Output Reference Tracking for MISO Positive Systems in General Anesthesia ⋆

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Abstract: In this paper a nonlinear positive control law is proposed for reference tracking in multi-input positive systems. This law proves to have a good performance in the control of the depth of anesthesia (DoA) by means of *propofol* and *remifentanil*, which is illustrated by several simulations.

Keywords: Positive systems, control, DoA, anesthesia.

1. INTRODUCTION

Positive systems describe processes that involve inherently positive quantities, with applications in various areas of science and technology. This is the case of drug administration models for which it only makes sense to consider positive control laws.

In this context, the goal of automatically controlled drug administration is to determine the dosage to be administered to achieve a certain level of plasma concentration and consequently a certain effect of a drug in the patient.

This is modeled as an output reference tracking problem. More specifically, after modeling the phenomenon in question by a control system in which the control input is the dosage of drug to be administered and the output is the corresponding effect, one seeks a control law that forces the system output to converge to the desired reference value.

In this paper we consider single output positive systems with multiple inputs and design a nonlinear positive control law that ensures asymptotic tracking of a desired output reference value. This control law can be viewed as a generalization of the one proposed in Bastin and Provost (2002) for the control of the total mass in SISO compartmental systems. Moreover it can also be adapted to the case of positive systems with multiple outputs.

Our results prove to be useful for the control of the depth of anesthesia, a problem that has lately deserved much attention (Hemmerling et al. (2010), Ionescu et al. (2008), Dumont et al. (2008), Furutani et al. (2005), Soltesz et al. (2011)). This is illustrated by means of several simulations using the minimally parameterized model for the effect of *propofol* and *remifentanil* administration, introduced in Silva et al. (2010)

2. OUTPUT REFERENCE TRACKING FOR MISO POSITIVE SYSTEMS

In this section the general problem of reference tracking for multi-input/single-output (MISO) positive systems is presented. The application to the control of anesthesia will be presented in Section 3.

2.1 Problem Description

Consider a positive system with m inputs and a single output described by the state-space model

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ y(t) = Cx(t), \end{cases} \tag{1}$$

where A is a $n \times n$ Meztler matrix, i.e., a matrix in which all the off-diagonal components are nonnegative, and B and C are matrices with nonnegative entries (Godfrey (1983)) of dimension $n \times m$ and $1 \times m$, respectively. Here, for short, in the sequel (1) is denoted by (A, B, C). Moreover, for a vector v, the notations $v \geq 0$ ($v > 0$) and $v \leq 0$

⋆ This work was supported by *FEDER* founds through *COMPETE*–Operational Programme Factors of Competitiveness ("Programa Operacional Factores de Competitividade") and by Portuguese funds through the *Center for Research and Development in Mathematics and Applications* (University of Aveiro) and the Portuguese Foundation for Science and Technology ("FCT–Fundação para a Ciência e a Tecnologia"), within project PEst-C/MAT/UI4106/2011 with COMPETE number FCOMP-01-0124-FEDER-022690. The authors also acknowledges GALENO - Modeling and Control for personalized drug administration, Funding Agency: FCT,Programme: FCT PTDC/SAU-BEB/103667/2008. Additionally, Filipa Nogueira acknowledges the support of FCT - Portugal through the grant SFRH/BD/48314/2008.

($v < 0$) mean that all its entries are respectively positive (strictly positive) and negative (strictly negative). The same applies to matrices.

Given a desired reference value y^* for the output, a control law $u = Kx + L$ is sought such that the closed loop system

$$\begin{cases} \dot{x}(t) = (A + BK)x(t) + BL \\ y(t) = Cx(t), \end{cases} \tag{2}$$

has bounded trajectories and tracks the reference, i.e., it verifies $\lim_{t\to\infty} y(t) = y^*$.

2.2 Controller design

Here we solve the problem of reference tracking, by regarding it as a problem of controlling the system to a level set $\Omega_{y^*} = \{x \in \mathbb{R}^n_+ : Cx = y^*\}$ in the state space, where $\mathbb{R}^n_+ = \{x \in \mathbb{R}^n : x \geq 0\}$.

For this purpose we first design an auxiliary control law, $\tilde{u}$, and then impose positivity to $\tilde{u}$ in order to obtain a positive control input u. We also make the following assumptions: $(A1)$ A is stable, $(A2)$ CB is a nonzero row matrix and $(A3)$ $CA < 0$.

Let

$$\tilde{u}(t) = -ECAx(t) + E\lambda(y^* - y(t)),$$

where $\lambda > 0$ is a design parameter, and E is a column matrix with nonnegative entries such that $CBE = 1$. Note that such a matrix always exists since CB has nonnegative entries, at least one of each is strictly positive. The application of this control input leads to the closed-loop dynamics

$$\dot{x}(t) = Ax(t) + B(E\lambda(y^* - y(t)) - ECAx(t))$$

which implies that

$$\begin{aligned} \dot{y}(t) &= C\dot{x}(t) = CAx(t) + \lambda(y^* - y(t)) - CAx(t) \\ &= -\lambda(y(t) - y^*) \end{aligned}$$

and therefore

$$\dot{y(t)} - y^* = -\lambda(y(t) - y^*).$$

Hence, $y(t) - y^* = e^{-\lambda t}(y(0) - y^*)$ and

$$\lim_{t\to\infty} y(t) = y^*,$$

which means that the reference value is asymptotically tracked.

In the sequel it is shown that reference tracking can still be achieved even when a positivity restriction to the control input is imposed. This positivity restriction is made componentwise and corresponds to taking the control input as $u = [\, u_1 \ \cdots \ u_m \,]^T$ with $u_i = max(\tilde{u}_i, 0)$, where $\tilde{u}_i$ denotes the $i-th$ component of $\tilde{u}$. Note that $\tilde{u}_i = E_i(-CAx + \lambda(y^* - y))$, where $E_i \geq 0$ is the $i-th$ entry of E. Therefore if $\tilde{u}_i < 0$ then $-CAx + \lambda(y^* - y) < 0$, and all the other components $\tilde{u}_j$ of $\tilde{u}$ corresponding to nonzero E_j are negative as well. This allows to conclude that either $u = \tilde{u}$ or $u = 0$. In this latter case

$$\lambda(y^* - y) < CAx. \tag{3}$$

Since, by assumption $(A3)$, $CA < 0$ and $x \geq 0$, then $CAx \leq 0$ and (3) implies that $y^* - y < 0$.

To prove that all trajectories converge to y^*, we apply the LaSalle's invariance principle (LaSalle (1976)) to the Lyapunov function

$$V(x) = \frac{1}{2}(y^* - y)^2$$

for the system (1) on $\mathbb{R}^n_+$.

For $u = \tilde{u}$:

$$\begin{aligned} \dot{V}(x) &= -(y^* - y)\dot{y} = -(y^* - y)C\dot{x} \\ &= -(y^* - y)C\left(Ax + B\left[E\lambda(y^* - y) - ECAx\right]\right) \\ &= -\lambda(y^* - y)(y^* - y) = -\lambda(y^* - y)^2 \ \leq \ 0 \end{aligned}$$

For $u = 0$:

$$\dot{V}(x) = -(y^* - y)C\dot{x} = -\underbrace{(y^* - y)}_{\leq 0}\underbrace{CAx}_{\leq 0} \ \leq \ 0$$

By the LaSalle's invariance principle, all system trajectories converge to the largest set contained in

$$W = \{x \in \mathbb{R}^n_+ : \dot{V}(x) = 0\}$$

which is forward-invariant under the closed-loop dynamics.

It can be shown that

$$W = \{x \in \mathbb{R}^n_+ : y = y^* \text{ or } (y^* < y \text{ and } CAx = 0)\}.$$

Moreover, the set Ω_{y^*} of positive states for which the corresponding output y equals y^* is forward-invariant under the closed-loop dynamics. In fact, let $F(x)$ be the vector field associated with the closed-loop system

$$\begin{cases} \dot{x} = Ax + Bu \\ u = max(\tilde{u}, 0). \end{cases}$$

When $Cx = y^*$, $u = \tilde{u} = -ECAx \geq 0$ and $F(x) = Ax - BECAx$. As a consequence $CF(x) = 0$ showing that $F(x)$ is tangent to Ω_{y^*} in its interior points. So Ω_{y^*} is forward-invariant under the closed-loop dynamics.

On the other hand, the trajectories starting in a state x for which $Cx > y^*$ and $CAx = 0$ converge to Ω_{y^*}, because

$$\begin{aligned} Cx > y^* \ &\Rightarrow u = 0 \\ &\Rightarrow \dot{x}(t) = Ax(t) \end{aligned}$$

Since A is assumed to be stable, if the control would remain zero, $\lim_{t\to\infty} Cx(t)$ would be zero. This implies that at a certain time instant t^* $Cx(t^*)$ reaches the value $Cx(t^*) = y^*$, i.e. $x(t^*) \in \Omega_{y^*}$. From this instant on the trajectories remain indefinitely in the forward-invariant set Ω_{y^*}. Therefore, the largest invariant subset contained in W is Ω_{y^*} and, by LaSalles's invariance principle, all the closed-loop system trajectories converge to this set, which means that $\lim_{t\to\infty} y(t) = y^*$ as desired.

The study just developed leads to the following result.

Theorem 1. Let (A, B, C) be a positive MISO linear system, such that A is stable, $CA < 0$ and $CB \neq 0$. If $u = max(\tilde{u}, 0)$, $\tilde{u} = -ECAx + E\lambda(y^* - y)$, with $\lambda > 0$, and $E \geq 0$ such that $CBE = 1$, then the closed-loop system output $y(t)$ verifies $\lim_{t\to\infty} y(t) = y^*$.

3. CONTROL OF THE DEPTH OF ANESTHESIA

Combinations of drugs are used in general anesthesia because no single drug is able to provide all its necessary components (namely, analgesia, hypnosis, areflexia) without seriously compromising hemodynamic and/or respiratory function, impairing operating conditions, or delaying postoperative recovery. Ideal combination of dosing facilitates optimal therapeutic effect without producing significant side effects.

Here, a control law is designed to administer the hypnotic agent *propofol* and the opioid analgesic *remifentanil* to patients during surgery, in order to achieve a desired level of unconsciousness. This is measured in terms of the depth of anesthesia (DoA), usually denoted by $z(t)$, which is a feature that can be related to the quantities of administered drugs as explained next.

In what concerns DoA, the response for the administration of hypnotics and analgesics is commonly modeled as a high order pharmacokinetic/pharmacodynamic (PK/PD) Wiener model (Bailey and Haddad (2005)). However, a new Wiener model (minimally parameterized model) with a minimal number of parameters describing the join effect of *propofol* and of *remifentanil* as been introduced in Silva et al. (2010). Here, the main goal of this section is to design a controller for the DoA based on this minimally parameterized model. The perfomance of this controller on simulated and real patients will be analyzed in a further stage.

The effect concentration of *propofol* (c_e^p) and of *remifentanil* (c_e^r) can be modeled by the state space model (see Silva et al. (2010)):

$$\begin{cases} \dot{x^i} = A^i x^i + B^i u^i \\ c_e^i = [\,0\ 0\ 1\,]\, x^i, \end{cases}$$

where

$$i = p, r,\ x^i = \begin{bmatrix} x_1^i \\ x_2^i \\ x_3^i \end{bmatrix},$$

$$A^p = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix},\ A^r = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix},$$

$$B^p = \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix} \text{ and } B^r = \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix}.$$

When *propofol* and *remifentanil* are simultaneously administered, the corresponding DoA $z(t)$ is approximately given by the expression (see Silva et al. (2010)):

$$z(t) \approx \frac{z_0}{1 + (\mu U^p + U^r)^\gamma},$$

where μ, γ are parameters, z_0 is the effect at zero concentration and U^p and U^r respectively denote the potencies of *propofol* and *remifentanil*, which are obtained by normalizing the effect concentrations with respect to the concentrations that produces half the maximal effect (denoted by EC_{50}^p and EC_{50}^r, respectively), being given by (see Silva et al. (2010)):

$$U^p = \frac{c_e^p}{EC_{50}^p} \text{ and } U^r = \frac{c_e^r}{EC_{50}^r}.$$

Defining $\theta^p = \frac{\mu}{EC_{50}^p}$, $\theta^r = \frac{1}{EC_{50}^r}$ and $U = \mu U^p + U^r$ yields $z(t) \approx \frac{z_0}{1+U^\gamma}$, with $U = \theta^p c_e^p + \theta^r c_e^r$. This leads to the following model

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ U(t) = \theta^p c_e^p(t) + \theta^r c_e^r(t) = Cx(t) \\ z(t) \approx \dfrac{z_0}{1 + U^\gamma}, \end{cases} \tag{4}$$

where

$$x(t) = \begin{bmatrix} x^p(t) \\ x^r(t) \end{bmatrix}, \quad A = \begin{bmatrix} A^p & 0_{3\times3} \\ 0_{3\times3} & A^r \end{bmatrix},$$

$$B = \begin{bmatrix} B^p & 0_{3\times1} \\ 0_{3\times1} & B^r \end{bmatrix},\ C = [\,0\ 0\ \theta^p\ 0\ 0\ \theta^r\,]$$

For surgery purposes it is desirable to maintain the depth of anesthesia close to a certain reference level z^*. This can be achieved by designing a control law that forces $U(t)$ to follow the reference level $U^* = \sqrt[\gamma]{\frac{z_0}{z^*} - 1}$.

In order to apply the design method of the previous section, the product CB should be a nonzero row. However, here $CB = [\,0\ 0\,]$ and the condition is not met. To overcome this problem, instead of the output $U(t)$, the output

$$M(x(t)) = \theta^p M^p(x^p(t)) + \theta^r M^r(x^r(t)) = C_M x(t),$$

with

$$M^p(x^p) = [\,1\ 1\ 1\,]\, x^p,\ M^r(x^r) = [\,1\ 1\ 1\,]\, x^r \text{ and}$$

$$C_M = [\,\theta^p\ \theta^p\ \theta^p\ \theta^r\ \theta^r\ \theta^r\,],$$

is considered. Moreover a connection between the reference value U^* and an adequate reference value M^* for M will be established, in such a way that when $\lim_{t\to\infty} M(x(t)) = M^*$ then $\lim_{t\to\infty} U(t) = U^*$ and $\lim_{t\to\infty} z(t) = z^*$, as desired. It is noteworthy that now, for the new output matrix C_M, $C_M B = [\,10\theta^p\alpha\ \ 3\theta^r\eta\,]$ is nonzero guaranteeing the applicability of the proposed controller design method. Thereby, if the matrix $E \overset{def}{=} \begin{bmatrix} e^p \\ e^r \end{bmatrix} \geq 0$ is such that $C_M BE = 1$, which is equivalent to have $10\theta^p\alpha e^p + 3\theta^r\eta e^r = 1$, by Theorem 1, applying the control law $u = max(0, \tilde{u})$, with

$$\tilde{u} = -EC_M Ax + E\lambda(M^* - M) \text{ and } \lambda > 0 \tag{5}$$

to the system (A, B, C_M), forces the output $M(x(t))$ to converge to M^* as t goes to infinity.

In order to determine which value of M^* should be chosen in the control law (5), an analysis is made of the values $U(t)$ obtained for the closed-loop system. For this purpose it will be first proved that the state of the closed-loop system converges to an equilibrium point x^*. In order to show this, since, as mentioned in the previous section, the trajectories $x(t)$ converge to the forward-invariant set $\Omega_{M^*} = \{x \in \mathbb{R}^6_+ : M(x) = M^*\}$, it is enough to prove that, for the restriction of the closed-loop system to this set, the state trajectories converge to an equilibrium point x^*. Note that this restriction is well defined as Ω_{M^*} is forward-invariant under the closed-loop dynamics.

When $M(x) = M^*$, $\tilde{u} = -ECAx$ and the closed-loop system can be described as

$$\dot{x} = \tilde{A}x \tag{6}$$

with

$$\begin{aligned}\tilde{A} &= A - BEC_M A \\ &= \begin{bmatrix} a_1 - 10\alpha & 8a_1 & a_1 & a_2 & a_2 & a_2 \\ 9\alpha & -9\alpha & 0 & 0 & 0 & 0 \\ 0 & \alpha & -\alpha & 0 & 0 & 0 \\ a_3 & 8a_3 & a_3 & a_4 - 3\eta & a_4 & a_4 \\ 0 & 0 & 0 & 2\eta & -2\eta & 0 \\ 0 & 0 & 0 & 0 & \eta & -\eta \end{bmatrix}\end{aligned}$$

where

$$\begin{array}{llll} a_1 = & 10\alpha^2\theta^P\rho g, & a_2 = & 10\alpha\eta\theta^r\rho g, \\ a_3 = & 3\alpha\eta\theta^P g, & a_4 = & 3\eta^2\theta^r g, \\ \rho = & \frac{e^p}{e^r}, & g = & \frac{1}{3\eta\theta^r + 10\alpha\theta^p\rho}. \end{array}$$

It is not difficult to check that the equilibria of (6) are the states of the form $x^{eq} = (x_3^p, x_3^p, x_3^p, x_3^r, x_3^r, x_3^r)$ with $x_3^p = \rho x_3^r$. Therefore, $x^* = (\frac{M^{p*}}{3}, \frac{M^{p*}}{3}, \frac{M^{p*}}{3}, \frac{M^{r*}}{3}, \frac{M^{r*}}{3}, \frac{M^{r*}}{3})$ with $M^{p*} = \rho M^{r*}$ and $M^{r*} = \frac{M^*}{\theta^p\rho + \theta^r}$, i.e.

$$x^* = (\rho, \rho, \rho, 1, 1, 1)\frac{M^{r*}}{3},$$

is the only equilibrium point of the closed-loop system in the set Ω_{M^*}.

In order to analyze the stability of the closed-loop system restricted to Ω_{M^*}, the evolution equations of this restriction are next obtained.

When $M(x) = M^*$, $x_1^p = M^* - x_2^p - x_3^p - \frac{\theta^r}{\theta^p}(x_1^r + x_2^r + x_3^r)$ and $\dot{x} = \tilde{A}x$ becomes

$$\begin{cases} \dot{x_1^p}(t) = M^* - \dot{x_2^p} - \dot{x_3^p} - \dot{x_1^r} - \dot{x_2^r} - \dot{x_3^r} \\ \dot{x_2^p}(t) = 9\alpha(M^* - x_2^p - x_3^p - \dfrac{\theta^r}{\theta^p}(x_1^r + x_2^r + x_3^r)) - 9\alpha x_2^p \\ \dot{x_3^p}(t) = \alpha x_2^p - \alpha x_3^p \\ \dot{x_1^r}(t) = a_3 M^* + 7a_3 x_2^p + (a_4 - a_3\theta^r/\theta^p - 3\eta)x_1^r + \\ \qquad +(a_4 - a_3\theta^r/\theta^p)(x_2^r + x_3^r) \\ \dot{x_2^r}(t) = 2\eta x_1^r - 2\eta x_2^r \\ \dot{x_3^r}(t) = \eta x_2^r - \eta x_3^r. \end{cases}$$

Therefore the closed-loop system dynamics restricted to Ω_{M^*} can be described by the evolution of the vector

$$\Delta\bar{x} = \begin{bmatrix} x_2^p \\ x_3^p \\ x_1^r \\ x_2^r \\ x_3^r \end{bmatrix} - \bar{x}^*$$

with

$$\bar{x}^* = \begin{bmatrix} \rho \\ \rho \\ 1 \\ 1 \\ 1 \end{bmatrix} \frac{M^{r*}}{3},$$

which is given by $\dot{\Delta\bar{x}} = \bar{A}\Delta\bar{x}$ with

$$\bar{A} = \begin{bmatrix} -18\alpha & -9\alpha & -9\alpha & -9\alpha & -9\alpha \\ \alpha & -\alpha & 0 & 0 & 0 \\ 7a_3 & 0 & a_4 - a_3 - 3\eta & a_4 - a_3 & a_4 - a_3 \\ 0 & 0 & 2\eta & -2\eta & 0 \\ 0 & 0 & 0 & \eta & -\eta \end{bmatrix}$$

Now it can be shown that, given fixed values of $\alpha, \eta, \theta^p, \theta^r$, it is always possible to find suitable values for ρ such that $\bar{A}$ is stable. For such values, $\Delta\bar{x}(t)$ converges to zero, i.e., $\bar{x}(t)$ converges to $\bar{x}^* = (\rho, \rho, 1, 1, 1)\frac{M^{r*}}{3}$. Consequently $x(t)$ converges to $x^* = (\rho, \rho, \rho, 1, 1, 1)\frac{M^{r*}}{3}$ under the closed-loop dynamics.

Now, as mentioned before, in order to track a certain level of depth of anesthesia z^*, the reference value for U must be equal to

$$U^* = \sqrt{\frac{z_0}{z^*} - 1}. \tag{7}$$

Since $U(t) = \theta^p c_e^p(t) + \theta^r c_e^r(t) = \theta^p x_3^p(t) + \theta^r x_3^r(t)$, the value U^* can be achieved by driving the output $M(t)$ to $M^* = 3(\theta^p\rho + \theta^r)x_3^{r*}$, with $x_3^{r*} = \frac{U^*}{\theta^p\rho + \theta^r}$, which is equivalent to have

$$M^* = 3U^*. \tag{8}$$

Simulation results are presented in the next section

4. SIMULATIONS

In this section the performance of the control law presented in the previous sections is illustrate by means of several simulations. For this purpose, we consider: $z_0 = 97.7; \alpha = 0.1013; \eta = 0.7588; \mu = 3.3040; \gamma = 1.4592; EC_{50}^p = 10mg/ml; EC_{50}^r = 0.01mg/ml$. These values were used in the work developed in Silva (2011), to which we refer for further explanation. We also assume that it is intended that the DoA of a patient, evaluated by BIS measurements, follows the reference value of 50. By (7), this means that U must follow the reference $U^* = 0.9682$, or equivalently, by (8), M must follow the reference $M^* = 2.9047$. Once these values are fixed, the control law only depends on the design parameters $\lambda > 0$ and $\rho \geq 0$. The parameter λ influences the speed of convergence to the reference value, as can be seen in Fig. 1 where the values $\lambda = 0.02, \lambda = 1$ were respectively taken for a fixed value of $\rho = 2$ (corresponding to proportion of 2 : 1 for *propofol* and *remifentanil*). On

the other hand the parameter ρ specifies the desired proportion between the administered amounts of propofol and remifentanil, which may be chosen according to clinical criteria. Fig. 2 illustrates DoA effect for different drug proportions (namely, $\rho = 0, \rho = 2$, and $\rho = 10$) and Figures 3, 4, and 5 present the evolution of the corresponding drug dosages. As can be seen in Fig. 2, in spite of the variation of the drug proportion (ρ) the desired effect is practically the same. It turns out that this may constitute an advantage, since the choice of the proportion can be made in order to accommodate clinical restrictions or considerations, without significative consequences in terms of the effect. Finally Fig. 6 illustrates the performance of the control algorithm in the presence of a change of the reference profile. In the first thirteen minutes it is intended that the BIS follows the reference 50, in the following thirteen minutes the BIS reference level is set to 30 and in the last twenty minutes the BIS should again follow the reference level 50. It may be seen that the controller has a good performance also in this case. As expected, when the reference decreases there is a bolus of *propofol* and *remifentanil* and when it increases no drug is administered.

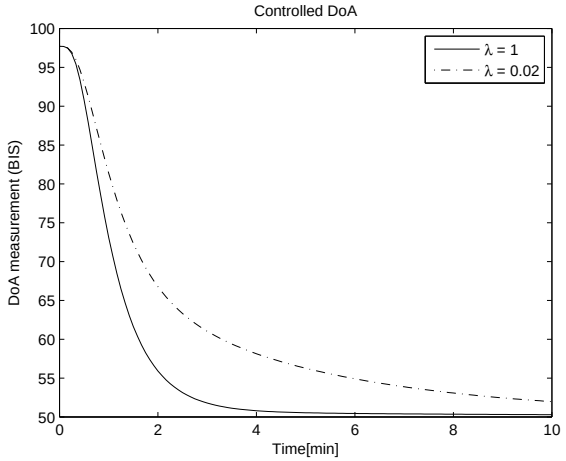

Fig. 1. Evolution of DoA, for $\rho = 2, \lambda = 0.02$ and $\lambda = 1$.

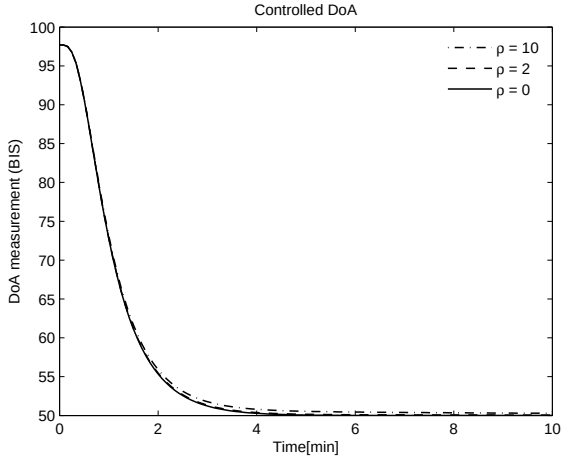

Fig. 2. Evolution of DoA for different values of drugs proportion, i.e., $\rho = 0, \rho = 2, \rho = 10$ and for $\lambda = 1$.

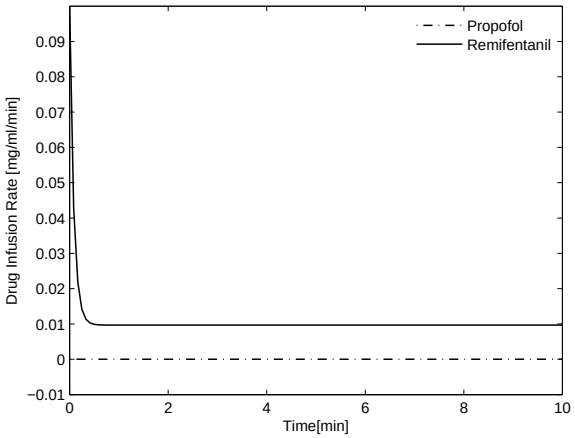

Fig. 3. Evolution of the dosage of *propofol* and of *remifentanil*, for $\lambda = 1, \rho = 0$ (without *propofol* infusion dose).

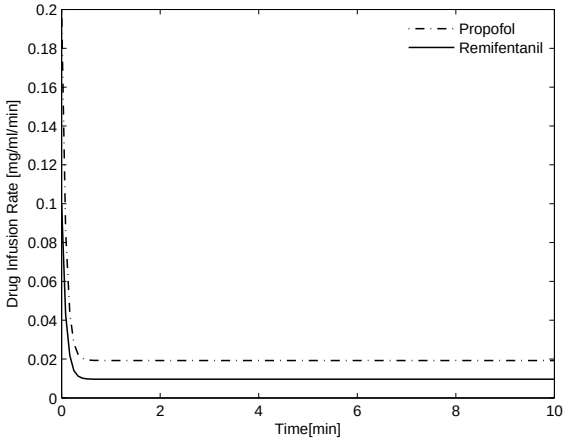

Fig. 4. Evolution of the dosage of *propofol* and of *remifentanil*, for $\lambda = 1, \rho = 2$.

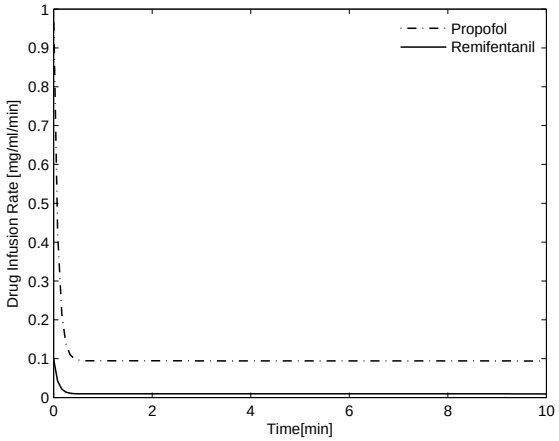

Fig. 5. Evolution of the dosage of *propofol* and of *remifentanil*, for $\lambda = 1, \rho = 10$.

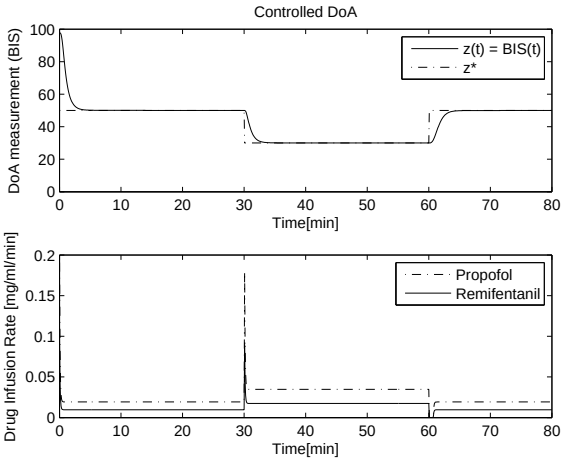

Fig. 6. Evolution of DoA and of the dosages of *propofol* and of *remifentanil*, assuming changes in reference profiles ($z^* = 50$ from the beginning till $t = 40\,min$ and $z^* = 30$ from then on), for $\lambda = 1, \rho = 2$.

5. CONCLUSION

In this paper, a nonlinear control law for multi-input positive systems was proposed in order to track a desired output reference value. This control law has a good performance for the control of the DoA by means of simultaneous administration of *propofol* and *remifentanil*. Moreover it can be tuned in order to achieve different convergence rates as well as a desired proportion between the dosages of these two drugs.

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