Olivia Ada Obi

A BI-GEOMETRIC FRACTIONAL MODEL OF THE COMPETITION BETWEEN HEALTHY AND CANCEROUS CELLS AND THE EFFECT OF RADIOTHERAPY ON BOTH CELLS

PhD THESIS

2022

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June, 2022

Approval

We certify that we have read the thesis submitted by Olivia Ada OBI titled **"A STUDY OF BI-GEOMETRIC FRACTIONAL MODEL FOR THE COMPETITION BETWEEN CANCEROUS AND HEALTHY CELLS AND THE EFFECT OF RADIOTHERAPY ON BOTH CELLS"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Doctor of Philosophy in Mathematics.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Olivia Ada OBI

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Acknowledgments

Apart from my efforts, the success of any thesis largely depends on the guidelines and encouragements of many others. I hereby use this opportunity to express my profound gratitude to all those who have been instrumental to the successful completion of this thesis and by extension, my PhD.

I offer my sincerest gratitude to my supervisor, Prof. Dr. Evren Hınçal for his suggestions, patience and guidance and also allowing me the room to work in my own way. Special gratitude also goes to Assist. Prof. Dr. Mohammad Momenzadeh of Mathematics department, who guided me throughout my thesis with his knowledge and patience, he was a great asset who provided outstanding mentoring experience.

I will also like to express my unreserved gratitude to all my instructors at the department of mathematics, Near East University, Cyprus. For the inestimable knowledge imparted on me throughout the period of my PhD program, which enhanced my research skills in mathematics, my ability to work independently, my critical thinking and analytical ability amongst many others. The experience was an interesting and rewarding one which immensely facilitated my skills and knowledges in achieving a remarkable academic progress, fulfilling my aspiration to become an accomplished professional in the field of mathematics.

Lastly, all these would have been impossible without the love, patience and support of my family, especially my two lovely daughters; Victoria and Jessica, they have been with me during my PhD journey and have been a constant source of love, strength and support all these years.

Olivia Ada Obi

Abstract

A Bi-Geometric Fractional Model for The Competition Between Cancerous and Healthy Cells and The Effect of Radiotherapy on Both Cells.

Ada Obi, Olivia

PhD, Department of Mathematics

June, 2022, 70 Pages

We established our model based on the modification of a well-known predator-prey simulation. The Lotka–Volterra competition model also known as a system of differential equations that describes the population of healthy and cancerous cells within the tumor tissue of a patient that is struggling with cancer. Besides, fractional differentiation implies a meticulous model with more flexible parameters. Furthermore, studying fractional differential operators on non-Newtonian calculi obtains different types of fractional operators with distinct singularities. Bi-geometric calculus is a famous example of these calculi which is equipped with the Hadamard fractional differential operator. The model is extended in these criteria and in the first step, the existence and uniqueness of the model are considered and guaranteed by applying the Arzela-Ascoli theorem. The bi-geometric analogue of the numerical method has provided a suitable tool to solve the model approximately. In the end, the visual graphs are obtained by using the MATLAB program.

Key Words*:* Bi-Geometric Calculus, Fractional Differential Operator, Prey-Predator Model, Hadamard fractional operator

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List of Abbreviations

TRNC: Turkish Republic of North Cyprus

MNE: Ministry of National Education

FDE: Fractional differential equation

ODE: Ordinary differential equation

IVE: Integral Volterra equation

CHAPTER I

Introduction

1. What is Cancer?

There are many reasons to be interested in the study of cancer. For me specifically, it was triggered by the loss of my mother to cancer. Even glimpses of mundane incident rate of death due to cancer can convince any researcher to spend time to investigate the disease. The last updates of cancer incidence and mortality showed an estimated 19.3 million new cancer cases and almost 10 million cancer deaths occurred in 2020. [Sung et. al (2020)]

In this section, we present some of the key biological concepts that are necessary to understand the tumor models introduced in this literature. The cooperation of more than ten million cells needs to meet to maintain the healthy life of a human being. On the most basic level of definition, cancer is caused by rebellious, selfish cells that impact the harmony between cells. Eventually, the absence of treatment leads to the death of the organism. Although, understanding the mechanism of cancer and cancer biology which involves many components is sophisticated, we focus on the molecular and cellular biology of cancer in any specific tissue. An interested reader can find a comprehensive overview of cancer biology in some standard textbooks [Vogelstein et. al (2004)]. Roughly speaking, cancer is the disease of the DNA that causes alterations or mutations in the genetic material and imminent uncontrolled growth of cells. Once a cancerous cell has emerged, it undergoes a process known as clonal expansion. The population of cancerous cells increases by cell division. However, cells can acquire a variety of further mutations which lead to more advanced progression. The process by which cancerous cells migrate and start growing in another organ is referred to as metastasis.

The division patterns of tissue stem cells and the interactions between these two populations have been studied [Vogelstein et. al (2004)]. The increase of cancerous cells population leads to emerging tumors. Tumor evolution is a sophisticated process involving many different phenomena which occur at different scales. Three natural viewpoints in medicine or biology are remarkable in describing the phenomena occurring during the evolution of tumors. These are sub-cellular level (microscopic scale), the cellular level (mesoscopic scale), and the tissue level (macroscopic scale) [Wang (2010)]. The mesoscopic scale refers to the cellular level and therefore to the main activities of the cell populations. E.g., statistical description of the progression and activation state, interactions among tumor cells, and the other types of cells present in the body such as endothelial cells, macrophages, lymphocytes, proliferative and destructive interactions, aggregation and disaggregation properties. Most of the published articles refer to two main methods of cancer treatments; chemotherapy and radiotherapy. Radiotherapy or radiation therapy is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink the tumor by damaging their DNA. This procedure is not the immediate consequence of irradiation. Indeed, it takes days or weeks of treatment before DNA is damaged enough for cancer cells to die.

2. Mathematical Model and Different Approaches

Similar to [Dominik (2014)], we follow the same categorization in the area of mathematical modeling of tumorigenesis. Indeed, broadly speaking, there are three major areas where theory has contributed the most to cancer research

(i) Using the context of epidemiology and other statistical data to describe the model. Furthermore, using the available incident statistics and creating models to explain the observations are one of the oldest and most successful methodologies in theoretical cancer research. This field, in general, has not been very fruitful and there have been some hesitations in applying the technique to the study of cancer originated by [Armitage and Doll (1954)], and then taken to the next level by Moolgavkar and colleagues [Moolgavkar and Knudson (1981)].

(ii) Mechanistic modeling of tumor growth, including multi-scale modeling. An entirely different approach to cancer modeling is to look at the mechanistic aspects of the tumor material and use physical properties of biological tissues to describe the tumor growth. In series of articles, the various methods were studied and biochemical kinetics were modeled, see [Preziosi (2003); Cristini and Lowengrub (2010)] for review.

(iii) Modeling of cancer initiation and progression as somatic evolution. In this area of research, methods of population dynamics and evolutionary game theory are applied to study cancer. First developed by ecologists and evolutionary biologists, these methods have been used to understand the collective behavior of a population of cancer cells, see [Gatenby and Gawlinski (2003); Gatenby and Vincent (2003b)].

Mathematical modeling of growth, differentiation and mutation of cells in tumor are one of the oldest and best developed topics in biomathematics [Bellomo and Maini (2007)]. Let us view cancer as a population of cells that evolves deterministically and has some potential to grow. For a successful discussion, we need to overview the different types of mathematical model population. The simplest case could be considered as the given differential equation;

$$\frac{dX}{dt} = birth - death + migration.$$

Here, X denotes the number of the population. If we assume the birth and death as a constant coefficient of population, by neglecting the immigration, the result gives the exponential growth of the population

$$\frac{dX}{dt} = bX - dX$$

$$\Rightarrow X(t) = X_o exp\big((b-d)t\big).$$

Obviously, $b > d$ implies the exponential growth of the population while $d > b$ leads to extinction. This model is not realistic and in the long run, there must be some adjustment to such exponential growth. Verhulst (1834) proposed that a self-limiting process should operate when a population becomes too large

$$\frac{dX}{dt} = rX\left(1 - \frac{X}{K}\right) \qquad r, K > 0$$

This model is called the logistic growth equation and it has two steady states or equilibrium states, namely $X = K$ and $X = 0$. The carrying capacity, K, determines the size of the stable population while $r,$ is a measure of the rate at which it is reached. That is, it is a measure of the dynamics. Applying the Bernoulli method of ODE with $V = X^{-1}$, solve the logistic growth equation in terms of terms of X_0, the initial population

$$X(t) = \frac{X_0 K e^{rt}}{K + X_0(e^{rt} - 1)} \ approaches\ to\ K,\ \ as\ \ \ t\ approaches\ to\ \infty.$$

3. Predator and Prey Model

In this section, we study a few things about Lotka–Volterra equation or as it is known predator-prey equation. This equation is a couple of first order nonlinear differential equation which was inspired during the conversation about ecology. For the prey species, it is assumed that the prey growth, if left alone, is Malthusian. It means that the specific growth rate is constant. Furthermore, in this model, the specific growth rate diminishes by an amount proportional to the predator density. This leads to the prey equation

$$\frac{dX_1}{dt}(t) = X_1(t)(\alpha - \beta X_2(t)) \qquad \alpha, \beta > 0,$$

for the predator species, it is assumed that the predator will become extinct exponentially just as a radioactive decay in the absence of prey, inversely their growth rate is enhanced by an amount proportional to the prey density which leads to the predator equation as

$$\frac{dX_2}{dt}(t) = X_2(t)(-\gamma + \delta X_1(t)) \qquad \gamma, \delta > 0$$

There are some remarkable comments about this system of first order nonlinear differential equation. First, we assume that the prey species (rabbits) is growing exponentially at the rate of $\alpha X_1(t)$. In the absence of predators, $X_2 = 0$ and at the equilibrium point where $\frac{dX_2}{dt} = 0$, and when the coefficient of the interaction X_1X_2 is added, the sign of interaction factor determines the type of Lotka–Volterra equation. If the sign of interaction factor is negative, then it means that after the equilibrium point the population of that species will decline. Conversely, if the interaction factor is positive, then the population of the species will increase after the equilibrium point. For instance, if $\delta < 0$, then both species will decline after the equilibrium point and that means we will have a competition form like sheep-rabbits. Furthermore, if $\beta < 0$ then both species will grow after the equilibrium point and the cooperation between them can be constructed. Now let X_1 and X_2 determine the population of healthy and cancerous cells respectively. In the first step, we should let healthy cells grow logistically in the absence of cancerous cells. Thus, we have

$$\frac{dX_1}{dt}(t) = \alpha_1 X_1(t)\left(1 - \frac{X_1(t)}{K_1}\right),$$

here, α_1 is the proliferation coefficient and K_1 denotes the carrying capacity. In the next step, we should add the interaction factor which determines the competition between cancerous cells and healthy cells. This interaction is similar to the attitude of sheep-rabbits that compete for the same resources. There are some restrictions in each model which should be implemented eventually. Here, we assume that the concentration of cancerous and healthy cells exists in the same region of the organism. Thus, the system can be rewritten as

$$\begin{cases} \dfrac{dX_1}{dt} = \alpha_1 X_1(t)\left(1 - \dfrac{X_1(t)}{K_1}\right) - \beta_1 X_1(t) X_2(t) \\ \dfrac{dX_2}{dt} = \alpha_2 X_2(t)\left(1 - \dfrac{X_2(t)}{K_2}\right) - \beta_2 X_1(t) X_2(t) \end{cases}$$

Here, $\beta_i,\ i = 1,2$ describe the coefficients of interaction factor or competition coefficients. This model determines the competition between cancerous and healthy cells. In the next step, we can plug in the treatment effects and study the efficiency of different treatments on the population of cancerous and healthy cells. For instance, in [Nani and et. al. (2000)], the effect of the treatment by immunotherapy on the population of cancer and healthy cells is studied. So, the plugged-in part is a function $-h(X_2(t), w)$ of the population of cancerous cells. w is defined by another ODE and describes the effect of immunotherapy.

Now, let us see the effect of two other main treatments; radiotherapy and chemotherapy. In radiotherapy, the struggling tissue is affected by the exposure to radiation. Indeed, the radiation causes mutation on the DNA of the cells and in that period of time, the affected cells die. This is like harvesting the population of both healthy and cancerous cells. In this circumstance, [Liu et. al. (2016)] describes the effect of radiotherapy in two phases. If n denotes the number of times that the radiation is administrated and w denotes the period of administration, then we can split the interval of $[nw, (n+1)w]$ to two parts and the model will be as follows for $t \in [nw, L]$,

$$\begin{cases} \dfrac{dX_1}{dt} = \alpha_1 X_1(t)\left(1 - \dfrac{X_1(t)}{K_1}\right) - \beta_1 X_1(t) X_2(t) - \varepsilon\gamma X_1(t) \\ \dfrac{dX_2}{dt} = \alpha_2 X_2(t)\left(1 - \dfrac{X_2(t)}{K_2}\right) - \beta_2 X_1(t) X_2(t) - \gamma X_2(t) \end{cases}$$

In the remainder of the interval, the patient is in resting, and the normal growth without the plugged-in part is considered in $t \in [L, (n+1)w]$. Here, γ describes the efficiency of the radiation and ε is the suitable location of the radiation. Moreover, we can add the effect of chemotherapy in the resting period by plugging in $-\eta_i \Delta e^{-\sigma(t-(nw+L))} X_i(t)$ in both equations.

CHAPTER II

Non-Newtonian Calculi and Fractional Differentiation

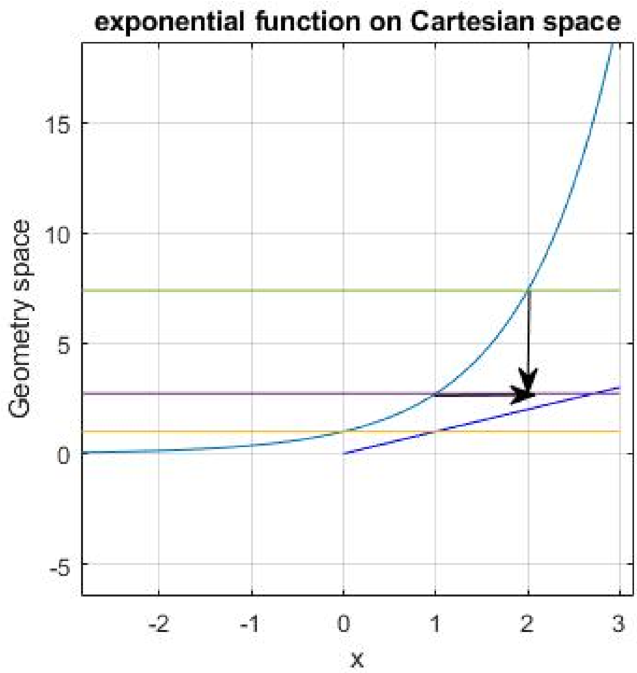
1. Non-Newtonian Calculi

In this section, the progress of non-Newtonian calculus and the origin of the debate are investigated. A successful discussion on this topic could be considered by investigating the structure of real numbers. The real numbers can be assumed as a complete set with two binary operators and the order on the set. Most mathematical systems are sets with some binary operations, some relations or distinguished subsets. In this analogy, we can demonstrate the real set as a quadruple $(R, +, -, <)$. Here, the real system with these binary operators and inequality satisfies the axioms of a complete Archimedean ordered field. Let us simplify the idea of non-Newtonian calculus roughly as applying product instead of addition and division instead of subtraction. At first glance, this structure can interpret the proportions of changes instead of differences of changes, especially when we consider the derivative. To construct the general form of this structure, we should apply a function, let's say $\alpha(x)$ such that, the binary operators are redefined by them. As far as we know, the original idea belongs to Michael Grossman and Robert Katz, who introduced the non-Newtonian calculus in 1972 in a book titled non-Newtonian calculi [Grossman et al. (1972)]. Almost Simultaneously, E. Pop was inspired by $t - conorm$ decomposable measures and defined g-calculus by putting $g^{-1}(x)$ instead of $\alpha(x)$ and these binary operators were named Pseudo-operators [Dubois (1982) and Pop (1993)]. These two different analogies of the same concept were developed quite separately in different aspects. It is safe to say that researchers in these two branches have not found out the similarities of the concepts, and the consequence is that many articles with the same purpose have been published with different notations [Kirisci (2017), Babakhani (2018)].

Furthermore, there is not a consensus about the conditions of $\alpha(x)$ generally in both approaches. Indeed, the function $\alpha(x)$ plays the role of transformation between different calculi and maintaining the algebraic structure of real numbers provided by properties of $\alpha(x)$ as an invertible function. Naturally, we can consider $\alpha(x)$ as a bijection making sure about the transformation of topological properties, or as we mentioned before, the main example could be exponential function, and to meet the need for differentiation, we can generally extend the concept and consider $\alpha(x)$ as an analytic function. In this literature, we assume the function $\alpha(x)$ as a differentiable monotone function from real line to $\mathbb{R}^+$. This assumption is freely developed to the analytic function for complex cases. In this circumstance, the arithmetic operators can be redefined as follows

$$a \oplus_\alpha b = \alpha\left(\alpha^{-1}(a) + \alpha^{-1}(b)\right)$$
$$a \ominus_\alpha b = \alpha\left(\alpha^{-1}(a) - \alpha^{-1}(b)\right)$$
$$a \otimes_\alpha b = \alpha\left(\alpha^{-1}(a) \times \alpha^{-1}(b)\right)$$
$$a \oslash_\alpha b = \alpha\left(\alpha^{-1}(a) \div \alpha^{-1}(b)\right)$$

Needless to say, that the substitution of $\alpha(x)$ by an exponential function implies the replacement of addition with multiplication and subtraction with division, and consequently, it leads to geometric calculus [Grossman et al. (2006)]. Moreover, this branch is well-developed to the complex space [Bashirov et al. (2018)]. Furthermore, the special case of $\alpha(x) = \exp(x)$ shrinks the whole real line in $\mathbb{R}^+$. This operator obtains the new vision to Cartesian coordinate, which can be seen in the following figure



The figure describes the action of bi-geometric calculus. Here, we deal with $e^0, e^1, e^2, \ldots$ instead of $0,1,2, \ldots$ and the Y-coordinate can merge with these values. The given function is $y = \exp(x)$ that has a value of $e^0, e^1, e^2, \ldots$ at the given points

$0,1,2,\ldots$ respectively. That means that the corresponding function at Newtonian calculus should be $y = x$. On the other hand, the differences of the values in the Y-axis can be evaluated by ratio. For instance, the vertical arrow shows the distance between e^2 and e^1 which is one unit in Bi-geometric calculus or $\frac{e^2}{e^1} = e^1$. Thus, we need to redefine the derivative and replace differences with ratios. In this circumstance, we can define the derivative as

$$^{exp}D^o(f)(x) = f^o(x) = \lim_{h\to 0} \sqrt[h]{\frac{f(x+h)}{f(x)}} = exp\left(\frac{(f(x))'}{f(x)}\right)$$

Therefore, the derivative of $y = exp(x)$ will be $y^o = e^1$ and this function similar to $y = x$ has a constant slope of 1. In recent decades, geometric calculus as Grossman called it or multiplicative calculus got its niche in researches. [Florack et. Al. (2012)] Indeed, the multiplicative derivative $f^o(x)$ has its interpretation as a positive number which represents how many times $f(x)$ increases at the moment x, or the growth factor at the moment x in comparison with the Newtonian derivative that determines the rate of growth. [Bashirov et. Al. (2011)] There is another way to define the derivative which equips the Bi-geometric calculus as

$$^{exp}D(f)(x) = f^*(x) = \lim_{y\to x} \sqrt[\frac{y}{x}]{\frac{f(y)}{f(x)}} = exp\left(\frac{x(f(x))'}{f(x)}\right)$$

The meaning of multiplicative derivative as the growth factor leads to many applications in actuarial science, economics, biology, demography, etc. For instance, the basic model of population, logistic growth law can be rewritten as follows

$$exp\left(\frac{N'(t)}{N(t)}\right) = {}^{exp}D^o(N)(t) = exp\left(\beta\left(1 - \frac{N}{K}\right)\right), \qquad N(t=0) = N_o > 0$$

Where $K > 0$ represents the carrying capacity of the population and in the case of catching the value K, the multiplicative derivative equals to one that interprets the only single increase in the population function. Almost the exponential growth of small tumors and growth saturation can be predicted by the logistic growth law. However, the second Newtonian derivative of this expression shows the symmetry of $N(t)$ about its point of inflection and this is not particularly flexible when it is used to describe experimental data. The modified model involves the exponential factor which controls how rapid the saturation is, and can be expressed as follows

$$^{exp}D^o(N)(t) = exp\left(\frac{\beta}{a}\left(1 - \left(\frac{N}{K}\right)^a\right)\right), \qquad N(t=0) = N_o > 0 \quad (1)$$

This model represents the general case in which $a = 1$ and it gives the logistic growth law, and $a \rightarrow 0^+$ recovers to Gompertzian growth law. The Gompertz model is studied in terms of non-Newtonian calculus comprehensively [Bashirov et. Al. (2011)]. Besides, the model of study of the population of healthy and cancerous cells in a struggling tissue can be simplified as

$$\begin{cases} {X_1}^* = exp\left(\alpha_1\left(1 - \dfrac{X_1(t)}{K_1}\right) - \beta_1 X_2(t) - \varepsilon\gamma\right) \\ {X_2}^* = exp\left(\alpha_2\left(1 - \dfrac{X_2(t)}{K_2}\right) - \beta_2 X_1(t) - \gamma\right) \end{cases}$$

Here, the terms inside the exponential determines the instantaneous ratio rate of growth. For instance, in the absence of X_2 and radiation, X_1 will grow at the ratio of $\alpha_1\left(1 - \frac{X_1(t)}{K_1}\right)$, this means that the proportion grows at the rate of α_1 and can be controlled by $\left(1 - \frac{X_1(t)}{K_1}\right)$. The multiplicative derivative inspires the alternative insight in understanding the model of simulation, and it is worth investigating the general formula for non-Newtonian derivative. Derivative and integral of non-Newtonian calculus satisfy the fundamental theorem of calculus and can be presented as

$$^{\alpha(x)}D(f)(x) = f^{\widehat{\alpha}}(x) = \lim_{y \to x}\big((f(y) \ominus_\alpha f(x)) \oslash_\alpha (y \ominus_\alpha x)\big) = \alpha\left(\frac{\alpha^{-1}(f(x))'}{\alpha^{-1}(x)'}\right),$$

$$^{\alpha(x)}I(f)(x) = \int_a^x f(t)d^{\widehat{\alpha}}t = \lim_{n\to\infty} {}^{i=1}_{n}\oplus_\alpha \Big(\big(f(c_i)\otimes_\alpha(x_{i+1} \ominus_\alpha x_i)\big)\Big)$$

$$= \alpha\left(\int_a^x \alpha^{-1}(f(t))\alpha^{-1}(t)'dt\right).$$

2. Fractional Differentiation and Abel Equation

The origin of fractional calculus can be traced back to a letter that was written to Guillaume de l'Hôpital by Gottfried Wilhelm Leibniz in 1695. The structure of fractional derivative or at least related integral equation has appeared in different fields of science since it was introduced and investigated. For instance, in 1823, N. H. Abel studied the solution of a mechanical problem where one of the first integral equations appeared. [Gorenflo et. Al. (1980)] That problem was stated to find the curve of a path with regards to the place of falling bead such that the amount of time consumed is the same. The solution of this mechanical problem is cycloid with the parametric equation as

$$\begin{cases} x = a(t - sint) \\ y = a(1 - cost) \end{cases}$$

It is easy to see the reason for demonstrating the solution as cycloid. Indeed, the term ds or length differentiation is $ds = \sqrt{x'^2 + y'^2} = a\sqrt{2}(1 - cost)$ and equating the kinetic $\left(\frac{1}{2}mv^2\right)$ and potential energy (mgy) for two different positions of the bead show the same amount of time consumed. $\left(v = \frac{ds}{dt} \rightarrow t = \sqrt{\frac{a}{g}}\pi\right)$ Here, we just showed that the cycloid is a solution of this problem. Although, finding the time consumed in general, regarding to parameterization of curve, can be expressed by integral equation as

$$t(y) = \frac{1}{\sqrt{2g}}\int_0^y \frac{\sqrt{1 + \varphi'^2(z)}dz}{\sqrt{y - z}} = \frac{1}{\sqrt{2g}}\int_0^y (u - z)^{-\frac{1}{2}}u(z)dz$$

Here, $x = \varphi(y)\, where\, y \in [0, H]$, expresses the curve equation (cycloid) and $t(y)$ describes the consumed time where initial position of y is applied. In fact, Abel treated a more general equation as

$$\frac{1}{\Gamma(\mu)}\int_0^x (x - \tau)^{\mu-1}\, u(\tau)d\tau = f(x), \;\; 0 < \mu < 1$$

In fact, in honor of V. Volterra, the more general type of this equation is named singular Volterra equation of the first kind. This integral equation has a kernel with singularity of the type $(x - \tau)^{\mu-1}$.

Roughly speaking, fractional differentiation is the extension of natural order derivative to a more general order preferably the complex case. In this circumstance, we can see the integral and derivative as two operators and fractional order integral can appear by using Cauchy iterated integral. Indeed, the integral operator of natural order n can be expressed as following iterated integral

$${}_aI_x^n(f)(x) = \int_a^x \int_a^{x_1} \dots \int_a^{x_{n-1}} f(x_n)dx_n \dots dx_2dx_1 = \frac{1}{(n-1)!}\int_a^x (x - \tau)^{n-1}f(\tau)d\tau$$

The order of this operator can be extended to any complex number with positive real part by substituting n and using gamma function $\Gamma(\mu)$ instead of $(n-1)!$. This extension obtains non-integer order of integral operator. Furthermore, according to the fundamental theorem of calculus, we can consider the derivative as an inverse operator of integral, which inspires the fractional differentiation and integration as one unifying operator. Indeed, the unique extension of analytic continuation in fractional order leads to Riemann-Liouville derivative as

$$ {}_aD_x^{\mu}(f)(x) = \frac{d^n}{dx^n}\left({}_aI_x^{n-\mu}(f)(x)\right) = \frac{d^n}{dx^n}\left(\frac{1}{\Gamma(n-\mu)}\int_a^x (x-\tau)^{n-\mu-1} f(\tau)d\tau\right) $$

Here, n denotes the ceiling function, the least integer greater than or equal to μ and expresses the derivative as a negative order of integration. Due to the uniqueness of extension of analytic continuation in fractional order, the only possibility of defining analytic continuation of fractional derivative as an inverse operator is Riemann-Liouville derivative. However, if we look at fractional derivative as a part of an equation, then the boundary values should be written in terms of fractional integral which does not suitably fit reality. The Caputo derivative remedies the situation and can be considered as follows

$$ {}_a^CD_x^{\mu}(f)(x) = {}_aI_x^{n-\mu}\left(\frac{d^n}{dx^n}(f)(x)\right) = \frac{1}{\Gamma(n-\mu)}\int_a^x (x-\tau)^{n-\mu-1}\frac{d^n}{dx^n}\big(f(\tau)\big)d\tau $$

This derivative is more suitable to determine the real phenomena since the initial value can be considered as the initial values of normal ODE. However, this operator is not the extension of analytic continuation in fractional order. These operators are concluded directly from the definition of fractional integral. However, we could focus on fractional derivative individually and find the formula. In this circumstance, we can extend the general Leibniz formula for the product rule to fractional form. The Leibniz formula for the derivative of two differentiable functions can be written as

$$ D^n\big(u(x).v(x)\big) = \sum_{k=0}^{n}\binom{n}{k} D^k\big(u(x)\big)D^{n-k}\big(v(x)\big) $$

Similarly, the general Leibniz formula for derivative of products in terms of any function can be rewritten as

$$ \begin{aligned} {D_{g(z)}}^n\big(u(x).v(x)\big) &= \sum_{k=0}^{n}\binom{n}{k} {D_{g(z)}}^k\big(u(x)\big){D_{g(z)}}^{n-k}\big(v(x)\big) \\ &= \sum_{k=0}^{n}\binom{n}{k}\left(\frac{1}{g(x)'}\frac{d}{dx}\right)^k\big(u(x)\big)\left(\frac{1}{g(x)'}\frac{d}{dx}\right)^{n-k}\big(v(x)\big) \end{aligned} $$

This generalization of Leibniz formula inspired Osler to find the fractional derivative operator in terms of an arbitrary function. [Osler (1970)] There is a striking resemblance between this generalization and product rule of non-Newtonian calculus which can be seen as

$$^{\alpha(x)}D^n\big(u(x)\otimes_\alpha v(x)\big) = \alpha\left(\left(\frac{1}{\alpha^{-1}(x)'}\frac{d}{dx}\right)^n\big(\alpha^{-1}ou(x).\alpha^{-1}ov(x)\big)\right)$$

$$= {}_{k=0}^{\ n}\!\bigoplus{}_{\alpha(x)}\left(\alpha\left(\frac{n!}{k!\,(n-k)!}\right)\otimes_\alpha D^k\big(u(x)\big)\otimes_\alpha D^{n-k}\big(v(x)\big)\right)$$

$$= \alpha\left(\sum_{k=0}^{n}\binom{n}{k}\left(\frac{1}{\alpha^{-1}(x)'}\frac{d}{dx}\right)^k\big(\alpha^{-1}ou(x)\big)\left(\frac{1}{\alpha^{-1}(x)'}\frac{d}{dx}\right)^{n-k}\big(\alpha^{-1}ov(x)\big)\right)$$

Considering the special case of $u(x)$ and $v(x)$, combining with Cauchy formula for complex function, we obtain the derivative with respect to any function. Moreover, replacing n by any complex number with positive real part makes the fractional differential operator with respect to any function which is named ψ −fractional differential operator as

$$^{\psi(x)}{}_zD_a^\mu\big(f(z)\big) = \frac{1}{\Gamma(-\mu)}\int_{\psi^{-1}(a)}^{z}\frac{f(t)\psi'(t)dt}{(\psi(z)-\psi(t))^{\mu+1}}$$

This generalization can be obtained by putting more general functions in the chains of iterated Cauchy integral which was determined in Katugampola's work. [Katugampola (2011)] This iterated Cauchy integral is presented as

$$\int_a^x {t_1}^r dt_1 \int_a^{t_1} {t_2}^r dt_2 \dots \int_a^{t_{n-1}} {t_n}^r f(t_n) dt_n$$

$$= \frac{(r+1)^{1-n}}{(n-1)!}\int_a^x (t^{r+1}-s^{r+1})^{n-1}\, s^r f(s) ds$$

This formula can be extended to the fractional integral operator of any order and the result is the specific case of operator with respect to any function. The same method in non-Newtonian calculus can be applied and

$$\int_a^x d^{\hat{\alpha}}t_1 \int_a^{t_1} d^{\hat{\alpha}}t_2 \dots \int_a^{t_{n-1}} f(t_n) d^{\hat{\alpha}}t_n$$

$$= \alpha\left(\frac{1}{(n-1)!}\int_a^x \big(\alpha^{-1}(x)-\alpha^{-1}(s)\big)^{n-1}\,\alpha^{-1}\big(f(s)\big)\alpha^{-1}(s)'ds\right)$$

Besides, the special cases of ψ −fractional differential operator are considered. For instance, in 1892, Hadamard began the publication of series of articles under the common title [Hadamard (1892)]. The third section of the article gave an underlying idea for creating different forms of fractional integral operators. The main purpose of the study in those publications was investigating the relationship between coefficients of series with the unit radius of convergence and consequently, singularity of kernel was transformed to point one. We recap some definitions as follows

Definition 2.1 Let $[a,b]$ be the real interval and $x \in [a,b]$, then for $\mu \in \mathbb{C}\ (Re(\mu) > 0)$ the Riemann-Liouville, Hadamard, ψ −fractional, and non-Newtonian integral operators are defined as follows respectively

$$ {}_aI_x^{\mu}(f)(x) = \frac{1}{\Gamma(\mu)}\int_a^x (x-\tau)^{\mu-1} f(\tau)d\tau, $$

$$ {}_a^HI_x^{\mu}(f)(x) = \frac{1}{\Gamma(\mu)}\int_a^x \left(ln\frac{x}{\tau}\right)^{\mu-1} f(\tau)\frac{d\tau}{\tau}, $$

$$ {}_a^{\psi(x)}I_x^{\mu}(f)(x) = \frac{1}{\Gamma(\mu)}\int_a^x \left(\psi(x)-\psi(\tau)\right)^{\mu-1} f(\tau)\psi'(\tau)d\tau, $$

$$ {}_a^{\alpha(x)}I_x^{\mu}(f)(x) = \alpha\left(\frac{1}{\Gamma(\mu)}\int_a^x \left(\alpha^{-1}(x)-\alpha^{-1}(\tau)\right)^{\mu-1} \alpha^{-1} o f(\tau)\alpha^{-1\prime}(\tau)d\tau\right). $$

The negative order of these operators obtains the derivative operators. Indeed, the continuum analytics of their order implies the following definition of their derivative as follows, respectively

$$ {}_aD_x^{\mu}(f)(x) = \frac{1}{\Gamma(n-\mu)}\left(\frac{d^n}{dx^n}\right)\int_a^x (x-\tau)^{n-\mu-1} f(\tau)d\tau, $$

$$ {}_a^HD_x^{\mu}(f)(x) = \frac{1}{\Gamma(n-\mu)}\left(x\frac{d}{dx}\right)^n\int_a^x \left(ln\frac{x}{\tau}\right)^{n-\mu-1} f(\tau)\frac{d\tau}{\tau}, $$

$$ {}_a^{\psi(x)}D_x^{\mu}(f)(x) = \frac{1}{\Gamma(n-\mu)}\left(\frac{1}{\psi'(x)}\frac{d}{dx}\right)^n\int_a^x \left(\psi(x)-\psi(\tau)\right)^{n-\mu-1} f(\tau)\psi'(\tau)d\tau, $$

$$ {}_a^{\alpha(x)}D_x^{\mu}(f)(x) = $$

$$\alpha\left(\frac{1}{\Gamma(n-\mu)}\left(\frac{1}{\alpha^{-1}(x)'}\frac{d}{dx}\right)^{n}\int_{a}^{x}\left(\alpha^{-1}(x)-\alpha^{-1}(\tau)\right)^{n-\mu-1}\alpha^{-1}of(\tau)\alpha^{-1\prime}(\tau)d\tau\right).$$

We can reach Caputo derivative operator by moving the derivative part inside the integral. We emphasize that Caputo is not the analytic continuum of order, but it is more suitable to make equations for real phenomena. The semi group property and more information about their comparisons were studied in [Momenzadeh (2021)].

We recap different types of non-Newtonian Calculi, their derivatives, integrals and fractional operators in the following table

Table 1: Comparison of differentiation operators in different Calculi

Type of calculus	***Derivative*** **(μ = 1)**	***Integral*** **(μ = − 1)**
Newtonian	$f'(x)$	${}_aI_x(f)(x)=\int_a^x \mathrm{f(s)}ds$
Bi-Geometric	$f^{*}(x)=exp\left(\frac{x(f(x))'}{f(x)}\right)$	${}^{exp(x)}_{\ \ a}I_x(f)(x)=\exp\left(\int_a^x \ln(\mathrm{f(s)})\frac{ds}{s}\right)$
t^p − calculus	$f^{(\mathrm{p})}(x)=\frac{(f(x))^{\mathrm{q}}(f(x)')^{\mathrm{p}}}{x^q}$, $\quad \frac{1}{\mathrm{p}}+\frac{1}{\mathrm{q}}=1$	${}^{x^p}_{\ a}I_x(f)(x)=\left(\frac{1}{\mathrm{p}}\int_a^x f^{\frac{1}{\mathrm{p}}}(s)s^{\frac{1}{\mathrm{q}}}\mathrm{ds}\right)^{\mathrm{p}}$
Bi-Positive Calculus	$f^{(\ell)}(x)=ln(f(x)')+f(x)-x$	${}^{ln(x)}_{\ \ a}I_x(f)(x)=ln\left(\int_a^x \exp(sf(s))\mathrm{ds}\right)$
α- Calculus	${}^{\alpha(x)}D(f)(x)=\alpha\left(\frac{\alpha^{-1}(f(x))'}{\alpha^{-1}(x)'}\right)$	${}^{\alpha(x)}_{\ \ a}I_x(f)(x)=\alpha\left(\int_a^x \alpha^{-1}(f(s))\alpha^{-1}(s)'ds\right)$

Type of calculus	***Fractional Integral*** **(μ)**
Newtonian	${}_aI_x^{\mu}(f)(x)=\frac{1}{\Gamma(\mu)}\int_a^x (x-s)^{\mu-1}f(s)ds$
Bi-Geometric	${}^{exp}_{\ \ a}I_x^{\mu}(f)(x)=exp\left(\frac{1}{\Gamma(\mu)}\int_a^x \left(ln\left(\frac{x}{s}\right)\right)^{\mu-1} ln(f(s))\frac{ds}{s}\right)$

t^p – calculus	${}^{x^p}_{a}I^{\mu}_{x}(f)(x)=\left(\frac{1}{\mathrm{p}\Gamma(\mu)}\int_a^x\left(x^{\frac{1}{\mathrm{p}}}-s^{\frac{1}{\mathrm{p}}}\right)^{\mu-1}f^{\frac{1}{\mathrm{p}}}(s)s^{\frac{1}{\mathrm{q}}}\mathrm{ds}\right)^{\mathrm{p}}$
Bi-Positive Calculus	${}^{ln}_{a}I^{\mu}_{x}(f)(x)=ln\left(\frac{1}{\Gamma(\mu)}\int_a^x(e^x-e^s)^{\mu-1}exp(f(s)+s)ds\right)$
α- Calculus	${}_{a}I^{\mu}_{x}(f)(x)=\alpha\left(\frac{1}{\Gamma(\mu)}\int_a^x\left(\alpha^{-1}(\mathrm{x})-\alpha^{-1}(\mathrm{s})\right)^{\mu-1}\alpha^{-1}\left(f(s)\right)\alpha^{-1}(s)'ds\right)$

Type of calculus	***Caputo Fractional derivative** (−μ)*
Newtonian	${}^{C}_{a}D^{\mu}_{x}(f)(x)=\frac{1}{\Gamma(n-\mu)}\int_a^x(x-s)^{n-\mu-1}f^{(n)}(s)ds$
Bi-Geometric	${}^{exp}_{a}D^{\mu}_{x}(f)(x)=exp\left(\frac{1}{\Gamma(n-\mu)}\int_a^x\left(ln\left(\frac{x}{s}\right)\right)^{n-\mu-1}\left(s\frac{d}{ds}\right)^{n}ln\left(f(s)\right)\frac{ds}{s}\right)$
t^p – calculus	${}^{x^p}_{a}D^{\mu}_{x}(f)(x)=\left(\frac{1}{\Gamma(n-\mu)}\int_a^x\left(x^{\frac{1}{\mathrm{p}}}-s^{\frac{1}{\mathrm{p}}}\right)^{n-\mu-1}\left(\frac{1}{p}s^{\frac{1}{q}}\frac{d}{ds}\right)^{n}f^{\frac{1}{\mathrm{p}}}(s)s^{\frac{1}{q}}\mathrm{ds}\right)^{\mathrm{p}}$
Bi-Positive Calculus	${}^{ln}_{a}D^{\mu}_{x}(f)(x)=ln\left(\frac{1}{\Gamma(n-\mu)}\int_a^x(e^x-e^s)^{n-\mu-1}\left(e^s\frac{d}{ds}\right)^{n}exp\left(f(s)\right)e^sds\right)$
α- Calculus	${}_{a}D^{\mu}_{x}(f)(x)=\alpha\left(\frac{1}{\Gamma(n-\mu)}\int_a^x\left(\alpha^{-1}(\mathrm{x})-\alpha^{-1}(\mathrm{s})\right)^{n-\mu-1}\left(\frac{1}{\alpha^{-1}(\mathrm{s})'}\frac{d}{ds}\right)^{n}\alpha^{-1}\left(f(s)\right)\alpha^{-1}(s)'ds\right)$

Our study in this literature is focused on bi-geometric calculus, so it is necessary to investigate the properties of the fractional operators in this calculus. Indeed, the relationship between bi-geometric fractional operators and Hadamard operators when $0<\mu<1$, can be rewritten as

$$
{}^{exp}_{a}I^{\mu}_{x}(f)(x)=exp\left({}^{H}_{a}I^{\mu}_{x}\left(ln(f)\right)(x)\right)=exp\left(\frac{1}{\Gamma(\mu)}\int_a^x\left(ln\left(\frac{x}{s}\right)\right)^{\mu-1}ln\left(f(s)\right)\frac{ds}{s}\right)
$$

$$
{}^{exp}_{a}I^{1}_{x}(f)(x)=exp\left(\int_a^x ln\left(f(s)\right)\frac{ds}{s}\right)
$$

$$
{}^{exp}_{a}D^{\mu}_{x}(f)(x)=exp\left({}^{H}_{a}D^{\mu}_{x}\left(ln(f)\right)(x)\right)=exp\left(\frac{1}{\Gamma(1-\mu)}\left(x\frac{d}{dx}\right)\int_a^x\left(ln\left(\frac{x}{s}\right)\right)^{-\mu}ln\left(f(s)\right)\frac{ds}{s}\right)
$$

$$
{}^{exp}_{a}D^{1}_{x}(f)(x)=exp\left(\delta\left(ln(f)\right)(x)\right)=exp\left(x\frac{d}{dx}\left(ln(f)\right)(x)\right)=exp\left(x\frac{f'}{f}(x)\right)
$$

As we mentioned before, this derivative is an analytic continuous extension of the order and we can see this in the following lemma.

Lemma 2.2 The operators ${}^{exp}_{a}I^{\mu}_{x}$ and ${}^{exp}_{a}D^{\mu}_{x}$ are the continuations of each other with respect to μ on the respective half line or half plane in complex case. If $f(x)$ is differentiable by bi-geometric calculus, so that ${}^{exp}_{a}I^{\mu}_{x}f(x)$ and ${}^{exp}_{a}D^{\mu}_{x}f(x)$ are defined, then, they coincide at $\mu = 0$. In particular, we have

$$\lim_{\mu\to 0^-}\left({}^{exp}_{a}I^{\mu}_{x}f(x)\right) = \lim_{\mu\to 0^+}\left({}^{exp}_{a}D^{\mu}_{x}f(x)\right) = f(x)$$

Proof: The proof can be obtained due to continuity of exponential function and property 2.27 of [Kilbas et. al. (2006)].

Interchanging the order of derivative and integration in the definition of fractional differentiation leads to Caputo derivative. We emphasize that the analytic continuation of fractional integral operator is unique, thus applying the fractional integral on Caputo derivative will not give the identity function. Indeed, the properties of Caputo type derivative on bi-geometric calculus can be listed in the following lemma.

Lemma 2.3 The fractional Caputo derivative for differentiable function $f(x)$ on bi-geometric calculus is defined as

$${}^{exp,C}_{a}D^{\mu}_{x}(f)(x) = exp\left(\frac{1}{\Gamma(n-\mu)}\int_a^x \left(ln\left(\frac{x}{s}\right)\right)^{n-\mu-1}\left(s\frac{d}{ds}\right)^n ln(f(s))\frac{ds}{s}\right) = exp\left({}^{H}_{a}I^{n-\mu}_{x}\delta^n lnf(x)\right)$$

Moreover, this operator has the following properties

- ${}^{exp,C}_{a}D^{\mu}_{x}(f)(x) = {}^{exp}_{a}D^{\mu}_{x}\left(f(t) - \sum_{k=0}^{n-1}\frac{\delta^k f(a)}{k!}\left(ln\frac{t}{a}\right)^k\right)(x)$

  In particular, for $0 < \mu < 1$, we have

  $${}^{exp,C}_{a}D^{\mu}_{x}(f)(x) = {}^{exp}_{a}D^{\mu}_{x}(f(t) - f(a))(x)$$

- ${}^{exp}_{a}I^{\mu}_{x}\left({}^{exp,C}_{a}D^{\mu}_{x}\right)(f)(x) = exp\left(lnf(x) - \sum_{k=0}^{n-1}\frac{\delta^k lnf(a)}{k!}\left(ln\frac{x}{a}\right)^k\right)$

Proof: The first property is a direct consequence of Theorem 2.1 of [Jarad et. al. (2012)] and for the second one we have

$${}^{exp}_{a}I^{\mu}_{x}\left({}^{exp,C}_{a}D^{\mu}_{x}\right)(f)(x) = exp\left({}^{H}_{a}I^{\mu}_{x}\ln\left(exp\left({}^{H,C}_{a}D^{\mu}_{x}\right)(lnf)\right)\right)(x)$$

Now applying lemma 2.5 in [Jarad et. al. (2012)] leads to the conclusion.

3. Equicontinuous Functions and Arzela-Ascoli Theorem

In this section, we prepare the background study to prove the existence and uniqueness of the introduced model. There are many approaches for determining the existence of system of differential equations and one of them is using the concepts of mathematical analysis which are used in Arzela-Ascoli theorem. Our main reference here is Conway's book. [Conway (2012)]

Consider G as an open set in complex plane $\mathbb{C}$, which is equipped with the metric function (Ω, d). The metric space (Ω, d) is complete in the sense of convergence of Cauchy sequences, then designate by $C(G, \Omega)$ the set of all continuous functions from G to Ω. The definition of Equicontinuous family of the functions can be described as follows:

Definition 2.4 A set $\mathfrak{I} \subseteq C(G, \Omega)$ is Equicontinuous at a point $\omega \in G$ if and only if for every non-negative ε, there is a non-negative δ such that for $|z - \omega| < \delta$, we have $d\big(f(z), f(\omega)\big) < \varepsilon$. Moreover, $\mathfrak{I}$ is Equicontinuous over a set $E \subseteq G$ instead of only one single point. If for any given $\varepsilon > 0$, there exist $\delta > 0$ such that for any two closed enough points in E (i. e. $|z - z'| < \delta$), the inequality $d\big(f(z), f(z')\big) < \varepsilon$ is satisfied for all $f \in \mathfrak{I}$.

Definition 2.5 A set $\mathfrak{I} \subseteq C(G, \Omega)$ is normal if each sequence in $\mathfrak{I}$ has a subsequence which converges to a function $f \in \mathfrak{I}$ in $C(G, \Omega)$. This condition (being normal) is equivalent to the statement that the closure of $\mathfrak{I} \subseteq C(G, \Omega)$ is compact. Indeed, compactness in Hausdorff space is equivalent to sequential compactness.

Definition 2.6 A sequence of the functions $f_k: \Omega \subseteq \mathbb{R} \to \mathbb{R}^n$ is uniformly bounded if there exists $M > 0$ such that $|f_k(t)| \leq M$ for every $t \in \Omega$ and every $k \in \mathbb{N}$.

Now, we state the Arzela-Ascoli theorem and the equivalent forms for real functions. First, let's state the original form

Theorem 2.7 A set $\mathfrak{I} \subseteq C(G, \Omega)$ is normal if and only if the following two conditions are satisfied

1. For each z in G, $\{f(z): f \in \mathfrak{I}\}$ has compact closure in Ω;
2. $\mathfrak{I}$ is equicontinuous at each point of G.

Corollary 2.8 Every uniformly bounded, uniformly Equicontinuous sequence of functions $f_k: \Omega \subseteq \mathbb{R} \to \mathbb{R}^n$ has a subsequence that converges uniformly on compact sets. (Here compactness is equivalent to closed and bounded sets due to Hine-Borel Theorem)

It is noticeable that uniformly convergent implies the interchange of limit and integral, thus

$$\lim_{n\to\infty}\int_b^c f_n(s)ds = \int_b^c f(s)ds$$

The corollary 2.8 clarifies the method of the proof for existence. Indeed, after stating the fractional model, we should follow some steps to determine the solution of the system as a sequence of the functions. In the next step, we should check if the introduced operator is uniformly bounded and uniformly Equicontinuous or not.

In the end, we should be concerned about suitable norm and space of discussion. Let I be the closed interval and $X = C(I)$ denotes the space of all continuous functions defined on I endowed with the maximum norm

$$\|f\| = max_{t\in I}|f(t)|$$

Definitely, the maximum norm induces the Banach space. (The complete norm space in the sense that any Cauchy sequence is convergent)

Moreover, for any $(u, v) \in X \times X$ the product topology induces the norm in X^2 as

$$\|(f, g)\| = max\{\|f\|, \|g\|\}$$

Clearly, this space with given norm is a Banach space.

Definition 2.9 Let (H, d) be the metric space equipped with metric function d, then $T: H \to H$ is a contraction mapping if there exist $0 < \rho < 1$ such that

$$d\big(T(h_2), T(h_1)\big) < \rho d(h_2, h_1) \qquad (1)$$

Moreover, if $T: H \to H$ is a contraction mapping, then, for any h in H, the sequence $\{h_n\}_{n=1}^{\infty}$ of iterations of h under T is a Cauchy sequence. This iteration is defined as

$$h_1 = h, \qquad h_n = T(h_{n-1}) = T^n(h)$$

In addition, if the space is complete then the Banach theorem obtains the exact fixed point for this operator. There are fixed-point theorems for operators that satisfies (1) with $\rho = 1$ and even for arbitrary continuous operator on certain matric spaces. For example, the Schauder fixed point theorem states that a continuous operator on a convex, compact subset of a Banach space has a fixed point. In this literature, we use the Banach fixed-point theorem to obtain the uniqueness of solution for our model.

CHAPTER III
Mathematical Method

1. Fractional Bi-Geometric Model

In this section, we introduce our model in terms of bi-geometric calculus. Also, the existence and uniqueness of this model are discussed. In the previous chapter we constructed the model of healthy and cancerous cells based on Lotka–Volterra competition which can be rewritten in terms of bi-geometric calculus as

$$\begin{cases} {X_1}^* = exp\left(\alpha_1 t\left(1-\frac{X_1(t)}{K_1}\right) - \beta_1 t X_2(t) - \varepsilon t D(t)\right) \\ {X_2}^* = exp\left(\alpha_2 t\left(1-\frac{X_2(t)}{K_2}\right) - \beta_2 t X_1(t) - t D(t)\right) \end{cases}$$

Here, $\alpha_i,\ i = 1,2$ are respective proliferation coefficients, $K_i,\ i = 1,2$ denotes carrying capacities, $\beta_i,\ i = 1,2$ denotes the coefficients of interaction factor or competition coefficients, $X_1(t)$ is the population of healthy cells at the time t and $X_2(t)$ is the population of cancerous cells at time t. The effect of radiotherapy is determined by the function $D(t)$ with

$$D(t) = \begin{cases} \gamma > 0 & t \in [nw, L] \\ 0 & t \in [L, (n+1)w] \end{cases}$$

In fact, the n^{th} time radiotherapy with the duration of w is administrated and the period of treatment is divided to two stages. The first period is determined by the positive value γ and the second period is the rest time with the value of fractional operators, and replace the fractional operator with bi-geometric derivative of this calculus.

There are some attempts to fit this model with Hadamard fractional operator [Awadalla et. al. (2019)]. However, the most suitable way of extension is to consider the Hadamard operator as a plugged part of a bigger scale (i.e., bi-geometric calculus) to have a successful mathematical model. We should recall that Hadamard derivative operator tends to $\delta = x\frac{d}{dx}$ when the fractional order tends to 1. This expression was not considered in the said article and therefore, leads to an unsuitable extension of the model. Now, let us introduce our model based on fractional operators of bi-geometric calculus. Indeed, the model can be developed for $0 < \mu < 1$ as follows:

$$\begin{cases} \left({}^{exp,C}_{\ a}D^{\mu}_{x}\right)(X_1)(t) = exp\left(\alpha_1 t\left(1-\dfrac{X_1(t)}{K_1}\right)-\beta_1 tX_2(t)-\varepsilon tD(t)\right) \\ \left({}^{exp,C}_{\ a}D^{\mu}_{x}\right)(X_2)(t) = exp\left(\alpha_2 t\left(1-\dfrac{X_2(t)}{K_2}\right)-\beta_2 tX_1(t)-tD(t)\right) \end{cases} \quad (1)$$

Now, applying the lemma 2.3 on these equations obtains the following expression for left hand side of the equation

$$\left({}^{exp,C}_{\ a}D^{\mu}_{x}\right)(X_1)(t) = \left({}^{exp}_{\ a}D^{\mu}_{t}\right)\left((X_1)(t)-(X_1)(a)\right)$$

Administrating the integral operator, ${}^{exp}_{\ a}I^{\mu}_{t}$, in addition of lemma 2.3 shows

$$\begin{cases} exp(lnX_1(t)-lnX_1(a)) = {}^{exp}_{\ a}I^{\mu}_{t}\left(exp\left(\alpha_1 t\left(1-\dfrac{X_1(t)}{K_1}\right)-\beta_1 tX_2(t)-\varepsilon tD(t)\right)\right) \\ exp(lnX_2(t)-lnX_2(a)) = {}^{exp}_{\ a}I^{\mu}_{t}\left(exp\left(\alpha_2 t\left(1-\dfrac{X_2(t)}{K_2}\right)-\beta_2 tX_1(t)-tD(t)\right)\right) \end{cases}$$

Due to the definition of ${}^{exp}_{\ a}I^{\mu}_{x}f(t) = exp\left({}^{H}_{a}I^{\mu}_{t}ln(f(t))\right)$, we can rewrite the system of nonlinear equations as

$$\begin{cases} ln\left(\dfrac{X_1(t)}{X_1(a)}\right) = {}^{H}_{a}I^{\mu}_{t}\left(\alpha_1 t\left(1-\dfrac{X_1(t)}{K_1}\right)-\beta_1 tX_2(t)-\varepsilon tD(t)\right) \\ ln\left(\dfrac{X_2(t)}{X_2(a)}\right) = {}^{H}_{a}I^{\mu}_{t}\left(\alpha_2 t\left(1-\dfrac{X_2(t)}{K_2}\right)-\beta_2 tX_1(t)-tD(t)\right) \end{cases}$$

The related integral equation can be expressed as

$$\begin{cases} ln\left(\dfrac{X_1(t)}{X_1(a)}\right) = \dfrac{1}{\Gamma(\mu)}\displaystyle\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\left(\alpha_1\left(1-\dfrac{X_1(s)}{K_1}\right)-\beta_1 X_2(s)-\varepsilon D(t)\right)ds \\ ln\left(\dfrac{X_2(t)}{X_2(a)}\right) = \dfrac{1}{\Gamma(\mu)}\displaystyle\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\left(\alpha_2\left(1-\dfrac{X_2(s)}{K_2}\right)-\beta_2 X_1(s)-D(t)\right)ds \end{cases} \quad (2)$$

This integral equation describes the converted model to bi-geometric calculus and we will investigate the existence and uniqueness of the solution in the next section. Due to biological interpretation, we will only consider the non-negative solutions. Hence, we suppose that both initial values for the population of healthy and cancerous cells, $X_1(a)$ and $X_2(a)$ are positive. One of the advantages of using bi-geometric calculus then appears by determining only the non-negative solutions. The next proposition describes this property.

Proposition 3.1 Non-negative quadrant of $\mathbb{R}^2$ is invariant for system (2).

Proof: The first equation in (2), expresses the population in terms of exponential function, this means

$$X_1(t) = X_1(a)exp\left(\frac{1}{\Gamma(\mu)}\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\left(\alpha_1\left(1-\frac{X_1(s)}{K_1}\right)-\beta_1 X_2(s)\right.\right.$$
$$\left.\left.-\varepsilon D(s)\right)\frac{ds}{s}\right)$$

Thus $X_1(t)$ should be positive for any positive $X_1(a)$. Moreover, this formula shows that if $X_1(\tau) = 0$ at some $\tau \geq 0$ then the population should be identically zero after that.

2. Existence of solution

In this section, we apply the results of Arzela-Ascoli theorem to provide the conditions of existence. First, let us state the equivalence of integral equations (2) and our model (1).

Lemma 3.1 The system of fractional nonlinear equations (1) and integral equations (2) are equivalent. In other words, if $(u, v) \in X^2$ is a solution of integral equations (2) then (u, v) is a solution of (1) and vice versa.

Proof: The procedure of finding the system of integral equations in the previous section obtains one side of the proof which (u, v) as a solution of (1) implies the solution of (2). If we apply bi-geometric fractional derivative to both sides of (2) then it will result in system (1).

Proposition 3.2 The given equation (1) has a solution $(u, v) \in X^2$.

Proof: Let define the operator $T: X^2 \to X^2$ for $u, v \in X$ as

$$T(u,v)(t) = \frac{1}{\Gamma(\mu)}\left(\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\left(\varphi(u,v)\right)\frac{ds}{s}, \int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\left(\psi(u,v)\right)\frac{ds}{s}\right)$$
$$= (T_1(u,v)(t),\ T_2(u,v)(t)\ )$$

Here, $\varphi(u, v)$ and $\psi(u, v)$ are defined as

$$\varphi(u,v) = \alpha_1 s\left(1-\frac{u(s)}{K_1}\right) - \beta_1 s v(s) - \varepsilon s D(s)$$

$$\psi(u,v) = \alpha_2 s\left(1-\frac{v(s)}{K_2}\right) - \beta_2 s u(s) - s D(s)$$

These two functions are bounded because

$$|\varphi(u,v)| \leq |\alpha_1||s|\left(1+\frac{|u(s)|}{K_1}\right) + |\beta_1||s||v(s)| + \varepsilon\gamma|s| = M_1$$

$$|\psi(u,v)| \le |\alpha_2||s|\left(1+\frac{|v(s)|}{K_2}\right)+|\beta_2||s||u(s)|+\gamma|s| = M_2$$

We emphasize that $u, v \in X = C(I)$ and I is a closed interval with the positive values greater than $e^0 = 1$. Moreover, we can see that the operator is bounded with respect to its norm and consequently, the first condition of Arzela-Ascoli theorem is verified. It is correct because

$$|T_1(u(t),v(t))| \le \frac{1}{\Gamma(\mu)}\left|\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s}\right|$$

$$\le \frac{M_1}{\Gamma(\mu)}\left|\int_a^t \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1} \frac{ds}{s}\right| = \frac{M_1}{\Gamma(\mu+1)}\left(ln\left(\frac{t}{a}\right)\right)^{\mu} \le N_1$$

Therefore, $\|T_1(u,v)\| = max_{t\in I}|T_1(u(t),v(t))| \le N_1$ and similarly we can see $\|T_2(u,v)\| \le N_2$ for some positive constant N_2. This implies that

$$\|T(u,v)\| = \big\|\big(T_1(u,v),T_2(u,v)\big)\big\| = max(\|T_1(u,v)\|,\|T_2(u,v)\|) \le N$$

Where $N = max(N_1, N_2)$. Furthermore, the given operator is Equicontinuous because

$$\big|T_1\big(u(t_2),v(t_2)\big) - T_1\big(u(t_1),v(t_1)\big)\big|$$

$$= \left|\frac{1}{\Gamma(\mu)}\int_a^{t_2} \left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s}\right.$$

$$-\frac{1}{\Gamma(\mu)}\int_a^{t_1} \left(ln\left(\frac{t_1}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s}$$

$$\left.\mp\frac{1}{\Gamma(\mu)}\int_a^{t_1} \left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s}\right|$$

$$= \left|\frac{1}{\Gamma(\mu)}\int_a^{t_1} \left(\left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1} - \left(ln\left(\frac{t_1}{s}\right)\right)^{\mu-1}\right)\varphi\big(u(s),v(s)\big)\frac{ds}{s}\right.$$

$$\left.+\frac{1}{\Gamma(\mu)}\int_{t_1}^{t_2} \left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s}\right|$$

$$\leq \frac{M_1}{\Gamma(\mu)}\left(\int_a^{t_1}\left(\left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1}-\left(ln\left(\frac{t_1}{s}\right)\right)^{\mu-1}\right)\frac{ds}{s}+\int_{t_1}^{t_2}\left(ln\left(\frac{t_2}{s}\right)\right)^{\mu-1}\frac{ds}{s}\right)$$

$$=\frac{M_1}{\Gamma(\mu+1)}\left(\left(ln\left(\frac{t_2}{t_1}\right)\right)^{\mu}-\left(ln\left(\frac{t_1}{a}\right)\right)^{\mu}\right)$$

Similarly, we can see

$$\left|T_2\big(u(t_2),v(t_2)\big)-T_2\big(u(t_1),v(t_1)\big)\right|$$

$$\leq \frac{M_2}{\Gamma(\mu+1)}\left(\left(ln\left(\frac{t_2}{t_1}\right)\right)^{\mu}-\left(ln\left(\frac{t_1}{a}\right)\right)^{\mu}\right)$$

Now, using the fact that logarithmic function in closed interval I is uniformly continuous to obtain that the operator T in X^2 is equicontinuous. Therefore T is completely continuous and the equation (1) has a solution in $U \subseteq X$.

3. Uniqueness of solution

In this section, we state the uniqueness theorem based on Banach fixed-point theorem. In this case, we apply some restrictions on the coefficients and have the following theorem:

Theorem 3.4 Consider the following constants

$$\xi_1=\frac{1}{\Gamma(\mu+1)}max_{t\in I}\left\{\frac{\alpha_1}{K_1}\left(ln\left(\frac{t}{a}\right)\right)^{\mu},\beta_1\left(ln\left(\frac{t}{a}\right)\right)^{\mu}\right\}$$

$$\xi_2=\frac{1}{\Gamma(\mu+1)}max_{t\in I}\left\{\frac{\alpha_2}{K_2}\left(ln\left(\frac{t}{a}\right)\right)^{\mu},\beta_2\left(ln\left(\frac{t}{a}\right)\right)^{\mu}\right\}$$

Have the properties that $\xi=max\{\xi_1,\xi_2\}<1$ then the given system (1) has a unique solution.

Proof. Let $(u(t),v(t))$ and $(x(t),y(t))$ be two couples of ordered pairs in X^2, then, we can see

$$\left|T_1\big(u(t),v(t)\big)-T_1\big(x(t),y(t)\big)\right|$$

$$=\left|\frac{1}{\Gamma(\mu)}\int_a^t\left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}\Big(\varphi\big(u(s),v(s)\big)\right.$$

$$\left.-\varphi\big(x(s),y(s)\big)\Big)\frac{ds}{s}\right|$$

$$= \left| \frac{1}{\Gamma(\mu)} \int_a^t \left(ln \left(\frac{t}{s} \right) \right)^{\mu-1} \left(\frac{\alpha_1}{K_1} \big(x(s) - u(s) \big) + \beta_1 (y(s) - v(s)) \right) \frac{ds}{s} \right|$$

$$\leq \frac{1}{\Gamma(\mu+1)} \left(ln \left(\frac{t}{a} \right) \right)^{\mu} \left(\frac{\alpha_1}{K_1} \|u - v\| + \beta_1 \|v - y\| \right)$$

$$\leq \xi \|(u,v) - (x,y)\|$$

We should emphasize that the norm on the ordered pair of continuous functions was defined as

$$\|(u,v) - (x,y)\| = \|(u - x, v - y)\| = max\{\|u - x\|, \|v - y\|\}$$

$$= max\{max_{t\in I}|u(t) - x(t)|, max_{t\in I}|v(t) - y(t)|\}$$

Similarly, we can see

$$\left| T_2\big(u(t), v(t)\big) - T_2\big(x(t), y(t)\big) \right| \leq \xi \|(u,v) - (x,y)\|$$

Hence, for the Euclidean distance d on $\mathbb{R}^2$, we get

$$d\big(T(u,v), T(x,y)\big) = d\left(\big(T_1(u,v), T_2(u,v)\big), \big(T_1(x,y), T_2(x,y)\big) \right)$$

$$= \sqrt{\big(T_1(u,v) - T_1(x,y)\big)^2 + \big(T_2(u,v) - T_2(x,y)\big)^2}$$

$$\leq \xi d\big((u,v), (x,y)\big)$$

That is, T is a contraction and Banach contraction principle guarantees the uniqueness of solution.

CHAPTER IV

Numerical Solution

1. Numerical Methods in Bi-geometric Calculus

In this section, we will discuss the numerical solution of (1) which is the nonlinear system of fractional differential equation (FDE). As we mentioned in the previous chapter, the solution of (1) leads to Volterra integral equation (VIE) of the first type which was presented as equation (2). It is a straight way to approximate the given integral with numerical methods to find the solution of the system (1). But this procedure is not that much trivial since we have the non-local nature of FDE. The presence of a real power ($\mu \in \mathbb{R}$) in the kernel of integral equation as $\left(ln\left(\frac{t}{s}\right)\right)^{\mu-1}$ makes it impossible to divide the solution at some previous point $t_n - h$ plus the increment term related to the interval $[t_n - h, t_n]$, as is common with ordinary differential equations. Besides, these partitions of interval seem not suitable to be considered in this case. Indeed, the steps are defined by differences but division describes better meshes which is more practical for logarithmic function.

Furthermore, the absence of smoothness at some point, poses some problems for the numerical computation since methods based on polynomial approximations fail to provide accurate results when there are some lacks of smoothness. Indeed, as Lubich mentioned in his works, the solution of VIE which is totally equivalent to Reimann FDE can be presented as expansion in mixed (integer and fractional) powers. [Lubich (1983)]

Roughly speaking, the step-by-step numerical methods mainly can be divided into two main methods.

- One-step method:

Just one approximation of the solution at the previous step is used to evaluate the solution. They are particularly used when it is necessary to dynamically change the step size in order to adapt the integration process to the behavior of solution.

- Multiple steps method:

  In these classes of methods, it is necessary to use more previously computed approximations to evaluate the solution. Because of the persisting memory of fractional operators, multi-step methods are clearly a natural choice of solving FDE.

  Therefore, we apply the multiple-step method to find our model solutions. Before we go forward, it is necessary to describe the interpolation function in Newtonian and Bi-geometric calculus. Let us describe the situation for the first and second order interpolation polynomials.

  Example 4.1 One of the oldest methods of solving FDE is by applying the approximation method for integration on relevant VIE. Product integration rules were introduced by Young [Young (1954)] to numerically solve second type of weak singular VIEs. They hence apply in a natural way to FDEs due to their formulation as integral presentation. In this method, the given integral splits to different partitions and different order of interpolation polynomials are used to approximate the integral. Here, we show both cases:

- constant interpolation polynomial:

$$\int_{t_0}^{t_n} f(\tau)d\tau = \sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} f(\tau)d\tau$$

$$\cong \sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} f(t_i)d\tau = \sum_{i=0}^{n-1}(t_{i+1}-t_i)f(t_i) = \sum_{i=0}^{n-1} hf(t_i)$$

  Here, the allocated terms in summation determines the area of rectangle with side of $h = t_{i+1} - t_i$ and height of $f(t_i)$. In fact, the function $y = f(t)$ is approximated by the constant values $f(t_i)$ in the interval of $[t_i, t_{i+1}]$. The interval $[a, b]$ splits with the steps of h and $t_i = a + ih$.

- first order interpolation polynomial:

$$\int_{t_0}^{t_n} f(\tau)d\tau = \sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} f(\tau)d\tau$$

$$\cong \sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} f(t_i) + \frac{f(t_{i+1}) - f(t_i)}{t_{i+1} - t_i}(\tau - t_i)d\tau$$

$$= \sum_{i=0}^{n-1} hf(t_i) + \frac{\Delta f}{h}\frac{h}{2}(t_{i+1} + t_i) - \frac{\Delta f}{h}ht_i$$

$$= \frac{h}{2}\sum_{i=0}^{n-1}\left(f(t_i) + f(t_{i+1})\right)$$

Here, the function $y = f(t)$ is approximated by first order interpolation polynomial which is the line that passes through $\left(t_i, f(t_i)\right)$ and $\left(t_{i+1}, f(t_{i+1})\right)$ in the interval $[t_i, t_{i+1}]$. That is $y = f(t_i) + \frac{f(t_{i+1})-f(t_i)}{t_{i+1}-t_i}(t - t_i)$ and the integral of this line in the given interval determines the area of trapezoid.

Now, let us consider the Bi-geometric partitions in the given interval. Since the exponential function is an onto function, without losing the generality, we can assume that the interval is $[e^a, e^b]$. Here the steps are defined as e^h and changes in steps by multiplying instead of adding. By another word, the nodes define as $t_i = e^a \otimes_{exp} \left(e^i \otimes_{exp} e^h\right) = e^a\left(e^{ih}\right)$. That means the nodes are $e^a, e^{a+h}, e^{a+2h}, \ldots, e^b$. The first order interpolation polynomial of $y = f(t)$ in the interval $[t_i, t_{i+1}]$ is the line that connects $\left(t_i, f(t_i)\right)$ to $\left(t_{i+1}, f(t_{i+1})\right)$ with the slope of $\left(f(t_{i+1}) \ominus_{exp} f(t_i)\right) \oslash_{exp} e^h = \sqrt[h]{\frac{f(t_{i+1})}{f(t_i)}}$ and the analogue of the given line will be $y = f(t_i).\left(\frac{t}{t_i}\right)^{\left(\frac{lnf(t_{i+1})-lnf(t_i)}{h}\right)}$. Thus, approximation of bi-geometric integral in terms of the first order interpolation polynomial can be expressed as

$$\int_{t_0}^{t_n} f(\tau)d^{\tau} = \bigoplus_{i=0}^{n-1} {}_{exp}\int_{t_i}^{t_{i+1}} f(\tau)d^{\tau} = exp\left(\sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} f(\tau)d^{\tau}\right)$$

$$= exp\left(\sum_{i=0}^{n-1} ln\left(\int_{t_i}^{t_{i+1}} f(t_i).\left(\frac{t}{t_i}\right)^{\left(\frac{lnf(t_{i+1})-lnf(t_i)}{h}\right)} d^{\tau}\right)\right)$$

$$= exp\left(\sum_{i=0}^{n-1}\int_{t_i}^{t_{i+1}} \left(lnf(t_i)\right.\right.$$

$$\left.\left.+\left(\frac{lnf(t_{i+1})-lnf(t_i)}{h}\right)(ln\tau - lnt_i)\right)\frac{d\tau}{\tau}\right)$$

$$= exp\left(\sum_{i=0}^{n-1}\left(ln\left(\frac{t_{i+1}}{t_i}\right).lnf(t_i)\right.\right.$$

$$\left.\left.+\left(\frac{\Delta lnf}{h}\right)\left(\frac{(lnt_{i+1})^2}{2} - \frac{(lnt_i)^2}{2}\right) - \frac{\Delta lnf}{h} lnt_i ln\left(\frac{t_{i+1}}{t_i}\right)\right)\right) =$$

$$= exp\left(\sum_{i=0}^{n-1} h\big(lnf(t_i) + lnf(t_{i+1})\big)\right)$$

Here, we can see the bi-geometric analogue of this approximation. In this literature we apply the same nodes which we described before. Indeed, the interval of $[a = e^{lna}, t = e^{lnt}]$ can be split by the steps e^h as we mentioned before. Given a grid $t_n = a(e^{nh})$, with constant step size $h > 0$, in product integration rules, the solution of (2) at t_n is first written in a piece-wise way as

$$\begin{cases} ln\left(\dfrac{u(t_n)}{u(a)}\right) = \dfrac{1}{\Gamma(\mu)}\displaystyle\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\varphi\big(u(s),v(s)\big)\frac{ds}{s} \\ ln\left(\dfrac{v(t_n)}{v(a)}\right) = \dfrac{1}{\Gamma(\mu)}\displaystyle\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\psi\big(u(s),v(s)\big)\frac{ds}{s} \end{cases}$$

And $\varphi\big(u(s),v(s)\big)$ and $\psi\big(u(s),v(s)\big)$ is approximated, in each subinterval $[t_j, t_{j+1}]$, by means of some interpolation polynomials. The resulting integrals are hence computed in an exact way to lead to $u(t_n)$ and $v(t_n)$. Explicit or implicit methods refer to the way in which the approximation is made. This is the most straightforward way to generalize Adams multi-steps methods commonly used for ordinary differential equations. Roughly speaking, the iterated numerical methods can be categorized to two methods, explicit and implicit methods. In an explicit method, y_n would be computed in terms of known quantities at the previous time step n. An implicit method, in contrast, would compute some or all of the terms in iteration in terms of known quantities at the new step $n+1$.

In the first step, to make the implicit forward Euler method, we approximate the integrand $\varphi\big(u(.),v(.)\big)$ and $\psi\big(u(.),v(.)\big)$ with the weight function $\left(ln\left(\frac{t_n}{.}\right)\right)^{\mu-1}$ by the constant values $\varphi\big(u(t_i),v(t_i)\big)$ and $\psi\big(u(t_i),v(t_i)\big)$ in the interval $[t_i,t_{i+1}]$ respectively. Indeed, this is the first order interpolation polynomial approximation. This leads to the following

$$\begin{cases} ln\left(\dfrac{u(t_n)}{u(a)}\right) = \dfrac{h^\mu}{\Gamma(\mu+1)}\displaystyle\sum_{j=0}^{n-1}\varphi\left(u(t_j),v(t_j)\right)\left((n-j)^\mu-(n-j-1)^\mu\right) \\ ln\left(\dfrac{v(t_n)}{v(a)}\right) = \dfrac{h^\mu}{\Gamma(\mu+1)}\displaystyle\sum_{j=0}^{n-1}\psi\left(u(t_j),v(t_j)\right)\left((n-j)^\mu-(n-j-1)^\mu\right) \end{cases}$$

We set the coefficients by using the following definition

$$b_n^{(\mu)} = \frac{h^\mu}{\Gamma(\mu+1)}\left((n+1)^\mu - n^\mu\right)$$

Therefore, the given model can be rewritten as

$$\begin{cases} ln\left(\dfrac{u(t_n)}{u(a)}\right) = \displaystyle\sum_{j=0}^{n-1} b_{n-j-1}^{(\mu)}\varphi\left(u(t_j),v(t_j)\right) \\ ln\left(\dfrac{v(t_n)}{v(a)}\right) = \displaystyle\sum_{j=0}^{n-1} b_{n-j-1}^{(\mu)}\psi\left(u(t_j),v(t_j)\right) \end{cases} \quad (3)$$

This approximation is called the explicit product integral rectangular method and the rectangular terms refer to underlying quadrature rules used for the integration as we mentioned in the given example. It is remarkable that the values of $\varphi\left(u(t_j),v(t_j)\right)$ and $\psi\left(u(t_j),v(t_j)\right)$ present the non-smoothness in the interval with intersection with $[nw,L]$ and $[L,(n+1)w]$. Similarly, when integrands $\varphi\big(u(.),v(.)\big)$ and $\psi\big(u(.),v(.)\big)$ are approximated by the first order interpolation polynomials, we reach to

$$\begin{cases} ln\left(\frac{u(t_n)}{u(a)}\right) = \frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\begin{pmatrix} \varphi\left(u(t_{j+1}), v(t_{j+1})\right) + \left(\frac{lns - ln(t_{j+1})}{ln(e^h)}\right) \\ \left(\varphi\left(u(t_{j+1}), v(t_{j+1})\right) - \varphi\left(u(t_j), v(t_j)\right)\right)\end{pmatrix}\frac{ds}{s} \\ ln\left(\frac{v(t_n)}{v(a)}\right) = \frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\begin{pmatrix} \psi\left(u(t_{j+1}), v(t_{j+1})\right) + \left(\frac{lns - ln(t_{j+1})}{ln(e^h)}\right) \\ \left(\psi\left(u(t_{j+1}), v(t_{j+1})\right) - \psi\left(u(t_j), v(t_j)\right)\right)\end{pmatrix}\frac{ds}{s} \end{cases} \quad (4)$$

Given terminology of bi-geometric calculus determines the reason for this presentation of first order interpolation polynomials. We use the abbreviation of φ_j for $\varphi\left(u(t_j), v(t_j)\right)$ and ψ_j for $\psi\left(u(t_j), v(t_j)\right)$, then the right-hand side of the first equation can be rewritten as

$$\frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\left(\varphi_{j+1} + ln\left(\frac{s}{t_{j+1}}\right)\left(\frac{\Delta\varphi}{h}\right)\right)\frac{ds}{s}$$

$$= \frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1} -\left(\frac{\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu}}{\mu(\mu+1)}\right)\left(\varphi_{j+1}(\mu+1)\right.$$

$$\left.\left. + \frac{\Delta\varphi}{h}\left((\mu+1)ln\left(\frac{s}{t_{j+1}}\right) + ln\left(\frac{t_n}{s}\right)\right)\right)\right|_{t_j}^{t_{j+1}}$$

$$= \frac{1}{\Gamma(\mu+2)}\sum_{j=0}^{n-1}\left((n-j)^{\mu}h^{\mu}\left(\varphi_{j+1}(\mu+1)\right.\right.$$

$$\left. + \frac{\Delta\varphi}{h}(-(\mu+1)h + (n-j)h)\right)$$

$$\left. - (n-j-1)^{\mu}h^{\mu}\left(\varphi_{j+1}(\mu+1) + \frac{\Delta\varphi}{h}\left((n-j-1)h\right)\right)\right)$$

$$= \frac{h^{\mu}}{\Gamma(\mu+2)}\sum_{j=0}^{n-1}\left(((n-j)^{\mu}(\mu+1) - (n-j-1)^{\mu}(\mu+1)\right.$$

$$+ (n-j)^{\mu}(-\mu+n-j-1) - (n-j-1)^{\mu+1})\varphi_{j+1}$$

$$\left. + \left((n-j-1)^{\mu+1} + (n-j)^{\mu}(\mu-n+j+1)\right)\varphi_j\right)$$

Now, we recap the coefficients of φ_j by splitting the first and last term and gathering the similar indexes. Therefore,

$$\frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\left(\varphi_{j+1}+ln\left(\frac{s}{t_{j+1}}\right)\left(\frac{\Delta\varphi}{h}\right)\right)\frac{ds}{s}$$
$$=\frac{h^{\mu}}{\Gamma(\mu+2)}\left((n-1)^{\mu+1}+n^{\mu}(\mu-n+1)\right)\varphi_0+\frac{h^{\mu}}{\Gamma(\mu+2)}\varphi_n$$
$$+\frac{h^{\mu}}{\Gamma(\mu+2)}\sum_{i=1}^{n-1}\left(((n-i-1)^{\mu+1}-2(n-i)^{\mu+1}+(n-i+1)^{\mu+1})\varphi_j\right)$$

Moreover, we can use these terms to summarize our calculation by using the following introduced coefficients:

$$\tilde{c}_n^{(\mu)}=\frac{(n-1)^{\mu+1}+n^{\mu}(\mu-n+1)}{\Gamma(\mu+2)},$$

$$c_n^{(\mu)}=\begin{cases}\dfrac{1}{\Gamma(\mu+2)} & n=0\\ \dfrac{(n-1)^{\mu+1}-2n^{\mu+1}+(n+1)^{\mu+1}}{\Gamma(\mu+2)} & n=1,2,..\end{cases}$$

These coefficients can summarize the result as

$$\frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}}\left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1}\left(\varphi_{j+1}+ln\left(\frac{s}{t_{j+1}}\right)\left(\frac{\Delta\varphi}{h}\right)\right)\frac{ds}{s}=h^{\mu}\left(\tilde{c}_n^{(\mu)}\varphi_0+\sum_{i=1}^{n}c_{n-i}^{(\mu)}\varphi_i\right)$$

Similarly, we can write the same for the second equation of (4). The iteration formula can be reformed as

$$\begin{cases}ln\left(\dfrac{u(t_n)}{u(a)}\right)=h^{\mu}\left(\tilde{c}_n^{(\mu)}\varphi_0+\displaystyle\sum_{i=1}^{n}c_{n-i}^{(\mu)}\varphi_i\right)\\ ln\left(\dfrac{v(t_n)}{v(a)}\right)=h^{\mu}\left(\tilde{c}_n^{(\mu)}\psi_0+\displaystyle\sum_{i=1}^{n}c_{n-i}^{(\mu)}\psi_i\right)\end{cases}\quad(5)$$

Unlike what one would expect, using interpolation polynomials of higher degree (i.e., more than one) does not necessarily improve the accuracy of the obtained approximation. This issue has been already studied in [Dixon, J. (1985)], due to behavior of the solution of FDEs, which with few exceptions [Diethelm, K. (2007)] have a non-smooth behavior even in the presence of a smooth given function as an integrand.

2. Predictor-Corrector Method

The main problem in equation (5) is the presence of $u(t_n)$ in both sides of the equation as well as $v(t_n)$ in both sides of the second equation. Indeed, we made the equation (5) to find the value of $u(t_n)$ and $v(t_n)$, and these terms appear in the right sides of equations as $\varphi_n = \varphi(u(t_n)\,, v(t_n)\,)$ and $\psi_n = \psi(u(t_n)\,, v(t_n)\,)$. Due to the nonlinearity of these function, this leads to solving the system of non-linear equations which is not acceptable. Therefore, we use the equation (3), the explicit product integral rectangular approximation in an iterated process as a predictor, then we insert a preliminary approximation for implicit trapezoidal φ_n and ψ_n in the right-hand side of (5) to get a better approximation that can then be used.

In the numerical approaches to the given model, we apply the equation (3) for finding φ_n and ψ_n which is the so-called predictor-corrector term and then we use (5) for the main approximation. In this situation, we have

$$\begin{cases} u_n{}^{(p)} = u(a) \prod_{j=0}^{n-1} exp\left(b_{n-j-1}^{(\mu)} \varphi\left(u(t_j), v(t_j)\right)\right) \\ v_n{}^{(p)} = v(a) \prod_{j=0}^{n-1} exp\left(b_{n-j-1}^{(\mu)} \psi\left(u(t_j), v(t_j)\right)\right) \end{cases} \quad (4)$$

$$\begin{cases} u(t_n) = u(a) exp\left(h^\mu \left(\tilde{c}_n^{(\mu)} \varphi\big(u(a), v(a)\big)\right)\right) exp\left(h^\mu \left(c_0^{(\mu)} \varphi\big(u_n{}^{(p)}, v_n{}^{(p)}\big)\right)\right) \\ \qquad \prod_{j=0}^{n-1} exp\left(h^\mu c_{n-i}^{(\mu)} \varphi\left(u(t_j), v(t_j)\right)\right) \\ v(t_n) = u(a) exp\left(h^\mu \left(\tilde{c}_n^{(\mu)} \psi\big(u(a), v(a)\big)\right)\right) exp\left(h^\mu \left(c_0^{(\mu)} \psi\big(u_n{}^{(p)}, v_n{}^{(p)}\big)\right)\right) \\ \qquad \prod_{j=0}^{n-1} exp\left(h^\mu c_{n-i}^{(\mu)} \psi\left(u(t_j), v(t_j)\right)\right) \end{cases} \quad (5)$$

Here, we used the fractional variant of the trapezoidal formula, which is also called the Adams–Moulton method. In addition, the implicit relationship is remedied by using predictor terms. Whereas, the non-Newtonian calculus is homomorphic with the Newtonian calculus, we may pursue the convergency of the numerical method in this calculus. The error analysis of this method is given in the following proposition:

Proposition 4.1. For the given dynamic system, the following relations hold true:

$$\left| \frac{1}{\Gamma(\mu)} \int_a^b \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1} \varphi\big(u(s), v(s)\big) \frac{ds}{s} - \sum_{j=0}^{n-1} b_{n-j-1}^{(\mu)} \varphi\left(u(t_j), v(t_j)\right) \right| \le \frac{Ah\xi}{\mu} \left(ln\left(\frac{b}{a}\right)\right)^\mu$$

$$\left|\frac{1}{\Gamma(\mu)}\int_a^b \left(ln\left(\frac{t}{s}\right)\right)^{\mu-1} \varphi\big(u(s),v(s)\big)\frac{ds}{s} - h^{\mu}\left(\tilde{c}_n^{(\mu)}\varphi_0 + \sum_{i=1}^{n} c_{n-i}^{(\mu)}\varphi_i\right)\right| \leq \frac{Bh^2\xi}{4\mu}\left(ln\left(\frac{b}{a}\right)\right)^{\mu}$$

Here, ξ is the same as the introduced constant in theorem (3.4). Furthermore, constants A and B represent the maximums of u(x) and v(x), and their derivatives in the interval [a, b], respectively. A similar relationship can be written for the second equation of (2).

Proof. The first equation determines the error of zero interpolation polynomial approximation or rectangular method. The proof is straight-forward and can be derived by partitioning the integral into the given intervals. We can rewrite the first inequality as:

$$\left|\frac{1}{\Gamma(\mu)}\sum_{j=0}^{n-1}\int_{t_j}^{t_{j+1}} \left(ln\left(\frac{t_n}{s}\right)\right)^{\mu-1} \left(\varphi\big(u(s),v(s)\big) - \varphi\left(u(t_j),v(t_j)\right)\right)\frac{ds}{s}\right|$$
$$\leq hA\xi\int_a^b \left(ln\left(\frac{b}{s}\right)\right)^{\mu-1}\frac{ds}{s}$$

In the proposition 3, we chose ξ such that

$$\left|\varphi\big(u(s),v(s)\big) - \varphi\left(u(t_j),v(t_j)\right)\right| \leq \xi\left|\big(u(s),v(s)\big) - \left(u(t_j),v(t_j)\right)\right| \leq \xi Ah$$

As we mentioned before, the $u(t)$ and $v(t)$ determine the population of healthy and cancerous cells respectively, and are continuous. Therefore, these functions are bounded within the interval $[a, b]$, and "A" denotes the maximum of both. Moreover, we assume that their derivatives are bounded in the allocated interval and the maximum of $u'(t)$ and $v'(t)$ is denoted by B. The proof of the second inequality is similar and can be derived by using extended Taylor expansion for the functions of two variables. Indeed, the first interpolation polynomial can be considered as a truncated Taylor expansion of the first degree, and the extended mean value theorem leads us to the result.

Furthermore, proposition (4.1) achieves the sufficient conditions for convergence of the given numerical method. By tending the bi-geometric partitions to zero, equations in (4) and (5) approach the solution of (2). A comprehensive study of different numerical methods for fractional differential equations in Newtonian calculus is investigated in [Garrappa, R. (2018)].

3. Computer Program

In this section, we focus on computer program of our model. All the experiments are carried out in MATLAB Ver. 8.3.0.532 (R2014a) on a computer equipped with a CPU Intel i5- 10210U at 2.11 GHz running under the operating system Windows 10. Many MATLAB routines for solving FDE can be found on the software section of the webpage (https://www.dm.uniba.it/Members/garrappa/Software). However, most of the possible codes were written for Reimann-Liouville FDE and the bi-geometric models which are based on Hadamard FDE rarely are discussed in the available papers. One of the comprehensive discussions on MATLAB programs for FDE can be seen in [Garrappa, R. (2018)].

In the first step, we determine all inputs which the solution is based on these parameters. Generally, the index 1 determines the corresponding properties of healthy cells and index 2 is for determining the corresponding properties of cancerous cells. We list the input parameters that should be defined in our program as follows

1) a1 and a2: respective proliferation coefficients,
2) b1 and b2: interaction factor or competition coefficients,
3) k1 and k2: respective carrying capacities,
4) r1 and r2: respective efficiency of radiotherapy coefficients,
5) q: efficiency of radiotherapy in the function $D(t)$,
6) L: determines the rest time in the procedure of radiotherapy,
7) u0 and v0: the initial values for healthy and cancerous cells populations in the initial time $t_0 = e^0 = 1$,
8) h: the partition length which describes the accuracy of the approximation and the interval is meshed based on this value,
9) mu: the fractional order of the model.

The main purpose of coding MATLAB for this model can be described in three steps. First, we apply the allocated numerical methods to find the values of the healthy and cancerous cells in the specific time. Second, we plot the graph of these functions with respect to time in the horizontal line. Last, we determine the phase graph that shows the healthy and cancerous cells in X and Y axes respectively. In these criteria, both populations are considered as a functions of parameter time and the result is called the phase diagram.

The introduced nonlinear system of ordinary differential equations in chapter 1, determines the population of healthy and cancerous cells by using the classic Lotka-Volterra equation. The analytic solution of this system when the cancerous cells are eradicated and their corresponding graphs are given in [Liu et. al. (2014)]. The corresponding Newtonian fractional model can be simulated by the MATLAB code FDE12.m [Guiot, C. et. al. (2003)]. However, we present the bi-geometric FDE solution here by using the predictor-corrector method of Adams-Bashforth-Moulton for Hadamard FDE.

The disease is diagnosed when some 30 cells doubling from the progenitor cancer cells occur. At this stage, a tumor is clinically detectable with conventional diagnostic tools at approximately 1 cm^3 in volume, representing a population of about 1 billion cells. [Guiot, C. et. al. (2003)] Regardless of the different masses and development times, mammals, birds and fish all share a common growth pattern. [West, G. B., et. al. (2001)] However, this value for different types of cancer and situations can be changed. Individual responses to radiation therapy for cervical cancer (Tumor type: Adenocarcinoma, Squamous Cell Carcinoma) in practice are published, and we use the same data to compute our initial values. [Belfatto, et. al. (2016)] The carrying capacities of healthy and cancerous cells determine the maximum population that can be accommodated and are chosen to be e^1. According to the construction of the model, when the population reaches e^1, then profiling stops. The value 1 signified a population of approximately 100 billion cells. The rates of proliferation are obtained primarily by using values of growth fraction. Many experiments have been carried out to determine the growth fractions of different cancer cells, and the rate of proliferation has been computed by multiplying growth fractions by ln2. [Belostotski. Et. al. (2005)] As a result, we assume growth fractions of 0.49 and 1.4e-03 for cancerous and healthy cells, respectively. The associated α_i in the bi-geometric analogue can be calculated as $\alpha_1 = exp(9.7041 \times 10^{-4})$ and $\alpha_2 = exp(0.3396)$. In the absence of radiation, cancer wins, resulting in the following conditions: [Freedman, H. I. (1980)]

$$K_1 < \frac{\alpha_2}{\beta_2}, \qquad K_2 > \frac{\alpha_1}{\beta_1}$$

Therefore, we assume $\beta_1 = exp(0.0433)$ and $\beta_1 = exp(0.2385)$ to obtain the necessary conditions for our model. The advantage of conformal radiotherapy is that it is less harmful to healthy cells, and we control the effect of radiation by putting $\varepsilon = exp(0.0008)$ based on the assumption that e is less than 0.1%. [Belostotski. Et. al. (2005)] In the end, for the initial values of healthy and cancerous cells, we assume the approximation values [Guiot, C. et. al. (2003)] and gross tumor volume in cm^3 multiplied by a billion.

It is noticeable that the radiotherapy is implemented 5 days of the week and the duration of radiation is 15 to 20 minutes. This period of treatment is called fractions. The effects of radiotherapy are determined by the ξ function in the original equation. For simplicity of calculations, we assume ξ is a Heaviside step function for our discussion. However, we can improve the details of our model by using more parameters in ξ. [Farayola et. al. (2020)] We remedy the situation by considering the proportion of treatment in the time interval. We refer to the effect of fractions (estimated as 0.25-hour times 25 times implementations) as a proportion of 0.26 day in comparison to 7 weeks of second monitoring. In addition, the given data in [Belfatto, et. al. (2016)] is categorized into 16 cases, and only 2 patients were treated by radiotherapy with staging N_0M_0. (The N factor denotes the number of nearby lymph nodes that have cancer, and M denotes the metastasis.) The results are summarized in the following table:

	Patient 1	***Patient 2***
Tumor	SCC	SCC
Staging	$T1bN_0M_0$	$T1bN_0M_0$
therapy	RT	RT
Initial and final population	24.1e9-3.59e9	17.4e9-8.61e9
Final population by model	3.26e9	8.16e9

Moreover, the graph of the cancerous cell population with respect to time is sketched in the next figure. We set initial values and constants according to the previous discussion, and the cell population is stored in the vectors B and C.

Since the original equation is autonomous, we can rewrite that system of ODE into one single equation. Consequently, we have an ODE that is based on the derivative of healthy cells in terms of cancerous cells. The phase diagram in this case shows the population of one species with respect to another one.

These constants are defined in our program at first and can be changed according to the case of study. In the next step, we define a vector of size 600 to put the time values inside it. In fact, the n^{th} column of this vector is equal to the value of the time in bi-geometric calculus as e^{n}.

```
A=zeros(1,400);
B=zeros(1,400);
C=zeros(1,400);
for m=1:400
    A(1,m)=exp(m);
end
for s=1:400
t=A(1,s);
end
```

To avoid the resizing of matrix and making the longtime of progression, we put the initial zero values for the matrices A, B and C. The matrices B and C later will be filled by the values of X_n and Y_n which are the healthy and cancerous cells populations. The size of the time matrix is selected according to the performance of computer and can be extended to the larger interval. With the last given loop, time is selected as an element of a matrix A one by one. In the next step, we determine the steps of iterations based on the value of $h = 0.1$. Since the time at the step s is equal to $t = t_m = e^m$ and at the initial time $t_0 = 1$, then the steps will be $\left\lceil \frac{ln(t)}{h} \right\rceil$. Moreover, we put the initial values for the predictor-corrector factors as

```
n=round(log(t)/h);
Un=u0;
Vn=v0;
```

In the next step, we use another loop to define the productions of predictor-corrector and at the end, we will multiply the final values by the initial terms, as is mentioned in the equation (4). In this part of the program, we replace the coefficients b_n and $\varphi(u(t), v(t))$ and $\psi(u(t), v(t))$ by the given values in previous chapter

```
for i=0:n-1
if (1<=exp(i*h)) && (exp(i*h)<=L)
Un=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a1*(1-
Un/k1)-(b1*Vn)-(e*q))*exp(i*h));
Vn=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a2*(1-
Vn/k2)-(b2*Un)-q)*exp(i*h));
else
Un=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a1*(1-
Un/k1)-(b1*Vn))*exp(i*h));
Vn=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a2*(1-
Vn/k2)-(b2*Un))*exp(i*h));
end
X=X*Un;Y=Y*Vn;
end
Un=X; Vn=Y;
% the predictor value is reserved to Un and Vn
for k=0:n0-1
if (0<=k*h) && (k*h<=L)
Om=((h^mu)/(gamma(mu+1)))*(((n-k)^mu)-((n-k-1)^mu))*(a1*(1-
Om/k1)*Om-(b1*Om*Lm)-(e*q)*Om);
Lm=((h^mu)/(gamma(mu+1)))*(((n-k)^mu)-((n-k-1)^mu))*(a2*(1-
Lm/k2)*Lm-(b2*Om*Lm)-q*Lm);
else
Om=((h^mu)/(gamma(mu+1)))*(((n-k)^mu)-((n-k-1)^mu))*(a1*(1-
Om/k1)*Om-(b1*Om*Lm));
Lm=((h^mu)/(gamma(mu+1)))*(((n-k)^mu)-((n-k-1)^mu))*(a2*(1-
Lm/k2)*Lm-(b2*Om*Lm));
end
Z=Z+Om;N=N+Lm;
end
```

Om=Z; Lm=N;;

We note that the $\varphi(u(t), v(t))$ and $\psi(u(t), v(t))$ are written in terms of $D(t)$ and the time interval is divided to three partitions of radiotherapy. These partitions are given in the program by $[1, L], [w, wL], [w^2, w^2L]$. Indeed, the rest time after radiotherapy was defined as w and we assumed three times of radiotherapy in our program. The if statement's command checks the value of $t_i = e^{ih}$ for being included in the radiotherapy periods. The last values of Un and Vn in this part determines the predictor-corrector values.

In the next step, we apply the same method to find X_n and Y_n, but this time the loop has $n-1$ steps and after defining the product parts, more terms will be multiplied by the result to get the equation (5). Again, we expand the form of (5) by substituting the values of c_n and $\widetilde{c_n}$ in the program.

```
Xn=u0; Yn=v0;
for j=1:(n-1)
   if (w<exp(j*h)) && (exp(j*h)<w*L)
      if (w^2<exp(j*h)) && (exp(j*h)<(w^2)*L)
         if (1<exp(j*h)) && (exp(j*h)<L)
         Xn=exp(((h^mu)/(gamma(mu+2)))*(((n-j-1)^(mu+1))-(2*(n-
j)^(mu+1))+((n-j+1)^(mu+1)))*(a1*(1-Xn/k1)-(b1*Yn)-(r1*q/Xn)));
         Yn=exp(((h^mu)/(gamma(mu+1)))*(((n-j-1)^(mu+1))-(2*(n-
j)^(mu+1))+((n-j+1)^(mu+1)))*(a2*(1-Yn/k2)-(b2*Xn)-(r2*q/Yn)));
         end
      end
      else
         Xn=exp(((h^mu)/(gamma(mu+2)))*(((n-j-1)^(mu+1))-(2*(n-
j)^(mu+1))+((n-j+1)^(mu+1)))*(a1*(1-Xn/k1)-(b1*Yn)));
         Yn=exp(((h^mu)/(gamma(mu+1)))*(((n-j-1)^(mu+1))-(2*(n-
j)^(mu+1))+((n-j+1)^(mu+1)))*(a2*(1-Yn/k2)-(b2*Xn)));
   end
end
Xn=Xn*u0*exp((h^mu)/(gamma(mu+2))*((n-1)^(mu+1)+(n^mu)*(mu-
n+1))*(a1*(1-u0/k1)-b1*v0-r1*q/u0))*exp((h^mu)/(gamma(mu+2))*(a1*(1-
Un/k1)-(b1*Vn)-(r1*q/Un)));
```

```
Yn=Yn*v0*exp((h^mu)/(gamma(mu+2))*((n-1)^(mu+1)+(n^mu)*(mu-n+1))*(a1*(1-v0/k1)-b1*u0-r1*q/v0))*exp((h^mu)/(gamma(mu+2))*(a2*(1-Vn/k2)-(b1*Un)-(r2*q/Vn)));
B(1,s)=real(Xn);
C(1,s)=real(Yn);
end
```

In the last step, we put the values of healthy and cancerous cells in the vectors B and C respectively. The final step is plotting the curves of each population separately and move the phase curve which determines the changes in both populations in chronological way, when time varies in the vector A. This can be done by plot command as

```
plot(A,B);
plot(A,C);
plot(B,C);
```

The following figures are given as a result of this program:

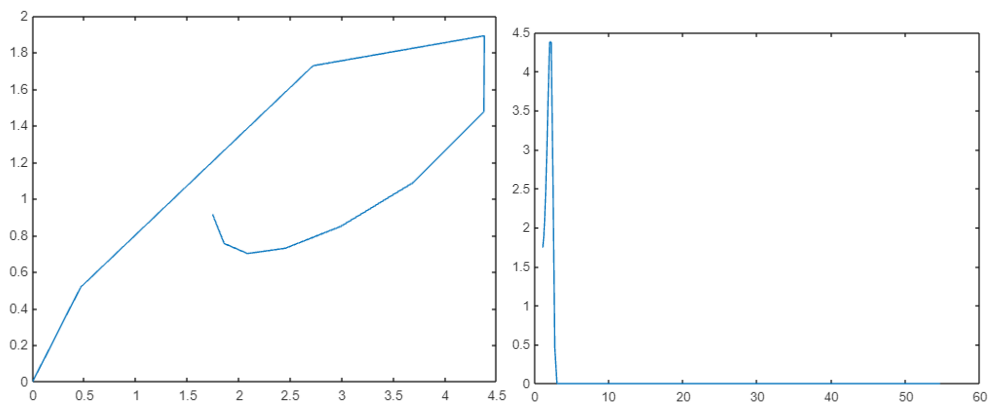


Figure 1. The results sample for phase diagram and cancerous cell populations according to the given constants in Appendix A: (a) The phase diagram; (b) Cancerous cell population.

CHAPTER V
Discussion

One of the main applications of mathematics can be considered as modeling real life phenomena with the help of mathematical tools. Since 16th century that Newton determined the rate of growth with derivative of the function, this powerful tool has been used to describe the dynamic system. The origin of discussion traces back to the applications in mechanics when the derivative is interpreted as a rate of distance or velocity. Any dynamic apparatus is based on some changes and these changes are associated with the derivative of one or more functions. Furthermore, the profound investigation in dynamic system obtains equations of independent variable, dependent variable and their derivatives. Thus, the ordinary differential equation can describe a dynamic system and predict the attitude of the system.

Later, the fractional derivative as a derivative of a given function in any complex order was defined and many dynamic systems were reformulated with this new definition of derivative. There are many benefits of using fractional differentiation to model the dynamic system, such as; having memory effects, better fitting functions, etc. Besides, the non-Newtonian calculi prepared the alternative view to Newtonian calculus by modifying the arithmetic operators and made new interpretations to the growth rate. The mixture of fractional differential operators and non-Newtonian calculi, especially the bi-geometric calculus obtains the operators with respect to any analytic function.

The bi-geometric calculus as an old calculus was used in different fields of mathematics especially in statistics where we use geometric mean instead of arithmetic mean. In fact, rate was described as a proportion instead of difference, and this modification leads to many applications in different aspects. We apply the bi-geometric analogues to describe the population of healthy and cancerous cells in a dynamic system. This approach leads to competition equations of Lotka-Volterra type, but this time in bi-geometric analogue and the fractional case equipped with Hadamard operator. Many articles were investigated the Reimann-Liouville operator as a suitable form of fractional operator for modelling the real phenomena. However, the Hadamard operator was considered rarely and the origin of this operator was not considered. Therefore, the results were not reliable and not even understandable. Our work in this aspect is unique and opens a new aspect of working in this area. However, there are many difficulties with working with Hadamard operators such as singularity behavior of weight function and so on. Working in the field of biomathematics needs many backgrounds in different fields. First, the biological background for mathematic student would be an obvious obstacle since he/she studies many mathematics courses with different nature. For instance, to make a satisfactory complete study, we spent over three months to study the biological part. Secondly, understanding the relationship between different parts of the system needs accurate consideration in previous studies and finding the best cohesive model.

CHAPTER VI

Conclusion and Recommendations

In this chapter we summarize our results and present conclusions based on the research findings according to the objective of the research and give recommendations accordingly. In this literature, we apply the bi-geometric calculus to model the population of healthy and cancerous cells. There are some benefits of using this calculus which were mentioned in the text and we can list them as follows:

- The bi-geometric calculus deals with positive numbers and it can be seen in proposition 3.1
- The bi-geometric calculus uses proportion instead of differences and this property summarizes the equation as we can see in the first equation of chapter 3.
- Before analyzing the model, it is essential, or rather obligatory, to express it in non-dimensional terms. This has several advantages. For example, the units used in the analysis becomes unimportant and the adjectives small and large have a definite relative meaning. It also always reduces the number of relevant parameters to dimensionless groupings which determine the dynamics. A pedagogical article with several practical examples by Segel (1972) discusses the necessity and advantages for non dimensionalization and scaling in general. The bi-geometric model describes non-scale parameters and this can be considered as a main advantage.
- The singularity of fractional operator is transferred from the point zero and the new operator is based on Hadamard operator with singularity 1.

The new model based on bi-geometric calculus gives a different view to the model and prepares new methods in different fields as numerical calculation etc. One of the important usages of this calculus is simplifying the calculations, especially for numerical solutions. This discussion can be used for different models which were studied before with the help of Reimann-Liouville operators and with same logic, many investigations can be followed.

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Appendices

Appendix A

MATLAB code Figure 1

```
v = @(t) exp(t);
t = linspace(-3, 3);
figure(1)
plot(t, v(t))
grid on
title('exponential function on Cartesian space')
xlabel('x');
ylabel('Geometry space');
hold on
fplot(@(x) (x), [0,3], 'b')
hold on
plot(t,exp(0)+0*t);
hold on
plot(t,exp(1)+0*t);
hold on
plot(t,exp(2)+0*t);
hold on
plot(t,exp(3)+0*t);
hold off
```

MATLAB code for program section

```
% Defining the constants for the model
a1=exp(0.1); a2=exp(0.45); b1=exp(0.11); b2=exp(0.15); k1=exp(0.65); k2=exp(1);
r1=exp(0.05);
r2=exp(0.01); q=exp(0.35); L=exp(50); u0=exp(0.44); v0=exp(0.22); h=0.01; mu=0.7;
w=exp(150);
% Defining the time variable as a vector
A=zeros(1,400); B=zeros(1,400); C=zeros(1,400);
for m=1:400
     A(1,m)=exp(m);
end
for s=1:400
t=A(1,s);
% Defining the partition
n=ceil(log(t)/h);Un=u0; Vn=v0;
% Finding the predictor-corrector by applying 3 times radiotherapy
    for i=1:n
        if (w<exp(i*h)) && (exp(i*h)<w*L)
            if (w^2<exp(i*h)) && (exp(i*h)<(w^2)*L)
                if (1<exp(i*h)) && (exp(i*h)<L)
            Un=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a1*(1-Un/k1)-
(b1*Vn)-(r1*q/Un)));
            Vn=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a2*(1-Vn/k2)-
(b2*Un)-(r2*q/Vn)));
                end
            end
                  else
```

```
            Un=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a1*(1-Un/k1)-
(b1*Vn)));
            Vn=exp(((h^mu)/(gamma(mu+1)))*(((n-i)^mu)-((n-i-1)^mu))*(a2*(1-Vn/k2)-
(b2*Un)));
        end
    end
Un=Un*u0;
Vn=Vn*v0;
% Finding the value of healthy cells population Xn and cancerous cells population Yn
Xn=u0; Yn=v0;
for j=1:(n-1)
    if (w<exp(j*h)) && (exp(j*h)<w*L)
        if (w^2<exp(j*h)) && (exp(j*h)<(w^2)*L)
            if (1<exp(j*h)) && (exp(j*h)<L)
            Xn=exp(((h^mu)/(gamma(mu+2)))*(((n-j-1)^(mu+1))-(2*(n-j)^(mu+1))+((n-
j+1)^(mu+1)))*(a1*(1-Xn/k1)-(b1*Yn)-(r1*q/Xn)));
            Yn=exp(((h^mu)/(gamma(mu+1)))*(((n-j-1)^(mu+1))-(2*(n-j)^(mu+1))+((n-
j+1)^(mu+1)))*(a2*(1-Yn/k2)-(b2*Xn)-(r2*q/Yn)));
            end
        end
        else
            Xn=exp(((h^mu)/(gamma(mu+2)))*(((n-j-1)^(mu+1))-(2*(n-j)^(mu+1))+((n-
j+1)^(mu+1)))*(a1*(1-Xn/k1)-(b1*Yn)));
            Yn=exp(((h^mu)/(gamma(mu+1)))*(((n-j-1)^(mu+1))-(2*(n-j)^(mu+1))+((n-
j+1)^(mu+1)))*(a2*(1-Yn/k2)-(b2*Xn)));
    end
end
Xn=Xn*u0*exp((h^mu)/(gamma(mu+2))*((n-1)^(mu+1)+(n^mu)*(mu-n+1))*(a1*(1-u0/k1)-b1*v0-
r1*q/u0))*exp((h^mu)/(gamma(mu+2))*(a1*(1-Un/k1)-(b1*Vn)-(r1*q/Un)));
Yn=Yn*v0*exp((h^mu)/(gamma(mu+2))*((n-1)^(mu+1)+(n^mu)*(mu-n+1))*(a1*(1-v0/k1)-b1*u0-
r1*q/v0))*exp((h^mu)/(gamma(mu+2))*(a2*(1-Vn/k2)-(b1*Un)-(r2*q/Vn)));
B(1,s)=real(Xn);
C(1,s)=real(Yn);
end
plot(A,B);
plot(A,C);
plot(B,C);
```

Appendix B

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CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name: Obi, Olivia Ada

Nationality: Nigerian
Date of Birth: 10th October, 1986

EDUCATION

Degree	**Institution**	**Year of Graduation**
M.Sc. Mathematics	Eastern Mediterranean University, Cyprus	2013
B.Sc. Mathematics Ed.	Ahmadu Bello University, Nigeria.	2009

WORK EXPERIENCE

Year	**Place**	**Enrollment**
2021 – present	Department of Mathematics, Near East University, Cyprus.	Part time Instructor
2013 – 2020	Department of Mathematics, Federal College of Education, Zaria, Nigeria.	Lecturer II
2010 – 2012	Department of Mathematics, Eastern Mediterranean University, Cyprus	Teaching Assistant
2008 – 2009	Demonstration Secondary School, ABU, Zaria	Mathematics Teacher

2004 –2005	Comprehensive Secondary School, Zaria, Nigeria	Teaching Practice

FOREIGN LANGUAGES

English, fluently spoken and written, Turkish (Little)

HONORS AND AWARDS

- EMU scholarship award (M.Sc. Mathematics), EMU, Cyprus 2010 –2012
- Best graduating student, Mathematics /Computer science, FCE, Zaria, 2005.
- Appreciation Letter for selfless services, Demonstration Secondary School, ABU, Zaria.

MEMBERSHIP OF PROFESSIONAL ORGANIZATIONS

- Member, Mathematics Association of Nigeria (MAN).
- Member, Institute of Mathematics and its Application (IMA), UK.
- Member, National Union of Teachers (NUT), Nigeria.

PUBLICATIONS

ARTICLES PUBLISHED IN JOURNALS

- Momenzadeh, M., Obi, O.A., Hincal, E. (2022). A Bi-Geometric Fractional Model for the Treatment of Cancer Using Radiotherapy. MDPI journal, fractal fract. 2022. https://doi.org/10.3390/fractal fract 6060287
- Stability of Autonomous Systems of Equations and Lotka-Volterra Competition Model. NIJOSSER 2013, 2nd Edition.

CONFERENCES PRESENTATIONS

- Obi, O. (2022). A Bi-Geometric Fractional Model for the Treatment of Cancer Using Radiotherapy. A Paper presented at the 63rd annual conference of British Applied Mathematics Colloquium, Loughborough Campus, UK. https://bamc2022.lboro.ac.uk

- Obi, O. (2015). Using Queuing Theory to Optimize Healthcare Performance and Patient's Satisfaction. A paper presented at the 52nd Annual Conference of the Mathematics Association of Nigeria held at the University of Nigeria, Enugu Campus, Nigeria.

- Obi, O. (2014). Application of Mathematics in Works and Industry. A paper presented at the Faculty of Sciences, Federal College of Education, Zaria, Nigeria.

THESIS

Masters

- Obi, O.A. (2013). Stability of Autonomous and non-Autonomous Differential Equations. Master's Thesis, Department of Mathematics, Faculty of Sciences, Eastern Mediterranean University, Cyprus.

Project

- Obi, O.A. (2009). Gender Inequality in Mathematics Education at College level; possible causes and solutions. Bachelor Degree project, Department of Mathematics Education, Faculty of Science Education, Ahmadu Bello University, Nigeria.

COURSES GIVEN (from 2010 to date)

- Calculus I and II
- Differential Equations
- Numerical Analysis
- Advanced Calculus
- Engineering Mathematics
- Statistics and Probability
- Trigonometry
- Basic General Mathematics
- Introduction to Computer Studies

HOBBIES

Reading, Football, Music, Tennis

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Fractional Calculus, Multiplicative Calculus, Artificial Intelligence, Python programming language.

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