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Constrained Control of Semilinear Fractional-Order Systems: Application in Drug Delivery Systems

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Abstract— **This paper proposes an approach to control fractional-order semilinear systems which are subject to linear constraints. The design procedure consists of two stages. First, a linear state-feedback control law is proposed to prestabilize the system in the absence of constraints. The stability and convergence properties are proved using Lyapunov theory. Then, a constraint-handling unit is utilized to enforce the constraints at all times. In particular, we use the Explicit Reference Governor (ERG) scheme. The core idea behind ERG is, first, to translate the linear constraints into a constraint on the value of the Lyapunov function, and then to manipulate the auxiliary reference such that the Lyapunov function is smaller than a threshold value at all times. The proposed method is applied in a drug delivery system to control the drug concentration, and its performance is assessed through extensive simulation results.**

I. Introduction

Fractional-order systems are the generalization of the traditional integer-order systems. Fractional-order systems have been used in control theory and applications thanks to their capabilities in accurate modeling of dynamical systems, the bigger stability regions, and the achievement of more control requirements [1]. During the last years, numerous control schemes have been developed for fractional-order systems, e.g., fractional PID controller [2], fractional CRONE controller [3], and fractional lead-lag controller [4]. Similarly, in order to improve the control performance of nonlinear systems, quite a few number of control methods are developed based on fractional calculus, such as sliding mode control [5], model reference adaptive control [6], backstepping control [7], and fuzzy control [8].

Similar to integer-order systems, fractional-order systems can be subject to operational constraints, which need to be satisfied. Feasibility of controlling the fractional-order systems in the presence of such constraints are studied widely (see [9], [10] and references within for more details). Also, some schemes are presented in the literature to address the constrained control problem of fractional-order systems. These schemes are mostly developed based on Model Predictive Control (MPC) framework [11]–[13]. It is well-known that MPC usually leads to a good performance, as it solves an optimization problem at each time instant to obtain the control action. However, this increases the computational cost, which might be impractical/unrealistic in many applications.

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This paper mainly focuses on constrained control of a class of fractional-order systems, called semilinear fractional-order systems. A semilinear system can be seen as a combination of a linear system and a nonlinear system. Examples of such systems are: DC motor [14], heat equation [15], electric circuit [16], duffing system [17], and Lorenz attractor [18]. The proposed control scheme consists of two parts. The first part stabilizes the system in the absence of constraints, by proposing a linear state-feedback control law. Second part enforces the constraints satisfaction at all times. In this paper, we will use the recently introduced Explicit Reference Governor (ERG) framework [19], [20] to ensure that constraints are never violated. The main idea behind the ERG framework is to determine an invariant set that would contain the state trajectory if the currently auxiliary reference were to remain constant. If the distance between this invariant set and the boundary of the constraints is strictly positive, it follows from the continuity that the derivative of the auxiliary reference can be nonzero without leading to constraint violations. If this distance is zero, the satisfaction of the constraints is ensured by maintaining the current reference constant. One of the main strengths of the ERG is that it requires very limited computational capabilities, since it does not make use of any online optimization.

In order to verify the effectiveness of the proposed constrained scheme, we will study its performance in a drug delivery system. In particular, we will use the proposed scheme to control the concentration of propofol, a hypnotic drug used in general anesthesia. First, we will discuss that the so-called Pharmacokinetic (PK) model, which described the relationship between the administrated drug and the plasma concentration, can be expressed as a smilinear fractional-order system. We will then formulate the overdosing prevention as a constraint on the states of the system that must be satisfied at all times. Finally, simulation results will be carried out on 44 patients with real clinical data.

The rest of this paper is organized as follows: In Section II, basic definition of fractional-order derivative is presented, and Lyapunov stability of the fractional-order systems is discussed. The problem is stated in Section III. Section IV explains the design procedure: Subsection IV-A proposes a linear state-feedback control law to prestabilize the system in the absence of constraints, and Subsection IV-B briefly summarizes the ERG framework, and provides a guideline to apply it to semilinear fractional-order systems. In Section V the proposed constrained control scheme is applied to a drug delivery system and simulation results are reported. Finally, Section VI concludes the main results of the paper.

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II. Preliminary Concepts

Since the time Leibniz introduced non-integer order derivatives, several definitions have been generated by several mathematicians. In this section, preliminary materials used in this paper are briefly explained.

Definition 1: The Caputo fractional derivative of order α is defined as follows

$$ {}_0^C D_t^\alpha f(t) = \begin{cases} \frac{1}{\Gamma(k-\alpha)} \int_0^t \frac{f^{(k)}(\tau)}{(t-\tau)^{\alpha+1-k}} d\tau; & k-1 < \alpha < k \\ \frac{d^k}{dt^k} f(t); & \alpha = k \end{cases}, \quad (1) $$

where $\Gamma(\cdot)$ is the gamma function, and $f^{(k)}(t)$ is the derivative of order k [21]. In the rest of this paper, for the sake of brevity, we will use D_t^α to represent the operator ${}_0^C D_t^\alpha$.

Theorem 1: (Fractional-order extension of Lyapunov direct method) [22] Using the Caputo derivative, a fractional-order nonlinear system can be represented by:

$$ D_t^\alpha x = f(t, x), \quad (2) $$

Let $x = 0$ be an equilibrium point for fractional-order system (2). Let $V(t, x(t))$ be a continuously differentiable function as a Lyapunov function candidate, and $\gamma_i (i = 1, 2, 3)$ be class-K functions such that

$$ \gamma_1(\|x\|) \leq V(t, x(t)) \leq \gamma_2(\|x\|), \quad (3) $$

$$ D_t^\alpha V(t, x(t)) \leq -\gamma_3(\|x\|), \quad (4) $$

where $\alpha \in (0, 1)$. Then, system (2) is asymptotically stable.

Lemma 1: Let $x(t) \in \mathbb{R}^n$ be a vector of continuously differentiable functions. Then, the following inequality holds true $\forall t \geq 0$ and $\forall \alpha \in (0, 1)$:

$$ D_t^\alpha (x^T P x) \leq (D_t^\alpha x)^T P x + x^T P D_t^\alpha x, \quad (5) $$

where $P \in \mathbb{R}^{n \times n}$ is a symmetric positive definite matrix [23].

III. Problem Statement

Consider the following commensurate fractional-order semi-linear system:

$$ D_t^\alpha x(t) = Ax(t) + g(x) + Bu(t) \quad (6) $$

where α represents the order of fractional derivatives of the system and belongs to interval $(0, 1)$; $x \in \mathbb{R}^n$ is the system state vector; $g(\cdot)$ is a nonlinear function; $A \in \mathbb{R}^{n \times n}$ and $B \in \mathbb{R}^{n \times p}$ are known matrices; and $u(t) \in \mathbb{R}^p$ is the input of the system. It is assumed that $g(\cdot)$ is ϵ-Lipschitz continuous, *i.e.*, $\|g(x_1) - g(x_2)\| \leq \epsilon(\|x_1 - x_2\|)$, where $x_1, x_2 \in \mathbb{R}^n$, and $\epsilon > 0$. The control problem is to track a desired reference $r \in \mathbb{R}^m$.

Assume that system (6) is subject to linear constraints at all times. This condition can be expressed by the following inequality:

$$ \beta_x^T x + \beta_r^T r \leq h. \quad (7) $$

where $\beta_x \in \mathbb{R}^{n \times n_c}$, $\beta_r \in \mathbb{R}^{m \times n_c}$, and $h \in \mathbb{R}^{n_c}$, with n_c as the number of the constraints.

At this stage, we define the following problem.

Problem 1: Consider system (6) which is subject to constraint (7). Find an auxiliary reference $v(t)$ such that for a given desired reference $r(t)$, the constraints are satisfied at all times, and the auxiliary reference converges to the desired one.

In this paper, we will use the ERG framework to solve Problem 1. As shown in [20], the ERG can solve the mentioned problem in two stages. First, the system should be prestabilized in the absence of the constraints. Then, the ERG unit will be added on top to enforce the constraints. Next section will detail these two stages separately.

IV. Proposed Control Scheme

In this section, the prestabilization and constraints enforcement will be studied.

A. Prestabilization

This subsection will study the prestabilization of system (6). By prestabilization, we mean that the system can converge to the desired reference, r, in the absence of the constraints. In this paper, we will propose a linear state-feedback controller to prestabilize system (6), as it is easy to determine the Lyapunov function that proves the stability (see Subsection IV-B). The following theorem addresses this issue.

Theorem 2: Let r be the desired reference signal. Consider the following control input:

$$ u(t) = -Kx(t) + Gr, \quad (8) $$

where $K \in \mathbb{R}^{p \times n}$ and $G \in \mathbb{R}^{p \times m}$ are design gains. Then, if $\mathrm{Re}\{\lambda(A - BK)\} < 0$, and if there are $P = P^T > 0$ ($P \in \mathbb{R}^{n \times n}$) and $\theta > 0$ ($\theta \in \mathbb{R}$) such that $P(A - BK) + (A - BK)^T P = -\theta I$ and $\theta - 2\epsilon \|P\| > 0$, the equilibrium point $\bar{x}_r$ is globally asymptotically stable. Note that $\mathrm{Re}\{\cdot\}$ represents the real part of a complex number, and $\lambda(\cdot)$ is the eigenvalue of a matrix.

Proof: By substituting control input (8) into system (6), it implies that

$$ D_t^\alpha x(t) = (A - BK)x(t) + g(x) + BGr. \quad (9) $$

Consider the following Lyapunov function

$$ V = (x - \bar{x}_r)^T P (x - \bar{x}_r), \quad (10) $$

where according to Lemma 1, its time derivative satisfies the following inequality

$$ \begin{aligned} D_t^\alpha V \leq & (x - \bar{x}_r)^T P \left(D_t^\alpha x - D_t^\alpha \bar{x}_r \right) \\ & + \left((D_t^\alpha x - D_t^\alpha \bar{x}_r) \right)^T P (x - \bar{x}_r). \end{aligned} \quad (11) $$

Since the equilibrium point $\bar{x}_r$ satisfies

$$ D_t^\alpha \bar{x}_r = (A - BK)\bar{x}_r + g(\bar{x}_r) + BGr = 0, \quad (12) $$

it follows from (9) and (11) that

$$
\begin{aligned}
D_t^\alpha V \leq &(x-\bar{x}_r)^T P\Big[(A-BK)x+g(x)+BGr \\
&-(A-BK)\bar{x}_r-g(\bar{x}_r)-BGr\Big] \\
&+\Big[(A-BK)x+g(x)+BGr \\
&-(A-BK)\bar{x}_r-g(\bar{x}_r)-BGr\Big]^T P(x-\bar{x}_r) \\
\leq &(x-\bar{x}_r)^T[P(A-BK)+(A-BK)^T P](x-\bar{x}_r) \\
&+2(x-\bar{x}_r)^T P(g(x)-g(\bar{x}_r)). \qquad (13)
\end{aligned}
$$

Now, by using the Lipschitz continuity of function $g(\cdot)$, one can obtain:

$$
\begin{aligned}
D_t^\alpha V \leq &(x-\bar{x}_r)^T[P(A-BK)+(A-BK)^T P](x-\bar{x}_r) \\
&+2\left\|x-\bar{x}_r\right\|\left\|P\right\|\epsilon\left\|x-\bar{x}_r\right\| \\
\leq &-\theta\left\|x-\bar{x}_r\right\|^2+2\epsilon\left\|P\right\|\left\|x-\bar{x}_r\right\|^2 \\
\leq &-(\theta-2\epsilon\left\|P\right\|)\left\|x-\bar{x}_r\right\|^2, \qquad (14)
\end{aligned}
$$

which completes the proof, as $\theta - 2\epsilon\left\|P\right\| > 0$.

■

B. Constraints Enforcement

As mentioned before, we will use the ERG framework to enforce the constraints at all times. The ERG does so by modifying the auxiliary reference through the following differential equation:

$$\dot{\nu} = \kappa \cdot \Delta(x,\nu) \cdot \rho(\nu, r), \qquad (15)$$

where $\kappa > 0$ is a tuning parameter, and $\Delta(\cdot)$ and $\rho(\cdot)$ are two fundamental components of the ERG, called Dynamic Safety Margin (DSM) and Navigation Function (NF), respectively.

The NF represents the direction along a feasible path that leads from the current auxiliary reference ν to the desired reference r. As discussed in [20], the problem of finding a suitable NF is equivalent to the path planning problem. This component will not be studied in this paper, as it is the subject of an intensive literature.

The DSM represents a "distance" between the constraints and the system trajectory that would emanate from the state $x(t)$ for a constant reference ν. As shown in [19], a systematic way to build a DSM is using the Lyapunov theory. More precisely, given a Lyapunov function $V(x(t),\nu)$ which proves the stability of $\bar{x}_\nu$, if there exists a threshold value $\Gamma(\nu)$ continuous in ν such that $V(x(t),\nu) \leq \Gamma(\nu)$ implies that $c(x(t),v) \geq 0,\ \forall t \geq t_0$, then a possible DSM can be defined as $\Delta(x,\nu) = \Gamma(\nu) - V(x(t),\nu)$.

In general, the optimal choice of $\Gamma(\nu)$ for the i-th constraint can be computed via the following optimization problem:

$$\Gamma_i(\nu) = \left\{ \begin{array}{ll} & \min\limits_{z} V(z,\nu) \\ \text{s.t.} & \beta_{x,i}^T z + \beta_{r,i}^T r \geq h_i \end{array} \right. ,\ i \in \{1,2,\cdots,n_c\}, \qquad (16)$$

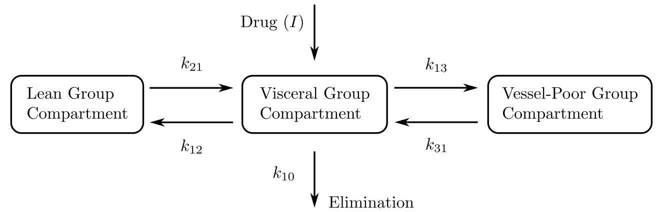

Fig. 1. Three-compartment pharmacokinetic model.

where $\beta_{x,i}$ is the i-th column of β_x, $\beta_{r,i}$ is the i-th column of β_r, and h_i is the i-th element of h. As shown in [19], (16) provides a closed-form solution in the following form:

$$\Gamma_i(\nu) = \frac{(\beta_{x,i}^T \bar{x}_\nu + \beta_{r,i}^T r - h_i)^2}{\beta_{x,i}^T P^{-1} \beta_{x,i}}, \qquad (17)$$

and the final DSM can be computed as

$$\Gamma(\nu) = \min_{i\in\{1,2,\cdots,n_c\}} \Gamma_i(\nu). \qquad (18)$$

V. Simulation Study: Control of Drug Concentration

In this section, the effectiveness of the proposed scheme will be demonstrated through intensive simulation studies carried out to control the drug concentration.

The relationship between the administrated dose of a drug and its concentration can be expressed through the so-called pharmacokinetic model [24]. This model is developed considering three-compartments and is depicted in Fig. 1 [25], [26]. We use V_1 to denote the volume of the plasma compartment (visceral group), V_2 to denote the volume of the shallow peripheral compartment (lean group), and V_3 to denote the volume of the deep peripheral compartment (vessel-poor group). Moreover, we use $C_1(t)$, $C_2(t)$, and $C_3(t)$ to denote the propofol concentration in the plasma, fast peripheral, and slow peripheral compartments, respectively. As shown in [27], fractional calculus describes drug absorption and disposition processes accurately. In particular, the state-space representation of the PK model is [28]

$$D_t^\alpha x = Ax + BI. \qquad (19)$$

where $x = \begin{bmatrix} C_1 & C_2 & C_3 \end{bmatrix}^T$, I is the infusion rate, and matrices A and B are

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{12} & k_{13} \\ k_{21} & -k_{21} & 0 \\ k_{31} & 0 & -k_{31} \end{bmatrix}, \qquad (20)$$

$$B = \begin{bmatrix} \frac{1}{V_1} & 0 & 0 \end{bmatrix}^T, \qquad (21)$$

with the distribution rates k_{10}, k_{12}, k_{21}, k_{13}, and k_{31} defined as

$$
\begin{aligned}
&k_{10} = \frac{Cl_1}{V_1},\ k_{12} = \frac{Cl_2}{V_1},\ k_{21} = \frac{Cl_2}{V_2}, \\
&k_{13} = \frac{CL_3}{V_1},\ k_{31} = \frac{Cl_3}{V_3}, \qquad (22)
\end{aligned}
$$

in which parameter Cl_1 is the elimination clearance, and Cl_2 and Cl_3 are the inter-compartmental clearances.

In general, matrix A given in (20) is uncertain, as parameters Cl_1, Cl_2, Cl_3, V_2 and V_3 depend on the patient's characteristics (i.e., age, weight, height, etc) which differ from one to another. Thus, for each patient, the matrix A can be expressed in the form $A = \bar{A} + \Delta A$, where $\bar{A}$ represents the nominal matrix calculated with nominal values, and ΔA represents the uncertainty. Hence, (19) can be rewritten as

$$D_t^\alpha x = \bar{A}x + BI + g(x), \tag{23}$$

where $g(x) = \Delta A x$. It is easy to show that $g(x)$ is $\|\Delta A\|$-Lipschitz continuous.

In this paper, we assume that the understudy drug is propofol, which is a well-known hypnotic drug. Moreover, we will use the dataset presented in [29] which includes real clinical data of 44 patients. Parameters Cl_i and V_i, $i = 1, 2, 3$ can be calculated using the relations presented in [24]. As a result, we have

$$\bar{A} = \begin{bmatrix} -1.0450 & 0.3950 & 0.1960 \\ 0.0667 & -0.0667 & 0 \\ 0.0035 & 0 & -0.0035 \end{bmatrix}, \tag{24}$$

$$\|\Delta A\| \leq 0.2057. \tag{25}$$

As shown in [30], [31], propofol concentration in the central compartment should not exceed 10 [μg/ml], as it increases the risk of overdosing. Hence, in order to prevent overdosing in patients, it is recommended to constrain the concentration to be less than 10, i.e., $C_1(t) \leq 10$ [32].

In order to prestabilize system (23), we use the linear state-feedback control scheme presented in Theorem 2. The obtained feedback gain is $K = [-3.18 \quad 1.53 \quad 32.54]^T$. Simulation results are shown in Fig. 2, where the order of the system is $\alpha = 0.9$. As seen in this figure, the system is stable and the concentration in the central compartment converges to the desired value. However, the safety constraint is violated in all patients, meaning that the patients are in the danger of overdosing.

Now, we use the ERG scheme discussed in Subsection IV-B to prevent overdosing. The DSM can be computed through (16) with $V(\cdot)$ as in (10). For what concerns NF, we use the most intuitive one [33]:

$$\rho(\nu, r) = \frac{r - \nu}{\max\{|r - \nu|, \eta\}}, \tag{26}$$

where $\eta > 0$ is a smoothing factor.

Using $\kappa = 0.001$ and $\eta = 0.01$ simulation results are shown in Fig. 3 for two values of α (0.8 and 0.9, as discussed in [34]), and simulation results for $\alpha = 1$ are presented for comparison purposes. These results demonstrate the effectiveness of the proposed method in tracking the desired reference, while the safety constraint is satisfied at all times, i.e., $C_1(t) \leq 10, \ \forall t \geq 0$.

Note that the distribution rates are expressed in [1/s$^\alpha$], which means that high values of α lead to fast changes in the concentration. This fact can be seen in Fig. 3, where the dynamic behavior for $\alpha = 0.8$ is slower than that of $\alpha = 0.9$.

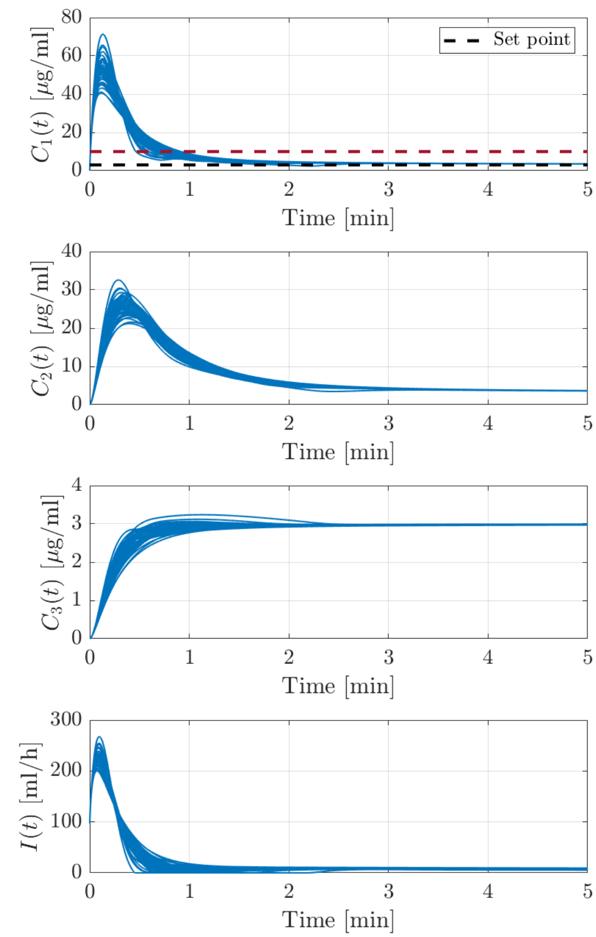

Fig. 2. Closed-loop response of all 44 patients using the linear state-feedback control law, without enforcing safety.

VI. Conclusion

This paper proposed a control scheme for fractional-order semilinear systems subject to linear constraints. The design procedure has two stages: (i) prestabilization, and (ii) constraint enforcement. Regarding the prestabilization stage, we proposed a linear state-feedback control law, where stability and convergence properties are proved analytically. For what concerns the second stage, we used the so-called explicit reference governor scheme. This control scheme is an *add-on* unit that modifies the time derivative of the auxiliary reference, whenever needed, such that constraints satisfaction is guaranteed at all times. The effectiveness of the proposed constrained control scheme was studied in drug delivery systems, where drug concentration needs to be bounded to ensure overdosing prevention. Simulation results showed that the proposed method effectively ensures patient's safety, though it increases the time to converge to the desired reference.

References

[1] A. T. Azar, S. Vaidyanathan, and A. Ouannas, *Fractional order control and synchronization of chaotic systems*. Springer, 2017, vol. 688.

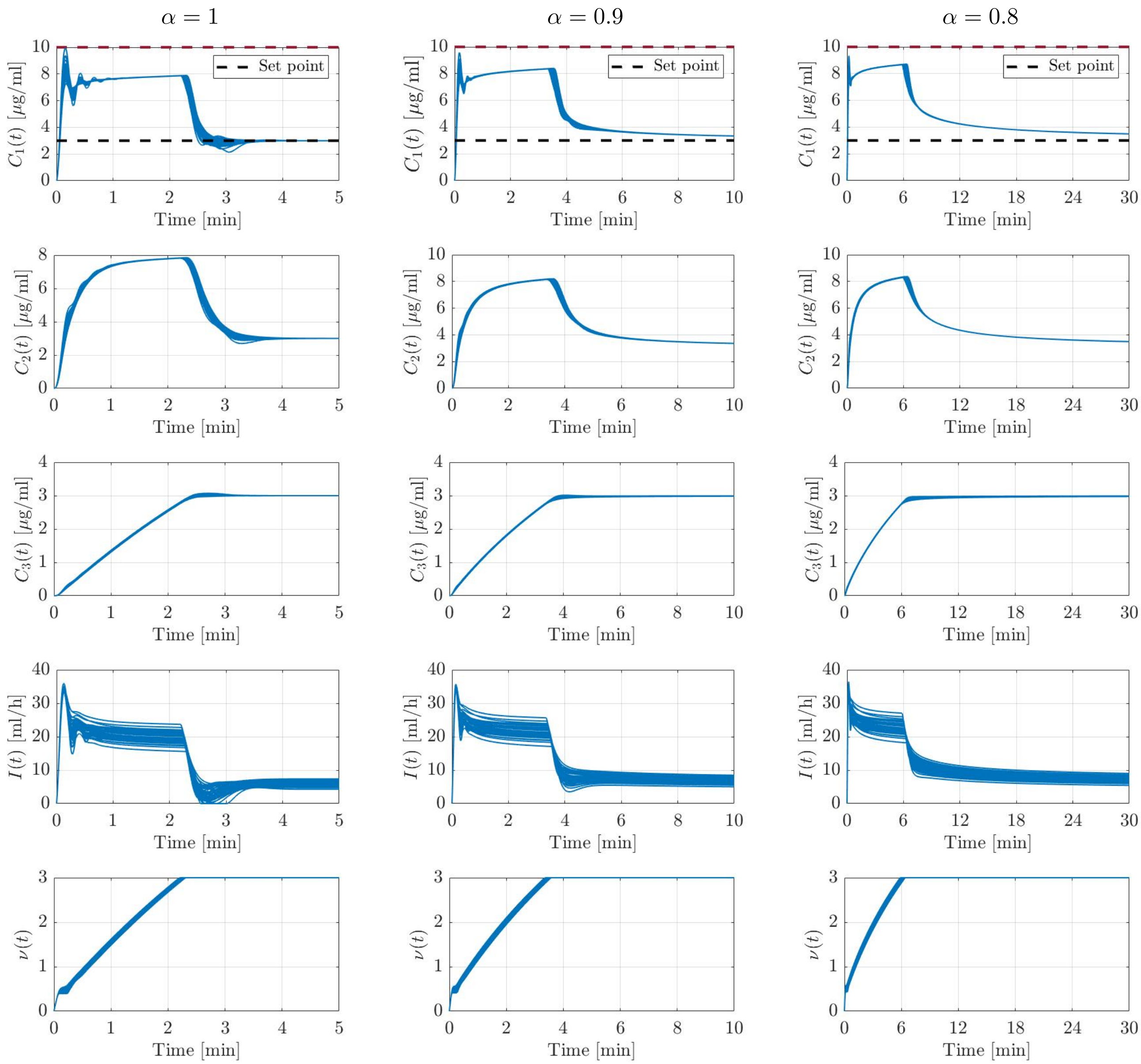

Fig. 3. Closed-loop response of all 44 patients using the proposed constrained control scheme.

[2] B. Yaghooti and H. Salarieh, "Robust adaptive fractional order proportional integral derivative controller design for uncertain fractional order nonlinear systems using sliding mode control," *Proceedings of the Institution of Mechanical Engineers, Part I: Journal of Systems and Control Engineering*, vol. 232, no. 5, pp. 550–557, 2018.

[3] A. Kumari and I. Gupta, "Design of fractional order controller via crone principle for time delayed systems," in *2019 9th Annual Information Technology, Electromechanical Engineering and Microelectronics Conference (IEMECON)*. IEEE, 2019, pp. 5–11.

[4] T. Dogruer and N. Tan, "Lead and lag controller design in fractional-order control systems," *Measurement and Control*, p. 0020294019858094, 2019.

[5] B. Yaghooti, A. Siahi Shadbad, K. Safavi, and H. Salarieh, "Adaptive synchronization of uncertain fractional-order chaotic systems using sliding mode control techniques," *Proceedings of the Institution of Mechanical Engineers, Part I: Journal of Systems and Control Engineering*, vol. 234, no. 1, pp. 3–9, 2020.

[6] M. Abedini, M. A. Nojoumian, H. Salarieh, and A. Meghdari, "Model reference adaptive control in fractional order systems using discrete-time approximation methods," *Communications in Nonlinear Science and Numerical Simulation*, vol. 25, no. 1-3, pp. 27–40, 2015.

[7] Y. Wei, W. T. Peter, Z. Yao, and Y. Wang, "Adaptive backstepping output feedback control for a class of nonlinear fractional order systems," *Nonlinear Dynamics*, vol. 86, no. 2, pp. 1047–1056, 2016.

[8] A. Mohammadzadeh and O. Kaynak, "A novel fractional-order fuzzy control method based on immersion and invariance approach," *Applied Soft Computing*, vol. 88, p. 106043, 2020.

[9] B. Sikora and J. Klamka, "Constrained controllability of fractional linear systems with delays in control," *Systems & Control Letters*, vol. 106, pp. 9–15, 2017.

[10] R. J. Nirmala, K. Balachandran, and J. J. Trujillo, "Null controllability of fractional dynamical systems with constrained control," *Fractional Calculus and Applied Analysis*, vol. 20, no. 2, pp. 553–565, 2017.

[11] A. Rhouma, F. Bouani, B. Bouzouita, and M. Ksouri, "Model predictive control of fractional order systems," *Journal of Computational and Nonlinear Dynamics*, vol. 9, no. 3, p. 031011, 2014.

[12] S. Domek, "Switched state model predictive control of fractional-order nonlinear discrete-time systems," *Asian Journal of Control*, vol. 15, no. 3, pp. 658–668, 2013.

[13] P. Sopasakis and H. Sarimveis, "Stabilising model predictive control for discrete-time fractional-order systems," *Automatica*, vol. 75, pp. 24–31, 2017.

[14] I. Petráš, "Fractional-order feedback control of a dc motor," *Journal of electrical engineering*, vol. 60, no. 3, pp. 117–128, 2009.

[15] A. Shukla, N. Sukavanam, and D. Pandey, "Approximate controllability of fractional semilinear control system of order $\alpha \in (1, 2]$ in hilbert spaces," *Nonlinear Studies*, vol. 22, no. 1, pp. 131–138, 2015.

[16] U. Arora and N. Sukavanam, "Controllability of retarded semilinear fractional system with non-local conditions," *IMA Journal of Mathematical Control and Information*, vol. 35, no. 3, pp. 689–705, 2017.

[17] Z.-M. Ge and C.-Y. Ou, "Chaos in a fractional order modified duffing system," *Chaos, Solitons & Fractals*, vol. 34, no. 2, pp. 262–291, 2007.

[18] I. Grigorenko and E. Grigorenko, "Chaotic dynamics of the fractional lorenz system," *Physical review letters*, vol. 91, no. 3, p. 034101, 2003.

[19] E. Garone, M. Nicotra, and L. Ntogramatzidis, "Explicit reference governor for linear systems," *International Journal of Control*, vol. 91, no. 6, pp. 1415–1430, 2018.

[20] M. Hosseinzadeh and E. Garone, "An explicit reference governor for the intersection of concave constraints," *IEEE Transactions on Automatic Control*, vol. 65, no. 1, pp. 1–11, 2020.

[21] I. Podlubny, *Fractional differential equations: an introduction to fractional derivatives, fractional differential equations, to methods of their solution and some of their applications*. Elsevier, 1998, vol. 198.

[22] Y. Li, Y. Chen, and I. Podlubny, "Stability of fractional-order nonlinear dynamic systems: Lyapunov direct method and generalized mittag–leffler stability," *Computers & Mathematics with Applications*, vol. 59, no. 5, pp. 1810–1821, 2010.

[23] M. A. Duarte-Mermoud, N. Aguila-Camacho, J. A. Gallegos, and R. Castro-Linares, "Using general quadratic lyapunov functions to prove lyapunov uniform stability for fractional order systems," *Communications in Nonlinear Science and Numerical Simulation*, vol. 22, no. 1-3, pp. 650–659, 2015.

[24] J. Schüttler and H. Ihmsen, "Population pharmacokinetics of propofola multicenter study," *Anesthesiology: The Journal of the American Society of Anesthesiologists*, vol. 92, no. 3, pp. 727–738, 2000.

[25] N. Sadati, M. Hosseinzadeh, and G. A. Dumont, "Multi-model robust control of depth of hypnosis," *Biomedical Signal Processing and Control*, vol. 40, pp. 443–453, 2018.

[26] M. Hosseinzadeh, "Robust control applications in biomedical engineering: Control of depth of hypnosis," in *Control Applications for Biomedical Engineering Systems*. Academic Press, 2020, pp. 89–125.

[27] A. Dokoumetzidis and P. Macheras, "Fractional kinetics in drug absorption and disposition processes," *Journal of pharmacokinetics and pharmacodynamics*, vol. 36, no. 2, pp. 165–178, 2009.

[28] D. Copot, C.-M. Ionescu, A. Chevalier, and R. De Keyser, "Remifentanil pharmacokinetics: a fractional order modeling approach," in *Proc. 8th European Nonlinear Oscillations Conference*, 2014.

[29] S. Bibian, G. A. Dumont, M. Huzmezan, and C. R. Ries, "Patient variability and uncertainty quantification in clinical anaesthesia: part I, PKPD modelling and identification," in *Proc. 6th IFAC Symp. Modelling and Control in Biomedical Systems*, Reims, France, Sep. 20-22, 2006.

[30] M. Hosseinzadeh, G. A. Dumont, and E. Garone, "Constrained control of depth of hypnosis during induction phase," *IEEE Transactions on Control Systems Technology*, 2019.

[31] M. Hosseinzadeh, K. Van Heusden, G. A. Dumont, and E. Garone, "An explicit reference governor scheme for closed-loop anesthesia," in *Proc. 18th European Control Conference*, 2019, pp. 1294–1299.

[32] M. Hosseinzadeh and E. Garone, "Constrained control in closed-loop anesthesia," in *Proc. 38th Benelux Meeting on Systems and Control*, 2019.

[33] M. Hosseinzadeh, A. Cotorruelo, D. Limon, and E. Garone, "Constrained control of linear systems subject to combinations of intersections and unions of concave constraints," *IEEE Control Systems Letters*, vol. 3, no. 3, pp. 571–576, 2019.

[34] A. Almusharrf, "Development of fractional trigonometry and an application of fractional calculus to pharmacokinetic model," 2011.