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# h-Discrete Fractional Model of Tumor Growth and Anticancer Effects of Mono and Combination Therapies

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# $h$–DISCRETE FRACTIONAL MODEL OF TUMOR GROWTH AND ANTICANCER EFFECTS OF MONO AND COMBINATION THERAPIES

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"But how could you live and have no story to tell?"- Fyodor Dostoevsky. This quote has always been my motivation when I faced difficult days in my life. It pushes me to think that obstacles and unhappy moments in our lives should not stop us from improving ourselves and to creating our own stories.

I would like to dedicate my first academic work to my dear mother who has put a great deal of effort in raising and supporting us in over the years. I would like to express my thanks for everything you have done for me, Mom.

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Contents

$h$–DISCRETE FRACTIONAL MODEL OF TUMOR GROWTH AND ANTICANCER EFFECTS OF MONO AND COMBINATION THERAPIES

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In this thesis, we focus on $h$–discrete and $h$–discrete fractional representation of a pharmacokinetics-pharmacodynamics (PK-PD) model which describes tumor growth considering time on $h\mathbb{N}_a$, where $h > 0$. First, we introduce some definitions, lemmas and theorems on both $h$–discrete and $h$–discrete fractional calculus in the preliminary section. In Chapter 3, we work on the PD model with delay by examining nabla $h$–discrete equations and nabla $h$–discrete fractional equations as well as variation of constants formulas, accordingly. We introduce our model and solve it using theorems we proved in the last section of the indicated chapter. When we do simulation for the solutions we found that jumps occur when drug was given the first time. Therefore, we decide to work on PD model without delay in Chapter 4. We also obtain theorems regarding nabla $h$–discrete equations and nabla $h$–discrete fractional equations ignoring delay. We apply our results to the tumor growth model to find solutions. We observe that jumps disappear on this model once we put new solutions into code. Although, we do not attain our wanted goal for tumor growth model having delay, we decide to write it as a chapter in this thesis because the theorems and lemmas found in Chapter 3 might be useful for another research work in the future. In Chapter 5, we give our PK model considering both delay and without delay case, then solutions of the models are stated accordingly. In the last chapter, we summarize what we have done so far and mention future works regarding continuation of this work.

# Chapter 1
# INTRODUCTION

Discretization in applied mathematics is a procedure which transfers continuous models, functions and equations into discrete form using operators, namely both delta and nabla operators. Our first aim in starting this process is to make them appropriate for numerical calculation and implementation on computers. Fractional calculus studies some various potentials which define the complex number or real number powers of the differentiation operator and of the integration operator. It has many applications for fields such as finance, medicine and engineering [29],[3],[7],[9],[10].

Fractionalization of mathematical models in the area of phamacodynamics and phamacokinetics is not new but it has not really prevailed [30],[33]. Mathematical complexity is one of the reasons that creates difficulties when numerical methods are implemented by the users. In clinical setting with populations comprising of several hundreds of patients, the run-time involved would be a second reason. In paper [3], the authors worked on PK-PD model starting with discretizing and then fractionalizing. An explicit solution was found for the indicated model without implementing any numerical methods. Nevertheless, as the authors stated in their paper [3], some limitations of the discretization approach appeared in the discrete model for $h = 1$.

The first property of the tumor growth model, which states that tumor growth is inhibited while its treatment, fails in simulation process once obtained the solution is implemented. Simulation demonstrates that as dose is increasing the tumor volume is increasing in the beginning after decrease is observed in treatment. In discrete model, the effect of the drug is seen after the day the drug is administrated to the blood because of the nature of solutions. The graph of the discrete model does not show any decrease in tumor volume right away after drug administration.

The second property of the model,that tumor volume will never be negative, holds true for the discrete model $h = \frac{1}{24}$ on $h\mathbb{N}_0^h$ but not for $h = 1$. Tumor volume is going to be negative while increasing doses significantly. The authors stated in the paper [3] that this is not reasonable not only from the mathematical side but also from the biological point of view.

As the authors maintained, the discrete model for $h = 1$ loses some important properties that hold true for the continuous model. Our motivation to write this thesis is based on removing these limitations in the model. While simulation was done for daily drug concentration, we now consider $c(t)$-drug concentration values for each hour rather than only one time in a day.

# Chapter 2
# PRELIMINARIES

In this chapter, we give fundamental theorems, lemmas and definitions on $h$–discrete calculus and $h$–discrete fractional calculus. In order to acquire basic knowledge regarding discrete fractional calculus, we refer [20] to the readers.

**Definition 2.1.** *Let $a \in \mathbb{R}$. Nabla operator $(\nabla)$ which is also known as the backward difference operator for a function $f : \mathbb{N}_a \longrightarrow \mathbb{R}$ is defined by*

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

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

**Definition 2.2.** *Let $a \in \mathbb{R}$ and $h > 0$. Nabla $h$–operator $(\nabla_h)$ which is also known as the backward $h$–difference operator for a function $f : h\mathbb{N}_a \longrightarrow \mathbb{R}$ with a domain $h\mathbb{N}_a = \{a, a+h, a+2h, ....\}$ is defined by*

$$\nabla_h f(t) := \frac{f(t) - f(\rho_h(t))}{t - \rho_h(t)} = \frac{f(t) - f(t-h)}{h},$$

*where $\rho_h(t) = t - h$ is backward jump operator on time scale calculus [20].*

**Definition 2.3.** *[3] Let $\alpha \in \mathbb{R}$. $t^{\overline{\alpha}}$ is known as a rising factorial power (read as 't to the $\alpha$ rising') is defined by*

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

*such that $t \in \mathbb{R} \setminus \{..., -2, -1, 0\}$, $0^{\overline{\alpha}} = 0$ and $\Gamma$ denotes the Gamma function [24].*

**Definition 2.4.** *Let $\alpha \in \mathbb{R}$ and $h > 0$. The nabla $h$-factorial of $t$ is defined by*

$$t_h^{\overline{\alpha}} := h^{\alpha} \frac{\Gamma(\frac{t}{h} + \alpha)}{\Gamma(\frac{t}{h})}$$

*where* $t \in \mathbb{R} \setminus \{...., -2h, -h, 0\}$, $0_h^{\overline{\alpha}} = 0$, *and* $\Gamma$ *denotes the Gamma function [24].*

We present the $\alpha$-th order fractional sum of $f$ defined as in [5]

$$\nabla_a^{-\alpha} f(t) := \sum_{s=a}^{t} \frac{(t-\rho(s))^{\overline{\alpha-1}}}{\Gamma(\alpha)} f(s), \tag{2.0.1}$$

where $\alpha \geq 0$, $\rho(t) = t-1$, and $t \in \mathbb{N}_a$. In addition, we recall the definition of $\alpha$-th order fractional difference of $f$ which is also known as a Riemann-Liouville (RL) fractional difference

$$\nabla^{\alpha} f(t) := \nabla^n (\nabla^{-(n-\alpha)} f(t)),$$

where $\alpha > 0$, $n-1 < \alpha < n$, $n$ is a positive integer [5].

**Definition 2.5** (Nabla h–fractional sum). *Let* $\alpha > 0$ *and* $a$ *be any real number. For a function* $f : h\mathbb{N}_a \longrightarrow \mathbb{R}$, *the nabla h–fractional sum with order* $\alpha$ *is defined by*

$$\left({}_a\nabla_h^{-\alpha} f\right)(t) := \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^{t/h} \left(t - \rho_h(sh)\right)_h^{\overline{\alpha-1}} f(sh)h, \quad t \in h\mathbb{N}_a.$$

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

**Definition 2.6** (Nabla $h$–fractional difference.). *The nabla* $h$*–fractional difference of order* $\alpha$ *is defined by*

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

*where* $a \in \mathbb{R}$, $\alpha, h > 0$, $n-1 < \alpha < n$, *and* $n$ *is a positive integer.*

Let us introduce the properties of the rising factorial power functions. While the proof of the first property is given in [31], we make a generalization and give the general power rule as a second property.

**Lemma 2.7.** *Let $a$ be any real number and $h > 0$, $\alpha > 0$, $\mu > 0$ be positive numbers. Whenever the expressions on each side of the equality are valid, these succeeding properties hold.*

*(i)* $\nabla_h t_h^{\overline{\mu}} = \mu t_h^{\overline{\mu-1}}$ *where* $t \in h\mathbb{N}_a$.

*(ii)* ${}_a\nabla_h^{-\alpha}(t-a+h)_h^{\overline{\mu}} = \dfrac{\Gamma(\mu+1)}{\Gamma(\mu+\alpha+1)}(t-a+h)_h^{\overline{\mu+\alpha}}$ *where* $t \in h\mathbb{N}_a$.

*Proof.* $(ii)$ By using the definition of the nabla $h$–fractional sum operator, we obtain

$$\begin{aligned}
{}_a\nabla_h^{-\alpha}(t-a+h)_h^{\overline{\mu}} &= \frac{1}{\Gamma(\alpha)}\sum_{s=a/h}^{t/h}\big(t-\rho_h(sh)\big)_h^{\overline{\alpha-1}}(sh-a+h)_h^{\overline{\mu}}h \\
&= \frac{1}{\Gamma(\alpha)}\sum_{s=a/h}^{t/h} h^{\alpha-1}\frac{\Gamma(\frac{t-sh+h}{h}+\alpha-1)}{\Gamma(\frac{t-sh+h}{h})}h^{\mu}\frac{\Gamma(\frac{sh-a+h}{h}+\mu)}{\Gamma(\frac{sh-a+h}{h})}h \\
&= \frac{h^{\alpha+\mu}}{\Gamma(\alpha)}\sum_{s=a/h}^{t/h}\frac{\Gamma(\frac{t}{h}-s+\alpha)}{\Gamma(\frac{t}{h}-s+1)}\frac{\Gamma(s-\frac{a}{h}+\mu+1)}{\Gamma(s-\frac{a}{h}+1)} \\
&= \frac{h^{\alpha+\mu}}{\Gamma(\alpha)}\sum_{s=0}^{(t-a)/h}\frac{\Gamma(\frac{t-a}{h}-s+\alpha)}{\Gamma(\frac{t-a}{h}-s+1)}\frac{\Gamma(s+\mu+1)}{\Gamma(s+1)} \\
&= \frac{h^{\alpha+\mu}}{\Gamma(\alpha)}\sum_{s=0}^{(t-a)/h}\binom{\frac{t-a}{h}}{s}\frac{\Gamma(s+\mu+1)\Gamma(\frac{t-a}{h}-s+\alpha)}{\Gamma(\frac{t-a}{h}+1)},
\end{aligned}$$

where we used the formula

$$\binom{u}{v} = \frac{\Gamma(u+1)}{\Gamma(v+1)\Gamma(u-v+1)},$$

where $u$ and $v$ are natural numbers. Next, we apply the following identity given in [2] into our problem

$$\sum_{v=0}^{u}\binom{u}{v}\alpha^{\overline{v}}\beta^{\overline{u-v}} = (\alpha+\beta)^{\overline{u}},$$

where $u, v$ are natural numbers and $\alpha, \beta$ are positive real numbers.

Hence, we have

$$\frac{h^{\alpha+\mu}}{\Gamma(\alpha)}\sum_{s=0}^{(t-a)/h}\binom{\frac{t-a}{h}}{s}\frac{\Gamma(s+\mu+1)\Gamma(\frac{t-a}{h}-s+\alpha)}{\Gamma(\frac{t-a}{h}+1)} = h^{\alpha+\mu}\frac{\Gamma(\mu+1)}{\Gamma(\frac{t-a}{h}+1)}\sum_{s=0}^{t-a/h}\binom{\frac{t-a}{h}}{s}(\mu+1)^{\overline{s}}\alpha^{\overline{\frac{t-a}{h}-s}}$$

$$= h^{\alpha+\mu}\frac{\Gamma(\mu+1)}{\Gamma(\frac{t-a}{h}+1)}(\mu+1+\alpha)^{\overline{\frac{t-a}{h}}}.$$

Using the definition of nabla rising factorial and nabla $h$–factorial, we get the following result which completes the proof.

$$h^{\alpha+\mu}\frac{\Gamma(\mu+1)}{\Gamma(\frac{t-a}{h}+1)}(\mu+1+\alpha)^{\overline{\frac{t-a}{h}}} = h^{\alpha+\mu}\frac{\Gamma(\mu+1)}{\Gamma(\frac{t-a}{h}+1)}\frac{\Gamma(\mu+1+\alpha+\frac{t-a}{h})}{\Gamma(\mu+1+\alpha)}$$

$$= \frac{\Gamma(\mu+1)}{\Gamma(\mu+\alpha+1)}(t-a+h)_h^{\overline{\mu+\alpha}}.$$

□

**Theorem 2.8** (Leibniz rule on $h\mathbb{N}_a$)**.** *Let $a$ be any real number, $h > 0$, and $t \in h\mathbb{N}_a$. Then for a function $f : h\mathbb{N}_a \longrightarrow \mathbb{R}$ the following identities are true.*

*(i)* $\nabla_h \sum_{s=a}^{t/h} f(t,s) = \sum_{s=a}^{t/h} \nabla_h f(t,s) + \dfrac{f(t-h,\frac{t}{h})}{h}.$

*(ii)* $\nabla_h \sum_{s=a}^{t/h} f(t,s) = \sum_{s=a}^{(t/h)-1} \nabla_h f(t,s) + \dfrac{f(t,\frac{t}{h}-1)}{h}.$

*Proof.* $(i)$ We can rewrite the right hand side of the equation by means of the backward difference operator,

$$\nabla_h \sum_{s=a}^{t/h} f(t,s) = \frac{\sum_{s=a}^{t/h} f(t,s) - \sum_{s=a}^{(t-h)/h} f(t-h,s) + f(t-h,\frac{t}{h}) - f(t-h,\frac{t}{h})}{h}$$

$$= \frac{\sum_{s=a}^{t/h} f(t,s) - \sum_{s=a}^{t/h} f(t-h,s)}{h} + \frac{f(t-h,\frac{t}{h})}{h}$$

$$= \sum_{s=a}^{t/h} \nabla_h f(t,s) + \frac{f(t-h, \frac{t}{h})}{h}.$$

$(ii)$ Using backward difference operator, we have

$$\nabla_h \sum_{s=a}^{(t/h)} f(t,s) = \frac{\sum_{s=a}^{(t/h)} f(t,s) - \sum_{s=a}^{(t-h)/h-1} f(t-h,s)}{h}$$

$$= \frac{\sum_{s=a}^{(t/h)-1} f(t,s) - \sum_{s=a}^{(t/h)-1} f(t-h,s) + f(t, \frac{t}{h} - 1)}{h}$$

$$= \sum_{s=a}^{(t/h)-1} \nabla_h f(t,s) + \frac{f(t, \frac{t}{h} - 1)}{h}.$$

□

Subsequently, we introduce the connection between the nabla $h-$ the discrete operator and the discrete operator. Additionally, we present the relationship between nabla $h$–fractional difference operator and the discrete fractional difference operator. To the best of our knowledge, those connections are not found elsewhere in the literature.

**Lemma 2.9.** *Let $a$ be any real number, $h > 0$, and $t \in h\mathbb{N}_a$. Define the function $k : \mathbb{N}_{a/h} \longrightarrow h\mathbb{N}_a$*

$$k(u) := uh$$

*and $y : h\mathbb{N}_a \longrightarrow \mathbb{R}$. Then*

$$\nabla_h y(uh) = \frac{\nabla (y \circ k)(u)}{h}$$

*where $u = \frac{t}{h} \in \mathbb{N}_{a/h}$.*

*Proof.* Using the definition of nabla operator,

$$\nabla_h y(t) = \frac{y(t) - y(t-h)}{h}$$

we substitute $t = uh$ and obtain ,

$$\begin{aligned}\nabla_h y(uh) &= \frac{y(uh) - y(uh-h)}{h} \\ &= \frac{y(k(u)) - y(k(u-1))}{h} \\ &= \frac{\nabla(y \circ k)(u)}{h},\end{aligned}$$

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

□

**Lemma 2.10.** *Let $\alpha, h > 0$, $a$ be any real number,and the function $k$ be defined as $k : \mathbb{N}_{a/h} \longrightarrow h\mathbb{N}_a$*

$$k(u) := uh.$$

*And let $y : h\mathbb{N}_a \longrightarrow \mathbb{R}$. Then*

$$_a\nabla_h^{\alpha} y(uh) = h^{-\alpha} \nabla_{a/h}^{\alpha} (y \circ k)(u)$$

*where $u = \frac{t}{h} \in \mathbb{N}_{a/h}$.*

*Proof.* We first find a relation between $\nabla_h^{-\alpha}$ and $\nabla^{-\alpha}$

$$\begin{aligned}_a\nabla_h^{-\alpha} y(uh) &= \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^{u} \left(uh - \rho_h(sh)\right)_h^{\overline{\alpha-1}} y(sh)h \\ &= \frac{1}{\Gamma(\alpha)} \sum_{s=a/h}^{u} \frac{\Gamma(\frac{uh-sh+h}{h} + \alpha - 1)}{\Gamma(\frac{uh-sh+h}{h})} h^{\alpha} y(sh)\end{aligned}$$

$$= \frac{h^{\alpha}}{\Gamma(\alpha)} \sum_{s=a/h}^{u} \frac{\Gamma(u-s+\alpha)}{\Gamma(u-s+1)} y(sh)$$

$$= \frac{h^{\alpha}}{\Gamma(\alpha)} \sum_{s=a/h}^{u} (u-s+1)^{\overline{\alpha-1}} y(sh)$$

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

$$= h^{\alpha} \nabla_{a/h}^{-\alpha} (y \circ k)(u)$$

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

With help of Definition 2.6 and Lemma 2.9, we obtain

$$_{a}\nabla_{h}^{\alpha} y(uh) = (\nabla_{h}({}_{a}\nabla_{h}^{-(1-\alpha)}))y(uh)$$

$$= \frac{\nabla(({}_{a}\nabla_{h}^{-(1-\alpha)})y \circ k)(u)}{h}$$

$$= \frac{\nabla({}_{a}\nabla_{h}^{-(1-\alpha)} y(uh))}{h}$$

$$= \frac{\nabla(h^{1-\alpha} \nabla_{a/h}^{-(1-\alpha)} (y \circ k)(u))}{h}$$

$$= h^{-\alpha} \nabla_{a/h}^{\alpha} (y \circ k)(u)$$

where $u \in \mathbb{N}_{a/h}$. □

**Theorem 2.11** (Integration by parts). *[22] Let $f, g : h\mathbb{N}_a \longrightarrow \mathbb{R}$ are given, then the following identity*

$$\sum_{s=a}^{t/h} \nabla f(s) g(s) = f(s)g(s)\Big|_{s \to a-1}^{s \to \frac{t}{h}} - \sum_{s=a}^{t/h} f(\rho(s)) \nabla g(s)$$

*holds.*

## Chapter 3

# THE PHARMACODYNAMICS MODEL WITH DELAY

The pharmacodynamics (PD) is a field that focuses on studying biological and physiologic effects of drugs, the relation of the effects to drug exposure and the system of drug movement. Indicated effects can comprise of those observed within microorganisms, animals, or humans. Main significance in PD is the connecting of the drug at the receptor (target) since receptors are the most consequential targets for therapeutic drugs [12, 23].

The main goal of PD modeling is to predict the time curve of the drug effect potency in natural conditions in health and disease [11]. In the process of discovering and developing drugs, the PD modeling has been a principal success factor. As an illustration, optimization of the dosing administration and the delivery profile of new or presenting drugs can be given which demonstrates that PD modeling has a benefit as the theoretical basis [13].

Looking back to history, it was discerned that the answer to pharmacological questions can be found by clinicians and pharmacists employing mathematical models [14], [15]. Despite this fact, it is significant to emphasize that the development of the mathematical PD modeling theory was liberated from the mathematical group. The interpretation of pharmacological concepts in the PD models is the main pivot. Thus, clinical representation of model parameters can be created and rational model performance can be used for simulations. Over the past decades, mathematicians began to make significant contributions to PD modeling with effectual input. Furthermore, a small mathematical group that develops more progressive mathematical and computational approaches has been established within the PD field [28].

Another important ambition of the PD model is to provide an answer to certain clinical questions. For the sake of being more precise, it has been shown that the attainment of mathematical modeling such as in the biopharma industry is contingent on acquiring the correct question, correct model, and correct analysis [1]. Ordinary differential equations play the main role in formulating PD models and they can be improved in such a way that depends on data which means characterizing existing data, or in a more mechanistic perspective, where elaborate underlying physiological mechanisms are depicted [3].

In this chapter, we will consider the PD delayed model for tumor growth. A. K. Laird [27] started mathematical modeling of tumor growth in the 1960s using the application of the Gombertz [19] function to fit data from various animals. By observing the sigmoidal curve, it appeared that the curve fits perfectly to the common tumor growth behaviour which generally passes through three phases, exponential growth at the initial step followed by linear growth and ultimately saturation. Detailed information concerning the delayed model problem is given in Section 3.3 of this chapter. In the beginning, the model is given as a system of differential equations and we use nabla $h$–discrete and nabla $h$–discrete fractional operators to write the model on $h$–discrete calculus and $h$–discrete fractional calculus. Therefore, we introduce the solution of nabla $h$–discrete equations and its variation of constants formula in Section 3.1, and the solution of nabla $h$–discrete fractional equation and its variation of constants formula in Section 3.2. We present the new tumor growth model in Section 3.3 and solve it using theorems obtained in the previous sections.

## 3.1 Nabla $h$–Discrete Equations with Delay

**Theorem 3.1.** *Let $\lambda, c, t_0 \in \mathbb{R}$. The solution of the following initial value problem (IVP)*

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

$$y(t_0) = c$$

*is given by*

$$y(t) = c(1+h\lambda)^{\frac{t-t_0}{h}}$$

*where $h > 0$ and $h\lambda \neq -1$.*

*Proof.* By using the definition of the nabla $h$-discrete operator, we can write

$$\frac{y(t) - y(t-h)}{h} = \lambda y(t-h)$$

$$y(t) = y(t-h)(1+h\lambda).$$

Setting $t = t_0 + h$, the equation yields

$$y(t_0+h) = y(t_0)(1+h\lambda) = c(1+h\lambda),$$

since $y(t_0) = c$. Setting $t = t_0 + 2h$, we have

$$y(t_0+2h) = c(1+h\lambda)^2.$$

Proceeding forward gives us

$$y(t_0 + nh) = c(1 + h\lambda)^n \quad for \quad n \in \mathbb{N}.$$

The above expression can be rewritten as in the following,

$$y(t) = c(1 + h\lambda)^{\frac{t-t_0}{h}}$$

for all $t \in h\mathbb{N}_{t_0+h}$ and $h\lambda \neq -1$. □

Next, we state and prove the variation of constants formula for the non-homogeneous linear equation.

**Theorem 3.2** (Variation of Constants Formula)**.** *Assume $\lambda \in \mathbb{R} \setminus \{-\frac{1}{h}\}$ and $t_0 \in \mathbb{R}$. Then, the first order nabla h–difference equation*

$$(\nabla_h y)(t) = \lambda y(t-h) + f(t-h) \quad for \quad t = t_0 + h, t_0 + 2h, ..., \tag{3.1.1}$$

*has the general solution*

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

*where $h > 0$ and $c \in \mathbb{R}$ constant number.*

*Proof.* Using direct substitution of the solution into (3.1.1), we obtain

$$\begin{aligned}\nabla_h y(t) =& \nabla_h c(1 + h\lambda)^{\frac{t-t_0}{h}} + \nabla_h \sum_{s=t_0/h}^{\frac{t}{h}-1} (1 + h\lambda)^{\frac{t}{h}-s-1} f(sh)h \\ =& c\lambda(1 + h\lambda)^{\frac{t-h-t_0}{h}} + \sum_{s=t_0/h}^{\frac{t}{h}-2} \nabla_h (1 + h\lambda)^{\frac{t}{h}-s-1} f(sh)h\end{aligned}$$

$$+\frac{(1+h\lambda)^{\frac{t}{h}-s-1}f(sh)h}{h}\Big|_{t\to t, s\to\frac{t}{h}-1}$$

$$=c\lambda(1+h\lambda)^{\frac{t-t_0}{h}-1}+\sum_{s=t_0/h}^{\frac{t}{h}-2}\lambda(1+h\lambda)^{\frac{t}{h}-s-2}f(sh)h+f(t-h)$$

$$=\lambda[c(1+h\lambda)^{\frac{t-t_0}{h}-1}+\sum_{s=t_0/h}^{\frac{t}{h}-2}(1+h\lambda)^{\frac{t}{h}-s-2}f(sh)h]+f(t-h)$$

$$=\lambda y(t-h)+f(t-h),$$

where we use Theorem 2.8 $(ii)$ and Theorem 3.1. □

## 3.2 Nabla $h$–Discrete Fractional Equations with Delay

**Theorem 3.3.** *Let $\lambda, c, t_0 \in \mathbb{R}$, $h>0$, and $\alpha \in (0,1)$. A solution of the following initial value problem*

$$_{t_0}\nabla_h^\alpha y(t)=\lambda y(t-h) \quad t=t_0+h, t_0+2h, ..., \tag{3.2.1}$$

$$y(t_0)=c \tag{3.2.2}$$

*is given by*

$$y(t)=\frac{c}{h^{\alpha-1}}\sum_{n=t_0/h}^{t/h}\frac{\lambda^{n-\frac{t_0}{h}}(t-nh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}.$$

*Proof.* We directly substitute the given solution into the equation (3.2.1) and use the definition of rising factorial power

$$_{t_0}\nabla_h^\alpha y(t)={}_{t_0}\nabla_h^\alpha\frac{c}{h^{\alpha-1}}\sum_{n=t_0/h}^{t/h}\frac{\lambda^{n-\frac{t_0}{h}}(t-nh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$={}_{t_0}\nabla_h^{\alpha}\frac{c}{h^{\alpha-1}}\sum_{n=t_0/h}^{t/h}\lambda^{n-\frac{t_0}{h}}\frac{h^{(n-\frac{t_0}{h}+1)\alpha-1}\Gamma(\frac{t-nh+h}{h}+n\alpha-\frac{t_0}{h}\alpha+\alpha-1)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)\Gamma(\frac{t-nh+h}{h})}$$

$$=I.$$

Using Definition 2.5 and Definition 2.6, we obtain

$$I=\nabla_h\,{}_{t_0}\nabla_h^{-(1-\alpha)}\frac{c}{h^{\alpha-1}}\sum_{n=t_0/h}^{t/h}\lambda^{n-\frac{t_0}{h}}\frac{h^{n\alpha-\frac{t_0}{h}\alpha+\alpha-1}\Gamma(\frac{t-nh+h}{h}+n\alpha-\frac{t_0}{h}\alpha+\alpha-1)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)\Gamma(\frac{t-nh+h}{h})}$$

$$=\nabla_h\frac{c}{h^{\alpha-1}}\sum_{s=t_0/h}^{t/h}\frac{(t-\rho_h(sh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)}h\sum_{n=t_0/h}^{s}\lambda^{n-\frac{t_0}{h}}\frac{h^{n\alpha-\frac{t_0}{h}\alpha+\alpha-1}\Gamma(\frac{sh-nh+h}{h}+n\alpha-\frac{t_0}{h}\alpha+\alpha-1)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)\Gamma(\frac{sh-nh+h}{h})}.$$

Subsequently, we interchange the order of summation and get

$$I=\frac{c}{h^{\alpha-1}}\nabla_h\sum_{n=t_0/h}^{t/h}\sum_{s=n}^{t/h}\frac{h^{-\alpha}\Gamma(\frac{t-sh+h}{h}-\alpha)}{\Gamma(\frac{t-sh+h}{h})\Gamma(1-\alpha)}\lambda^{n-\frac{t_0}{h}}h^{n\alpha-\frac{t_0}{h}\alpha+\alpha}\frac{\Gamma(s-n+1+n\alpha-\frac{t_0}{h}\alpha+\alpha-1)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)\Gamma(s-n+1)}$$

$$=\frac{c}{h^{\alpha-1}}\nabla_h\sum_{n=t_0/h}^{t/h}\sum_{s=0}^{t/h-n}\frac{\Gamma(\frac{t-nh-sh+h}{h}-\alpha)}{\Gamma(\frac{t-nh-sh+h}{h})\Gamma(1-\alpha)}\lambda^{n-\frac{t_0}{h}}h^{(n-\frac{t_0}{h})\alpha}\frac{\Gamma(s+n\alpha-\frac{t_0}{h}\alpha+\alpha)}{\Gamma(s+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$=\frac{c}{h^{\alpha-1}}\nabla_h\sum_{n=t_0/h}^{t/h}\frac{\lambda^{n-\frac{t_0}{h}}h^{(n-\frac{t_0}{h})\alpha}}{\Gamma(\frac{t}{h}-n+1)}\sum_{s=0}^{t/h-n}\binom{\frac{t}{h}-n}{s}(1-\alpha)^{\overline{\frac{t}{h}-n-s}}(n\alpha-\frac{t_0}{h}\alpha+\alpha)^{\overline{s}},$$

where we used the formula

$$\binom{u}{v}=\frac{\Gamma(u+1)}{\Gamma(v+1)\Gamma(u-v+1)},$$

where $u$ and $v$ are natural numbers. By using the identity below

$$\sum_{s=0}^{t/h-n}\binom{\frac{t}{h}-n}{s}(1-\alpha)^{\overline{\frac{t}{h}-s-n}}(n\alpha+\alpha)^{\overline{s}}=(n\alpha+1)^{\overline{\frac{t}{h}-n}}.$$

we obtain

$$I = \frac{c}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h})\alpha} (n\alpha - \frac{t_0}{h}\alpha + 1)^{\overline{\frac{t}{h}-n}}}{\Gamma(\frac{t}{h} - n + 1)}$$

$$= \frac{c}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h})\alpha} (\frac{t}{h} - n + 1)^{\overline{(n-\frac{t_0}{h})\alpha}}}{\Gamma(n\alpha - \frac{t_0}{h}\alpha + 1)}$$

$$= \frac{c}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h})\alpha} \Gamma(\frac{t}{h} - n + 1 + n\alpha - \frac{t_0}{h}\alpha)}{\Gamma(n\alpha - \frac{t_0}{h}\alpha + 1)\Gamma(\frac{t}{h} - n + 1)}$$

$$= \frac{c}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} (t - nh + h)_h^{\overline{(n-\frac{t_0}{h})\alpha}}}{\Gamma(n\alpha - \frac{t_0}{h}\alpha + 1)}.$$

Next, we apply Theorem 2.8 $(i)$ on the final expression, and we get

$$I = \frac{c}{h^{\alpha-1}} \sum_{n=t_0/h}^{t/h} \nabla_h \lambda^{n-\frac{t_0}{h}} \frac{(t - nh + h)_h^{\overline{(n-\frac{t_0}{h})\alpha}}}{\Gamma(n\alpha - \frac{t_0}{h}\alpha + 1)}$$

$$+ \frac{c\lambda^{n-\frac{t_0}{h}}}{h^{\alpha-1}\Gamma(n\alpha - \frac{t_0}{h}\alpha + 1)} \frac{(t - nh + h)_h^{\overline{(n-\frac{t_0}{h})\alpha}}}{h}\Big|_{t\to t-h, n\to \frac{t}{h}}$$

$$= \frac{c}{h^{\alpha-1}} \sum_{n=t_0/h}^{t/h} \frac{(n - \frac{t_0}{h})\alpha\lambda^{n-\frac{t_0}{h}} (t - nh + h)_h^{\overline{n\alpha-\frac{t_0}{h}\alpha-1}}}{\Gamma(n\alpha - \frac{t_0}{h}\alpha)(n\alpha - \frac{t_0}{h}\alpha)}$$

$$= \frac{c}{h^{\alpha-1}} \sum_{n=t_0/h+1}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} (t - nh + h)_h^{\overline{n\alpha-\frac{t_0}{h}\alpha-1}}}{\Gamma(n\alpha - \frac{t_0}{h}\alpha)},$$

where we used the definition of rising power factorial and assumption on the Gamma function, $\frac{1}{\Gamma(0)} = 0$. Hence we have

$$I = \frac{c}{h^{\alpha-1}} \sum_{n=t_0/h}^{(t-h)/h} \frac{\lambda^{n-\frac{t_0}{h}+1} (t - (n+1)h + h)_h^{\overline{(n+1-\frac{t_0}{h})\alpha-1}}}{\Gamma((n + 1 - \frac{t_0}{h})\alpha)}$$

$$= \frac{c\lambda}{h^{\alpha-1}} \sum_{n=t_0/h}^{(t-h)/h} \frac{\lambda^{n-\frac{t_0}{h}} (t-nh)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= \lambda y(t-h),$$

as desired. □

Subsequently, we give an alternative proof for the initial value problem given above.

*Proof.* (Alternative proof.)
We prove above theorems by means of Lemma 2.9 and Lemma 2.10.
The given equation,

$${}_{t_0}\nabla_h^{\alpha} y(t) = \lambda y(t-h)$$

can be written as the following

$${}_{t_0}\nabla_h^{\alpha} y(t) = {}_{t_0}\nabla_h^{\alpha} y(uh) = h^{-\alpha} \nabla_{t_0/h}^{\alpha} (y \circ k)(u)$$

$$\lambda y(t-h) = \lambda y(h(u-1)) = \lambda (y \circ k)(u-1)$$

$$\nabla_{t_0/h}^{\alpha} (y \circ k)(u) = \lambda h^{\alpha} (y \circ k)(u-1),$$

where $k(u) = uh$ and $u \in \mathbb{N}_{t_0/h}$. Next, we consider the following IVP and its solution given in [34]

$$\nabla_a^{\nu} y(t) = \lambda y(t-1) \quad for \quad t = a+1, a+2, a+3, ...,$$

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

Hence, we have

$$(y \circ k)(u) = c \sum_{n=t_0/h}^{u} \frac{(\lambda h^{\alpha})^{n-\frac{t_0}{h}} (u-n+1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$y(uh) = c \sum_{n=t_0/h}^{u} \frac{(\lambda h^{\alpha})^{n-\frac{t_0}{h}} (u-n+1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$y(t) = c \sum_{n=t_0/h}^{t/h} \frac{(\lambda h^{\alpha})^{n-\frac{t_0}{h}} (\frac{t}{h}-n+1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

Next, using the definition of rising factorial power, the following result is obtained

$$\begin{aligned} y(t) =& c \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} h^{\alpha(n-\frac{t_0}{h})} \Gamma(\frac{t-nh+h}{h} + (n-\frac{t_0}{h}+1)\alpha - 1)}{\Gamma(\frac{t-nh+h}{h})\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\ =& \frac{c}{h^{\alpha-1}} \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} (t-nh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}. \end{aligned}$$

□

Let us define the following nabla function which will be used for the succeeding theorem

$$\hat{y}_{\lambda}(t,t_0) := \frac{1}{h^{\alpha-1}} \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}} (t-nh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}.$$

**Theorem 3.4** (Variation of Constants Formula)**.** *Assume* $\lambda, t_0 \in \mathbb{R}$ *and* $h > 0$. *The fractional* $h$*–difference equation of order* $\alpha \in (0,1)$

$$_{t_0}\nabla_h^{\alpha} y(t) = \lambda y(t-h) + f(t-h) \quad for \quad t = t_0 + h, t_0 + 2h, ...,$$

*has the general solution*

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

*where c is constant and*

$$\hat{y}_\lambda(t,t_0) = \frac{1}{h^{\alpha-1}} \sum_{n=t_0/h}^{t/h} \frac{\lambda^{n-\frac{t_0}{h}}(t-nh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}.$$

*Proof.* Our aim is to show the following

$${}_{t_0}\nabla_h^\alpha \sum_{s=t_0/h}^{t/h-1} \hat{y}_\lambda(t+t_0-sh-h,t_0)f(sh)h^\alpha = \lambda \sum_{s=t_0/h}^{t/h-2} \hat{y}_\lambda(t+t_0-sh-2h,t_0)f(sh)h^\alpha + f(t-h).$$

Using Definition 2.5 and Definition 2.6, we can write the left side of the equation given above as the following,

$$\begin{aligned}
I =& {}_{t_0}\nabla_h^\alpha \sum_{s=t_0/h}^{t/h-1} \hat{y}_\lambda(t+t_0-sh-h,t_0)f(sh)h^\alpha \\
=& \nabla_h \, {}_{t_0}\nabla_h^{-(1-\alpha)} \sum_{s=t_0/h}^{t/h-1} \hat{y}_\lambda(t+t_0-sh-h,t_0)f(sh)h^\alpha \\
=& \nabla_h \sum_{u=t_0/h}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \sum_{s=t_0/h}^{u-1} \hat{y}_\lambda(uh+t_0-sh-h,t_0)f(sh)h^{\alpha+1}.
\end{aligned}$$

Next, we interchange the order of summation and get

$$I = \nabla_h \sum_{s=t_0/h}^{t/h-1} \sum_{u=s+1}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(uh+t_0-sh-h,t_0)f(sh)h^{\alpha+1}.$$

Using Theorem 2.8 $(ii)$, we obtain

$$I = \sum_{s=t_0/h}^{t/h-2} \nabla_h \sum_{u=s+1}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(uh+t_0-sh-h,t_0) f(sh) h^{\alpha+1}$$

$$+ \sum_{u=s+1}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \frac{\hat{y}_\lambda(uh+t_0-sh-h,t_0) f(sh) h^{\alpha+1}}{h} \Big|_{t\to t, s\to \frac{t}{h}-1}.$$

Since $\hat{y}_\lambda(t_0,t_0)=1$, we rewrite

$$I = \sum_{s=t_0/h}^{t/h-2} \nabla_h \sum_{u=s+1}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(uh+t_0-sh-h,t_0) f(sh) h^{\alpha+1} + f(t-h).$$

Next we use substitution $\tau h = uh+t_0-sh-h$, we obtain

$$\sum_{u=s+1}^{t/h} \frac{(t-\rho(uh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(uh+t_0-sh-h,t_0) f(sh) h^{\alpha+1}$$

$$= \sum_{\tau=t_0/h}^{\frac{t+t_0}{h}-s-1} \frac{(t-(\tau h+sh+h-t_0-h))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(\tau h,t_0) f(sh) h^{\alpha+1}$$

$$= \sum_{\tau=t_0/h}^{\frac{t+t_0}{h}-s-1} \frac{((t+t_0-sh-h)-\rho(\tau h))^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \hat{y}_\lambda(\tau h,t_0) f(sh) h^{\alpha+1}$$

$$= {}_{t_0}\nabla_h^{-(1-\alpha)} \hat{y}_\lambda(t+t_0-sh-h,t_0) f(sh) h^{\alpha}.$$

Hence, we obtain

$$I = \sum_{s=t_0/h}^{t/h-2} \nabla_h \big( {}_{t_0}\nabla_h^{-(1-\alpha)} \hat{y}_\lambda(t+t_0-sh-h,t_0) f(sh) h^{\alpha} \big) + f(t-h)$$

$$= \sum_{s=t_0/h}^{t/h-2} {}_{t_0}\nabla_h^{\alpha} \hat{y}_\lambda(t+t_0-sh-h,t_0) f(sh) h^{\alpha} + f(t-h)$$

$$= \lambda \sum_{s=t_0/h}^{t/h-2} \hat{y}_\lambda(t+t_0-sh-2h,t_0) f(sh) h^{\alpha} + f(t-h)$$

$$= \lambda y(t-h) + f(t-h).$$

We use Theorem 3.3 to complete the proof. □

## 3.3 Solving Tumor Growth Model with Delay Using Nabla $h$–Discrete and Nabla $h$–Fractional Operators

As a result of replacement of the unperturbed growth component of PK-PD model in [25] with the Gombertz growth component, the following form [3] of the PK-PD model in continuous time was obtained.

$$\begin{aligned}
x_1'(t) &= (a - bln(x_1(t))x_1(t) - k_2c(t)x_1(t), \qquad x_1(0) = w_0 \\
x_2'(t) &= k_2c(t)x_1(t) - k_1x_2(t), \quad x_2(0) = 0 \\
x_3'(t) &= k_1x_2(t) - k_1x_3(t), \qquad x_3(0) = 0 \\
w(t) &= x_1(t) + x_2(t) + x_3(t),
\end{aligned}$$

This model describes unperturbed and perturbed tumor growth and consists of five parameters $(w_0, a, b, k_1, k_2)$ [3]:

- $k_1$ is the transit rate between compartments of the non-proliferating cells.
- $a$ and $b$ control the growth of the proliferating cells.
- $w_0$ is the initial tumor weight.
- $k_2$ is the the potency factor of the drug.

We presume that cells instantaneously cease proliferating depending on drug concentration once affected by drug action and get through certain phases with rate $k_1$ before

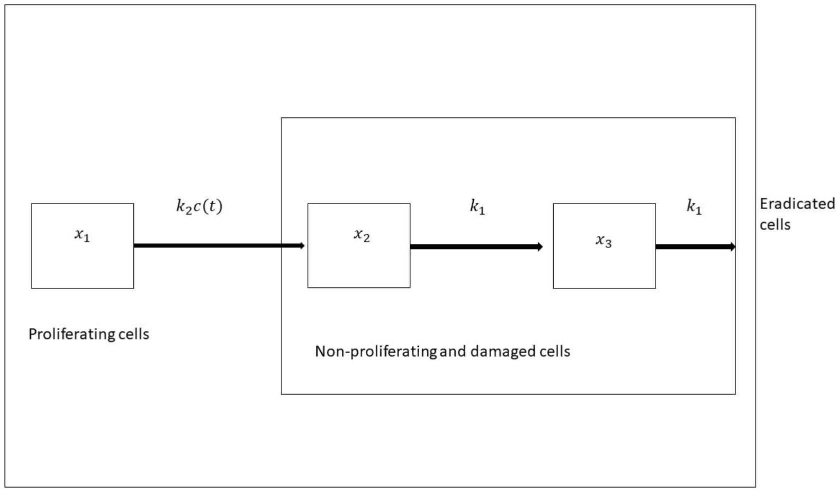


**Figure 3.3.1:** Schematic representation of transit compartment model to evaluate anticancer effect of single therapy.

they die. Considering that non-proliferating cells still give additional weight to total tumor mass, total tumor $w(t)$ is the sum of proliferating $x_1$ and non-proliferating tumor cells $(x_2, x_3)$. But, there are only remaining $x_1$ cells that are proliferating and not affected by drug action which add to the tumor growth. Here, $c(t)$ is the drug concentration in plasma and $w(t)$ is total tumor weight.

In the process of constructing the tumor growth inhibition model, two fundamental properties are considered [3]:

1. The tumor growth will be prevented while the drug is administrated, i.e. $c(t) > 0$.

2. The tumor volume will always be positive, i.e. $w(t) > 0$ for all $t \geq 0$.

We first write the delayed model indicated above as nabla $h$–discrete equations

$$(\nabla_h u)(t) = a - bu(t-h) - k_2 c(t-h), \qquad x_1(0) = w_0$$

$$(\nabla_h x_2)(t) = k_2 c(t-h) x_1(t-h) - k_1 x_2(t-h), \qquad x_2(0) = 0$$

$$(\nabla_h x_3)(t) = k_1 x_2(t-h) - k_1 x_3(t-h), \qquad x_3(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t),$$

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

We solve the above system of difference equations by using Theorem 3.1 and Theorem 3.2. We obtain the following solutions

$$u(t) = u(0)(1-bh)^{\frac{t}{h}} + h \sum_{s=0}^{\frac{t}{h}-1} (1-bh)^{\frac{t}{h}-s-1}(a - k_2 c(sh))$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = k_2 h \sum_{s=0}^{\frac{t}{h}-1} (1-k_1 h)^{\frac{t}{h}-s-1}(c(sh)x_1(sh))$$

$$x_3(t) = k_1 h \sum_{s=0}^{\frac{t}{h}-1} (1-k_1 h)^{\frac{t}{h}-s-1} x_2(sh)$$

Next, we write the delayed model on $h$–discrete fractional calculus

$$\nabla_h^\alpha u(t) = a - bu(t-h) - k_2 c(t-h), \qquad x_1(0) = w_0$$

$$\nabla_h^\alpha x_2(t) = k_2 c(t-h)x_1(t-h) - k_1 x_2(t-h), \qquad x_2(0) = 0$$

$$\nabla_h^\alpha x_3(t) = k_1 x_2(t-h) - k_1 x_3(t-h), \qquad x_3(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t),$$

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

Using Theorem 3.3 and Theorem 3.4 as tools, we obtain the following solutions for $x_1(t), x_2(t), x_3(t)$. We obtain:

$$u(t) = \hat{y}_{-b}(t,0)u(0) + \sum_{s=0}^{(t/h)-1} \hat{y}_{-b}(t - sh - h, 0)(a - k_2 c(sh))h^{\alpha}$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = \sum_{s=0}^{(t/h)-1} \hat{y}_{-k_1}(t - sh - h, 0)(k_2 c(sh) x_1(sh))h^{\alpha}$$

$$x_3(t) = \sum_{s=0}^{(t/h)-1} \hat{y}_{-k_1}(t - sh - h, 0)(k_1 x_2(sh))h^{\alpha}$$

where

$$\hat{y}_{-b}(t,0) = \sum_{n=0}^{(t/h)} \frac{(-b)^n h^{n\alpha} \Gamma(\frac{t}{h} + n\alpha - n + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h} - n + 1)}$$

$$\hat{y}_{-k_1}(t,0) = \sum_{n=0}^{(t/h)} \frac{(-k_1)^n h^{n\alpha} \Gamma(\frac{t}{h} + n\alpha - n + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h} - n + 1)}.$$

## 3.4 Combination Therapy for Tumor Growth Model with Delay

Patients having cancer are widely treated by combination therapy. The principal purpose of combining anticancer agents in the clinic is to acquire a better reaction with decreased destructive effects. Starting from early drug development, evaluating the nature and severity of combination drug therapy in the laboratory has always been a considerable challenge. A substantial number of reports can be found in the literature concerning the definition and categorization of pharmacological drug cooperation [8], [21]. Furthermore, PK-PD modeling was suggested to quantify in vivo drug interactions in order to remove these challenging features of combination therapy. Working with this modelling approach gives an opportunity to select the most advantageous combination therapies [25].

We replace unperturbed growth component given in the paper [25] with the Gombertz growth component, and we get the model equations for combination therapies in the form of differential equations which are shown below,

$$
\begin{aligned}
x_1'(t) &= (a - bln(x_1(t))x_1(t) - (k_2^a c_1(t) + k_2^b c_2(t)\psi)x_1(t), \qquad x_1(0) = w_0 \\
x_2'(t) &= (k_2^a c_1(t) + k_2^b c_2(t)\psi)x_1(t) - k_1 x_2(t), \quad x_2(0) = 0 \\
x_3'(t) &= k_1 x_2(t) - k_1 x_3(t), \qquad x_3(0) = 0 \\
w(t) &= x_1(t) + x_2(t) + x_3(t).
\end{aligned}
$$

Parameters are listed as below,

- $k_1$ is the transit rate between the compartments of the non-proliferating cells.
- $k_2^a$ is the potency of the drug $A$.

- $k_2^b$ is the potency of the drug $B$.

- $c_1(t)$ is the concentration of drug $A$.

- $c_2(t)$ is the concentration of drug $B$.

It would be worthwhile to mention that $\psi$ was included the model so as to determine the interaction during joint administration. The value of $\psi$ either greater or less than 1 shows the degree of rise or decrease in the anti-tumor effect. In this section, we first write the model indicated above as nabla $h$-discrete equations

$$\begin{aligned}(\nabla_h u)(t) &= a - bu(t-h) - (k_2^a c_1(t-h) + k_2^b c_2(t-h)\psi), \qquad x_1(0) = w_0\\ (\nabla_h x_2)(t) &= (k_2^a c_1(t-h) + k_2^b c_2(t-h)\psi)x_1(t-h) - k_1 x_2(t-h), \quad x_2(0) = 0\\ (\nabla_h x_3)(t) &= k_1 x_2(t-h) - k_1 x_3(t-h), \qquad x_3(0) = 0\\ w(t) &= x_1(t) + x_2(t) + x_3(t)\end{aligned}$$

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

We solve above system of difference equations by using Theorem 3.1 and Theorem 3.2. The following solutions are obtained:

$$u(t) = u(0)(1-bh)^{\frac{t}{h}} + h\sum_{s=0}^{\frac{t}{h}-1}(1-bh)^{\frac{t}{h}-s-1}(a - (k_2^a c_1(sh) + k_2^b c_2(sh)\psi))$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = h\sum_{s=0}^{\frac{t}{h}-1}(1-k_1 h)^{\frac{t}{h}-s-1}(k_2^a c_1(sh) + k_2^b c_2(sh)\psi)x_1(sh))$$

$$x_3(t) = h\sum_{s=0}^{\frac{t}{h}-1}(1-k_1 h)^{\frac{t}{h}-s-1}k_1 x_2(sh)$$

Next, we write the delayed model for combination therapy on $h$–discrete fractional calculus

$$\nabla_h^\alpha u(t) = a - bu(t-h) - (k_2^a c_1(t-h) + k_2^b c_2(t-h)\psi), \qquad x_1(0) = w_0$$

$$\nabla_h^\alpha x_2(t) = (k_2^a c_1(t-h) + k_2^b c_2(t-h)\psi)x_1(t-h) - k_1 x_2(t-h), \qquad x_2(0) = 0$$

$$\nabla_h^\alpha x_3(t) = k_1 x_2(t-h) - k_1 x_3(t-h), \qquad x_3(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t),$$

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

Using Theorem 3.3 and Theorem 3.4 as tools, we obtain the following solutions for $x_1(t), x_2(t), x_3(t)$. We obtain:

$$u(t) = \hat{y}_{-b}(t,0)u(0) + \sum_{s=0}^{(t/h)-1} \hat{y}_{-b}(t-sh-h,0)(a - (k_2^a c_1(sh) + k_2^b c_2(sh)\psi))h^\alpha$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = \sum_{s=0}^{(t/h)-1} \hat{y}_{-k_1}(t-sh-h,0)(k_2^a c_1(sh) + k_2^b c_2(sh)\psi))x_1(sh))h^\alpha$$

$$x_3(t) = \sum_{s=0}^{(t/h)-1} \hat{y}_{-k_1}(t-sh-h,0)(k_1 x_2(sh))h^\alpha$$

where

$$\hat{y}_{-b}(t,0) = \sum_{n=0}^{(t/h)} \frac{(-b)^n h^{n\alpha}\Gamma(\frac{t}{h} + n\alpha - n + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h} - n + 1)}$$

$$\hat{y}_{-k_1}(t,0) = \sum_{n=0}^{(t/h)} \frac{(-k_1)^n h^{n\alpha}\Gamma(\frac{t}{h} + n\alpha - n + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h} - n + 1)}.$$

# Chapter 4

# THE PHARMACODYNAMICS MODEL WITHOUT DELAY

Even though we get solutions for delay case of our model, try different drug doses, do parameter estimations and simulations, we still see jumps on the graph. Therefore, in this chapter, we investigate our tumor growth model by getting rid of delay from model equations. In order to obtain solutions for indicated problem, we first introduce several theorems including variation of constants formulas for nabla $h$–discrete and discrete fractional equations by neglecting delay. In the final section, we solve our model which does not have delay with help of those theorems we prove in Section 4.1 and Section 4.2. As a result, we are able to eliminate occurring jumps from graph for tumor growth model without delay.

## 4.1 Nabla $h$–Discrete Equations without Delay

**Theorem 4.1.** *Let $h > 0$ and $\lambda, c, t_0 \in \mathbb{R}$ be constants. The solution of the following initial value problem (IVP)*

$$(\nabla_h y)(t) = -\lambda y(t) \quad for \quad t \in h\mathbb{N}_{t_0} \tag{4.1.1}$$

$$y(t_0) = c \tag{4.1.2}$$

*is given by*

$$y(t) = c(1 + h\lambda)^{-\frac{t-t_0}{h}}$$

*where $h\lambda \neq -1$.*

*Proof.* By using the definition of nabla $h$-discrete operator, we can write

$$\frac{y(t) - y(t-h)}{h} = -\lambda y(t)$$

$$y(t) = y(t-h)(1 + h\lambda)^{-1}.$$

Setting $t = t_0 + h$, the equation yields

$$y(t_0 + h) = y(t_0)(1 + h\lambda)^{-1} = c(1 + h\lambda)^{-1}$$

since $y(t_0) = c$. Setting $t = t_0 + 2h$, we have

$$y(t_0 + 2h) = c(1 + h\lambda)^{-2}.$$

Proceeding forward gives us

$$y(t_0 + nh) = c(1 + h\lambda)^{-n} \quad for \quad n \in \mathbb{N}.$$

The above expression can be rewritten as follows ,

$$y(t) = c(1 + h\lambda)^{-\frac{t-t_0}{h}}$$

for all $t \in h\mathbb{N}_{t_0}$ and $h\lambda \neq -1$. □

Next, we give variation of constants formula for the equation 4.1.1 and its proof.

**Theorem 4.2** (Variation of Constants Formula)**.** *Assume* $h > 0$, $\lambda \in \mathbb{R} \setminus \{-\frac{1}{h}\}$ *and* $t_0$

*are any real numbers. Then, the first order nabla h–difference equation*

$$(\nabla_h y)(t) = -\lambda y(t) + f(t) \quad for \quad t = t_0, t_0 + h, t_0 + 2h, ..., \tag{4.1.3}$$

*has the general solution*

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

*where $c \in \mathbb{R}$ constant number.*

*Proof.* Using direct substitution into (4.1.3), we obtain

$$\begin{aligned}
\nabla_h y(t) =& \nabla_h c(1+h\lambda)^{-\frac{t-t_0}{h}} + \nabla_h \sum_{s=t_0/h+1}^{\frac{t}{h}} (1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h \\
=& -c\lambda(1+h\lambda)^{-\frac{t-t_0}{h}} + \sum_{s=t_0/h+1}^{\frac{t}{h}} \nabla_h (1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h \\
&+ \frac{(1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h}{h}\Big|_{t\to t-h, s\to\frac{t}{h}} \\
=& -c\lambda(1+h\lambda)^{-\frac{t-t_0}{h}} + \sum_{s=t_0/h+1}^{\frac{t}{h}} -\lambda(1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h + f(t) \\
=& -\lambda[c(1+h\lambda)^{-\frac{t-t_0}{h}} + \sum_{s=t_0/h+1}^{\frac{t}{h}} (1+h\lambda)^{-(\frac{t}{h}-s+1)} f(sh)h] + f(t) \\
=& -\lambda y(t) + f(t),
\end{aligned}$$

where we use Theorem 2.8 $(i)$ and Theorem 4.1. □

## 4.2 Nabla $h$–Discrete Fractional Equations without Delay

**Theorem 4.3.** *Let $h > 0$, $\lambda, c \in \mathbb{R}$. and $\alpha \in (0,1)$. A solution of the following initial value problem*

$$ {}_{t_0}\nabla_h^{\alpha} y(t) = -\lambda y(t) \quad t = t_0, t_0 + h, t_0 + 2h, ..., \tag{4.2.1}$$

$$ y(t_0) = c \tag{4.2.2}$$

*is given by*

$$y(t) = \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

*where* $|\lambda h^{\alpha}| < 1$.

*Proof.* We directly substitute the given solution into the equation (4.2.1) and use definition of rising factorial power. Hence, we have

$$\begin{aligned} {}_{t_0}\nabla_h^{\alpha} y(t) &= {}_{t_0}\nabla_h^{\alpha} \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\ &= {}_{t_0}\nabla_h^{\alpha} \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha+\alpha-1} \Gamma(\frac{t-t_0+h}{h} + n\alpha - \frac{t_0}{h}\alpha + \alpha - 1)}{\Gamma(\frac{t-t_0+h}{h})\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\ &= I. \end{aligned}$$

Using Definition 2.5 and Definition 2.6, we obtain

$$I = \nabla_{h\ t_0}\nabla_h^{-(1-\alpha)} c(1+\lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha - \frac{t_0}{h}\alpha} \Gamma(\frac{t-t_0}{h} + n\alpha - \frac{t_0}{h}\alpha + \alpha)}{\Gamma(\frac{t-t_0}{h}+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= \nabla_h c(1+\lambda h^{\alpha}) \sum_{s=t_0/h}^{t/h} \frac{(t-\rho_h(sh))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} h \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha} \Gamma(\frac{sh-t_0}{h} + n\alpha - \frac{t_0}{h}\alpha + \alpha)}{\Gamma(\frac{sh-t_0}{h}+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= \nabla_h c(1+\lambda h^{\alpha}) \sum_{s=t_0/h}^{t/h} \frac{h^{-\alpha}\ \Gamma(\frac{t-sh+h}{h} - \alpha)}{\Gamma(\frac{t-sh+h}{h})\Gamma(1-\alpha)} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}}\ h^{n\alpha-\frac{t_0}{h}\alpha+1}}{\Gamma(s-\frac{t_0}{h}+1)}$$

$$\times \frac{\Gamma(s-\frac{t_0}{h}+n\alpha-\frac{t_0}{h}\alpha+\alpha)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= \nabla_h c(1+\lambda h^{\alpha}) \sum_{s=t_0/h}^{t/h} \frac{\Gamma(\frac{t}{h}-s+1-\alpha)}{\Gamma(\frac{t}{h}-s+1)\Gamma(1-\alpha)} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha+1-\alpha}}{\Gamma(s-\frac{t_0}{h}+1)}$$

$$\times \frac{\Gamma(s-\frac{t_0}{h}+n\alpha-\frac{t_0}{h}\alpha+\alpha)}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}.$$

Subsequently, we interchange the order of summation and get

$$I = \nabla_h c(1+\lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \sum_{s=t_0/h}^{t/h} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h}-1)\alpha+1} \Gamma(s-\frac{t_0}{h}+(n-\frac{t_0}{h}+1)\alpha)}{\Gamma(s-\frac{t_0}{h}+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$\times \frac{\Gamma(\frac{t}{h}-s+1-\alpha)}{\Gamma(\frac{t}{h}-s+1)\Gamma(1-\alpha)}$$

$$= \nabla_h c(1+\lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \sum_{s=0}^{\frac{t-t_0}{h}} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h}-1)\alpha+1} \Gamma(s+(n-\frac{t_0}{h}+1)\alpha)}{\Gamma(s+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$\times \frac{\Gamma(\frac{t}{h}-s-\frac{t_0}{h}+1-\alpha)}{\Gamma(\frac{t}{h}-s-\frac{t_0}{h}+1)\Gamma(1-\alpha)}.$$

Next, we apply the following formulas

$$\binom{u}{v} = \frac{\Gamma(u+1)}{\Gamma(v+1)\Gamma(u-v+1)},$$

where $u$ and $v$ are natural numbers.

$$\sum_{s=0}^{t/h-n} \binom{\frac{t}{h}-n}{s} (1-\alpha)^{\overline{\frac{t}{h}-s-n}} (n\alpha+\alpha)^{\overline{s}} = (n\alpha+1)^{\overline{\frac{t}{h}-n}}.$$

and obtain

$$I = \nabla_h \frac{c(1+\lambda h^{\alpha})}{\Gamma(\frac{t-t_0}{h}+1)h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha} \sum_{s=0}^{\frac{t-t_0}{h}} \binom{\frac{t-t_0}{h}}{s} (1-\alpha)^{\overline{\frac{t-t_0}{h}-s}} (n\alpha - \frac{t_0}{h}\alpha + \alpha)^{\overline{s}}$$

$$= \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha}}{\Gamma(\frac{t-t_0}{h}+1)} (1+n\alpha-\frac{t_0}{h}\alpha)^{\overline{\frac{t-t_0}{h}}}$$

$$= \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha} (\frac{t-t_0}{h}+1)^{\overline{n\alpha-\frac{t_0}{h}\alpha}}}{\Gamma(1+n\alpha-\frac{t_0}{h}\alpha)}.$$

Now we use Definition 2.3 and Definition 2.4,

$$I = \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha-\frac{t_0}{h}\alpha} \frac{\Gamma(\frac{t-t_0}{h}+1+n\alpha-\frac{t_0}{h}\alpha)}{\Gamma(\frac{t-t_0}{h}+1)\Gamma(1+n\alpha-\frac{t_0}{h}\alpha)}$$

$$= \frac{c(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \nabla_h \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{n\alpha-\frac{t_0}{h}\alpha}}}{\Gamma(1+n\alpha-\frac{t_0}{h}\alpha)}.$$

Using Lemma 2.7 $(i)$, the following is obtained

$$I = \frac{c(1+\lambda h^\alpha)}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (n\alpha - \frac{t_0}{h}\alpha)(t-t_0+h)_h^{\overline{n\alpha-\frac{t_0}{h}\alpha-1}}}{(n\alpha-\frac{t_0}{h}\alpha)\Gamma(n\alpha-\frac{t_0}{h}\alpha)}$$

$$= \frac{c(1+\lambda h^\alpha)}{h^{\alpha-1}} \sum_{n=t_0/h+1}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{n\alpha-\frac{t_0}{h}\alpha-1}}}{\Gamma(n\alpha-\frac{t_0}{h}\alpha)}$$

since $\frac{1}{\Gamma(0)} = 0$. Hence we have

$$I = \frac{c(1+\lambda h^\alpha)}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n+1-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n+1)\alpha-\frac{t_0}{h}\alpha-1}}}{\Gamma((n+1)\alpha-\frac{t_0}{h}\alpha)}$$

$$= -\lambda \frac{c(1+\lambda h^\alpha)}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= -\lambda y(t)$$

as desired. □

*Proof.* (Alternative proof) Using Lemma 2.10, we introduce a second proof of the theorem mentioned above.

$${}_{t_0}\nabla_h^\alpha y(t) = -\lambda y(t)$$

$${}_{t_0}\nabla_h^\alpha y(uh) = -\lambda y(uh)$$

$$\frac{\nabla_{t_0/h}^\alpha (y \circ k)(u)}{h^\alpha} = -\lambda (y \circ k)(u)$$

$$\nabla_{t_0/h}^\alpha (y \circ k)(u) = -\lambda h^\alpha (y \circ k)(u)$$

where $k(u) = uh = t$ and $u \in \mathbb{N}_{t_0/h}$. We use solution of the following IVP given in [4]

$$\nabla^{\alpha} y(t) = -\lambda y(t) \quad for \quad t = 1, 2, 3, ...,$$

$$y(0) = c$$

Hence we have,

$$(y \circ k)(u) = c(1 + \lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda h^{\alpha})^{n-\frac{t_0}{h}} (u - \frac{t_0}{h} + 1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n - \frac{t_0}{h} + 1)\alpha)}$$

$$y(uh) = c(1 + \lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda h^{\alpha})^{n-\frac{t_0}{h}} (u - \frac{t_0}{h} + 1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n - \frac{t_0}{h} + 1)\alpha)}$$

$$y(t) = c(1 + \lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda h^{\alpha})^{n-\frac{t_0}{h}} (\frac{t-t_0}{h} + 1)^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n - \frac{t_0}{h} + 1)\alpha)}$$

Now we use Definition 2.3 and rewrite the equation

$$\begin{aligned} y(t) =& c(1 + \lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda h^{\alpha})^{n-\frac{t_0}{h}} \Gamma(\frac{t-t_0+h}{h} + 1 + n\alpha - \frac{t_0}{h}\alpha + \alpha - 1)}{\Gamma(\frac{t-t_0+h}{h} + 1)\Gamma((n - \frac{t_0}{h} + 1)\alpha)} \\ =& c(1 + \lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} h^{n\alpha - \frac{t_0}{h}\alpha} (t - t_0 + h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{h^{n\alpha - \frac{t_0}{h}\alpha + \alpha - 1}\Gamma((n - \frac{t_0}{h} + 1)\alpha)} \\ =& \frac{c(1 + \lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t - t_0 + h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n - \frac{t_0}{h} + 1)\alpha)} \end{aligned}$$

as desired. □

Let us define

$$y_{\lambda}^{*}(t, t_0) := \frac{1}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t - t_0 + h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n - \frac{t_0}{h} + 1)\alpha)}.$$

**Theorem 4.4** (Variation of Constants Formula)**.** *Assume $h > 0$ and $\lambda, c, t_0 \in \mathbb{R}$. The fractional difference equation of order $\alpha \in (0,1)$*

$$ {}_{t_0}\nabla_h^{\alpha} y(t) = -\lambda y(t) + f(t)) \quad t = t_0, t_0 + h, t_0 + 2h, ..., \tag{4.2.3}$$

*has the general solution*

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

*where $c$ is constant and*

$$y_\lambda^*(t,t_0) = \frac{1}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}.$$

*Proof.* We need to show

$$\sum_{s=t_0/h+1}^{t/h} y_\lambda^*(t+t_0-sh, t_0) f(sh) h^\alpha$$

is a solution of equation (4.2.3). Using the definition of $y_\lambda^*(t,t_0)$ and Definition 2.5, we write

$$\begin{aligned}
y_p(t) &= \sum_{s=t_0/h+1}^{t/h} y_\lambda^*(t+t_0-sh, t_0) f(sh) h^\alpha \\
&= \sum_{s=t_0/h+1}^{t/h} \frac{1}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-sh+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh) h^\alpha \\
&= \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{s=t_0/h+1}^{t/h} \frac{(t-\rho(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh) h \\
&= \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \; {}_{t_0+h}\nabla_h^{-(n-\frac{t_0}{h}+1)\alpha} f(t)
\end{aligned}$$

Next, we plug in $y_p(t)$ into equation (4.2.3) and use Definition 2.6

$$\begin{aligned}
{}_{t_0}\nabla_h^{\alpha} y_p(t) &= {}_{t_0}\nabla_h^{\alpha} \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-(n-\frac{t_0}{h}+1)\alpha} f(t) \\
&= \nabla_h \, {}_{t_0}\nabla_h^{-(1-\alpha)} \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-(n-\frac{t_0}{h}+1)\alpha} f(t) \\
&= \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0}\nabla_h^{-(1-\alpha)} \, {}_{t_0+h}\nabla_h^{-(n-\frac{t_0}{h}+1)\alpha} f(t) \\
&= I.
\end{aligned}$$

Using Definition 2.6, we obtain

$$\begin{aligned}
I &= \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0}\nabla_h^{-(1-\alpha)} \sum_{s=t_0/h+1}^{t/h} \frac{(t-\rho(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh)h \\
&= \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{\tau=t_0/h}^{t/h} \frac{(t-\rho(\tau h))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \sum_{s=t_0/h+1}^{\tau h/h} \frac{(\tau h-\rho(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh)h^2
\end{aligned}$$

Next, we interchange the order of summation and get

$$\begin{aligned}
I &= \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{s=t_0/h+1}^{t/h} \sum_{\tau=s}^{t/h} \frac{(t-\rho(\tau h))_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)} \frac{(\tau h-\rho(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh)h^2 \\
&= \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{s=t_0/h+1}^{t/h} {}_{sh}\nabla_h^{-(1-\alpha)} (t-\rho_h(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}} \frac{f(sh)h}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}
\end{aligned}$$

Next, we use Lemma 2.7 $(ii)$ and obtain

$$
\begin{aligned}
I =& \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{s=t_0/h+1}^{t/h} \frac{\Gamma((n-\frac{t_0}{h}+1)\alpha-1+1)}{\Gamma((n-\frac{t_0}{h}+1)\alpha-1+1+1-\alpha)} \\
&\times \frac{(t-\rho_h(sh))_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1+1-\alpha}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} f(sh)h \\
=& \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \sum_{s=t_0/h+1}^{t/h} \frac{(t-\rho_h(sh))_h^{\overline{(n-\frac{t_0}{h})\alpha}}}{\Gamma((n-\frac{t_0}{h})\alpha+1)} f(sh)h \\
=& \nabla_h \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-((n-\frac{t_0}{h})\alpha+1)} f(t) \\
=& \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, \nabla_h \, {}_{t_0+h}\nabla_h^{-((n-\frac{t_0}{h})\alpha+1)} f(t).
\end{aligned}
$$

Using Definition 2.6, the following result is obtained

$$
\begin{aligned}
I =& \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-((n-\frac{t_0}{h})\alpha)} f(t) \\
=& \sum_{n=t_0/h+1}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-((n-\frac{t_0}{h})\alpha)} f(t) + f(t) \\
=& \sum_{n=t_0/h}^{\infty} (-\lambda)^{n+1-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-((n+1-\frac{t_0}{h})\alpha)} f(t) + f(t) \\
=& -\lambda \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} \, {}_{t_0+h}\nabla_h^{-(n-\frac{t_0}{h}+1)\alpha} f(t) + f(t) \\
=& -\lambda y_p(t) + f(t).
\end{aligned}
$$

We use Theorem 4.3 to complete the proof. □

Now, we focus on the following problem,

$$ {}_{t_0}\nabla_h^{\alpha} y(t) = -\lambda y(t) \quad t = t_0, t_0 + h, t_0 + 2h, ..., \tag{4.2.4}$$

$$ y(t_0) = 1 \tag{4.2.5}$$

We define the solution of (4.2.4)-(4.2.5) as indicated below,

$$\hat{e}_{\alpha}(-\lambda, (t-t_0)_h^{\overline{\alpha}}) = \frac{(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

**Theorem 4.5.** *Let* $0 < \alpha < 1$ . *The following are valid:*

*(i)* $\hat{e}_{\alpha}(-\lambda, 0) = 1, \quad t \in h\mathbb{N}_a.$

*(ii)* ${}_{t_0}\nabla_h^{\alpha} \hat{e}_{\alpha}(-\lambda, (t-t_0)_h^{\overline{\alpha}}) = -\lambda \hat{e}_{\alpha}(-\lambda, (t-t_0)_h^{\overline{\alpha}}), \quad t \in h\mathbb{N}_a.$

*(iii)* $\hat{e}_{\alpha}(-\lambda, (t-t_0)_h^{\overline{\alpha}}) \geq 0, \quad t \in h\mathbb{N}_a.$

*(iv)* $\hat{e}_{\alpha}(0, (t-t_0)_h^{\overline{\alpha}}) = \dfrac{(t-t_0+h)^{\overline{\alpha-1}}}{\Gamma(\alpha) h^{\alpha-1}}, \quad t \in h\mathbb{N}_a.$

*(v)* $\hat{e}_{\alpha}(-\lambda, (t-t_0)_h^{\overline{\alpha}})$ *converges absolutely if* $|\lambda h^{\alpha}| < 1$.

*Proof.* $(i)$ We use the Definition 2.4 to prove $(i)$,

$$\begin{aligned}
\hat{e}_{\alpha}(-\lambda, 0) &= \frac{(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} (h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\
&= \frac{(1+\lambda h^{\alpha})}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}} \Gamma(1+n\alpha-\frac{t_0}{h}\alpha+\alpha-1) h^{n\alpha-\frac{t_0}{h}\alpha+\alpha-1}}{\Gamma(1)\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\
&= (1+\lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} (-\lambda)^{n-\frac{t_0}{h}} h^{(n-\frac{t_0}{h})\alpha} \\
&= (1+\lambda h^{\alpha}) \sum_{n=t_0/h}^{\infty} (-\lambda h^{\alpha})^{n} = (1+\lambda h^{\alpha}) \frac{1}{(1+\lambda h^{\alpha})} = 1
\end{aligned}$$

$(ii)$ We first use the definition of $\hat{e}_\alpha(-\lambda,(t-t_0)_h^{\overline{\alpha}})$,

$$
\begin{aligned}
{}_{t_0}\nabla_h^\alpha \hat{e}_\alpha(-\lambda,(t-t_0)_h^{\overline{\alpha}}) =& \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}} {}_{t_0}\nabla_h^\alpha\left(\frac{(t-t_0+h)_h^{\overline{\alpha-1}}}{\Gamma(\alpha)}\right) \\
&+ \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}} {}_{t_0}\nabla_h^\alpha\left(\sum_{n=t_0/h+1}^{\infty}\frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}\right) \\
=& \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\left(\nabla_h\, {}_{t_0}\nabla_h^{-(1-\alpha)}\frac{(t-t_0+h)_h^{\overline{\alpha-1}}}{\Gamma(\alpha)}\right) \\
&+ \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\sum_{n=t_0/h+1}^{\infty}\nabla_h\, {}_{t_0}\nabla_h^{-(1-\alpha)}\frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)} \\
=& I
\end{aligned}
$$

where we used Definition 2.6.

Next, we use Lemma 2.7 $(ii)$ and obtain the following,

$$
\begin{aligned}
I =& \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\nabla_h\left(\frac{\Gamma(\alpha-1+1)(t-t_0+h)_h^{\overline{\alpha-1+1-\alpha}}}{\Gamma(\alpha-1+1+1-\alpha)\Gamma(\alpha)}\right) \\
&+ \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\sum_{n=t_0/h+1}^{\infty}\nabla_h\left(\frac{(-\lambda)^{(n-\frac{t_0}{h})}\Gamma((n-\frac{t_0}{h}+1)\alpha)(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h})\alpha}}}{\Gamma(n\alpha-\frac{t_0}{h}\alpha+1)\Gamma((n-\frac{t_0}{h}+1)\alpha)}\right).
\end{aligned}
$$

Subsequently, Lemma 2.7 $(i)$ is used as a tool. We simplify and get,

$$
\begin{aligned}
I =& \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\sum_{n=t_0/h+1}^{\infty}\frac{(-\lambda)^{(n-\frac{t_0}{h})}(n-\frac{t_0}{h})\alpha(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h})\alpha-1}}}{(n-\frac{t_0}{h})\alpha\Gamma((n-\frac{t_0}{h})\alpha)} \\
=& \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\sum_{n=t_0/h}^{\infty}\frac{(-\lambda)^{(n-\frac{t_0}{h}+1)}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}
\end{aligned}
$$

$$= -\lambda\frac{(1+\lambda h^{\alpha})}{h^{\alpha-1}}\sum_{n=t_0/h}^{\infty}\frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= -\lambda\hat{e}_{\alpha}(-\lambda,(t-t_0)_h^{\overline{\alpha}})$$

$(iii)$ In order to prove third property, we plug in the solution into the equation 4.2.4. Using Definition 2.6, the following is obtained

$$\begin{aligned}
{}_{t_0}\nabla_h^{\alpha}\hat{e}_{\alpha}(-\lambda,(t-t_0)_h^{\overline{\alpha}}) =& \big(\nabla_h\, {}_{t_0}\nabla_h^{-(1-\alpha)}\hat{e}_{\alpha}(-\lambda,(t-t_0)_h^{\overline{\alpha}})\\
=& \nabla_h\sum_{s=t_0/h}^{t/h}\frac{(t-sh+h)_h^{\overline{-\alpha}}}{\Gamma(1-\alpha)}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h\\
=& \frac{1}{\Gamma(1-\alpha)}\sum_{s=t_0/h}^{t/h}\nabla_h(t-sh+h)_h^{\overline{-\alpha}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h\\
&+\frac{(t-sh+h)_h^{\overline{-\alpha}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h}{\Gamma(1-\alpha)h}\Big|_{t\to t-h,s\to\frac{t}{h}} = I
\end{aligned}$$

where we use Theorem 2.8 $(i)$.

We simplify and use Theorem 2.7,

$$\begin{aligned}
I =& \frac{1}{\Gamma(1-\alpha)}\left(\sum_{s=t_0/h}^{t/h}\nabla_h(t-sh+h)_h^{\overline{-\alpha}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h+0\right)\\
=& \frac{-\alpha}{\Gamma(1-\alpha)}\sum_{s=t_0/h}^{t/h}(t-sh+h)_h^{\overline{-\alpha-1}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h
\end{aligned}$$

Next, we make the above result equal to the right hand side of 4.2.4 and obtain,

$$\frac{-\alpha}{\Gamma(1-\alpha)}\sum_{s=t_0/h}^{t/h}(t-sh+h)_h^{\overline{-\alpha-1}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h = -\lambda\hat{e}_{\alpha}(-\lambda,(t-t_0)_h^{\overline{\alpha}})$$

$$\frac{-\alpha}{\Gamma(1-\alpha)}\left(\sum_{s=t_0/h}^{t/h-1}(t-sh+h)_h^{\overline{-\alpha-1}}\hat{e}_{\alpha}(-\lambda,(sh-t_0)_h^{\overline{\alpha}})h+(h)_h^{\overline{-\alpha-1}}\hat{e}_{\alpha}(-\lambda,(t-t_0)_h^{\overline{\alpha}}h\right)$$

$$= -\lambda \hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}})$$

We use the definition of the nabla $h$–factorial as a succeeding step,

$$\frac{-\alpha}{\Gamma(1-\alpha)} \sum_{s=t_0/h}^{t/h-1} (t - sh + h)_h^{\overline{-\alpha-1}} \hat{e}_{\alpha}(-\lambda, (sh - t_0)_h^{\overline{\alpha}})h + \frac{-\alpha\Gamma(-\alpha)h^{-\alpha-1}}{\Gamma(1-\alpha)\Gamma(1)} \hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}} h)$$

$$= -\lambda \hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}})$$

Since $\Gamma(1-\alpha) = -\alpha\Gamma(-\alpha)$, we get the following

$$\frac{-\alpha}{\Gamma(1-\alpha)} \sum_{s=t_0/h}^{t/h-1} (t - sh + h)_h^{\overline{-\alpha-1}} \hat{e}_{\alpha}(-\lambda, (sh - t_0)_h^{\overline{\alpha}})h + \hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}})h^{-\alpha}$$

$$= -\lambda \hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}})$$

$$\hat{e}_{\alpha}(-\lambda, (t - t_0)_h^{\overline{\alpha}}) = \frac{\alpha}{(\lambda + h^{-\alpha})\Gamma(1-\alpha)} \sum_{s=t_0/h}^{t/h-1} (t - sh + h)_h^{\overline{-\alpha-1}} \hat{e}_{\alpha}(-\lambda, (sh - t_0)_h^{\overline{\alpha}})$$

Since $0 < \alpha < 1$ and $|\lambda h^{\alpha}| < 1$, it is obvious that $(\lambda + h^{-\alpha}) > 0$ and $\Gamma(1-\alpha) > 0$. Using Definition 2.4, we can show that

$$(t - sh + h)_h^{\overline{-\alpha-1}} = \frac{h^{-\alpha-1}\Gamma(\frac{t}{h} - s - \alpha)}{\Gamma(\frac{t}{h} - s + 1)} \geq 0$$

for $t_0 \leq sh \leq t - h$. Thus, using the fact that $\hat{e}_{\alpha}(-\lambda, 0) = 1$, we obtained

$$\hat{e}_{\alpha}(-\lambda, (t - t_0)^{\overline{\alpha}}) \geq 0 \quad t \in h\mathbb{N}_{t_0}.$$

$(iv)$ We first rewrite the solution of 4.2.4-4.2.5 as the following,

$$\hat{e}_\alpha(-\lambda,(t-t_0)_h^{\overline{\alpha}}) = \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\sum_{n=t_0/h}^{\infty}\frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$$

$$= \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}}\left(\frac{(t-t_0+h)_h^{\overline{\alpha-1}}}{\Gamma(\alpha)}+\sum_{n=t_0/h+1}^{\infty}\frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}\right)$$

set $\lambda = 0$

$$\hat{e}_\alpha(0,(t-t_0)_h^{\overline{\alpha}}) = \frac{(t-t_0+h)_h^{\overline{\alpha-1}}}{h^{\alpha-1}\Gamma(\alpha)}.$$

We write generalization of the theorem given in the paper [16]. If we take $h = 1$, we obtain the result shown in the paper indicated above.

$(v)$ We prove that ${}_{t_0}\nabla_h^\alpha \hat{e}_\alpha(-\lambda,(t-t_0)_h^{\overline{\alpha}})$ is convergent using the ratio test. We will use the following property of the Gamma function [6]

$$\lim_{n\to\infty}\frac{\Gamma(n+\alpha)}{\Gamma(n)n^\alpha} = 1$$

where $\alpha \in \mathbb{R}$. Then

$$\lim_{n\to\infty}\frac{\Gamma(\frac{t-t_0}{h}+(n+2-\frac{t_0}{h})\alpha)}{\Gamma(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)^\alpha} = 1 \tag{4.2.6}$$

and

$$\lim_{n\to\infty}\frac{\Gamma((n-\frac{t_0}{h}+1)\alpha)((n-\frac{t_0}{h}+1)\alpha)^\alpha}{\Gamma((n+1)-\frac{t_0}{h}+1)\alpha)} = 1. \tag{4.2.7}$$

Define $a_n = \frac{(1+\lambda h^\alpha)}{h^{\alpha-1}} \sum_{n=t_0/h}^{\infty} \frac{(-\lambda)^{n-\frac{t_0}{h}}(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1}}}{\Gamma((n-\frac{t_0}{h}+1)\alpha)}$. Then we have

$$\lim_{n\to\infty}\left|\frac{a_{n+1}}{a_n}\right| = \lim_{n\to\infty}\left|\frac{\lambda(t-t_0+h)_h^{\overline{(n+1-\frac{t_0}{h}+1)\alpha-1)}}\Gamma((n-\frac{t_0}{h}+1)\alpha)}{\Gamma((n+1-\frac{t_0}{h}+1)\alpha)(t-t_0+h)_h^{\overline{(n-\frac{t_0}{h}+1)\alpha-1)}}}\right|$$

$$= \lim_{n\to\infty}\left|\frac{h^{n\alpha+2\alpha-\frac{t_0}{h}\alpha-1}\Gamma(\frac{t-t_0}{h}+n\alpha+2\alpha-\frac{t_0}{h}\alpha)\Gamma((n-\frac{t_0}{h}+1)\alpha)\Gamma(\frac{t-t_0}{h}+1)}{h^{n\alpha-\frac{t_0}{h}\alpha+\alpha-1}\Gamma(\frac{t-t_0}{h}+1)\Gamma((n-\frac{t_0}{h}+2)\alpha)\Gamma(\frac{t-t_0}{h}+n\alpha+\alpha-\frac{t_0}{h}\alpha)}\right|$$

$$= \lim_{n\to\infty}\left|\lambda h^\alpha\frac{\Gamma(\frac{t-t_0}{h}+n\alpha+2\alpha-\frac{t_0}{h}\alpha)\Gamma((n-\frac{t_0}{h}+1)\alpha)}{\Gamma((n-\frac{t_0}{h}+2)\alpha)\Gamma(\frac{t-t_0}{h}+n\alpha+\alpha-\frac{t_0}{h}\alpha)}\right|$$

$$= \lim_{n\to\infty}\Bigg|\ \lambda h^\alpha\frac{\Gamma(\frac{t-t_0}{h}+(n+2-\frac{t_0}{h})\alpha)}{\Gamma(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)^\alpha} \times\frac{\Gamma((n-\frac{t_0}{h}+1)\alpha)((n-\frac{t_0}{h}+1)\alpha)^\alpha}{\Gamma((n+1-\frac{t_0}{h}+1)\alpha)}\cdot\frac{(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)^\alpha}{((n-\frac{t_0}{h}+1)\alpha)^\alpha}\ \Bigg|$$

$$= \lim_{n\to\infty}\left|\ \lambda h^\alpha\frac{(\frac{t-t_0}{h}+(n+1-\frac{t_0}{h})\alpha)^\alpha}{((n-\frac{t_0}{h}+1)\alpha)^\alpha}\ \right|$$

$$= \left|\lambda h^\alpha\frac{\alpha^\alpha}{\alpha^\alpha}\right| = |\lambda h^\alpha| < 1,$$

where we used (4.2.6)-(4.2.7) and Definition 2.4. □

## 4.3 Solving Tumor Growth Model without Delay Using Nabla $h$–Discrete and Nabla $h$–Fractional Operators

In this section, we give solutions to the model given in Section 3.3 but without the delay condition. We first write the model on $h$–discrete calculus as the following

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

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

Using Theorem 4.1 and Theorem 4.2, we obtain the following solutions

$$
\begin{aligned}
u(t) &= u(0)\frac{1}{(1+hb)^{\frac{t}{h}}} + h\sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hb)^{\frac{t}{h}-s+1}}(a - k_2 c(sh))\\
x_1(t) &= e^{u(t)}\\
x_2(t) &= k_2 h \sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hk_1)^{\frac{t}{h}-s+1}}(c(sh)x_1(sh))\\
x_3(t) &= k_1 h \sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hk_1)^{\frac{t}{h}-s+1}} x_2(sh).
\end{aligned}
$$

Next, we write the representation of our model on $h$–discrete fractional calculus below

$$\nabla_h^\alpha u(t) = a - bu(t) - k_2 c(t), \qquad x_1(0) = w_0$$

$$\nabla_h^\alpha x_2(t) = k_2 c(t) x_1(t) - k_1 x_2(t), \qquad x_2(0) = 0$$

$$\nabla_h^\alpha x_3(t) = k_1 x_2(t) - k_1 x_3(t), \qquad x_3(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t),$$

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

Then, we solve the model utilizing Theorem 4.3 and Theorem 4.4 and get the following outcome

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

$$x_1(t) = e^{u(t)}$$

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

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

where

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

$$y_{k_1}^*(t,0) = \sum_{n=0}^{\infty} \frac{(-k_1)^n h^{n\alpha} \Gamma(\frac{t}{h} + n\alpha + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h} + 1)}.$$

## 4.4 Combination Therapy for Tumor Growth without Delay Model

In this section, we focus on the tumor growth model for without delay form for combination therapy as we did in Section 3.4. First, we write the model on $h$–discrete calculus. Then we introduce solutions using theorems we present in Section 4.1. Moreover, we continue to write our model on $h$–fractional calculus and give its solutions.

$$
\begin{aligned}
(\nabla_h u)(t) &= a - bu(t) - (k_2^a c_1(t) + k_2^b c_2(t)\psi), \qquad x_1(0) = w_0 \\
(\nabla_h x_2)(t) &= (k_2^a c_1(t) + k_2^b c_2(t)\psi)x_1(t) - k_1 x_2(t), \quad x_2(0) = 0 \\
(\nabla_h x_3)(t) &= k_1 x_2(t) - k_1 x_3(t), \qquad x_3(0) = 0 \\
w(t) &= x_1(t) + x_2(t) + x_3(t)
\end{aligned}
$$

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

Using Theorem 4.1 and Theorem 4.2, we obtain the following solutions

$$u(t) = u(0)\frac{1}{(1+hb)^{\frac{t}{h}}} + h\sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hb)^{\frac{t}{h}-s+1}}(a - (k_2^a c_1(sh) + k_2^b c_2(sh)\psi))$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = h\sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hk_1)^{\frac{t}{h}-s+1}}(k_2^a c_1(sh) + k_2^b c_2(sh)\psi)x_1(sh))$$

$$x_3(t) = k_1 h\sum_{s=1}^{\frac{t}{h}} \frac{1}{(1+hk_1)^{\frac{t}{h}-s+1}} x_2(sh).$$

Next, we write the representation of our model on $h$–discrete fractional calculus below

$$\nabla_h^\alpha u(t) = a - bu(t) - (k_2^a c_1(t) + k_2^b c_2(t)\psi), \qquad x_1(0) = w_0$$

$$\nabla_h^\alpha x_2(t) = (k_2^a c_1(t) + k_2^b c_2(t)\psi)x_1(t) - k_1 x_2(t), \qquad x_2(0) = 0$$

$$\nabla_h^\alpha x_3(t) = k_1 x_2(t) - k_1 x_3(t), \qquad x_3(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t),$$

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

As a following step, we solve the model with help of Theorem 4.3 and Theorem 4.4 and get the following result

$$u(t) = y_b^*(t,0)(1+bh^\alpha)u(0) + \sum_{s=1}^{(t/h)} y_b^*(t-sh,0)(a - (k_2^a c_1(sh) + k_2^b c_2(sh)\psi))h^\alpha$$

$$x_1(t) = e^{u(t)}$$

$$x_2(t) = \sum_{s=1}^{(t/h)} y_{k_1}^*(t-sh,0)(k_2^a c_1(sh) + k_2^b c_2(sh)\psi)x_1(sh))h^\alpha$$

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

where

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

$$y_{k_1}^*(t,0) = \sum_{n=0}^{\infty} \frac{(-k_1)^n h^{n\alpha}\Gamma(\frac{t}{h} + n\alpha + \alpha)}{\Gamma((n+1)\alpha)\Gamma(\frac{t}{h}+1)}.$$

# Chapter 5
# THE PHARMACOKINETIC MODEL

Pharmacokinetics (PK) is one of the fields of pharmacology which studies the behaviour of the drugs that are administrated to the body over time. To put another way, PK determines the fate of substances given to a living organism. These substances include pesticides, cosmetics, pharmaceutical drugs, food additives, and so on. Clinical pharmacokinetics [17] is the application of pharmacokinetic rules to the secure and productive therapeutic control of drugs in an single patient. It forms a reasonable basis for administrating proper amounts of the drug for a sensible amount of time to attain desired beneficial effects while minimizing detrimental events. PK's aim is to analyze chemical metabolism and to uncover the future of a chemical from the time it is administered till the moment it is completely removed from the body.

The PK model consists of the following the processes: liberation, absorption, distribution, metabolism, and elimination of a drug [18]. Liberation is the procedure that pharmaceutical formulation release drug. Absorption is the procedure in which the substance enters to blood circulation. Distribution is the process whereby substances circulate or diffuse throughout fluids and tissues of the body. Metabolism or biotransformation is the process whereby an organism recognizes a foreign substance is present. Elimination or excretion is the removal of substances from the body.

Patient-related factors and a drug's chemical properties define the pharmacokinetics of the drug. With the aim of predicting pharmacokinetics parameters in populations some patient-related factors such as renal function, sex and age can be used. For instance, some drugs, especially those demanding both metabolism and excretion are noticeably long in the elderly.

In 1937, Swedish physiologist T. Teorell [32] published first pharmacokinetic model which describes the circulatory system. In addition, F. H. Dost who was a

German pediatrist is considered to be the founder of the term pharmacokinetic, we refer the reader to [35] for further information. "Der Blutspiegel" [14] in 1953 and "Grundlagen der Pharmakokinetik" [15] in 1968 were two of his famous books in which he gave elaborate information and detailed analysis concerning drug behavior in time based on a linear differential equation [23].

The drug concentration in blood within given time is measured in pharmacokinetic experiments. For the sake of improving the PK model, the body is usually divided into several parts. In this chapter, we focus on a two-compartment model approach which is broadly used. The model is based on linear differential equations and from a modeling perspective forms a verifiable method to determine the drug concentration. The time curve of many drugs can be represented by such models.

In this chapter, we first introduce our tumor pharmacokinetic model with two compartments. Subsequently, we consider model for delay and without delay cases. We give solutions for two forms of the models in the final section of this chapter, accordingly.

## 5.1 Two-Compartment PK Model without Delay

In this section, we consider two-compartment pharmacokinetic model. We study oral absorption and endovenous control of the drug. Blood samples have to be taken from patients in order to measure drug concentration. However, existence of data is restricted due to moral limits. It is observed that two compartments are adequate to suitably illustrate the time curve in blood for most drugs. To acquire more knowledge regarding it, we refer the reader to [18].

A two-compartment model should be comprise of two physiological sensible parts [26]:

- The main compartment is recognized with the blood and organs greatly provided with blood like liver or kidney.
- The peripheral compartment represents as an illustration tissue or typically, the section of the body which is severely supplied with blood.

The compartments are linked with each other and thus sharing between main and peripheral compartments occurs. Essential assumptions in pharmacokinetics are as follows:

- The drug is completely removed (metabolism and excretion) from the body via the main compartment.

Now we give our two-compartment tumor growth PK model.

$$
\begin{aligned}
A'(t) &= -k_a A(t), & A(t_D) &= f * dose \\
C'(t) &= k_a \frac{A(t)}{V} - (k_{el} + k_{12})C(t) + k_{21}P(t), & C(t_D) &= 0 \\
P'(t) &= k_{12}C(t) - k_{21}P(t), & P(t_D) &= 0
\end{aligned}
$$

where $0 < f \leq 1$ is a parameter describing the amount of drug which reaches the blood. Without loss of generality, we take $f = 1$. The model has the parameters

$$\mu = (k_a, k_{el}, k_{12}, k_{21})$$

and dose as a variable.

- $V$ is volume of distribution in the model.
- $k_a > 0$ is absorption rate constant.
- $k_{el} > 0$ is elimination rate from the body.
- $k_{12}, k_{21} > 0$ stand for the distribution between main and peripheral compartment.
- $C(t)$ is the drug concentration in the blood.
- $A(t)$ is the absorption amount.

It is worthwhile to mention that while for the two-compartment model $k_{12}, k_{21} > 0$, for the one compartment model $k_{12} = k_{21} = 0$.

As it is seen above, the model is given in the form of differential equations and our aim is to find the solution by rewriting the model as a nabla $h$–discrete equation.

$$\begin{aligned}
&\nabla_h A(t) = -k_a A(t), && A(t_D) = dose \\
&\nabla_h C(t) = k_a \frac{A(t)}{V} - (k_{el} + k_{12})C(t) + k_{21}P(t), && C(t_D) = 0 \\
&\nabla_h P(t) = k_{12}C(t) - k_{21}P(t), && P(t_D) = 0
\end{aligned}$$

In order to find the solution for nabla $h$–discrete equations indicated above, we use theorems that we prove in Section 4.1 and Section 4.2. Using Theorem 4.1, we obtain the solution of the first equation as follows,

$$A(t) = dose \cdot (1 + hk_a)^{-\frac{t-t_D}{h}}.$$

Regarding the second and third equations, we first write them as a system,

$$\nabla_h \begin{bmatrix} C(t) \\ P(t) \end{bmatrix} = \begin{bmatrix} -(k_{el} + k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} \begin{bmatrix} C(t) \\ P(t) \end{bmatrix} + \begin{bmatrix} \frac{k_a A(t)}{V} \\ 0 \end{bmatrix}$$

By means of variation of constants formula, more precisely, Theorem 4.2, we obtain

$$\begin{bmatrix} C(t) \\ P(t) \end{bmatrix} = h \sum_{s=t_D/h+1}^{(t/h)} (I - hM)^{-(\frac{t}{h}-s+1)} \begin{bmatrix} \frac{k_a A(sh)}{V} \\ 0 \end{bmatrix} \tag{5.1.1}$$

where $M$ is an $2 \times 2$ matrix and $I$ is an $2 \times 2$ identity matrix.

$$M = \begin{bmatrix} -(k_{el} + k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix}$$

The characteristic equation for matrix $M$ is

$$\lambda^2 + (k_{el} + k_{12} + k_{21})\lambda + k_{el}k_{21} = 0.$$

Our eigenvalues are

$$\lambda_1 = \frac{-(k_{el} + k_{12} + k_{21}) + \sqrt{(k_{el} + k_{12} + k_{21})^2 - 4k_{el}k_{21}}}{2}$$

$$\lambda_2 = \frac{-(k_{el} + k_{12} + k_{21}) - \sqrt{(k_{el} + k_{12} + k_{21})^2 - 4k_{el}k_{21}}}{2}.$$

Next step is to use the Putzer algorithm in order to achieve solution; therefore, we introduce the Putzer algorithm for delayed form equation.

**Theorem 5.1.** *The unique solution of the initial value problem*

$$\nabla_h y(t) = Ay(t) \quad t = t_0 + h, t_0 + 2h, ..., \tag{5.1.2}$$

$$y(t_0) = c \tag{5.1.3}$$

*is given by*

$$y(t) = (I - hA)^{-\frac{t-t_0}{h}} c$$

*where $A$ is an $n \times n$ constant matrix, and $c$ and $y(t)$ are $n \times 1$ vectors.*

Now, we define the following nabla function

$$y_A^*(t, t_0) := (I - hA)^{-\frac{t-t_0}{h}} \tag{5.1.4}$$

**Theorem 5.2** (Variation of Constants Formula)**.** *Assume $t_0 \in \mathbb{R}$ and $h > 0$. The fractional $h$–difference equation*

$$\nabla_h y(t) = Ay(t) + f(t) \quad for \quad t = t_0 + h, t_0 + 2h, ...,$$

*has the general solution*

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

*where $A$ is an $n \times n$ constant matrix, $c$ is $n \times 1$ vector.*

Next, we introduce the Putzer Algorithm on $h$–discrete calculus. The indicated algorithm is a method used for calculating matrix exponential functions analytically using eigenvalues and components in the solution of a simple linear system. Hence, we first introduce the matrix exponential function.

**Definition 5.3.** *(Matrix Exponential Function without Delay) Let $A$ be an $n \times n$ constant matrix. The unique matrix valued solution of the initial value problem(IVP)*

$$\nabla_h Y(t) = AY(t) \quad for \quad t \in h\mathbb{N}_a \tag{5.1.5}$$

$$Y(a) = I_n, \tag{5.1.6}$$

*where $I_n$ denotes the $n \times n$ identity matrix, is called the matrix exponential function.*

Now, we introduce the theorem regarding the Putzer algorithm and its proof for $h$–discrete calculus.

**Theorem 5.4.** *Let $\lambda_1, \lambda_2, ..., \lambda_n$ be (not necessarily distinct) eigenvalues of the $n \times n$ matrix $A$, with each eigenvalue repeated as many times as its multiplicity, then*

$$y_A^*(t, a) = \sum_{i=0}^{n-1} p_{i+1}(t) M_i,$$

*where*

$$\begin{aligned} &M_0 = I_n \\ &M_i = (A - \lambda_i I_n) M_{i-1}, \quad (1 \le i \le n-1) \\ &M_n = 0 \end{aligned}$$

*and the vector valued function $p$ defined by*

$$p(t) = \begin{bmatrix} p_1(t) \\ p_2(t) \\ p_3(t) \\ \vdots \\ p_n(t) \end{bmatrix}$$

*is the solution of the initial value problem*

$$\nabla_h p(t) = \begin{bmatrix} \lambda_1 & 0 & 0 & \cdots & 0 \\ 1 & \lambda_2 & 0 & \cdots & 0 \\ 0 & 1 & \lambda_3 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & 1 & \lambda_n \end{bmatrix} p(t) \qquad for \qquad t \in h\mathbb{N}_a \tag{5.1.7}$$

$$p(a) = \begin{bmatrix} 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{5.1.8}$$

*Proof.* Define $\Phi(t) = \sum_{i=0}^{n-1} p_{i+1}(t)M_i$. Firstly, we show that $\Phi$ solves the IVP (5.1.5)-(5.1.6). It is good to demonstrate that

$$\begin{aligned} \Phi(a) &= p_1(a)M_0 + p_2(a)M_1 + \cdots + p_n(a)M_{n-1} \\ &= I_n \end{aligned}$$

since the given initial values $p(a) = \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \end{bmatrix}^T$.

$$\nabla_h \Phi(t) - A\Phi(t) = \nabla_h \sum_{i=0}^{n-1} p_{i+1}(t) M_i - A \sum_{i=0}^{n-1} p_{i+1}(t) M_i$$

$$= \nabla_h p_1(t) M_0 + \nabla_h p_2(t) M_1 + \cdots \nabla_h p_n(t) M_{n-1} - A \sum_{i=0}^{n-1} p_{i+1}(t) M_i,$$

since $\nabla_h$ is a linear operator. Subsequently, we use (5.1.7) and obtain

$$\nabla_h \Phi(t) - A\Phi(t) = \lambda_1 p_1(t) M_0 + [p_1(t) + \lambda_2 p_2(t)] M_1 + [p_2(t) + \lambda_3 p_3(t)] M_2$$

$$+ \cdots + [p_{n-1}(t) + \lambda_n p_n(t)] M_{n-1} - A \sum_{i=0}^{n-1} p_{i+1}(t) M_i$$

$$= [\lambda_1 M_0 + M_1 - AM_0] p_1(t) + [\lambda_2 M_1 + M_2 - AM_1] p_2(t)$$

$$+ \cdots + [\lambda_n M_{n-1} - AM_{n-1}] p_n(t)$$

$$= [\lambda_n I_n - A] M_{n-1} p_n(t),$$

since $M_i = (A - \lambda_i I_n) M_{i-1}$ for $(1 \le i \le n)$. Using the Cayley-Hamilton Theorem, we get zero for the last quantity.

In other words,

$$(\lambda_n I_n - A) M_{n-1} p_n(t) = -(A - \lambda_n I_n)(A - \lambda_{n-1} I_n) \cdots (A - \lambda_1 I_n) p_n(t)$$

$$= 0_{n \times n}.$$

Since $y^*_{A,}(t, a)$ satisfies the IVP (5.1.5)-(5.1.6), we have

$$\Phi(t) = y^*_A(t, a)$$

by the unique solution of the given initial value problem. □

Now, we apply the Putzer algorithm indicated above for our problem,

$$M_0 = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}.$$

$$M_1 = \begin{bmatrix} -(k_{el} + k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} - \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_1 \end{bmatrix} = \begin{bmatrix} -(k_{el} + k_{12} + \lambda_1) & k_{21} \\ k_{12} & -(k_{21} + \lambda_1) \end{bmatrix}.$$

Now, the vector function given by,

$$y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix}$$

must be a solution of the IVP,

$$\nabla_h y = \begin{bmatrix} \lambda_1 & 0 \\ 1 & \lambda_2 \end{bmatrix} y, \quad y(0) = \begin{bmatrix} 1 \\ 0 \end{bmatrix}.$$

So, $y_1(t)$ is a solution of the IVP

$$\nabla_h y_1(t) = \lambda_1 y_1(t)$$

$$y_1(0) = 1$$

and we obtain

$$y_1(t) = (1 - h\lambda_1)^{-\frac{t}{h}}.$$

Next, $y_2(t)$ is a solution of the IVP

$$\nabla_h y_2(t) = \lambda_2 y_2(t) + y_1(t)$$

$$y_2(0) = 0$$

It follows that

$$y_2(t) = \sum_{s=1}^{t/h} (1 - h\lambda_2)^{-(\frac{t}{h}-s+1)} (1 - h\lambda_1)^{-s} h$$

Hence,

$$(I - hM)^{\frac{t}{h}} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} (1 - h\lambda_1)^{-\frac{t}{h}} \tag{5.1.9}$$

$$+ \begin{bmatrix} -(k_{el} + k_{12} + \lambda_1) & k_{21} \\ k_{12} & -(k_{21} + \lambda_1) \end{bmatrix} \sum_{s=1}^{t/h} (1 - h\lambda_2)^{-(\frac{t}{h}-s+1)} (1 - h\lambda_1)^{-s} h \tag{5.1.10}$$

Subsequently, we take the last the sum from the expression indicated above and call it $Q$,

$$\begin{aligned} Q &= \sum_{s=1}^{t/h} (1 - h\lambda_2)^{-(\frac{t}{h}-s+1)} (1 - h\lambda_1)^{-s} h \\ &= \sum_{s=1}^{t/h} (1 - h\lambda_2)^{-(\frac{t}{h}-s+1)} \frac{h}{h\lambda_1} \nabla (1 - h\lambda_1)^{-s} \\ &= \frac{1}{\lambda_1} \sum_{s=1}^{t/h} \nabla (1 - h\lambda_1)^{-s} (1 - h\lambda_2)^{-(\frac{t}{h}-s+1)} \end{aligned}$$

where we use Definition 2.1 as a tool.

Next, we apply integration by parts formula given in Theorem 2.11 to the last equality and we obtain,

$$Q = \frac{1}{\lambda_1}((1-h\lambda_1)^{-s}(1-h\lambda_2)^{-(\frac{t}{h}-s+1)})\Big|_{s\to 0}^{s\to\frac{t}{h}} - \frac{1}{\lambda_1}\sum_{s=1}^{t/h}(1-h\lambda_1)^{-s+1}\nabla(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}$$

We simplify and get the following result

$$Q = \frac{1}{\lambda_1}\left(\frac{(1-h\lambda_1)^{-\frac{t}{h}} - (1-h\lambda_2)^{-\frac{t}{h}}}{1-h\lambda_2}\right) + \frac{(1-h\lambda_1)\lambda_2}{(1-h\lambda_2)\lambda_1}\sum_{s=1}^{t/h}(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}(1-h\lambda_1)^{-s}h$$

$$Q = \frac{1}{\lambda_1}\left(\frac{(1-h\lambda_1)^{-\frac{t}{h}} - (1-h\lambda_2)^{-\frac{t}{h}}}{(1-h\lambda_2)}\right) + \frac{(1-h\lambda_1)\lambda_2}{(1-h\lambda_2)\lambda_1}Q$$

$$Q = \frac{(1-h\lambda_1)^{-\frac{t}{h}} - (1-h\lambda_2)^{-\frac{t}{h}}}{\lambda_1 - \lambda_2}.$$

We plug in result into equation 5.1.9 and obtain

$$(I-hM)^{\frac{t}{h}} = \begin{bmatrix} (1-h\lambda_1)^{-\frac{t}{h}} & 0 \\ 0 & (1-h\lambda_1)^{-\frac{t}{h}} \end{bmatrix} + \frac{(1-h\lambda_1)^{-\frac{t}{h}} - (1-h\lambda_2)^{-\frac{t}{h}}}{\lambda_1-\lambda_2}\begin{bmatrix} -(k_{el}+k_{12}+\lambda_1) & k_{21} \\ k_{12} & -(k_{21}+\lambda_1) \end{bmatrix}$$

Finally, we rewrite equation 5.1.1 and the following result is achieved

$$\begin{aligned} C(t) = & \frac{k_a \cdot dose}{V}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{-(\frac{sh-t_D}{h})}h \\ & - \frac{(k_{el}+k_{12}+\lambda_1)k_a \cdot dose}{(\lambda_1-\lambda_2)V}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{-(\frac{sh-t_D}{h})}h \\ & + \frac{(k_{el}+k_{12}+\lambda_1)k_a \cdot dose}{(\lambda_1-\lambda_2)V}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{-(\frac{sh-t_D}{h})}h \end{aligned}$$

For the sake of simplification, we take the first sum in the above expression,

$$
\begin{aligned}
I &= \sum_{s=t_D/h+1}^{t/h} (1-h\lambda_1)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{(-s+\frac{t_D}{h})}h \\
&= \sum_{s=t_D/h+1}^{t/h} (1-h\lambda_1)^{-(\frac{t}{h}-s+1)} \frac{-\nabla(1+hk_a)^{(-s+\frac{t_D}{h})}}{hk_a} h
\end{aligned}
$$

since $\nabla(1+hk_a)^{(-s+\frac{t_D}{h})} = -hk_a(1+hk_a)^{(-s+\frac{t_D}{h})}$.

$$
I = \sum_{s=t_D/h+1}^{t/h} -\frac{1}{k_a}\nabla(1+hk_a)^{(-s+\frac{t_D}{h})}(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}
$$

Successively, we apply Theorem 2.11 to the last equality and get the following outcome

$$
\begin{aligned}
I = &-\frac{1}{k_a}\left((1+hk_a)^{(-s+\frac{t_D}{h})}\ (1-h\lambda_1)^{-(\frac{t}{h}-s+1)}\right)\Big|_{s\to\frac{t_D}{h}}^{s\to\frac{t}{h}} \\
&+\frac{1}{k_a}\sum_{s=t_D/h+1}^{t/h}(1+hk_a)^{(-s+1+\frac{t_D}{h})}\ \nabla(1-h\lambda_1)^{-(\frac{t}{h}-s+1)} \\
= &-\frac{1}{k_a}\left(\frac{(1+hk_a)^{-(\frac{t-t_D}{h})}-(1-h\lambda_1)^{-(\frac{t-t_D}{h})}}{1-h\lambda_1}\right) \\
&-\frac{\lambda_1(1+hk_a)}{k_a(1-h\lambda_1)}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{(-s+\frac{t_D}{h})}h.
\end{aligned}
$$

We simplify and obtain

$$
I = -\frac{1}{k_a}\left(\frac{(1+hk_a)^{-(\frac{t-t_D}{h})}-(1-h\lambda_1)^{-(\frac{t-t_D}{h})}}{1-h\lambda_1}\right) - \frac{\lambda_1(1+hk_a)}{k_a(1-h\lambda_1)}I
$$

$$
I = \frac{(1-h\lambda_1)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}}{k_a+\lambda_1}. \tag{5.1.11}
$$

Similarly, we get the following result for the third sum in the equation for $C(t)$

$$\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{-(\frac{sh-t_D}{h})}h = \frac{(1-h\lambda_2)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}}{k_a+\lambda_2}. \tag{5.1.12}$$

Thus,

$$C(t) = \frac{k_a\cdot dose}{V}\frac{(1-h\lambda_1)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}}{k_a+\lambda_1} \tag{5.1.13}$$

$$-\frac{(k_{el}+k_{12}+\lambda_1)k_a\cdot dose}{(\lambda_1-\lambda_2)V(k_a+\lambda_1)}\left((1-h\lambda_1)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}\right) \tag{5.1.14}$$

$$+\frac{(k_{el}+k_{12}+\lambda_1)k_a\cdot dose}{(\lambda_1-\lambda_2)V(k_a+\lambda_2)}\left((1-h\lambda_2)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}\right). \tag{5.1.15}$$

And we get the solution for $P(t)$ as follows,

$$P(t) = \sum_{s=t_D+1}^{t/h}\left(\frac{(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}-(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}k_{12}}{\lambda_1-\lambda_2}\right)\frac{dose\cdot k_a(1+hk_a)^{-(\frac{sh-t_D}{h})}}{V}h$$

$$=\frac{dose\cdot k_a\cdot k_{12}}{V(\lambda_1-\lambda_2)}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_1)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{(-s+\frac{t_D}{h})}h$$

$$-\frac{dose\cdot k_a\cdot k_{12}}{V(\lambda_1-\lambda_2)}\sum_{s=t_D/h+1}^{t/h}(1-h\lambda_2)^{-(\frac{t}{h}-s+1)}(1+hk_a)^{(-s+\frac{t_D}{h})}h$$

From previous calculation, more precisely, using Equation 5.1.11 and Equation 5.1.12, the following result is obtained

$$P(t) = \frac{dose\cdot k_a\cdot k_{12}}{V(\lambda_1-\lambda_2)(k_a+\lambda_1)}\left((1-h\lambda_1)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}\right)$$

$$-\frac{dose\cdot k_a\cdot k_{12}}{V(\lambda_1-\lambda_2)(k_a+\lambda_2)}\left((1-h\lambda_2)^{-(\frac{t-t_D}{h})}-(1+hk_a)^{-(\frac{t-t_D}{h})}\right).$$

## 5.2 Two-Compartment PK Model with Delay

In this section, we analyze the model shown in Section 5.1 but in the delay case. Firstly, we write the model for the nabla $h$–discrete calculus. Then, we use theorems which we proved in Section 3.1 and Section 3.2. Furthermore, we use the definition of $e^{Mt}$ where $M$ is $n \times n$ matrix and the Putzer algoritm for the solution of the delayed two-compartment PK model.

We first introduce the Putzer algorithm for the delayed form equations. So, we state the subsequent theorem and the proof follows similar techniques as Theorem 3.3.

**Theorem 5.5.** *The unique solution of the initial value problem*

$$\nabla_h y(t) = Ay(t-h) \quad t = t_0 + h, t_0 + 2h, ..., \tag{5.2.1}$$

$$y(t_0) = c \tag{5.2.2}$$

*is given by*

$$y(t) = (I + hA)^{\frac{t-t_0}{h}} c$$

*where $A$ is an $n \times n$ constant matrix, $c$ and $y(t)$ are $n \times 1$ vectors.*

Now, we define the following nabla function

$$\widehat{y}_A(t, t_0) := (I + hA)^{\frac{t-t_0}{h}} \tag{5.2.3}$$

**Theorem 5.6** (Variation of Constants Formula)**.** *Assume $t_0 \in \mathbb{R}$ and $h > 0$. The* *fractional h–difference equation*

$$\nabla_h y(t) = Ay(t-h) + f(t-h) \quad for \quad t = t_0 + h, t_0 + 2h, ...,$$

*has the general solution*

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

*where $A$ is an $n \times n$ constant matrix, $c$ is $n \times 1$ vector.*

**Definition 5.7.** *(Matrix Exponential Function with Delay) Let $A$ be an $n \times n$ constant matrix. The unique matrix valued solution of the initial value problem(IVP)*

$$\nabla_h Y(t) = AY(t-h) \quad for \quad t \in h\mathbb{N}_a \tag{5.2.4}$$

$$Y(a) = I_n, \tag{5.2.5}$$

*where $I_n$ denotes the $n \times n$ identity matrix, is called the matrix exponential function.*

Now, we introduce theorem regarding the Putzer algorithm and its proof.

**Theorem 5.8.** *Let $\lambda_1, \lambda_2, ..., \lambda_n$ are (not necessarily distinct) eigenvalues of the $n \times n$ matrix $A$, with each eigenvalue repeated as many times as its multiplicity, then*

$$\widehat{y}_A(t, a) = \sum_{i=0}^{n-1} p_{i+1}(t) M_i,$$

*where*

$$M_0 = I_n$$

$$M_i = (A - \lambda_i I_n) M_{i-1}, \quad (1 \le i \le n-1)$$

$$M_n = 0$$

*and the vector valued function p defined by*

$$p(t) = \begin{bmatrix} p_1(t) \\ p_2(t) \\ p_3(t) \\ \vdots \\ p_n(t) \end{bmatrix}$$

*is the solution of the initial value problem*

$$\nabla_h p(t) = \begin{bmatrix} \lambda_1 & 0 & 0 & \cdots & 0 \\ 1 & \lambda_2 & 0 & \cdots & 0 \\ 0 & 1 & \lambda_3 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & 1 & \lambda_n \end{bmatrix} p(t-h) \qquad for \qquad t \in h\mathbb{N}_a \tag{5.2.6}$$

$$p(a) = \begin{bmatrix} 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{5.2.7}$$

*Proof.* Define $\Phi(t) = \sum_{i=0}^{n-1} p_{i+1}(t)M_i$. Firstly, we show that $\Phi$ solves the IVP (5.2.4)-

(5.2.5). It is good to demonstrate that

$$\Phi(a) = p_1(a)M_0 + p_2(a)M_1 + \cdots + p_n(a)M_{n-1}$$

$$= I_n$$

since the given initial values $p(a) = \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \end{bmatrix}^T$.

$$\nabla_h \Phi(t) - A\Phi(t-h) = \nabla_h \sum_{i=0}^{n-1} p_{i+1}(t)M_i - A\sum_{i=0}^{n-1} p_{i+1}(t-h)M_i$$

$$= \nabla_h p_1(t)M_0 + \nabla_h p_2(t)M_1 + \cdots \nabla_h p_n(t)M_{n-1} - A\sum_{i=0}^{n-1} p_{i+1}(t-h)M_i,$$

since $\nabla_h$ is a linear operator. Subsequently, we use (5.2.6) and obtain

$$\nabla_h \Phi(t) - A\Phi(t-h) = \lambda_1 p_1(t-1)M_0 + [p_1(t-h) + \lambda_2 p_2(t-h)]M_1$$

$$+ [p_2(t-h) + \lambda_3 p_3(t-h)]M_2 + \cdots + [p_{n-1}(t-h) + \lambda_n p_n(t-h)]M_{n-1}$$

$$- A\sum_{i=0}^{n-1} p_{i+1}(t-h)M_i$$

$$= [\lambda_1 M_0 + M_1 - AM_0]p_1(t-h) + [\lambda_2 M_1 + M_2 - AM_1]p_2(t-h)$$

$$+ \cdots + [\lambda_n M_{n-1} - AM_{n-1}]p_n(t-h)$$

$$= [\lambda_n I_n - A]M_{n-1}p_n(t-h),$$

since $M_i = (A - \lambda_i I_n)M_{i-1}$ for $(1 \le i \le n)$. Using Cayley-Hamilton Theorem, we get zero for the last quantity.

In other words,

$$(\lambda_n I_n - A)M_{n-1}p_n(t-h) = -(A-\lambda_n I_n)(A-\lambda_{n-1}I_n)\cdots(A-\lambda_1 I_n)p_n(t-h)$$

$$= 0_{n\times n}.$$

Since $\widehat{y}_{A,}(t,a)$ satisfies the IVP (5.2.4)-(5.2.5), we have

$$\Phi(t) = \widehat{y}_A(t,a)$$

by the unique solution of the given initial value problem. □

Now, we first rewrite our tumor growth PK model by taking delay into consideration.

$$\nabla_h A(t) = -k_a A(t-h), \qquad A(t_D) = dose$$

$$\nabla_h C(t) = k_a \frac{A(t-h)}{V} - (k_{el}+k_{12})C(t-h) + k_{21}P(t-h), \qquad C(t_D) = 0$$

$$\nabla_h P(t) = k_{12}C(t-h) - k_{21}P(t-h), \qquad P(t_D) = 0$$

From first equation, we obtain a solution for $A(t)$ as follows

$$A(t) = dose \cdot (1-hk_a)^{\frac{t-t_D}{h}}.$$

where we use Theorem 3.1. Subsequently, we write equation second and third as a system,

$$\nabla_h \begin{bmatrix} C(t) \\ P(t) \end{bmatrix} = \begin{bmatrix} -(k_{el}+k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} \begin{bmatrix} C(t-h) \\ P(t-h) \end{bmatrix} + \begin{bmatrix} \dfrac{k_a A(t-h)}{V} \\ 0 \end{bmatrix}$$

Using variation of constants formula given in Theorem 3.2, we obtain

$$\begin{bmatrix} C(t) \\ P(t) \end{bmatrix} = h \sum_{s=t_D/h}^{(t/h-1)} (I + hM)^{(\frac{t}{h}-s-1)} \begin{bmatrix} \frac{k_a A(sh)}{V} \\ 0 \end{bmatrix} \tag{5.2.8}$$

where $M$ is an $2 \times 2$ matrix and $I$ is $2 \times 2$ identity matrix.

$$M = \begin{bmatrix} -(k_{el} + k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix}$$

and we use definition of $e^{Mt}$. The characteristic equation for matrix $M$ is

$$\lambda^2 + (k_{el} + k_{12} + k_{21})\lambda + k_{el}k_{21} = 0.$$

Our eigenvalues are

$$\lambda_1 = \frac{-(k_{el} + k_{12} + k_{21}) + \sqrt{(k_{el} + k_{12} + k_{21})^2 - 4k_{el}k_{21}}}{2}$$

$$\lambda_2 = \frac{-(k_{el} + k_{12} + k_{21}) - \sqrt{(k_{el} + k_{12} + k_{21})^2 - 4k_{el}k_{21}}}{2}.$$

Next, we apply the Putzer algorithm given in Theorem 5.8,

$$M_0 = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}.$$

$$M_1 = \begin{bmatrix} -(k_{el} + k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} - \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_1 \end{bmatrix} = \begin{bmatrix} -(k_{el} + k_{12} + \lambda_1) & k_{21} \\ k_{12} & -(k_2 1 + \lambda_1) \end{bmatrix}.$$

Now, the vector function given by,

$$n(t) = \begin{bmatrix} n_1(t) \\ n_2(t) \end{bmatrix}$$

must be the solution of the IVP,

$$\nabla_h n = \begin{bmatrix} \lambda_1 & 0 \\ 1 & \lambda_2 \end{bmatrix} n, \quad n(0) = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

So, $n_1(t)$ is a solution of IVP

$$\nabla_h n_1(t) = \lambda_1 n_1(t-h)$$

$$n_1(0) = 1$$

and we obtain

$$n_1(t) = (1 + h\lambda_1)^{\frac{t}{h}}.$$

Next, $n_2(t)$ is a solution of IVP

$$\nabla_h n_2(t) = \lambda_2 n_2(t-h) + n_1(t-h)$$

$$n_2(0) = 0$$

It follows that

$$n_2(t) = \sum_{s=0}^{t/h-1} (1 + h\lambda_2)^{(\frac{t}{h}-s-1)}(1 + h\lambda_1)^s h$$

Hence,

$$(I + hM)^{\frac{t}{h}} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} (1 + h\lambda_1)^{\frac{t}{h}} \tag{5.2.9}$$

$$+ \begin{bmatrix} -(k_{el} + k_{12} + \lambda_1) & k_{21} \\ k_{12} & -(k_{21} + \lambda_1) \end{bmatrix} \sum_{s=0}^{t/h-1} (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} (1 + h\lambda_1)^s h \tag{5.2.10}$$

Next, we take the last sum and define it as a $L$,

$$\begin{aligned} L &= \sum_{s=0}^{t/h-1} (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} (1 + h\lambda_1)^s h \\ &= \sum_{s=0}^{t/h-1} (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} \frac{(1 + h\lambda_1)}{h\lambda_1} \nabla (1 + h\lambda_1)^s h \\ &= \frac{1 + h\lambda_1}{\lambda_1} \sum_{s=0}^{t/h-1} \nabla (1 + h\lambda_1)^s (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} \end{aligned}$$

where we use Definition 2.1 as a tool.

Subsequently, we apply Theorem 2.11 to last equality and we obtain,

$$L = \frac{1 + h\lambda_1}{\lambda_1} \left( ((1 + h\lambda_1)^s (1 + h\lambda_2)^{(\frac{t}{h}-s-1)}) \Big|_{s \to -1}^{s \to \frac{t}{h}-1} - \sum_{s=0}^{t/h-1} (1 + h\lambda_1)^{s-1} \nabla (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} \right)$$

We simplify and get the following result

$$L = \frac{1 + h\lambda_1}{\lambda_1} \left( \frac{(1 + h\lambda_1)^{\frac{t}{h}} - (1 + h\lambda_2)^{\frac{t}{h}}}{1 + h\lambda_1} \right) + \frac{(1 + h\lambda_1)\lambda_2}{(1 + h\lambda_1)\lambda_1} \sum_{s=0}^{t/h-1} (1 + h\lambda_2)^{(\frac{t}{h}-s-1)} (1 + h\lambda_1)^s h$$

$$L = \frac{1}{\lambda_1} \left( (1 + h\lambda_1)^{\frac{t}{h}} - (1 + h\lambda_2)^{\frac{t}{h}} \right) + \frac{\lambda_2}{\lambda_1} L$$

$$L = \frac{(1 + h\lambda_1)^{\frac{t}{h}} - (1 + h\lambda_2)^{\frac{t}{h}}}{\lambda_1 - \lambda_2}.$$

We plug this result into equation 5.2.9 and obtain

$$
\begin{aligned}
(I+hM)^{\frac{t}{h}} =& \begin{bmatrix} (1+h\lambda_1)^{\frac{t}{h}} & 0 \\ 0 & (1+h\lambda_1)^{\frac{t}{h}} \end{bmatrix} \\
&+ \frac{(1+h\lambda_1)^{\frac{t}{h}} - (1+h\lambda_2)^{\frac{t}{h}}}{\lambda_1 - \lambda_2} \begin{bmatrix} -(k_{el}+k_{12}+\lambda_1) & k_{21} \\ k_{12} & -(k_{21}+\lambda_1) \end{bmatrix}
\end{aligned}
$$

Consequently, we rewrite equation 5.2.8 and the following result is achieved

$$
\begin{aligned}
C(t) =& \frac{k_a \cdot dose}{V} \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_1)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(\frac{sh-t_D}{h})} h \\
&- \frac{(k_{el}+k_{12}+\lambda_1)k_a \cdot dose}{(\lambda_1-\lambda_2)V} \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_1)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(\frac{sh-t_D}{h})} h \\
&+ \frac{(k_{el}+k_{12}+\lambda_1)k_a \cdot dose}{(\lambda_1-\lambda_2)V} \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_2)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(\frac{sh-t_D}{h})} h
\end{aligned}
$$

By taking the first sum from expression above, we simplify and get

$$
\begin{aligned}
W &= \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_1)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(s-\frac{t_D}{h})} h \\
&= \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_1)^{(\frac{t}{h}-s-1)} \frac{\nabla(1-hk_a)^{(s-\frac{t_D}{h})}(1-hk_a)}{-hk_a} h
\end{aligned}
$$

since $\nabla(1-hk_a)^{(s-\frac{t_D}{h})} = \frac{-hk_a}{1-hk_a}(1-hk_a)^{(s-\frac{t_D}{h})}$.

$$
W = -\frac{1-hk_a}{k_a} \sum_{s=t_D/h}^{t/h-1} \nabla(1-hk_a)^{(s-\frac{t_D}{h})} (1+h\lambda_1)^{(\frac{t}{h}-s-1)}
$$

Successively, we apply Theorem 2.11 to last equality and get the following outcome

$$
W = -\frac{1-hk_a}{k_a} \left( (1-hk_a)^{(s-\frac{t_D}{h})} \, (1+h\lambda_1)^{(\frac{t}{h}-s-1)} \right) \Big|_{s\to\frac{t_D}{h}-1}^{s\to\frac{t}{h}-1}
$$

$$+\frac{1-hk_a}{k_a}\sum_{s=t_D/h}^{t/h-1}(1-hk_a)^{(s-1-\frac{t_D}{h})}\nabla(1+h\lambda_1)^{(\frac{t}{h}-s-1)}$$

$$=-\frac{1-hk_a}{k_a}\left(\frac{(1-hk_a)^{(\frac{t-t_D}{h})}-(1+h\lambda_1)^{(\frac{t-t_D}{h})}}{1-hk_a}\right)$$

$$+\frac{(-\lambda_1)(1-hk_a)}{k_a(1-hk_a)}\sum_{s=t_D/h}^{t/h-1}(1+h\lambda_1)^{(\frac{t}{h}-s-1)}(1-hk_a)^{(s-\frac{t_D}{h})}h$$

We simplify and obtain

$$W=-\frac{1-hk_a}{k_a}\left(\frac{(1-hk_a)^{(\frac{t-t_D}{h})}-(1+h\lambda_1)^{(\frac{t-t_D}{h})}}{1-hk_a}\right)-\frac{\lambda_1}{k_a}W$$

$$W=\frac{(1+h\lambda_1)^{(\frac{t-t_D}{h})}-(1-hk_a)^{(\frac{t-t_D}{h})}}{k_a+\lambda_1}. \tag{5.2.11}$$

Similarly, we get the following result for the third sum in the equation for $C(t)$

$$\sum_{s=t_D/h}^{t/h-1}(1+h\lambda_2)^{(\frac{t}{h}-s-1)}(1-hk_a)^{(\frac{sh-t_D}{h})}h=\frac{(1+h\lambda_2)^{(\frac{t-t_D}{h})}-(1-hk_a)^{(\frac{t-t_D}{h})}}{k_a+\lambda_2}. \tag{5.2.12}$$

Hence, we obtain solution of $C(t)$. Thus,

$$C(t)=\frac{k_a\cdot dose}{V}\frac{(1+h\lambda_1)^{(\frac{t-t_D}{h})}-(1-hk_a)^{(\frac{t-t_D}{h})}}{k_a+\lambda_1}$$

$$-\frac{(k_{el}+k_{12}+\lambda_1)k_a\cdot dose}{(\lambda_1-\lambda_2)V(k_a+\lambda_1)}\left((1+h\lambda_1)^{(\frac{t-t_D}{h})}-(1-hk_a)^{(\frac{t-t_D}{h})}\right)$$

$$+\frac{(k_{el}+k_{12}+\lambda_1)k_a\cdot dose}{(\lambda_1-\lambda_2)V(k_a+\lambda_2)}\left((1+h\lambda_2)^{(\frac{t-t_D}{h})}-(1-hk_a)^{(\frac{t-t_D}{h})}\right).$$

And we get solution for $P(t)$ as follows,

$$P(t) = \sum_{s=t_D/h}^{t/h-1} \left( \frac{(1+h\lambda_1)^{(\frac{t}{h}-s-1)} - (1+h\lambda_2)^{(\frac{t}{h}-s-1)} k_{12}}{\lambda_1 - \lambda_2} \right) \frac{dose \cdot k_a (1-hk_a)^{(\frac{sh-t_D}{h})}}{V} h$$

$$= \frac{dose \cdot k_a \cdot k_{12}}{V(\lambda_1 - \lambda_2)} \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_1)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(s-\frac{t_D}{h})} h$$

$$- \frac{dose \cdot k_a \cdot k_{12}}{V(\lambda_1 - \lambda_2)} \sum_{s=t_D/h}^{t/h-1} (1+h\lambda_2)^{(\frac{t}{h}-s-1)} (1-hk_a)^{(s-\frac{t_D}{h})} h$$

From previous calculation, more precisely, using Equation 5.2.11 and Equation 5.2.12, the following result is obtained

$$P(t) = \frac{dose \cdot k_a \cdot k_{12}}{V(\lambda_1 - \lambda_2)(k_a + \lambda_1)} \left( (1+h\lambda_1)^{(\frac{t-t_D}{h})} - (1-hk_a)^{(\frac{t-t_D}{h})} \right)$$

$$- \frac{dose \cdot k_a \cdot k_{12}}{V(\lambda_1 - \lambda_2)(k_a + \lambda_2)} \left( (1+h\lambda_2)^{(\frac{t-t_D}{h})} - (1-hk_a)^{(\frac{t-t_D}{h})} \right).$$

## 5.3 Application of the Pharmacokinetics Model

In this section, we illustrate an example where one can see how we do calculate the concentration over time. A drug is administered to the body daily in four consecutive days at the times $t = 360, 384, 408, 432$. We calculate the concentration in the following way:

Before the drug is administered, there is no concentration. So we have

$$C(t) = 0 \quad for \quad t < 360.$$

After the first dose is given at $t = 360$, we define

$$C_1(t) := C(t, dose_1) \quad for \quad t \in \mathbb{N}_{360}$$

Subsequently, a second dose is administered to the body at $t = 384$. The concentration includes two parts: the first part is the remaining concentration from the first dose and the second part is the concentration due to the second dose.

$$C_2(t) := C_1(t) + C(t, dose_2) \quad for \quad t \in \mathbb{N}_{384}$$

Finally, a third dose is administered at time $t = 408$. Now, we consider two parts in order to determine drug concentration in the blood: the first part is the remaining concentration from the first and the second doses, namely $C_2(t)$, the second part is the concentration due to the third dose.

$$C_3(t) := C_2(t) + C(t, dose_3) \quad t \in \mathbb{N}_{408}$$

We continue to the process and write

$$C_4(t) := C_3(t) + C(t, dose_4) \quad for \quad t \in \mathbb{N}_{432} \quad .$$

# Chapter 6
# CONCLUSION AND FUTURE WORK

In this thesis, we worked on $h$–discrete calculus and $h$–discrete fractional calculus for the sake of finding solutions to our tumor growth model for both mono and combination therapies. To put it another way, we first introduced some basics and fundamental knowledge about $h$–discrete calculus and $h$–discrete fractional calculus as preliminaries. We then focus on the nabla $h$–discrete equation for delayed form and introduce the variation of constants formula accordingly. Following to this, we examine $h$–discrete fractional equation with delay and its variation of constants formula, too. We write our tumor growth model for both mono and combination therapies and find solutions for them in Chapter 3. Since our aim was to eliminate jumps from our tumor growth model's graph, as a following step we applied the same procedure for the model not having delay in Chapter 4 and we achieve our goal,in other words, we are able to remove those jumps from our tumor growth graph. In the last chapter, we consider PK model. Furthermore, we write the PK model on $h$–discrete calculus and find solutions for it. In order to obtain solutions we had to use the Putzer algorithm, therefore, we introduced the Putzer algorithm on $h$–discrete calculus. We give an application of PK model in the final section of Chapter 5.

In future work, we would like to fractionalize PK model and examine its effects for parameter estimations as well. Additionally, we will work on our PK model for combination therapy on both $h$–discrete calculus and $h$–discrete fractional calculus.

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