ON THE ROLE OF PHARMACOMETRICS AND THE OBJECTIVE IN OPTIMIZING CANCER THERAPIES

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ABSTRACT
In the optimization of mathematical models for cancer chemotherapies, the controls are given by the drug-dosages and the objective minimizes some compromise between tumor kill and side effects. In simple models, the dosage, concentration and effect of the drugs are identified. Here we discuss the role of pharmacometric models which describe the links between these quantities. The choice of the mathematical representation of the objective also has an effect on the solutions of the problem. Both of these aspects will be discussed.

KEYWORDS: optimal control, cancer chemotherapy, pharmacometrics of drugs, linear (L^1) and quadratic (L^2) objectives

MSC: 62P10

RESUMEN
Los modelos de optimización son útiles para determinar las dosis en los tratamientos de cáncer mediante quimioterapias. Considerando como sontroles estas dosis, el objetivo es minimizar un compromiso entre la eliminación del tumor y los efectos secundarios. En el caso más simple se identifican la dosis, la concentracón y el efecto. En este trabajo discutimos sobre el papel de los modelos farmacométricos que describen las relaciones entre estas cantidades y como afecta el resultado la representación matemática de la función objetivo.

PALABRAS CLAVE: control optimal, quimioterapia para el cáncer, farmacometría, funciones objetivo lineales (L^1) y cuadráticas (L^2).

1. INTRODUCTION

Optimal control for mathematical models for chemotherapy has a long history dating back to the 1970s and 1980s and the fundamental work by Eisen [4], Swierniak and Kimmel [7, 26] and Swan [28, 29], continuing throughout the 1990s (e.g., see the monograph by Martin and Teo [16] or [27]), revitalizing in the 2000s when novel approaches to cancer therapy such as angiogenic treatments (e.g., [11]) or immunotherapies (e.g., [19]) became available, and continuing strongly into the present time (e.g., see

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[23] and the many references therein). During these years, tremendous progress has been made in medicine in understanding cancer which indeed has led to numerous significant novel approaches including anti-angiogenic treatment, cancer viruses, and, currently at the forefront of medical research, immuno-therapies. While these developments are reflected in the fact that increasingly more sophisticated mathematical models are formulated and analyzed (e.g., [3, 14]), one of the most important and basic underlying questions—how should drug doses be scheduled in time in order to achieve a in a certain way 'best' outcome—still in many cases remains unanswered. For mathematical models, optimal control theory addresses this topic.

Already in the formulation of the dynamics, a reasonable compromise will need to be made between medical accuracy and mathematical tractability of the model. While ever increasing medical knowledge makes it tempting to try and formulate mathematical models that so-to-speak incorporate all biological facts, the reality is that such models have an unsurmountable number of parameters that simply cannot be established. From this point of view, it is therefore preferable to formulate minimally parameterised models which also have the advantage of allowing some analytical mathematical methods to be used. These are the type of models we are discussing in our paper, but without considering one particular model of which many are available in the literature (e.g., see [23]).

In this paper, we want to focus on another crucial aspect in the optimization of mathematical models for cancer therapies: the formulation of the objective. While it is commonly agreed upon that the objective needs to strike a balance between tumor kill which one wants to maximize (and this generally correlates with increased drug dosages) and limiting side effects (and this generally correlates with limiting these drug dosages), there exist many and often non-equivalent ways to translate this into a mathematical objective. In our opinion, it is quintessential that any such formulation reasonably accurately reflects the underlying aim, i.e., measuring tumor size and side-effects. As such, it needs to be tied in with the total use of drugs and the properties these drugs have. Pharmacometrics is a rather novel term in the pharmacological industry which tries to quantify both the pharmacokinetics (PK) and pharmacodynamics (PD) of the drugs (see Fig. 1). Pharmacokinetic models describe the relations between the drug dosage, u, and the drug's concentration in the blood stream, c, ("what the body does to the drug") while pharmacodynamic models describe the actual effects that the drug has on the disease ("what the drug does to the body"). One underlying question of interest in our research is whether, and if so, to what extent, the mathematical models used in the modeling determine the structure of optimal controls.

Our topic in this paper is a discussion of the effects which the choice of the objective functional and the pharmacometric models have on the structure of optimal controls. In Section 2 we briefly describe different formulations for the pharmacometric models in the dynamics depending on the time horizon to be modelled and then, in Section 3, we discuss the effects which the choice of an appropriate objective functional to be minimized has on the structure of optimal controls. We also give examples that illustrate the changes and similarities that arise from different such modeling approaches.

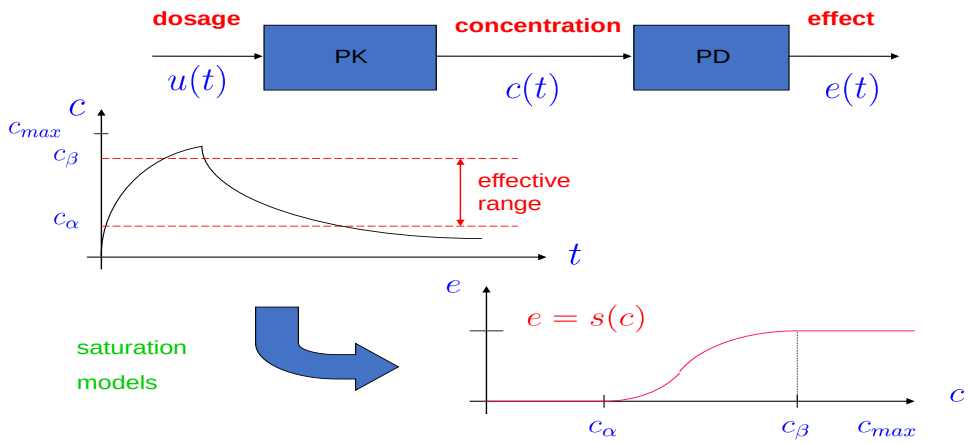

Figure 1: Pharmacometrics: PK and PD.

2. MATHEMATICAL MODELS FOR PHARMACOMETRICS

As a general rule, the pharmacokinetics of drugs are well-understood. As a matter of fact, no drug would be allowed on the market without a very good understanding of its pharmacokinetics and its side effects. Typically, low-dimensional, linear differential equations with a small number of compartments (typically ranging from 1 to 3) are sufficient to provide an adequate modeling [6]. If u denotes the drug's dose rate and c its concentration in the bloodstream, a 1-compartment model for PK is simply given by exponential increase and decay of the form

$$\dot{c} = -\gamma c + u, \qquad c(0) = 0, \tag{2.1}$$

with γ the *clearance rate* of the drug related to the half-life of the agent. A 2-compartment model distinguishes between the concentrations c_1 of the agent in a central compartment (blood) and c_2 in a peripheral compartment (organ) and is modelled by a linear system $\dot{c}(t) = Ac(t) + bu(t)$ of the form

$$\dot{c}(t) = \begin{pmatrix} -\gamma - \alpha & \beta \\ \alpha & -\beta \end{pmatrix} c + \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} u(t) \tag{2.2}$$

where γ again denotes the clearance rate, α and β are positive rates that describe the interactions between the two compartments, and the coefficients b_i ($b_i \geq 0$, $b_1 + b_2 = 1$) describe the relative influx of the drug into the compartments. Note that both eigenvalues of the matrix A are negative reals and the general solution thus has the form

$$c_1(t) = ae^{-\lambda_1 t} + be^{-\lambda_2 t} \tag{2.3}$$

with $0 < \lambda_1 < \lambda_2$ the negatives of the eigenvalues. Higher dimensional models for PK are rare, but are used, for example, in insulin pumps. In this paper, for simplicity we only consider a 1-compartment model.

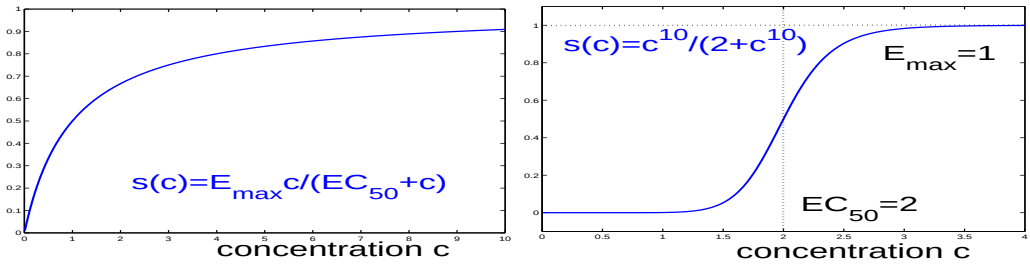

Figure 2: Mathematical models for pharmacodynamics.

The pharmacodynamics of drugs, on the other hand, is a much more intricate and less understood subject. Pharmacodynamic models are generally described by functional relations of the form $s(c)x$ where x represents a compartment of cells on which the drugs are acting (e.g., tumor cells, vasculature, immune system, healthy cells, etc.) and the coefficient $s(c)$ models the effect of the drug at concentration c (see Fig. 2). Over a limited range of concentrations (not too low and, particularly, not too high), linear models are adequate. These are based on the log-kill hypothesis [25] and take the simple form

$$s_1(c) = Gc \tag{2.4}$$

with G a positive constant. However, drug effects saturate with increasing concentrations and also require some minimum concentration levels to be effective at all. In the pharmaceutical industry these aspects are typically modelled by Hill-type functions. Michaelis-Menten type relations of the form

$$s_2(c) = E_{\max}\frac{c}{UC_{50} + c} \tag{2.5}$$

with $E_{\max}$ denoting the maximum effect the drug can have and UC_{50} the concentration at which half of this effect is realized, called the $E_{\max}$ model in pharmacology, are commonly used to model saturating effects at higher concentrations while sigmoidal functions of the form

$$s_3(c) = E_{\max}\frac{c^n}{UC_{50} + c^n} \tag{2.6}$$

with exponents $n > 1$ also model the ineffectiveness of drugs at low concentrations [15, 21]. Naturally, these equations can be linearized over certain ranges giving back the model s_1, but the resulting slopes (i.e., the coefficients G to be used) will be very different if one linearizes around a point on the upper end of the Hill curve or say the point UC_{50}. This may significantly alter the structure of solutions [10, 23].

The time horizon plays an important role in considering which of these models should be taken. If the therapy horizon is large, e.g., several months or even years, then there is no need to include a model for the PK of a drug as these processes act on a much faster time scale, e.g., minutes compared with days, hours compared with months. In such a case, it suffices to identify the drug's dose rate with its concentrations, $c = u$, and simply consider the dynamics by itself. If we denote the state of the system by an n-dimensional vector x which represents cell numbers in various compartments (e.g.,

tumor, vasculature, healthy cells etc.) and consider a chemotherapy model with one drug whose dose rate/concentration is denoted by u, then the dynamics just takes the form

$$\dot{x} = f(x) + s(u)g(x), \quad x(0) = x_0, \tag{2.7}$$

with $s(u)$ denoting one of the PD models above. As it is natural that saturation effects will take place over extended time periods, here the $E_{\max}$ model s_2 is the most likely candidate, but the sigmoidal model s_3 also is reasonable since such prolonged time periods necessarily need to include drug holidays when the concentrations will be very low. For a short time period (e.g., lab experiments or when controlling insulin levels in a patient) the PK time scale will be relevant and in such a case PK models need to be included. If we incorporate the 1-compartment model for PK into equation (2.7), then the system takes the following form:

$$\dot{x} = f(x) + s(c)g(x), \qquad x(0) = x_0, \tag{2.8}$$

$$\dot{c} = -\gamma c + u, \qquad c(0) = 0. \tag{2.9}$$

We note that the dynamics in the latter case is linear in the control while it is the PD model s which determines such properties in the first case.

3. LINEAR (L_1) VERSUS QUADRATIC (L_2) OBJECTIVE FORMULATIONS IN THE CONTROL

Given a mathematical model for the evolution of cancer cells under drug treatment such as (2.7) or (2.8)-(2.9), the problem of cancer chemotherapy can then be formulated as the optimal control problem to minimize some criterion $J = J(u)$ which is imposed on this dynamics. If we allow in principle arbitrary treatment schedules with a limited dose rate, $0 \leq u \leq u_{\max}$, the problem can formally be stated as follows:

[OC] Among all Lebesgue measurable functions $u : [0, T] \to [0, u_{\max}]$ defined over an interval $[0, T]$, find a control $u(\cdot)$ (representing the dosage of the drug) which minimizes the objective $J = J(u)$, subject to the dynamics (2.7), respectively (2.8)-(2.9), and possible constraints.

While the main aim naturally is to kill cancer cells, side effects cannot be neglected and must be taken into account in the modeling. This can either be done directly by imposing constraints or indirectly by including terms in the objective that limit the total amount of drugs given. In the direct approach, it is assumed that the amount of drugs to be given, A, has been determined a priori (with the understanding that it was predetermined by medical professionals that this is a safe amount) and then the question becomes how to schedule these drugs (e.g., [5, 11]). In such a case, side effects are incorporated as an isoperimetric constraint,

$$\int_0^T u(t)dt \leq A, \tag{3.1}$$

and the terminal time can be fixed (if a specific therapy horizon is considered) or free (if the problem simply becomes how to best use the specified amount of drugs). By varying the value A, the solutions

allow to assess the effects of the total dosages. In the indirect approach (e.g., [8, 9, 16, 28]), such considerations are incorporated by including a measure related to the amount of drugs given into the objective as one of the aspects to be minimized. Commonly used formulations are of the form

$$J_1 = rx(T) + \int_0^T qx(t) + pu(t)dt \to \min \tag{3.2}$$

or

$$J_2 = rx(T) + \int_0^T qx(t) + pu^2(t)dt \to \min \tag{3.3}$$

with the difference in the formulations lying in how the control is measured. The penalty term $rx(T) = \sum_{i=1}^n r_i x_i(T)$ represents a weighted average of the number of cells in various compartments (e.g., cells in different phases of the cell cycle, cells with different resistance properties with respect to the drug, etc.) at the end of treatment and the integral term over $qx = \sum_{i=1}^n q_i x_i$ represents a weighted average of the number of cells in these compartments during treatment. We highlight some of the pitfalls that should be avoided in the formulation of the objective:

- The term $\int_0^T qx(t)dt$ is included to prevent that the tumor grows to unacceptably high levels during treatment. If the emphasis in the objective is solely put on the number of cancer cells at the end of therapy, generally optimal controls postpone giving drugs and excessively high intermediate tumor volumes may become an unintended and unacceptable consequence of the choice of the objective.

- The formulation of the objectives (3.2) and (3.3) attempts to make a reasonable compromise between minimizing the tumor kill and restricting the side effects of treatment which are measured indirectly through the integral of the control. Obviously, the weights p, q and r determine the optimal solutions. If the weight s on the drug is too small, optimal solutions will simply give drugs all the time at full dose; if the weights are too high, no drugs will be given. It clearly is necessary to calibrate the weights to obtain meaningful results. For example, if we take q small relative to r, then the emphasis is all on the terminal condition and this may (and indeed again will) lead to unacceptable behaviors during the therapy interval. Thus, a biologically meaningful calibration of these weights always needs to be undertaken.

- The main difference in these two approaches lies in how the side effects are measured by the integrals on the controls. While the integral $\int_0^T u(t)dt$ has clear pharmacological meaning, the integral $\int_0^T u^2(t)dt$ does not and distorts such interpretations.

Before describing the mathematical differences between these two approaches, in Fig. 3 we compare two examples of optimal solutions. These solutions are for a mathematical model for a cell-cycle specific 3-compartment model of cancer chemotherapy when both a cytotoxic (killing) agent u and a cytostatic (blocking) agent v are administered [9, 23]. The maximum dose rate for the cytotoxic agent is normalized to 95% and the maximum blocking capability of the cytostatic agent is set to 30%. The figure shows that controls for the L_2-type objective are continuous, more in line with an interpretation of the controls as concentrations, while controls for the L_2-type objective are discontinuous (bang-bang) in line with an interpretation of the controls as dose rates. There is a significant difference in

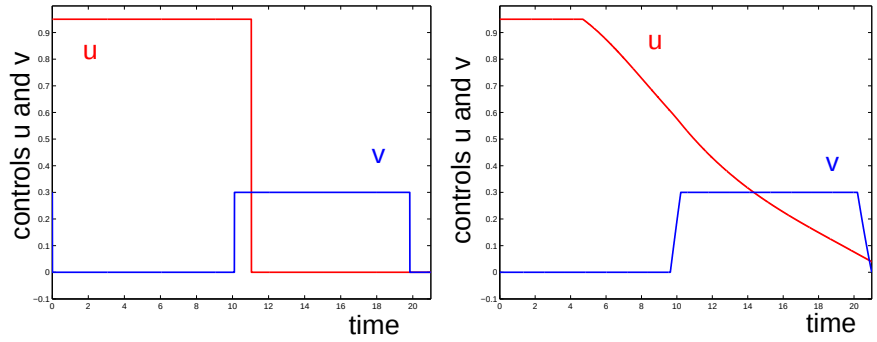

Figure 3: Locally optimal controls (with the cytotoxic agent u shown in red and the cytostatic agent v shown in blue) for the objectives J_1 (left) and J_2 (right) [23]

the administration schedules for the cytotoxic agent: the L_2-type objective has a built in bias towards lower doses and the optimal control is at maximum dose for just over 4 days and then gradually decays to a small dose at the end of the fixed therapy horizon (3 weeks); the L_1-type objective does not have an a priori built in bias towards specific doses and here the optimal control is of the MTD (maximum tolerated dose) type with upfront dosing and the maximum dose session lasting for about 11 days. In the control literature, such piecewise constant controls are called bang-bang controls and for medical problem formulations they play a major role corresponding to the standard MTD protocols with rest-periods. We only remark that such controls, which actually are the most commonly used protocols in medical practice, are automatically eliminated if an L_2-type modeling is done. On the other hand, with an L_1-type objective, they can be confirmed or rejected as the optimal ones through an analysis of the problem. While there are significant differences in the administration schedule for the cytotoxic agent, the schedules for the cytostatic agents are very similar and clearly the optimal L_2 control mimics the optimal L_1 control modulo the switchings which cannot be optimal for a quadratic objective. The reason for this behavior lies in the generally much shorter times that cells spend in the synthesis phase of the cell-cycle where the cytostatic agent is active.

The popularity of using a quadratic objective in the control has its origin in the necessary conditions for optimality given by the Pontryagin Maximum Principle [20]. One essential aspect of these conditions is the minimization of the Hamiltonian H of the optimal control problem over the control set $[0, u_{\max}]$. For a general optimal control problem with Lagrangian L and dynamics f, the Hamiltonian takes the form

$$H = \lambda_0 L(x, u) + \lambda f(x, u) \tag{3.4}$$

where λ_0 is a constant multiplier associated with the objective J and λ is a time-varying multiplier associated with the dynamics. It is one of the conditions of the maximum principle that if (x_*, u_*) is an optimal controlled trajectory, then for almost every time $t \in [0, T]$ the optimal control $u_*(t)$ minimizes the Hamiltonian H pointwise over the control set,

$$H(\lambda_0, \lambda(t), x_*(t), u_*(t)) = \min_{0 \le u \le u_{\max}} H(\lambda_0, \lambda(t), x_*(t), u). \tag{3.5}$$

The formulation with J_2 is favored in many papers for the simple reason that it offers significant mathematical advantages. In this case, the Hamiltonian H of the optimal control problem becomes quadratic in the control which makes this minimization an easy problem to solve. However, solving (3.5) for the control only defines u_* as a function of the state x and the multiplier λ, not as a feedback function of the state. Thus, even if this simpler approach is taken, it is not clear a priori that the computed control will be optimal, even locally, as this function still needs to be projected into the state space. Here overlaps (conjugate points) may occur in which case the extremal is not optimal. This is a highly non-trivial aspect and we refer to our paper [24] where second-order conditions to prove the optimality of such extremals have been developed. These have been applied to a class of problems modeling cell-cycle specific cancer chemotherapies like the example given in Fig. 3 to verify the local optimality of the computed extremals.

On the other hand, for the formulation with J_1, and also assuming that the dynamics is linear in u, the Hamiltonian takes the form

$$H(\lambda_0, \lambda(t), x_*(t), u) = \Psi(t) + \Phi(t)u \tag{3.6}$$

and here a degenerate case arises when the function

$$\Phi(t) = \frac{\partial H}{\partial u}(\lambda_0, \lambda(t), x_*(t), u_*(t)) \tag{3.7}$$

multiplying the control, called the *switching function*, vanishes. For such times the minimization condition (3.5) gives no information about the optimal control. Indeed, it is possible that $\Phi(t)$ vanishes over a non-empty interval I giving rise to so-called *singular controls*. These are computed by successively differentiating $\Phi(t)$ along the dynamics until the control u explicitly appears and then solving the resulting equation for the control. It follows from Lie-algebraic properties that the control can only appear for the first time in en even derivative, say of order $2k$, and then it is a higher-order necessary condition for optimality, the *Legendre-Clebsch condition*, that the following condition be satisfied:

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \frac{\partial H}{\partial u}(\lambda_0, \lambda(t), x_*(t), u_*(t)) \geq 0. \tag{3.8}$$

Rather than being an aberration, these often are the determining structures in optimal solutions [11]. Unfortunately, establishing the optimality of singular controls and their corresponding trajectories requires a delicate mathematical analysis. In addition, no good numerical procedures exist that would be able to locate these structures which often are only supported on lower-dimensional submanifolds in the state-space [11]. In a nut-shell, the mathematical problem with a linear L_1-type objective leads to a mathematically much more difficult problem to analyze than the problem when a quadratic L_2-type objective is chosen.

Mathematical simplicity, and the wide availability of standard numerical algorithms, are the sole reason for selecting a quadratic function of the control in the objective. In our opinion, there does not exist a single valid reason for justifying such a choice from a modeling perspective. By squaring the dosage, values which are higher than 1 are penalized excessively while values below 1 are favored. For example, as seen in Fig. 3, lower doses are favored simply because of the choice of the objective, not because they may inherently be the better choice. This actually is an important aspect of metronomic

chemotherapies, but no such claim is justified based on solutions of optimal control problems with L_2-type objectives. More importantly, there is no relation between the integral

$$\int_0^T u(t)^2 dt \tag{3.9}$$

and the total drug dosage (3.1). Thus, no matter how generic an argument about "systemic cost" is made, integrals of the type (3.9) do not represent pharmacologically relevant or meaningful parameters. On the other hand, the integrals

$$\int_0^T u(t)dt, \qquad \text{respectively} \qquad \int_0^T c(t)dt, \tag{3.10}$$

have immediate pharmacological meaning and are the AUC (area under the curve) that are used to measure the efficacy of drugs.

4. MATHEMATICAL MODELS WITH E_{MAX} PD

An important aspect of the overall modeling is that it is not necessary to revert to an arbitrary formulation of the objective using quadratic terms to harvest the advantages that convexity/concavity properties bring to the system. If we consider a mathematical model without PK and employ the saturating $E_{\max}$-model for PD, also normalizing the control in terms of UC_{50}, i.e., setting $UC_{50} = 1$, then the Hamiltonian of the problem takes the form

$$H(\lambda, x, u) = \lambda_0 (pu + qx) + \langle \lambda, f(x) \rangle + \frac{u}{1+u} \langle \lambda, g(x) \rangle \tag{4.1}$$

which, depending on the sign of $\lambda(t)$ is either convex or concave in the control leading to similar simple solutions for minimizing the Hamiltonian over the control set as when quadratic control terms are used. In fact, for this model we have the following result:

Theorem 4.1. [13] *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 u_* satisfies the following conditions:*

$$u_*(t) = \begin{cases} u_{max} & \text{if } \langle \lambda(t), g(x_*(t)) \rangle \leq -p(u_{max}+1)^2, \\ \sqrt{-\frac{\langle \lambda(t), g(x_*(t)) \rangle}{p}} - 1 & \text{if } -p(u_{max}+1)^2 \leq \langle \lambda(t), g(x_*(t)) \rangle \leq -p, \\ 0 & \text{if } -p \leq \langle \lambda(t), g(x_*(t)) \rangle. \end{cases} \tag{4.2}$$

In particular, optimal controls are continuous.

For this situation, all the benefits that a quadratic term in the control brings to the optimization are provided by the concavity properties of the $E_{\max}$ model for PD. The controls here are continuous in line with an interpretation of the controls as concentrations while if a linear log-kill model is used, controls are discontinuous in line with dose rates. Figure 4 shows two optimal solutions for a mathematical model for anti-angiogenic therapy that shows these features [11, 12].

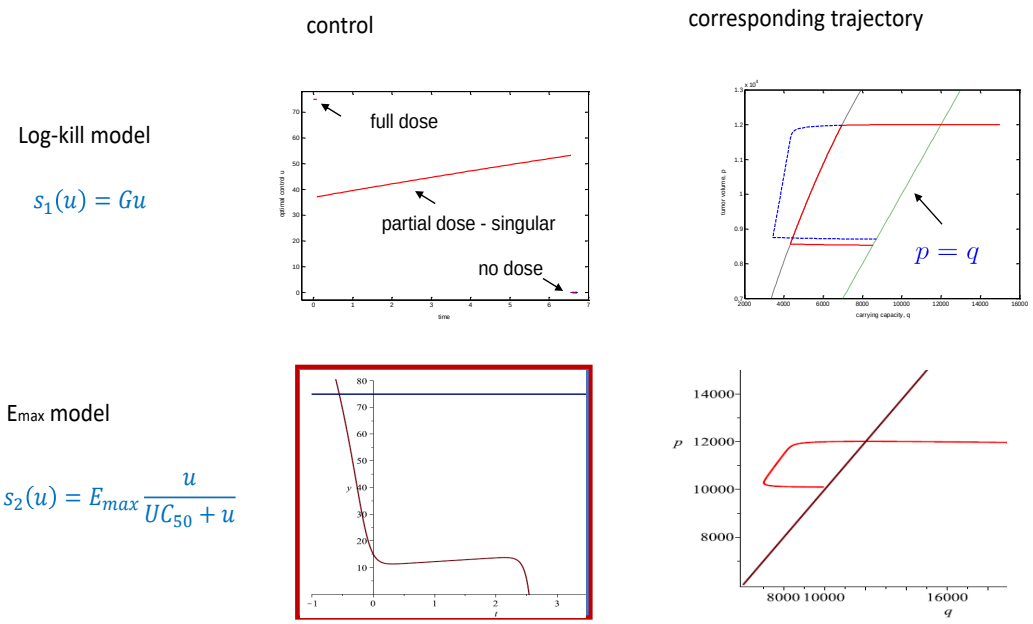

Figure 4: Optimal controls for a mathematical model for minimizing the tumor volume $p(T)$ with an a priori given amount of anti-angiogenic agents [11]. The top row shows the optimal control (left) and corresponding trajectory (right) for a linear log-kill model for PD [11] while the bottom row shows the same objects for an $E_{\max}$ model for PD [12]. The trajectories are displayed in (p, q)-space with p denoting the tumor volume and q the carrying capacity of the vasculature. The total amounts of anti-angiogenic inhibitors to be given are different in the two simulations.

5. CONCLUSION

Two aspects of optimizing cancer therapies, the choice of the objective and the incorporation of pharmacometric models, have interesting connections. In the choice of the objective, biological relevance and interpretation, not mathematical simplicity should be the most important and driving aspect. This favors the approach of choosing an L_1-type objective which leads to a more complicated mathematical structure, but not to unsurmountable difficulties. On the other hand, choosing an L_2-type objective simplifies the mathematical analysis as it induces convexity properties in the control on the Hamiltonian, but it distorts the biological meaning. In this paper, we point out that similar convexity properties can be achieved by incorporating the $E_{\max}$ model for PD without losing any of the biological realism. This proposed modeling thus has the double benefits of making the model more realistic and of allowing to pursue mathematically simpler arguments without using the biologically unjustified or even erroneous L_2 approach.

RECEIVED: MAY, 2018.
REVISED: JULY, 2018.

REFERENCES

[1] B. BONNARD & M. CHYBA (2003): Singular Trajectories and their Role in Control Theory, **Mathématiques & Applications,** vol. 40, Springer Verlag, Paris.

[2] A. BRESSAN & B. PICCOLI (2007): **Introduction to the Mathematical Theory of Control**, American Institute of Mathematical Sciences.

[3] M. DELITALA & T. LORENZI (2013): Formations of evolutionary patterns in cancer dynamics, in: **Pattern Formation in Morphogenesis: Problems and Mathematical Issues,** (V. Capasso et al., Eds.), Springer Proceedings in Mathematics, Vol. 15, pp. 179–190.

[4] M. EISEN (1979): Mathematical Models in Cell Biology and Cancer Chemotherapy, **Lecture Notes in Biomathematics**, Vol. 30, Springer Verlag, Berlin.

[5] A. ERGUN, K. CAMPHAUSEN & L.M. WEIN (2003): Optimal scheduling of radiotherapy and angiogenic inhibitors, **Bulletin of Mathematical Biology**, **65**, pp. 407–424.

[6] A. KÄLLÉN (2007): **Computational Pharmacokinetics**, Chapman and Hall, CRC, London, .

[7] M. KIMMEL & A. SWIERNIAK (1983): An optimal control problem related to leukemia chemotherapy, **Scientific Bulletins of the Silesian Technical University**, **65**, pp. 120–130.

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

[9] U. LEDZEWICZ & H. SCHÄTTLER (2002): Analysis of a cell-cycle specific model for cancer chemotherapy, **J. of Biological Systems**, **10**, pp. 183–206.

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

[11] U. LEDZEWICZ & H. SCHÄTTLER (2007): Antiangiogenic therapy in cancer treatment as an optimal control problem, **SIAM J. on Control and Optimization**, **46**(3), pp. 1052–1079.

[12] M. LESZCZYŃSKI,U. LEDZEWICZ & H. SCHÄTTLER (2019): Optimal control for a mathematical model for anti-angiogenic treatment with Michaelis-Menten pharmacodynamics, **Discr. and Cont. Dyn. Syst., Series B**, to appear

[13] M. LESZCZYŃSKI, E. RATAJCZYK, U. LEDZEWICZ & H. SCHÄTTLER (2017): Sufficient conditions for optimality for a mathematical model of drug treatment with pharmacodynamics, **Opuscula Math.**, **37**(3), pp. 403-–419.

[14] A. LORZ, T. LORENZI, J. CLAIRAMBAULT, A. ESCARGUEIL & B. PERTHAME (2015): Effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors, **Bull. Math. Biol.**, **77**, pp. 1–22.

[15] P. MACHERAS & A. ILIADIN (2016): Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics, **Interdisciplinary Applied Mathematics**, Vol. 30, 2nd ed., Springer, New York, .

[16] R. MARTIN & K.L. TEO (1994): **Optimal Control of Drug Administration in Cancer Chemotherapy**, World Scientific Press, Singapore.

[17] L. NORTON & R. SIMON (1977): Tumor size, sensitivity to therapy, and design of treatment schedules, **Cancer Treatment Reports**, **61**, pp. 1307–1317.

[18] L. NORTON & R. SIMON (1986): The Norton-Simon hypothesis revisited, **Cancer Treatment Reports**, **70**, pp. 41–61.

[19] L.G. DE PILLIS & A. RADUNSKAYA (2001): A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, **J. of Theoretical Medicine**, **3**, pp. 79–100.

[20] L.S. PONTRYAGIN, V.G. BOLTYANSKII, R.V. GAMKRELIDZE, & E.F. MISHCHENKO (1964): **The Mathematical Theory of Optimal Processes**, Macmillan, New York.

[21] M. ROWLAND & T.N. TOZER (1995): **Clinical Pharmacokinetics and Pharmacodynamics**, Wolters Kluwer Lippicott, Philadelphia.

[22] H. SCHÄTTLER & U. LEDZEWICZ (2012): **Geometric Optimal Control**, Interdisciplinary Applied Mathematics, vol. 38, Springer.

[23] H. SCHÄTTLER & U. LEDZEWICZ (2015): bf Optimal Control for Mathematical Models of Cancer Therapies, Interdisciplinary Applied Mathematics, vol. 42, Springer.

[24] H. SCHÄTTLER & U. LEDZEWICZ & H. MAURER, Sufficient conditions for strong local optimality in optimal control problems with L_2-type objectives and control constraints, **Discr. and Cont. Dyn. Syst., Series B**, **19** (8), 2014, pp. 2657–2679, doi:10.3934/dcdsb.2014.19.2657

[25] H.E. SKIPPER (1986): 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**, pp. 253–278.

[26] A. SWIERNIAK (1988): Optimal treatment protocols in leukemia - modelling the proliferation cycle, **Proc. of the 12th IMACS World Congress, Paris, 4**, pp. 170–172.

[27] A. SWIERNIAK (1995): Cell cycle as an object of control, **Journal of Biological Systems**, **3**, pp. 41–54.

[28] G.W. Swan (1984): **Applications of Optimal Control Theory in Medicine**, Marcel Dekker, New York.

[29] G.W. SWAN (1988): General applications of optimal control theory in cancer chemotherapy, **IMA J. of Mathematical Applications in Medicine and Biology**, **5**, pp. 303–316.