A Geometric Analysis of Bang-Bang Extremals in Optimal Control Problems for Combination Cancer Chemotherapy*

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***Abstract*— Cell-cycle specific compartmental models for the growth of cancer cells under combination chemotherapies are considered as multi-input optimal control problems over a fixed therapy interval. The controls are the dose rates of various chemotherapeutic agents, such as cytotoxic (killing) and cytostatic (blocking) drugs or recruiting agents. Singular controls are not optimal for the models under consideration and thus bang-bang controls become the natural candidates for optimality. We use a geometric approach based on the construction of a field of bang-bang extremals to determine the strong local optimality of extremals. If the flows of trajectories at a junction cross the switching surface transversally (*transversal crossing*), then local optimality is retained while it ceases if the two flows cross the switching surface in opposite directions (*transversal folds*). In the latter case, switching points are conjugate points for the combined flow. A simple algorithm will be described that allows us to verify if a junction is a transversal crossing or fold.**

I. Introduction

We formulate a geometric, field-theoretic approach to analyze the strong local optimality of bang-bang extremals in optimal control problems. The practical motivation for this work comes from the analysis of mathematical models for chemotherapy over a fixed therapy interval. For these problems, and consistent with medical practice, optimal protocols typically are bang-bang leading to therapy sessions consisting of periods of full dose treatment interlaced with rest periods when no drugs are given. We describe a geometric approach that is based on the construction of a field of bang-bang extremals and allows us to determine the strong local optimality of extremals by means of a simple algorithmic procedure. It was shown in our earlier work [10], [15] that a solution to the Hamilton–Jacobi–Bellman equation can be propagated across a switching surface if the two flows at the junction cross the switching surface transversally (*transversal crossing*) and in such a case local optimality is retained. On the other hand, if the flows cross the switching surface in opposite directions (*transversal folds*), the switching surface becomes an envelope for the control system. In this case, the switching points are conjugate points for the combined flow and local optimality ceases. We outline a simple computational procedure that allows us to distinguish between transversal crossings and folds.

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In recent years, there has been strong renewed activity analyzing the local optimality of bang-bang extremals. A. Sarychev [14] and A. Agrachev, G. Stefani and P.L. Zezza [1] employed a symplectic framework to define and analyze a second variation along bang-bang extremals. L. Poggiolini, G. Stefani and M. Spadini extended this framework to study both simple [12] and multiple [11] switchings at the junctions. U. Felgenhauer gave conditions that guarantee for the strong stability of these bang-bang structures [3], [4], [5]. Naturally, the various conditions that are obtained, including ours, are closely related. Our approach differs from the others in its direct geometric appeal and that it leads to a rather simple algorithmic determination of conjugate points that allows us to determine the strong local optimality of a bang-bang reference trajectory.

II. Cell-Cycle Specific Compartmental Models for Combination Chemotherapy

Every cell passes through a sequence of phases from cell birth to cell division. After an initial growth phase G_1, the cell enters a phase S where DNA synthesis occurs. Following a second growth phase G_2, the cell prepares for mitosis (phase M) that leads to cell division. Each of the two daughter cells can either reenter phase G_1 or for some time may simply lie dormant in a separate phase G_0 until reentering G_1, thus starting the entire process all over again.

While the simplest mathematical models for optimal control of cancer chemotherapy treat the entire cell cycle as one compartment, multi-compartment models cluster phases of the cell cycle with the purpose of effectively modeling the actions of different types of chemotherapeutic agents used [17], [18], [19]. Cytotoxic (killing) agents generally act in the G_2/M phase since the cell walls become thin and porous in mitosis M and thus the cell is more vulnerable to an attack. Cytostatic (blocking) agents, on the other hand, aim to synchronize the transitions of cells through the cell cycle by causing brief and invisible inhibition of DNA synthesis in the phase S and holding cells in G_1. Recruitment agents make cells leave the dormant compartment G_0 where they simply are not vulnerable to the attacks of any chemotherapeutic drugs. This classification of agents is broad and several drugs (e.g., paclitaxel), depending on the concentrations, show both cytotoxic and cytostatic effects.

A. Bilinear Dynamics

Depending on the specific type of tumor that is considered, and on the drugs that are administered, an appropriate clustering of the phases of the cell cycle is undertaken. The dynamics consist of balance equations that describe the transitions between the compartments with the state N a vector that gives the average number of cancer cells in the compartments. The transit times of cells through phases of the cell cycle vary, especially in malignant tumors. In a first approximation, an exponential distribution is used to model these transit times [18] and the expected number of cells exiting the ith compartment is simply given by $a_i N_i(t)$, where a_i is the inverse transit time through compartment i. The controls represent the administered dose rates of the drugs with the value 0 corresponding to no treatment and the upper limit $\bar{u}_i$ corresponding to a maximum dose. Overall, these assumptions lead to a bilinear dynamics of the form

$$\dot{N}(t) = (A + \sum_{i=1}^{m} u_i B_i) N(t), \quad N(0) = N_0. \qquad (1)$$

with the matrices describing the various in- and outflows from the compartments.

Example: Combination of a cytotoxic and a cytostatic drug. The cell-cycle is clustered into the compartments G_0/G_1, S, and G_2/M with a killing agent u_1 acting in G_2/M and a blocking agent u_2 active in the synthesis phase S. The matrices in the dynamics (1) are given by

$$A = \begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix},$$

$$B_1 = \begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix},$$

with the coefficient 2 accounting for cell division. In this paper, no pharmacokinetic model for the concentrations of the drugs in the blood stream is included and with respect to pharmacodynamics, the standard log-kill assumption is made. It implies that the dose rate stands in a direct relation to the fraction of cells that are killed in the G_2/M phase. Thence only the fraction $1 - u_1$ of the outflow of cells from the last compartment undergoes cell division and reenters the first compartment. The blocking agent u_2 is applied to slow the transit times of cancer cells during the synthesis phase S. As a result, the flow of cancer cells from the second into the third compartment is reduced by a factor u_2 of its original flow $a_2 N_2(t)$ to $(1 - u_2(t))a_2 N_2(t)$, $0 \le u_2(t) \le \bar{u}_2 < 1$.

B. Optimal Control Formulation

The problem of finding an optimal chemotherapy protocol is a multi-input optimal control problems over a fixed therapy horizon $[0, T]$ with the aim to minimize the number of cancer cells, both over the course of therapy and at the end of therapy, while limiting the side effects of the drugs. These side effects of the therapy can be included by either explicitly limiting the amounts of drugs to be given a priori (based on medical expertise) or by implicitly restricting their use by including an integral of the control over the therapy interval as a penalty term in the objective. In such a model minimizing controls will have to balance the amount of drugs given with the conflicting objective to kill cancer cells.

The choice of the objective is one persistent issue in modeling. The amounts of drugs administered are measured by integrals of the form $\int_0^T u(t)dt$ that are linear in u and under standard cell-cycle kinetic assumptions (log-kill hypothesis), these integrals also are a measure for the ineffective cell divisions and thus also for the side effects sustained during therapy. It therefore seems questionable to use models that are quadratic in the control. Clearly, these so-called L_2-objectives offer mathematical advantages in that the Hamiltonian of the resulting optimal control problem is strictly convex with a unique minimum, but they generally lack a biological justification. Therefore, we take as objective to be minimized the following one:

$$J = rN(T) + \int_0^T \left(qN(t) + \sum_{i=1}^{m} s_i u_i(t) \right) dt \qquad (2)$$

The penalty term $rN(T)$ represents a weighted average of the total number of cancer cells at the end of therapy $[0, T]$ while the term qN in the running cost is a weighted average of the number of cancer cells in the compartments during therapy. This term is included to prevent that this number increases to unacceptably high levels during the intermediate course of therapy. The number of cancer cells that do not undergo cell division at time t, and are considered killed, is modeled by the fraction of ineffective cell divisions. Since the drugs kill healthy cells at a proportional rate, the controls $u_i(t)$ are thus also used to model the negative effect of the drug on the normal tissue or its toxicity. The coefficients s_i are various nonnegative weights that model the degree of side effects which can be attributed to the specific chemotherapeutic agents.

Solutions to these models can be constructed based on applications of the Pontryagin maximum principle [13], a multiplier type collection of necessary conditions for optimality. For models that are linear in the controls with bounded control sets, like the one considered here, these conditions single out candidates for optimality that apply the controls at full or no dose, so-called *bang-bang controls*, or controls with values in the interior of the control set that follow specific time-varying formulas, so-called *singular controls*. For cell-cycle specific compartmental models, it typically is possible, like for the model formulated above [7], but also for other formulations [6], [8], to exclude the optimality of singular controls by means of higher order necessary conditions for optimality such as the generalized Legendre–Clebsch conditions [2], [15]. Thus bang-bang controls become the natural candidates for optimality. In the next section we develop a simple algorithmic procedure that allows us to determine their local optimality.

III. Transversal Crossings and Folds in Flows of Bang-Bang Extremals

More generally, we consider the following optimal control problem: For a fixed terminal time T and given initial conditions $(t_0, x_0) \in \mathbb{R} \times \mathbb{R}^n$, minimize the functional

$$\mathcal{J}(u) = \int_{t_0}^{T} L(x(s), u(s))ds + \varphi(x(T)) \tag{3}$$

over all locally bounded, Lebesgue measurable functions u that take values in a prescribed control set U,

$$u : [t_0, T] \to U \subset \mathbb{R}^m, \quad t \mapsto u(t),$$

for which the solution x of the initial value problem

$$\dot{x}(t) = f(x(t), u(t)), \qquad x(t_0) = x_0, \tag{4}$$

exists over the full interval $[t_0, T]$.

We make standard assumptions on the data and call a locally bounded, Lebesgue measurable function u with values in U (a.e.) an *admissible control*. The solution x of the differential equation (1) for u is the *corresponding trajectory* and the pair (x, u) is called a *controlled trajectory*. Also, the control Hamiltonian H is defined as

$$H = H(t.\lambda_0, \lambda, x, u) = \lambda_0 L(t, x, u) + \lambda f(t, x, u). \tag{5}$$

with $\lambda_0 \in \mathbb{R}$ and λ an n-dimensional row vector, $\lambda \in (\mathbb{R}^n)^*$.

A. Parameterized Families of Extremals and Solutions to the Hamilton–Jacobi–Bellman Equation

Necessary conditions for optimality are given by the Pontryagin maximum principle [13], [15] and a parameterized family of extremals is a collection of controlled trajectories and multipliers that satisfy these conditions. Specifically, we require that the parameterizations are "smooth" and we first assume that with p a parameter, the controls $u = u(t, p)$ are continuous and r-times continuously differentiable in the parameter p with the partial derivatives continuous in (t, p). We write $u \in C^{0,r}$ for this class of functions. In principle, the parameter can be anything, but for problem [OC] there is a canonical choice for the parametrization taking the value of the trajectory at the endpoint, $p = x(T)$, and then integrating the dynamics and adjoint equation backward from the terminal T while maintaining the minimum condition. This leads to the following formal definition:

Definition 3.1: Given an open subset P of $\mathbb{R}^n$ and an r-times continuously differentiable function $t_- \in C^r(P)$, let

$$D = \{(t, p) : p \in P,\, t_-(p) \le t \le T\}.$$

A *C^r-parameterized family $\mathcal{E}$ of extremals* (or extremal lifts) with domain D consists of

1) a family of controlled trajectories

$$(x, u) : D \to \mathbb{R}^n \times U, \quad (t, p) \mapsto (x(t, p), u(t, p)),$$

such that $u \in C^{0,r}(D)$ and

$$\dot{x}(t, p) = f(x(t, p), u(t, p)), \quad x(T, p) = p. \tag{6}$$

2) a non-negative multiplier $\lambda_0 \in C^{r-1}(P)$ and co-state $\lambda : D \to (\mathbb{R}^n)^*$, $\lambda = \lambda(t, p)$, so that $(\lambda_0(p), \lambda(t, p)) \neq (0, 0)$ for all $(t, p) \in D$ and the adjoint equation,

$$\dot{\lambda}(t, p) = -\frac{\partial H}{\partial x}(\lambda_0(p), \lambda(t, p), x(t, p), u(t, p)), \tag{7}$$

is satisfied on $[t_-(p), T]$ with terminal condition

$$\lambda(T, p) = \lambda_0(p)\frac{\partial \varphi}{\partial x}(p) \tag{8}$$

3) and $u(t, p)$ is a solution to the minimization problem

$$\begin{aligned} &H(\lambda_0(p), \lambda(t, p), x(t, p), u(t, p)) \\ &\qquad = \min_{v \in U} H(\lambda_0(p), \lambda(t, p), x(t, p), v). \end{aligned} \tag{9}$$

This definition provides the framework for our constructions and it merely formalizes that all controlled trajectories in the family $\mathcal{E}$ satisfy the conditions of the maximum principle while some smoothness properties are satisfied by the parametrization. The degree r in the definition denotes the smoothness of the parametrization of the controls in the parameter p, $u \in C^{0,r}$, and it follows from standard results on ODEs that the states x lie in $C^{1,r}$ and the multiplier λ lies in $C^{1,r-1}$. If $\lambda_0(p) > 0$ for all $p \in P$, then all extremals are normal and by diving by $\lambda_0(p)$ we may assume that $\lambda_0(p) \equiv 1$ and we call such a family *normal*.

Definition 3.2: Let $\mathcal{E}$ be a C^r-parameterized family of extremals. The flow associated with the controlled trajectories (x, u) is the mapping

$$F : D \to \mathbb{R} \times \mathbb{R}^n, \quad (t, p) \longmapsto F(t, p) = \begin{pmatrix} t \\ x(t, p) \end{pmatrix},$$

i.e., is defined in terms of the graphs of the corresponding trajectories. We say the flow F is a $C^{1,r}$-mapping on an open set $Q \subset D$ if the restriction of F to Q is continuously differentiable in (t, p) and r times differentiable in p with derivatives that are jointly continuous in (t, p). If $F \in C^{1,r}(Q)$ is injective and the Jacobian matrix $DF(t, p)$ is nonsingular everywhere on Q, then we say F is a $C^{1,r}$-diffeomorphism onto its image $F(Q)$.

Definition 3.3: Given a C^r-parameterized family $\mathcal{E}$ of extremals with domain D, the corresponding *parameterized cost* or *cost-to-go function* is the function $C : D \to \mathbb{R}$,

$$(t, p) \mapsto C(t, p) = \int_t^T L(x(s, p), u(s, p))\, ds + \varphi(p).$$

Thus C is the value of the objective $J(u)$ for $u = u(\cdot, p)$ if the initial condition at time t is given by $x(t, p)$.

Note that we do not assume in our definitions that the flow F covers the state space injectively. If this is the case, we call the corresponding family a field.

Definition 3.4: A C^r-parameterized local field of extremals $\mathcal{F}$ for problem [OC] is a C^r-parameterized family of normal extremals such that the associated flow $F : D \to \mathbb{R} \times \mathbb{R}^n$, $(t, p) \mapsto F(t, p)$, is a $C^{1,r}$-diffeomorphism. Note that F is locally a $C^{1,r}$-diffeomorphism if and only if the Jacobian matrix $\frac{\partial x}{\partial p}$ is non-singular on D.

In this case, the value $V^{\mathcal{E}}$ corresponding to the parameterized family $\mathcal{E}$ can be defined in the state space as

$$V^{\mathcal{E}} : G \to \mathbb{R}, \quad V^{\mathcal{E}} = C \circ F^{-1},$$

and is a continuously differentiable function. It is shown in [10], [15] that $V^{\mathcal{E}}$ is a solution to the Hamilton–Jacobi–Bellman equation on the region G of the state space that is covered injectively by the flow of trajectories and this leads to the following sufficient condition for strong local optimality:

Proposition 3.1: [10] Let $\mathcal{F}$ be a C^r-parameterized local field of extremals for problem [OC] and suppose the associated flow F covers a domain G. Then, given any initial condition $(t_0, x_0) \in G$, $x_0 = x(t_0, p_0)$, the open-loop control $\bar{u}(t) = u(t, p_0)$, $t_0 \le t \le T$, is optimal when compared with any other admissible controlled trajectory (x, u) with the same initial condition whose graph lies in G. □

Hence the strong local optimality of a controlled trajectory $(x(\cdot, p_0), u(\cdot, p_0))$ is connected with the local injectivity of the flow F along this trajectory and thus closely related to the regularity of the differential of the flow, $DF(\cdot, p_0)$. There exist well-known classical results that date back to Legendre and express the regularity of the function $t \mapsto \frac{\partial x}{\partial p}(t, p_0)$ in terms of the existence of a solution to a Riccati differential equation (for example, see [2], [15]).

B. Parameterized Families of Broken Extremals

As for bang-bang controls, optimal controls are rarely continuous and it becomes necessary to concatenate parameterized families of extremals. Without loss of generality, we simply consider two flows. For the same parameter set P, let $\mathcal{E}_1$ and $\mathcal{E}_2$ be C^r-parameterized families of extremals with domains $D_1 = \{(t, p) : p \in P,\, t_1(p) \le t \le \tau(p)\}$ and $D_2 = \{(t, p) : p \in P,\, \tau(p) \le t \le T\}$, and denote the associated controls, trajectories and multipliers by the corresponding subscript. These two C^r-parameterized families of extremals can be concatenated if for all $p \in P$ the states and the multipliers agree at the junction. The concatenated family $\mathcal{E} = \mathcal{E}_1 * \mathcal{E}_2$ then is defined as the family of extremals with domain

$$D = \{(t, p) : p \in P,\, t_1(p) \le t \le T\},$$

and the controls u, trajectories x and adjoint variable λ are defined piecewise.

Definition 3.5: A C^r-parameterized family of broken extremals is a finite concatenation $\mathcal{E} = \mathcal{E}_1 * \cdots * \mathcal{E}_k$ of C^r-parameterized families of extremals.

The set $\mathcal{T} = \{(t, p) : t = \tau(p),\ p \in P\}$ defining the junction is an embedded hypersurface in D and its image in the (t, x)-space is the switching surface

$$\mathcal{S} = \{(t, x) : t = \tau(p),\ x = x(\tau(p), p),\ p \in P\}.$$

If the differential $DF_i(t, p)$ of the flow F_i for $i = 1$ or $i = 2$ is nonsingular for $t = \tau(p)$, then the switching surface $\mathcal{S}$ is an embedded n-dimensional submanifold near $(t, x) = (\tau(p), x(\tau(p), p))$ and the flow F_i is transversal to $\mathcal{S}$.

Definition 3.6: We say the C^r-parameterized family $\mathcal{E} = \mathcal{E}_1 * \mathcal{E}_2$ of broken extremals has a *regular switching point* at $(t_0, p_0) = (\tau(p_0), p_0)$ if both flow maps F_1 and F_2 are nonsingular at (t_0, p_0). We call such a switching point a *transversal crossing* if the graphs of the trajectories $t \mapsto x_i(t, p)$, $i = 1, 2$, cross the switching surface $\mathcal{S}$ in the same direction and a *transversal fold* if they cross it in opposite directions.

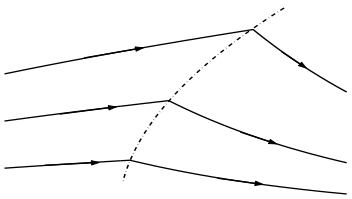

Fig. 1. The flow of a parameterized family of broken extremals near a transversal crossing.

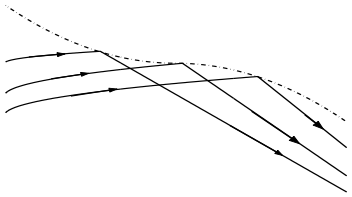

Fig. 2. The flow of a parameterized family of broken extremals near a transversal fold.

We give a characterization of transversal crossings and folds in the parameter space. Since we typically integrate the family of extremals backward from the terminal manifold, here we take the second parameterized family $\mathcal{E}_2$ as our starting point.

Proposition 3.2: [15] Suppose $\frac{\partial x_2}{\partial p}(\tau(p), p)$ is nonsingular and with $\xi(p) = x_1(\tau(p), p) = x_2(\tau(p), p)$ and $u_i(p) = u_1(\tau(p), p))$ for $i = 1, 2$, let

$$k(p) = f(\tau(p), \xi(p), u_2(p)) - f(\tau(p), \xi(p), u_1(p)).$$

The point $(\tau(p), p)$ is a regular switching point if and only if

$$1 + \frac{\partial \tau}{\partial p}(p) \left(\frac{\partial x_2}{\partial p}(\tau(p), p) \right)^{-1} k(p) \neq 0. \tag{10}$$

The concatenated family $\mathcal{E} = \mathcal{E}_1 * \mathcal{E}_2$ of normal broken extremals has a transversal crossing at $(\tau(p), p)$ if the expression in (10) is positive and a transversal fold if it is negative. □

It can be shown that local optimality properties of the flow of extremals are preserved at transversal crossings—in fact, in this case the value $V^{\mathcal{E}}$ remains a continuously differentiable solution of the Hamilton–Jacobi–Bellman equation at the switching surface $\mathcal{S}$ [10], [15]—while typically optimality ceases at a switching surface consisting of transversal folds. Essentially, under some regularity assumptions, in the latter case the switching surface $\mathcal{S}$ is made up of controlled trajectories (ξ, η) that are envelopes [16], [15]. If it can be

argued that controlled trajectories that lie in $\mathcal{S}$ cannot be optimal, then using an envelope theorem, it can be shown that $\mathcal{S}$ consists of conjugate points and optimality ceases. For example, the following result holds:

Theorem 3.1: [15] Let $\mathcal{E} = \mathcal{E}_1 * \mathcal{E}_2$ be a C^1-parameterized family of normal broken extremals for the optimal control problem [OC] for a single-input control-affine system of the form $\dot{x} = f(x) + ug(x)$, $0 \leq u \leq u_{max}$, $x \in \mathbb{R}^n$, and suppose that the controls have a bang-bang switch at time $\tau(p)$. If the flow undergoes a transversal fold at $\mathcal{T} = \{(t,p) : t = \tau(p),\ p \in P\}$, then through every point q on the switching surface

$$\mathcal{S} = \{(t,x) : t = \tau(p),\ x = x(\tau(p),p),\ p \in P\} = F(\mathcal{T}),$$

passes a controlled trajectory corresponding to a singular control. If singular controlled trajectories that lie in $\mathcal{S}$ violate the Legendre–Clebsch condition, then optimality of the flow ceases at $\mathcal{S}$. □

Altogether, the following result holds:

Proposition 3.3: Let $\mathcal{E}$ be an n-dimensional C^r-parameterized family of normal broken extremals for the optimal control problem [OC] with switching times

$$t_-(p) = \tau_0(p) < \tau_1(p) < \cdots < \tau_k(p) < \tau_{k+1}(p) = T.$$

If (i) the matrix $\frac{\partial x_i}{\partial p}(t, p_0)$ is nonsingular on the intervals $\tau_i(p_0) \leq t \leq \tau_{i+1}(p_0)$ for $i = 0, \ldots, k$, and if (ii) the trajectory $x(\cdot, p_0)$ has transversal crossings at all switchings, then there exists a neighborhood P of p_0 such that the parameterized family $\mathcal{E}$ with domain $D = \{(t,p) : t_-(p) \leq t \leq T,\ p \in P\}$ defines a field of normal broken extremals. In particular, the cost-to-go function gives rise to a continuously differentiable solution to the Hamilton–Jacobi–Bellman equation on $G = F(D)$ and the associated local optimality results hold. □

C. Local Analysis of a Flow of Bang-Bang Extremals

The situation simplifies considerably in case of *bang-bang controls*. It is clear from the uniqueness of solutions to a differential equation that the flow F corresponding to a constant control cannot have singularities and $\frac{\partial x}{\partial p}(\cdot, p_0)$ is nonsingular over an interval $[t_-(p), t_+(p)]$ if and only if it is nonsingular at the initial (or terminal) time. *Conjugate points can thus occur only at the switching points, and these are transversal folds.*

While for some problems it may be easy to check directly whether switchings are transversal crossings or folds, Proposition 3.2 allows us to do this in an effective way in general. Note that we keep the formulation here general, but for multi-input systems it is realistic only if only one of the components switches. This, however, is the typical case. Simultaneous switchings of the controls become much more difficult to analyze [11], but they are the exception and here we assume that all switchings are in only one of the controls.

For simplicity, and in line with our problem formulation for the compartmental models for chemotherapy, we assume that the dynamics is of the form $\dot{x} = f(x) + ug(x)$ with a scalar control u, $0 \leq u \leq u_{\max}$. Also, we integrate trajectories backward and denote the left- and right-hand limits of functions at the switching surface by a $-$ and $+$ sign, respectively. The parametrization $t = \tau(p)$ defining the switching surface $\mathcal{S}$ then is the solution of the equation

$$\Phi(t,p) = c + \langle \lambda(t,p), g(x(t,p)) \rangle = 0$$

for t with c a constant. By the implicit function theorem, this solution exists if the time derivative $\dot{\Phi}(t,p)$ does not vanish for $t = \tau(p)$. Consider a reference extremal determined by the parameter value p_0 and let $t_0 = \tau(p_0)$ and $x_0 = x(t_0, p_0)$. Using implicit differentiation, and taking into account the special form of the dynamics, it can be shown (e.g., see [10], [15]) that the transversality condition (10) is equivalent to

$$\begin{aligned} |\dot{\Phi}(t_0,p_0)| + u_{\max} \{ & \lambda(t_0,p_0) Dg(x_0) \\ & + g^T(x_0) Z_+(t_0,p_0) \} \, g(x_0) \neq 0 \end{aligned} \tag{11}$$

where, more generally,

$$Z_\pm(t,p) = \frac{\partial \lambda^T}{\partial p}(t\pm,p) \left(\frac{\partial x}{\partial p}(t\pm,p) \right)^{-1},$$

and the switching is a crossing if the sign in (11) is positive and a fold if it is negative. Except for the value of the matrix $Z_+(t_0,p_0)$, all the quantities in (11) are continuous at the switching time and are readily available. Neither is it difficult to compute the values of the matrix Z. For a constant control u, it follows from the variational equations that Z satisfies the Lyapunov equation

$$\begin{aligned} \dot{Z} + Z(DF(x) + uDg(x)) + (DF(x) + uDg(x))^T Z \\ + H_{xx}(\lambda, x, u) \equiv 0, \end{aligned} \tag{12}$$

along the extremal $(\lambda, x, u) = (\lambda(\cdot,p), x(\cdot,p), u(\cdot,p))$ corresponding to the parameter p. Hence the values of Z are easily propagated backward from its terminal value

$$Z(T,p) = \frac{\partial^2 \varphi}{\partial x^2}(p).$$

However, the partial derivatives $\frac{\partial x}{\partial p}$ and $\frac{\partial \lambda^T}{\partial p}$ are discontinuous at the switching surface, and it becomes necessary to update the values of Z at switching points. This can be done using standard results from matrix algebra about inversion of rank-1 perturbations of nonsingular matrices and we just give the result (see [10], [15]):

$$\begin{aligned} Z_-(t_0,p_0) \quad = \quad & \left(Z_+(t_0,p_0) + Dg(x_0)^T \lambda(t_0,p_0)^T R(p_0) \right) \\ & \times \left(\mathrm{Id} + \frac{g(x_0) R(p_0)}{1 - R(p_0) g(x_0)} \right) \end{aligned} \tag{13}$$

where

$$R(p_0) = \frac{u_{\max}}{\left| \dot{\Phi}(t_0,p_0) \right|} \left(\lambda(t_0,p_0) Dg(x_0) + g^T(x_0) Z_+(t_0,p_0) \right). \tag{14}$$

Also, the expression $1 - R(p_0)g(x_0)$ in the denominator in (13) is an equivalent expression for the transversality condition (10) and thus is nonzero.

IV. Mathematical Models for Chemotherapy with Blocking and Recruiting Agents

We return to the example formulated earlier. It has been shown in [7] that singular controls cannot be optimal and thus transversal folds limit the optimality of any flow of bang-bang extremals. The algorithmic procedure outlined above has been used to verify the strong local optimality of the bang-bang flow around the reference extremal given below. The inverse cell cycle transit times were taken as $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$ [18] and the coefficients in the objective were chosen as $r_1 = 1$, $r_2 = 0.5$, $r_3 = 1$, $q_1 = 0.01$, $q_2 = 0.2$, $q_3 = 0.01$, and $s_1 = 100$, $s_2 = 0.2$. The therapy horizon was $[0, 50]$ (in days). Figure 3 shows the optimal cytotoxic and cytostatic agents and the time course of the corresponding states N_i, $i = 1, 2, 3$. The dotted curves which are included in the plots of the controls show the respective switching functions. As initial conditions we used the steady state proportions of the uncontrolled dynamics. In this scenario, initially both blocking and killing agents are used at maximum rates in order to prevent further cell divisions as much as possible. As the cancer shrinks, the more toxic killing agent gets replaced by an on-and-off regime for the weaker cytostatic agent.

V. Conclusion

In the paper, we described a geometric approach to sufficient conditions for strong local optimality of bang-bang extremals. The procedure is applicable regardless of whether single-input or multi-input control systems are considered as long as switchings arise in only one of the controls. The required transversality conditions at the corresponding switching surfaces can easily be determined algorithmically and this makes this an effective procedure to check optimality of bang-bang extremals. These results were developed in the context of the analysis of bang-bang extremals in mathematical models for cell-cycle specific cancer chemotherapy.

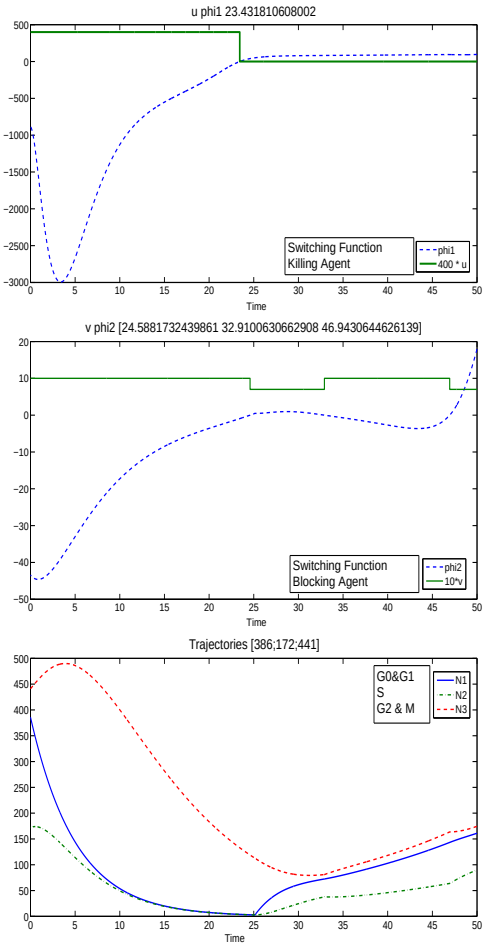

Fig. 3. Optimal cytotoxic (top) and cytostatic (middle) agents and time course (bottom) of the corresponding bang-bang trajectory.

References

[1] A. Agrachev, G. Stefani, and P.L. Zezza, Strong optimality for a bang-bang trajectory, *SIAM J. Contr. and Opt.*, **41** (2002), pp. 991–1014.

[2] A.E. Bryson, Jr. and Y.C. Ho, *Applied Optimal Control*, Revised Printing, Hemisphere Publishing Company, New York, 1975.

[3] U. Felgenhauer, On stability of bang-bang type controls, *SIAM J. Control Optim.*, **41** (2003), pp. 1843–1867.

[4] U. Felgenhauer, Lipschitz stability of broken extremals in bang-bang control problems, in: Large-Scale Scientific Computing (Sozopol 2007), (I. Lirkov et al., eds.), Lecture Notes in Computer Science, vol. 4818, Springer-Verlag (2008), pp. 317–325.

[5] U. Felgenhauer, L. Poggiolini, and G. Stefani, Optimality and stability result for bang-bang optimal controls with simple and double switch behaviour. in: *50 Years of Optimal Control*, (A. Ioffe, et al., eds.), *Control and Cybernetics*, **38** (4B) (2009), pp. 1305–1325.

[6] U. Ledzewicz and H. Schättler, Optimal bang-bang controls for a 2-compartment model in cancer chemotherapy, *J. of Optimization Theory and Applications - JOTA*, **114**, (2002), pp. 609–637.

[7] U. Ledzewicz and H. Schättler, Analysis of a cell-cycle specific model for cancer chemotherapy, *J. of Biol. Syst.*, **10**, 2002, pp. 183–206.

[8] U. Ledzewicz and H. Schättler, Optimal control for a bilinear model with recruiting agent in cancer chemotherapy, Proceedings of the 42nd IEEE Conference on Decision and Control (CDC), Maui, Hawaii, December 2003, pp. 2762–2767.

[9] R. Martin and K.L. Teo, *Optimal Control of Drug Administration in Cancer Chemotherapy*, World Scientific, Singapore, 1994.

[10] J. Noble and H. Schättler, Sufficient conditions for relative minima of broken extremals, *J. of Mathematical Analysis and Applications*, **269**, 2002, pp. 98–128.

[11] L. Poggiolini and M. Spadini, Strong local optimality for a bang-bang trajectory in a Mayer problem, *SIAM J. Control and Optimization*, **49** (2011), pp. 140–161.

[12] L. Poggiolini and G. Stefani, Sufficient optimality conditions for a bang-bang trajectory, in: *Proc. 45th IEEE Conference on Decision and Control*, (2006).

[13] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze and E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*, MacMillan, 1964.

[14] A. Sarychev, Morse index and sufficient optimality conditions for bang-bang Pontryagin extremals, in: *System Modeling and Optimization*, Lecture Notes in Control and Information Sciences, Vol. 180, (1992), pp. 440–448.

[15] H. Schättler and U. Ledzewicz, *Geometric Optimal Control—Theory, Methods and Examples*, Springer-Verlag, New York, 2012.

[16] H.J. Sussmann, Envelopes, high-order optimality conditions and Lie brackets, Proc. of the 28th IEEE Conference on Decision and Control, Tampa, Florida, December 1989, pp. 1107–1112.

[17] A. Swierniak, Some control problems for simplest differential models of proliferation cycle, *Appl. Math. and Comp. Sci.*, **4**, 1994, pp. 223–232.

[18] A. Swierniak, Cell cycle as an object of control, *J. of Biol. Syst.*, **3**, 1995, pp. 41–54.

[19] A. Swierniak, U. Ledzewicz, and H. Schättler, Optimal control for a class of compartmental models in cancer chemotherapy, *Int. J. Applied Math. and Computer Sci.*, **13**, (2003), pp. 357–368