Master of Applied Mathematics Program
Professional Master's Project Report
Department of Applied Mathematics
Illinois Institute of Technology

Pharmacodynamic Models in Cancer with Treatment

Submitted by

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Abstract

Tumor growth often follows simple laws that can expressed as mathematical models. The models that are comprised in this study include the Gompertz Equation, the Logistic Equation and the Hahnfeldt Model that describe the relationship between a tumors carrying capacity and the carrying capacity of the vasculature. To understand the Hahnfedlt Model, it is necessary to explore the relationship that the Gompertz Equation and Logistic Equation have in regards to the carrying capacity of the tumor and the vasculature, respectively. The mathematical models explored use anti-angiogenic agents in two settings that involve continuous injection, and time varying injection. The former is not ideal for a patient, but is still studied, likewise, the latter is studied when a same sized dose is administered to a patient.

Contents

1 Introduction

Mathematical modeling is rapidly developing in pharmacokinetics and pharmacodynamics. Mathematical models of tumor growth provide the potential for personalized treatment therapies for cancers. These models capture dynamics between the cancer and the cancer therapy agent(s) used for identifying therapy for cancer treatment. Various model types such as, the fixed effect model, the linear model, the log-linear model, the E_{max} model (Michaelis-Menton Equation) and the sigmoid E_{max} model (Generalized Hill Functions) contribute to finding wider applications in drug therapy. Pharmacokinetics (PK) and Pharmacodynamics (PD) establish procedures for measuring pharmacokinetic drug levels of standard chemotherapeutic agents. Mathematical models in pharmacokinetics and pharmacodynamics emphasize the relations between a drugs dose rate, concentration in compartments within the body, and the overall effect the drug has on the cancer. The pairing of a pharmacokinetics and pharmacodynamics model inhibit the study of the relationship that the drug dose has with the drugs concentration within the compartment and how the cancer responds to the drug.

Angiogenisis is the formation of new blood vessels that typically occur in multiple processes in the body, such as, pregnancy in the maternal and fetal placental tissues, wound healing to help grow a multi-vascular network, and in tumors which help support the tumor with blood supply for growth [8]. With the essential role of angiogenesis in tumor growth, incorrect structures and poor vessel growth are common features in tumor growth.[3]In this project, a variety of pharmacodynamic models analyze the chemotherapeutic and anti-angiogenic therapy drug effects in the cancer tumor and the vasculature, respectively. The Gompertz Equation is used to analyze the effect of the chemotherapeutic drug on the cancer tumor, and the logistic equation is used to analyze the anti-angiogenic therapy drug on the vasculature. A one-compartment pharmacokinetic model is considered for a a single anti-angiogenic therapy agent. The objective is to determine how the single agent can be used to minimize the overall progression of the tumor volume and the vasculature of a tumor through the injection of anti-angiogenic cancer therapy agents. Classic tumor growth models and tumor growth models coupled with growth models of the carrying capacity of the vasculature will be analyzed to determine how the pharmacodynamic relationship of chemotherapeutic and anti-angiogenic agents affect the growth.

2 Classic Tumor Growth Models

Mathematical models play a role in various ways in modeling the growth and treatment of cancer tumors [2]. There are numerous models that have been proposed which are often specific to the type of cancer being studied. We consider two of the most popular models: Gompertz and Logistic.To

understand the nature of the system of ordinary differential equations, the analyticsolutions to each differential equation will provide an underlying understanding to the pharmacodynamic models.

2.1 The Gompertz Equation

The Gompertz Equation is a multifaceted equation used to fit growth data from population growth to tumor and bacterial growth. The Gompertz Equation was used by A.K Laird [4] in 1964 by fitting it to tumor growth data. Laird discovered that the model is useful when the starting value of the tumor growth is present. The model has been used for modeling tumor growth in breast cancer and lung cancer [9] .The defining feature for the Gompertz Equation is that the growth rate decays exponentially as the tumor volume increases. The Gompertz equation is used to describe the growth of the volume $p(t)$ of a tumor

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}),\ p(0) = p_0 \tag{2.1}$$

where α is the tumor growth rate, p is the volume of the tumor, and q is the carrying capacity of the vasculature, which is a constant. The solution of (2.1) is given by

$$p(t) = p_0 e^{\ln(\frac{k}{p_0})(1-e^{-\alpha t})} \tag{2.2}$$

The analytic solution and its graph show the characteristics of the Gompertz Equation . An essential characteristic of Figure 1 shows that the graph has quick exponential growth on a small time interval and stabilizes as the time interval increases. This is due to the fact that the volume of the tumor approaches the carrying capacity of the vasculature. Next, pharmacodynamic models will explore the affect the chemotherapeutic drug agent have on the volume of the tumor through continuous infusion and periodic infusion of the chemotherapeutic drug agent.

2.1.1 The Gompertz Equation with Continuous Chemotherapeutic Infusion

The Gompertz equation with continuous chemotherapeutic infusion is a pharmacodynamic model that is used to describe the growth of the tumor when there is a treatment used to minimize the volume. We include an additional term, up, in the Gompertz equation to describe the continuous infusion of a chemotherapeutic agent to reduce the tumor size. The infusion of the chemotherapeutic drug agent will show the pharmacodynamic relationship the chemotherapeutic drug agent has with the tumor cells. The pharmacodynamic model, (2.3) and the solution, (2.4) reflect how the concentration of the chemotherapeutic drug agent minimizes the tumor volume with respect to time. The solution to the pharmacodynamic model shows that with the inclusion of the chemotherapeutic drug agent will decrease the volume of the tumor due to the interaction of the chemotherapeutic

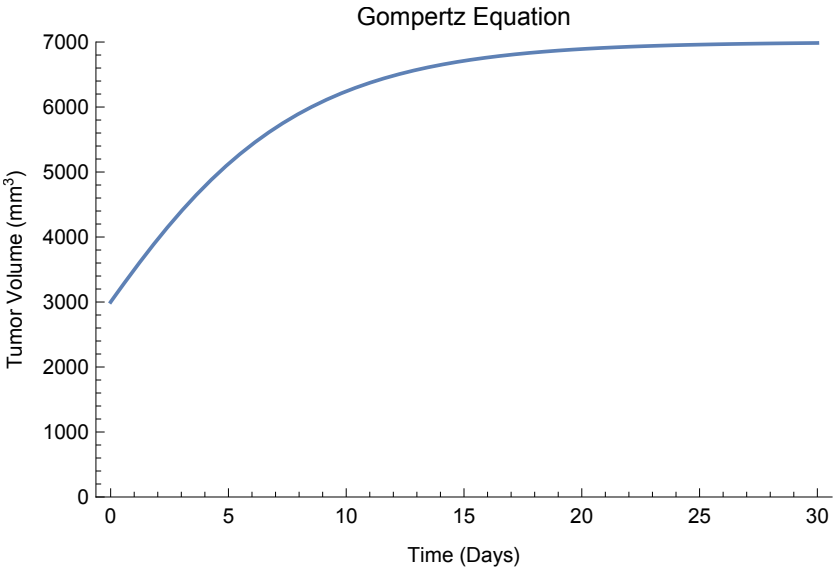

Figure 1: The Gompertz Equation with parameters:
$p_0 = 3000, q = 7000, \alpha = 0.2$

drug agent and the tumor cells. The pharmacodynamic model is

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}) - up,\ p(0) = p_0. \tag{2.3}$$

Here u is the concentration of the chemotherapeutic drug agent. The solution of (2.3) is

$$p(t) = p_0^{e^{-\alpha t}} e^{(\ln(q) - (\frac{u}{\alpha}))(1-e^{-\alpha t})} \tag{2.4}$$

The pharmacodynamic model displays how the presence of the continuous infusion of a chemotherapeutic agent can affect the cancer cell proliferation. When the concentration of the chemotherapeutic agent is minimal, the proliferation of the cancer cells reach a lower threshold compared to the untreated proliferation in Figure 1. As the concentration of the chemotherapeutic agent increases the proliferation of the cancer cells, and the volume of the cancer tumor decrease to a smaller, yet present size. When the concentration of the chemotherapeutic agent increases from the previous concentration, the necrosis of the cancer cells is most effective, due to the volume of the tumor minimizing to a negligible size, shown in Figure 2. The concentration of the chemotherapeutic agent minimizes the size of the cancer tumor within a thirty day interval when there is continuous infusion. Next, the concentration of a chemotherapeutic agent with periodic injections will analyze how it minimizes the proliferation of cancer cells.

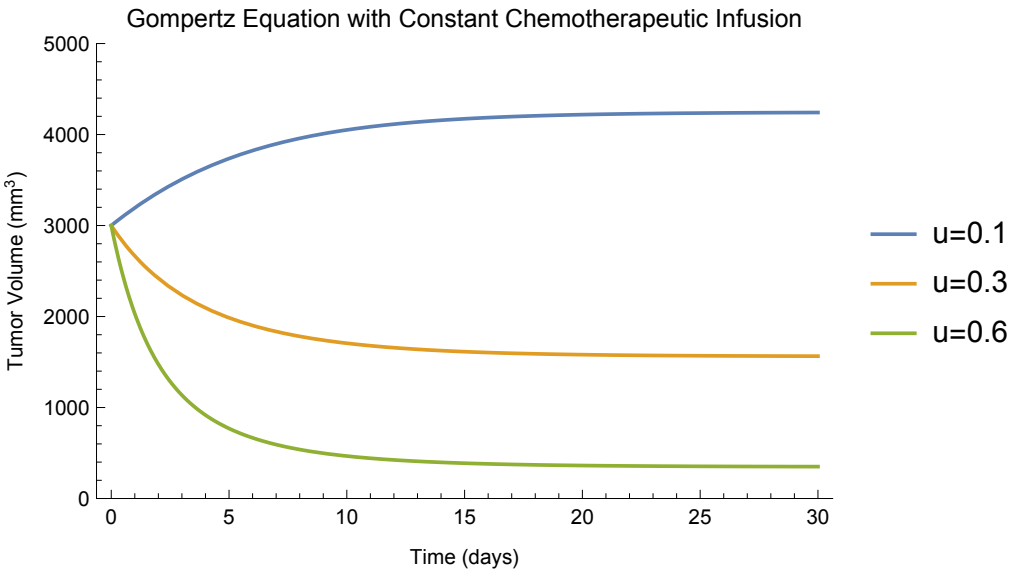

Figure 2: The Gompertz Equation with parameters:
$p_0 = 3000, q = 7000, \alpha = 0.2$

2.1.2 The Gompertz Equation with Periodic Chemotherapeutic Injections

We now consider the Gompertz equation where the chemotherapeutic agent is administered through intravenous injection. This model will provide the foundation for determining the minimum or maximum safe level for selecting the therapeutic dosing regimen on a given time interval. The equal dosing of the same chemotherapeutic agent will provide a therapeutic window that will maximize the dosing regimen, so that the volume of the tumor will decrease without harming the patient. The Gompertz Equation described below and the analytical solution provide an equal dosing regimen of the same chemotherapeutic agent on a fixed time interval.

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}) - u(t)p,\ p(0) = p_0 \tag{2.5}$$

The sum of Dirac delta functions is utilized to describe the frequency in which the same dose concentration,D, is administered to the patient. The Dirac delta function models the time interval in which a chemotherapeutic cancer agent is given to the patient through intravenous injection.

$$u(t) = D\sum_{i=1}^{n} \delta(t - t_i) \tag{2.6}$$

The solution of (2.5) is given by

$$p(t) = q \cdot q^{-e^{-\alpha t}} e^{-D\sum_{i=1}^{n} e^{-\alpha(t-t_i)} H(t-t_i)} p_0^{e^{-\alpha t}} \tag{2.7}$$

Where $H(t)$ represents the Heaviside function in solution (2.7). With the equal time dosing regimen of the same chemotherapeutic drug a tumor volume window is created, in which, the concentrations of the agent will diminish the volume of the tumor without significant adverse effects to the patient. The value D represents the equal dose of the chemotherapeutic drug that is administered at the periodic intervals. As the concentration of the dose increases the volume of the tumor decreases. The concentration of the dose has multiple implications on the model. When the dosing concentration exceeds a threshold, the dosing concentration can inversely effect the patients health. A dosing concentration that is too small will be ineffective against the tumor, therefore, optimizing the dosing concentration is vital towards the overall health of the patient. In Figure 3 the concentrations of the dose are compared. When the concentration is low, $D = 0.0025\frac{mg}{kg}$ the volume of the tumor still increases with the equal time dosing of the chemotherapeutic agent. As the value of the dosing concentration increases from $0.0025\frac{mg}{kg}$ to $0.0200\frac{mg}{kg}$, the size of the tumor decreases within the thirty day interval.With these chemotherapeutic concentrations, a treatment regimen greater than thirty days will be needed to minimize the tumor to a negligible size. In Figure 3 the concentration of the chemotherapeutic agent is $0.0400\frac{mg}{kg}$. This dosing regimen allows for the necrosis of the cancer cells minimizing the volume of the cancer tumor to a size of no consequence. The Gompertz equation with continuous chemotherapeutic infusion regimen is different from the periodic injection of the chemotherapeutic agent regimen. The time interval in which the volume of the tumor decreases approaches faster with continuous infusion than periodic infusion.

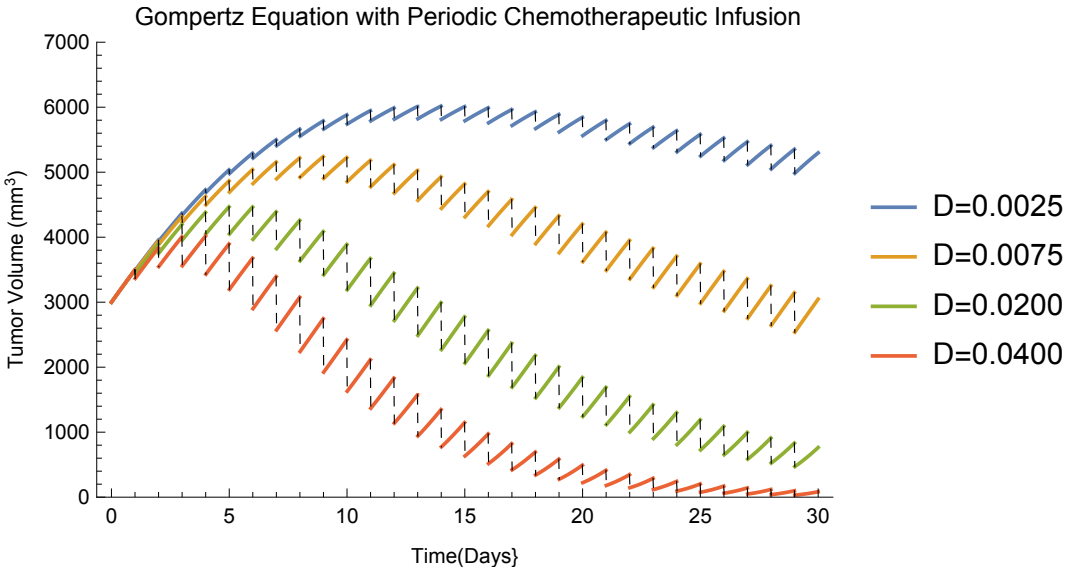

Figure 3: The Gompertz Equation with Periodic Injection with parameters:
$p_0 = 3000, q = 7000, \alpha = 0.2$

The Gompertz equation described the volume of the cancer tumor. The absence of the

chemotherapeutic agent allowed the volume of the cancer tumor to grow to the carrying capacity of the tumor. When the chemotherapeutic agent is introduced into the pharmacodynamic models, the volume of the cancer tumor decreases with varying concentrations of the chemotherapeutic agent. The continuous infusion of the chemotherapeutic agent decreases the volume of the tumor on a smaller time interval than the periodic injection of the chemotherapeutic agent. The next section will explore how the carrying capacity of the vasculature will change with the implementation of an anti-angiogenic therapy regimen in a set of pharmacodynamic models.

2.2 The Logistic Equation

The logistic equation is a prominently used equation in various applications of mathematical modeling. It has been used primarily for modeling population growth. The model can be fitted to data involving tumor growth with consistency. The logistic equation can be used to describe the volume of the vasculature, $q(t)$

$$\frac{dq}{dt} = \beta q(1 - \frac{q}{k}), q(0) = q_0 \tag{2.8}$$

Where the solution of (2.8) is given by

$$q(t) = \frac{q_0 k}{q_0 + (k - q_0)e^{-\beta t}} \tag{2.9}$$

The equation of interest, which shows bounded tumor growth, is a model that assumes that the vasculature of the tumor will approach an equilibrium point. The growth rate of the carrying capacity of the vasculature is described by the parameter β , and k represents the volume of the the vasculature in Equation (2.8). The model describes the vasculature in a tumor with no cancer therapy agents present. The logistic equation shows a limiting growth of the cancer tumor, because as the tumor volume increases the rate of growth of the tumor becomes less and less. In turn, the vasculature can only supply nutrients to parts of the tumor. The model and the analytic solution of the logistic equation is shown above. It is a first order differential equation that is a separable equation.

The graph of the logistic equation shows how there is bounded growth of the vasculature is shown in Figure 4.The growth of the vasculature grows exponentially as time increases during a small interval. As the time increases, the growth is bounded by the carrying capacity of the vasculature. The pharmacodynamic models show the relationship the anti-angiogenic agent has with the growth of the vasculature when there is continuous infusion of the agent and when there is periodic injection of the agent. These pharmacodynamic models explore the effects of the ability for the vasculature to efficiently carry blood, nutrients and oxygen to the tumor.

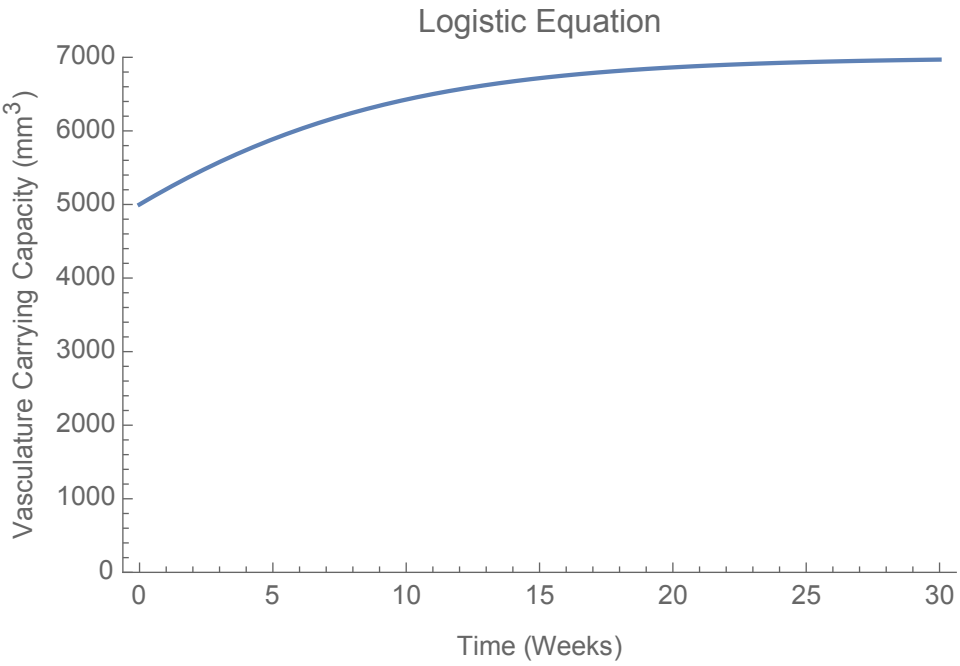

Figure 4: The Logistic Equation with parameters:
$q_0 = 5000, k = 7000, \beta = 0.15$

2.2.1 The Logistic Equation with Continuous Anti-Angiogenic Infusion

The logistic equation describes the change in the carrying capacity of the vasculature that supplies the tumor with nutrients, oxygen and blood. The pharmacodynamic model analyzed shows the effect of continuously infusion of anti-angiogenic cancer therapy treatment to the vasculature. The pharmacodynamic model represented in (2.10) shows the addition of the anti-angiogenic cancer therapy agent, with the term uq. The pharmacodynamic model is

$$\frac{dq}{dt} = \beta q(1 - \frac{q}{k}) - uq, q(0) = q_0 \tag{2.10}$$

Where the solution of (2.10) is given by

$$q(t) = \frac{(1 - \frac{u}{\beta})kq_0}{q_0 + ((1 - \frac{u}{\beta}) - q_0)e^{(\beta - u)t}} \tag{2.11}$$

The solution (2.11) reflects how the addition of continuous infusion of an anti-angiogenic cancer therapy agent will decrease the the carrying capacity of the vasculature. This analytic solution of provides some foundation for understanding how the injection of anti-angiogenic cancer therapy agent will effect the tumor growth when coupled with the Gompertz equation (2.1).The solution of the pharmacodynamic model (2.11) is similar to that of the logistic equation with the only

difference is the addition of the anti-angiogenic cancer therapy agent in the exponent and the change of the value of the carrying capacity of the vasculature, k. The solution reflects how the continuous infusion of the anti-angiogenic agent will affect the growth of the vasculature.

Figure 5 displays how the concentration of the anti-angiogenic agent affects the carrying capacity of the vasculature. The carrying capacity of the vasculature is affected when the concentrations of the anti-angiogenic agent vary. Figure 5 depicts that the minimal presence of a dose $u = 0.05\frac{mg}{kg}$ will not enable the proliferation of the vasculature, but maintain its initial size. When the concentration of the anti-angiogenic dose increases, the necrosis of the vasculature begins. When the concentration of the dose is $u = 0.3\frac{mg}{kg}$ the carrying capacity of the vasculature is minimized to a size that will prevent the supply of blood, oxygen and nutrients to the cancer cells in the tumor. The affects of the anti-angiogenic cancer therapy drug agent will be explored when the drug dose is administered on a periodic dosing regimen.

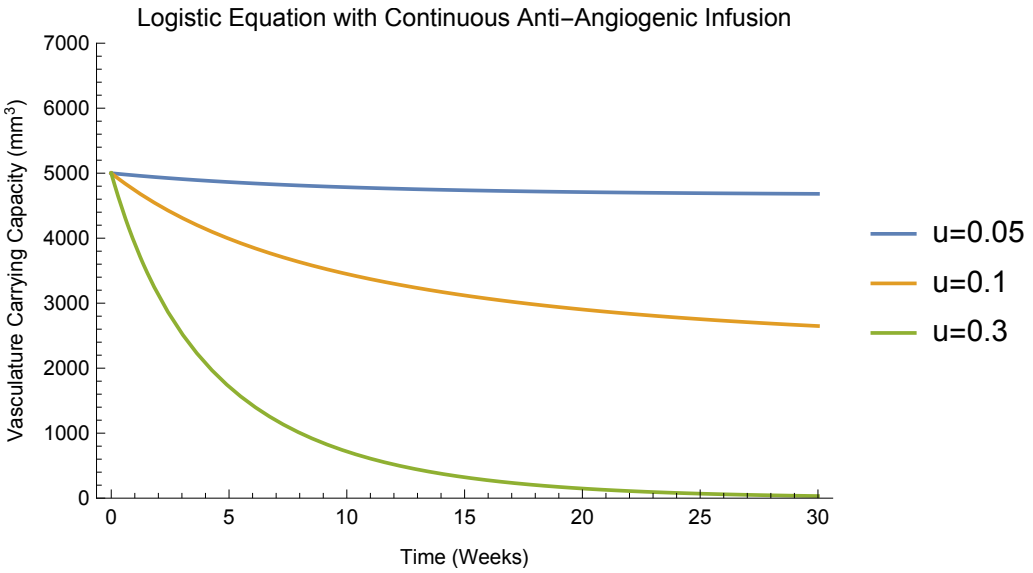

Figure 5: The Logistic Equation with Continuous Injection with parameters: $q_0 = 5000, k = 7000, \beta = 0.15$

2.2.2 The Logistic Equation with Periodic Anti-Angiogenic Injections

The pharmacodynamic model (2.12) describes the relationship between the change in the carrying capacity of the vasculature and the periodic dosing of anti-angiogenic drug agent. The pharmacodynamic relationship explores the adequate dosing regimen that will appropriately diminish the carrying capacity of the vasculature. Analyzing the effects of periodic injection of anti-angiogenic cancer therapy agent provides a basis for the Hahnfeldt Model. The implication of having the

periodic injection with the logistic equation emphasizes the choice to limit the carrying capacity of the vasculature around the tumor. The equation (2.12) shows how the addition of the periodic injection to the logistic equation will effect the carrying capacity of the vasculature.In the pharmacodynamic model the term $u(t)q$ is the log-kill term, which represents a measure of how thoroughly the anti-angiogenic agent reduces the carrying capacity of the vasculature. Analytically solving the pharmacodynamic model by transforming (2.12) to the Riccatti Differential Equation provided the procedures to analytically solve the pharmacodynamic model with its solution reflected in equation (2.13).

$$\frac{dq}{dt} = \beta q\left(1 - \frac{q}{k}\right) - u(t)q, q(0) = q_0 \tag{2.12}$$

Let $e^{\int_0^t u(t)}$ be the piecewise defined function to represent the dosing regiment of the anti-angiogenic cancer therapy drug. The piecewise defined function can be represented as a recursive sequence bounded by the number of doses, n.

$$e^{\int_0^t u(t)dt} = \begin{cases} 1 & t < t_i \\ e^{-i\cdot D} & t_i < t < t_{i+1} \\ e^{-(i+1)\cdot D} & t_{i+1} < t < t_{i+2} \\ \vdots & \vdots \\ e^{-(i+(n-1))\cdot D} & t_{i+(n-1)} < t < t_n \end{cases}$$

Before the first time varying injection of the anti-angiogenic cancer therapy drug, there is no injection, so 1 is used to represent the absence of injection. after the first injection of the anti-angiogenic cancer therapy drug of dose D, it is represented by e^{-D} in the piecewise function described.

$$q(t) = \frac{q_0 k e^{\beta t}\prod_{i=1}^{n} e^{-DH(t-t_i)}}{k + q_0\int_0^t \frac{\beta}{k} e^{\beta T}\prod_{i=1}^{n} e^{-DH(T-t_i)}dT} \tag{2.13}$$

Figure 6 depicts the regular logistic growth of the carrying capacity of the vasculature on the time interval from zero to one, due to the fact that there is no anti-angiogenic cancer therapy agent. The presence of the anti-angiogenic cancer therapy drug shows how it has an impact on the growth of carrying capacity of the vasculature. By introducing a periodic injection of the anti-angiogenic cancer therapy drug, the vasculature's carrying capacity reduces when there is a high concentration of the anti-angiogenic cancer therapy agent. As the concentration minimizes in the dosing interval, the carrying capacity of the vasculature increases until the next dosing period begins. This continues to occur, however, the carrying capacity of the vasculature decreases as the periodic dosing regimen continues until there is a critical point reached in which the carrying

capacity of the vasculature ceases to grow.

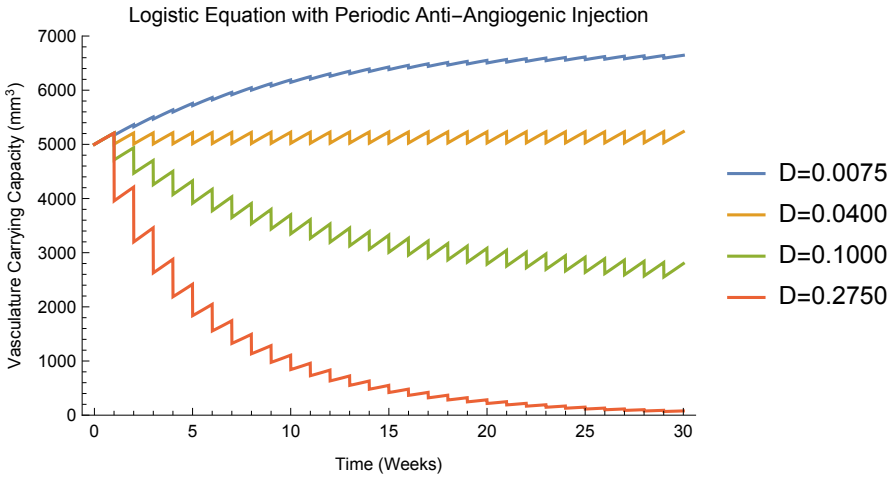

Figure 6: Logistic Equation with Periodic Injection of Anti-Angiogenic Agent. with parameters: $q_0 = 5000, k = 7000, \beta = 0.15$

An important characteristic of Figure 6 shows that the relative size of each jump after the periodic injection of the anti-angiogenic cancer therapy agent is the same. The distance between each jump is $1 - e^{-D}$. This shows that the same ratio of the vasculature is killed regardless of the size of the vasculature at the given period of the treatment. This phenomena is known as the *log-kill hypothesis* [10]. The logistic equation modeled the carrying capacity of the vasculature. The model depicts how the carrying capacity of the vasculature grows to a bounded volume. The pharmacodynamic models of the logistic equation depict how the carrying capacity of the vasculature is affected with the continuous infusion and periodic injection of an anti-angiogenic agent into the system. In both cases, the carrying capacity of the vasculature is decreased with appropriate anti-angiogenic agent concentrations. The next section is going to study how the Gompertz equation with the logistic equation will affect the size of the cancer tumor. Pharmacodynamic models with continuous infusion and periodic injection of the anti-angiogenic agent on the vasculature will be compared as to how the pharmacodynamic models minimize the tumor volume.

3 Tumor Growth Models Including Vasculature

The relationship between the Gompertz equation and the logistic equation will be analyzed from multiple pharmacodynamic perspectives to explore how the carrying capacity of the vasculature will aid or inhibit the proliferation of the cancer cells when there is chemotherapeutic drug present on the tumor or when there is an anti-angiogenic cancer therapy agent on the vasculature. The

pharmacodynamic models will explore how the implementation of a continuous chemotherapeutic drug regimen on the cancer tumor cells will affect the growth of the tumor given the carrying capacity of the vasculature is untreated. Conversely, another pharmacodynamic model will explore how the implementation of an anti-angiogenic drug regimen on the vasculature will affect the proliferation of the tumor when the cancer cells are untreated.

3.1 The Gompertz Equation with Logistic Carrying Capacity

The relationship between the cancer tumor and the carrying capacity of the vasculature will be analyzed to determine how the growth of the tumor is affected when there is no chemotherapeutic drug agent or anti-angiogenic therapy agent present in the tumor or the vasculature. This substitution will show how the logistic carrying capacity interacts with the Gompertz equation, and the affect on the growth of the tumor. The model is given by

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}) \tag{3.1}$$

$$\frac{dq}{dt} = \beta q(1 - \frac{q}{k}) \tag{3.2}$$

The solution from (3.2) has been previously found with solution (2.9). This solution is substituted into (3.1). This substitution will show how the logistic carrying capacity interacts with the Gompertz equation, and show the affect on the growth of the tumor. The solution of (3.1) is given by

$$p(t) = \frac{q_0 k(\frac{p_0}{q_0})^{e^{-\alpha t}} \exp\left(\frac{\beta\left(e^{-\alpha t}\cdot {}_2F_1\left(1,\frac{\alpha}{\beta};\frac{\alpha+\beta}{\beta};-\frac{q_0}{k-q_0}\right)-{}_2F_1\left(1,\frac{\alpha}{\beta};\frac{\alpha+\beta}{\beta};-\frac{e^{t\beta}q_0}{k-q_0}\right)+\alpha t\right)}{\alpha}\right)}{k + q_0(e^{\beta t} - 1)} \tag{3.3}$$

The solution, (3.3), contains a generalized hypergeometric function, ${}_2F_1$, known as Gauss' hypergeometric function.

$${}_2F_1(a; b; c; z) = \sum_{n=0}^{\infty} \frac{(a)_n (b)_n z^n}{(c)_n n!} \tag{3.4}$$

The generalized hypergeometric function is the sum of a hypergeometric series defined by a special case where a,b,c, are independent of z. Where a,b,c are the parameters of the function and z is the variable[1]. Here $(a)_n$,$(b)_n$ and $(c)_n$ represent the Pochhammer symbol which is used to denote the falling factorial when $n \geq 0$ for any parameter [11]. Then the Pochhammer symbol is given by

$$(x)_n = \frac{\Gamma(x + n)}{\Gamma(x)} = x(x + 1) \dots (x + n - 1) \tag{3.5}$$

Figure 7 graphically displays the affect the carrying capacity of the vasculature has on the volume of the tumor. Figure 1 and Figure 7 display how the the proliferation of the cancer cells reach the carrying capacity of the tumor size, however, Figure 7 shows a slower growth, because the the carrying capacity of the vasculature is represented by the equation (2.9) where Figure 1 characterizes the carrying capacity of the vasculature as a constant. The proliferation of the cancer cells in the tumor will be studied in pharmacodynamic models when there is continuous chemotherapeutic infusion and when there is periodic injection of the anti-angiogenic agent.

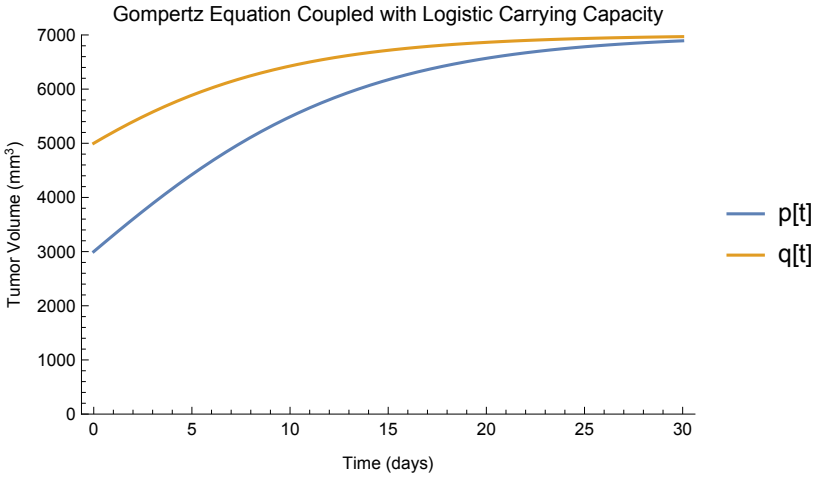

Figure 7: The Gompertz Equation with the Logistic Carrying Capacity with parameters: $p_0 = 3000, q_0 = 5000, k = 7000, \alpha = 0.2, \beta = 0.15$

In the proceeding sections, the Gompertz equation with the logistic equation will be analyzed when there is continuous infusion of chemotherapeutic agent, and when there is continuous infusion of anti-angiogenic cancer therapy agent. The relationship that the therapeutic agents have on their respective region will be analyzed to show affects on the growth of the tumor.

3.2 The Gompertz Equation with Continuous Chemotherapeutic Injection and Logistic Carrying Capacity

The pharmacodynamic model explores the relationship between the growth of the volume of the tumor when there is continuous infusion of the chemotherapeutic agent with logistic carrying capacity of the vasculature. The pharmacodynamic system is given by

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}) - up \tag{3.6}$$

$$\frac{dq}{dt} = \beta q(1 - \frac{q}{k}) \tag{3.7}$$

The pharmacodynamic model, featured in (3.6) and (3.7), utilizes the solution (2.9) to reflect the relationship the tumor volume and the carrying capacity of the vasculature share. The solution of equation (3.6) provides insight on how the volume of the tumor is affected by the continuous infusion of the chemotherapeutic agent with logistic carrying capacity of the vasculature. The solution contains the hypergeometric functions (3.4) observed in the previous section.

$$p(t) = \frac{q_0 k \exp\left(\frac{\beta e^{-\alpha t}\left(\cdot {}_2F_1\left(1, \frac{\alpha}{\beta}; \frac{\alpha+\beta}{\beta}; -\frac{q_0}{k-q_0}\right) - {}_2F_1\left(1, \frac{\alpha}{\beta}; \frac{\alpha+\beta}{\beta}; -\frac{e^{t\beta} q_0}{k-q_0}\right) + \alpha \ln(\frac{p_0}{q_0}) + \alpha\beta t e^{\alpha t} - u(e^{\alpha t} - u)\right)}{\alpha}\right)}{k + q_0(e^{\beta t} - 1)} \tag{3.8}$$

Figure 8 displays how the chemotherapeutic agent affects the volume of the tumor when the concentration of the dose of the chemotherapeutic agent varies. In Figure 8 three unique concentrations ($u = 0.1\frac{mg}{kg}$,$u = 0.2\frac{mg}{kg}$ and $u = 0.6\frac{mg}{kg}$) of a chemotherapeutic agent are compared. When the concentration of the chemotherapeutic agent is small the figure displays growth of the tumor on the thirty day interval. When the concentration of the chemotherapeutic agent increases, the volume of the tumor is smaller than the initial size after the thirty day interval, yet the small dose does not shrink the size of the tumor towards eradication. When the concentration of the dose increases to the largest concentration compared Figure 8 the volume of the tumor decreases towards eradication throughout the thirty day interval. Figure 8 shows how a larger concentration influences the necrosis of the cancer cells. When a large concentration of a chemotherapeutic agent is continuously infused into the tumor, the volume of the tumor rapidly decreases. The volume of the tumor is more than four times smaller than the initial volume of the tumor. By having a continuous infusion of a higher concentration of the chemotherapeutic agent, the tumor volume decreased to a negligible volume. The pharmacodynamic model expresses how the volume of the tumor reduces when the chemotherapeutic agent is continuously infused. Figure 8 progressively shows how the higher concentration of the chemotherapeutic agent minimizes the proliferation of the cancer cells so the tumors volume decreases below the initial volume. The next pharmacodynamic model involves the periodic injection of the anti-angiogenic agent on the carrying capacity of the vasculature.

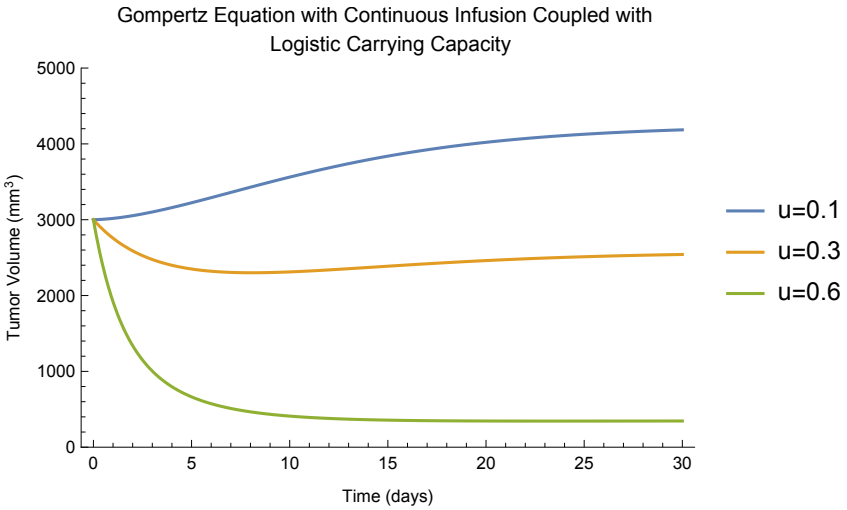

Figure 8: The Gompertz Equation with Logistic Carrying Capacity with Continuous Infusion with parameters:
$p_0 = 3000, q_0 = 5000, k = 7000, \alpha = 0.2, \beta = 0.15$

3.3 The Gompertz Equation with Logistic Carrying Capacity and Periodic Anti-Angiogenic Injection

The Gompertz equation with the logistic carrying capacity and periodic injection of anti-angiogenic agent is the pharmacodynamic model that will explore how the size of the tumor with logistic carrying capacity is affected when there is a periodic, same sized dose anti-angiogenic agent.

$$\frac{dp}{dt} = -\alpha p \ln(\frac{p}{q}) \tag{3.9}$$

$$\frac{dq}{dt} = \beta q(1 - \frac{q}{k}) - u(t)q \tag{3.10}$$

The analytic solution from (2.13) will be substituted into (3.9) to show how the inclusion of the anti-angiogenic cancer therapy drug agent impacts the growth of the tumor with logistic carrying capacity of the vasculature. Introducing the anti-angiogenic cancer therapy drug agent provides further opportunity to explore the effects it has on the growth of both the tumor and the vasculature.Figure 9 describes the pharmacodynamic relationship between the growth of the tumor and the growth of the carrying capacity of the vasculature when there is anti-angiogenic agents periodically injected for the vasculature. Figure 9 show how the concentration of a periodic injection of the anti-angiogenic agent affects the proliferation of the cancer cells in the tumor. The figure displays how the carrying capacity of the vasculature decreases when there is periodic injection

of a same sized dose of an anti-angiogenic agent compared to the size of the tumor when there is logistic carrying capacity of the vasculature and periodic injection of an anti-angiogenic agent. The carrying capacity is affected greatly by the same sized dose concentration of the agent, and that is seen in the decrease in the tumor size after each injection in the regimen. The dose of $D = 0.975\frac{mg}{kg}$ of the anti-angiogenic agent were to continue on a longer dosing regimen, these doses would be considered effective, due to the decreasing volume of the tumor and the decreasing carrying capacity of the vasculature.

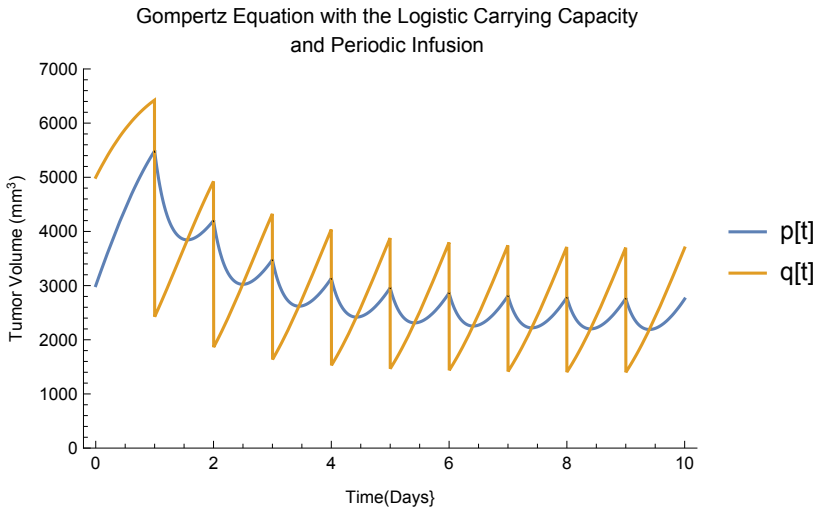

Figure 9: The Gompertz Equation with Logistic Carrying Capacity and Periodic Anti-Angiogenic Injection with parameters:
$p_0 = 3000, q_0 = 5000, k = 7000, \alpha = 2, \beta = 1.5, D = 0.975$

The various pharmacodynamic models studied in this section depict how the growth of the cancer tumor is impeded when there is continuous infusion and periodic injection of a anti-angiogenic agent. In previous sections, the continuous infusion and periodic injection eradicated the carrying capacity of the vasculature, which supplies oxygen, blood and nutrients to the cancer cells in the tumor. By comparing the growth of the volume of the tumor when there was no treatment, continuous infusion, and periodic injection of anti-angiogenic agent displayed how the growth of the volume of the tumor is directly related to the carrying capacity of the vasculature. Section 3.1 displayed that when there was no treatment on the vasculature, the volume of the tumor grew to the carrying capacity of the tumor. When there was continuous infusion of the anti-angiogenic agent on the vasculature with varying concentrations, the volume of the tumor decreased in half the time interval compared to the periodic injection of the anti-angiogenic treatment.

The Gompertz pharmacodynamic models that were analyzed displayed the affect that the concentration of the chemotherapeutic agent had on the proliferation of the cancer cells. Simi-

larly, the logistic pharmacodynamic models that were analyzed related the affect the concentration of the anti-angiogenic agent had on the carrying capacity of the vasculature. The aim of these pharmacodynamic models were to identify the appropriate dosing concentration to minimize the tumor volume and the carrying capacity of the vasculature to a negligible size. When the volume of the tumor was dependent on the vasculature, the Gompertz equation and the logistic equation were coupled together to further understand how the growth of the tumor is related to the carrying capacity of the vasculature. Pharmacodynamic models were analyzed to determine how the growth of the tumor is affected with continuous dosing of a chemotherapeutic agent, and periodic dosing of an anti-angiogenic agent. Analyzing these pharmacodynamic models identified an appropriate dosing concentration and dosing regimen for both cancer therapy agents. The pharmacodynamic models that were studied share a similar relationship to the Hahnfeldt Model studied in the next section.

4 Hahnfeldt Model

We consider three pharmacodynamic models to understand the how the anti-angiogenic agent affects the growth of the vasculature under different models. The system of differential equations describes the change in volume of the tumor and the change in the varrying capacity of the vasculature when there is no anti-angiogenic treatment. The model is:

$$\frac{dp}{dt} = -\alpha p \ln \frac{p}{q} \tag{4.1}$$

$$\frac{dq}{dt} = bp - (\mu + dp^{\frac{2}{3}})q \tag{4.2}$$

In the system of differential equations, the variable p represents the primary tumor volume measured in mm^3, and q is the carrying capacity of the vasculature - new blood vessels formed from pre-existing blood vessels measured in mm^3. When the carrying capacity of the vasculature is less than the tumor volume the tumor shirks, conversely, the tumor grows due to the increase in vasculature. The variable c represents the concentration of the cancer therapy agent measured in $\frac{mg}{kg}$. The variables b and d represent the proliferation of the tumor cells and the necrosis of the tumor cells respectively both measured in day^{-1} and $mm^{-1}day^{-1}$. The ordinary differential equation (4.1) is a the Gompertz equation where α is the constant related to the proliferation of the tumor cells. The Gompertz equation describes the growth of the tumor cells with a confined amount of nutrients. The ordinary differential equation (4.2) represents the dynamics of the carrying capacity of the vasculature where bp represents the stimulation of the vasculature by the tumor. The

middle term, $-(\mu + dp^{\frac{2}{3}})$ represents the Bertalanffy Model, which shows that the volume of the tumor decreases with cell death and increases related to surface area [9] .The terms μ and $dp^{\frac{2}{3}}q$ in the Bertalanffy Model represent the growth rate, and the inhibition an interaction term between the tumor and vasculature,respectively. The parameter u represents the rate of elimination of the cancer therapy agent. In Leszczynski's tumor growth model, (4.1)and (4.2) is a known system of differential equations referred to as the Hahnfeldt Model. The Hahnfeldt Model describes the growth of a tumor under angiogenic signalling. The development of the Hahnfedlt Model explores the relationship the tumor volume has with the carrying capacity of the vasculature around the tumor. Hahnfedlt's Model describes how implementing an anti-angiogenic drug will prevent the vasculature from supplying the tumor blood. By stunting the blood supply to a tumor, through anti-angiogenic agents, the tumors carrying capacity will decrease. Ultimately, the anti-angiogenic agent is implemented on the vasculature to ensure that the tumor will not grow [7].

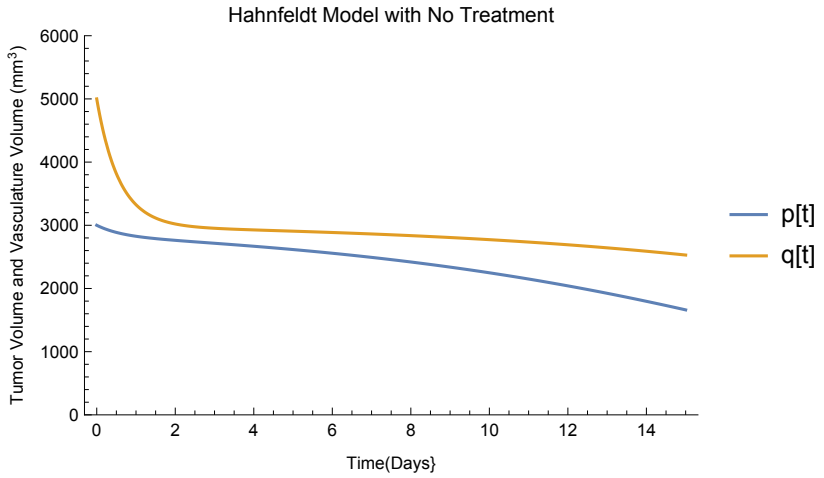

Figure 10: The Hahnfeldt Model with no Anti-Angiogenic Therapy with parameters: $p_0 = 3000, q_0 = 5000, \alpha = 0.2, \beta = 0.15, \mu = 0.02, d = 0.0087, b = 2.3$

The Hahnfeldt Model with no anti-angiogenic treatment, in Figure 10, displays how the volume of the tumor is smaller than the carrying capacity of the vasculature. This relationship is similar to that of Figure 7 when the Gompertz equation with logistic carrying capacity was analyzed. The similiarity in the two figures shows how the volume of the tumor is less than the carrying capacity of the vasculature. The relationship the volume of the tumor has with the carrying capacity of the vasculature will be explored when an anti-angiogenic agent regimen is applied to the vasculature. Next, a regimen of continuous infusion of the anti-angiogenic agent will show how the agent affects the carrying capacity of the vasculature and the volume of the tumor.

4.1 Hahnfeldt Model with Continuous Anti-Angiogenic Infusion

We consider the tumor models by Leszczynski et al.[5] . The model involves a system of ordinary differential equations that describe the progression of the tumor and the change in the carrying capacity of the vasculature with the continuous inclusion of the anti-angiogenic drug agent.The model [5] is given by

$$\frac{dp}{dt} = -\alpha p \ln \frac{p}{q} \tag{4.3}$$

$$\frac{dq}{dt} = bp - (\mu + dp^{\frac{2}{3}} + u)q \tag{4.4}$$

Figure 11 displays how the concentration of an anti-angiogenic agent affects the carrying capacity of the vasculature and the volume of the tumor when there is a continuous infusion of an anti-angiogenic agent. The carrying capacity of the vasculature with continuous infusion of an anti-angiogenic agent increases on a fixed time interval and then decreases to a size of insignificance, so that any oxygen, blood or nutrients cannot be supplied to the tumor. Similarly, the volume of the tumor decrease to an insignificant size on a shorter time interval than that of the vasculature. This shows how the continuous infusion of the anti-angiogenic agent reduces the volume of the tumor when there is continuous infusion of an anti-angiogenic agent. The next pharmacodynamic model will analyze how the periodic injection of an anti-angiogenic agent can reduce the volume of the tumor.

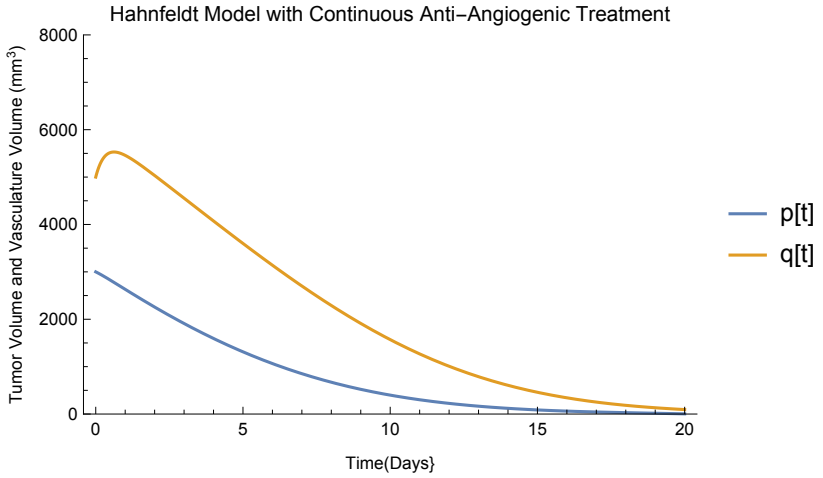

Figure 11: The Hahnfeldt Model with Periodic Anti-Angiogenic Therapy with parameters: $p_0 = 3000, q_0 = 5000, \alpha = 0.2, \beta = 0.015, \mu = 0.02, d = 0.0087, b = 5.85, u = 1.2$

4.2 Hahnfeldt Model with Periodic Anti-Angiogenic Injection

The pharmacodynamic model of interest explores the relationship the volume of the tumor has with logistic carrying capacity when a same sized dose of an anti-angiogenic agent is administered in a periodic dosing regimen. The model is given by

$$\frac{dp}{dt} = -\alpha p \ln \frac{p}{q} \tag{4.5}$$

$$\frac{dq}{dt} = bp - (\mu + dp^{\frac{2}{3}} + u(t))q \tag{4.6}$$

Where $u(t)$ is given by the equation (2.6). Figure 12 shows how the carrying capacity of the vasculature with a periodic dosing regimen affects the volume of the tumor. The graph describes how the dosing regimen directly affects the carrying capacity of the vasculature and the volume of the tumor. When a same sized anti-angiogenic dose is administered the carrying capacity of the vasculature is reduced to a size smaller than the volume of sthe tumor, as the concentration of the anti-angiogenic agent becomes less effective on the fixed time interval, the carrying capacity of the vasculature and the volume of the tumor increase at varying rates. As seen in Figure 10 and Figure 11 the carrying capacity of the vasculature is greater than the volume of the tumor when there was no treatment regimen, a continuous anti-angiogenic infusion regimen, and a periodic dosing regimen of an anti-angiogenic agent.

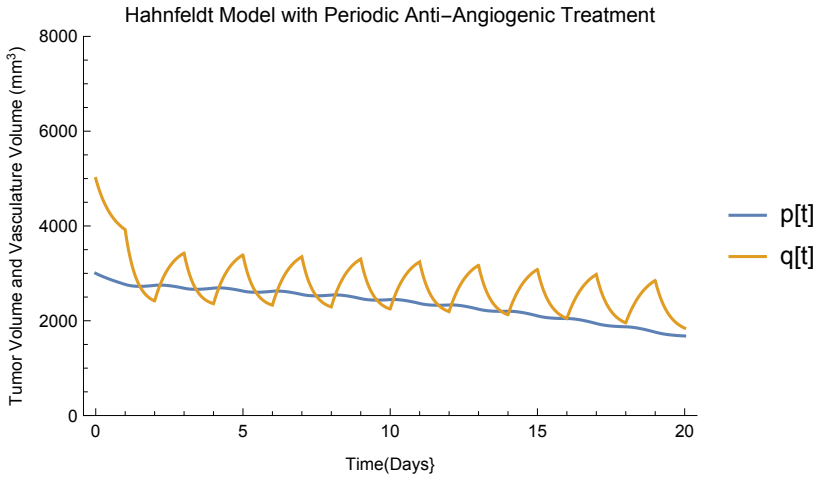

Figure 12: The Hahnfeldt Model with Periodic Anti-Angiogenic Therapy with parameters: $p_0 = 3000, q_0 = 5000, \alpha = 0.2, \beta = 0.015, \mu = 0.02, d = 0.0087, b = 2.3$

Figure 12 and Figure 8 show how the periodic dosing of an anti-angiogenic agent afffects the size of the tumor . Both figures show how the carrying capacity of the vasculature is affected with periodic

and same sized dosing of an anti-angiogenic agent, and shows how the tumor volume is directly related to the decrease in the carrying capacity when the anti-angiogenic agent is administered on a periodic dosing regimen. The pharmacodynamic models shown in each of the figures (Figure 12 and Figure 8) show that the anti-angiogenic agent used in the periodic injection reduce the carrying capacity of the vasculature, and the volume of the tumor decreases due to the reduction in the carrying capacity.

5 Conclusion

Classical tumor growth models have been analyzed for cancer therapy treatments with a same size dosing regimen. The Gompertz pharmacodynamic models explored how the size of the dosing concentration can inhibit the proliferation of the cancer cells with varying concentrations of chemotherapeutic agents. The logistic pharmacodynamic models explored how the size of the dosing concentration can inhibit the carrying capacity of the vasculature that grows from the cancer tumor by varying the concentrations of the anti-angiogenic agents. When the Gompertz and Logistic pharmacodynamic models are coupled the relationship between the proliferation of the cancer cells and the carrying capacity of the vasculature were analyzed when a a dosing regimen was introduced to either system. The Hahnfeldt pharmacodynamic models analyzed how the presence of an anti-angiogenic agent can afffect the carrying capacity of the vasculature and impede the growth of the tumor. The periodic same sized dose of the anti-angiogenic agent in Figure **??**This paper analyzed how to identify the same size dosing concentration of a chemotherapeutic agent and an anti-angiogenic agent to minimize the volume of a cancer tumor and minimize the carrying capacity of the vasculature.

References

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A Mathematica Code

2.1 | Gompertz Equation

```
Quit[]
```

```
q0 = 5000; p0 = 3000; k = 7000; α = 0.2; β = 0.15;
```

```
p[t_] := p0 * Exp[Log[k / p0] * (1 - Exp[-α * t])]
```

```
Plot[p[t], {t, 0, 30}, PlotRange → {0, 7000},
 PlotLabel → "Gompertz Equation", Frame → {True, True, False, False},
 FrameLabel → {"Time (Days)", "Tumor Volume (mm^3)"}]
```

2.1.1 | Gompertz Equation with Constant Infusion

```
Quit[]
```

```
p0 = 3000; k = 7000; α = 0.2; u = 0.6;
```

```
p1[t_] = p0^{Exp[-α * t]} * Exp[(Log[k] - (u / α)) * (1 - Exp[-α * t])]
```

```
Plot[p1[t], {t, 0, 30}, PlotRange → {0, 4000},
 PlotLabel → "Gompertz Equation with Constant Chemotherapeutic Infusion",
 Frame → {True, True, False, False},
 FrameLabel → {"Time (days)", "Tumor Volume (mm^3)"}]
```

2.1.2 | Gompertz Equation with Time Varying Injection

```
Quit[]
```

```
q0 = 5000; p0 = 3000; k = 7000; α = 0.2; d = 0.0075;
```

```
p2[t_] := k * k^{-Exp[-α * t]} * Product[
    Exp[-d * Exp[-α * (t - i)] * HeavisideTheta[t - i] i], {i, 1, 30}] * p0^{Exp[-α * t]}
```

```
Plot[p2[t], {t, 0, 30}, PlotRange → {0, 7000}, AxesLabel → Automatic,
 PlotLabel → " Gompertz Equation with Time Varying Chemotherapeutic Infusion",
 ExclusionsStyle → Dashed, Frame → {True, True, False, False},
 FrameLabel → {"Time(Days}", "Tumor Volume (mm^3)"}]
```

Verifying the relative jump on each time interval, to determine the linear log kill term is the same.

```
l11 = Limit[p2[t], t → 1, Direction → "FromBelow"]
```

```
l12 = Limit[p2[t], t → 1, Direction → "FromAbove"]
```

```
j1 = Simplify[(l11 - l12) / l12]
```

```
l21 = Limit[p2[t], t → 2, Direction → "FromBelow"]
```

```
l22 = Limit[p2[t], t → 2, Direction → "FromAbove"]
```

```
In[•]:= j2 = Simplify[(l21 - l22) / l21]
```

2.2 | Logistic Equation

```
In[•]:= Quit[]

In[•]:= q0 = 5000; k = 7000; β = 0.15;

In[•]:= q[t_] := (q0 * k) / ((q0 + (k - q0) * Exp[-β * t]))

In[•]:= Plot[q[t], {t, 0, 30}, PlotRange → {0, 7000}, AxesLabel → Automatic,
 PlotLabel → "Logistic Equation", Frame → {True, True, False, False},
 FrameLabel → {"Time (Weeks)", "Vasculature Carrying Capacity (mm^3)"}]
```

2.2.1 | Logistic Equation with Constant Injection

```
In[•]:= Quit[]

In[•]:= q0 = 5000; k = 7000; β = 0.15; u = 0.3;

In[•]:= A = (β - u)

        B = (1 - (u / β)) * k

In[•]:= q2[t_] := (B * q0) / (q0 + (B - q0) * Exp[-A * t])

In[•]:= Plot[q2[t], {t, 0, 30}, PlotRange → {0, 7000},
 PlotLabel → "Logistic Equation with Continuous Anti-Angiogenic Infusion",
 Frame → {True, True, False, False},
 FrameLabel → {"Time (Weeks)", "Vasculature Carrying Capacity (mm^3)"}]
```

2.2.2 | Logistic Equation with Periodic Injection

```
In[•]:= Quit[]

In[•]:= $Assumptions = β > 0 && k > 0 && d > 0 && t ≥ 0 ;

In[•]:= Block[{x}, Do[f[i][d_] = Exp[-i * d], {i, 0, 30}]]
        Definition @ f;

In[•]:= Block[{t}, h[t_] = Piecewise[Table[{f[i][d], i < t < i + 1}, {i, 1, 30}]]]
        Definition @ h;

In[•]:= g[t_] := Piecewise[{{1, t < 1}, {h[t]}, {Exp[-31 * d], t > 31}}]

In[•]:= q[t_] := q0 * k * Exp[β * t] * g[t] /
            (k + q0 * Integrate[β * Exp[β * T] * g[T], {T, 0, t}, Assumptions → Element[t, Reals]])
```

Verifying that the relative jump on each time interval is the same.

```
In[•]:= Limit[q[t], t → 0]
```

```
l11 = Limit[q[t], t → 1, Direction → "FromBelow"]
```

```
l12 = Limit[q[t], t → 1, Direction → "FromAbove"]
```

```
j1 = Simplify[(l11 - l12) / l11]
```

```
q0 = 5000; p0 = 3000; k = 7000; β = 0.15; d = 0.275;
```

```
Plot[q[t], {t, 0, 30}, PlotRange → {0, 7000},
 ExclusionsStyle → Dashed, AxesLabel → Automatic,
 PlotLabel → "Logistic Equation with Periodic Anti-Angiogenic Injection",
 Frame → {True, True, False, False},
 FrameLabel → {"Time (Days)", "Vasculature Carrying Capacity (mm^3)"}]
```

3.1 Gompertz Equation Coupled with Logistic Equation

```
Quit[]
```

```
q0 = 5000; p0 = 3000; k = 7000; α = 0.2; β = 0.15;
```

Gompertz Coupled with Logistic when $\alpha = \beta$

```
p3[t_] := (q0 * k) ^ {-Exp[-α * t]} * ((q0 * k) / (q0 + (k - q0) * Exp[-α * t])) *
   (k) ^ {Exp[-α * t]} * (q0 * Exp[α * t] + (k - q0)) ^ {(-Exp[-α * t] * (k - q0)) / (q0)} *
   (k) ^ {(Exp[-α * t] * (k - q0)) / (q0)} * (p0) ^ {Exp[-α * t]}
```

```
Plot[p3[t], {t, 0, 40}, PlotRange → {0, 7000},
 PlotLabel → "Gompertz Equation Coupled with Logistic Equation (α=β)",
 AxesLabel → Automatic]
```

Gompertz Coupled with Logistic when $\alpha \neq \beta$

```
Quit[]
```

```
sol = DSolve[
   {p'[t] == -α * p[t] * Log[p[t] / ((q0 * k) / (q0 + (k - q0) * Exp[-β * t]))], p[0] == p0},
   p[t], t]
```

```
sol1 = Simplify[sol]
```

```
q0 = 5000; p0 = 3000; k = 7000; α = 0.1; β = 0.2;
```

```
p31[t_] := Evaluate[p[t] /. sol1]
```

```
Plot[p31[t], {t, 0, 40}, PlotRange → {0, 7000},
 PlotLabel → "Gompertz Equation Coupled with the Logistic Equation (α <β)",
 Frame → {True, True, False, False},
 FrameLabel → {"Time (days)", "Tumor Volume (mm^3)"}]
```

3.2 | Gompertz Equation with Continuous Injection Coupled with Logistic Equation

```
In[•]:= Quit[]

In[•]:= sol =
 DSolve[{p'[t] == -α * p[t] * Log[p[t] / ((q0 * k) / (q0 + (k - q0) * Exp[-β * t]))] - u * p[t],
   p[0] == p0}, p[t], t]

In[•]:= sol1 = Simplify[sol]

In[•]:= q0 = 5000; p0 = 3000; k = 7000; α = 0.2; β = 0.15; u = 0.6;

In[•]:= p31[t_] := Evaluate[p[t] /. sol1]

In[•]:= Plot[p31[t], {t, 0, 30}, PlotRange → {0, 5000},
 PlotLabel → "Gompertz Equation with Continuous Infusion Coupled with
the Logistic Equation", Frame → {True, True, False, False},
 FrameLabel → {"Time (days)", "Tumor Volume (mm^3)"}]
```

3.3 | Gompertz Equation with Coupled with the Logistic Equation with Periodic Anti-Angiogenic Injection

```
In[•]:= Quit[];

In[•]:= $Assumptions = β > 0 && k > 0 && d > 0 ; && t ≥ 0 ;

In[•]:= Block[{x}, Do[f[i][d_] = Exp[-i * d], {i, 0, 30}]]
Definition @ f;

In[•]:= Block[{t}, h[t_] = Piecewise[Table[{f[i][d], i < t < i + 1}, {i, 0, 30}]]]
Definition @ h

In[•]:= q0 = 5000; p0 = 3000; k = 7000; α = 0.2; β = 0.15; d = 0.0075;

In[•]:= q[t_] = Simplify[q0 * k * Exp[β * t] * h[t] / (k +
       q0 * Integrate[β * Exp[β * T] * h[T], {T, 0, t}, Assumptions → Element[t, Reals]])]

In[•]:= qq[t_] = Simplify[Log[q[t]]]

In[•]:= sol = DSolve[{w'[t] == -α * w[t] + α * qq[t], w[0] == Log[p0]}, w[t], t]

In[•]:= p[t_] = Exp[w[t]] /. sol
```

```
Plot[p[t], {t, 0, 30}, PlotRange → {0, 7000},
 PlotLabel → "Gompertz Equation Coupled with the Logistic Equation
with Periodic Anti-Angiogenic Injection",
 ExclusionsStyle → Dashed, Frame → {True, True, False, False},
 FrameLabel → {"Time(Days}", "Tumor Volume (mm^3)"}]
```

4 | Hahnfeldt Model with No Treatment

```
Quit[]
```

```
p0 = 3000; q0 = 5000; α = 0.2; β = 0.015; μ = 0.02; d = 0.0087; b = 5.85;
```

```
sol = NDSolve[
  {p'[t] == α * p[t] * Log[p[t] / q[t]], q'[t] == b * p[t] - (μ + d * p[t] ^ (2 / 3)) * q[t],
   p[0] == p0, q[0] == q0}, {p, q}, {t, 0, 15}]
```

```
graph = Plot[Evaluate[{p[t], q[t]} /. sol], {t, 0, 15}, PlotRange → {0, 10 000},
  ExclusionsStyle → Dashed, Frame → {True, True, False, False},
  PlotLabel → "Hahnfeldt Model with No Treatment",
  FrameLabel → {"Time(Days}", "Tumor Volume and Vasculature Volume (mm^3)"},
  PlotLegends → LineLegend[{"p[t]", "q[t]"}]]
```

4.1 Hahnfeldt Model with Continuous Anti-Angiogenic Infusion

```
Quit[]
```

```
p0 = 3000;
q0 = 5000;
α = 0.2;
β = 0.015;
μ = 0.02;
d = 0.0087;
b = 5.85;
u = 1.2;
```

```
sol = NDSolve[
  {p'[t] == α * p[t] * Log[p[t] / q[t]], q'[t] == b * p[t] - (μ + d * p[t] ^ (2 / 3) + u) * q[t],
   p[0] == p0, q[0] == q0}, {p, q}, {t, 0, 15}]
```

```
graph = Plot[Evaluate[{p[t], q[t]} /. sol], {t, 0, 20}, PlotRange → {0, 8000},
  ExclusionsStyle → Dashed, Frame → {True, True, False, False},
  PlotLabel → "Hahnfeldt Model with Continuous Anti-Angiogenic Treatment",
  FrameLabel → {"Time(Days}", "Tumor Volume and Vasculature Volume (mm^3)"},
  PlotLegends → LineLegend[{"p[t]", "q[t]"}]]
```

4.2 | Hahnfeldt Model with Periodic Anti-Angiogenic Treatment

```
In[•]:= Quit[];

In[•]:= p0 = 3000; q0 = 5000; α = 0.2; β = 0.015; μ = 0.02; d = 0.0087; b = 2.3;

In[•]:= sol = NDSolve[
          {p'[t] == α * p[t] * Log[p[t] / q[t]], q'[t] == b * p[t] - (μ + d * p[t] ^ (2 / 3)) * q[t] -
              (Sum[HeavisideTheta[t - (2 * j - 1)] - HeavisideTheta[t - (2 * j)], {j, 1, 20}]) *
               q[t], p[0] == p0, q[0] == q0}, {p, q}, {t, 0, 20}]

In[•]:= graph = Plot[Evaluate[{p[t], q[t]} /. sol], {t, 0, 20}, PlotRange → {0, 8000},
          ExclusionsStyle → Dashed, Frame → {True, True, False, False},
          PlotLabel → "Hahnfeldt Model with Periodic Anti-Angiogenic Treatment",
          FrameLabel → {"Time(Days)", "Tumor Volume and Vasculature Volume (mm³)"},
          PlotLegends → LineLegend[{"p[t]", "q[t]"}]]
```