Control of uncertain compartmental systems

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***Abstract*— A study of the performance of mass control for compartmental systems, under the presence of uncertainties, is presented. Bounds for the asymptotical mass offset are derived as a functional of the uncertainty bounds. The obtained results are illustrated by simulations for the case of neuromuscular blockade control of patients undergoing surgery.**

***Index Terms*—Compartmental systems, positive control, uncertain systems, neuromuscular blockade control.**

I. Introduction

Compartmental models have been successfully used to model biomedical and pharmacokinetical systems, see, for instance, [2] or [4]. Compartmental systems consist of a finite number of subsystems, the compartments, which exchange matter with each other and with the environment. Such systems form a subclass of positive systems (i.e., systems for which the state and output variables remain nonnegative whenever the input is nonnegative). As is well-known, in this case, the design of suitable control laws is more delicate, since one has to guarantee the positivity of the control input. In this framework, a nonnegative adaptive control law is proposed in [3], in order to guarantee the partial asymptotic set-point stability of the closed loop system. On the other hand, a positive feedback control law is proposed in [1], in order to stabilise the total system mass at an arbitrary set-point. This law was used in [8] for the control of the neuromuscular blockade (see [6], [7] and [9]) of patients undergoing surgery, but no analysis was made of the effect of parameter uncertainty in its performance.

In this paper, we try to fill in this gap, not only for the neuromuscular blockade model, but for a wide class of compartmental systems. More concretely, we consider that the control law is tuned for a nominal process model that contains an additive uncertainty with respect to the real model, and analyse the behavior of the total mass in the controlled system. It turns out that, in this case, bounds for the asymptotical mass offset can be easily expressed in terms of the system uncertainties.

II. Compartmental Systems

Compartmental systems are dynamical systems described by a set of equations of the form

$$\dot{x}_i = \sum_{j\neq i} f_{ji}(x) - \sum_{l\neq i} f_{il}(x) - f_{i0}(x) + f_{0i}(x)$$
$$i = 1, \ldots, n$$

(see [2] or [10]) where $x = (x_1, \ldots, x_n)^T$ is the state variable and x_i and f_{ij} take nonnegative values. Each equation describes the evolution of the quantity or concentration of material within a subsystem, called compartment. Since the compartments exchange with each other and with the environment, in the above equation, x_i is the amount (or concentration) of material in compartment i, f_{ij} is the flow rate from compartment j to compartment i and the subscript 0 denotes the environment (see [2]). In this paper, we consider the class of linear time-invariant compartmental systems described by

$$\dot{x}_i = \sum_{j\neq i} k_{ji}x_j - \sum_{l\neq i} k_{il}x_i - q_i x_i + b_i u, \; i = 1, \ldots, n, \quad (1)$$

where x_i and the input u take nonnegative values, $k_{ij}, q_i, b_i \in \mathbb{R}_+$ and at least one b_i is positive (see Fig. 1). Note that, in this case, $f_{ji} = k_{ji}x_j, f_{0i} = b_i u$ and $f_{i0} = q_i x_i$, and it can be easily proved that the system is positive, this is, if we consider an input u that remains nonnegative, then the state variable also remains nonnegative. Moreover, (1) can also be written in matrix form as

$$\dot{x} = Ax + bu, \quad (2)$$

where A (called compartmental matrix) is so that

$$a_{ii} = -q_i - \sum_{j\neq i} k_{ij} \text{ and, if } i \neq j, a_{ij} = k_{ji},$$

and $b = (b_1, b_2, \ldots, b_n)^T$.

The total mass of the system in a given state x is defined as $M(x) = \sum_{i=1}^{n} x_i$. For an arbitrary positive value M^*, the set $\Omega_{M^*} = \left\{x \in \mathbb{R}_+^n : M(x) = M^*\right\}$ of all the points x in the state space with mass M^* is called an *iso-mass*.

An important issue in the context of the control of compartmental systems is to design a control law which yields a positive input that steers the system mass $M(x)$ to a desired value.

In [1], the following positive control law is proposed to guarantee that the trajectories converge to a set Ω_{M^*}:

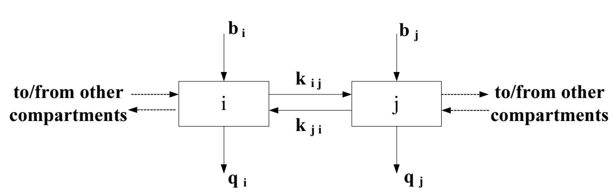


Fig. 1. Two compartments of a linear time-invariant compartmental model, as described by (1).

$$\begin{array}{l} u(x) = \max\left(0, \tilde{u}(x)\right) \\ \tilde{u}(x) = \left(\sum_{i=1}^{n} b_i\right)^{-1} \left(\sum_{i=1}^{n} q_i x_i + \lambda\left(M^* - M(x)\right)\right), \end{array} \tag{3}$$

where λ is an arbitrary design parameter.

In order to state the corresponding theorem, we need to introduce the following concept of full outflow connectedness. A compartmental system (1) is said to be *fully outflow connected* if at every state x there is a path $i \to j \to k \to \cdots \to l$ with positive k_{ij}'s from every compartment i to some compartment l such that $q_l > 0$ (see [1]).

Theorem 1: [1] Let (2) be a fully outflow connected compartmental system. Then, for the closed loop system (2)-(3) with arbitrary initial conditions $x(0) \in \mathbb{R}_+^n$:

$i)$ the iso-mass Ω_{M^*} is forward invariant;

$ii)$ the state $x(t)$ is bounded for all $t > 0$ and converges to the iso-mass Ω_{M^*}.

The proof of this result is based on the application of LaSalle's invariance principle (see [5], pg.30), by considering the Lyapunov function

$$V(x) = \frac{1}{2}\left(M^* - M(x)\right)^2$$

of (2) on $\mathbb{R}_+^n$.

In [8], the control law (3) was applied for the control of the neuromuscular blockade of patients undergoing surgery, by means of the infusion of *atracurium*. In fact, it is possible to model this problem as a three compartmental model that can be described as depicted in Fig. 2, where u is the drug infusion dose administered in the central compartment, and $k_{12}, k_{21}, k_{13}, q_3$ are positive micro-rate constants and q_1, q_2 are nonnegative micro-rate constantes that vary from patient to patient. In this case, the set of equations (1) becomes

$$\left\{ \begin{array}{lcl} \dot{x}_1 & = & -(k_{12} + k_{13} + q_1)x_1 + k_{21}x_2 + u \\ \dot{x}_2 & = & k_{12}x_1 - (k_{21} + q_2)x_2 \\ \dot{x}_3 & = & k_{13}x_1 - q_3 x_3 \end{array} \right. \tag{4}$$

where x_1, x_2 and x_3 are the drug amounts in the central, peripheral and effect compartments, respectively. However, even after a satisfactory identification of the patients characteristics, it was necessary to consider an additional integrator, in order to achieve good results. This might be explained by the fact that (contrary to what happens, for instance, with state feedback stabilisers, which are not uniquely defined from the system matrices) the control law (3) strongly depends on the system parameters. Since parameter uncertainty is present not only in this case, but in most of the applications, it is relevant to analyse the robustness of that control law.

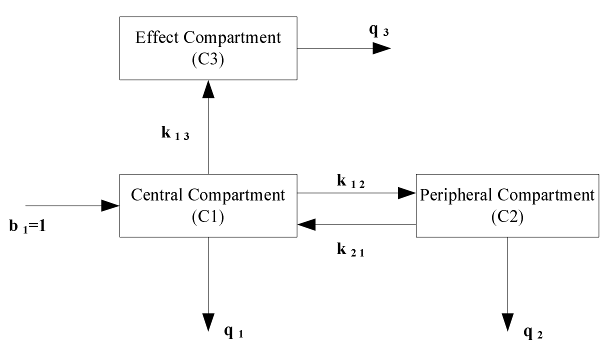


Fig. 2. Compartmental model for the neuromuscular blockade effect of the drug *atracurium*.

III. Uncertain Compartmental Systems

In this section, we analyse the performance of the control law (3), proposed in [1], in the presence of parameter uncertainties.

If we consider that we can measure precisely what is injected from the outside into the system, the parameters b_i are not subject to uncertainties. On the other hand, since the control law does not depend on the k_{ij}'s, we may assume that the only uncertain parameters are $q_1, \ldots, q_n$. Therefore, we shall assume that a control law (3) is designed for a nominal system

$$\dot{x} = (A + \Delta A)\, x + bu, \tag{5}$$

while the real system is given by

$$\dot{x} = Ax + bu, \tag{6}$$

being

$$\Delta A = diag(-\Delta q_1, -\Delta q_2, \ldots, -\Delta q_n)$$

the matrix of parameter uncertainties. Note that, in this case, the control law (3) becomes

$$\begin{array}{ll} u(x) & = \max\left(0, \tilde{u}(x)\right) \\ \tilde{u}(x) & = \left(\sum_{i=1}^{n} b_i\right)^{-1} \left(\sum_{i=1}^{n} \left(q_i + \Delta q_i\right) x_i + \right. \\ & \left. + \lambda\left(M^* - M(x)\right)\right). \end{array} \tag{7}$$

It turns out that, for suitable values of the design parameter λ, when the control law (7) is applied to (6), the asymptotical values of the system mass lay in an interval which is related to M^* as stated in the next theorem.

Theorem 2: Let (6) be a fully outflow connected compartmental system, $\Delta_{qmin} = \min\{\Delta q_i\}$, $\Delta_{qmax} = \max\{\Delta q_i\}$ and take the design parameter λ in (7) larger than Δ_{qmax}. Then, the state trajectories $x(t)$ of the closed loop system (6)-(7), with arbitrary initial conditions $x(0) \in \mathbb{R}_+^n$, converge to the forward invariant set

$$\Omega = \left\{x \in \mathbb{R}_+^n : M(x) \in I(M^*)\right\},$$

with $I(M^*) = \left[\frac{\lambda}{\lambda - \Delta_{qmin}} M^*, \frac{\lambda}{\lambda - \Delta_{qmax}} M^*\right]$.

Proof: Let $\overline{M}_{min} = \frac{\lambda}{\lambda - \Delta_{qmin}} M^*$ and $\overline{M}_{max} = \frac{\lambda}{\lambda - \Delta_{qmax}} M^*$. Consider the function $V : \mathbb{R}^n \to \mathbb{R}$ defined by

$$V(x) = \left\{ \begin{array}{ll} \frac{1}{2}\left(M(x) - \overline{M}_{min}\right)^2 & \text{if } M(x) < \overline{M}_{min} \\ \frac{1}{2}\left(M(x) - \overline{M}_{max}\right)^2 & \text{if } M(x) > \overline{M}_{max} \\ 0 & \text{otherwise.} \end{array} \right.$$

Note that V is a Lyapunov function of the system on $\mathbb{R}_+^n$ because it is continuous and $\dot{V}(x) \leq 0, \forall x \in \mathbb{R}_+^n$ (see [5], pg.30). In fact, if $x \in \mathbb{R}_+^n$,

$$\dot{V}(x) = \begin{cases} \left(M(x) - \overline{M}_{min}\right) \frac{dM(x)}{dt} & \text{if } M(x) < \overline{M}_{min} \\ \left(M(x) - \overline{M}_{max}\right) \frac{dM(x)}{dt} & \text{if } M(x) > \overline{M}_{max} \\ 0 & \text{otherwise} \end{cases}$$

is nonpositive, as we next show.

- Suppose that $M(x) < \overline{M}_{min}$. Since

$$\begin{aligned} &\textstyle\sum_{i=1}^n (q_i + \Delta q_i) x_i + \lambda (M^* - M(x)) \geq \\ &\geq \textstyle\sum_{i=1}^n q_i x_i + \Delta_{qmin} M(x) + \lambda (M^* - M(x)) \\ &= \textstyle\sum_{i=1}^n q_i x_i + (\lambda - \Delta_{qmin}) \left(\overline{M}_{min} - M(x)\right) \\ &> 0, \end{aligned}$$

it follows that $\tilde{u}(x) > 0$. Thus,

$$\begin{aligned} u(x) &= \tilde{u}(x) \\ &= \left(\textstyle\sum_{i=1}^n b_i\right)^{-1} \left(\textstyle\sum_{i=1}^n (q_i + \Delta q_i) x_i + \right. \\ &\quad \left. + \lambda (M^* - M(x))\right). \end{aligned}$$

In this case,

$$\begin{aligned} \frac{dM(x)}{dt} &= \textstyle\sum_{i=1}^n \Delta q_i x_i + \lambda (M^* - M(x)) \\ &\geq \Delta_{qmin} M(x) + \lambda (M^* - M(x)) \\ &= (\lambda - \Delta_{qmin}) \left(\overline{M}_{min} - M(x)\right) \\ &> 0 \end{aligned}$$

and

$$\dot{V}(x) = \left(M(x) - \overline{M}_{min}\right) \frac{dM(x)}{dt} < 0.$$

- Suppose that $M(x) > \overline{M}_{max}$. If $\tilde{u}(x) < 0$, $u(x) = 0$ and

$$\frac{dM(x)}{dt} = -\textstyle\sum_{i=1}^n q_i x_i \leq 0.$$

Thus, in this case,

$$\dot{V}(x) = \left(M(x) - \overline{M}_{max}\right) \frac{dM(x)}{dt} \leq 0.$$

If $\tilde{u}(x) \geq 0$, since $u(x) = \tilde{u}(x)$, it follows that

$$\begin{aligned} \frac{dM(x)}{dt} &= \textstyle\sum_{i=1}^n \Delta q_i x_i + \lambda (M^* - M(x)). \\ &\leq \Delta_{qmax} M(x) + \lambda (M^* - M(x)) \\ &= (\lambda - \Delta_{qmax}) \left(\overline{M}_{max} - M(x)\right) \\ &< 0 \end{aligned}$$

and

$$\dot{V}(x) = \left(M(x) - \overline{M}_{max}\right) \frac{dM(x)}{dt} < 0.$$

Applying LaSalle's invariance principle (see [5], pg.30), it turns out that $x(t)$ converges to the largest invariant set contained in

$$\left\{x \in \mathbb{R}_+^n : \dot{V}(x) = 0\right\} = I_1 \cup I_2,$$

where

$$I_1 = \left\{x \in \mathbb{R}_+^n : M(x) \in I(M^*)\right\}$$

and

$$\begin{aligned} I_2 = \; &\left\{x \in \mathbb{R}_+^n : u(x) = 0, \textstyle\sum_{i=1}^n q_i x_i = 0 \text{ and} \right. \\ &\left. M(x) > \overline{M}_{max}\right\}. \end{aligned}$$

It can be shown that the set I_2 has no invariant subset. Indeed, if this would be the case, u would be zero and the assumption of full outflow connectedness would imply that $M(x) \to 0$, meaning that x would leave the subset (see [1]). On the other hand, I_1 is an invariant set, which concludes the proof of the theorem. ■

Remark 3:

i) If $\Delta q_1 = \Delta q_2 = \ldots = \Delta q_n = \Delta q$, since $\Delta_{qmin} = \Delta_{qmax} = \Delta q$, the state trajectory $x(t)$ converges to the iso-mass $\Omega_{\overline{M}}$, with $\overline{M} = \frac{\lambda}{\lambda - \Delta_q} M^*$.

ii) When $\Delta q_i = 0$, $i = 1, \ldots, n$, we recover the result from Theorem 1.

Using the same kind of techniques as in Theorem 2, it is possible to show that:

Proposition 4: Let (6) be a fully outflow connected compartmental system. Then, the state trajectories $x(t)$ of the closed loop system (6)-(7), with arbitrary initial conditions $x(0) \in \mathbb{R}_+^n$, converge to the forward invariant set

$$\tilde{\Omega} = \left\{x \in \mathbb{R}_+^n : M(x) \in \tilde{I}(M^*)\right\},$$

where $\tilde{I}(M^*) = \left[\frac{\lambda}{\lambda + \Delta q} M^*, \frac{\lambda}{\lambda - \Delta q} M^*\right]$ and $\Delta q = \max\{|\Delta q_i|\}$, if the design parameter λ is taken to be larger than Δq.

Note that, contrary to what happens with the set $I(M^*)$ in Theorem 2 (which may even not contain the value M^*), the set $\tilde{I}(M^*)$ in Proposition 4 is a neighborhood of M^*. This allows to bound the absolute mass offset by

$$\begin{aligned} &\max\left\{M^* - \frac{\lambda}{\lambda + \Delta q} M^*, \frac{\lambda}{\lambda - \Delta q} M^* - M^*\right\} = \\ &= \frac{\Delta q}{\lambda - \Delta q} M^*, \end{aligned}$$

leading the bound $\frac{\Delta q}{\lambda - \Delta q}$ for the relative mass offset. Clearly, increasing the parameter λ contributes to increase the robustness of the control law.

Remark 5: Note that other bounds for the relative mass offset can be derived from set $I(M^*)$, namely $\max\left\{\frac{|\Delta_{qmin}|}{\lambda - \Delta_{qmin}}, \frac{|\Delta_{qmax}|}{\lambda - \Delta_{qmax}}\right\}$.

IV. Simulations

In this section, some simulation examples are presented for the neuromuscular blockade control. We consider that the patient's real model is given by (4), with the following values for the parameters (units $= min^{-1}$): $k_{12} = 0.1928, k_{13} = 0.0017, k_{21} = 0.1556, q_1 = 0.1047, q_2 = 0, q_3 = 0.0836$.

Our aim is to stabilise the system mass on the value $M^* = 1.1169$ (corresponding to a 10% level of neuromuscular blockade), using the control law (7). We start by taking the design parameter $\lambda = 0.2$.

In the first simulation, depicted in Fig. 3, it is assumed that the nominal patient model coincides with the real one, i.e., $\Delta q_i = 0, i = 1, 2, 3$. As expected, the system mass converges to M^*.

Fig. 4 shows the result of a simulation scenario, where the Δq_i's are taken to be all equal, namely $\Delta q_1 = \Delta q_2 = \Delta q_3 = 0.03$. In this case, illustrating Remark 3*i*), the system mass reaches the set-point $\overline{M} = \frac{\lambda}{\lambda - \Delta_q} M^* = 1.3141$.

The simulations in Fig. 5 correspond to the case where the Δq_i's are different. The three illustrated cases correspond to the following situations: M^* lies outside $I(M^*)$, M^* lies in the interval $I(M^*)$ and M^* coincides with one of the bounds of this interval.

Fig. 6 illustrates the case where not only the q_i's are subject to uncertainties, but also the other parameters, showing that the controller performance only depends on the Δq_i's.

Finally, Fig. 7 illustrates the behavior of the mass of the controlled system for different values of the parameter λ, under a fixed uncertainty for the system parameters. According to the definition of $I(M^*)$, one observes that the increasing of λ corresponds to the decrease of the final mass offset.

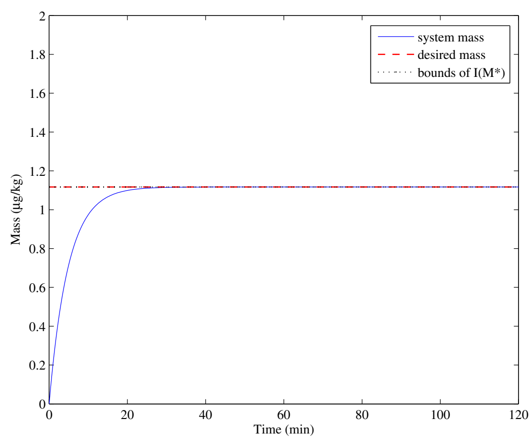


Fig. 3. Simulation for the neuromuscular blockade control, considering $\Delta q_i = 0, i = 1, 2, 3$.

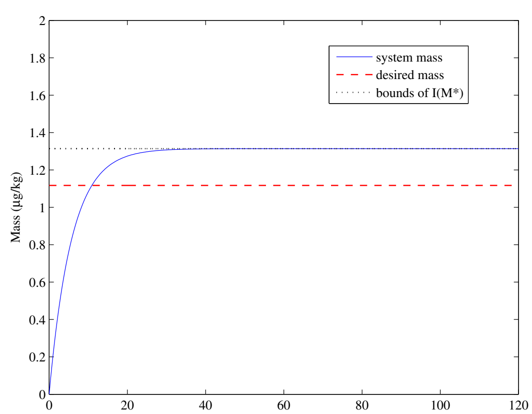
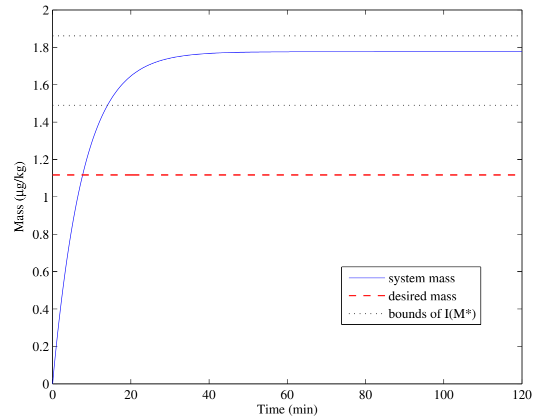
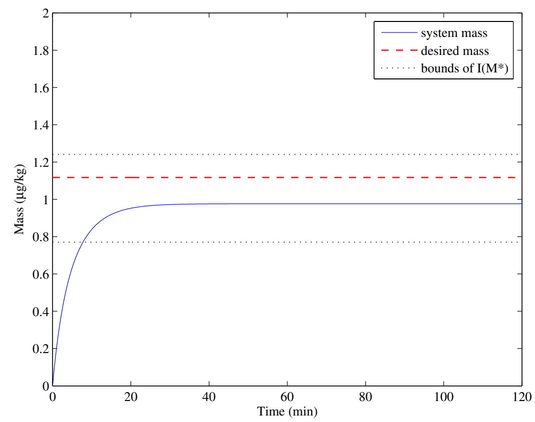


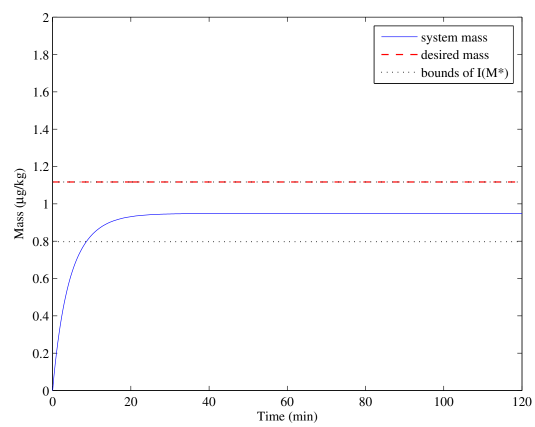
Fig. 4. Simulation for the neuromuscular blockade control, considering $\Delta q_i = 0.03, i = 1, 2, 3$.



(a)

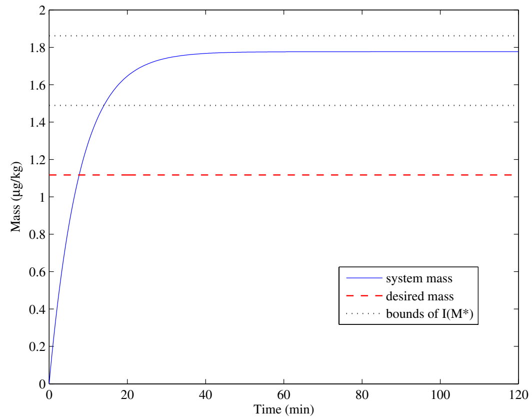


(b)



(c)

Fig. 5. Simulations for the neuromuscular blockade control. (a) Simulation with $\Delta q_1 = 0.08, \Delta q_2 = 0.07$ and $\Delta q_3 = 0.05$; the system mass lays asymptotically in the interval $I(M^*) = [1.4893, 1.8616]$. (b) Simulation with $\Delta q_1 = -0.09, \Delta q_2 = 0.02$ and $\Delta q_3 = 0.01$; the system mass lays asymptotically in the interval $I(M^*) = [0.7703, 1.2411]$. (c) Simulation with $\Delta q_1 = -0.08, \Delta q_2 = 0$ and $\Delta q_3 = -0.01$; the system mass lays asymptotically in the interval $I(M^*) = [0.7978, 1.1169]$.



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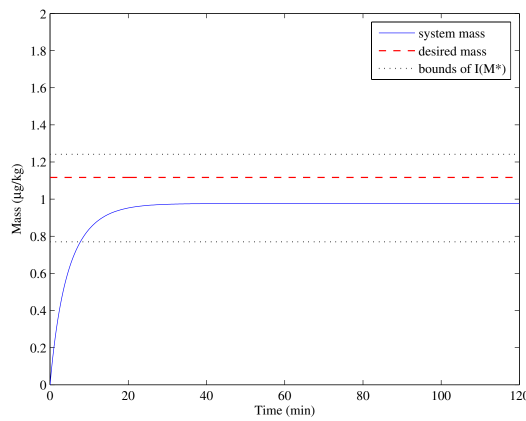

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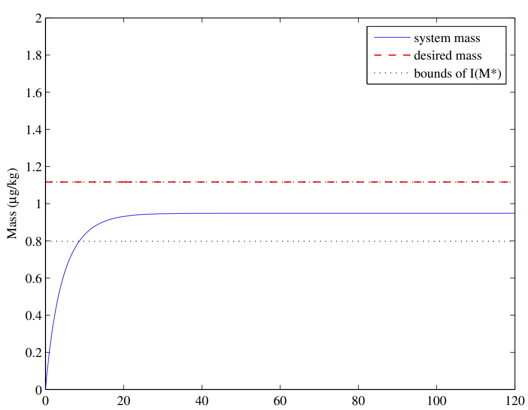
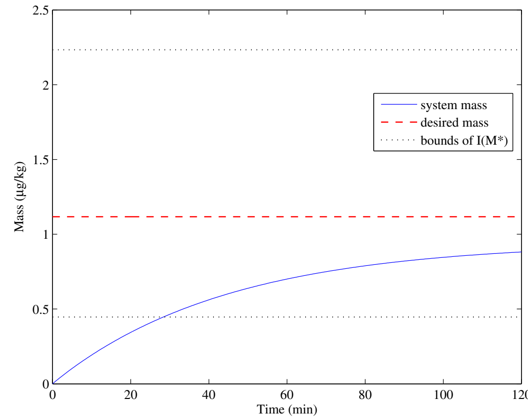
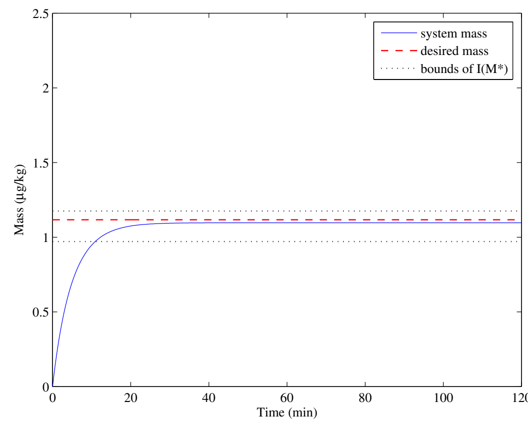


(c)

Fig. 6. Simulations for the neuromuscular blockade control when all the parameters are subject to uncertainties. These simulations where obtained considering the same Δq_i's as in the simulations in Fig. 5 and other parameters uncertainties, namely $\Delta k_{13} = 0.02, \Delta k_{12} = 0.04$ and $\Delta k_{21} = -0.03$. Notice that the simulation results are exactly the same as the corresponding ones in Fig. 5.



(a)



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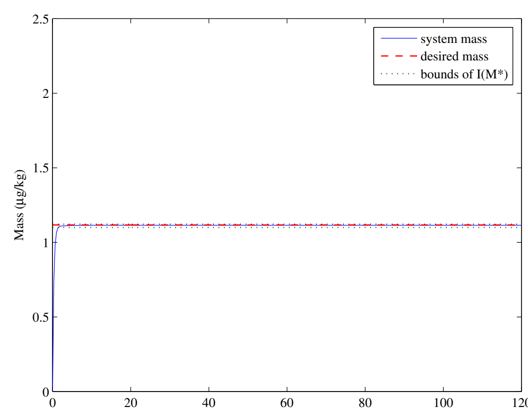

(c)

Fig. 7. Simulations for the neuromuscular blockade control. These simulations where obtained considering $\Delta q_1 = -0.02, \Delta q_2 = 0.01$ and $\Delta q_3 = -0.03$, and different values of λ. (a) Simulation for $\lambda = 0.02$. (b) Simulation for $\lambda = 0.2$. (c) Simulation for $\lambda = 2$.

CONCLUSION

This paper presents a study of the performance of the control law (3) proposed in [1] when applied to the mass control of compartmental systems with parameters uncertainties.

It turns out that the asymptotical mass values lay in an interval whose limits can be expressed in terms of the uncertainty bounds. This allows to derive bounds for the asymptotical mass offset.

In order to illustrate the obtained results, simulations for the case of neuromuscular blockade automatic control by *atracurium* infusion were carried out. These simulations suggest that, in this case, the asymptotical values of the drug mass reach a constant value in the aforementioned interval. This issue is currently under further investigation.

ACKNOWLEDGMENT

This work was partially supported by FCT through the Unidade de Investigação Matemática e Aplicações (UIMA), Universidade de Aveiro, Portugal.

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