Progress in Fractional Differentiation and Applications
An International Journal

http://dx.doi.org/10.18576/pfda/080103

The Drug Administration via Fractional-order $PI^{\lambda}D^{\delta}$-Controller

Reyad El-Khazali[1,*], *Iqbal M. Batiha*[2,3] *and Shaher Momani*[3,4]

[1]ECSE Department, Khalifa University, Abu-Dhabi, UAE
[2]Department of Mathematics, Faculty of Science and Technology, Irbid National University, 2600 Irbid, Jordan
[3]Nonlinear Dynamics Research Center (NDRC), Ajman University, Ajman 346, UAE
[4]Department of Mathematics, Faculty of Science, The University of Jordan, Amman 11942, Jordan

Received: 2 Mar. 2020, Revised: 10 Jul. 2020, Accepted: 12 Jul. 2020
Published online: 1 Jan. 2022

Abstract: Amiodarone is a commonly used antiarrhythmic drug which may induce pulmonary toxicity. To achieve high quality medical treatment, it is necessary to supervise a well-controlled medical protocol to avoid anomalies in such a drug and in any similar one. This work proposes the use of a fractional-order $PI^{\lambda}D^{\delta}$ controllers to maintain a consistent pharmacokinetics for drug administration. The additional fractional-order parameters, $0 < \lambda, \delta \leq 1$, which provide additional features to such controller, are determined using the Particle Swarm Optimization (PSO) algorithm. This is accomplished by approximating $s^{-\lambda}$ or s^{δ} by 1^{st}- or 2^{nd}-order rational transfer functions to minimize the ITAE, IAE, ISE, and ITSE error functions. The study includes a comparison between Oustaloup's and El-Khazalis' approximations to show the effectiveness and the cost of each controller design. All results are verified via numerical simulations.

Keywords: Fractional-order pharmacokinetic model for Amiodarone, $PI^{\lambda}D^{\delta}$-controller, particle swarm optimization algorithm, Laplacian operator, Oustaloup's and El-Khazali's approximation.

1 Introduction

Many applications in our real-life have been developed based on integer-order differential equations. Such applications and many complex phenomena, such as viscoelastic material, biological membrane, biomedical and electrochemical processes, have been accurately modeled and well established using fractional calculus, see [1]. In this field, it is necessary to know when and how we can fractionalize these classic applications. For example, an ordinary differential equation can be easily fractionalised by replacing a suitable fractional-order derivative instead of its integer counterpart. In general, modeling by the fractional calculus can describe several ordinary calculus phenomena in an efficient way. Recently, the fractional calculus was well utilized to introduce the pharmacokinetics (PK) model in its new fractional dynamic form [2]. Consequently, several researchers have handled this subject in a significant number of publications (see e.g. [3,4,5]). The mass balance equation of Physiologically Based Pharmacokinetics Models (PBPK) is well described by fractional-order dynamics [2,3]. It allows one to understand the interplay of the main factors of the drug distribution, identifies its concentration time profile, and explores the drug interactions [3]. All these points effectively contribute to understand the action of the drug which implies an efficient treatment and effective administration.

In medical fields, the implementations of the control theory have been widely accepted for many linear models, (see e.g. [3,6]). In particular, the drug administration problem can be considered as a control problem. This is due to the need of having precise and accurate composition of drugs. In fact, the aim of such process is to keep the drug concentration at specific organs in the body. This concentration must be close to the wished therapeutically setpoints, while the concentration in the other organs and tissues does not overrun safety limits [3,7]. However, the administered dosage is considered as a manipulated variable in PK model, while the concentration of the drug in some organs of the body is considered as the controlled variable [3]. In [2], Dokometzidis et al. have proposed a PK distribution for the Amiodarone

* Corresponding author e-mail: reyad.elkhazali@ku.ac.ae

drug that enjoys a fractional-order dynamics by following a single intravenous single oral dose. Sopasakis et al. have proposed the same model for the Amiodarone drug intravenous administration, and used a fractional-order PID ($PI^{\lambda}D^{\delta}$) controller that shows juxtaposed accuracy with actual data [3].

To improve the efficacy of the PK model, a robust control system is proposed here and carried out using the PSO algorithm. The objective is to optimize the five parameters of the $PI^{\lambda}D^{\delta}$ controller (K_p, K_i, K_d, λ, and δ) using the minimum order realization of such fractional-order dynamics. This is accomplished by replacing $s^{\pm\alpha}$ by either a 1^{st}- or 2^{nd}-order rational transfer function of order $\alpha \in (0,1]$, i.e. $s^{\pm\alpha} = N(s,\alpha)/D(s,\alpha)$ [8].

This paper is organized as follows: Basic concepts and background is presented in the next section. A brief overview of the fractional-order PK model for Amiodarone is presented in Section III, while some basic preliminaries of the $PI^{\lambda}D^{\delta}$-controller are presented in Section IV. Section V introduces some optimum $PI^{\lambda}D^{\delta}$ -controllers, followed by Section VI that presents some comparisons of numerical simulation of the results. Section VII is devoted to conclusion.

2 Fractional-order models

Linear systems with hereditary effect are described by fractional-order dynamics [9]. Integer-order systems, however, are a subset of the fractional-order ones. Moreover, fractional-order controllers outperform their integer-order counterparts [9,10,11] due to the increase in the controlled system bandwidth, and the flexibility in choosing its parameters. The fractional-order LTI (FoLTI) systems that are considered in this work are described by the following fractional-order differential equation [9]:

$$a_n D^{\alpha_n} y(t) + \ldots + a_0 D^{\alpha_0} y(t) = b_m D^{\beta_m} u(t) + \ldots + b_0 D^{\beta_0} u(t) \tag{1}$$

where $u(t)$ and $y(t)$ are, respectively, the control and output variables, and D^{α_k} (or D^{β_ℓ}) denotes the Cuputo's differential operator for different incommensurate fractional orders, $\alpha_k; k = 1,2,3,\ldots,n$, and $l = 1,2,3,\ldots,m$, for arbitrary constants $n, m \in \mathbb{N}$.

System (1) is said to be of commensurate order if all its fractional orders are multiples of rational number $p/q \equiv k_q$, $q \in \mathbb{N}$. The system is then described as [12]:

$$\sum_{k=0}^{n} a_k D^{k_q} y(t) = \sum_{k=0}^{m} b_k D^{k_q} u(t) \tag{2}$$

Clearly, if one takes $p/q = 1/n$, where $n > 1$, then (2) defines systems of commensurate fractional orders. Since fractional-order linear time-invariant (FoLTI) systems enjoy hereditary effect; i.e, of infinite dimensions, one may approximate such systems with realizable finite-order rational transfer functions that exhibit almost the same frequency response of the original system within the desired bandwidth of the rational approximation [13]. The input-output relationships of LTI systems are defined by:

The frequency response of systems is usually carried out using transfer functions. The transfer function of a LTI system is defined as the ratio of the Laplace transform of the output (system output response) to the Laplace transform of the input (system input) under the assumption that all initial conditions are zero [13], i.e.

$$G(s) = \frac{\mathscr{L}(\text{output})}{\mathscr{L}(\text{input})}\bigg|_{\text{zero initial conditions}} = \frac{Y(s)}{U(s)} \tag{3}$$

A typical form of FoLTI system (1) can be described by the following transfer function [13]:

$$G(s) = \frac{b_m s^{\beta_m} + b_{m-1} s^{\beta_{m-1}} + \ldots + b_1 s^{\beta_1} + b_0 s^{\beta_0}}{a_n s^{\alpha_n} + a_{n-1} s^{\alpha_{n-1}} + \ldots + a_1 s^{\alpha_1} + a_0 s^{\alpha_0}} \tag{4}$$

3 The PK model for Amiodarone

Amiodarone, which is an antiarrhythmic drug, has many significant clinical implications because of its singularity in a long-term accumulation pattern, and its highly nonlinear non-exponential dynamics [2,3]. Such drug can be administered either intravenously or orally. In [2], a PK model for this drug has been proposed considering a fractional compartmental model based on a single intravenous and a single oral dose [2,3]. Sopasakis et al. in [3] supposed a direct administration of the drug into the central compartment (plasma). They also assumed that the control objective is the concentration of the drug in the target tissues or organs. Anyhow, the fractional-order PK model for Amiodarone has the following form [2,3]:

$$\frac{dA_1}{dt} = -(k_{12}+k_{10})A_1 + k_{21}.D^{1-\alpha}A_2 + u$$
$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}.D^{1-\alpha}A_2 \tag{5}$$

where A_1 and A_2 are the amounts of Amiodarone [ng] in the plasma and the tissues respectively, u is the administration rate [ng/day], $\alpha \in (0,1)$, and k_{10}, k_{12} and k_{21} are the parameters of the model. In fact, $k_{21}D^{1-\alpha}A_2$ defines the fractional-order diffusion of Amiodarone from the tissues to the central compartment, $k_{12}A_1$ represents the rate at which Amiodarone is transferred from the plasma to the tissues, and $k_{10}A_1$ is the excretion rate [3]. Typical values of the model's parameters are presented in Table I [3]. Now, taking Laplace transform to (5) yields the following transfer function:

$$G(s) = \frac{U(s)}{\mathscr{L}(A_2(t))} = \frac{\frac{1}{k_{10}}\left(\frac{1}{k_{21}}s^{\alpha}+1\right)}{\frac{1}{k_{10}k_{21}}s^{\alpha+1} + \frac{1}{k_{10}}s + \frac{k_{10}+k_{12}}{k_{10}k_{21}}s^{\alpha}+1} \tag{6}$$

where $U(s)$ is the Laplace transform of the administration rate, $\mathscr{L}(u(t))$, and $\mathscr{L}(A_2(t))$ is the Laplace transform of the concentration of Amiodarone in the tissues.

Table 1: Parameters of the PK model for Amiodarone

Parameter	Value
α	0.5870
k_{10}	1.4913
k_{12}	2.9522
k_{21}	0.4854

One can use, respectively, the following El-Khazali's 1^{st}- and 2^{nd}-order approximations of s^{α} given in [14,15,16], where $\alpha = 0.5870$;

$$s^{0.5870} = \frac{2.974s+1}{s+2.974} \tag{7}$$

and

$$s^{0.5870} = \frac{2.905s^2+4.727s+0.5575}{0.5575s^2+4.727s+2.905} \tag{8}$$

Substituting both (7) and (8) into (6) yields two different transfer functions, $G_1(s)$ that corresponds to the 1^{st}-order El-Khazali's approach, and $G_2(s)$ that corresponds to the 2^{nd}-order El-Khazali's approach; i.e.

$$G_1(s) = \frac{s+0.7064}{s^2+4.736s+1.907} \tag{9}$$

$$G_2(s) = \frac{s^2+2.211s+0.6196}{s^3+6.403s^2+8.311s+1.442} \tag{10}$$

Observe that such two transfer functions represent two approximations for the plant of the fractional-order PK model constructed for Amiodarone under the given values of the parameters. Later on, we will introduce robust techniques to tune the $PI^{\lambda}D^{\delta}$-controller for these models.

4 $PI^{\lambda}D^{\delta}$-controller

The concept of $PI^{\lambda}D^{\delta}$-controller was introduced by Podlubny in [9,17]. Recently, this controller has been used for many industrial applications to improve systems' performance. It provides extra degrees of freedom by adding two more parameters (λ and δ) to the original three parameters, (K_p, K_i, K_d), and so increasing the complexity of tuning its parameters [9]. The fractional-order integro-differential equation that describes the $PI^{\lambda}D^{\delta}$ controllers is given by [9,18, 19]:

$$u(t) = K_p e(t) + K_i J^{\lambda} e(t) + K_d D^{\delta} e(t), \tag{11}$$

where J^{λ} is the Riemann-Liouville operator of order λ, and D^{δ} is the Caputo operator of order δ. The Laplace transform of (11) is given by:

$$C(s) = \frac{U(s)}{E(s)} = K_p + K_i s^{-\lambda} + K_d s^{\delta}. \tag{12}$$

However, the closed-loop system for the fractional-order PK model for Amiodarone with unity feedback is shown in Figure 1.

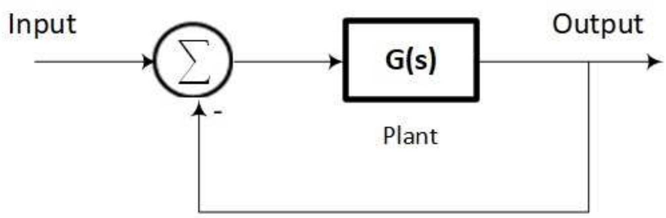

Fig. 1: Closed-loop uncontrolled system

In Figure 2, the variable e is the tracking error which represents the difference between the desired input value r and the actual output, the transfer functions $G_i(s)$, given in (9) and (10), $i = 1,2$, represent the plant of the model.

In this work, the $PI^{\lambda}D^{\delta}$-controller will be taken along with the fractional-order PK model for Amiodarone. This means that we will try to optimize the system performance under consideration to improve its unit-step response. This optimization will be done by employing the PSO algorithm using El-Khazali's approximations. For a complete description of the PSO algorithm, one may find more details in [19] and its references.

To improve the performance of the controlled system one has to minimize the error, $e(t)$, which is the difference between the desired and the actual system outputs [19]. To appreciate the different tuning mechanisms, one could minimize several error functions, such as ITAE, IAE, ISE, and ITSE, to generate the best set of parameters for the desired $PI^{\lambda}D^{\delta}$ controller. These error functions are listed here for completeness:

–Integral Square Error (ISE)

$$ISE = \int_0^{\infty} e^2(t)dt. \tag{13}$$

–Integral Time-Absolute Error (ITAE)

$$ITAE = \int_0^{\infty} t|e(t)|dt. \tag{14}$$

–Integral Absolute Error (IAE)

$$IAE = \int_0^{\infty} |e(t)|dt. \tag{15}$$

–Integral Time Square Error (ITSE)

$$ITSE = \int_0^{\infty} te^2(t)dt. \tag{16}$$

5 Optimum $PI^{\lambda}D^{\delta}$-controller

To illustrate the proposed design technique of the $PI^{\lambda}D^{\delta}$-controller, let us return to the two transfer functions $G_1(s)$ and $G_2(s)$ given in (9) and (10), respectively, which yield two different approximations for the fractional-order PK Amiodarone model. Hence, it is required to find the optimal parameters of the $PI^{\lambda}D^{\delta}$-controller (K_p, K_i, K_d, λ and δ). Such parameters will minimize the four types of the performance indices, ITAE, IAE, ISE and ITSE.

The PSO algorithm is initialized by taking a population size of 20, and the maximum number of iterations is 50. Furthermore, let us assume the following search spaces for every parameter of the $PI^{\lambda}D^{\delta}$-controller:

$$0 < K_p,\ K_i,\ K_d < 50, \quad 0 < \lambda,\ \delta < 1 \tag{17}$$

The PSO algorithm is carried out using the two approaches of El-Khazali's approximations, and the two approximated forms of the PK models $G_1(s)$ and $G_2(s)$ given by (9) and (10), respectively. Two sets of optimum parameters that correspond to these two functions have been then obtained. Each set consists of the required five parameters (K_p, K_i, K_d, λ and δ), and forms two $PI^{\lambda}D^{\delta}$-controllers; $C_1(s)$ and $C_2(s)$, which correspond to El-Khazalis' 1^{st}- and 2^{nd}-order approximations.

For more insight about such two controllers $C_1(s)$ and $C_2(s)$, we have found that the corresponding optimum parameters when developing $C_1(s)$ are $K_p = 45.23$, $K_i = 49.82$, and $K_d = 35.87$ with $\lambda = 0.792$, and $\delta = 0.106$, while the optimal parameters of $C_2(s)$ are $K_p = 18.4563$, $K_i = 49.39$, and $K_d = 0.1$ with $\lambda = 0.90659$, and $\delta = 0.210$. In other words,

$$C_1(s) = 45.23 + \frac{49.82}{s^{0.792}} + 35.87s^{0.106} \tag{18}$$

and

$$C_2(s) = 18.4563 + \frac{49.39}{s^{0.90659}} + 0.1s^{0.210}. \tag{19}$$

One remark should be made here, all optimum parameters of the above two controllers have been tuned by including the ITAE index through PSO algorithm for a reason that will be stated in Section VI. Both $s^{0.792}$ and $s^{0.106}$ in (18) have been approximated using the 1^{st}-order El-Khazali's approach, and similarly for both $s^{0.90659}$ and $s^{0.210}$ in (19) that have been approximated using the 2^{nd}-order El-Khazali's approach. All these approximations should be then substituted in both controllers; $C_1(s)$ and $C_2(s)$ to yield the following integer-order structures of the two controllers, perspectively:

$$C_{1_i}(s) = \frac{95.84s^2 + 163.3s + 73.65}{s^2 + 1.347s + 0.1949} \tag{20}$$

and

$$C_{2_i}(s) = \frac{19.97s^4 + 153.9s^3 + 379.7s^2 + 319.5s + 82.11}{s^4 + 5.006s^3 + 6.046s^2 + 1.961s + 0.04494} \tag{21}$$

In reference [3], P. Sopasakis et al. designed a $PI^{\lambda}D^{\delta}$-controller (denoted here by $C_3(s)$) to regulate the dynamic behavior of the system at hand. Its optimal tuning parameters were found to be: $K_p = 50.5197$, $K_i = 151.0551$, and $K_d = 0.0756$ with $\lambda = 0.9170$, and $\delta = 0.7590$. That is,

$$C_3(s) = 50.5197 + \frac{151.0551}{s^{0.9170}} + 0.0756s^{0.7590} \tag{22}$$

However, they did not use any of well-known approaches such as Oustaloup's, Matsuda's and Carlson's approaches to approximate the Laplacian operators $s^{0.5870}$, $s^{0.9170}$ nor $s^{0.7590}$ that are given in (22) (see [8,20]). From this perspective, we find a needed motivation for employing one of these approaches to obtain suitable integer-order approximations for such operators, and then perform some numerical comparisons between the results of this work and Oustaloup's approach (One of most popular approaches) through reference [3]. For implementing this task, $s^{0.5870}$, given by (6), is first approximated using Oustaloup's approach to formulate an integer-order PK model.

Since a 1^{st}-order Oustaloup approximation to $s^{0.587} \approx (57.68s+1)/(s+57.68)$; $0.01 \leq \omega \leq 100\ rad/s$, yields a large phase error of 35° at $\omega_c = 1\ rad/s$, then it is necessary to jump to the next 3^{rd}-order Oustaloup's approximation to present a fair comparison with the 2^{nd}-order El-Khazali's approximation (10), i.e.

$$s^{0.587} = \frac{57.68s^3 + 1508s^2 + 390.3s + 1}{s^3 + 390.3s^2 + 1508s + 57.68} \tag{23}$$

Now, substituting from (23) into (6) yields the following minimum 8^{th}-order approximation to the PK model after removing the common poles and zeros:

$$G_3(s) = \frac{s^7 + 809.7s^6 + 1.781e05s^5 + 5.712e06s^4 + 3.923e07s^3 + 8.76e07s^2 + 4.359e07s + 1.111e06}{s^8 + 814.1s^7 + 1.817e05s^6 + 6.492e06s^5 + 6.306e07s^4 + 2.449e08s^3 + 3.679e08s^2 + 1.103e08s + 1.77e06} \tag{24}$$

One may use El-Khazali 1^{st}- and 2^{nd}-order approximations, and Oustaloup's approximation to replace $s^{0.917}$ and $s^{0.759}$ in (22), and so generating three different forms of integer-order controllers for (22). Figure 2 shows the unit-step response of the PK model using its integer-order representations given by $G_1(s)$, $G_2(s)$, and $G_3(s)$.

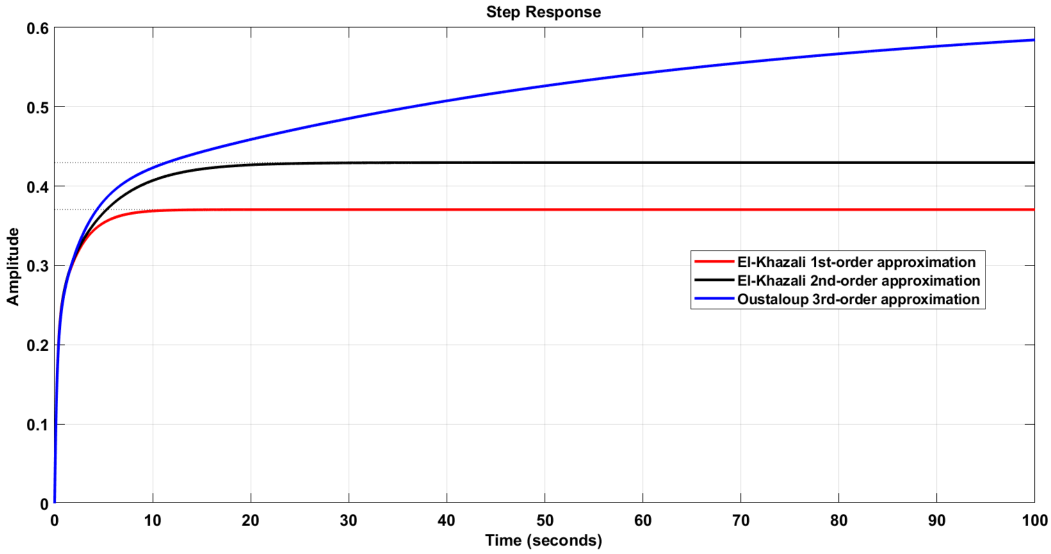

Fig. 2: Unit-step response of uncontrolled system

Obviously, the uncontrolled system output does not reach its expected reference input. Furthermore, using Oustaloup's 3^{rd}-order approximations of $s^{0.917}$ and $s^{0.759}$, the $PI^{0.917}D^{0.759}$ controller given by (22) takes the following equivalent integer-order form:

Hence, for comparison purposes, using 3^{rd}-order Oustaloup's approximation to (22) yields:

$$C_{3_i}(s) = \frac{\begin{array}{c}3.669e04s^6+1.732e07s^5+3.732e08s^4+2.213e09s^3\\+3.746e09s^2+4.886e08s+1.612e07\end{array}}{\begin{array}{c}563.6s^6+3.338e05s^5+5.874e06s^4+2.354e07s^3\\+4.083e06s^2+1.612e05s+189.2\end{array}} \tag{25}$$

The order reduction in the plant models given by (9) and (10) over (24) is obvious. This also led to a reduced-order controllers given by (20) and (21) compared to that of (25).

6 Numerical simulation

When minimizing the four object functions, ITAE, IAE, ISE, and ITSE, the step-response of the controlled system is investigated using the different forms of controllers and model transfer functions as depicted in Figure (3). When using (9) and (20), the numerical results of the closed-loop transfer function $T_1(s) = C_{1_i}(s)G_1(s)/(1+C_{1_i}(s)G_1(s))$ is depicted in Figure (4) and Table II. Similarly, when using (10) and (21), the results of its step response are shown in Figure (5) and Table III. The same numerical results when using (24) and (25) to form $T_3(s) = C_{3_i}(s)G_3(s)/(1+C_{3_i}(s)G_3(s))$ are shown in Figure (6) and Table IV.

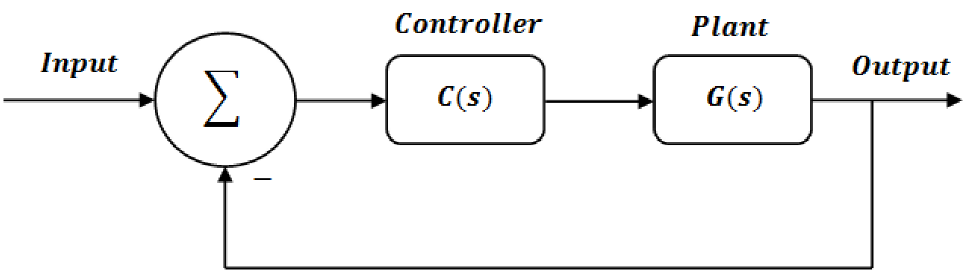

Fig. 3: Closed-loop controlled system

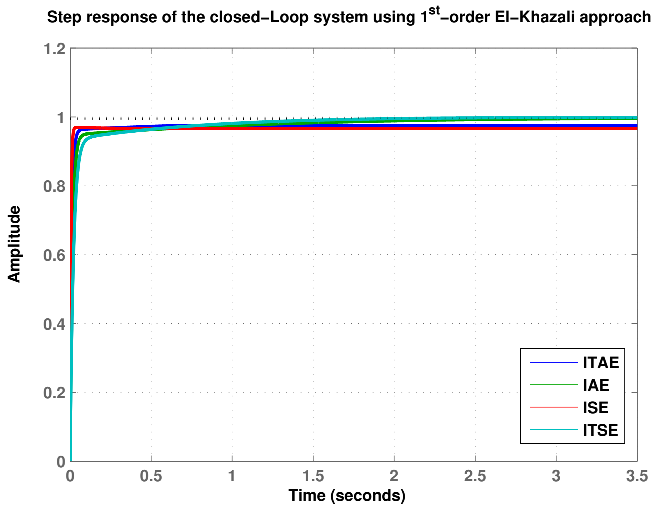

Fig. 4: The closed-loop system $T_1(s)$ with respect to the four performance indices

Table 2: Step response specifications of $T_1(s)$ with respect to the four performance indices

Step Response	ITAE	IAE	ISE	ITSE
Rise Time	0.0253	0.0391	0.0118	0.0621
Settling Time	0.5280	1.0631	1.0019	0.8477
Settling Min.	0.8976	0.8990	0.9024	0.8988
Settling Max.	0.9753	0.9965	0.9699	0.9983
Overshoot	0.0000	0.0480	0.0000	0.1272
Peak	0.9753	0.9965	0.9699	0.9983
Peak Time	0.6702	3.8659	0.0446	2.9422

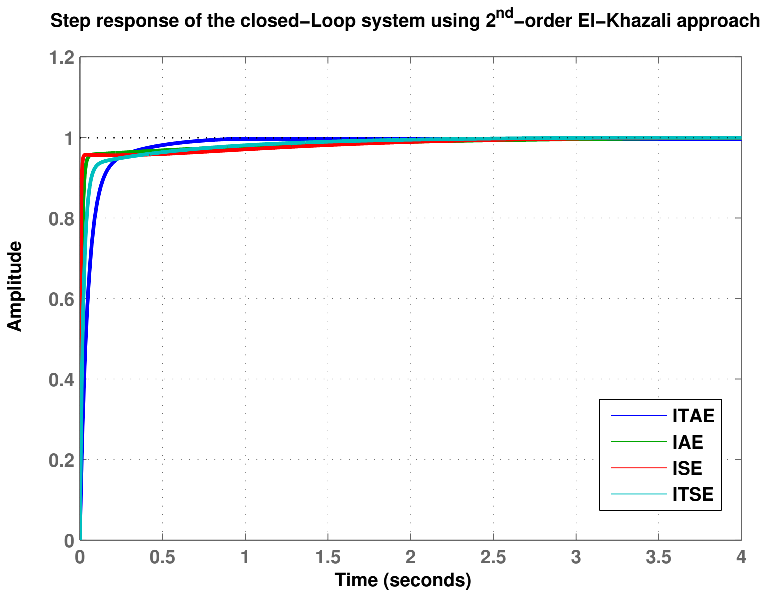

Fig. 5: The closed-loop system $T_2(s)$ with respect to the four performance indices

Table 3: Step response specifications of $T_2(s)$ with respect to the four performance indices

Step Response	ITAE	IAE	ISE	ITSE
Rise Time	0.1377	0.0273	0.0114	0.0667
Settling Time	0.4674	1.1596	1.3590	0.9372
Settling Min.	0.9007	0.9001	0.9098	0.8997
Settling Max.	0.9957	0.9999	0.9994	0.9994
Overshoot	0.0000	0.0159	0.1027	0.0541
Peak	0.9957	0.9999	0.9994	0.9994
Peak Time	0.8905	4.5262	3.6543	3.2528

For compactness, the closed-loop transfer functions of $T_1(s)$, $T_2(s)$, and $T_3(s)$ are respectively given by (26), (27), and (28).

$$T_1(s) = \frac{95.84s^3 + 231s^2 + 189s + 52.03}{s^4 + 101.9s^3 + 239.5s^2 + 192.5s + 52.4} \tag{26}$$

$$T_2(s) = \frac{\begin{array}{c}19.97s^6+198.1s^5+732.3s^4+1254s^3\\+1024s^2+379.5s+50.88\end{array}}{\begin{array}{c}s^7+31.37s^6+244.4s^5+816s^4+1324s^3\\+1049s^2+382.7s+50.94\end{array}} \tag{27}$$

$$T_3(s) = \frac{\begin{array}{c}3.669e04s^{13}+4.702e07s^{12}+2.093e10s^{11}+3.598e12s^{10}\\+1.686e14s^9+3.211e15s^8+2.947e16s^7+1.418e17s^6\\+3.599e17s^5+4.443e17s^4+2.092e17s^3\\+2.687e16s^2+1.246e15s+1.791e13\end{array}}{\begin{array}{c}563.6s^{14}+8.293e05s^{13}+4.27e08s^{12}+9.002e10s^{11}\\+6.886e12s^{10}+2.322e14s^9+3.817e15s^8+3.254e16s^7\\+1.5e17s^6+3.702e17s^5+4.484e17s^4+2.097e17s^3\\+2.69e16s^2+1.246e15s+1.791e13\end{array}} \tag{28}$$

A closer look to the above figures and tables shows that the ITAE one has more ability than others to provide the closed-loop response with minimal overshoot and fast settling time. However, we find that it does not give us a fast rise time compared to the others. Generally, one may conclude that the ITAE index satisfies excellent results, and we would like here to choose it out of all indices to get us optimal parameters of $C_1(s)$ and $C_2(s)$ corresponding to both $G_1(s)$ and $G_2(s)$, respectively.

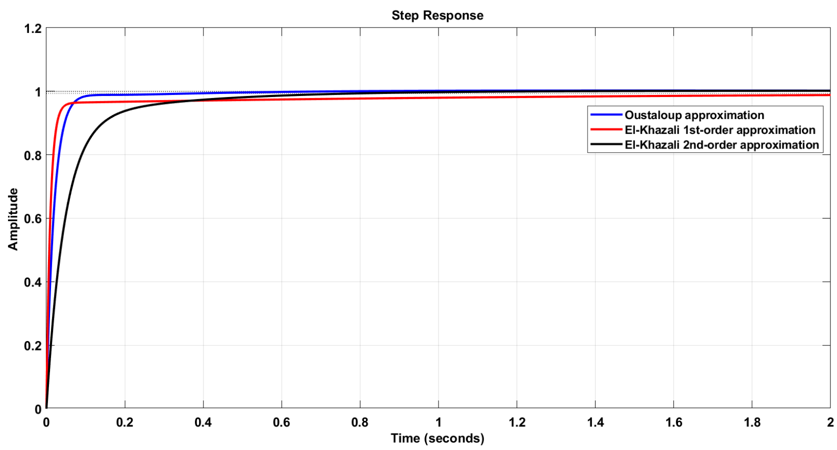

Fig. 6: A comparison between $T_1(s)$, $T_2(s)$ and $T_3(s)$

Table 4: Step response specifications of $T_1(s)$, $T_2(s)$ and $T_3(s)$

Step Response	$T_1(s)$	$T_2(s)$	$T_3(s)$
Rise Time	0.0252	0.1377	0.0529
Settling Time	0.5280	0.4674	0.1232
Settling Min.	0.8976	0.9007	0.9009
Settling Max.	0.9753	0.9957	1.0051
Overshoot	0.0000	0.0000	0.5315
Peak	0.9753	0.9957	1.0051
Peak Time	0.6702	0.8906	0.2846

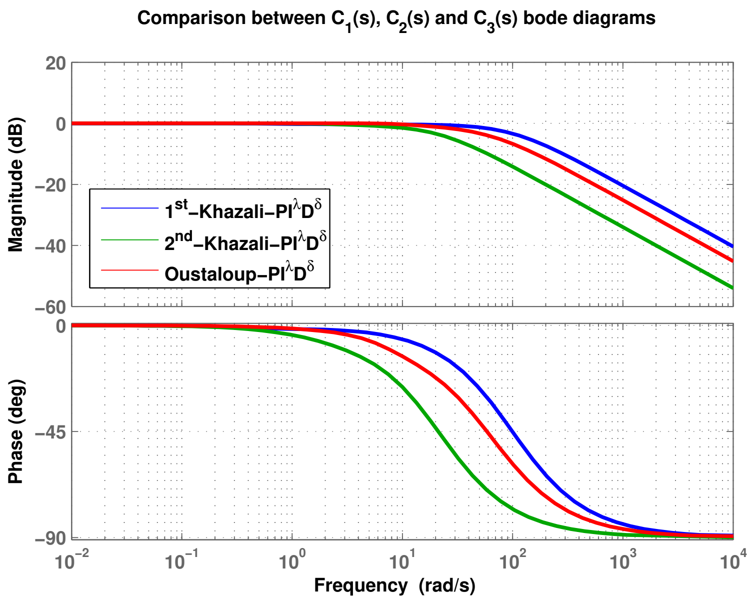

Fig. 7: A Comparison of the bode diagrams between $T_1(s)$, $T_2(s)$ and $T_3(s)$

Based on the above results, one can deduce that all three controllers are fiercely competing in providing the closed-loop system response specifications with a best performance. In particular, $C_1(s)$ and $C_2(s)$ demonstrate a higher efficacy than the third one in providing the closed-loop system with minimal overshoot, although the settling time is slightly higher in both of them than the settling time in $C_3(s)$. Regarding the rise time, one might observe that the first controller, $C_1(s)$, returns back again to show itself as the best.

7 Conclusion

Three robust $PI^{\lambda}D^{\delta}$-controllers based on PSO algorithm via El-Khazali's and Oustaloup's approximations have been designed for controlling the concentration of Amiodarone drug level, which is described by a fractional-order pharmacokinetic model. These designs have been proposed to satisfy set of time and frequency domain constraints, such as overshoot, rise time, and settling time. The different types of approximations affected the size and the complexity of the controller dynamics. Besides reducing the order of the controlled system, it was shown that with the lowest order of approximation to the fractional-order Laplacian operator, i.e. first-order approximation, the controlled system exhibits a satisfactory and competitive behavior to that of other higher order ones.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] R. Magin, *Fractional calculus in bioengineering*, Begell House Publishers Inc., U.S., 2006.

[2] A. Dokoumetzidis, R. Magin and P. Macheras, Fractional kinetics in multi-compartmental systems, *J. Pharmacokinet. Pharmacodyn.* **37**, 507-524 (2010).

[3] P. Sopasakis and H. Sarimveis, Controlled drug administration by a fractional PID, *IFAC Proc. Vol.* **47**(3), 8421-8426 (2014).

[4] A. Dokoumetzidis, R. Magin and P. Macheras, A commentary on fractionalization of multi-compartmental models, *J. Pharmacokinet. Pharmacodyn.* **37**, 203-207 (2010).

[5] J. K. Popović, M. Poša, K. J. Popović, D. J. Popović, N. Milošević and V. Tepavčević, Individualization of a pharmacokinetic model by fractional and nonlinear fit improvement, *Eur. J. Drug Metab. Pharmacokinet.* **38**, 69–76 (2013).

[6] P. Sopasakis and H. Sarimveis, An integer programming approach for optimal drug dose computation, *Comput. Meth. Progr. Biomed.* **108**, 1022-1035 (2012).

[7] H. Sarimveis, P. Sopasakis, A. Afantitis and G. Melagraki, A model predictive control approach for optimal drug administration, *Chem. Eng. Trans.* **17**, 1311-1316 (2009).

[8] R. El-Khazali, I. M. Batiha and S. Momani, Approximation of fractional-order operators, In: P. Agarwal, D. Baleanu, Y. Chen, S. Momani, J. Machado (eds) Fractional calculus (ICFDA 2018), *Springer Proceedings in Mathematics & Statistics* **303**, Springer, Singapore 2019.

[9] I. Podlubny, Fractional-order systems and $PI^{\lambda}D^{\mu}$ controllers, *IEEE Trans. Automat. Control* **44**, 208-214 (1999).

[10] W. Lin and Z. Chongquan, Design of optimal fractional-order PID controllers using particle swarm optimization algorithm for DC motor system, *2015 IEEE Advanced Information Technology, Electronic and Automation Control Conference (IAEAC)* (Chongqing, China; Dec. 19-20, 2015) IEEE Publishers, pp. 175-179 (2015).

[11] R. El-Khazali, Fractional-order $PI^{\lambda}D^{\mu}$ controller design, *Comp. Math. Appl.* **66**, 639-646 (2013).

[12] A. M. Abdel-Aty, A. S. Abdel-Aty, A. G. Radwan, C. Psychalinos and B. J. Maundy, Approximation of the fractional-order Laplacian s^{α} as a weighted sum of first-order high-pass filters, *IEEE Trans. Circ. Sys. II: Express Briefs* **65**, 1114-1118 (2018).

[13] A. Tepljakov, *Fractional-order modeling and control of dynamic systems* (Ph.D Thesis), Tallin University of Technology, Tallinn, 2015.

[14] A. K. Gilmutdinov, P. A. Ushakov and R. El-Khazali, *Fractal elements and their applications*, Springer, Switzerland, 2017.

[15] R. El-Khazali, On the biquadratic approximation of fractional-order Laplacian operators, *Analog Int. Circ. Sign. Proc.* **82**, 503-517 (2015).

[16] R. El-Khazali, Fractional-order $LC^{\alpha}L$ filter-based grid connected PV systems, *2019 IEEE 62nd International Midwest Symposium on Circuits and Systems (MWSCAS)* (Dallas, TX, USA; August 4-7, 2019) IEEE Publishers, pp. 533-536 (2019).

[17] C. A. Monje, Y. Q. Chen, B. M. Vinagre, D. Xue and V. Feliu, *Fractional-order systems and controls: Fundamentals and applications*, Springer, London, New York, 2010.

[18] I. Podlubny, *Fractional differential equations*, Academic Press, San Diego, 1999.

[19] S. Momani, R. El-Khazali and I. M. Batiha, Tuning PID and $PI^{\lambda}D^{\delta}$ controllers using particle swarm optimization algorithm via El-Khazali's approach, *AIP Conf. Proc.* **2172**, Article ID 050003 (2019).

[20] A. Oustaloup, F. Levron, B. Mathieu and F. M. Nanot, Frequency band complex noninteger differentiator: characterization and synthesis, *IEEE Trans. Circuit. Syst. I. Fund. Theor. Appl.* **47**, 25–39 (2000).