Chapter 8

Advanced Fractional Mathematical Model for Tumor Growth Dynamics

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8.1 Introduction

Cancer is one of the most frequently encountered diseases that can lead to the end of human life despite the advances in science and medicine. It is a multi-staged disease which occurs because of changes in DNA formation (mutation) of abnormal cells. Cancer become second in terms of rate of mortality in the world today and approximately 9.6 million people died due to cancer in year 2018 (`http://www.who.int/topics/cancer/en/`). A lot of research is going on to understand this abnormality in behavior of cancer cells. Normal healthy cells do their job systematically and stop cell division. They are replaced by newly formed daughter cells, while on the other hand cancerous cells keep dividing uncontrollably unlike normal cells and work differently. Most cancerous cells form a mass of tissue that is called a tumor. The word tumor comes from the Latin 'tumor' referring to the swelling that occurs as a consequence of these abnormal growths and is now used interchangeably with 'neoplasm', meaning new or abnormal cell growth. This definition of neoplasm leads to a major division of cancers into malignant and benign. The terms 'tumor' and 'cancer' have also come to be used synonymously but a distinction might be made in that metastatic cancer occurs because a tumor has acquired the capacity to invade its surroundings, the first step in spreading to secondary sites. This involves the destruction of other cells, critically some that make up the vessels of the circulatory (blood and lymphatic) systems. Once the tumor cell can get into the circulation it can be carried to other locations: it has become malignant. The implication, of course, is that there are tumors that are not malignant.

We introduced a fractional mathematical model of tumor growth and its treatment processes to provide a more agreeable solution. This model considers various factors present in the Hahnfeldt et al. [55] model, utilizing the Caputo fractional derivative operator with a power-law kernel. In this chapter, initially, we provide some preliminaries in section 8.2. Section 8.3 covers mathematical modelling of fractional tumor growth model. The solution of fractional tumor growth mathematical model is in section 8.6. In section 8.4, we provide existence & uniqueness of the solution of the system. Stability analysis, simulation, experimental results and conclusion are discussed in section 8.5, 8.7 and 8.8 respectively.

8.2 Preliminaries

Applications of Fractional calculus require the definition of fractional derivatives and integrals [79].

Definition 8.2.1. *For a function $f : \mathbb{R}^+ \to \mathbb{R}$, the Riemann-Liouville fractional integral of order $\alpha > 0$ is given by*

$$I_t^\alpha(f(t)) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-z)^{\alpha-1} f(z)\, dz,$$

where, Γ denotes the Gamma function and α is the fractional order parameter.

Definition 8.2.2. *For a function $f \in C^n$, the Caputo derivative with order α is defined as*

$$c_{D_t^\alpha}(f(t)) = I^{n-\alpha} D^n f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(z)}{(t-z)^{\alpha-n+1}}\, dz,$$

that is defined for the absolutely continuous functions and $n-1 < \alpha < n$, $n \in \mathbb{N}$. Obviously, $D_t^\alpha(f(t))$ tends to $f'(t)$ as $\alpha \to 1$.

8.3 Mathematics in cancer biology

In cancer biology, the Malthusian growth model is one of the basic models that describe the tumor growth in terms of growth rate and death rate in tumor population. The *Malthusian Model* or *Exponential Model* is the natural description of early stages of cancer growth. In the exponential model, each cancer cell splits into two daughter cells in the affected area at the rate of constant a. The exponential model is given by

$$\frac{dp(t)}{dt} = ap(t),$$

where a is the kinetic parameter and $p(t)$ is the volume of the cancer cells. The cancer cell growth in the exponential model is proportional to the population of the cancer. The

exponential model estimates the maximum tumor growth volume at doubling time. However, at the last stages, the exponential model fails to predict the angiogenesis process (formation of new blood vessels) and reduction of the nutrient. Extension of the exponential model to predict the early stage of cancer cell proliferation (process by which a cell grows and divides to produce two daughter cells) and its angiogenesis process thus is required.

The exponential model has limitations to predict the long-term growth rate of cancer cell proliferation. To overcome these problems, a logistic model was introduced to explain the behavior of cancer cell growth and proliferation. The general equation for the logistic model was first introduced by Pierre Francois Verhulst in 1883. The model was proposed to find out the elements of organic population, concentrating on the inherent development rate a, whose entire size is limited by carrying capacity of k.

The logistic model equation describes that the growth is proportional linearly with size until the growth of the cells reaches the carrying capacity, b. The logistic equation produces an S-shape curve for the volume of cancer cells. This model can interpret the mutual competition between the cells. The generalized logistic equation is

$$\frac{dp}{dt} = ap \ln\left(1 - \frac{p}{k}\right), \quad p(0) = p_0.$$

The Gompertz growth model is a generalization of the logistic model with an asymmetric curve with the point of inflection. This model has the ability to draw the latent stages of cancer tumor. It has a sigmoidal curve and was applied to ultimately model the size of the cell growth for the entire organisms. This model was first developed by Gompertz in 1825 to explain the human mortality curve, which further was employed by many researchers to fit and describe the tumor growth data. The mathematical equation for the model is

$$\frac{dp}{dt} = ap \ln\left(\frac{b}{p + c}\right),$$

where a, b and c are parameters that can be adjusted to describe a particular data set, p is the volume of tumor and t is function of time. $\frac{dp}{dt}$ is directly proportional to the number of

cells in the tumor. This model is popular for modelling the tumor growth as it slows down the process of tumor growth as the size of the tumor increases.

Hahnfeldt et al. [55] focused on introducing as simple as possible mathematical model that would incorporate the effect of angiogenesis on solid tumor development. They characterized vascularized tumor by two time-dependent variables:

- p — tumor volume, (in mm^3)
- k — vessels carrying capacity, that is the maximal tumor size that can be supplied with nutrients by the present vasculature (arrangement of blood vessels in the body or in an organ or body part) (in mm^3).

According to the experimental data, the most rapid growth of both tumor and normal tissue is observed in the initial stage of their growth. In addition, it is observed that the size of the tumor has a negative effect on the rate of its growth and there exists a limitation for the maximal size of the tumor. Therefore, it seems that the growth of the tumor can be described by the Gompertzian or logistic type of equation. Hahnfeldt et al. (which assumes time-dependent capacity to account for dynamic changes in the vascular support available to the tumor) assumed the Gompertzian type of tumor growth. This model considers the Gompertz model as a tumor growth model and further includes time-dependent carrying capacity in terms of stimulation and inhibition. Also confirmed the validity of the model in vivo lab experiments [55].

The change in carrying capacity with time will depend on the following four assumptions:

1. $g_2(p, k) = \eta p$: increase in carrying capacity due to stimulatory signals from tumor cells (angiogenesis) where η is the rate at which stimulator is released per day, p is tumor volume at a given time.
2. $\theta g_1(p, k) = \theta k p^{2/3}$: decrease in the carrying capacity with time due to inhibitory signals from the tumor cells. The term 2/3 was derived by Hahnfeldt using the diffusion-consumption equation.

3. δk: decrease in the carrying capacity due to natural death of endothelial cells.

4. $fkD_r(t)$: decrease in the carrying capacity due to antiangiogenic drugs. f is the rate at which the drug is administered. D_r can be further defined as

$$D_r(t) = \int_0^t A(T)e^{-c_r(t-T)}\,dT,$$

where T is the time at which the drug is administered, c_r is the clearance rate of any drug and $A(T)$ is the dosage given during treatment. Hahnfeldt et al. experimented with different treatment modules of TNP-470, angiostatin, or endostatin.

The differential equations describing the system are as

$$\frac{dp}{dt} = -\gamma p \ln\left(\frac{p}{k}\right), \tag{8.1}$$

$$\frac{dk}{dt} = \eta p - \theta k p^{2/3} - \delta k - fkD_r(t). \tag{8.2}$$

Equation (8.1) shows that the change in the number of tumor cells is dependent on the ratio of p/k i.e., the number of cells present to the carrying capacity. If the ratio of tumor volume to carrying capacity is greater than 1, then there will be inhibition of tumor growth, and if it is less than 1, then there is stimulation. Equation (8.2) shows the change in carrying capacity with time due to various factors taken into consideration.

Equations (8.1) and (8.2) remain the same for the "Modified Hahnfeldt model," but the only difference is the value of the parameter δ. In the case of the Hahnfeldt model, the value of $\delta = 0$, but in the Modified Hahnfeldt model, it lies between the range 0.005 to 0.05 [98]. In this paper, we have only considered untreated tumors.

$$\frac{dp}{dt} = -\gamma p \ln\left(\frac{p}{k}\right), \tag{8.3}$$

$$\frac{dk}{dt} = \eta p - \theta k p^{2/3} - \delta k, \tag{8.4}$$

with initial conditions $p(0) = p_0, k(0) = k_0$.

To present the consequence of aforesaid expressed parameters numerically and for the best understanding of Tumor growth, it is necessary to replace the integer-order Tumor Growth model with an arbitrary-order model. In our study, we re-develop the model (8.1) and (8.2) by replacing the classical time derivative using the Caputo derivative, which gives the fractional modified Hahnfeldt model:

$$^{C}D_t^{\alpha}\left(p(t)\right) = -\gamma p \ln\left(\frac{p}{k}\right), \quad p(0) = p_0 \tag{8.5}$$

$$^{C}D_t^{\alpha}\left(k(t)\right) = \eta p - \theta k p^{2/3} - \delta k, \quad k(0) = k_0 \tag{8.6}$$

Now, we consider tumor growth treatment models. Tumor growth reduction depends upon various treatments:

- Anti-tumor treatment.
- Anti-angiogenesis treatment.
- Immunotherapy.
- Radiation.
- Surgery.

In this model, we consider only Anti-Tumor therapy and Anti-Angiogenesis therapy. We have defined spontaneous loss of carrying capacity which happens due to the natural death of endothelial cells.

$$^{C}D_t^{\alpha}\left(p(t)\right) = -\gamma p \ln\left(\frac{p}{k}\right) - \omega p.$$

According to Enderling et al., where $(-\omega p)$ is added for chemotherapy treatment. Here ω is defined as the killing strength in the range of [0,1].

$$^{C}D_t^{\alpha}\left(k(t)\right) = \eta p - \theta k p^{2/3} - \delta k - f k D_r(t),$$

where, we introduce spontaneous loss as a δk in this equation. Here f is the rate at which the drug is administered and $D_r(t)$ is the drug concentration at a given time inside the body of the patient.

8.4 Existence and Uniqueness

Theorem 8.4.1. *[126] The following functions:*

$$G_1(t,p) = -\gamma p \ln\left(\frac{p}{k}\right), \tag{8.7}$$

$$G_2(t,p) = \eta p - \theta k p^{2/3} - \delta k. \tag{8.8}$$

fulfill the Lipschitz condition and are contractions when:

(i) $0 < L_1 < 1$,

(ii) $0 < L_2 < 1$.

Proof. Let p_1 and p_2 be two functions of $G_1(t,P)$ and K_1 and K_2 be two functions of $G_2(t,P)$, then

$$\begin{aligned}
&\|G_1(t,p_1) - G_1(t,p_2)\| \\
&\quad = \left\|-\gamma\left[p_1 \ln\left(\frac{p_1}{k}\right) - p_2 \ln\left(\frac{p_2}{k}\right)\right]\right\| \\
&\quad = \|\gamma\| \, \|p_1 \ln(p_1) - p_2 \ln(p_2) + p_2 \ln(p_1) - p_2 \ln(p_1) + \ln(k)(p_1 - p_2)\| \\
&\quad = \|\gamma\| \, \|(p_1 - p_2)(\ln(p_1) - \ln(k)) + p_2(\ln(p_1) - \ln(p_2))\| \\
&\quad \leq \|\gamma\| \, \|(p_1 - p_2)(\ln(p_1) - \ln(k))\| + \|\gamma\| \, \|p_2\| \, \|\ln(p_1) - \ln(p_2)\| \\
&\quad \leq \|\gamma\| \, \|(p_1 - p_2)\| \frac{1}{\min\{p_1,k\}} \|p_1 - k\| + \|\gamma\| \, \|p_2\| \frac{1}{\min\{p_1,p_2\}} \|p_1 - p_2\| \\
&\quad \leq (\|\gamma\| \, \|p_1\| \, \|k\| + \|\gamma\| \, \|p_2\|) \, \|p_1 - p_2\| .
\end{aligned}$$

Let $l_1 = \sup_t \|p_1(t)\|$, $l_2 = \sup_t \|p_2(t)\|$ and $l_3 = \sup_t \|k(t)\|$, then

$$\|G_1(t,p_1) - G_1(t,p_2)\| \leq L_1 \|p_1 - p_2\| ,$$

where, $L_1 = \|\gamma\| \, (l_1 + 2l_2)$.

Similarly, we get

$$\begin{aligned}\|G_1(t,k_1) - G_1(t,k_2)\| &= \left\|(-\theta k_1 p^{2/3} - \delta)(k_1 - k_2)\right\| \\ &\leq \left(\theta \left\|p^{2/3}\right\| + \|\delta\|\right) \|k_1 - k_2\| .\end{aligned}$$

Let $l_3 = \sup_t \|p(t)\|$ and $L_2 = (\theta l_3^{2/3} + \|\delta\|)$, then $\|G_1(t,k_1) - G_1(t,k_2)\| \leq L_2 \|k_1 - k_2\|$.

Hence, the Lipschitz condition for $G_1(t,p)$ and $G_2(t,k)$ hold, and if $0 < L_1 < 1$ and $0 < L_2 < 1$, then the contraction holds for both $G_1(t,p)$ and $G_2(t,k)$. □

8.5 Stability analysis

We have a system of nonlinear fractional differential equations in the fractional tumor growth model, and therefore, first, we must linearize this system and find the eigenvalue of the Jacobian matrix at the equilibrium point [121]. We will analyze the stability of untreated tumors, i.e., $D_r(t) = 0$ and $\omega = 0$. The equilibrium is found when the system is independent of time. ${}^{C}D_t^{\alpha}\left(p(t)\right) = 0$ and ${}^{C}D_t^{\alpha}\left(k(t)\right) = 0$.

The equilibrium point of the given nonlinear system of ordinary differential equations is:

$$E = \left(\left(\frac{\eta - \delta}{\theta}\right)^{3/2}, \left(\frac{\eta - \delta}{\theta}\right)^{3/2}\right)$$

From equations (8.11) and (8.12), we have $q_1 = -\gamma p \ln\left(\frac{p}{k}\right), \quad q_2 = \eta p - \theta k p^{2/3} - \delta k$.

The Jacobian matrix is as follows:

$$J = \begin{pmatrix} -\gamma & \gamma \\ \frac{1}{3}\eta + \frac{2}{3}\delta & -\eta \end{pmatrix}$$

The eigenvalues of the Jacobian matrix at its equilibrium points are:

$$E_1 = \frac{1}{2}\left(-(\gamma + \eta) + \sqrt{(\gamma^2 + \eta^2) - \frac{2}{3}\gamma\eta + \frac{8}{3}\gamma\delta}\right),$$

$$E_2 = \frac{1}{2}\left(-(\gamma+\eta) - \sqrt{(\gamma^2+\eta^2) - \frac{2}{3}\gamma\eta + \frac{8}{3}\gamma\delta}\right).$$

Using the eigenvalues, we predict the stability of the given system.

Table 8.1: Eigenvalue with corresponding parameter taken from Table 8.2

Data set or Cell line	**Eigenvalue**
Lewis lung carcinoma (Hahnfeldt et.al.) [55]	$[-0.12547915, -5.91652085]$
Breast adenocarcinoma xenografts-1. [58]	$[-4.78536872, -0.08573128]$
Breast adenocarcinoma xenografts-2 [58]	$[-0.08149756, -1.20280244]$
H226 (lung cancer cell line). [59]	$[-0.0644368, -0.7647632]$
HT29 (Human colon cancer cell line) [123]	$[-0.11469448, -0.60520552]$

As all eigenvalues are real and negative, it is concluded that the system is asymptotically stable. This means the value will remain stable with time.

8.6 Numerical algorithm

We consider the Fractional modified Hahnfeldt model (8.5) and (8.6). Where $p(t_j)$, $k(t_j)$ are computed with the fractional Euler's method approximation scheme,

$$p(t_{j+1}) = p(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_1(t_j, p(t_j), k(t_j)), \tag{8.9}$$

$$k(t_{j+1}) = k(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f_2(t_j, p(t_j), k(t_j)). \tag{8.10}$$

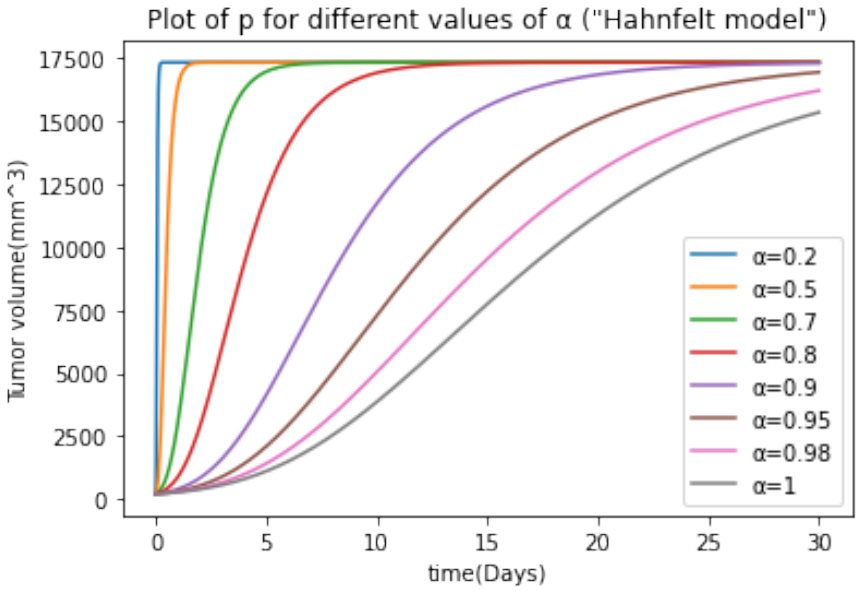
The functions $f_1(t_j, p(t_j), k(t_j))$ and $f_2(t_j, p(t_j), k(t_j))$ are given by

$$f_1(t_j, p(t_j), k(t_j)) = -\gamma p \ln\left(\frac{p}{k}\right), \tag{8.11}$$

$$f_2(t_j, p(t_j), k(t_j)) = \eta p - \theta k p^{2/3} - \delta k, \tag{8.12}$$

where, $0 \leq j \leq n$, $t_{j+1} = t_j + h$ and h is the step size.

8.7 Simulations and Experimental results



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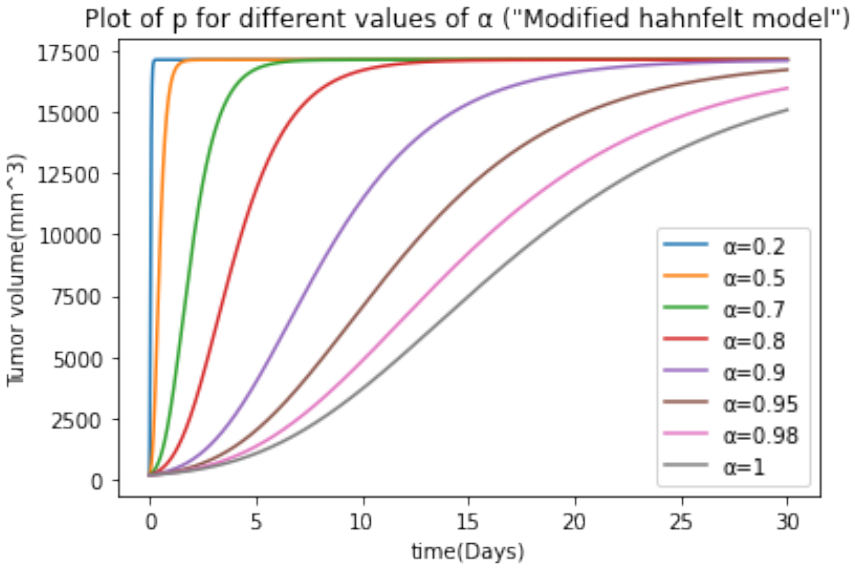
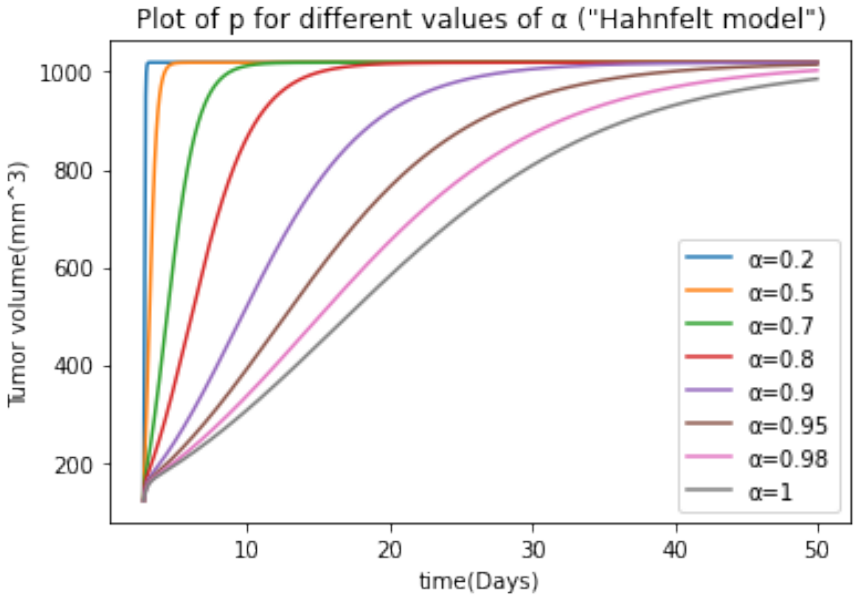


(b)

Figure 8.1: Tumor Volume vs Time plotted for Lewis Lung Carcinoma

In figure 8.1, the data is taken from [55] when $\alpha = 0.2, 0.5, 0.7$ the value of carrying capacity (k) and tumor volume (p) remain the same for their respective model, but when

$\alpha = 0.8, 0.9, 0.95, 0.98, 1.00$ the tumor volume starts decreasing. When $\alpha = 0.8, 0.9$, the difference between k and p is not much, but when $\alpha = 0.95, 0.98, 1.00$ the tumor volume starts decreasing more rapidly.



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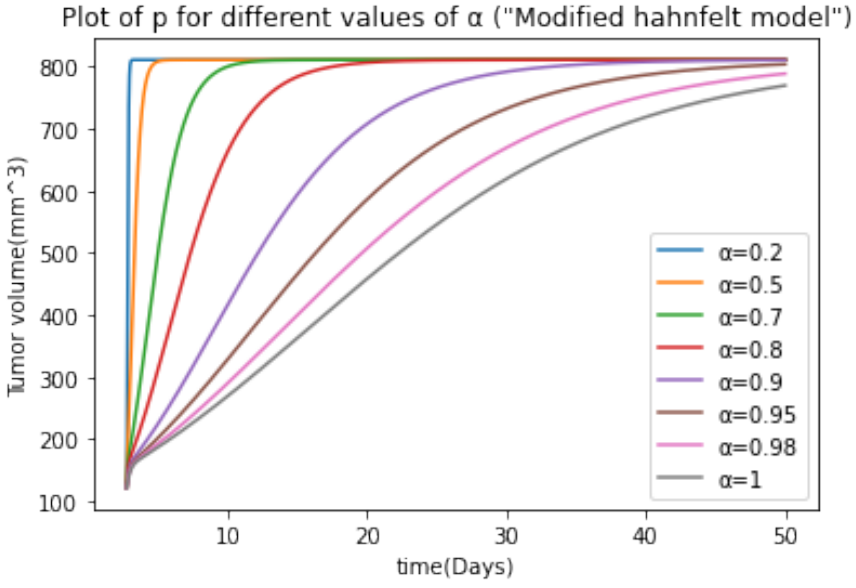
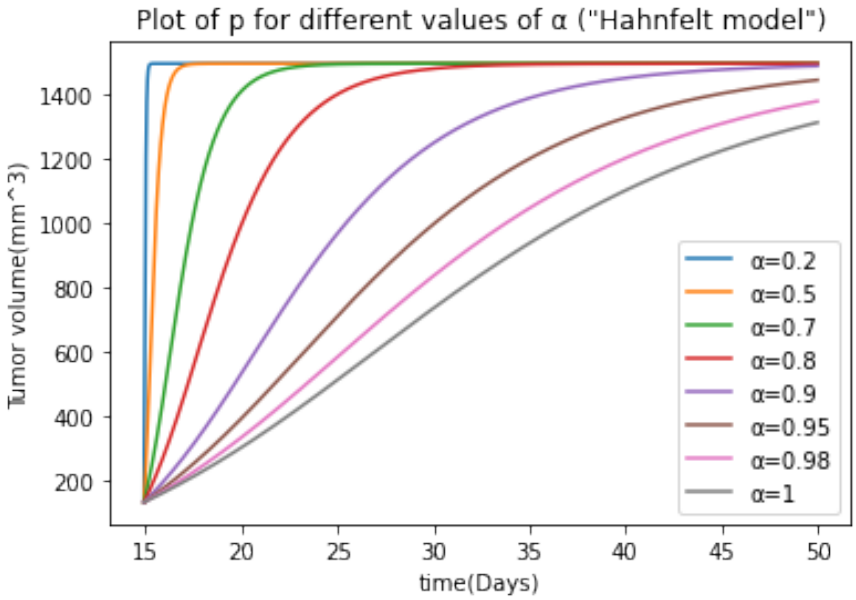


(b)

Figure 8.2: Breast adenocarcinoma xenografts-1

In figure 8.2, the data from Higgins et al. for Breast adenocarcinoma xenografts-1 is used to compare both models. Tumor volume versus time for different values of α is plotted, which shows the comparison between them [58].



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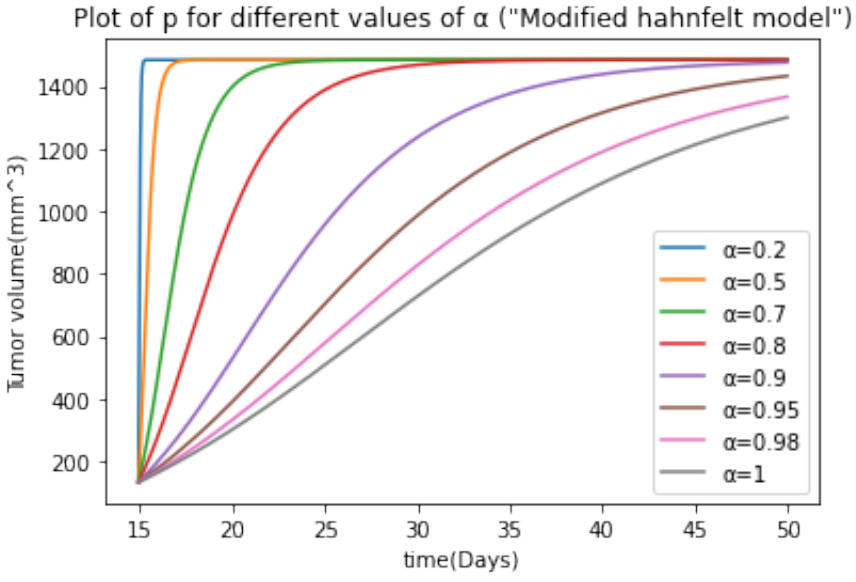

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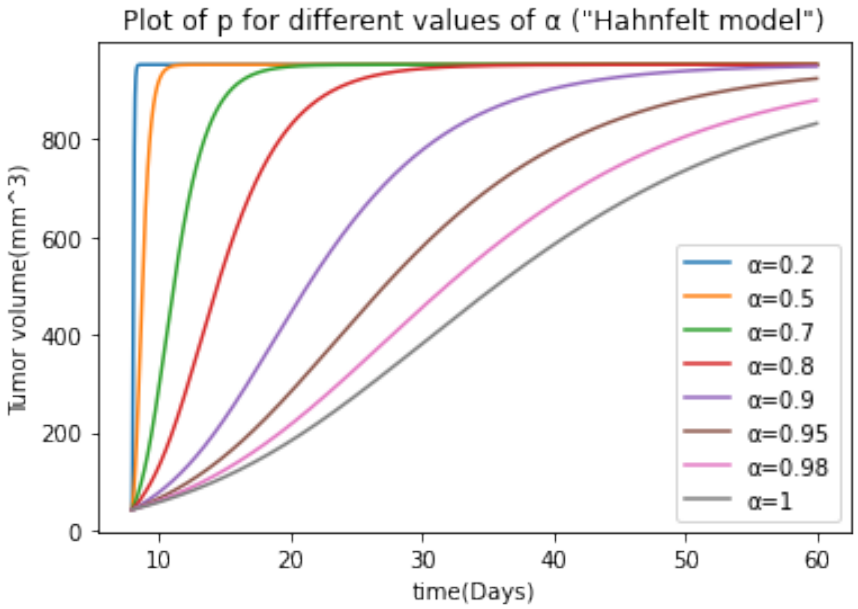
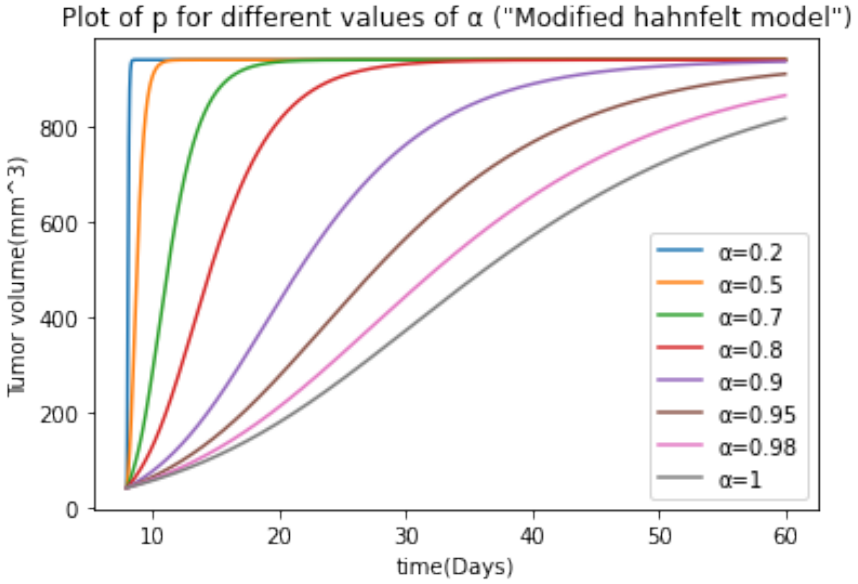
Figure 8.3: Breast adenocarcinoma xenografts-2

In figure 8.3, the data from Higgins et al. for Breast adenocarcinoma xenografts-2 is used to compare both models. A graph of tumor volume versus time for different values of α is plotted, which shows the comparison between them [58].



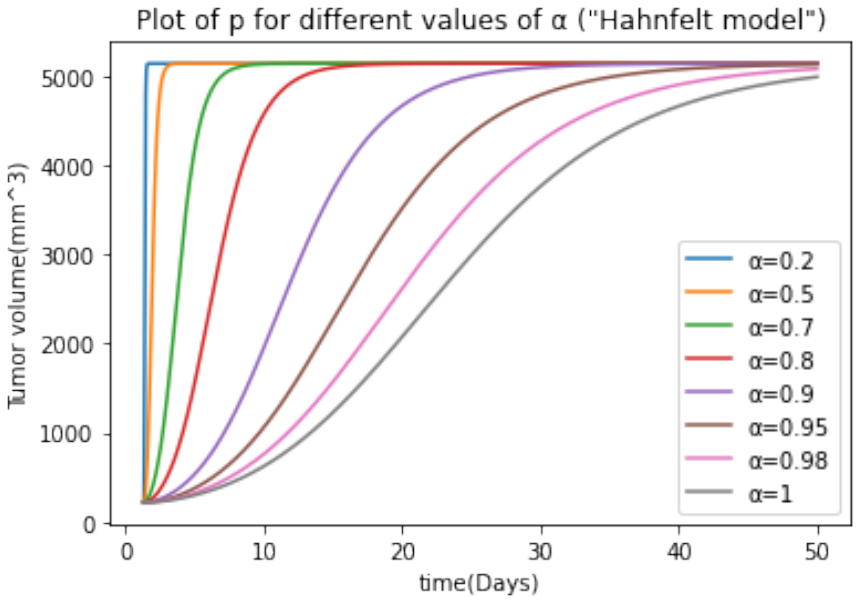
(a)



(b)

Figure 8.4: H226 (lung cancer cell line)

In figure 8.4, the data from Higgins et al. for H226 (lung cancer cell line) is used to compare both models. A graph of tumor volume versus time for different values of α is plotted, which shows the comparison between them [58].



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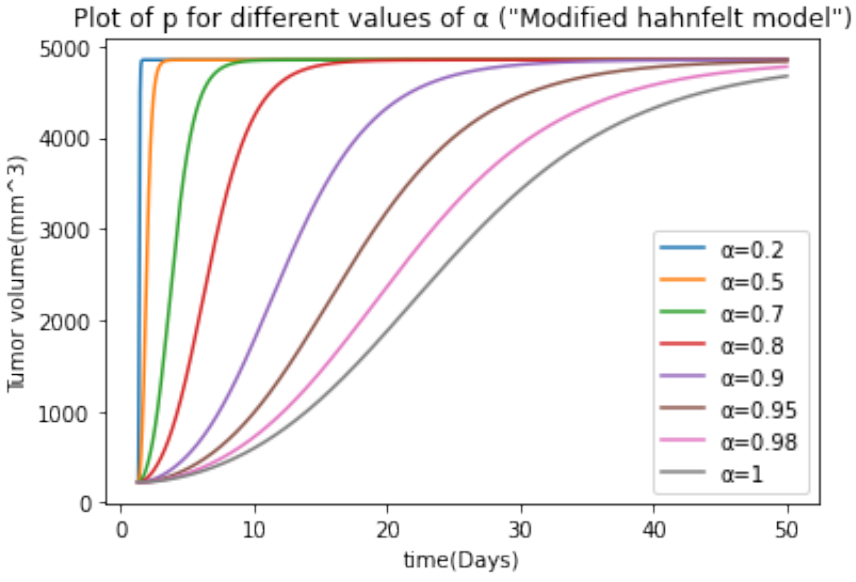

(b)

Figure 8.5: HT29 (Human colon cancer cell line)

In figure 8.5, the data from Higgins et al. is used to compare both models. A graph of tumor volume versus time for different values of α is plotted, which shows the comparison between them [58].

Table 8.2: Tumor volume (p) and carrying capacity (k) for different α of Hahnfeldt and Modified Hahnfeldt tumor growth model

α	Hahnfeldt		Modified Hahnfeldt	
	k	p	k	p
0.2	17346.52289121	17346.52289121	17124.60744631	17124.60744631
0.5	17346.52289121	17346.52289121	17124.60744631	17124.60744631
0.7	17346.52289121	17346.52289121	17124.60744631	17124.60744631
0.8	17346.52004186	17346.51452813	17124.60410319	17124.59779701
0.9	17334.39963687	17310.96524778	17111.38505586	17086.47298831
0.95	17212.76807887	16956.99366168	16981.78883312	16715.82102584
0.98	16956.34860784	16227.17218965	16712.04978131	15962.32766499
1.00	16642.49589481	15363.76536699	16384.368048	15079.16483903

Table 8.3: Root Mean Squared Error (RMSE) for different cancers

HCP40	HCT116	HP40	HSCC1 (Head and Neck)
1399.794731	1408.761879	1324.142429	223.1626791
1468.874815	1508.304317	1399.232823	235.942092
1477.774751	1525.827741	1409.945128	238.7935126
1477.006596	1528.047396	1409.81285	239.3355936
1476.057045	1528.128634	1409.059338	239.4007466

In below mentioned figure 8.6, we have calculated the RMSE for cancers: HCP40, HCT116, HP40, and HSCC1 (Head and Neck) with different values of α. In this computation, we have used the Fractional Hahnfeldt mathematical model [58]. Results indicate that $\alpha = 0.1$ gives the minimum RMSE compared to the classical model.

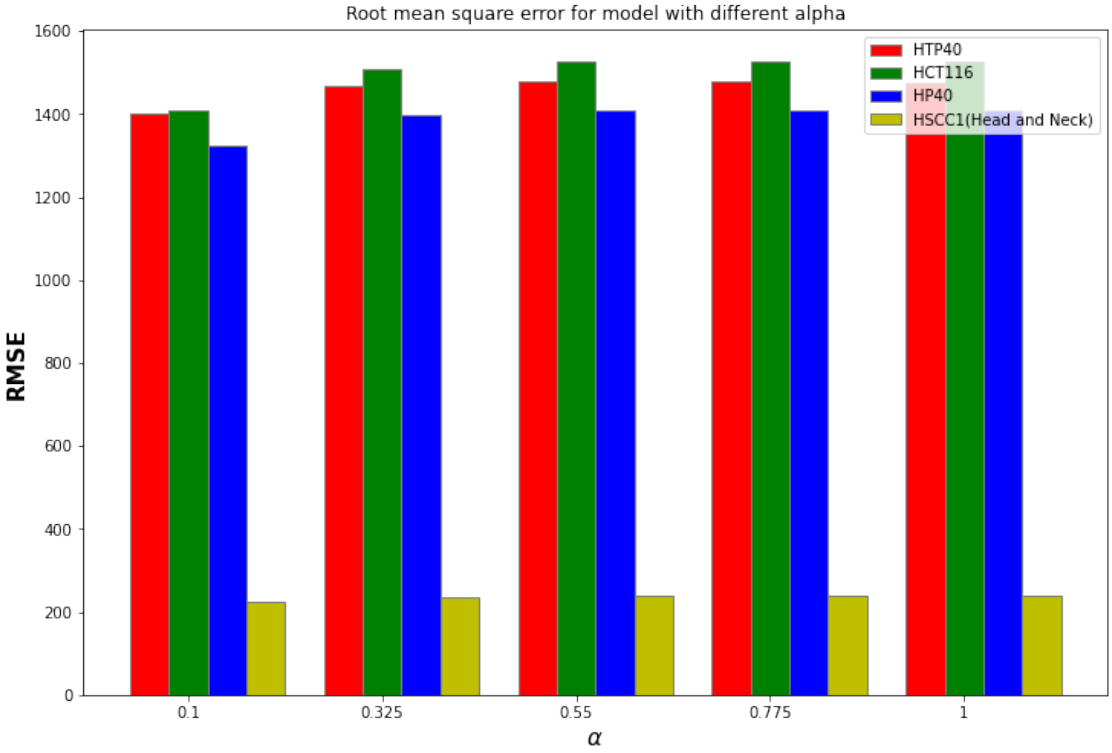

Figure 8.6: Bar chart of RMSE for cancer model with different α

8.8 Conclusion

We introduced a fractional mathematical model of tumor growth and its treatment processes to provide a more agreeable solution. This model considers various factors present in the Hahnfeldt et al. model, utilizing the Caputo fractional derivative operator with a power-law kernel. The existence and uniqueness of the arbitrary order system were investigated by applying the Lipschitz condition, and system stability was ensured. We investigated the numerical solution of the nonlinear arbitrary order tumor growth using the fractional Euler method. Room mean square error (RMSE) calculations were performed for cancers HCP40, HCT116, HP40, and HSCC1 (Head and Neck), with different values of α. The impact of the arbitrary order α on the dynamics of tumor growth and numerical simulations were provided for distinct values of the arbitrary power α. Results indicate that the fractional-order model yields superior outcomes compared to the classical model.