Neural Network Adaptive Dynamic Output Feedback Control for Nonlinear Nonnegative Systems using Tapped Delay Memory Units

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***Abstract*— The potential applications of neural adaptive 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 nonlinear uncertain nonnegative and compartmental systems. The proposed framework is Lyapunov-based and guarantees ultimate boundedness of the error signals. In addition, the neural adaptive controller guarantees that the physical system states remain in the nonnegative orthant of the state space. Finally, the proposed approach is used to control the infusion of the anesthetic drug propofol for maintaining a desired constant level of depth of anesthesia for noncardiac surgery.**

I. Introduction

Neural networks offer an ideal framework for on-line system identification and control of many complex uncertain nonlinear dynamical systems. One of the key aspects of neural networks is that a very rich class of continuous nonlinear maps can be approximated from the collective action of very simple, autonomous processing units interconnected in simple ways. This massively parallel and highly redundant processing architecture has resulted in concrete accomplishments in pattern recognition, system identification, and adaptive control.

Given the complexity, uncertainties, and nonlinearities inherent in pharmacokinetic and pharmacodynamic models needed to capture the wide effects of pharmacological agents and anesthetics in the human body, neural networks can provide an ideal framework for addressing adaptive control for clinical pharmacology [1]. 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 [2] 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.

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In this paper, we extend the results of [3] to nonnegative and compartmental dynamical systems with applications to the specific problem of automated anesthesia. Specifically, we develop an output feedback neural network adaptive controller that operates over a tapped delay line of available input and output measurements. The neuro adaptive laws for the neural network weights are constructed using a linear observer for the nominal normal form system error dynamics. The approach is applicable to general class of nonlinear nonnegative dynamical systems without imposing a strict positive real requirement on the transfer function of the linear error normal form dynamics. Furthermore, since in pharmacological applications involving active drug administration control inputs as well as the system states need to be nonnegative, the proposed neuro adaptive output feedback controller also guarantees that the control signal remains nonnegative. We emphasize that the proposed framework addresses adaptive *output feedback* controllers for nonlinear compartmental systems with *unmodeled dynamics* of *unknown dimension* while guaranteing ultimate boundedness of the error signals corresponding to the physical system states as well as the neural network weighting gains. Output feedback controllers are crucial in clinical pharmacology since key physiological (state) variables cannot be measured in practice.

II. Mathematical Preliminaries

In this section we introduce notation, several definitions, and some key results concerning linear and nonlinear nonnegative dynamical systems [2], [4] that are necessary for developing the main results of this paper. Specifically, for $x \in \mathbb{R}^n$ we write $x \geq\geq 0$ (resp., $x >> 0$) to indicate that every component of x is nonnegative (resp., positive). In this case we say that x is *nonnegative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n\times m}$ is *nonnegative* or *positive* if every entry of A is nonnegative or positive, respectively, which is written as $A \geq\geq 0$ or $A >> 0$, 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 $x >> 0$. Furthermore, we write $(\cdot)^{\mathrm{T}}$ to denote transpose, $\mathrm{tr}(\cdot)$ for the trace operator, $\lambda_{\min}(\cdot)$ to denote the minimum eigenvalue of a Hermitian matrix, $\|\cdot\|$ for a Euclidean vector norm, $\|\cdot\|_{\mathrm{F}}$ for the Frobenius matrix norm, and $V'(x)$ for the Fréchet derivative of V at x. Finally, $M \otimes N$ denotes the Kronecker product of matrices M and N. The following definition introduces the notion of a nonnegative (resp., positive) function.

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

The next definition introduces the notions of essentially nonnegative matrices and compartmental matrices.

Definition 2.2 ([2]): Let $A \in \mathbb{R}^{n\times n}$. A is *essentially nonnegative* if $A_{(i,j)} \geq 0$, $i, j = 1, \cdots, n$, $i \neq j$. A is *compartmental* if A is essentially nonnegative and $\sum_{i=1}^{n} A_{(i,j)} \leq 0$, $j = 1, \cdots, n$.

The following definition introduces the notion of essentially nonnegative vector fields [2].

Definition 2.3: Let $f = [f_1, \cdots, f_n]^{\mathrm{T}} : \mathcal{D} \to \mathbb{R}^n$, where $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ that contains $\overline{\mathbb{R}}^n_+$. Then f is *essentially nonnegative* if $f_i(x) \geq 0$, 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.

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

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

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

The following definition and proposition are needed for the main results of the paper.

Definition 2.4: 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.

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

In this section we consider the problem of characterizing neural adaptive dynamic 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 square nonlinear uncertain dynamical system $\mathcal{G}$ given by

$$\dot{x}(t) = f(x(t)) + G(x(t))u(t), \quad x(0) = x_0, \quad t \geq 0, \tag{2}$$
$$y(t) = h(x(t)), \tag{3}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, is the state vector, $u(t) \in \mathbb{R}^m$, $t \geq 0$, is the control input, $y(t) \in \mathbb{R}^m$, $t \geq 0$, is the system output, $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative but otherwise unknown and satisfies $f(0) = 0$, $G : \mathbb{R}^n \to \mathbb{R}^{n\times m}$ is an unknown nonnegative input matrix function, and $h : \mathbb{R}^n \to \mathbb{R}^m$ is a nonnegative function and satisfies $h(0) = 0$. We assume that $f(\cdot)$, $G(\cdot)$, and $h(\cdot)$ are smooth (i.e., C^∞ mappings) and the control input $u(\cdot)$ in (2) 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 dynamic output feedback control laws for essentially nonnegative systems with nonnegative control inputs. Specifically, for a given desired set point $y_{\mathrm{d}} \in \overline{\mathbb{R}}^m_+$ and for a given $\varepsilon > 0$, our aim is to design a nonnegative control input $u(t)$, $t \geq 0$, predicated on the system measurement $y(t)$, $t \geq 0$, such that $\|y(t) - y_{\mathrm{d}}\| < \varepsilon$ for all $t \geq T$, where $T \in [0, \infty)$, and $x(t) \geq\geq 0$, $t \geq 0$, and $u(t) \geq\geq 0$, $t \geq 0$, for all $x_0 \in \overline{\mathbb{R}}^n_+$.

In this paper, we assume that for the nonlinear dynamical system (2), (3), the conditions for the existence of a globally defined diffeomorphism transforming (2), (3) into normal form [5], [6] are satisfied so that there exists a global diffeomorphism $\mathcal{T} : \mathbb{R}^n \to \mathbb{R}^n$, a C^∞ function $f_\xi : \mathbb{R}^r \times \mathbb{R}^{n-r} \to \mathbb{R}^r$, and a C^∞ function $f_z : \mathbb{R}^r \times \mathbb{R}^{n-r} \to \mathbb{R}^{n-r}$ such that, in the coordinates

$$\begin{bmatrix} \xi \\ z \end{bmatrix} \triangleq \mathcal{T}(x), \tag{4}$$

where $\xi \triangleq [y_1, \dot{y}_1, \cdots, y_1^{(r_1-2)}, \cdots, y_m, \dot{y}_m, \cdots, y_m^{(r_m-2)}; y_1^{(r_1-1)}, \cdots, y_m^{(r_m-1)}] \in \mathbb{R}^r$, $z \in \mathbb{R}^{n-r}$, and $r \triangleq r_1 + \cdots + r_m$ is the (vector) relative degree of $\mathcal{G}$, $\mathcal{G}$ given by (2), (3) is equivalent to

$$\dot{\xi}(t) = f_\xi(\xi(t), z(t)) + G_\xi(\xi(t), z(t))u(t), \quad \xi(0) = \xi_0, \quad t \geq 0, \tag{5}$$
$$\dot{z}(t) = f_z(\xi(t), z(t)), \quad z(0) = z_0, \tag{6}$$
$$y(t) = C\xi(t), \tag{7}$$

with appropriate initial conditions $\xi_0 \in \mathbb{R}^r$ and $z_0 \in \mathbb{R}^{n-r}$, where

$$f_\xi(\xi, z) = A\xi + \tilde{f}_{\mathrm{u}}(\xi, z), \; G_\xi(\xi, z) = \begin{bmatrix} 0_{(n-m)\times m} \\ G_{\mathrm{s}}(\tilde{x}) \end{bmatrix}, \tag{8}$$

$$A = \begin{bmatrix} A_0 \\ \hat{A} \end{bmatrix}, \quad \tilde{f}_{\mathrm{u}}(\xi, z) = \begin{bmatrix} 0_{(n-m)\times 1} \\ f_{\mathrm{u}}(\tilde{x}) \end{bmatrix}, \tag{9}$$

$\tilde{x} \triangleq [\xi^{\mathrm{T}}, z^{\mathrm{T}}]^{\mathrm{T}}$, $A_0 \in \mathbb{R}^{(r-m)\times r}$ is a known matrix of zeros and ones capturing the multivariable controllable canonical form representation [7], $\hat{A} \in \mathbb{R}^{m\times r}$ is such that A is asymptotically stable, $f_{\mathrm{u}} : \mathbb{R}^n \to \mathbb{R}^m$ is an unknown function and satisfies $f_{\mathrm{u}}(0) = 0$, $C \in \mathbb{R}^{m\times r}$ is a known matrix of zeros and ones capturing the system output, and $G_{\mathrm{s}} : \mathbb{R}^n \to \mathbb{R}^{m\times m}$ is an unknown matrix function such that $\det G_{\mathrm{s}}(\tilde{x}) \neq 0$, $\tilde{x} \in \mathbb{R}^n$. Furthermore, we assume that for a given $y_{\mathrm{d}} \in \overline{\mathbb{R}}^m_+$ there exist $z_{\mathrm{e}} \in \mathbb{R}^{n-r}$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}^m_+$ such that $x_{\mathrm{e}} \triangleq \mathcal{T}^{-1}(\tilde{x}_{\mathrm{e}}) \geq\geq 0$ and

$$0 = f_\xi(\xi_{\mathrm{e}}, z_{\mathrm{e}}) + G_\xi(\xi_{\mathrm{e}}, z_{\mathrm{e}})u_{\mathrm{e}}, \tag{10}$$
$$0 = f_z(\xi_{\mathrm{e}}, z_{\mathrm{e}}), \tag{11}$$

where $\tilde{x}_{\mathrm{e}} \triangleq [\xi_{\mathrm{e}}^{\mathrm{T}}, z_{\mathrm{e}}^{\mathrm{T}}]^{\mathrm{T}}$ and ξ_{e} is given with $y_i = y_{\mathrm{d}i}$, $i = 1, \cdots, m$, and $\dot{y}_i = \cdots = y_i^{(r_i-1)} = 0$, $i = 1, \cdots, m$. In addition, we assume that (6) is input-to-state stable at $z(t) \equiv z_{\mathrm{e}}$ with $\xi(t) - \xi_{\mathrm{e}}$ viewed as the input; that is, there exist a class $\mathcal{KL}$ function $\eta(\cdot, \cdot)$ and a class $\mathcal{K}$ function $\gamma(\cdot)$ such that

$$\|z(t) - z_{\mathrm{e}}\| \leq \eta(\|z_0 - z_{\mathrm{e}}\|, t) + \gamma\left(\sup_{0\leq\tau\leq t} \|\xi(\tau) - \xi_{\mathrm{e}}\|\right), \quad t \geq 0. \tag{12}$$

Note that $(\xi_{\rm e}, z_{\rm e}) \in \mathbb{R}^r \times \mathbb{R}^{n-r}$ is an equilibrium point of (5), (6) if and only if there exists $u_{\rm e} \in \overline{\mathbb{R}}_+^m$ such that (10), (11) hold. Furthermore, we assume that, for a given $\varepsilon^* > 0$, the functions $f_{\rm u}(\mathcal{T}(x)) - f_{\rm u}(\mathcal{T}(x_{\rm e})) - G_{\rm s}(\mathcal{T}(x_{\rm e}))u_{\rm e}$ and $G_{\rm s}(\mathcal{T}(x)) - B_{\rm s}$, where $B_{\rm s} \in \mathbb{R}^{m\times m}$, can be approximated over a compact set $\mathcal{D}_{\rm c} \subset \overline{\mathbb{R}}_+^n$ by a linear in the parameters neural network up to a desired accuracy so that there exist $\varepsilon_1 : \mathbb{R}^n \to \mathbb{R}^m$ and $\varepsilon_2 : \mathbb{R}^n \to \mathbb{R}^{m\times m}$ such that $\|\varepsilon_1(x)\| < \varepsilon^*$ and $\|\varepsilon_2(x)\|_{\rm F} < \varepsilon^*$, $x \in \mathcal{D}_{\rm c}$, and

$$f_{\rm u}(\mathcal{T}(x)) - f_{\rm u}(\mathcal{T}(x_{\rm e})) - G_{\rm s}(\mathcal{T}(x_{\rm e}))u_{\rm e} = W_1^{\rm T}\sigma_1(x) + \varepsilon_1(x), \quad x \in \mathcal{D}_{\rm c}, \tag{13}$$

$$G_{\rm s}(\mathcal{T}(x)) - B_{\rm s} = W_2^{\rm T}[I_m \otimes \sigma_2(x)] + \varepsilon_2(x), \quad x \in \mathcal{D}_{\rm c}, \tag{14}$$

where $W_1 \in \mathbb{R}^{s_1\times m}$ and $W_2 \in \mathbb{R}^{ms_2\times m}$ are optimal *unknown* (constant) weights that minimize the approximation errors over $\mathcal{D}_{\rm c}$, $\sigma_1 : \mathbb{R}^n \to \mathbb{R}^{s_1}$ and $\sigma_2 : \mathbb{R}^n \to \mathbb{R}^{s_2}$ are sets of basis functions such that each component of $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$ takes values between 0 and 1, and $\varepsilon_1(\cdot)$ and $\varepsilon_2(\cdot)$ are the modeling errors. Since $f_{\rm u}(\cdot)$ and $G_{\rm s}(\cdot)$ are continuous, we can choose $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$ from a linear space $\mathcal{X}$ of continuous functions that forms an algebra and separates points in $\mathcal{D}_{\rm c}$. In this case, it follows from the Stone-Weierstrass theorem [8, p. 212] that $\mathcal{X}$ is a dense subset of the set of continuous functions on $\mathcal{D}_{\rm c}$. Now, as is the case in the standard neuro adaptive control literature, we can construct the signal $u_{\rm ad} = F(\hat{W}_1, \hat{W}_2, \sigma_1(x), \sigma_2(x))$ involving the estimates of the optimal weights and basis functions as our adaptive control signal. However, in order to develop an output feedback neural network, we use the recent approach given in [9] for reconstructing the system states via the system delayed inputs and outputs. Specifically, we use a *memory unit* as a particular form of a tapped delay line that takes a scalar time series input and provides a vector output consisting of the present values of the system outputs and system inputs and their delayed values. As shown in [9], such a memory unit can be used to characterize an equivalent input-output representation for (2), (3) in the sense of guaranteeing the existence of a function $g(\cdot)$ and a number d such that the future outputs of (2), (3) can be determined based on a number of past observations of the inputs and outputs of (2), (3). The following theorem is given in [9].

Theorem 3.1 ([9]): Consider the nonlinear dynamical system $\mathcal{G}$ given by (2), (3). Assume that the state vector $x(t)$, $t \geq 0$, of (2), (3) evolves on $\mathcal{B}_r(0) \triangleq \{x \in \mathbb{R}^n : \|x\| \leq r\}$ and $\mathcal{G}$ is observable. Furthermore, assume that the system output $y(t)$, $t \geq 0$, and its derivatives up to the order $(n-1)$ are bounded for all $t \geq 0$. Then, given an arbitrary $\varepsilon^* > 0$, there exists a set of bounded weights W and a positive scalar $d > 0$ such that any continuous function $g(x,u) : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^p$ can be approximated over the compact set $\mathcal{B}_r(0)$ by a linear in the parameters neural network of the form

$$g(x(t),u(t)) = W^{\rm T}\sigma(\zeta(t)) + \varepsilon(x(t),\zeta(t)), \quad \|\varepsilon(x(t),\zeta(t))\| \leq \varepsilon^*, \quad t \geq 0, \tag{15}$$

where $x(t)$, $t \geq 0$ is the solution to (2),

$$\zeta(t) \triangleq [y_1(t), y_1(t-d), \cdots, y_1(t-(n-1)d), \cdots, y_m(t), y_m(t-d), \cdots, y_m(t-(n-1)d); u_1(t), u_1(t-d), \cdots, u_1(t-(n-r_1-1)d), \cdots, u_m(t), u_m(t-d), \cdots, u_m(t-(n-r_m-1)d)]^{\rm T}, \quad t \geq 0, \tag{16}$$

$\|\zeta(t)\| \leq \zeta^*$, $t \geq 0$, and $\zeta^* > 0$ is a uniform bound of $\zeta(\cdot)$ over $\mathcal{B}_r(0)$.

In light of the above theorem, it follows that if the dynamical system $\mathcal{G}$ is observable and its state trajectory $x(t)$, $t \geq 0$, evolves on $\mathcal{D}_{\rm c}$, then there exist $\varepsilon_1 : \mathbb{R}^n \times \mathbb{R}^{2nm-r} \to \mathbb{R}^m$ and $\varepsilon_2 : \mathbb{R}^n \times \mathbb{R}^{2nm-r} \to \mathbb{R}^{m\times m}$ such that $\|\varepsilon_1(x(t),\zeta(t))\| < \varepsilon^*$ and $\|\varepsilon_2(x(t),\zeta(t))\|_{\rm F} < \varepsilon^*$, $t \geq 0$, and, for all $t \geq 0$,

$$f_{\rm u}(\mathcal{T}(x(t))) - f_{\rm u}(\mathcal{T}(x_{\rm e})) - G_{\rm s}(\mathcal{T}(x_{\rm e}))u_{\rm e} = W_1^{\rm T}\sigma_1(\zeta(t)) + \varepsilon_1(x(t),\zeta(t)), \tag{17}$$

$$G_{\rm s}(\mathcal{T}(x(t))) - B_{\rm s} = W_2^{\rm T}[I_m \otimes \sigma_2(\zeta(t))] + \varepsilon_2(x(t),\zeta(t)). \tag{18}$$

For the statement of the next result, define the projection operator $\mathrm{Proj}(\tilde{W}, Y)$ given by

$$\mathrm{Proj}(\tilde{W}, Y) \triangleq \begin{cases} Y, & \text{if } \mu(\tilde{W}) < 0, \\ Y, & \text{if } \mu(\tilde{W}) \geq 0 \text{ and } \mu'(\tilde{W})Y \leq 0, \\ Y - \frac{\mu'^{\rm T}(\tilde{W})\mu'(\tilde{W})Y}{\mu'(\tilde{W})\mu'^{\rm T}(\tilde{W})}\mu(\tilde{W}), & \text{otherwise,} \end{cases} \tag{19}$$

where $\tilde{W} \in \mathbb{R}^{s\times m}$, $Y \in \mathbb{R}^{n\times m}$, $\mu(\tilde{W}) \triangleq \frac{\mathrm{tr}\,\tilde{W}^{\rm T}\tilde{W} - \tilde{w}_{\max}^2}{\varepsilon_{\tilde{W}}}$, $\tilde{w}_{\max} \in \mathbb{R}$ is the norm bound imposed on $\tilde{W}$, and $\varepsilon_{\tilde{W}} > 0$. Note that, given the matrices $\tilde{W} \in \mathbb{R}^{s\times m}$ and $Y \in \mathbb{R}^{s\times m}$, it follows that

$$\begin{aligned} &\mathrm{tr}[(\tilde{W} - W)^{\rm T}(\mathrm{Proj}(\tilde{W}, Y) - Y)] \\ &\quad = \sum_{i=1}^{n}[\mathrm{col}_i(\tilde{W} - W)]^{\rm T}(\mathrm{Proj}(\mathrm{col}_i(\tilde{W}), \mathrm{col}_i(Y)) \\ &\qquad -\mathrm{col}_i(Y)) \\ &\quad \leq 0, \end{aligned} \tag{20}$$

where $\mathrm{col}_i(X)$ denotes the ith column of the matrix X.

Theorem 3.2: Consider the nonlinear uncertain dynamical system $\mathcal{G}$ given by (2) and (3) 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. For a given $y_{\rm d} \in \overline{\mathbb{R}}_+^m$ assume there exist nonnegative vectors $x_{\rm e} \in \overline{\mathbb{R}}_+^n$ and $u_{\rm e} \in \overline{\mathbb{R}}_+^m$ such that

$$0 = f(x_{\rm e}) + G(x_{\rm e})u_{\rm e}, \tag{21}$$

$$y_{\rm d} = h(x_{\rm e}). \tag{22}$$

Furthermore, assume that the equilibrium point $x_{\rm e}$ of (2) is globally asymptotically stable with $u(t) \equiv u_{\rm e}$. In addition, assume that there exists a global diffeomorphism $\mathcal{T} : \mathbb{R}^n \to \mathbb{R}^n$ such that $\mathcal{G}$ can be transformed into the normal form given by (5) and (6), and (6) is input-to-state stable at $z_{\rm e}$ with $\xi(t) - \xi_{\rm e}$ viewed as the input. Finally, let $Q_1, Q_2 \in \mathbb{R}^{m\times m}$ be positive definite. Then the neural adaptive output feedback control law

$$u(t) = \begin{cases} \hat{u}(t), & \text{if } \hat{u}(t) \geq\geq 0, \\ 0, & \text{otherwise,} \end{cases} \tag{23}$$

where

$$\hat{u}(t) = -\left(B_{\rm s} + \hat{W}_2^{\rm T}(t)[I_m \otimes \sigma_2(\zeta(t))]\right)^{-1}\hat{W}_1^{\rm T}(t)\sigma_1(\zeta(t)), \tag{24}$$

$B_{\rm s} \in \mathbb{R}^{m\times m}$ is positive definite, $\zeta(t)$, $t \geq 0$, is given by (16), $\hat{W}_1(t) \in \mathbb{R}^{s_1\times m}$, $t \geq 0$, and $\hat{W}_2(t) \in \mathbb{R}^{ms_2\times m}$, $t \geq 0$, with update laws

$$\dot{\hat{W}}_1(t) = Q_1 \mathrm{Proj}(\hat{W}_1(t), \sigma_1(\zeta(t))\xi_{\rm c}^{\rm T}(t)\tilde{P}B_0), \quad \hat{W}_1(0) = \hat{W}_{10}, \tag{25}$$

$$\dot{\hat{W}}_2(t) = Q_2 \mathrm{Proj}(\hat{W}_2(t), [I_m \otimes \sigma_2(\zeta(t))]u(t)\xi_{\rm c}^{\rm T}(t)\tilde{P}B_0), \quad \hat{W}_2(0) = \hat{W}_{20}, \tag{26}$$

where $\tilde{P} \in \mathbb{R}^{r\times r}$ is a positive-definite solution of the Lyapunov equation

$$0 = (A - LC)^{\rm T}\tilde{P} + \tilde{P}(A - LC) + \tilde{R}, \quad \tilde{R} > 0, \tag{27}$$

and $\xi_{\rm c}(t)$, $t \geq 0$, is the solution to the estimator dynamics

$$\dot{\xi}_{\rm c}(t) = A\xi_{\rm c}(t) + L(y(t) - y_{\rm c}(t) - y_{\rm d}), \quad \xi_{\rm c}(0) = \xi_{\rm c0}, \quad t \geq 0, \tag{28}$$

$$y_{\rm c}(t) = C\xi_{\rm c}(t), \tag{29}$$

where $\xi_{\rm c}(t) \in \mathbb{R}^r$, $t \geq 0$, $A \in \mathbb{R}^{r\times r}$ is asymptotically stable, $L \in \mathbb{R}^{r\times m}$ is such that $A - LC$ is asymptotically stable, and $B_0 \triangleq [0_{m\times(r-m)}, I_m]^{\rm T}$, guarantees that there exists a compact positively invariant set $\mathcal{D}_\alpha \subset \mathbb{R}^n \times \mathbb{R}^r \times \mathbb{R}^{s_1\times m} \times \mathbb{R}^{ms_2\times m}$ such that $(x_{\rm e}, 0, W_1, W_2) \in \mathcal{D}_\alpha$, where $W_1 \in \mathbb{R}^{s_1\times m}$ and $W_2 \in \mathbb{R}^{ms_2\times m}$, and the solution $(x(t), \xi_{\rm c}(t), \hat{W}_1(t), \hat{W}_2(t))$, $t \geq 0$, of the closed-loop system given by (2), (23), (25), (26), (28), and (29) is ultimately bounded for all $(x(0), \xi_{\rm c}(0), \hat{W}_1(0), \hat{W}_2(0)) \in \mathcal{D}_\alpha$ with ultimate bound $\|y(t) - y_{\rm d}\|^2 < \varepsilon$, $t \geq T$, where

$$\varepsilon > \left[\left(\sqrt{\frac{\nu}{\lambda_{\min}(RP^{-1})}} + \alpha_1\right)^2 + \left(\sqrt{\frac{\nu}{\lambda_{\min}(\tilde{R}\tilde{P}^{-1})}} + \alpha_2\right)^2 + \lambda_{\max}(Q_1^{-1})\hat{w}_{1\max}^2 + \lambda_{\max}(Q_2^{-1})\hat{w}_{2\max}^2\right]^{\frac{1}{2}} \tag{30}$$

$$\nu \triangleq \frac{\alpha_1^2}{\lambda_{\min}(RP^{-1})} + \frac{\alpha_2^2}{\lambda_{\min}(\tilde{R}\tilde{P}^{-1})}, \tag{31}$$

$$\alpha_1 \triangleq [\sqrt{s_1}\hat{w}_{1\max} + (b_{\rm s} + m\sqrt{s_2}\hat{w}_{2\max})u^*] \cdot \|P^{-1/2}(P - \tilde{P})B_0\| + (\sqrt{s_1}\hat{w}_{1\max} + (\varepsilon_1^* + \varepsilon_2^* u^*))\|P^{1/2}B_0\|, \tag{32}$$

$$\alpha_2 \triangleq [3\sqrt{s_1}\hat{w}_{1\max} + 2(b_{\rm s} + m\sqrt{s_2}\hat{w}_{2\max})u^* + (\varepsilon_1^* + \varepsilon_2^* u^*)]\|\tilde{P}^{1/2}B_0\|, \tag{33}$$

$u^* \triangleq \sup_{t\geq 0}\|u(t)\|$, $b_{\rm s} \triangleq \lambda_{\max}(B_{\rm s})$, $\hat{w}_{i\max}$, $i = 1, 2$, are norm bounds imposed on $\hat{W}_i$, and $P \in \mathbb{R}^{r\times r}$ is a positive-definite solution of the Lyapunov equation

$$0 = A^{\rm T}P + PA + R, \quad R > 0. \tag{34}$$

Furthermore, $u(t) \geq\geq 0$, $t \geq 0$, and $x(t) \geq\geq 0$, $t \geq 0$, for all $x_0 \in \overline{\mathbb{R}}_+^n$.

Remark 3.1: It is important to note that the existence of a global neural network approximator for an uncertain nonlinear map using the system outputs and inputs and its delayed values (as in (17), (18)) cannot in general be established. In the proof of Theorem 3.2, as is common in the neural network literature, we assume that for a given arbitrarily large compact set $\mathcal{D}_{\rm c} \subset \mathbb{R}^n$, there exists an approximator for the unknown nonlinear map up to a desired accuracy. This assumption ensures that in the error space $\tilde{\mathcal{D}}_{\rm e}$ there exists at least one Lyapunov level set such that $\tilde{\mathcal{D}}_\eta \subset \tilde{\mathcal{D}}_\alpha$. In the case where $f_{\rm u}(\cdot)$ and $G_{\rm s}(\cdot)$ are continuous on $\mathbb{R}^n$, it follows from the Stone-Weierstrass theorem that $f_{\rm u}(\cdot)$ and $G_{\rm s}(\cdot)$ can be approximated over an arbitrarily large compact set $\mathcal{D}_{\rm c}$ in the sense of (13) and (14) and hence (17) and (18) hold with sufficiently small d. In addition, we assume that $\hat{W}_2(0)$ is sufficiently close to the optimal weight W_2 so that $B_{\rm s} + \hat{W}_2(t)[I_m \otimes \sigma_2(\zeta(t))]$ is nonsingular for all $t \geq 0$.

Remark 3.2: Implementation of (24) requires a fixed-point iteration at each integration step; that is, the controller contains an algebraic constraint on u. For each choice of $\sigma_1(\cdot)$ and $\sigma_2(\cdot)$ this equation must be examined for solvability in terms of u. It is more practical to avoid this iteration by using one-step delayed values of u in calculating $\hat{u}$. Implementations using both approaches result in imperceptible differences in our numerical studies.

Remark 3.3: In the case of systems of unknown dimension but with known relative degree, Theorem 3.2 applies with a slight modification to the input vector of the neural network; that is, n in (16) should be replaced by a sufficiently large value that is greater than the largest possible system dimension.

In Theorem 3.2 we assumed that the equilibrium point $x_{\rm e}$ of (2) is globally asymptotically stable with $u(t) \equiv u_{\rm e}$. In general, however, unlike linear nonnegative systems with asymptotically stable plant dynamics, a given set point $x_{\rm e} \in \mathbb{R}_+^n$ for the nonlinear nonnegative dynamical system (2) may not be asymptotically stabilizable with a constant control $u(t) \equiv u_{\rm e} \in \overline{\mathbb{R}}_+^m$. However, if $f(x)$ is homogeneous, cooperative; that is, the Jacobian matrix $\frac{\partial f(x)}{\partial x}$ is essentially nonnegative for all $x \in \overline{\mathbb{R}}_+^n$, the Jacobian matrix $\frac{\partial f(x)}{\partial x}$ is irreducible for all $x \in \overline{\mathbb{R}}_+^n$ [4], and the zero solution $x(t) \equiv 0$ of the undisturbed ($u(t) \equiv 0$) system (2) is globally asymptotically stable, then the set point $x_{\rm e} \in \mathbb{R}_+^n$ satisfying (10), (11) is a unique equilibrium point with $u(t) \equiv u_{\rm e}$ and is also asymptotically stable for all $x_0 \in \overline{\mathbb{R}}_+^n$ [10]. This implies that the solution $x(t) \equiv x_{\rm e}$ to (2) with $u(t) \equiv u_{\rm e}$ is asymptotically stable for all $x_0 \in \overline{\mathbb{R}}_+^n$.

IV. Nonlinear Adaptive Output Feedback Control for General Anesthesia

To illustrate the application of our adaptive control framework we consider a hypothetical model for the intravenous anesthetic propofol. The pharmacokinetics of propofol are described by a three-compartment model [11]. The model is shown in Figure 1. The mass of the drug in the intravascular blood volume 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.

A mass balance of the three-state compartmental model yields

$$\dot{x}_1(t) = -[a_{\rm e}(c(t)) + a_{21}(c(t)) + a_{31}(c(t))]x_1(t) + a_{12}(c(t))x_2(t) + a_{13}(c(t))x_3(t) + u(t), \quad x_1(0) = x_{10},\ t \geq 0, \tag{35}$$

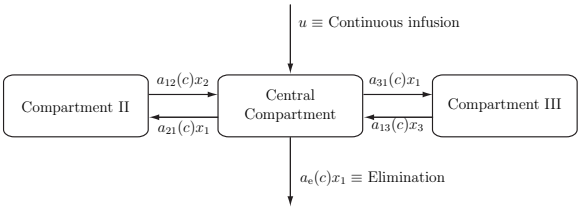

Fig. 1. Pharmacokinetic model for drug distribution during anesthesia

$$\dot{x}_2(t) = a_{21}(c(t))x_1(t) - a_{12}(c(t))x_2(t), \quad x_2(0) = x_{20}, \tag{36}$$

$$\dot{x}_3(t) = a_{31}(c(t))x_1(t) - a_{13}(c(t))x_3(t), \quad x_3(0) = x_{30}, \tag{37}$$

where $c(t) = x_1(t)/V_{\mathrm{c}}$, V_{c} is the volume of the central compartment, $a_{21}(c)$ is the rate of transfer of drug from the central compartment to Compartment II, $a_{12}(c)$ is the rate of transfer of drug from Compartment II to the central compartment, $a_{31}(c)$ is the rate of transfer of drug from the central compartment to Compartment III, $a_{13}(c)$ is the rate of transfer of drug from Compartment III to the central compartment, $a_{\mathrm{e}}(c)$ 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 the anesthetic drug propofol into the central compartment. In order to formulate a physiologically realistic nonlinear model we assume that the rate of transfer and the rate of metabolism are proportional to the cardiac output; that is, we assume $a_{21}(c) = A_{21}Q(c)$, $a_{12}(c) = A_{12}Q(c)$, $a_{31}(c) = A_{31}Q(c)$, $a_{13}(c) = A_{13}Q(c)$, and $a_{\mathrm{e}}(c) = A_{\mathrm{e}}Q(c)$, where A_{12}, A_{21}, A_{13}, A_{31}, and A_{e} are positive constants and $Q(c)$ representing the cardiac output given by

$$Q(c) = \frac{Q_0 \mathrm{C}_{50}^{\alpha}}{\mathrm{C}_{50}^{\alpha} + c^{\alpha}}, \tag{38}$$

where the effect is related to c (since c is the presumed concentration in the highly perfused myocardium), $Q_0 > 0$ is a constant, and $\mathrm{C}_{50} > 0$ 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, c). Even though the transfer and loss coefficients A_{12}, A_{21}, A_{13}, A_{31}, and A_{e} are nonnegative, and $\alpha > 1$, $\mathrm{C}_{50} > 0$, 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 neuro adaptive control to regulate intravenous anesthetics during surgery is essential.

Even though propofol concentrations in the blood are known to be correlated with lack of purposeful responsiveness (and presumably consciousness) [12], 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 [1]. 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. Recently, a new EEG indicator, the

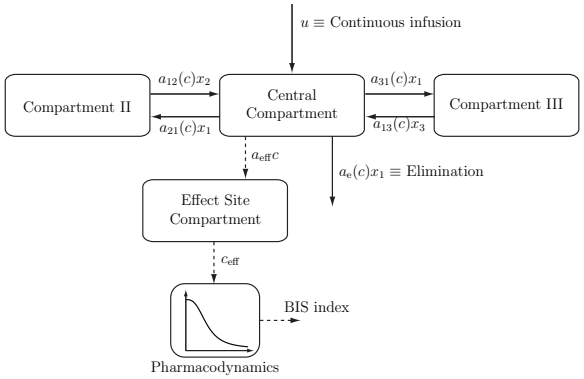

Fig. 2. Combined pharmacokinetic/pharmaco-dynamic model

Bispectral Index (BIS), has been proposed as a measure of anesthetic effect. This index quantifies the nonlinear relationships between the component frequencies in the electroencephalogram, as well as analyzing their phase and amplitude. The BIS signal is a nonlinear monotonically decreasing function of the level of consciousness and is given by

$$\mathrm{BIS}(c_{\mathrm{eff}}) = \mathrm{BIS}_0 \left(1 - \frac{c_{\mathrm{eff}}^{\gamma}}{c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma}}\right), \tag{39}$$

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 micrograms/mililiter 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 (39). 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

$$\dot{c}_{\mathrm{eff}}(t) = a_{\mathrm{eff}}(c(t) - c_{\mathrm{eff}}(t)), \quad c_{\mathrm{eff}}(0) = c(0), \quad t \geq 0, \tag{40}$$

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

$$c_{\mathrm{eff}}(t) = \int_0^t e^{-a_{\mathrm{eff}}(t-s)} a_{\mathrm{eff}} c(s)\, \mathrm{d}s. \tag{41}$$

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; while the range between 40 and 60 indicates a moderate hypnotic state. Figure 2 shows the combined pharmacokinetic/pharmacodynamic model for propofol distribution.

For set-point regulation define $e(t) \triangleq x(t) - x_{\mathrm{e}}$, where $x_{\mathrm{e}} \in \mathbb{R}^3$ is the set point satisfying the equilibrium condition for (35)–(37) and (40) with $x_1(t) \equiv x_{\mathrm{e}1}$, $x_2(t) \equiv x_{\mathrm{e}2}$, $x_3(t) \equiv x_{\mathrm{e}3}$, $c_{\mathrm{eff}} \equiv \mathrm{EC}_{50}$, and $u(t) \equiv u_{\mathrm{e}}$, so that $f_{\mathrm{e}}(e) = [f_{\mathrm{e}1}(e), f_{\mathrm{e}2}(e), f_{\mathrm{e}3}(e), f_{\mathrm{e}4}(e)]^{\mathrm{T}}$ is given by

$$\begin{aligned} f_{\mathrm{e}1}(e) = {} & -[a_{\mathrm{e}}(c) + a_{21}(c) + a_{31}(c)](e_1 + x_{\mathrm{e}1}) \\ & + a_{12}(c)(e_2 + x_{\mathrm{e}2}) + a_{13}(c)(e_3 + x_{\mathrm{e}3}) \\ & - [a_{\mathrm{e}}(c_{\mathrm{e}}) + a_{21}(c_{\mathrm{e}}) + a_{31}(c_{\mathrm{e}})]x_{\mathrm{e}1} \\ & + a_{12}(c_{\mathrm{e}})x_{\mathrm{e}2} + a_{13}(c_{\mathrm{e}})x_{\mathrm{e}3}, \end{aligned} \tag{42}$$

$$f_{e2}(e) = a_{21}(c)(e_1 + x_{e1}) - a_{12}(c)(e_2 + x_{e2}) - [a_{21}(c_e)x_{e1} - a_{12}(c_e)x_{e2}], \quad (43)$$

$$f_{e3}(e) = a_{31}(c)(e_1 + x_{e1}) - a_{13}(c)(e_3 + x_{e3}) - [a_{31}(c_e)x_{e1} - a_{13}(c_e)x_{e3}], \quad (44)$$

$$f_{e4}(e) = a_{eff}(c - (e_4 + EC_{50})) - a_{eff}(e_e - EC_{50}), \quad (45)$$

where $c_e \triangleq x_{e1}/V_c$. 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.

In the following numerical simulation we assume $BIS_0 = 100$ and the target (desired) BIS value, BIS_{target}, is set at 50. Now, using the adaptive output feedback controller

$$u(t) = \max\{0, \hat{u}(t)\}, \quad (46)$$

where

$$\hat{u}(t) = -\frac{\hat{W}_1^T(t)\sigma_1(\zeta(t))}{b_s + \hat{W}_2^T(t)\sigma_2(\zeta(t))}, \quad (47)$$

$$\zeta(t) = [BIS(t-d), BIS(t-2d), u_1(t-d), u_1(t-2d)]^T, \quad (48)$$

$b_s > 0$, with update laws (25) and (26), where $\xi_c(t) \in \mathbb{R}^2$, $t \geq 0$, is the solution to the estimator dynamics

$$\dot{\xi}_c(t) = A\xi_c(t) + L(-BIS(t) - y_c(t) + BIS_{target}), \quad \xi_c(0) = \xi_{c0}, \quad t \geq 0, \quad (49)$$

$$y_c(t) = \xi_c(t), \quad (50)$$

where $A \in \mathbb{R}^{2\times 2}$ and $L \in \mathbb{R}^{2\times 1}$, it follows from Theorem 3.2 that there exist positive constants ε and T such that $|BIS(t) - BIS_{target}| \leq \varepsilon$, $t \geq T$, for any (uncertain) nonnegative values of the pharmacokinetic transfer and loss coefficients $(A_{12}, A_{21}, A_{13}, A_{31}, A_e)$ as well as any (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 (39). Furthermore, since our adaptive controller only requires the error signal $BIS(t) - BIS_{target}$, we do not require knowledge of the pharmacodynamic parameters γ and EC_{50}. For our simulation we assume $V_c = (0.228\ \ell/\text{kg})(M\ \text{kg})$, where $M = 70$ kg is the weight (mass) of the patient, $A_{21}Q_0 = 0.112\ \text{min}^{-1}$, $A_{12}Q_0 = 0.055\ \text{min}^{-1}$, $A_{31}Q_0 = 0.0419\ \text{min}^{-1}$, $A_{13}Q_0 = 0.0033\ \text{min}^{-1}$, $A_eQ_0 = 0.119\ \text{min}^{-1}$, $\alpha = 3$, and $C_{50} = 4\ \mu\text{g/m}\ell$ [11]. 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 robustness of the proposed adaptive controller we switch the pharmacodynamic parameters EC_{50} and γ, respectively, from 5.6 μg/mℓ and 2.39 to 7.2 μg/mℓ and 3.39 at $t = 15$ min and back to 5.6 μg/mℓ and 2.39 at $t = 30$ min. Here, we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $A = \begin{bmatrix} 0 & 1 \\ -1 & -1 \end{bmatrix}$, $L = [0, 1]^T$, $b_s = 1$, $Q_1 = \times 10^{-5}$ g/min^2, $Q_2 = 2.0 \times 10^{-5}$ g/min^2, $d = 0.005$ min, and initial conditions $x(0) = [0,\ 0,\ 0]^T$ g, $c_{eff}(0) = 0$ g/mℓ, and $\xi_c(0) = [0,\ 0]^T$. Figure 3 shows the masses of propofol in the three compartments versus time. Figure 4 shows the concentrations in the central and effect site compartments versus time. Figure 5 shows the compensator states versus time. Finally, Figure 6 shows the BIS index and the control signal (propofol infusion rate) versus time.

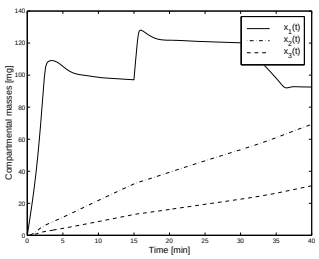

Fig. 3. Compartmental masses versus time

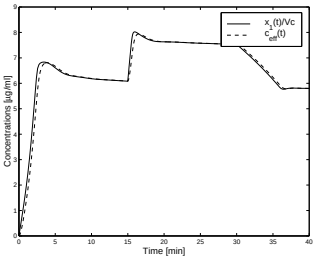

Fig. 4. Concentrations in the central and effect site compartments versus time

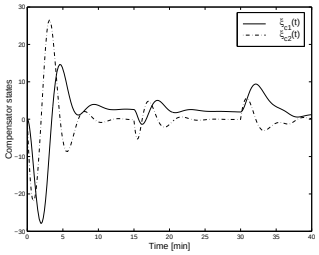

Fig. 5. Compensator states versus time

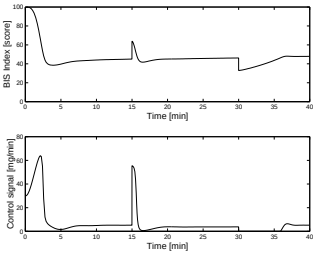

Fig. 6. BIS Index versus time and control signal (infusion rate) versus time

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