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Optimal Control for a Mathematical Model of Glioma Treatment with Oncolytic Therapy and TNF-α Inhibitors

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Abstract A mathematical model for combination therapy of glioma with oncolytic therapy and TNF-α inhibitors is analyzed as an optimal control problem. In the objective, a weighted average between the tumor volume and the total amount of viruses given is minimized. It is shown that optimal controls representing the virus administration are generically of the bang-bang type, i.e., the virus should be applied at maximal allowed dose with possible rest periods. On the other hand, optimal controls representing the dosage of TNF-α inhibitors follow a continuous regimen of concatenations between pieces that lie on the boundary and in the interior of the control set.

Keywords Optimal control · Oncolytic therapy · Singular control · High order necessary conditions for optimality

Mathematics Subject Classification 49K15 · 93C15

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1 Introduction

Cancer treatment by means of oncolytic viruses is an active area of medical research with several clinical trials and many different types of viruses being tested [1–3]. Oncolytic viruses are genetically altered replication-competent viruses which infect and reproduce in cancer cells, but in principle do not harm normal cells. When an infected cell dies, many newly formed viruses are released and spread infecting neighboring tumor cells. Ideally, this process eventually will eradicate the tumor. However, and although based on promising assumptions, there exist serious obstacles to such treatment approaches with the main one that the innate immune system recognizes the infected cells and destroys them before the viruses get a chance to multiply [4]. Experiments for glioblastoma xenografts have shown that CD 163+ macrophages inhibited the viruses [5] and pointed to the inhibition of these macrophages as a possibility to enhance the effectiveness of the therapy. A system of PDEs to model these processes has been formulated and studied by Friedman et al. [6]. More recently, Auffinger et al. [7] have shown that inhibition of TNF-α significantly enhances virus replication and the efficacy of the overall treatment . In [8], a mathematical model that captured the interactions between uninfected tumor cells, infected tumor cells, the viruses, macrophages and TNF-α they produce was proposed. This model, which is based on the work of Friedman et al. [6], was formulated as a population-type ODE model, and the efficacy of treatments that combine viral injections with TNF-α inhibitors was analyzed relative to the objective of minimizing the tumor radius.

In [9], an analysis of the dynamical systems properties of the system under constant infusions of viruses and TNF-α inhibitors is given. The model turns out to exhibit a rich geometric structure including interesting behaviors like transcritical bifurcations, Hopf bifurcations and period orbits. Other ODE-type mathematical models for glioma and its treatment were also formulated and analyzed as a dynamical system in [10–14] for different modeling approaches and different combination treatments. Generally, it is evident from the past literature on the topic that the tools of dynamical systems theory can be highly successful in providing insights into the structure and the properties of mathematical models for various cancers and their therapies (e.g., [15,16]). However, this analysis requires to assume that the treatment protocols represented by the controls are constant, which in practice does not have to be the case. Introduction of time-varying controls opens a wide range of possibilities for their choices and leads to natural questions about the search of the optimal protocols for these treatments.

Optimal control theory has a long history as a tool in the search for optimal cancer treatments starting in the early 1970s and 1980s (e.g., [17–20]). In recent years, more advanced tools of geometric optimal control have been employed to analyze the models for cancer treatments in the case of both mono- and combination therapies (e.g., [21]). This included models for cell-cycle-specific chemotherapy (e.g., [22,23]), therapy with antiangiogenic inhibitors alone [24,25] as well as in combination with chemotherapy [26] and radiotherapy [27]. Some models including tumor–immune interactions and immunotherapy of cancer have been analyzed as optimal control problems as well (e.g.,[28,29]), but the treatment discussed here, a combination therapy for glioma including the viral injection with TNF-α inhibitors, has not been the subject of such studies so far.

In this paper, the model for combination therapy formulated in [8] is analyzed as an optimal control problem. The maximum principle, a classical tool providing the necessary conditions of optimality, is employed to determine candidates for optimal controls. Then the analysis is pursued further with the application of Lie algebraic methods involving Lie bracket computations. High-order conditions for optimality, like the Legendre–Clebsch conditions, are applied to determine the local optimality of singular controls. The problem is analyzed in the case of monotherapy as well as in combination with the administration of TNF-α inhibitors. It is shown that generically singular controls are not optimal for the virus application and that this control follows a bang-bang structure of full-dose administrations and rest periods.

2 A Mathematical Model for the Treatment of Glioma with Virotherapy and TNF-α Inhibitors

The mathematical model below for glioma treatment with virotherapy and TNF-α inhibitors has been introduced in [8]. The system is five-dimensional with the following states for the system: the density of (uninfected) cancer stem cells, x, the density of infected cancer cells, y, the density of the virus, v, the density of the macrophages, M, and the concentration of TNF-α, T. The model contains two controls that describe treatment actions. The first one, u_1, represents the amount of virus that is injected, and the second one, u_2, stands for the concentration of TNF-α inhibitors. The dynamics of the model is expressed mathematically in the following system of ODEs:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \alpha x - \beta x v - \delta_x x, \tag{1}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \beta x v - \xi y \frac{T}{K+T} - \delta_y y, \tag{2}$$

$$\frac{\mathrm{d}M}{\mathrm{d}t} = A + s y M - \delta_M M, \tag{3}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \frac{\eta}{1+u_2} M - \omega y \frac{T}{K+T} - \delta_T T, \tag{4}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = b\delta_y y - \rho x v - \delta_v v + u_1. \tag{5}$$

All the densities and concentrations are in units of $\frac{\mathrm{g}}{\mathrm{cm}^3}$. Equation (1) describes the proliferation of uninfected tumor cells with α representing their proliferation rate and δ_x their death rate. The dynamics only depends on the net effect $\alpha - \delta_x$, but we retain this more typical form of writing the parameters. The interaction term $\beta x v$ describes the infection of the tumor cells x by the virus with virus-dependent infection rate βv. Second Eq. (2) models the time evolution of the infected cancer cells y. Here $\beta x v$ simply is the influx of infected cancer cells from Eq. (1) and δ_y is the natural death rate. The term $\xi y \frac{T}{K+T}$ represents the necrotic death of infected cells caused by TNF-α, T. This effect is modeled by a saturating Michaelis–Menten-type function with carrying capacity K. When a cell infected with virus particles y dies due to bursting, a number of new viruses are released. This number, the burst size, is denoted by b.

Table 1 States of the model

States	Description	Dimension
x	Density of uninfected cancer stem cells	$\frac{\text{g}}{\text{cm}^3}$
y	Density of infected cancer stem cells	$\frac{\text{g}}{\text{cm}^3}$
M	Density of macrophages	$\frac{\text{g}}{\text{cm}^3}$
T	Density of TNF-α	$\frac{\text{g}}{\text{cm}^3}$
v	Density of virus	$\frac{\text{g}}{\text{cm}^3}$
z	$z = (x, y, M, T, v)^\dagger$	

If infected tumor cells die by necrosis, this number is small compared with b and in this paper we set this effect to zero. Thus, the term $b\delta_y y$ in Eq. (5) models the new supply of viruses released upon death of infected cancer cells. In that equation, the term $\rho x v$ models the loss of virus through absorption by uninfected tumor cells. Lastly, $\delta_v v$ represents natural degradation and clearance of the virus. The variable u_1 is a control in the system, and it represents injection of new viruses. Equation (3) describes the evolution of macrophages with A representing a constant source and δ_M the death rate of macrophages under healthy normal conditions. The term syM accounts for the tumorigenic response of the immune system invoked by the infected cells y. Equation (4) models the evolution of TNF-α. The first term describes the production of TNF-α by macrophages, while the remaining two terms are loss by absorption within y cells and loss by natural degradation. In the first term, an injection u_2 of TNF-α inhibitors represents a second control of the system. Table 1 summarizes the notation for the states, and Table 2 gives the parameters and specific values that will be used in numerical calculations below.

3 Formulation of the Optimal Control Problem

We consider the following optimal control problem:

[OC] Minimize the functional

$$J = J(u) = \sigma_1 x(t_f) + \sigma_2 y(t_f) + \int_0^{t_f} (\theta x(s) + \gamma_1 u_1(s) + \gamma_2 u_2(s))\, \mathrm{d}s \qquad (6)$$

subject to dynamics (1)–(5) and initial conditions $x(0) = x_0$, $y(0) = y_0$, $M(0) = M_0$, $T(0) = T_0$ and $v(0) = v_0$ over all Lebesgue measurable functions $u_1 : [0, t_f] \to [0, u_1^{\max}]$ and $u_2 : [0, t_f] \to [0, u_2^{\max}]$. The terminal time t_f can be fixed or free; the weights σ_1 and σ_2 are nonnegative, while θ, γ_1 and γ_2 are positive.

The objective is a weighted average of the tumor volume at the end of therapy, the uninfected tumor cells over the therapy interval and the total amounts of drugs given. Generally, minimizing this quantity generates a compromise between two competing

Table 2 Parameters of the model and numerical values used in computations

Parameter	Description	Dimension	Num. value(s)
α	Proliferation rate of uninfected tumor cells	1/day	0.2
β	Infection rate of tumor cells by viruses	$\frac{\text{cm}^3}{\text{g}\cdot\text{day}}$	2×10^4
ρ	Rate of loss of viruses during infection	$\frac{\text{cm}^3}{\text{g}\cdot\text{day}}$	4×10^{-2}
ξ	Effectiveness of the inhibitory action of TNF-α	1/day	0.4
δ_y	Infected tumor cell death rate	1/day	0.2
η	TNF-α production rate	1/day	2.86×10^{-3}
δ_T	TNF-α cell degradation rate	1/day	55.45
δ_M	Macrophages death rate	1/day	0.015
b	Burst size of infected cells during apoptosis	$\times 10^{-6}$	50–150
K	Carrying capacity of the TNF-α	$\frac{\text{g}}{\text{cm}^3}$	5×10^{-7}
ω	Degradation of TNF-α due to its action on infected cells	1/day	4×10^{-10}
δ_v	Virus lysis rate	1/day	0.5
A	Constant source of macrophages	$\frac{\text{g}}{\text{cm}^3\cdot\text{day}}$	0.9×10^{-6}
s	Stimulation rate of macrophages by infected cells without stimulus	$\frac{\text{cm}^3}{\text{g}\cdot\text{day}}$	0.15
δ_x	Death rate of uninfected cancer cells	1/day	0.1
u_1	Infusion of the virus	$\frac{g}{\text{cm}^3\cdot\text{day}} \times 10^{-6}$	0–2.5
u_2	Infusion of a TNF-α inhibitor		

aims of treatment. On the one hand, the aim is to reduce the tumor size which represents the severity of the disease and this requires to give as much drugs as possible. On the other hand, side effects need to be limited and so the aim also is to give as little drugs as possible. Clearly, the balance will be determined by the weights σ_1, $\sigma_2\theta$, γ_1 and γ_2 in the objective, and generally, these coefficients are variables of choice which often need to be selected carefully to obtain a meaningful behavior.

We would like to point out some specific features of the chosen functional. Firstly, we use the L_1-norm on the controls to measure the side effects of treatment. This term is in direct relation to the total doses given and as such has a meaningful pharmacological and biologically relevant interpretation. Mathematically, it would be easier to deal with L_2-type objectives in the control, but the interpretation of such terms is questionable. Secondly, in the integral term we include the uninfected stem cells x, but do not incorporate the infected cancer cells y. The aim of the type of treatment considered here is precisely to infect the cancer cells, i.e., to raise y and in this way generate more viruses which then attack the tumor. Thus, it is not desired to limit y during treatment. On the other hand, and for simple reasons of caution, it is also not a desired objective to put as high as possible a virus load into the system. For this reason, we included the infected tumor cells at the terminal time, $y(t_f)$, in the penalty term to keep this

number small toward the end of therapy. If the viral load at the terminal time is of no concern, we take $\sigma_2 = 0$.

We denote the state of the system by $z = (x, y, M, T, v)^\dagger$ and rewrite the dynamics in the form

$$\dot{z} = f(z) + u_1 g_1(z) + \frac{u_2}{1+u_2} g_2(z), \tag{7}$$

where

$$f(z) = \begin{bmatrix} \alpha x - \beta x v - \delta_x x \\ \beta x v - \xi y \frac{T}{K+T} - \delta_y y \\ A + s y M - \delta_M M \\ \eta M - \omega y \frac{T}{K+T} - \delta_T T \\ b\delta_y y - \rho x v - \delta_v v \end{bmatrix}, \quad g_1(z) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \quad \text{and} \quad g_2(z) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ -\eta M \\ 0 \end{bmatrix}. \tag{8}$$

The vector field f, called the *drift*, describes the evolution of the system when no drugs are given ($u_1 \equiv u_2 \equiv 0$), while the vector fields g_1 and g_2, the *control vector fields*, in combination with the control terms describe the effects of oncolytic therapy and injection of TNF-α inhibitors, respectively. We note that the control vector field g_1 is constant. This considerably simplifies the required Lie algebraic computations and enables a theoretical analysis.

4 Analysis of the Problem for Oncolytic Monotherapy

In this section, we consider the single-input problem when only oncolytic therapy is applied. We set $u_2 \equiv 0$ and label the control u_1 as u. Similarly, we write $g = g_1$ and $\gamma = \gamma_1$ and the system becomes control-affine:

$$\dot{z} = f(z) + u g(z). \tag{9}$$

The optimal control problem thus has the following form:

[V] Minimize the functional

$$J = J(u) = \sigma_1 x(t_f) + \sigma_2 y(t_f) + \int_0^{t_f} (\theta x(s) + \gamma u(s))\, \mathrm{d}s \tag{10}$$

subject to dynamics (9) and initial conditions $x(0) = x_0$, $y(0) = y_0$, $M(0) = M_0$, $T(0) = T_0$ and $v(0) = v_0$ over all Lebesgue measurable functions $u : [0, t_f] \to [0, u^{\max}]$.

4.1 Necessary Conditions for Optimality

First-order necessary conditions for optimality of a control u_* are given by the *Pontryagin's maximum principle* [30] (also see [31–33] for some more recent references). Define the Hamiltonian function $H : \mathbb{R} \times (\mathbb{R}^5)^* \times \mathbb{R}^5 \times \mathbb{R} \to \mathbb{R}$ as

$$H(\lambda_0, \lambda, x, u) = \lambda_0(\theta x + \gamma u) + \langle \lambda, f(z) + ug(z) \rangle, \tag{11}$$

with $\langle \lambda, v \rangle = \lambda v$ denoting the inner product of a row vector λ with a column vector v. If u_* is an optimal control and z_* denotes the corresponding trajectory, then there exist a constant $\lambda_0 \geq 0$ and a covector $\lambda : [0, t_f] \to (\mathbb{R}^5)^*$ which satisfy the adjoint equation

$$\dot{\lambda} = -\lambda_0(\theta, 0, 0, 0, 0) - \lambda(Df(z_*) + uDg(z_*)) \tag{12}$$

with terminal condition $\lambda(t_f) = (\sigma_1, \sigma_2, 0, 0, 0)$ such that H is minimized almost everywhere on $[0, t_f]$ by u_* along $(\lambda(t), z_*(t))$, i.e.,

$$H(\lambda_0, \lambda(t), z_*(t), u_*(t)) = \min_{0 \leq v \leq u_{max}} H(\lambda_0, \lambda(t), z_*(t), v). \tag{13}$$

Furthermore, the Hamiltonian is constant along $(\lambda(t), z_*(t), u_*(t))$ and this constant is zero if the terminal time is free.

In coordinates, the adjoint equations read

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial H}{\partial x} = -\lambda_0\theta - \lambda_1(\alpha - \beta v - \delta_x) - (\lambda_2\beta - \lambda_5\rho)v, \\
\dot{\lambda}_2 &= -\frac{\partial H}{\partial y} = (\lambda_2\xi + \lambda_4\omega)\frac{T}{K+T} - \lambda_3 sM + (\lambda_2 - \lambda_5 b)\delta_y, \\
\dot{\lambda}_3 &= -\frac{\partial H}{\partial M} = \lambda_3(\delta_M - sy) - \lambda_4\eta, \\
\dot{\lambda}_4 &= -\frac{\partial H}{\partial T} = (\lambda_2\xi + \lambda_4\omega)\frac{yK}{(K+T)^2} + \lambda_4\delta_T, \\
\dot{\lambda}_5 &= -\frac{\partial H}{\partial v} = (\lambda_1 - \lambda_2)\beta x + \lambda_5(\rho x + \delta_v),
\end{aligned}$$

and all the states are evaluated along the optimal trajectory z_*.

Controlled trajectories (z, u) for which there exist multipliers λ_0 and λ such that the conditions of the maximum principle are satisfied are called *extremals*, and the triples $(x, u, (\lambda_0, \lambda))$ including the multipliers are called *extremal lifts* (to the cotangent bundle). If $\lambda_0 > 0$, then the extremal lift is called *normal*, while it is called abnormal if $\lambda_0 = 0$. It is easy to see that extremals for problem [V] are normal: If $\lambda_0 = 0$, then the adjoint Eq. (12) is a time-varying homogeneous linear differential equation with terminal condition $\lambda(t_f) = 0$ and thus $\lambda(t) \equiv 0$ contradicting the nontriviality of the multipliers. Without loss of generality we therefore normalize $\lambda_0 = 1$.

Optimal controls are determined by the minimization property on the Hamiltonian function. For problem [V] this minimization problem is linear in u and, defining the *switching function* $\Phi : [0, t_f] \to \mathbb{R}$ as

$$\Phi(t) = \gamma + \langle \lambda(t), g(z(t)) \rangle = \gamma + \lambda_5(t), \tag{14}$$

it follows that

$$u_*(t) = \begin{cases} u^{\max}, & \text{if } \Phi(t) < 0, \\ 0, & \text{if } \Phi(t) > 0, \end{cases} \tag{15}$$

while the control is not determined through the minimization property if $\Phi(t) = 0$. This leads to the notion of bang-bang controls (controls which switch at isolated zeroes of the switching function) and singular controls which arise when the switching function is identically zero over a nonempty open interval I.

4.2 Singular Controls

In this section, we will analyze further the optimality of the singular controls for problem [V]. If an optimal control u_* is singular on a nonempty open interval I, then the switching function Φ and all its derivatives vanish on I. In particular, by Eq. (14) we have that

$$\lambda_5(t) \equiv -\gamma = \text{const.} \tag{16}$$

Furthermore, since the Hamiltonian H is constant over $[0, t_f]$, say $H \equiv \nu$, along a singular arc it follows that

$$\langle \lambda(t),\, f(z(t)) \rangle \equiv \nu - \theta x(t). \tag{17}$$

It is clear that we need the derivatives of the switching function in order to compute singular controls. The following result provides an efficient formalism for this.

Proposition 4.1 *Let k be a differentiable vector field and $\varphi(t) = \langle \lambda(t), k(z(t)) \rangle$, where z is a solution of the dynamics and λ is a solution of the corresponding adjoint equation. Setting $e_1 = (1, 0, \ldots, 0)$, the derivative of φ is given by*

$$\dot{\varphi}(t) = -\theta \, \langle e_1, k(z(t)) \rangle + \langle \lambda(t), [f + ug, k](z(t)) \rangle \tag{18}$$

with

$$[h, k](z) = Dk(z)h(z) - Dh(z)k(z)$$

denoting the Lie bracket of two differentiable vector fields h and k.

Proof This is a direct verification: From (12) we have that $\dot{\lambda} = -\theta e_1 - \lambda(Df(z) + uDg(z))$ and thus

$$\begin{aligned} \dot{\varphi} &= \langle \dot{\lambda}, k(z) \rangle + \langle \lambda, Dk(z)\dot{z} \rangle \\ &= -\theta \langle e_1, k(z) \rangle - \langle \lambda(Df(z) + uDg(z)), k(z) \rangle + \langle \lambda, Dk(z)(f(z) + ug(z)) \rangle \\ &= -\theta \langle e_1, k(z) \rangle + \langle \lambda, Dk(z)f(z) - Df(z)k(z) \rangle + u \langle \lambda, Dk(z)g(z) - Dg(z)k(z) \rangle \\ &= -\theta \langle e_1, k(z) \rangle + \langle \lambda, [f, k](z) \rangle + u \langle \lambda, [g, k](z) \rangle \end{aligned}$$

verifying Eq. (18). □

We apply this proposition to compute the derivatives of the switching function. Since $\langle e_1, g\rangle \equiv 0$, the first derivative is given by

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](z(t))\rangle\,. \tag{19}$$

Furthermore, since $g(z) = (0, 0, 0, 0, 1)^\dagger$, it follows for any differentiable vector field k that $[g, k](z) = Dk(z)g(z) = \frac{\partial k}{\partial v}(z)$ and thus

$$[f, g](z) = -\frac{\partial f}{\partial v}(z) = (\beta x, -\beta x, 0, 0, \rho x + \delta_v)^\dagger\,. \tag{20}$$

Since $[f, g]$ does not depend on v, it immediately also follows that $[g, [f, g]] \equiv 0$. This implies that the control u does not appear in the second derivative of the switching function and singular controls are of intrinsic order $k > 1$. A singular control u is said to be of intrinsic order k if the first $2k - 1$ derivatives of the switching function do not depend on u, but u appears linearly in the $2k$th derivative (e.g., see [33, Definition 2.8.6]). Since $\Phi(t) = \frac{\partial H}{\partial u}(z(t))$, these conditions can be expressed in the compact form (e.g., see [34])

$$\begin{aligned}
&\frac{\partial}{\partial u}\frac{d^j}{\mathrm{d}t^j}\frac{\partial H}{\partial u}(z(t)) \equiv 0 \quad \text{for } j = 1, \ldots, 2k-1,\\
&\frac{\partial}{\partial u}\frac{d^{2k}}{\mathrm{d}t^{2k}}\frac{\partial H}{\partial u}(z(t)) \neq 0 \quad \text{for all } t \in I.
\end{aligned}$$

In fact, we shall show below that singular controls are of intrinsic order $k > 2$. Essentially, this imposes too many restrictions on singular controls so that they generically do not exist for problem [V]. This requires to compute a large number of derivatives of the switching function and associated Lie brackets. We list these results below, but refer the reader to [35] for the details.

We apply Proposition 4.1 to compute the higher derivatives of the switching function. Using the notation $\mathrm{ad}\, f(g) = [f, g]$ to denote higher-order Lie brackets, the second and third derivatives of the switching function are given by

$$\begin{aligned}
\ddot{\Phi}(t) &= -\theta\langle e_1, [f, g](z(t))\rangle + \langle \lambda(t), [f, [f, g]](z(t))\rangle\\
&= -\theta\beta x(t) + \left\langle \lambda(t), \mathrm{ad}^2 f(g)(z(t))\right\rangle
\end{aligned} \tag{21}$$

$$\begin{aligned}
\Phi^{(3)}(t) &= -\theta\beta\dot{x}(t) - \theta\langle e_1, [f, [f, g]](z(t))\rangle + \langle \lambda(t), \mathrm{ad}^3 f(g)(z(t))\rangle\\
&= -\theta\beta x(t)(\alpha - \delta_x - \beta v(t) + \rho x(t) + \delta_v) + \langle \lambda(t), \mathrm{ad}^3 f(g)(z(t))\rangle.
\end{aligned} \tag{22}$$

Here we already used that $[g, [f, g]] \equiv 0$ which implies that also the Lie brackets $[f, [g, [f, g]]]$, $[g, [g, [f, g]]]$ and $[g, [f, [f, g]]]$ vanish identically. We note that

$$[f,[f,g]](z)=\begin{pmatrix}\beta x(\rho x+\delta_v)\\ -\beta x\left(\alpha-\delta_x+\frac{\xi T}{K+T}+\delta_y+\rho x+\delta_v\right)\\ sM\beta x\\ -\frac{\omega T}{K+T}\beta x\\ \rho x(\alpha-\delta_x)+b\delta_y\beta x+(\rho x+\delta_v)^2\end{pmatrix} \tag{23}$$

and $\mathrm{ad}^3 f(g)(z)$ is given by

$$-\beta x\begin{pmatrix}x\rho\left(\beta v-2(\alpha-\delta_x)\right)-b\delta_y\beta x-(\rho x+\delta_v)^2\\ \left(\frac{\xi T}{K+T}+\delta_y\right)\left(2(\alpha-\delta_x)-\beta v+\frac{\xi T}{K+T}+\delta_y+\rho x+\delta_v\right)\\ +(\alpha-\delta_x)(\alpha-\delta_x-\beta v+3\rho x+\delta_v)\\ -\beta x(\rho v-b\delta_y)+\frac{\xi K}{(K+T)^2}(M\eta-T\delta_T)+(\rho x+\delta_v)^2\\ -s\left(M\left(2(\alpha-\delta_x)-\beta v+\frac{\xi T}{K+T}+\delta_y+\rho x+\delta_v\right)+A\right)\\ \frac{\omega}{K+T}\left(\frac{K\eta M}{K+T}+T\left(2(\alpha-\delta_x)-\beta v+\frac{\xi T-K\delta_T}{K+T}+\delta_y+\rho x+\delta_v+\delta_T\right)\right)+\eta Ms\\ \\ -\frac{1}{\beta}(\rho x+\delta_v)\left(\rho(3(\alpha-\delta_x)-\beta v)-2b\delta_y\beta\right)-\frac{1}{\beta x}(\rho x+\delta_v)^3\\ -b\delta_y\big(2(\alpha-\delta_x)-\beta v+\frac{\xi T}{K+T}+\delta_y\big)-\frac{\rho}{\beta}(\alpha-\delta_x)(\alpha-\delta_x-\beta v)\end{pmatrix}. \tag{24}$$

Differentiating once more, we get for the fourth derivative of the switching function that

$$\begin{aligned}\Phi^{(4)}(t)=&\frac{d}{dt}\left(-\theta\beta x(t)(\alpha-\delta_x-\beta v(t)+\rho x(t)+\delta_v)\right)\\ &-\theta\langle e_1,\mathrm{ad}^3 f(g)(z(t))+\Big\langle\lambda(t),[f+ug,\mathrm{ad}^3 f(g)](z(t))\Big\rangle.\end{aligned} \tag{25}$$

Proposition 4.2 *The Lie bracket* $[g,ad^3 f(g)]$ *is a linear combination of the brackets* $[f,g]$ *and* $[f,[f,g]]$*:*

$$[g,ad^3 f(g](z)=\beta\delta_v[f,g](z)-\beta[f,[f,g]](z). \tag{26}$$

Proof We have that

$$[g,ad_f^3(g)](z)=\frac{\partial}{\partial v}\mathrm{ad}^3 f(g)(z)=\begin{pmatrix}-\beta^2x^2\rho\\ \beta^2x\left(\frac{\xi T}{K+T}+\delta_y+\alpha-\delta_x+\rho x\right)\\ -\beta^2xsM\\ \beta^2x\frac{\omega T}{K+T}\\ -\beta x\left(\rho(\rho x+\delta_v)+b\delta_y\beta+\rho(\alpha-\delta_x)\right)\end{pmatrix}.$$

Comparing this relation with Eqs. (20) and (23) the result follows. □

Corollary 4.1 *Singular controls for problem* [V] *are of order greater than* 2.

Proof The coefficient at the control u in Eq. (25) is given by

$$\begin{aligned}\frac{\partial}{\partial u}\frac{d^4}{dt^4}\frac{\partial H}{\partial u}(z(t)) &= \frac{\partial}{\partial u}\Phi^{(4)} = \theta\beta^2 x(t) + \langle\lambda(t), [g, ad_f^3(g)](z(t))\rangle \\ &= \theta\beta^2 x(t) + \langle\lambda(t), \beta\delta_v[f,g](z(t0)\rangle - \langle\lambda(t), \beta[f,[f,g]](z(t))\rangle \\ &= \theta\beta^2 x(t) - \beta(\theta\beta x(t)) \equiv 0,\end{aligned}$$

where we have used that $\dot{\Phi}(t) = \langle\lambda(t), [f,g](z)\rangle \equiv 0$ and $\ddot{\Phi}(t) \equiv 0$. The latter, by means of Eq. (21), is equivalent to

$$\langle\lambda(t), [f,[f,g]](z(t) = \theta\beta x(t). \tag{27}$$

This proves the result. □

Theorem 4.1 *For parameter values in an open and dense subset of the parameter space, there do not exist singular controls for problem* [V].

Proof Summarizing our computations, if a control u is singular on an open interval I, then the following 6 equations must be satisfied on I:

$$\langle\lambda(t), f(z(t))\rangle = \nu - \theta x(t), \tag{28}$$
$$\langle\lambda(t), g(z(t))\rangle = -\gamma, \tag{29}$$
$$\langle\lambda(t), [f,g](z(t))\rangle = 0, \tag{30}$$
$$\langle\lambda(t), [f,[f,g]](z(t))\rangle = \theta\beta x(t), \tag{31}$$
$$\langle\lambda(t), \mathrm{ad}^3 f(g)(z(t))\rangle = \theta\beta x(t)(\alpha - \delta_x - \beta v(t) + \rho x(t) + \delta_v), \tag{32}$$
$$\langle\lambda(t), \mathrm{ad}^4 f(g)(z(t))\rangle = \zeta(z(t)). \tag{33}$$

Here ν denotes the constant value of the Hamiltonian function and the function ζ is determined by Eq. (25). The second equation determines the multiplier $\lambda_5 = -\gamma \neq 0$. The fact that this multiplier is constant allows us to rewrite the remaining five equations as a system of homogeneous equations of the form $\langle\lambda(t), W_i(z(t))\rangle \equiv 0$, where the W_i, $i = 1, \ldots, 5$, are smooth vector fields. For example, if we define $W_1 = f + \frac{\nu-\theta x}{\gamma} g$, then we have that

$$\begin{aligned}\langle\lambda(t), W_1(z(t))\rangle &= \langle\lambda(t), f(z(t))\rangle + \frac{\nu - \theta x(t)}{\gamma}\langle\lambda(t), g(z(t))\rangle \\ &= \nu - \theta x(t) + \frac{\nu - \theta x(t)}{\gamma}(-\gamma) \equiv 0.\end{aligned}$$

For $W_2 = [f,g](z)$ this directly follows from Eq. (30). Similarly, Eq. (31) implies that

$$\left\langle\lambda(t), [f,[f,g]](z(t)) + \frac{\theta\beta x(t)}{\gamma} g(z(t))\right\rangle \equiv 0 \tag{34}$$

and we could take W_3 as the vector field $[f, f, g]] + \frac{\theta\beta x}{\gamma} g$. However, it is of advantage to still subtract an appropriate multiple of $[f, g]$ from this vector field to simplify the relations. In principle, it is straightforward to define these vector fields W_3, W_4 and W_5, but the calculations are lengthy and the resulting vector fields do not have a simple form. We therefore refer to [35] for the details. Since $\lambda_5 \neq 0$, it follows that these five vector fields W_i need to be linearly dependent along a singular trajectory (i.e., the corresponding solution of the dynamics). We thus have the following result:

Lemma 4.1 *Singular trajectories necessarily lie in the set*

$$S = \{(x, y, M, T, v) \in \mathbb{R}^5 : \det(W_1, W_2, W_3, W_4, W_5) \equiv 0\}, \tag{35}$$

where the matrix has ordered columns given by $W_1, \ldots, W_5$.

More is true. Indeed, since $\Phi^{(4)}(t) \equiv 0$, by differentiating the switching function further, at least one additional relation exists that needs to be satisfied by a singular control. This follows from Lie algebraic relations which imply that the control u only appears for the first time in an even-numbered derivative of the switching function (e.g., see [34, p. 260]). Thus, at least one more equality relation follows from its fifth derivative. This generates a seventh equation for λ. Putting aside that $\lambda_5 = -\gamma \neq 0$, one can form at least 6 collections of 5 vector fields that all need to be linearly dependent. The vector fields $W_1, \ldots, W_5$ in Lemma 4.1 are just one of these collections. For every time $t \in I$ this gives rise to 6 hypersurfaces in a five-dimensional space.

It follows from Thom's transversality theorem [36] that the set of all parameters for which there exists a point that lies on all these hypersurfaces is a residual set in $\mathbb{R}^p$ with p the dimension of the parameter space. We recall that a set A in a topological space is *residual* if it can be written as an at most countable intersection of open and dense subsets and a property is said to be generic if it holds on a residual set. In our case, a finite number of such intersections suffice and thus the statement follows. □

We further note that Lemma 4.1 defines a hypersurface S in the state space on which singular trajectories need to lie and away from S singular controls are not possible. Even stronger, the above computations verify that at any point $(x, y, M, T, v) \notin S$, one of the first four derivatives of the switching function is nonzero if $\Phi(t) = 0$. This implies that either the control remains constant (if the second or fourth derivative is nonzero) or that it has a bang-bang switch (if the first or third derivative is nonzero). Hence, for example, the following stronger result holds:

Corollary 4.2 *Optimal controls corresponding to trajectories that lie outside of S are bang-bang.*

4.3 Numerical Example for the Oncolytic Monotherapy Problem

We give a numerical example that demonstrates the bang-bang character of the solution. We consider the following specification of problem [V]: Minimize

$$J = x(50) + 5y(50) + \int_0^{50} \left(\frac{x(s)}{10} + 20000u(s) \right) \mathrm{d}s \tag{36}$$

over all Lebesgue measurable functions $u : [0, 50] \to [0, u^{\max} = 2.5 \times 10^{-6}]$ subject to dynamics (1)–(5) and initial conditions:

$$x(0) = 0.7, \quad y(0) = 0.1, \quad M(0) = 0.1, \quad T(0) = 10^{-7}, \quad v(0) = 0.$$

The terminal time $t_f = 50$ is fixed, and the parameter values for the dynamics are taken from Table 2 with $b = 10^{-4}$.

From a practical perspective often protocols which are constant for a prolonged period of time followed by a rest period (i.e., bang-bang controls with one switching) are preferred. In many cancer therapies that is the structure of initial induction therapy simply since at the beginning it generally becomes imperative to kill as many cancer cells as possible. In addition, the prolonged effects better allow doctors to judge a particular dose, while the corresponding levels of concentrations can be realized by simple pharmacological procedures like administering a pill a day. Also, it should be pointed out that the therapy horizon generally considers only one therapy interval with subsequent therapy intervals clearly separated in time. It is therefore of interest to consider such protocols and to check whether they are locally optimal (within the class of all controls, not just those that have one switching).

Mathematically, it is easy to minimize the objective functional directly if one restricts the controls to functions which are bang-bang with exactly one switching from full dose to no dose of the form

$$u_{bb}(t) = \begin{cases} 2.5 \cdot 10^{-6}, & \text{if } t \in [0, \tau], \\ 0, & \text{if } t \in (\tau, 50]. \end{cases} \tag{37}$$

A direct numerical optimization gives the best solution of this form for $\tau = 36$. In Fig. 1 we show the profile of the variables of the model for the first 50 days under this control. Figure 2 shows the graph of the multiplier λ_5 (and the constant level $-\gamma$) which has been computed as solutions of the adjoint equation along the corresponding trajectory. These calculations verify that this control along with its trajectory and multiplier indeed defines an extremal for the system. Furthermore, since the control is bang-bang with only one switching, arguments similar to those in Appendix B in [37] for bilinear systems can be used to verify that *this controlled trajectory indeed is a strong relative minimum for control problem* [V] within the class of all admissible controls.

Note also that the trajectories clearly show that the viral load decreases once the control is set to zero. The number of infected tumor cells also diminishes further, and the number of uninfected cells is again on the rise. In order to achieve a long-time control of the tumor, thus, multiple therapy intervals and repeated applications in a similar bang-bang style are required.

We only briefly comment on the important aspect of parameter sensitivity. In the paper [9] an analysis of the number and stability of the equilibrium points for the

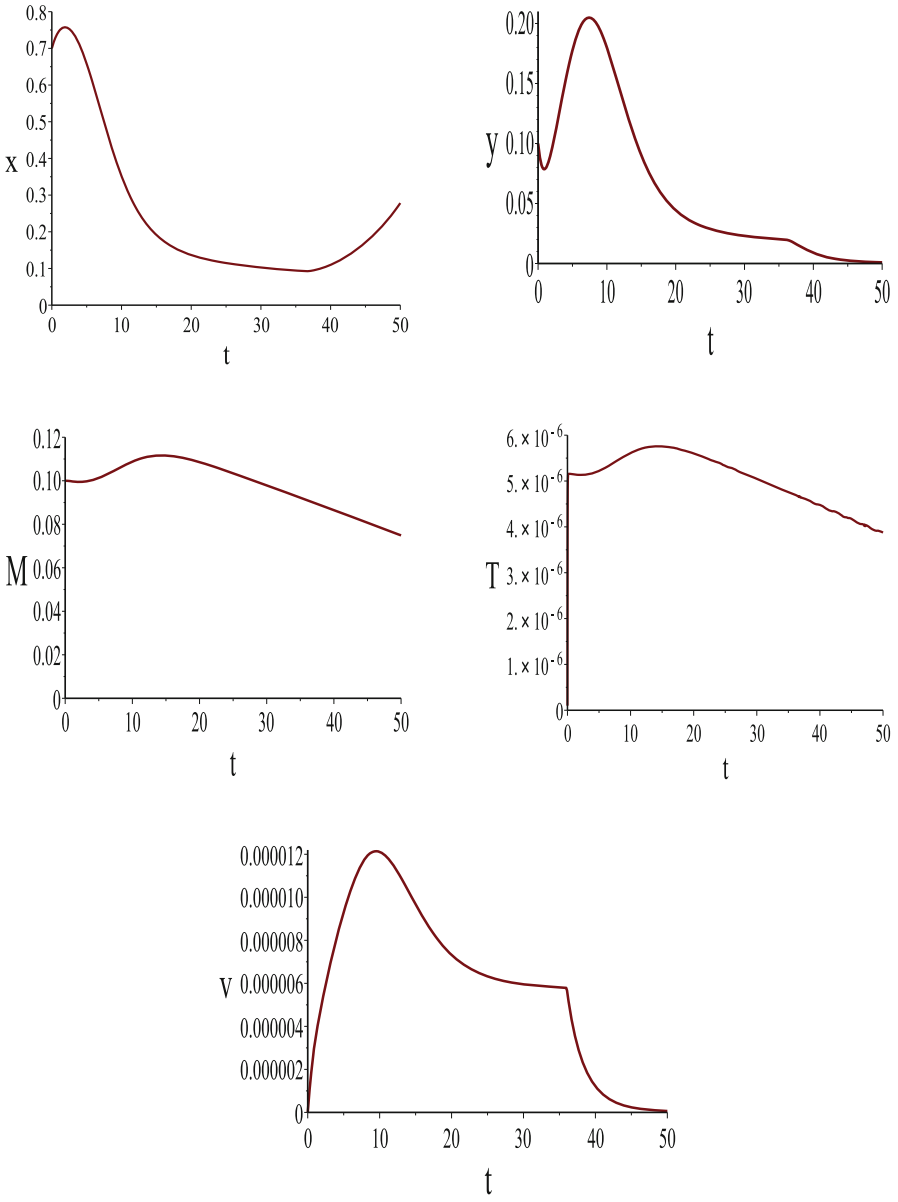

Fig. 1 Graphs of the model variables under control u_{bb} with one switching at $\tau = 36$

dynamical system under constant controls was given and, especially, the effects of the burst size b on the dynamics were investigated. Various bifurcations exist (e.g., transcritical, Hopf bifurcations which generate periodic orbits), and generally, with a relatively large number of parameters, a full-blown sensitivity analysis requires a significant amount of numerical computations which has not yet been done. It is

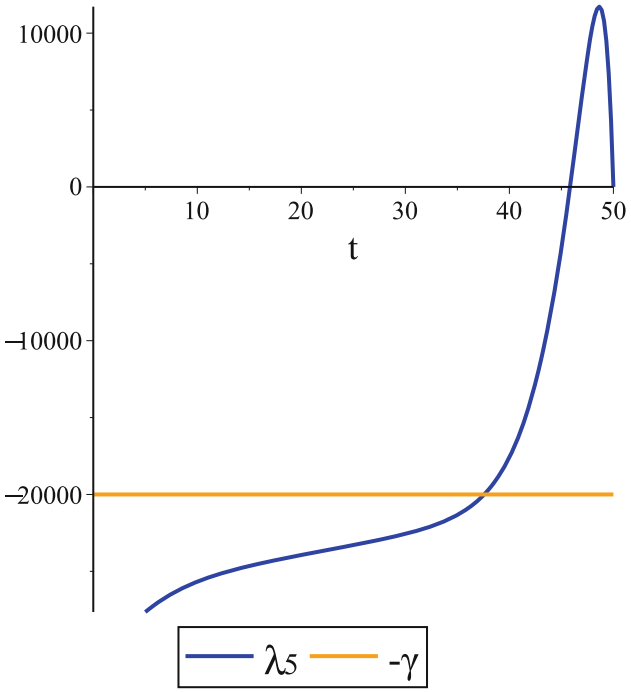

Fig. 2 Multiplier λ_5 along an extremal bang-bang control with one switching

easier to do this for a particular set of parameters, but obviously then also of limited interpretational value. For the example here, the qualitative structure (an optimal bang-bang control with one switching) persists and changes in the switching time are small, but, again, this is just for one particular scenario. It is the fact that generally such a sensitivity analysis is only feasible numerically for selected parameter values which make theoretical results like the one obtained here (that optimal controls are bang-bang) of value.

5 Analysis of the Optimal Control Problem for Combination Therapy

We now incorporate the second control representing the TNF-α inhibitor into our problem. Since optimal controls for the virotherapy generically are bang-bang, we focus on a time period when the first control is constant and consider the single-input control problem when we assume that either $u_1 \equiv 0$ or $u_1 \equiv u_1^{\max}$. We write

$$\dot{z} = f(z) + \frac{u_2}{1+u_2} g_2(z), \tag{38}$$

where

$$f(z) = \begin{bmatrix} \alpha x - \beta x v - \delta_x x \\ \beta x v - \xi y \frac{T}{K+T} - \delta_y y \\ A + s y M - \delta_M M \\ \eta M - \omega y \frac{T}{K+T} - \delta_T T \\ b\delta_y y - \rho x v - \delta_v v \end{bmatrix},$$

respectively,

$$f(z) = \begin{bmatrix} \alpha x - \beta x v - \delta_x x \\ \beta x v - \xi y \frac{T}{K+T} - \delta_y y \\ A + s y M - \delta_M M \\ \eta M - \omega y \frac{T}{K+T} - \delta_T T \\ b\delta_y y - \rho x v - \delta_v v + u_1^{max} \end{bmatrix}$$

and

$$g_2(z) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ -\eta M \\ 0 \end{bmatrix}.$$

We consider the following optimal control problem:

[W] Minimize the functional

$$J = J(u) = \sigma_1 x(t_f) + \sigma_2 y(t_f) + \int_0^{t_f} (\theta x(s) + \gamma_2 u_2(s))\, \mathrm{d}s \tag{39}$$

subject to dynamics (1)–(5) with initial conditions $x(0) = x_0$, $y(0) = y_0$, $M(0) = M_0$, $T(0) = T_0$ and $v(0) = v_0$ over all Lebesgue measurable functions $u_2 : [0, t_f] \to [0, u_2^{\max}]$. The terminal time t_f can be fixed or free.

The current formulation for the problem allows us to carry out the analysis using results from [38]. The fundamental necessary conditions for optimality for problem **[W]** are again given by the Pontryagin's maximum principle [30]. Since the problem does not involve terminal constraints on the state, as for the oncolytic monotherapy problem, extremals are normal and without loss of generality we already define the Hamiltonian function $H : (\mathbb{R}^n)^* \times \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}$ for the control problem as

$$H(\lambda, z, u_2) = \theta x + \gamma_2 u_2 + \left\langle \lambda, f(z) + \frac{u_2}{1+u_2} g_2(z) \right\rangle. \tag{40}$$

It follows from the Pontryagin maximum principle that, if u_2^* is an optimal control and z_* denotes the corresponding trajectory, then there exists a covector $\lambda : [0, t_f] \to (\mathbb{R}^5)^*$ which is a solution to the *adjoint equation*,

$$\dot{\lambda} = -\theta e_1 - \lambda\left(Df(z) + \frac{u_2}{1+u_2}Dg_2(z)\right) \tag{41}$$

with terminal condition $\lambda(t_f) = (\sigma_1, \sigma_2, 0, 0, 0)$ such that the Hamiltonian H is minimized almost everywhere on $[0, t_f]$ by u_2^* along $(\lambda(t), z_*(t))$, i.e.,

$$H(\lambda(t), z_*(t), u_2^*(t)) = \min_{0\le v\le u_2^{\max}} H(\lambda(t), z_*(t), v), \tag{42}$$

and the Hamiltonian is constant along the optimal solution and its corresponding multiplier.

In coordinates, for both versions of the vector fields f, the adjoint equations read

$$\begin{aligned}
\dot{\lambda_1} &= -\frac{\partial H}{\partial x} = -\theta - \lambda_1(\alpha - \beta v - \delta_x) - (\lambda_2\beta - \lambda_5\rho)v,\\
\dot{\lambda_2} &= -\frac{\partial H}{\partial y} = (\lambda_2\xi + \lambda_4\omega)\frac{T}{K+T} - \lambda_3 sM + (\lambda_2 - \lambda_5 b)\delta_y,\\
\dot{\lambda_3} &= -\frac{\partial H}{\partial M} = \lambda_3(\delta_M - sy) - \lambda_4\eta,\\
\dot{\lambda_4} &= -\frac{\partial H}{\partial T} = (\lambda_2\xi + \lambda_4\omega)\frac{yK}{(K+T)^2} - \lambda_3\eta\frac{u_2}{1+u_2} + \lambda_4\delta_T,\\
\dot{\lambda_5} &= -\frac{\partial H}{\partial v} = (\lambda_1 - \lambda_2)\beta x + \lambda_5(\rho x + \delta_v).
\end{aligned}$$

Theorem 5.1 *Let u_2^* be an optimal control with corresponding trajectory x_*, and let λ be an adjoint vector such that the conditions of the maximum principle are satisfied. Then we have that*

$$u_2^*(t) = \begin{cases} 0, & \text{if } \eta\lambda_4(t)M(t) \le \gamma_2,\\ \sqrt{\frac{\eta\lambda_4(t)M(t)}{\gamma_2}} - 1, & \text{if } \gamma_2 \le \eta\lambda_4(t)M(t) \le \gamma_2(u_2^{\max}+1)^2,\\ u_2^{max}, & \text{if } \gamma_2(u_2^{\max}+1)^2 \le \eta\lambda_4(t)M(t). \end{cases} \tag{43}$$

Proof We need to minimize the Hamiltonian H as a function of the control u_2 over the control set $[0, u_2^{\max}]$. Since

$$\frac{\partial H}{\partial u_2} = \gamma_2 + \frac{\langle\lambda, g_2(z)\rangle}{(1+u_2)^2},$$

it follows that $H(\lambda(t), z_*(t), u_2)$ is strictly increasing in u_2 if the function

$$\Psi(t) = \langle\lambda(t), g_2(z_*(t))\rangle \tag{44}$$

is nonnegative. In this case, the minimum over the control set $[0, u_2^{\max}]$ therefore is attained for $u_2^* = 0$. If $\Psi(t)$ is negative, then it follows from

$$\frac{\partial^2 H}{\partial u_2^2} = -\frac{2\langle \lambda, g_2(z)\rangle}{(1+u_2)^3}$$

that the Hamiltonian $H(\lambda(t), x_*(t), u_2)$ is a strictly convex function of u_2 on $\mathbb{R}$. Hence, it has a unique stationary point and this point is the global minimum of the function. Solving $\frac{\partial H}{\partial u_2} = 0$, the stationary point is given by

$$u_{st}(t) = \sqrt{-\frac{\Psi(t)}{\gamma_2}} - 1. \tag{45}$$

Depending on the location of $u_{st}(t)$ we have the following three cases: If $u_{st}(t) < 0$, then the function $H(\lambda(t), x_*(t), \cdot)$ is strictly increasing on $[0, u_2^{\max}]$ with minimum at $u_2^* = 0$; if $0 \le u_{st}(t) \le u_2^{\max}$, then the global minimum lies in the control set and thus u_2^* is given by the stationary point; and if $u_{st}(t) > u_2^{\max}$, then $H(\lambda(t), x_*(t), \cdot)$ is strictly decreasing over $[0, u_2^{\max}]$ with minimum at $u_2^* = u_2^{\max}$. This proves the result. □

Corollary 5.1 *Optimal controls u_2^* are continuous.*

Proof Using the notation from the proof above, as long as $\Psi(t)$ is negative, the point $u_{st}(t)$ where the Hamiltonian $H(\lambda(t), x_*(t), \cdot)$ attains its minimum over $\mathbb{R}$ varies continuously with t. For this case we can represent the control in the form

$$u_2^*(t) = \max\{0, \min\{u_{st}(t), u_2^{\max}\}\}, \tag{46}$$

and thus, u_2^* is continuous as long as $\Psi(t)$ is negative. For $\Psi(t) \ge 0$ the optimal control is given by $u_2^* \equiv 0$ which is also the optimal control for $\Psi(t) \ge -\gamma_2$. Hence, optimal controls remain continuous as Ψ becomes nonnegative. □

Thus, and in line with the interpretation of this control as a concentration, optimal controls continuously change between the limiting values $u_2^{\max}$ and 0 and values that lie in the interior of the control set as the function Ψ crosses the levels $-\gamma_2$ and $-\gamma_2(1+u_2^{\max})^2$. We therefore call the function Ψ the *indicator function* for the optimal control. Clearly, it is this function that determines the optimal controls. For example, we have the following result:

Proposition 5.1 *If the indicator function Ψ is strictly increasing on $[0, t_f]$, then optimal controls are concatenations of boundary and interior controls of at most the sequence $u_2^{\max} \to u_{st}(t) \to 0$, i.e., possibly starting with a full-dose segment, $u_2^*(t) \equiv u_2^{\max}$, controls switch to the interior control $u_2^*(t) = u_{st}(t)$ and end with a segment where no drugs are given, $u_2^*(t) \equiv 0$. For some initial conditions this sequence may be shorter and not all pieces need to be present. If present, the interior control $u_{st}(t)$ is strictly decreasing. Analogously, if Ψ is strictly decreasing on*

$[0, t_f]$, *then optimal controls are at most concatenations that follow the sequence* $0 \to u_{st}(t) \to u_2^{\max}$ *and in this case the interior control is strictly increasing.* □

Overall, monotonicity and convexity properties of the indicator function determine the concatenation structure of the optimal controls. It is therefore of importance to be able to compute the derivatives of the indicator function effectively.

Proposition 5.2 *Given a continuously differentiable vector field k, define the function* $\varphi(t) = \langle \lambda(t), k(z(t)) \rangle$, *where z is a solution of the dynamics and* λ *is a solution of the corresponding adjoint equation. Then the derivative of* φ *is given by*

$$\dot{\varphi}(t) = -\theta \langle e_1, k(z(t)) \rangle + \langle \lambda(t), [f, k](z(t)) \rangle + \frac{u_2(t)}{1 + u_2(t)} \langle \lambda(t), [g_2, k](z(t)) \rangle . \tag{47}$$

Proof Using (41), and dropping the dependence of the variables on time t in our notation, we obtain

$$\begin{aligned}
\dot{\varphi} &= \langle \dot{\lambda}, k(z) \rangle + \langle \lambda, Dk(z)\dot{z} \rangle \\
&= -\theta \langle e_1, k(z) \rangle - \left\langle \lambda \left(Df(z) + \frac{u_2}{1 + u_2} Dg_2(z) \right), k(z) \right\rangle \\
&\quad + \left\langle \lambda, Dk(z) \left(f(z) + \frac{u_2}{1 + u_2} g_2(z) \right) \right\rangle \\
&= -\theta \langle e_1, k(z) \rangle + \langle \lambda, Dk(z) f(z) - Df(z) k(z) \rangle \\
&\quad + \frac{u_2}{1 + u_2} \langle \lambda, Dk(z) g_2(z) - Dg_2(z) k(z) \rangle \\
&= -\theta \langle e_1, k(z) \rangle + \langle \lambda, [f, k](z) \rangle + \frac{u_2}{1 + u_2} \langle \lambda, [g_2, k](z) \rangle
\end{aligned}$$

verifying the result. □

Proposition 5.3 *The control vector fields commute, i.e.,* $[g_1, g_2](z) = 0$, *and we have that*

$$[f, g_2](z) = \begin{bmatrix} 0 \\ -\eta M \frac{\xi y K}{(K+T)^2} \\ 0 \\ -\eta \left(A + M \left(sy - \delta_M + \frac{\omega y K}{(K+T)^2} + \delta_T \right) \right) \\ 0 \end{bmatrix}.$$

Corollary 5.2 *The first derivative of the indicator function* Ψ *is given by*

$$\dot{\Psi}(t) = \langle \lambda(t), [f, g_2](z(t)) \rangle , \tag{48}$$

i.e., and again dropping the t-dependence of the variables,

$$\dot{\Psi}(t) = -\eta \left(\frac{MyK}{(K+T)^2} (\lambda_2 \xi + \lambda_4 \omega) + \lambda_4 \left(A + M \left(sy - \delta_M + \delta_T \right) \right) \right). \tag{49}$$

As we can see, the formula for the derivative of the indicator function involves a number of parameters, some variables of the system as well as the adjoint variables λ_2 and λ_4 and so its sign will depend on all this complex structure. For a specific choice of parameters it may be possible to determine it uniquely or, because of the adjoint variables involved, it may still exhibit changes of signs. This will consequently imply that the two types of concatenations described in Proposition 5.1 may be present in the solutions of the problem in different parts of the state space. Such investigations will be pursued in future work on this topic.

6 Conclusions

In this paper, we continued the analysis of the model for combination therapy of glioma initiated in [8]. We formulated it as an optimal control problem with a proper objective which reflects the underlying biology and initiated the complex task of determining the full structure of optimal solutions. We proved that the optimal control representing the application of the virus is generically of the bang-bang type, i.e., the virus should be applied in sessions of maximum dose with possible rest periods. Regarding the second control which represents the concentration of a TNF-α inhibitor, we showed that optimal controls will be continuous consisting of concatenations of boundary and interior pieces. We singled out two types of scenarios which appear in the problem if the indicator function is monotone. Classes of optimal controls for both treatments have been determined and provide a good base for further work on constructing these controls and corresponding optimal responses of the system for specific parameter values of the model.

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