Cancer Treatment Using Multiple Chemotheraputic Agents Subject to Drug Resistance

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Abstract

A compartment model for the evolution of cancer subject to multiple chemotherapeutic agents is presented. The formulation accounts for the heterogeneous nature of cancer and drug resistance, leading to a system that can be used as a tool for optimizing treatments. Chemotherapeutic or cytotoxic agents have limited effectiveness due to of toxicity and the development of drug resistance. Toxicity limits the amount of the agent that can be used and acts as an upper bound on the dosage. Drug resistance causes the clinical value of the cytotoxic agent to become nominal after a small number of treatments. Therefore, several non-cross resistant cytotoxic agents are used to extend the number of treatments that can be administered.

1 Introduction

One of the most challenging aspects of treating cancer with chemotherapy is the development of resistance to the cytotoxic agents. Drug resistance, whether intrinsic or acquired, ultimately leads

to the ineffectiveness of the agent where there is nominal clinical benefit compared to the side effects of the treatment. To counter the development of the resistance, other treatment modes or options are used that destroy the resistant and sensitive cells. The use of multimode treatments, for example chemotherapy and radiotherapy, leads to a more effective treatment plan. One of these multimode options is to use another cytotoxic agent that utilizes a different mechanism to destroy the cells and therefore should not be cross resistant, i.e., cells should not share all of the same drug resistance mechanisms. Treatment therapies utilizing multiple cytotoxic agents are commonly used in practice, see for example [1, 2, 3].

This paper extends the four compartment model presented in [4] for the evolution of cancer subjected to chemotherapy to account for the use of multiple cytotoxic agents. For concreteness, we examine the case of two non-cross resistant cytotoxic agents (say agents A and B) which yields an eight compartment model. This can be extended rather easily to M non-cross resistant cytotoxic agents, where the number of compartments would be given by

$$2\sum_{i=0}^{M}\left(\begin{array}{c} M \\ i \end{array}\right) = 2^{M+1}.$$

The resulting set of ordinary differential equations is viewed as a system which describes the evolution of the compartment populations. For the sake of brevity, the reader is referred to [4] for model details.

2 Compartmental Model

Cancer can be viewed as a system consisting of three types of cells: proliferating, clonogenic and end cells. The division is based on the cells' function. The first type is the *proliferating fraction*, which consists of cells that are currently undergoing cell division and represents the mechanism by which the cancer grows and spreads. During the cell life cycle, a number of checkpoints exist to ensure that the resulting daughter cells will be viable after mitosis. For each viable daughter cell, there exists a positive probability for the daughter cell to become any one of the three types of cells. The quiescent or *clonogenic fraction* consists of *stem cells* that are capable of propagating the cancer but are currently inactive. Given a proper stimulus, the cells in the clonogenic fraction can be recruited into the other two groups. The final type are the *end cells* which consists of necrotic tissue and terminally differentiated somatic tissues such as vascular structures which can support but not propagate the cancer. The goal of most treatments is to move all of the cells from the growth and clonogenic fractions into the end compartment. The end cells are not accounted for in this model since they cannot generate new cancerous cells.

Drug resistance can either be intrinsic or acquired. Intrinsic resistance is resistance that exists prior to treatment. Acquired resistance to a cytotoxic agent evolves as a result of treatment with the cytotoxic agent and develops after mitosis, *randomly* providing the cell with mechanisms to defeat the actions of cytotoxic agents via mutations. Mutations can only occur in cells that are actively dividing, therefore only cells in the proliferating fraction can mutate. Either kind of drug resistance is assumed to be inherited by the daughter cells and their progeny. Note that resistance to a particular drug normally implies that resistance should exist for all drugs in the same category that act with the same mechanism. Thus, two drugs which use the same mechanism to attack the

cancerous cell are referred to as cross resistant.

A treatment consists of administering both agents at specified times. For example, a typical treatment period is 28 days with agent A administered on day 1 and agent B on day 14. A treatment cycle consists of n treatments, and at most m cycles can be administered. Therefore a total of $N = n \times m$ treatments may be given. Regimens for treatment normally start with a single treatment cycle and continue until the patient goes into remission or all of the available treatments have been administered. Upon recurrence of the cancer, a new treatment cycle begins provided a treatment is available. Figure 1 represents the eight compartment model for the evolution of heterogeneous cancer with treatment. In the figure, the solid lines represent the evolutionary dynamics of the cancer and the the dashed lines show the effects of treatments.

2.1 Mathematical Model

Cancer is a stochastic evolutionary process for the various types of cells. The physical process for the development of cancer is an intractable problem since all cells and their evolution would need to be followed. Therefore, the mathematical model presented here is based on macroscopic or bulk actions and is not necessarily related to the biological processes of the individual cancerous cells. However, the bulk dynamics may be observed through means such as clinical *in vitro* trials or *in vivo* methods such as imaging.

Define the unit dose impulse function, $\Delta_{j,k}(t)$ for the time $t = t_{j,k}$ at which a treatment j of cytotoxic agent X_k is administered by

$$\Delta_{j,k}(t) = \left\{ \begin{array}{ll} 1 & t = t_{j,k} \\ 0 & \text{otherwise} \end{array} \right\}, \tag{2.1}$$

where $X_1 = A$ and $X_2 = B$. Define the indicator set

$$\mathcal{I} \equiv \{ \ 0, \ \ 1, \ \ 2, \ \ 3\} \tag{2.2}$$

to represent the classification of the cells and their resistance to the cytotoxic agents, where $P_i(t)$ and $C_i(t)$ for $i \in \mathcal{I}$ denote the number of cells in the proliferating and clonogenic fractions, respectively, where the index i denotes no resistance if $i = 0$, resistance to agent A if $i = 1$, resistance to agent B if $i = 2$, resistance to both agents if $i = 3$. The model that is generated predicts the evolution of the cancer starting from a single cell. Let time $t = 0$ be the time of the appearance of the first malignant cell from which a colony will form. This first cell must be in the growth fraction, which yields the initial conditions for the model as

$$P_0(0) = 1, \qquad P_i(0) = 0 \ \text{ for } \ i = 1, \ 2, \ 3, \qquad C_i(0) = 0 \ \text{ for } \ i \in \mathcal{I}. \tag{2.3}$$

For the remainder of this section let $i, s \in \mathcal{I}$ be the indicator for the drug resistance, $X_k \in \{A, B\}$ be the cytotoxic agent administered, $Y \in \{P, \ C\}$ represent proliferating or clonogenic fraction, and $j = 1, \ 2, \ \ldots, \ N$ denote the treatment number. The overall growth dynamics for the untreated cancer is assumed to be Gompertzian in nature with relative rate of change form

$$f(P_0, P_1, P_2, P_3, C_0, C_1, C_2, C_3) = \lambda \log\Big(\frac{K}{P_0 + P_1 + P_2 + P_3 + C_0 + C_1 + C_2 + C_3}\Big), \tag{2.4}$$

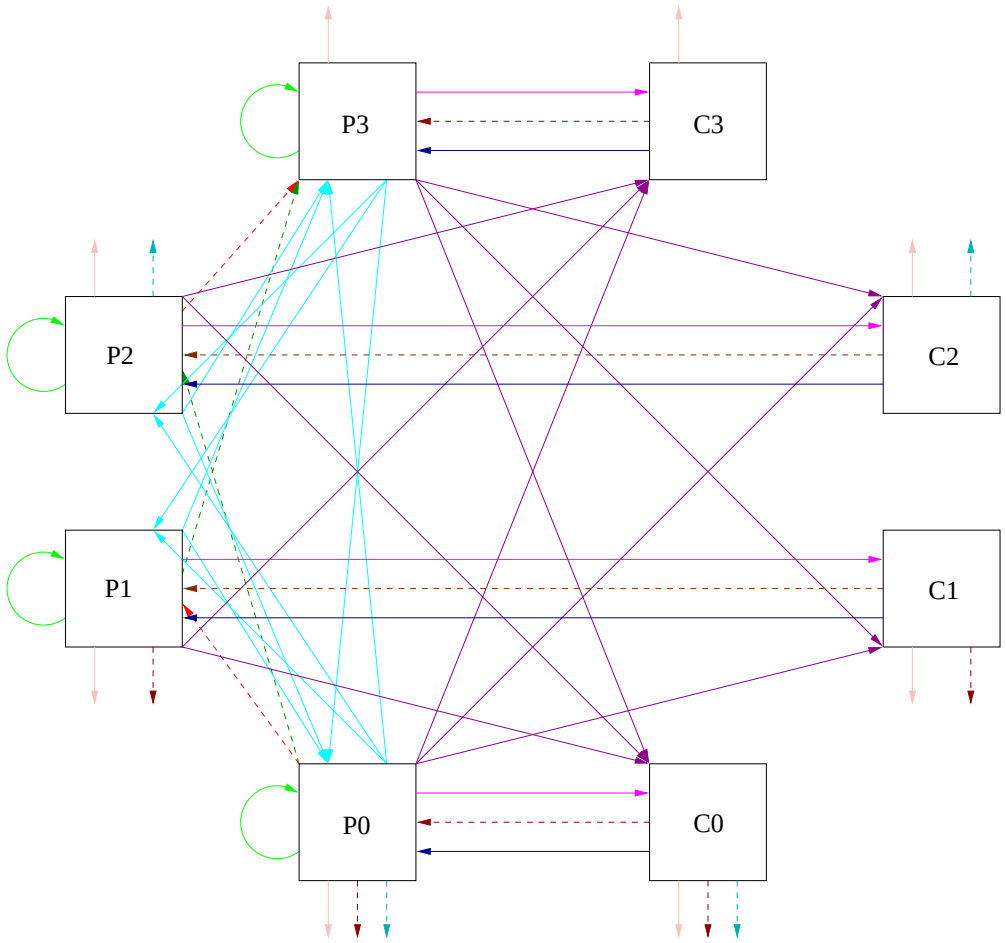

Figure 1: Schematic representation of the eight compartmental model subject to chemotherapy with cytotoxic agents A and B. The dashed lines are chemotherapy terms. Compartments to the left of the figure's center denote the proliferating compartments P_i, and similarly, those on the right denote the clonogenic compartments C_i, for $i = 0,\ 1,\ 2,\ 3$. Compartments aligned in rows are susceptible to neither agent (P_0, C_0), to agent A only (P_1, C_1), to agent B only (P_2, C_2), or both cytotoxic agents (P_3, C_3).

where the time dependence of $P_i(t)$ and $C_i(t)$ has been suppressed. The evolutionary rates for the growth of the cancer are α_i denoting natural migration of daughter cells after mitosis from the proliferating to the clonogenic fraction, β_i the natural back migration of clonogenic cells which restart the cell life cycle, and $\delta_{P,i}$ or $\delta_{C,i}$ the natural loss of cells either from the proliferating or clonogenic compartments to the end cell compartment. All of these rates are, in general, functions of $(P_0, P_1, P_2, P_3, C_0, C_1, C_2, C_3, t)$. The probabilistic mutation rates for the viable mutated cells are denoted by μ_{Y_i,Y_s}, where Y_i is the compartment for the parent cell and Y_s is the compartment of the daughter cell. All possible mutations are allowed, except for those mutations that have zero probability of occurring. Transitions from mutations are not allowed to stay in the same compartment, therefore $\mu_{Y_i,Y_i} \equiv 0$, and mutations are not allowed where resistance to one agent is lost and the resistance to the other is gained, therefore $\mu_{Y_1,Y_2} \equiv 0$ and $\mu_{Y_2,Y_1} \equiv 0$.

Let $\Delta_{j,k}\kappa_{Y_i,j,k}$ denote the loss of cells in the Y_i compartment due to treatment j of agent X_k. A feature of this model is that only susceptible cells to a given agent X_k are killed by the administration of the treatment, which is assumed to be uniform. However, the kill rates can vary to account for semi-cross resistance of cytotoxic agents. For the model in Figure 1, the nonzero kill rates are $\Delta_{j,k}\kappa_{P_0,j,k}$, $\Delta_{j,2}\kappa_{P_1,j,2}$, and $\Delta_{j,1}\kappa_{P_2,j,1}$. As a result of the large numbers of cells killed by the administration of cytotoxic agent X_k, a stimulus is generated that recruits cells form the clonogenic fraction into the proliferating fraction to ensure the viability of the cancer at rate $\Delta_{j,k}\gamma_{C_i,Y_i,j,k}$. Side effects of treatment include the development acquired resistance at a rate $\Delta_{j,k}\mu_{Y_i,Y_s,j,k}$. It is assumed, without loss of generality, that those cells that acquire resistance stay in the proliferating fraction. The only nonzero rates for the development of acquired resistance are $\Delta_{j,1}\mu_{P_0,P_1,j,1}$, $\Delta_{j,1}\mu_{P_2,P_3,j,1}$, $\Delta_{j,2}\mu_{P_0,P_2,j,2}$, and $\Delta_{j,2}\mu_{P_1,P_3,j,2}$.

The equations for the proliferating compartments of the compartment model are

$$\begin{aligned}\frac{dP_i}{dt} &= \left[\Big\{1-\alpha_i-\sum_{s=1}^{4}(\mu_{P_i,P_s}+\mu_{P_i,C_s})\Big\}P_i+\sum_{s=1}^{4}\mu_{P_s,P_i}P_s\right]f+\beta_i C_i-\delta_{P,i}P_i \\ &\quad+\sum_{j=1}^{N}\sum_{k=1}^{2}\Bigg\{\Big(-\Delta_{j,k}\kappa_{P_i,j,k}-\sum_{s=i}^{4}\Delta_{j,k}\mu_{P_i,P_s,j,k}\Big)P_i \\ &\qquad\qquad+\sum_{s=1}^{i}\Delta_{j,k}\mu_{P_s,P_i,j,k}P_s+\gamma_{C_i,P_i,j,k}C_i\Bigg\},\end{aligned} \tag{2.5}$$

where $i \in \mathcal{I}$. The corresponding equations for the clonogenic compartments are

$$\frac{dC_i}{dt} = \left[\alpha_i P_i+\sum_{s=1}^{4}\mu_{P_s,C_i}P_s\right]f-\beta_i C_i-\delta_{C,i}C_i-\sum_{j=1}^{N}\sum_{k=1}^{2}\Delta_{j,k}\Big(\kappa_{C_i,j,k}+\gamma_{C_i,P_i,j,k}\Big)C_i, \tag{2.6}$$

where $i \in \mathcal{I}$. Therefore, the system of equations which represents the dynamics as illustrated in Figure 1 are given by (2.5) and (2.6), which are subject to the initial condition (2.3).

3 Discussion

Ultimately, the majority of cells reside in the P_3 and C_3 compartments so that if any cytotoxic agent is administered the change in the number of cells is algebraic at best. This suggests that

alternate treatment modes should be sought to reduce the drug resistant populations and the number of cancerous cells. Such treatment modalities as the use of surgery, radiotherapy, and immunotherapies using cytokines, angio-genesis inhibitors, and anti-metastatic agents could be employed in a comprehensive treatment plan for the patient.

The formulation of the cancer evolution and the subsequent treatment focuses on the heterogenous nature of the cancer and the effects drug resistance. Thus, this provides a system that can be utilized by clinicians to determine the effectiveness of treatment regimens employing multiple cytotoxic agents to predict the response of the cancer to a given strategy. Additionally, the model presents a framework in which alternate treatment strategies can be evaluated. A future direction is to solve numerically the optimal control problem for the treatment schedule in order to maximize the life expectancy and quality of life of the patient.

Modeling the treatment of cancer has difficulties since a number of the underlying biological mechanisms are not clearly understood, for example, the development of resistance to a given treatment. Typically, tumors are not composed of a single strain of cancer cell but consist of several prominent strains, due to mutations, which will react differently to the various cytotoxic agents utilized for treatment. These mutations greatly complicate the model and need to be included for a better understanding of the effects of a given treatment plan. Future research directions include the addition of more realism in the model to account for mutations in the cancer cells and a more comprehensive treatment plan, including considerations of pharmacokinetics and toxicity of treatments, to include all possible modes, in particular radiotherapy and angiogenesis inhibitors, for combatting the cancer and retarding its development. Additionally, an optimal control problem needs to be developed, tailored to every patient, that determines the most effective treatment plan for the patient that accounts for the disease and the patients' health and mental state. We believe that the use of a tailored individual comprehensive treatment plan using multimode treatments should lead to a better quality of life for the patient as well as a longer life expectancy.

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