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Mathematical Modeling of Cancer Chemotherapy

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Abstract

The complexity of the tumor system presents a formidable challenge in developing an optimal cancer treatment. Mathematical modeling and computer simulation are increasingly being utilized to predict tumor growth and investigate the efficacy of cancer therapeutic strategies, such as chemotherapy, in suppressing its growth. Along with laboratory experiments, this approach has been utilized to develop an optimal treatment for individual patients. This paper presents a system of ordinary differential equations consisting of the Gompertz and exponential decay models that describe the dynamics of tumor growth and chemotherapy drug concentration. A numerical method was utilized to simulate and solve the model and was further used to examine the effectiveness of various treatment schedules and dosages in suppressing overall tumor growth. The results suggested that frequent smaller dosages of the chemotherapy drug are more efficient than less frequent larger dosages. This study illustrates the use of mathematical model as a predictive tool to help guide laboratory experiments in developing an optimal cancer treatment.

Keywords: Math model, Differential equations, Cancer, Chemotherapy, Numerical simulation

1. Introduction

According to the World Health Organization, cancer is the leading cause of death worldwide, causing about 10 million deaths annually. More than 40% of these deaths could have been prevented through routine screening, earlier detection, and effective treatment (World Health Organization, 2022).

Cancer is caused when normal cells transform into cancerous cells through uncontrollable cell division and the creation of gene mutations. Genetic factors and carcinogens interact to induce these transformations (Matthews, 2022). Groups of cancerous cells are classified as malignant tumors, meaning they can spread rapidly and invade other parts of the body through the process of metastasis. In metastasis, cancerous cells spread into surrounding tissue and organs through the lymphatic system and the bloodstream, making it more difficult to treat (Cancer Research UK, 2020).

To this date, scientists are still searching for a cure for cancer. Innovative research has fueled the development of new medications and treatments. One of the most well-known cancer treatments is chemotherapy. Paclitaxel is a specific type of chemotherapy drug that aims to eliminate cancer by preventing the cell division of cancerous cells, shrinking the malignant tumors significantly. A protein known as tubulin polymerizes into microtubules, which are responsible for cell division. Paclitaxel stabilizes and boosts the polymerization of tubulin and thus the production of microtubules. The microtubules formed by paclitaxel are exceptionally unstable and dysfunctional, promoting apoptosis or cell death of the cancerous cells (Meštrović, 2023). Although paclitaxel appears to be one of the most promising cancer therapeutic drugs, its clinical toxicity and side effects cannot be ignored, especially when given at high doses. Thus, it is important that the anticancer drug is administered strategically to ensure its efficiency while at the same time minimizing its toxicity (Rowinsky, 1993; Marupudi, 2007).

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Laboratory experiments for cancer research can be costly and are often quite challenging to perform as each experiment can only be done for a specific type of cancer and cannot be easily modified to investigate others (Errington, 2021). Interdisciplinary research that combines cancer biology, mathematical modeling, and computer simulation has been initiated and done in the last decade. Various modeling techniques, such as cellular automaton, agent-based, and Potts model, have been used to simulate cancer growth (Stott, et al., 1999; Kansal, et al., 2000; Sherratt and Chaplain, 2001; Jiang, 2005). Other math modeling works conducted by (Gevertz, 2011; Sun, et al., 2012; Hendrata and Sudiono, 2019; Lai and Friedman, 2019) focused on investigating the effect of therapeutic strategies, such as antiangiogenic treatments, chemotherapy, TKI treatment, and cell-based therapy, on tumor growth. This interdisciplinary approach has become popular as it can provide additional insights into the tumor system that would complement the experimental results and aid the development of cancer treatments.

Although computational models for cancer published in literature have been able to qualitatively mimic cancer growth and development, such models are generally extensive and may be limited in their clinical applicability as they require parameter values and input data that are impossible to obtain from experiments. Moreover, the simulation of such complex models requires large-scale computing power which may not be easily accessible. Simpler mathematical models with fewer parameters that also exhibit good agreement with experimental observations can potentially be used as a more accessible predictive tool to assess the efficacy of therapeutic drugs and help design an optimal treatment schedule.

The objective of this research is to develop a computational model for tumor growth with few but physically relevant parameters to investigate the efficacy of treatment schedules under various dosages of the chemotherapy drug paclitaxel to determine the most effective approach to reducing tumor growth. The model consists of a system of differential equations which can be simulated using a numerical method implemented in accessible software, such as Excel or Python. The simulation results suggested that frequent smaller dosages of the chemotherapy drug are more efficient than less frequent higher dosages, which agree with the observations in many clinical experiments.

This paper is organized as follows: Section 2 discusses the mathematical model that is used to illustrate the dynamics of the tumor cell population along with the chemotherapy drug (paclitaxel) concentration that influences the growth. The derivation and implementation of Euler's method that is used to obtain the numerical solution to the proposed model are also discussed in this section. The results of this study are presented and discussed in Sections 3 and 4, respectively. Section 5 concludes the paper.

2. Materials and Methods

The two main components in the proposed model are the tumor cell density and the paclitaxel drug concentration in the tumor system. Both dynamics can be represented by first order differential equations described below.

2.1 Tumor Growth Model

Several classical mathematical models have been developed and used to predict how population changes over time. The simplest of such models is the exponential growth model. In this model, the rate of change of the population is assumed to be proportional to the current population size. The differential equation for the exponential growth model is given by

$$\frac{dc}{dt} = rc,$$

where $c(t)$ represents the population size at time t and r is the growth rate of the population. Using the technique of separation of variables, one can derive the analytical solution

$$c(t) = c(0)\, e^{rt},$$

where $c(0)$ denotes the initial population size. In regard to cancer, the exponential growth model can be used to model

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the initial growth of cancer, where the cells undergo cell division continuously regardless of the tumor size. However, as nutrients and oxygen deplete over time due to cells' consumption, the growth eventually slows down, making this model physically unrealistic.

An alternative to this model is the Gompertz model. This model was first developed in 1825 by Benjamin Gompertz and later became one of the most widely used models for tumor growth (Gerlee, 2013; Laird, 1964). In the Gompertz model, the population does not grow indefinitely, but its growth slows down as population size increases. The population size eventually plateaus at a certain value known as the *carrying capacity.* One can think of the carrying capacity as the maximum population size that the environment can sustain. The Gompertz model can be described by the following differential equation

$$\frac{dc}{dt} = -rc\ln(c/K), \tag{1}$$

where $r$and K represent the growth rate and the carrying capacity, respectively. To see why this model is indeed more realistic, first note that when the tumor size is small, that is, when $c(t) < K$, the ratio $c/K < 1$ and the rate of change $dc/dt > 0$. This implies that tumor size $c(t)$ is increasing. However, as the tumor grows and reaches the carrying capacity, that is $c(t) = K$, the rate of change $dc/dt = 0$ and the tumor stops growing. Lastly, if the tumor size $c(t)$ is bigger than the carrying capacity K, the ratio $c/K > 1$, and the tumor size will decrease as $dc/dt < 0$.

2.2 Drug Decay Model

An ordinary differential equation that describes the rate of change of drug concentration over time can be employed to study how chemotherapy drug, such as paclitaxel, affects tumor growth. It is assumed that once administered intravenously, drug diffuses into the tissue and decays naturally as time progresses. A simple exponential decay model

$$\frac{dD}{dt} = -aD$$

can be used to describe the changes in drug concentration in the tumor tissue. In this equation, $D(t)$ represents the concentration of the drug at a time t and a is the decay rate. In many cancer treatments, chemotherapy drugs are administered periodically to maintain their effectiveness in suppressing cancer growth. To incorporate periodic drug administration, the exponential decay model can be modified by adding the drug injection term as follows:

$$\frac{dD}{dt} = -aD + I(t). \tag{2}$$

Here $I(t)$ denotes the amount of drug administered at each injection.

Lastly, to incorporate the effect of chemotherapy drug on tumor growth, the interaction term bcD needs to be subtracted from equation (1). Here b can be interpreted as the killing rate of the cancer cells due to the chemotherapy drug. Therefore, the tumor growth equation becomes

$$\frac{dc}{dt} = -rc\ln\left(\frac{c}{K}\right) - bcD. \tag{3}$$

2.3 Euler's Mothod

Many differential equations that model a real-life situation can be too complicated to solve analytically or do not even have an exact solution. In such cases, numerical methods, such as Euler's method, can be employed to approximate the solution to the initial value problem (IVP) of the form $y' = f(t, y), y(t_0) = y_0$.

The Euler's method computes the approximation to the solution at discrete time in the interval $[t_0, t_f]$. The method starts by dividing this time interval into n subintervals, each of which has length h. That is, $t_0 < t_1 < \cdots < t_f$, where

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$h = t_n - t_{n-1}$. Euler's method uses the tangent line to the solution curve $y(t)$ at t_0 to approximate the value $y(t_1)$. Recall that the equation of the tangent line to the curve $y(t)$ at the point $(t_0, y(t_0))$ is given by:

$$y - y(t_0) = y'(t_0)(t - t_0).$$

Evaluating this equation at t_1 gives the approximate value of $y(t_1)$:

$$y(t_1) \approx y(t_0) + y'(t_0)(t_1 - t_0).$$

Since $y'(t_0) = f(t_0, y_0)$ and $t_1 - t_0 = h$, the above equation can be written as

$$y(t_1) \approx y(t_0) + h\, f(t_0, y_0).$$

Repeating this process, the approximate value at t_2 can be obtained by

$$y(t_2) \approx y(t_1) + h\, f(t_1, y_1)$$

and in general, $y(t_n) \approx y(t_{n-1}) + h\, f(t_{n-1}, y_{n-1})$.

If y_n denotes the approximation to the actual value $y(t_n)$, Euler's formula can then be defined recursively as

$$y_n = y_{n-1} + h\, f(t_{n-1}, y_{n-1}) \tag{4}$$

2.4 Implementation

The tumor-paclitaxel model discussed in Sections 2.1 and 2.2 consists of a coupled system of two ODEs:

$$\frac{dc}{dt} = -rc \ln\left(\frac{c}{K}\right) - bcD \tag{5}$$

$$\frac{dD}{dt} = -aD + I(t) \tag{6}$$

where $I(t)$, the amount of paclitaxel drug administered periodically, is the control parameter that can be varied to test the efficacy of different dosages. For example, if a certain amount I_0 of paclitaxel is administered weekly, then $I(t) = I_0$, when $t = 7, 14, 21, \ldots$, and $I(t) = 0$ otherwise.

In the model simulation, dimensionless quantities for the parameters and variables were used to compare the relative influence of the drug concentration in suppressing tumor growth. Implementing Euler's method (4) to approximate the solution to the tumor-paclitaxel model (5)-(6) would yield the following recurrence relations:

$$c_n = c_{n-1} + h\,(-r\, c_{n-1} \ln(c_{n-1}/K) - b\, c_{n-1}\, D_{n-1}) \tag{7}$$

$$D_n = D_{n-1} + h\,(-a\, D_{n-1} + I_{n-1}) \tag{8}$$

with initial tumor volume $c(0) = c_0$ and initial drug dosage $D(0) = D_0$. The values of c_n and D_n generated by the above recurrence relations were computed using Excel.

Table 1. Parameter values used in the model simulation.

Parameters	Description	Dimensionless value used in baseline simulation
r	Tumor growth rate	0.2
K	Tumor carrying capacity	1
b	Drug killing rate	0.5
a	Drug decay rate	0.1

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Table 2. Simulation scenarios performed in this study.

Scenario	Description	Initial conditions	Dosing schedule
1	Tumor growth without chemotherapy	$c(0) = 0.1$, $D(0) = 0$	$I(t) = 0, t > 0$
2	Tumor growth under single high dose of drug	$c(0) = 0.75$, $D(0) = 0.75$	$I(t) = 0, t > 0$
3	Tumor growth under moderate drug dose administered every 3 weeks	$c(0) = 0.75$, $D(0) = 0.25$	$I(t) = \begin{cases} 0.25, for\ t = 21, 42 \\ 0, otherwise \end{cases}$
4	Tumor growth under small drug dose administered weekly	$c(0) = 0.75$, $D(0) = 0.083$	$I(t) = \begin{cases} 0.083, for\ t = 7, 14, \ldots, 56 \\ 0, otherwise \end{cases}$

Using the Euler's method with step size size $h = 0.2$ and parameter values listed in Table 1, four scenarios were simulated for a period of 60 days as shown in Table 2. The first scenario was tumor growth simulation without chemotherapy. In this simulation, the initial tumor volume $c(0) = c_0 = 0.1$, initial drug dosage $D(0) = D_0 = 0$, and the amount of drug administered $I(t) = I_n = 0$ for all n.

The second scenario was tumor growth simulation under a high dose of paclitaxel administered once. As cancer needs to reach a certain size to be detected and for chemotherapy treatment to be performed, the initial tumor volume was set to $c(0) = c_0 = 0.75$. The paclitaxel dosage was set to be $D(0) = D_0 = 0.75$ administered once at $t = 0$ and $I(t) = I_n = 0$ for all n.

The third scenario was tumor growth simulation under a moderate dose of paclitaxel administered every 3 weeks. The initial tumor volume was set to $c(0) = c_0 = 0.75$. The paclitaxel dosage was set to be $D(0) = D_0 = 0.25$ and $I(t) = 0.25$ for $t = 21, 42$ and $I(t) = 0$ otherwise. Such dosage was chosen to standardize the total amount of drug administered throughout the 60-day period in all simulation scenarios.

The last scenario was tumor growth under a small dose of paclitaxel administered weekly. Likewise, the initial tumor volume was set to $c(0) = c_0 = 0.75$. The paclitaxel dosage was set to be $D(0) = D_0 = 0.083$ and $I(t) = 0.083$ for $t = 7, 14, \ldots, 49, 56$ and $I(t) = 0$ otherwise. This dosage was chosen so that the total amount of drug administered during the 60-day period would not be higher than 0.75.

Sensitivity analysis needs to be performed to determine which parameter plays the most critical role in affecting the model output. Tumor carrying capacity $K = 1$ was used to normalize the tumor volume so that $0 \leq c(t) \leq K$ for all t. To perform sensitivity analysis of the tumor growth rate r, the simulation of tumor growth without chemotherapy (scenario 1) was done with the growth rate r modified by ±10% while keeping the other parameters at their baseline values. For the sensitivity analysis of the other two parameters, the drug killing rate b and drug decay rate a, the simulation of tumor growth under a single drug dosage (scenario 2) was performed with one parameter value increased or decreased by 10%, while keeping the other parameters at their baseline values.

3. Results

3.1 Tumor Growth Simulations

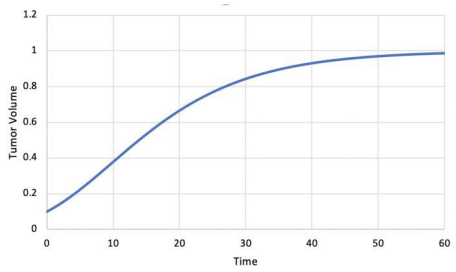

Figure 1. The Gompertz model simulation for tumor growth without chemotherapy.

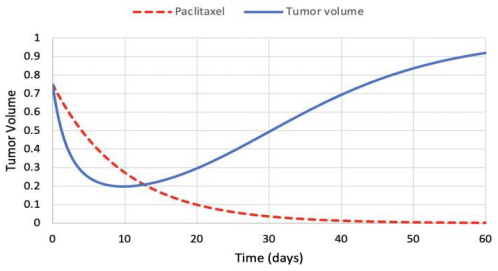

Figure 2. Tumor growth under paclitaxel treatment with a high dose administered once.

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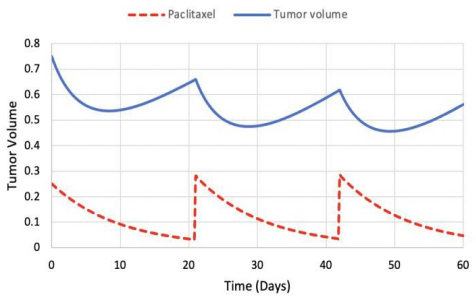

Figure 3. Tumor growth under paclitaxel treatment at a moderate dose administered every three weeks.

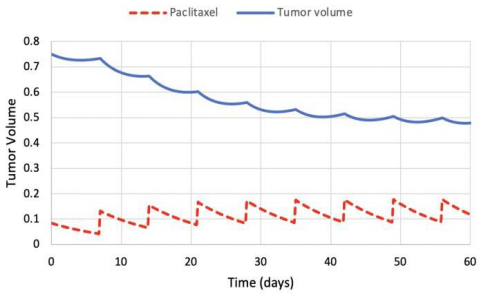

Figure 4. Tumor growth under paclitaxel treatment at a small dose administered weekly.

3.2 Sensitivity Analysis

Table 3. Sensitivity analysis of tumor growth rate r.

Percentage used	Tumor growth rate	Final tumor volume	% change
90%	0.18	0.9795	-0.84%
100%	0.2	0.9878	
110%	0.22	0.9928	0.51%

Table 4. Sensitivity analysis of drug killing rate b.

Percentage used	Drug killing rate	Final tumor volume	% change
90%	0.45	0.9269	0.84%
100%	0.5	0.9192	
110%	0.55	0.9116	-0.83%

Table 5. Sensitivity analysis of drug decay rate a.

Percentage used	Drug decay rate	Final tumor volume	% change
90%	0.09	0.8951	-2.62%
100%	0.1	0.9192	
110%	0.11	0.9361	1.84%

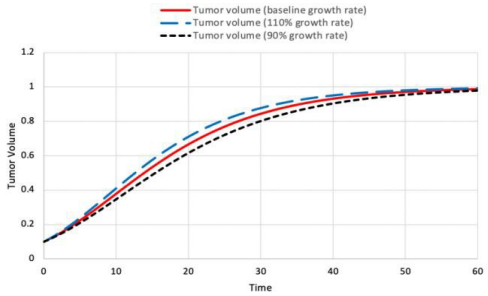

Figure 5. Sensitivity analysis plot for tumor growth rate r.

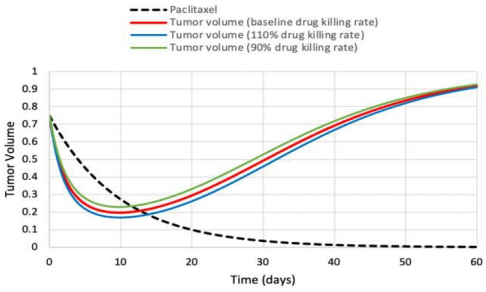

Figure 6. Sensitivity analysis plot for drug killing rate b.

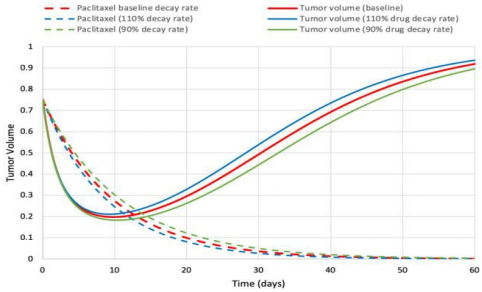

Figure 7. Sensitivity analysis plot for drug decay rate a.

4. Discussion

In all four simulation scenarios described in Section 2, Euler's method was employed to solve the model by computing the equations (7)-(8) recursively with the given initial conditions c_0 and D_0.

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In the first simulation without chemotherapy (Figure 1), the initial conditions $c(0) = c_0 = 0.1$ and $D(0) = D_0 = 0$. This corresponds to a relatively small tumor that can quickly grow due to uncontrollable cell division and plenty of nutrients and oxygen in the tumor tissue. As the tumor volume got bigger, nutrients eventually started to deplete and competition among tumor cells increased. The growth eventually slowed down, and the tumor size reached its carrying capacity $c(t) \approx K = 1$, as shown in Figure 1.

In the second simulation (Figure 2), the effect of a single dose of paclitaxel in reducing tumor size was simulated. As cancer needs to reach a certain size to be detected and for chemotherapy treatment to be performed, the initial tumor volume was set to $c(0) = c_0 = 0.75$. A high dosage of paclitaxel $D(0) = D_0 = 0.75$ was administered once at the beginning of the simulation. Figure 2 showed that paclitaxel can reduce the tumor volume from 0.75 to 0.2 in about 10 days. However, as paclitaxel concentration decreased, its efficacy significantly decreased and the tumor could grow again, reaching a volume that is greater than 0.9 at the end of 60 days.

The third and fourth simulations were performed to investigate whether a repeated dose of paclitaxel is needed to suppress tumor growth for a longer period. Starting with the same initial tumor volume of 0.75 as in the previous scenario, Figure 3 showed the simulation result when paclitaxel was administered in a moderate dose of 0.25 every 3 weeks. During the 60-day period, the drug was administered three times (day 0, day 21, and day 42). The dosage of 0.25 was chosen so that the total dosage of drug administered during the 60-day period would be 0.75, which was consistent with the second simulation scenario. It showed that although the tumor size fluctuated and got smaller rather slowly, this chemotherapy regimen could reduce the tumor volume to below 0.6 by the end of 60 days. However, this 3-weekly treatment schedule was still partially ineffective because the growth of the tumor drastically increased every 20 days.

In the last scenario (Figure 4), a weekly administration of paclitaxel at a small dose of 0.083 was simulated. This dosage was chosen so that the total amount of drug administered during the 60-day period would not be higher than 0.75. As shown in Figure 4, the tumor size in general decreased steadily and was around 0.5 at the end of 60 days. Moreover, the fluctuations in tumor size, although still visible, were not as prominent as in the previous scenario, making this treatment schedule by far the most effective. These results were in alignment with those analyses obtained through laboratory experiments performed in (Lin, et al., 2022).

Since the parameters used in the model were estimated, there was a degree of flexibility and uncertainty in their values which remained to be explored. Sensitivity analysis can help determine which model parameter is the most important in controlling the model output. This can help determine where future research and efforts in laboratory experiments would be most beneficial in suppressing tumor growth.

Table 3 and Figure 5 showed that when the tumor growth rate r was varied by ±10% from the baseline value of 0.2 while all other parameters remained fixed, the changes in final tumor volume were less than 1%. Likewise, Table 4 and Figure 6 showed that when the drug killing rate b was increased or decreased by 10% from its baseline value of 0.5, the changes in final tumor volume were also less than 1%. However, when the drug decay rate a was varied by ±10% from its baseline value of 0.1, the final tumor volume changed by more than 2%, as shown in Table 5 and Figure 7. This indicated that the drug decay rate is the parameter that affected the result the most. Periodic drug administration is a way to prevent the drug concentration from being too low due to drug decay. This aligns with the simulation result that suggested that more frequent administration is the most effective in suppressing tumor growth.

5. Conclusion

In this project, a system of ordinary differential equations consisting of the Gompertz model and the exponential decay model were employed to describe the dynamics of tumor growth and chemotherapy drug concentration in the tumor tissue, respectively. Euler's method was implemented to numerically solve the system and simulate the growth of the tumor with and without chemotherapy treatment. The treatment using paclitaxel with different dosages and schedules were simulated to examine their efficacies in suppressing the overall growth of the tumor. The simulation results suggested that weekly administration of paclitaxel with a small dosage is more efficient than either one-time administration with a high dosage or 3-weekly administration with a medium dosage.

The model presented in this study can be applied to any type of cancer and chemotherapy drug if the parameter

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values specific to the cell type and drug are adjusted accordingly. Techniques, such as the least squares method, can be performed to estimate these parameter values from the available experimental data to obtain a more accurate and reliable prediction for how a chemotherapy drug affects a specific type of cancer. This project illustrated how mathematical modeling and computer simulation can be used as a tool to investigate the effectiveness of certain treatment regimens and can potentially help develop an optimal treatment strategy.

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