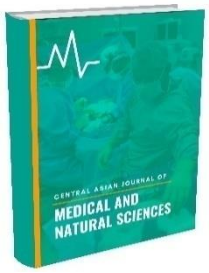
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 03 Issue: 06 | Nov-Dec 2022 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

Modeling Tumor Cell Proliferation and Therapeutic Treatment Simulation

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Received 6th Oct 2022,
Accepted 5th Nov 2022,
Online 19th Dec 2022

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Keywords: Modeling, simulation, chemo-immunotherapy, Tumour growth, cell proliferation, carcinogenic, therapeutic treatment.

Annotation: **Background and Objectives:** Tumor growth and cell proliferation have been global health concerns over the years. This research involves the formulation of mathematical models to investigate tumor cell proliferation and the application of treatments to control and reduce cell proliferation. **Materials and Methods:** The study is divided into two parts: first, the model depicts the tumor spreading through the cell proliferation caused by a carcinogenic substance (agent), which causes the tumor to grow exponentially, thereby putting lives at risk and facilitating death. Secondly, chemo-immunotherapeutic models were formulated and used to modify the tumor spread, and cell proliferation models were developed to control and reduce the proliferation rate. The formulated models were solved analytically. Graphical and tabular results were generated from the simulation using Wolfram Mathematica software, where we studied cases of a steady supply of chemo-immunotherapeutic drugs, the fading rate of chemo-immunotherapeutic drugs, the increase in carcinogenic substances, and the variation of growth rates on cell proliferation. **Results:** The study showed that cell proliferation increased, indicating the fast spread of the tumor as the carcinogenic substance exposure rate increased. However, it is seen that the steady supply of chemo-immunotherapeutic drugs helps in reducing and controlling cell proliferation. In addition, the fading rate of chemo-immunotherapeutic drugs, independently and combined, also decreases cell proliferation in the presence of a quantified carcinogenic substance. The study concludes that carcinogenic substances and the use of chemo-immunotherapeutic drugs in controlling and reducing cell proliferation can cause tumor spread.

1. Introduction

A mathematical model is being extensively used in medical processes to develop a quantitative balance of bio-medical phenomena. This quantitative orientation is useful both clinically and experimentally, and the most prominent application of mathematical modeling is in the area of cancer biology [1]. Significant progress has been made in theoretical, experimental, and clinical approaches to understanding tumor dynamics and interactions with the immune system and bodily tissues, leading to the development of important cancer therapy methods such as virotherapy, immunotherapy, and chemotherapy [2].

Cancer develops when normal cells are damaged and do not undergo programmed cell death as quickly as they divide through mitosis.

Carcinogens may increase the risk of cancer by altering cellular metabolism or directly damaging DNA in cells, which interferes with biological processes and induces uncontrolled, malignant division, eventually leading to the formation of a tumor [3].

Over the years, researchers have worked on tumor growth problems and proposed mathematical modeling of tumor growth in mice following low-level direct electric current [4]. A numerical study of the nonlinear fractional mathematical model of tumor cells in the presence of chemotherapeutic treatment was proposed [5]. Research has investigated tumor growth in oncology, where oncology is the study of cancer. He developed mathematical models of preclinical and clinical tumor growth [6] and investigated using the physical laws of tumour growth to model cancer processes [7]. Other researchers have proposed an optimal control and pattern formation for a haptotaxis model of solid tumour invasion [8]. The aspects of modelling and simulating tumour growth and treatment were developed; their model is based on the hypothesis that the proliferation of malignant cells may be simulated by an unstable closed-loop control circuit. Researchers also proposed progress in modelling and simulation of three-dimensional tumour growth and treatment [9]. Their work showed how tumor treatment may be optimized in the long run using computer simulation experiments as a powerful new tool. They evaluated virtual growth tumors with varying growth kinetics and observed tumours with lower proliferation rates will have the most reduction in swelling from their applied treatments.

Mathematical modeling, analysis, and simulation of tumor dynamics with drug interventions were carried out, and the results indicate their usefulness for studying the dynamics of tumor cells and for providing dynamic interactions between tumor cells, the immune system, and drug-response systems [10]. Tumor growth in mice after electrotherapy and bleomycin treatment was also modeled mathematically [11]. The effect of bleomycin on tumor growth was obtained by introducing the influential parameter, which transferred the bleomycin concentration in tumor tissue obtained from the pharmacokinetic model to the effect on tumor growth. It was possible to model tumor cell regression in response to chemotherapeutic treatment [12]. They observed that the response of three different levels of immune system strength to the pulsed chemotherapy was better if a chemotherapeutic drug was injected near the invasive fronts of the tumor. An application of the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives to a mathematical model of the chemotherapy effect was derived [13]. They obtained approximate analytical solutions for a cancer chemotherapy effect model involving fractional derivatives with an exponential kernel. Stochastic modeling of tumor growth within an organ during chemotherapy was performed using bivariate birth, death, and migration processes [14]. A carcinogenic substance is a material such as a radionuclide or radiation that promotes carcinogenesis, the formation of cancer due to the ability to damage the genome or disruption of the cellular metabolic process.

Chemotherapy is the administration of any drug to treat a disease. The term "chemotherapy" (or "chemo") also refers to cancer-treatment drugs. It's critical to understand that not all cancer medications and drugs work the same way.

Traditional or standard chemotherapy used to be the only type of drug that could treat cancer, but now there are many different types of drugs used to treat it. Cancer therapeutic drugs have three major goals: cure, control, and palliative [15].

The goals of this study are to develop novel models that represent tumor cell proliferation caused by a carcinogenic agent (substance) and to apply treatments to reduce or control cell proliferation. Secondly, solve the models analytically with the initial concentration of tumor cells and the application of the initial dosage of the therapeutic drugs. Perform a numerical simulation using Wolfram Mathematica software, study the impact of the steady supply of chemo- and immunotherapeutic drugs on cell proliferation and other contributing carcinogenic factors on cell proliferation, and make appropriate recommendations based on the model output.

2. Materials and Methods

Data Availability

Previous literature is used to obtain the dynamics of the mathematical models as well as the parameter values. The research was divided into two parts.

The first segment is concerned with the mathematical formulation of cell proliferation caused by carcinogenic agents or substances in the absence of treatment; we assume that the cell proliferation rate is proportional to the available volume.

The second segment entails the use of treatments to combat cell proliferation. Chemotherapy and immunotherapy are being considered as treatments (chemo-immunotherapy).

Following the previously mentioned segmentation, we present the models as follows:

2.1 Untreated Cell Proliferation

To model the effect of therapy on cancer growth, one should first, model the kinetics of the growth of an untreated growth. The model that describes an untreated cancer cell proliferation, we present

$$\frac{dy}{dt} = \gamma_1 e^{\alpha_1 t} y \qquad (1)$$

$$y(t=0) = y_0$$

γ_1 is the Tumour-causing agent or substance in the body, α_1 is the growth of proliferating cell, y is the tumour cell, y_0 is the initial cell population of the tumour cell, t is time.

2.2 Treated Cell Proliferation with Chemo-Immunotherapeutic

$$\frac{dy}{dt} = \gamma_1 e^{\alpha_1 t} y - \alpha_2 My - \alpha_3 Iy \qquad (2)$$

$$\frac{dM}{dt} = v_M - d_4 M \qquad (3)$$

$$\frac{dI}{dt} = v_I - d_5 I \qquad (4)$$

$y(t=0)=y_0$, $M(t=0)=M_0$ and $I(t=0)=I_0$

v_M is constant supply of chemotherapeutic drug, v_I is constant supply of immunotherapeutic drug, d_4 and d_5 is the fading rates of chemo-immunotherapeutic drugs, M and I is the concentrations of chemo-immunotherapeutic drugs, t is time.

3. Method of Solution

Now, we need to solve equation (1) to get the untreated cell proliferation by separable variable technique, which is:

$$\int \frac{dy}{y} = \gamma_1 \int e^{\alpha_1 t} dt \tag{5}$$

$$\log_e y = \frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + C_1 \tag{6}$$

$$y = e^{\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + C_1} \tag{7}$$

$$y = e^{C_1} e^{\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t}} \tag{8}$$

Applying the initial condition to solve equation (8), we have:

$$y = y_0 e^{-\frac{\gamma_1}{\alpha_1}} e^{\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t}} \tag{9}$$

Also, to investigate the effect of the chemo-immunotherapeutic drugs on the cancer cell density, we modify equation (1) to include the treatments as follows:

$$\frac{dy}{dt} = \gamma_1 e^{\alpha_1 t} y - \alpha_2 M y - \alpha_3 I y \tag{10}$$

Since we are considering the chemo-immunotherapeutic treatment, we can s well solve them independently with a specific dose as follows:

$$\frac{dM}{dt} + d_4 M = v_M \tag{11}$$

$$\frac{dI}{dt} = v_I - d_5 I \tag{12}$$

where $M(t)$ and $I(t)$ denote the chemotherapy and immunotherapy drugs concentrations over time respectively.

Solving equation (11), we obtained:

$$M = M_c + M_p$$

$$M = Ae^{-d_4 t} + \frac{v_M}{d_4} \tag{13}$$

$$M = \left(M_0 - \frac{v_M}{d_4} \right) e^{-d_4 t} + \frac{v_M}{d_4} \tag{14}$$

$$M = M_0 e^{-d_4 t} + \frac{v_M}{d_4}\left(1 - e^{-d_4 t}\right) \tag{15}$$

Solving equation (12), we obtained:

$$I = I_c + I_p$$

$$I = Ae^{-d_4 t} + \frac{v_I}{d_5} \tag{16}$$

$$I = \left(I_0 - \frac{v_I}{d_5}\right)e^{-d_5 t} + \frac{v_I}{d_5} \tag{17}$$

$$I = I_0 e^{-d_5 t} + \frac{v_I}{d_5}\left(1 - e^{-d_5 t}\right) \tag{18}$$

For us to investigate the effect of the chemo-immunotherapeutic drug on cancer proliferation, we substitute equations (15) and (18) into equation (10) so that it becomes:

$$\frac{dy}{y} = \left(\gamma_1 e^{\alpha_1 t} - \alpha_2\left(M_0 e^{-d_4 t} + \frac{v_M}{d_4}\left(1 - e^{-d_4 t}\right)\right) - \alpha_3\left(I_0 e^{-d_5 t} + \frac{v_I}{d_5}\left(1 - e^{-d_5 t}\right)\right)\right)dt \tag{19}$$

Integrating both sides of equation (19), we obtained:

$$\int \frac{dy}{y} = \left(\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} - \alpha_2\left(-\frac{M_0}{d_4} e^{-d_4 t} + \frac{v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) - \alpha_3\left(-\frac{I_0}{d_5} e^{-d_5 t} + \frac{v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right)\right) \tag{20}$$

Simplifying equation (20), we obtained:

$$\log_e y = \frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + \left(\frac{\alpha_2 M_0}{d_4} e^{-d_4 t} - \frac{\alpha_2 v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} e^{-d_5 t} - \frac{\alpha_3 v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right) + C_2 \tag{21}$$

Taking the exponentials of equation (21), we obtained:

$$y = e^{\left(\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + \left(\frac{\alpha_2 M_0}{d_4} e^{-d_4 t} - \frac{\alpha_2 v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} e^{-d_5 t} - \frac{\alpha_3 v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right) + C_2\right)} \tag{22}$$

Simplifying equation (22), we have:

$$y = e^{C_2} e^{\left(\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + \left(\frac{\alpha_2 M_0}{d_4} e^{-d_4 t} - \frac{\alpha_2 v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} e^{-d_5 t} - \frac{\alpha_3 v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right)\right)} \tag{23}$$

Upon further simplification, we obtained:

$$y = Be^{\left(\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + \left(\frac{\alpha_2 M_0}{d_4} e^{-d_4 t} - \frac{\alpha_2 v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} e^{-d_5 t} - \frac{\alpha_3 v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right)\right)} \tag{24}$$

Applying the initial condition $y(t=0) = y_0$, we obtained

$$y = \left(y_0 e^{-\left(\frac{\gamma_1}{\alpha_1} + \left(\frac{\alpha_2 M_0}{d_4} - \frac{\alpha_2 v_M}{d_4}\left(\frac{1}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} - \frac{\alpha_3 v_I}{d_5}\left(\frac{1}{d_5}\right)\right)\right)}\right) e^{\left(\frac{\gamma_1}{\alpha_1} e^{\alpha_1 t} + \left(\frac{\alpha_2 M_0}{d_4} e^{-d_4 t} - \frac{\alpha_2 v_M}{d_4}\left(t + \frac{e^{-d_4 t}}{d_4}\right)\right) + \left(\frac{\alpha_3 I_0}{d_5} e^{-d_5 t} - \frac{\alpha_3 v_I}{d_5}\left(t + \frac{e^{-d_5 t}}{d_5}\right)\right)\right)} \tag{25}$$

4. Results and Discussion

We investigate the dynamics of tumor cell proliferation by observing the effect of the various parameters on the model. In particular, the variation in carcinogenic substances showed the effects of changes in carcinogenic substances $\gamma_1 = 0,5,10,15$ in Table 1. Table 2 shows the results of the variation of tumor growth rate and carcinogenic substance observation. The effect of the variation of the carcinogenic substance and tumor growth rate was investigated, and the results are presented in Table 3. The effect of a steady increase in chemotherapeutic drugs on cell proliferation was illustrated using Table 4. Table 5 shows the steady supply of immunotherapeutic drugs on cell proliferation. The decrease in the effectiveness of the chemotherapeutic drug on cell proliferation was investigated, and the results are illustrated in Table 6. The variation of the immunotherapeutic drug on cell proliferation was shown in Table 7. Finally, the effect of chemo-immunotherapeutic drug variation on tumor cell proliferation was studied, and the results are shown in Table 8.

Table 1: The Effect of a Carcinogenic Substance Variation on Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$\gamma_1 = 0$	$\gamma_1 = 5$	$\gamma_1 = 10$	$\gamma_1 = 15$
0.0	50	50	50	50
0.1	50	82.5083	136.152	224.674
0.2	50	136.392	372.054	1014.9
0.3	50	225.862	1020.28	4608.84
0.4	50	374.686	2807.79	21040.8
0.5	50	622.676	7754.51	96570.9
0.6	50	1036.64	21492.7	445605
0.7	50	1728.92	59783.1	2.0672000
0.8	50	2888.66	166888	9.6416400
0.9	50	4835.06	467555	4.5213100
1.0	50	8107.56	1.3146500	2.1317300

$y(t)$ = tumor cell over time

Table 1 showed that if there is no carcinogenic agent triggering abnormal tissue growth, there could be no cancer. However, it is seen that an increase in carcinogenic agents could result in the growth of the tumor at different levels; the tumor size could be 50, 82.5083, 136.152, or 224.674, respectively, based on this research over a period of time. The result obtained in this research agrees with Shannon *et al*. [16].

Table 2: Effects of Growth Rate Variation and Carcinogenic Substance on Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$\alpha_1 = 0.035, \gamma_1 = 0$	$\alpha_1 = 0.045, \gamma_1 = 5$	$\alpha_1 = 0.055, \gamma_1 = 5$	$\alpha_1 = 0.065, \gamma_1 = 5$
0.0	50	50	50	50
0.1	50	82.529	82.5497	82.5704
0.2	50	136.529	136.666	136.804
0.3	50	226.375	226.89	227.407
0.4	50	375.204	377.732	379.271
0.5	50	626.632	630.627	634.661
0.6	50	1046.17	1055.82	1065.6

0.7	50	1750.63	1772.72	1795.2
0.8	50	2936.27	2984.92	3034.64
0.9	50	4936.4	5040.49	5147.43
1.0	50	8318.44	8536.27	8761.32

$y(t)$ = tumor cell over time

The first column in Table 2 showed that without carcinogenic substances, there is no risk of tumors before we talk of cell proliferation. The table showed that the tumor cell began to proliferate with the presence of a carcinogenic substance, and a faster growth rate also increased the cell proliferation rate. The result is in agreement with Sanga *et al*. [17], which talked about mathematical modeling of cancer progression and response.

Table 3: Carcinogenic Substance Variation and Cell Proliferation Growth Rate

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$\gamma_1 = 0, \alpha_1 = 0$	$\gamma_1 = 5, \alpha_1 = 0.045$	$\gamma_1 = 10, \alpha_1 = 0.055$	$\gamma_1 = 15, \alpha_1 = 0.065$
0.0	50	50	50	50
0.1	50	82.529	136.289	225.182
0.2	50	136.529	373.554	1024.14
0.3	50	226.375	1029.58	4704.08
0.4	50	376.204	2853.63	21822.6
0.5	50	626.632	7953.63	102255
0.6	50	1046.17	22295.1	483994
0.7	50	1750.63	62850.8	2.314170000
0.8	50	2936.27	178195	1.117850000
0.9	50	4936.4	508131	5.455460000
1.0	50	8318.44	1.457360000	2.690100000

$y(t)$ = tumor cell over time

Peer *et al*. [18] investigated the age-dependent growth rate of primary breast cancer, where the increase in growth rate caused an increase in cell proliferation. However, in Table 3, it is seen that tumor cell proliferation reduces over time due to different changes in carcinogenic substances.

Table 4: The Effect of Chemotherapeutic Drug Supply Variation on Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$v_M = 5$	$v_M = 10$	$v_M = 15$	$v_M = 20$
0.0	50	50	50	50
0.1	23.5748	23.5422	23.5095	23.477
0.2	11.7356	11.6714	11.6075	11.5439
0.3	6.15013	6.07537	6.00151	5.92856
0.4	3.38374	3.31166	3.24112	3.17209
0.5	1.9495	1.88563	1.82384	1.76409
0.6	1.1733	1.11886	1.06695	1.01745
0.7	0.735963	0.69031	0.647488	0.607323
0.8	0.480093	0.441924	0.40679	0.374448
0.9	0.325036	0.292975	0.264077	0.238029
1.0	0.227948	0.200763	0.176821	0.155734

$y(t)$ = tumor cell over time

In Table 4, the increase in the constant supply of chemotherapeutic drugs on tumor cell proliferation was seen to be increasing without any treatment for a different carcinogenic substance, and this result agrees with Mukhopadhyay and Bhattacharyya [19], which talked about viruses that specifically destroy tumor cells that could be used as a therapeutic agent to arrest tumors.

Table 5: Changes in the Consistent Supply of Immunotherapeutic Drug Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$v_I = 5$	$v_I = 10$	$v_I = 15$	$v_I = 20$
0.0	50	50	50	50
0.1	23.5748	23.4595	23.3448	23.2307
0.2	11.7356	11.5122	11.293	11.078
0.3	6.15013	5.89471	5.6499	5.41526
0.4	3.38374	3.14249	2.91844	2.71036
0.5	1.9495	1.74053	1.55396	1.38739
0.6	1.1733	0.999607	0.851629	0.725556
0.7	0.735963	0.594167	0.479691	0.38727
0.8	0.480093	0.364885	0.277323	0.210774
0.9	0.325036	0.231127	0.16435	0.116867
1.0	0.227948	0.150769	0.099729	0.065951

$y(t)$ = tumor cell over time

We noticed in Table 5 that, with the application of the immunotherapeutic treatment at 5 units, the tumor cell quantity reduced from 50 to 0.227948 over time. However, the process repeated itself as the immunotherapeutic treatment was increased from 5 to 20 units. This is an indication that the immunotherapeutic treatment was effective in reducing the size of the tumor, which, as stated earlier by Bru and Herre [7].

Table 6: Effect of a Chemotherapeutic Drug on Tumor Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$d_4 = 0.3$	$d_4 = 0.5$	$d_4 = 0.7$	$d_4 = 0.9$
0.0	50	50	50	50
0.1	23.5746	23.5238	23.4721	23.4196
0.2	11.7356	11.6359	11.5339	11.4296
0.3	6.15013	6.03494	5.91654	5.79543
0.4	3.38374	3.27353	3.16032	3.04506
0.5	1.9495	1.8526	1.75362	1.65388
0.6	1.1733	1.0914	1.00858	0.926465
0.7	0.735963	0.667864	0.599997	0.534152
0.8	0.480093	0.42366	0.36847	0.316354
0.9	0.325036	0.278063	0.233169	0.192122
1.0	0.227948	0.188487	0.151777	0.119443

$y(t)$ = tumor cell over time

As seen in Table 6, the effect of chemotherapeutic drugs on the tumor cell proliferation and size was investigated, and the treatment was found to be effective because as the dosage of the chemotherapeutic drug increased from 0.3 to 0.9, the tumor size also decreased from 50 to 0.227948, 0.188487, 0.151777, and 0.119443, respectively, and this is in line with the previous study by Piere and Ghalamie [1].

Table 7: Effect of an Immunotherapeutic Drug on Tumor Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$d_5 = 0.6$	$d_5 = 0.7$	$d_5 = 0.8$	$d_5 = 1.0$
0.0	50	50	50	50
0.1	23.5748	23.5729	23.571	23.6815
0.2	11.7356	11.7283	11.721	11.9281
0.3	6.15013	6.13757	6.12523	6.35534
0.4	3.38374	3.3679	3.35244	3.356466
0.5	1.9495	1.93227	1.9156	2.0956
0.6	1.1733	1.15598	1.1394	1.28612
0.7	0.735963	0.719311	0.703562	0.821061
0.8	0.480093	0.464451	0.449871	0.543464
0.9	0.325036	0.310504	0.297184	0.371859
1.0	0.227948	0.214489	0.202385	0.26232

$y(t)$ = tumor cell over time

The effect of the immunotherapeutic drug on the tumor size and cell proliferation was investigated, as seen in Table 7. The table showed that the tumor cells decreased as the immunotherapeutic rate increased, and the tumor cells decreased from 50 to 1.9495, 0.214489, 0.202385, and 0.26232, respectively, which Wang and Deisbieck [20] agree to, and they elucidated that mathematical models have the potential to help discover new therapeutic targets and treatment strategies.

Table 8: Variation of Chemo-Immunotherapeutic Drugs on Tumor Cell Proliferation

Time(Year)	$y(t)$	$y(t)$	$y(t)$	$y(t)$
t	$d_4 = 0.3, d_5 = 0.6$	$d_4 = 0.5, d_5 = 0.7$	$d_4 = 0.7, d_5 = 0.8$	$d_4 = 1.0, d_5 = 1.0$
0.0	50	50	50	50
0.1	23.6995	23.5748	23.6375	23.8106
0.2	11.971	11.7356	11.8544	12.1825
0.3	6.4143	6.15013	6.28359	6.65527
0.4	3.6303	3.38374	3.50834	3.86011
0.5	2.16172	1.9495	2.05668	2.36484
0.6	1.34939	1.1733	1.26213	1.52314
0.7	0.880014	0.735963	0.808529	1.02698
0.8	0.597728	0.480093	0.539265	0.722082
0.9	0.421624	0.325036	0.37356	0.527569
1.0	0.30803	0.227948	0.268148	0.399251

$y(t)$ = tumor cell over time

Table 8 depicts the decaying growth of tumor cells as chemo-immunotherapeutic drugs were administered. It is seen that the tumor size shrank from 50 to 0.30803, 0.227948, 0.268148, and 0.399251, and this result is in agreement with previous results obtained by Hawkins [21,13].

5. Conclusions

We conclude this investigation by saying: To begin with, there can be no tumor without carcinogenic substances triggering the body's tissues. Second, the tumor growth rate allowed for continuous growth while using only a small amount of a carcinogenic substance. Third, the increase in carcinogenic substances and rate of growth caused the tumor to grow

uncontrollably. Fourth, a steady supply of chemotherapeutic and immunotherapeutic drugs aids in the control and treatment of tumors while also slowing tumor cell proliferation. Finally, the fading rates of chemo-immunotherapeutic drugs aided in tumor cell proliferation control, demonstrating the importance of always increasing your dosage and adhering to your prescription.

6. Significance Statement

We used mathematical models to represent tumor cell proliferation and the application of treatment in controlling and reducing proliferating cells in this study. This study is significant because we have been able to use dynamic mathematical models to represent tumor cell proliferation, and obtain exact solutions denoting the cells as well as the treatments. The study has been able to show the importance of chemotherapeutic, and immunotherapeutic treatments as well as their combined treatment.

Author Contributions: The research idea was shared and contributed by all authors, mathematical formulation and analytical solution was done by KW Bunonyo, literature and biochemical validation was done by Odinga Tamuno-Boma and C.G. Ikimi, finally, the conclusion was written and harmonized by all authors.

Conflicts of Interest: The authors declared that there is no conflict of interest.

References

1. Peirce, S. M. (2008). Computational and mathematical modeling of angiogenesis. *Microcirculation*, *15*(8), 739-751. **https://doi.org/10.1080/10739680802220331**
2. Unni, P., & Seshaiyer, P. (2019). Mathematical modeling, analysis, and simulation of tumour dynamics with drug interventions. *Computational and mathematical methods in medicine*. https://doi.org/10.1155/2019/4079298.
3. Hunt, K. K. (2008). Breast Cancer 2nd edition. In *Breast Cancer 2nd edition*, doi: 10.1007/978-0-387-34952-7_7. https://link.springer.com/book/10.1007/978-0-387-34952-7
4. Cabrales, L. E. B., Aguilera, A. R., Jiménez, R. P., Jarque, M. V., Ciria, H. M. C., Reyes, J. B., & Ávila, M. G. (2008). Mathematical modeling of tumour growth in mice following low-level direct electric current. *Mathematics and Computers in Simulation*, 78(1), 112-120, doi:10.1016/j.matcom.2007.06.004.
5. Kumar, S., & Atangana, A. (2020). A numerical study of the nonlinear fractional mathematical model of tumour cells in presence of chemotherapeutic treatment. *International Journal of Biomathematics*, 13(03), 2050021, https://doi.org/10.1142/S1793524520500217.
6. Bonate, P. L. (2011). Modeling tumour growth in oncology. *Pharmacokinetics in drug development*, 1-19, doi: 10.1007/978-1-4419-7937-7_1.
7. Bru, A., & Herrero, M. A. (2006). From the physical laws of tumour growth to modelling cancer processes. *Mathematical Models and Methods in Applied Sciences*, 16(supp01), 1199-1218,http://www.worldscinet.com/m3as/16/preserveddocs/16supp01/S0218202506001510.pdf.
8. Dai, F., & Liu, B. (2019). Optimal control and pattern formation for a haptotaxis model of solid tumour invasion. *Journal of the Franklin Institute*, *356*(16), 9364-9406, https://doi.org/10.1016/j.jfranklin.2019.08.039.
9. Düchting, W., & Vogelsaenger, T. (1985). Recent progress in modelling and simulation of three-dimensional tumour growth and treatment. Biosystems, 18(1), 79-91, https://doi.org/10.1016/0303-2647(85)90061-9.

10. Miklavčič, D., Jarm, T., Karba, R., & Serša, G. (1995). Mathematical modelling of tumour growth in mice following electrotherapy and bleomycin treatment. *Mathematics and computers in simulation*, *39*(5-6), 597-602, https://doi.org/10.1016/0378-4754(95)00123-6.

11. Ansarizadeh, F., Singh, M., & Richards, D. (2017). Modelling of tumour cells regression in response to chemotherapeutic treatment. *Applied Mathematical Modelling*, *48*, 96-112, https://doi.org/10.1016/j.apm.2017.03.045.

12. Morales-Delgado, V. F., Gómez-Aguilar, J. F., Saad, K., & Escobar Jiménez, R. F. (2019). Application of the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives to mathematical model of cancer chemotherapy effect. *Mathematical Methods in the Applied Sciences*, *42*(4), 1167-1193, https://doi.org/10.1002/mma.5421.

13. Padi, T. R., Jayabharathiraj, J., Kumar, B. N., Usha, C. L., & Reddy, P. R. (2014). Stochastic Modelling of Tumour Growth within Organ during Chemotherapy Using Bivariate Birth, Death and Migration Processes. IOSR Journal of Mathematics, 10(3), 01-08

14. Zhu, Q., Zhang, A., Liu, P., & Xu, L. X. (2012). Study of tumour growth under hyperthermia condition. Computational and mathematical methods in medicine, 2012, doi: 10.1155/2012/198145.

15. Stanculeanu, D. L., Daniela, Z., Lazescu, A., Bunghez, R., & Anghel, R. (2016). Development of new immunotherapy treatments in different cancer types. *Journal of Medicine and Life*, *9*(3), 240-248, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5154307.

16. Shannon J, Ray R, Wu C, Nelson Z, Gao DL, Li W, Hu W, Lampe J, Horner N, Satia J, Patterson R. (2005). Food and botanical groupings and risk of breast cancer: a case-control study in Shanghai, China. Cancer Epidemiology Biomarkers & Prevention. 14(1):81-90. https://web.archive.org/web/20200319112457id_/https://cebp.aacrjournals.org.

17. Peer PG, Van Dijck JA, Verbeek AL, Hendriks JH, Holland R. (1993). Age-dependent growth rate of primary breast cancer. Cancer. 71(11):3547-51. https:// doi/pdf/10.1002/1097-0142(19930601)71.

18. Mukhopadhyay B, Bhattacharyya R. (2009). A nonlinear mathematical model of virus-tumor-immune system interaction: deterministic and stochastic analysis. Stochastic Analysis and Applications. 27(2):409-29. https://doi.org/10.1080/07362990802679067.

19. Sanga S, Sinek JP, Frieboes HB, Ferrari M, Fruehauf JP, Cristini V. (2006). Mathematical modeling of cancer progression and response to chemotherapy. Expert review of anticancer therapy.6(10):1361-76. https://doi.org/10.1586/14737140.6.10.1361.

20. Wang Z, Deisboeck TS (2014). Mathematical modeling in cancer drug discovery. Drug discovery today. 19(2):145-50. https://doi.org/10.1016/j.drudis.2013.06.015.

21. Hawkins-Daarud, A., Rockne, R. C., Anderson, A. R., & Swanson, K. R. (2013). Modeling tumour-associated edema in gliomas during anti-angiogenic therapy and its impact on imageable tumour. *Frontiers in oncology*, *3*, 66, https://doi.org/10.3389/fonc.2013.00066.