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A study on discrete and discrete fractional pharmacokinetics-pharmacodynamics models for tumor growth and anti-cancer effects

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Abstract: We study the discrete and discrete fractional representation of a pharmacokinetics - pharmacodynamics (PK-PD) model describing tumor growth and anti-cancer effects in continuous time considering a time scale $h\mathbb{N}_0^h$, where $h > 0$. Since the measurements of the tumor volume in mice were taken daily, we consider $h = 1$ and obtain the model in discrete time (i.e. daily). We then continue with fractionalizing the discrete nabla operator to obtain the model as a system of nabla fractional difference equations. The nabla fractional difference operator is considered in the sense of Riemann-Liouville definition of the fractional derivative. In order to solve the fractional discrete system analytically we state and prove some theorems in the theory of discrete fractional calculus. For the data fitting purpose, we use a new developed method which is known as an improved version of the partial sum method to estimate the parameters for discrete and discrete fractional models. Sensitivity analysis is conducted to incorporate uncertainty/noise into the model. We employ both frequentist approach and Bayesian method to construct 90 percent confidence intervals for the parameters. Lastly, for the purpose of practicality, we test the discrete models for their efficiency and illustrate their current limitations for application.

Keywords: Discrete Fractional Calculus, Parameter Estimations, Data Fitting, Sensitivity Analysis, Markov Chain Monte Carlo, Random Walk Metropolis, Delayed Rejection Adaptive Metropolis

MSC: 39A12, 34A25, 26A33, 62G05, 65C05, 65C20

1 Introduction

Mathematical modeling of pharmacokinetics (PK) and pharmacodynamics (PD) deals with (i) the distribution and elimination of a drug, the pharmacokinetics [17], and (ii) the therapeutic effect of a drug on a specific target, the pharmacodynamics [24]. Mathematical PK-PD models became an essential part in drug development and clinical pharmacology in the last 20-30 years. The U.S. Food and Drug Administration recognized such

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computational modeling and simulation tools as an improvement of the efficiency for developing safe and effective drugs [18].

Historically, clinicians and pharmacists [15], [16] realized very early that mathematical models are useful tools to answer pharmacological questions. However, it is important to point out that the development of the mathematical PK-PD modeling theory was quite independent from the mathematical community. PK-PD modeling is a field where the representation of pharmacological concepts in the models is the main focus. Therefore, clinical interpretation of model parameters can be made and reasonable model behavior can be used for simulations. In the last 2-3 decades, mathematicians started to contribute with valuable input to the PK-PD field. Moreover, a small mathematical community that promotes more advanced mathematical and computational approaches has been established within the PK-PD field [25].

The main purpose of a PK-PD model is to be a tool to answer specific clinical questions. More precisely, Allen et al. [1] pointed out recently that the success of mathematical modeling, for example in the biopharma industry, depends on getting the (i) right question, (ii) right model, and (iii) right analysis. Usually, PK-PD models are formulated by ordinary differential equations and can be developed in a more data-driven approach, i.e. simply characterizing available data, or in a more mechanistic approach, where detailed underlying physiological mechanisms are represented. In this paper, we consider a PK-PD model for tumor growth and anti-cancer drug effects that can be considered as a hybrid of both approaches, which is often also called a semi-mechanistic model. In general, the complexity of the PK-PD model structure strongly depends on available data, prior knowledge and most important on the specific questions that need to be answered.

Mathematical modeling of tumor growth started in the 1960s by A. K. Laird [23] with the application of the Gompertz function [19] to fit data from different animals, see e.g. Bonate et al. [13] for more details. It turned out that this sigmoidal curve fits well to the general tumor growth behavior which usually has three phases, exponential growth in the beginning followed by linear growth and finally saturation. Nowadays the Gompertz function is a common tool in PK-PD modeling although it is a more data-driven than mechanistic approach. The major goal in anti-cancer drug development is to assess the anti-cancer effect of different drug candidates and consequently to early identify promising drug candidates. Therefore, the PK-PD models have to characterize the drug potency and need the capability to perform simulations of tumor growth behavior for different doses. For these reasons, tumor growth models were extended with (i) PK models describing the drug concentration, and (ii) effect models relating the action of the drug on the tumor growth [26], [21], [22] and again see Bonate et al. [13] for a broader overview.

Development of advanced and effective mathematical models which describe and predict tumor growth kinetics is an ongoing research area for scientists, especially for applied mathematicians [2], [6]-[10], [14]-[19], and [21]-[29]. Motivated by recently studied models in fractional calculus [14, 28], we aim (i) to discretize a PK-PD model in continuous time and obtain a system of fractional difference equations in discrete time, and (ii) to investigate the properties of the discrete and discrete fractional model representation.

For the purpose of analyzing the estimated parameters, sensitivity analysis is conducted to incorporate uncertainty/noise into the model. Uncertainty could be resulted from measurements and/or intrinsic variability in experimental units and environment. By accounting for uncertainty in a mathematical model, applied mathematicians can attach measures of reliability to estimated quantities using experiment data sets. The standard procedure involves obtaining confidence intervals for model parameters. In this study, we employ both frequentist approach and Bayesian method to construct 90 percent confidence intervals for the parameters.

The plan of the paper is as follows: In Section 2, we give some preliminaries so that the reader will be familiar with the mathematical formulations in the later sections. We state and prove some theorems that will serve as main tools to obtain the explicit solutions of the system of discrete fractional equations. In Section 3, we first demonstrate the construction principle of our continuous tumor growth model and present important model properties. Then we obtain both discrete and discrete fractional models after discretizing the PK-PD model in continuous time. For estimating parameters, we use the improved version of the partial sum method after solving each model explicitly. A pseudo-code for the discrete fractional model outlines the algorithm we write in Mathematica-11. We close this section by presenting our findings with sensitivity analysis on the model parameters. In Section 4, we discuss limitations and advantages of the discrete model representation.

In the models, we consider a nabla (backward) discrete fractional operator of Riemann-Liouville type. We refer the reader to some recent work by Atıcı and co-authors [3]-[5] for the use of the discrete fractional operators in modeling and a book by Goodrich and Peterson [20] for the theory of discrete fractional calculus.

2 Preliminaries

In this section, we present sufficient fundamental definitions and formulas so that the article is self-contained. In addition, we state and prove some theorems in discrete fractional calculus so that we explicitly solve the discrete fractional models introduced in the later sections.

Definition 2.1. Let $a \in \mathbb{R}$. The backward difference operator, or nabla operator (∇) for a function $f : \mathbb{N}_a \rightarrow \mathbb{R}$ is defined by

$$(\nabla f)(t) = f(t) - f(t-1),$$

where $\mathbb{N}_a = \{a, a+1, a+2, \dots\}$.

Definition 2.2. Let μ be any real number. The rising factorial power $t^{\overline{\mu}}$ (read ‘ t to the μ rising’) is defined as

$$t^{\overline{\mu}} = \frac{\Gamma(t+\mu)}{\Gamma(t)},$$

where $t \in \mathbb{R} \setminus \{\dots, -2, -1, 0\}$, $0^{\overline{\mu}} = 0$ and Γ denotes the Gamma function.

Lemma 2.1. ([20]) The formula

$$\nabla(t-a)^{\overline{\mu}} = \mu(t-a)^{\overline{\mu-1}}$$

holds whenever the expressions on each side of the equality are sensible.

We consider the ν -th order fractional sum of f defined as

$$\nabla_a^{-\nu} f(t) = \sum_{s=a}^t \frac{(t-\rho(s))^{\overline{\nu-1}}}{\Gamma(\nu)} f(s) \quad (2.1)$$

where $\nu \geq 0$, $\rho(t) = t-1$, and $t \in \mathbb{N}_a$. Further, we consider the ν -th order fractional difference (a Riemann-Liouville fractional difference) of f defined by

$$\nabla^{\nu} f(t) = \nabla^n (\nabla^{-(n-\nu)} f(t)) \quad (2.2)$$

where $\nu > 0$, $n-1 < \nu < n$, n denotes a positive integer.

Let $\lambda, c \in \mathbb{R}$ and $\nu \in (0, 1)$. We study the following the initial value problem (IVP)

$$\nabla_0^{\nu} y(t) = \lambda y(t-1) \quad \text{for } t = 1, 2, 3, \dots, \quad (2.3)$$

$$\nabla_0^{-(1-\nu)} y(t)|_{t=0} = y(0) = c. \quad (2.4)$$

Theorem 2.3. The solution of the IVP (2.3)- (2.4) is uniquely determined.

Proof. We use the definition of the fractional nabla difference operator (2.2) to obtain the following iteration schema.

$$\nabla_0^\nu y(t) = \lambda y(t-1)$$

$$\nabla \nabla_0^{-(1-\nu)} y(t) = \lambda y(t-1)$$

$$\nabla \sum_{s=0}^t \frac{(t-\rho(s))^{-\bar{\nu}}}{\Gamma(1-\nu)} y(s) = \lambda y(t-1)$$

$$\sum_{s=0}^t \frac{(t-\rho(s))^{-\bar{\nu}}}{\Gamma(1-\nu)} y(s) - \sum_{s=0}^{t-1} \frac{(t-1-\rho(s))^{-\bar{\nu}}}{\Gamma(1-\nu)} y(s) = \lambda y(t-1)$$

$$y(t) = - \sum_{s=0}^{t-1} \frac{(t-\rho(s))^{-\bar{\nu}-1}}{\Gamma(-\nu)} y(s) + \lambda y(t-1),$$

for $t = 1, 2, \dots$. This iteration schema ensures that the solution of the IVP (2.3)-(2.4) is uniquely determined. \square

Theorem 2.4. *The unique solution of the initial value problem (2.3)-(2.4) is given by*

$$y(t) = c \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{(n+1)\nu-1}}}{\Gamma((n+1)\nu)}. \quad (2.5)$$

Proof. We show that

$$c \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{(n+1)\nu-1}}}{\Gamma((n+1)\nu)}$$

satisfies the IVP (2.3)-(2.4). Indeed, we have

$$\begin{aligned} & \nabla_0^\nu c \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{(n+1)\nu-1}}}{\Gamma((n+1)\nu)} \\ &= c \nabla \nabla_0^{-(1-\nu)} \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{(n+1)\nu-1}}}{\Gamma((n+1)\nu)} \\ &= c \nabla \sum_{s=0}^t \frac{(t-\rho(s))^{-\bar{\nu}}}{\Gamma(1-\nu)} \sum_{n=0}^s \frac{\lambda^n (s-n+1)^{\overline{(n+1)\nu-1}}}{\Gamma((n+1)\nu)} \\ &= I. \end{aligned}$$

Next we interchange the order of sums and obtain

$$\begin{aligned} I &= c \nabla \sum_{n=0}^t \sum_{s=n}^t \frac{\lambda^n \Gamma(t-s+1-\nu) \Gamma(s-n+\nu)}{\Gamma(1-\nu) \Gamma(t-s+1) \Gamma(s-n+1) \Gamma(n\nu+\nu)} \\ &= c \nabla \sum_{n=0}^t \sum_{s=0}^{t-n} \frac{\lambda^n \Gamma(t-s-n+1-\nu) \Gamma(s+n\nu+\nu)}{\Gamma(1-\nu) \Gamma(t-s-n+1) \Gamma(s+1) \Gamma(n\nu+\nu)}. \end{aligned}$$

By using the formula $\binom{t}{r} = \frac{\Gamma(t+1)}{\Gamma(r+1)\Gamma(t-r+1)}$ and the definition of the rising factorial power we get,

$$\begin{aligned} I &= c \nabla \sum_{n=0}^t \sum_{s=0}^{t-n} \binom{t-n}{s} \frac{\lambda^n \Gamma(t-s-n+1-\nu) \Gamma(s+n\nu+\nu)}{\Gamma(1-\nu) \Gamma(t-n+1) \Gamma(n\nu+\nu)} \\ &= c \nabla \sum_{n=0}^t \frac{\lambda^n}{\Gamma(t-n+1)} \sum_{s=0}^{t-n} \binom{t-n}{s} (1-\nu)^{\overline{t-s-n}} (n\nu+\nu)^{\bar{s}} \end{aligned}$$

$$\begin{aligned}
&= c \nabla \sum_{n=0}^t \frac{\lambda^n}{\Gamma(t-n+1)} (nv+1)^{\overline{t-n}} \\
&= c \nabla \sum_{n=0}^t \frac{\lambda^n}{\Gamma(nv+1)} (t-n+1)^{\overline{nv}},
\end{aligned}$$

where we used the identity $\sum_{s=0}^{t-n} \binom{t-n}{s} (1-v)^{\overline{t-s-n}} (nv+v)^{\overline{s}} = (nv+1)^{\overline{t-n}}$.

Next we apply the following rule to the above expression

$$\nabla \sum_{n=0}^t f(t, n) = \sum_{n=0}^t \nabla f(t, n) + f(\rho(t), t).$$

Hence, we have

$$\begin{aligned}
I &= c \sum_{n=0}^t \nabla \frac{\lambda^n}{\Gamma(nv+1)} (t-n+1)^{\overline{nv}} + \frac{c\lambda^n}{\Gamma(nv+1)} (t-n+1)^{\overline{nv}} \Big|_{t=t-1, n=t} \\
&= c \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{nv-1}}}{\Gamma(nv)} \\
&= c\lambda \sum_{n=0}^{t-1} \frac{\lambda^n (t-n)^{\overline{(n+1)v-1}}}{\Gamma((n+1)v)} \\
&= c\lambda y(t-1).
\end{aligned}$$

Uniqueness of this solution follows from Theorem 2.3. \square

Theorem 2.5. Assume $\lambda \in \mathbb{R}$. The fractional difference equation of order v where $v \in (0, 1)$

$$\nabla_0^v y(t) = \lambda y(t-1) + f(t-1) \quad \text{for } t = 1, 2, 3, \dots, \quad (2.6)$$

has the general solution

$$y(t) = \hat{y}_\lambda(t)c + \sum_{s=0}^{t-1} \hat{y}_\lambda(t-s-1)f(s), \quad t = 0, 1, 2, \dots, \quad (2.7)$$

where c is constant and

$$\hat{y}_\lambda(t) = \sum_{n=0}^t \frac{\lambda^n (t-n+1)^{\overline{(n+1)v-1}}}{\Gamma((n+1)v)}.$$

Proof. A direct substitution gives that $\sum_{s=0}^{t-1} \hat{y}_\lambda(t-s-1)f(s)$ is a particular solution of equation

$$\nabla_0^v y(t) = \lambda y(t-1) + f(t-1).$$

We show that

$$\nabla_0^v \sum_{s=0}^{t-1} \hat{y}_\lambda(t-s-1)f(s) = \lambda \sum_{s=0}^{t-2} \hat{y}_\lambda(t-s-2)f(s) + f(t-1).$$

Using the definition of the nabla fractional difference operator we have

$$\begin{aligned}
\nabla_0^v \sum_{s=0}^{t-1} \hat{y}_\lambda(t-s-1)f(s) &= \nabla \nabla_0^{-(1-v)} \sum_{s=0}^{t-1} \hat{y}_\lambda(t-s-1)f(s) \\
&= \nabla \sum_{u=0}^t \frac{(t-\rho(u))^{\overline{-v}}}{\Gamma(1-v)} \sum_{s=0}^{u-1} \hat{y}_\lambda(u-s-1)f(s) = I.
\end{aligned}$$

Next we interchange the order of sums and obtain

$$I = \nabla \sum_{s=0}^{t-1} \sum_{u=s+1}^t \frac{(t-\rho(u))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(u-s-1)f(s).$$

Next we apply the following rule to the above expression

$$\nabla \sum_{s=0}^{t-1} f(t, s) = \sum_{s=0}^{t-2} \nabla f(t, s) + f(t, t-1). \quad (2.8)$$

Hence, we have

$$\begin{aligned} I &= \sum_{s=0}^{t-2} \nabla \sum_{u=s+1}^t \frac{(t-\rho(u))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(u-s-1)f(s) \\ &\quad + \sum_{u=s+1}^t \frac{(t-\rho(u))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(u-s-1)f(s) \big|_{t=t, s=t-1} \\ &= \sum_{s=0}^{t-2} \nabla \sum_{u=s+1}^t \frac{(t-\rho(u))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(u-s-1)f(s) + f(t-1) \end{aligned}$$

since $\hat{y}_\lambda(0) = 1$.

Next we use the substitution $u-s-1 = \tau$, we obtain

$$\begin{aligned} \sum_{u=s+1}^t \frac{(t-\rho(u))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(u-s-1) &= \sum_{\tau=0}^t \frac{(t-(\tau+s+1-1))^{-\bar{\nu}}}{\Gamma(1-\nu)} \hat{y}_\lambda(\tau) \\ &= \nabla_0^{-(1-\nu)} \hat{y}_\lambda(t-s-1). \end{aligned}$$

Thus,

$$\begin{aligned} I &= \sum_{s=0}^{t-2} \nabla \nabla_0^{-(1-\nu)} \hat{y}_\lambda(t-s-1)f(s) + f(t-1) \\ &= \sum_{s=0}^{t-2} \nabla_0^\nu \hat{y}_\lambda(t-s-1)f(s) + f(t-1) \\ &= \lambda \sum_{s=0}^{t-2} \hat{y}_\lambda(t-s-2)f(s) + f(t-1). \end{aligned}$$

We use Theorem 2.4 to complete the proof. \square

Theorem 2.6. Assume $\lambda \in \mathbb{R} \setminus \{-1\}$. The first order nabla difference equation

$$\nabla y(t) = \lambda y(t-1) + f(t-1) \quad \text{for } t = 1, 2, 3, \dots, \quad (2.9)$$

has the general solution

$$y(t) = (1+\lambda)^t c + \sum_{s=0}^{t-1} (1+\lambda)^{t-s-1} f(s), \quad t = 0, 1, 2, \dots, \quad (2.10)$$

where c is constant.

Definition 2.7. Let $a \in \mathbb{R}$ and $h \in \mathbb{R}^+$. The backward h -difference operator for a function $f : h\mathbb{N}_a^h \rightarrow \mathbb{R}$ is defined by

$$f^\nabla(t) = \frac{f(t) - f(t-h)}{h}, \quad t = a+h, a+2h, \dots$$

where $h\mathbb{N}_a^h = \{a, a+h, a+2h, \dots\}$.

Theorem 2.8. [12] Assume $\lambda \in \mathbb{R} \setminus \{-\frac{1}{h}\}$. The first order nabla h -difference equation

$$y^\nabla(t) = \lambda y(t-h) + f(t-h) \quad \text{for } t = h, 2h, 3h, \dots, \quad (2.11)$$

has the general solution

$$y(t) = (1 + h\lambda)^{\frac{t}{h}} c + h \sum_{s=0}^{\frac{t}{h}-1} (1 + h\lambda)^{\frac{t}{h}-s-1} f(sh), \quad t = 0, h, 2h, \dots, \quad (2.12)$$

where c is constant.

For further reading on time scale calculus which includes $h\mathbb{N}_a^h$, we refer the reader to a book by Bohner and Peterson [11].

3 The tumor growth inhibition model with drug effect

3.1 Development of the continuous tumor growth inhibition model

Replacing the unperturbed growth component of the PK-PD model in [21] with the Gompertz growth component, results in the following representation of the PK-PD model in continuous time

$$\begin{aligned} x_1'(t) &= (a - b \ln(x_1(t)))x_1(t) - k_2 c(t)x_1(t), & x_1(0) &= w_0 \\ x_2'(t) &= k_2 c(t)x_1(t) - k_1 x_2(t), & x_2(0) &= 0 \\ x_3'(t) &= k_1 x_2(t) - k_1 x_3(t), & x_3(0) &= 0 \\ w(t) &= x_1(t) + x_2(t) + x_3(t), \end{aligned}$$

where a, b, k_1, k_2 are model parameters to estimate and $c(t)$ represents the drug concentration in plasma described by mono- or bi-exponential PK models [22].

During anticancer treatment it is assumed that the growth dynamics of the tumor will be perturbed by the anticancer drug effect described with the model parameter k_2 . Due to drug action, proliferating cells become non-proliferating depending on the drug concentration. The model assumes that cells affected by drug action immediately stop proliferating and pass through apoptotic stages (x_2, x_3) with a rate k_1 before they die. Since these non-proliferating cells still add to total tumor mass, total tumor volume $w(t)$ is the sum of proliferating x_1 and non-proliferating tumor cells (x_2, x_3) .

The tumor growth inhibition model was constructed in such a way that two fundamental properties hold:

- (P.1) During drug administration, i.e. $c(t) > 0$, the tumor growth will be inhibited.
- (P.2) The tumor volume will never become negative, i.e. $w(t) > 0$ for all $t \geq 0$.

We first discretize the above model considering the time scale $h\mathbb{N}_0^h$ with $h > 0$. Hence we have

$$\begin{aligned} u^\nabla(t) &= a - bu(t-h) - k_2 c(t-h), & x_1(0) &= w_0 \\ x_2^\nabla(t) &= k_2 c(t-h)x_1(t-h) - k_1 x_2(t-h), & x_2(0) &= 0 \\ x_3^\nabla(t) &= k_1 x_2(t-h) - k_1 x_3(t-h), & x_3(0) &= 0 \\ w(t) &= x_1(t) + x_2(t) + x_3(t), \end{aligned}$$

where $u(t) = \ln x_1(t)$.

We solve the above system of difference equations by using Theorem 2.8. Hence we have

$$u(t) = (1 - hb)^{\frac{t}{h}} u(0) + h \sum_{s=0}^{\frac{t}{h}-1} (1 - hb)^{\frac{t}{h}-s-1} (a - k_2 c(sh)), \quad t = 0, h, 2h, \dots,$$

$$x_1(t) = e^{u(t)} \quad t = 0, h, 2h, \dots$$

$$x_2(t) = hk_2 \sum_{s=0}^{\frac{t}{h}-1} (1 - hk_1)^{\frac{t}{h}-s-1} (c(sh)x_1(sh)), \quad t = 0, h, 2h, \dots,$$

$$x_3(t) = hk_1 \sum_{s=0}^{\frac{t}{h}-1} (1 - hk_1)^{\frac{t}{h}-s-1} x_2(sh), \quad t = 0, h, 2h, \dots$$

If $h = 1$, the perturbed discrete tumor growth model with three compartments reads:

$$\begin{aligned} \nabla u(t) &= a - bu(t-1) - k_2 c(t-1), & x_1(0) &= w_0 \\ \nabla x_2(t) &= k_2 c(t-1)x_1(t-1) - k_1 x_2(t-1), & x_2(0) &= 0 \\ \nabla x_3(t) &= k_1 x_2(t-1) - k_1 x_3(t-1), & x_3(0) &= 0 \\ w(t) &= x_1(t) + x_2(t) + x_3(t), \end{aligned}$$

where $u(t) = \ln x_1(t)$ and a, b, k_1, k_2 are model parameters to estimate.

We solve the above system of difference equations by using Theorem 2.6. Hence we have

$$u(t) = (1-b)^t u(0) + \sum_{s=0}^{t-1} (1-b)^{t-s-1} (a - k_2 c(s)), \quad t = 0, 1, 2, \dots,$$

$$x_1(t) = e^{u(t)} \quad t = 0, 1, 2, \dots$$

$$x_2(t) = (1-k_1)^t x_2(0) + k_2 \sum_{s=0}^{t-1} (1-k_1)^{t-s-1} (c(s)x_1(s)), \quad t = 0, 1, 2, \dots,$$

$$x_3(t) = (1-k_1)^t x_3(0) + k_1 \sum_{s=0}^{t-1} (1-k_1)^{t-s-1} x_2(s), \quad t = 0, 1, 2, \dots$$

The perturbed discrete fractional tumor growth model with three compartments reads:

$$\begin{aligned} \nabla^v u(t) &= a - bu(t-1) - k_2 c(t-1), & x_1(0) &= w_0 \\ \nabla^v x_2(t) &= k_2 c(t-1)x_1(t-1) - k_1 x_2(t-1), & x_2(0) &= 0 \\ \nabla^v x_3(t) &= k_1 x_2(t-1) - k_1 x_3(t-1), & x_3(0) &= 0 \\ w(t) &= x_1(t) + x_2(t) + x_3(t), \end{aligned}$$

where $u(t) = \ln x_1(t)$ and v, a, b, k_1, k_2 are model parameters to estimate. Here we assume that v is a real number such that $v \in (0, 1)$.

For the first equation in the above system, we use some properties of the nabla-difference operator and the Gamma function, we obtain the following iteration formula for $u(t)$.

$$u(t+1) = a - bu(t) - k_2 c(t) - \sum_{s=-1}^{t-1} \frac{(t-s+1)^{\overline{-v-1}}}{\Gamma(-v)} u(s+1),$$

for $t = 0, 1, 2, \dots$

We use Theorem 2.5 as a tool to obtain the solutions.

$$u(t) = \hat{y}_{-b}(t)u(0) + \sum_{s=0}^{t-1} \hat{y}_{-b}(t-s-1)(a - k_2 c(s)), \quad t = 0, 1, 2, \dots,$$

$$x_1(t) = e^{u(t)} \quad t = 0, 1, 2, \dots$$

$$x_2(t) = \hat{y}_{-k_1}(t)x_2(0) + k_2 \sum_{s=0}^{t-1} \hat{y}_{-k_1}(t-s-1)[c(s)x_1(s)], \quad t = 0, 1, 2, \dots$$

$$x_3(t) = \hat{y}_{-k_1}(t)x_3(0) + k_1 \sum_{s=0}^{t-1} \hat{y}_{-k_1}(t-s-1)x_2(s), \quad t = 0, 1, 2, \dots$$

3.2 Tumor growth and drug concentration data

Data was taken from the supplemental material of [21]. These data describe the tumor volume measurements in Xenograft mice treated with different compounds. For more details see [21].

3.3 Parameter Estimations

In our study we used the improved partial sum method in Mathematica to estimate the parameters for the discrete and discrete fractional models. We include a pseudo-code of the algorithm for discrete fractional model in Algorithm 3 (see Appendix). This algorithm outlines how the improved partial sum method ([7]) works for the system of equations. In Table 1, we list the parameter estimates and residual sum of squares (RSS) values for the discrete and the discrete fractional PK-PD models. Comparing the RSS values between the discrete and the discrete fractional model, the discrete fractional model results in better fitting for all drugs.

Table 1: Parameter estimates and RSS values for the discrete and the discrete fractional models

<i>Model</i>	\hat{a}	\hat{b}	\hat{k}_1	\hat{k}_2	\hat{v}	<i>RSS</i>
<i>DrugA2 – 120</i>						
<i>Discrete</i>	0.0602508	0.0310842	0.428171	0.00017402		0.055199
<i>DiscreteFractional</i>	0.0841445	0.00344602	0.737472	0.000525139	0.97	0.0352125
<i>DrugA1 – 180</i>						
<i>Discrete</i>	0.0879982	0.00515473	2.02997	0.000124896		0.107967
<i>DiscreteFractional</i>	0.0921663	0.0000332075	1.87965	0.0000951145	0.9924	0.0972591
<i>DrugB – 100</i>						
<i>Discrete</i>	0.103846	0.0733249	0.471986	0.00075884		0.0053611
<i>DiscreteFractional</i>	0.155291	0.0481064	0.214043	0.00442623	0.97619	0.00218639
<i>DrugC – 100</i>						
<i>Discrete</i>	0.087694	0.0147851	0.00378922	0.000102413		0.044971
<i>DiscreteFractional</i>	0.104413	0.000148219	0.00676393	0.000825508	0.9917	0.0441995
<i>DrugC – 150</i>						
<i>Discrete</i>	0.129083	0.0105822	0.391106	0.00042877		0.0213876
<i>DiscreteFractional</i>	0.142964	0.0000000796487	0.367953	0.000697642	0.9813	0.0183728

3.4 Analyzing the Model Statistically

After the model parameters are estimated, sensitivity analysis is conducted to incorporate uncertainty/noise into the model. Uncertainty could be resulted from measurements and/or intrinsic variability in experimental units and environment. By accounting for uncertainty in mathematical model, applied mathematicians can attach measures of reliability to estimated quantities using experiment data sets. The standard procedure involves obtaining point estimates for the model parameters and then either obtain the corresponding stan-

dard error of the estimates or construct confidence intervals. In this study, we employ both the frequentist approach and Bayesian method to construct 90% confidence intervals for the model parameters.

We assume that n scalar longitudinal observations are represented by the statistical model

$$W_j = f_j(\beta) + \epsilon_j; j = 1, \dots, n, \quad (3.1)$$

where $f_j(\beta)$ is the model for the observations in terms of the state variables and $\beta \in \mathbb{R}^p$ is a vector of theoretical true parameter values. The error terms $\epsilon_j, j = 1, \dots, n$ represent noise, measurement error, or uncontrol variables that can potentially influence the deterministic relationship represented by $f_j(\beta)$.

For our statistical model of the observation or measurement process (3.1) we assume that the errors $\epsilon_j, j = 1, 2, \dots, n$, are independent identically distributed random variables with mean $E[\epsilon_j] = 0$ and constant variance $\text{Var}[\epsilon_j] = \sigma_0^2$, where σ_0^2 is unknown.

Thus we use the realized data w_j from observations of three-compartment model to seek a value $\hat{\beta}$ that minimizes

$$SS(\beta) = \sum_{i=1}^n (f_j(\beta) - y_j)^2. \quad (3.2)$$

The estimator $\hat{\beta}(W)$ is a random variable whose realized value depends on the observed data w_j of random variables W_j . The distribution of $\hat{\beta}(W)$ (through repeated sampling) is called the sampling distribution. Knowledge of this sampling distribution provides uncertainty information (e.g., standard errors) for the numerical values of $\hat{\beta}$ obtained using a specific data set. Under the regularity assumptions, as the sample size n approaches infinity, the sampling distribution of $\hat{\beta}(W)$ is approximately $N_p(\beta, \sigma_0^2[\chi^T(\beta)\chi(\beta)]^{-1})$, where $\chi(\beta)$ is a $n \times p$ sensitivity matrix with elements

$$\chi_{jk}(\beta) = \frac{\partial f_j(\beta)}{\partial \beta_k}; j = 1, \dots, n; k = 1, \dots, p.$$

Since β and σ_0 are not known, we must approximate them using the parameter estimates to obtain the estimate for the variance-covariance matrix $\Sigma_0 = \sigma_0^2[\chi^T(\hat{\beta})\chi(\hat{\beta})]^{-1}$

$$\Sigma_0 \approx \Sigma(\hat{\beta}) = \hat{\sigma}^2[\chi^T(\hat{\beta})\chi(\hat{\beta})]^{-1},$$

where $\hat{\sigma}^2$ is given by

$$\sigma_0^2 \approx \hat{\sigma}^2 = \frac{1}{n-p} \sum_{i=1}^n (f_j(\hat{\beta}) - y_j)^2.$$

Standard errors of the estimate $\hat{\beta}_k$ are thus given by $SE(\hat{\beta}_k) = \sqrt{\Sigma_{kk}(\hat{\beta})}, k = 1, \dots, p$. Then a $(1 - \gamma)100\%$ confidence interval for β_k is readily given by $\hat{\beta}_k \pm t_{n-p, \gamma/2} * SE(\hat{\beta}_k)$, where the critical value $t_{n-p, \gamma/2}$ is computed from the Student's t distribution with $n - p$ degrees of freedom.

The 90% confidence intervals for the parameters in the model is computed as follows: The least squares estimates $\hat{a}, \hat{b}, \hat{k}_1$, and \hat{k}_2 for parameters a, b, k_1 and k_2 of the discrete model and estimates $\hat{a}, \hat{b}, \hat{v}, \hat{k}_1$, and \hat{k}_2 for parameters a, b, v, k_1 and k_2 of the discrete fractional model are obtained from iterative computational scheme. Then the sensitivity matrix $\chi(\hat{\beta})$ can be derived. The results of 90% confidence intervals of parameters for the discrete model are included in Table 2 and those for the discrete fractional model are in Table 3.

After obtaining the sensitivity matrix, we utilize the Markov Chain Monte Carlo (MCMC) technique which constructs the Markov chain whose stationary distribution is the posterior distribution of the model parameters. The specific algorithm is called the Delayed Rejection Adaptive Metropolis [27]. The algorithm starts with an initial vector β_0 and is iterated M times. In each iteration, a new candidate β^* is chosen from a Normal distribution that centers at the value β from the previous iteration and the variance-covariance matrix $\Sigma(\hat{\beta})$ where $\hat{\beta}$'s are the estimates of the parameters. Whether this candidate is either accepted as the new value for β or not depends on how more likely the candidate is compared to the previous value of β with respect to the posterior distribution. If the candidate is rejected, the delayed rejection algorithm provides a mechanism

for constructing alternative candidate β rather than retaining the previous value. Also, during a nonadaptive period of length k_0 , chain values β are computed using the initial covariance matrix $\Sigma(\hat{\beta})$. Once adaptation starts, the variance-covariance matrix is adapted according to the covariance matrix of the accepted candidates β s in the previous steps. The results of 90% Bayesian interval estimates of parameters for two models are included in Table 2 and 3.

Based on Table 2 and 3, we can see that in most cases, the model parameters are significant (confidence intervals do not contain zero). Also, the Bayesian approach gives remarkably narrower confidence intervals in most cases considered. The reason is that the construction of confidence intervals using frequentist approach is based upon the asymptotic theory of estimators which assumes that the sample size has to be sufficiently large. When the sample size is not large enough, the frequentist asymptotic confidence interval is relatively wide. On the other hand, in the Bayesian inference, the sample size is often not of concern.

Table 2: Confidence intervals of parameters for discrete model, A2-120 drug.

<i>Parameter</i>	$\hat{\beta}$	<i>FrequentistCI</i>	<i>BayesianCI</i>
<i>a</i>	0.0602508	(0.0438067, 0.0766949)	(0.04483548, 0.07527723)
<i>b</i>	0.0310842	(0.0163216, 0.0458468)	(0.01691371, 0.04493783)
<i>k</i> ₁	0.428171	(−0.638645, 1.49499)	(0.02814296, 1.1982126)
<i>k</i> ₂	0.00017402	(−0.0000380704, 0.00038611)	(0.0000801619, 0.00040083)

Table 3: Confidence intervals of parameters for discrete fractional model, A2-120 drug.

<i>Parameter</i>	$\hat{\beta}$	<i>FrequentistCI</i>	<i>BayesianCI</i>
<i>a</i>	0.0841445	(0.0348417, 0.133447)	(0.03514273, 0.12066398)
<i>b</i>	0.00344602	(−0.0528842, 0.0597763)	(−0.03928112, 0.05883459)
<i>v</i>	0.97	(0.913687, 1.02631)	(0.9299219, 1.0178996)
<i>k</i> ₁	0.737472	(0.30457, 1.17037)	(0.3790513, 1.1573647)
<i>k</i> ₂	0.000525139	(0.00045256, 0.000597718)	(0.0004778875, 0.0005829522)

4 Limitations in Discrete Models

Fractionalization of mathematical models in the PKPD field is not new [28, 30] but has not really prevailed. One reason might be the raising mathematical complexity and consequently the difficulties in numerical implementation for the user and probably also in run-time. We have to keep in mind that, e.g. in a clinical setting with a population consisting of several hundreds of patients run-time is an issue. As we are presenting here, first discretizing and then fractionalizing a PK-PD model is an approach which can be resulted in a simple explicit solution for which direct implementation without any numerical solvers is possible. However, simulations of the discrete model ($h = 1$) showed some limitations of the discretization approach which will be discussed in this paragraph:

First, property (P.1) (tumor growth is always inhibited during treatment) partially fails in discrete models. Simulations showed that for increasing doses the tumor volume can be slightly increased in the very beginning of the treatment and then decreases during treatment as illustrated in Figure 1. In discrete models, because of the nature of the solutions, the effect of the drug occurs in the following day after the drug is administered. The graph in discrete time does not decrease immediately after drug administration.

Second, property (P.2) (tumor volume will never become negative) holds for the discrete model on $h\mathbb{N}_0^h$ with $h = \frac{1}{24}$, and does not hold for the discrete model ($h = 1$). As in Figure 2, the simulations showed that for strongly increasing doses the tumor volume can become negative. On one hand this is obviously not reasonable from a biological perspective. On the other hand, the model on $h\mathbb{N}_0^h$ recovers the property (P.2) as illustrated in Figure 3. In addition to all these, we also want to point out that in practice model predictions are usually only reliable for a local range of parameters.

Third, since the PK is on a different time scale than the PD, this may have an impact on the chosen discretization step size. Please note, an absorption compartment in a PK model is necessary, if it takes some time for the drug to reach the blood. Typical examples are orally administered drugs with a delay between administration and appearance in blood of e.g. several hours. In contrast, intravenously administered drugs appear immediately in blood. In this paper, we simplified the PK from [21] and omitted the absorption component for two reasons: First, absorption was rapid and can be neglected from a pharmacological perspective. Second, we have to be aware that the drug was administered every day and at the same time when the tumor was measured. Because $c(t)$ describes the drug concentration in blood, c would be zero at the time of administration, since it takes a very short time to reach the blood due to the absorption component. Hence, without an absorption component, c at the time of administration characterizes always the peak of the drug concentration. Because the discrete models always evaluate c every day, this ensures that we always use the maximal drug concentration at the discretization steps. Without this modification, c would be always zero in the discrete models. However, it is possible to take such characteristic of $c(t)$ into account in the discrete model on $h\mathbb{N}_0^h$ by choosing h in a smaller value.

Forth, the solution representation introduces the restriction of $\lambda \neq -1$ (as stated in Theorem 2.6) which is then translated to our discrete tumor growth model for the parameters b and k_1 .

In summary, the discrete model ($h = 1$) loses some necessary properties that hold in the continuous model representation. As we illustrated in Figure 3, the second property can be recovered by a model on $h\mathbb{N}_0^h$ which reads $c(t)$ in every hour not only one time in a day as in the discrete model. However the graph of the model in $h\mathbb{N}_0$ increases immediately at the time of drug administration starts. This issue may lead to the question that maybe the discretization of the continuous model has to be constructed in a different way to assure that (P.1) and (P.2) become valid in the discrete model ($h = 1$) and no jump occurs for the $h\mathbb{N}_0^h$ model.

A Appendix

Algorithm 1

Input: Unperturbed data: Array L of tumor volume.

Output: L'

/* This code takes unperturbed data L and fills all missing data on each time unit using Gombertz curve and FindFit in Mathematica */

Define $model = e^{\log_e(a) - e^b(e^{-c})^t}$

/*Determine a , b , and c using FindFit in Mathematica*/

FindFit[L,model,{ a , b , c },t]

For($i=0$ to $|L|$)

if $L[i]$ has no data

$L'[i] = model[i]$

else

$L'[i] = L[i]$

Algorithm 2

Input: Array L computed by Algorithm 1. Values in L are between first day of experiment and last day in

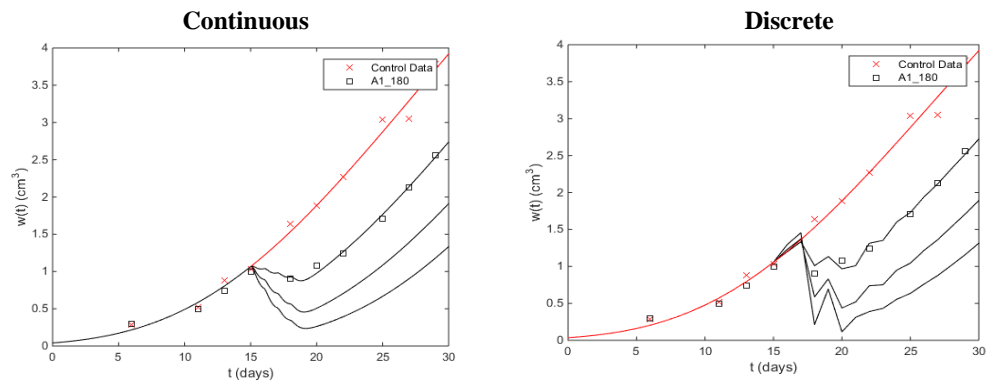


Figure 1. Tumor growth and the effect of drug concentration are shown for the continuous and discrete ($h=1$) model. Drug concentration $c(t)$ was multiplied with factor 0, 1, 2 and 3.

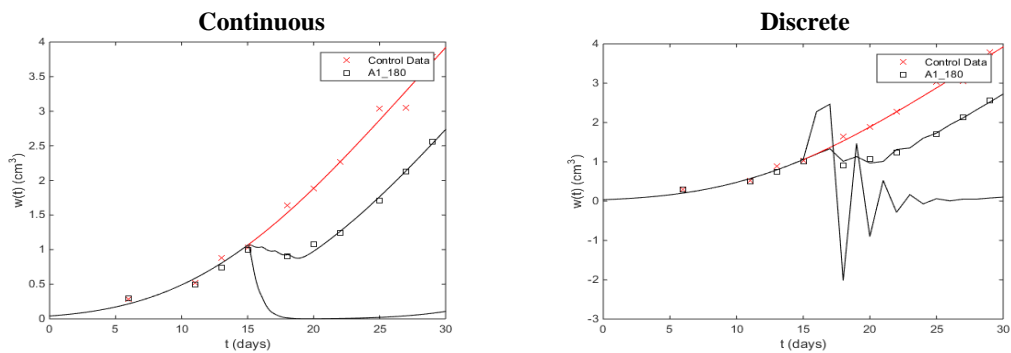


Figure 2. Tumor growth and the effect of drug concentration are shown for the continuous and discrete ($h=1$) model. Drug concentration $c(t)$ was multiplied with factor 10.

Hourly time scale model

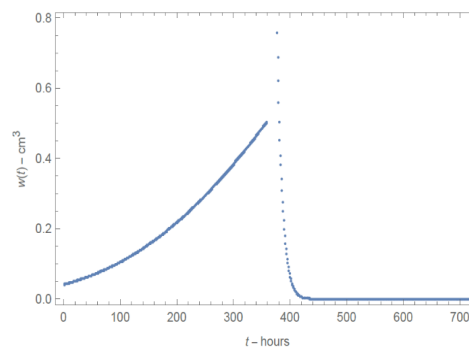


Figure 3. Tumor growth and the effect of drug concentration is shown for the model on hN ($h=1/24$). Drug concentration $c(t)$ was multiplied by a factor 10 in the hourly time scale model.

which CT is 0.

Output: a and b

We refer the improved partial sum algorithm

Algorithm 3

Input: Array L computed by **Algorithm 1**. Array CT of drug concentration rate, and constants a , b , and v determined by **Algorithm 2**

Output: k_1 , k_2 , and RSS

$$X_1[1] = L[1]$$

$$U_1[1] = \text{Loge}(X_1[1])$$

$$\text{Define } Y_1[t] := a - b * U_1[t-1] - \frac{1}{\Gamma[-v]} \sum_{s=0}^{t-2} \frac{\Gamma[t-v-s-1]}{\Gamma[t-s]} U_1[s+1] - k_2 CT[t-1]$$

For $j = 2$ to $|L|$

$$X_1[j] = e^{Y_1[j]}$$

$$\text{Define } Y_2[t] := \sum_{s=1}^t (\sum_{n=1}^{t+1-s} (-k_1)^{n-1} \frac{\Gamma[t+1-s-n+nv]}{\Gamma[t+2-n-s]\Gamma[nv]}) k_2 CT[s-1] X_1[s-1]$$

For $j = 1$ to $|L|$

$$X_2[j] = Y_2[j]$$

$$\text{Define } Y_3[t] := \sum_{s=1}^t (\sum_{n=1}^{t+1-s} (-k_1)^{n-1} \frac{\Gamma[t+1-s-n+nv]}{\Gamma[t+2-n-s]\Gamma[nv]}) k_1 X_2[s-1]$$

For $j = 1$ to $|L|$

$$X_3[j] = Y_3[j]$$

$$S = X_1 + X_2 + X_3$$

For $j=1$ to $|L|$

$$WS[j] = X_1[j] + X_2[j] + X_3[j]$$

/* After certain index, say k , values in WS are functions of k_1 , k_2 Using **FindRoot** in Mathematica determine k_1 , k_2 values for **inVa1** and **inVa2**. We have chosen these initial values by trial and error */

For **inVa1**= n_1 to n_2 by incrementing ϵ

For **inVa2**= m_1 to m_2 to by incrementing γ

For index= k to $|L| - 2$

Determine k_1 , k_2 for each index. Replace k_1 , k_2 in WS

$$RSS = \sum_{i=1}^{|L|} (S[i] - L[i])^2, \text{ where } L[i] \text{ is measured data}$$

Return minimum RSS with corresponding k_1 , k_2 values

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References

- [1] R. Allen, H. Moore, Perspectives on the role of mathematics in drug discovery and development, *Bull. Math. Biol.*, doi: 10.1007/s11538-018-00556-y (2019).
- [2] G. Annadurai, S. Rajesh Babu, and V. R. Srinivasamoorthy, Development of Mathematical Models (Logistic, Gompertz and Richards Models) Describing the Growth Pattern of Pseudomonas Putida (NCM 2174), *Bioprocess Engineering*, **23** (2000), 607–612.
- [3] F. M. Atıcı and P. W. Elloe, Linear Systems of Fractional Nabla Difference Equations, *The Rocky Mountain Journal of Mathematics*, Special issue honoring Prof. Lloyd Jackson, Vol. 41, bf 2(2011), pp. 353–370.
- [4] F. M. Atıcı and P. W. Elloe, Discrete fractional calculus with the nabla operator, *Electronic Journal of Qualitative Theory of Differential Equations, Spec. Ed. I* (2009) No. 3, 1–12.
- [5] F. M. Atıcı and N. Acar, Exponential functions of discrete fractional calculus, *Applicable Analysis and Discrete Mathematics*, Vol. 7, 2 (2013), 343–353.
- [6] F. M. Atıcı, M. Atıcı, W. M. Hrushesky, and N. Nguyen, Modeling Tumor Growth with Basic Functions of Fractional Calculus, *Progress in Fractional Differentiation and Applications*, **1** (2015), No. 4, 1–13.
- [7] F. M. Atıcı, M. Atıcı, M. Belcher, and D. Marshall, A New Approach for Modeling with Discrete Fractional Equations, *Fundamenta Informaticae*, **151** (2017), 313–324. doi:10.3233/FI-2017-1494
- [8] I. D. Bassukas, B. M. Schultze, The recursion formula of the Gompertz function: A simple method for the estimation and comparison of tumor growth curves, *Growth Dev. Aging*, **52** (1988), 113–122.

- [9] I. D. Bassukas, Comparative Gompertzian analysis of alterations of tumor growth patterns, *Cancer Research*, **54** (1994), 4385-4392.
- [10] S. Benzekry, C. Lamont, A. Beheshti, A. Tracz, J. M. L. Ebo, L. Hlatky and P. Hahnfeldt, Classical Mathematical Models for Description and Prediction of Experimental Tumor Growth, *PLOS Computational Biology*, **10** (2014), 1–19.
- [11] M. Bohner and A. Peterson, Dynamic Equations on Time Scales, *Birkhäuser, Basel* (2001).
- [12] M. Bohner and A. C. Peterson, Advances in dynamic equations on time scales, *Birkhäuser Boston, MA*, (2003).
- [13] P.L. Bonate, D.R. Howard, Pharmacokinetics in Drug Development: Advances and Applications, Volume 3, Springer (2011).
- [14] A. Dokoumetzidis, R. Magin and P. Macheras, Fractional kinetics in Multi-Compartmental Systems, *J. Pharmacokinet. Pharmacodyn.*, **37** (2010), 507–524.
- [15] F.H. Dost, Der Blutspiegel, Leipzig, Thieme (1953).
- [16] F.H. Dost, Grundlagen der Pharmakokinetik, Stuttgart, Thieme (1968).
- [17] M. Gibaldi, D. Perrier, Pharmacokinetics, Boca Raton, CRC Press Taylor & Francis Group (1982).
- [18] J. V. S. Gobburu and P. J. Marroum, Utilisation of pharmacokinetic - pharmacodynamic modeling and simulation in regulatory decision making, *Clinical Pharmacokinetics*, **40** (2001), 883–892.
- [19] B. Gompertz, On the Nature of the Function Expressive of the Law of Human Mortality, and on a New Mode of Determining the Value of Life Contingencies, *Philos. Trans. R. Soc. Lond.*, **115** (1825), 513–585.
- [20] C. Goodrich and A. C. Peterson, Discrete Fractional Calculus, *Springer* (2016), doi: 10.1007/978-3-319-25562-0.
- [21] G. Koch, A. Walz, G. Lahu, and J. Schropp, Modeling of tumor growth and anticancer effects of combination therapy, *J. Pharmacokinet Pharmacodyn.*, **36** (2009), 179–197.
- [22] G. Koch, J. Schropp, Mathematical concepts in pharmacokinetics and pharmacodynamics with application to tumor growth, In: P. Kloeden, C. Pötzsche, eds. Nonautonomous dynamical systems in the life sciences, New York, Springer (2013), 225–250.
- [23] A.K. Laird, Dynamics of tumor growth, *Br. J. Cancer* **18** (3) (1964), 490–502.
- [24] D. E. Mager, E. Wyska, W. J. Jusko, Diversity of mechanism-based pharmacodynamics, *Drug Metabolism and Disposition*, **31** (2003), 510–519.
- [25] H. Moore, The mathematical and computational sciences (MCS) special interest group (SIG) of the international society of pharmacometrics (ISoP), *CPT Pharmacometrics Syst Pharmacol*, accepted, doi.org/10.1002/psp4.12410, (2019).
- [26] M. Simeoni, P. Magni, C. Cammia, G. De Nicolao, V. Croci, E. Pesenti, M. Germani, I. Poggesi, and M. Rocchetti, Predictive pharmacokinetic pharmacodynamic modeling of tumor growth kinetics in Xenografi models after administration of Anti-cancer Agents, *Cancer Research*, **64** (2004), 1094–1101.
- [27] R. C. Smith, Uncertainty Quantification: Theory, Implementation, and Applications, *SIAM*, (2014).
- [28] P. Sopasakis, H. Sarimveis, P. Macheras, A. Dokoumetzidis, Fractional calculus in pharmacokinetics, *J. Pharmacokinet Pharmacodyn.*, **45**(1) (2018), 107–125.
- [29] Y. N. Sun and W. J. Jusko, Transit compartments versus gamma distribution function to model signal transduction processes in pharmacodynamics, *J. Pharm. Sci.*, **87** (1998), 732–737.
43(5) (2016), 461–479.
- [30] D. Verotta, Fractional dynamics pharmacokinetics - pharmacodynamic models, *J Pharmacokinet Pharmacodyn*, **37**(3) (2010), 257–276.