Modeling the Growth of Cancerous Tumors

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1 Introduction

Cancer is one of the leading causes of death in America. Nearly 2 million people have been diagnosed with cancer in the last year [1]. Mathematical modeling has become a useful tool in understanding the growth of cancer and how well certain remedies, like chemotherapy, reduce the growth of said cancer. The paper "Model-based Tumor Growth Dynamics and Therapy Response in a Mouse Model of *De Novo* Carcinogenesis" looks into using a Gompertz growth model to model the growth of cancerous tumors in mice and a two-compartment pharmacokinetic/pharmacodynamic model to describe the effects of therapy in mice treated with 5-Fluorouracil (5-FU) [5]. This project recreates the models used in the paper and tests them on a similar set of data provided by Dr. Wang of Union College .

2 Experiment Info

2.1 Goals and Reasoning

Tumor growth is complex and has many parameters that are specific to type, tissue, initial growth, immune system, and more. Mathematical modeling helps determine cancer growth using pre-existing biological knowledge.

Currently, many of the studies conducted on cancer growth using mathematical modelling don't have validating clinical or experimental data for their models. For the studies that do, they use experimental data taken from xenograft mice. This process has two main drawbacks: (1) the tumors are transplanted, meaning the critical information of tumor initiation and starting growth is lost, and (2) they are immunodeficient, meaning they are incapable of initiating an immune response, which is a critical piece in fighting cancer [5].

The research paper's goal was to use mice that didn't fall into this category and show that a Gompertz growth model adequately modeled the growth of *in vivo* tumors in mouse models of *de novo* carcinogenesis both with and without treatment [5]. Another new idea implemented was to use the doubling rate of each mouse's tumors so that the model would become more accurate. Our goals are to reproduce these models and use them on the data we have and analyze whether or not

they perform well.

2.2 Background

This particular research avoided the aforementioned drawbacks by using immunocompetent E6/E7 double transgenic mice that were treated with DMBA/TPA. This means that the response of their immune system was taken into account, and the cancer was initiated by 12-dimethylbenzanthracene (DMBA), a polycyclilc aromatic hydrocarbon (PAH) and a carcinogen that initiates and promotes tumorigenesis [2]. DMBA was then paired with 12-O-tetradecanoylphorbol 13-acetate (TPA), a tumor promoter that stimulates cell proliferation [6]. This allows for *de novo* carcinogenesis capturing the critical tumor initiation. The researchers then based their models on the idea of tumor progression and maintanence *in vivo*.

2.3 Experiment Process

The experiment started with creating two groups of the E6/E7 mice, a DMBA/TPA treatment group and a non-DMBA/TPA treatment group. The non-treated group had no tumors while the DMBA/TPA group developed cancerous tumors.

From the DMBA/TPA group the mice were split into therapy treatment and no treatment. Three tumors were selected randomly at the beginning of the experiment to monitor on each mouse and were measured twice a week once visible. These measurements were of the length and width of the tumor and conducted three times each measurement session. Once the tumors reached a length of 3mm, 50mg/kg or 100mg/kg of 5-FU were given to the therapy treatment group. Once any of the tumors on a mouse was measured to be over 1cm, the mouse was euthanized.

From these measurements, the volume of each tumor was estimated. The researchers then modeled the growth of the tumors by taking the initial volume and compared their models to the actual data.

It is important to note that we deviated from the paper by using the formula for the volume of an ellipsoid to estimate the volume of the tumors:

$$V = \frac{4}{3}\pi r_1 r_2 r_3$$

Note: The third radius was computed by averaging the distance of the length and width measurements.

While the paper used the following to calculate the volume of the tumors:

$$V = \frac{\pi}{6}(xy)^{\frac{3}{2}}$$

Here is a pictorial breakdown of the experiment:

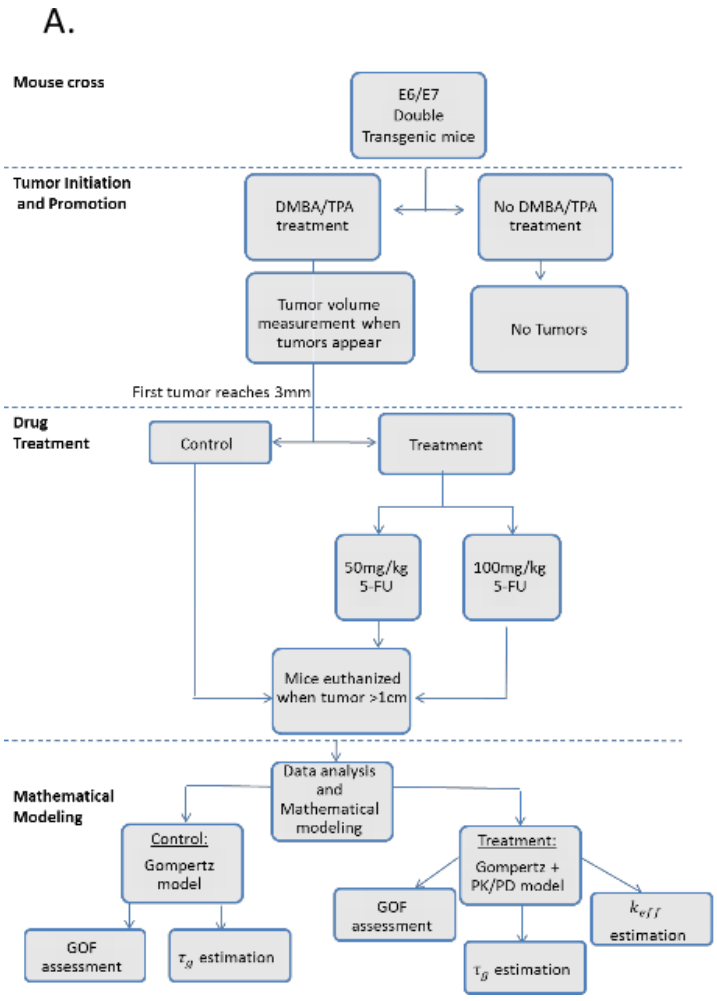

Figure 1: Experiment Process

3 Mathematical Model

3.1 Gompertz Growth Model

The model used is a Gompertz growth model which was previously used in "Clinically relevant cancer chemotherapy dose scheduling via mixed-integer optimization" [3].

$$\frac{dT(t)}{dt} = \frac{1}{\tau_g} \ln \left[\frac{\ln(\theta_g/T_0)}{\ln(\theta_g/2T_0)} \right] T(t) \ln \left(\frac{\theta_g}{T(t)} \right) - L(T(t), C_2(t))$$

with the following parameters:

- $T(t)$, tumor volume (mm^3) at time t
- θ_g, plateau size (mm^3)
- τ_g, tumor doubling time (days)
- T_0, initial tumor size (mm^3)

The first term on the RHS represents the increase in cells due to proliferation (rapid reproduction of cells). The second term on the RHS, $L(T(t), C_2(t))$, describes the decrease in cells due to therapy. Note: When L = 0, the equation represents an untreated cancer cell growth model.
$L(T(t), C_2(t))$ is a function of drug concentration at the tumor site, $C_2(t)$:

$$L(T(t), C_2(t)) = k_{eff}(C_2(t) - C_{2,thr})H(C_2(t) - C_{2,thr})T(t)$$

with the following parameters:

- $C_2(t)$, drug concentration in tumor site (ng/ml)
- $C_{2,thr}$, therapeutic threshold under which drug has no effect (ng/ml)
- k_{eff}, drug kill rate (ml/(days·ng))

- Heaviside function:

$$H(C_2(t) - C_{2,thr}) = \begin{cases} 0, \text{if } C_2(t) < C_{2,thr} \\ 1, \text{if } C_2(t) \geq C_{2,thr} \end{cases} \tag{1}$$

$L(T(t), C_2(t)) = 0$ if the drug amount in the tumor site is below a certain threshold. After the threshold is reached, the remaining amount is multiplied by a drug kill rate and the current tumor volume.

3.2 Pharmacokinetic/Pharmacodynamic Model

Pharmacokinetic refers to the movement of drugs within the body and pharmacodynamic refers to the effects of drugs and the mechanism of their action [9], [8]. To model these types of interactions we assume that the body is a well-mixed tank meaning that all spatial derivatives go to 0, making our model turn into a system of ordinary differential equations. We use a 2-compartmental model since it describes the kinetic behavior of the drug and it's corresponding concentration profile. The two ODEs are as follows:

$$\frac{dC_1(t)}{dt} = k_{21}C_2(t)\frac{V_2}{V_1} - k_{10}C_1(t) + \frac{d(t)}{V_1}$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t)\frac{V_1}{V_2} - k_{21}C_2(t)$$

with the following parameters:

- $C_1(t)$, drug concentration in the plasma (blood) (ng/ml)
- $C_2(t)$, drug concentration in the tumor site (ng/ml)
- V_1, distributed volume of the drug after injection in plasma (blood) (ml)
- V_2, distributed volume of the drug after injection in tumor site (ml)
- k_{21} rate constant of drug moving from tumor site to plasma (1/days)
- K_{12} rate constant of drug moving from plasma to tumor site (1/days)

- k_{10} other elimination processes (1/days)
- $d(t)$ drug dosage (ng/days)

It is important to note that the value of $C_{2,thr}$ and the function $d(t)$ were not mentioned in the paper. Because of this, we researched values for $C_{2,thr}$ for our specific drug and created a function $d(t)$ accounting for the drug injection based on time. These two will be explained in further detail in the following section.

4 Simulations

4.1 Untreated Growth

In this portion we will be investigating the growth of the mouse CM37. The mouse was in the DMBA/TPA group but was not given 5-FU therapy therefore this mouse falls into the category of untreated cancer cell growth. The model used for this type needs θ_g, τ_g, and T_0. The research paper states the following parameters for the three tumors of CM37 ($T_{0,i}$ are determined by the data set):

- $\theta_g = 10^6\ mm^3$, (this is the same for all mice)
- $\tau_{g,1} = 6.650\ days$
- $\tau_{g,2} = 8.256\ days$
- $\tau_{g,3} = 9.868\ days$
- $T_{0,1} = 1.05734512817826\ mm^3$
- $T_{0,2} = 1.64845213386851\ mm^3$
- $T_{0,3} = 0.848010046805851\ mm^3$

The figures produced are shown below in order from CM37 tumor 1 to tumor 3.
The code for these models can be found in the appendix (A.1).

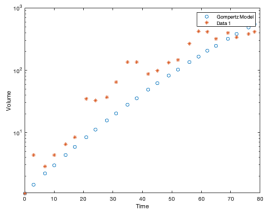

Figure 2: CM37 T1 Personal Gompertz Model

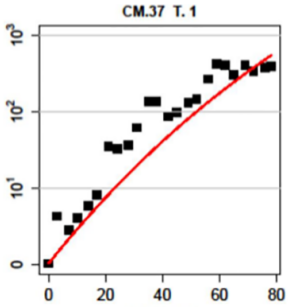

Figure 3: CM37 T1 Paper Gompertz Model

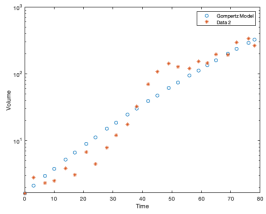

Figure 4: CM37 T2 Personal Gompertz Model

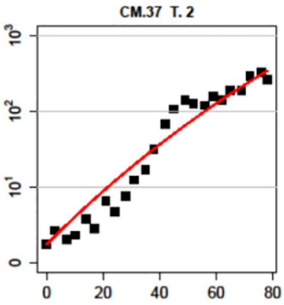

Figure 5: CM37 T2 Paper Gompertz Model

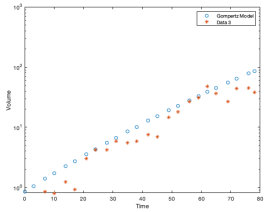

Figure 6: CM37 T3 Personal Gompertz Model

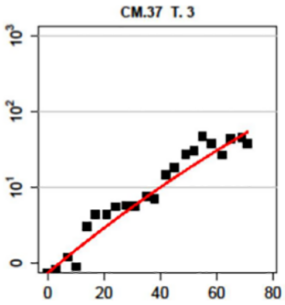

Figure 7: CM37 T3 Paper Gompertz Model

Note: Variance between personal and paper in model 3 may be due to different initial volumes.

4.2 Growth with Chemotherapy Treatment

For the chemotherapy treatment model we will be investigating the growth of the mouse CM41. This mouse was treated with DMBA/TPA and after the tumors reached 3mm in length/width 5-FU was given weekly based on the weight of the mouse at the specific time of injection. The

parameters needed for the model are as follows:

- $\theta_g = 10^6\ mm^3$, (this is the same for all mice)
- $\tau_{g,1} = 7.373\ mm^3$
- $\tau_{g,2} = 6.574\ mm^3$
- $\tau_{g,3} = 3.704\ mm^3$
- $T_{0,1} = 0.878996389635191\ mm^3$
- $T_{0,2} = 1.69648563110085\ mm^3$
- $T_{0,3} = 0.904771702916853\ mm^3$
- $k_{eff,1} = 5.02 \cdot 10^{-5}\ ml/(days \cdot ng)$
- $k_{eff,2} = 7.52 \cdot 10^{-5}\ ml/(days \cdot ng)$
- $k_{eff,3} = 1.16 \cdot 10^{-4}\ ml/(days \cdot ng)$
- $C_{2,thr,opt1} = 10 \cdot 10^3\ ng/ml$
  This estimation was taken from [3].
- $C_{2,thr,opt2} = 20 \cdot 10^3\ ng/ml$
  This estimation was taken from [7].
- $k_{10} = 151.2\ (1/days)$
- $k_{12} = 5.62\ (1/days)$
- $k_{21} = 2.31\ (1/days)$
- $V_1 = 0.71 \cdot 10^3\ ml$
- $V_2 = 0.1 \cdot 10^3\ ml$
- Dosage $= 50mg/kg$ for all tumors

- $d(t) = \chi_E(x)$ where E = Set of days that injections were given. (Characteristic function)

Since there are two estimation of the $C_{2,thr}$, two series of simulations were ran for this model. For $d(t)$ there was no explanation of the function in the paper so we decided to create a characteristic function that became activated only on the days of the injections. These dates and the corresponding weights of the mice on these dates can be found in the code of the appendix (A.2). Because of this, we must iteratively use ODE45 in our code to run from the start of each new injection date. Note that injection dates and weights (of mouse) are the same for all three tumors.

4.2.1 Models using Paper's Parameters

This section shows the simulations with the paper's given parameters compared to the paper's findings. Note that the $C_1(t)$ and $C_2(t)$ models are the same for each tumor as their ODEs are not affected by $\frac{dT(t)}{dt}$. The code for the models can be found in the appendix (A.2).

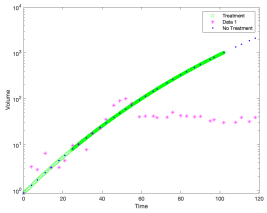

Figure 8: CM41 T1 Personal PK/PD Model Paper's Parameters

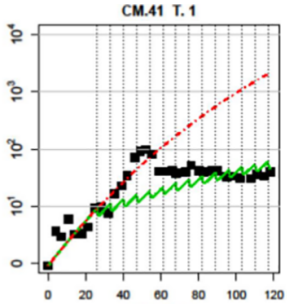

Figure 9: CM41 T1 Paper PK/PD Model

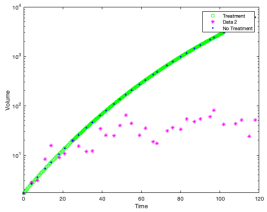

Figure 10: CM41 T2 Personal PK/PD Model Paper's Parameters

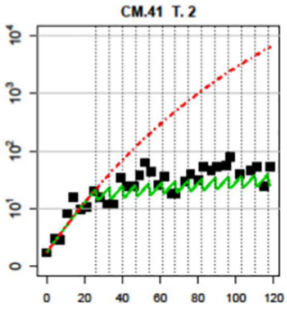

Figure 11: CM37 T2 Paper PK/PD Model

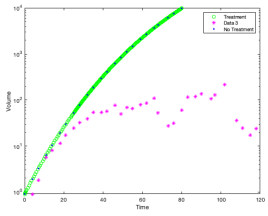

Figure 12: CM41 T3 Personal PK/PD Model Paper's Parameters

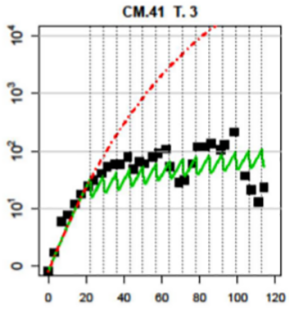

Figure 13: CM37 T3 Paper PK/PD Model

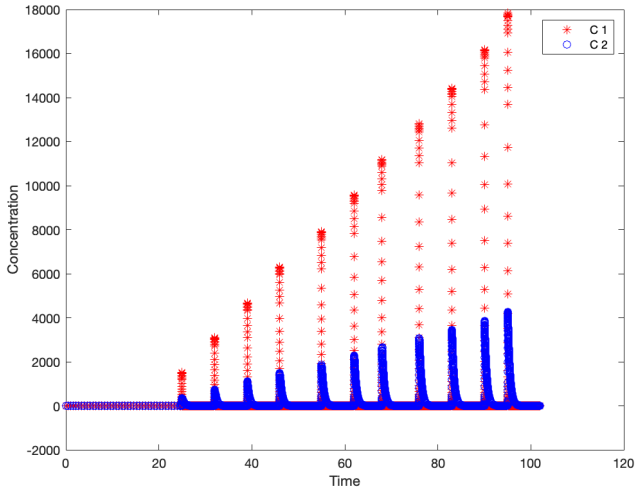

Figure 14: $C_1(t)$, $C_2(t)$ Model vs time $t(days)$ with Paper's Parameters

The models with the current parameters do not fit the figures of the paper. We see that our therapy term is never activated, because of this we have neglected to put in graphs using the parameter $C_{2,thr,2} = 20 \cdot 10^3\ ng/ml$ since the graphs with this parameter would be identical to those shown. Since these parameters seem to be non satisfactory, we decided to change the following parameters to fit the graph as desired.

4.2.2 Models using New Parameters

The previous section seemed to have problems with creating a well-activated therapy term. This brings us into investigation two parameters:

- k_{10} other elimination processes (1/days)
- $C_{2,thr}$, therapeutic threshold under which drug has no effect (ng/ml)

The k_{10} parameter accounts for the natural depletion of 5-FU and it seems to be depleting the chemotherapy too quickly.
The $C_{2,thr}$, the activation threshold, also seems to be too high as the amount of 5-FU after reaching the baseline activation requirement in the tumor site is insufficient to create any real therapy effect.

To combat these problems, we have chosen the following parameters for each tumor:

- $k_{10,1} = 22\ (1/days)$
- $C_{2,thr,1} = 10\ ng/ml$
- $k_{10,2} = 24\ (1/days)$
- $C_{2,thr,2} = 10\ ng/ml$
- $k_{10,3} = 22\ (1/days)$
- $C_{2,thr,3} = 10\ ng/ml$

CM41 Tumor 1:

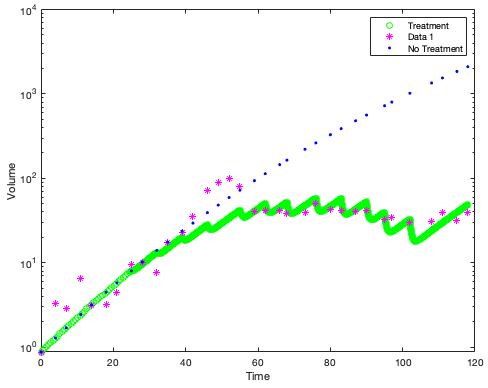

Figure 15: CM41 T1 Personal with New Parameters

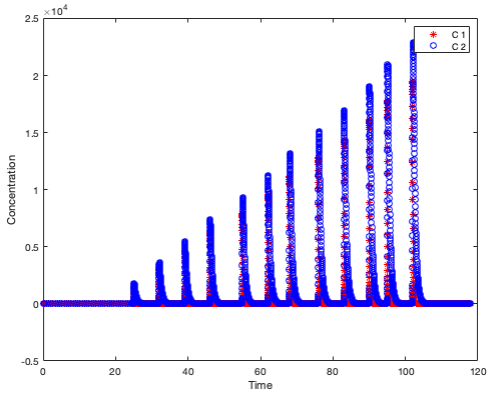

Figure 16: $C_1(t)$, $C_2(t)$ T1 Model vs time $t(days)$ with New Parameters

CM41 Tumor 2:

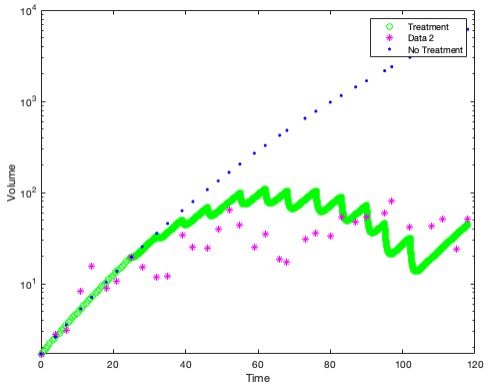

Figure 17: CM41 T2 Personal with New Parameters

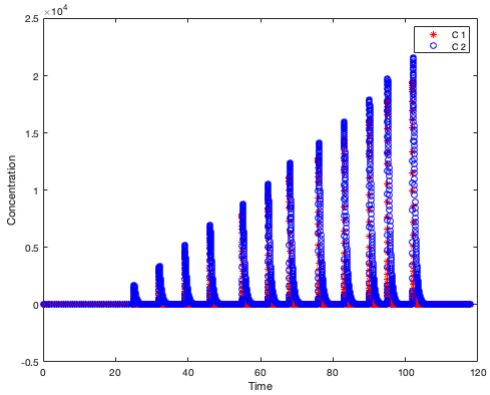

Figure 18: $C_1(t)$, $C_2(t)$ T2 Model vs time $t(days)$ with New Parameters

CM41 Tumor 3:

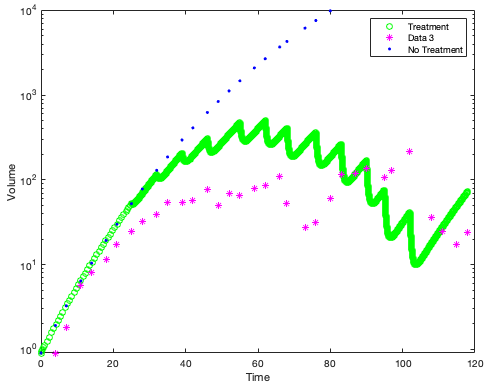

Figure 19: CM41 T3 Personal with New Parameters

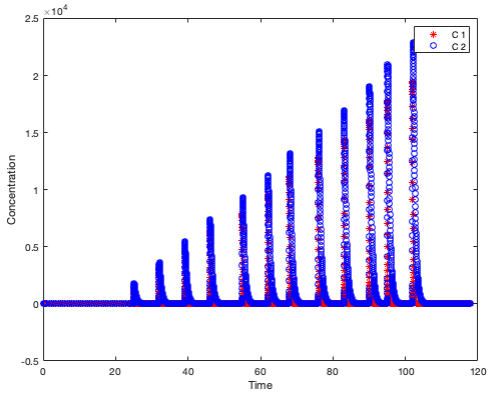

Figure 20: $C_1(t)$, $C_2(t)$ T3 Model vs time $t(days)$ with New Parameters

The code for the models can be found in the appendix (A.2).

5 Findings and Concluding Thoughts

5.1 Analysis of Models

The Gompertz growth model performs very well when it come to untreated cancer growth. The models produced in **4.1** perform adequately and gives a good estimation to the growth of the tumor with just the initial volume, plateau size, and tumor doubling time.

The Gompertz model coupled with the pharmacokinetic/pharmacodynamic model produces results that are not satisfactory when used with the parameters given in the research paper [5]. When parameters are adjusted, the system creates models that follow the trends of cancerous tumor growth with a chemotherapy treatment element. This discrepancy suggests further research into parameters and how they differ between mice. The experiment found that chemotherapy treatment is very specific to each patient and that a mathematical model holds well for intra-mouse variability but suffers when looking at inter-mouse variability as cancer is very specific to each mouse. This said, it is much harder and ineffective to create a blanket model for all mice affected by the specific cancer as the growth of the tumors is highly variable for each mouse, therefore specific growth models for each patient perform much better.

5.2 Possible Future Research

Future research options include looking into the parameters of the pharmacokinetic/pharmacodynamic model and seeing which values can be changed to find a better fitting model. Another interesting option is to try to construct a system of ODEs based off of fibroblast cell growth activation as it's been recently found that they can provide oncogenic signals to old or damaged cells resulting in cancerous tumors [4]. Lastly, more analysis of the growths of other mice can be done from the given data set.

A Appendix

A.1 Code for 4.1

```
clear vars; close all; format long;
% 12/13/23 UMASS Fall 2023 - Math 690 Cell Bio
% Modeling growth of Chinese Hamster V79 Fibroblast tumors in mice
% Gompertz Growth Model (with NO treatment term)from:
% "Model-Based Tumor Growth Dynamics and Therapy Response in a Mouse Model
% of De Novo Carcinogenesis"

% Parameters:
Time_CM37 = [0 3 7 10 14 17 ...
             21 24 28 31 35 38 ...
             42 45 49 52 56 59 ...
             62 65 69 72 76 78];

Volume_CM37_1 = [1.05734512817826 4.29427945618071 2.82813710498522...
                 4.30311514673383 6.42532492146200 8.40385808679081...
                 34.7400876687410 32.9032352318492 36.8464703905686...
                 64.4300841127476 134.377518590330 134.535474785537...
                 87.7878261903194 97.3210180119256 132.128260248874...
                 147.772649317043 265.707876574662 420.251808038243...
                 412.169458216514 317.361302313402 401.904398274764...
                 336.657719556933 381.773221679249 413.379479569847];

Volume_CM37_2 = [1.64845213386851 2.80387144332889 2.34896097310745...
    2.51716727369388 3.84278385838863 3.08751490662487...
    6.77988541741200 4.46657543166296 7.84237501991580...
    12.1591829727632 17.4407196334331 32.3509985508928...
    69.8816094818062 108.588856856017 143.466037519508...
    126.673962288551 120.313125886687 155.247129118280...
    146.129096264207 195.686202345380 192.095110498560...
    298.358981154917 336.839192260304 267.331042475290];


Volume_CM37_3 = [0 0 0.848010046805851 ...
    0.806274919245178 1.24342241735973 0.927136642840116...
    3.04225543570564 4.17683586296306 4.19925054477001...
    5.85465950285933 5.49397953348599 5.88577224631160...
    7.60478678132267 6.96940542672067 14.8190770864626...
    18.0395109165764 26.7638933681529 30.8522663259214...
    47.9143459314166 37.0036567210430 27.0261948290002...
    44.1492645385703 45.3293852602236 38.0922949627555];
```

```
% Plateau size (mm^3)
theta_g = (10^6);

% Tumor doubling time (days)
tau_g = 6.650;

% Initial tumor size (mm^3)
T_o = 1.05734512817826;

%%
v1 = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) )).*...
    x .* log(theta_g/x));
[t1, za] = ode45(v1,Time_CM37,T_o);
figure
% plot(t1,za(:,1),'o')
sem1 = semilogy(t1,za(:,1),'o');
hold on
% plot(Time_CM37,Volume_CM37_1,'*')
sem2 = semilogy(Time_CM37,Volume_CM37_1,'*');
ylim([0 10^3])
xlabel('Time')
ylabel('Volume')
% legend('Gompertz','Data 1')
legend([sem1(1),sem2(1)],'Gompertz Model', 'Data 1')

%%
tau_g = 8.256;
T_o = 1.64845213386851;
v2 = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) )).*...
    x .* log(theta_g/x));
[t2, zb] = ode45(v2,Time_CM37,T_o);
figure
% plot(t2,zb(:,1),'o')
sem11 = semilogy(t2,zb(:,1),'o');
hold on
% plot(Time_CM37,Volume_CM37_2,'*')
sem22 = semilogy(Time_CM37,Volume_CM37_2,'*');
ylim([0 10^3])
xlabel('Time')
ylabel('Volume')
%legend('Gompertz','Data 2')
legend([sem11(1),sem22(1)],'Gompertz Model', 'Data 2')

%%
```

```
tau_g = 9.868;
T_o = 0.848010046805851;
v3 = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) )).*...
    x .* log(theta_g/x));
[t3, zb] = ode45(v3,Time_CM37,T_o);
figure
% plot(t3,zb(:,1),'o')
sem111 = semilogy(t3,zb(:,1),'o');
hold on
% plot(Time_CM37,Volume_CM37_3,'*')
sem222 = semilogy(Time_CM37,Volume_CM37_3,'*');
ylim([0 10^3])
xlabel('Time')
ylabel('Volume')
% legend('Gompertz','Data 3')
legend([sem111(1),sem222(1)],'Gompertz Model', 'Data 3')
```

A.2 Code for 4.2.1 and 4.2.2

Note that each section uses the same code with different parameters.

```
    clear vars; close all; format long;
% 12/13/23 UMASS Fall 2023 - Math 690 Cell Bio
% Modeling growth of Chinese Hamster V79 Fibroblast tumors in mice
% Gompertz Growth Model (with treatment term)from:
% "Model-Based Tumor Growth Dynamics and Therapy Response in a Mouse Model
% of De Novo Carcinogenesis"
% System of ODEs

% Parameters:

% CM41 Tumor 1:

Volume_CM41_1 = [0.878996389635191 3.26805804763647 2.86878227442802...
    6.44116832227991 3.16520676444380 3.20800592228668...
    4.47244344192618 9.57806441120787 10.1901846574933...
    7.74757395154267 17.5623284743031 22.8521576984554...
    35.4933509463060 71.9319223184681 89.5046952308661...
    100.582502858711 79.6921542704108 40.4972376625088...
    41.6744219258733 41.9782627853019 38.5713314682931...
    39.7470244059893 50.4665632368223 43.1484215748283...
    41.8766525281702 40.4240740420417 41.3200673205974...
    32.7717433865195 34.7679350175181 30.3386451516282...
    30.5971711744152 39.2034816172807 31.7746126411338...
```

```
    39.0625034226527];


% CM41 Tumor 2:
Volume_CM41_2 = [1.69648563110085 2.78219073065005 3.10395218480958...
    8.27956522041937 15.4445405494125 8.94011893522412...
    10.6922868720414 19.8280523682773 15.0212111138742...
    11.8900642558576 12.1712682142805 34.2409638779540...
    25.1102895459313 24.5192148870098 40.3031735139597...
    64.4058616770791 44.3150529569737 24.9396016392516...
    34.6410701369982 18.7680141388856 17.2785338654939...
    30.9232394806072 36.3593895461532 33.0243362788696...
    54.3045864381805 47.5225233540683 54.0691128792942...
    58.9960941054689 79.9931659511220 41.3796578063600...
    43.4792883147328 50.6755557100626 23.9702681710860...
    51.7423058939811];


% CM41 Tumor 3:
Volume_CM41_3 = [0 0.904771702916853 1.81109989046063...
    5.73619975955862 7.99458722019968 11.5063260242119...
    17.3674785785247 24.2777044281663 31.9035036355972...
    38.9470877081004 53.8453901180553 54.7580402372157...
    57.6783823302744 77.5769225547427 49.3517682692090...
    68.4838627442720 65.0850436400562 79.0961122299053...
    85.1360971147118 110.060247955264 52.9086335112664...
    27.2263283600231 31.2106199653273 60.0860519906288...
    116.690395312355 117.957510554918 135.519082118710...
    107.372291972430 129.887215950477 215.132521710182...
    36.1781784094593 24.8450430940743 17.2557170598273...
    24.2385095691543];


CM41_total_time = [0 4 7 11 14 18 ...
                   21 25 28 32 35 39 ...
                   42 46 49 52 55 59 ...
                   62 66 68 73 76 80 ...
                   83 87 90 95 97 102 ...
                   108 111 115 118];

CM41_inj_time = [25, 32, 39,...
                 46, 55, 62,...
                 68, 76, 83,...
                 90, 95, 102];
```

```
CM41_inj_weight = [ 21.74 22.01 22.75...
                23.26 22.72 23.55...
                22.87 23.14 22.90...
                24.88 23.63 23.58];

Drug_amount = 50; %(mg)
%ODE Parameters:

% ODE 1:

% Plateau size (mm^3)
theta_g = (10^6);

% Tumor doubling time (days)
tau_g = 7.373;

% Initial tumor size (mm^3)
T_o = 0.878996389635191;

% Drug killing rate
K_eff = 5.02*(10^(-5));

% ODE 2 and 3:

% Other elimination processes
% K_10 = 151.2; % given in paper
K_10 = 22; % Amount for T1

% Rate corresponding to drug concentration in plasma(blood)
K_12 = 5.62;

% Rate corresponding to drug concentration in area of drug action(tumor)
K_21 = 2.31;

% Distributed volume of drug after injection in plasma
V_1 = 0.71*(10^3);

% Distributed volume of drug after injection in tumor site
V_2 = 0.1*(10^3);

% Concentration threshold:
% C_thresh = 10*10^(3); %(ng/ml) First Reccomendation
% C_thresh = 20*10^(3) %(ng/ml) First Reccomendation
C_thresh = 10; % Amount for T1
```

```
%% TUMOR 1
% ODE45 Iterative Loop
t_tracker = [];
T_new = T_o;
t_start = 0;
ST = CM41_inj_time;
final_outputs = [];
C1_new = 0;
C2_new = 0;
for i = 1:length(ST)

    dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
        )).* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*...
        heav_1(X(3), C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
    [t1, X] = ode45(dXdt,[t_start ST(i)],[T_new; C1_new; C2_new]);
    final_outputs = [final_outputs; X];
    t_start = ST(i);
    t_tracker = [t_tracker; t1];
    T_new = X(end, 1);
    C2_new = X(end, 3);
    C1_new = C1_new + (dj(CM41_inj_weight, Drug_amount, ST, ST(i))./V_1);
end
dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) ))...
    .* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*heav_1(X(3),...
    C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
[t2, X1] = ode45(dXdt,[ST(end) CM41_total_time(end)], [T_new; C1_new; C2_new]);
t_tracker = [t_tracker; t2];
final_outputs = [final_outputs; X1];


% Untreated ODE
v_no_treat = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
    )).* x .* log(theta_g/x));
[t2, x] = ode45(v_no_treat,CM41_total_time,T_o);



figure
```

```
sem1 = semilogy(t_tracker,final_outputs(:,1),'go');
hold on
sem2 = semilogy(CM41_total_time,Volume_CM41_1,'m*');
hold on
sem3 = semilogy(t2, x, 'b.');
ylim([0 10^4])
xlabel('Time')
ylabel('Volume')
legend([sem1(1),sem2(1),sem3(1)],'Treatment', 'Data 1', 'No Treatment')

figure
sem11 = plot(t_tracker,final_outputs(:,2),'r*');
hold on
sem22 = plot(t_tracker,final_outputs(:,3),'bo');
xlabel('Time')
ylabel('Concentration')
legend([sem11(1),sem22(1)], 'C 1', 'C 2')


%% TUMOR 2

tau_g = 6.574;

T_o = 1.69648563110085;

K_eff = 7.52*(10^(-5));

K_10 = 24; % Amount for T2

C_thresh = 10; % Amount for T2




% ODE45 Iterative Loop
t_tracker = [];
T_new = T_o;
t_start = 0;
ST = CM41_inj_time;
final_outputs = [];
C1_new = 0;
C2_new = 0;
for i = 1:length(ST)
```

```
    dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
        )).* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*...
        heav_1(X(3), C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
    [t1, X] = ode45(dXdt,[t_start ST(i)],[T_new; C1_new; C2_new]);
    final_outputs = [final_outputs; X];
    t_start = ST(i);
    t_tracker = [t_tracker; t1];
    T_new = X(end, 1);
    C2_new = X(end, 3);
    C1_new = C1_new + (dj(CM41_inj_weight, Drug_amount, ST, ST(i))./V_1);


end
dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) ))...
    .* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*heav_1(X(3),...
    C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
[t2, X1] = ode45(dXdt,[ST(end) CM41_total_time(end)], [T_new; C1_new; C2_new]);
t_tracker = [t_tracker; t2];
final_outputs = [final_outputs; X1];


% Untreated ODE
v_no_treat = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
    )).* x .* log(theta_g/x));
[t2, x] = ode45(v_no_treat,CM41_total_time,T_o);



figure
sem1 = semilogy(t_tracker,final_outputs(:,1),'go');
hold on
sem2 = semilogy(CM41_total_time,Volume_CM41_2,'m*');
hold on
sem3 = semilogy(t2, x, 'b.');
ylim([0 10^4])
xlabel('Time')
ylabel('Volume')
legend([sem1(1),sem2(1),sem3(1)],'Treatment', 'Data 2', 'No Treatment')

figure
sem11 = plot(t_tracker,final_outputs(:,2),'r*');
```

```
hold on
sem22 = plot(t_tracker,final_outputs(:,3),'bo');
xlabel('Time')
ylabel('Concentration')
legend([sem11(1),sem22(1)], 'C 1', 'C 2')



%% TUMOR 3

tau_g = 3.704;

T_o = 0.904771702916853;

K_eff = 1.16*(10^(-4));

K_10 = 22; % Amount for T3

C_thresh = 10; % Amount for T3




% ODE45 Iterative Loop
t_tracker = [];
T_new = T_o;
t_start = 0;
ST = CM41_inj_time;
final_outputs = [];
C1_new = 0;
C2_new = 0;
for i = 1:length(ST)

    dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
        )).* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*...
        heav_1(X(3), C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
    [t1, X] = ode45(dXdt,[t_start ST(i)],[T_new; C1_new; C2_new]);
    final_outputs = [final_outputs; X];
    t_start = ST(i);
    t_tracker = [t_tracker; t1];
    T_new = X(end, 1);
    C2_new = X(end, 3);
```

```
    C1_new = C1_new + (dj(CM41_inj_weight, Drug_amount, ST, ST(i))./V_1);


end

dXdt = @(t,X) [((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o)) ))...
    .* X(1) .* log(theta_g./(X(1))) - (K_eff.*(X(3)-C_thresh).*heav_1(X(3),...
    C_thresh).*X(1)));...
        (K_21.*X(3).*(V_2/V_1) - K_12.*X(2) - K_10.*X(2));...
        (K_12.*X(2).*(V_1/V_2) - K_21.*X(3))];
[t2, X1] = ode45(dXdt,[ST(end) CM41_total_time(end)], [T_new; C1_new; C2_new]);
t_tracker = [t_tracker; t2];
final_outputs = [final_outputs; X1];


% Untreated ODE
v_no_treat = @(t,x) ((1/tau_g).*log(( log(theta_g/T_o) / log(theta_g/(2*T_o))...
    )).* x .* log(theta_g/x));
[t2, x] = ode45(v_no_treat,CM41_total_time,T_o);



figure
sem1 = semilogy(t_tracker,final_outputs(:,1),'go');
hold on
sem2 = semilogy(CM41_total_time,Volume_CM41_3,'m*');
hold on
sem3 = semilogy(t2, x, 'b.');
ylim([0 10^4])
xlabel('Time')
ylabel('Volume')
legend([sem1(1),sem2(1),sem3(1)],'Treatment', 'Data 3', 'No Treatment')

figure
sem11 = plot(t_tracker,final_outputs(:,2),'r*');
hold on
sem22 = plot(t_tracker,final_outputs(:,3),'bo');
xlabel('Time')
ylabel('Concentration')
legend([sem11(1),sem22(1)], 'C 1', 'C 2')
```

```
%% Plotting Heaviside function piece
% func = -(K_eff.*(final_outputs(:,3)-C_thresh).*heav_1(final_outputs(:,3),...
% C_thresh).*final_outputs(:,1));
% figure
% plot(t_tracker, func)


%% Characteristic Function for drug injection
function drug_injection = dj(inj_weight, amount, inj_time, current_t)
% Weight is coming in as grams, need to convert to kg
kg_weight = (1/1000).*inj_weight; % Turns weight to kg
if ismember(current_t,inj_time)
    activator = 1;
    time_location = inj_time==current_t;
    kg_weight_value = kg_weight(time_location);
    drug_injection = amount.*kg_weight_value.*(10^6).*activator;
else
    drug_injection = 0;
end
end
%% Heaviside function for x>= 0
function heav_output = heav_1(C_2, C_threshold)
value = C_2-C_threshold;
if value < 0
    heav_output = 0;
else
    heav_output = 1;
end
end
```

References

[1] "Cancer Facts and Figures 2023." American Cancer Society, www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2023-cancer-facts-figures.html. Accessed 17 Dec. 2023.

[2] El-Masry, Omar S, et al. "Oral Intragastric DMBA Administration Induces Acute Lymphocytic Leukemia and Other Tumors in Male Wistar Rats." Journal of Experimental Pharmacology, U.S. National Library of Medicine, 25 Feb. 2022, www.ncbi.nlm.nih.gov/pmc/articles/PMC8887968/#:~:text=have%20been%20made.-,7%2C12%2Ddimethylbenz%5Ba%5D%2Danthracene%20(DMBA),that%20initiates%20and%20promotes%20tumorigenesis.

[3] Harrold, John M., and Robert S. Parker. "Clinically relevant cancer chemotherapy dose scheduling via mixed-integer optimization." Computers & Chemical Engineering, vol. 33, no. 12, 2009, pp. 2042–2054, https://doi.org/10.1016/j.compchemeng.2009.06.005.

[4] Kalluri, Raghu, and Michael Zeisberg. "Fibroblasts in Cancer." Nature News, Nature Publishing Group, 30 Mar. 2006, www.nature.com/articles/nrc1877.

[5] Loizides, C., Iacovides, D., Hadjiandreou, M. M., Rizki, G., Achilleos, A., Strati, K., and Mitsis, G. D. (n.d.). Model-based tumor growth dynamics and therapy response in a mouse model of de novo carcinogenesis. PLOS ONE. https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0143840#pone.0143840.ref007

[6] MA;, Kolb TM;Davis. "The Tumor Promoter 12-O-Tetradecanoylphorbol 13-Acetate (TPA) Provokes a Prolonged Morphologic Response and ERK Activation in TSC2-Null Renal Tumor Cells." Toxicological Sciences: An Official Journal of the Society of Toxicology, U.S. National Library of Medicine, pubmed.ncbi.nlm.nih.gov/15178807/. Accessed 17 Dec. 2023.

[7] Morawska, Katarzyna, et al. "5-Fu Therapeutic Drug Monitoring as a Valuable Option to Reduce Toxicity in Patients with Gastrointestinal Cancer." Oncotarget, U.S. National Library of Medicine, 30 Jan. 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5837758/#: :text=Several%20previous%20studies%20proposed%20a,therapy%20%5B14%2C%2018%5D.

[8] Pharmacodynamics - StatPearls - NCBI Bookshelf, www.ncbi.nlm.nih.gov/books/NBK507791/. Accessed 18 Dec. 2023.

[9] Pharmacokinetics - Statpearls - NCBI Bookshelf, www.ncbi.nlm.nih.gov/books/NBK557744/. Accessed 18 Dec. 2023.