Preliminary Design for Reference tracking feedback for Medical Cyber-Physical Pharmacokinetic Systems

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***Abstract*—This paper addresses the reference tracking control problem for Medical Cyber-Physical Systems (MCPS). The control theory is employed to guarantee the suitable concentration of drugs in the body of patients to guarantee a safe treatment. The MCPS is modeled as a switched system, and the modes consider the different scenarios for the problem. A discrete-time model is utilized for the pharmacokinetic process, and the zero input control strategy is employed to design state-feedback controllers with a guaranteed exponential convergence rate. A numerical experiment is presented to illustrate the validity and effectiveness of our method.**

***Index Terms*—cyber-physical systems, medical systems, pharmacokinetic, communication constraints, lyapunov theory**

I. Introduction

The suitable concentration and permanence of drugs in the body of patients is fundamental to guarantee a safe treatment. The pharmacokinetic (PK) process of a drug involves evaluating the Absorption, Distribution, Metabolism, Excretion, and Toxicity (also called ADMET) within the body on the dependence of time [1], [2]. Current technological advances outline pharmacological processes to *Precision Medicine* [3]–[5], which consists of the customization of medical decisions depending on the specific needs of the patients. This scheme can be seen as a classic automated system where the patient is the plant and the drug scheduling incorporates parameters such as age, weight, and base pathologies, to mention a few. Additionally, it is possible to optimize the drug dose by minimizing toxicity or maintaining a reference drug concentration level in the body.

This context presents us with the emerging topic of Medical Cyber-Physical Systems (MCPS) [6]–[8]. In this structure, the MCPS algorithm (or intelligence, as called in [6]) must adapt the drug supply based on the specific characteristics of the patient and is dependent on a computational element connected via communication channels, which transmits the patient readings and calculates the best dosage.

In this context, control theory offers techniques that can be applied to this class of problems. Among others, one may cite full-order filters, Luenberger-based observers, and static and dynamic output feedback controllers. However, the control law (intelligence) in the MCPS must be able to operate locally or remotely, in addition to guaranteeing an efficient supply of the drug even when against: forgetfulness of the patients; communication problems with the medical-server; Denial-of-Service (DoS) attacks; among other problems inherent to the Cyber-physical design and/or networking control systems.

This paper outlines a theoretical framework for a realistic model of precision medicine approach for reference tracking control design for drug delivery. The reference tracking control proposed consists of the use of state-feedback controllers that utilize an integral action and the zero-input strategy. The proposed approach is tolerant to MCPS problems and vulnerabilities, seeking to guarantee the tracking asymptotic or exponential stability. The technique is specialized and applied in the context of discrete-time pharmacokinetic systems composed of three compartments (body parts). The theoretical foundations of the system structure are shown in detail, and also how to obtain the parameters and the feasibility of the state's measurement. The MCPS is modeled as a switched system, and the modes consider the different scenarios for the problem. The Lyapunov theory is employed to get the conditions, which are written in the form of parameter-

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dependent Linear Matrix Inequalities (LMIs). The obtained conditions can guarantee an exponential convergence rate for the augmented system, ensuring the ability to track the desired signal correctly. The conditions are used in the design stage, and a theoretical numerical experiment is conducted to prove the designed control's effectiveness.

II. Problem Statement

Consider the following discrete-time uncertain MCPS in state-space representation:

$$\begin{aligned} x(k+1) &= A(\alpha_k)x(k) + B(\alpha_k)u(k), \\ y(k) &= Cx(k), \end{aligned} \tag{1}$$

where $x \in \mathbb{R}^{n_x}$ is the state vector $u \in \mathbb{R}^{n_u}$ is the control input and $y \in \mathbb{R}^{n_y}$ is the system output. The matrices $A(\alpha_k) \in \mathbb{R}^{n_x \times n_x}$ and $B(\alpha_k) \in \mathbb{R}^{n_x \times n_u}$ are part of a polytopic domain in the function of the time-varying parameter α_k. k represents the referred time instant. A generic matrix $M(\alpha_k)$ is defined as:

$$\begin{aligned} M(\alpha_k) &= \sum_{z=1}^{Z} \alpha_{k,z} H_z, \quad \alpha_k \in \Lambda_Z, \\ \Lambda_Z &= \left\{ \alpha \in \mathbb{R}^Z : \sum_{z=1}^{Z} \alpha_{k,z} = 1;\ \alpha_{k,z} \geq 0,\ z = 1, \ldots, Z \right\}, \end{aligned} \tag{2}$$

and the output matrix is $C \in \mathbb{R}^{n_y \times n_x}$.

The goal is to design robust state-feedback controllers that aim to render the steady-error null for constant references, representing a desirable drug concentration in a given body tissue. The proposed control strategy may contemplate drug administrations in each considered time instant or every N instants. This interval between drug deliveries seeks to contemplate possible communication problems in the MCPS, DoS attacks, or the patient's forgetfulness.

The DoS attacks originate from a malicious agent and aim to jam the system's communication channels, and may make it impossible to update the measured state received by the controller, the control signal, and the parameter α_k (more details in [9]). The following is established about the attacks.

Assumption 1: The attacker is energetically bounded, thus the DoS attacks may last up to N time instants.

Considering attacks with limited maximum duration is a reasonable assumption found in other works in the literature [10], [11].

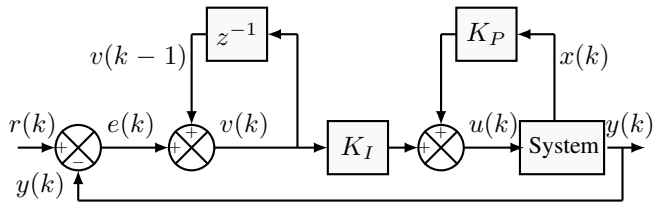

Fig. 1. Diagram of the proposed reference tracking control.

Following the diagram of the closed-loop system presented in Fig. 1, the error can be computed as:

$$e(k) = r(k) - y(k), \tag{3}$$

being $r(k) \in \mathbb{R}^{n_y}$ the reference to be tracked. An integral action is considered via the construction of an augmented system defining $\eta(k) = [x(k) \quad v(k)]^T$ with

$$v(k) = e(k) + v(k-1),$$

resulting in

$$\begin{aligned} \eta(k+1) &= \bar{A}(\alpha_k)\eta(k) + \bar{B}(\alpha_k)\bar{u}(k), \\ \bar{y}(k) &= \bar{C}\eta(k), \end{aligned} \tag{4}$$

where

$$\bar{A}(\alpha_k) = \begin{bmatrix} A(\alpha_k) & 0 \\ -CA(\alpha_k) & I \end{bmatrix},\ \bar{B}(\alpha_k) = \begin{bmatrix} B(\alpha_k) \\ -CB(\alpha_k) \end{bmatrix},\ \bar{C} = \begin{bmatrix} C & 0 \end{bmatrix}.$$

Dimension-wise, $n_\eta = n_x + n_y$, resulting in $\eta \in \mathbb{R}^{n_\eta}$, $\bar{A}(\alpha_k) \in \mathbb{R}^{n_\eta \times n_\eta}$, $\bar{B} \in \mathbb{R}^{n_\eta \times n_u}$, and $\bar{C} \in \mathbb{R}^{n_y \times n_\eta}$.

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To consider that the control inputs are applied at every N time instants, a zero-input control strategy [12] is utilized to represent the absence of drug administration in the time instants in between, being the interval caused by any of the aforementioned reasons. A switched system to represent the closed-loop dynamics for (4) is also built. This approach is akin to what was used in other Cyber-Physical Systems [9], [10], [13], [14].

With that stated, the following control law is then considered for (4), where $K_s \in \mathbb{R}^{n_u \times n_\eta}$:

$$u(k+s) = K_s\eta(k), \quad K_s = \begin{cases} [K_{P0}\ K_{I0}], & \text{if } s = 0, \\ 0, & \text{if } s > 0. \end{cases} \tag{5}$$

Where the employed gain depends on the switching point $s = 0, 1, \ldots, \iota(k)$, with the switching signal $\iota(k)$ drawing values from the finite set $L \triangleq \{0, 1, \ldots, N\}$, where N represents the maximum interval between doses. It is important to highlight that when $\iota(k) = 0$, there is no interval. Also, the zero-input nature of the control strategy defines that $K_s = 0$, when $s > 0$.

Given the presented assumptions, the closed-loop system dynamics modes are as follows. The modes are selected, one at a time, successively and relative to the instant concerning the drug application or its absence.

- Case 0: No interval between doses

$$\begin{aligned} \eta(k+1) &= \left(\bar{A}(\alpha_k) + \bar{B}(\alpha_k)K_0\right)\eta(k), \\ &= F_0(\alpha_k)\eta(k), \\ F_0(\alpha_k) &\triangleq \bar{A}(\alpha_k) + \bar{B}(\alpha_k)K_0. \end{aligned} \tag{6}$$

- Case 1: 1 time instant-interval between doses. $\eta(k+1)$ as in Case 0 and

$$\begin{aligned} \eta(k+2) &= \bar{A}(\alpha_{k+1})\eta(k+1), \\ &= F_1(\alpha_k, \alpha_{k+1}), \\ F_1(\alpha_k, \alpha_{k+1}) &\triangleq \bar{A}(\alpha_{k+1})F_0(\alpha_k). \end{aligned} \tag{7}$$

- Case N: N time instant-interval between doses. $\eta(k+1)$ as in Case 0, $\eta(k+2)$ as in Case 1 and

$$\begin{aligned}\eta(k+N+1) &= \bar{A}(\alpha_{k+N})\eta(k+N),\\ &= F_N(\alpha_k,\ldots,\alpha_{k+N}),\\ F_N(\alpha_k,\ldots,\alpha_{k+N}) &\triangleq \bar{A}(\alpha_{k+N})F_{N-1}(\alpha_k,\ldots,\alpha_{k+N-1}).\end{aligned} \tag{8}$$

Remark 1: Given the zero-input strategy utilized to model the dynamics of the drug delivery, and as stated in (5), the input is only applied in Case 0, as in (6). On the subsequent modes, the input matrix $\bar{B}$ would also be present, however, since in these modes $K = 0$, i.e. $u(k) = 0$, this matrix can be disregarded.

Remark 2: To simplify the notation, the dependency of $F_N(\alpha_k, \alpha_{k+1}, \ldots, \alpha_{k+N})$, as in (6)-(8), on the time-varying parameter will be omitted from now on. Thus, only F_i, $i = 0, 1, \ldots, N$, will be employed.

In summary, the resulting switched system is as follows.

$$\eta(k+1) = F_{\iota(k)}\eta(k), \tag{9}$$

Where $\iota(k)$ is a switching signal that draws from the set $L \triangleq \{0, 1, \ldots, N\}$. Since only one mode of (9) is activated at a time, the indicator function $\zeta(k) = [\zeta_0(k), \ldots, \zeta_N(k)]^T$ is used.

$$\zeta_i(k) = \begin{cases} 1, & \text{if } \iota(k) = i,\\ 0, & \text{otherwise.}\end{cases}$$

Resulting in

$$\eta(k+1) = F_{\iota(k)}(\zeta(k))\eta(k). \tag{10}$$

III. Pharmacokinetic absorption model

The pharmacokinetic process of a drug involves evaluating the Absorption, Distribution, Metabolism, Excretion, and Toxicity (also called ADMET) within the body on the dependence of time [1], [2]. The biomathematical models, which describe the drug distribution processes through organs connected by the vascular system in an integrated physiological context, are called The Physiologically Based Pharmacokinetic Methods [15], and correspond to a middle-point between the in silico and in vivo approach. Since the vascular system is equal in humans and pretty similar in other mammals, these models are widely transferable [16], expanding their applicability. Additionally, the distribution of a drug within the body can be described in good agreement with experimental data by using simplified biomathematical models, more specifically the compartment model [17]. The compartmental model is an extensively used technique, which assumes the percolation of the drug dynamic between body parts (called compartment). This structure reduces the complexity and reaches accurate results in practice.

In the state-of-the-art, the Pharmacokinetic Absorption Model can be formulated in the state-space representation for the set of ordinary differential equations [18]–[22]). The states for dynamic systems corresponding to drug concentration in the body part and the exogenous input is the drug (injection or oral) consequently, we can formulate performance criteria based on linear combinations of the states and/or inputs. In the case of discrete-time systems, the coefficients of the model correspond to absorption or delivery rates between states (body parts) [18] and/or physiological parameters [23]. In this paper the general compartmental model for the pharmacokinetic process is used, where the absorption or delivery rates are bounded time-varying parameters (11). The discrete-time pharmacokinetic systems are composed of the following three-compartments; blood $b(k)$, organ $o(k)$, and muscle $m(k)$ being in the latter the drug entry compartment, injection $w(k)$ exogenous input in (11). The bounded time-varying parameters correspond to the delivery rate of the muscle to blood $\gamma_{mb}(\alpha_k)$, blood to organ $\gamma_{bo}(\alpha_k)$, organ to blood $\gamma_{ob}(\alpha_k)$, blood to muscle $\gamma_{bm}(\alpha_k)$. And, the absorption rate to muscle, organ and blood by $\mu_m(\alpha_k)$, $\mu_o(\alpha_k)$ and $\mu_b(\alpha_k)$ respectively.

State-space representation: The $x(k) \in \mathbb{R}^3$ is the state vector by $x(k) = [m(k)\ b(k)\ o(k)]^T$ and $u(k) \in \mathbb{R}$ is the control drug input (injection). The dynamic matrices $A(\alpha_k) \in \mathbb{R}^{3\times3}$ defined as (12).

$$A(\alpha_k) = \begin{bmatrix} \binom{1-\gamma_{mb}(\alpha_k)}{-\mu_m(\alpha_k)} & \gamma_{bm}(\alpha_k) & 0\\ \gamma_{mb}(\alpha_k) & \binom{1-\gamma_{bo}(\alpha_k)}{-\gamma_{bm}(\alpha_k)-\mu_b(\alpha_k)} & \gamma_{ob}(\alpha_k)\\ 0 & \gamma_{bo}(\alpha_k) & 1-\gamma_{ob}(\alpha_k)-\mu_o(\alpha_k)\end{bmatrix} \tag{12}$$

The input matrix $B(\alpha_k) \in \mathbb{R}^{3\times1}$ by $B(\alpha_k) = [D_m(\alpha_k)\ 0\ 0]^T$. The proposed system is inspired by the [24], [25]. The proposed structure allows mapping the behavior in the continuous-time pharmacokinetic absorption systems.

IV. Main Results

In this section the new control theory-inspired methodology to track drug concentration in MCPS is proposed, being said matter modeled after a reference tracking control problem. An LMI-based approach is utilized to design the state-feedback controller that will define the most appropriate dosage to be administered, which will be calculated through the current drug concentration in the body. This approach uses a zero-input strategy that seeks to be robust even in the presence of communication faults, DoS attacks, or patient forgetfulness.

The new LMI condition to compute the gain of the proposed control law (5) is presented in the sequel. An exponential decay rate is considered in the design stage, as a way to speed up the response. For the sake of clarity, the particular case considering drug administrations with one time instant interval, i.e. $L \triangleq \{0, 1\}$ is presented in the following Lemma.

Lemma 1: If there exists $P_i(\alpha_k) \in \mathbb{R}^{n_\eta\times n_\eta}$, where $P_i(\alpha_k) = P_i^T(\alpha_k) > 0$ and the matrices $X \in \mathbb{R}^{n_\eta\times n_\eta}$, $Z \in \mathbb{R}^{n_u\times n_\eta}$ with a given scalar $0 < \rho \leq 1$ such that

$$\begin{bmatrix} -\rho^2 P_0(\alpha_k) & X^T\bar{A}(\alpha_k)^T + Z^T\bar{B}(\alpha_k)^T\\ \star & P_j(\alpha_{k+1}) - X - X^T\end{bmatrix} < 0, \tag{13}$$

$$\begin{bmatrix} -\rho^2 P_1(\alpha_k) & X^T\bar{A}(\alpha_k)^T\bar{A}(\alpha_{k+1})^T + Z^T\bar{B}(\alpha_k)^T\bar{A}(\alpha_{k+1})^T\\ \star & P_j(\alpha_{k+1}) - X - X^T\end{bmatrix} < 0, \tag{14}$$

$$
\begin{aligned}
m(k+1) &= m(k) - \gamma_{mb}(\alpha_k)m(k) + \gamma_{bm}(\alpha_k)b(k) - \mu_m(\alpha_k)m(k) + D_m(\alpha_k)w(k),\\
b(k+1) &= b(k) + \gamma_{mb}(\alpha_k)m(k) - \gamma_{bo}(\alpha_k)b(k) - \gamma_{bm}(\alpha_k)b(k) + \gamma_{ob}(\alpha_k)o(k) - \mu_b(\alpha_k)b(k),\\
o(k+1) &= o(k) + \gamma_{bo}(\alpha_k)b(k) - \gamma_{ob}(\alpha_k)o(k) - \mu_o(\alpha_k)o(k).
\end{aligned} \tag{11}
$$

with $i, j \in L$, $L \triangleq \{0, 1\}$, then $K_0 = ZX^{-1}$ is the state-feedback control gain from (5) that assure that the closed-loop system (10) (with F_0 and F_1 given as in (6)-(7) for $N = 1$) is asymptotically stable if $\rho = 1$, and exponential stable with convergence rate at least ρ if $0 < \rho < 1$, for all $(\alpha_k, \alpha_{k+1}) \in \Lambda_Z \times \Lambda_Z$.

Proof: By performing the change of variables $Z = K_0X$, (13) and (14) can be rewritten as

$$
\begin{bmatrix} -\rho^2 P_0(\alpha_k) & X^T {F_0}^T \\ \star & P_j(\alpha_{k+1}) - X - X^T \end{bmatrix} < 0,
\begin{bmatrix} -\rho^2 P_1(\alpha_k) & X^T {F_1}^T \\ \star & P_j(\alpha_{k+1}) - X - X^T \end{bmatrix} < 0. \tag{15}
$$

Considering $\mathcal{R} = diag(X^{-1}, X^{-1})$, pre- and post multiplying (15) by its transpose and by itself, respectively, results in

$$
\begin{bmatrix} -\rho^2 X^{-T} P_0(\alpha_k) X^{-1} & {F_0}^T X^{-1} \\ \star & P_j(\alpha_{k+1}) - X^{-1} - X^{-T} \end{bmatrix} < 0, \tag{16}
$$

$$
\begin{bmatrix} -\rho^2 X^{-T} P_1(\alpha_k) X^{-1} & {F_1}^T X^{-1} \\ \star & P_j(\alpha_{k+1}) - X^{-1} - X^{-T} \end{bmatrix} < 0. \tag{17}
$$

Given ${\mathcal{M}_0}^T = [I \quad F_0]$, ${\mathcal{M}_1}^T = [I \quad F_1]$, pre-and post multiplying (16) by ${\mathcal{M}_0}^T$ and its transpose, and (17) by ${\mathcal{M}_1}^T$ and its transpose results in

$$
{F_0}^T X^{-T} P_j(\alpha_{k+1}) X^{-1} F_0 - \rho^2 X^{-T} P_0(\alpha_k) X^{-1} < 0, \tag{18}
$$

$$
{F_1}^T X^{-T} P_j(\alpha_{k+1}) X^{-1} F_1 - \rho^2 X^{-T} P_1(\alpha_k) X^{-1} < 0. \tag{19}
$$

Multiplying (18) by $\zeta_0(k)$, (19) by $\zeta_1(k)$, summing up the results leads to

$$
\begin{aligned}
&F\left(\zeta(k)\right)^T X^{-T} P_j(\alpha_{k+1}) X^{-1} F\left(\zeta(k)\right) \\
&\qquad - \rho^2 X^{-T} P(\zeta(k), \alpha_k) X^{-1} < 0.
\end{aligned} \tag{20}
$$

The same strategy is considered once again, and multiplying (20) by $\zeta_j(k+1)$, $j = 0, 1$ and summing up the results it is obtained

$$
\begin{aligned}
&F(\zeta(k))^T X^{-T} P(\zeta(k+1), \alpha_{k+1}) X^{-1} F(\zeta(k)) \\
&\qquad - \rho^2 X^{-T} P(\zeta(k), \alpha_k) X^{-1} < 0.
\end{aligned} \tag{21}
$$

At last, pre- and post multiplying (21) by $\eta(k)^T$ and its transpose, it is possible to infer that (21) is equivalent to $\Delta V(\eta(k)) < (\rho^2 - 1)V(\eta(k))$, where $V(\eta(k)) = \eta(k)^T \left(X^{-T} P(\zeta(k), \alpha_k) X^{-1}\right) \eta(k)$. With (13) and (14), it is possible to assure that $P(\zeta(k), \alpha_k) > 0$, therefore, the Lyapunov function $V(\eta(k))$ is positive definite and F_i as seen in (6)-(8) is asymptotically stable if $\rho = 1$, and exponential stable with convergence rate of at least ρ if $0 < \rho < 1$. With that, the proof is concluded.

In the sequel, a generic approach that considers an arbitrary N time instants interval between the doses is presented.

Theorem 1: If there exists $P_i(\alpha_k) \in \mathbb{R}^{n_\eta \times n_\eta}$, where $P_i(\alpha_k) = P_i^T(\alpha_k) > 0$ and the matrices $X \in \mathbb{R}^{n_\eta \times n_\eta}$, $Z \in \mathbb{R}^{n_u \times n_\eta}$ with a given scalar $0 < \rho \leq 1$ such that

$$
\begin{bmatrix} -\rho^2 P_i(\alpha_k) & {\Psi_i}^T \\ \star & P_j(\alpha_{k+1}) - X - X^T \end{bmatrix} < 0, \tag{22}
$$

where

$$
\Psi_i = \prod_{l=0}^{i} \left(\bar{A}(\alpha_{k+(i-l)})\right) X + \Theta_i \bar{B}(\alpha_k) Z, \tag{23}
$$

$$
\Theta_i = \prod_{r=1}^{i} A(\alpha_{k+(i-r+1)}), \quad \Theta_0 = I, \tag{24}
$$

with $i, j \in L$, $L \triangleq \{0, \ldots, N\}$, then $K_0 = ZX^{-1}$ is the state-feedback control gain from (5) that assure that the closed-loop system (10) (with F_i as given by (6)-(8)) is asymptotically stable if $\rho = 1$, and exponential stable with convergence rate of at least ρ if $0 < \rho < 1$, for all $(\alpha_k, \ldots, \alpha_{k+N}) \in \Lambda_Z \times \cdots \times \Lambda_Z$.

Proof: The proof of Lemma 1 introduces the basis for this proof. However here $\mathcal{M}_i = [I \quad F_i]^T$ is considered.

Remark 3: By applying Theorem 1 with $N = 0$, the reference tracking for the discrete-time LPV pharmacokinetic MCPS is considered with inputs at every time instant. In this case, there is no switching, and only (13) is taken into account.

Remark 4: It is worth noting that every controller gain designed for $N > 0$ will be able to adapt the dosage with guaranteed asymptotic or exponential stability for every interval equal to or lesser than N time instants between doses.

Corollary 1: By setting $(\alpha_k, \ldots, \alpha_{k+N}) = \alpha$, a control law (5) that assures the asymptotic stability of linear time-invariant (LTI) systems with polytopic uncertainties is obtained.

Corollary 2: In Theorem 1, by rendering constant every matrix dependent on the α_k parameter (i.e. $M_i(\alpha_k) = M_i$), a control law (5) that assures asymptotic stability of a single precisely known operating point of a pharmacokinetic absorption system is obtained.

V. Numerical Experiments

A numerical example is chosen to test the effectiveness of the proposed method. The conditions were implemented in MATLAB. Parsers YALMIP [26] and ROLMIP [27] and the solver MOSEK [28] were utilized. Considering the previously presented discrete-time 3-compartment model, described by (11), the parameters displayed in Table I are considered.

The state matrix (12) is utilized, considering 8 vertices. To represent the drug being injected into the muscle, the input

TABLE I
3-COMPARTMENT MODEL PARAMETERS

Parameters	Values
γ_{mb}	0.095
γ_{bo}	0.095
$\begin{bmatrix}\underline{\gamma}_{ob} & \bar{\gamma}_{ob}\end{bmatrix}$	$\begin{bmatrix}0.037 & 0.17\end{bmatrix}$
γ_{bm}	0.03
$\begin{bmatrix}\underline{\mu}_m & \bar{\mu}_m\end{bmatrix}$	$\begin{bmatrix}0.1 & 0.21\end{bmatrix}$
$\begin{bmatrix}\underline{\mu}_o & \bar{\mu}_o\end{bmatrix}$	$\begin{bmatrix}0.1 & 0.11\end{bmatrix}$
μ_b	0.2

matrix is $B = \begin{bmatrix}D_m & 0 & 0\end{bmatrix}^T$, with $D_m = 1000$ and our aim is to control the drug concentration in the organs, thus, $C = \begin{bmatrix}0 & 0 & 1\end{bmatrix}$. A controller considering this LPV system, after converting it to its augmented form (4), is obtained through Theorem 1, considering an interval of $N = 4$ time instants between doses, and an exponential decay rate of $\rho = 0.9$.

The desired concentration is $r(k) = 0.5$, as seen in (3). To reflect the time-varying nature of the system in its time-based simulation, a new set of α_k, as seen in (2) is randomly generated at each time instant. Because of the time-varying parameter randomness, the mean of 1000 simulations was calculated to test the controller performance. In Fig. 2 a scenario where a dose is applied during every time instant is described, while in Fig. 3, there is an interval of 4 time instants between inputs.

The proposed control strategy was able to calculate inputs that assured the reference tracking to the desired drug concentration in the organs in both scenarios. Note that the input signal in each time instant refers to the amount of drug administrated in each time instant of the considered time scale. In Fig. 2, administrating doses every time instant provided an almost stationary response in the reference, being, however, not a viable option in some practical instances. Applying doses divided by 4 time instant intervals, as seen in Fig. 3, is a less conservative and practical approach, which presents an oscillatory response that orbits the reference. This is a satisfactory and expected response when using a zero-input strategy, proving to be a robust control system even under drug administration disruption. In conclusion, the proposed technique was successful in providing a solution to the pharmacokinetic absorption reference tracking problem.

VI. CONCLUSIONS

Keeping the suitable concentration of drugs in the body during treatment is vital to ensure its efficacy. In this context, emerging MCPS can be applied in order to integrate technological solutions to medical applications, as well as utilize control theory fundamentals to help define the appropriate drug dosages. This work proposed a zero-input state-feedback control strategy for MCPS that assures exponential or asymptotic stability to a reference tracking problem, which keeps the

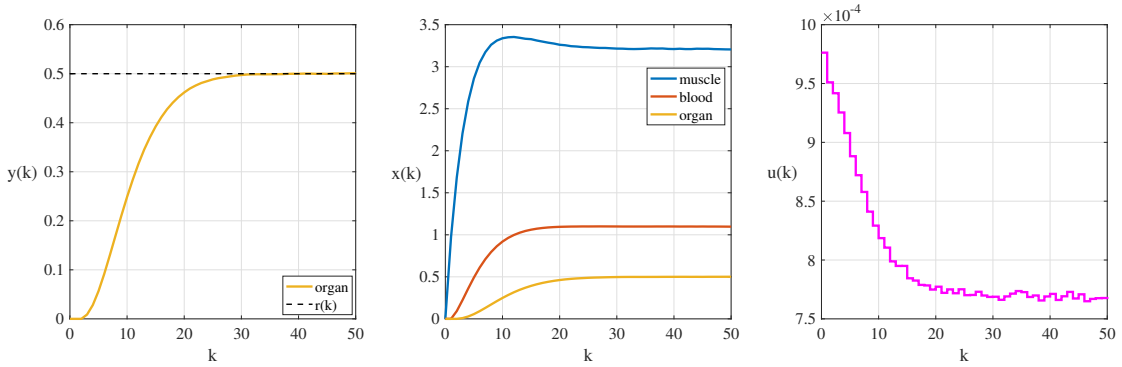

Fig. 2. Mean output, states and inputs of 1000 time-based simulations considering doses every time instant ($N = 0$); Initial conditions are $\eta(0) = \begin{bmatrix}0 & 0 & 0 & r(0)\end{bmatrix}^T$. $K_0 = \begin{bmatrix}-0.0010 & -0.0028 & -0.0083 & 0.0020\end{bmatrix}$.

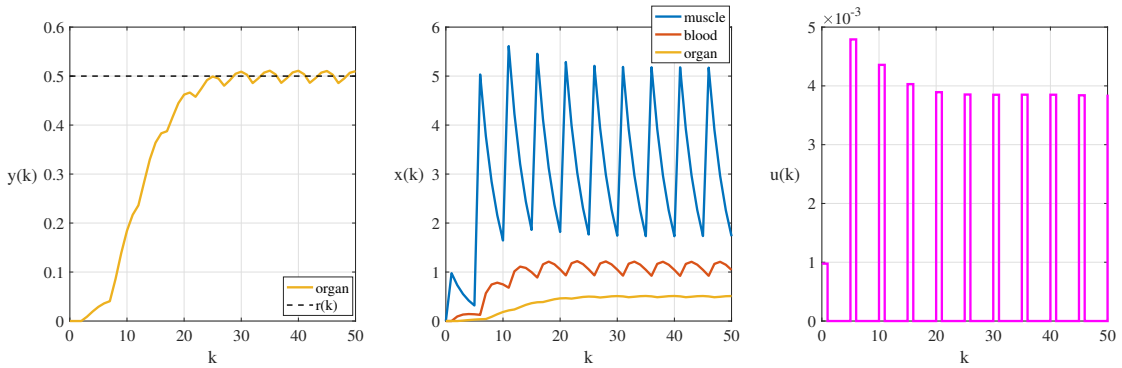

Fig. 3. Mean output, states and inputs of 1000 time-based simulations considering doses with intervals of 4 time instants ($N = 4$). Initial conditions are $\eta(0) = \begin{bmatrix}0 & 0 & 0 & r(0)\end{bmatrix}^T$. $K_0 = \begin{bmatrix}-0.0010 & -0.0028 & -0.0083 & 0.0020\end{bmatrix}$.

drug concentration at the desired value. The proposed control strategy was designed to be resilient against communication faults in the system, DoS attacks, or even patient forgetfulness.

The most important future work is to ensure the positivity of the system, given that drug concentrations as control signals can only be positive. The general solution to this problem involves guaranteeing the positivity of the closed loop, which poses a significant challenge.

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