5-2022

Modeling Intra-patient Planned Dose Change to Better Understand Dose Response in Cancer

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May 3, 2022

Abstract

In this paper, we attempt to find the most efficient trial design to determine the optimal dose of cancer treatment. The two trial designs being evaluated are a standard trial design and intra-patient dose-switching trial. The optimal dose is the lowest dose that still causes a decrease in the tumor size. The most efficient trial is defined as the trial in which the distribution of parameters from the data set mostly closely matches the distribution from a simulated trial. We developed an ordinary differential equation to model the change in the sum of the length of tumor diameters over time. This equation takes into account resistance of the tumor to the drug, the carrying capacity of the tumor, the growth rate of the the tumor and the decay rate of the tumor due to the drug dose. This equation was used to fit the parameters and run simulations. We determined that the intra-patients dose switching trial had a parameter distribution that mostly closely matched the original data in comparison to the standard trial.

1 Introduction

Standard practice in the field of oncology is to subject cancer patients to the maximum tolerable dose of chemotherapeutic drugs. The maximum tolerable dose is the highest dose a patient can tolerate without experiencing unacceptable levels of toxicity [2]. Chemotherapeutic drugs are highly toxic, and pose serious risks to the patient, as excessive doses can cause more adverse reactions in cancer patients. A potential alternative is to find an optimal dose rather than maximum tolerable dose. An optimal dose is a lower dose that sacrifices drug efficacy in exchange for a notable reduction in the occurrences of severe adverse events. Since individual patients respond differently to treatment, it is challenging to

find an optimal dose. In order to compensate for this high patient variability, large clinical trials are required. The sample size used in a drug trial is directly correlated to the cost, which is why the maximum tolerable dose is often used instead of the optimal dose [4].

One way to remedy the challenges of increased resources needed to find the optimal dose is to experiment with different trial designs [4]. A commonly used trial design is a standard steady dosage trial is which dosages are not altered unless adverse side effects occur. Another trial design is intra-patient dose switching trial in which dosages are intentionally changed throughout the course of treatment. In this work, we will explore the hypothesis that the intra-patient trial design may give us more information about the dose-response relationship.

Through an exploration of dosage efficacy in different trial designs, we seek to find an optimal dose while using fewer resources. The quantifiable question we set out to answer is which trial design results in the lowest error among the fitted growth rate and drug effect term in simulations based on a model fitted to data. To answer this question, we create a mathematical model to predict efficacy of treatment with respect to different dosage options. We use this model to simulate the two different trial designs by drawing from a distribution of parameters determined from fitting the model to data. For each of the trial designs, we analyze the efficacy of treatment and the variability between drug effect in trial simulations. The trial design with lowest error in change in the fitted decay rate of the lesion due to treatment is the most efficient trial design which will require the smallest amount of resources to find the optimal dose.

2 Data

We used the data set listed as "DDMODEL00000198: Tumor growth inhibition model for Sunitinib Treatment in GIST" containing cancer patient data with tumor sizes, time, treatment, and dosage data [3]. The data set tracks standard steady-dose treatment of 80 cancer patients with a gastrointestinal stromal tumor. The data set includes the change in the sum of tumor diameters, with the corresponding treatment the patient was given. The data set is used to find the parameters for the model, introduced below, by fitting a curve through each patient's data. This data set should be sufficient in generating the distributions of each parameter due to the size of 80 patients over a treatment period of up to 40 weeks.

3 Mathematical Model

3.1 Assumptions

The biological processes underlying oncology are very complex. Thus, it is necessary to make simplifying assumptions to streamline model development. There are three different drug concentrations used, which are 0, 37, and 50 picograms/ mL [3]. We assume the 50 pg/ml dose is 50% as effective as the

37 pg/ml. This is because there was a lack of data points to fit the drug effect parameter for the 37 pg/ml dose. We chose 50% because the trends in the initial data suggested the 37 pg/ml dose was approximately half as effective as the 50 pg/ml dose. We also assume there will be no change in body's ability to metabolize the drug throughout the trial period. The model applies only to solid tumor cancers and we assume the tumor will continue to grow until it reaches a carrying capacity, that is, until the tumor runs out of space to grow. The carrying capacity is patient dependent. We ignore non-target lesions; that is, only tumor size will be measured. We assume that the tumor develops resistance to treatment gradually over time [7]. Finally, patients are removed from the clinical trial simulations if their tumor increases in size by 50%.

3.2 Model Formulation

Tumor size is characterized by the sum of the diameters of the target lesions for patient i and represented by the variable L^i, which is dependent on time t. The index i represents a patient number because the model will be fitted to each patient. We are modeling the change in the sum of the diameters of the target lesions over time, which can be described simply by the following equation:

$$\frac{dL^i}{dt} = \text{Growth Rate} - \text{Decay Rate}. \tag{1}$$

There are several model types that are frequently used to model tumor growth. The most commonly used growth models utilize exponential growth, logistic growth, or a Gompertz equation. Of these common growth curves, the best practice is for the model type to be decided based upon the specific context of the tumor you are trying to model [6]. Exponential growth comes with certain limitations. An exponential growth curve does not account for any slowing in growth rate due to a natural carrying capacity. In the case of trial designs, some patients will be placed into a placebo group and receive no treatment for an extended period of time. In this scenario, the use of an exponential growth curve would not be appropriate because it would not reflect the slowing in growth when the patient's tumor approaches the carrying capacity. Therefore, with no justification to use a more complex growth curve, we elect to use logistic growth [7].

The logistic model estimates growth based on a growth rate k_g^i and a maximum carrying capacity V^i. The logistic growth model accurately reflects the situation where the tumor size becomes stable over a period of time, as once the tumor length is getting close to parameter V^i, the carrying capacity, the tumor growth rate will approach zero. Taking these factors into consideration, we developed the following equation, which can be used to calculate natural growth of the tumor:

$$\frac{dL^i}{dt} = k_g^i \left(1 - \frac{L^i}{V^i}\right) L^i. \tag{2}$$

The effect of the drug on the tumor is represented by a decay rate k_d^i. Patients are given different dosages D at various times, therefore we must consider multiple decay rates $k_{d_D}^i$ for each dosage. The drug effect is given by $k_d^i(t)$ which is defined by the following piece-wise function:

$$k_d^i(t) = \begin{cases} 0, & \text{if } D = 0 \\ k_{d_{37}}^i, & \text{if } D = 37 \\ k_{d_{50}}^i, & \text{if } D = 50. \end{cases} \tag{3}$$

The decay rate of the tumor is given by

$$\frac{dL^i}{dt} = -k_d^i(t)L^i. \tag{4}$$

Equation 2 can be modified by subtracting the decay rate due to drug effect which causes the tumor size to shrink.

$$\frac{dL^i}{dt} = k_g^i \left(1 - \frac{L^i}{V^i}\right) L^i - k_d^i(t)L^i. \tag{5}$$

Finally, as the patient is given continued doses of the drug, the cancer builds up resistance, R^i, to the treatment. Equation 6 can be used to model the change in resistance to the oncology drug where λ^i is the parameter that we will fit for each of the patients.

$$R^i(t) = e^{\lambda^i \int_0^t k_d^i(s)\, ds} \tag{6}$$

The resistance R^i is being modeled by using exponential growth with initial condition of $R(0) = 1$. The exponent of the function, $\int_0^t k_d^i(s)\, ds$, was chosen to represent the accumulation of respective drug dosage over time, multiplied by the rate, λ^i; this accounts for the effect of drug dosage on change in resistance.

$$\frac{dL^i}{dt} = \left[k_g^i \left(1 - \frac{L^i}{V^i}\right) - \frac{k_d^i(t)}{R^i(t)}\right] L^i. \tag{7}$$

Equation 7 shows the extension of the standard logistic tumor growth rate model after we take into consideration the treatment and resistance. We divide the decay rate due to drug effect by R^i, resistance, because we wanted to model an inverse relationship between resistance and drug effect. Therefore, as resistance increases, the drug effect decreases. We note that for the purposes of fitting to data, the initial condition $L(0)$ is known, and when simulating trials, the initial condition is defined by a log-normal population distribution.The variables and parameters have been summarized in the Tables 1 and 2:

Variables	Description	Units
t	Time	Days
$L^i(t)$	Sum of the length of tumor diameters of patient i	Millimeters
$R^i(t)$	Resistance of the tumor to the drug of patient i	Dimensionless

Table 1: Variables

Parameter	Description	Units
V^i	Carrying capacity of tumor in patient i	Millimeters
k_g^i	Growth rate of the tumor in patient i	1/day
$k_{d_{37}}^i$	Decay rate of the tumor in patient i due to the 37 picograms/mL drug dose	1/day
$k_{d_{50}}^i$	Decay rate of the tumor in patient i due to the 50 picograms/mL drug dose	1/day
λ^i	Resistance growth rate for patient i	Dimensionless
D	Drug dose	Picograms/milliliter

Table 2: Parameters

3.3 Assessing Variability

For all of these parameters, we expect values to vary considerably between patients. To account for this, we generate a set of parameters for each patient i, by applying a curve fitting algorithm using our data set. For every patient i, we use their tumor growth data to determine a value for k_g^i, $k_{d_{37}}^i$, $k_{d_{50}}^i$, λ^i, and V^i. We treat each patient's response as samples of random variables. We then use the patient values for each parameter to determine a mean value and a distribution of the parameter. We show that variation in growth and response rates would be consistent with a normal distribution [1]. To ensure that model parameters cannot be negative, we will assume our population parameter distributions to be log-normal. In Figure 1, we include the distribution for the parameter k_g^i which you can see is approximately log-normal. The other parameters had a similar distribution. We sample from these distributions to run simulations of the trial design. We assess variance by comparing the error amongst the fitted growth rate and drug effect term in simulations based on a model fitted to data.

Continuing onward, we simulate case-by-case results from both standard and intra-patient dose switching designs. We sample from the distribution of parameters to simulate patient data. From the simulated patient data, we fit the

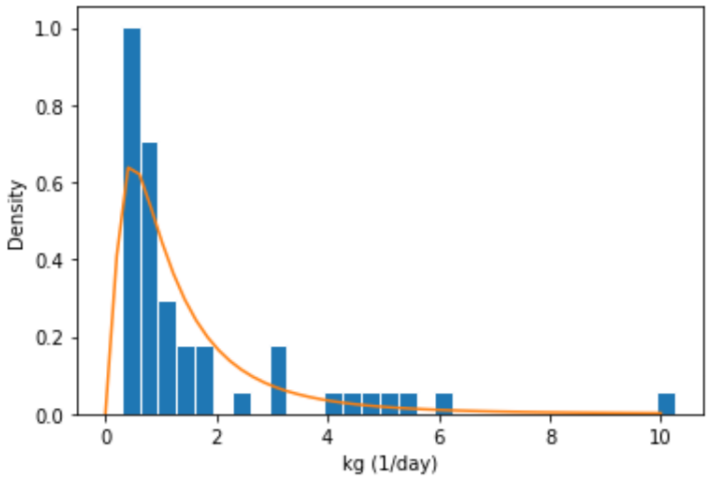

Figure 1: Histogram of parameter k_g^i which is approximately log-normal

parameters to the simulated patient data set to see which trial design produces the lowest error between the parameter distribution when comparing the original fitted parameters to the simulation.

4 Results

4.1 Calculated Parameter Values

The procedure for fitting the parameters to the data and running the simulations is outlined in Figure 2.

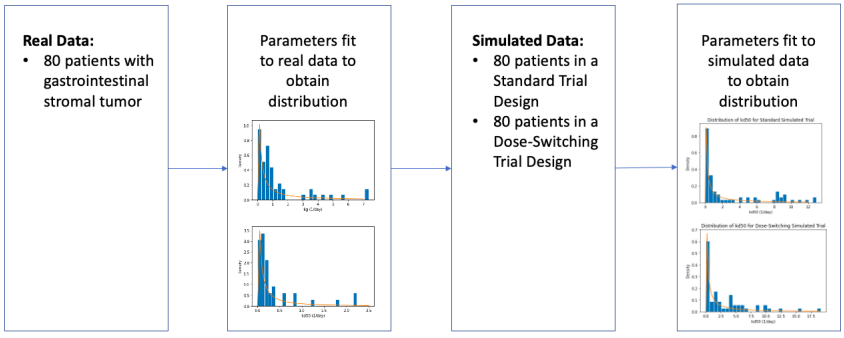

Figure 2: Outline of Process of Fitting Parameters

In order to use Equation 7 to find patient-specific model parameters, we implement a numerical method. We use MATLAB's built-in functions to find the parameters in Equation 7. We implement the function `lsqcurvefit` and "ode45" to find the estimated parameters V^i, k_g^i, $k_{d_{37}}^i$, $k_{d_{50}}^i$, and λ^i. The fitted parameters for five patients can be seen in Table 3.

Id	k_g^i	$k_{d_{37}}^i$	$k_{d_{50}}^i$	V^i	λ^i	$Error$
1	0.43	None	0.249	150.13	0.0893	0.000236
2	2.22	1.43	1.0893	120.012	0.0001	17480
3	2.29	None	3.438	189.05	0.94	255.20
6	82.55	None	56.17	435	1.3168	24317
7	0.558	None	0.2813	372.876	2.647	0.0048
9	2.706	2.9	1.72	162	0.001	2309

Table 3: Estimated parameters for the first 5 patients

Table 3 includes most, but not all of the patients' dose response parameters, as some patients lack data points. For example, patients 4 and 5 only have two data points for the entire trial, which is not sufficient in obtaining the estimated parameters. In addition, some of the fits have high error despite a somewhat simple model. From the table, patients 2 and patients 6 have such error. Figure 3 is the graph fitting of the patient 9 dosage response for dose switching and 4 is the graph fitting of the patient 3 dosage response for standard trial.

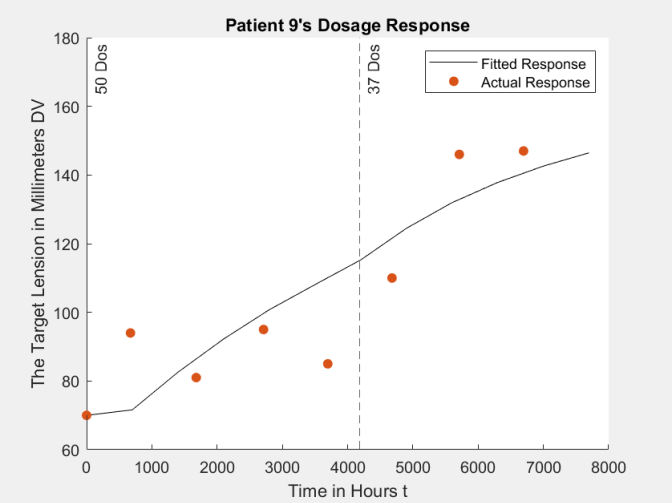

Figure 3: The graph of the Patient 9 dosage response

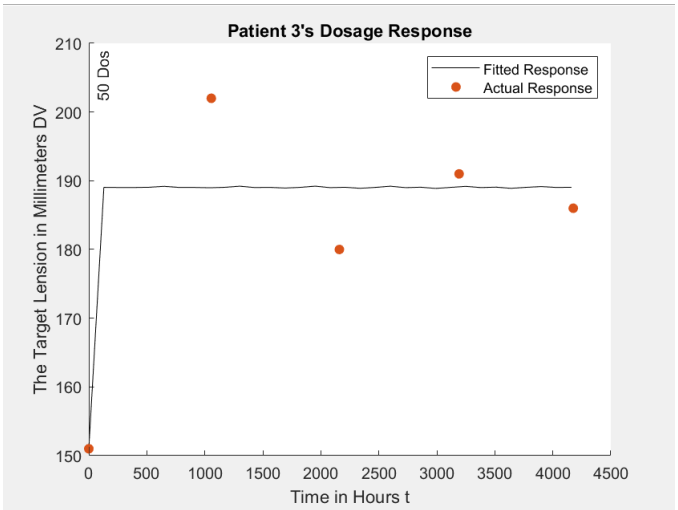

Figure 4: The graph of the Patient 3 dosage response

For patient 9 in figure 3, the kink at the start of trial was due to the time step issues with the fitting function and also because the break in between each of the measurement. In the data set, patients tend to have 2 weeks without treatment. Patient 3 seems to be reaching the carrying capacity after 3 weeks, The main cause of such sudden increase is the unusual high measure of the targeted lesion at week 6. This could be a measurement error since at week 12, there is a significant decrease in the tumor sizes.

Figure 1 shows an example of the distribution of k_g^i values for all 80 patients. It can be seen that the distribution is approximately log-normal; the rest of the parameters had a similar distribution. Table 4 is a summary of the μ and σ of the distribution for each model parameter. It also includes $\tilde{\mu}$ and $\tilde{\sigma}$ values for each parameter. The values $\tilde{\mu}$ and $\tilde{\sigma}$ are parameters of the log-normal distribution for each model parameter which were found by taking the natural log of each patient's estimated parameter value and then calculating the mean and standard deviation. The log-normal parameters $\tilde{\mu}$ and $\tilde{\sigma}$ are used for the random sampling from the log-normal distribution in the simulations.

Parameter	μ	σ	$\tilde{\mu}$	$\tilde{\sigma}$
k_g^i	1.628	1.933	-1.081	2.729
$k_{d_{37}}^i$	0.360	0.713	-7.214	7.354
$k_{d_{50}}^i$	1.660	2.778	-0.744	1.877
V^i	352.371	473.390	5.329	1.006
λ^i	1.08	2.903	-5.694	6.813

Table 4: Mean and standard deviation of parameters and their fitted log-normal distributions

$$\mu = \frac{k_g^1 + k_g^2 + ... + k_g^n}{n}$$

$$\sigma = \sqrt{\frac{(k_g^1 - \mu)^2 + (k_g^2 - \mu)^2 + ... + (k_g^n - \mu)^2}{n}}$$

$$\tilde{\mu} = \frac{\ln k_g^1 + \ln k_g^2 + ... + \ln k_g^n}{n}$$

$$\tilde{\sigma} = \sqrt{\frac{(\ln k_g^1 - \tilde{\mu})^2 + (\ln k_g^2 - \tilde{\mu})^2 + ... + (\ln k_g^n - \tilde{\mu})^2}{n}}$$

where the lognormal curve in Figure 1 is defined by

$$f(x) = \frac{1}{x\tilde{\sigma}\sqrt{2\pi}} \exp\left\{\frac{-(\ln(x) - \tilde{\mu})^2}{2\tilde{\sigma}^2}\right\} \tag{8}$$

4.2 Model Simulation of Treatment

A Python program was written to simulate the model and treatment. Using the values of the parameters calculated for each patient, a log-normal distribution was constructed for each parameter. Then, 80 patients were generated by sampling the parameter values from these distributions. Their treatments were then simulated in MATLAB by the use of the "ode45" function. Some of the results of the simulations can be seen in Figures 5 and 9.

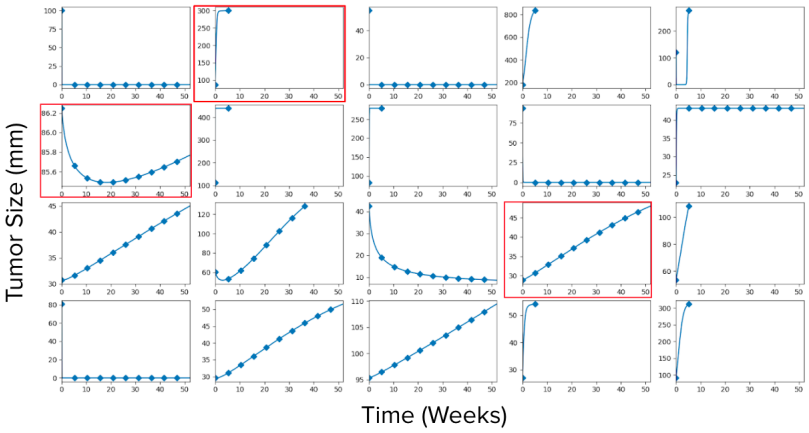

Figure 5: Graphs generated from the random simulation of 20 patients in standard dose trials.

Figure 5 displays the simulation of 20 patients participating in a standard dose trial. The graphs represent the tumor size in millimeters over 52 weeks.

The patients receive the 50 ml/pg dose over the entire trial period. Patients that experience tumor growth in which the tumor size increases by over 50% are removed from the trial. The dots in the graphs represent each time the tumor size was measured during the trial. There are some important trends that can be seen in the graphs surrounded by a red box which are enlarged in Figures 6, 7, and 8 for further examination.

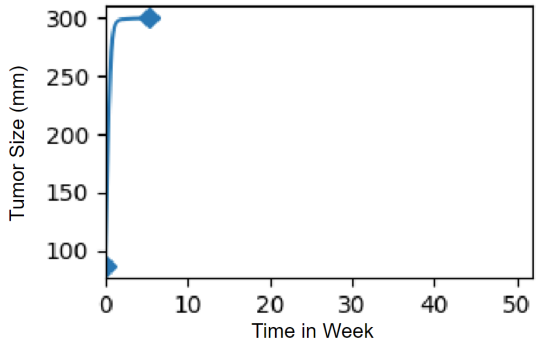

Figure 6: Example of patient in standard simulated trial with logistic growth that is removed from trial

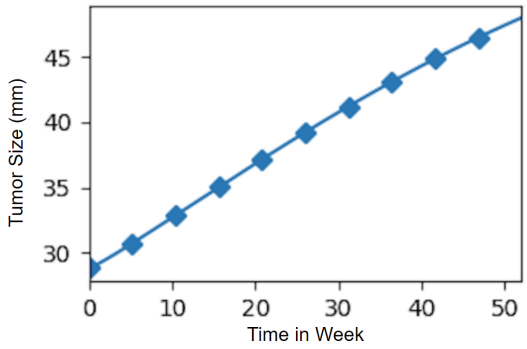

Figure 7: Example of patient in standard simulated trial with linear growth

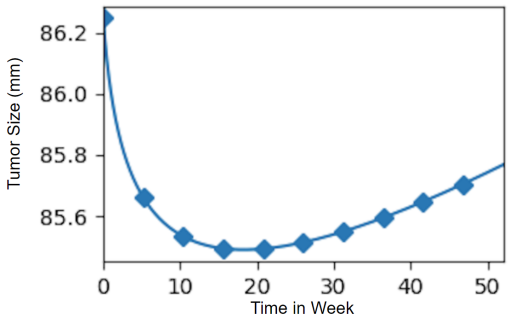

Figure 8: Example of patient in standard simulated trial with drug resistance

In Figure 6 we see a patient with a high growth rate parameter which leads to logistic growth where the tumor size quickly approaches carrying capacity. Since the tumor grew by more than 50%, the patient was removed from the trial period after the first tumor measurement. The next trend is linear growth of the tumor which can be seen Figure 7. In Figure 8 we see a patient with a higher tumor decay rate than growth rate as there is exponential decay for the first 20 weeks, although it is on a small scale of only approximately 0.8 mm. At week 20, we see the patients tumor size begin to increase again. This is the result of the patient developing resistance to the tumor.

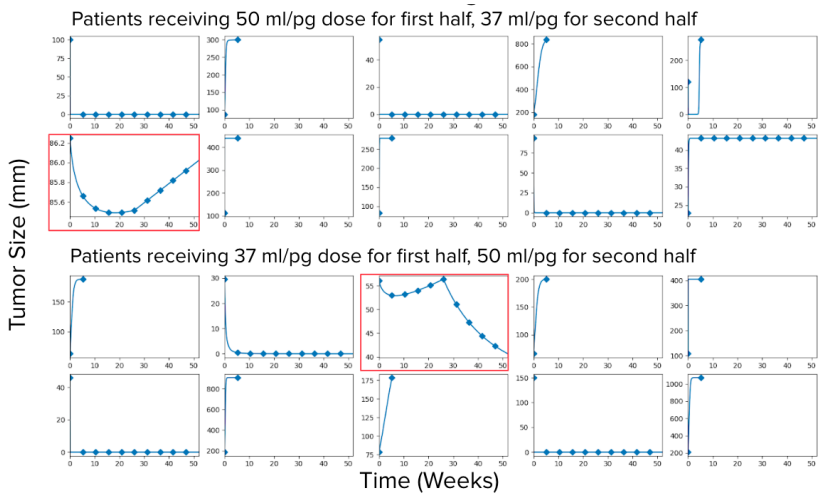

Figure 9: Graphs generated from the random simulation of 20 patients in dose-switching trials. The top two rows contain patients that switched from a high dose to a low dose, while the bottom two rows contain patients that switched from a low dose to a high dose

Figure 9 shows the simulation of 20 patients participating in the dose-switching trial over six weeks. The patients in the top two rows receive the 50 pg/ml dose for the first 26 weeks and the 37 pg/ml for the last 26 weeks. The patients in the bottom two rows receive the 37 pg/ml for the first 26 weeks and then receive the 50 pg/ml for the last 26 weeks. The dots represent the each time the tumor size was measured during the trial. The two graphs outlined in red are enlarged in Figures 10 and 11 to show key characteristics.

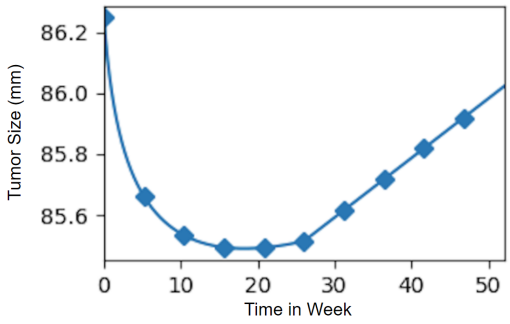

Figure 10: Example of patient in dose-switching simulated trial that first received the 50 ml/pg dose

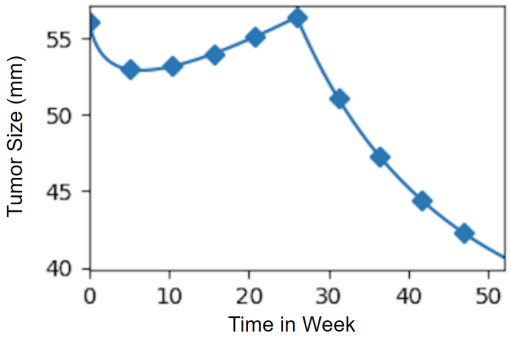

Figure 11: Example of patient in dose-switching simulated trial that first received the 37 ml/pg dose

In Figure 10 the patient initially received the 50 ml/pg dose for the first 26 weeks. During this period the tumor size decayed exponentially, although it was on a small scale. However, at the 26 week point the patient the patient switched to the 37 pg/ml treatment which was only 50% as effective and saw a linear increase in tumor growth over the rest of the trial period. This growth from the change in drug dose was less gradual than the growth we saw in Figure

8 due to the development of drug resistance. In Figure 11 the patient initially received the 37 pg/ml dose for the first 26 weeks and then received the 50 pg/ml dose for the second 26 weeks. It can be seen that the tumor developed resistance quickly to the 37 pg/ml dose as the tumor size decreased slightly but then started to increase again. However, the 50 ml/pg dose was highly effective at the 26 week point and cause a decrease in the tumor size by 15 mm.

After the simulations have been performed, the output of the data from the simulations will be fit using the `lsqcurvefit` and "ode45" similar to the original data.

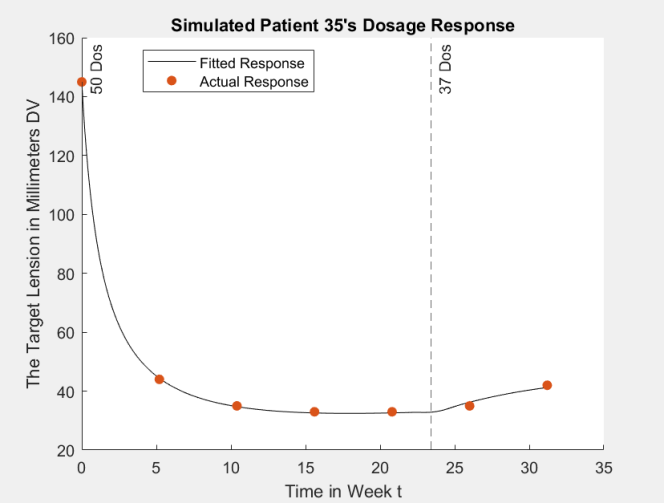

Figure 12: The graph of the Simulated Patient 35 dosage response

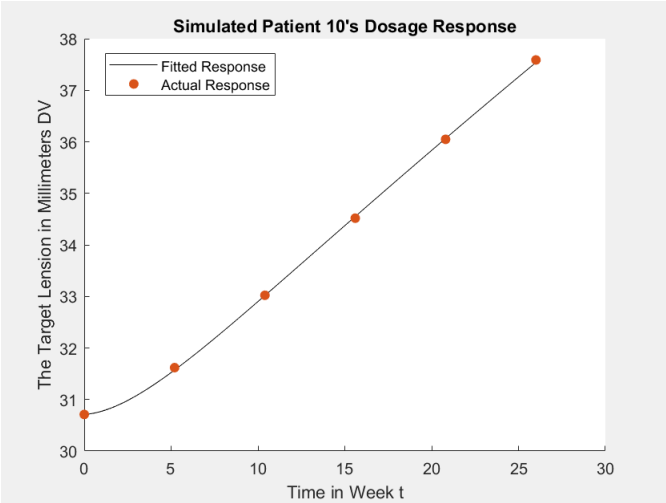

Figure 13: The graph of the Simulated Patient 10 dosage response

Figure 12 and Figure 13 represent the fit of dose switching patients and standard dose patients. It's not a surprise to see that the fit is almost perfect as the model capture the entire dosage response of the patients since the simulation does take into account for error in measurement.

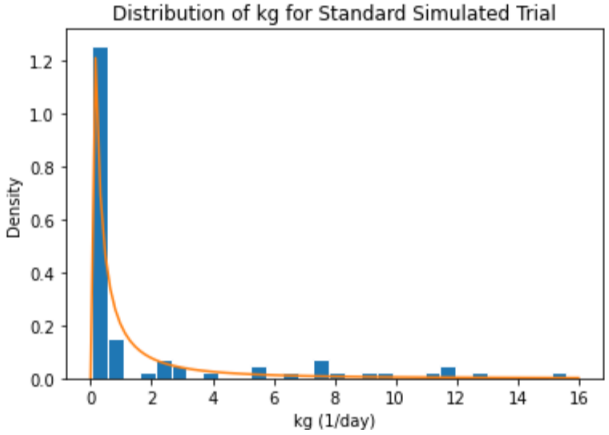

Figure 14: Log-normal distribution of the simulated standard trial for k_g

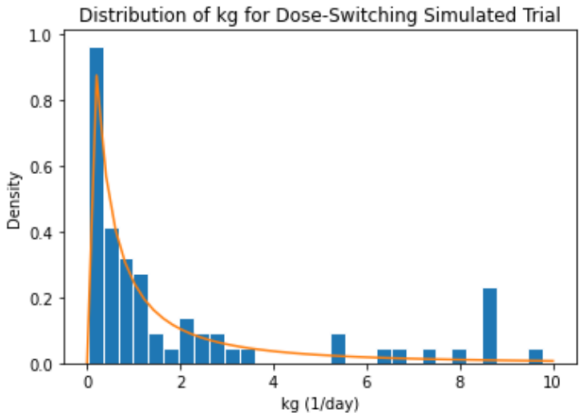

Figure 15: Log-normal distribution of the simulated dose switching trial for k_g

Figures 14 and 15 are the distribution of the k_g parameters generated from the standard and simulated trial, respectively. These are compared to Figure 1 which shows the distribution of the parameter from original fitted data set. The same process was completed for the parameter $k_{d_{50}}$. A comparison is between these distributions is in Section 4.2.1.

4.2.1 Analysis Of Variability In Treatment

Our overall goal of the aforementioned code, generated parameters, and simulations collectively is to assess the error of projected drug effect between the two treatment methods. The values of the parameter distributions that were fitted to the simulated patient data set are given in Tables 5 and 6.

Parameter	μ	σ	$\tilde{\mu}$	$\tilde{\sigma}$
k_g^i	2.065	3.684	-0.8788	1.7762
$k_{d_{50}}^i$	1.045	2.061	-2.035	3.334

Table 5: Mean and standard deviation of parameters and their fitted log-normal distributions for the standard simulation

Parameter	μ	σ	$\tilde{\mu}$	$\tilde{\sigma}$
k_g^i	2.093	2.816	-0.2791	1.6097
$k_{d_{50}}^i$	1.660	2.778	-0.744	1.877

Table 6: Mean and standard deviation of parameters and their fitted log-normal distributions for the dose-switching simulation

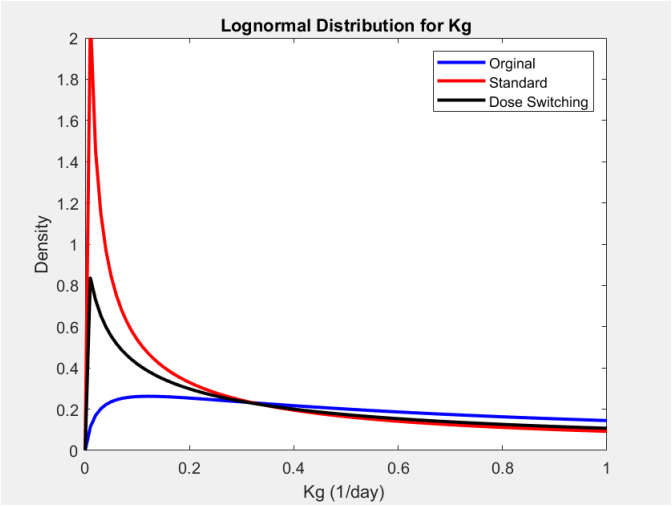

Figure 16: Log-normal distributions of k_g for the original and simulated trials.

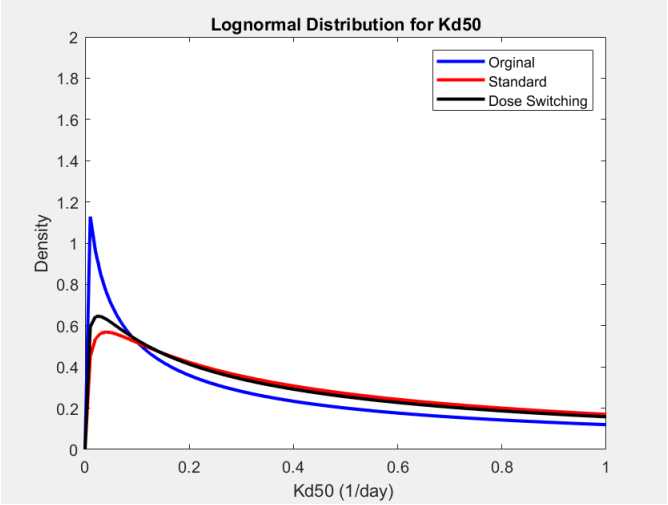

Figure 17: Log-normal Distribution of $k_{d_{50}}$ for the original and simulated trials.

To better visualize these values, the lognormal distributions that $\tilde{\mu}$ and $\tilde{\sigma}$ describe for each trial design can be plotted against each other, as well as against that of the original data, as seen in figure 16 and 17. In these plots, the plots for the standard and dose-switching parameters can be seen to be similar, though the dose-switching plot has peaks that are slightly closer to that of the original data set.

4.3 Analysis of the Model

$$\text{Relative Error} = \frac{|\text{Simulation Value} - \text{Experimental Value}|}{\text{Experimental Value}}$$

To assess the accuracy of the two trial methods, fitted distributions for the parameters of each trial type can be compared against the actual data to measure the relative error.

Trial Type	k_g Error in μ	$k_{d_{50}}$ Error in μ	k_g Error in σ	$k_{d_{50}}$ Error in σ
Standard	26.84%	37.04%	90.58%	25.81%
Switching	28.56%	30.90%	8.11%	20.81%

Table 7: Relative error among parameters

As seen in Table 7, the dose-switching method resulted in lower error in all but the mean of the k_g distribution, in which it was only slightly higher than the standard trial. Specifically, it performed significantly better than the standard trial design with regards to the drug effect. Because of this lower error, the results point towards the dose-switching method being the better method for reducing error in calculated drug effect.

5 Discussion

Our model is able to give a clear answer to which trial design will give the lowest error in the parameter distributions. However, there are limitations in our model. The data set used is mostly limited to one kind of dosage response which is $k^i_{d_{50}}$, and not many patients have $k^i_{d_{37}}$. The complexity of the model with the addition of the resistance term make the fitting of the patients highly sensitive to the initial guesses. For example, different initial guesses can lead to multiple possible minimum least square value and in rare occasion the estimated parameters can be unreasonable compared to a clinical trial. This model never considered the possibility of measurement error. The k^i_g, $k^i_{d_{37}}$, and $k^i_{d_{50}}$ may not behave as desired in the model. This is due to the data and fitting process where patients can be given a higher k^i_d than k^i_g or $k^i_{d_{37}}$ being greater than $k^i_{d_{50}}$. The model has room for improvement, where a different fitting function can be tested or to use a different data set and see how that varies from the result. Another possible way of improving this model is to reduce the complexity of the model by picking a different function to model the resistance of the tumor.

6 Conclusion

The motivation of the simulated trials and the underlying mathematical model are to determine which trial design is the most efficient at determining

the optimal dose of cancer treatment; that is the treatment with the lowest error in simulated model productions from empirical data. The model was hence developed to capture the growth rate of the tumor in relationship to the drug effect. It was also designed to account for the biological nature of the body to have a carrying capacity in the development of a tumor. From the model and simulated parameters, we obtain that the dose switching trials have lower error in parameters between the simulated and actual data compared to the standard trial. Therefore, we conclude that the dose switching trial is more efficient in finding the optimal dose of cancer treatment for solid tumors such as a gastrointestinal stromal tumor.

7 Acknowledgement

We thanks Dr.Andy Stein from Novartis for the problem statement and mentorship during the academic semester.

8 Appendix of Code

8.1 File "Testing.m"

The main code for getting the estimate parameters for the patients who receives dosage 50. Multiple iteration is needed to be done to get the estimate parameters by picking a different initial values. (lsqcurve fit function)

The code use "function500.m" and "function500p.m"

8.2 File "function500.m"

The code correspond to the ordinary differential equation.

8.3 File "function500p.m'

The code correspond to the solving of the ordinary differential equation using ode45 and pass the values.

8.4 File "DoseSwitching.m"

The main code for getting the estimate parameters for the patients who receives dosage 50 then dosage 37 and who receives dosage 37 then dosage 50. Multiple iteration is needed to be done to get the estimate parameters by picking a different initial values. (lsqcurve fit function)

The code use "function50037.m", "function50037p.m", "function500372.m", and "function500372p.m"

8.5 File "function50037.m"

The code correspond to the ordinary differential equation for dosage 50 and 37.

8.6 File "function50037p.m"

The code correspond to the solving of the ordinary differential equation using ode45 and pass the values. (Patients who get dose 50, then dose 37)

8.7 File "function500372.m"

The code correspond to the ordinary differential equation for dosage 37 and 50.

8.8 File "function500372p.m"

The code correspond to the solving of the ordinary differential equation using ode45 and pass the values. (Patients who get dose 37, then dose 50)

8.9 File "TrialSim.py"

Contains all code related to simulated trials. Samples from log-normal distributions using `scipy.stats.lognorm` to generate patients for the purposes of simulating trials. Differential equations are solved on a per-patient basis using `scipy.integrate.odeint` and then graphed using `matplotlib.pyplot`. Data output is done using `csv` in a format mirroring the original data set.

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The main purpose of this paper was to gain understanding on the resistance modeling of the tumor. Stochastic model and deterministic model were introduced to characterize the evolution of the tumor cell.