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Pharmacokinetics and Pharmacodynamics Models of Tumor Growth and Anticancer Effects in Discrete Time

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Abstract: We study the h -discrete and h -discrete fractional representation of a pharmacokinetics-pharmacodynamics (PK-PD) model describing tumor growth and anticancer effects in continuous time considering a time scale $h\mathbb{N}_0$, where $h > 0$. Since the measurements of the drug concentration in plasma were taken hourly, we consider $h = 1/24$ and obtain the model in discrete time (i.e. hourly). We then continue with fractionalizing the h -discrete nabla operator in the h -discrete model to obtain the model as a system of nabla h -fractional difference equations. In order to solve the fractional h -discrete system analytically we state and prove some theorems in the theory of discrete fractional calculus. After estimating and getting confidence intervals of the model parameters, we compare residual squared sum values of the models in one table. Our study shows that the new introduced models provide fitting as good as the existing models in continuous time.

Keywords: Discrete Fractional Calculus, Parameter Estimations, Data Fitting

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

1 Introduction

In a typical pharmacokinetics and pharmacodynamics (PK-PD) model, which describes the impact of anti-cancer treatment on the dynamics of tumor growth, a transit compartment model consists of a system of first order differential equations. A first order differential equation is an equation that includes an unknown function of time t (call f) and its first order derivative, which stands for the instantaneous rate of change of f at time t . In this regard, the PK-PD model can be viewed as a relation between unknown functions of time, their first order derivatives that include some estimated parameters, and drug concentration as a function of time.

In this paper, we introduce the PK-PD model as a system of h -fractional difference equations of non-integer order α , where α is any real number between zero and one. A fractional difference equation is an equation which includes an unknown function of time (call f); and is defined as the rate of change of the $(1 - \alpha)$ -th order sum of the function f at time t . From a practical point of view, the mentioned non-integer order sum can be considered as the history of the function f from the initial time t_0 to t . Hence it is worth

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mentioning that the fractional difference of a function depends on function's whole time history from initial time t_0 to t ; and not on its instantaneous behavior at time t . Additionally, the models with fractional difference equations in discrete time provide the possibility of expressing the solution as an iteration schema. Hence there will be no need to search for numerical approximation methods to solve the equations. Because of such characteristics, we believe that introducing a system of fractional difference equations into the PK-PD research area will serve as a base for more applicable models in cancer research. In contrast to the previously-introduced PK-PD models with ordinary differential equations (ODE) and fractional differential equations (FDE) in the literature [1, 2, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 22, 23, 24, 25, 26, 27, 28, 29], here we take a different approach which yields new insights in modeling.

In the paper [5], the authors introduced and then fractionalized the following model on the time scale $h\mathbb{N}_0 = \{0, h, 2h, \dots\}$ with $h > 0$

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

where $u(t) = \ln x_1(t)$. While the models in [5] were serving as good candidates for the purpose of data fitting, some limitations on the models were pointed out such as the discrete model ($h = 1$) loses some necessary properties that hold in the continuous model, a jump occurs in the h -discrete model ($h > 0$) after drug administered. In this work, we aim to keep the data fitting capability of the models and to remove the mentioned limitations by introducing and studying the following model in discrete time ($h > 0$):

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

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

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 h -discrete fractional equations. The nabla h -fractional difference operator is considered in the sense of Riemann-Liouville definition of the fractional derivative. In Section 3, we first demonstrate the construction principle of our continuous tumor growth model and present important model properties. Then we obtain both h -discrete and h -discrete fractional models after discretizing the PK-PD model in continuous time. In Section 4, for estimating parameters, we use Nelder-Mead algorithms in R and MatLab after solving each h -discrete and fractional h -discrete models explicitly. We close this section by presenting our findings with confidence intervals on the model parameters. In Section 5, we discuss advantages of the models in discrete time.

2 Preliminaries

Definition 2.1. Let $a \in \mathbb{R}$ and $h \in \mathbb{R}^+$. The backward h -difference operator for a function $f : h\mathbb{N}_a \rightarrow \mathbb{R}$ is defined by

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

where $h\mathbb{N}_a = \{a, a+h, a+2h, \dots\}$, and the n th-order backward h -difference operator for f is defined recursively by

$$\nabla_h^n f(t) = \nabla_h \nabla_h^{n-1} f(t), \quad t = a+nh, a+(n+1)h, \dots$$

We note that if $h = 1$, we have the backward difference operator, or nabla operator (∇)

$$(\nabla f)(t) = f(t) - f(t-1), \quad t \in \mathbb{N}_a$$

Definition 2.2. [21] For any $t, r \in \mathbb{R}$ and $h > 0$, the h -rising factorial function is defined by

$$t_{\bar{h}} = h^r \frac{\Gamma(\frac{t}{h} + r)}{\Gamma(\frac{t}{h})},$$

where the quotient is well-defined. Here $\Gamma(\cdot)$ denotes the Euler gamma function.

Definition 2.3. [7] Let $\alpha > 0$ and a be two real numbers. For a function $f : h\mathbb{N}_a \rightarrow \mathbb{R}$, the nabla h -fractional sum with order α is defined by

$$\nabla_{h,a}^{-\alpha} f(t) := \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^{t/h} (t - \rho(sh))_{\bar{h}}^{\alpha-1} f(sh)h, \quad t \in h\mathbb{N}_a.$$

where $h > 0$ and $\rho(t) = t - h$.

We note that if $h = 1$, then we have the α -th order fractional sum operator [4]

$$\nabla_{1,a}^{-\alpha} f(t) = \sum_{s=a}^t \frac{(t - \rho(s))^{\alpha-1}}{\Gamma(\alpha)} f(s), \quad t \in \mathbb{N}_a. \quad (2.1)$$

In the rest of the paper, we write $\nabla_a^{-\alpha}$ for $\nabla_{1,a}^{-\alpha}$.

Definition 2.4. [7] The nabla h -fractional difference of order α in the sense of Riemann-Liouville is defined by

$$\nabla_{h,a}^{\alpha} f(t) := \nabla_h^n \nabla_{h,a}^{-(n-\alpha)} f(t), \quad t \in h\mathbb{N}_a.$$

where $a, \alpha \in \mathbb{R}$, $n-1 < \alpha < n$, and n is a positive integer.

Lemma 2.1. Let a be any real number and $\alpha \in (0, 1)$. Let function $k : \mathbb{N}_{a/h} \rightarrow h\mathbb{N}_a$ be defined by

$$k(u) := uh$$

and $y : h\mathbb{N}_a \rightarrow \mathbb{R}$. Then the following hold:

- i) $\nabla_h y(uh) = \frac{\nabla(y \circ k)(u)}{h}$
- ii) $\nabla_{h,a}^{\alpha} y(uh) = h^{-\alpha} \nabla_{a/h}^{\alpha} (y \circ k)(u)$

where $u \in \mathbb{N}_{a/h+1}$.

Proof. The proof i) is straightforward. Hence we omit its proof here. To prove ii), we claim that $\nabla_{h,a}^{-\alpha} y(uh) = h^{\alpha} \nabla_{a/h}^{-\alpha} (y \circ k)(u)$ for $u \in \mathbb{N}_{a/h}$. Indeed, we have

$$\begin{aligned} \nabla_{h,a}^{-\alpha} y(uh) &= \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^u (uh - \rho(sh))_{\bar{h}}^{\alpha-1} y(sh)h \\ &= \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^u \frac{\Gamma(\frac{uh-sh+h}{h} + \alpha - 1)}{\Gamma(\frac{uh-sh+h}{h})} h^{\alpha} y(sh) \\ &= \frac{h^{\alpha}}{\Gamma(\alpha)} \sum_{s=a/h}^u \frac{\Gamma(u-s+\alpha)}{\Gamma(u-s+1)} y(sh) \end{aligned}$$

$$\begin{aligned}
&= \frac{h^\alpha}{\Gamma(\alpha)} \sum_{s=a/h}^u (u-s+1)^{\overline{\alpha-1}} y(sh) \\
&= h^\alpha \sum_{s=a/h}^u \frac{(u-s+1)^{\overline{\alpha-1}}}{\Gamma(\alpha)} (y \circ k)(s) \\
&= h^\alpha \nabla_{a/h}^{-\alpha} (y \circ k)(u)
\end{aligned}$$

where $u \in \mathbb{N}_{a/h}$.

We use Definition 2.4 and i) to obtain the desired identity. Indeed, we have

$$\begin{aligned}
\nabla_{h,a}^\alpha y(uh) &= \nabla_h \nabla_{h,a}^{-(1-\alpha)} y(uh) \\
&= \nabla_h (\nabla_{h,a}^{-(1-\alpha)} \circ y)(uh) \\
&= h^{-1} \nabla (\nabla_{h,a}^{-(1-\alpha)} \circ y \circ k)(u) \\
&= h^{-1} \nabla (\nabla_{h,a}^{-(1-\alpha)} y(uh)) \\
&= h^{-1} \nabla h^{1-\alpha} \nabla_{a/h}^{-(1-\alpha)} (y \circ k)(u) \\
&= h^{-\alpha} \nabla_{a/h}^\alpha (y \circ k)(u),
\end{aligned}$$

where $u \in \mathbb{N}_{a/h+1}$. □

The following theorem states the variation of constant formula in $h\mathbb{N}_a$. This theorem has been stated and proved for any time scale in [11].

Theorem 2.5. Assume $h > 0$, $\lambda \in \mathbb{R} \setminus \left\{-\frac{1}{h}\right\}$ and t_0 is any real number. Then the first order nabla h -difference equation

$$\nabla_h y(t) = -\lambda y(t) + f(t) \quad \text{for } t \in h\mathbb{N}_{t_0+h}, \quad (2.2)$$

has the general solution

$$y(t) = c(1+h\lambda)^{\frac{t_0-t}{h}} + \sum_{s=t_0/h+1}^{\frac{t}{h}} (1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h,$$

where c is constant.

The following theorem states the variation of constant formula for α -th order discrete fractional equation in $\mathbb{N}_a$. For the proof of the theorem we refer the reader to an article by Atıcı and Eloe [3]. Let α be a real number between zero and one.

Theorem 2.6. Let A be a $n \times n$ constant matrix with eigenvalues of modulus less than one and suppose f is a vector valued function. Then the initial value problem

$$\nabla_0^\alpha y(t) = Ay(t) + f(t) \quad \text{for } t \in \mathbb{N}_1, \quad (2.3)$$

$$\nabla_0^{-(1-\alpha)} y(t)|_{t=0} = y(0), \quad (2.4)$$

has a unique solution. Moreover, this solution is given by

$$y(t) = (t+1)^{\overline{\alpha-1}} F_{\alpha,\alpha}(A(t+\alpha)^{\overline{\alpha}})(I-A)y(0) + \sum_{s=1}^t (t-\rho(s))^{\overline{\alpha-1}} F_{\alpha,\alpha}(A(t+\alpha-1-\rho(s))^{\overline{\alpha}})f(s),$$

where

$$F_{\alpha,\alpha}(A(t+\alpha)^{\bar{\alpha}}) = \sum_{k=0}^{\infty} \frac{A^k(t+\alpha)^{\bar{k}\alpha}}{\Gamma((k+1)\alpha)}.$$

Now we are in a position to state and prove the variation of constant formula for fractional h -difference equations.

Theorem 2.7. Assume $h > 0$ and $\lambda, c \in \mathbb{R}$ such that $|\lambda h^\alpha| < 1$. The h -fractional difference equation

$$\nabla_{h,0}^\alpha y(t) = -\lambda y(t) + f(t) \quad \text{for } t \in h\mathbb{N}_h \quad (2.5)$$

has the general solution

$$y(t) = y_\lambda^*(t, 0)(1 + \lambda h^\alpha)c + \sum_{s=1}^{t/h} y_\lambda^*(t - sh, 0)f(sh)h^\alpha$$

where c is constant and

$$y_\lambda^*(t, 0) = \frac{1}{h^{\alpha-1}} \sum_{n=0}^{\infty} \frac{(-\lambda)^n (t+h)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)}.$$

Proof. Replacing t by uh and using Lemma 2.1-(ii), we write the Equation (2.5) as a fractional difference equation

$$\nabla_0^\alpha (y \circ k)(u) = -\lambda h^\alpha (y \circ k)(u) + h^\alpha (f \circ k)(u),$$

for $u \in \mathbb{N}_h$. Then we use Theorem 2.6 to obtain the desired result. $\square$

Next we consider the following initial value problem

$$\nabla_{h,0}^\alpha y(t) = -\lambda y(t) \quad t \in h\mathbb{N}_h \quad (2.6)$$

$$y(0) = 1 \quad (2.7)$$

where $|\lambda h^\alpha| < 1$. By Theorem 2.7, the unique solution of this IVP is

$${}_h\hat{e}_{\alpha,\alpha}(-\lambda, t_h^{\bar{\alpha}}) := (1 + \lambda h^\alpha) \frac{1}{h^{\alpha-1}} \sum_{n=0}^{\infty} \frac{(-\lambda)^n (t+h)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)},$$

for $t \in h\mathbb{N}_0$.

Lemma 2.2. Let $0 < \alpha < 1$. The following are valid:

- i) ${}_h\hat{e}_{\alpha,\alpha}(-\lambda, t_h^{\bar{\alpha}})$ converges absolutely if $|\lambda h^\alpha| < 1$.
- ii) ${}_h\hat{e}_{\alpha,\alpha}(-\lambda, t_h^{\bar{\alpha}}) \rightarrow 0$ as $t \rightarrow \infty$ if $0 \leq |\lambda h^\alpha| < 1$.

Proof. One can easily see that ${}_h\hat{e}_{\alpha,\alpha}(-\lambda, t_h^{\bar{\alpha}}) = \hat{e}_{\alpha,\alpha}(-\lambda h^\alpha, (\frac{t}{h})^{\bar{\alpha}})$, where $\hat{e}_{\alpha,\alpha}(-\lambda, t^{\bar{\alpha}})$ is the unique solution the IVP

$$\begin{aligned} \nabla_0^\alpha y(t) &= -\lambda y(t) \quad \text{for } t \in \mathbb{N}_1, \\ y(0) &= 1. \end{aligned}$$

Hence the proof (i) and (ii) follow from Theorem 3.2 in [6] and Theorem 2.4 in [16], respectively. $\square$

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 [22] 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 [23].

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 $h\mathbb{N}_0$ with $h > 0$. Hence we have

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

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

We solve the above system of difference equations by using Theorem 2.5. Hence we have

$$\begin{aligned}u(t) &= u(0) \frac{1}{(1 + hb)^{\frac{t}{h}}} + h \sum_{s=1}^{\frac{t}{h}} \frac{1}{(1 + hb)^{\frac{t}{h}-s+1}} (a - k_2 c(sh)), \quad t = 0, h, 2h, \dots, \\ x_1(t) &= e^{u(t)} \quad t = 0, h, 2h, \dots\end{aligned}$$

$$\begin{aligned}x_2(t) &= k_2 h \sum_{s=1}^{\frac{t}{h}} \frac{1}{(1 + hk_1)^{\frac{t}{h}-s+1}} (c(sh)x_1(sh)), \quad t = 0, h, 2h, \dots, \\ x_3(t) &= k_1 h \sum_{s=1}^{\frac{t}{h}} \frac{1}{(1 + hk_1)^{\frac{t}{h}-s+1}} x_2(sh), \quad t = 0, h, 2h, \dots\end{aligned}$$

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

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

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

We use Theorem 2.7 as a tool to obtain the following solutions.

$$u(t) = y_b^*(t, 0)(1 + bh^\alpha)u(0) + \sum_{s=1}^{(t/h)} y_b^*(t - sh, 0)(a - k_2 c(sh))h^\alpha, \quad t = 0, h, 2h, \dots,$$

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

$$x_2(t) = \sum_{s=1}^{(t/h)} y_{k_1}^*(t - sh, 0)(k_2 c(sh)x_1(sh))h^\alpha, \quad t = 0, h, 2h, \dots$$

$$x_3(t) = \sum_{s=1}^{(t/h)} y_{k_1}^*(t - sh, 0)(k_1 x_2(sh))h^\alpha, \quad t = 0, h, 2h, \dots,$$

where

$$y_\lambda^*(t, 0) = \sum_{n=0}^{\infty} \frac{(-\lambda)^n h^{n\alpha} \Gamma(\frac{t}{h} + n\alpha + \alpha)}{\Gamma((n+1)\alpha) \Gamma(\frac{t}{h} + 1)}.$$

3.2 The construction principle for the discrete equations

We briefly explain the idea behind the construction principle for the discrete equations we introduced here and in the paper [5]. We consider two possible discretization techniques:

T1. First order derivatives in the continuous model can be approximated by use of the Δ_h operator, i.e. $x'(t) \simeq \Delta_h x(t)$, where $\Delta_h x(t) = \frac{x(t+h) - x(t)}{h}$. Since $\Delta_h x(t) = \nabla_h x(t+h)$, the discrete equations can be written with $\nabla_h x(t)$ following by h unit back shift on the time dependent variables on the right side of the equations.

T2. First order derivatives in the continuous model can be approximated by use of the ∇_h operator, i.e. $x'(t) \simeq \nabla_h x(t)$, where $\nabla_h x(t) = \frac{x(t) - x(t-h)}{h}$.

In [5], the authors employed the technique T1 to discretize the first order differential equations in the continuous model. Later in the simulations, some limitations occurred in the discrete models. One of the concern was the jump in the hourly model when the drug concentration $c(t)$ was multiplied by some numbers 10, 20, 100, as it was illustrated in Figure 3 in [5]. In this paper, we employ the technique T2. In the later sections, we justify that the new discrete models are as good as the continuous model in data fitting, and even better for some cases. As we illustrate in Figure 1, the new discrete models address all shortcomings listed in [5]. In this sense, the discrete models which are introduced in this paper can be considered as the improved PK-PD models in discrete time.

3.3 Tumor growth and drug concentration data

Data was taken from the supplemental material of [22]. These data describe the tumor volume measurements in Xenograft mice treated with different compounds. For more details see [22].

4 Parameter estimates

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

$$W_j = f_j(\beta) + \epsilon_j; j = 1, \dots, n, \quad (4.1)$$

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 $\epsilon_j, j = 1, \dots, n$ represents 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 from the tumor growth inhibition model, 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 $Var[\epsilon_j] = \sigma_0^2$, 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

$$SS(\beta) = \sum_{i=1}^n (f_j(\beta) - y_j)^2. \quad (4.2)$$

Since the realized data for both unperturbed and perturbed tumor growth are available, both sets are utilized simultaneously in fitting the growth curves (with and without drugs) and obtaining estimated parameters. The unperturbed growth curves are similar to the perturbed counterpart excepts for concentration $c(t) = 0$ for all t .

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 $\Sigma_0 = \sigma_0^2[\chi^T(\beta)\chi(\beta)]^{-1}$

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

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 $\hat{\beta}_k$ 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 $\hat{a}, \hat{b}, \hat{\alpha}, \hat{k}_1$, and $\hat{k}_2$ for parameters a, b, α, k_1 and k_2 of the discrete fractional model are obtained based on the exact solutions for the h -discrete and h -discrete fractional models. The estimates of parameters can be obtained by minimizing the residual sum of squares SS using the statistical software package R. Then the sensitivity matrix $\chi(\hat{\beta})$ can be derived. The point estimates and the 90% confidence intervals of the parameters for the discrete model are included in Table 1 and those for the discrete fractional model are in Table 2. Table 3 gives residual sum of squares RSS values for all drugs being fitted using continuous, discrete, and discrete fractional models using unperturbed and perturbed data simultaneously.

Comparing the RSS values between the discrete model and the discrete fractional model for the same drugs, we can see that the discrete fractional models give better fit compared to the discrete counterpart for three drugs A2-120, B-100, and C-150. In three out of five drugs, the discrete models gives slightly better fit than the continuous models. Note that the estimated parameters and thus RSS for the continuous model are obtained from the numerical ODE solver, while the estimated parameters and RSS are obtained from fitting the exact solutions for the discrete and discrete fractional models.

Table 1: Parameter estimates for the discrete models

<i>Drug</i>	<i>Parameter</i>	<i>PointEstimate</i>	<i>90%ConfidenceInterval</i>
A – 180	u_0	–3.175632	(–3.239106, –3.112158)
	a	0.136117	(0.13504, 0.137194)
	b	0.060554	(0.05917, 0.061938)
	k_1	4.482323	(2.603571, 6.361074)
	k_2	0.308696	(0.303989, 0.313403)
A2 – 120	u_0	–3.241787	(–3.358222, –3.125352)
	a	0.136932	(0.135004, 0.13886)
	b	0.059379	(0.056922, 0.061836)
	k_1	1.885773	(1.676879, 2.094667)
	k_2	0.008851	(0.008215, 0.009487)
B – 100	u_0	–5.108226	(–5.200344, –5.016108)
	a	0.1518	(0.151254, 0.152346)
	b	0.083937	(0.082233, 0.085641)
	k_1	0.407038	(0.38491, 0.429166)
	k_2	0.013888	(0.013546, 0.01423)
C – 100	u_0	–3.312055	(–3.312337, –3.311773)
	a	0.138427	(0.130744, 0.14611)
	b	0.0643	(0.059691, 0.068908)
	k_1	996.996848	(994.5671, 999.4265)
	k_2	0.018319	(0.017376, 0.019262)
C – 150	u_0	–4.688894	(–4.767446, –4.610342)
	a	0.147844	(0.147328, 0.14836)
	b	0.078886	(0.077287, 0.080485)
	k_1	7.114879	(4.32558, 9.904178)
	k_2	0.013196	(0.013031, 0.013361)

5 Conclusions

Calculus on a time scale $h\mathbb{N}_0$ serves as a bridge between calculus on $\mathbb{R}^+$ and calculus on $\mathbb{N}_0$. In applied mathematics, there are many problems where h -difference equations are obtained by approximating either ordinary differential equations (ODEs) or partial differential equations (PDEs). The main goal is to simplify the problem so that the qualitative behavior of solutions of ODEs or PDEs can be obtained accordingly.

In this study, we discretize the PK-PD model in continuous time. Since the concentration of each drug was measured hourly, we have $h\mathbb{N}_0$ as the domain of the discrete model. We introduce a new set of PK-PD models which behave similar to the PK-PD models in continuous time. These new models bring some advantages compared to previously known models. They are elementary to work with and they also are quite accurate in data fitting. The latest techniques in data fitting require us to use ODE solver which applies some numerical approximations to the model in continuous time. Here the new models do not require us to use any approximation techniques. We solve them analytically and use their explicit solutions directly in our codes. As we demonstrated in Figure 1 the new models possess the fundamental properties of PK-PD model when we increase the dose.

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Table 2: Parameter estimates for the discrete fractional models

<i>Drug</i>	<i>Parameter</i>	<i>PointEstimate</i>	<i>90%ConfidenceInterval</i>
A – 180	u_0	–9.758875	(–14.031835, –5.485915)
	a	0.218072	(0.178465, 0.257679)
	b	0.070423	(0.06946, 0.071386)
	k_1	1	(0.74683, 1.25317)
	k_2	0.512681	(0.409866, 0.615496)
	α	0.83298	(0.766106, 0.899854)
A2 – 120	u_0	–30.70348	(–33.509097, –27.897863)
	a	0.348938	(0.336292, 0.361583)
	b	0.077499	(0.069408, 0.08559)
	k_1	0.000603	(–0.025396, 0.026602)
	k_2	0.000744	(–0.0006, 0.002088)
	α	0.669374	(0.651485, 0.687263)
B – 100	u_0	–13.092971	(–14.127705, –12.058237)
	a	0.235815	(0.227604, 0.244026)
	b	0.092708	(0.089948, 0.095468)
	k_1	0.157305	(0.128354, 0.186256)
	k_2	0.028494	(0.027016, 0.029972))
	α	0.849753	(0.837448, 0.862058)
C – 100	u_0	–74.563004	(–102.15329, –46.97272)
	a	0.48059	(0.4184, 0.54278)
	b	0.043052	(0.028323, 0.057781)
	k_1	0.898381	(0.681062, 1.1157)
	k_2	0.067926	(0.056684, 0.079168)
	α	0.505903	(0.44559, 0.566216)
C – 150	u_0	–125.967968	(–146.49701, –105.43899)
	a	0.598447	(0.564046, 0.632848)
	b	0.057664	(0.04402, 0.071308)
	k_1	0.489675	(0.365487, 0.613863)
	k_2	0.059227	(0.053655, 0.064799)
	α	0.475421	(0.447283, 0.503559)

Table 3: RSS values for different models

<i>Drug</i>	<i>Continuous(ODESolver)</i>	<i>Discrete</i>	<i>DiscreteFractional</i>
A – 180	0.151127	0.151114	0.163661
A2 – 120	0.2699	0.268172	0.255162
B – 100	0.034676	0.034689	0.031645
C – 100	0.166268	0.166281	0.192427
C – 150	0.033695	0.033694	0.029003

Figure 1: Simulations with the dose multiplied by the factors 1, 10 and 100

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