}(\tilde{e}(t))-\sum_{i=1}^{m}\tilde{y}_i(t)g_i(x(t))\varepsilon_i(x(t))\\&\quad+\sum_{i=1}^{m}|\tilde{y}_i(t)|\Big(\sqrt{s_i}\mu w_i^*+(\sqrt{s_i}+\gamma_i w_i^*)\|\tilde{W}_i(t)\|-\gamma_i\|\tilde{W}_i(t)\|^2\Big)\\&\leq\|\tilde{e}(t)\|\Bigg[-\rho\alpha\|\tilde{e}(t)\|+\sum_{i=1}^{m}(\sqrt{s_i}w_i^*+\varepsilon_i^*)\mu\\&\quad+\sum_{i=1}^{m}(\sqrt{s_i}+\gamma_i w_i^*)\|\tilde{W}_i(t)\|-\sum_{i=1}^{m}\gamma_i\|\tilde{W}_i(t)\|^2\Bigg].\end{aligned} \tag{41}$$

Next, completing squares yields

$$\begin{aligned}&\dot{V}(\tilde{e}(t),\tilde{W}(t))\\&\leq\|\tilde{e}(t)\|\Bigg[-\rho\alpha\|\tilde{e}(t)\|+\sum_{i=1}^{m}(\sqrt{s_i}w_i^*+\varepsilon_i^*)\mu\\&\quad-\sum_{i=1}^{m}\gamma_i\Big(\|\tilde{W}_i(t)\|-\frac{\sqrt{s_i}+\gamma_i w_i^*}{2\gamma_i}\Big)^2+\sum_{i=1}^{m}\frac{(\sqrt{s_i}+\gamma_i w_i^*)^2}{4\gamma_i}\Bigg]\\&=\|\tilde{e}(t)\|\Bigg[-\rho\alpha\|\tilde{e}(t)\|-\sum_{i=1}^{m}\gamma_i\Big(\|\tilde{W}_i(t)\|-\frac{\sqrt{s_i}+\gamma_i w_i^*}{2\gamma_i}\Big)^2+\nu\Bigg]\end{aligned} \tag{42}$$

$$\begin{aligned}\dot{V}(\tilde{e}(t),\tilde{W}(t))=&V_{\mathrm{s}}'(\tilde{e}(t))\Big[[\tilde{f}(\tilde{e})+\tilde{G}(\tilde{e}(t))\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]\\&+[\tilde{G}(\tilde{e}(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]G(x(t))[\hat{W}^{\mathrm{T}}(t)\sigma(y(t))-\alpha_{\tilde{\mathcal{D}}_{\mathrm{c}}}(x(t)-y_{\mathrm{d}})-G^{-1}(x(t))G(y_{\mathrm{d}})u_{\mathrm{e}}]\\&+[\tilde{G}(e(t))\beta_{\tilde{\mathcal{D}}_{\mathrm{c}}}(e_x(t))]G(x(t))(\hat{W}_{\mathrm{u}}(t)-\hat{W}(t))^{\mathrm{T}}\sigma(y(t))\Big]+2\operatorname{tr}\tilde{W}^{\mathrm{T}}(t)Q^{-1}\dot{\hat{W}}(t)\\\leq&-\rho V_{\mathrm{s}}(\tilde{e}(t))-\sum_{i=1}^{m}\tilde{y}_i(t)g_i(x(t))\varepsilon_i(x(t))\\&+\sum_{i=1}^{m}\Big[\tilde{y}_i(t)g_i(x(t))(\hat{W}_{\mathrm{u}i}(t)-W)^{\mathrm{T}}\sigma_i(y(t))-\tilde{y}_i(t)\tilde{W}_i^{\mathrm{T}}(t)\sigma_i(y(t))-\gamma_i|\tilde{y}_i(t)|\tilde{W}_i^{\mathrm{T}}(t)\hat{W}_i(t)\Big].\end{aligned} \tag{40}$$

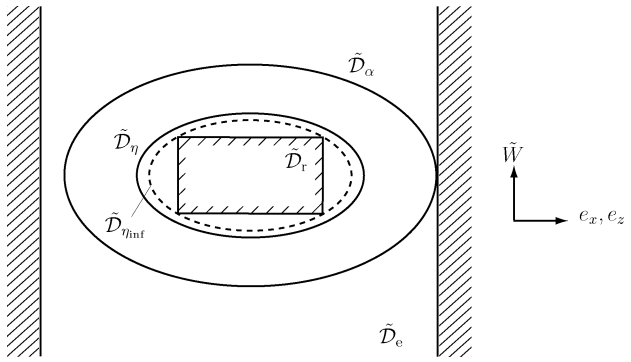

Fig. 1. Visualization of sets used in the proof of Theorem 3.1.

where ν is given by (30). Now, for

$$\|\tilde{e}\| \geq \frac{\nu}{\rho\alpha} \triangleq \alpha_{\tilde{e}} \tag{43}$$

or

$$\|\tilde{W}\|_F \geq \sqrt{\sum_{i=1}^{m}\Big(\frac{\sqrt{s_i}+\gamma_i w_i^*}{2\gamma_i}\Big)^2} + \sqrt{\frac{\nu}{\gamma_{\min}}} \triangleq \alpha_{\tilde{W}} \tag{44}$$

it follows that $\dot{V}(\tilde{e}(t),\tilde{W}(t)) \leq 0$ for all $t \geq 0$; that is, $\dot{V}(\tilde{e}(t),\tilde{W}(t)) \leq 0$ for all $(e_x(t),e_z(t),\tilde{W}(t)) \in \tilde{\mathcal{D}}_e \backslash \tilde{\mathcal{D}}_r$ and $t \geq 0$, where

$$\tilde{\mathcal{D}}_e \triangleq \Big\{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : x \in \mathcal{D}_{cx}\Big\} \tag{45}$$

$$\tilde{\mathcal{D}}_r \triangleq \Big\{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : \|\tilde{e}\| \leq \alpha_{\tilde{e}},\ \|\tilde{W}\|_F \leq \alpha_{\tilde{W}}\Big\}. \tag{46}$$

Next, define

$$\tilde{\mathcal{D}}_\alpha \triangleq \Big\{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : V(\tilde{e},\tilde{W}) \leq \alpha\Big\} \tag{47}$$

where α is the maximum value such that $\tilde{\mathcal{D}}_\alpha \cap \tilde{\mathcal{D}}_e = \tilde{\mathcal{D}}_\alpha$, and define

$$\tilde{\mathcal{D}}_\eta \triangleq \Big\{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : V(\tilde{e},\tilde{W}) \leq \eta\Big\} \tag{48}$$

where

$$\eta > \max_{\|\tilde{e}\|=\alpha_{\tilde{e}}} V_s(\tilde{e}) + \max_{\|\tilde{W}\|_F=\alpha_{\tilde{W}}} \operatorname{tr}\tilde{W}Q^{-1}\tilde{W}^T = \beta\alpha_{\tilde{e}}^2 + q_{\min}\alpha_{\tilde{W}}^2. \tag{49}$$

To show ultimate boundedness of the closed-loop system (28) and (38), assume[2] that $\tilde{\mathcal{D}}_\eta \subset \tilde{\mathcal{D}}_\alpha$ (see Fig. 1). Now, since $\dot{V}(\tilde{e},\tilde{W}) \leq 0$ for all $(e_x,e_z,\tilde{W}) \in \tilde{\mathcal{D}}_e \backslash \tilde{\mathcal{D}}_r$ and $\tilde{\mathcal{D}}_r \subset \tilde{\mathcal{D}}_\alpha$, it follows that $\tilde{\mathcal{D}}_\alpha$ is positively invariant. Hence, if $(e_x(0),e_z(0),\tilde{W}(0)) \in \tilde{\mathcal{D}}_\alpha$, then the solution $(e_x(t),e_z(t),\tilde{W}(t))$, $t \geq 0$, to (28) and (38) is ultimately bounded. Furthermore, since $\tilde{\mathcal{D}}_\alpha$ is positively invariant, it follows that:

$$\mathcal{D}_\alpha \triangleq \Big\{(x,z,\hat{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : (x-y_d, z-z_e, \hat{W}-W) \in \tilde{\mathcal{D}}_\alpha\Big\} \tag{50}$$

is also positively invariant. Now, to show that $\|y(t)-y_d\|^2 < \epsilon_1$, $t \geq T = T(x_0,z_0,\hat{W}_0,\epsilon_1)$, suppose there exists $t^* \geq 0$ such that $\tilde{e}(t^*) = 0$ and $\tilde{W}(t^*) = 0$. In this case, $\tilde{e}(t) = 0$ and $\tilde{W}(t) = 0$ for all $t \geq t^*$ and, hence, $\|y(t)-y_d\|^2 < \epsilon_1$ is trivially satisfied for all $t \geq t^*$. Alternatively, suppose there does not exist $t^* \geq 0$ such that $e(t^*) = 0$ and $\tilde{W}(t^*) = 0$. In this case, consider the Lyapunov-like function

$$\tilde{V}(\tilde{e},\tilde{W}) = \begin{cases} V(\tilde{e},\tilde{W}) - \eta_{\inf}, & (e_x,e_z,\tilde{W}) \in \mathcal{D}_\alpha \backslash \mathcal{D}_{\eta_{\inf}} \\ 0, & (e_x,e_z,\tilde{W}) \in \mathcal{D}_{\eta_{\inf}} \end{cases} \tag{51}$$

where $\eta_{\inf} \triangleq \beta\alpha_{\tilde{e}}^2 + q_{\min}\alpha_{\tilde{W}}^2$ and

$$\tilde{\mathcal{D}}_{\eta_{\inf}} \triangleq \{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : V(\tilde{e},\tilde{W}) \leq \eta_{\inf}\}.$$

Note that $\tilde{V}(\tilde{e},\tilde{W})$ is continuous on $\mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m}$ and $\tilde{\mathcal{D}}_\eta$ is positively invariant. Furthermore, note that

$$\tilde{V}(\tilde{e}(t),\tilde{W}(t)) \leq \tilde{V}(\tilde{e}(\tau),\tilde{W}(\tau)), \quad 0 \leq \tau \leq t. \tag{52}$$

Now, it follows from the generalized Krasovskii–LaSalle invariant set theorem [33, Th. 2.3] that $(e_x(t),e_z(t),\hat{W}(t)) \to \mathcal{M} \triangleq \cup_{\gamma>0}\mathcal{M}_\gamma$ as $t \to \infty$, where $\mathcal{M}_\gamma$ denotes the largest invariant set contained in $\mathcal{R}_\gamma \triangleq \{(e_x,e_z,\tilde{W}) \in \mathbb{R}^m \times \mathbb{R}^{n-m} \times \mathbb{R}^{s\times m} : \tilde{V}(\tilde{e},\tilde{W}) = \gamma\}$. Hence, since $\mathcal{M}_\gamma = \emptyset$, $\gamma > 0$, and $\mathcal{R}_0 = \tilde{\mathcal{D}}_{\eta_{\inf}} \subset \tilde{\mathcal{D}}_\eta$, there exists $T = T(x_0,z_0,\hat{W}_0,\epsilon_1) \geq 0$ such that $(e_x(t),e_z(t),\hat{W}(t)) \in \tilde{\mathcal{D}}_\eta$ for all $t \geq T$ and, hence

$$\|\tilde{e}(t)\|^2 < \max\{\|\tilde{e}\|^2 \in \mathbb{R} : V_s(\tilde{e}) = \eta\} = \frac{\eta}{\alpha}, \quad t \geq T. \tag{53}$$

Since $\|e_x\| \leq \|\tilde{e}\|$, (53) implies $\|y(t)-y_d\|^2 < \epsilon_1$, $t \geq T$.

Finally, $u(t) \geq\geq 0$, $t \geq 0$, is a restatement of (26). Now, since $f(\tilde{x}) \triangleq [f_x^T(x,z), f_z^T(x,z)]^T$ is essentially nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^m$, and $u(t) \geq\geq 0$, $t \geq 0$, it follows from Proposition 2.1 that $x(t) \geq\geq 0$ and $z(t) \geq\geq 0$ for all $t \geq 0$ and $(x_0,z_0) \in \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m}$. □

Remark 3.1: It follows from Theorem 2.2 that if $\mathcal{G}$ given by (8)–(10) is exponentially minimum phase, then $\mathcal{G}$ is semiglobally output feedback exponentially passive. Hence, for any arbitrarily large compact set $\tilde{\mathcal{D}}_c$ there exists an output feedback control law of the form (14) that renders the closed-loop system (8)–(10) exponentially passive. For this compact set $\tilde{\mathcal{D}}_c$, as is common in the neural network literature, we assume that there exists an approximator for the unknown nonlinear map $\alpha_{\mathcal{D}_c}(x-y_d) - G^{-1}(x)G(y_d)u_e$ up to a desired accuracy. Furthermore, we assume that in the error space $\tilde{\mathcal{D}}_e$ there exists at least one Lyapunov level set such that $\tilde{\mathcal{D}}_\eta \subset \tilde{\mathcal{D}}_\alpha$.

A block diagram showing the neuro adaptive control architecture given in Theorem 3.1 is shown in Fig. 2. In Theorem 3.1, we assumed that the equilibrium point (y_d,z_e) of (8), (9) is globally asymptotically stable with $u(t) \equiv u_e$. In general, however, unlike linear nonnegative systems with asymptotically stable plant

[2]This assumption is standard in the neural network literature and ensures that in the error space $\tilde{\mathcal{D}}_e$ there exists at least one Lyapunov level set $\tilde{\mathcal{D}}_\eta \subset \tilde{\mathcal{D}}_\alpha$. In the case where the neural network approximation holds in $\mathbb{R}^m \times \mathbb{R}^{n-m}$, this assumption is automatically satisfied. See Remark 3.1 for further details.

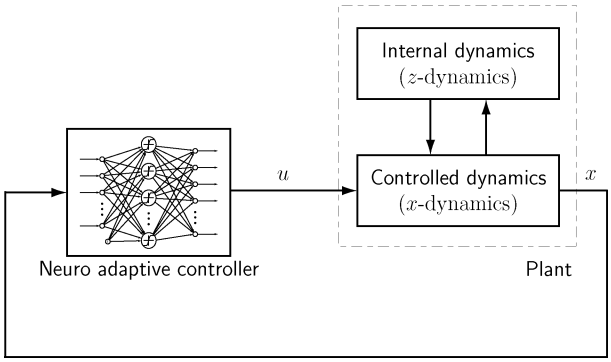

Fig. 2. Block diagram of the closed-loop system.

dynamics, a given set point $(y_{\rm d}, z_{\rm e}) \in \mathbb{R}_+^m \times \mathbb{R}_+^{n-m}$ for the nonlinear nonnegative dynamical system (8), (9) may not be asymptotically stabilizable with a constant control $u(t) \equiv u_{\rm e} \in \overline{\mathbb{R}}_+^h$. However, if $f(\tilde{x}) \triangleq [f_x^{\rm T}(x,z), f_z^{\rm T}(x,z)]^{\rm T}$ is homogeneous, cooperative; that is, the Jacobian matrix $\partial f(\tilde{x})/\partial \tilde{x}$ is essentially nonnegative for all $\tilde{x} \triangleq [x^{\rm T}, z^{\rm T}]^{\rm T} \in \overline{\mathbb{R}}_+^n$, the Jacobian matrix $\partial f(\tilde{x})/\partial \tilde{x}$ is irreducible for all $\tilde{x} \in \overline{\mathbb{R}}_+^n$ [29], and the zero solution $(x(t), z(t)) \equiv 0$ of the undisturbed $(u(t) \equiv 0)$ system (8), (9) is globally asymptotically stable, then the set point $(y_{\rm d}, z_{\rm e}) \in \mathbb{R}_+^m \times \mathbb{R}_+^{n-m}$ satisfying (20) and (21) is a unique equilibrium point with $u(t) \equiv u_{\rm e}$ and is also asymptotically stable for all $(y_0, z_0) \in \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m}$ [34]. This implies that the solution $(x(t), z(t)) \equiv (y_{\rm d}, z_{\rm e})$ to (8), (9) with $u(t) \equiv u_{\rm e}$ is asymptotically stable for all $(y_0, z_0) \in \overline{\mathbb{R}}_+^m \times \overline{\mathbb{R}}_+^{n-m}$.

IV. Neural Adaptive Control for General Anesthesia

Almost all anesthetics are myocardial depressants which lower cardiac output (i.e., the amount of blood pumped by the heart per unit time). As a consequence, decreased cardiac output slows down redistribution kinetics; that is, the transfer of blood from the central compartments (heart, brain, kidney, and liver) to the peripheral compartments (muscle and fat). In addition, decreased cardiac output could increase drug concentrations in the central compartments causing even more myocardial depression and further decrease in cardiac output. To study the effects of pharmacological agents and anesthetics we propose the nonlinear two-compartment model shown in Fig. 3, where x_1 denotes the mass of drug in the central compartment, which is the site for drug administration and is generally thought to be comprised of the intravascular blood volume as well as highly perfused organs such as the heart, brain, kidney, and liver. These organs receive a large fraction of the cardiac output. Alternatively, x_2 is the mass of drug in the peripheral compartment, comprised of muscle and fat which receive a smaller proportion of the cardiac output.

A mass balance of the two-state compartment model yields

$$\dot{x}_1(t) = -a_{21}(c(t))x_1(t) - a_{\rm e}(c(t))x_1(t) + a_{12}(c(t))x_2(t) + u(t), \quad x_1(0) = x_{10}, \quad t \geq 0 \tag{54}$$

$$\dot{x}_2(t) = a_{21}(c(t))x_1(t) - a_{12}(c(t))x_2(t), \quad x_2(0) = x_{20} \tag{55}$$

where $c \triangleq x_1/V_{\rm c}$ is the drug concentration in the central compartment, $V_{\rm c}$ is the volume of the central compartment, $a_{21}(c)$ is the rate of transfer of drug from Compartment I to Compartment II, $a_{12}(c)$ is the rate of transfer of drug from Compartment II to Compartment I, $a_{\rm e}(c)$ is the rate of drug metabolism and elimination (metabolism typically occurs in the liver), and $u(t)$, $t \geq 0$, is the infusion rate of an anesthetic drug. In order to formulate a physiologically realistic nonlinear model, we assume that the rate transfers are proportional to the cardiac output. This reflects the fact that the drug transfer from the central compartment to the peripheral compartment (or *vice versa*) requires physical transport via the blood stream from the heart, brain, etc., to muscle and fat (or *vice versa*). It is generally assumed that this transport in the vascular tree will be proportional to the cardiac output $Q(c)$. Furthermore, for many drugs the rate of metabolism (i.e., $a_{\rm e}(c)$) will be proportional to the rate of transport of drug to the liver and, hence, we assume that $a_{\rm e}(c)$ is also proportional to the cardiac output. Thus, we assume $a_{21}(c) = A_1 Q(c)$, $a_{12}(c) = A_2 Q(c)$, and $a_{\rm e}(c) = A_{\rm e} Q(c)$, where A_1, A_2, and $A_{\rm e}$ are positive constants. Many anesthetics depress the heart, decreasing the cardiac output. Furthermore, the transfer coefficients are functions of the concentration c in the central compartment. Thus, to develop a physiologically plausible model we assume a sigmoid relationship between drug concentration in the central compartment and effect so that $Q(c) = Q_0 {\rm C}_{50}^{\alpha}/({\rm C}_{50}^{\alpha} + c^{\alpha})$, where the effect is related to c (since that is the presumed concentration in the highly perfused myocardium), $Q_0 > 0$ is a constant, ${\rm C}_{50} > 0$ is the drug concentration associated with a 50% decrease in the cardiac output, and $\alpha > 1$ determines the steepness of this curve (that is, how rapidly the cardiac output decreases with increasing drug concentration). Furthermore, this model assumes instantaneous mixing and as c increases, the rate coefficients decrease through their dependence on the cardiac output. Even though the transfer and loss coefficients A_1, A_2, and $A_{\rm e}$ are nonnegative, and $\alpha > 1$, ${\rm C}_{50} > 0$, 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 crucial.

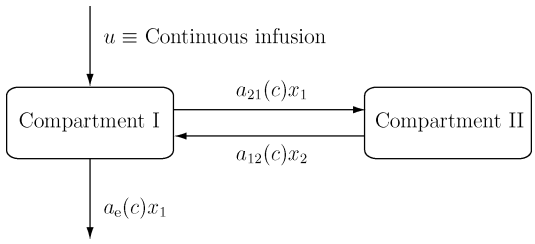

Fig. 3. Pharmacokinetic model for drug distribution during anesthesia.

Midazolam is an intravenous anesthetic that has been used for both induction and maintenance of general anesthesia. A simple yet effective patient model for the disposition of midazolam is based on the two-compartment model shown in Fig. 3 with the first compartment acting as the central compartment. Here, we use the BIS as a measure of anesthetic effect. The BIS signal is a nonlinear monotonically decreasing function of the level of consciousness and is given by

$${\rm BIS}(c_{\rm eff}) = {\rm BIS}_0 \left(1 - \frac{c_{\rm eff}^{\gamma}}{c_{\rm eff}^{\gamma} + {\rm EC}_{50}^{\gamma}}\right) \tag{56}$$

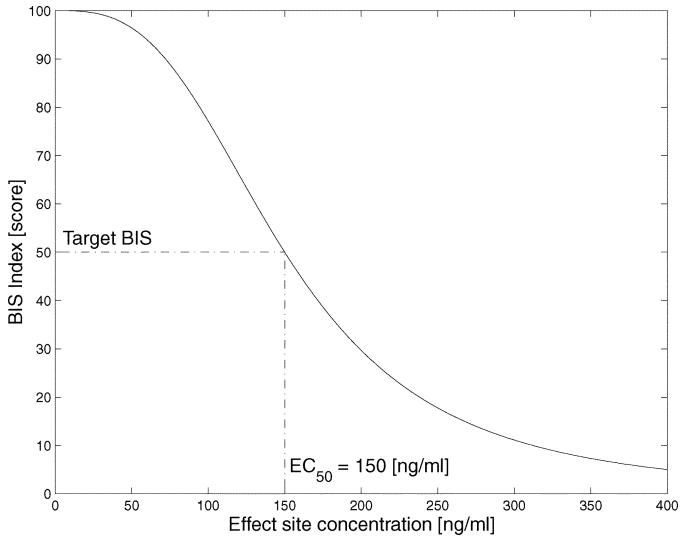

Fig. 4. BIS index versus effect site concentration.

where BIS_0 denotes the baseline (awake state) value and, by convention, is typically assigned a value of 100, c_{eff} is the midazolam concentration in nanograms/liter in the effect site compartment (brain), EC_{50} is the concentration at half maximal effect and represents the patient's sensitivity to the drug, and γ determines the degree of nonlinearity in (56). Here, the effect site compartment is introduced as a correlate between the central compartment concentration and the central nervous system concentration. The effect site compartment concentration is related to the concentration in the central compartment by the first-order delay model

$$\dot{c}_{\mathrm{eff}}(t) = a_{\mathrm{eff}}(c(t) - c_{\mathrm{eff}}(t)), \quad c_{\mathrm{eff}}(0) = x_1(0), \quad t \geq 0 \tag{57}$$

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

$$c_{\mathrm{eff}}(t) = \int_0^t e^{-a_{\mathrm{eff}}(t-s)} a_{\mathrm{eff}} c(s)\, \mathrm{d}s. \tag{58}$$

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

In the following numerical simulation we set $\mathrm{EC}_{50} = 150\ \mathrm{ng/m}\ell$, $\gamma = 3$, and $\mathrm{BIS}_0 = 100$, so that the BIS signal is shown in Fig. 4. The target (desired) BIS value, $\mathrm{BIS}_{\mathrm{target}}$, is set at 50. Furthermore, for simplicity of exposition, we assume that the effect site compartment equilibrates instantaneously with the central compartment; that is, we assume that $a_{\mathrm{eff}} \to \infty$, so that (57) gives $c_{\mathrm{eff}}(t) = c(t)$, $t \geq 0$. Now, defining $x \triangleq \mathrm{BIS}_0 - \mathrm{BIS}(c) = h(c)$ and $z \triangleq x_2$, where $h(c) \triangleq c^\gamma/(c^\gamma + \mathrm{EC}_{50}^\gamma)$, (54), (55) can be written in form of (8)–(10) with

$$f_x(x,z) = h'(c)\Big[-a_{21}(c)h^{-1}(x) - a_{\mathrm{e}}(c)h^{-1}(x) + \frac{a_{12}(c)z}{V_{\mathrm{c}}}\Big] \tag{59}$$

$$f_z(x,z) = V_{\mathrm{c}}[a_{21}(c)h^{-1}(x) - a_{12}(c)z] \tag{60}$$

$$G(x) = \frac{h'(c)}{V_{\mathrm{c}}}. \tag{61}$$

Note that $f_x(x,z)$ is essentially nonnegative with respect to x, $f_z(x,z)$ is essentially nonnegative with respect to z, and $G(x)$ is nonnegative. In addition, note that since $h(\cdot)$ is a monotonically increasing function, the mapping $(x_1, x_2) \mapsto (x,z)$ is diffeomorphic. Furthermore, note that since

$$\tilde{f}_z(0, e_z) = -a_{12}\left(\frac{y_{\mathrm{d}1}}{V_{\mathrm{c}}}\right) e_z \tag{62}$$

where

$$\tilde{f}_z(e_x, e_z) = f_z(e_x + y_{\mathrm{d}}, e_z + z_{\mathrm{e}}) - f_z(y_{\mathrm{d}}, z_{\mathrm{e}}) \tag{63}$$

and $a_{12}(y_{\mathrm{d}1}/V_{\mathrm{c}}) > 0$, it follows that the system zero dynamics are exponentially stable and, hence, the system given by (54), (55) is exponentially minimum phase at $(y_{\mathrm{d}}, z_{\mathrm{e}})$. Thus, since the input matrix function satisfies (17), it follows from Theorem 2.2 that (54), (55) is semiglobally output feedback exponentially passive. Now, using the adaptive output feedback controller

$$u(t) = \max\{0, \hat{u}(t)\} \tag{64}$$

where

$$\hat{u}(t) = \hat{W}^{\mathrm{T}}(t)\sigma(\mathrm{BIS}(t)) \tag{65}$$

$\hat{W}(t) \in \mathbb{R}^s$, $t \geq 0$, and $\sigma : \mathbb{R} \to \mathbb{R}^s$ is a given basis function, with update law

$$\dot{\hat{W}}(t) = q_{\mathrm{BIS}}\Big[(-\mathrm{BIS}(t) + \mathrm{BIS}_{\mathrm{target}})\sigma(\mathrm{BIS}(t)) - \gamma|\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}|\hat{W}(t)\Big], \quad \hat{W}(0) = \hat{W}_0 \tag{66}$$

where q_{BIS} is an arbitrary positive constant, it follows from Theorem 3.1 that the control input (anesthetic infusion rate) $u(t)$ is nonnegative for all $t \geq 0$ and there exist positive constants ε and T such that $|\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}| \leq \varepsilon$, $t \geq T$, for all (uncertain) positive values of the transfer and loss coefficients $(A_1, A_2, A_{\mathrm{e}})$ as well as all (uncertain) nonnegative coefficients α, C_{50}, and Q_0. It is important to note that during actual surgery the BIS signal is obtained directly from the EEG and not (56). For our simulation we assume $V_{\mathrm{c}} = 31\ \ell$, $A_1 Q_0 = 0.018\,95\ \mathrm{min}^{-1}$, $A_2 Q_0 = 0.010\,03\ \mathrm{min}^{-1}$, $A_{\mathrm{e}} Q_0 = 0.016\,51\ \mathrm{min}^{-1}$, $\alpha = 3$, and $\mathrm{C}_{50} = 200\ \mathrm{ng/m}\ell$. Note that these parameter values for α and C_{50} probably exaggerate the effect of midazolam on cardiac output. They have been

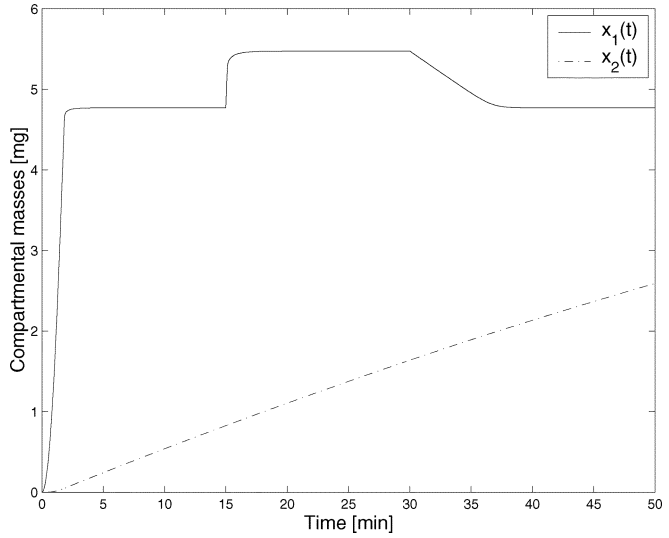

Fig. 5. Compartmental concentrations versus time.

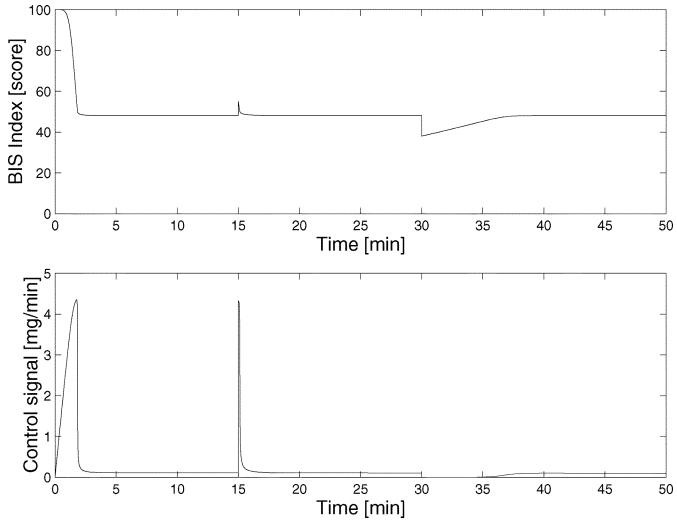

Fig. 6. BIS index versus time and control signal (infusion rate) versus time.

selected to accentuate nonlinearity but they are not biologically unrealistic. To illustrate the efficacy of the proposed neuro adaptive controller we switch the pharmacodynamic parameters EC_{50} and γ, respectively, from 150 $\mathrm{ng/m}\ell$ and 3 to 170 $\mathrm{ng/m}\ell$ and 2 at $t = 15$ min and back to 150 $\mathrm{ng/m}\ell$ and 3 at $t = 30$ min. Furthermore, here we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $q_{\mathrm{BIS}} = 1 \times 10^4$, $\gamma = 1 \times 10^{-10}$, $s = 6$

$$\sigma(\mathrm{BIS}) = \left[\frac{1}{1+e^{-a(\mathrm{BIS}-\mathrm{BIS}_{\mathrm{target}})}}, \ldots, \frac{1}{1+e^{-6a(\mathrm{BIS}-\mathrm{BIS}_{\mathrm{target}})}}\right]^{\mathrm{T}}$$

$a = 1$, and initial conditions $x_1(0) = 0$ mg, $x_2(0) = 0$ mg, $\hat{W}(0) = 0_{6\times 1}$ mg/min, Fig. 5 shows the concentrations of midazolam in the two compartments versus time. Fig. 6 shows the BIS index and the control signal (midazolam infusion rate) versus time.

Even though we did not calculate the analytical bounds given by (29) due to the fact that one has to solve an optimization problem with respect to (25) to obtain ε_i^* and w_i^*, $i = 1, \ldots, 6$, the closed-loop BIS signal response shown in Fig. 6 is clearly acceptable. Furthermore, the basis functions for $\sigma(\mathrm{BIS})$ are chosen to cover the domain of interest of our pharmacokinetic/pharmacodynamic problem since we know that the BIS index varies from 0 to 100. Hence, the basis functions are distributed over that domain. The number of basis functions, however, is based on trial and error. This goes back to the Stone–Weierstrass theorem, which only provides an existence result without any constructive guidelines. Finally, we note that simulations using a larger number of neurons resulted in imperceptible differences in the closed-loop system performance.

V. Conclusion

Nonnegative and compartmental systems are widely used to capture system dynamics involving the interchange of mass and energy between homogenous subsystems or compartments. Thus, it is not surprising that nonnegative and compartmental models are remarkably effective in describing the dynamical behavior of biological systems, physiological systems, and pharmacological systems. In this paper, we developed a neural adaptive output feedback control framework for adaptive set-point regulation of nonlinear uncertain nonnegative and compartmental systems. Using Lyapunov methods, the proposed framework was shown to guarantee ultimate boundedness of the error signals corresponding to the physical system states and the neural network weighting gains while additionally guaranteeing the nonnegativity of the closed-loop system states associated with the plant dynamics. Finally, using a nonlinear two-compartment patient model for the disposition of anesthetic drug midazolam, the proposed adaptive control framework was used to monitor and control 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. 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.

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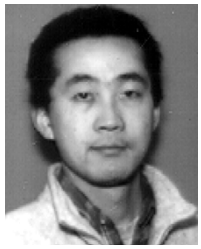

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