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Mathematical Models for MC and MTD Chemotherapy

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The goal of the project is to construct a mathematical model for Metronomic and Maximum Tolerated Dose Chemotherapy that will optimize the efficacy and reduce the toxicity of the treatment. In doing so, we allowed for a variety of treatment protocols. We studied variables such as dose schedule, compartmental models of varying state variable amounts, and tumor density. All results have been reported. It is of note that negative results are viewed as successes, as they allow future experiments to streamline testing. In an effort to easily display our data, we included each of the tested mathematical equations and models with their corresponding graphs of results when applicable.

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INTRODUCTION

Chemotherapy is widely used in treating diseases such as cancer because of its ability to kill all cells, whether cancerous or healthy. Problems arise for the patient during treatment due to chemotherapy attacking all cells instead of the tumor cells exclusively [13]. Due to chemotherapy's inability to target the cancerous cells it is said to be toxic to the body. As a consequence the chemotherapy has to be given in amounts that will not be overly toxic to the patient, while still reducing the size of the tumor. To reduce the amount of stress chemotherapy puts on the human body mathematical models are used to determine the levels of chemotherapy that are effective in killing the tumor [1,7]. Along with determining the correct levels of chemotherapy to use in treatment, it is necessary to find a proper schedule to give doses of the drug that would maximize efficacy and have a low overall toxicity [1].

There are two types of existing chemotherapy treatments commonly used, Maximum Tolerated Dose (MTD) and Metronomic Chemotherapy (MC) [2]. MTD chemotherapy is given in high doses with periods of rest between treatments in order to use the maximum amount of drug that is tolerated by the patient [2, 3]. Metronomic chemotherapy is the lowest amount of toxicity of chemotherapy administered over a longer period of time [2]. Both types of chemotherapy have specific benefits when treating certain types of cancer; for example, a higher dose may cease tumor growth when the

converse, a low continuous dose, may have no effect on the tumor [14]. When taking into consideration the different types of chemotherapy it is useful to develop a mathematical model to determine which type of chemotherapy has the greatest efficacy in treating the tumor.

To track the movement and toxic build-up of chemo-therapy throughout the tumor and the body, experimenters have developed imaging agents that can bind to certain proteins to mimic the movement of chemotherapy [4, 5, 6]. The imaging agents are able to show where in the body, aside from the tumor, the chemotherapy has accumulated. The build-up of the imaging agent shows experimenters where the chemotherapy becomes lethally toxic [6]. The lethality of chemotherapy occurs when it has accumulated in an area that contains healthy cells, the cell death that occurs is considered harmful because the cells were not cancerous. It is important to develop a mathematical model that can compartmentalize the effects of chemotherapy in regard to toxicity in order to have less invasive procedures [6, 7].

Compartmentalized models are able to show the movement of the drug in and out of the tumor and various other organs such as the kidneys, which are involved in the filtering of the blood and excretion of waste [6]. Gompertz-type growth models take into account the slowing of tumor growth as the mass reaches a certain cell population level [1, 7]. It is important to take into consideration, when creating a mathematical model, that the tumor will decrease and increase in growth rates as the drug is being administered and the cells become resistant to the drug [7, 8]. The fluctuation of growth rates of cells in the tumor are due to the administration of the chemotherapy, especially the Maximum Tolerated Dose (MTD) treatment and the Gompertz style of growth [1,7,8]. The MTD chemotherapy treatment has a characteristic side-effect of fluctuating mass size due to the manner it is administered because of it is given in high doses and requires a rest period afterward to reduce toxicity [2,3].

It is our goal to develop a mathematical model for our PIC Math sponsor, the Moffitt Cancer Center, that has an optimal schedule that will maximize drug efficacy with the minimal amount of toxicity required. Such a model would be effective in suppressing tumor growth and be minimally harmful to the healthy cells. Due to the importance of toxicity outside of the tumor, a compartmental model is necessary to track the movement and build-up of the drug in the body. The mathematical models created will take into consideration both types of chemotherapy treatment, the Maximum Tolerated Dose (MTD) and the Metronomic Chemotherapy (MC) because each are important in showing the effects each type have on a tumor.

MATHEMATICAL MODELS

In designing the models, we begin with a simplistic approach. Drawing heavily from [7], the first model simply shows how tumor size changes over time. The only variables the model includes are a rate constant k(Day^{-1}), cell population T (mm^3), and the carrying capacity T_∞(mm^3). See appendix I for a table containing the variables described.

$$\frac{dT}{dt} = kT\left(1 - \frac{T}{T_\infty}\right) \tag{1}$$

Based on the previously listed simplistic mathematical model, we constructed our alternative models with regard to the simple models. In this mathematical model we start with the logistic growth model:

$$\frac{dT(t)}{dt} = \lambda_L T(t)\left(1 - \frac{T(t)}{T_\infty}\right) - L(T(t), C(t)) \tag{2}$$

The logistic growth model describes the relationship between the tumor growth and the effect of the anticancer drug. The first term

$$\lambda_L T(t)\left(1-\frac{T(t)}{T_\infty}\right)$$

describes the increase in cells due to proliferation with carrying capacity T_∞.

$$\lambda_L = \frac{1}{\tau} ln\left(\frac{T_\infty - T_0}{T_\infty/2 - T_0}\right)$$

λ_L, the tumor growth rate is a constant and is calculated from the tumor doubling time τ. Initially, the solution explodes exponentially at a rate λ_L (tumor growth rate), which eventually converge to the equilibrium value $T(t)= T_\infty$ for the population over time. The second term

$$L(T(t), C(t)) = k(C(t) - C_{thr})H(C(t) - C_{thr})T(t)$$

describes the decrease in cells due to drug. We begin the equation with the drug's specific kill rate, k_{eff}, which is a major determining factor in the effects of the drug. We then multiply by the amount the concentration is above the threshold, $C(t) - C_{thr}$, to prevent errors from occurring when the concentration is below the drug's threshold, we multiply by the output of our Heaviside function, H. Thus far, we are essentially representing how much of a given volume would be killed by the drug, finally we multiply by the tumor's volume at time *t*, $T(t)$, to reach a complete model for cells lost due to drug treatment. *H* is a Heaviside function where:

$$H = \begin{cases} 0 & if: C(t) - C_{thr} < 0 \\ 1 & if: C(t) - C_{thr} \geq 0 \end{cases}$$

As mentioned in [1, 7], such simple models are unable to accurately portray complex growth dynamics. Merely utilizing a rate constant to control growth rate is a rather naive method of constructing a model, when in experiments growth of a cancer does not resemble a linear function. Instead, a Gompertz style equation, one which replicates the results of tumor growth slowing due to decreased nutrients and increased cell density, is used to more accurately reproduce experimental data. The second equation thus shows how tumor volume at a given time, $T(t)$ (mm^3), changes with time *t* (days).

$$\frac{dT(t)}{dt} = \frac{1}{\tau_g}\frac{\ln[\theta_g/T_0]}{\ln[\theta_g/2T_0]}T(t)\ln\left[\frac{\theta_x}{T(t)}\right] - L(T(t), C(t)) \quad (3)$$

In this equation, we have two contributing parts. The first we will detail is the first half:

$$\frac{1}{\tau_g}\frac{\ln[\theta_g/T_0]}{\ln[\theta_g/2T_0]}T(t)\ln\left[\frac{\theta_x}{T(t)}\right]$$

Growth is modeled using variables of plateau size θ_g (mm^3), tumor doubling size τ_g (days), initial tumor volume (mm^3), and "θ_x" which was incorrectly typed in [7], as it was meant to be θ_g (mm^3). These are input into a standard Gompertz growth model, representing the natural growth of the tumor unimpaired by the introduction of the drug. As such, inputting *L=0* (Cell number) would model an untreated tumor giving a starting point for our mathematical models [7].

The later half, $-L(T(t),C(t))$, represents the efficacy of the treatment, measured as tumor cell loss due to therapy. The function $L(a,b)$ is a measurement of the cells lost, with inputs $a=T(t)$ being the tumor volume at time *t* and $b=C(t)$ (ng/mm^3) being drug concentration at the tumor site.

The assumptions for the drug concentration mathematical models are, drug is administered by

infusion, there is an instantaneous mixing of the drug with plasma, there is an immediate delivery of the drug to the tumor site, and the drug fluid dynamics mimic the florescence used in the mouse model graphic simulation data given by the client.

DRUG CONCENTRATION PROFILE

There are three compartments being considered for the drug concentration profile. The three compartments are concentration of drug in the blood, the tumor, and the other tissues. The following tables give the parameters and the description used in the drug concentration profile. See appendix I for a comprehensive legend of variables and parameters used.

Variable	Unit	Parameter
$BL(t)$	ng/mm^3	[Drug in Blood]
$TL(t)$	ng/mm^3	[Drug in Tumor]
$NL(t)$	ng/mm^3	[Drug in Other Tissues]
$T(t)$	mm^3	Tumor Volume

The values for the parameters used are obtained from [7]:

Variable	Value (d^{-1})	Parameter (Rate)
k_{10}	151.2 d^{-1}	Blood Outbound
k_{12}	5.62 d^{-1}	Tumor Inbound
k_{21}	2.31 d^{-1}	Tumor Outbound
k_{13}	5.62 d^{-1}	Other Tissue Inbound
k_{31}	2.31 d^{-1}	Other Tissue Outbound

The drug concentration profile in each of the compartments is as follows:

$$\frac{dBL}{dt} = (k_{21})(TL)\left(\frac{T}{VB}\right) + (k_{31})(NL)\left(\frac{VN}{VB}\right) \quad (4)$$

$$-(k_{12} + k_{13})(BL) - k_{10}(BL)\left(\frac{d}{VB}\right)$$

$$\frac{dTL}{dt} = (k_{12})(BL)\left(\frac{VB}{T}\right) - (k_{21})(TL) \quad (5)$$

$$\frac{dNL}{dt} = (k_{13})(BL)\left(\frac{VB}{VN}\right) - (k_{31})(NL) \quad (6)$$

The first compartment (4) is the concentration of the drug in the blood leaving the tumor and other tissues. The second compartment (5) is the amount of drug in the tumor as it enters and exits the tumor. The third compartment (6) is the amount of drug as it enters and exits the other tissues.

TOXICITY MODEL

The following table gives values to the parameters used in the toxicity model. These values were obtained from [7]:

Parameter	Value
$NL_{max}(t)$	50 d
$NL_{cum}(t)$	2.1x10^3d days
t	84 days

The model

$$0 \leq NL(t) \leq NL_{max} \quad (7)$$

limits the drug concentration in nonspecific tumor site between a lower and an upper bound at each drug administration. The model

$$\int_0^T NL(t)dt \leq NL_{cum} \quad (8)$$

places an upper bound on the total cumulative toxicity at the end of the treatment period.

In the toxicity model our group takes into account drug decay rate. We assume drug decay rate to be equivalent to recovery from toxicity in order to have a more accurate model for toxicity, since toxicity recovery cannot be implemented directly. The equation below depicts how we take into account the drug decay rate.

$$(k_{13})(BL)\left(\frac{VB}{VN}\right) - (d)(DK) \qquad (9)$$

This is a measure of the amount of drug entering the body minus the current concentration of the drug multiplied by its decay rate (days^{-1}), (d)(DK).

RESULTS

Our immediate results with the mathematical models were very basic in terms of what was modeled and the parameters used. Initially we developed two basic graphs in order to test the Gompertz model code without the drug included. Our group did this to see the uninhibited tumor growth in the model we used. The parameters that differed between the two models were initial tumor volume and time.

Figure 1 depicts the tumor initial volume starting at an arbitrarily selected 80 mm^3 and measures the growth rate without drug for a span of 180 hours. This graph is able to portray a correct Gompertz growth style curve, which indicated a successful simple mathematical model.

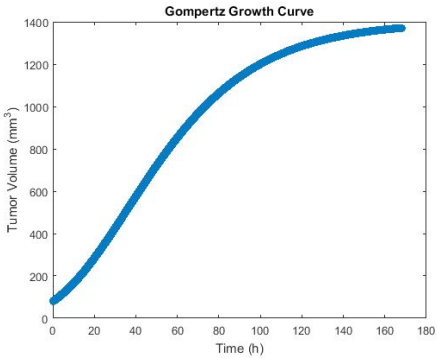

Figure 1: Gompertz Model Without Drug (80 mm^3).

Figure 2 shows the second graph developed; which is measured for a longer period of time, 350 hours, and has a tumor initial volume of one cell. The one cell start size was chosen to replicate a cancerous cell that begins over replication from a simple mutation of a healthy cell.

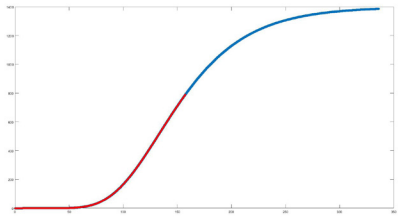

Figure 2: Gompertz Model Without Drug (One Cell).

Both graphs are a comparison of tumor volume (y-axis) and time (x-axis) to show the uninhibited tumor growth over time. By using the different tumor initial volume sizes our group was able to see the importance of the parameter in our development of accurate mathematical models for drug efficacy and toxicity.

The next graph (figure 3), we developed upon client request. Our client requested we test our mathematical model by matching the data provided in graph E (figure 9). The data provided by the client was obtained through bicarbonate therapy experimentation with mice. The data in the graph were the points we compared all data produced by our

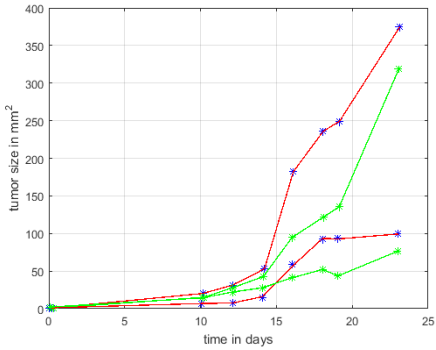

Figure 3: Graph E with Data Points.

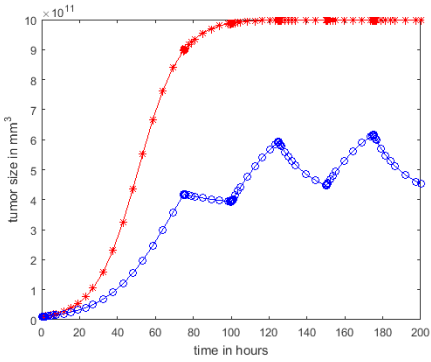

Figure 4: Drug in Tumor.

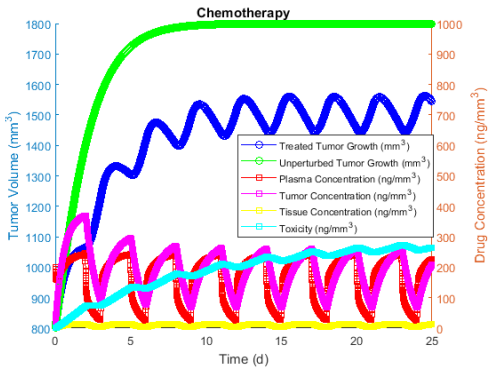

Figure 5: Early Graph of Chemotherapy Treatment.

models to, in order to have a more accurate depiction of the drug efficacy. The bicarbonate therapy data in the graph was given to our group by the client as a comparison for the florescent dye we were to model in our mathematical models created.

Figure 4 is an early graph of our group's attempts at modeling uninhibited tumor volume and tumor volume when treated with the drug. In figure 4 uninhibited tumor size is measured by the red line and the treated tumor is measured by the blue line. In this early iteration of drug scheduling, the tumor volume is affected by each dose of the drug which is denoted by each peak in the blue line on the graph. The graph's only successes are in showing tumor volume and the effects of the drug.

Figure 5 shows an early iteration of our attempts at trying different options with the drug scheduling and toxicity levels, the first option being Maximum Tolerated Dose (MTD) treatment. In this graph dosing is based on set time intervals, which can be changed as seen fit by experimenters. The graph demonstrates the tumor volume beginning to be affected by the drug scheduling, showing that our group was on the right track as far as scheduling and drug concentration were concerned for a MTD type of treatment.

Figure 6 was our next option for drug scheduling and toxicity measurement, Metronomic Chemotherapy (MC) treatment, which caps dosing when toxicity threshold is reached. Figure 6 had less peaks and had much smoother lines because of the constant drug administration due to the specifications of metronomic chemotherapy. Therefore, the graph accurately depicts the administration of drug over a constant time interval, only stoping drug treatment when the toxicity threshold is reached.

In the graph the light blue lines show what happens once the toxicity threshold has been reached. That is, the drug administration will stop until toxicity has decreased and then will begin again once

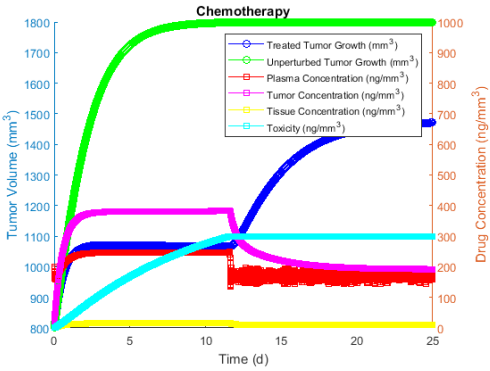

Figure 6: Early Toxicity Graph.

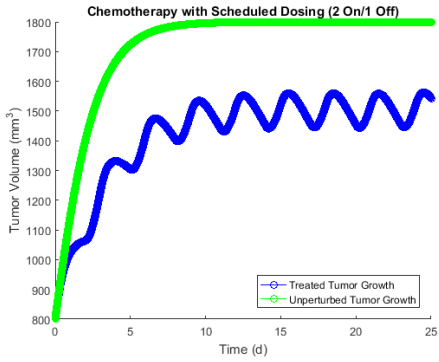

Figure 7: Chemotherapy with Scheduled Dosing (2 On/1 Off) Dose amount: 4000ng

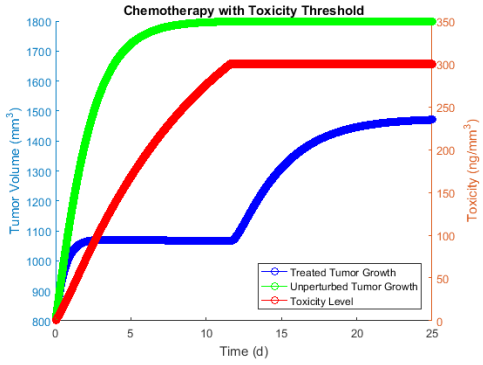

Figure 8: Chemotherapy with Toxicity Threshold. Dose amount: 4000ng.

toxicity is below threshold, creating the appearance of a line with many points close together on it. Due to this feature of toxicity and drug concentration levels explained by metronomic chemotherapy treatment our group tried to stray away from it in our final models.

For both of the early attempts of our modeling all six compartments are shown in the graphs (figures 5 and 6) by a different colored line. The green line in each of the graphs shows the uninhibited tumor growth, while the purple line is the tumor treated with drug. The orange line on the graphs is the drug concentration in the non-specific tissues. The red and light blue lines show drug concentration in the blood and toxicity respectively. The dark blue line depicted the drug efficacy for the treatment being used.

In figure 7, modeling a MTD drug schedule, we implemented a two day on, one day off schedule. Simply put we administered drug for two days and left treatment alone for one day. The graph shows uninhibited tumor growth in green, and treated tumor growth in blue. Again, the graph compares tumor volume, with a maximum of 1800 (mm^3), (y-axis) and time for twenty-five days, (x-axis).

The final graph (figure 8) modeling a MC treatment schedule shows that the tumor responds to treatment until the toxicity threshold has been reached. Once the toxicity threshold has been reached the tumor begins to stop responding to treatment due to there not being enough drug administered to affect it. The green line, again, displays an untreated tumor with the blue line representing a treated tumor. The red line shows the toxicity levels where the y-axis on right side of the graph shows the toxicity levels in ng/mm^3.

See appendix I - Tables and Graphs, for further simulations of the mathematical models for MTD and MC chemotherapy, along with a graphic of a mouse model at three days of tumor treatment.

DISCUSSION AND CONCLUSIONS

The two Gompertz growth model graphs have shown our group an important aspect of the research we are doing. That is the starting point and data we use are critical in developing a working and accurate model to use in cancer research.

Another important aspect we learned as we created the models was that toxicity levels compared to drug concentration have a great impact on how much the tumor will react to the treatment being given. The Metronomic (MC) treatment schedule, shown in figure eight, is a good example of that because once the toxicity threshold has been reached the tumor does not react as much to the drug administration. The model shows that the tumor begins to start growing again, showing that it is not an affective treatment for the cancer. While, the Maximum Tolerate Dose (MTD) schedule (figure 7) appears to have more of an affect on the tumor by decreasing the amount that it can grow by. The tumor is immediately affected by the drug and does decrease in size and growth, but as soon as the drug stops being administered the tumor begins to grow again, therefore, causing the treatment to not be affective enough to completely eradicate the tumor.

In attempting to develop a toxicity measure our group has come across an issue with the method in which drug toxicity is measured, which is through a standard weight loss model. The main problem with the weight loss model is that cancer patients naturally loose weight due to the disease, so it is hard to determine what weight is lost due to the drug alone. When the tumor is responding properly to treatment, it should be shrinking as well, which in turn can cause an amount of weight loss. Thus, we cannot correctly assume all weight lost is due to the tumor loosing mass. Due to the unknowns that come with the weight loss models, it is incorrect to assume that all weight lost during treatment is due to toxicity of the drug. Therefore, in order to implement a toxicity model that had less assumptions we used a model that accounts for the drug decay rate and the amount of drug that is in the non-specific tissue. The model allows us to get a better picture of the drug concentration of the entire body and not just the tumor, therefore giving us a more accurate toxicity measure.

LIMITATIONS

Throughout our equations, we assume a compartmentalized model. As mentioned previously, this is both a more simplistic and more accurate representation of tumor-drug dynamics. In this manner, we are able to study the effects of the chemotherapeutic toxicity on each compartment. A limitation of our modeling is the requirement of representing flow of near infrared florescent dyes, as their flows are the only data we were provided. We are aware that the dynamics of these dyes may not mimmic the flow of the drug, and have taken measures to report the differences between the dye and drug accordingly.

Another limitation of our model is the inability to properly compare our data produced from our models to that of the florescent imaging agent due to the lack of ability to interconvert the data. Due to that fact, we reached out to our client to determine the best possible solution to our problem. At this point we have decided to compare them based off of equivalence.

Our greatest limitation in our models has stemmed primarily from the lack of usable data. In reaching out to our client, we were discouraged from looking into particular parameters (namely results from an unspecified paper on bicarbonate therapy).

The reason for our interest in the parameters from the bicarbonate therapy were due to the fact that the data given to us from the client stemmed from that research. Therefore, all data has been suggested to be extrapolated from the following graph; Graph E:

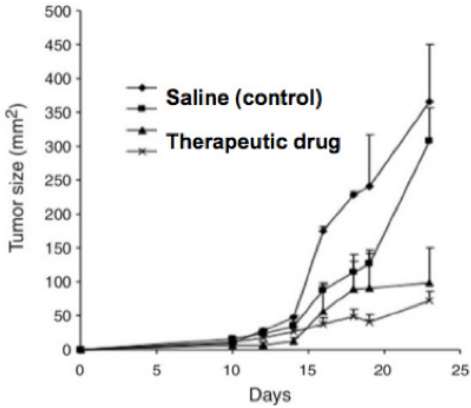

Figure 9: Graph E.

FUTURE WORK

In future work our group aims to create an alternative model that can better incorporate additional parameters such as: vasculature of the tumor and surrounding organs, tumor density, drug uptake patterns and resistance. Upon completion of our alternative model we intend to produce a mouse model graphic simulation that can take into consideration the different veins and arteries that will come into contact with the tumor. The proximal vasculature is important to model due to the complexities that arise because the tumor has the ability to restrict blood flow, which will effect how much drug is able to get into the tumor.

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REFERENCES

Traina, T. A., Dugan, U., Higgins, B., Kolinsky, K., Theodoulou, M., Hudis, and C. A., Norton, L., "Optimizing Chemotherapy Dose and Schedule by Norton-Simon Mathematical Modeling," *Breast Dis.,* vol. 31, no. 1, p. 7-18.

Shah, A. B., Rejniak, K. A., and Gevertz, J. L., "Limiting the Development of Anti-cancer Drug Resistance in a Spatial Model of Micrometastases," *Math Biosci Eng.,* vol. 13, no. 6, p. 1185-1206.

Vanhoefer, U., Cao, S., Harstrick, A., Seeber, S., and Rustum, Y. M., "Comparative antitumor efficacy of docetaxel and paclitaxel in nude mice bearing human tumor xenografts that overexpress the multidrug resistance protein (MRP)," *Annals of Oncology,* vol 8, p. 1221-1228.

Tafreshi, N. K., Enkemann, S. A., Bui, M. M., Lloyd, M. C., Abrahams, D., Huynh, A. S., Kim, J., Grobmyer, S. R., Carter, W. B., Vagner, J., Gillies, R. J., and Morse, D. L., "A Mammaglobin-A Targeting Agent for Noninvasive Detection of Breast Cancer Metastasis In Lymph Nodes," *Cancer Research,* vol. 71 no. 3, p. 1050-1059.

Bradshaw-Pierce, E. L., Eckhardt, S. G., and Gustafson, D. L., "A Physiological Based Pharmacokinetic Model of Docetaxel Disposition: From Mouse to Man," *Cancer Therapy: Preclinical,* vol. 13 no. 9, p. 2768-2776

Tafreshi, N. K., Silva, A., Estrella, V. C., McCardle, T. W., Chen, T., Jeune-Smith, Y., Lloyd, M. C., Enkemann, S. A., Smalley, K. S. M., Sondak, V. K., Vagner, J., and Morse, D. L., "In Vivo and in Silico Pharmacokinetics and Biodistribution of a Melanocortin Receptor 1 Targeted Agent in Preclinical Models of Melanoma," *Molecular Pharmaceutics,* vol. 10, p. 3175-3185.

Hadjiandreou, M. M., and Mitsis, G. D., "Mathematical Modeling of Tumor Growth, Drug-resistnace, Toxicity, and Optimal Therapy Design," *IEEE Transactions on Biomedical Engineering*, vol. 61 no. 2, p. 415-425.

Au, J. L.-S., Guo, P., Gao, Y., Lu, Z., Wientjes, M. G., Tsai, M., and Wientjes, M. G., "Multiscale Tumor Spatiokinetic Model for Intraperitoneal Therapy," *The AAPS Journal,* vol 16 no. 3, p. 424-439.

Stolfi, R. L., Martin, D. S., Sawyer, R. C., and Spiegelman, S., "Modulation of 5-Fluorouracil-induced Toxicity in Mice with Interferon or with the Interferon Inducer, Polyinosinic-Polycytidylic Acid," *Cancer Research,* vol. 43, p. 561-566.

Hadjiandreou, M. M., and Mitsis, G. D., "Towards tumor growth control subject to reduced toxicity," *American Control Conference,* vol. 2012. p. 5592-5597.

Loizides, C., Lacovides, D., Hadiandreou, M. M., Rizki, G., Achilleos, A., Strati, K., and Mitsis, G. D., "Model-Based Tumor Growth Dynamics and Therapy Response in a Mouse Model of De Novo Carcinogenesis," *Plos One,* p. 1-18.

Ishikawa, T., Utoh, M., Sawada, N., Nishida, M., Fukase, Y., Sekiguchi, F., and Ishitsuka, H., "Tumor Selective Delivery of 5-Fluorouracil by Capecitabine, a New Oral Fluoropyrimidine Carbamate, in Human Cancer Xenografts," *Biochemical Pharmacology,* vol. 55, p. 1091-1097

The American Cancer Society medical and editorial content team. "How Chemotherapy Drugs Work" https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html (Updated February 15, 2016)

The American Cancer Society medical and editorial content team. "How is Chemotherapy used to treat Cancer?" https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-is-chemotherapy-used-to-treat-cancer.html (Updated February 16, 2016)

APPENDIX I - TABLES, GRAPHS, AND ADDITIONAL FIGURES

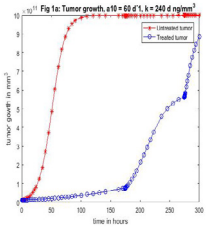
Variables and Parameters for Mathematical Models 1, 2, 3

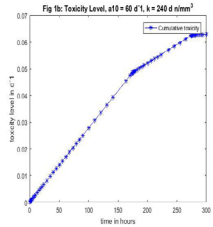
Variable	Value	Unit	Parameter
t	-	days	Time
t_0	0	days	Initial Time
t_f	25	days	Final Time
$T(t)$	-	mm^3	Tumor Volume
k	8.4×10^{-3}	cells $days^{-1}$	Rate Constant
θ_g	2400	mm^3	Plateau Size
τ_g	1.88	days	Tumor Doubling Time
T_0	1	mm^3	Initial Tumor Size
T_m	800	$days^{-1}$	Tumor Size at Treatment
L	-	Cell Number	Decrease in Cells Due to Therapy
$C(t)$	-	ng/mm^3	Drug Concentration at Tumor Site
C_{thr}	75	ng/mm^3	Therapeutic Threshold
H	-	-	Heaviside Function
k_{eff}	0.001	d ng/mm^3	Drug Kill Rate
d	900	$ng\ d^{-1}$	Dosage
λ_L	9.9×10^{-4}	Day^{-1}	Tumor Growth Rate
T	10^{10}	mm^3	Initial Population
T_∞	10^{12}	cells	Carrying Capacity
τ	-	days	Tumor Doubling Time
k_{10}	5.62	$days^{-1}$	Tumor Inbound Rate
k_{12}	2.31	$days^{-1}$	Tumor Outbound Rate
k_{21}	6.67	$days^{-1}$	Other Tissue Inbound Rate
k_{13}	2.9	$days^{-1}$	Other Tissue Outbound Rate
k_{31}	151.2	$days^{-1}$	Blood Outbound Rate
VB	710	mm^3	Blood Volume
VN	25900	mm^3	Tissue Volume
DK	0.10416	$days^{-1}$	Drug Decay Rate
T_{Xthr}	500	ng/mm^3	Toxicity Threshold

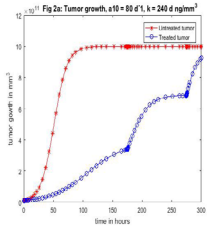
0.0.1 Scheduling and drug concentration 1:

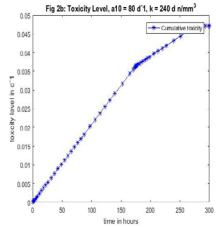
$$U = \begin{cases} 0.02 & \text{if} t < 175 \\ 0.01 & \text{if} 175 \leq t < 275 \\ 0.001 & \text{if} 275 \leq t < 300 \end{cases}$$

Vary drug exit rate, $a10$ from the system, fix drug kill efficiency $k = 240$:

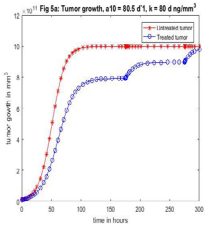


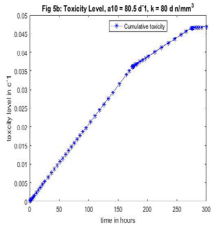


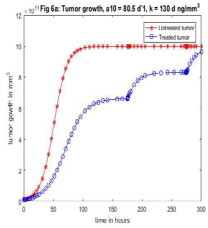


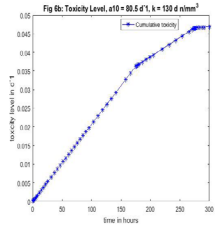


Vary drug kill efficiency, k and fix drug exit rate $a10 = 80.5d^-1$:





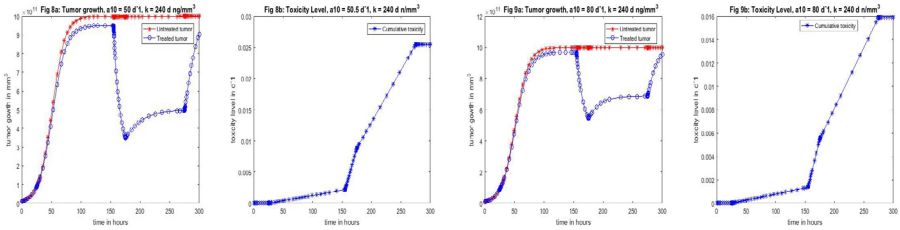




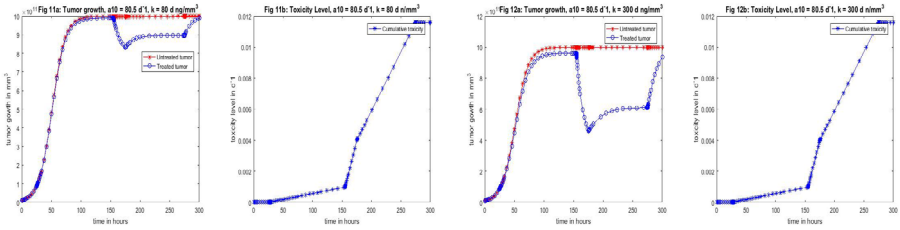
0.0.2 Scheduling and drug concentration 2:

$$U = \begin{cases} 0.0 & \text{if} t < 25 \\ 0.001 & \text{if} 25 \leq t < 155 \\ 0.02 & \text{if} 155 \leq t < 175 \\ 0.01 & \text{if} 175 \leq t < 275 \\ 0.0 & \text{if} 275 \leq t < 300 \end{cases}$$

Vary drug exit rate, $a10$ from the system, fix drug kill efficiency $k = 240$:



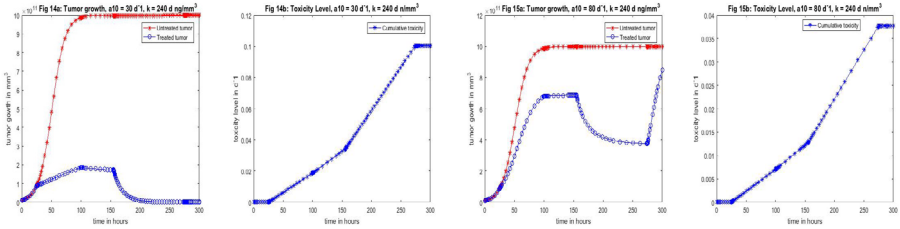
Vary drug kill efficiency, k and fix drug exit rate $a10 = 80.5d^-1$:



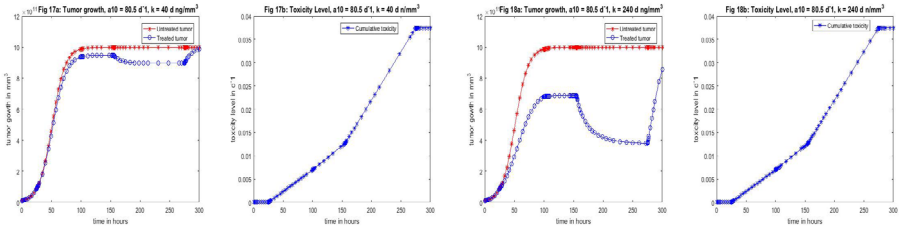
0.0.3 Scheduling and drug concentration 3:

$$U = \begin{cases} 0.0 & \text{if} t < 25 \\ 0.009 & \text{if} 25 \leq t < 100 \\ 0.01 & \text{if} 100 \leq t < 155 \\ 0.02 & \text{if} 155 \leq t < 275 \\ 0.0 & \text{if} 275 \leq t < 300 \end{cases}$$

Vary drug exit rate, $a10$ from the system, fix drug kill efficiency $k = 240$:



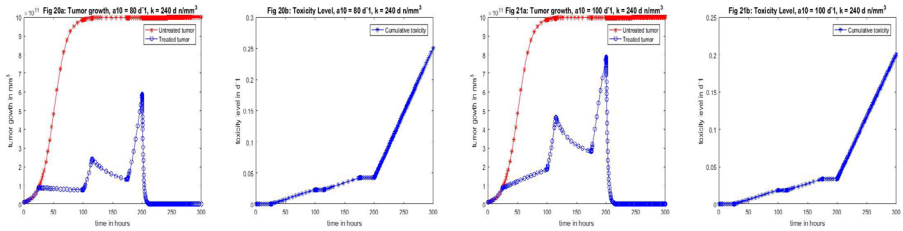
Vary drug kill efficiency, k and fix drug exit rate $a10 = 80.5d^{-}1$:



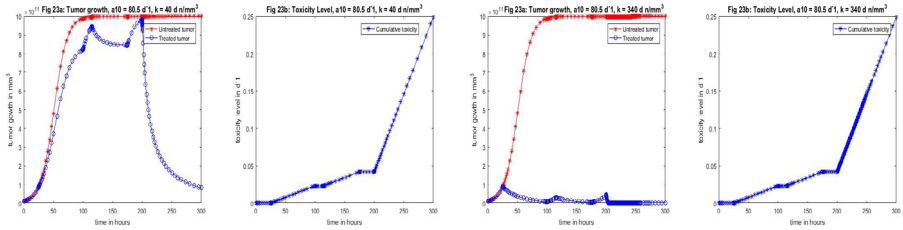
0.0.4 Scheduling and drug concentration 4:

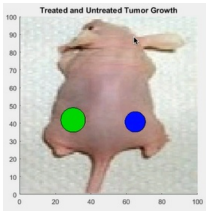
$$U = \begin{cases} 0.0 & \text{if} t < 25 \\ 0.03 & \text{if} 25 \leq t < 100 \\ 0.0 & \text{if} 100 \leq t < 115 \\ 0.03 & \text{if} 115 \leq t < 175 \\ 0.0 & \text{if} 175 \leq t < 200 \\ 0.2 & \text{if} 200 \leq t < 300 \end{cases}$$

Vary drug exit rate, $a10$ from the system, fix drug kill efficiency $k = 240$:



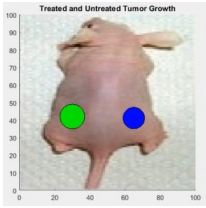
Vary drug kill efficiency, k and fix drug exit rate $a10 = 80.5d^-1$:





mouse.png

Figure 10: MTD Mouse Model. (Green dot - untreated tumor; Blue dot - treated tumor.)



mouse.png

Figure 11: MC Mouse Model. (Green dot - untreated tumor; Blue dot - treated tumor.)