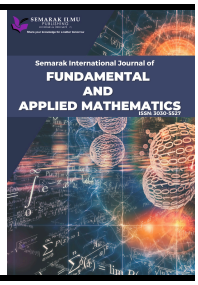
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Optimal Control Applied to Cell-Cycle-Specific Chemotherapy Drugs Focusing on Bone Marrow Preservation

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ABSTRACT

Chemotherapy is an essential cancer treatment, but it often causes severe bone marrow toxicity. Cell-cycle-specific drugs target proliferating cells more selectively, yet inappropriate dosing can still lead to bone marrow toxicity. This study develops an optimal control framework to design chemotherapy strategies that balance treatment effectiveness and bone marrow preservation. A compartmental model based on ordinary differential equations describes the dynamics of proliferating and quiescent bone marrow cells under chemotherapy. Treatment intensity is introduced as a bounded control acting on proliferating cells only. An objective function is defined to minimize chemotherapy-induced bone marrow damage while regulating drug administration. Pontryagin's Maximum Principle is employed to derive the optimal treatment control, resulting in a coupled state-adjoint system. The optimality system is solved numerically using the forward-backward sweep method in conjunction with the fourth-order Runge-Kutta scheme. Numerical results demonstrate that optimal dosing strategies can significantly reduce bone marrow damage while maintaining effective chemotherapy treatment.

1. Introduction

Cancer encompasses a range of diseases in which abnormal cells proliferate uncontrollably and may spread throughout the body. Mathematical descriptions of cancer chemotherapy have been extensively investigated within the field of mathematical biology [1,2]. Cancer can affect any organ or tissue, including the lungs, skin, colon, breast, bones, and blood. The cell cycle comprises several main stages, including phases G_1 (Gap 1), S (Synthesis), G_2 (Gap 2), M (Mitosis), and G_0. Proliferating cells actively pass through all the major phases of the cell cycle, which are G_1, S, G_2, and M [3].

Cell-cycle-specific chemotherapy drugs are medications that target cancer cells only during specific phases of the cell cycle. Cyclophosphamide, Taxol (Paclitaxel), and Vincristine are widely used chemotherapy drugs. Cyclophosphamide is a cell-cycle non-specific alkylating agent that disrupts DNA replication across all phases, making it effective but also highly toxic to healthy tissues,

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especially bone marrow [4,5]. Taxol and Vincristine are cell-cycle-specific drugs that target cells during the mitotic (M) phase. Taxol stabilizes microtubules, preventing cell division, while Vincristine inhibits microtubule formation, also stopping mitosis [6,7]. All three drugs are used to treat various cancers, but their differing toxicity profiles and phase-specific actions make them highly relevant to mathematical modeling in chemotherapy research.

The dynamics that represent the numbers of cancer-cell populations across the different cell-cycle stages, and the objective is to reduce the corresponding cell population by the end of the prescribed treatment period in mathematical models [8-10]. The adverse impact on healthy cells is incorporated indirectly through a penalty associated with drug administration in the objective function.

Chemotherapy remains a cornerstone in the treatment of many types of cancer [11,12]. However, its non-selective cytotoxic effects often result in damage to healthy, rapidly dividing cells, most notably, bone marrow tissue. Excessive dosages or poorly optimized treatment schedules can lead to bone marrow suppression.

Severe bone marrow suppression not only compromises a patient's immune system and oxygen-carrying capacity but can also result in treatment delays, dose reductions, or complete discontinuation of therapy, ultimately affecting patient survival. Optimal control theory offers a mathematical approach to designing such balanced treatment protocols. By modeling the interaction between chemotherapy drugs and healthy tissues like bone marrow, it becomes possible to determine drug dosing strategies that maximize the treatment of chemotherapy while keeping the number of proliferating cells that die due to chemotherapy low.

The objective of this study is to focus on the application of optimal control theory to manage chemotherapy dosing in a way that balances the chemotherapy treatment with the preservation of bone marrow function. The objective function is defined to minimize the number of proliferating cells that die due to chemotherapy and maximize the chemotherapy treatment. The equations are solved using the Forward-Backward Sweep Method with the fourth-order Runge-Kutta method. The graphical results are produced using MATLAB software.

After this introductory section, the relevant literature is discussed in Section 2. Section 3 presents a new model, building on the work of Panetta and Fister [10]. Section 4 presents the numerical simulations of the proposed model, and lastly, Section 5 concludes the findings.

2. Literature Review

2.1 Mathematical Modeling in Cancer Treatment

Mathematical modeling has been widely used to describe the dynamics of cancer cells developing resistance to chemotherapy drugs and the effects on both malignant and healthy cell populations. This resistance is a significant challenge in cancer treatment, as it can make the drugs less effective over time [9]. By separating drug-sensitive and drug-resistant populations, the authors developed a model incorporating two cytotoxic agents that give rise to distinct resistant cell groups. An optimal-control formulation for chemotherapy is subsequently established, together with an analysis of the qualitative properties of its optimal controls.

Two important difficulties in chemotherapy are the dependence of treatment response on the cell-cycle phase and the development of resistance to cytotoxic drugs. Apply optimal control theory to mathematical models of cell cycle dynamics to overcome these two problems. The results focused on mathematical modelling and control of the cell cycle, mechanisms of gene amplification associated with drug resistance, and parameter estimation for the developed models [13].

2.2 Mathematical Modeling in Cancer Treatment

Kimmel and Swiernak [13] applied optimal control theory to formulate chemotherapy protocols. This involves defining a control problem where the goal is to maximize the effectiveness of drug treatment while minimizing harm to normal cells. In optimal control models for cancer chemotherapy, the state represents the number of cancer cells, and the control input reflects drug dosage. This is done by balancing drug effects and side effects through an optimized control strategy over a fixed treatment period [13].

Cojocaru and Agur [14] developed the Z-method, using a parameter Z=Tm/Th where Tm is the elimination time for cancer cells, and T_h that for healthy cells. Their studies showed that treatment is most effective when the drug is given in short pulses at specific intervals. This method can even reduce toxicity [14], especially when cancer and healthy cells have similar average cycle times but differ in variability.

3. The Mathematical Model

3.1 The Mathematical Model Formulation

Figure 1 shows the compartmental diagram of a bone marrow cell that includes proliferating cells ($P(t)$), quiescent (resting) cells ($Q(t)$), and proliferating cells that died due to cell-cycle-specific chemotherapy drugs ($C(t)$).

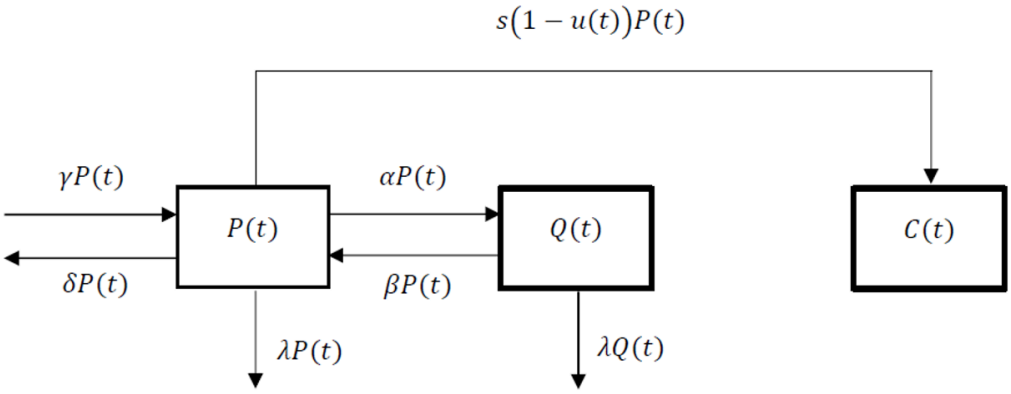


Fig. 1. Compartmental diagram of proliferating cells and quiescent cells in bone marrow

The system of ordinary differential equations associated with Figure 1 is as follows

$$\frac{dP(t)}{dt} = \gamma P(t) - (\delta + \alpha + \lambda)P(t) - s\big(1-u(t)\big)P(t) + \beta Q(t), \quad P(0) > 0, \tag{1a}$$

$$\frac{dQ(t)}{dt} = \alpha P(t) - (\lambda + \beta)Q(t), \quad Q(0) > 0, \tag{1b}$$

$$\frac{dC(t)}{dt} = s\big(1-u(t)\big)P(t), \quad C(0) = 0, \tag{1c}$$

where γ is the growth rate of cycling cells, α is the transition rate from proliferating to resting cells, δ is the natural death rate of the cells, β is the transition rate from resting to proliferating cells, λ is the cell differentiation rate where the mature bone marrow cell leaves the bone marrow and enters the bloodstream as various types of blood cells, s is the effectiveness of the treatment, and u(t) is a dummy variable associated with the control variable ϒ(t).

Model (1) describes a biologically realistic process as proliferating cells either die, transition to a resting state, or are killed by chemotherapy. Resting cells may return to proliferation or differentiate into blood cells and leave the bone marrow.

The control variable ϒ(t)=1-u(t), where u(t) is a dummy variable. We assume that our control variable ϒ(t) is defined on t∈[0,t_f] with the condition that 0≤ ϒ(t)≤1. Note that

ϒ(t)=1 represents maximal chemotherapy and ϒ(t)=0 represents no chemotherapy. Thus, the variable u(t) lies between 0 and 1 as follows

$$0 \leq u(t) \leq 1, \quad \text{for} \quad 0 \leq t \leq t_f.$$

The admissible control set for ϒ(t)=1-u(t) is defined as follows

$$W = \{u(t) | 0 \leq u(t) \leq 1\}.$$

Under the action of ϒ(t) to the bone marrow, there are s(1-u(t))P(t) proliferating cells that are destroyed.

To properly pose the control-based problem, the designed goal to be minimized is defined as follows

$$J\big(u(t)\big) = \int_0^{t_f} C(t) + B\big(u(t)\big)^2 \quad dt, \tag{2}$$

Where B is the weightage parameter. The weight B describes the importance of each term in the objective function. The assumption here is the importance of each term in the objective function. The assumption here is to minimize the total amount of proliferating cells that died due to the side effect of cell-cycle-specific chemotherapy drugs (refer to the first term of equation (2)) and maximize the amount of drug given through minimizing the second term in equation (2). The two minimization terms create a trade-off, as administering higher doses of the drug tends to decrease the bone marrow population. This objective function equation (2) represents balancing these two effects.

The objective function J(u(t)) formulates an optimization problem, that is, to identify the optimal profile of treatment without over-destruction of the bone marrow during the period of

t ∈ [0,t_f].

An optimal control variable is denoted by ϒ^* (t)=1-u^* (t) where J(u^* (t)) achieves its minimum. The formulation of the control-based model allows us to find the optimal control ϒ^* (t) such that the accumulated number of proliferating cells that died due to cell-cycle-specific chemotherapy drugs is minimized during the time period t∈[0,t_f] and the amount of drugs given is maximized during the same period.

The goal, therefore, is to characterize ϒ^* (t)=1-u^* (t) satisfying

$$J\big(u^*(t)\big) = \min_{u(t) \in W} \int_0^{t_f} C(t) + Bu^2(t) \quad dt. \tag{3}$$

3.2 Characterization of the Optimal Control Variable

Form the Hamiltonian function Ψ(t) as follows

$$\Psi(t) = C + Bu^2(t) + \lambda_1(t)\frac{dP(t)}{dt} + \lambda_2(t)\frac{dQ(t)}{dt} + \lambda_3(t)\frac{dC(t)}{dt}, \tag{4}$$

where λ_1 (t), λ_2 (t), and λ_3 (t) are the adjoint variables. Expanding Equation (4) gives

$$\Psi = C + Bu^2 + \gamma P\lambda_1 - (\delta + \alpha)P\lambda_1 - sP\lambda_1 + suP\lambda_1 + \beta Q\lambda_1 - \lambda P\lambda_1 + \alpha P\lambda_2 \\ -(\lambda + \beta)Q\lambda_2 + sP\lambda_3 - suP\lambda_3.$$

Then, using the Pontryagin's Maximum Principle [15] to find the adjoint function for each variable (P(t), Q(t), and C(t)) with zero transversality, λ_1 (t_f)=0, λ_2 (t_f)=0, and λ_3 (t_f)=0, as follows

$$\frac{d\lambda_1(t)}{dt} = -\frac{\partial\Psi}{\partial P}, \qquad \lambda_1(t_f) = 0,$$
$$\frac{d\lambda_2(t)}{dt} = -\frac{\partial\Psi}{\partial Q}, \qquad \lambda_2(t_f) = 0,$$
$$\frac{d\lambda_3(t)}{dt} = -\frac{\partial\Psi}{\partial C}, \qquad \lambda_3(t_f) = 0.$$

Then, we obtain the system of adjoint variables λ_1 (t), λ_2 (t), and λ_3 (t), as follows:

$$\frac{d\lambda_1}{dt} = -\gamma\lambda_1 + (\delta + \alpha + \lambda)\lambda_1 + s(1-u)(\lambda_1 - \lambda_3) - \alpha\lambda_2, \qquad \lambda_1(t_f) = 0,$$
$$\frac{d\lambda_2}{dt} = -\beta\lambda_1 + (\lambda + \beta)\lambda_2, \qquad \lambda_2(t_f) = 0,$$
$$\frac{d\lambda_3}{dt} = -1, \qquad \lambda_3(t_f) = 0.$$

Next, we find the characterization of the optimal control variable u^* (t). The variable u^* (t) is determined from the optimality condition, ∂Ψ/∂u=0 giving

$$u = \frac{sP(\lambda_3 - \lambda_1)}{2B}.$$

Next, using the bounds on the control variable u(t), where 0≤u(t)≤1, we obtain the following characterization

$$u^*(t) = \min\left\{\max\left\{0, \frac{sP(\lambda_3 - \lambda_1)}{2B}\right\}, 1\right\}.$$

This ensures that the control variable stays within the allowable bounds.

Therefore, the equations to be solved numerically are as follows:

$$\frac{dP(t)}{dt} = \gamma P(t) - (\delta + \alpha + \lambda)P(t) - s\big(1 - u(t)\big)P(t) + \beta Q(t), \quad P(0) > 0, \tag{5a}$$
$$\frac{dQ(t)}{dt} = \alpha P(t) - (\lambda + \beta)Q(t), \quad Q(0) > 0, \tag{5b}$$
$$\frac{dC(t)}{dt} = s\big(1 - u(t)\big)P(t), \qquad C(0) = 0, \tag{5c}$$

$$\frac{d\lambda_1(t)}{dt} = -\gamma\lambda_1(t) + (\delta + \alpha + \lambda)\lambda_1(t) + s\big(1 - u(t)\big)\big(\lambda_1(t) - \lambda_3(t)\big) - \alpha\lambda_2(t), \quad \lambda_1\big(t_f\big) = 0, \tag{5d}$$

$$\frac{d\lambda_2(t)}{dt} = -\beta\lambda_1(t) + (\lambda + \beta)\lambda_2(t), \qquad \lambda_2\big(t_f\big) = 0, \tag{5e}$$

$$\frac{d\lambda_3(t)}{dt} = -1, \qquad \lambda_3\big(t_f\big) = 0. \tag{5f}$$

$$u^*(t) = \min\left\{\max\left\{0, \frac{sP(t)\big(\lambda_3(t) - \lambda_1(t)\big)}{2B}\right\}, 1\right\}. \tag{5g}$$

This model (5) is solved numerically using the forward-backward sweep method coupled with the fourth-order Runge-Kutta scheme. The reader can refer to Lenhart *et al*., [15], Nasir *et al*., [16] and Nasir *et al*., [17] for the details of the Forward-Backward Sweep Method.

4. Numerical Simulation

4.1 Simulation 1: Baseline Optimal Treatment

In this section, we study the baseline optimal control solution using the initial conditions and parameter values in Table 1.

Table 1
The initial conditions and parameter values

Initial conditions / parameters	Value
$P(0)$	200000
$Q(0)$	2000
$C(0)$	0
t_f	14
δ	0.01
α	0.15
s	0.5
β	0.1
λ	0.1
B	10000000

The corresponding simulation of the model in Equation (5) using the values in Table 1 is shown in Figure 2.

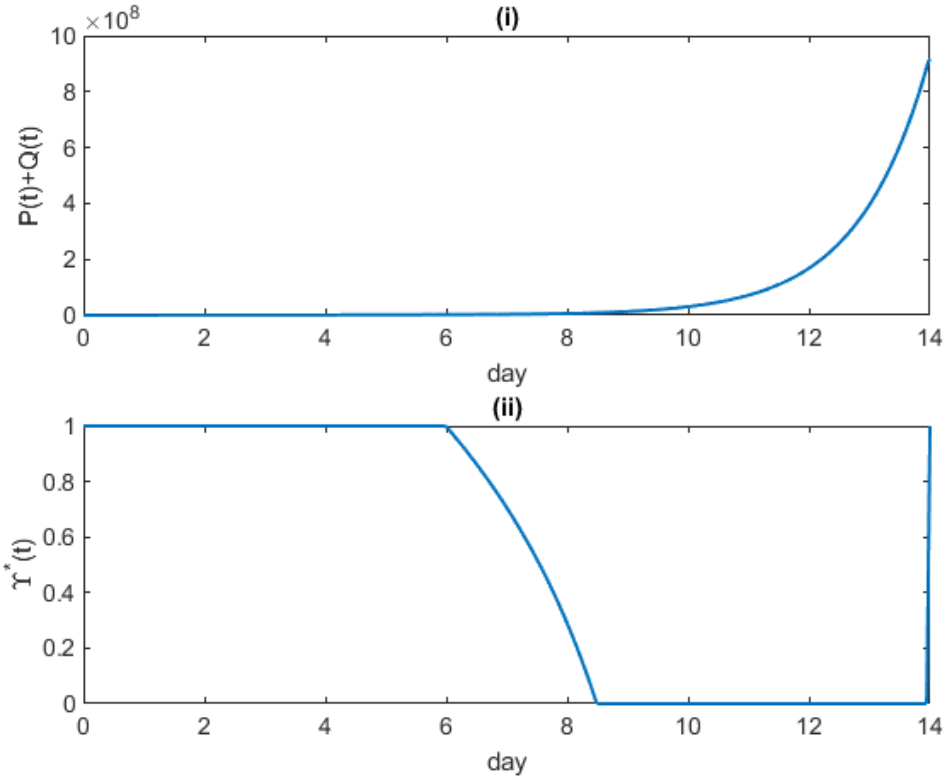


Fig. 2. (i) Simulation of the total bone marrow cells, both proliferating and quiescent cells. (ii) The optimal control profile

We aim to maximize the total number of bone marrow cells (P(t)+Q(t)) by minimizing the cells that die due to chemotherapy (C(t)) along with maximizing drug (Υ^* (t)) over the interval t_f. As can be seen in Figure 2, the treatment is maximal for approximately 6 days, then gradually stops. After the treatment stops, it allows the bone marrow to grow larger. As we will see in the next section, modifying the weight B allows us to adjust for an acceptable bone marrow loss for the interval of t∈[0,14].

4.2 Simulation 2: Effect of Varying the Weight Parameter B

In this section, we analyse model (5) with respect to changes in the weight parameter B. The numerical values are the same as in Table 1, but with different values of B as follows:

$$B = 10000000, B = 11000000, B = 12500000$$

By changing the weight B signifies that it is more important to maximize the bone marrow mass rather that the dose. As shown in Figure 3, we observe that when B is increased, more drug is used and the bone marrow cells are decreased. Similarly, decreasing B signifies that it is more important to maximize the bone marrow mass rather than the chemotherapy dose.

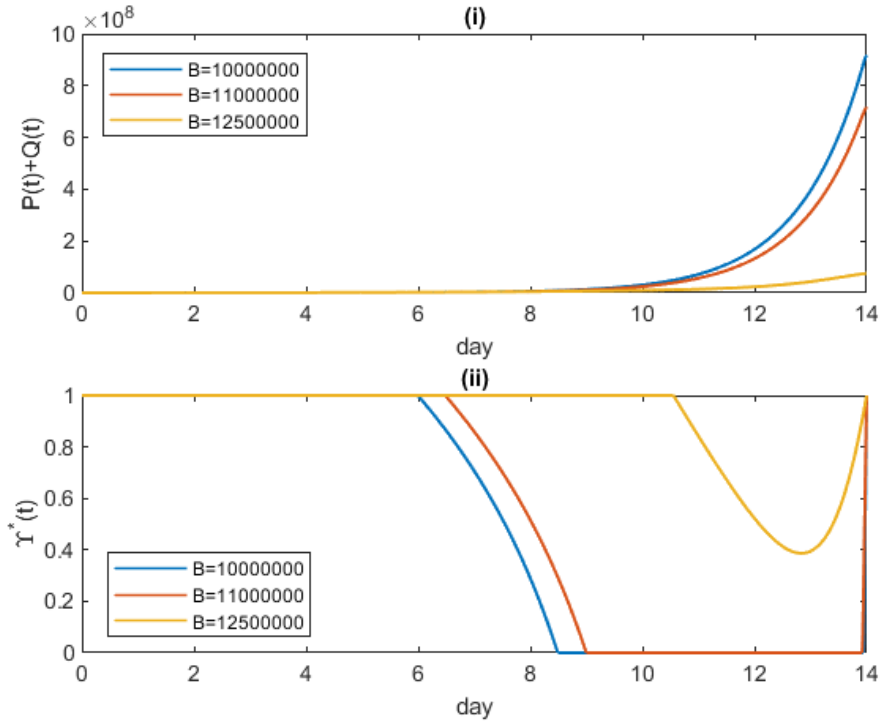


Fig. 3. (i) Simulation of the total bone marrow cells, both proliferating and quiescent cells, with varying B values. (ii) The optimal control profile with varying B values

In general, the weight B should be selected according to the patient's condition. For patients who have not previously undergone treatment and have normal bone marrow levels, a higher value of B may be appropriate, allowing a higher drug dosage to be administered. In contrast, for patients who have undergone multiple treatment cycles and have reduced bone marrow levels, a lower value of B should be considered to place greater emphasis on preserving bone marrow mass.

4.3 Simulation 3: Comparison between Single and Periodic Treatments

In this section, we compare the effects of continuous and periodic treatment regimens. The numerical values are the same as in Table 1, but model (5) is simulated with two different cases, where the first case is about a single treatment period of 14 days, while the second case is about a two-time treatment period of 7 days. The corresponding simulation results are shown in Figure 4.

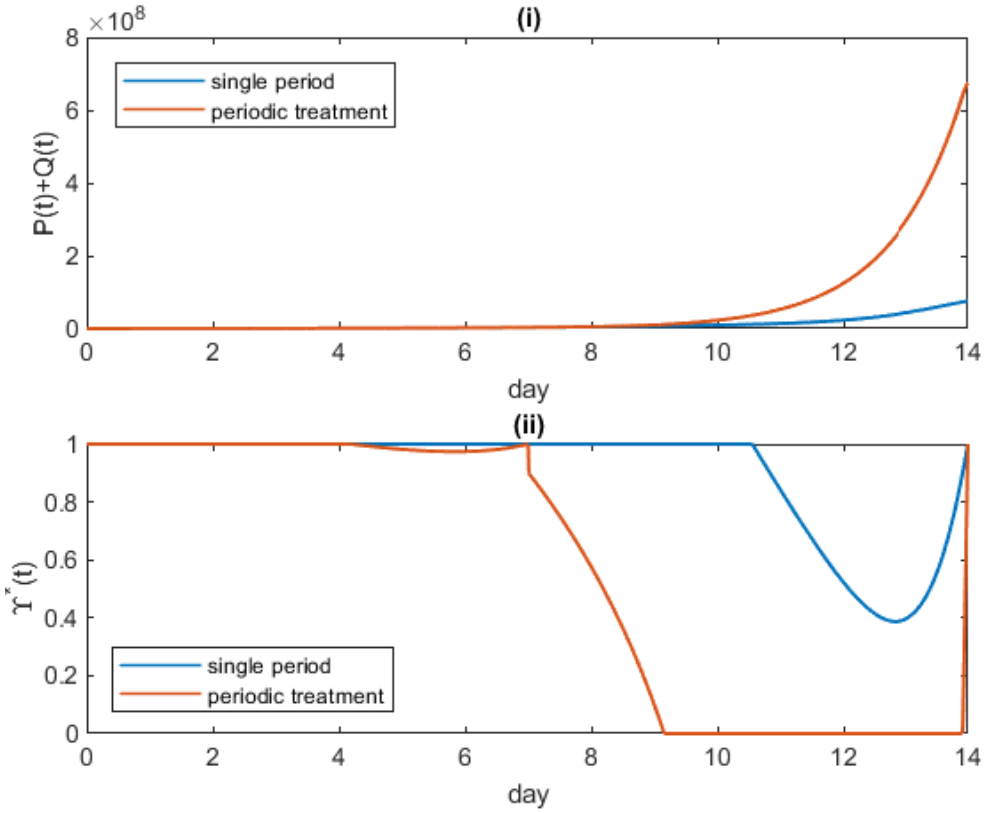


Fig. 4. (i) Simulation of the total bone marrow cells, both proliferating and quiescent cells, with two different treatment periods. (ii) The optimal control profile with two different cases of treatment period

In Figure 4, a periodic treatment consisting of two intervals of t_f=7 days are compared to a single period consisting of one interval of t_f=14 days. For the first period, where 0≤t≤7, we choose B=12500000 which allows a larger dose and a larger bone marrow kill. Then, for the second period, where 7≤t≤14, we decrease the parameter to B=11500000 because the bone marrow is depressed from the first period of treatment. Therefore, in this second period, the treatment involves fewer drugs. Hence, the bone marrow grows (refer to the orange line in Figure 4(i)).

If we instead consider one interval of t_f=14 days with B=12500000, we obtain a high amount of reduction in the bone marrow. In this case, the bone marrow stays at lower levels since treatment is given at the highest dose for nearly 11 days.

Initially, the periodic treatment regimen appears more favorable because it results in less overall bone marrow damage, as indicated by the larger area under the bone marrow curve. However, several factors suggest that this may not be the optimal strategy. In particular, the absence of treatment after day 9 allows the cancer cell population to continue increasing. Since cancer cells proliferate more rapidly than bone marrow cells, this treatment gap may have adverse effects on the patient. Therefore, the single 14-day treatment interval may be a more appropriate option, although it requires a longer treatment duration and a higher total drug dosage.

5. Conclusions

The results demonstrate an optimal control framework for chemotherapy scheduling that accounts explicitly for bone marrow preservation under cell-cycle-specific chemotherapy treatment. A compartmental mathematical model describing the dynamics of proliferating and quiescent bone marrow cells was formulated and coupled with a bounded control representing treatment intensity. Pontryagin's Maximum Principle was employed to characterize the optimal control strategy, and the

resulting optimality system was solved using the forward-backward sweep method with the fourth-order Runge-Kutta scheme.

Numerical simulations demonstrate that the optimal control strategy effectively balances chemotherapy efficacy and bone marrow toxicity by adaptively modulating treatment intensity over time. The results highlight the importance of incorporating the dynamics of proliferating and quiescent cells in bone marrow into chemotherapy optimization and show that appropriate weighting of the control can significantly reduce treatment-induced damage while maintaining effective therapy.

The proposed framework provides a flexible mathematical tool for investigating toxicity-aware chemotherapy scheduling. Future work may extend the model to induce tumor dynamics, treatment delays, or patient-specific parameters to enhance clinical relevance.

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