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Optimal Chemotherapy Scheduling under an Isoperimetric Constraint: Analysis and Simulation

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Abstract

This study examines an optimal control model for chemotherapy scheduling under an isoperimetric constraint that limits the total administered drug. The model is formulated using a system of ordinary differential equations and analyzed using Pontryagin's Maximum Principle. Analytical expressions for the optimal control are derived, and numerical simulations are performed to explore system behavior under varying parameters. Sensitivity analysis is conducted with respect to the tumor growth rate α and total drug amount β. The results show that constrained dosing significantly influences control structure, promoting early intensive treatment when resources allow. The findings highlight the importance of incorporating cumulative drug limits into treatment design and provide insights for personalized therapy planning.

Keywords: Optimal control; Pontryagin's Maximum Principle; Isoperimetric constraint; mathematical oncology; Chemotherapy; Tumor growth; optimal dosing strategy; Sensitivity analysis.

1 Introduction

The theoretical framework of optimal control (Optimal Control Theory) has become a powerful framework for generating methodologies to develop strategies that optimize the therapeutic advantage in biomedical processes [2, 4]. The ability of the theory to determine the best possible intervention over time, while considering biological and physiological constraints, makes it particularly suitable for designing treatment protocols. In oncology, where tumor progression and patient health are highly sensitive to drug dosing schedules, controlling both the intensity and timing of drug administration is critical. Incorrect or unsuitable dosing can either fail to sufficiently reduce tumor growth or even cause severe adverse effects to the patient.

The mathematical models integrated with optimal controls have been commonly used and employed to explore chemotherapy scheduling and strategies for cancer therapy [1, 5, 9]. These approaches allow researchers to make drug administration policies that minimize tumor size while reducing the harmful side effects associated with excessive treatment. Several studies have shown that optimal control techniques can significantly improve treatment efficiency compared with fixed dosing strategies [10, 11, 7].

To meet these considerations, realistic constraints similar to those seen in clinical practice represent an essential consideration. One such constraint is the total allowable drug dosage over a treatment period, which ensures that the cumulative drug given does not surpass safe limits. This type of restriction is formalized mathematically as an *isoperimetric constraint* in the optimal control problem [6]. Incorporating this constraint allows us to enforce a strict limit

on the total amount of therapeutic agent while still optimizing the treatment trajectory for maximal tumor reduction.

The present work describes a model of cancer treatment governed by an ordinary differential equation (ODE), capturing the essential dynamics of tumor growth and drug effects. By applying optimal control techniques, we analyze how to distribute the drug over time in order to minimize the tumor size while respecting the total dosage limit. Both analytical methods, through Pontryagin's Maximum Principle, and numerical approaches are employed to explore the behavior of the system under varying conditions [2, 3, 8]. In particular, sensitivity analyses are also performed to investigate the effects of changes in tumor growth rate and total allowable drug on the optimal control strategies, providing insights that are directly relevant to personalized treatment planning.

In general, this study demonstrates how integrating mathematical modeling, optimal control and clinically realistic constraints can guide the design of more effective and safer cancer therapies, bridging the gap between theoretical analysis and practical application to derive and analyze optimal control strategies under a fixed cumulative drug constraint.

2 Isoperimetric Optimal Control Problem

2.1 Problem Formulation

We study a simple cancer growth model in which tumor dynamics are influenced by an externally administered drug $u(t)$. Mathematical models based on ordinary differential equations are commonly used to describe tumor growth and treatment response [11, 7]. The goal is to minimize the tumor burden at the end of treatment while controlling the cumulative amount of drug:

$$\min_u \; J(u) = \int_0^T u^2(t)\,dt + x(T), \tag{2.1}$$

$$\text{s.t. } x'(t) = \alpha x(t) + \beta u(t), \quad x(0) = x_0, \tag{2.2}$$

$$\int_0^T u(t)\,dt = B, \quad 0 \le u(t) \le M. \tag{2.3}$$

Here, $\alpha > 0$ represents the natural tumor growth rate, $\beta < 0$ models the cytotoxic effect of the drug, B denotes the total allowable dose over the treatment horizon, and M is the maximum instantaneous drug dose. The integral constraint (2.3) is an example of an *isoperimetric constraint*, enforcing a fixed total dosage in accordance with clinical safety limits [6].

2.2 Incorporating the Isoperimetric Constraint

To handle the integral constraint efficiently, we introduce an auxiliary state variable:

$$z(t) = \int_0^t u(s)\,ds \quad \Rightarrow \quad z'(t) = u(t), \quad z(0) = 0, \quad z(T) = B. \tag{2.4}$$

With this transformation, the optimal control problem can be reformulated as:

$$\min_u J(u) = \int_0^T u^2(t)\,dt + x(T), \tag{2.5}$$

$$x'(t) = \alpha x(t) + \beta u(t), \quad x(0) = x_0, \tag{2.6}$$

$$z'(t) = u(t), \quad z(0) = 0, \quad z(T) = B, \quad 0 \le u(t) \le M. \tag{2.7}$$

This form allows the use of standard optimal control techniques while explicitly enforcing the total dose constraint [1, 4].

2.3 Pontryagin's Maximum Principle

To derive the necessary conditions for optimality, we apply Pontryagin's Maximum Principle, a fundamental result in optimal control theory [2, 4]. We define the Hamiltonian:

$$H = u^2 + \lambda_1(\alpha x + \beta u) + \lambda_2 u, \tag{2.8}$$

where $\lambda_1(t)$ and $\lambda_2(t)$ are the adjoint variables corresponding to $x(t)$ and $z(t)$, respectively. The adjoint system is then:

$$\lambda_1'(t) = -\frac{\partial H}{\partial x} = -\alpha\lambda_1, \quad \lambda_1(T) = 1, \tag{2.9}$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial z} = 0, \quad \lambda_2(T) = 0. \tag{2.10}$$

The necessary optimality condition for $u(t)$ is obtained by differentiating the Hamiltonian with respect to the control:

$$\frac{\partial H}{\partial u} = 2u + \beta\lambda_1 + \lambda_2 = 0 \quad \Rightarrow \quad u^*(t) = -\frac{1}{2}(\beta\lambda_1 + \lambda_2), \tag{2.11}$$

with the control constrained to $0 \le u^*(t) \le M$.

2.4 Analytical Characterization of the Optimal Control

The adjoint equations can be solved explicitly:

$$\lambda_1(t) = e^{\alpha(T-t)}, \quad \lambda_2(t) = C, \tag{2.12}$$

Where the constant C is determined by enforcing the isoperimetric constraint $z(T) = B$ and respecting the control bounds. Substituting back, the optimal drug profile $u^*(t)$ can be expressed in closed form, allowing direct computation of the corresponding tumor trajectory $x^*(t)$.

2.5 Sensitivity Analysis

To explore the impact of key parameters on treatment outcomes, sensitivity analyses with respect to α (tumor growth rate) and B (total drug dose) are performed. Changes in α influence the rate of tumor progression, while variations in B alter the intensity and distribution of the optimal control. These analyses provide insights into robust therapeutic strategies under varying patient-specific conditions.

2.6 Effect of Total Drug Dose B

We conclude that the total allowable of the drug, B, directly constrains the cumulative amount of therapy over the treatment horizon. larger values of B provide greater flexibility, allowing higher initial dosing that can rapidly reduce tumor burden. However, excessive drug quantities may increase the risk of adverse effects, underscoring the clinical importance of respecting safety limits. On the other hand, smaller B values limit the overall therapeutic input, resulting in slower tumor reduction and a more evenly distributed control profile. The sensitivity of the optimal control to B highlights the trade-off between treatment intensity and cumulative drug exposure.

2.7 Effect of Tumor Growth Rate α

The tumor growth rate α determines the intrinsic aggressiveness of the tumor. So, with respect to a higher α values, the optimal strategy typically involves stronger initial dosing to counter rapid proliferation, with the control decreasing over time once the immediate threat is mitigated. On the contrary, slower-growing tumors (α smaller) can permit a more gradual and uniform administration schedule, reducing the intensity of drug delivery without compromising long-term tumor control. These observations emphasize the need to tailor dosing strategies according to patient-specific tumor kinetics.

2.8 Numerical Illustration

In order to study and measure these effects, we will perform simulations for the optimal control problem for a range of B and α values by using the following different values :

$$B = 0.5, \quad B = 1, \quad B = 1.5, \quad \alpha = 0.3, \quad \alpha = 0.5, \quad \alpha = 0.8, \quad \beta = -1, \quad M = 10 \tag{2.13}$$

Using the parameter values given in Table (2.13), we now examine the sensitivity of the optimal control with respect to B.

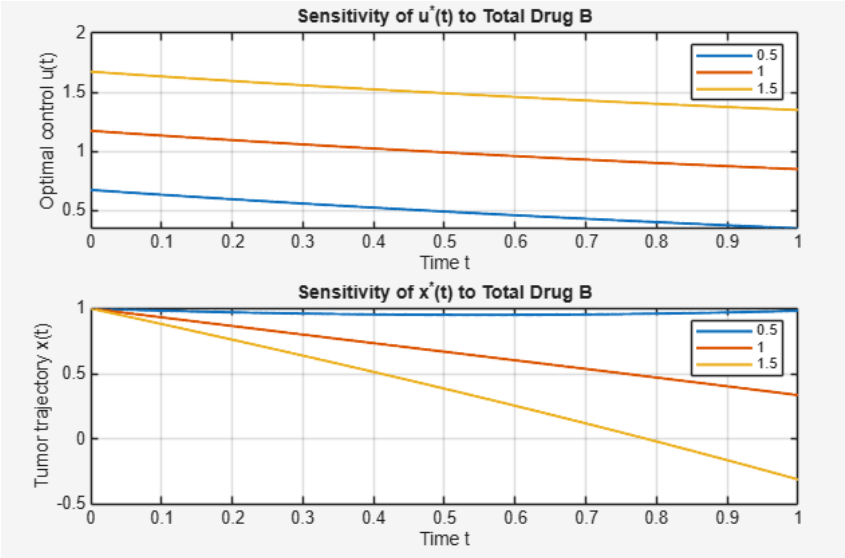

Figure 1: Sensitivity of optimal control $u^*(t)$ and tumor trajectory $x^*(t)$ to variations in total drug B.

2.9 Discussion of Figure 1

Figure 1 reveals the following important observations :

1. **Shift toward early intensive dosing:** When the allowable total drug amount B is increasing, the optimal strategy allocates a larger portion of the dose at the beginning of the treatment horizon. In other words, greater drug availability makes it optimal to intensify therapy in the early phase to quickly reduce the tumor burden. on the other hand , when B is limited, the control profile becomes smoother and more evenly distributed over time in order to satisfy the overall dosage constraint.

2. **Enhanced tumor suppression for larger B:** The optimal state trajectory $x^*(t)$ demonstrate a faster decline as B grows. This indicates that expanding the total drug

budget strengthens the overall therapeutic effect, especially during the initial phase of treatment. The acceleration decrease in tumor size is a direct consequence of the stronger early intervention permitted by higher values of B.

3. **Balance between treatment intensity and safety limits:** Although increasing B allows for a more aggressive early dosing strategy, practical considerations such as toxicity and patient tolerance must be taken into consideration. So, The isoperimetric constraint plays a crucial role in modeling these limitation by capping the cumulative drug administration, thereby ensuring that the optimal strategy remains within clinically acceptable bounds.

4. **Nonlinear relationship between B and tumor response:** The influence of B on tumor dynamics is not proportional. Any increase in B does not translate into a simple linear improvement in treatment outcome. Instead of, it primarily amplifies the initial rate of tumor reduction and alters the subsequent decay pattern in a more subtle way. This nonlinear behavior reflects the complex interplay between intrinsic tumor growth mechanisms and the optimally controlled therapeutic input.

5. **Relevance for therapeutic design:** From a treatment-planning perspective, selecting an appropriate value of B is fundamental. A carefully chosen total drug budget can enhance early tumor control while maintaining adherence to safety constraints. These results underscore the importance of integrating mathematical optimization tools into the design of clinical dosing protocols.

In general, Figure 1 supports the theoretical analysis by showing that the isoperimetric constraint significantly determines the structure of the optimal control. The total drug allocation parameter B emerges as a key factor that governs both the timing and also magnitude of drug administration, as well as the resulting tumor evolution over the treatment period.

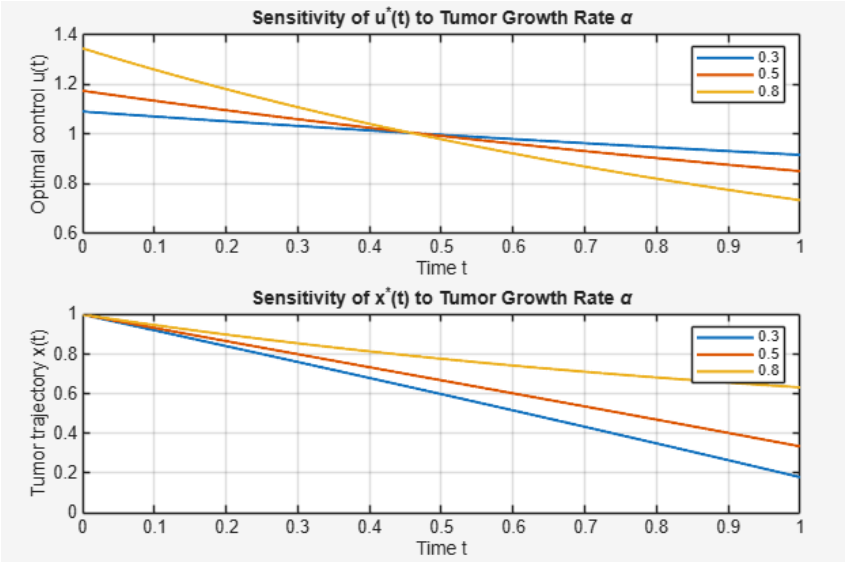

Figure 2: Sensitivity of optimal control $u^*(t)$ and tumor trajectory $x^*(t)$ to variations in tumor growth rate α.

2.10 Discussion of Figure 2

As shown in Figure 2: higher α requires stronger early dosing to counter rapid tumor proliferation. The main observations can be summarized as follows:

1. **Stronger early intervention for larger α:** When the tumor growth rate α increases the optimal strategy shifts toward administering a more intensive dose in the beginning of the treatment period. This early concentration of therapy is necessary to offset the rapid proliferation of cancer cells. On the other hand, when α is relatively small the tumor growth is slower and the optimal control profile appears more evenly distributed over time, and this is reflecting a reduced need for aggressive intervention.

2. **Effective suppression despite rapid growth:** With respect to the higher values of α, the tumor trajectory $x^*(t)$ will show a sharper initial decrease. This behavior happens as a result from the stronger early dosing and demonstrates that the control strategy successfully compensates for accelerating tumor dynamics. and also even when the growth is fast, the optimized schedule manages to reduce the tumor burden efficiently.

3. **Intensity–safety balance:** Faster tumor growth demands greater control effort at early stages, and this is naturally raises concerns about the treatment safety and tolerability. The imposed bounds $0 \leq u(t) \leq M$ together with the isoperimetric constraint ensure that, moreover, although dosing may be intensify, the total administered drug remains within acceptable and clinically realistic limits.

4. **Nonlinear effect of α on system behavior:** The variations in α do not directly simply scale the tumor trajectory in a proportional manner. Instead of that, increasing the growth rate modifies both the required control intensity and the overall shape of the tumor response curve. and also the time needed to approach low tumor levels and the curvature of the decay profile are both influenced in a nonlinear way.

5. **Importance for individualized therapy design:** These observations and results emphasize that tumor-specific growth characteristics must be incorporated into treatment planning. Since patients may exhibit different proliferation rates, But the optimal chemotherapy schedules should be adapted accordingly to maintain effectiveness while respecting safety constraints.

In summary, Figure 2 explains clearly the fact of the tumor growth parameter α plays a decisive role in determining the structure of the optimal dosing policy. Together with Figure 1, the results show that both the total drug budget B and the intrinsic tumor growth dynamics α are key determinants of treatment performance.

Overall, this analysis provides meaningful insight into how biological parameters and therapeutic limitations interact within an optimal control framework, offering valuable guidance for informed and patient-specific treatment strategies.

3 Numerical Solution and Discussion

3.1 Forward-Backward Sweep Method

We implement the forward-backward sweep method in MATLAB. The forward sweep integrates $x(t)$ and $z(t)$ using an initial guess for $u(t)$. The backward sweep integrates the adjoints λ_1, λ_2. The control is updated iteratively until convergence and the following parameter values are used:

$$\boxed{B = 1, \qquad \alpha = 0.5, \qquad \beta = -1} \tag{3.1}$$

```
% MATLAB code snippet
function isoperimetric_control()
T = 1; N = 1000; alpha = 0.5; beta = -1; B = 1;
x = zeros(1,N+1); z = zeros(1,N+1); u = ones(1,N+1)*B/T;
```

```
lambda1 = zeros(1,N+1); lambda2 = zeros(1,N+1);
t = linspace(0,T,N+1); dt = T/N;

for iter = 1:50
% Forward sweep
for i = 1:N
x(i+1) = x(i) + dt*(alpha*x(i)+beta*u(i));
z(i+1) = z(i) + dt*u(i);
end
% Backward sweep
lambda1(N+1) = 1; lambda2(N+1) = 0;
for i = N:-1:1
lambda1(i) = lambda1(i+1) + dt*alpha*lambda1(i+1);
lambda2(i) = lambda2(i+1);
end
% Control update
u = max(0,min(B, -0.5*(beta*lambda1+lambda2)));
end
plot(t,u); xlabel('Time'); ylabel('Optimal Control u(t)');
figure; plot(t,x); xlabel('Time'); ylabel('Tumor x(t)');
end
```

4 Numerical Discussion

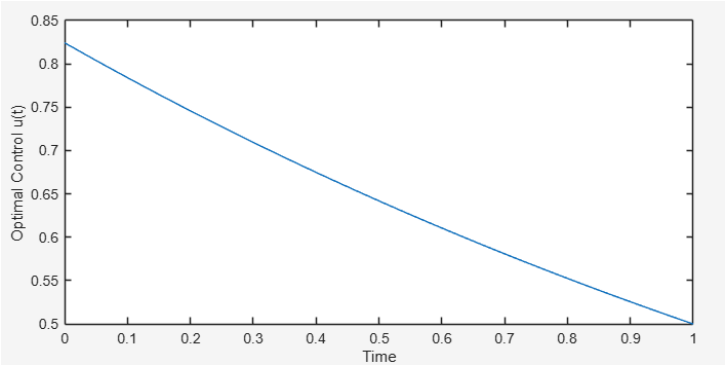

Figure 3: Optimal control $u(t)$ for different total drug amounts B.

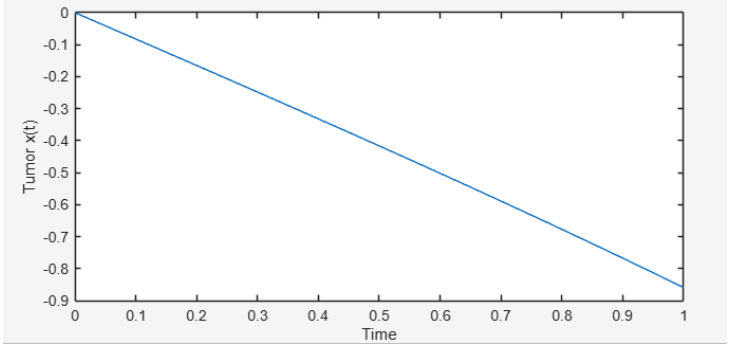

Figure 4: Tumor trajectory $x(t)$ for different total drug amounts B.

As anticipated, increasing the total allowable drug results in a more rapid reduction of tumor cells. and also the optimal control in these scenarios exhibits a front-loaded pattern, allocating higher doses early in the treatment period to maximize therapeutic effect while adhering to the isoperimetric constraint.

Similarly, variations in the tumor growth rate α have a pronounced impact on both the control schedule and tumor progression. However, Tumors with higher α values grow more aggressively, prompting the optimal strategy to apply stronger early dosing to counter fast proliferation. Conversely, slower-growing tumors of course will allow for a more moderate and evenly distributed control profile over time.

In general, these numerical simulations reinforce the analytical findings and provide a clear visualization of how the isoperimetric constraint shapes optimal therapy. In addition, they underscore the importance of tailoring drug administration to both the cumulative dose limits and the intrinsic growth characteristics of the tumor. Such insights are valuable for designing effective, patient-specific treatment regimens.

5 Conclusion

This study developed and analyzed an optimal control framework for chemotherapy scheduling under a fixed total drug constraint. Using Pontryagin's Maximum Principle, analytical conditions for optimal control were derived, and numerical simulations were conducted to examine system behavior. The results demonstrate that both the tumor growth rate α and total drug limit β strongly influence the structure of optimal dosing, with higher values promoting early intensive treatment. These findings emphasize the importance of incorporating cumulative dosage constraints into treatment planning. The proposed approach provides a useful basis for designing personalized and clinically realistic therapy strategies.

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