A Mathematical Model to Predict Tumor Responses to Cancer Drugs Based on Dose Response Curves in the Continuous Case

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This project is associated with the PIC Math Program of the Mathematical Association of America (MAA). This project investigates how to mathematically model the drug concentration that kills 50 percent of the 3-D tumor cells and generate a dose response curve. These curves allow us to more accurately predict effective drug dosages, such as, the ideal balance between the drug toxicity and drug effectiveness. The PDEs developed in this paper allow us to vary multiple variables (like tumor density and drug concentration) at once within a set of coupled equations, which can reduce the amount of time spent planning experiments and allow for greater accuracy in drug dosages. In future applications, we can develop a discrete model to further analyze independent parameters.

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INTRODUCTION

Cancer is one of the leading causes of death worldwide. Various modalities are used as a cure for cancer, mainly chemotherapy, radiation therapy, surgery and immuno-therapy. In chemotherapy, the drug is injected into the patient's body to kill tumor cells (Marios, 2014).

Different mathematical models have been developed to depict the growth of cancer cells and the effect of drugs on them. These take into account factors like the diffusion coefficients, which influence how easily drugs permeate the cell, drug resistance, which is the cell's lack of reaction to treatment, and drug toxicity, which is the cell's death rate after drug administration. In this study, two aspects are being considered; the first is the development of the tumor cells in the form of a spheroid, a manufactured tumor-like mass without vasculature, and the second part is the efficacy of drugs administered to the tumor cells. Multicellular spheroids are considered a surrogate for solid tumors and are commonly used to study drug delivery and tumor sensitivity to specified drugs (Marios, 2014).

The goal of this project is to develop a continuous mathematical model to investigate how to use dose response curves to control the growth of solid tumors. Dose response curves show the relationship between the drug dosage and the change in tumor size. To do this, we graph dose response curves for

various drug efficacy rates to find the IC_{50} curve which displays the ideal balance between effectively killing the tumor cells and reducing unintentional damage to the surrounding healthy tissue. The IC_{50} concentration is the standard measure of the drug dose needed to inhibit the growth of the tumor cell population by half (Friedrich, 2009). Our control case is the tumor growth model without any drugs. We use this to see the total cell growth possible in 3 days. Then, the cell growth with varying drug efficacy rates will be graphed against the total cell growth (without drugs) in order to find the dose response curves. We chose 3 days as the max time because our industrial partner, The Moffitt Cancer Center of Tampa, used this time constraint for their research. For our study, we simulate multicellular spheroids, which are the classic approach for 3D cell culturing. Throughout the past three decades, multiple article reviews have highlighted the potential of this model system in cancer research and treatment (Wientjesa, 2014). Early investigations in the 1970s not only triggered the study of basic biological mechanisms in multicellular tumor spheroids (MCTS), such as the regulation of tumor cell proliferation, differentiation and cell death processes, but also initiated the progressive entry of the MCTS model into various new fields of therapeutic interest (Friedrich, 2009).

In fact, tumor cells grown as 3D structures can acquire clinically relevant multicellular resistance to apoptosis-inducing drugs that may mimic the chemo-resistance found in solid tumors (Friedrich, 2009). Spheroids are aggregates of tumor cells without blood vessels, retaining many properties of solid tumors (e.g., multicellular structures, extracellular matrix, tight junctions between cells, gradients of nutrient and oxygen concentrations, and heterogeneous cell proliferation rate) (Gao, 2013). The absence of vasculature in spheroids ascertains that the transport was due to diffusion and not convection. This is important because our model is set up for diffusion. If needed, the convection terms can be added in at a later date. The model we consider here is the simplest possible model of a spatially structured multicellular tumor spheroid.

DEVELOPMENT OF MODEL

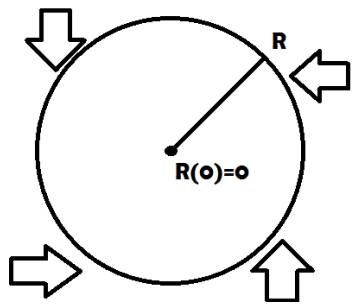


Figure 1. Tumor radius and flux of drug on the boundary

Tumor Growth

There are two models commonly used to mimic spheroids, the Logistic and Gompertz models. When creating a spherical 3D model, we first looked at the logistic growth, $\lambda T(1-\frac{T}{T_\infty})$. According to Nguimkeu, a parameter significance test based on linear regression can determine which

model is more accurate in a given circumstance. For our purposes, we chose the linear model and simplified it to be defined in a single region sphere of radius 0 to *R*, where *R* is the maximum radius at *t=72* hours. Later, our simple single region model can be adapted to more accurately reflect a real tumor, with three regions of cells (a dying cell core, a dormant layer, and a layer of growing cells).This is more accurate than the Gompertz model, because a typical tumor spheroid has three phases to its growth (Murray, 2002). The first is an exponential phase, then a linear phase with a constant growth rate, which later transitions into a declining growth rate (Goodman, 2008). As time progresses, cells in the core begin to die at an increasing rate. At the same time, healthy cells in the uppermost growth layer continue to increase. Since the growth rate of the necrotic core is greater than the growth rate of the proliferating top layer, the overall growth rate declines. In this study, the surface plot diagrams will show the tumor composition in tumor cells per million. The cell number may be computed by integrating over the radius for the function modeling the tumor, as will be shown in section 3.5. To create the initial dose response curve, we're looking at the volume of the tumor when it reaches the max radius (*R=72 hours*) with no drugs administered. This becomes the control case.

Drug Diffusion in the Spheroid

Next we'll look at the initial conditions for the drug diffusion and the behavior of the drug on the tumor's boundaries, R_0 and *R*. Let $C(r, t)$ be the drug concentration. To ensure smooth function behavior,the drug diffusion on the boundaries is constant (Yang, 2016). At the center, R_0, the diffusion is 0. At the outer edge, the diffusion of the drug is at a constant concentration, C_∞. If one takes the limit of the equation as r goes to 0, the diffusion term becomes increasingly large. Placing boundary conditions on the equation keeps the model manageable.

For the initial conditions, at radius 0, the drug concentration is $C(0, t) = C_0(0, t) = C_0$.

Next we looked at the flux of the drug diffusion on the boundary and converted it to spherical coordinates which are easier to work with (Yang, 2016). This is done by thinking of *r*, the radius (where $r \in [0,R]$), in terms of

$$r = \sqrt{x^2 + y^2 + z^2} \tag{2.1}$$

and allowing $x=r\sin\phi\cos\theta$, $y=r\sin\phi\cos\theta$ and $z=r\cos\phi$. Assuming the tumor is symmetrical, the values of θ and ϕ will cancel each other out in this general Laplacian representation of a sphere, and reduce the equation to the first term.

$$\nabla^2 C = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) + \frac{1}{r^2 \sin\phi}\frac{\partial^2 C}{\partial \theta^2} + \frac{1}{r^2\sin\phi}\frac{\partial}{\partial\phi}\left(\sin\phi\frac{\partial C}{\partial\phi}\right) \tag{2.2}$$

$$\frac{\partial C}{\partial t} = \frac{d_c}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) = \text{flux of drug concentration} \tag{2.3}$$

The tumor is similar to the following figure 1. Here, d_c is the diffusion coefficient for the drug. In our Matlab code, we base this value on averages found in a study performed by Gao (1). We chose to use pre-existing data since we don't have the resources to run the month long tests needed to create spheroid cultures.

COUPLING TUMOR GROWTH AND DRUG DIFFUSION

Next, we couple the drug diffusion with tumor growth to find a model that connects tumor growth and drug treatments.

Let $T(r, t)$ be the tumor density and $C(r, t)$ be the drug concentration. For this model, we're looking for the effect of the drug up to 72 hours (3 days). We chose this time limit in conjunction with our industrial partner, The Moffitt Cancer Center of Tampa, Florida. The overarching purpose of this project is to find the dose response curves which are used to find the IC_{50} curve. IC_{50} is the ideal balance between effectively killing the tumor cells and reducing unintentional damage to the surrounding healthy tissue. To create the dose response curves, we graph the tumor volume generated with varying drug efficacy rates against the tumor volume with no drugs administered. From each graph, we extract the data point which is half the tumor's total growth. Then, these points are compiled into the IC_{50} concentration graph.

Equations

$$\frac{\partial T}{\partial t} = \text{diffusion rate} + \text{logistic growth rate} = \text{tumor growth without drug} \tag{3.1}$$

$$\frac{\partial T}{\partial t} = \frac{d_T}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right) + \lambda T\left(1 - \frac{T}{T_\infty}\right) \tag{3.2}$$

$$\frac{\partial T}{\partial t} = \text{diffusion rate} + \text{logistic growth rate} - \text{drug efficacy rate} \tag{3.3}$$

$$\frac{\partial T}{\partial t} = \text{tumor growth with drug} \tag{3.4}$$

$$\frac{\partial T}{\partial t} = \frac{d_T}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right) + \lambda T\left(1 - \frac{T}{T_\infty}\right) - aCT \tag{3.5}$$

$$\frac{\partial C}{\partial t} = \text{drug diffusion rate} - \text{rate of clearance} \tag{3.6}$$

$$\frac{\partial C}{\partial t} = \frac{d_c}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) - \delta C \tag{3.7}$$

Initial Conditions

For the tumor: $T(0, r) = T_0(r) = T_0$

For the drug: $C(0, r) = C_0(r) = C_0$

Boundary Conditions

For the tumor: $\frac{\partial T}{\partial r}(0, t) = 0$ and $\frac{\partial T}{\partial r}(R, t) = 0$

For the drug: $\frac{\partial C}{\partial r}(0, t) = 0$ and $C(R, t) = C_\infty$

Variable and Parameter Definitions

Variable	Meaning	Units
$T(r,t)$	The tumor density	$\frac{cells}{mm^3}$
T_∞	The max tumor density	$\frac{cells}{mm^3}$
$C(r,t)$	The drug concentration	$\frac{mol}{mm^3}$
r	The radius of the tumor	mm
λ	Growth coefficient for the logistic growth	$\frac{1}{hour}$
a	The killing rate due to chemotherapy	$\frac{mm}{mol*hour}$

Parameter	Meaning	Units
d_T	The coefficient of diffusion for tumor cells held constant at 0.5	$\frac{mm^2}{hour}$
d_C	The coefficient of diffusion of the drug held constant at 0.5	$\frac{mm^2}{hour}$
δ	The rate of drug clearance held constant at 0.5	$\frac{1}{hour}$

Max Density of Tumor, T_∞

In order to find the max tumor density, which will be used as a basis of comparison for the overall tumor growth and cell kill efficacy, the tumor growth model is simulated for *t*=72 hours. This value is then used to graph a dose response curve, which can also be computed by

$$\int_0^R T(r,72)dr \tag{3.8}$$

According to Gao (2013), the determined max tumor cell quantity is roughly 1 million cells for a tumor of radius 1mm.

MATLAB CODE AND SIMULATION RESULTS

Objectives

The objective of this primary code is to see how the tumor grows up until *t*=72 hours (3 days), then to run the simulation while varying the drug efficacy. In MatLab, the drug concentration will be held constant at 1 to reduce the amount of data to sort through. Then, we monitor the cell death volume as a fraction of the total tumor volume. This graph becomes the IC_{50} curve after aggregating midpoints from the dose response curves. In this code, we can vary the values of λ, a, and δ which represent the tumor growth coefficient, the drug efficacy rate and the drug clearance rate. To generate our graphs, we run the tumor growth surface plots with varying drug efficacy rates, and hold the drug concentration $C(r, t)$ at 1 while varying the drug efficacy, a, from 0.1 to 1. As shown in the chart above, d_T, d_C, and δ are held constant at 0.5 in our code. To generate the

accompanying dose response curves, we chose the critical values of λ for which the surface plot behavior changed from tumor shrinkage to growth. Other curves can be generated by holding these critical λ values fixed and varying the drug concentration.

Methods

To solve this system of partial differential equations, we used the add-on PDEP within Matlab (Tseng, 2012). We imputed the principle pde, its boundary conditions and initial conditions, then added a graphing function that will display each change made in an iterative loop for the variable being studied. Based upon the literature listed in our references, we set arbitrary values for d_T and d_C which are equal to the average of the values found in our readings (Gao, 2013).

In our coupled drug and tumor growth pde, our surface plots present a graph of tumor density and drug concentration with drug already administered. For these surface plots, the x-axis is the radius of the tumor, the y-axis is time, and the z-axis is the quantity of tumor cells per million. For the drug concentration graph, the x-axis is the radial distance and the y-axis is also time.

In the code for the tumor growth alone, we ran our code using the PDEP module in Matlab, set our initial and boundary conditions and plotted a surface profile to more easily study the growth. By placing multiple loops inside our code, we can easily vary two or three variables at once, resulting in roughly 100 graphs. The values will grow according to this format:

$$(\lambda_i, a_i),\ i = +1\ \rightarrow (\lambda_{i+1}, a_i) \rightarrow (\lambda_{i+1}, a_{i+1}), \ldots,\ i = +n\ \rightarrow (\lambda_{i+n}, a_{i+n}) \tag{4.1}$$

These graphs will show the tumor growth and drug concentration. The graphs can be saved manually, but Matlab is capable of automatically saving and labeling the files with the appropriate code.

Another possibility with our code is to find the equation for the original tumor growth, then take the integral with respect to the radius to find the total area under the curve or the number of cells grown up to time, *t*.

Critical Values of λ, the Growth Rate, for Different Efficacy Rates, a

As the drug efficacy rate, a, increases, the critical point of the growth rate, λ, increases proportionately. This implies that as the drug is more effective, the point at which the tumor's growth pattern changes from concave (shrinking) to convex (growing) increases as well. This is because in the absence of the drug, equation (3.2) only, the tumor grows and reaches its carrying capacity. When the tumor growth is modeled with drug treatment, equations (3.5) and (3.7), the tumor will either shrink or grow depending on the tumor growth rate, λ, or the efficacy of the drug killing the tumor cells, a. As shown in Table 4.3 and shown in Figures 2-11, there exists a critical growth rate of the tumor in which, below

a Value	Critical Value of λ
a = 0.1	λ ∈ (0.11, 0.12)
a = 0.2	λ ∈ (0.23, 0.24)
a = 0.3	λ ∈ (0.35, 0.36)
a = 0.4	λ ∈ (0.46, 0.47)
a = 0.5	λ ∈ (0.58, 0.59)
a = 0.6	λ ∈ (0.70, 0.71)
a = 0.7	λ ∈ (0.81, 0.82)
a = 0.8	λ ∈ (0.93, 0.94)
a = 0.9	λ ∈ (1.05, 1.06)
a = 1.0	λ ∈ (1.17, 1.18)

that, the tumor shrinks in response to drug treatment, but when the growth rate is above the critical value then the tumor does not respond to treatment. For the dose response curves which measure the tumor cell survival at different drug dosages , the point at which the tumor shrank 50% occurred at larger drug doses when λ increased. The tumor growth surface plots with drug administered are found on page 13 in figures 2-11. For the corresponding dose curves, please refer to figures 12-21 on page 16. Each figure is labeled in increasing λ order to facilitate comparisons.

GRAPHS AND RESULTS

Tumor Growth Surface Plots With Drug for Varying Values of λ

Fig 2 - λ =0.11, **a** =0.1

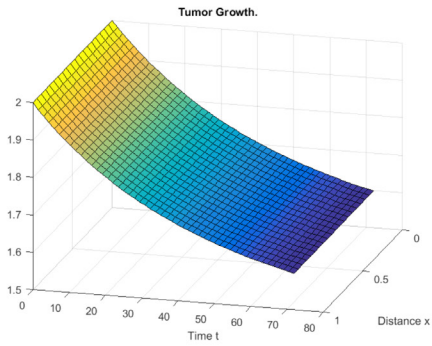


Fig 3- λ =0.12, **a** =0.1

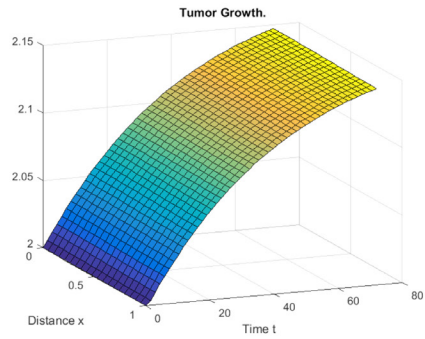


Fig 4 - λ =0.35, **a** =0.3

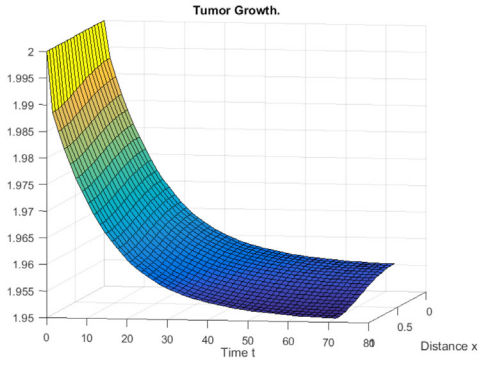
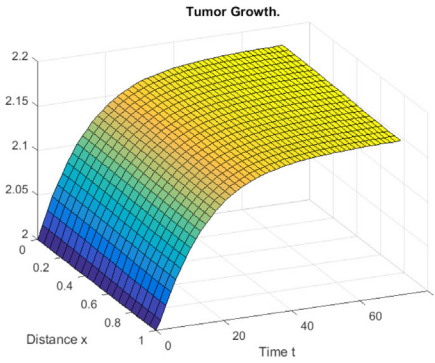


Fig 5- λ =0.36, **a** =0.3



Tumor Growth Surface Plots With Drug for Varying Values of λ

Fig 6- λ =0.58, **a** =0.5

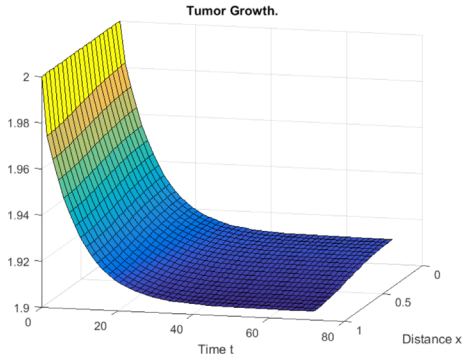


Fig 7- λ =0.59, **a** =0.5

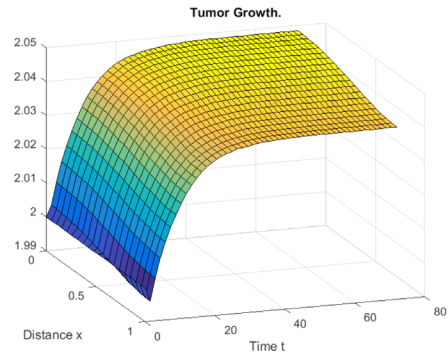


Fig 8 - λ =0.93, **a** =0.8

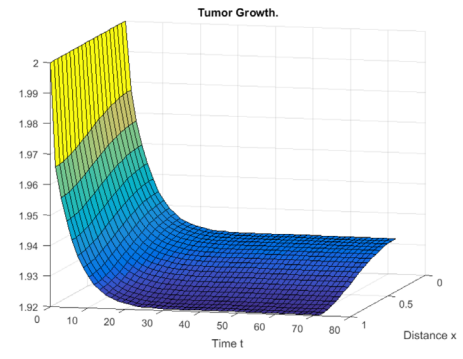
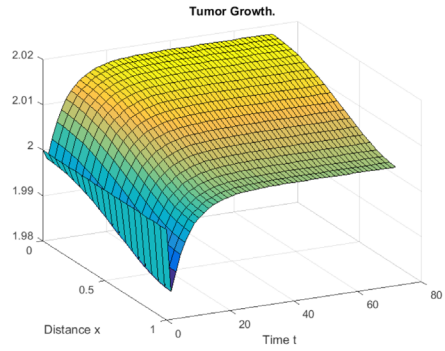


Fig 9- λ =0.94, **a** =0.



Tumor Growth Surface Plots With Drug for Varying Values of λ

Fig 10- λ =1.17, **a** =1.0

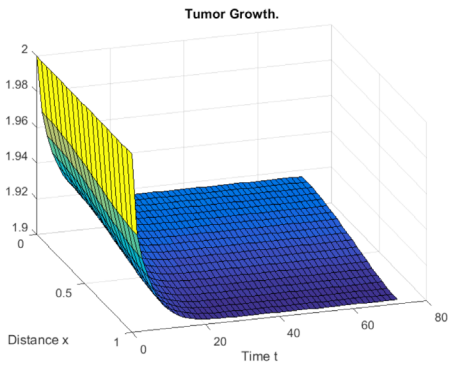
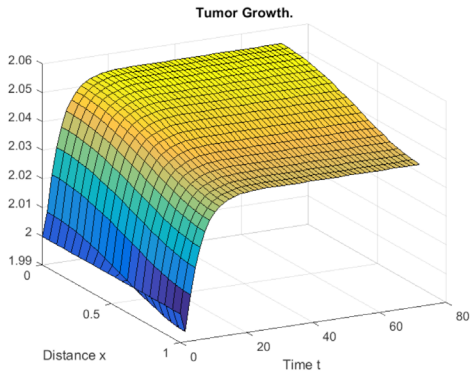


Fig 11 - λ =1.18, **a** =1.0



Figures 2-11: The following are the tumor growth surface plots for increasing drug efficacy rates. For these surface plots, the x-axis is the radius of the tumor, the y-axis is time and the z-axis is the quantity of tumor cells per million. Here drug concentration C(r,t) is held fixed at 1 and we vary the drug efficacy, a, between 0.1 and 1 to control the drug amount administered.

The λ values isolated display the critical points in tumor growth where behavior switches from shrinkage to growth. This is because in the absence of the drug, equation (3.2) only, the tumor grows and reaches its carrying capacity. When the tumor growth is modeled with drug treatment, equations (3.5) and (3.7), the tumor will either shrink or grow depending on the tumor growth rate, λ, or the efficacy of the drug killing the tumor cells, a. As shown in Table 4.3 and in the above figures, there exists a critical growth rate of the tumor in which, below that, the tumor shrinks in response to drug treatment, but when the growth rate is above the critical value, then the tumor does not respond to treatment.

Dose Response Curves for Varying Values of λ

Fig 12 - λ =0.11

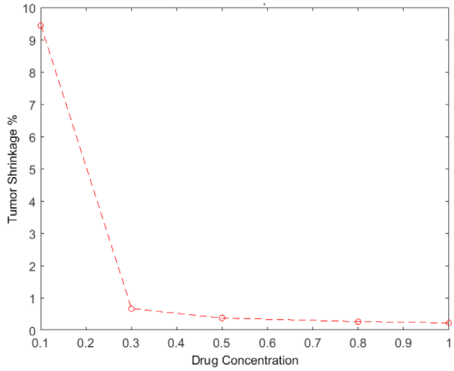


Fig 13- λ =0.12

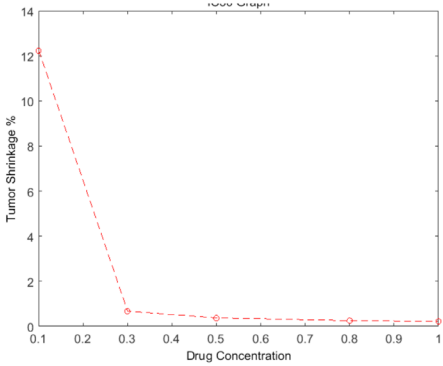


Fig 14 - λ =0.35

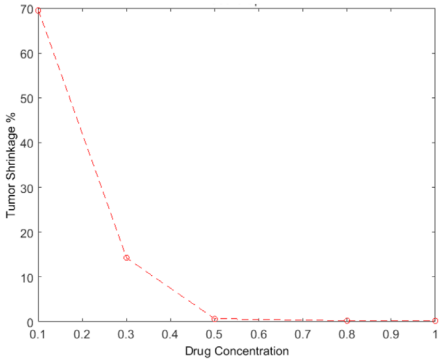
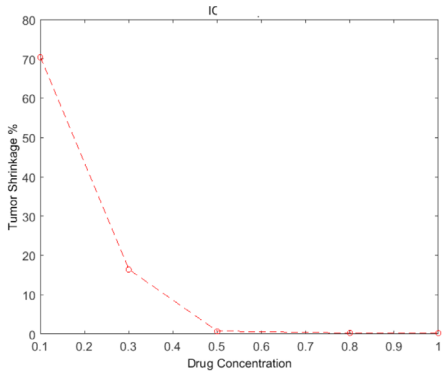


Fig 15- λ =0.36



Dose Response Curves for Varying Values of λ

Fig 16 - λ =0.58

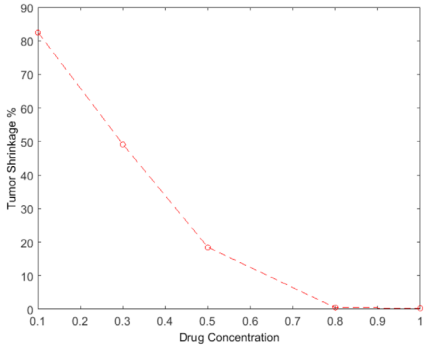


Fig 17- λ =0.59

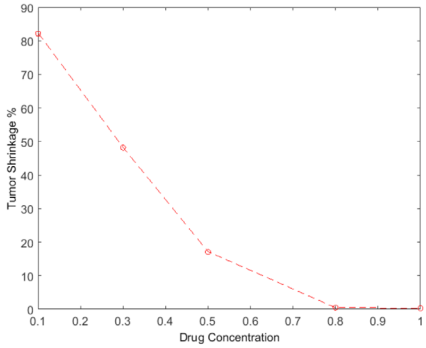


Fig 18 - λ =0.93

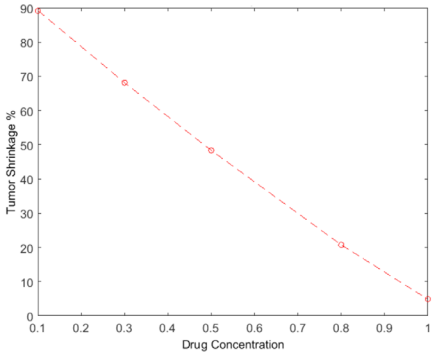
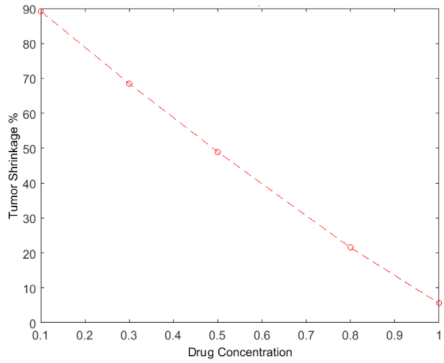


Fig 19- λ =0.94



Dose Response Curves for Varying Values of λ

Fig 20 - λ =1.17

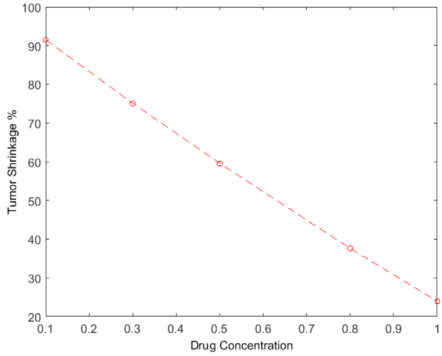
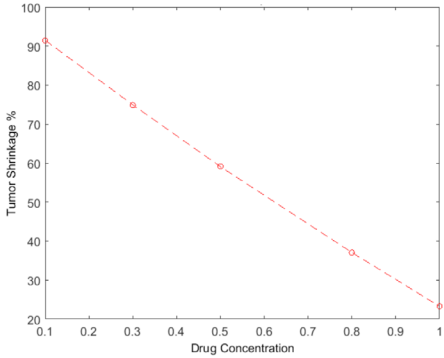


Fig 21- λ =1.18



Figures 12-21: The following are the dose response curves for the tumor growth at different drug concentrations for $\lambda \in (0.11, 1.18)$. Dose response curves show the relationship between the drug dosage and the change in tumor size. As λ, the growth rate, increases, the data point where the tumor volume is one half of the original volume occurs with greater drug dosages. This leads to the IC_{50} concentration, which is the standard measure of the drug dose needed to inhibit the growth of the tumor cell population by half (Friedrich, 2009). Our control case is the tumor growth model without any drugs. We use this to establish the total cell growth possible in 3 days. Then, the cell growth with varying drug efficacy rates will be graphed against the total cell growth (without drugs) in order to find the dose response curves. These points are later aggregated to create the IC_{50} curve.

CONCLUSIONS

This project allows us to study the simulated tumor growth and dose response curves for a spheroid to find the IC_{50} concentration, the ideal balance between the drug toxicity and the efficacy of drug induced cell death. This model provides a more accurate representation of drug diffusion and clearance in 3D spheroids prior to running physical experiments. This also enables us to find the rate of drug clearance, drug efficacy and tumor growth carrying capacity more efficiently. With these coupled PDEs, we can vary multiple variables like tumor radius, tumor growth, drug concentration, and diffusion at once for the continuous case. In a discrete model, each variable would need its own ordinary differential equation to model parameter behavior in individual cells, which is more complicated.

From this study, we looked at how the drug diffuses into the tumor, tumor growth, and the resultant dose response curves. In the future, this could be extended to a 3D discrete model,which allows for closer independent parameter studies.

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