

# Neuroadaptive Output Feedback Control for Nonlinear Nonnegative Dynamical Systems with Actuator Amplitude and Integral Constraints

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**Abstract**—A neuroadaptive output feedback control architecture for nonlinear nonnegative dynamical systems with input amplitude constraints is developed. Specifically, the neuroadaptive controller guarantees that the imposed amplitude and integral input constraints are satisfied and the physical system states remain in the nonnegative orthant of the state space. 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 in the face of infusion rate constraints and a drug dosing constraint over a specified period.

## I. INTRODUCTION

Actuator nonlinearities arise frequently in practice and can severely degrade closed-loop system performance, and in some cases drive the system to instability, if not accounted for in the control design process. These effects are even more pronounced for adaptive controllers which continue to adapt when the feedback loop has been severed due to the presence of actuator saturation causing unstable controller modes to drift, which in turn leads to severe windup effects leading to unacceptable transients after saturation. Direct adaptive controllers for adaptive tracking of multivariable nonlinear uncertain systems with amplitude saturation constraints have been developed in the literature (see [1] and the references therein).

The presence of control rate saturation may further exacerbate the problem of control amplitude saturation. To address amplitude and rate saturation constraints the authors in [1] construct a reference system (governor or supervisor) to address tracking and regulation in the face of actuator constraints by deriving adaptive update laws that guarantee that the error system dynamics are asymptotically stable and the adaptive controller gains are Lyapunov stable. In the case where the actuator amplitude and rate are limited, the adaptive control signal to the reference system is modified to effectively robustify the error dynamics to the saturation constraints, and hence, guaranteeing asymptotic stability of the error states.

Even though adaptive and neuroadaptive controllers for drug delivery systems have been developed in the literature [2]–[6], adaptive control for drug dosing with actuator saturation effects is rather limited [7]. An implicit assumption inherent in most adaptive control frameworks for clinical pharmacology is that the adaptive control law is implemented without any regard to actuator amplitude and rate saturation constraints. Of course, any electromechanical control actuation device (e.g., infusion pump) is subject to amplitude and/or rate constraints leading to saturation nonlinearities

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enforcing limitations on control amplitudes and control rates. More importantly, in physiological applications, drug infusion rates can vary from patient to patient, and, to avoid overdosing, it is vital that the infusion rate does not exceed patient-specific threshold values. As a consequence, actuator constraints (e.g., infusion pump rate constraints) need to be accounted for in drug delivery systems.

Nonnegative and compartmental systems are essential in capturing the behavior of a wide range of dynamical systems involving dynamic states whose values are nonnegative [8]. While nonnegative and compartmental systems have wide applicability in biology and medicine, their use in the specific field of pharmacokinetics is essential in developing models for closed-loop control drug administration [8]. In this paper, we develop a neuroadaptive control framework for nonnegative dynamical systems with actuator amplitude and control integral constraints. Specifically, building on the work of [6] we develop an output feedback neural network controller that operates over a tapped delay line (TDL) of available input and output measurements. The neuroadaptive laws for the neural network weights are constructed using a linear observer for the nominal normal form system error dynamics.

The proposed approach is applicable to a specific class of nonlinear nonnegative dynamical systems with control amplitude saturation constraints as well as control integral constraints. In addition, since in pharmacological applications involving active drug administration control inputs as well as the system states need to be nonnegative, the proposed neuroadaptive output feedback controller also guarantees that the control signal as well as the physical system states remain nonnegative. Using an electroencephalogram (EEG) measurement as an objective, quantitative measure of consciousness, the proposed framework is used to control the infusion of an anesthetic drug for maintaining a desired constant level of depth of anesthesia during surgery in the face of infusion rate constraints and a drug dosing constraint over a specified time interval.

## II. MATHEMATICAL PRELIMINARIES

In this section, we introduce notation, several definitions, and some key results concerning nonlinear nonnegative dynamical systems [8] that are necessary for developing the main results of this paper. Specifically, for  $x \in \mathbb{R}^n$  we write  $x \geq 0$  (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* or *positive* if every entry of  $A$  is nonnegative or positive, respectively, which is written as  $A \geq 0$  or  $A \gg 0$ , respectively. Let  $\mathbb{R}_+^n$  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  $x \geq 0$  and  $x \gg 0$ . Furthermore, we write  $(\cdot)^T$  to denote transpose,  $\text{tr}(\cdot)$  for the trace operator,  $\lambda_{\min}(\cdot)$  to denote the minimum eigenvalue of a Hermitian matrix, and  $\|\cdot\|$  for a vector norm in  $\mathbb{R}^n$ .

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

(resp.,  $u(t) \gg 0$ ) on the interval  $[0, T]$ .

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

**Definition 2.2:** Let  $f = [f_1, \dots, f_n]^T : \mathcal{D} \subseteq \overline{\mathbb{R}}_+^n \rightarrow \mathbb{R}^n$ . Then  $f$  is *essentially nonnegative with respect to*  $\hat{x} = [x_1, \dots, x_r]^T$ ,  $r \leq n$ , if  $f_i(x) \geq 0$  for all  $i = 1, \dots, r$  and  $x \in \overline{\mathbb{R}}_+^n$  such that  $x_i = 0$ ,  $i = 1, \dots, r$ , where  $x_i$  denotes the  $i$ th component of  $x$ .  $f$  is *essentially nonnegative* if  $f_i(x) \geq 0$  for all  $i = 1, \dots, n$  and  $x \in \overline{\mathbb{R}}_+^n$  such that  $x_i = 0$ .

Note that if  $f(x) = Ax$ , where  $A \in \mathbb{R}^{n \times n}$ , then  $f$  is essentially nonnegative if and only if  $A$  is *essentially nonnegative*, that is,  $A_{(i,j)} \geq 0$ ,  $i, j = 1, \dots, n$ ,  $i \neq j$ , where  $A_{(i,j)}$  denotes the  $(i, j)$ th entry of  $A$ .

### III. NEUROADAPTIVE OUTPUT FEEDBACK CONTROL WITH ACTUATOR CONSTRAINTS

In this section, we consider the problem of characterizing neuroadaptive dynamic output feedback control laws for nonlinear uncertain dynamical systems with actuator amplitude constraints to achieve reference model output tracking. Specifically, consider the controlled nonlinear uncertain dynamical system  $\mathcal{G}$  given by

$$\begin{aligned} \dot{x}(t) &= A_0 x(t) + B\Lambda [h(u(t)) + f(x(t), z(t), \hat{u}(t))], \\ x(0) &= x_0, \quad t \geq 0, \quad (1) \\ \dot{z}(t) &= f_z(x(t), z(t)), \quad z(0) = z_0, \quad (2) \\ y(t) &= Cx(t) + W_y^T \sigma_y(\hat{y}(t), \hat{u}(t)), \quad (3) \end{aligned}$$

where  $x(t) \in \mathbb{R}^r$ ,  $t \geq 0$ , 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,  $\hat{u}(t) \triangleq [u(t - \tau_u), u(t - 2\tau_u), \dots, u(t - p\tau_u)]$  is a vector of  $p$ -delayed values of the control input with  $p \geq 1$  and  $\tau_u > 0$  given,  $\hat{y}(t) \triangleq [y(t - \tau_y), y(t - 2\tau_y), \dots, y(t - q\tau_y)]$  is a vector of  $q$ -delayed values of the system output with  $q \geq 1$  and  $\tau_y > 0$  given,  $A_0 \in \mathbb{R}^{r \times r}$  is a known Hurwitz and essentially nonnegative matrix,  $B \in \mathbb{R}^{r \times m}$  is a known nonnegative input matrix,  $\Lambda \in \mathbb{R}^{m \times m}$  is an *unknown* nonnegative and positive-definite matrix,  $h(u(t)) = [h_1(u_1(t)), \dots, h_m(u_m(t))]^T$  is the constrained control input given by

$$h_i(u_i) \triangleq \begin{cases} 0, & \text{if } u_i \leq 0, \\ u_i^*, & \text{if } u_i \geq u_i^*, \\ u_i, & \text{otherwise,} \end{cases} \quad i = 1, \dots, m, \quad (4)$$

where  $u_i^* > 0$ ,  $i = 1, \dots, m$ , are given constants,  $f : \mathbb{R}^r \times \mathbb{R}^{n-r} \times \mathbb{R}^{mp} \rightarrow \mathbb{R}^m$  is Lipschitz continuous, bounded, and essentially nonnegative with respect to  $x$  for all  $z \in \mathbb{R}^{n-r}$  and  $\hat{u} \in \mathbb{R}^{mp}$  but otherwise *unknown*, that is,  $f(\cdot, \cdot)$  is such that  $f_i(x, \hat{u}) \geq 0$  if  $x_i = 0$ ,  $i = 1, \dots, n$ , for all  $z \in \mathbb{R}^{n-r}$  and  $\hat{u} \in \mathbb{R}^{mp}$ ,  $f_z : \mathbb{R}^r \times \mathbb{R}^{n-r} \rightarrow \mathbb{R}^{n-r}$  is such that (2) is input-to-state stable for all  $z \in \mathbb{R}^{n-r}$  with  $x(t)$  viewed as the input,  $C \in \mathbb{R}^{m \times r}$  is a known output matrix,  $W_y \in \mathbb{R}^{l \times m}$  is an *unknown* matrix, and  $\sigma_y : \mathbb{R}^{mq} \times \mathbb{R}^{mp} \rightarrow \mathbb{R}^l$  is a known Lipschitz continuous function that is bounded on  $\mathbb{R}^{mq} \times \mathbb{R}^{mp}$ .

In order to achieve output tracking, we construct a reference nonnegative dynamical system  $\mathcal{G}_{\text{ref}}$  given by

$$\begin{aligned} \dot{x}_{\text{ref}}(t) &= A_{\text{ref}} x_{\text{ref}}(t) + B_{\text{ref}} r(t), \quad x_{\text{ref}}(0) = x_{\text{ref}0}, \quad t \geq 0, \quad (5) \\ y_{\text{ref}}(t) &= C x_{\text{ref}}(t), \quad (6) \end{aligned}$$

where  $x_{\text{ref}}(t) \in \mathbb{R}^r$ ,  $t \geq 0$ , is the reference state vector,  $r(t) \in \mathbb{R}^d$ ,  $t \geq 0$ , is a bounded piecewise continuous nonnegative reference input,  $A_{\text{ref}} \in \mathbb{R}^{r \times r}$  is a Hurwitz and essentially nonnegative matrix, and  $B_{\text{ref}} \in \mathbb{R}^{r \times d}$  is a nonnegative matrix.

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 neuroadaptive dynamic output feedback control laws for nonnegative systems with nonnegative control inputs. In addition, to account for infusion rate constraints we develop neuroadaptive control laws with actuator constraints. Specifically, for the reference model output tracking problem our goal is to design a nonnegative control input  $u(t)$ ,  $t \geq 0$ , predicated on the system measurement  $y(t)$ ,  $t \geq 0$ , such that  $\|y(t) - y_{\text{ref}}(t)\| < \gamma$  for all  $t \geq T$ , where  $\|\cdot\|$  denotes the Euclidean vector norm on  $\mathbb{R}^m$ ,  $\gamma > 0$  is sufficiently small, and  $T \in [0, \infty)$ ,  $x(t) \geq 0$ ,  $t \geq 0$ , for all  $x_0 \in \overline{\mathbb{R}}_+^n$ , and the control input  $u(\cdot)$  in (1) is restricted to the class of *admissible controls* consisting of measurable functions  $u(t) = [u_1(t), \dots, u_m(t)]^T$ ,  $t \geq 0$ , such that (4) holds and

$$\eta_i(t) \triangleq \int_{t-\tau_s}^t h_i(u_i(s)) ds \leq \eta_i^*, \quad i = 1, \dots, m, \quad t \geq 0, \quad (7)$$

where  $\tau_s > 0$  and  $\eta_i^* > 0$ ,  $i = 1, \dots, m$ , are given constants, and  $u_i(t) \equiv 0$  for all  $t \in [-\tau_s, 0]$  and  $i = 1, \dots, m$ . Note that  $\eta_i(t)$ ,  $i = 1, \dots, m$ ,  $t \geq 0$ , given by (7) satisfies

$$\dot{\eta}_i(t) = h_i(u_i(t)) - h_i(u_i(t - \tau_s)), \quad \eta_i(0) = 0, \quad t \geq 0. \quad (8)$$

Here, we assume that the function  $f(x, z, \hat{u})$  can be approximated over a compact set  $\mathcal{D}_x \times \mathcal{D}_z \times \mathcal{D}_{\hat{u}}$  by a linear in parameters neural network up to a desired accuracy. In this case, there exists  $\hat{\varepsilon} : \mathbb{R}^r \times \mathbb{R}^{n-r} \times \mathbb{R}^{mp} \rightarrow \mathbb{R}^m$  such that  $\|\hat{\varepsilon}(x, \hat{u})\| < \varepsilon^*$  for all  $(x, z, \hat{u}) \in \mathcal{D}_x \times \mathcal{D}_z \times \mathcal{D}_{\hat{u}}$ , where  $\varepsilon^* > 0$ , and

$$f(x, z, \hat{u}) = W_f^T \hat{\sigma}(x, z, \hat{u}) + \hat{\varepsilon}(x, z, \hat{u}), \quad (x, z, \hat{u}) \in \mathcal{D}_x \times \mathcal{D}_z \times \mathcal{D}_{\hat{u}}, \quad (9)$$

where  $W_f \in \mathbb{R}^{s \times m}$  is an optimal *unknown* (constant) weight that minimizes the approximation error over  $\mathcal{D}_x \times \mathcal{D}_z \times \mathcal{D}_{\hat{u}}$ ,  $\hat{\sigma} : \mathbb{R}^r \times \mathbb{R}^{n-r} \times \mathbb{R}^{mp} \rightarrow \mathbb{R}^s$  is a vector of basis functions such that each component of  $\hat{\sigma}(\cdot, \cdot, \cdot)$  takes values between 0 and 1, and  $\hat{\varepsilon}(\cdot, \cdot, \cdot)$  is the modeling error. Note that  $s$  denotes the total number of basis functions or, equivalently, the number of nodes of the neural network.

In order to develop an *output* feedback neuroadaptive controller, we use the approach developed 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 an  $(2mn - r)$ -dimensional vector output consisting of the present values of the system outputs and system inputs, and their  $2(n-1)m - r$  delayed values given by

$$\zeta(t) \triangleq [y(t), y(t-d), \dots, y(t-(n-1)d), \dots, y(t), y(t-d), \dots, y(t-(n-1)d); u_1(t), u_1(t-d), \dots, u_1(t-(n-r_1-1)d), \dots, u_m(t), u_m(t-d), \dots, u_m(t-(n-r_m-1)d)]^T, \quad t \geq 0, \quad (10)$$

where  $r_i$  denotes the relative degree of  $\mathcal{G}$  with respect to the output  $y_i$ ,  $i = 1, \dots, m$ .

The following matching conditions are needed for the main result of this paper.

*Assumption 3.1:* There exist  $K_y \in \mathbb{R}^{m \times m}$  and  $K_r \in \mathbb{R}^{m \times d}$  such that  $A_0 + BK_y C = A_{\text{ref}}$  and  $BK_r = B_{\text{ref}}$ .

Using the parameterization  $\Lambda = \hat{\Lambda} + \Delta\Lambda$ , where  $\Delta\Lambda \in \mathbb{R}^{m \times m}$  is an unknown symmetric matrix, the dynamics in (1) can be rewritten as

$$\dot{x}(t) = A_0 x(t) + B\hat{\Lambda}h(u(t)) + B[\Lambda f(x(t), z(t), \hat{u}(t)), + \Delta\Lambda h(u(t))], \quad x(0) = x_0, \quad t \geq 0. \quad (11)$$

Define  $W \triangleq [W_1^T, W_2^T]^T \in \mathbb{R}^{(s+m) \times m}$ , where  $W_1 \triangleq W_f \Lambda$  and  $W_2 \triangleq \Delta\Lambda^T$ . Using (9), (11) can be rewritten as

$$\begin{aligned} \dot{x}(t) &= A_0 x(t) + B\hat{\Lambda}u(t) + BW^T \sigma(\zeta(t), h(u(t))) \\ &\quad + B\hat{\Lambda}\Delta h(t) + B\Lambda\hat{\varepsilon}(x(t), z(t), \hat{u}(t)) \\ &\quad + BW_1^T [\hat{\sigma}(x(t), z(t), \hat{u}(t)) - \sigma_\zeta(\zeta(t))], \\ x(0) &= x_0, \quad t \geq 0, \end{aligned} \quad (12)$$

where

$$\sigma(\zeta(t), h(u(t))) \triangleq [\sigma_\zeta^T(\zeta(t)), h^T(u(t))]^T, \quad t \geq 0, \quad (13)$$

$\sigma_\zeta : \mathbb{R}^{2mn-r} \rightarrow \mathbb{R}^s$  is a vector of basis functions such that each component of  $\sigma_\zeta(\cdot)$  takes values between 0 and 1, and  $\Delta h(u(t)) \triangleq h(u(t)) - u(t)$ ,  $t \geq 0$ .

Next, consider a sequence of positive numbers  $\{\rho_i\}_{i=1}^\infty$  such that  $\lim_{i \rightarrow \infty} \rho_i = 0$  and define the time-dependent set  $\Omega_{t,i}$  and saturation impact times  $\tau_i^*(t)$  by

$$\begin{aligned} \Omega_{t,i} &\triangleq \{\tau \geq 0 : \eta_i(\tau) = \eta_i^* \text{ and there exists } N > 0 \\ &\quad \text{such that for all } i \geq N, \eta_i(\tau - \rho_i) < \eta_i^*\}, \\ &\quad t \geq 0, \quad i = 1, \dots, m, \end{aligned} \quad (14)$$

$$\tau_i^*(t) \triangleq \begin{cases} \theta_i + \max\{\tau : \tau \in \Omega_{t,i}\}, & \text{if } \Omega_{t,i} \neq \emptyset, \\ 0, & \text{otherwise,} \end{cases} \quad t \geq 0, \quad i = 1, \dots, m, \quad (15)$$

where  $\theta_i > 0$ ,  $i = 1, \dots, m$ , are design parameters.

Now, consider the control input  $u(t)$ ,  $t \geq 0$ , given by

$$u(t) = \Phi(\eta(t))\psi(t), \quad t \geq 0, \quad (16)$$

where  $\Phi(\eta(t)) \triangleq \text{diag}[\phi_1(\eta_1(t)), \dots, \phi_m(\eta_m(t))]$ ,  $t \geq 0$ , and

$$\begin{aligned} \phi_i(\eta_i(t)) &\triangleq \begin{cases} 1, & \text{if } 0 \leq \eta_i(t) \leq \eta_i^* - \delta_i \text{ and } t \geq \tau_i^*(t), \\ \frac{1}{\delta_i}(\eta_i^* - \eta_i(t)), & \text{if } \eta_i^* - \delta_i \leq \eta_i(t) \leq \eta_i^* \text{ and } t \geq \tau_i^*(t), \\ 0, & \text{otherwise,} \end{cases} \\ &\quad t \geq 0, \quad i = 1, \dots, m, \end{aligned} \quad (17)$$

$0 < \delta_i < \eta_i^*$ ,  $i = 1, \dots, m$ , are design constant parameters (chosen to be sufficiently small), and  $\psi(t) \in \mathbb{R}^m$ ,  $t \geq 0$ , is given by

$$\psi(t) = \psi_n(t) - \psi_{\text{ad}}(t), \quad t \geq 0, \quad (18)$$

where

$$\psi_n(t) = \hat{\Lambda}^{-1}[K_y y(t) + K_r r(t)], \quad t \geq 0, \quad (19)$$

$$\begin{aligned} \psi_{\text{ad}}(t) &= \hat{\Lambda}^{-1} \left[ \hat{W}^T(t) \sigma(\zeta(t), h(u(t))) \right. \\ &\quad \left. + K_y \hat{W}_y^T(t) \sigma_y(\hat{y}(t), \hat{u}(t)) \right], \quad t \geq 0, \end{aligned} \quad (20)$$

and  $\hat{W}(t) \in \mathbb{R}^{(s+m) \times m}$ ,  $t \geq 0$ , and  $\hat{W}_y(t) \in \mathbb{R}^{l \times m}$ ,  $t \geq 0$ , are update weights. Note that for all  $t \geq 0$  and  $i = 1, \dots, m$ ,  $0 \leq \phi_i(\eta_i(t)) \leq 1$ . Furthermore, if  $\eta_i(\hat{t}) = \eta_i^*$  for every  $\hat{t} \geq 0$ , then  $h_i(u_i(\hat{t})) = 0$ , and hence, it follows from (8) that the integral constraint (7) is satisfied.

*Remark 3.1:* The choice of  $\phi_i(\eta_i)$ ,  $i = 1, \dots, m$ , is not limited to the piecewise linear continuous function given by (17). In particular, on the interval  $\eta_i^* - \delta_i \leq \eta_i \leq \eta_i^*$ ,  $\phi_i(\eta_i)$  can be any decreasing continuous function such that  $\phi_i(\eta_i^* - \delta_i) = 1$  and  $\phi_i(\eta_i^*) = 0$ .

Defining the tracking error state  $e(t) \triangleq x(t) - x_{\text{ref}}(t)$ ,  $t \geq 0$ , and using (16), (18)–(20), and Assumption 3.1, the error dynamics are given by

$$\begin{aligned} \dot{e}(t) &= A_{\text{ref}} e(t) + B\tilde{W}^T(t) \sigma(\zeta(t), h(u(t))) \\ &\quad + BK_y \tilde{W}_y^T(t) \sigma_y(\hat{y}(t), \hat{u}(t)) + B\hat{\Lambda}\Delta h(u(t)) + \varepsilon(t), \\ e(0) &= x_0 - x_{\text{ref}0}, \quad t \geq 0, \end{aligned} \quad (21)$$

where

$$\begin{aligned} \varepsilon(t) &\triangleq B\hat{\Lambda}(\Phi(t) - I_m)\psi(t) + B\Lambda\hat{\varepsilon}(x(t), z(t), \hat{u}(t)) \\ &\quad + BW_1^T [\hat{\sigma}(x(t), z(t), \hat{u}(t)) - \sigma_\zeta(\zeta(t))], \quad t \geq 0, \end{aligned}$$

$\tilde{W}(t) \triangleq W - \hat{W}(t)$ ,  $t \geq 0$ , and  $\tilde{W}_y(t) \triangleq W_y - \hat{W}_y(t)$ ,  $t \geq 0$ .

Next, to remove the effects due to saturation on the error state  $e(t)$ ,  $t \geq 0$ , consider the dynamical system given by

$$\begin{aligned} \dot{e}_s(t) &= A_{\text{ref}} e_s(t) + B\hat{\Lambda}\Delta h(u(t)), \quad e_s(0) = e_{s0}, \quad t \geq 0, \quad (22) \\ y_s(t) &= C e_s(t), \end{aligned} \quad (23)$$

where  $e_s(t) \in \mathbb{R}^r$ ,  $t \geq 0$ , and define the augmented error state  $\tilde{e}(t) \triangleq e(t) - e_s(t)$ ,  $t \geq 0$ . Now, it follows from (21) and (22) that

$$\begin{aligned} \dot{\tilde{e}}(t) &= A_{\text{ref}} \tilde{e}(t) + B \left[ K_y \tilde{W}_y^T(t) \sigma_y(\hat{y}(t), \hat{u}(t)) \right. \\ &\quad \left. + \tilde{W}^T(t) \sigma(\zeta(t), h(u(t))) \right] + \varepsilon(t), \quad \tilde{e}(0) = 0, \quad t \geq 0. \end{aligned} \quad (24)$$

For the statement of our main result, define the projection operator  $\text{Proj}(\tilde{W}, Y)$  by

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

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

Consider the update laws given by

$$\begin{aligned} \dot{\hat{W}}(t) &= \Gamma_W \text{Proj}[\hat{W}(t), \sigma(\zeta(t), h(u(t))) \xi_C^T(t) P B], \\ \hat{W}(0) &= \hat{W}_0, \quad t \geq 0, \end{aligned} \quad (25)$$

$$\begin{aligned} \dot{\hat{W}}_y(t) &= \Gamma_y \text{Proj}[\hat{W}_y(t), \sigma_y(\hat{y}(t), \hat{u}(t)) \xi_C^T(t) (P B K_y \\ &\quad + \tilde{P} L)], \quad \hat{W}_y(0) = \hat{W}_{y0}, \end{aligned} \quad (26)$$

where  $\Gamma_W \in \mathbb{R}^{(s+m) \times (s+m)}$  and  $\Gamma_y \in \mathbb{R}^{l \times l}$  are positive definite matrices,  $P \in \mathbb{R}^{r \times r}$  is a positive-definite solution of the Lyapunov equation

$$0 = A_{\text{ref}}^T P + P A_{\text{ref}} + R, \quad (27)$$

where  $R > 0$ , and  $\tilde{P} \in \mathbb{R}^{n_\xi \times n_\xi}$  is a positive-definite solution of the Lyapunov equation

$$0 = (\hat{A} - L\hat{C})^T \tilde{P} + \tilde{P}(\hat{A} - L\hat{C}) + \tilde{R}, \quad (28)$$

where  $\tilde{R} > 0$ ,  $\hat{A} \in \mathbb{R}^{n_\xi \times n_\xi}$  is Hurwitz,  $L \in \mathbb{R}^{n_\xi \times m}$ ,  $\hat{C} \in \mathbb{R}^{m \times n_\xi}$ , and  $\xi_c(t) \in \mathbb{R}^{n_\xi}$ ,  $t \geq 0$ , is the solution to the estimator dynamics

$$\begin{aligned} \dot{\xi}_c(t) &= \hat{A}\xi_c(t) + L[y(t) - y_{\text{ref}}(t) - y_c(t) - y_s(t)], \\ \xi_c(0) &= \xi_{c0}, \quad t \geq 0, \end{aligned} \quad (29)$$

$$y_c(t) = \hat{C}\xi_c(t) + \hat{W}_y^T(t)\sigma_y(\hat{y}(t), \hat{u}(t)). \quad (30)$$

Note that since  $h(u)$  is bounded for all  $u \in \mathbb{R}^m$  and  $f(x, z, \hat{u})$  is bounded for all  $(x, z, \hat{u}) \in \mathbb{R}^r \times \mathbb{R}^{n-r} \times \mathbb{R}^{mp}$ , it follows that  $x(t)$ ,  $t \geq 0$ , is bounded for all  $t \geq 0$ , and hence,  $\psi_n(t)$  is bounded for all  $t \geq 0$ . Now, since the projection operator used in the update laws (25) and (26) guarantees the boundness of the update weights  $\hat{W}(t)$ ,  $t \geq 0$ , and  $\hat{W}_y(t)$ ,  $t \geq 0$ , it follows that there exist  $u^* > 0$  and  $\delta^* > 0$  such that  $\|u(t)\| \leq u^*$  and  $\|\Delta h(u(t))\| \leq \delta^*$  for all  $t \geq 0$ . Furthermore, note that there exists  $\varepsilon^* > 0$  such that  $\|\varepsilon(t)\| \leq \varepsilon^*$  for all  $t \geq 0$  such that  $(x(t), z(t), \hat{u}(t)) \in \mathcal{D}_x \times \mathcal{D}_z \times \mathcal{D}_{\hat{u}}$ . Finally, there exist  $\alpha_1 > 0$  and  $\alpha_2 > 0$  such that  $\|\tilde{W}^T(t)\sigma(\zeta(t), h(u(t)))\| \leq \alpha_1$  and  $\|\tilde{W}_y^T(t)\sigma_y(\hat{y}(t), \hat{u}(t))\| \leq \alpha_2$  for all  $t \geq 0$ .

For the statement of the main result of this paper, let  $\|\cdot\|^* : \mathbb{R}^{n_\xi \times n_\xi} \rightarrow \mathbb{R}$  be the matrix norm equi-induced by the vector norm  $\|\cdot\|^{**} : \mathbb{R}^{n_\xi} \rightarrow \mathbb{R}$ .

**Theorem 3.1:** Consider the nonlinear uncertain dynamical system  $\mathcal{G}$  given by (1)–(3) with  $u(t)$ ,  $t \geq 0$ , given by (16) and reference model  $\mathcal{G}_{\text{ref}}$  given by (5) and (6) with tracking error dynamics given by (21). Assume Assumption 3.1 holds,  $\lambda_{\min}(R) > 1$ , and  $\lambda_{\min}(\tilde{R}) > \|\tilde{P}L\hat{C}\|^{*2}$ . Then there exists a compact positively invariant set  $\mathcal{D}_\alpha \subset \mathbb{R}^r \times \mathbb{R}^m \times \mathbb{R}^{(s+m) \times m} \times \mathbb{R}^{l \times m}$  such that  $(0, 0, 0, W, W_y) \in \mathcal{D}_\alpha$ , where  $W \in \mathbb{R}^{(s+m) \times m}$  and  $W_y \in \mathbb{R}^{l \times m}$ , and the solution  $(e(t), e_s(t), \xi_c(t), \hat{W}(t), \hat{W}_y(t))$ ,  $t \geq 0$ , of the closed-loop system given by (1)–(3), (16), (22), (23), (25), (26), (29) and (30) is ultimately bounded for all  $(e(0), e_s(0), \xi_c(0), \hat{W}(0), \hat{W}_y(0)) \in \mathcal{D}_\alpha$  with ultimate bound  $\|y(t) - y_{\text{ref}}(t)\| < \gamma$ ,  $t \geq T$ , where  $\gamma > 0$ . Furthermore,  $u(t)$ ,  $t \geq 0$ , satisfies (7) for all  $t \geq 0$ ,  $h(u(t)) \geq 0$ ,  $t \geq 0$ , and  $x(t) \geq 0$ ,  $t \geq 0$ , for all  $x_0 \in \mathbb{R}_+^n$ .

A block diagram showing the neuroadaptive control architecture given in Theorem 3.1 is shown in Figure 1.

**Remark 3.2:** To apply Theorem 3.1 to the set-point regulation problem, let  $x_e \in \mathbb{R}_+^r$  and  $r(t) \equiv r^*$  be such that  $0 = A_{\text{ref}}x_e + B_{\text{ref}}r^*$  and  $y_{\text{ref}}(t) \equiv y_d = Cx_e$ , where  $y_d \in \mathbb{R}_+^m$  is a given desired set-point. In this case, the controller signal is given by (16) and (18) with  $\psi_n(t) \equiv 0$ .

#### IV. NEUROADAPTIVE OUTPUT FEEDBACK CONTROL FOR GENERAL ANESTHESIA WITH DRUG INFUSION CONSTRAINTS

To illustrate the application of the neuroadaptive control framework presented in Section III for general anesthesia we develop a model for the intravenous anesthetic propofol. The pharmacokinetics of propofol are described by the three compartment model [8] shown in Figure 2, 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* (blood within

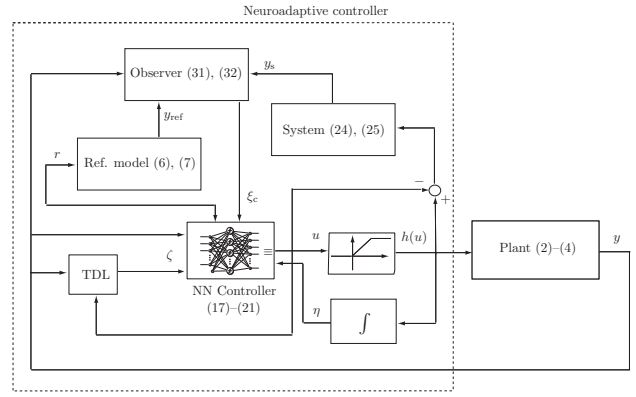


Fig. 1. Block diagram of the closed-loop system.

arteries and veins) as well as *highly perfused* organs (organs with high ratios of blood flow to weight) such as the heart, brain, kidney, and liver. These organs receive a large fraction of the cardiac output. The remainder of the drug in the body is assumed to reside in two peripheral compartments, one identified with muscle and one with fat; the masses in these compartments are denoted by  $x_2$  and  $x_3$ , respectively. These compartments receive less than 20% of the cardiac output.

A mass balance of the three-state compartmental model yields

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

$$\begin{aligned} \dot{x}_2(t) &= a_{21}(c(t))x_1(t) - a_{12}(c(t))x_2(t), \\ x_2(0) &= x_{20}, \quad t \geq 0, \end{aligned} \quad (32)$$

$$\begin{aligned} \dot{x}_3(t) &= a_{31}(c(t))x_1(t) - a_{13}(c(t))x_3(t), \\ x_3(0) &= x_{30}, \quad t \geq 0, \end{aligned} \quad (33)$$

where  $c(t) = x_1(t)/V_c$ ,  $V_c$  is the volume of the central compartment (about 15 l for a 70 kg patient),  $a_{ij}(c)$ ,  $i \neq j$ , is the rate of transfer of drug from the  $j$ th compartment to the  $i$ th compartment,  $a_{11}(c)$  is the rate of drug metabolism and elimination (metabolism typically occurs in the liver), and  $h(u(t))$ ,  $t \geq 0$ , is the constrained infusion rate of the anesthetic drug propofol into the central compartment. The transfer coefficients are assumed to be functions of the drug concentration  $c$  since it is well known that the pharmacokinetics of propofol are influenced by cardiac output [8] and, in turn, cardiac output is influenced by propofol plasma concentrations, both due to *venodilation* (pooling of blood in dilated veins) and myocardial depression.

Experimental data indicate that the transfer coefficients  $a_{ij}(\cdot)$  are nonincreasing functions of the propofol concentration [8]. The most widely used empirical models for pharmacodynamic concentration-effect relationships are modifications of the Hill equation [8]. Applying this almost ubiquitous empirical model to the relationship between transfer coefficients implies that

$$a_{ij}(c) = A_{ij}Q_{ij}(c), \quad Q_{ij}(c) = Q_0 C_{50,ij}^{\alpha_{ij}} / (C_{50,ij}^{\alpha_{ij}} + c^{\alpha_{ij}}),$$

where, for  $i, j \in \{1, 2, 3\}$ ,  $i \neq j$ ,  $C_{50,ij}$  is the drug concentration associated with a 50% decrease in the transfer coefficient,  $\alpha_{ij}$  is a parameter that determines the steepness of the concentration-effect relationship, and  $A_{ij}$  are positive constants. Note that both pharmacokinetic parameters are functions of  $i$  and  $j$ , that is, there are distinct Hill equations for each transfer coefficient. Furthermore, since for many

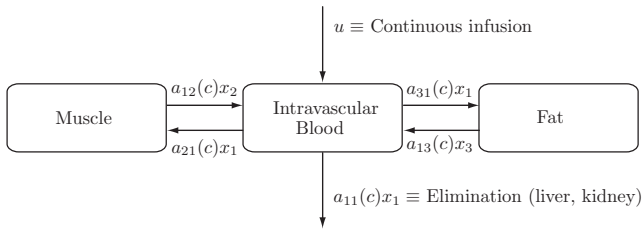


Fig. 2. Pharmacokinetic model for drug distribution during anesthesia

drugs the rate of metabolism  $a_{11}(c)$  is proportional to the rate of transport of drug to the liver we assume that  $a_{11}(c)$  is also proportional to the cardiac output so that  $a_{11}(c) = A_{11}Q_{11}(c)$ .

To illustrate the neuroadaptive control of propofol, we assume that  $C_{50,ij}$  and  $\alpha_{ij}$  are independent of  $i$  and  $j$ . Also, since decreases in cardiac output are observed at clinically-utilized propofol concentrations we arbitrarily assign  $C_{50}$  a value of  $4 \mu\text{g/ml}$  since this value is in the mid-range of clinically utilized values. We also assign  $\alpha$  a value of 3 [10]. This value is within the typical range of those observed for ligand-receptor binding (see the discussion in [11]). The nonnegative transfer and loss coefficients  $A_{12}$ ,  $A_{21}$ ,  $A_{13}$ ,  $A_{31}$ , and  $A_{11}$ , and the parameters  $\alpha > 1$ ,  $C_{50} > 0$ , and  $Q_0 > 0$ , are uncertain due to patient gender, weight, pre-existing disease, age, and concomitant medication.

Even though propofol concentration levels in the blood plasma will lead to the desired depth of anesthesia, they cannot be measured in real-time during surgery. Furthermore, we are more interested in drug *effect* (depth of hypnosis) rather than drug *concentration*. Hence, we consider a model involving *pharmacokinetics* (drug concentration as a function of time) and *pharmacodynamics* (drug effect as a function of concentration) for controlling consciousness. Specifically, we use an electroencephalogram (EEG) signal as a measure of hypnotic drug effect of anesthetic compounds on the brain [12]. 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 control in general anesthesia.

The Bispectral Index (BIS), an EEG indicator, has been proposed as a measure of hypnotic 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 related to drug concentration by the empirical relationship

$$\text{BIS}(c_{\text{eff}}(t)) = \text{BIS}_0 \left( 1 - \frac{c_{\text{eff}}^\gamma(t)}{c_{\text{eff}}^\gamma(t) + \text{EC}_{50}^\gamma} \right), \quad (34)$$

where  $\text{BIS}_0$  denotes the baseline (awake state) value and, by convention, is typically assigned a value of 100,  $c_{\text{eff}}$  is the propofol concentration in  $\mu\text{g/ml}$  in the effect-site compartment (brain),  $\text{EC}_{50}$  is the concentration at half maximal effect and represents the patient's sensitivity to the drug, and  $\gamma$  determines the degree of nonlinearity in (34). Here, the effect-site compartment is introduced to account for finite equilibration time 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 model ([8])

$$\dot{c}_{\text{eff}}(t) = a_{\text{eff}}(c(t) - c_{\text{eff}}(t)), \quad c_{\text{eff}}(0) = c(0), \quad t \geq 0, \quad (35)$$

where  $a_{\text{eff}}$  in  $\text{min}^{-1}$  is an unknown positive time constant. In reality, the effect-site compartment equilibrates with the

central compartment in a matter of a few minutes. The parameters  $a_{\text{eff}}$ ,  $\text{EC}_{50}$ , and  $\gamma$  are determined by data fitting and vary from patient to patient. BIS index values of 0 and 100 correspond, respectively, to an *isoelectric* EEG signal (no cerebral electrical activity) and an EEG signal of a fully conscious patient; the range between 40 and 60 indicates a moderate hypnotic state.

Next, using a globally defined diffeomorphism we transform the system given by (31)–(33) and (35) into the normal form given by (1)–(3) and consider a set-point regulation problem with a desired level of hypnosis corresponding to  $\text{BIS}_{\text{Target}} = 50$ . In the following simulation involving the infusion of the anesthetic drug propofol we set  $\text{EC}_{50} = 5.6 \mu\text{g/ml}$ ,  $\gamma = 2.39$ , and  $\text{BIS}_0 = 100$ . Here, we use the neuroadaptive output feedback controller  $u(t) = \phi(\eta(t))\psi(t)$ ,  $t \geq 0$ , where

$$\phi(\eta(t)) = \begin{cases} 1, & \text{if } 0 \leq \eta(t) \leq \eta^* - \delta \text{ and } t \geq \tau^*(t), \\ \frac{1}{\delta}(\eta^* - \eta(t)), & \text{if } \eta^* - \delta \leq \eta(t) \leq \eta^* \text{ and } t \geq \tau^*(t), \\ 0, & \text{otherwise,} \end{cases} \quad t \geq 0, \quad (36)$$

$$\eta(t) = \int_{t-\tau_s}^t h(u(s))ds, \quad t \geq 0, \quad (37)$$

$$h(u(t)) = \begin{cases} 0, & \text{if } u(t) \leq 0, \\ u^*, & \text{if } u(t) \geq u^*, \\ u(t), & \text{otherwise,} \end{cases} \quad t \geq 0, \quad (38)$$

$\delta = 0.005$ ,  $\eta^* = 0.15 \text{ g}$ ,  $\tau_s = 10 \text{ sec}$ ,  $\theta = 5 \text{ sec}$ , and  $u^* = 0.32 \text{ g/min}$ . Note that (38) guarantees an infusion rate constraint of  $0.32 \text{ g/min}$ , whereas (37) ensures a drug dosing constraint of  $0.15 \text{ g}$  over a period of 10 seconds.

Next, let

$$\psi(t) = \psi_n(t) - \psi_{\text{ad}}(t), \quad (39)$$

where  $\psi_n(t) \equiv 0$  and  $\psi_{\text{ad}}(t) = \hat{W}^T(t)\sigma(\zeta(t))$ ,  $t \geq 0$ , where

$$\zeta(t) = [\text{BIS}_f(t-d), \text{BIS}_f(t-2d), h(u(t-d)), h(u(t-2d))]^T, \quad (40)$$

$d > 0$ , and

$$\dot{\hat{W}}(t) = Q_{\text{BIS}} \text{Proj}[\hat{W}_1(t), \sigma(\zeta(t))\xi_c^T(t)PB], \quad \hat{W}(0) = \hat{W}_0, \quad t \geq 0, \quad (41)$$

where  $Q_{\text{BIS}}$  is a positive constant and  $\xi_c(t) \in \mathbb{R}^2$ ,  $t \geq 0$ , is the solution to the estimator dynamics

$$\dot{\xi}_c(t) = \hat{A}\xi_c(t) + L(\text{BIS}(t) - \text{BIS}_{\text{Target}} - y_c(t) - y_s(t)), \quad \xi_c(0) = \xi_{c0}, \quad t \geq 0, \quad (42)$$

$$y_c(t) = \hat{C}\xi_c(t), \quad (43)$$

where  $\hat{A} \in \mathbb{R}^{2 \times 2}$ ,  $L \in \mathbb{R}^{2 \times 1}$ ,  $\hat{C} \in \mathbb{R}^{1 \times 2}$ , and  $y_s(t)$ ,  $t \geq 0$ , is the output of the dynamical system

$$\dot{e}_s(t) = A_0 e_s(t) + B\Delta h(u(t)), \quad e_s(0) = e_{s0}, \quad t \geq 0, \quad (44)$$

$$y_s(t) = C e_s(t). \quad (45)$$

Here, we assume that  $W_y = 0$  so that  $\hat{W}(t) \equiv 0$ . Now, it follows from Theorem 3.1 that there exist positive

constants  $\gamma$  and  $T$  such that  $|\text{BIS}(t) - \text{BIS}_{\text{target}}| \leq \gamma$ ,  $t \geq T$ , where  $\text{BIS}(t)$  is given by (34), for all nonnegative values of the pharmacokinetic transfer and loss coefficients  $A_{12}, A_{21}, A_{13}, A_{31}, A_{11}$  as well as all nonnegative coefficients  $\alpha, C_{50}$ , and  $Q_0$ .

For our simulation we assume  $V_c = (0.228 \text{ l/kg})(M \text{ kg})$ , where  $M = 70 \text{ kg}$  is the mass of the patient,  $A_{21}Q_0 = 0.112 \text{ min}^{-1}$ ,  $A_{12}Q_0 = 0.055 \text{ min}^{-1}$ ,  $A_{31}Q_0 = 0.0419 \text{ min}^{-1}$ ,  $A_{13}Q_0 = 0.0033 \text{ min}^{-1}$ ,  $A_eQ_0 = 0.119 \text{ min}^{-1}$ ,  $a_{\text{eff}} = 3.4657 \text{ min}^{-1}$ ,  $\alpha = 3$ , and  $C_{50} = 4 \text{ } \mu\text{g/ml}$  [10]. Note that the parameter values for  $\alpha$  and  $C_{50}$  probably exaggerate the effect of propofol on cardiac output. They have been selected to accentuate nonlinearity but they are not biologically unrealistic. Furthermore, to illustrate the efficacy of the proposed neuroadaptive controller we switch the pharmacodynamic parameters  $\text{EC}_{50}$  and  $\gamma$ , respectively, from  $5.6 \text{ } \mu\text{g/ml}$  and  $2.39$  to  $7.2 \text{ } \mu\text{g/ml}$  and  $3.39$  at  $t = 15 \text{ min}$  and back to  $5.6 \text{ } \mu\text{g/ml}$  and  $2.39$  at  $t = 30 \text{ min}$ . Here, we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal.

With  $B = [1, 0, 0]^T$ ,  $C = [1, 0, 0]$ ,  $\hat{A} = \begin{bmatrix} 0 & 1 \\ -1 & -1 \end{bmatrix}$ ,  $L = [0, 1]^T$ ,  $\hat{C} = [1, 0]$ ,  $Q_{\text{BIS}} = 2.0 \times 10^{-4} \text{ g/min}^2$ ,  $d = 0.005$ , and initial conditions  $x_1(0) = x_2(0) = x_3(0) = 0 \text{ g}$ ,  $c_{\text{eff}}(0) = 0 \text{ g/ml}$ ,  $\xi_c(0) = [0, 0]^T$ ,  $e_{s0} = [0, 0, 0]^T$ , and  $\hat{W}(0) = 1 \times 10^{-3}[-3_{12 \times 1}, 1_{12 \times 1}]^T$ , Figure 3 shows the concentrations in the central and effect-site compartments versus time. Note that the effect-site compartment equilibrates with the central compartment in a matter of several minutes. Figure 4 shows the BIS signal and the amount of propofol delivered over a 10-second window versus time. Note that during the controller operation  $\eta(t)$  is far below the clinical critical value  $\eta^*$ . Finally, Figure 5 shows the constrained  $h(u(t))$  and unconstrained  $u(t)$  propofol infusion rate versus time.

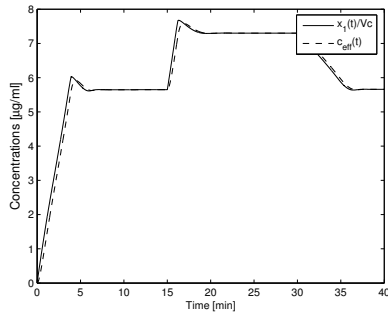


Fig. 3. Concentrations in the central and effect site compartments versus time

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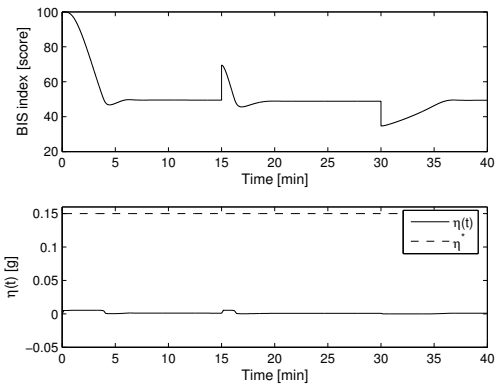


Fig. 4. BIS signal and  $\eta$  versus time

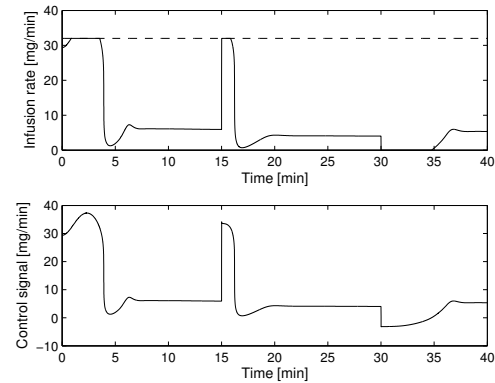


Fig. 5. Infusion rate and control signal versus time

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