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OPTIMAL CONTROL FOR A MATHEMATICAL MODEL OF CHEMOTHERAPY WITH MICHAELIS-MENTEN TYPE PHARMACODYNAMICS

Maciej Leszczyński[1], Elżbieta Ratajczyk[1], Urszula Ledzewicz[1,2], Heinz Schättler [3]

[1] Institute of Mathematics, Lodz University of Technology,
ul. Wólczańska 215, 90-924 Łódź, Poland
[2] Dept. of Mathematics and Statistics, Southern Illinois University Edwardsville
Edwardsville, Il, 62026-1653, USA
[3] Dept. of Electrical and Systems Engineering, Washington University
St. Louis, Mo, 63130, USA
[1]Leszczynskimaciej@10g.pl;elaratajczyk@onet.pl
urszula.ledzewicz@p.lodz.pl
[2]uledzew@siue.edu, [3]hms@wustl.edu

ABSTRACT

We consider an optimal control problem for a general mathematical model for chemotherapy with a single agent. The control represents the concentration of the agent and its effect (pharmacodynamics) is modelled by a Michaelis-Menten type relation. 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.

INTRODUCTION

We consider optimal control problems for chemotherapy (not necessarily restricted to cancer). The controls u in the formulation represent the dosages of various chemotherapeutic 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 [4]. 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 [11]) as well as Michaelis-Menten or sigmoidal functional relations are commonly used [6, 8]. The latter 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 non-trivial problem [5, 10] 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

$$E_{\max}\frac{c}{C_{50}+c} \tag{1}$$

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. Then, 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.

FORMULATION OF THE OPTIMAL CONTROL PROBLEM

We consider a general system of differential equations of the form

$$\dot{x} = f(x) + \frac{u}{1+u}g(x) \tag{2}$$

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) 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

$$J = J(u) = \alpha x(T) + \int_0^T \beta x(s) + \gamma u(s) ds \tag{3}$$

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 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).

NECESSARY CONDITIONS FOR OPTIMALITY

The fundamental necessary conditions for optimality for problem [MM] are given by the Pontryagin Maximum Principle [7] (for some more recent references on optimal control, see [1, 2, 9]). Since the optimal control problem [MM] does not involve terminal constraints on the state, without loss of generality we define the Hamiltonian function H for the control problem as

$$\begin{aligned} H \quad &: \quad (\mathbb{R}^n)^* \times \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \\ &\quad (\lambda, x, u) \to H(\lambda, x, u) = \beta x + \gamma u + \left\langle \lambda, f(x) + \frac{u}{1+u} g(x) \right\rangle \end{aligned} \tag{4}$$

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

$$\dot{\lambda} = -\beta - \lambda \left(Df(x) + \frac{u}{1+u} Dg(x) \right), \tag{5}$$

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

$$H(\lambda(t), x_*(t), u_*(t)) = \min_{0 \le v \le u_{max}} H(\lambda(t), x_*(t), v) \equiv 0. \tag{6}$$

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 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*

$$u_*(t) = \begin{cases} u_{max} & \text{if } \langle \lambda(t), g(x_*(t)) \rangle \leq -\gamma(u_{max}+1)^2, \\ \sqrt{-\frac{\langle \lambda(t), g(x_*) \rangle}{\gamma}} - 1 & \text{if } -\gamma(u_{max}+1)^2 \leq \langle \lambda(t), g(x_*(t)) \rangle \leq -\gamma, \\ 0 & \text{if } -\gamma \leq \langle \lambda(t), g(x_*(t)) \rangle. \end{cases} \tag{7}$$

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

$$\Phi(t) = \langle \lambda(t), g(x_*(t)) \rangle \tag{8}$$

is non-negative. Hence in this case the minimum over the control set $[0, u_{max}]$ 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

$$u_{st}(t) = \sqrt{-\frac{\Phi(t)}{\gamma}} - 1. \tag{9}$$

Depending on the location of $u_{st}(t)$ we get 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. □

Corollary 1. *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

$$u_*(t) = \max\{0, \min\{u_{st}(t), u_{\max}\}\} \tag{10}$$

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. □.

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 and, for example, we have the following result:

Proposition 1. *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. Analogously, if Φ is strictly decreasing on $[0,T]$, then optimal controls are at most concatenations that follow the sequence $\mathbf{0} \to \mathbf{u_{st}(t)} \to \mathbf{u}_{\max}$. □

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. This is accomplished by direct computations:

Proposition 2. *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*

$$\dot{\Psi}(t) = -\langle \beta, h(x(t)) \rangle + \langle \lambda(t), [f,h](x(t)) \rangle + \frac{u(t)}{1+u(t)} \langle \lambda(t), [g,h](x(t)) \rangle \tag{11}$$

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

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 [3]. 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 [3] or [10] for a detailed development of the mathematical model. The optimal control problem [MM] for this model takes the following form:

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

$$J = J(u) = p(T) + \int_0^T \theta p(s) + \gamma u(s) ds$$

subject to the dynamics

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{12}$$

$$\dot{q} = bp - dp^{\frac{2}{3}} q - \mu q - \frac{Guq}{1+u}, \qquad q(0) = q_0. \tag{13}$$

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 $\alpha = (1,0)$ normalizing the weight for the tumor volume at the end of the therapy interval and $\beta = (\theta, 0)$ putting the emphasis on tumor reductions. The drift and control vector fields in the general description [MM] are, with $x = (p,q)$, given by

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

and the Hamiltonian function H for the control problem is

$$H(\lambda, x, u) = \theta p + \gamma u - \lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - \left(\mu + dp^{\frac{2}{3}}\right) q - \frac{Gu}{1+u} q \right). \tag{14}$$

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

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p} = -\theta + \lambda_1 \xi \left(\ln\left(\frac{p}{q}\right) + 1 \right) - \lambda_2 \left(b - \frac{2}{3} p^{-\frac{1}{3}} q \right), \tag{15}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial q} = -\lambda_1 \xi \frac{p}{q} + \lambda_2 \left(\mu + d p^{\frac{2}{3}} + \frac{Gu}{1+u} \right), \tag{16}$$

with terminal conditions

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

and, by Theorem 1, optimal controls satisfy

$$u_*(t) = \begin{cases} u_{max} & \text{if } Gq(t)\lambda_2(t) \geq \gamma(u_{max}+1)^2, \\ \sqrt{\frac{Gq(t)\lambda_2(t)}{\gamma}} - 1 & \text{if } \gamma(u_{max}+1)^2 \geq Gq(t)\lambda_2(t) \geq \gamma, \\ 0 & \text{if } \gamma \geq Gq(t)\lambda_2(t). \end{cases} \tag{17}$$

It follows from the transversality condition that $\Phi(T) = -G\lambda_2(T)q(T) = 0$ and 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.

CONCLUSION

Optimal controls for the problems considered in this paper are continuous concatenations of segments that consist of full or no dose controls connected by interior segments. This structure allows for efficient numerical computations of extremals. Second-order conditions for local optimality of such extremals can then be formulated based on the method of characteristics as it is developed in [9]. This will be done in future work.

REFERENCES

[1] B. Bonnard and M. Chyba, *Singular Trajectories and their Role in Control Theory*, Mathématiques & Applications, vol. 40, Springer Verlag, Paris, 2003.

[2] A. Bressan and B. Piccoli, *Introduction to the Mathematical Theory of Control*, American Institute of Mathematical Sciences, 2007.

[3] P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Research*, **59**, (1999), pp. 4770âĂŞ4775.

[4] A. Källén, Computational Pharmacokinetics, Chapman and Hall, CRC, London, 2007.

[5] U. Ledzewicz and H. Schättler, The influence of PK/PD on the structure of optimal control in cancer chemotherapy models, *Mathematical Biosciences and Engineering (MBE)*, **2**(3), (2005), pp. 561–578.

[6] P. Macheras and A. Iliadin, Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics, Interdisciplinary Applied Mathematics, Vol. 30, 2nd ed., Springer, New York, 2016.

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

[8] M. Rowland and T.N. Tozer, Clinical Pharmacokinetics and Pharmacodynamics, Wolters Kluwer Lippicott, Philadelphia, 1995.

[9] H. Schättler and U. Ledzewicz, *Geometric Optimal Control*, Interdisciplinary Applied Mathematics, Vol. 38, Springer, New York, 2012.

[10] H. Schättler and U. Ledzewicz, *Optimal Control for Mathematical Models of Cancer Therapies*, Interdisciplinary Applied Mathematics, Vol. 42, Springer, New York, 2015.

[11] H.E. Skipper, On mathematical modeling of critical variables in cancer treatment (goals: better understanding of the past and better planning in the future), *Bulletin of Mathematical Biology*, **48**, (1986), pp. 253–278.