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Modeling and optimization of combined cytostatic and cytotoxic cancer chemotherapy

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ABSTRACT

Objectives: This study extends a previous mathematical model of cancer cytotoxic chemotherapy, which considered cycling tumor cells and interactions with the immune system, by incorporating a different type of drug: a cytostatic agent. The effect of a cytostatic drug is to arrest cells in a phase of their cycle. In consequence, once tumor cells are arrested and synchronized they can be targeted with a cytotoxic agent, thus maximizing cell kill fraction and minimizing normal cell killing. The goal is to incorporate the new drug into the chemotherapy protocol and devise optimal delivery schedules.
Methods: The problem of designing efficient combined chemotherapies is formulated as an optimal control problem and tackled using a state-of-the-art evolutionary algorithm for real-valued encoding, namely the *covariance matrix adaptation* evolution strategy. Alternative solution representations and three formulations of the underlying objective function are proposed and compared.
Results: The optimization problem was successfully solved by the proposed approach. The encoding that enforced non-overlapping (simultaneous) application of the two types of drugs produced competitive protocols with significant less amount of toxic drug, thus achieving better immune system health. When compared to treatment protocols that only consider a cytotoxic agent, the incorporation of a cytostatic drug dramatically improved the outcome and performance of the overall treatment, confirming *in silico* that the combination of a cytostatic with a cytotoxic agent improves the efficacy and efficiency of the chemotherapy.
Conclusion: We conclude that the proposed approach can serve as a valuable decision support tool for the medical practitioner facing the complex problem of designing efficient combined chemotherapies.

1. Introduction

The main goal in cancer chemotherapy is to cure the patient, and it is important to do so as efficiently as possible. Several alternatives to enhance chemotherapy treatments have been proposed [1] such as using combinations of toxic drugs, immunotherapy and more recently virotherapy [2]. This article focuses on the use of a cytostatic drug to aid a cytotoxic drug in chemotherapy. There is evidence in the medical literature [3], that this type of combined therapy has increased effectiveness.

The model formulated by Villasana and Radunskaya [4] considers the tumor growth, its interaction with the immune system and the action of a cycle-specific cytotoxic drug. In [5] this model is used in an optimal control formulation of the chemotherapy scheduling problem, which is successfully solved using modern heuristic search methods. A more recent study [6] considered the effect of different terms in the objective function of the optimal control formulation (such as the tumor levels, the immune system level, and the number of treatment cycles) on the overall features and efficacy of the obtained treatments.

Other authors have formulated the design of chemotherapy schedules from the point of view of optimal control [7–9], solving the stated optimization problem either analytically or numerically. However, for increasingly complex and realistic cancer models, analytical or traditional numerical methods are no longer applicable, and some authors have turned to meta-heuristics to optimize chemotherapy schedules. Petrovski, McCall and colleagues, have extensively and successfully used evolutionary algorithms and other modern heuristics in this domain [10–12]. Their work differs from the approach in [5], mainly in the underlying mathematical model of tumor growth. While Petrovski et al. considered the Gompertz growth model with linear cell-loss effect [10], without including interactions with the immune system;

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Villasana et al. employed a more realistic cancer model [4]. Specifically, our model includes the interactions between tumor cells and immune cells; and differentiates between cell phases for subsequent treatment with a cycle-phase-specific drug. In a more recent book chapter, McCall et al. present a survey of approaches employing heuristic search methods to solve the cancer chemotherapy scheduling problem via optimal control. Examples of these approaches include the use of simulated annealing on a model of tumor and host cell interaction, a parallelized genetic algorithm, and multimodal optimization genetic algorithms (see [13] and the references therein for further details). More recently, Liang and colleagues have applied several algorithms to the chemotherapy scheduling problem using optimal control, where the underlying dynamics follows a modification of Martin's original model [14]. In [15], the authors use a genetic algorithm to solve the proposed optimal control problem, while in [16], they combine the genetic algorithm with the forward iterative dynamic programming as the local search in a memetic approach. However, none of these published studies based on heuristics search methods considers a drug that is not cytotoxic nor do the models incorporate the tumor interaction with the body's natural defense system.

Swierniak et al. [17] published a series of models for tumor growth using cycle-phase-specific drugs. The authors also developed analytical relations for the optimal drug scheduling on the simpler of those problems. In their exposition, a model that incorporates a cytostatic drug is included and the numerical solution for the optimal control model using Pontryagin's Maximum Principle is obtained. The optimal solution encountered was bang–bang (i.e. a solution that only takes upon the maximum and minimum values on a bounded range) with non-overlapping applications of the two types of drugs. Some of the models considered were simple enough to be still mathematically tractable, and thus, analytic solutions were readily available. However, the model that took into account the cell arrest, considered a single treatment cycle, while in practice cancer treatments are composed of multiple cycles. For more complex models of tumor growth, and multiple drug applications, mathematical manipulation becomes prohibitive. In consequence, an understanding of the qualitative features of the treatments that would be obtained in those cases is still lacking.

The present study extends our previous work [4–6] with the goal of suggesting more efficient cancer treatments. Specifically, a modification of the model presented in [4] is carried out so that it incorporates a different type of drug, which would act as a cytostatic agent in conjunction with the original cytotoxic agent. The idea behind combining these two agents, is that the cytostatic drug can halt the rapid progression of the cancerous cells through their cell cycle at a certain phase. Thus, when the cells are released, they are mostly arrested in the most vulnerable stage to the action of cytotoxic drugs. The overall strategy is that once cells are arrested and synchronized in the cell cycle, these can be targeted with a cytotoxic agent, thus maximizing cell kill fraction and minimizing normal cell killing. An example of a cycle-phase-specific cytotoxic drug is Taxol (paclitaxel), and an example of a cytostatic drug is Iressa (gefitinib). These are the drugs that were identified and modeled in our approach. Our study proposes and compares several treatment encodings and optimal control formulations of the chemotherapy scheduling problem. We present a detailed analysis of the treatments obtained, and a comparison with previous treatments that do not include the cytostatic agent.

The article is organized as follows. Section 2 presents the mathematical formulation of the problem, including the relevant biomedical background, the mathematical model describing the patient dynamics and the optimal control formulation. Thereafter, Section 3 details the methodology, including the alternative problem encodings and objective functions, and the evolutionary algorithm employed. Section 4 outlines the results, while Section 5 summarizes and discusses the main findings.

2. Problem formulation

2.1. Biomedical background

Most chemotherapy drugs work by attacking cells that are dividing rapidly. Normal cells divide at a self-regulated rate with tight controls in its progression in the cell cycle. In cancer cells, these controls are bypassed giving way to defective cells unable to control their reproduction, thus leading to the formation of a tumor or blood cancer. Chemotherapy drugs interfere with the division of these cells and may cause the cancer to recede completely. The treatment reduces the number of cancerous cells to a minimum level, at which point other mechanisms (e.g. programmed cell death) will remove the remaining tumor cells.

The cell cycle is the process leading to cell division. It encompasses four stages: G_1, S, G_2, and M, where G_1 and G_2 are resting phases (or Gap periods), S is the synthetic period, and M or mitosis is the time during which cells segregate the duplicated DNA material between daughter cells. Cycle-phase-specific drugs are those acting on a specific phase of the cell cycle. These drugs are either *cytotoxic*, or *cytostatic*. Cytotoxic drugs are toxic to the cells, thus killing them, while cytostatic drugs are not aimed at killing cancer cells but rather at stopping them from multiplying and trapping them in the cell cycle progression. When the concentration levels of the cytostatic drug fades, the cells are then released to continue in the cell cycle.

An example of a cytotoxic phase-specific drug is Taxol (paclitaxel) which has shown high efficacy in the treatment of breast, ovarian, head, and neck cancer. The action of this drug is carried through different mechanisms: it inhibits mitosis, induces apoptosis (programmed cell death), and enhances tumor radiosensitivity. Today, paclitaxel is used either as a single agent or accompanied by other drugs. The optimal scheduling and possible drug interactions for paclitaxel are not yet fully understood [18]. An example of a cytostatic drug is Iressa (gefitinib). Gefitinib is the first selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain. Over-expression of EGFR is observed in certain types of carcinomas (for example lung and breast) leading to uncontrolled cell proliferation. Gefitinib inhibits EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP) binding site of the enzyme. Thus the function of the EGFR tyrosine kinase in activating the Ras signal transduction cascade is inhibited, and malignant cells are inhibited. The study presented in [3] confirmed that the combination of these two drugs (paclitaxel and gefitinib) produces higher toxicity for the cancer cells. The Iressa drug acts by inducing a delay in cell cycle progression, with a complete arrest of G_1 cell phase growth after 72 h of treatment (daily dose of a 250 mg tablet). Iressa has been used with Taxol in clinical trials on mice obtaining better results than those treated exclusively with Taxol [19].

2.2. Mathematical model

The patient model used [4] is a competition model of tumor growth that includes the immune system response. The model considers three populations of cells: immune system, tumor during interphase (period comprising G_1 through G_2), and tumor during mitosis. Delay differential equations are used to take into account the phases of the cell cycle.

In the model, $T_1(t)$ and $T_M(t)$ denote the population of tumor cells during interphase and mitosis at time t respectively. $I(t)$ represents the immune system population at time t, that we take