Controlled Drug Administration by a Fractional PID [*]

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Abstract: Amiodarone is an antiarrhythmic drug that exhibits highly complex and non-exponential dynamics whose controlled administration has important implications for its clinical use especially for long-term therapies. Its pharmacokinetics has been accurately modelled using a fractional-order compartmental model. In this paper we design a fractional-order PID controller and we evaluate its dynamical characteristics in terms of the stability margins of the closed loop and the ability of the controlled system to attenuate various sources of noise and uncertainty.

Keywords: Biomedical control; Biomedical systems; Pharmacokinetics and drug delivery; Control of physiological and clinical variables; Physiological model; Fractional control.

1. INTRODUCTION

1.1 Motivation

It is characteristic how Machado et al. [2011] open their review on the recent history of fractional calculus saying that "fractional calculus may be considered an old and yet novel topic." Although lots of mathematicians have worked on this field, many fundamental questions remain unanswered. From the point of view of applied research the field is nowadays very active – it has been only the last few decades that the scientific community turned to fractional calculus seeking for a modeling solution for phenomena that ordinary calculus had a hard time to approach. Such complex phenomena are biological membranes, viscoelastic materials, certain electrochemical processes and biomedical phenomena (see Magin [2006]).

In 2010, Kytariolos et al. [2010] introduced fractional dynamics in the field of pharmacokinetic modelling pointing out the main reasons for the failure of the classical IVIVC (In-Vitro In-Vivo Correlations) theory. The first step to this direction was taken by Dokoumetzidis and Macheras [2009]. In practice, non-linearities, anomalous diffusion, fractional-order kinetics, diffusion accross fractal manifolds, synergetic and competitive action and a great many other factors render this approach not applicable (see Dokoumetzidis and Macheras [2008]). Recently, a significant number of relevant publications has emerged; see Popović et al. [2012], Verotta [2010a,b], Pereira [2010], Dokoumetzidis et al. [2010b], Popović et al. [2010].

Fractional-order derivatives – which we shall define properly in the sequel – although seem to be a mere mathematical construction and a method of nonlinear modelling, possess, in fact, physical meaning and occur naturally through physical phenomena. Hilfer [2000a] called attention on the fact that such operators emerge naturally from the study of anomalous diffusion and other phenomena (Hilfer [2000b]).

Fractional dynamics can be cast as Physiologically Based Pharmacokinetic Models (PBPK) with fractional-order derivatives (see Dokoumetzidis et al. [2010a]) where the mass balance equations are rewritten using fractional-order derivatives. This offers a mechanistic understanding of the interplay among the main factors of drug distribution, allows us to draw individualized concentration-time profiles and study drug-drug interactions using the fractional calculus approach. The "fractionalisation" of pharmacokinetic equations though has to be done in a way so that the mass preservation holds.

The problem of drug administration is purely a control problem where the aim is to keep the drug concentration at certain organs in the body close to the desired therapeutical set-points while the concentration in other organs and tissues does not exceed certain safety limits (see Sarimveis et al. [2009]). The manipulated variable is the administered dosage and the controlled variable is the concentration of the drug in some tissue or organ of the body.

It is nowadays clear that accurate pharmacokinetic modelling is essential for the understanding of the action of a drug and is of major importance for of the establishment of an efficient therapeutical administration course. Feedback control is concededly a practice that enjoys wide acceptance in medicine (see Sopasakis and Sarimveis [2012]

and Dua et al. [2006]), though using linear integer-order pharmacokinetic models.

In this paper we employ a fractional pharmacokinetic model to describe the distribution of Amiodarone upon intravenous administration, which has proven to be very accurate when juxtaposed to actual data. Amiodarone follows anomalous, non-exponential pharmacokinetic dynamics with major clinical implications as the drug may overaccumulate in a long-term administration course. We propose the use of a fractional PID controller and we explore the dynamical characteristics of the closed-loop system.

1.2 Fractional Dynamical Systems

The most exotic property of non-integer order derivatives is that they are not *local* properties. The calculation of $(D^n f)(x_0)$ (with $n \in \mathbb{N}$) requires the knowledge of f in an arbitrarily small region around x_0, say $(x_0 - \varepsilon, x_0 + \varepsilon)$; this is not true for non-integer order derivatives $(D^a f)(x_0)$ (with $a \in \mathbb{R}$). This property proves invaluable when modeling phenomena with memory or other complex dynamics. Using fractional calculus, one obtains some peripheral vision in contrast to the local approach that ordinary derivatives offer and the process is now modeled using integro-differential equations.

Let us first define the generalised Riemann-Liouville fractional-order integral operator which extends the n-th order ($n \in \mathbb{N}$) integral I^n which is given by the Cauchy formula:

$$(I^n f)(t) = \frac{1}{(n-1)!} \int_0^t (t-\tau)^{n-1} f(\tau) \mathrm{d}\tau, \ t \geq 0. \quad (1)$$

Using the property of the Gamma function that $\Gamma(n) = (n-1)!$ for all $n \in \mathbb{N}$ we arrive at the following generalised integral of real order $\alpha \in \mathbb{R}$:

$$(I^\alpha f)(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) \mathrm{d}\tau, \ t \geq 0. \quad (2)$$

For $\alpha \in \mathbb{R}$ let us denote by $m = \lceil \alpha \rceil$ the smallest natural number m so that $m \geq \alpha$. The following operator is known as the Caputo derivative of order α:

$$(D^\alpha f)(t) = I^{m-\alpha} \frac{\mathrm{d}^m f(t)}{\mathrm{d}t^m}. \quad (3)$$

This operator enjoys a number of good properties such that it extends the integer-order derivative to arbitrary real orders, it preserves analiticity, it is a linear operator, it has the semigroup property (i.e., $D^\alpha D^\beta f = D^{\alpha+\beta} f$) and D^0 is the identity operator. It is of central importance that the Laplace transformation of the Caputo fractional derivative can be calculated by the following formula:

$$\mathcal{L}\left[D^\alpha f\right](s) = s^\alpha F(s) - \sum_{k=0}^{m-1} s^{\alpha-k-1} \left.\frac{\mathrm{d}^k f}{\mathrm{d}t^k}\right|_0, \quad (4)$$

where $F(s) = (\mathcal{L}f)(s)$.

Such generalized derivation operators give rise to the corresponding class of functional relations known as *fractional differential equations* and have the general form:

$$F(t, x, D^{\alpha_1} x, \ldots, D^{\alpha_n} x) = 0. \quad (5)$$

Dynamical systems with fractional derivatives can be represented in the following form:

$$H(D^{\alpha_1}, \ldots, D^{\alpha_n})x = T(D^{\beta_1}, \ldots, D^{\beta_m})u \quad (6)$$

where x and u stand for the output and input variables. In this paper we consider the case of *linear fractional dynamical systems*, i.e., we assume that H and T are linear functions. Linear fractional dynamical systems can be represented in the Laplace domain in terms of their tranfer functions:

$$G(s) = \frac{X(s)}{U(s)} = \frac{P(s)}{Q(s)}, \quad (7)$$

where P and Q are *fractional polynomials*, i.e., functions of the form $P(s) = \sum_{i=0}^n a_i s^{b_i}$ with $b_i > 0$ for all $i = 0, \ldots, n$, and $X(s) = (\mathcal{L}x)(s)$ and $U(s) = (\mathcal{L}u)(s)$. A very interesting fact is that the achievement of equilibrium for the output of the system (i.e., $\dot{x}(t) = 0$) does not imply that the input is also in equilibrium (i.e., $\dot{u}(t) = 0$). This, however, does not hinder us from studying the stability of such systems in the BIBO (Bounded-Input Bounded-Output) sense. To this end, let us define the *open-loop transfer function* of the system:

$$G_{\mathrm{ol}}(s) = G(s)G_{\mathrm{c}}(s), \quad (8)$$

where $G_c(s)$ is the transfer function of the controller. The *closed-loop transfer function*, which relates the set-point x^{sp} with the response x, is:

$$G_{\mathrm{cl}}(s) = \frac{G_{\mathrm{c}}(s)G(s)}{1 + G_{\mathrm{c}}(s)G(s)}. \quad (9)$$

Various stability criteria have been postulated; in this paper we shall use a Bode-type criterion which applies to G_{ol} (see Monje et al. [2010]):

Criterion 1. (BIBO Stability Criterion). Assume there exists a frequency $\omega_{\mathrm{co}} > 0$ so that $\arg G_{\mathrm{ol}}(\imath\omega_{\mathrm{co}}) = -\pi$ (This will be referred to as the *crossover frequency* of the system). If $|G_{\mathrm{ol}}(\imath\omega_{\mathrm{co}})| < 0$db, then G_{cl} is BIBO-stable.

1.3 Numerical Simulations

In certain simple cases, the solution of fractional differential equations and initial value problems can be performed analytically – usually in terms of the Mittag-Leffler special function:

$$\mathcal{E}_{a,b}(z) = \sum_{k \in \mathbb{N}} \frac{z^k}{\Gamma(ak+b)}. \quad (10)$$

For instance, it is:

$$\mathcal{L}^{-1} \frac{s^{a-b}}{s^a - \lambda} = t^{b-1} \mathcal{E}_{a,b}(\lambda t^a). \quad (11)$$

In a more general case, however, it is not possible to derive analytical expressions for the solution. Aoun et al. [2004] provide a thorough review of numerical methods for the solution of fractional differential equations. A very widespread approach consists in approximating the fractional dynamics by some integer one. The Oustaloup filter (see Oustaloup et al. [2000], Merrikh-Bayat [2012]) is a well established technique for the approximation of fractional transfer functions by integer ones in a specified range of operating frequencies.

1.4 Fractional-PID Controllers

Fractional PID controllers were introduced by Podlubny [1999] and are generalisations of the standard PID. A

fractional PID controller, or $PI^\lambda D^\mu$ has a tranfer function of the following form:

$$G_c(s) = K_p + \frac{K_i}{s^\lambda} + K_d s^\mu, \qquad (12)$$

where K_p, K_i, K_d, λ and μ are positive tuning parameters, and it produces the control action:

$$u(t) = K_p \epsilon(t) + K_i I^\lambda \epsilon(t) + K_d D^\mu \epsilon(t), \qquad (13)$$

where $\epsilon(t)$ is the *deviation* of the system's output from the set-point $x_{sp}(t)$ defined as $\epsilon(t) := x_{sp}(t) - x(t)$. A fractional PID controller involves 5 tuning parameters so it offers greater flexibility by enabling us to determine both its low and high-frequency gains. One of the most well-established methods for the tuning of fractional PID controller is the minimisation of a performance index involving the step response of the closed-loop sytem. A standard choice is the ITAE (Integral Time Absolute Error) index defined as:

$$J_{itae} := \int_0^\infty \tau \epsilon(\tau) d\tau. \qquad (14)$$

This leads to the formulation of the following optimisation problem:

$$J_{itae}^\star := \min_{K_p, K_i, K_d, \lambda, \mu} J_{itae}, \qquad (15)$$

provided that the choice of parameters leads to a stable closed-loop system. Such optimisation problems are non-convex and their numerical solution depends on the initial estimate; it is therefore recommended to try a multiplitude of initial values. Monje et al. [2010] suggest that there may be more than one acceptable parametrization.

The optimisation of the ITAE criterion can be carried out along with some additional requirements so as to guarantee certain desirable dynamical characteristics for the closed-loop. Valério and da Costa [2006] prescribe a set of 5 requirements for the tuning of fractional PID controllers which attenuate the in-loop noise and damp external noises. Noise rejection in the closed loop is guaranteed by the following condition:

$$M_h := |G_{cl}(\imath \omega_h)| < \eta, \qquad (16)$$

where ω_h is an arbitrarily chosen high frequency and η is a design parameter. We also require that there should be a crossover frequency ω_{co} and the gain margin be equal to a given value (greater than 1). What is the same we postulate a similar requirement for the phase margin. The controller has also to compensate parametric uncertainties that can be the cause of inaccurate modelling or time-varying dynamics of the controlled process. To enforce this robustness qualification we require that:

$$M_z := \frac{d}{d\omega} \arg\left(G_{ol}(\imath \omega)\right)\Big|_{\omega = \omega_{co}} < \zeta, \qquad (17)$$

where $\zeta > 0$ is a design parameter. Finally, the closed-loop system has to compensate for output disturbances, which are in principle of low frequency (see Åström [2002]). To this end, we require that the sensitivity function of the system, defined as

$$G_{sens}(s) := \frac{1}{1 + G_{ol}(s)}, \qquad (18)$$

exhibit low gain at low frequencies, i.e.,

$$M_\ell := |G_{sens}(\imath \omega_\ell)| < \vartheta \qquad (19)$$

where ω_ℓ is some, arbitrarily chosen, low frequency and ϑ is a properly small design parameter.

Table 1. PK Parameters of Amiodarone

Parameter	Value
a	0.5870
k_{10}	1.4913day^{-1}
k_{12}	2.9522day^{-1}
k_{21}	0.4854day^{-a}

These requirements need to be taken into account while tuning a fractional PID controller. This way, the optimisation problem (15) is solved subject to the nonlinear constraints (16) to (19).

2. FEEDBACK CONTROL OF AMIODARONE ADMINISTRATION

Amiodarone is an antiarrhythmic agent (see Kühlkamp et al. [1999]) which can be administered either intravenously (*i.v.*) or orally. Amiodarone is well-known for its highly nonlinear non-exponential dynamics and singular long-term accumulation pattern. Recently, Dokoumetzidis et al. [2010a] modelled the pharmacokinetic distribution of Amiodarone with a fractional compartmental model following a single *i.v.* and a single oral dose. The compartmental topology of the model is presented in Figure 1.

Let A_1 and A_2 be the amounts of Amiodarone (in ng) in the plasma and the tissues respectively and u be the administration rate (in ng/day). We assume that the drug is administered directly into the central (plasma) compartment while the control objective is the concentration of the drug in the tissues attains a prescribed value (set-point). The fractional dynamical model we employ reads as follows:

$$\frac{dA_1}{dt} = -(k_{12} + k_{10})A_1 + k_{21} \cdot D^{1-a}A_2 + u, \qquad (20a)$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21} \cdot D^{1-a}A_2, \qquad (20b)$$

with $a < 1$. The terms "$k_{21} \cdot D^{1-a}A_2$" correspond to the fractional-order diffusion of Amiodarone from the tissues to the central compartment, the term "$k_{12}A_1$" is the rate at which Amiodarone is transfered from the central compartment to the tissues and "$k_{10}A_1$" defines the excretion rate. This dynamics is graphically presented in Fig. 1. The parameters of the aforementioned model are presented in Table 1. The transfer function of the system which links the administration rate $U(s) = \mathcal{L}u(t)$ to the concentration of Amiodarone in the tissues $\hat{A}_2(s) = \mathcal{L}A_2(t)$ is:

$$G(s) = \frac{\frac{1}{k_{10}}\left(\frac{1}{k_{21}}s^a + 1\right)}{\frac{1}{k_{10}k_{21}}s^{a+1} + \frac{1}{k_{10}}s + \frac{k_{10}+k_{12}}{k_{10}k_{21}}s^a + 1} \qquad (21)$$

Before the commencement of the administration course we assume that the initial concentration of Amiodarone in the organism is zero, i.e., $A_1(t) = A_2(t) = 0$ for all $t \leq 0$.

We tuned a fractional PID controller for the control of the concentration of Amiodarone in the central compartment the parameters of which were chosen using the ITAE criterion along with the additional constraints outlined above. We chose the characteristic frequencies $\omega_\ell = 0.01 \text{rad/day}$, and $\omega_h = 100 \text{rad/day}$ and required that $\vartheta = -10 \text{db}$, $\eta = -20 \text{db}$ and we also imposed the robustness requirement

Table 2. Optimal Tuning Parameters

Parameter	Value
K_p	50.5197
K_i	151.0551
K_d	0.0756
λ	0.9170
μ	0.7590

$\zeta = 1\text{deg} \cdot \text{rad}^{-1} \cdot \text{day}$. The optimal tuning parameters of the fractional controller are given in Table 2. The optimal value of J_{itae} following the excitation of the system with a step pulse of amplitude $x^{\text{sp}} = +0.1$ was found to be $3.9713 \cdot 10^{-4}$ng. Using the Bode diagram of G_{ol} shown in Fig 4
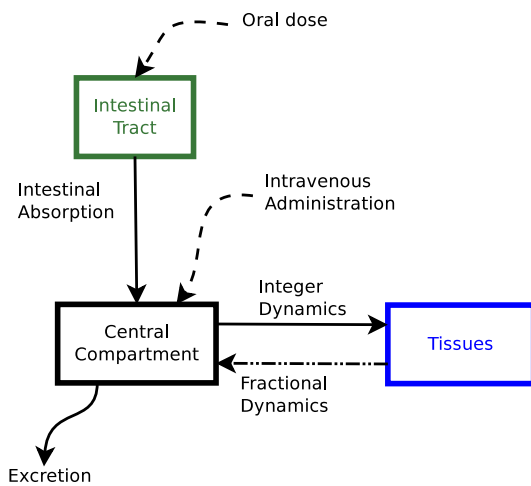
Fig. 1. Topology of the pharmacokinetic system used for the derivation of the pharmacokinetic model (20).
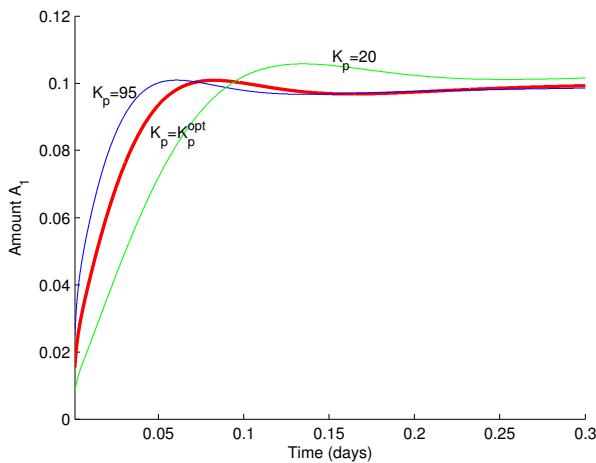

Fig. 2. Step-response of the closed-loop system for a change of the set-point by $+0.1$ for various values of K_p. The thick red line corresponds to the optimal value $K_p^\star = 50.52$. The amount of Amiodarone is in ng.

we calculated the phase and gain margins of the closed loop as well as the crossover frequency. A gain margin as high as 43.9db should be considered excellent and implies that the closed loop will remain stable even in presence of delay element as it is well away from instability. We may
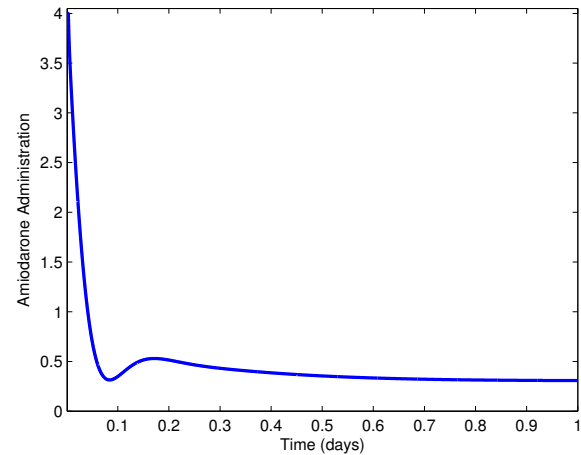

Fig. 3. The control action produced by the optimally tuned fractional controller. The administration rate is in ng/day.
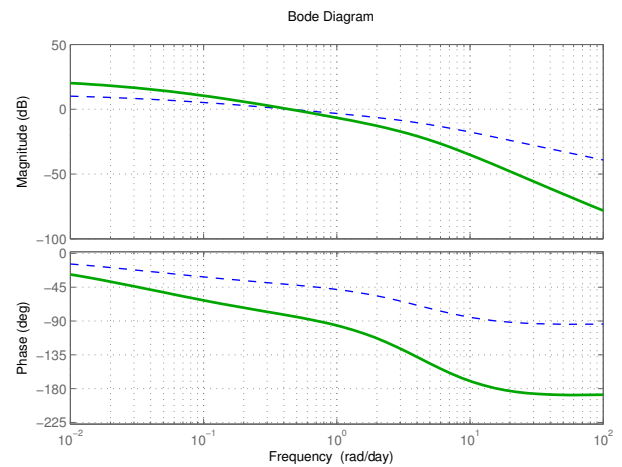

Fig. 4. Bode diagram: The blue dashed line corresponds to the pharmacokinetic system and the thick green solid line to the open-loop system in presence of the optimally tuned $\text{PI}^\lambda\text{D}^\mu$ controller. The phase margin is 98° and the gain margin is 43.9db. The crossover frequency is 16rad/day. It was found that $M_z = 0.5\text{deg} \cdot \text{rad}^{-1} \cdot \text{day}$

draw the same conclusion observing the high phase margin of 98°. The phase margin translates into the maximum delay that the closed-loop can take remaining stable; this is calculated by the formula:

$$\tau_{d,\max} = \frac{M_p}{\omega_1} = 3.37\text{day} \qquad (22)$$

where $\omega_1 = 0.43\text{rad/day}$ is the frequency at which $|G_{\text{ol}}(\imath\omega_1)| = 0$db and M_p is the phase margin in rad.

As one can see in Fig. 5, the closed-loop transfer function exhibits very low gain (<-60db) at high frequencies ($>\omega_h$), thus filtering out high-frequency noise signals in the closed loop and/or noise that comes with the set-point. Despite of the quite high values of the stability margins, the system responds satisfactorily fast. Due to the high gain margin, we can increase the controller's gain so as
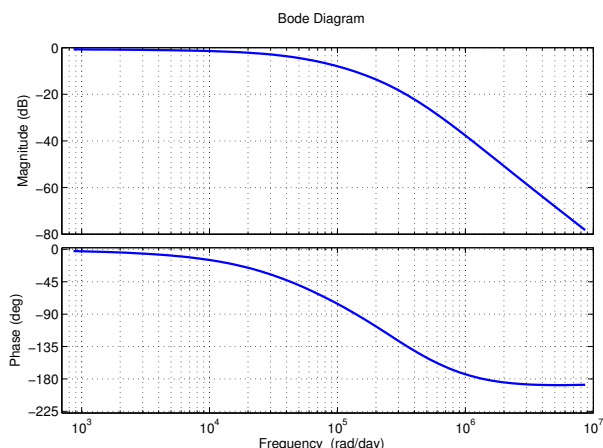
Bode Diagram

Fig. 5. Bode diagram of the closed-loop transfer function. Note that at high frequencies the gain is lower than -60db, thus, the controller attenuates the high-frequency noise in the closed-loop or possible noise that comes with x^{sp}.
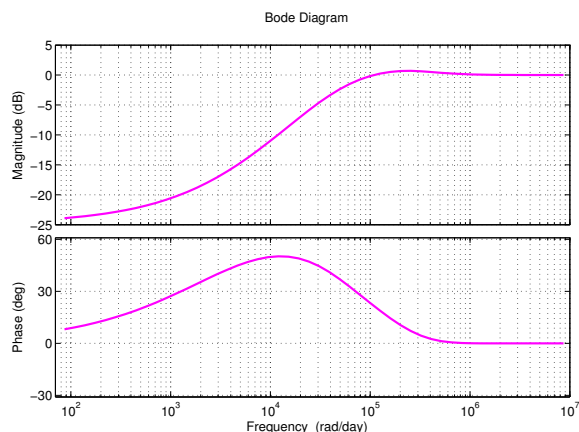
Bode Diagram

Fig. 6. Bode diagram of the sensitivity function of the system.

to obtain faster responses at the cost of a higher ITAE value. The sensitivity function of the system exhibits low gain (lower than -20db) at low frequencies as one can see in Fig. 6 which, in turn, implies that the system can attenuate output disturbacens.

All time-domain simulations were performed using an Oustaloup filter in the frequency range $10^{-3} \sim 10^3$rad/day. For the frequency-domain calculations no approximation was necessary.

3. CONCLUSION

Fractional Systems theory enables us to model nonlinear processes with (infinite) memory such as anomalous diffusion and deep tissue trapping and presents great perspectives for pharmacokinetic modelling. Such systems can be used for the formulation of control problems where the goal is to maintain a constant drug concentration in a tissue of organ of the body.

In this paper we designed a fractional-order $PI^\lambda D^\mu$-type controller for the stabilisation of the concentration of Amiodarone whose pharmacokinetic distribution in the organism is described by a fractional-order model and we presented closed-loop simulations. The designed controller not only has a high gain margin but also exhibits excellent behaviour with respect to noise rejection in the closed loops and attenuation of externally applied disturbances. The proposed control approach is a good candidate for the control of other drugs that follow such fractional-order dynamics such as Mibefradil (Fuite et al. [2002]) or Diclofenac (Popović et al. [2010]).

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