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Optimization of chemotherapy regimens using mathematical programming

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ABSTRACT

Cancer is a leading cause of death and a cost burden on healthcare systems worldwide. The mainstay of treatment is chemotherapy which is most often administered empirically. Optimizing the frequency of drug administration would benefit patients by avoiding overtreatment and reducing costs. In this work, the optimization of chemotherapy regimens using mathematical programming techniques is demonstrated by developing a simple mathematical programming model for the administration of a fictitious drug. The question to be answered by the solution of the model is how often the drug should be administered so that the tumor size does not exceed a predefined size and the treatment cost reaches a minimum value. The proposed mathematical programming model is computer-implemented using a well-established mathematical programming system, thus keeping the cost and effort of obtaining the optimization results low. An example is used to demonstrate the superiority of the proposed optimization approach over the mainstay approach.

1. Introduction

Despite significant advances in cancer research, cancer remains a fatal disease with a poor prognosis (Ferlay et al., 2021; Siegel et al., 2024). Current treatment options range from surgery, (radio-)chemotherapy, palliative care, and combinations of these. Every day, oncologists are faced with choosing the best treatment option for an individual patient. Drug regimens are selected according to state-of-the-art guidelines based on clinical trials.

An important principle of chemotherapy is cytoreduction, i.e. the elimination of the tumorous (neoplastic) cell population. Because many therapies cannot fully discriminate between tumorous and non-tumorous cells, healthy (proliferative) cells also undergo cell death. Thereby, treatment itself can induce organ dysfunction and may significantly reduce quality of life. This has led to the common practice of administering chemotherapy in cycles with specific and individually tailored dosage(s). However, little is known on optimal dosing and how individuals benefit from variation in administration cycles.

"Treatment scheduling" refers to the concept of allocating appropriate treatment to a patient in a suitable (i.e. gold standard therapy and administration mode), optimized (optimal frequency of administration) and timely (treatment duration and total time frame) manner (National Cancer Institute). Scheduling models have to consider and integrate several non-negligible parameters and constraints, respectively (Majidi et al., 1993). These parameters shall reflect tumor biology as accurately as possible. The importance of treatment scheduling may be underlined by the fact, that the leading causes of cancer death, i.e. lung and colorectal cancer (Ferlay et al., 2021), are both sensitive to chemotherapy.

In recent decades, the growing interest in tumor modeling (Brady & Enderling, 2019; Kuznetsov et al., 2021; Rockne et al., 2019; Victori & Buffa, 2019) has led to several attempts to mathematically model tumor growth and thereby optimize treatment regimens in a more individualized and targeted way (Enderling & Wolkenhauer, 2021; Shi et al., 2014). Optimal control approaches predominate (Lecca, 2021), with most models expressed as sets of differential equations (Moore & Allen, 2019). These models are then reformulated in order to make them amenable to mathematical programming techniques such as mixed integer linear programming (MILP). The main reason for using differential equations is to be able to model the tumor dynamics: Tumor growth as a function of time, evolution of drug clearance over time, etc.

Tumor growth is biologically complex and any modeling attempt is inherently approximate. It is generally accepted that tumors grow in three phases: In the initial phase, the tumor starts growing exponentially from a small size (Fig. 1). After reaching its maximum growth acceleration, the tumor continues growing in larger rates. Finally, growth rates decrease as the tumor approaches a lethal size (Gompertz, 1825; Laird, 1964). Importantly, tumor growth rates of human neoplasms are extremely heterogeneous, depending on the entity, inherent biological aggression, and host factors (Spratt et al., 1995, 1996). Tumor growth dynamics are most commonly modeled using exponential, power law, logistic, Gompertz and Bertalanffy functions, depending on the cancer type (Beckman et al., 2020; Benzekry et al., 2014; Soerensen et al., 2018; Tabassum et al., 2019; Vaghi et al., 2020).

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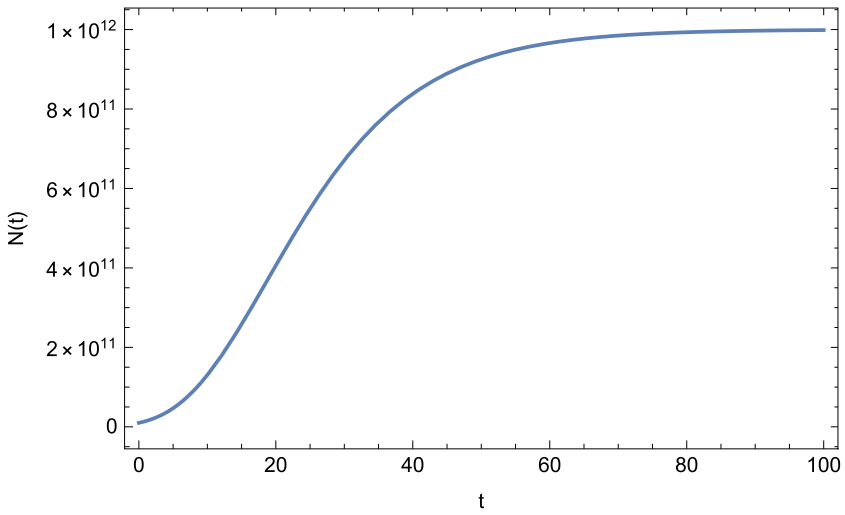

Fig. 1. Tumor growth over time (t: time, $N(t)$: amount of tumor cells over time t).

Patient death can be considered the most critical clinical endpoint in oncology and inevitably marks the point of no return. Death occurs when the tumor size exceeds a critical value. Therefore, the definition of a value for the tumor mass beyond which the quality of life for the patient may be considered unbearable, is useful for the purposes of treatment optimization. A total tumor burden of one kilogram, equivalent to one trillion cells, has been postulated to be lethal (Del Monte, 2009). Tumor cell populations smaller than 10^3 cells are considered as biologically tolerable due to efficient host defense mechanisms (e.g. via apoptosis, immune surveillance, etc.) (Petrovski & McCall, 2001). In addition to tumor size, resistance to chemotherapy critically limits any scheduling efforts (Werner et al., 2014) as it unequivocally predicts treatment failure. Lastly, while scheduling models are becoming increasingly complex and multi-parametric (Laleh et al., 2022), financial affordability can significantly hinder treatment access and delivery (Fundytus et al., 2021). In 2018, the cost of cancer in the European Union was €199 billion (Hofmarcher et al., 2020). Despite being important especially in low-income countries (Ruff et al., 2016), budget constraints have so far been neglected in treatment scheduling.

Besides optimal control, other approaches have found their way into treatment scheduling. In recent years, there has been an increased research effort to apply metaheuristics to optimize treatment scheduling (Horne et al., 2016). Various metaheuristic optimization approaches have been put into practice, such as swarm intelligence (e.g. Dhieb et al., 2023), a multiobjective gray wolf optimizer (Chen et al., 2023), etc. Dhieb et al. propose an optimized chemotherapy scheduling and drug administration protocol that aims to minimize tumor cell size, drug consumption, and total therapy duration (Dhieb et al., 2023). Their protocol consists of a series of chemotherapy and relaxation sessions. While drug administration is optimized according to an optimal control approach, the duration of each session is optimized using the Particle Swarm Optimization metaheuristic. Shindi et al. combine optimal control theory with multiobjective swarm intelligence and evolutionary algorithms to minimize tumor and drug concentration (Shindi et al., 2020). They claim that their hybrid approach is performing better than methodologies that are based purely on swarm or evolutionary algorithms. The metaheuristic multiobjective "gray wolf optimizer" (Chen et al., 2023), which mimics predator–prey behavior, was used to establish a drug administration protocol that minimizes the concentration of cancer cells and the concentration of the drug within the body of the patient. It should be noted though, that while metaheuristic approaches provide "good enough" solutions, they suffer from their inherent inability to claim mathematically proven global optimality (INFORMS, 2021; Soerensen et al., 2018).

In recent years, artificial intelligence (AI) methods have been applied to healthcare (Padmanabhan et al., 2017; Shiranthika et al., 2022). Yang et al. review applications of Reinforcement Learning (RL) in cancer chemotherapy. They conclude that RL could be of practical value, but there are still many issues to be resolved for these techniques to benefit oncological studies (Yang et al., 2023). A more recent application of RL to drug dose control in chemotherapy is reported by Mashayekhi et al. The authors report promising results, but point out that several challenges still need to be addressed before RL can be applied to real medical cases (Mashayekhi et al., 2024).

Mathur et al. provide a classification of cancer therapy optimization approaches based on the accumulated knowledge of previous research (Mathur et al., 2022). This classification is intended to aid decision making when determining the most appropriate treatment regimen for a given cancer patient. Another excellent critical review and assessment of research to date is provided by Strobl et al. (Strobl et al., 2023). Both papers provide invaluable views on future research directions.

This work addresses the scheduling of drug dose administration for cancer patients over a longer treatment horizon. The treatment horizon is divided into a number of shorter treatment periods at the beginning of which a drug dose may or may not be administered. Dose administration decisions are outcomes of a mathematical programming problem that is solved to global optimality. The goal of the drug administration schedule is to ensure an acceptable level of quality of life for the patient at a minimum drug cost. Quality of life is ensured by forcing the size of the tumor of the patient not to exceed a prespecified upper bound. The tumor size is controlled by assuming that the treatment drug reduces the size of the tumor and that it resets the function describing tumor growth evolution back to an earlier time state. The result of the optimization is thus, how often and when a given drug should be administered in order to guarantee an acceptable quality of life while financial cost is kept at a minimum.

Main assumption of our approach is that drug administration leads to tumor shrinkage. The ability to keep the tumor size below a given upper bound determines the success or failure of a treatment. The developed model can be mathematically classified as a MILP resp. mixed-integer nonlinear programming (MINLP) model and is computer-implemented using the mathematical programming modeling system GAMS (GAMS Development Corporation, 2021). The optimization problem is solved to global optimality usling the optimization solver CPLEX (IBM Inc, 2021) resp. the global optimization solver BARON (Sahinidis, 1996).

Formulating the drug administration scheduling problem as a multi-period global optimization problem, addressing both therapeutic and economic issues, and solving it to global optimality is a novel approach.

Determining the tumor size during optimization by moving back and forth on the function describing its evolution, is another novelty.

The optimization approach makes it possible to assess treatability, to avoid overtreatment and to ensure a good quality of life for the patient. Moreover, the healthcare system can reduce treatment costs.

2. A mathematical programming approach for treatment scheduling in Oncology

In the following section an optimization model for drug administration for a patient suffering from a solid tumor is developed. If the patient does not receive medical treatment, he will die when the tumor reaches a critical size. In order to keep the tumor size at a level that allows the patient to live a comfortable life, the patient is treated with drugs. The effect of the drug treatment on the tumor is to reduce the size of the tumor. The treatment does not reduce the size of the tumor to zero. If the treatment is stopped, the tumor will continue to grow until either the patient dies or the treatment is restarted.

The problem is to minimize the cost of treatment while ensuring an acceptable quality of life for the patient. To achieve this goal, decisions must be made about whether or not to administer the drug at predetermined time points over the treatment horizon.

2.1. Assumptions

For the purposes of modeling the following assumptions are made:

- The treatment horizon consists of a predefined number of intervals of constant length (e.g. weeks)
- The drug can be administered at most once at the beginning of each interval
- Each dose of the drug is of the same amount
- The tumor grows according to a prespecified growth model during the time periods
- The effect of the drug on the tumor is that it reduces its size by a constant factor
- The drug cannot reduce the size of the tumor below a minimum value

2.1.1. Notation

In this section we introduce the notation for expressing the problem as a mathematical programming model. This concerns the indices, the constants as well as the decision variables involved in the model.

2.1.2. Indices

k index indicating the number of treatment periods.

2.1.3. Constants

p	price for a dose of drug
$\overline{G}(k)$	upper bound on size of the tumor
$\underline{G}(k)$	lower bound on the size of the tumor
S_{Tol}	maximum size of tumor tolerated
S_{min}	minimum possible size of the tumor after treatment
S_0	initial size of the tumor
A	constant factor by which the tumor size has grown after a period of time elapsed
RF	factor expressing the reduction in tumor size when a dose of drug is administered

2.1.4. Decision variables

$X(k)$	binary variable indicating weather ($X(k) = 1$) or not ($X(k) = 0$) the drug is administered
$G(k)$	tumor size before treatment
$R(k)$	reduction of tumor when drug is administered
$S(k)$	tumor size after the drug has been administered

2.1.5. Constraints

In the following, we mathematically express the constraints that characterize the treatment scheduling problem. First we describe the objective function, and then the problem constraints.

2.1.6. Objective function

The goal of the optimization is to minimize the total cost of the drug treatment while keeping the size of the tumor below a certain level S^{max}. The total cost of the drug treatment is the sum of the cost of the drug that need to be administered during the treatment horizon H. The objective function may be expressed mathematically as

$$Min \sum_{k=1}^{K} p\, X(k) \tag{1}$$

2.1.7. Treatment horizon

The treatment horizon H consists of K periods of equal length, which are indexed from 1 to K.

2.2. Tumor size

2.2.1. Size of tumor before treatment (tumor growth)

We use an exponential model to express tumor growth. More specifically we assume that the untreated tumor size at period k equals A times the treated tumor size at the previous period $S(k-1)$. This is expressed mathematically as

$$G(k) = A\, S(k-1) \qquad \forall k > 1 \tag{2}$$

2.2.2. Size of tumor after treatment

The size of the tumor at period k, $S(k)$, equals the size of the tumor because of tumor growth $G(k)$ minus the reduction in size of the tumor because of treatment in period k. Expressed mathematically

$$S(k) = G(k) - R(k) \qquad \forall k = 1, \ldots, K \tag{3}$$

2.2.3. Reduction of tumor size

The effect of drug treatment is shown by a reduction in the size of the tumor. We assume that the size of the tumor is reduced by a constant factor RF each time the drug is administered. Expressed mathematically

$$R(k) = RF\, X(k)\, G(k) \qquad \forall k = 1, \ldots, K \tag{4}$$

2.2.4. Tumor size limit

As already stated, the model aims at finding a drug administration schedule that keeps the size of tumor below value S_{Tol}.

$$S(k) \leq S_{Tol} \qquad \forall k = 1, \ldots, K \tag{5}$$

2.3. Mathematical properties of the model

Besides the linear constraints, the model contains the nonlinear constraints (4). Further, the model contains the discrete (binary) variables X_k, all other variables being continuous, non-negative. The model is therefor a Mixed Integer Non-Linear Programming (MINLP) problem.

The problem can either be solved as a MINLP, or efforts can be made to linearize constraints (2) and (4), thus transforming the MINLP problem into an MILP. Fortunately, constraints (4) can be linearized exactly, so the linearization does not therefore change the optimal solution of the problem. The linearization leads to a MILP amenable to currently available MILP solvers.

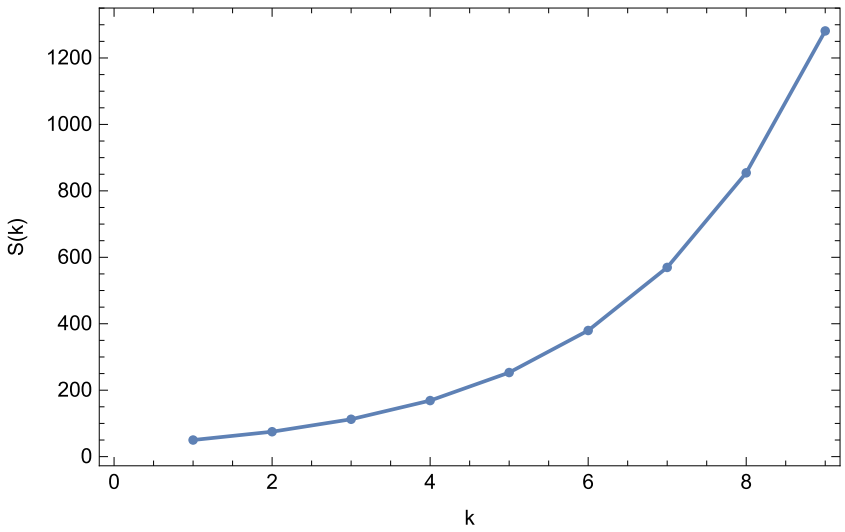

Fig. 2. Evolution of tumor size $S(k)$ when the tumor is not treated (identical to $G(k)$).

Linearization of Eq. (4)

The following set of constraints linearizes constraints (4) exactly (Hu & Kahng, 2016, page 128)

$$\underline{G}(k)X(k) \leq \frac{R(k)}{RF} \qquad \forall k = 1, \ldots, K \tag{6}$$

$$\frac{R(k)}{RF} \leq \overline{G}(k)X(k) \qquad \forall k = 1, \ldots, K \tag{7}$$

$$\underline{G}(k)(1 - X(k)) \leq G(k) - \frac{R(k)}{RF} \qquad \forall k = 1, \ldots, K \tag{8}$$

$$G(k) - \frac{R(k)}{RF} \leq \overline{G}(k)(1 - X(k)) \qquad \forall k = 1, \ldots, K \tag{9}$$

This concludes the description of the model. In the following we describe an example of an instance of the model, we implement it in the mathematical programming language GAMS (GAMS Development Corporation, 2021), and solve it using the commercial state of the art MILP solver interfaced by GAMS.

3. Results

3.1. Model parameters

In the following the parameters of the model instance are being described

Tumor growth parameters
Growth rate: $A = 1.5$
Initial value: $S_0 = 50$

Tumor size parameters
Initial value of the tumor size: $S_0 = 50$
Maximum acceptable tumor size before treatment: $S^{max} = 500$
Minimum size of the tumor after treatment: $S_{min} = 10$

Time parameters
Treatment horizon: $H = 52$
Period length: $L = 1$

Drug parameters
Tumor size reducing factor: $RF = 0.6$
Cost for a dose: $p = 10$

3.2. Solution of the optimization problem

In the following, we show that the tumor size reaches the lethal size without treatment. A simple heuristic solution to the problem is then presented. Finally, an attempt is made to solve the problem to optimality using state-of-the-art optimization software.

3.2.1. No drug treatment

When the tumor is left untreated its size grows by a factor of $A = 1.5$ period by period. At period $k = 9$ the size of the tumor reaches the value of 1281.4453 exceeding the lethal value of 1000 (gram). Thus not treating cannot be an option since the patient dies after 8 periods of time. The evolution of $S(k)$ when the tumor is not treated is depicted in Fig. 2.

3.2.2. Heuristic solution

A simple heuristic approach to address the problem would be to administer the drug just when the tumor size $G(k)$ is about to exceed the value S_{Tol}. This approach leads to an objective value of 210, which means, that the drug needs to be administered 21 times within the treatment horizon at the appropriate periods. The evolution of $S(k)$ when the heuristic is applied is shown in Fig. 3. Fig. 3 shows that the tumor size remains at tolerable but high values during the treatment horizon. We are interested in solutions that ensure small tumor size and are economically viable.

3.2.3. Solution of the example using optimization software

The example instance of the model is implemented using GAMS. GAMS is a mathematical modeling system, that allows the computer implementation of optimization models by using human readable algebraic statements. The modeling system provides interfaces to implementations of state-of-the-art mathematical optimization algorithms, referred to as solvers. The model is developed to be a MILP since it contains both continuous and discrete variables and only linear constraints. For the solution of the problem we use the state-of-the-art MILP solver CPLEX (IBM Inc, 2021).

The MILP solver CPLEX returns for the model instance described above a feasible solution of 210, which corresponds to 21 doses of drug. The solver is not able to determine the optimal solution to the problem within the allocated time of 3 h (10,800 s).

The evolution of the tumor size $S(k)$ is shown in Fig. 4.

Further arbitrary modifications of S_{Tol} cannot answer the question concerning the optimal value of drug cost subject to a predefined S_{Tol}. This question can only be answered if we enable CPLEX to obtain the optimal solution to the problem.

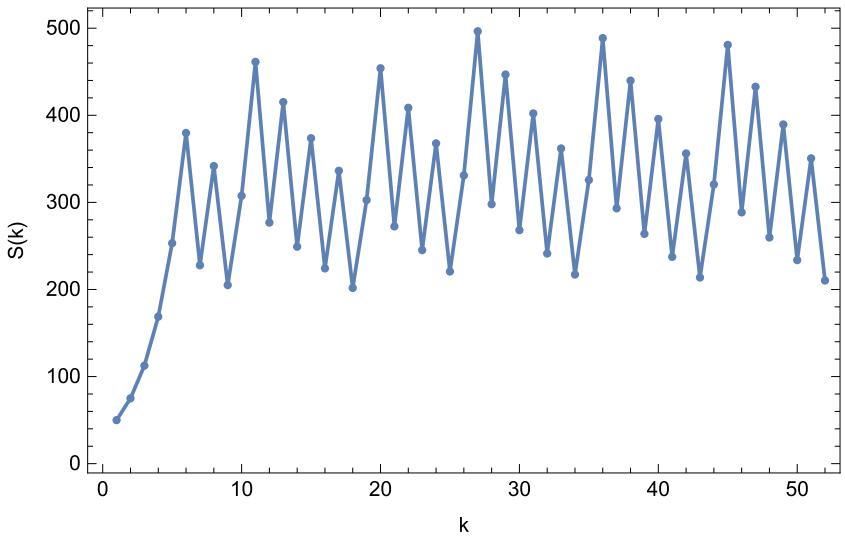

Fig. 3. Evolution of tumor size $S(k)$ after the drug has been administered when the heuristic is applied.

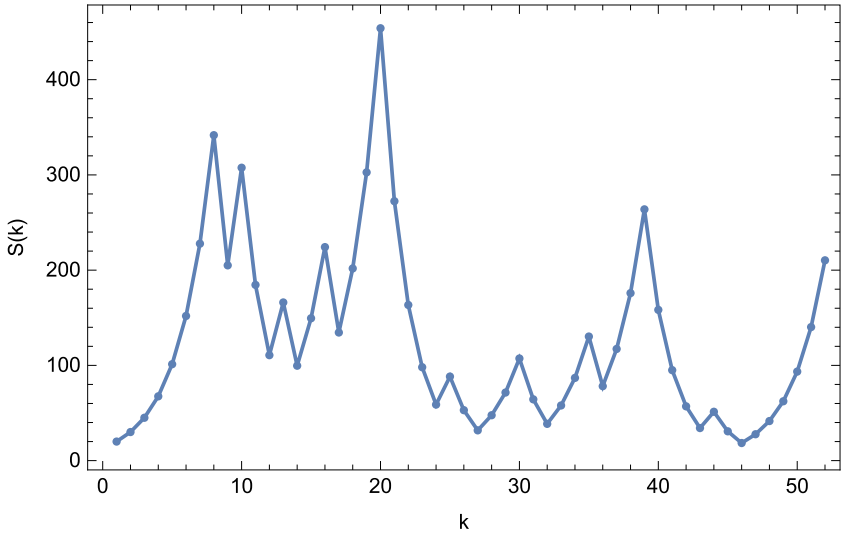

Fig. 4. Evolution of $S(k)$ after the drug has been administered.

3.3. Model refinement

In this section we take another look at the model aiming to strengthen the constraints involved, with the objective to be able to obtain the optimal solution to the model within an acceptable time period. We focus on constraints (4), which are restated here:

$$R(k) = RF\ X(k)\, G(k) \qquad \forall k = 1, \ldots, K \tag{10}$$

Eq. (10) can be relaxed to

$$R(k) \leq RF\ X(k)\, G(k) \qquad \forall k = 1, \ldots, K \tag{11}$$

which does not affect the optimal solution of the problem because optimization will always force this inequality to be satisfied as an equality. This is because it is optimal to reduce the tumor size as much as possible, whenever the drug is administered.

With constraint (11) we want to enforce

$$X(k) = 0 \implies R(k)/RF \leq 0 \qquad \forall k = 1, \ldots, K \tag{12}$$

and

$$X(k) = 1 \implies \frac{R(k)}{RF} \leq G(k) \qquad \forall k = 1, \ldots, K \tag{13}$$

The last two constraints (12), (13) may be reformulated to

$$R(k)/RF \leq M_1 X(k) \qquad \forall k = 1, \ldots, K \tag{14}$$

and

$$\frac{R(k)}{RF} - G(k) \leq M_2(1 - X(k)) \qquad \forall k = 1, \ldots, K \tag{15}$$

where M_1, M_2 are numbers big enough to make the constraints redundant when appropriate and as small as possible to keep the feasible region tight. A first choice for these numbers is $M_1 = M2 = \overline{G}(k) = \frac{S_{Tol}}{RF}$.

Eq. (15) shows that M_2 needs only be an upper bound on $\frac{R(k)}{RF} - G(k)$ when $X(k) = 0$ (when $X(k) = 1$, the expression is bounded by 0). When $X(k) = 0$ from Eq. (14) follows that $\frac{R(k)}{RF} = 0$ and Eq. (15) becomes $-G(k) \leq 0$. M_2 can therefore be set to $M_2 = 0$.

Eqs. (14), (15) become

$$R(k) \leq S_{Tol} X(k) \qquad \forall k = 1, \ldots, K \tag{16}$$

and

$$\frac{R(k)}{RF} - G(k) \leq 0.0 \qquad \forall k = 1, \ldots, K \tag{17}$$

With the help of constraint (2) constraint (17) can be rewritten as

$$R(k) \leq RF\ A\ S(k-1) \qquad \forall k > 1 \tag{18}$$

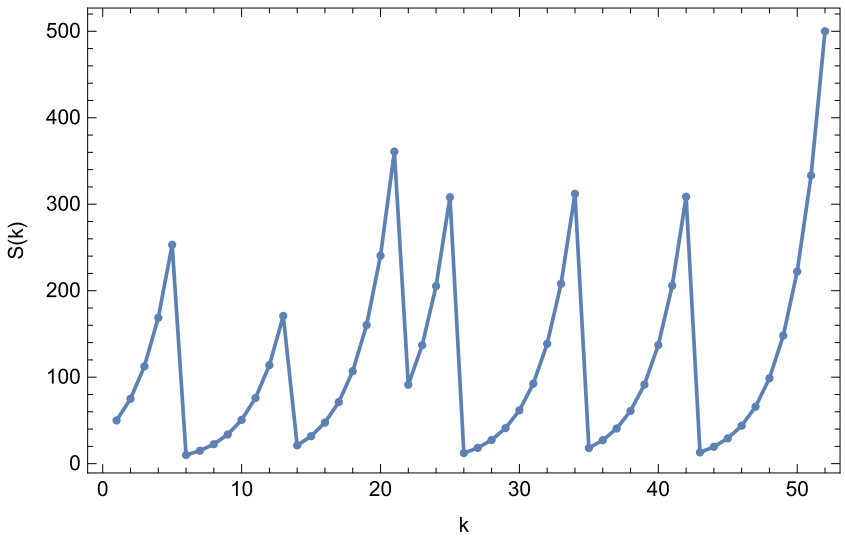

Fig. 5. Optimal solution for the evolution of $S(k)$ after model refinement.

and since $S(k) \leq S_{Tol}$ constraint (18) can be written as

$$R(k) \leq RF\ A\ S_{Tol}\ X(k) \qquad \forall k = 1, \ldots, K \tag{19}$$

Recapitulating, the analysis leads to the following two constraint sets, which replace the non-linear constraints (4).

$$R(k) \leq S_{Tol} X(k) \qquad \forall k = 1, \ldots, K \tag{20}$$

$$R(k) \leq RF\ A\ S_{Tol}\ X(k) \qquad \forall k = 1, \ldots, K \tag{21}$$

Solving the problem stated in Section 3 using constraints (20), (21) leads to the optimal solution of the problem within a solution time of 2.714 s on a desktop equipped with a Intel Pentium 4.3 GHz CPU and 4 GB of RAM.

The value of the objective function is 60, indicating that administering 6 doses of drug maintain the size of the tumor below $S_{Tol} = 500$.

The evolution of the tumor size $S(k)$ is depicted in Fig. 5.

4. Treatment optimization using the Gompertz tumor growth model

Since much of the scientific community considers modeling tumor growth using the Gompertz growth function to be a more appropriate way to mathematically model tumor growth (e.g. Beckman et al., 2020; Benzekry et al., 2014; Tabassum et al., 2019; Vaghi et al., 2020), we adapt the mathematical optimization model presented in the previous section to model tumor growth using the Gompertz function. To do so, we refer to Benzekry et al. (2014) and adapt the values of the parameters used by those authors for the growth function to obtain similar values to those obtained in Section 3.1 where we assume exponential tumor growth.

More specifically, we assume tumor growth according to the following function (see Benzekry et al., 2014, page 3):

$$G(t) = V_0 \exp(\frac{a}{b}(1 - \exp(-bt))) \tag{22}$$

For the purpose of this work, parameters V_0, a, b are as follows: $V_0 = 50$, $a = 0.72$, $b = 0.18$.

Eq. (2) becomes now:

$$G(k) = V_0\ \exp(\frac{a}{b}(1 - \exp(-b(t(k-1)+1)))) \qquad \forall k > 1 \tag{23}$$

where,

$$t(k) = -\frac{1}{b}\ ln(1 - \frac{b}{a} ln(\frac{S(k)}{V_0})) \tag{24}$$

In Eqs. (23), (24) $t(k)$ denotes the time at which the size of the tumor equals the value $S(k)$ if the tumor is not treated. Put differently, $t(k)$ denotes the time at which treatment at period k sets back the evolution of the tumor size. This value is attained by solving Eq. (22) for t, when fixing $G(t)$ to $S(k)$.

In terms of its mathematical programming properties the modified model classifies to be a MINLP problem. The problem is computer implemented using GAMS and solved using the global optimization software tool BARON (Sahinidis, 1996).

All parameter values remain as in Section 3.1 apart from the initial size of the tumor which is set to $S_0 = 3V_0 = 150$ and the minimum acceptable size of the tumor after treatment which is set to $S_{min} = 60$. These modifications are necessary to avoid mathematical problems because of Eq. (24) (negative t_k values, undefined logarithm operation).

The solution of the problem is depicted in Fig. 6. The value of the objective function assumes its optimal value at a value of 200, which means that the patient is administered a drug dose 20 times within the planing horizon of 52 time periods. The time points at which the drug needs to be administered are shown in Fig. 6; these are the beginning of the periods: 3, 6, 9, 11, 14, 17, 18, 21, 23, 26, 27, 30, 33, 36, 38, 41, 43, 45, 46, 50.

The solution was obtained on a desktop equipped with a Intel Pentium 4.3 GHz CPU and 4 GB of RAM after a processing time of 30350.16 s. The magnitude of the consumed computation time reflects the difficulty of solving MINLPs to optimality and gives rise to the need for research to developing ways to improving computational performance.

5. Discussion and conclusion

Mathematical modeling has long been used in cancer research and has led to invaluable insights into cancer biology (Anderson & Quaranta, 2008; Barbolosi et al., 2016; Strobl et al., 2023). The first mathematical optimization approaches to treatment planning in oncology were developed in the mid-twentieth century. Since then, important discoveries in cancer genetics, evolution and metabolism have been made (Hanahan, 2022; Hanahan & Weinberg, 2000, 2011; Nature, 2020).

Mathematical modeling of treatment has several significant advantages. First, in contrast to an experimental setup, it is low cost (Shi et al., 2014). Second, mathematical models have proven their ability to predict advantageous treatment doses (Moore, 2018). Third, in silico modeling allows for the testing of a considerable number of mathematical hypotheses. Finally, mathematical models challenge

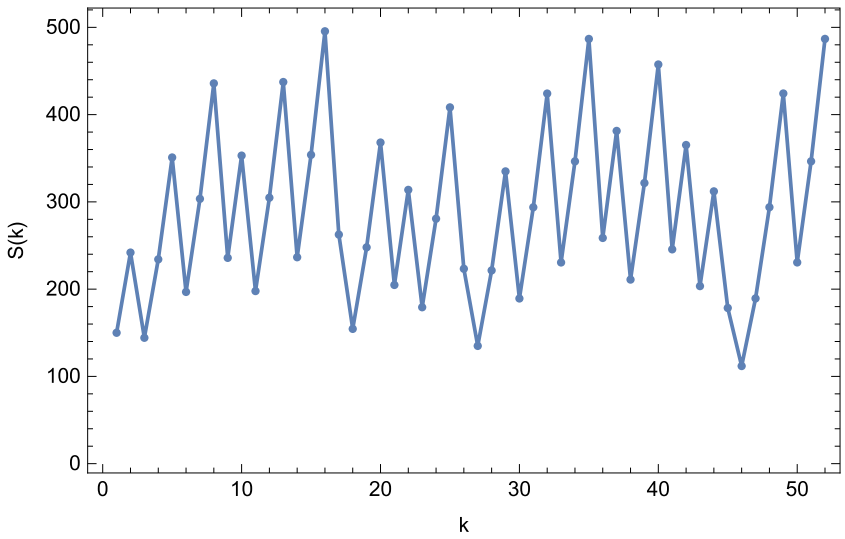

Fig. 6. Optimal solution for the evolution of tumor size $S(k)$ after treatment(s) in the case of Gompertz tumor growth.

empirical results from clinical trials (Altrock et al., 2015) and may lead to further investigation. Nevertheless, important biological phenomena are still largely unaddressed, either due to poor understanding or due to difficult implementation in models. These phenomena include, for instance, metastases and relapse tumors, both of which imply greater innate resistance and usually higher biological aggressiveness.

The MILP and MINLP approaches presented here demonstrate that mathematical programming can be of great value in developing optimal treatment schedules. This approach is natural because dichotomous decisions are common in scheduling algorithms and linear resp. non-linear constraints may capture the underlying problem realistically. Furthermore, these approaches have been described as "flexible" in that previously unprecedented clinically important constraints can be incorporated with relative ease (Harrold & Parker, 2004). The models developed here are only applicable to solid neoplasms with an identifiable tumor size. The latter is, however, not critically limiting as the vast majority of malignant tumors are solid (Siegel et al., 2024). The developed model provides fast optimization which is necessary in routine practice.

Budget constraints have been largely neglected in treatment scheduling models. Treatment costs are, however, not negligible with increasing economic pressure and expensive targeted therapies (Hofmarcher et al., 2020; Tsimberidou et al., 2020). Treatment costs have been included by Bazrafshan and Lotfi in their optimization model, which seeks to maximize the sum of the predicted expected survival time of the patient for each drug that is a candidate for a drug mix to be administered during chemotherapy treatment. The survival time is calculated using statistical methods and subsequently a MILP is formulated to maximize the expected survival time of a drug mix subject to budget and other constraints. The tumor dynamics are not included in their model, which is a key difference from our approach (Bazrafshan & Lotfi, 2016). The approach presented here explicitly considers the cost of each dose to be administered and attempts to minimize the total cost, while taking into account tumor growth dynamics and patient quality of life constraints. Simultaneously addressing therapeutic and economic issues and solving to global optimality is a novel approach.

As previously stated, our mathematical programming model addresses both therapeutic and economic aspects. The therapeutic aspects are unambiguously related to the modeling of tumor growth dynamics. It is assumed that the size of the tumor increases steadily in the absence of drug administration. When a dose is administered, the function that describes tumor growth is set to an earlier time status, indicating a reduction in tumor size as a result of the treatment. The presented optimization approach allows for the assessment of the treatability of the disease. An infeasible solution to the model would indicate that treatment cannot be successful. Additionally, the model may suggest not administering a drug dose at the beginning of a treatment period to avoid overtreatment. Finally, by limiting the tumor size to a predefined upper bound, the patient may be promised a good quality of life.

Although novel, the presented model has some limitations. First, the capabilities of the model are demonstrated by using fictitious values. Patient data is protected by privacy laws, requires ethical approval, and is generally difficult to obtain. Previous research has mainly relied on experimental data, i.e. from cell lines or mice (Murphy et al., 2016). The use of data from case reports is limited as it typically represents a single time point. Bazrafshan and Lotfi (2016) incorporated trial data into their work, but only demographic data, a toxicity score, and dosage levels of a specific drug (Bazrafshan & Lotfi, 2016). Additionally, the issue of drug resistance was not explicitly addressed, but it could be included in the model as a reduction in the drug's ability to reduce tumor size. Lastly, Gompertz tumor growth is used, which is generally well accepted but does not perform well for any type of cancer. Tumor growth varies considerably depending on the model used (Murphy et al., 2016). However, accuracy testing of published cell line data from ten different mass-forming cancers confirms Gompertz growth is reliable (Sarapata & de Pillis, 2014). Selecting the appropriate model is crucial for predicting tumor growth and determining the necessary therapeutic interventions for the disease.

A classification of our approach according to Mathur et al. (2022) is difficult because no assumptions are made, e.g. about the frequency or density of dose administration. The drug is administered according to the result of the optimization process, which does not take into account the heuristic knowledge accumulated from previous research. The closest class of therapy to our approach (according to Mathur et al., 2022) would be "adaptive therapy", i.e. dynamic alteration of doses in response to the tumor evolution. The model presented here aims at control rather than cure. We limit the tumor size which allows for competition between treatment-sensitive and -resistant cells (West et al., 2023).

Current treatment practices, make the appropriate time to initiate treatment controversial. While some have advocated early treatment for smaller tumors (Coldman & Goldie, 1983), others suggest higher doses for larger tumors at the end of the treatment period (Harrold & Parker, 2004). Although larger tumors might become more vulnerable due to constrained nutrient supply, administration at the end of treatment periods is ethically problematic as it implies hitting tumor growth arbitrarily only at a very late stage of disease (Iliadis & Barbolosi, 2000). "Metronomic chemotherapy", i.e. the repeated administration

of low doses to avoid toxicity while keeping the tumor size constantly small (Ledzewicz & Schaettler, 2017), might reduce side effects but does not imply optimal doses or respect budget constraints. This work concludes that it is feasible to keep tumor size constantly within a critical tolerated boundary by computing optimal treatment doses.

Some authors (e.g. De Pillis & Radunskaya, 2001; Ghaffari et al., 2016; Heydarpoor et al., 2020; Sharifi et al., 2019) model interactions with immune cells in order to protect the immune system from the drug effect. Immunotherapies, such as checkpoint inhibitors, are state-of-the-art for many cancers (Mahoney et al., 2015). However, immune cells can be hijacked by cancer to create a tumor-promoting milieu (Vinay et al., 2015). The goal of preserving the immune infiltrate must be viewed with caution and must be modeled accurately. Cancer is heterogeneous and the complexity of tumor evolution highlights the need for dynamic decision making (Strobl et al., 2023). This of course has implications for the modeling efforts. For example, allowing for relaxation and cell recovery during the treatment schedule must take into account that cancer cells also recover during treatment arrests. This makes careful modeling to correctly capture reality very important.

Many approaches to treatment scheduling aim for a complete response, i.e. a tumor reduction to zero with no evidence of residual tumor. Resistance is a phenomenon that makes complete response a rare event. Tumor cells (can) acquire resistance (Murray, 1997) during treatment arrests by inducing sub-clones with different biological behavior (Marusyk et al., 2014; Michor & Beal, 2015; Prager et al., 2019). In addition, resistance is also a matter of statistical chance (Coldman & Murray, 2000) and can be intrinsic, i.e. not acquired, with immediate non-response and treatment failure (Patwardhan et al., 2021). Modeling a therapy-resistant (insensitive) population is an accurate means of depicting cancer biology as the sensitive and the insensitive tumor clones directly compete with each other for nutrients, access to blood flow, defense mechanisms against the host immune response, etc. (Hadjiandreou & Mitsis, 2014). However, as resistance is an inherent and plastic property of cancer, we prefer to use critical tumor size as the primary endpoint.

It becomes apparent that the mathematical modeling effort needs to be increased in order to be able to obtain applicable optimization results. It is imperative to correctly capture the biology of cancer if optimal treatment schedules are to be mathematically derived. Combining model development with synchronous clinical triage could be a step forward (Mathur et al., 2022). On the other hand, complex, multi-parameter models make it difficult to optimize with real-world data because this data is difficult to obtain (Kuznetsov et al., 2021). A therapeutic approach that adapts cancer biology to what is algorithmically possible, is unacceptable in the context of cancer treatment, as it may jeopardize a patient's life.

Novel studies on treatment scheduling will depend on stronger interdisciplinary collaboration (Anderson & Maini, 2018; Balaz et al., 2021; Kuznetsov et al., 2021) to bridge gaps and to validate models with clinical data (Brady & Enderling, 2019; Hadjiandreou & Mitsis, 2014; Meille et al., 2016; Moore, 2018). While clinicians do not understand the mathematical complexity of optimization approaches, modeling experts cannot reliably identify and implement the most important parameters for treatment. The lack of synergy results in a considerable loss of information. In addition, the treatment schedule must obey economical and technical constraints. Appropriate methods have to be developed in order to be able to cope with the complexities that the models may exhibit such as averse mathematical properties, problem size, solution speed, and many others. Thus, future research will have to address the problem of modeling these aspects as accurately as necessary in order to robustly support the decision making process in oncology.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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