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Analyzing the quality robustness of chemotherapy plans with respect to model uncertainties

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ABSTRACT

Mathematical models of chemotherapy planning problems contain various biomedical parameters, whose values are difficult to quantify and thus subject to some uncertainty. This uncertainty propagates into the therapy plans computed on these models, which poses the question of robustness to the expected therapy quality. This work introduces a combined approach for analyzing the quality robustness of plans in terms of dosing levels with respect to model uncertainties in chemotherapy planning. It uses concepts from multi-criteria decision making for studying parameters related to the balancing between the different therapy goals, and concepts from sensitivity analysis for the examination of parameters describing the underlying biomedical processes and their interplay. This approach allows for a profound assessment of a therapy plan, how stable its quality is with respect to parametric changes in the used mathematical model.

1. Introduction

The term chemotherapy refers to the treatment of cancer with cytotoxic anti-cancer drugs and aims for tumor control with acceptable side effects. Cancerous cells have found a way to escape from the mechanisms which usually precisely control cell division and start to reproduce and grow rapidly in an uncontrolled fashion [1]. In such cases, the immune response of the human body, which should usually detect and destroy abnormal cells, does often not succeed in controlling the growing tumor. Anti-cancer drugs that are used for a chemotherapy treatment act by effectively targeting fast-dividing cells such as tumor cells. An important advantage of chemotherapy compared to radiation therapy and surgery is the fact that chemotherapy does not only decrease the tumor size but does also kill cancer cells that have spread from the primary tumor to other parts of the body as metastases [2]. However, apart from cancer cells, also other cells in the human body, which divide rapidly under normal circumstances, are killed by anti-cancer drugs. The cell death of these non-cancerous cells is one of the most important side effects of a chemotherapy treatment.

In common practice, the specification of therapy plans in terms of medication, dose and time schedule happens according to standardized guidelines [3]. This obviously results in a poor adaption of therapy plans to the individual patient case in terms of specific cancer growth behavior or drug efficacy. This clearly leaves scope for improvement, when it comes to the specification of the best possible plan for the considered patient case. As an improvement of common practice, literature lists various optimization approaches based on chemotherapy simulation models, which allow for the computation of an optimal therapy plan for the individual patient [4–10]. Numerical computation happens with certain values for the biomedical parameters included in the mathematical model. However, these biomedical parameters usually originate from numerical fits or are chosen due to biological or medical assumptions and are thus liable to some uncertainty, which propagates into the computed therapy plans. This raises the question of robustness to the expected therapy plan.

This paper analyzes the quality robustness with respect to parameter uncertainties in chemotherapy planning basically in two different ways. It uses concepts from multi-criteria decision making in order to investigate parameters related to the balancing between the different therapy goals and concepts from sensitivity analysis in order to study modeling parameters which describe biomedical processes in the simulation model. As a basis for further analysis this work introduces an exemplary mathematical model for the simulation of a chemotherapy treatment, which allows for the formulation of a chemotherapy planning problem. This optimization problem is solved using numerical computations. A profound analysis of different simulation models and the corresponding planning problems regarding parameter uncertainties is conducted in [11].

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2. The general approach

This section introduces the concepts which allow for an analysis of the quality robustness with respect to model uncertainties in chemotherapy planning. All assumptions on the specific realization of the mathematical model or the precise formulation and structure of the optimization problem are quite general. This fact allows for a wide applicability of the introduced concepts.

2.1. Mathematical modeling

Literature lists several models for simulating a cancer chemotherapy treatment, which rely on (ordinary or partial) differential equations and basically differ in the level of detail [4–10,12,13]. Each model prominently contains the dynamics of cell growth and cell death induced by the administration of cytostatics. Modeling the dynamics of one cell population via ordinary differential equations yields

$$\dot{n}(t) = g(n(t)) - l(d_c(t))n(t), \quad n(0) = n_0, \tag{1}$$

where $n(t)$ is the number of cells at time t and "˙" indicates its time derivative. Furthermore, g is the function describing cell growth and l is the loss function of the cell population, where $l(d_c)$ represents the drug kill rate at plasma drug concentration d_c.

Eq. (1) describes the evolution of one single cell population over time at presence of one specific drug. However, a reasonable mathematical model in chemotherapy planning typically considers the dynamics of at least two different cell populations, normal cells and tumor cells, which can be coupled by including interaction of the different cell populations. Furthermore, the mathematical model might consider the administration of several different drugs. A very general approach for modeling an arbitrary number of cell population dynamics yields

$$\dot{\mathbf{n}}(t) = g(\mathbf{n}(t)) - l(\mathbf{d}_c(t))\mathbf{n}(t) - c(\mathbf{n}(t)), \quad \mathbf{n}(0) = \mathbf{n}_0, \tag{2}$$

where $\mathbf{n}(t) = (n_1(t), \dots, n_m(t))^T$ are the number of cells for m different cells populations, $\mathbf{d}_c(t) = (d_{c_1}(t), \dots, d_{c_e}(t))^T$ are the different plasma drug concentrations when administering e different drugs, and c is the function describing the coupling of the different cell populations.

The plasma drug concentrations $\mathbf{d}_c(t) = (d_{c_1}(t), \dots, d_{c_e}(t))^T$ at time t' depend on the rates of drug administration $\mathbf{d}_a(t) = (d_{a_1}(t), \dots, d_{a_e}(t))^T$ at all $t \in [0, t']$. Based on this assumption, various kinds of drug administration (e.g. intravenous injection/infusion, oral dosing) and different dynamics of plasma drug concentrations can be modeled.

The system (2) can be easily applied to the case of several tumors and normal cell populations as well as the case of additionally modeling the patient's immune response by incorporating the dynamics of immune cells. Furthermore, the choice for a certain growth or loss function can be made individually for every cell population. Equation (2) can thus be considered as a very general and flexible modeling approach which is only based on a few standard assumptions. A specific model will be exemplarily introduced in Section 3.1.

2.2. Plan optimization

In a chemotherapy planning problem, the different anatomic entities affected by a chemotherapy treatment have to be taken into account in combination with the respective goals, i.e. the reduction of tumor cells or the sparing of organs at risk. Aiming for a good therapy plan, one has to balance the tradeoff between the different optimization goals, some of which enter the optimization as constraints, whereas other goals contribute to the objective function. Therefore, the chemotherapy planning problem can be regarded as a multi-criteria optimization problem [14,15].

In order to spare the organs at risk, constraints are included in the optimization problem. On the one hand, the toxic effect of the cytostatics is limited by introducing upper bounds on the instantaneous and cumulative plasma drug concentration [5]

$$\mathbf{d}_c(t) \le \mathbf{d}_{c,\max} \quad \text{for all} \quad t \in [0, T_f], \tag{3}$$

and

$$\int_0^{T_f} \mathbf{d}_c(t)dt \le \mathbf{d}_{c,\mathrm{cum}}, \tag{4}$$

where T_f is the length of the total treatment period.

On the other hand, the number of normal cells n_N is required to be above a certain level during the treatment

$$n_N(t) \ge n_{\min,N} \quad \text{for all} \quad t \in [0, T_f]. \tag{5}$$

Table 1
Typical values for the constraint parameters and their source. D is the unit of plasma drug concentration.

Constraint parameter	Typical value	Unit	Source
$n_{\min,N}$	2.5×10^9	cells	[5]
$d_{c,\max}$	50	D	[5]
$d_{c,\mathrm{cum}}$	4.1×10^3	D	[5]

Table 1 introduces typical values for the constraint parameters.

The chemotherapy planning problem can be summarized as

$$\begin{aligned} \min_{\mathbf{d}_a \ge 0} \quad & J(\mathbf{d}_a) \qquad \text{s.t.} \\ & n_N(t) \ge n_{\min,N} \quad \text{for all} \quad t \in [0, T_f], \\ & \mathbf{d}_c(t) \le \mathbf{d}_{c,\max} \quad \text{for all} \quad t \in [0, T_f], \\ & \int_0^{T_f} \mathbf{d}_c(t)dt \le \mathbf{d}_{c,\mathrm{cum}}, \end{aligned}$$

with $n_N(t)$ fulfilling (2) and an arbitrary objective function J.

Evaluation of the objective function and the constraints for this general type of planning problem requires computation of cell population dynamics and plasma drug concentrations over time. Depending on the specific choice of model this can be done either analytically or numerically by solving (systems of) differential equations with any appropriate numerical scheme. Depending on the realization of (2), this planning problem is a linear, nonlinear, or optimal control problem.

Besides the global optimum, the specific planning problem can feature a number of local optima and finding the global optimum might be too costly. Hence, the optimization algorithm usually computes a local optimum. This raises the question which local optimum one wants to aim at. For acceptability reasons, the optimum which is found by an optimization algorithm should be a local optimum which is close to clinical practice. Therefore, the starting point for the optimization procedure is usually chosen to be consistent with the standardized guidelines that are applied in clinical practice. This approach is assumed to compute a local optimum which shows similarity to these standardized guidelines.

2.3. Quality robustness

The biomedical parameters introduced in a mathematical model are liable to some uncertainty, which propagates into the computed therapy plans. These parameters can be divided into optimization and modeling parameters. The first group balances the tradeoff between the different planning goals. This work mainly concentrates on those parameters introduced as constraints in the planning problem in Eqs. (3)–(5). In order to analyze quality robustness with respect to these optimization parameters, concepts from multi-criteria optimization are used. Furthermore, modeling parameters are parameters that appear in the chemotherapy simulation model and the corresponding robustness of the therapy quality is investigated using concepts from sensitivity analysis.