A Model for Cancer Chemotherapy with State Space Constraints*

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Abstract. The analysis of optimal control problems is significantly more difficult when state space constraints are imposed and thus in many modelling approaches explicit constraints are handled by including penalty terms in the objective. In this paper we use the example of a simple model for cancer chemotherapy to compare the structure of extremals when upper limits on the total number of cancer cells are imposed (a) implicitly through a penalty term in the objective and (b) explicitly in the form of state space constraints.

1. Introduction

More recent models for cancer chemotherapy are cell-cycle specific and treat the cell cycle as the object of control [13]. Drug treatment influences the cell cycle in many possible ways and here only the most fundamental aspect is considered, *cell-killing*. Most drugs are active in a specific phase of the cell-cycle. For example, spindle poisons destroy the mitotic spindle and are active in mitosis. Depending on the type of drug modelled and the degree of detail in mathematical models the phases of the cell cycle are combined into clusters. In this more mathematical paper we consider a model for cancer chemotherapy treatment with a single G_2/M specific killing agent. This applies to many drugs which affect cells during their division when cell walls become porous and are more vulnerable to attack. The remaining phases of the cell cycle (G_0, G_1 and S) are combined into the other compartment. Cancer chemotherapy is modelled as a control system with the *state* of the system given by the *number of cancer cells* in these compartments. The *control* represents the drug dosage which in this model is identified with its concentration and proportionally generates the killing effect in the dynamics. The active ingredient in the

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drug is a cytostatic agent which kills cancer cells and healthy cells alike. The medical goal is to maximize the number of cancer cells which the agent kills while keeping the toxicity to the normal tissue acceptable. Mathematically there are many (non-equivalent) ways of modelling this. The model which forms the basis of our study here was proposed and originally analyzed as an optimal control problem by Swierniak [13] and then reconsidered in [4] with the objective to minimize the number of cancer cells at the end of a fixed therapy interval. In this model the negative effects on the healthy cells are represented only indirectly by also minimizing the drug dosage in the objective. In order to guarantee that cancer cells do not grow to unacceptably high levels in between, here we also postulate an upper bound on the number of cancer cells, but consider two variations of the model. In the first one we include a weighted average of the number of cancer cells at any time as penalty term in the objective, a so-called *soft* modelling of the constraint; in the second model we explicitly postulate an upper limit on the total number of cancer cells. Mathematically the analysis of these two models is quite different with the case of explicit constraints much more difficult because of the presence of measures as multipliers.

2. A Two-Compartment Model with State Constraints

In this model (c.f. Swierniak [13,14]) two compartments are distinguished which combine G_0, G_1 and S and G_2 and M, respectively. Let $N_i(t)$, $i = 1, 2$, denote the number of cancer cells in the i-th compartment at time t. Admissible controls are Lebesgue measurable functions $u : [0, T] \to [0, 1]$ representing the dose of the drug administered with $u = 0$ corresponding to no treatment and $u = 1$ corresponding to a maximum dose. It is assumed that the drug dissipates instantaneously, i.e. its concentration is equal to the dosage and consequently pharmaco-kinetic equations are not modelled. It is assumed that the effect of the drug represented by the number of ineffective cell-divisions in the G_2/M phase is proportional to the control u with an effectiveness factor s, $0 < s \leq 1$. This provides the simplest pharmaco-dynamic model. An exponential distribution is used to model the transit times of cells through the compartments and the expected number of cells exiting the i-th compartment is given by $a_i N_i(t)$, where a_i is the parameter of the exponential distribution related to the inverse of the transit time. Therefore while all cells $a_2 N_2$ leave the compartment G_2/M, only the fraction $(1 - su)a_2 N_2$ of surviving cells undergoes cell division and reenters the first compartment. Hence the controlled mathematical model becomes

$$\dot{N}_1 = -a_1 N_1 + 2(1 - su)a_2 N_2, \qquad N_1(0) = N_{10}, \tag{1}$$

$$\dot{N}_2 = a_1 N_1 - a_2 N_2, \qquad N_2(0) = N_{20}, \tag{2}$$

with all initial conditions positive. It is easily seen that if each component of $N(t_0)$ is positive, then all components of $N(t)$ remain positive for all times $t \geq t_0$ [4, Prop. 3.1]. It is therefore not necessary to add this positivity condition as extra state-space constraint. Note that

$$\dot{N}_1 + \dot{N}_2 = (1 - 2su)a_2 N_2 \tag{3}$$

and thus for $s \leq \frac{1}{2}$ the total number of cancer cells cannot be reduced. Thus we **assume** that $s > \frac{1}{2}$.

If we set $N = (N_1, N_2)^T$, then the general form of the dynamics is described by a bilinear system of the form

$$\dot{N}(t) = (A + suB)N(t), \quad N(0) = N_0, \tag{4}$$

where A and B are fixed (2×2)-matrices given by

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix} \text{ and } B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix} \tag{5}$$

In [13] the performance index or objective is chosen as

$$J = rN(T) + \int_0^T u(t)dt \to \min. \tag{6}$$

where $r = (r_1, r_2)$ and the coefficients r_1 and r_2 are positive numbers. The penalty term $rN(T) = r_1N_1(T) + r_2N_2(T)$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$. The side effects of treatment are only modelled indirectly through the control term. The number of cancer cells which do not undergo cell division at time t and are killed are given by $su(t)a_2N_2(t)$, i.e. $u(t)$ is proportional to the fraction of ineffective cell divisions. Since the drug kills healthy cells at a proportional rate, the control $u(t)$ is also used to model the negative effect of the drug on the normal tissue or its toxicity. Thus the integral in the objective models the cumulative negative effects of the treatment. An objective of this form which only minimizes the number of cancer cells at the end of therapy is prone to generate solutions which allow the number of cancer cells to grow to unacceptably high levels at intermediate points. Typical optimal controls for this problem are bang-bang with one switching from $u = 0$ to $u = 1$ [4]. If this switching occurs too late, high levels of cancer cells are incurred earlier and upper limits on the total number of cancer cells need to be imposed to avoid such an overshoot.

In a formulation which avoids the introduction of explicit state space constraints a penalty term $\int_0^T qN(t)dt$ where $q = (q_1, q_2)$ again is a vector of positive weights is added. This leads to the problem

(P_{soft}) minimize the objective

$$J = rN(T) + \int_0^T qN(t) + u(t)dt \to \min \tag{7}$$

over all Lebesgue-measurable functions $u : [0, T] \to [0, 1]$ subject to the dynamics (4).

In an alternate formulation an explicit upper bound on the number of cancer cells is postulated. Mathematically, the problem then can be formulated as follows:

(P_{hard}) minimize the objective

$$J = rN(T) + \int_0^T u(t)dt \to \min \tag{8}$$

over all Lebesgue-measurable functions $u : [0, T] \to [0, 1]$ subject to the dynamics (4) and state-space constraint

$$N_1(t) + N_2(t) \leq \bar{N}. \tag{9}$$

3. Extremals for (P_{soft})

First-order necessary conditions for optimality are given by the Pontryagin maximum principle. For (P_{soft}) the analysis of extremals and results are a small extension of those from [4,5] and we only briefly indicate the steps: If u_* is an optimal control with corresponding trajectory N_*, then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous function λ, which we write as row-vector, $\lambda : [0,T] \to (\mathbb{R}^2)^*$, satisfying the adjoint equation with transversality condition,

$$\dot{\lambda} = -\lambda(A + suB) - \lambda_0 q, \qquad \lambda(T) = \lambda_0 r, \tag{10}$$

such that $(\lambda_0, \lambda(t)) \neq (0,0)$ for all $t \in [0,T]$ and the following minimum condition is satisfied: the optimal control minimizes the Hamiltonian

$$H = \lambda_0(qN + u) + \lambda(A + suB)N \tag{11}$$

over the control set $[0,1]$ along $(\lambda_0, \lambda(t), N_*(t))$.

We call control-trajectory pairs (N,u) for which there exist multipliers such that these conditions are satisfied *extremals*. In general it cannot be excluded that λ_0 vanishes and extremals with $\lambda_0 = 0$ are called abnormal, while those with $\lambda_0 > 0$ (and then we can normalize $\lambda_0 = 1$) are called normal. For this model the multiplier λ_0 cannot vanish: otherwise $\lambda(T) = 0$ and thus $\lambda(t) \equiv 0$ contradicting the non-triviality of the multipliers. Without loss of generality we therefore normalize $\lambda_0 = 1$.

It is not difficult to see that the first quadrant in the dual space is negatively invariant for the adjoint flow (10) and thus since $r_i > 0$ all states N_i and costates λ_i are positive over $[0,T]$. Optimal controls minimize the Hamiltonian H. If we define the so-called switching function Φ by

$$\Phi(t) = 1 + s\lambda(t)BN(t), \tag{12}$$

then the optimal controls are given as

$$u_*(t) = \begin{cases} 1 & \text{if } \Phi(t) < 0 \\ 0 & \text{if } \Phi(t) > 0 \end{cases}. \tag{13}$$

We call the constant controls $u = 0$ and $u = 1$ *bang* controls. A priori the control is not determined by the minimum condition at times when $\Phi(t) = 0$. However, if $\Phi(t)$ vanishes on an open interval, then also all its derivatives must vanish and this may determine the control. The corresponding controls are called *singular*. Optimal controls then need to be synthesized from these candidates. If Φ vanishes identically on an interval I, then it can be shown by a direct computation that

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = 4a_1a_2 > 0. \tag{14}$$

Thus the strengthened Legendre-Clebsch condition [3] is violated and singular controls are not optimal. In fact, they are locally maximizing. Consequently, and although more complicated structures cannot be excluded a priori, bang-bang controls become the prime candidates for optimality. Necessary and sufficient optimality conditions for bang-bang controls developed in [5] directly apply and can be used to establish local optimality properties of bang-bang arcs.

4. Extremals for (P_{hard})

In this model we have $q = 0$, but otherwise no changes are made in H. The presence of explicit state-space constraint complicates matters in that it brings in an additional multiplier which a priori is only known to be a non-negative Radon measure. There exist several formulations of the necessary conditions, not all equivalent in their details. Here we use a formulation adapted from [15]: If $u_* : [0, T] \to [0, 1]$ is an optimal control with corresponding trajectory N_*, such that the state-space constraint is not active at the terminal time, then there exist a constant $\lambda_0 \geq 0$, an absolutely continuous function η, which we write as row-vector, $\eta : [0, T] \to (\mathbb{R}^2)^*$, and a non-negative Radon measure $\mu \in C^*([0, T]; \mathbb{R})$, which do not all vanish simultaneously, (in the sense that $\lambda_0 + \|\eta\|_\infty + \mu([0, T]) > 0$) such that with

$$\lambda(t) = \eta(t) - c \int_{[0,t]} d\mu(s), \qquad c = (1, 1), \tag{15}$$

the following conditions hold:

(a) The optimal control minimizes the Hamiltonian over the control set $[0, 1]$ along $(\lambda_0, \lambda(t), N_*(t))$, i.e.

$$H(\lambda_0, \lambda(t), N_*(t), u_*(t)) = \min_{0 \leq w \leq 1} H(\lambda_0, \lambda(t), N_*(t), w). \tag{16}$$

(b) The multiplier λ satisfies the adjoint equation with transversality condition in the following form,

$$\dot{\eta}(t) = -\lambda(t)(A + su_*(t)B), \qquad \lambda(T) = \lambda_0 r. \tag{17}$$

(c) The measure μ is only active when the state lies on the constraint: supp $\mu \subseteq \{t \in [0, T] : cN_*(t) = \bar{N}\}$.

We can still restrict the analysis to normal extremals, but now the argument is more involved:

Lemma 4.1 *If u_* is an optimal control, then a corresponding extremal is normal.*

Proof. This can be seen using, for example, results of [11, Thm. 4.4]. The conditions in [11, Thm. 4.4] can be verified by rewriting problem (P_{hard}) as a Mayer problem, call it (P'). The only condition which requires verification is part (b) of the Constraint Qualification (CQ) of [11, Thm. 4.4]. Defining $h(t, N) = N_1 + N_2 - \bar{N}$, it needs to be shown that there exist positive constants ϵ, β, γ, and δ, and a continuous function $\nu : [0, T] \times \mathbb{R}^3 \to [0, 1]$ such that whenever $(t, (\xi_1, \xi_2, \xi_3)) \in [0, T] \times \mathbb{R}^3$ satisfies

$$\left\| (\xi_1, \xi_2, \xi_3) - (N_1^*(t), N_2^*(t), \int_0^t u_*(s)ds) \right\|_\infty \leq \epsilon \tag{18}$$

and

$$N_1^*(t) + N_2^*(t) - \bar{N} \geq -\delta, \tag{19}$$

then

$$h_t(t,\xi_1,\xi_2) + h_N(t,\xi_1,\xi_2)(A + s\nu(t,\xi)B)(\xi_1,\xi_2)^T = a_2\xi_2(1 - 2s\nu(t,\xi)) < -\gamma. \quad (20)$$

Since $N_2^*(t)$ remains positive, we have $m = \min\{N_2^*(t) : \ t \in [0,T]\} > 0$. Take any $\delta > 0$, $\epsilon \in (0, \frac{m}{2})$, and let $\gamma = a_2\frac{m}{2}(s - \frac{1}{2})$ and $\nu(t,x_1,x_2,x_3) = \frac{1}{2} + \frac{1}{4s}$. Since we assume $s > \frac{1}{2}$ this value is an admissible control. Now let $\xi = (\xi_1,\xi_2,\xi_3)$ be such that (18) and (19) are satisfied. Since $\epsilon < \frac{m}{2}$ we deduce from (18) that $\xi_2 > \frac{m}{2}$ and thus $a_2\xi_2 > a_2\frac{m}{2} = \gamma/(s - \frac{1}{2})$ which implies (20). ■

Let $M = \{(t,N) \in [0,T] \times \mathbb{R}^2_+ : cN_*(T) = \bar{N}\}$ denote the constraint manifold and let $A = \{t \in [0,T] : cN_*(t) = \bar{N}\} = \{t \in [0,T] : (t, N_*(t)) \in M\}$ denote the set of times when the constraint is active. Since admissible controls are only Lebesgue-measurable, in principle A could be an arbitrarily complicated closed set. Nevertheless, in most practical situations this set often is a union of intervals. We derive more stringent necessary conditions for optimality for this case which then can be used to prove sufficient conditions for local optimality as well. Following the notation introduced by Maurer [7] we call a piece of a trajectory defined over an open interval I a boundary piece or *boundary arc* if $I \subset A$ and call pieces of the trajectory defined over open intervals which do not intersect the boundary *interior arcs*. The times τ when interior arcs and boundary arcs meet are called *junction times* and the corresponding values $N(\tau)$ junction points.

As for (P_{soft}), optimal controls satisfy the minimum condition (16) and consequently (13). Along interior arcs the extra multiplier is not active and thus extremals cannot be singular with bang-bang controls the most likely scenario. Let Γ_∂ be a boundary arc (∂-arc) defined over an open interval I. For problem (P_{hard}) the constraint manifold is control-invariant of relative degree 1. Specifically,

$$\dot{h}(t,N) := h_t(t,N) + h_N(t,N)\dot{N}(t) = (1 - 2su)a_2N_2(t) \quad (21)$$

and thus the control which keeps the boundary invariant is constant given by $u_\partial = \frac{1}{2s}$. This control is admissible since $s > \frac{1}{2}$.

Lemma 4.2 *If $I = (\tau_1,\tau_2)$ is the domain of a boundary arc, then the Radon measure μ is absolutely continuous on I with respect to Lebesgue measure with continuous and non-negative Radon-Nikodym derivative $\nu(t)$ given by*

$$\nu(t) = \frac{\lambda(t)[A,B]N(t)}{cBN(t)} \quad (22)$$

where $[A,B] = BA - AB$ denotes the commutator of the matrices A and B.

Proof. By the minimum condition we have $\Phi(t) = 1 + s\lambda(t)BN(t) \equiv 0$ and thus it follows from (15) that

$$\left(\eta(t) - c\int_{[0,t]} d\mu(\tau)\right) sBN(t) \equiv -1. \quad (23)$$

Since $cBN(t) = -2a_2N_2(t) < 0$ we therefore have that

$$\mu(t) = \int_{[0,t]} d\mu(\tau) = \frac{1 + \eta(t)sBN(t)}{csBN(t)} \quad (24)$$

is absolutely continuous on I. Writing $\mu(t) = \int_0^t \nu(\tau)d\tau$, the non-negativity of ν follows from the fact that μ is non-negative. Furthermore, we now can differentiate the switching function on I to obtain

$$\begin{aligned} 0 \equiv \dot{\Phi}(t) &= \dot{\lambda}(t)sBN(t) + \lambda(t)sB\dot{N}(t) \\ &= (-\lambda(t)(A + su_\partial B) - \nu(t)c)\, sBN(t) + \lambda(t)sB(A + su_\partial B)N(t) \\ &= s\lambda(t)[A, B]N(t) - \nu(t)csBN(t) \end{aligned}$$

which gives the explicit formula for ν. ■

This argument, which goes back to Maurer's paper [8], can be generalized to arbitrary constraint manifolds which are control-invariant of relative degree 1 [6]. For junction times the following continuity condition on the multiplier is an immediate consequence of Maurer's junction conditions [7, Cor. 5.2] (see also, [2, Prop. 4.2]).

Lemma 4.3 *The multiplier λ remains continuous at junction times τ between interior and boundary arcs.*

Proof. First assume that τ is a junction between a bang and boundary arcs, i.e. there exists an $\varepsilon > 0$ such that u is constant for $t \in (\tau - \varepsilon, \tau)$ and $t \in (\tau, \tau + \varepsilon)$. All junctions between bang and boundary arcs are transversal for problem (P_{hard}). For, we have $cAN = a_2N_2(t) > 0$ and thus 0-arcs transversally cross the constraint manifold M outward while $c(A + sB)N = (1 - 2s)a_2N_2(t) < 0$ and thus 1-arcs transversally cross M inward. Thus at an entry junction τ, a 0-arc concatenates with a ∂-arc and at exit-junctions a ∂-arc concatenates with a 1-arc. In each case [7, Cor. 5.2] applies and gives that λ remains continuous at τ. Specifically, without loss of generality consider an entry junction τ between $u = 0$ and $u = u_\partial$. In principle the measure μ could have an atomic part at $t = \tau$ which will generate a jump in λ at time τ. By (15) we must have that $\lambda(\tau-) = \lambda(\tau+) + c\upsilon$ with $\upsilon \geq 0$. Hence $\Phi(\tau-) = \Phi(\tau+) + \upsilon scBN(\tau)$. But at an entry junction τ we have $\Phi \equiv 0$ for $t > \tau$ and $\Phi > 0$ for $t < \tau$ near τ and thus

$$0 \leq \Phi(\tau-) = \upsilon scBN(\tau) = \upsilon s\,(-2a_2N_2(\tau)) \leq 0. \tag{25}$$

Hence $\upsilon = 0$.

Clearly this reasoning is equally valid if there exists a sequence of times $\{t_k\}_{k\in\mathbb{N}}$, $t_k < \tau$, with the properties that $\lim_{k\to\infty} t_k = \tau$ and $\Phi(t_k) > 0$. Choose $\varepsilon > 0$ so that the trajectory lies in the interior of the state space for $t \in (\tau - \varepsilon, \tau)$. (The existence of such an interval is part of the definition of an interior arc.) Since optimal controls cannot be singular for interior arcs, the switching function Φ cannot vanish on any subinterval of $(\tau - \varepsilon, \tau)$. If a sequence with the above properties does not exist, then indeed there exists a $\delta > 0$ so that $\Phi(t) < 0$ on $(\tau - \delta, \tau)$. But then the control is $u \equiv 1$ on $(\tau - \delta, \tau)$ which contradicts that τ is a junction time. Hence the Lemma holds for arbitrary junctions of interior and boundary arcs. ■

We summarize the necessary conditions for problem (P_{hard}). These conditions agree with "Informal Theorem 4.1" in [2].

Theorem 4.1 *Let $u_* : [0, T] \to [0, 1]$ be an optimal control for problem (P_{hard}) with corresponding trajectory N_* and assume N_* is a finite concatenation of interior and boundary*

arcs with junction times t_i^*, $i = 1, \ldots, m$, $0 = t_0^* < t_1^* < \ldots < t_m^* < t_{m+1}^* = T$ *such that the state-space constraint is not active at the terminal time. Then there exists a continuous function* λ_*, $\lambda_* : [0, T] \to (\mathbb{R}^2)^*$, $\lambda_*(T) = r$, *such that the following conditions hold:*

(1) *On each interval* (t_i^*, t_{i+1}^*), $i = 0, \ldots, m$, λ *is absolutely continuous and satisfies the adjoint equation in the form*

$$\dot{\lambda}_*(t) = -\lambda_*(t)(A + su_*(t)B) - c\nu_*(t) \tag{26}$$

where

$$\nu_*(t) \equiv 0 \qquad \text{if } (t_i^*, t_{i+1}^*) \text{ is the domain of an } \textit{interior arc} \tag{27}$$

and

$$\nu_*(t) \equiv \frac{\lambda(t)[A, B]N(t)}{cBN(t)} \geq 0 \qquad \text{if } (t_i^*, t_{i+1}^*) \text{ is the domain of a } \partial\textit{-arc;} \tag{28}$$

(2) *With* $\Phi_*(t) = 1 + s\lambda_*(t)BN_*(t)$ *the control satisfies*

$$u_*(t) = \begin{cases} 1 & \text{if } \Phi_*(t) < 0 \\ 0 & \text{if } \Phi_*(t) > 0 \end{cases} . \tag{29}$$

The control along a boundary arc is constant given by $u_\partial \equiv \frac{1}{2s}$ *and singular controls are not optimal along interior arcs.*

(3) *The Hamiltonian is constant along the optimal control,*

$$H(\lambda(t), N_*(t), u_*(t)) = u_*(t) + \lambda(t)\,(A + su_*(t)B)\,N_*(t) \equiv \text{const.} \tag{30}$$

The last statement is well-known. It can easily be verified on each interval (t_i^*, t_{i+1}^*) using the adjoint equation and then follows by the continuity of λ at entry- and exit-junctions for the full interval $[0, T]$. If the constraint is active at the terminal time T, then the transversality condition $\lambda_*(T) = r$ need not hold anymore.

5. Simulations and Conclusion

We include four simulations which compare the structure of solutions for the problems (P_{hard}) and (P_{soft}). The parameters for the dynamics are chosen as $a_1 = 0.197$ and $a_2 = 0.356$ [13,4], and we set $s = 0.8$. As initial condition we take $N_1^0 = 0.70$ and $N_2^0 = 0.30$ which correspond to the steady-state solution of the uncontrolled system with the total number of cancer cells normalized to 1. In the objective we chose $r = (1, 1)$ and compare solutions for $q = (1, 1)$, $q = (0.25, 0.25)$ and $q = (0.1, 0.1)$.

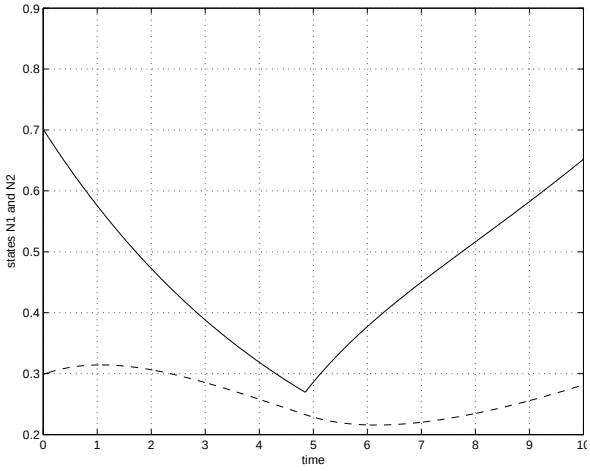

Fig. 1: States for (P_{soft}), $q = (1, 1)$

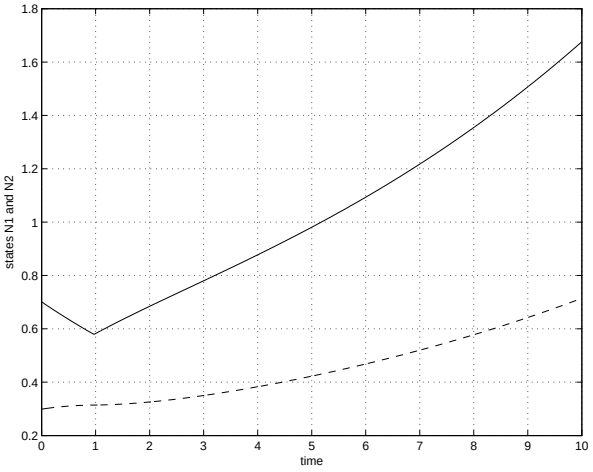

Fig. 2: States for (P_{soft}), $q = (0.25, 0.25)$

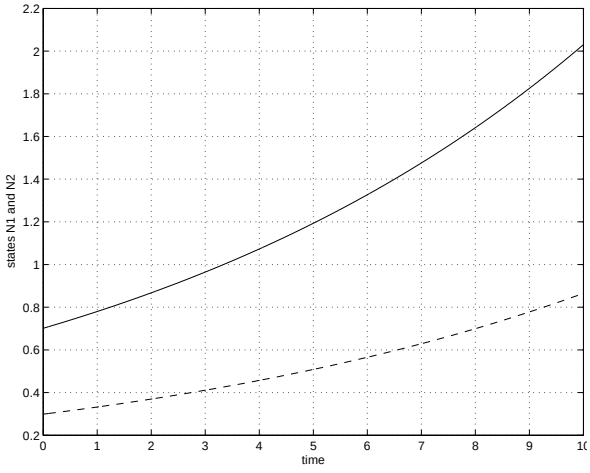

Fig. 3: States for (P_{soft}), $q = (0.1, 0.1)$

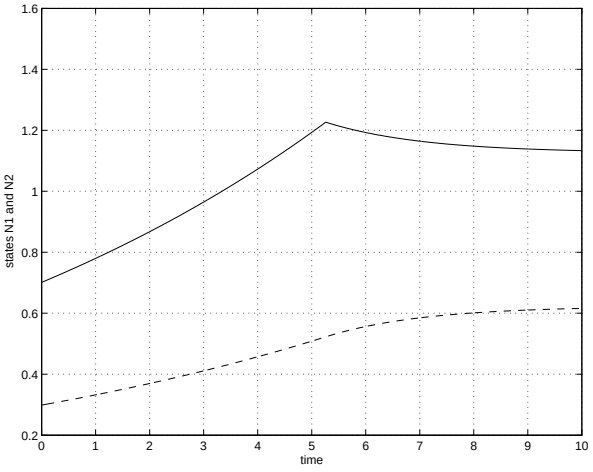

Fig. 4: States for (P_{hard})

The controls and trajectories given were computed using necessary conditions, but sufficient conditions developed in [4,5] apply to show that each control indeed is a strong local minimum. For high values of q optimal controls are bang-bang with one switching from $u = 1$ to $u = 0$. As the values for q are lowered the switching time approaches zero and has disappeared for $q = (0.1, 0.1)$. In particular, also for $q = (0, 0)$ the optimal control would be $u = 0$. This however, lets the total number of cancer cells grow exponentially. In the last simulation an explicit upper bound $N_1 + N_2 \leq \bar{N} = 1.75$ is imposed and as the system reaches this value, the control changes from $u = 0$ to the boundary control $u = \frac{1}{2s} = \frac{5}{8}$ which then leaves the value $\bar{N}$ invariant until the terminal time. For the parameters chosen, arguments from [6] can be used to again show that this solution is indeed locally optimal.

These simulations are only intended to show the changes of the structure of solutions for various values of q in the case of a soft state space constraint modelling and compare

with the case when hard limits are imposed. For high values of q the control is bang-bang with one switching with $u = 1$ initially. As q decreases the interval for which a full dose is given decreases until it disappears for small enough values of q. In this case the control is simply $u = 0$, i.e. the objective does not properly reflect the aims of treatment. The inclusion of a hard limit then still prevents the number of cancer cells to grow too high. But overall it is still the first approach of a soft modelling of the constraints with a reasonably large q which probably best represents the goals of treatment.

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