SUFFICIENT CONDITIONS FOR OPTIMALITY FOR A MATHEMATICAL MODEL OF DRUG TREATMENT WITH PHARMACODYNAMICS

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Communicated by Marek Galewski

Abstract. We consider an optimal control problem for a general mathematical model of drug treatment with a single agent. The control represents the concentration of the agent and its effect (pharmacodynamics) is modelled by a Hill function (i.e., Michaelis-Menten type kinetics). The aim is to minimize a cost functional consisting of a weighted average related to the state of the system (both at the end and during a fixed therapy horizon) and to the total amount of drugs given. The latter is an indirect measure for the side effects of treatment. It is shown that optimal controls are continuous functions of time that change between full or no dose segments with connecting pieces that take values in the interior of the control set. Sufficient conditions for the strong local optimality of an extremal controlled trajectory in terms of the existence of a solution to a piecewise defined Riccati differential equation are given.

Keywords: optimal control, sufficient conditions for optimality, method of characteristics, pharmacodynamic model.

Mathematics Subject Classification: 49K15, 93C15, 92C45.

1. INTRODUCTION

We consider optimal control problems for drug treatment. The controls u in the formulation represent the dosages of various therapeutic agents while pharmacokinetic models (PK) describe the relations between the dosages of the agents and their concentrations c in the blood stream ("what the body does to the drug") and pharmacodynamic models (PD) describe the effects that the drugs have on the disease ("what the drug does to the body"). Generally, PK is modelled by low-dimensional linear differential equations with real eigenvalues [7]. Pharmacodynamic models, on the other

hand, are simply given by functional relations of the form $\varphi(c)$ that model the effect the concentration c has. Here both linear models (based on the log-kill hypothesis [17]) as well as Michaelis-Menten or sigmoidal functional relations are commonly used [10,13]. While there exists a large literature on optimal control of mathematical models for chemotherapy going back to the early papers by Swierniak [19] and Swan [18], even including papers with state-space constraints (e.g., [5]), in most of these papers pharmacodynamic relations are not included. Yet, these type of functional relations are highly nonlinear and thus the dependence of optimal controls on the specific relations used in the modeling becomes a mathematically nontrivial problem [8, 9, 15] which at the same time is of great practical interest. These changes that *pharmacometrics* (i.e., both PK and PD) induce on the structure of optimal solutions are the scope of our research.

In this paper, we present results about the structure of optimal controls for a single chemotherapeutic agent when pharmacodynamics is modelled by a Michaelis-Menten type equation. This relation is based on enzyme kinetics and takes the form

$$E_{\max} \frac{c}{C_{50} + c}, \tag{1.1}$$

where $E_{\max}$ denotes the maximum effect the drug can have and C_{50} is the concentration for which half of this maximum effect is realized. These are standard parameters used in pharmacology to describe the effectiveness of drugs. This model, also called the $E_{\max}$-model in pharmacology, is appropriate for fast acting drugs that do not have a prolonged initial phase when the concentration builds up slowly. During such a phase the drug is still rather ineffective and a sigmoidal model would be more appropriate. Contrary to linear models of the form γc, a Michaelis-Menten form captures the typical saturation effects when the concentration becomes too large. As such it is the most commonly used model for PD in the industry. For simplicity, here we also do not include a pharmacokinetic model and thus identify the drug's dosage with its concentration in the blood stream. Once more, this is a reasonable modeling assumption for fast acting drugs.

For a fixed therapy horizon, we consider the optimal control problem to minimize a weighted average of quantities related to the state of the disease or infection and the total amount of drugs administered. The latter is given by the integral $\int_0^T u(s)ds$, the so-called AUC ("area under the curve") widely used in the pharmaceutical industry to describe the efficacy of treatment. It also represents an indirect assessment of the side effects of therapy and thus including it in the objective tends to limit these negative effects. We show in this paper that a Michaelis-Menten type expression for the pharmacodynamics induces enough convexity properties on the Hamiltonian function of the optimal control problem as a function of the control u to generate optimal controls which are continuous in time. This is consistent with an interpretation of the controls as concentrations (since no PK model is included) and it significantly simplifies numerical computations. Sufficient conditions for the strong local optimality of an extremal controlled trajectory in terms of the existence of a solution to a piecewise defined Riccati differential equation are given based on the method of characteristics.

2. FORMULATION OF THE OPTIMAL CONTROL PROBLEM

We consider a general system of differential equations of the form

$$\dot{x} = f(x) + \frac{u}{1+u}g(x), \tag{2.1}$$

where $f : D \to \mathbb{R}^n$ and $g : D \to \mathbb{R}^n$ are continuously differentiable vector fields defined on some domain $D \subset \mathbb{R}^n$. The dynamics represents an abstract formulation for chemotherapy with a single agent. The vector field f, called the *drift*, describes the evolution of the system when no drugs are given ($u \equiv 0$), while the vector field g, the *control vector field*, in combination with the control term describes the effects of drug treatment. The variable u, the *control* in the system, represents the *concentration* of the chemotherapeutic agent given. In this formulation we do not yet include a pharmacokinetic equation and thus identify the dosage with the concentration. The functional form used for the control u represents a Michaelis-Menten or $E_{\max}$-model with C_{50} normalized to 1 and the constant $E_{\max}$ subsumed in g.

Controls are Lebesgue measurable functions $u : [0, T] \to [0, u_{\max}]$ defined over an a priori fixed therapy horizon $[0, T]$ that take values in a compact interval $[0, u_{\max}]$. It follows from standard results on solutions of differential equations that for any $x_0 \in D$ the initial value problem for the dynamics (2.1) with initial condition $x(0) = x_0$ has a unique local solution $x(\cdot; x_0)$ which we call the corresponding trajectory. However, for general vector fields f and g there is no guarantee that this solutions will exist on all of $[0, T]$. *Admissible controls* thus are only those controls for which this solution exists over the full therapy horizon. For an admissible control we then define the *objective functional J* in the form

$$J = J(u) = \alpha x(T) + \int_0^T \beta x(s) + \gamma u(s)ds, \tag{2.2}$$

where α and β are n-dimensional row vectors, $\alpha, \beta \in (\mathbb{R}^n)^*$, and γ is a positive real number. The term $\alpha x(T)$ represents a weighted average of the variables x at the terminal time T (such as the total number of cancer cells at the end of therapy) while the integral term on the state x is included to prevent that this quantity would increase to unacceptably high levels in between. The integral of the control is the AUC-term of pharmacology and it is a measure for the side effects of treatment. Minimizing this quantity J generates a compromise between two competing aims of treatment. On one hand, the aim is to reduce the state x which represents the severity of the disease or infection (e.g., tumor volume) 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 α, β and γ in the objective and generally these coefficients are variables of choice which often need to be selected carefully to obtain a meaningful behavior.

We thus consider the following optimal control problem:

[MM] Minimize the functional J over all admissible controls $u : [0, T] \to [0, u_{max}]$ subject to the dynamics (2.1).

3. NECESSARY CONDITIONS FOR OPTIMALITY

The fundamental necessary conditions for optimality for problem [MM] are given by the Pontryagin maximum principle [12] (for some more recent references on optimal control, see [1,2,14]). Since the optimal control problem [MM] does not involve terminal constraints on the state, extremals are normal and without loss of generality we already define the Hamiltonian function H for the control problem as

$$H : (\mathbb{R}^n)^* \times \mathbb{R}^n \times \mathbb{R} \to \mathbb{R},$$

$$(\lambda, x, u) \to H(\lambda, x, u) = \beta x + \gamma u + \left\langle \lambda, f(x) + \frac{u}{1+u} g(x) \right\rangle \tag{3.1}$$

with $\langle \lambda, v \rangle = \lambda v$ denoting the inner product of a row vector λ with a column vector v. It follows from the Pontryagin maximum principle [12] that, if u_* is an optimal control and x_* denotes the corresponding trajectory, then there exists a covector $\lambda : [0, T] \to (\mathbb{R}^n)^*$ which is a solution to the *adjoint equation*,

$$\dot{\lambda} = -\beta - \lambda \left(Df(x) + \frac{u}{1+u} Dg(x) \right) \tag{3.2}$$

with terminal condition $\lambda(T) = \alpha$ such that the Hamiltonian H is minimized almost everywhere on $[0, T]$ by u_* along $(\lambda(t), x_*(t))$, i.e.,

$$H(\lambda(t), x_*(t), u_*(t)) = \min_{0 \leq v \leq u_{max}} H(\lambda(t), x_*(t), v). \tag{3.3}$$

Controlled trajectories (x, u) for which there exists a multiplier λ such that these conditions are satisfied are called *extremals* and the triples (x, u, λ) including the multipliers are called extremal lifts (to the cotangent bundle).

An important property for solutions to the optimal control problem [MM] is that optimal controls are continuous. More specifically, we have the following representation of optimal controls.

Theorem 3.1. *Let u_* 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*

$$u_*(t) = \begin{cases} u_{max} & \text{if } \langle \lambda(t), g(x_*(t)) \rangle \leq -\gamma(u_{max} + 1)^2, \\ \sqrt{-\frac{\langle \lambda(t), g(x_*(t)) \rangle}{\gamma}} - 1 & \text{if } -\gamma(u_{max} + 1)^2 \leq \langle \lambda(t), g(x_*(t)) \rangle \leq -\gamma, \\ 0 & \text{if } -\gamma \leq \langle \lambda(t), g(x_*(t)) \rangle. \end{cases} \tag{3.4}$$

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

$$\frac{\partial H}{\partial u} = \gamma + \frac{\langle \lambda, g(x) \rangle}{(1+u)^2},$$

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

$$\Phi(t) = \langle \lambda(t), g(x_*(t)) \rangle \tag{3.5}$$

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

$$\frac{\partial^2 H}{\partial u^2} = -\frac{2\langle \lambda, g(x) \rangle}{(1+u)^3}$$

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

$$u_{st}(t) = \sqrt{-\frac{\Phi(t)}{\gamma}} - 1. \tag{3.6}$$

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 $[0, u_{max}]$ with minimum at $u_* = 0$; if $0 \leq u_{st}(t) \leq u_{\max}$, then the global minimum lies in the control set and thus u_* is given by the stationary point, and if $u_{st}(t) > u_{\max}$, then $H(\lambda(t), x_*(t), \cdot)$ is strictly decreasing over $[0, u_{max}]$ with minimum at $u_* = u_{\max}$. This proves the result. $\square$

Corollary 3.2. *Optimal controls are continuous.*

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

$$u_*(t) = \max\{0, \min\{u_{st}(t), u_{\max}\}\} \tag{3.7}$$

and thus u_* is continuous as long as $\Phi(t)$ is negative. For $\Phi(t) \geq 0$ the optimal control is given by $u_* \equiv 0$ which is also the optimal control for $\Phi(t) \geq -\gamma$. Hence, optimal controls remain continuous as Φ becomes nonnegative. $\square$

Thus optimal controls continuously change between the limiting values $u_{\max}$ and 0 and values that lie in the interior of the control set as the function Φ crosses the levels $-\gamma$ and $-\gamma(1 + u_{\max})^2$. We therefore call the function Φ 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 3.3. *If the indicator function Φ is strictly increasing on $[0, T]$, then optimal controls are concatenations of boundary and interior controls of at most the sequence $\mathbf{u}_{\max} \to \mathbf{u_{st}(t)} \to \mathbf{0}$, i.e., possibly starting with a full dose segment, $u_*(t) \equiv u_{\max}$, controls switch to the interior control $u_*(t) = u_{st}(t)$ and end with a segment where no drugs are given, $u_*(t) \equiv 0$. 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 Φ is strictly decreasing on $[0, T]$, then optimal controls are at most concatenations that follow the sequence $\mathbf{0} \to \mathbf{u_{st}(t)} \to \mathbf{u}_{\max}$ and in this case the interior control is strictly increasing (see Figure 1).
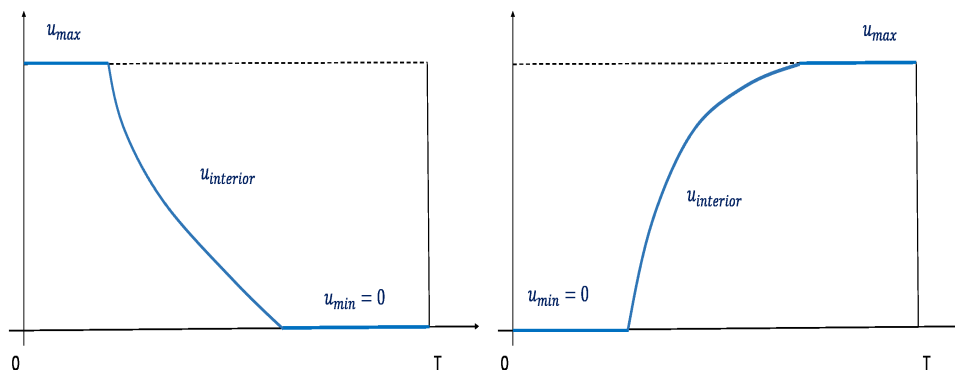

Fig. 1. Illustration of the structure of optimal controls if the indicator function Φ is strictly monotone (on the left for an increasing indicator function, on the right for a decreasing one). In this case the interior control is also strictly monotone, but in the opposite direction

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. The result below follows from a direct calculation.

Proposition 3.4. *Let (x, u, λ) be an extremal lift for the optimal control problem* [MM]. *Given a continuously differentiable vector field h, define the function $\Psi(t) = \langle \lambda(t), h(x(t)) \rangle$. Then the derivative of Ψ is given by*

$$\dot{\Psi}(t) = -\langle \beta, h(x(t)) \rangle + \langle \lambda(t), [f, h](x(t)) \rangle + \frac{u(t)}{1 + u(t)} \langle \lambda(t), [g, h](x(t)) \rangle, \quad (3.8)$$

where $[k, h](x) = Dh(x)k(x) - Dk(x)h(x)$ denotes the Lie bracket of the vector fields k and h.

4. EXAMPLE: A MATHEMATICAL MODEL FOR ANTI-ANGIOGENIC TREATMENT

We consider a dynamical system for tumor development under angiogenic signaling based on the equations by Hahnfeldt, Panigrahy, Folkman and Hlatky [6]. In this model, the spatial aspects of the underlying consumption-diffusion process that stimulate and inhibit angiogenesis are incorporated into a nonspatial 2-compartment model with the *primary tumor volume*, p, and the *carrying capacity* of the vasculature, q, as its

principal variables. The dynamics consists of two ODEs that describe the evolution of the tumor volume and its carrying capacity and we refer the reader to [6] or [15] for a detailed development of the mathematical model. The optimal control problem [MM] for this model takes the following form:

[H] For a fixed terminal time T, minimize the functional

$$J = J(u) = p(T) + \int\limits_0^T \theta p(s) + \gamma u(s)ds$$

subject to the dynamics

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad\qquad\qquad p(0) = p_0, \qquad\qquad (4.1)$$

$$\dot{q} = bp - dp^{\frac{2}{3}}q - \mu q - \frac{Guq}{1+u}, \qquad q(0) = q_0. \qquad\qquad (4.2)$$

over all Lebesgue measurable (respectively, piecewise continuous) functions $u : [0, T] \to [0, u_{\max}]$.

Administering anti-angiogenic drugs directly leads to a reduction of the carrying capacity q of the vasculature, but only indirectly effects the tumor volume p. For this reason here we have taken the weights in the objective as $\alpha = (1,0)$ and $\beta = (\theta, 0)$ normalizing the weight for the tumor volume at the end of the therapy interval and putting the emphasis on tumor reductions. The drift and control vector fields in the general description [MM] are, with $x = (p, q)$, given by

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bp - \left(\mu + dp^{\frac{2}{3}}\right)q \end{pmatrix}, \qquad g(x) = \begin{pmatrix} 0 \\ -Gq \end{pmatrix},$$

and the Hamiltonian function H for the control problem is

$$H(\lambda, x, u) = \theta p + \gamma u - \lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - \left(\mu + dp^{\frac{2}{3}}\right)q - \frac{Gu}{1+u}q\right). \qquad (4.3)$$

If u_* is an optimal control defined over an interval $[0, T]$ with corresponding trajectory (p_*, q_*), then there exists an absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^2)^*$, such that λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p} = -\theta + \lambda_1 \xi \left(\ln\left(\frac{p}{q}\right) + 1\right) - \lambda_2 \left(b - \frac{2}{3}dp^{-\frac{1}{3}}q\right), \qquad (4.4)$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial q} = -\lambda_1 \xi \frac{p}{q} + \lambda_2 \left(\mu + dp^{\frac{2}{3}} + \frac{Gu}{1+u}\right), \qquad (4.5)$$

with terminal conditions

$$\lambda_1(T) = \theta, \quad \lambda_2(T) = 0.$$

By Theorem 3.1, optimal controls satisfy

$$u_*(t) = \begin{cases} u_{max} & \text{if } Gq(t)\lambda_2(t) \geq \gamma(u_{max}+1)^2, \\[2ex] \sqrt{\frac{Gq(t)\lambda_2(t)}{\gamma}} - 1 & \text{if } \gamma(u_{max}+1)^2 \geq Gq(t)\lambda_2(t) \geq \gamma, \\[2ex] 0 & \text{if } \gamma \geq Gq(t)\lambda_2(t) \end{cases} \qquad (4.6)$$

and it follows from the transversality condition that $\Phi(T) = -G\lambda_2(T)q(T) = 0$. Thus optimal controls end with an interval $[\tau, T]$ where $u_*(t) \equiv 0$. The precise sequence of segments when the control lies on the boundary or in the interior still needs to be determined. It is expected that for biomedically realistic initial conditions optimal controls start with a full dose segment and then the dose is lowered to 0 at the end along one segment for which optimal controls take values in the interior of the control set.

5. SUFFICIENT CONDITIONS FOR STRONG LOCAL OPTIMALITY

We develop numerically verifiable sufficient conditions for the strong local optimality of an extremal controlled trajectory whose control consists of a finite number of concatenations of interior and boundary pieces.

Definition 5.1 (regular junction)**.** Let (x_*, u_*) be an extremal controlled trajectory for problem [MM] and denote the corresponding adjoint variable by λ. We call a time $\tau \in (0, T)$ a *junction time* if the control changes between a boundary value (given by 0 or u_{max}) and the interior control u_{st}; the point $x_*(\tau)$ is a *junction*. A junction is said to be *regular* if the derivative of the indicator function Φ, $\Phi(t) = \langle \lambda(t), g(x_*(t)) \rangle$, at the junction time τ does not vanish, i.e., $\dot{\Phi}(\tau) \neq 0$.

We call an extremal triple $\Gamma = (x_*, u_*, \lambda)$ for problem [MM] an *extremal lift with regular junctions* if it only has a finite number of junctions and if each junction is regular. Under these conditions, it is rather straightforward to embed the reference extremal into a parameterized family of broken extremals $(x(\cdot, p), u(\cdot, p), \lambda(\cdot, p))$ with regular junctions. We only note that a parameterized family of broken extremals essentially is, as the name indicates, a collection of extremal controlled trajectories along with their multipliers which piecewise satisfies some smoothness properties in the parameterization. We refer the reader to [14, Chapters 5 and 6] for the mathematically precise, but somewhat lengthy definitions. In our case, such a parameterized family of extremals is simply obtained by integrating the dynamics and the adjoint equation backward from the terminal time T with terminal conditions $x(T, p) = p$ and $\lambda(T, p) \equiv \alpha$ while choosing the control $u(t, p)$ to satisfy the minimality condition (3.4). The terminal value of the state takes over the role of the parameter p and for p in a sufficiently small neighborhood P of $p_* = x_*(T)$ the properties of the reference

extremal simply carry over onto the extremal for the parameter p. Specifically, states, controls and multipliers are defined by

$$\dot{x}(t,p) = f(x(t,p)) + \frac{u(t,p)}{1+u(t,p)} \cdot g(x(t,p)), \tag{5.1}$$

$$\dot{\lambda}(t,p) = -\beta - \lambda(t,p)\left(Df(x(t,p)) + \frac{u(t,p)}{1+u(t,p)}Dg(x(t,p))\right), \tag{5.2}$$

$$u(t,p) = \begin{cases} u_{max} & \text{if } \langle \lambda(t,p), g(x(t,p)) \rangle \leq -\gamma(u_{max}+1)^2, \\[2ex] \sqrt{-\frac{\langle\lambda(t,p),g(x(t,p))\rangle}{\gamma}} - 1 & \text{if } -\gamma(u_{max}+1)^2 \leq \langle \lambda(t,p), g(x(t,p)) \rangle \leq -\gamma, \\[2ex] 0 & \text{if } -\gamma \leq \langle \lambda(t,p), g(x(t,p)) \rangle \end{cases} \tag{5.3}$$

with terminal values

$$x(T,p) = p \quad \text{and} \quad \lambda(T,p) = \alpha. \tag{5.4}$$

Proposition 5.2. *Let $\Gamma_* = (x(\cdot,p_*), u(\cdot,p_*), \lambda(\cdot,p_*))$ be an extremal lift with regular junctions at times t_i, $i = 1, \ldots, k$, $0 = t_0 < t_1 < \cdots < t_k < t_{k+1} = T$, and suppose that the terminal time $t_{k+1} = T$ is not a junction time for the reference extremal. Then there exists a neighborhood P of p_* and continuously differentiable functions τ_i defined on P, $i = 1, \ldots, k$, that satisfy $\tau_i(p_*) = t_i$ such that the family $\Gamma_p = (x(\cdot,p), u(\cdot,p), \lambda(\cdot,p))$ for $p \in P$ is a parameterized family of broken extremals with regular junctions at times τ_i, $i = 1, \ldots, k$. All controls follow the same switching sequence (between interior and boundary controls) as the reference control $u(\cdot,p_*)$.*

Proof. For p in some open neighborhood P of p_* and $t \leq T$, let $x(t,p)$ and $\lambda(t,p)$ denote the solutions to equations (5.1) and (5.2) with terminal conditions (5.4) when the control $u = u(t,p)$ is given by the same type of control as the reference control $u(t,p_*)$ on the last interval $[t_k, T]$. That is, we choose $u(t,p)$ constant and with the same value as $u_*(t)$ if the $u_{ast}(t)$ is constant or we define

$$u(t,p) = \sqrt{-\frac{\langle\lambda(t,p), g(x(t,p))\rangle}{\gamma}} - 1$$

if $u_*(t)$ is given by the interior value. For values p close enough to $p_* = x_*(T)$, by the continuous dependence of solutions of an ODE on initial data and parameters, these solutions exist on an interval $[t_k - \varepsilon, T]$ for some $\varepsilon > 0$. Furthermore, since the terminal time T is not a junction for the reference extremal, it also follows that the triples $(x(\cdot,p), u(\cdot,p), \lambda(\cdot,p))$ are extremal lifts on a sufficiently small interval prior to T. At the last junction the control changes between a boundary value and the interior value and thus either $\Phi(t_k, p_*) = -\gamma$ or $\Phi(t_k, p_*) = -\gamma(1 + u_{max}^2)$. Since $\dot{\Phi}(t_k, p_*) \neq 0$, by the implicit function theorem the equation $\Phi(t,p) = -\gamma$, respectively $\Phi(t,p) = -\gamma(1 + u_{max}^2)$, whichever applies, can be solved for t by a continuously

differentiable function $\tau_k = \tau_k(p)$ near p_* which satisfies $\tau_k(p_*) = t_k$. By construction the controlled trajectories $(x(\cdot, p), u(\cdot, p))$ are extremals on the intervals $[\tau_k(p), T]$ and for p close enough to p_* we still have $\dot{\Phi}(\tau_k(p), p) \neq 0$. Hence for p close enough to p_* these functions define a parameterized family of extremals on $[\tau_k(p), T]$ which has a regular junction at the switching surface defined by $t = \tau_k(p)$. Then iterate this construction over the next interval $[t_{k-1}, t_k]$ by taking the values $x(\tau_k(p), p)$ and $\lambda(\tau_k(p), p)$ as terminal conditions on the junction surface. For P sufficiently small once more all required inequality relations will be satisfied. Since we only consider a finite number of junctions, there exists a small enough neighborhood P that works for all junctions. This proves the result.   □

The triples $\Gamma_p = (x(\cdot, p), u(\cdot, p), \lambda(\cdot, p))$, $p \in P$, define a parameterized family of broken extremals; that is, they satisfy all the necessary conditions for optimality of the maximum principle and are differentiable functions of the parameter between the junction times [14]. The associated flow map of the controlled trajectories is defined as

$$F : (t, p) \mapsto F(t, p) = (t, x(t, p)), \tag{5.5}$$

i.e., through the graphs of the corresponding trajectories. This is the correct formulation as our problem formulation overall is indeed time-dependent since there exists a fixed finite terminal time (e.g., see [14, pg. 324]). We emphasize that it is not required for a parameterized family of extremals that this flow defines an injective mapping. If it does, we call it a *field of extremals*. Obviously, since the trajectories for different parameter values typically obey different differential equations, it is quite possible that these graphs could intersect. In fact, conjugate points and associated loss of local optimality of extremals precisely correspond to fold singularities in this mapping while the reference controlled extremal will be a strong local minimum if this flow map is a diffeomorphism along the reference trajectory $t \mapsto x_*(t) = x(t, p_*)$ [14]. In principle, loss of injectivity of the flow can occur both in between the junction surfaces (and this corresponds to the classical conjugate points like in the calculus of variations) and at the junction surfaces (e.g., see [4, 11, 14]). In our case, however, since the controls remain continuous at junctions, the latter is not possible (also see [16]). Because of the continuity of the controls, trajectories before and after the junction point to the same side of the junction surface and thus the combined flow is injective near the junction surface (see Figure 2). In the terminology of [14], all junction surfaces are *transversal crossings*. Hence, the strong local optimality of an extremal lift with regular junctions reduces to determining *whether or not the flow map F is a diffeomorphism along the reference controlled trajectory on the segments between the junction times*. If this is the case, then a continuously differentiable solution to the Hamilton-Jacobi-Bellman equation can be constructed on the region covered by the flow F of extremals in the family by taking the cost along the extremals. The desired strong local optimality of the reference trajectory then follows from classical results.

It thus remains to check inductively whether the flow maps between the junction surfaces are diffeomorphisms. If the control is constant between two junction surfaces (given by either $u(t, p) \equiv 0$ or $u(t, p) \equiv u_{\max}$), this is immediate. For, in this case all

trajectories are solutions of the same differential equation and then this is merely the statement about uniqueness and smooth dependence on parameters for the solutions. It is the case when the controls lie in the interior of the control set that is the non-trivial one. However, in this case we are in the classical situation of neighboring feedback control laws (e.g., see [3, Chap. 6], [14, Sect. 5.3] or [16]). We briefly describe this theory and adjust its formulas to our problem formulation.
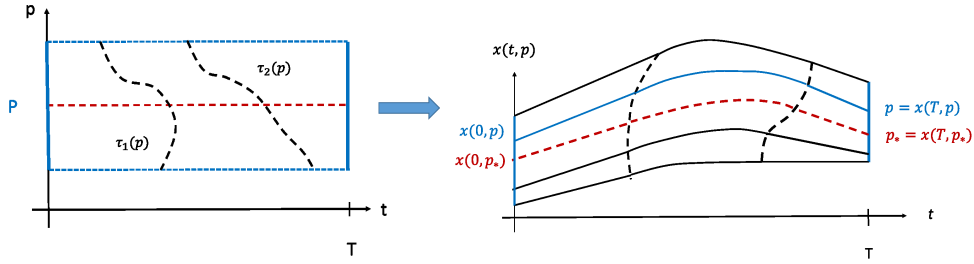

Fig. 2. A parameterized field of extremals with regular junctions

The mapping $F : (t, p) \to F(t, p) = (t, x(t, p))$ is a local diffeomorphism along the reference trajectory $t \to x(t, p_*)$ on the interval $[t_i, t_{i+1}]$ if and only if the Jacobian matrix DF is nonsingular on the interval $[t_i, t_{i+1}]$. If we denote by $\frac{\partial x}{\partial p}(t, p_*)$ the $n \times n$ matrix with (i, j) entry given by $\frac{\partial x_i}{\partial p_j}$, i.e., the ith row is the gradient of $x_i(t, p)$ with respect to the parameter p, then this is equivalent to $\frac{\partial x}{\partial p}(t, p_*)$ being non-singular on $[t_i, t_{i+1}]$. Note that this is automatic at the terminal time T because of the chosen parameterization, $x(T, p) \equiv p$, which gives $\frac{\partial x}{\partial p}(T, p_*) = Id$. Furthermore, $\frac{\partial x}{\partial p}(t, p_*)$ is non-singular over the interval $[t_i, t_{i+1}]$ if and only if the matrix

$$S_*(t) = \frac{\partial \lambda^T}{\partial p}(t, p_*) \left(\frac{\partial x}{\partial p}(t, p_*) \right)^{-1} \tag{5.6}$$

is well defined over this interval. Similarly as above, the ith row of $\frac{\partial \lambda^T}{\partial p}$ is the the gradient of $\lambda_i(t, p)$ and the transpose is taken since λ is a row vector. The partial derivatives $\frac{\partial x}{\partial p}(t, p)$ and $\frac{\partial \lambda^T}{\partial p}(t, p)$ are solutions of the *variational equations* of (5.1) and (5.2). Formally, these equations are obtained by differentiating equations (5.1) and (5.2) with respect to t and interchanging the partial derivatives with respect to p. Using the relations

$$\dot{x}(t, p) = \left(\frac{\partial H}{\partial \lambda^T}(\lambda^T(t, p), x(t, p), u(t, p)) \right)^T$$

and

$$\dot{\lambda}^T(t, p) = \left(-\frac{\partial H}{\partial x}(\lambda^T(t, p), x(t, p), u(t, p)) \right)^T$$

it follows that (e.g., see [14, Sect. 5.3] and [16])

$$\frac{d}{dt}\left(\frac{\partial x}{\partial p}\right) = H_{\lambda^T x}\frac{\partial x}{\partial p} + H_{\lambda^T u}\frac{\partial u}{\partial p}, \tag{5.7}$$

and

$$\frac{d}{dt}\left(\frac{\partial \lambda^T}{\partial p}\right) = -H_{x\lambda^T}\frac{\partial \lambda^T}{\partial p} - H_{xx}\frac{\partial x}{\partial p} - H_{xu}\frac{\partial u}{\partial p}. \tag{5.8}$$

Here x, u, λ and their partial derivatives are evaluated at (t, p) and the second-order partial derivatives of H are evaluated along the full extremals, $(\lambda(t, p), x(t, p), u(t, p))$. For notational clarity, however, we have dropped these arguments. Also, when differentiating the Hamiltonian H twice with respect to column vectors (x or λ^T), we write the corresponding matrices of second partial derivatives with the components of the first vector as row indices and the components of the second vector as column indices. Thus, the (i, j) entry of $\frac{\partial^2 H}{\partial x \partial \lambda^T}$ is given by $\frac{\partial^2 H}{\partial x_i \partial \lambda_j}$. We denote this matrix by $H_{x\lambda^T}$. Note that $H_{\lambda^T x} = (H_{x\lambda^T})^T$. Finally, we also have that $H_{\lambda^T \lambda^T} \equiv 0$ since H is linear in λ.

If the control u is constant on the domain $D_i = \{(t, p) : \tau_i(p) \le \tau_{i+1}(p), p \in P\}$, then $\frac{\partial u}{\partial p}(t, p) \equiv 0$ and we have that

$$\left(\begin{array}{c} \frac{d}{dt}\left(\frac{\partial x}{\partial p}\right) \\[2mm] \frac{d}{dt}\left(\frac{\partial \lambda^T}{\partial p}\right) \end{array}\right) = \left(\begin{array}{cc} H_{\lambda^T x} & 0 \\[2mm] -H_{xx} & -H_{x\lambda^T} \end{array}\right)\left(\begin{array}{c} \frac{\partial x}{\partial p} \\[2mm] \frac{\partial \lambda^T}{\partial p} \end{array}\right). \tag{5.9}$$

If the control u takes values in the interior of the control set on D_i, then, by the maximum principle, we have that

$$\frac{\partial H}{\partial u}(\lambda^T(t, p), x(t, p), u(t, p)) \equiv 0.$$

Differentiating in p, it follows that

$$H_{u\lambda^T}\frac{\partial \lambda^T}{\partial p} + H_{ux}\frac{\partial x}{\partial p} + H_{uu}\frac{\partial u}{\partial p} \equiv 0. \tag{5.10}$$

In our case,

$$\frac{\partial^2 H}{\partial u^2} = -\frac{2}{(1+u)^3}\langle \lambda, g(x)\rangle = -\frac{2\Phi}{(1+u)^3} \tag{5.11}$$

and this expression is positive if the control takes values in the interior of the control set (Theorem 3.1). Hence

$$\frac{\partial u}{\partial p} = H_{uu}^{-1}\left(H_{ux}\frac{\partial x}{\partial p} + H_{u\lambda^T}\frac{\partial \lambda^T}{\partial p}\right). \tag{5.12}$$

Substituting this expression into the variational equations gives the following homogeneous matrix linear differential equation:

$$
\begin{pmatrix} \frac{d}{dt}\left(\frac{\partial x}{\partial p}\right) \\[2mm] \frac{d}{dt}\left(\frac{\partial \lambda^T}{\partial p}\right) \end{pmatrix} = \begin{pmatrix} H_{\lambda^T x} - H_{\lambda^T u}H_{uu}^{-1}H_{ux} & -H_{\lambda^T u}H_{uu}^{-1}H_{u\lambda^T} \\[2mm] -H_{xx} + H_{xu}H_{uu}^{-1}H_{ux} & -\left(H_{x\lambda^T} - H_{xu}H_{uu}^{-1}H_{u\lambda^T}\right) \end{pmatrix} \begin{pmatrix} \frac{\partial x}{\partial p} \\[2mm] \frac{\partial \lambda^T}{\partial p} \end{pmatrix}.
$$

$$(5.13)$$

Note that

$$
H_{x\lambda^T} - H_{xu}H_{uu}^{-1}H_{u\lambda^T} = \left(H_{\lambda^T x} - H_{\lambda^T u}H_{uu}^{-1}H_{ux}\right)^T.
$$

Let $X(t) = \frac{\partial x}{\partial p}(t, p_*)$ and $Y(t) = \frac{\partial \lambda^T}{\partial p}(t, p_*)$ be the solutions of the variational equations along the reference extremal Γ_*. The variational equations are linear matrix differential equations with time-varying coefficients given by continuous functions and thus these solutions exist on the full interval $[t_i, t_{i+1}]$. It is a classical result in control theory, going back to Legendre and the calculus of variations, that if a pair of $n \times n$ matrices (X, Y) is a solution to a linear matrix differential equation of the form

$$
\begin{pmatrix} \dot{X} \\ \dot{Y} \end{pmatrix} = \begin{pmatrix} A & R \\ -M & -A^T \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix}, \tag{5.14}
$$

where A, R and M are matrices whose entries are continuous functions over $[t_i, t_{i+1}]$ and $X(t_{i+1})$ is nonsingular, then the matrix $X(t)$ is nonsingular over the interval $[t_i, t_{i+1}]$ if and only if there exists a solution to the matrix Riccati differential equation

$$
\dot{S} + SA(t) + A^T(t)S + SR(t)S + M(t) \equiv 0, \qquad S(t_{i+1}) = Y(t_{i+1})X(t_{i+1})^{-1} \tag{5.15}
$$

over the full interval $[t_i, t_{i+1}]$ while the matrix $X(\tau)$ is singular if this Riccati differential equation has a finite escape time $\tau \geq t_i$. (For example, a proof is given in [14, Proposition 2.4.1]). For an interior control we thus have the following result:

Proposition 5.3. *Suppose the control $u = u(t, p)$ takes values in the interior of the control set over the domain $D_i = \{(t, p) : \tau_i(p) \leq \tau_{i+1}(p), p \in P\}$. If the matrix matrix $X(t_{i+1}) = \frac{\partial x}{\partial p}(t_{i+1}, p_*)$ is nonsingular, then $X(t) = \frac{\partial x}{\partial p}(t, p_*)$ is nonsingular on the full interval $[t_i, t_{i+1}]$ if and only if there exists a solution S_* to the following matrix Riccati differential equation (all partial derivatives are evaluated along the reference extremal Γ_*)*

$$
\dot{S} + S\left(H_{\lambda^T x} - H_{\lambda^T u}H_{uu}^{-1}H_{ux}\right) + \left(H_{\lambda^T x} - H_{\lambda^T u}H_{uu}^{-1}H_{ux}\right)^T S \tag{5.16}
$$
$$
- SH_{\lambda^T u}H_{uu}^{-1}H_{u\lambda^T}S + \left(H_{xx} - H_{xu}H_{uu}^{-1}H_{ux}\right) \equiv 0
$$

with terminal condition $S_*(t_{i+1}) = Y(t_{i+1})X(t_{i+1})^{-1}$ over the full interval $[t_i, t_{i+1}]$. In this case, we have that $S_*(t) = Y(t)X(t)^{-1}$ for all $t \in [t_i, t_{i+1}]$.

In the case of a constant control, $u(t, p) \equiv const$, we have the same situation, but with $R(t) \equiv 0$. In this case the Riccati differential equation (5.16) reduces to the linear Lyapunov equation $\dot{S} + SA(t) + A^T(t)S + M(t) \equiv 0$ which always has a solution over the

full interval. This once more confirms that the flow is a diffeomorphism along intervals where the reference control is constant, but, more importantly, gives us the formula for how to propagate the matrix S along those intervals. We summarize the statement in the proposition below:

Proposition 5.4. *Suppose the control $u = u(t, p)$ takes the constant value $u(t, p) \equiv 0$ or $u(t, p) \equiv u_{\max}$ over the domain $D_i = \{(t, p) : \tau_i(p) \leq \tau_{i+1}(p), p \in P\}$. If the matrix $X(t_{i+1}) = \frac{\partial x}{\partial p}(t_{i+1}, p_*)$ is nonsingular, then $X(t) = \frac{\partial x}{\partial p}(t, p_*)$ is nonsingular over the full interval $[t_i, t_{i+1}]$ and the matrix $S_*(t) = Y(t)X(t)^{-1}$ can be computed as the solution to the linear Lyapunov equation*

$$\dot{S} + SH_{\lambda^T x} + H_{x\lambda^T}S + H_{xx} \equiv 0 \tag{5.17}$$

with terminal condition $S_*(t_{i+1}) = Y(t_{i+1})X(t_{i+1})^{-1}$.

Note that the Riccati differential equation (5.16) can be rewritten in the form

$$\dot{S} + SH_{\lambda^T x} + H_{\lambda^T x}^T S + H_{xx} - (SH_{\lambda^T u} + H_{xu}) H_{uu}^{-1} (H_{u\lambda^T}S + H_{ux}) \equiv 0$$

which brings out its relation with the Lyapunov equation (5.17) more clearly. These equations only differ in the addition of a rank 1 matrix which accordingly is added respectively deleted as the reference control takes values in the interior of the control or goes back to boundary values. We therefore can combine Propositions 5.3 and 5.4 to obtain the following result (c.f., also [15, Sect. 4.1]):

Theorem 5.5. *Let $\Gamma_* = (x_*(\cdot), u_*(\cdot), \lambda_*(\cdot))$ be an extremal lift with regular junctions at times t_i, $i = 1, \ldots, k$, $0 = t_0 < t_1 < \cdots < t_k < t_{k+1} = T$. Let S_* denote the solution to the terminal value problem for the matrix Riccati differential equation*

$$\dot{S} + SH_{\lambda^T x} + H_{x\lambda^T}S + H_{xx} - \iota (SH_{\lambda^T u} + H_{xu}) H_{uu}^{-1} (SH_{\lambda^T u+} + H_{xu})^T \equiv 0, \quad S_*(T) = 0, \tag{5.18}$$

where all partial derivatives are evaluated along the reference extremal Γ_* and $\iota = 1$ on intervals where the control u_* takes values in the interior of the control set and $\iota = 0$ otherwise. If the solution S_* exists on the full interval $[0, T]$, then there exists a neighborhood P of $x_*(T)$ such that the flow

$$\mathcal{F} : [0, T] \times P \to [0, T] \times \mathbb{P}, \quad (t, p) \mapsto (t, x(t, p)),$$

is a diffeomorphism on the domain $D = \{(t, p) : 0 \leq t \leq T, p \in P\}$. In this case, the reference control u_* is a strong local minimum for problem [MM]. Specifically, the reference controlled trajectory (x_*, u_*) is optimal relative to any other controlled trajectory (x, u) for which the graph of the trajectory x lies in the set $\mathcal{F}(D)$.

We still specify these formulas for model [MM]. Recall that

$$H = \beta x + \gamma u + \langle \lambda, f(x) + \frac{u}{1+u}g(x) \rangle.$$

Hence

$$\frac{\partial H}{\partial \lambda} = f(x) + \frac{u}{1+u}g(x)$$

and thus

$$H_{\lambda^T x} = Df(x) + \left(\frac{u}{1+u}\right)Dg(x)$$

and

$$H_{\lambda^T u} = \frac{1}{(1+u)^2}g(x).$$

Furthermore,

$$\frac{\partial H}{\partial u} = \gamma + \frac{\langle\lambda, g(x)\rangle}{(1+u)^2}$$

gives

$$H_{ux} = \frac{1}{(1+u)^2}\lambda Dg(x) \qquad \text{and} \qquad H_{uu} = -\frac{2}{(1+u)^3}\langle\lambda, g(x)\rangle.$$

In particular,

$$\left(SH_{\lambda^T u} + H_{xu}\right)H_{uu}^{-1}\left(SH_{\lambda^T u+} + H_{xu}\right)^T$$
$$= -\frac{1}{2(1+u)\langle\lambda, g(x)\rangle}\left(Sg(x) + Dg(x)^T\lambda^T\right)\left(Sg(x) + Dg(x)^T\lambda^T\right)^T.$$

Since the indicator function is negative when the control takes values in the interior, the matrix $-\left(SH_{\lambda^T u} + H_{xu}\right)H_{uu}^{-1}\left(SH_{\lambda^T u+} + H_{xu}\right)^T$ is negative semi-definite and the existence of a solution to the Riccati differential equation (5.18) is not guaranteed a priori by comparison results for solutions to Riccati differential equations. Indeed, this constitutes a true requirement for local optimality. In fact, it can also be shown that the existence of a solution on the interval $(0, T]$ (open at the initial time) is a necessary condition for strong local optimality of the reference trajectory and thus these statements correspond to the *Jacobi conditions* in the calculus of variations.

6. CONCLUSION

In this paper we considered optimal control problems for the administration of one therapeutic agent when pharmacodynamics was modelled by a Michaelis-Menten relation, probably the most commonly used model in the pharmaceutical industry. It was shown that optimal controls are continuous concatenations of segments that consist of full or no dose controls connected by interior segments. This is in agreement with an interpretation of the controls as concentrations. Second-order conditions for local optimality of such extremals were formulated based on the method of characteristics in terms of the existence of a solution to a piecewise defined Riccati differential equation.

In the current paper we have not yet included a pharmacokinetic model. This formulation is a good model for a fast-acting drug and it can be argued that this is always the case on the level of an extended therapy horizon. Nevertheless, for shorter time intervals such a model should be included. Also, the Michaelis-Menten relation used in this paper represents the steady-state of an enzyme kinetic reaction and could be replaced by a differential equation that more generally describes the transient behavior as well. These questions will be addressed in future work.

Acknowledgments

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