Compartmental Model for Cancer Evolution: Chemotherapy and Drug Resistance*

J. J. Westman[a], B. R. Fabijonas[b], D. L. Kern[c], and F. B. Hanson[d] †

[a] *Department of Mathematics, University of California, Box 951555, Los Angeles, CA 90095-1555, USA*
[b] *Department of Mathematics, Southern Methodist University, P.O. Box 750156, Dallas, TX 75275-0156, USA*
[c] *Institute for Mathematics and Its Applications, University of Minnesota, 207 Church Street SE, Minneapolis, MN 55455, USA*
[d] *Laboratory for Advanced Computing, University of Illinois at Chicago, 851 Morgan St.; M/C 249, Chicago, IL 60607-7045, USA*

December 20, 2001

Abstract

In this paper, a model is presented that explores the role of drug resistance in the evolution of cancer subject to treatment with a single cytotoxic agent. An important feature of this model is that it is designed to start from a single cell and generate the evolution of the cancer. From this perspective, the roles of intrinsic or natural occurring resistance as well as that of acquired resistance from chemotherapy can be seen at any stage of the development of the cancer or treatment history. Using this model, an empirical fit can be made to that of a given patient based on estimated parameters which can be updated as more observations become available. A focus is placed on the heterogeneous nature of the cancer and the effects of treatments, which suggests that this model should provide a reasonable tool to explore treatment options for cancer patients.

Keywords: Cancer; Chemotherapy; Drug resistance; Compartmental model

1 Introduction

One of the leading causes of death in the world is cancer. Even though there are a number of treatment options for cancer patients such as surgery, chemotherapy, immunotherapy, and radiotherapy, the life expectancy for the cancer patient will be diminished due to the disease and quite possibly the treatments as well. These treatment modalities cannot in general provide a cure for cancer but may bring about remission that can later relapse. The effects of these

*Corresponding author: John J. Westman, Department of Mathematics, University of California, Box 951555, Los Angeles, CA 90095-1555, USA, Phone: (310) 206-8094, Fax: (310) 206-6673, e-mail: jwestman@math.ucla.edu
†Work supported in part by the National Science Foundation Grant DMS-99-73231.

treatments can vary from cancer to cancer and individual to individual, which further complicates the situation for effective eradication of cancer in any given patient.

Currently, there exists a need for fundamental understanding of the properties and mechanisms involved in the genesis and evolution of cancers. Furthermore, the roles by which various treatment modalities effect the growth and spread of cancer needs to be understood in greater detail. This is an exceptionally difficult task since cancers are composed of a variety of cell types which may be in different phases of the cell cycle. The macroscopic properties for a given type of cancer can change depending on the number of cancerous cells present, with variation among how and where these properties are determined. This leads to confusion in terms of which values to use for parameters since there is a lack of consistent data about the properties for a given cancer. For example, Panetta [33] and references therein estimate the doubling time for breast cancer as 14.65 days from one group of studies and 150 days from another. In [2] and [3], the intrinsic growth rates used for a Gompertzian dynamic for leukemia have error bounds that are an order of magnitude greater than the estimate used, which is assembled from several sources. Clearly, this type of discrepancy would lead to radically different treatment methods since the underlying characteristics of the how cancer would evolve is radically different.

Two of the most crucial concerns with the use of chemotherapies and radiotherapies are toxicity and resistance. Toxicity limits the dose and frequency by which these treatments may be administered. Resistance, whether intrinsic or acquired, limits the effectiveness of the treatments. Therefore, if the roles of toxicity and resistance can be understood leading to a model which would relate their effects to the evolution of the cancer, then this information can be used to select appropriate treatments so as to minimize the spread of cancer and resistance while adhering to toxicity limits for a given patient with a given cancer. This paper examines the evolution of cancer subject to treatment with a single cytotoxic agent and drug resistance – toxicity will not be explored here. In Section 2, biological background and motivation are given to support the form of the models presented in Section 3. A numerical study is presented in Section 4 and a discussion of the model and the numerical results is in Section 5.

2 Basic biological cell dynamics, cancer evolution, and chemotherapy

The cell life cycle is shown in Figure 1. A brief description is given here, and a more detailed discussion can be found in [11, 16, 21, 37] and references therein. The cell life cycle begins in the G_1 gap phase in which protein and RNA syntheses are active. Once these processes are complete, the cell then enters the *synthetic* (S) phase where new DNA is generated. After the new DNA is formed, the duplicated chromosomes condense in the G_2 gap phase while cyclin-mediated activities create organelles and molecules necessary for the next and final phase, *mitosis* (M). Mitosis consists of a set of steps which leads to the development of two daughter cells. In all of these phases there are a number of *checkpoints* that the cell must pass through to insure the integrity of the DNA. Should the cell fail to meet the necessary requirements at the various checkpoints, the cell either repairs or destroys itself, a process referred to as apoptosis or programmed cell death. Should one of these checkpoint mechanisms fail, the result can be a malignant cell that has *mutated* from a normal cell and thus is a *germ* or initial proliferating cancerous cell which may potentially

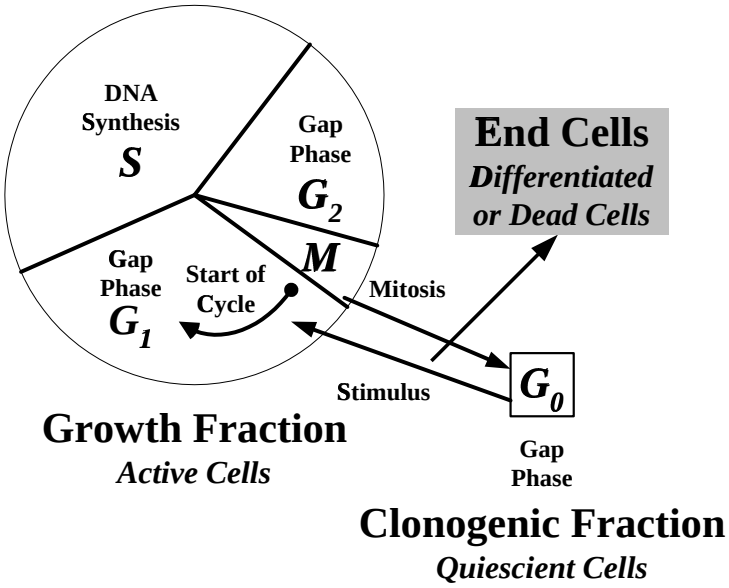

Figure 1: The cell life cycle. The active cells undergo a series of steps that culminate in the division of the parent cell into two daughter cells. The quiescent or stem cells are inactive and are in the gap phase G_0, which can be activated by appropriate stimulus.

develop into cancer. Volker [37] illustrates the multi-step process for the molecular basis of cancer from cells that have acquired chromosomal abnormalities. One cancerous cell has the potential to form cancer, for example see [22] for a stochastic model that can be used to model whether the germ cell forms a colony of cancer.

Cancerous cells can be compartmentalized according to their intrinsic proliferation capabilities: those actively engaged in the cell division form the proliferating or growth fraction, those in the G_0 quiescent phase form the clonogenic or cancer stem cell fraction, and those incapable of further cell division to propagate the cancer form the end cell fraction which consists of cells that have differentiated into support structures, primarily endothelial and vascular cells, and necrotic tissue. The allowable transitions among these three compartments are shown in Figure 2.

After a cell completes mitosis, either daughter cell may go to any of the three compartments with a given probability that can depend on the current population sizes of the compartments as well as other factors. The probabilistic transition rates of a daughter cell to the growth and clonogenic fractions, in the absence of treatment, depends on the aggressiveness of the cancer. For aggressive or fast growing cancers the transition rate of the daughter cells remaining in the proliferating fraction is high whereas slow developing cancers have a high rates entering the clonogenic fraction. Cells in the G_0 phase are in a resting or quiescent state and naturally will become active again entering the proliferating fraction which can be thought of as a natural *back migration*. A probabilistic equilibrium exists between the compartments that depends on the number of cells present. From a macroscopic perspective considering only bulk dynamics without treatments, the daughter cells that enter the clonogenic fraction can be thought of as a drift from the proliferating compartment after mitosis. Large migrations or *recruitment* of cells from the clonogenic to the growth fraction require an external stimulus. An example of such a stimulus would be the application of a cytotoxic agent, a

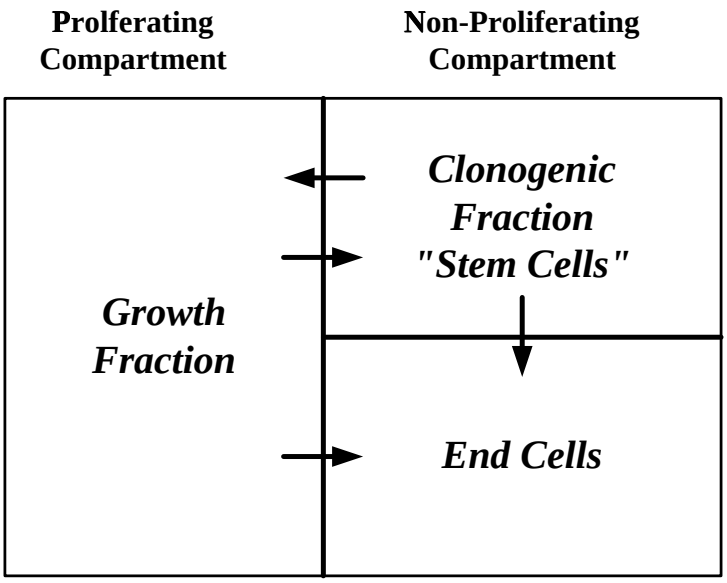

Figure 2: Cancer cell types and the allowable transitions among the compartments. Note that once a cell is in the end cell compartment it may never leave.

chemotherapeutic treatment, which would cause an abnormally large number of cells in either or both compartments to undergo apoptosis. The stimulus causes the recruitment of cells from the clonogenic to the growth fraction. In turn, the replenishment of the growth fraction tries to ensure the survival of the cancer. This source of cells for the growth fraction in conjunction with intrinsic or acquired drug resistance normally means that chemotherapy is a palliative treatment that cannot lead to a cure for cancer by itself.

The end cell compartment is a terminating compartment, due to lack of potential cancer proliferation. The model presented in this paper considers cells in the proliferating (P) and clonogenic (C) compartments only since these are the compartment which contain cells capable of proliferating the cancer. This is not to say that the members of the end cell compartment do not contribute to tumor evolution. On the contrary, the cells in this third group are either necrotic tissue or have differentiated to support structures such as vascularization, and play an important role in the development of the cancer, particularly in the size that the cancer can attain. Though there are treatment modalities which can affect the cells in the end cell fraction such as biomodulators (e.g. interferons and interleukins, see [17, 18, 20, 28, 35] and references therein), the present investigation focuses on treatment with cytotoxic agents which can only affect cells capable of proliferation. Thus, explicit dependence on the end cell compartment is neglected throughout the rest of this paper and model parameters are adjusted accordingly.

Traditional chemotherapeutic treatment schedules normally consist of a fixed number of treatments, for example 6 or 12, given at fixed intervals, typically 7 to 21 days apart, called a treatment cycle. The number of and the time between treatments is bounded by the cumulative effects of toxicity to normal tissue. For example, see Barbolosi and Iliadis [6] who consider a toxicity constraint based on the effects of cytotoxic agents on the level of white blood cells. These treatments are given in order to drive the number of cancer cells to a lower level so that the number of cells

cannot be detected *in vivo* clinically. The cancer is then referred to as being in remission. After the initial cycle, if the cancer is in remission no further treatments are given and the patient is monitored for recurrence. Upon recurrence, the first time the cancer is clinically detected, the treatment cycle is repeated. If the cancer does not recur after a sufficient period of time, then the claim is that the patient is cured.

The goal of chemotherapy in the framework of the three cellular compartments is to drive the cells in the proliferating and clonogenic fractions into the end cell fraction. The compartmental view of cancer also allows for the distinction of different types of cytotoxic agents, in particular cycle specific and nonspecific. Cycle specific drugs can only destroy cells in certain phases of the cell cycle and thus acts only on the proliferating fraction. Cycle nonspecific cytotoxic agents can destroy cells in either proliferating or clonogenic compartments; this formulation allows for different rates for the growth and clonogenic fractions since uptake of the agents in an active cell should be greater than that of a quiescent one.

One of the key difficulties encountered in treating cancers with chemotherapy is drug resistance. Every biological system exhibits drug resistance, and cancer is no exception. See Goldie and Coldman [21] for an introduction to this topic. Whether drug resistance is *intrinsic*, i.e. naturally occurring, or *acquired*, i.e. the result of exposure to the drug, is the topic of heated debate[25]. In either case, drug resistance hinders the effectiveness of a given cytotoxic agent. Thus, there is a finite number of treatments that can be given with significant impact. In order to combat drug resistance and yield a more effective treatment, multiple drugs typically are used that are not cross resistant. Thus, cells resistant to one of the cytotoxic agents can be killed by the others. If a single cycle of treatment does not lead to remission, additional applications of the cytotoxic agent(s) may be administered. Whether single or multiple cytotoxic agents are used, resistance to them will develop among the cancerous cells from each application of the agents which will diminish the benefits of treatments until they are negligible and should not be used.

3 Growth and treatment models for cancer

A number of models have been used to characterize the evolution and effects of treatments on cancers. These models can be categorized by the number of compartments considered. In one compartment models, the various types of cancer cells are thought of as a single type which are all included in the growth fraction. Treatments in these models either represent a *persistent kill* where a fixed percentage of cells are killed at every treatment, or a *reduced kill* in which the fraction of cells is reduced dependent on the number of treatments given. In Barbolosi and Iliadis [6], the single compartment model is considered for the cancer and two compartments are used for the pharmacokinetics for the drug concentrations as well as a model that considers white blood cells to impose a toxicity constraint on the concentration of drugs administered. Similarly, Afenya and coworkers [2, 3, 4, 6] use a *normal* or *good* cell population to limit the detrimental effects due to toxicity of the cytotoxic agents. Murray [29, 30, 31, 32] and others [26, 27] explore a number of optimal control problems for the administration of cytotoxic agents. In all of these models, only one compartment is used to model the cancer and therefore are limited in their practical value.

Two compartment models have been used to explore the effects of drug resistance using a single cytotoxic agent,

see for example [8, 12, 13, 14, 15, 33, 36], in which the compartments used are for drug resistant and sensitive cancer cells. A four compartment model is used in Abundo and Rossi [1] for cancer treatment with two cytotoxic agents, a natural extension to the two compartment models. Kirschner and Panetta [24] use two compartments to model the interaction of cancer and immune-effector cells using immunotherapy with the cytokine interleukin-2. Like the single compartment models, the cancer cells in all of these models are assumed to be in the growth fraction of the cancer. Two compartment models are used in Panetta [33] and Fister and Panetta [19] for the growth and clonogenic fractions. In these models, a more accurate description for the growth fraction is used and therefore the evolution of the number of cells is more reasonable. However, to the authors' knowledge, there is only one deterministic four compartment model Birkhead et al. [7] which considers drug resistance to a single cytotoxic agent of proliferating or cylcling (growth) and resting (clonogenic) main compartments with resistant and sensitive sub-populations governed by a system of four linear ordinary differential equations. The interactions between the various compartments are limited for simplicity and constant exponential growth dynamics are used. In this paper, a four compartmental model is developed in which the transitions between compartments are based on probabilities allowing for all possible interactions and the more realistic Gompertzian-like model for growth dynamics are employed which is valid for any population size. Distinctions between the growth dynamics is described in detail below.

3.1 Homogeneous cancer models

Homogeneous cancer models consist of a single cell type with all of the cells actively dividing, that is in the proliferating compartment. A key strength of these types of models is that growth parameters can be selected so that they match the results of a clinical assay or some reasonable aggregated values from a collection of assays. As discussed before, the lack of consistent clinical data makes this a reasonable assumption. However, the underlying reality of the system is not being accounted for. In using these models a greatly simplified problem can be cast and insight gained from the results generated. These concepts mirror those of standard population dynamics as do the assumptions necessary for model validation.

3.1.1 No treatment

The general form for the evolution of a cell population, $p(t)$, in absence of treatment, with general growth rate $f(p(t),t)$ per cell is given by:

$$\frac{dp(t)}{dt} = p(t)f(p(t),t). \tag{1}$$

The per cell growth rate function, $f(p,t) = \dot{p}/p$, represents the net growth, the difference between births of new cells and the loss of cells due to natural death or other causes, such as overcrowding. The form of the growth rate determines the characteristics by which the population will evolve. The following three forms for the growth rate in

(1) are typically used [1, 2, 3, 4, 6, 7, 9, 10, 19, 24, 26, 33, 34]:

$$f(p,t) = \left\{ \begin{array}{ll} c_1\,, & \text{Exponential Growth} \\ c_2\,(1-p/K)\,, & \text{Logistic Growth} \\ c_3 \log(K/p)\,, & \text{Gompertz Growth} \end{array} \right\}, \tag{2}$$

where c_i and K are positive constants that represent the leading order exponential growth and the carrying capacity, respectively. The population growth $p(t)$ for the three forms is displayed is versus time t in Figure 3. All populations start from a single cell, $p(0) = 1$ with carrying capacity $K = 1000$ where relevant and at the same slope of $\dot{p}$ relative to p, so that using $c_3 = 0.01$ implies that $c_1 = c_3 \log(K/(p(0)e)$ and $c_2 = c1/(1 - 2p(0)/K)$. For small population sizes, the exponential growth rate is the type of growth expected, that is one cell divides into two which subsequently divide into four and so on. Its main drawback is that the size of the population will grow without bound which clearly is not realistic for cancer in a finite host. The population size for the purely exponential growth model is plotted as the dash-dotted line in Figure 3. Cancer models which use exponential growth terms have two major

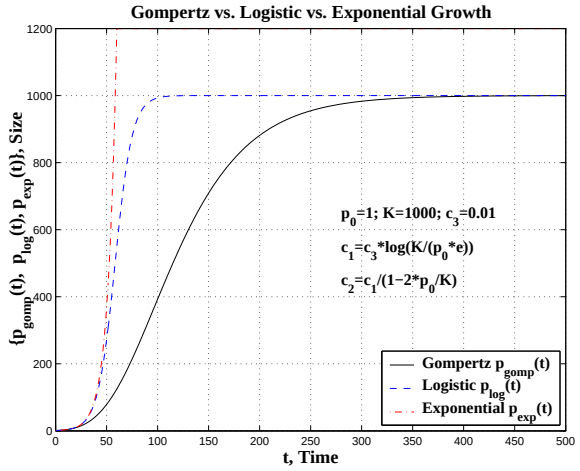

Figure 3: Graphs of the solutions to (1) for the three growth rate forms, in the absence of treatment. Note that the coefficients c_i of the growth rates are not identical, since the populations start at the same value and slope relative to the population size p.

flaws. The first is that the tumor size is relatively large at the time of detection (approximately 10^9 cells), a size which does not fit the *small-population* description and is close to the population saturation level (typically 10^{12} cells). The second flaw follows from the first: models which use this growth dynamic may indicate that treatments given are more effective than they actually are due to the exponential growth rates. Therefore, treatments with minimal clinical benefit may be given because of an inflated cancerous cell count whose major impact on the patient is to diminish the quality of life due to cumulative toxicity effects. The logistic growth exhibits a more realistic sigmoid curve (the dashed line in 3) which captures the exponential growth rates for small population sizes and limits the population to an appropriate carrying capacity or saturation level to approximate over-crowding effects. Logistic growth under these

controlled initial conditions is almost as aggressive as exponential growth, except near the tumor carrying capacity, so it might be a good model for extremely aggressive cancers. The Gompertz growth, like the logistic, is also sigmoid in shape (the solid line in 3), but differs in that the solution to (1) is an exponential of an exponential with saturation. The Gompertz growth is also more sensitive to saturation effects, when starting at the same initial value and slope. Additionally, the Gompertz growth dynamics are based on physical processes rather than population dynamics as discussed in [9, 10, 23]. The maximum per cell growth rate for the logistic is more than four times larger than that for the Gompertz growth form. Further, if the logistic and Gompertz models are fixed to have the same maximal per cell growth rate, at $K/4$ for logistic and K/e for Gompertz, rather than the same initial slopes, then the Gompertz growth surpasses the logistic growth. Upon treatment, additional loss terms must be added to (1).

3.1.2 Treatment

In developing treatments models the role of pharmacokinetics, the way in which the drugs interact with the human body, is paramount. See for example [11]. This entails many different concepts such as the mode by which the drug is to be administered, the effects of toxicity, the way in which the drug exits the system, and the development of resistance to the drug. The present investigation assumes that the drug administrations and the effects of chemotherapy are instantaneous. These assumptions, although not realistic, are somewhat justified because the model time scale used (one day) is relatively large enough for the majority of effects of treatment to be affected in one time unit. If the assumption of instantaneous effects are not reasonable, for example a 24-hour intravenous infusion of a cytotoxic agent, the average time at which the majority of the cytotoxic effects occurs can be used as the approximate time for the *effective* treatment. See [33] for an example of time dependent effects of chemotherapy administration.

The relationship between the quantity of cytotoxic agent given, limited by potential toxic effects, and the fraction of cells killed has been studied in a number of works, for example see [12, 13, 14, 15, 21, 34]. In this investigation, the maximum dose allowed will be given in order to kill as many cells as possible. Define $\Delta_i(t)$ to be a unit impulse function at time $t = t_i$, that is

$$\Delta_i(t) = \left\{ \begin{array}{ll} 1\,, & t = t_i \\ 0\,, & \text{otherwise} \end{array} \right\}, \tag{3}$$

which is used as the way in which the effects of treatments come into the model. Consider a treatment cycle of n treatments where at most m cycles can be given, therefore a total of $N = n \times m$ treatments may be given. Let the subscript $i = 1$ to N denote the individual treatments which are given at time t_i. The kill rate for treatment i is given by κ_i which represents the fraction of cells killed. The homogeneous cancer model (1) is augmented by a summation for the effects of the treatments. For treatment i at time t_i, the total number of cells killed is $\kappa_i p(t_i)$ and the treatment model is given by

$$\frac{dp(t)}{dt} = \left(f(p(t), t) - \delta(p(t), t) - \sum_{i=1}^{N} \Delta_i \kappa_i(t) \right) p(t), \tag{4}$$

where $\delta(p,t)$ denotes an additional, natural death rate. Due to the lack of information about the types of cells present and their status in terms of resistance, this model is quite limited.

3.2 Heterogeneous cancer model

3.2.1 No treatment

Let $P(t)$ and $C(t)$ represent the number of cells in the growth and clonogenic compartments, respectively. The model that is generated predicts the evolution of the cancer starting from a single growth cell. Let time $t = 0$ be the time for the appearance of the first malignant cell in the growth fraction from which a colony will form. This yields the initial conditions for the model as

$$P(0) = 1 \qquad \text{and} \qquad C(0) = 0. \tag{5}$$

Figure 4 represents the compartmental model for the evolution of heterogeneous cancer excluding the end cells and without treatment. Traditionally, in compartmental models the coefficients are multiplied by the value for the com-

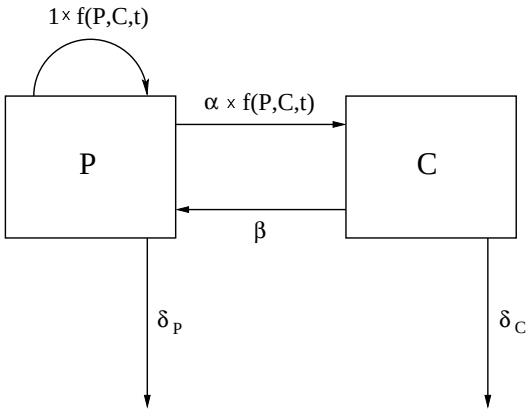

Figure 4: Schematic representation of the two compartmental model.

partment. The terms for the compartmental model are assumed to be functions with arguments (P,C,t). The compartmental form of the per cell growth rate $f(P,C,t)$ is used to select the form of the growth dynamics as in (2). The model presented here proposes that the growth rate be a Gompertzian relative rate of change form, based on the total population in the two compartments,

$$f(P,C,t) = \lambda \log\left(\frac{K}{P+C}\right), \tag{6}$$

where λ is the growth rate per unit time and K is the carrying capacity expressed as the total number of cells. This growth rate takes into consideration that only the cells in the proliferating compartment are actively undergoing cell division with the overall carrying capacity of the tumor being limited by the total cell population considered. The *death*

or *loss* rates, δ_P and δ_C, are used to account for natural losses from the respective compartments for reasons such as cell death, loss of the ability to divide, and recruitment to the end cell compartment to become stromal tissue. The value of 1 in the feedback loop for the proliferating compartment emphasizes that every cell in that compartment is currently undergoing division at rate $f(P, C, t)$. The factor $0 < \alpha(P, C, t) < 1$ is the probabilistic rate at which a daughter cell enters the G_0 resting phase of the cell life cycle after mitosis, i.e., migrates to the clonogenic compartment, which implies that $1 - \alpha(P, C, t)$ is the probability the cell remains in the growth fraction. Cells in the clonogenic fraction naturally recruited, in absence of treatment, into the growth fraction with a probabilistic rate $\beta(P, C, t)$. This leads to the following system of differential equations for the evolution of cancer in the absence of treatments:

$$\begin{aligned}
\frac{dP}{dt} &= \Big(1 - \alpha(P, C, t)\Big) f(P, C, t)P + \beta(P, C, t)C - \delta_P P \\
&= \Big(1 - \alpha(P, C, t)\Big) \lambda P \log\left(\frac{K}{P + C}\right) + \beta(P, C, t)C - \delta_P P, \\
\frac{dC}{dt} &= \alpha(P, C, t) f(P, C, t)P(t) - \beta(P, C, t)C - \delta_C C \\
&= \alpha(P, C, t)\lambda P \log\left(\frac{K}{P + C}\right) - \beta(P, C, t)C - \delta_C C
\end{aligned} \tag{7}$$

subject to the initial conditions (5) and the constraint $P(t) \geq 1$ for all time $t \geq 0$. A detailed discussion of the parameter forms can be found in later sections of this paper.

3.2.2 Treatment–two compartment model

Figure 5 represents the compartmental model for the evolution of heterogeneous cancer with treatment. The system of

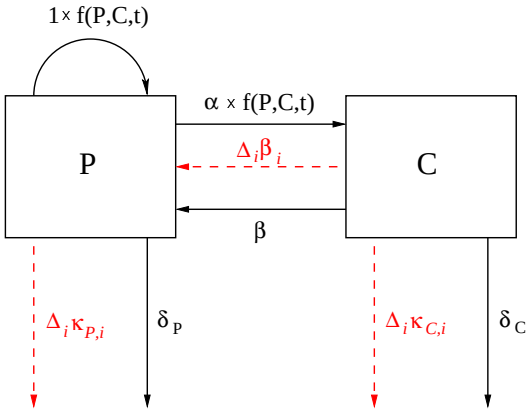

Figure 5: Schematic representation of the two compartmental model subject to chemotherapy. The dashed lines are chemotherapy terms.

equations for this model is

$$\begin{aligned}\frac{dP}{dt} &= \Big(1-\alpha(P,C,t)\Big)\lambda P\log\left(\frac{K}{P+C}\right)+\beta(P,C,t)C-\delta_P P-\sum_{i=1}^{N}\Delta_i(\kappa_{P,i}P-\beta_i C)\\ \frac{dC}{dt} &= \alpha(P,C,t)\lambda P\log\left(\frac{K}{P+C}\right)-\beta(P,C,t)C-\delta_C C-\sum_{i=1}^{N}\Delta_i C(\kappa_{C,i}+\beta_i)\end{aligned} \tag{8}$$

subject to the initial conditions (5). The term $\Delta_i\beta_i$ is used to model the large migrations of cells from the clonogenic to the growth fraction due to the effects of treatment. This recruitment increases the number of proliferating cells compensating for the loss of cells due to treatment. The terms $\Delta_i\kappa_{C,i}$ and $\Delta_i\kappa_{P,i}$ are the fraction of cells killed in the clonogenic and growth fractions, respectively. In this model, for each treatment i given, the values of $\kappa_{C,i}$ and $\kappa_{P,i}$ can form a monotone sequence of decreasing values to approximate the effects drug resistance. The values for the kill fractions are related to the type of cytotoxic agent administered, for example $\kappa_{C,i}=0$ for cycle specific cytotoxic agents if not administered at treatment i.

3.2.3 Treatment–four compartment model

A major drawback of the system (8) is that it is difficult to incorporate the effects of intrinsic and acquired drug resistance. As resistant cells develop, the overall fraction of cells that may be killed by the cytotoxic agent decreases. The system (8) has no way of determining the susceptible fraction of the population for the treatments, and only approximations for the kill rates $\kappa_{*,i}$ can be used to determine the effects of any given treatment. A new formulation is developed to track the development of drug resistant subpopulation of the cancer so that the effects of the treatments are accurate. Information from specific pharmacological studies can be used to determine the effects for a given cytotoxic agent for susceptible cells. In particular, the fraction of susceptible cells killed and the fraction of cells that acquire resistance to the agent are needed to model accurate effects of the treatments administered. Using this information, a model can be developed to determine the number of cells that are resistant and susceptible to the treatment. Here it is assumed that only a small fraction of the surviving cells from a treatment will develop acquired resistance. Resistance, whether intrinsic or acquired, is assumed to be inherited by the daughter cells and can be lost after mitosis due to another mutation of the daughter cells.

The model presented in this section assumes that drug resistance is complete rather than a spectrum, that is cells either are or are not resistant to a given cytotoxic agent. Furthermore, this paper focuses on the treatment of a tumor with a single cytotoxic agent. Let the subscripts R and S denote the subpopulation of each compartment which is resistant or susceptible to the administered cytotoxic agent, respectively. The growth term will be a compartmental Gompertzian relative rate of change form similar to (6):

$$f(P_R,P_S,C_R,C_S,t)=\lambda\log\left(\frac{K}{P_R(t)+P_S(t)+C_R(t)+C_S(t)}\right). \tag{9}$$

Let the natural rates α, β, δ_P and δ_C now be indexed by R and S, for resistant and susceptible, respectively, and are

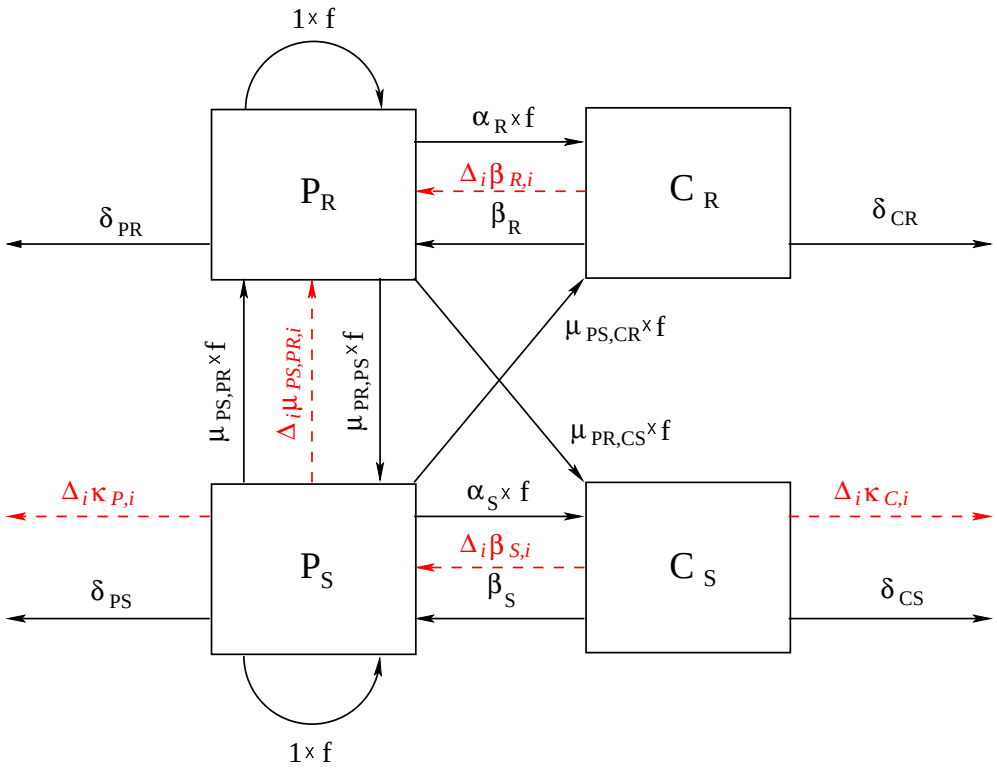

Figure 6: Schematic representation of the four compartmental model subject to chemotherapy. The dashed lines refer to chemotherapy. Compartments aligned in rows are either susceptible or resistant to the administered cytotoxic agent, and compartments aligned in columns are either proliferating or clonogenic sub-populations.

now functions of (P_R, P_S, C_R, C_S, t), as are all rates shown in Figure 6. The development of intrinsic or acquired drug resistance is assumed to require a mutation of the genetic material in a given cell. This resistance may be lost by further mutations or corrections to the corrupted portions of the cell's DNA. It is important to note that mutations may not lead to a viable cell and apoptosis may occur. The probabilistic mutation rates for the viable mutated cells are denoted by $\mu_{i,j}$ where i denotes the proliferating compartment of the parent cell and j denotes the destination of the daughter cell. In this formulation, all possible mutations are allowed. As before, $\Delta_i \kappa_{C(P)}$ denotes the loss of cells due to chemotherapy. The back migration of cells from the clonogenic to the proliferating compartments, modeled by the terms $\Delta_i \beta_{R,i}$ and $\Delta_i \beta_{S,i}$, now occurs in both the resistant and susceptible compartments. This is because the cells are recruited to replenish the total proliferating compartment population and not individual sub-populations. Finally, let $\Delta_i \mu_{PS,PR,i}$ denote acquired resistance. Then the equations for the four compartment model resembling the two compartment system (8) are

$$\begin{aligned} \frac{dP_R}{dt} &= \Big[(1-\alpha_R-\mu_{PR,CS}-\mu_{PR,PS})P_R+\mu_{PS,PR}P_S\Big]f+\beta_R C_R-\delta_{PR}P_R \\ &\quad +\sum_{i=1}^{N}\Delta_i(\mu_{PS,PR,i}P_S+\beta_{R,i}C_R), \end{aligned}$$

$$
\begin{aligned}
\frac{dP_S}{dt} &= \Big[(1-\alpha_S-\mu_{PS,CR}-\mu_{PS,PR})P_S+\mu_{PR,PS}P_R\Big]f+\beta_S C_S-\delta_{PS}P_S \\
&\qquad +\sum_{i=1}^{N}\Delta_i(-\mu_{PS,PR,i}P_S+\beta_{S,i}C_S-\kappa_{P,i}P_S), \\
\frac{dC_R}{dt} &= \Big[\alpha_R P_R+\mu_{PS,CR}P_S\Big]f-\beta_R C_R-\delta_{CR}C_R-\sum_{i=1}^{N}\Delta_i\beta_{R,i}C_R, \\
\frac{dC_S}{dt} &= \Big[\alpha_S P_S+\mu_{PR,CS}P_R\Big]f-\beta_S C_S-\delta_{CS}C_S-\sum_{i=1}^{N}\Delta_i(\beta_{S,i}+\kappa_{C,i})C_S. \qquad (10)
\end{aligned}
$$

It is clear that the number of compartments grows exponentially with the number of cytotoxic agents given. Specifically, the number of compartments for M non-cross resistant cytotoxic agents is

$$2\sum_{i=0}^{M}\binom{M}{i}=2^{M+1}.$$

4 Numerical example

From a macroscopic perspective, the movement of cells between the clonogenic and growth fractions can be simplified by considering the probabilistic bulk or net effects of the growth of cancer. In the case considered here, the proliferating compartments constitute 80% of the cancer. Thus, since most of the cells are actively proliferating, one expects little natural back migration from the clonogenic to the growth fraction compartments. It suffices to consider only a constant and small $\beta(P,C,t)$ term, i.e. $0<\beta(P,C,t)\approx\beta_{\text{const}}<<1$. The approach used also allows $\alpha(P,C,t)$ to capture the majority of the dynamics between the compartments in the absence of treatment, where the total populations for the growth and clonogenic fractions are given by $P(t)=P_R(t)+P_S(t)$ and $C(t)=C_R(t)+C_S(t)$, respectively. Thus, $\alpha(P,C,t)$ is the principal factor in determining the probabilistic relative sizes for the growth and clonogenic fractions. This formulation is meant to start with a single growth cell which further motivates the assumption on the roles of $\alpha(P,C,t)$ and $\beta(P,C,t)$. As the overall number of cells increases, the clonogenic fraction is assumed to be monotone increasing in the absence of treatment. As time passes the number of cells in the compartments is assumed to go to a limiting distribution given by

$$\lim_{t\to\infty}C(t)=K_C>0 \qquad \text{and} \qquad \lim_{t\to\infty}P(t)=K_P>0, \qquad (11)$$

where $K_C+K_P\equiv K$; hence

$$\lim_{t\to\infty}\frac{C(t)}{C(t)+P(t)}=\alpha_C>0 \qquad \text{and} \qquad \lim_{t\to\infty}\frac{P(t)}{C(t)+P(t)}=1-\alpha_C\equiv\alpha_P>0 \qquad (12)$$

are the limiting relative distributions of cells in the clonogenic and growth fractions, respectively. We define α in the two compartment model (8), or α_R and α_S in the four compartment model (10) to be α_C as defined above. Other parameter constraints are that $\max[\mu_{PS,CR},\mu_{PR,CS}]\ll\min[\mu_{PR,PS},\mu_{PS,PR}]\leq\max[\mu_{PR,PS},\mu_{PS,PR}]\ll 1$ since cells

in the first set require two mutations rather than one.

Parameter values used in the example	
$\alpha_R = \alpha_S = 0.20$	Probabilistic rate of migration from proliferating to clonogenic compartments
$\mu_{PR,PS} = \mu_{PS,PR} = 10^{-10}$	Probabilistic rate of intrinsic resistance
$\mu_{PR,CS} = \mu_{PS,CR} = 10^{-11}$	Probabilistic rate of cross compartment intrinsic resistance
$\beta_S = \beta_R = 10^{-10}$	Probabilistic rate of natural back migration from clonogenic to proliferating compartments
$\lambda = 0.00396, K = 5 \times 10^{14}$	Growth rate and overall carrying capacity used in f
$\delta_{PS} = \delta_{PR} = 0.01925$	Death rates for proliferating compartments
$\delta_{CS} = \delta_{CR} = 0.017325$	Death rates for clonogenic compartments
$P_S(0) = 1, P_R(0) = C_R(0) = C_S(0) = 0$	Initial conditions
10^{12} cells	Expected total population size at time of death
10^9 cells	Population size at which cancer can be detected
$\kappa_{P,i} = 98\%$	Cytotoxic agent's kill fraction for the proliferating compartment
$\beta_{R,i} = \beta_{S,i} = 50\%$	Probabilistic rate of cellular back migration from clonogenic to proliferating compartments due to chemotherapy
$\mu_{PS,PR,i} = 5 \times 10^{-9}$	Probabilistic rate of acquired drug resistance
$\kappa_{C,i} = 0$	Cytotoxic agent's kill fraction for the clonogenic compartment, i.e. cycle specific agent was used

Table 1: Summary of parameter values used in the numerical example.

The numerical example presented here considers the treatment cancer which began growing at time $t = 0$ with a single growth cell, so that the initial conditions for the system (10) are the extension of (5) given by

$$P_S(0) = 1 \text{ and } P_R(0) = C_R(0) = C_S(0) = 0.$$

Clinical detection requires a cancer burden of 10^9 cells, death is anticipated at a cancer burden of 10^{12} cells. The patient is diagnosed with the cancer and treatment begins at time $t = 600$ days with a cancer burden of 1.88×10^{10} cells.

In this example, the probabilistic rates of the system (10) are taken to be uniform since there is no conclusive evidence to suggest that the properties of resistant and susceptible cells behave differently in the way that they propagate. In the absence of treatment, the probabilistic limiting distributions for the cancer cells are 20% for clonogenic cells and 80% for proliferating cells. These values are used as the uniform probabilistic rates of migration after mitosis from the proliferating to the clonogenic fractions so that $\alpha_R = \alpha_S = 0.20$. The uniform probabilistic rate of natural back migration from the clonogenic to the proliferating fraction is $\beta_S = \beta_R = 10^{-10}$. The probabilistic loss terms, accounting for natural death and recruitment to develop stromal tissues, for the proliferating and clonogenic cells are $\delta_{PS} = \delta_{PR} = 0.01925$ and $\delta_{CS} = \delta_{CR} = 0.017325$, respectively. The growth rate and the carrying capacity for the Gompertzian dynamics (9) are $\lambda = 0.00396$ and $K = 5 \times 10^{14}$. Mutations that lead to viable cells may either acquire or loose natural or intrinsic resistance to all cytotoxic agents. The effects of the mutations

occur after mitosis and are inherited by the daughter cells which may either remain in the proliferating compartment or go into the quiescent phase. The probabilistic rate for the development of intrinsic resistance after mitosis is $\mu_{PR,PS} = \mu_{PS,PR} = 10^{-10}$ and the probabilistic rate for mutations or repair mechanisms to occur so that resistance is lost after mitosis is $\mu_{PR,CS} = \mu_{PS,CR} = 10^{-11}$.

Treatment of the cancer uses a single cycle-specific cytotoxic agent such that $m = 2$ clinically valuable treatment cycles of $n = 6$ treatments of the agent are given at intervals of 21 days for a total of $N = 12$ treatments with kill rates for each treatment i are $\kappa_{P,i} = 98\%$, and $\kappa_{C,i} = 0\%$, i.e., the therapeutic agent is cycle specific, so the treatment does not interfere with the clonogenic cells. Treatments cause a stimulus that recruits quiescent cells in the clonogenic fraction to become proliferating cells. This migration of cells is represented by $\Delta_i\beta_i$ in the two compartment model and similarly in the four compartment model. The probabilistic rates of migration for treatment i are uniform: $\beta_{R,i} = \beta_{S,i} = 50\%$. The probability that a surviving susceptible cell after treatment i acquires resistance is $\mu_{PS,PR,i} = 5 \times 10^{-9}$. The parameter values are summarized in Table 1.

In the absence of treatment, the model predicts that death will occur at time $t = 1667$ days. A two cycle regimen is depicted in Figure 7. The first treatment begins at time $t = 600$ days and concludes at $t = 705$ days with a cancer

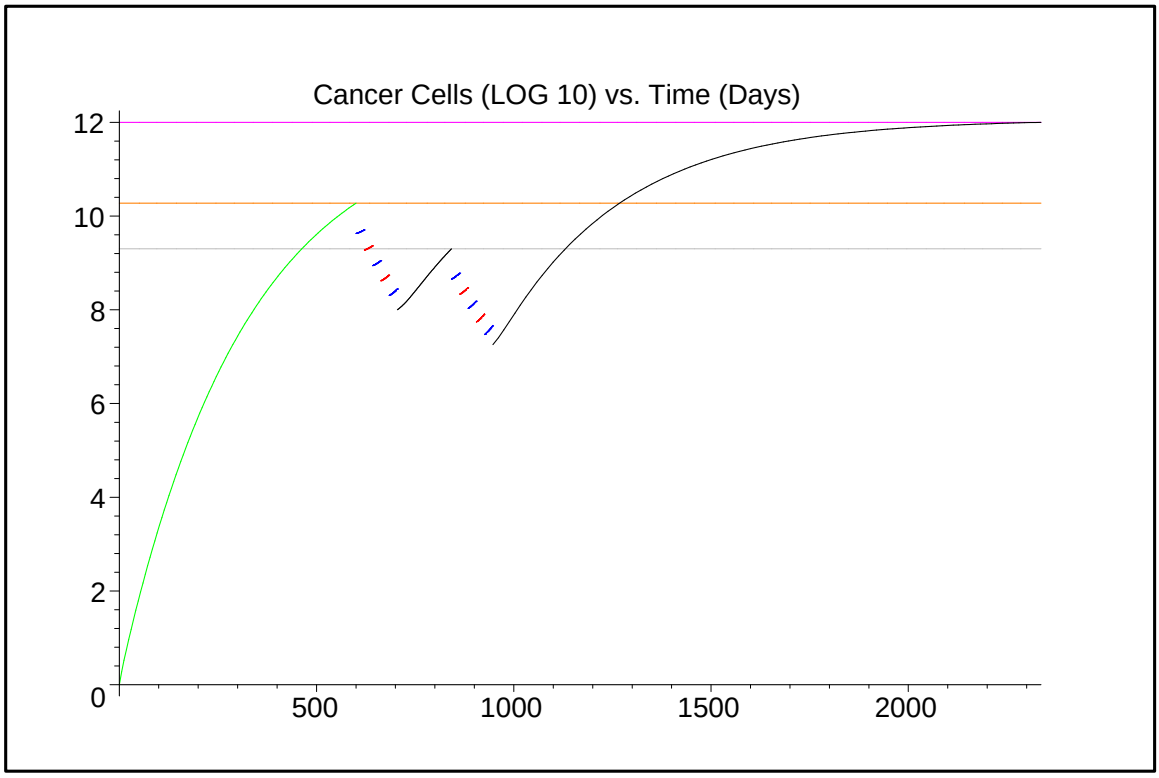

Figure 7: Logarithm of the total population size of cancer subjected to chemotherapeutic regimen of two cycles of a single cytotoxic agent using the four compartment model. The horizontal lines represent, from bottom to top, the number of cells for clinical detection, beginning of treatment, and anticipated death, respectively.

burden of approximately 2.81×10^8 cells, which is considered remission since the cancer burden is not clinically

detectable. Recurrence of the cancer occurs at time $t = 842$ days and another treatment cycle is administered. The cancer burden at the conclusion of the second treatment cycle is 4.65×10^7 cells and the patient is once again in remission. After the 2 treatment cycles have been administered death is anticipated at time $t = 2326$. Hence, the treatments lead to an increase in life expectancy of 659 days which is an increase of 39.53%. The cell counts for the various populations for the first two treatment cycles and the time at which death is anticipated are listed in Table 2. This example clearly illustrates the cumulative effects of drug resistance. Initially, the treatments drastically reduce

Event	Treatment	Day	P_S	C_S	P_R	C_R
Genesis		1	1	0	0	0
Detection	1	600	1.49×10^{10}	3.94×10^9	65	16
	2	621	3.28×10^9	1.82×10^9	213	35
	3	642	1.48×10^9	8.44×10^8	377	66
	4	663	7.22×10^8	4.00×10^8	668	122
	5	684	3.61×10^8	1.94×10^8	1230	231
	6	705	1.84×10^8	9.66×10^7	2372	454
Recurrence	7	842	1.58×10^9	4.19×10^8	79301	20859
	8	863	4.02×10^8	2.07×10^8	149720	30069
	9	884	1.95×10^8	1.03×10^8	288686	55901
	10	905	1.01×10^8	5.21×10^7	580532	113305
	11	926	5.37×10^7	2.70×10^7	1.22×10^6	241383
	12	947	2.90×10^7	1.43×10^7	2.67×10^6	535107
Recurrence		1131	4.38×10^8	1.15×10^8	1.15×10^9	3.02×10^8
Death		2336	5.67×10^{11}	1.57×10^{11}	2.16×10^{11}	5.98×10^{10}

Table 2: Population sizes of each compartment just after cytotoxic agent administration for a two cycle regimen.

the tumor size. Later treatments have significantly less effect on the overall tumor size. This is because the relative sizes of the resistant sub-populations are comparable to the susceptible populations.

Should the patient desire a third cycle upon second instance of recurrence, the model predicts that the patient will live one day less than the two cycle treatment. This second recurrence will be detected on day 1131. The first treatment of the third cycle will have a nominal affect and the rest of the treatments will have no clinical benefits, which can be seen in Figure 8. This result is not surprising since the total population that can be effectively treated, at the start of a third treatment cycle, is of the same order of magnitude as the resistant populations (see Table 2). In considering the patient, this additional treatment cycle would weaken the patient from side effects of the chemotherapy and yield a reduced quality of life and would most likely decrease the lifespan of the patient further than what is predicted by the model with the parameters given.

5 Discussion

The growth of cancer is erratic in nature and cannot be accurately described in terms of a simple mathematical model since every cell at each time t would need to be considered. Developing a model requires an understanding of the

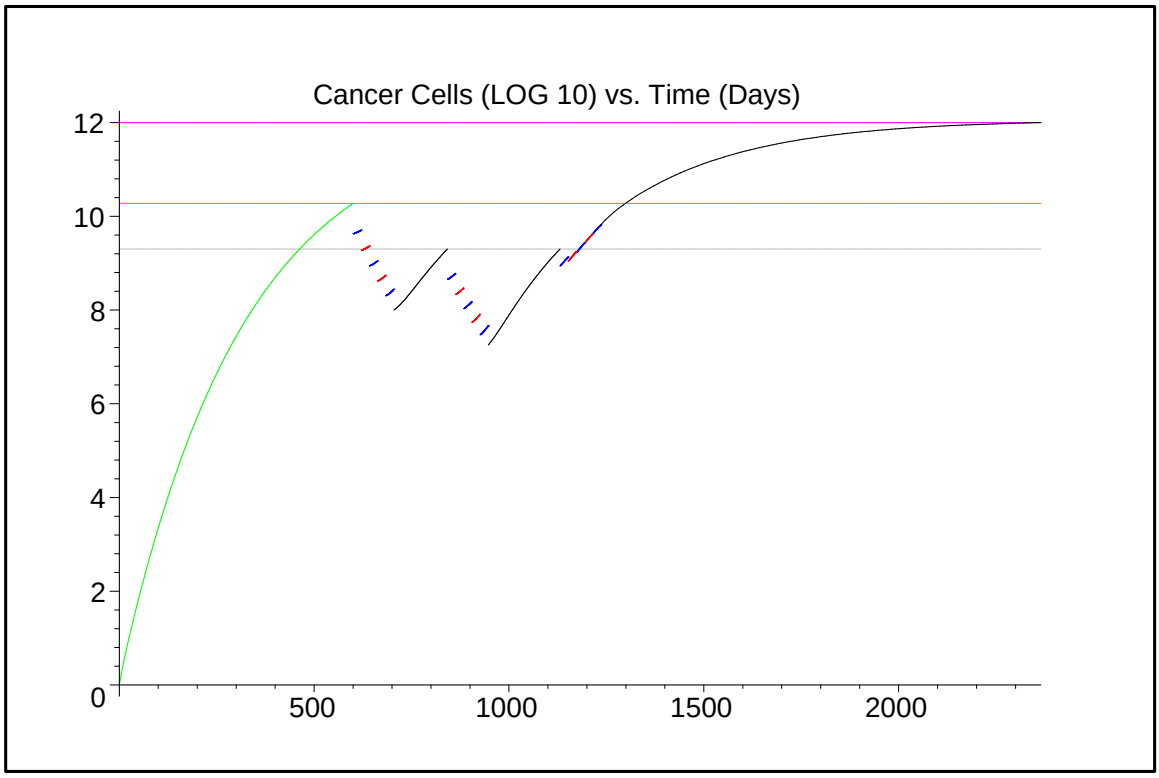

Figure 8: Logarithm of the total population size of cancer subjected to a chemotherapeutic regimen of three cycles of a single cytotoxic agent using the four compartment model. Notice that only the first treatment in the third cycle has any significant affect. The horizontal lines are as in Figure 7.

physical process and observations of the system. In cancer evolution, as mentioned earlier in the paper, there is a wide range of values for physically observed properties. It is important to note that various cancers behave differently and in the context of a given patient are a unique system.

To counter these difficulties, bulk dynamics are used to model the macroscopic evolution of the cancer in which the transition rates between the compartments are modeled using probabilistic rates. These transition rates may not be directly related to biological interpretation such as those in [7, 33] but describe the bulk dynamics of the cancer from a macroscopic perspective. The use of macroscopic properties which can be measured or estimated, for example blood serum level of key proteins or volume estimates from imaging instead of biologically based estimates, allows the model to capture key elements of the physical system. In this formulation for the development of cancer a focus is placed on the heterogeneous nature of cancer and the effects of drug resistance whether intrinsic or acquired.

In doing this, the work presented here is meant to be a diagnostic tool to aid in the assistance of determining and estimating the effects of treatments for a given patient. Ideally, the necessary parameters should come directly from data collected on the patient in question. However, this is not initially realistic, and aggregated clinical data is used that should be augmented by data collected from the patient over the course of treatment. Therefore, the values generated by the model should closely reflect the reality of the patient. The system (10) can be used as a tool for

clinicians to explore the development of cancer in the patient and the results of treatments, and can be used to weigh the benefits versus the side effects of the next treatment in order to determine whether or not the next treatment should be given. Additionally, this formulation could be used to explore alternate treatment scheduling for more effective use of cytotoxic agents.

The system (10) models cancer in a simplistic way. This formulation includes the heterogeneous nature of the cancer and the effects of drug resistance which are crucial for understanding the effects of treatment. The numerical example is used to illustrate these features with parameters selected to illustrate an aggressive cancer. The numerical parameters are constant and are meant to represent the asymptotic limiting values for the system. The evolution of cancer can be described as a stochastic dynamical system that is very complex with processes that depend on the relative population sizes among other factors, such as health and exposure to carcinogens. Therefore the parameters of the system (10) should vary with time and relative subpopulation sizes. The simplification of the treatments only approximates the true reality. The inclusion of pharmacokinetics would change the impulse formulation presented here into one which takes effect over a period of time. This would also allow for considerations such as various vectors of drug administration, duration of treatment, and dosage. Although the formulation is simple approximation of reality, it advances existing models and provides a better insight into this complex process. Future research directions include expanding the model to more accurately parallel the physical system.

As mentioned earlier in the paper, great variation has been observed in the physical parameters involved in cancer modeling. Additionally, one naturally expects great variation in different individuals not only for the evolution of cancer but the effects of treatment as well. From the perspective of the cancer patient, the model and parameters used for treatment should represent the *specific* patient and not some ideal generic cancer model tailored to some *idealized* patient. Therefore, we believe that methods need to be developed to estimate the various parameters that describe the evolution of the cancer for a given patient and the effects of treatments. These parameters should evolve in time, due to the cumulative effect of the cancer and treatment, the patient's health, and other factors that would need to be estimated. With the current parameters, a projection of the growth and potential metastasis of the cancer could be estimated. With this estimate more effective treatments could be given which should increase the patient's life expectancy and quality of life. This essentially leads to a dual problem of optimal control and estimation for the dynamical evolution of the cancer and of scheduling treatments. The control problem would need to have multiple objectives for reducing the cancer burden, maintaining a prescribed quality of life, protecting the health of the patient from both cancer and toxic effects of treatments, and determining the time when the next treatment should be given which is the control for the system. This way of determining when a treatment should be given leads to more effective treatments than traditional scheduling. This is a future direction of our research and beyond the scope of this paper.

References

[1] M. Abundo, C. Rossi, Numerical simulation of a stochastic model for cancerous cells submitted to chemotherapy, J. Math. Biol. 27 (1989) 81–90.

[2] E. K. Afenya, Acute leukemia and chemotherapy: a modeling viewpoint, Math. Biosci. 138 (1996) 79–100.

[3] E. K. Afenya, D. E. Bentil, Some perspectives on modeling leukemia, Math. Biosci. 150 (1998) 113–130.

[4] E. K. Afenya, C. P. Calderón, Normal cell decline and inhibition in acute leukemia: a biomathematical modeling approach, Cancer Detection and Prevention 20 (1996) 171–179.

[5] D. A. Anthoney, S. B. Kaye, Drug resistance, in: Cytotoxic Drug Resistance Mechanisms, R. Brown, U. Bvger-Brown, (Eds.), Totowa, New Jersey, 1999, Humana Press, pp. 1–15.

[6] D. Barbolosi, A. Iliadis, Optimizing drug regimens in cancer chemotherapy: a simulation study using a PK-PD model, Computers Bio. Med. 31 (2001) 157–172.

[7] B. G. Birkhead, E. M. Rakin, S. Gallivan, L. Dones, R. D. Rubens, A mathematical model for the development of drug resistance to cancer chemotherapy, Eur. J. Cancer Clin. Oncol. 23 (1987) 1421–1427.

[8] J. L. Boldrini, M. I. S. Costa, Therapy burden, drug resistance, and optimal treatment regimen for cancer chemotherapy, IMA J. Math. Appl. Med. Biol. 17 (2000) 33–51.

[9] C. P. Calderón, T. A. Kwembe, Modeling tumor growth, Math. Biosci. 103 (1991) 97–114.

[10] C. P. Calderón, T. A. Kwembe, Diverse ideas in modeling tumor growth, Acta Cientifica Venezolana 43 (1992) 64–75.

[11] K. C. Calman, J. F. Smyth, M. H. N. Tattersall, Basic principles of cancer chemotherapy, The Macmillan Press LTD, London, 1980.

[12] M. I. S. Costa, J. L. Boldrini, R. C. Bassanezi, Optimal control of populations developing drug resistance, IMA J. Math. Appl. Med. Biol. 9 (1992) 215–226.

[13] M. I. S. Costa, J. L. Boldrini, R. C. Bassanezi, Optimal chemotherapy: a case study with drug resistance, saturation effect, and toxicity, IMA J. Math. Appl. Med. Biol. 11 (1994) 45–59.

[14] M. I. S. Costa, J. L. Boldrini, R. C. Bassanezi, Chemotherapeutic treatments involving drug resistance and level of normal cells as a criterion of toxicity, Math. Biosci. 125 (1995) 211–228.

[15] M. I. S. Costa, J. L. Boldrini, R. C. Bassanezi, Drug kinetics and drug resistance in optimal chemotherapy, Math. Biosci. 125 (1995) 191–209.

[16] M. D. Cridland, Fundamentals of cancer chemotherapy, University Park Press, Baltimore, 1978.

[17] L. Cuaron, J. Thompson, The interferons, in: Biotherapy, P. T. Rieger, (Ed.), Jones and Bartlett Publishers, 2001, pp. 125–194.

[18] M. S. Ernstoff, Combination cytokine therapy in cancer, in: Tumor immunology and cancer therapy, R. H. Goldfarb, T. L. Whiteside, (Eds.), Marcel Dekker, 1994, pp. 273–279.

[19] K. R. Fister, J. C. Panetta, Optimal control applied to cell-cycle-specific cancer chemotherapy, SIAM J. Appl. Math. 60 (2000) 1059–1072.

[20] D. M. Gale, P. Sorokin, The interleukins, in: Biotherapy, P. T. Rieger, (Ed.), Jones and Bartlett Publishers, 2001, pp. 195–244.

[21] J. H. Goldie, A. J. Coldman, Drug resistance in cancer: mechanisms and models, Cambridge University Press, Cambridge, 1998.

[22] F. B. Hanson, C. Tier, A stochastic model of tumor growth, Math. Biosci. 61 (1982) 73–100.

[23] W. S. Kendal, Gompertzian growth as a consequence of tumor heterogeneity, Math. Biosci. 73 (1985) 103–107.

[24] D. Kirschner, J. C. Panetta, Modeling immunotherapy of the tumor-immune interaction, J. Math. Biol. 37 (1998) 235–252.

[25] T. Kuczek, T. C. K. Chan, Mathematical modeling for tumor resistance, J. Natl. Cancer Inst. 80 (1988) 146–147.

[26] R. B. Martin, M. E. Fisher, R. F. Minchin, K. L. Teo, A mathematical model of cancer chemotherapy with an optimal selection of parameters, Math. Biosci. 99 (1990) 205–230.

[27] A. S. Matveev, A. V. Savkin, Optimal chemotherapy regimens: influence of tumours on normal cells and several toxicity constraints, IMA J. Math. Appl. Med. Biol. 18 (2001) 25–40.

[28] M. S. Mitchell, Principles of combining biomodulators with cytotoxic agents in vivo, Seminars in Oncology 19 (1992) 51–56.

[29] J. M. Murray, Optimal control for a cancer chemotherapy problem with general growth and loss functions, Math. Biosci. 98 (1990) 273–287.

[30] J. M. Murray, Some optimal control problems in cancer chemotherapy with a toxicity limit, Math. Biosci. 100 (1990) 49–67.

[31] J. M. Murray, An example of the effects of drug resistance on the optimal schedule for a single drug in cancer chemotherapy, IMA J. Math. Appl. Med. Biol. 12 (1995) 55–69.

[32] J. M. Murray, The optimal scheduling of two drugs with simple resistance for a problem in cancer chemotherapy, IMA J. Math. Appl. Med. Biol. 14 (1997) 283–303.

[33] J. C. Panetta, A mathematical model of breast and ovarian cancer treated with Paclitaxel, Math. Biosci. 146 (1997) 89–113.

[34] J. C. Panetta, A mathematical model of drug resistance: heterogeneous tumors, Math. Biosci. 147 (1998) 41–61.

[35] K. Skalla, The interferons, Seminars in Oncology Nursing 12 (1996) 97–105.

[36] J. R. Usher, D. Henderson, Some drug-resistant models for cancer chemotherapy Part 1: Cycle-nonspecific drugs, IMA J. Math. Appl. Med. Biol. 13 (1996) 99–126.

[37] D. L. Volker, Normal cell biology and the biology of cancer, in: Biotherapy, P. T. Rieger, (Ed.), Jones and Bartlett Publishers, 2001, pp. 65–84.