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Brief Report

Optimization of Cancer Treatment: A Control Theory Approach

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ABSTRACT

In medical diagnostics and treatment, precise administration and monitoring are essential, especially in cancer therapy, where personalized drug dosage becomes critical due to varying patient responses. Human demographics exhibit diverse reactions to drug administration, necessitating individualized treatment regimens for cancer patients. The effects of drugs on cancer cells vary based on dosage, highlighting the need for a mathematical framework to model drug intake, absorption in the gastrointestinal tract, and eventual circulation in the bloodstream. For physicians, initial drug dosing and administration schedules-typically spanning a week-are observed before adjustment. This study mirrors this practical approach by proposing an optimal control therapy for cancer treatment, explicitly using chemotherapy. Through Pharmacokinetics (PK) modelling, one can explore dose optimization strategies to provide patient-specific, optimal drug regimens tailored to individual cancer patients. The research emphasizes the critical role of prior knowledge and control therapy in enhancing treatment outcomes.

Keywords: Oncology, Chemotherapy, Clinical care, Optimal therapy, Personalised medicine.

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INTRODUCTION

In medical examinations, each patient presents with unique demographics and medical history, resulting in distinct drug interactions. Consequently, it is vital to establish the correct therapeutic approach, particularly for complex diseases like cancer, where the dynamics of tumour cell generation and degeneration play a crucial role. Beyond disease-specific drug dosage, personalized drug administration is necessary to ensure accurate treatment for each patient.

Certain research investigates new methodologies for calculating optimal dose regimens in cancer treatment, specifically using chemotherapy. By delving into key results and exploring novel optimization techniques, one can aim to provide an optimal drug administration approach tailored to individual cancer patients. The study uses a cost function to minimize both the model's cost and resource usage, while achieving favourable outcomes through linear modelling. The balance between drug toxicity and tumour reduction is a focal point in this control therapy.

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LITERATURE REVIEW

Cancer treatments have evolved significantly over time. Research suggests that in 70% of cancer cases, there is a disruption in the survival mechanisms of specialized cells, particularly macrophages, which are responsible for regulating or eradicating dead and degenerative cells.[1-3] Studies have explored the role of macrophages in populating antigens and rejuvenating the immune system, with therapies leveraging this effect to combat cancer cells.[4,5] However, treatments using macrophage-based approaches have also been shown to sometimes increase tumour size.[6,7]

Chemotherapy, in conjunction with drug dosing, has proven to be a viable alternative to radiotherapy, which often results in harmful side effects by destroying healthy cells along with cancerous ones.[8-10] Optimal control therapy, in this context, ensures that drug administration is fine-tuned to minimize resource consumption while maximizing therapeutic efficacy.[11,12] This is achieved through Pharmacokinetic (PK) modelling, where drug concentration is carefully monitored and administered at stable infusion rates.[13,14]

While PK models offer a reliable method for drug administration, they face challenges in approximating induction phases and synchronizing drug delivery with the Pharmacodynamic (PD) response. Solutions have been proposed through the synchronization of drug administration intervals,[15] and these improvements have been complemented by

microprocessor-controlled drug infusions, which allow for more precise control.[16]

An alternative approach, Physiological-Based Pharmacokinetic (PBPK) modelling, predicts chemical concentrations in regions lacking data by leveraging the ADME (Absorption, Distribution, Metabolism, and Excretion) approach.[17,18] PBPK modelling has been widely studied for its applications in chemotherapy and its ability to handle physiological complexities.[19,20]

Non-negative and compartmental models have also proven useful in handling closed-loop control problems in drug administration, with interconnected subsystems providing better drug management.[21] Adaptive algorithms, incorporating PK/PD models and control systems, have shown promise in adjusting drug concentrations to patient responses.[22-24] However, these algorithms often assume fixed PK or PD models, which may limit their adaptability.[25]

Advances in genomics have provided further insights into cancer heterogeneity. Techniques such as DNA sequencing and machine learning models are now used to track cancer progression and predict cell behaviour based on genomic data.[26-28] Genomic profiling from resources like The Cancer Genome Atlas offers crucial data on tumour evolution, allowing for the development of patient-specific treatments.[29]

CHEMOTHERAPY

The earliest and most common form of cancer treatment, radiotherapy, often resulted in collateral damage to healthy cells. Chemotherapy emerged as an alternative that uses anti-cancer drugs to suppress cancer cell growth and division. Its effectiveness lies in its ability to target rapidly dividing cancer cells while preventing mutation and spread.

Chemotherapy integrates two models: Pharmacokinetics (PK) and Pharmacodynamics (PD). The PK model addresses the drug's administration and dosage, while the PD model focuses on its effects and mechanisms of action. In this study, we focus primarily on PK models, exploring their dynamics and multiple dosing strategies. This foundation will pave the way for future PD model studies.

REVIEW OF MATHEMATICAL MODELING

Mathematical modelling in medical research has progressed significantly, providing a quantitative mechanism to investigate complex biological phenomena like cancer. Cancer, being a genetic disease, is driven by evolutionary processes. The continuous mutation and accumulation of cancer cells make them more robust and challenging to treat, necessitating a detailed analysis of their behaviour through micro-level observations and quantitative mathematical models.

CANCER GROWTH AND EVOLUTION MODELS

Cancer cells undergo various genetic mutations, which impact their growth, spread, and survival within tissues. To understand these processes, mathematical models are essential for structuring biological dynamics. These models allow us to describe, predict, and analyse cancer development at cellular and tissue levels.

Branching processes are commonly used in cancer modelling to account for probabilistic cell growth. This process assumes that cancer cells follow similar growth patterns over time, simplifying the analysis. However, the key challenge remains patient-specific administration and the need for disease-specific data to tailor treatment to individual patients.

Critical Components of Mathematical Models for Cancer

Patient-specific administration: Tailored treatments based on individual patient characteristics.

Disease-specific data: The type of cancer informs accurate dosage patterns.

Adaptive models: Algorithms that adjust drug dosage based on patient demographics and medical history.

MODELING WITH ORDINARY DIFFERENTIAL EQUATIONS (ODES)

The mathematical foundation for modelling cell populations, especially in chemotherapy, often involves Ordinary Differential Equations (ODEs). These equations describe how healthy cells can transition into cancerous states and degrade over time. A more detailed multi-stage model for cancer growth accounts for cell susceptibility to mutation and metabolic influences.

Using these ODEs as a framework to simulate the tumour's reaction to drug treatments helps to better understand the interaction between healthy and cancerous cells during chemotherapy.

OPTIMIZATION IN CHEMOTHERAPY

Optimization plays a crucial role in chemotherapy by helping adjust drug dosages and intervals for each patient. A personalized dose regimen, informed by an optimized Pharmacokinetics (PK) model, ensures that the drug is administered with minimal side effects while maximizing its effectiveness.

The PK model focuses on drug movement and transformation within the body, which is influenced by various organs' absorption and metabolism rates. This model is paired with a Pharmacodynamic (PD) model that describes the drug's effect on cancer cells.

Optimization aims to balance the drug's impact on cancerous cells[30] while minimizing damage to healthy cells, a critical issue in chemotherapy. Researchers use Ordinary Differential Equations

to model the kinetics of drug interactions within the body and has seems to have fruitful results.

CHALLENGES AND FUTURE DIRECTIONS

Key challenges remain in incorporating patient-specific factors into these models. Future work will focus on improving the adaptability of mathematical models for individual treatment plans and integrating real-time data to optimize drug delivery.

An overview of the theoretical formulation in Section 3 provides a sufficient explanation of the Pharmacokinetic (PK) model used for drug delivery in chemotherapy, specifically Imatinib.[31]

THEORETICAL FORMULATION

Pharmacokinetic (PK) Model Overview

The PK model focuses on how the concentration of Imatinib, a drug used to target cancer cells, changes over time in the gastrointestinal tract and bloodstream. The two differential equations describe this behavior, modeling the drug's absorption from the gastrointestinal tract (Equation 1a) and its clearance from the bloodstream (Equation 1c). The equations provide a foundation for simulating drug administration and the resulting concentration over time.

$$\frac{dx_g}{dt} = -k_a x_g(t),\ t > 0 \qquad (1a)$$

Equation (1a): Describes how the concentration of Imatinib in the gastrointestinal tract decreases due to absorption.

Here, x_g is the concentration of Imatnib in the gastrointestinal tract as a function of time, with dimensions of mg, and k_a is a rate constant (dimensions: $[hr]^{-1}$) Equation (1a) is seeded with the initial condition:

$$x_g(0) = D_f \qquad (1b)$$

Here, D is the initial dose of Imatnib adminstered to the patient, and f is the bioavailability. Furthermore, the amount of Imatnib in the bloodstream changes over time according to the following model equation:

$$\frac{dx_b}{dt} = -k_a x_g(t) - CL\left(\frac{x_b(t)}{v}\right),\ t > 0 \qquad (1c)$$

Equation (1c): Models how the concentration of Imatinib in the bloodstream increases from absorption and decreases due to clearance.

Here, x_b is the concentration of Imatnib in the bloodstream as a function of time, with dimensions of mig, CL is the clearance rate, and v is the total volume of the patient's blood (in litres). The initial condition reads as:

$$x_b(0) = 0 \qquad (1d)$$

Equations (1) are set up for a once-off dose D delivered at time t = 0. However, in the present context, we wish to simulate repeated doses administered at times $\{t_0 = 0, t_1, t_2, ..., t_N = T\}$. Here, T is the time of the final dose chosen in the simulations so that the system reaches a quasi-steady state. Thus, similar to counting the zeroth dose, N doses are administered and Equation (1) modifies as the ordinary differential equations are solved piecewise between a time intervals.

DRUG ADMINISTRATION SCANERIOS

In the context of chemotherapy, drug administration involves repeated doses. In practice, the doses $\{D_0, D_1, \bullet\bullet\bullet, D_N{-}1\}$ can be distinct, although following are the two-dosing scenario considers:

Scenario 1: All doses are the same $D_j = D$, for all $j = 0, 1, 2, \bullet\bullet\bullet, N - 1$.

Scenario 2: The first dose differs, and subsequent doses are the same or follow a sequence.

In the second dose scenario, we might have:

$$Dj = D0,\ j = 0,\ D,\ j > 0,$$

or

$$Dj = D0,\ j = 0;\ D1,\ j = 1;\ D,\ j > 1,\ \text{etc.}$$

The intervals $\tau_j = t_j - t_j{-}1$ *(for j = 1, 2, ..., N)* between doses can also be variable, however, in this work we will mostly look at a fixed dose interval, e.g. $\tau = 24$ *hr,* $\tau = 12$ *hr,* $\tau = 8$ *hr*, etc. Therefore, in the following exposition, to fix ideas, we will assume a fixed dose interval τ.

OBJECTIVES AND COST FUNCTION

The aim of this work is to keep the concentration of the drug in the patient's body as close to a target level C_{targ} as possible. Here, the concentration is measured as $C = xb/v$, in mg/litre. As such, we introduce the Euclidean distance between the instantaneous concentration and the optimal target concentration:

$$\varepsilon(C, C_{targ}) = |C - C_{targ}|$$

We furthermore introduce cost function which penalizes the average deviation of the concentration from the target concentration, over the time interval of interest *[0, T]*.

$$J(D_0, D_1, ..., D_N, \tau) = \sum_{j=1}^{N} \int_{tj-1}^{tj} \varepsilon(C(t), Ctarg)dt$$

This setup allows flexibility in simulating different treatment regimens, which is crucial for optimizing drug delivery based on individual patient needs.

Therefore, in a nutshell, the aim of this project is to minimize the cost function.

$$J(D_0, D_1, ..., D_{N-1}, \tau)$$

as a function of the input parameters $\{D_0, D_1, ..., D_{N-1}\}$, and τ.

NUMERICAL APPROACH

Although analytical solutions to the equations exist, this work opts for a numerical solution using solvers like ODE45 in MATLAB or its equivalent in Python. This approach provides a general framework for other PK/PD models that may need to admit analytical solutions. Researchers compute the numerical cost function using a Riemann sum based on the interpolation of numerical solutions.

OPTIMIZATION TECHNIQUES

Two optimization approaches explore

Brute Force Computation: Suitable for low-dimensional optimizations, where the cost function evaluates for a range of dose values.

Built-in Optimization Methods: These are more sophisticated and involve function calls to MATLAB's `minion` or its Python equivalent to minimizing the cost function.

RESULTS AND REPRODUCTION OF PREVIOUS WORK

BCR-ABL% Analysis: Researchers model the mutation percentage observed over time for a cancer patient using piecewise linear regression on a logarithmic scale. It provides insight into the exponential decay of cancer markers due to chemotherapy.

Drug Dosage Administration: Simulations show how the concentration of Imatinib evolves both in the gastrointestinal tract and the bloodstream. Based on the PK model, the Figures illustrate standard and optimized drug dose administration for patient 0001 00002 RH.

The optimized drug administration design maintains the drug concentration close to the target level over time, minimizing side effects and maximizing treatment efficacy.

FUTURE WORK

The theoretical formulation can include more complex PK/PD models and patient-specific customization, such as varying clearance rates, bioavailability, and tumour growth dynamics.

This section discusses the production of new results related to drug dosage optimization for cancer treatment using a Pharmacokinetic (PK) model and optimization methods. It explores different drug administration schedules and dosages, analyzing their effectiveness in achieving an optimal therapeutic result with minimal side effects.

Required Work for the following Dose Administrations

- Single Drug Dose Administration.
- Double Drug Dose Administration.
- Triple Drug Dose Administration.
- Comparison Across Dosing Schedules.
- Four Drug Dose Administration.

CONCLUSION

Optimal Dosage Levels: Across all tested regimens, optimal dosages range between 200 and 400 mg, depending on the daily doses.

Future Work: Future investigations may incorporate Pharmacodynamic (PD) models, study the influence of cancer cell mutations, and explore personalized treatment plans by incorporating additional biological and clinical factors.

This study provides important insights into how multiple drug doses can be optimized for cancer therapy, improving patient outcomes while minimizing toxicity and side effects.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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