Optimal control for selected cancer chemotherapy ODE models: A view on the potential of optimal schedules and choice of objective function

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Abstract

In this article, four different mathematical models of chemotherapy from the literature are investigated with respect to optimal control of drug treatment schedules. The various models are based on two different sets of ordinary differential equations and contain either chemotherapy, immunotherapy, anti-angiogenic therapy or combinations of these. Optimal control problem formulations based on these models are proposed, discussed and compared. For different parameter sets, scenarios, and objective functions optimal control problems are solved numerically with Bock’s direct multiple shooting method.

In particular, we show that an optimally controlled therapy can be the reason for the difference between a growing and a totally vanishing tumor in comparison to standard treatment schemes and untreated or wrongly treated tumors. Furthermore, we compare different objective functions. Eventually, we propose an optimization-driven indicator for the potential gain of optimal controls. Based on this indicator, we show that there is a high potential for optimization of chemotherapy schedules, although the currently available models are not yet appropriate for transferring the optimal therapies into medical practice due to patient-, cancer-, and therapy-specific components.

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1. Introduction

While scientific computing has become an indispensable ingredient of research and every-day-practice in robotics and mechanics, chemical engineering, aerospace, transportation, and many other areas, the application of numerical methods to find answers to open questions in medicine is not yet as evolved.

Scientific computing, and in particular modeling, simulation, and optimization of processes, is often regarded as the third pillar of science, complementary to theory and experiment. In medicine however, experiments are not so easily reproducible as in mechanics, and the theoretic interpretation of drug influence is usually not as well understood as control parameters in physical systems.

There are many different levels on which tumor growth and possible control targets can be modeled. Inherently this is a complex multi-scale problem. A mathematical model can be stochastic or deterministic, spatially resolved or not, continuous or agent-based. Also the level of detail may vary. For example, there may be good reasons to include circadian rhythms and the cell cycle, [1]. A comprehensive overview can be found in the highly recommendable survey paper by Jean Clairambault [2].

We are aware of the fact that the influence of drugs is often not fully understood in medicine, and of course highly patient-dependent (e.g., see the parameter sets “human 9”/”human 10” in [3], respectively [4]). Hence it cannot be expected that currently available models of ordinary differential equations are a good match to clinical reality. A patient- and tumor-specific parameter estimation for well-understood mathematical models based on clinical data will hopefully lead the way and might allow application of optimized treatment schedules in the future.

This work is supposed to be another small step in the direction of analysis and understanding of optimal control chemotherapy models. The basic mathematical models that have been proposed in the literature over the last years (e.g., [3,5–11]) should already capture several important dynamic effects of chemotherapy treatments. Having in mind that the gap between simulated and real-world situation will still be large, we focus in this work on general qualitative insight that can be gained by optimization of available mathematical models. Examples for basic questions that are important in this context are

- What similarities and what differences arise for the different mathematical models? We discuss two mathematical models for cancer and cancer chemotherapy. Although they both contain some kind of chemotherapy, they differ in the kind of additional treatments and in type and amount of cell types they
include. For the two models, four parameter sets have been described in the literature. We present optimal control results for all of them (see Section 5), to the best of our knowledge three sets (see Sections 5.2–5.4) were not solved to optimality before.

- How large is the potential for the right timing of drug delivery? In general, the aim of a therapy, no matter what kind, is to minimize the tumor size, i.e., the tumor volume or the amount of tumor cells. To answer this question, we consider also therapies which, with a fixed amount of drugs, maximize the tumor size on a given time horizon. The result, a therapy which makes the tumor grow as big as possible under these constraints, can be considered the worst treatment one could apply. We compare these results to standard treatments or untreated tumors as well as the optimal control for a minimal tumor, the best treatment. It turns out that there are scenarios where the differences between worst and best treatments are small, but we also demonstrate scenarios where the same amount of drugs leads to a growing tumor on the one hand and a total disappearance on the other hand (see Figs. 2, 5, 7 and 9).

- How does the choice of the objective function influence the optimal control strategies? The formulation of a reasonable objective function is crucial for the optimal treatment schedules. We formulate new optimal control problems with non-standard objective functions for models for which such problems have not been published yet, see Sections 5.1–5.4.

- What role do local optima play? As the computational effort do perform a rigorous global optimization for all of the scenarios we considered is beyond the scope of this paper, we concentrated on some case studies with multiple initializations. Whereas for most scenarios the local optima seem to be the unique global ones, also multiple local optima were observed, compare Fig. 6 left and right. This effect is closely linked to the choice of the objective function. Including a penalization of tumor volume integrated over time in the objective function seems to favor multiple local optima.

Our approach to address these questions by numerical optimization is based on Bock's direct multiple shooting approach to solve optimal control problems. The underlying first **discretize**, then **optimize** concept allows for an efficient and fast solution of a multitude of different control problems.

This article is structured as follows. In the next two sections, we review and present the different models (Section 2) and control problems (Section 3) that have been investigated. Section 4 explains the direct multiple shooting techniques we used to solve the arising optimal control problems. Numerical results can be found in Section 5, where also some interpretations and comparisons between the different scenarios are discussed. We conclude with a summary of our results and an outlook on future work.

2. Cancer chemotherapy models

Two different models of cancer chemotherapy with a total of four different parameter sets have been investigated. The models consist of sets of ordinary differential equations and each feature a particular kind of medical treatment. In this section, an overview over the models is given and differences between them are highlighted. We also present their scientific context and give a survey of adjacent approaches we did not consider in detail. In general, we stick to the notation of the original articles if this does not conflict with the overall notation in this article.

2.1. d’Onofrio et al.

The model by d’Onofrio et al. [7] is based on the work by Hahnfeldt et al. [5] and in particular on a modification of the Hahnfeldt model by d’Onofrio and Gandolfi [12,13].

In [5], a model with two states and one control is proposed. The states are the volume of the tumor \( x_0 \) on the one hand and the volume of blood vessels in the neighborhood of the tumor \( x_1 \) on the other hand. This choice of state variables is due to the fact that the treatment strategy includes an anti-angiogenic therapy \( u_0 \) in this model, a concept introduced in the 1970s by Folkman [14]. As a tumor needs proliferating blood vessels to survive and to grow, the basic idea is to administer a drug that suppresses angiogenesis, the process of blood vessel formation from existing vessels. While the cytostatic agents applied in classical chemotherapy address the proliferation of tumor cells directly, anti-angiogenic drugs inhibit the stimulation of endothelial cells necessary for neo-vascularization.

The tumor volume equation contains a Gompertz-term

\[
-\xi x_0(t) \log \left( \frac{x_0(t)}{x_1(t)} \right)
\]

in which the limit has been replaced by the endothelial volume. **Gompertz growth** beside **logistic growth** is one of the two types of growth chosen in all models that have been investigated. Inserting the blood vessel volume as **carrying capacity** instead of a fixed value reflects that the growth of the tumor is limited by the vasculature volume. In [7] a classical chemotherapy treatment has been added, so that a combination therapy is possible and thus the model contains a second control \( u_1 \) representing a cytostatic drug:

\[
-\phi x_0(t) u_1(t).
\]

The equation for the blood vessel volume is more complex. It contains a term that represents the spontaneous loss of vasculature and one that represents the stimulation of **neo-vascularization** by the tumor (e.g., by the cytokine VEGF, **vascular endothelial growth factor**),

\[
-\mu x_1(t) + b x_0(t).
\]

The third term,

\[
-d x_0(t) x_1(t),
\]

reflects the effect of endogenous inhibition of angiogenesis. Finally, with

\[
-\gamma u_0(t) x_1(t) - \eta x_1(t) u_1(t),
\]

the response to the drugs is modeled. In contrast to [5], drug concentration is identified with dosage here. Hence, there is no concentration equation.

In d’Onofrio et al., the total amount of applied drugs is limited. To be able to treat this constraint in our optimization framework, we add two auxiliary states which sum up the amounts of given drugs:

\[
x_2(t) = u_0(t),
\]

\[
x_3(t) = u_1(t).
\]

Thus, the complete model is described by the system

\[
\dot{x}_0(t) = -\xi x_0(t) \ln \left( \frac{x_0(t)}{x_1(t)} \right) - \phi x_0(t) u_1(t),
\]

\[
\dot{x}_1(t) = b x_0(t) - \mu x_1(t) - d x_0(t) x_1(t)
- \gamma u_0(t) x_1(t) - \eta x_1(t) u_1(t),
\]

\[
\dot{x}_2(t) = u_0(t),
\]

\[
\dot{x}_3(t) = u_1(t)
\]

for \( t \in [t_0, t_f] \).

The parameters \( b, d, \mu, \xi, \gamma \) in [5] have been derived by about 1,000,000 runs of a Monte-Carlo algorithm based on data from...
experiments with mice that have been injected Lewis lung carcinoma cells. Note that the parameters and bounds ϕ, η, uimax, tlimax, ymax, zmax (compare also Section 3) are neither taken from [5] nor based on experimental data. These values have been used for numerical experiments only. All parameters are listed in Table 2 in the Appendix.

2.2. de Pillis et al. [3]

The model by de Pillis et al. [3] consists of six states, three controls and 29 parameters in three parameter sets. The work is based on previous work by the same or some of the authors [8,15,16]. As a major difference to the model above, it contains a combination of chemotherapy and immunotherapy. The first state is again the tumor population x0, but now measured in absolute cell count. Instead of the blood vessel volume, this model features three types of immune cell populations, all measured in absolute cell count. NK cells x1 - unspecific immune cells which are also present in a healthy body (‘natural killer’ cells) –, CD8+ T cells x2 – tumor-specific cytotoxic T-cells –, and circulating lymphocyte pool x3.

The fifth and the sixth state represent the chemotherapeutic drug concentration x4, respectively Interleukin-2 (IL-2) concentration x5. IL-2, which is one of the two immunotherapeutic controls, is a cytokine that stimulates CD8+ T activation cells and is used ‘to boost immune system function’ [3]. In addition, there is a control for a classic cytostatic drug u0 and one for a tumor infiltrating lymphocyte injection (TIL) u2. The latter means an injection of CD8+ T cells that have been stimulated against tumor cells outside the body.

The model features a logistic growth term in the tumor equation, here

$$\dot{x}_0(t) = (1 - b x_0(t))$$  (9)

NK cells x1 and CD8+ T cells x2 both kill tumor cells. The interaction between NK and tumor cells is modeled with a bilinear term, while the effect of CD8+ T cells introduces a quotient also used in other equations:

$$-\kappa x_1(t) x_0(t) - D x_0(t)$$  (10)

with

$$D = -\frac{(x_1(t)/x_0(t))^d}{s + (x_1(t)/x_0(t))^d}$$  (11)

Both terms are taken from de Pillis et al. [15]. The last summand in the tumor equation represents the effect of chemotherapy on the tumor where a saturation term $1 - e^{-ax(t)}$ is used. This term multiplied by different parameters is also contained in the immune cell equations:

- tumor x0: $-K_1 (1 - e^{-ax(t)}) x_0(t)$,  
- NK cells x1: $-K_1 (1 - e^{-ax(t)}) x_1(t)$,  
- CD8+ T cells x2: $-K_2 (1 - e^{-ax(t)}) x_2(t)$,  
- circ. lymphocytes x3: $-K_3 (1 - e^{-ax(t)}) x_3(t)$.

The equation for NK cells contains a recruitment term of circulating lymphocytes $e x_4(t)$ and an exponential decay term $-f x_3(t)$ representing the limited natural lifespan of each cell. Additionally, there is a term for recruitment of NK cells,

$$g \frac{x_0(t) ^2}{h + x_0(t)} x_1(t)$$  (13)

and one for the inactivation of NK cells after interaction with tumor cells

$$-p x_1(t) x_0(t).$$  (14)

Matching the assumption that there are no CD8+ T cells present in the absence of a tumor, there is no growth term but an exponential decay $-m x_2$ in the corresponding equation. However, there are several recruitment terms. One for the recruitment by tumor-CD8+ T cell interaction, one for the recruitment by tumor cells killed by NK cells (tumor debris), and one for the recruitment by encounters between tumor cells and circulating lymphocytes:

$$\frac{j}{k + D x_0(t) ^3} x_2(t) + r x_1(t) x_0(t) + r x_1(t) x_0(t).$$  (15)

Similar to the inactivation of NK cells there is a summand $-q x_3 x_2$ for the inactivation of CD8+ T cells after interacting with tumor cells. In addition, there is an inactivation term $-v x_1 x_2^2$ describing the regulation and suppression of CD8+ T cell activity at high cell levels. In the CD8+ T cell equation there is also a Michaelis-Menten-term for the influence of IL-2 and a simple input of the TIL control,

$$\frac{p x_2(t) x_4(t)}{g + x_2(t)} + u_2(t).$$  (16)

Circulating lymphocytes are expected to have a constant source and again a limited natural lifespan which leads – together with chemotherapeutic influence – to

$$\dot{x}_3(t) = \alpha - \beta x_3(t) - K_3 (1 - e^{-ax(t)}) x_3(t).$$  (17)

The last two equations – the ones for chemo- and immunotherapeutic drug concentration – are of simple exponential decay type with the corresponding controls as inputs:

$$\dot{x}_4(t) = -\gamma x_4(t) + u_0(t),$$  (18a)

$$\dot{x}_5(t) = -\mu x_5(t) + u_1(t).$$  (18b)

Thus, the model is described by the following system of ODEs. In favor of readability we omit the time dependence of states and controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>ϕ</td>
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</tr>
<tr>
<td>γ</td>
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</tr>
<tr>
<td>b</td>
<td>5.85</td>
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<tr>
<td>d</td>
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<tr>
<td>μ</td>
<td>0.02</td>
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<td>η</td>
<td>0.084</td>
</tr>
<tr>
<td>γmax</td>
<td>300</td>
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<td>tlimax</td>
<td>75</td>
</tr>
<tr>
<td>ymax</td>
<td>2/10</td>
</tr>
<tr>
<td>zmax</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Table 2: Parameters for the model by d’Onofrio et al. in [7].
\[ x_0 = ax_0(1 - bx_0) - cnx_0 - Dx_0 - K_T(1 - e^{-x_0})x_0, \]  
\[ \dot{x}_1 = \epsilon x_3 - f x_1 + g \frac{x_2}{h + x_0} x_1 - px_4 x_0 - K_N(1 - e^{-x_4})x_1, \]  
\[ \dot{x}_2 = -n x_2 + j \frac{D^2 x_2}{k + D^2 x_2} x_2 - qx_3 x_0 + (r x_1 + r_2 x_1) x_0 - qx_1 x_2 \]  
\[ - K_N(1 - e^{-x_4})x_2 + \frac{p x_3 x_0}{g_T + x_2} + u_2, \]  
\[ \dot{x}_3 = 2 - bx_3 - K_C(1 - e^{-x_3})x_3, \]  
\[ \dot{x}_4 = -\gamma x_4 + u_4, \]  
\[ \dot{x}_5 = -\mu x_5 + u_1 \]  
for \( t \in [t_0, t_f] \) and the shortcut \( D = \prod_{i=1}^{l} \frac{[x_i]}{[x_i]_0} \).

Three parameter sets from [3], mouse, human 9, and human 10, can be found in Table 3. As the name suggests, the mouse parameter set contains numerical values derived from murine experimental data. In fact, the parameters come from different papers treating different types of cancer and different types of mice. For example the tumor growth parameter \( a \) has been fitted to data from a paper by Diefenbach et al. [17]. In that article, EL4 thymoma, RMA lymphoma and B16-BL6 melanoma have been implanted into B6 - Rag\(^{-}\) mice. On the other hand, e.g., the death rate of NK cells \( I j \) is derived from Kuznetsov et al. [18], where a mathematical model is used to describe the kinetics of growth and regression of a BCl1 lymphoma in BABL/c mice. For the parameters \( r_2 \) and \( v \) no source is provided.

For the human parameter sets, the authors refer to an article by Dudley et al. [4]. This publication contains real proband data of 13 melanoma patients. The data of the ones numbered 9 and 10 have been used in [3] for fitting seven of the parameters. Again, for \( r_2 \) and \( v \) no source is provided. Actually, there are eight more references for the human parameter set, e.g., the two murine papers from the mouse parameter set. Another source [19] refers among others to Kuznetsov et al. Note that this means that about one third of the human parameters comes from murine experiments.

In [19] it is stated that the value of a certain parameter in their model \( \ldots \) varies greatly from patient to patient and cancer to cancer. So this model may generally not be adequate for generating useful treatment schedules – in particular for humans since there is only little human data used and the values may highly depend on the patient and the type of cancer. But it still may be useful for making general qualitative statements.

In summary, the heterogeneity of model parameters makes an applicability of numerical results obtained by us or other authors in clinical practice improbable.

2.3. Other approaches

Finally we give a short survey on models we did not consider in detail. There are lots of different mathematical modeling approaches in the cancer chemotherapy context, so we restrict ourselves to some that are conceptually close to the ones presented above.

2.3.1. Ergun et al.

The model in Ergun et al. [6] is – similar to the one presented in Section 2.1 – a modification of the Hahnfeldt-model [5]. In this article, a combination of radiotherapy and anti-angiogenic therapy is investigated. The major difference in the model is the decoupling of the vasculature equation from tumor volume by simply replacing tumor volume by vasculature volume. For the radiotherapy an LQ model is used. The authors report on several optimal control results. There is also a detailed analysis of the combination therapy for a slightly modified version of the model by Ledzewicz et al. [20].

2.3.2. Chareyron and Alamir

The work by Chareyron and Alamir [10] is based on the work of de Pillis et al. [8,15,16,3]. The authors use the model presented in Section 2.2 to apply non-linear model predictive control (NMPC) techniques.

However, only the chemotherapy control is considered for the NMPC scheme while both the immunotherapy and the TIL are derived by indirect methods independently from the chemotherapy. The chemotherapy itself is fixed to a finite set of values (0%, 20%, 40%, 60%, 80%, and 100% of maximum). This means that effectively chemotherapy is not a continuous control but a mixed–integer one. Since NMPC techniques are not part of our work, we did not further pursue the approach of Chareyron and Alamir.

2.3.3. de Pillis et al. [8]

The model of de Pillis et al. [8] is one of the ‘ancestors’ of de Pillis et al. [3]. It only includes a cytostatic chemotherapy control. An optimal control problem is formulated (minimize tumor size at end time subject to the number of ‘normal’ cells is above some lower bound) and optimal control results are presented. With one control and the constraint on normal cells, surprising results are not to be expected and indeed the optimal schedules show a bang–bang–structure.

We wanted to verify these results in our optimization framework, but some of the model’s parameters are only given in relations or intervals (e.g., ‘0 ≤ s ≤ 0.5’, ‘\( t_3 ≥ 0 \leq t_4 ≤ t_2 \)’). Since an exact parameter set was not available, this approach was not subject of further investigations.

2.3.4. de Pillis et al. [9]

In analogy to de Pillis et al. [3] essentially derived from previous work by the authors, de Pillis et al. [9] can be considered a descendant model of de Pillis et al. [3]. It contains the same controls and states as the one discussed in Section 2.2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mouse</th>
<th>Human 9</th>
<th>Human 10</th>
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<td>4.31 $10^{-3}$</td>
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<tr>
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</tr>
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<td>c</td>
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<td>d</td>
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<td>2.34</td>
<td>1.88</td>
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<td>l</td>
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<td>1.81</td>
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<td>2.08 $10^{-7}$</td>
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<td>4.12 $10^{-2}$</td>
<td>4.12 $10^{-2}$</td>
</tr>
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<td>g</td>
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</tr>
<tr>
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<td>2.02 $10^{-7}$</td>
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<tr>
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<td>1.42 $10^{-9}$</td>
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<tr>
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<tr>
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<td>2.00 $10^{-1}$</td>
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<td>( a_1 )</td>
<td>1.00 $10^{-1}$</td>
<td>1.00 $10^{-1}$</td>
<td>1.00 $10^{-1}$</td>
</tr>
</tbody>
</table>
In contrast to its predecessor, the latter article focuses on optimal control results. There are some modifications of the equations, but overall they are very similar. Most of the parameters have been adapted either from the mouse or the human 9/human 10 sets. At least some of the changes in the model equations compared to [3] may be due to the tractability with an indirect optimal control approach. As an example, the saturation term for the influence of chemotherapy \( (1 - e^{-x_0(t)}) \) has been replaced by the drug concentration \( x_0 \), significantly facilitating the analytical work of the first optimize, then discretize approach chosen by the authors.

We could not reproduce the numerical results on the basis of the equations and the parameter set given in the article. However, with a modified tumor growth parameter \( 4.0 \text{ instead of } 2.0 \cdot 10^{-3} \) we succeeded to reproduce some optimal controls result of a first scenario. For a second scenario, we could mostly reproduce the result choosing again a different tumor growth parameter \( 2.0 \). As it is not clear where the differences originate from, especially as they do not seem to derive from a single wrong parameter value, we eventually decided not to further investigate this model. Details on our simulation and optimization studies can be found in [21].

2.3.5. Isaeva and Osipov

The article by Isaeva and Osipov [11] is similar to de Pillis et al. [3] as it also takes classical chemotherapy and two types of immunotherapy into account, but the model also shows some differences. For example, they use Gompertz growth instead of logistic growth and just one state for immune cell populations. Because of the structural similarities to de Pillis et al. [3], we decided to investigate only one of the two similar approaches.

3. Chemotherapy control problems

Our goal is to investigate properties of optimal solutions based on the ODE models in Section 2. This includes the definition of an objective function, initial values, as well as constraints the trajectories have to fulfill.

d’Onofrio et al. formulated an optimal control problem for the model. The objective function supposed to be minimized is

\[
x_0(t_f) + z \int_{t_0}^{t_f} u_0(t)^2 \, dt,
\]

while the end time \( t_f \) is free and \( z \) is small. Apparently a value of \( z = 0.005 \) has been used in [7] to identify the correct control switching structure, whereas a value \( z = 0 \) has been used for the final calculation of the objective value. In [3] no control problem was specified, whereas in [9] a weighted sum was used. In our study we use the weighted sum

\[
p_0 \cdot x_0(t_f) + \int_{t_0}^{t_f} p_1 \cdot x_0(t)^2 dt + \sum_{i=0}^{n-1} \int_{t_0}^{t_i} p_{i+2} \cdot u_i(t) \, dt
\]

with a \( L^1 \) penalization of the positive controls. For \( z = 0 \) the Objective (20) is a special case of (21). We will compare the influence of different objective functions in Section 5, in particular,

\[
p_0 = 1, \quad p_1 = 10^{-6}, \quad p_2 = 10^{-2} \quad \text{(07)}
\]

with \( p_3 \) defined of \( p_4 = 0 \) in all cases. We will later identify these parameter sets with an objective function, e.g., refer in short to (O1) as the objective function (21) with values for \( p_0, p_1, p_2 \) defined by (01). The objective functions which correspond to maximization – (O2), (O4) and (O6) – have been used with total drug amount and (where applicable) terminal time fixed to the result of the corresponding minimization (see also Section 5).

The trajectories are constrained in the following way. For all control problems we have the inequalities

\[
0 \leq u_i(t) \leq u_i^{\text{max}}, \quad 0 \leq x_i(t).
\]

For the control problems based on the model of d’Onofrio et al.,

\[
u_i^{\text{max}} = u_{\text{max}}, \quad u_i^{\text{max}} = v_{\text{max}} \quad \text{(23)}
\]

and we furthermore consider a maximal dose over the whole time horizon in the form

\[
x_i(t) \leq y_{\text{max}}, \quad x_i(t) \leq z_{\text{max}}
\]

with the parameters \( u_{\text{max}}, v_{\text{max}}, y_{\text{max}}, z_{\text{max}} \) from [7] (see Section 2). We will consider different scenarios in Section 5. In our context a scenario consists of a set of initial values and values for the upper bounds in (22) and (24). For the control problems solved in Section 5.1 we fix \( x_0(t) = x_0(0) = 0 \text{ and } u_{\text{max}} = 75, v_{\text{max}} = 300 \text{ in all cases } \text{ and define}

\[
x_0(0) = 12000, \quad x_1(0) = 15000, \quad v_{\text{max}} = 1, \quad z_{\text{max}} = 2, \quad (51)
\]

\[
x_0(0) = 12000, \quad x_1(0) = 15000, \quad v_{\text{max}} = 2, \quad z_{\text{max}} = 10, \quad (52)
\]

\[
x_0(0) = 14000, \quad x_1(0) = 5000, \quad v_{\text{max}} = 1, \quad z_{\text{max}} = 2, \quad (53)
\]

\[
x_0(0) = 14000, \quad x_1(0) = 5000, \quad v_{\text{max}} = 2, \quad z_{\text{max}} = 10. \quad (54)
\]

For the solutions of the control problems presented in Sections 5.2–5.4 the upper bounds are given by \( u_{\text{max}}^1 = 1, u_{\text{max}}^2 = 5 \cdot 10^6 \text{, and } u_{\text{max}}^3 = 0 \). Note that for the tumor infiltrating lymphocytes (TIL) control \( u_{\text{IL}}(\cdot) \) no bounds were given in the original paper, therefore we fixed \( u_{\text{IL}}(\cdot) \) to zero for this study. The value of the fixed end time \( t_f \) varies in our scenarios and can be seen in the plots. The resulting scenarios are defined by different initial values listed in Table 1.

4. Numerical approach

We want to investigate the potential for optimal control in chemotherapy scheduling and the influence of the choice of objective function on the resulting tumor dynamics. To this end we will have to solve a number of optimal control problems of the type

\[
\min_{x \in \mathbb{R}^n} \int_{t_0}^{t_f} E(x(t), u(t), p) \, dt \quad \text{(25a)}
\]

subject to

\[
\dot{x}(t) = f(t, x(t), u(t), p), \quad \text{(25b)}
\]

\[
x(t_0) = x_0, \quad 0 = r_s(x(t_0), x(t_1), p), \quad \text{(25c)}
\]

\[
0 \leq r_i(x(t_0), x(t_1), p), \quad \text{(25d)}
\]

\[
0 \leq g(t, x(t), u(t), p) \quad \text{(25f)}
\]

for \( t \in [t_0, t_f] \) almost everywhere, with differential states \( x : [t_0, t_f] \rightarrow \mathbb{R}^n \), control functions \( u : [t_0, t_f] \rightarrow \mathbb{R}^m \), fixed model parameters \( p \in \mathbb{R}^p \), and an objective function of Bolza type, all functions assumed to be sufficiently smooth. Eq. (25b) represents the ODE model with a right hand side \( f(\cdot) \) depending on time \( t \in [t_0, t_f] \) and fixed initial values \( x(t_0), (25c) \). In (25d) and (25e) equality, respectively inequality boundary conditions are summarized, and (25f) contains state and path constraints.

There are different approaches to solve problem (25). An overview is given, e.g., in [22]. In the articles mentioned in Section 2,
mostly indirect methods have been used, when optimal control was considered. These methods build on the necessary conditions of optimality in function space, Pontryagin's maximum principle, and solve a resulting boundary value problem.

As we solve a larger number of control problems that have varying parameter sets and hence different solution structures, we decided to use a direct method for optimal control. Our choice is Bock's direct multiple shooting method [23]. This first discretize, then optimize approach transforms the control problem into a non-linear program (NLP) that is solved by tailored NLP solvers. Details and references can be found, e.g., in [24]. Finally, optimal solutions in a finite-dimensional approximation of the control space $L^\infty([t_0,t_f])$ are computed that depend on the chosen parametrization of the control functions and the choice of the multiple shooting time grid. Often applicability of drug scheduling severely limits the feasible choices of control functions and time resolution that are implementable in clinical practice (see also discussion in [25,26]). This issue can be addressed in a straightforward fashion in a multiple shooting setting, e.g., by piecewise constant control functions on a multiple shooting time grid corresponding to the minimum realizable time resolution.

References to related direct approaches and numerical solvers can be found, e.g., in [27–30]. A popular alternative is the usage of collocation, e.g., by combining problem-dependent modeling with AMPL [31] and a non-linear solver such as Ipopt [32].

In the sake of comparability of results, we solved all problems on a fixed control discretization grid with 100 or 200 intervals (model 1), respectively 40 or 120 intervals (model 2 – corresponding to a discretization of one interval per day). If one is interested in analyzing certain optimization instances in more depth, one might also consider an optimization of switching times and evaluation of second order sufficient conditions, [33], and analytical investigations, such as the order of singular arcs or explicit (feedback) expressions for singular arcs. This is beyond the scope of this paper, whenever we use ‘optimal solution’ in the following this will refer to KKT points of the discretized setting.

In direct methods, the differential equations for the adjoint variables are not explicitly derived and solved. However, in direct multiple shooting the Lagrange multipliers of the matching conditions approximate the adjoints pointwise, e.g., [24]. We use this property to approximate selected switching functions for illustrative purposes, compare Fig. 1.

5. Numerical results

In this section, we present numerical results for the control problems that have been introduced in Sections 2 and 3 obtained by applying Bock’s direct multiple shooting algorithm from Section 4. This section is split into a subsection for each model and parameter set we investigated.

5.1. d’Onofrio et al.

We tried to reproduce the results from the paper [7] first. Optimal solutions for each scenario are depicted in Figs. 2 left and Fig. 3. One can conclude from the plots that the results could be essentially reproduced on the whole, especially the control structure is the same. However, the end times in our results differ to some extent (0.13% or less) from those in d’Onofrio et al. – e.g., 6.653 vs. 6.648 (0.08%) in Scenario (S1). The differences between the tumor volumes are much smaller (in each case less than 0.01%), between vasculature volumes a little higher (1.47% or less): 7019.29 vs. 7019.09 for tumors and 7294.18 vs. 7365.33 for vasculature in Scenario (S1) for example, which corresponds to 0.003%, respectively 0.97%. The differences in the other scenarios are in a similar range and might be due to differences in the discretization. All solutions have been computed with 100 multiple shooting nodes in our case.

5.2. ‘Mouse’, de Pillis et al. [3]

In this section, we present optimal control results for the mouse parameter set, which is one of three parameter sets in de Pillis et al. [3].

For all three parameter sets we consider a fixed time horizon of either $t_f = 40$ or $t_f = 120$ days, as in [3]. In [21] also scenarios with free end time can be found. As stated before, we did not consider tumor infiltrating lymphocytes (TIL), as more modeling work is necessary to come up with realistic bounds here. For the mouse model which contains no IL-2 therapy, this means we consider a classical cyostatic chemo-monotherapy. As in de Pillis et al. we choose $\mu_{\text{max}} = 1$ for numerical experiments.

There are seven different initial value sets in [3], see Table 1. Note that only (T1) has been used for the ‘mouse’ model.

For the verification of the models’ implementations in our optimization framework we ran several simulations. The results of [3] for the mouse set could be reproduced, for chemotherapy as well as without any therapy, [21]. Optimal control results of the mouse model are shown in Figs. 5 and 6.

For $t_f = 40$ and the weighted sum objective (O3) we fixed the total amount of drugs applied to the values of the optimal solution, changed the sign of $p_0$ and $p_1$. This corresponds to a maximization of the tumor over the whole time horizon and at the end time in the given relative weighting under the constraint of a given total amount of drugs. We also compare the minimization result to a ‘standard treatment’ as applied by de Pillis et al. in Fig. 5. The potential benefit of optimal control is much higher in this scenario compared to the results in Section 5.1. While the maximized tumor at the end time is at about $2 \cdot 10^7$ cells, the minimal value is only
about 10^5 cells. This corresponds to 0.5% of the maximal value. The tumor size for the standard treatment is even higher than the maximized one, but again the total amount of drugs given is significantly lower here.

Fig. 1. Approximated switching functions based on Lagrange multipliers of multiple shooting matching conditions for d’Onofrio et al. and de Pillis et al. The upper row shows approximated switching functions, the lower row the corresponding controls. The approximated switching function fit to the control structure in general. Left: d’Onofrio et al., Scenario (S2), Objective (O1); the (analytic) switching functions for this model are \( S_0 = \frac{k_2}{C_0} x_1 \) and \( S_1 = \frac{k_3}{C_0} \frac{x_1}{x_0} \). Middle: de Pillis et al., mouse, Scenario (T1), Objective (O3); the (analytic) switching function for this model is \( S_0 = \frac{k_4}{C_0} p_2 \). Right: de Pillis et al., human 9, Scenario (T4), Objective (O5); first switching function is the same as for the mouse model, second switching function is \( S_1 = \frac{k_5}{C_0} p_3 \) (note that \( p_3 = 0 \) for all objective functions).

Fig. 2. Optimization results for d’Onofrio et al. Upper row: tumor (dark) and vasculature (bright) volume. Lower row: anti-angiogenic (bright, \( u_0 \)) and chemotherapy (dark, \( u_1 \)) controls. All results for Scenario (S1) for different objective functions. Left: minimization of tumor volume at end time, objective (O1). Middle: maximization of tumor volume at end time, (O2) (200 nodes). Right: no therapy (controls both at lower bound). The end value of the tumor population under maximization (with the same \( t_f \)) is about 10% higher than the minimized value, which is the maximal difference due to bad timing of drug admission.

Fig. 3. Trajectories as in Fig. 2. Optimization results for d’Onofrio et al., Scenarios (S2)-(S4) from left to right, all with Objective (O1), minimization of tumor at end time. All solutions are structurally similar.
Considering the high potential for correct timing of drug administration in this case, the question which objective function should be used becomes more important. In Fig. 6 left and right one observes that under the weighted sum Objective (O3) tumor cells are on a lower level in general whereas the end level is orders of magnitude lower with (O5) (middle plot).

Fig. 6 right shows an alternative local minimum to Fig. 6 left. While one solution applies chemotherapy early, hence reducing the tumor volume to a low value in the first half of the time horizon and letting it grow in the second half, the solution on the left allows for a higher value in the first part to reduce it in the second. Both strategies are related to the Gompertz growth of the tumor – if the tumor volume is high, the growth rate is considerably lower. Therefore a strategy distributing the chemotherapy over time would lead to a (non-optimal) higher average growth rate.

5.3. ‘Human 9’, de Pillis et al. [3]

The human 9 model is the second parameter set from de Pillis et al. [3]. We picked out two scenarios to verify our implementation, see [21]. The maximal dose of chemotherapy has been changed to 5.0, but there is no reason given for the higher dose. The immunotherapeutic pulses are said to be at $5.0 \times 10^6$ in one experiment and at $5.0 \times 10^5$ in another one. Maybe the latter is a typing error, as the upper bound of both IL-2 concentration plots is $5.0 \times 10^5$, which makes sense for a dosage of $5.0 \times 10^6$ with the corresponding Eq. (19f). Eventually we decided to adopt $1.0$, respectively $5.0 \times 10^6$ as upper bounds for the chemotherapeutic, respectively immunotherapeutic control. For chemotherapy, the drug amount applied in our solutions is notably higher than in the standard treatments investigated in [3], so it might be reasonable to consider a smaller upper bound. Additionally, note that the human parameter sets are based on mostly murine data. Some remarks on the immunotherapy level will follow below.

First, we have a look at the comparison between maximized and minimized tumor populations, see Fig. 7. The procedure was the same as in the mouse Section. We fixed the drug amount to the minimization value and changed the sign of the corresponding objective parameters, i.e., $p_0 = -1.0$ for the objective with a penalty on $u_0$. The difference is even higher here with a maximal tumor of almost $10^9$ and a minimum one with less than 1, which is less than 0.000001‰. Again the standard treatment is worse than the max-

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**Fig. 4.** Trajectories as in Fig. 3, now with Objective (O7) which includes impact of the $L^2$ norm. Although $x_0(t_f)$ is of comparable size, controls, end time $t_f$ and trajectories differ considerably compared to the Objective in Fig. 3.

**Fig. 5.** Optimization results for de Pillis et al. [3], mouse, Scenario (T1). Upper row: tumor population. Lower row: chemotherapy control $u_0$. Left: minimization of weighted Objective (O3). Middle: maximization of weighted Objective (O4). Right: standard therapy (example from [3], only simulation with given control – no optimization). The end value of the tumor population under minimization is about two orders of magnitude below the maximized (worst) one. Note that the given drug amount in the standard treatment is significantly lower, so that the result is even worse than for maximization.
imization, however, the drug amount for the maximization was about 250% of the standard treatment.

Fig. 8 contains representative optimization results for different initial values and objective functions. While Fig. 8 center features a full dose chemotherapy, in Fig. 8 left there is a full dose part at the beginning followed by a short singular arc leading into a zero part. A similar solution occurs in some more scenarios of human\footnote{data not shown} and a free end time scenario (\( t_f / C_25 \)) looks very similar, too. Fig. 8 right shows the problem of a delayed therapy – if the objective is to minimize tumor volume at the end time and the time horizon is large, the result may be long time periods (65 days Fig. 8 right) with a high tumor volume before therapy starts.

Except for one scenario, immunotherapy does not play a significant role in the treatment. Often it is at such a low levels (e.g., \( 10^7 / C_0 \)) with an upper bound of \( 5 \cdot 10^6 \)) that it might not be considered therapeutic at all. Note also that none of the objective functions contains a penalty on the immunotherapeutic control \( u_1 \), so immunotherapy might disappear completely with a penalty. However, there are also mathematical reasons for this low influence of immunotherapy. The control \( u_1 \) enters only in Eq. (19f), which reads

\[
\dot{x}_5 = -\mu_5 x_5 + u_1. \tag{26}
\]

With a full dose of \( u_1(t) = 5.0 \cdot 10^6 \) and \( \mu_1 = 10 \), \( x_5(t) \) should be at about \( 5.0 \cdot 10^5 \) close to a steady state. The state \( x_5 \) itself only plays a role in Eq. (19c), where the corresponding terms are

\[
\dot{x}_2 = \cdots + \frac{p_1}{g_7 + x_5} x_2 + \cdots \tag{27}
\]

with \( p_1 = 1.25 \cdot 10^{-1} \) and \( g_7 = 2 \cdot 10^7 \). For a \( x_2 \) which is most of the time at a level of at least \( 10^5 \), we have

\[
\frac{p_1 x_2 x_5}{g_7 + x_5} \approx \frac{10^{-1} \cdot 10^5}{10^7} \approx \frac{10^5}{10^7} \approx 10^2 \tag{28}
\]

and the influence of a \( 10^2 \) term on a \( 10^5 \) state indeed should be low. We conclude that additional work on the modeling of immunotherapy influences is necessary.

5.4. ‘Human 10’, de Pillis et al.\footnote{3} 

Like human 9, the human 10 parameter set shares the equations with the mouse model. Considering reproduction of the results in
the de Pillis et al. article, the first two scenarios without any treatment could be verified. In other scenarios, we observed some differences or they could not be reproduced at all. The differences seem to arise from the influence of IL-2, compare [21] for a detailed discussion.

In Figs. 9–11 we show optimal controls for different initial values from Table 1, end times $t_f$, and objective functions. We again compare maximization and minimization and a standard treatment in Fig. 9.

A selection of optimal solutions is presented in Figs. 10 and 11. Immunotherapy is again on a very low levels as expected. Many solutions for chemotherapy show a singular arc (Fig. 10 center and Fig. 11 throughout). Note that these solutions have been computed for the weighted sum objective. Only Fig. 11 right contains a singular solution with minimization of the tumor at the end time with a penalty on chemotherapy. Further results, including free end time scenarios and the calculation of sparse controls, can be found in [21].

6. Conclusion and outlook

We presented optimal control results for four different cancer chemotherapy models based on two sets of ordinary differential equations. Not all of the previous simulation results in the literature could be verified, e.g., de Pillis et al. [9], see [21] for a detailed discussion.

Our optimal control solutions of the d’Onofrio model quantitatively match the ones in their article [7]. But we also study additional optimization scenarios. The three different models based on de Pillis et al. [3] have been solved to optimality for the first time to the best of our knowledge.

Optimality refers here to the solution with a direct approach to optimal control. We recommend to investigate specific problems and instances also analytically in more depth in the future. For example, Eq. (19) lead to a vanishing of the controls in the second derivative of the switching function, hence the order of a singular
arc is greater than one. It should be further investigated if this leads to chattering junctions between bang–bang and singular arcs, as stated by McDanell and Powers, compare also [20]. In order to estimate the potential for the correct timing of chemotherapies we proposed to compare the results of a minimization to the ones of a maximization with the same total amount of drugs. The ratio between these two values is an indicator for the potential gain. For the d’Onofrio model in Section 5.1 this potential is rather low. A comparison to a maximization of the tumor at the end time with fixed drug amounts showed that tumor size is only about 15% larger in the worst treatment scenario, which can nevertheless be clinically significant. The optimal treatment yields a tumor 40% smaller than in the case without any treatment.

For the control problems based on the de Pillis model, Sections 5.2–5.4, the difference between minimal and maximal objective is several orders of magnitude, indicating a high potential for optimal timing. In this context the question of how to define the objective function naturally becomes more important. We considered different terms in a weighted sum objective function: tumor population at the end time and integrated over the whole time horizon, as well as possible penalizations of the controls. A high dependency of the results on the weights could be shown. For certain scenarios a control strategy leads to a complete removal of the tumor at the end time at the price of a higher average value, whereas an optimal control taking the $L^2$ norm into account generally does not lead to a removal. From the point of view of potential clinical applications, a tradeoff between minimal end size of the tumor and minimal average value (e.g., minimizing tumor invasiveness and destruction of surrounding tissue) should be important and will depend on the type of tumor, its location in the body and its absolute initial size.

The influence of the immunotherapy in the de Pillis models was surprisingly low. As the results are not fully convincing from a practical point of view in our opinion, further efforts should be devoted to a more detailed modeling of the interplay between immune system and cancer growth and its quantitative understanding. Generally, only few data are available for parameter sets, particularly in the case of human models, and obviously there is a significant variation from cancer type to cancer type and even from patient to patient. Therefore, we are aware that our current solutions are of no practical relevance for clinical applications, but they provide a proof of principles of what could be possible. It is obvious that an intense interdisciplinary cooperation between mathematicians, biologists, and physicians will be necessary to bridge this gap and to bring optimal control techniques into medical practice.

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**Fig. 10.** de Pillis et al. [3], human 10. Left: optimal control result for Scenario (T7) with end time $t_f = 40$ days under minimization of tumor at the end time (O1). Center: optimal control result for Scenario (T5) with end time $t_f = 120$ days under the weighted sum Objective (O3). Right: Simulation of Scenario (T6) with standard therapy including immunotherapy and TIL (given control, no optimization) – the results from [3] could not be reproduced.

**Fig. 11.** de Pillis et al. [3], human 10, different optimal control results for Scenario (T2). Upper row shows states, lower row controls. Left: weighted sum Objective (O3) with end time $t_f = 40$ days. Center: same Objective (O3) with end time $t_f = 120$ days. Right: minimization of tumor at end time with penalty on chemotherapy (O5), end time at 120 days. In contrast to Fig. 10 left, all solutions are dominated by singular arcs.
References


