Probabilistic Rate Compartment Cancer Model: Alternate versus Traditional Chemotherapy Scheduling

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Abstract. A four-compartment model for the evolution of cancer based on the characteristics of the cells is presented. The model is expanded to account for intrinsic and acquired drug resistance. This model can be explored to see the evolution of drug resistance starting from a single cell. Numerical studies are performed illustrating the palliative nature of chemotherapeutic treatments. Computational results are given for traditional treatment schedules. An alternate schedule for treatments is developed increasing the life expectancy and quality of life for the patient. A framework for the alternate scheduling is presented that addresses life expectancy, quality of life, and risk of metastasis. A key feature of the alternate schedule is that information for a particular patient can be used resulting in a personalized schedule of treatments. Alternate scheduling is compared to traditional treatment scheduling.

1 Introduction

Various treatment options may be open to the cancer patient such as surgery, chemotherapy, radiotherapy, and immunotherapy. These treatment modalities may be used in any combination and depend on the type and extent of the cancer in the patient. One of the most common modalities is chemotherapy which may be a primary treatment or a subsequent treatment following surgery as a suppressive therapy, see for example [10]. Chemotherapy is palliative in nature and most often cannot lead to a cure for the cancer due to drug resistance which may be either intrinsic, i.e. naturally occurring, or acquired in the presence of a cytotoxic or chemotherapeutic agent .[1]

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The four-compartment model used in this paper, described in detail in [29], allows for the exploration of treatment schedules so that a schedule may be determined that provides for the patient a greater life expectancy and higher quality of life such as the one proposed in [25]. A stochastic optimal scheduling or control problem can be used to determine such alternate schedules for treatments. In formulating a stochastic optimal control problem, the form for the dynamics of the system or for the cost functional can be structured in such a way as to obtain diverse results. The objectives that would be used for the cost functionals for traditional and alternate treatment scheduling are radically different. In traditional methods, as soon as the cancer is detected, the goal is to drive the cancer into remission as soon as possible. The goal of the alternate method is to increase the life expectancy of the patient and to maintain a minimum specified level for health and quality of life while ensuring that the risk of metastasis is kept to acceptable levels. Due to the nature of chemotherapeutic drugs and the development of resistance to them, both treatment strategies are subject to constraints based on the toxicity of the cytotoxic agent and the total number of treatments that can be administered. Additionally, traditional scheduling considers the time when a collection of treatments should be given whereas the alternate schedule uses individual treatments. The authors will do a more complete investigation of the optimal scheduling control problem in a future paper.

Two of the most crucial concerns with the use of chemotherapy are toxicity and drug resistance. The development of drug resistance occurs at the cellular level via several mechanisms [19,20]. Toxicity limits the dose and frequency by which treatments may be administered. Drug 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. One way to reduce the development of drug resistance of a cancer to a cytotoxic agent is to supplement the treatment with additional treatment modes, such as radiotherapy or another cytotoxic agent which is not cross resistant with the first agent. An extension of the model used in this paper can be found in [28] which considers multiple cytotoxic agents to reduce the effects of drug resistance.

Typically, a reduction in cancer is seen with the initial administration of cytotoxic agents, but eventually the tumor begins to grow and expand in the presence of the agent. This implies that the available effectiveness of the agent is limited to a finite number of applications after which it can no longer control the growth of the cancer. The application of cytotoxic agents also destroys normal or good cells which negatively impacts the patient's health. Therefore the determination whether or not to administer the cytotoxic agent needs to consider effects on the cancer as well as that of normal tissue, see

for example [1,2]. Traditional treatment schedules for chemotherapy consist of several applications of the cytotoxic agent relatively close together. After a treatment is administered, both the cancer cells and normal cells begin to grow again. The normal or good tissue used to measure the toxicity of the treatment is typically the white blood cell count, and indirectly the bone marrow cells responsible for it's production, see [11,3] for example. Clinically, it is easy to measure the white blood cell count before treatment, if the level of white blood cells is too small, the treatment may be delayed or given at a reduced dose.

Alternate optimal scheduling for cytotoxic agents has been the subject of many papers. However the dynamics employed for the evolution and treatment of the cancer have been lacking in the sense that, to the best of our knowledge, no source considers the heterogeneous nature of the cancer, the development of drug resistance, with appropriate Gompertzian growth dynamics. See [5,9,16–18,21–24,27] for various examples of optimal treatment scheduling for cytotoxic agents.

In Section 2 a summary of the compartment model for cancer subject to chemotherapy [29] is presented that accounts for the heterogenous nature of cancer and the evolution of drug resistance. A discussion of the alternate treatment scheduling is presented in Section 3 and a numerical example is given in Section 4 which is meant to provide a proof of concept for the optimal alternate scheduling.

2 Four-Compartment Model for Cancer Treatment

The following material is a summary of the four-compartment model presented in [29]. The compartments represent the heterogeneous nature of cancer subject to the development of drug resistance to a single cytotoxic agent. A key feature of this model is that the heterogeneous nature of the cancer as well as drug resistance are taken into account. To the best of the authors' knowledge, the only other treatment model to incorporate these factors is by Birkhead et al. [4] which is a deterministic system governed by exponential dynamics with limited interactions between the various compartments. In the model used here, more realistic Gompertzian dynamics (see [6,7,15]) are employed with all possible transitions between compartments allowed and the transition rates between compartments are both probabilistic in nature and dependent on the subpopulation sizes and time.

Cancer consists of three primary types of cells: the proliferating fraction, clonogenic fraction, and end cells (see for example [8]). End cells, denoted by E, primarily consist of somatic tissue, vascular and endothelial support cells, and necrotic tissue. These cells can not further propagate the cancer directly, but may play a fundamental support role in the development of the cancer. The proliferating or growth fraction cells, denoted by P, are actively dividing. After the completion of mitosis by the parent cell, the daughter cells

have a specified probability of becoming any of the primary types of cells which depends on the relative number of cells for each of the groups. The clonogenic cells, denoted by C, are quiescent or dormant cancer stem cells in the G_0 phase of the cell life cycle. With the proper stimulus, clonogenic cells can begin actively dividing, becoming proliferating cells, or can differentiate into support tissue.

The goal of chemotherapy is to move all of the cells from the proliferating and clonogenic fractions into the end cell compartment. Since end cells cannot directly propagate cancer, they are not considered in the model. The proliferating and clonogenic cells are further subdivided into susceptible and resistant subpopulations, denoted by the subscripts S and R, respectively. Define the indicator sets as

$$\mathcal{R} \equiv \{R,\ S\}\ , \qquad \mathcal{T} \equiv \{P,\ C\}\ , \qquad \text{and} \qquad \mathcal{I} \equiv \{PR,\ CR,\ PS,\ CS\}\ .$$

This results in a four-compartment model for the number of cells in the different subpopulations, $\{P_R(t),\ C_R(t),\ P_S(t),\ C_S(t)\}$, representing the *bulk* or *macroscopic* dynamics subject to treatment by a single cytotoxic agent. The effects of a given treatment is related to the quantity or dose of the cytotoxic agent given and is limited by potential toxic effects. In this formulation, the cytotoxic agent acts on the appropriate subpopulations and not on all cells. In this investigation, the maximum dose allowed for the cytotoxic agent will be given in order to kill as many cells as possible with effects assumed to be instantaneous. If the assumption of instantaneous effects is not realistic, for example intravenous infusion of the cytotoxic agent for 24 hours, then the mean time at which the majority of the agents act is used as the *effective* treatment time. The time at which treatment $i = 1, \ldots, N$ is given is denoted by $\delta(t - t_i)$. The resulting treatment model is illustrated in Figure 1 and is given by the following system of equations:

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

$$\frac{dC_R}{dt} = \left[\alpha_R P_R + \mu_{PS,CR} P_S\right] f - \beta_R C_R - \delta_{CR} C_R - \sum_{i=1}^{N} \delta(t - t_i)\beta_{R,i} C_R \ ,$$

where all coefficients are probabilistic rates and are functions related to the sizes of the subpopulations and time (P_R, P_S, C_R, C_S, t). The summation terms in (1) represent the effects of treatment. All daughter cells maintain

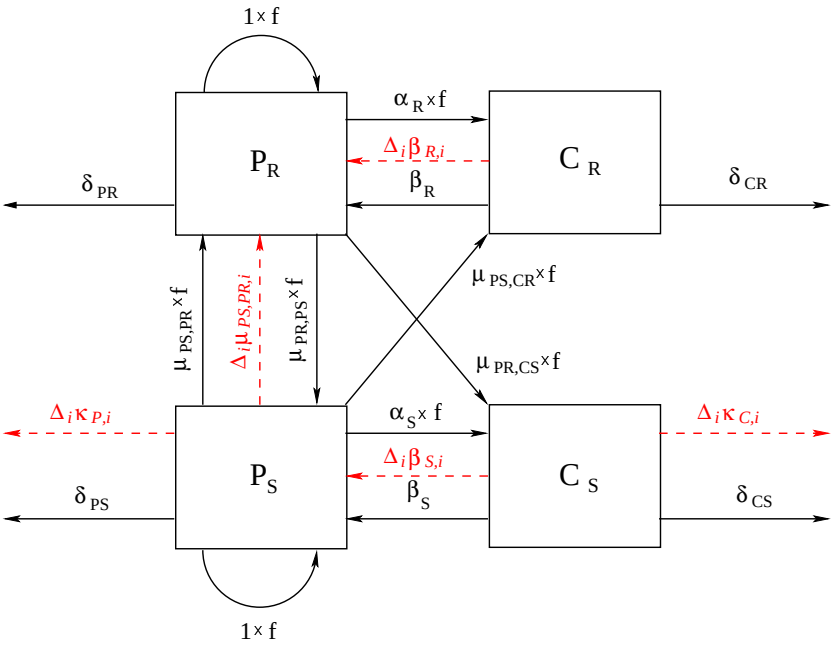

Fig. 1. Schematic representation of the four-compartment model subject to chemotherapy. The dashed lines refer to population migration due to chemotherapy. Compartments aligned in rows are either susceptible or resistant to the administered cytotoxic agent, and compartments aligned in columns are either proliferating or clonogenic sub-populations

their quality of drug resistance from the parent cell unless a mutation occurs in the parent cell which is inherited by the daughter cells after mitosis. The growth rate for the cancer is given by the Gompertzian form

$$f(P_R, P_S, C_R, C_S, t) = \lambda \log\left(\frac{K}{P_R(t) + P_S(t) + C_R(t) + C_S(t)}\right) , \qquad (2)$$

where λ is the growth rate and K is the carrying capacity for the proliferating and clonogenic cells. The allowed probabilities for the mutation rates are given by $\mu_{j,k}$ where $j, k \in \mathcal{I}$ are shown in Figure 1, if not shown then

$\mu_{j,k} \equiv 0$. The probabilistic rate α_* represents the fraction of cells that become quiescent, that is clonogenic, after mitosis which implies that the $1 - \alpha_*$ represents the fraction of cells that remain proliferating where $* \in \mathcal{R}$. Under the appropriate stimulus, clonogenic cells begin to proliferate with a probability given by β_* for $* \in \mathcal{R}$. The loss rates from a given compartment are denoted by δ_J where $J \in \mathcal{I}$ and account for apoptosis, natural death of cells, and cells recruited to the end cell compartment to become vascular and endothelial cells.

The probabilistic *death* or *kill* rate of cells due to the i^{th} treatment of the cytotoxic agent are given by $\kappa_{\star,i} \geq 0$ for $\star \in \mathcal{T}$. If either of $\kappa_{C,i} = 0$ then the cytotoxic agent is said to be *cycle-specific* otherwise the agent is *cycle-nonspecific*. A stimulus is created due to the death of a large number of cells by the cytotoxic agent which causes recruitment from the clonogenic to the proliferating fractions with a probabilistic rate for the i^{th} treatment given by $\beta_{*,i}$ for $* \in \mathcal{R}$. In the presence of a cytotoxic agent, proliferating cells may acquire resistance at the completion of mitosis with probability $\mu_{PS,PR,i}$ for the i^{th} treatment. In the treatment presented here, assuming the maximum dose for the cytotoxic agent, drug resistance is seen as semipermanent in the sense that once drug resistance is acquired a mutation must occur for the subsequent generation to lose or gain drug resistance. The concept of a drug resistance spectrum which depends on the dose of the cytotoxic agent is presented in Goldie and Coldman [14]. This implies that probabilities for both the kill rates and for acquiring resistance are dependent on the concentration of the drug at the site of the cancer. Note that all of the effects of treatment are indexed by the treatment number and therefore can change with the number of treatments given which allows for greater flexibility in modeling chemotherapy and can be used to generate the effects of the agents as presented in [14].

3 Alternate Treatment Scheduling

The ability for a cytotoxic agent to effectively treat cancer is limited by drug resistance, which can either be intrinsic or acquired. Drug resistance is inherited by daughter cells after mitosis and will be passed on to their progeny. This rapidly leads to a large subpopulation of the cancer cells that are *immune* to treatment. Cytotoxic agents destroy both cancerous and normal cells. Therefore, the benefit of a given treatment needs to consider the impact on the cancer as well as the overall health of the patient. This leads to a situation in which only a small number of treatments can be administered with overall positive impact such that additional treatments will have a nominal effect on the cancer and a negative impact on the patient.

Traditional treatment scheduling of cytotoxic agents is based on administering a *treatment cycle*. A treatment cycle consists of administering a fixed number of doses, denoted by n, of the cytotoxic agent at fixed time intervals

of $\Delta t_i \equiv t_{i+1} - t_i$, see for example [10]. If t_i denotes the time for the i^{th} treatment, then the next treatment would be given at time $t_{i+1} = t_i + \Delta t_i$. Only a few treatment cycles can be used with positive impact to the patient, the number of which is denoted by m. Thus, a total of $N = n \times m$ treatments may be given with positive impact to the patient. Once the decision is made to utilize chemotherapy, for example after initial detection or surgery, a treatment cycle is administered. If the treatment cycle does not lead to remission another treatment cycle is administered, provided one is available, until remission is achieved. Upon recurrence, clinical detection, of the cancer the process for administration of treatment cycles repeats. Treatment concludes when all of the m available treatments have been administered. The goal of traditional treatment schedules is to drive the cancer into remission. The use of a treatment cycle may have serious side effects in patients, leading to diminished quality of life due to cumulative toxic effects of the cytotoxic agents being administered relatively close together.

Traditional chemotherapy scheduling can waste the effectiveness of treatments by over-treating. That is, the benefit for the reduction of the cancer may be nominal or minimal relative to the detrimental side effects to the patient, reducing the patient's quality of life. Motivated by concepts of *managing* the cancer relative to the impact of treatment on the patient presented by Schipper et al. [25], an alternate treatment scheduling is considered. The goal is to determine the time at which the *next* treatment should be given. To do this, a *treatment level*, total number of cancer cells present, needs to be established. By doing this the time between treatments is expected to increase and should lead to an increased life expectancy and quality of life. The treatment level is then used to define a *next treatment time problem.* Additionally, a *stopping time problem* needs to be established to determine when treatments should be stopped because they are no longer beneficial in the overall sense to the patient.

A major concern for maintaining a large number of cancer cells is the risk of *metastasis*, the spread of the cancer to remote places in the body from the original site. This is a stochastic process that depends the size of the cancer, the level of angiogenesis (amount of vascularization and endothelial cells), as well as other factors. Metastasis is a process in which cancer cells detach, enter the blood stream, and are transported to remote locations where they attach and form new colonies of cancer. To counter the effects of metastasis, various investigators [12,13,26] suggest that angiogenesis inhibitors and antimetastatic drugs be given to the patient.

To determine when a treatment should be given, a stochastic optimal control problem needs to be solved for the maximum number of cancer cells present for treatment. This optimal control problem needs to based on the system (1) with extensions for stochastic effects such as metastasis which should be represented as a jump process as well as a background Gaussian random process to model small uncertainties and for a new state variables

that represent the time of expected death, quality of life, and measure of health. The cost functional should be designed to determine the maximum level of cancer cells necessary for a treatment to be given to maximize the time of expected death while minimizing the risk of metastasis and while maintaining a specified minimum level for quality of life and health. Additionally, constraints for toxicity need to be imposed.

The practical implementation of the alternate treatment scheduling must initially drive the the number of cancer cells below the treatment level using aggressive chemotherapy. Once this is achieved, the control problem should be implemented as a receding time horizon problem based on the discrete events of when treatments are given. In doing this, valuable information can be included about the patient in the decision making process for treatment scheduling. If the times between treatments is large enough, additional monitoring of the patient may be necessary to ensure the goals of treatment are met. This alternate scheduling should improve the life expectancy and quality of life for the patient by removing the cumulative negative side effects of chemotherapy. Hopefully, this new scheduling will lead to fewer patients who discontinue treatment.

The concepts presented here can be extended to consider the pharmacokinetic effects and properties of the treatments and allow for a new control variable in terms of the dose size. Another extension to this decision process would be the inclusion of multiple treatment modalities including for example, multiple cytotoxic agents, surgery, radiotherapy, and immunotherapy. The ultimate goal of cancer treatment should be to give the patient a near normal life expectancy and quality of life.

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. The values used in the numerical example are taken to be the constant limiting probabilities. Furthermore, the probabilistic rates of the system (1) 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.

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 (1) are given by

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

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 $t = 625$ days with a cancer burden of 2.58×10^{10}

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
$\beta_S = \beta_R = 10^{-5}$	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
$\delta_{PS} = \delta_{PR} = 0.01925$	Loss rates for proliferating compartments
$\delta_{CS} = \delta_{CR} = 0.017325$	Loss rates for clonogenic compartments
$P_S(0) = 1,$ $P_R(0) = C_R(0) = C_S(0) = 0$	Initial conditions
10^{12} cells	Expected number of cancer cells to cause death
10^9 cells	Population size at which cancer can be clinically detected
1.5×10^{10} cells	Number of cancer cells at which treatment is given for alternate scheduling
$\kappa_{P,i} = 98\%$	Cytotoxic agent's kill fraction for the proliferating compartment
$\kappa_{C,i} = 0$	Cytotoxic agent's kill fraction for the clonogenic compartment, i.e. cycle specific agent was used
$\beta_{R,i} = \beta_{S,i} = 90\%$	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

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

cells. In the absence of treatment, the probabilistic limiting distributions for the cancer cells are 20% for clonogenic cells and 80% for proliferating cells which represents an very aggressive cancer. 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 $\beta_S = \beta_R = 10^{-5}$. 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 (2) are $\lambda = 0.00396$ and $K = 5 \times 10^{14}$. Mutations that lead to viable cells may either acquire or lose 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 drug resistance is lost after mitosis is $\mu_{PR,CS} = \mu_{PS,CR} = 10^{-11}$.

Treatment of the cancer uses a single cytotoxic agent with kill rates for each treatment i given by $\kappa_{P,i} = 98\%$, and $\kappa_{C,i} = 0\%$, i.e., the chemotherapeutic agent is proliferating cycle specific, so the treatment does not kill any of the clonogenic cells. Treatments cause a stimulus from the large number of proliferating susceptible cells that are killed, which recruits quiescent cells from the clonogenic fraction to become proliferating cells with rates given by $\beta_{R,i} = \beta_{S,i} = 90\%$. The probability that a surviving susceptible cell after treatment i acquires drug resistance is $\mu_{PS,PR,i} = 5 \times 10^{-9}$. In the absence of treatment, the model predicts that death will occur at time $t = 1666$ days. The parameter values are summarized in Table 1.

4.1 Traditional Treatment Schedule

Treatment of the cancer uses a single cycle specific cytotoxic agent such that a maximum of $m = 2$ 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. This two treatment cycle regimen is depicted in Figure 2. The

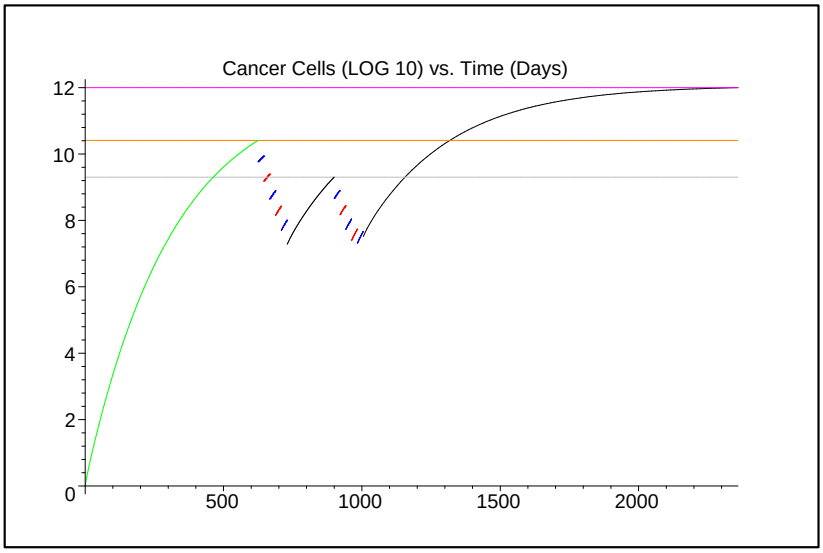

Fig. 2. Logarithm of the total population size of cancer subjected to chemotherapeutic regimen of two treatment cycles of a single cycle specific cytotoxic agent. The horizontal lines represent, from bottom to top, the number of cells for clinical detection, beginning of treatment, and anticipated death, respectively

first treatment begins at time $t = 625$ days and concludes at $t = 730$ days

with a cancer burden of approximately 1.90×10^7 cells, which is considered remission since the cancer burden is not clinically detectable. Recurrence of the cancer occurs at time $t = 900$ days and another treatment cycle is administered. The cancer burden at the conclusion of the second treatment cycle is approximately 3.27×10^7 cells and the patient is once again in remission. After the 2 treatment cycles have been administered death is anticipated at time $t = 2359$.

4.2 Alternate Treatment Schedule

In the alternate treatment scheduling, 12 treatments are used with a treatment level of 1.5×10^{10} cells. Initially, treatments are given spaced at the traditional schedule, $\Delta t_i = 21$ days, until the number of cancer cells is below the treatment level, that is aggressive treatment is used. Subsequent treatments are given when the number of cancer cells reaches treatment level, and a toxicity constraint for scheduling treatments is imposed. Let the treatment i be given at time t_i, and the next time that the number of cancer cells reaches the treatment level be τ_{i+1}. Then, the time for treatment $i+1$ is determined by the toxicity constraint:

$$t_{i+1} = t_i + \text{Max}[\Delta t_i, \quad \tau_{i+1} - t_i] \; . \tag{3}$$

The alternate scheduling corresponding to the two treatment cycle traditional schedule is depicted in Figure 3. After treatment ends death is anticipated at $t = 2661$ days.

4.3 Traditional vs. Alternate Treatment Scheduling

The goal of traditional treatment scheduling is to drive the cancer into remission as quickly as possible. In doing this, some treatments may be given without major benefit to the patient, that is the number of cancer cells killed is small relative to the remaining cancer cells. Alternate treatment scheduling seeks to have each treatment be as valuable as possible, however in doing this the patient is at risk for metastasis of the cancer. To minimize the risk of metastasis, angiogenic inhibitors and antimetastatic drugs should be used and the level of treatment should be selected so that the risk profile is acceptable to the patient.

A summary of the results for traditional and alternate is presented in Table 2. Note that 3 treatment cycles traditionally scheduled actually reduces the life expectancy of the patient which is attributed to drug resistance. In the alternate scheduling, even though 18 treatments leads to a longer life expectancy than 12 treatments the last 5 of the 18 treatments are scheduled at the toxicity threshold and above the treatment level which means that the quality of life for the patient would be diminished. Using 3 traditional

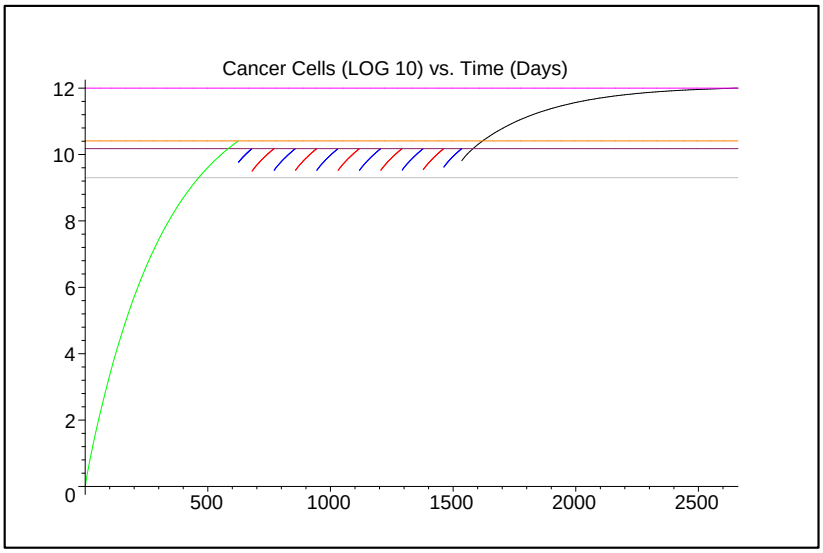

Fig. 3. Logarithm of the total population size of cancer subjected to 12 alternate scheduled chemotherapeutic treatments of a single cycle specific cytotoxic agent. The horizontal lines represent, from bottom to top, the number of cells for clinical detection, level for alternate treatment, beginning of treatment, and anticipated death, respectively

Traditional Scheduling			Alternate Scheduling		
Number of Treatment Cycles	Anticipated Death (days)	Percent Increase	Equivalent Number of Treatments	Anticipated Death (days)	Percent Increase
1	2103	26.23%	6	2200	32.05%
2	2359	41.60%	12	2661	59.72%
3	2308	38.54%	18	2686	61.22%

Table 2. Summary of traditional vs. alternate treatment scheduling, where 'percent increase' is relative to the anticipated death in the untreated case

treatment cycles or the equivalent of 18 alternate scheduled treatments is shown in Figure 4. In regions of traditional scheduling, the cumulative effects of the cytotoxic agents reduces the health of the patient since good or normal cells are killed as well weakening the patient, which may leave the patient susceptible to opportunistic infections. It is clear from Figure 4 that the third traditional treatment cycle and the last 5 alternate scheduled treatments provide no benefit to the patient and should have a significant negative impact on the patient's health, therefore they should not be administered. Table 3 lists the times for treatments for traditional and alternate

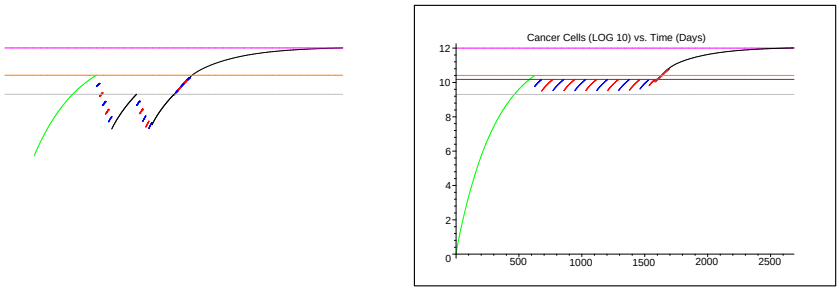

Fig. 4. Logarithm of the total population size of cancer subjected to (left figure) 3 traditional treatment cycles and (right figure) 18 alternate scheduled chemotherapeutic treatments of a single cycle specific cytotoxic agent. The horizontal lines correspond to those in Figures 2 and 3. Note that the last traditional treatment cycle is of nominal value and that the last 5 alternate treatments are above the level of treatment

schedules. The thirteenth alternate treatment is administered on day 1581, which accounts for the additional 25 extra days for anticipated death between the 12 and 18 treatments as listed in Table 2. Clearly, the alternate treatment schedule utilizing 13 treatments would be preferred mode of treatment scheduling. Note that the alternate treatment method not only increases the life expectancy and quality of life, but also allows for more treatments to be given with positive benefit to the patient.

Treatment Number	Traditional Schedule	Alternate Schedule
1	625	625
2	646	680
3	667	770
4	688	857
5	709	944
6	730	1031
7	900	1118
8	921	1205
9	942	1292
10	963	1378
11	984	1462
12	1005	1535

Table 3. Times of treatments for traditional and alternate scheduling

5 Conclusions

A compartment model for the evolution of cancer subject to chemotherapy should include aspects for the heterogeneous nature of cancer and for the development drug resistance. In using such a model, alternate treatment schedules can be tested against traditional schedules. Alternate treatment schedules allow for a better control of cancer management and can be tailored to the patient. The numerical example presented illustrates the benefit in terms of *life expectancy* as well as an increase in the *quality of life* since the times of treatments are spread over greater periods of time than that of traditional schedules.

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