ON THE ROLE OF PHARMACOMETRICS IN MATHEMATICAL MODELS FOR CANCER TREATMENTS

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Abstract. We review and discuss various aspects that the modeling of pharmacometric properties has on the structure of optimal solutions in mathematical models for cancer treatment. These include (i) the changes in the interpretation of the solutions as pharmacokinetic (PK) models are added, respectively deleted from the modeling and (ii) qualitative changes in the structures of optimal controls that occur as pharmacodynamic (PD) models are varied. The results will be illustrated with a sample of models for cancer treatment.

1. Introduction. Optimal control for mathematical models of cancer chemotherapy has a long history dating back to the 1970s and 1980s (e.g. [4, 9, 35, 36, 38]). This research has continued actively throughout the years to the present day (e.g., see [17, 26, 27, 39] and the many references in [31]). Although the literature is vast, relatively little attention has been given to the role that pharmacometric models have in determining the structure of optimal solutions [16]. The reason for this, on one hand, lies in the wide-held—and generally also correct assumption—that pharmacokinetic models (PK) can be added as an after thought while, on the other hand, good knowledge about pharmacodynamic models (PD) often is elusive with little data available.

Pharmacokinetic models (PK) describe the relations between a drug’s dose rate $u$ and its concentration $c$ in the bloodstream (or other central and peripheral compartments) while pharmacodynamic models (PD) describe the effects $e$ which a drug has on the disease at concentration $c$. Modeling assumptions made about these processes have a rather direct impact on the structure of optimal solutions. For example, it is convenient, and often useful initially, to identify the dose rate and concentrations of the drug. This, however, commonly leads to solutions which...
from a modeling perspective represent concentrations, but are discontinuous functions resembling dose rates. Mathematically, as we shall see, it is not as trivial as it may seem to close this gap by adding a simple pharmacokinetic model. Similarly, pharmacodynamic models are described by functional relations $e = s(c)x$ with $x$ representing the compartment on which the drug is acting (e.g., tumor cells, healthy cells etc.) and $s$ what can be a highly nonlinear function of the concentration (e.g., defined by a Michaelis-Menten relation or generalised Hill functions [25, 29]). This indeed can lead to vastly different optimal structures. The natural question underlying our research therefore is whether, and if so, to what extent, the mathematical models used in the modeling determine the structure of optimal controls. This question is not only on a mathematically non-trivial topic, but it is also of relevant practical interest [14, 16, 31].

In this paper, we review and illustrate features that arise as (i) a pharmacokinetic model for the drug action is ignored, respectively included, and (ii) as the modeling of the pharmacodynamic effects of the drug is changed. We include a brief review of the fundamentals of the pharmacometrics of a drug in Section 2 and formulate the general structure of a mathematical model for drug treatment which includes pharmacokinetics and pharmacodynamics in Section 3. We briefly summarize the main necessary conditions for optimality for this model in Section 4. Section 5 then discusses the relations between the optimal controls for such a model when a pharmacokinetic model is included, respectively, not incorporated into the model and illustrates the results with an example for anti-angiogenic therapy. Optimal control problems for models with a Michaelis-Menten type pharmacodynamics are discussed in Section 6. We conclude this review paper with a discussion of the robustness properties of solutions using a model for CML (chronic myeloid leukemia) in Section 7.

2. A brief discussion of pharmacometrics of drugs. Pharmacometrics is the field of pharmacology that quantifies how a substance administered to a living organism behaves in it. Mathematically, this is the study of the relationship between a drug’s dose rate $u$, its concentration $c$ and the effects $e$ the drug has on the body. Figure 1 gives a schematic representation of these processes as well as graphs of some commonly used functions to represent these mathematical relations. We briefly discuss the main models for these processes.

2.1. Pharmacokinetics (PK). Pharmacokinetic equations model the time evolution of a drug’s concentration in the blood plasma. The standard 1-compartment model that describes the concentration $c = c(t)$ of the drug in the bloodstream in response to a continuous dose rate $u = u(t)$ is one of exponential growth and decay given by

$$\dot{c} = -\rho c + u, \quad c(0) = 0,$$

with $\rho$ the clearance rate of the drug. If $u_{\text{max}}$ denotes the maximum dose rate, then the concentration $c_{\text{max}}$ saturates at the value

$$c_{\text{max}} = \frac{u_{\text{max}}}{\rho}. \quad (2)$$

When administration of the drug is stopped ($u \equiv 0$), the concentration dissipates at an exponential rate $\rho$. We note that the maximum concentration is proportional to the maximum dose rate and if this one is multiplied tenfold, then so is the
concentration in this model. While such a relation is a reasonable approximation over a specific range of dose rates, it is not if the dose rates become very high.

We merely remark that this 1-compartment model is the simplest way to model the relations between the dose rate and the concentration of the drug and that it is no problem to extend this structure to more detailed models where the concentrations in the bloodstream are separated from the concentrations in a peripheral compartment (such as tissue or an organ of interest) and the interactions between those compartments are taken into account. In such a case the quantity \( c \) simply becomes a vector and the interactions are modelled through linear systems \( \dot{c} = Ac + bu \) where the matrix \( A \) has negative real eigenvalues. Most commonly such models are 2-dimensional, but also higher dimensional models are in use if the peripheral compartment is divided further into a ‘shallow’ and ‘deep’ compartment. An example of such a structure is a 3-compartment model commonly used for insulin pumps [33].

In this paper, and this is mostly a matter of simplifying the presentation, we only consider a 1-compartment model. However, we propose to replace the standard linear model (1) with a slightly more general bilinear equation:

\[
\dot{c} = (\rho + \eta u) c + u = -\rho c + (1 - \eta c) u, \quad c(0) = 0.
\]

We introduced this form in [16] and have used it in some of our previous work. From a mathematical perspective, this generalization causes no additional difficulties in our framework and it reduces to the standard linear model if we choose \( \eta = 0 \). This approach offers some advantages which make the model more realistic. For example, the second parameter \( \eta \) allows us to differentiate between the clearance rate of the drug and the increase in the concentration. Clearly, when no drugs are administered, \( \rho \) is the clearance rate. At the same time, the maximum concentration exhibits a more realistic Michaelis-Menten type dependence on the maximum dose.
rate given by
\[ c_{\text{max}} = \frac{u_{\text{max}}}{\rho + \eta u_{\text{max}}} = \frac{1}{\eta + \frac{\rho}{u_{\text{max}}}}. \] (4)
It thus saturates at the value \( \frac{1}{\eta} \) which also gives some biological meaning to this quantity. Clearly, for the model to be meaningful, we need to impose the restriction \( \rho + \eta u_{\text{max}} > 0 \). In this modeling the clearance rate increases while drugs are given at a higher dose rate, but this need not invalidate the model as the probability of interactions goes up if more particles are confined into a fixed space. This would also seem to be a natural qualitative consequence of statistical mechanics. Furthermore, it is also interesting to note that the Michaelis-Menten shape arises in enzyme kinetics from the law of mass action between the substrate and the enzyme precisely through a bilinear relationship as postulated in equation (3). Derivations which clearly explain the connections between these structures are given, for example, in [3, pg. 109-111] or [13]. Thus we use this more general form for a 1-compartment model for PK in this paper.

2.2. Pharmacodynamics (PD). Pharmacodynamic models describe the effect \( e \) which a drug has at concentration \( c \). They are usually given by functional relations of the form \( e = s(c)x \) with \( x \) denoting the cells in a compartment on which the drug is acting (e.g., tumor cells, immune system, healthy cells, etc.) and the coefficient \( s(c) \) representing the concentration dependent killing rate of the drug. There exist several approaches to model the function \( s = s(c) \) with a linear relation \( s = \sigma c, \sigma > 0 \), based on the linear log-kill hypothesis [34] probably the most common model. This model is applicable over a specific range of concentrations, but generally it is not accurate if both low and high drug concentrations need to be considered. Commonly used functional forms are the so-called \( E_{\text{max}} \)-model which more accurately describes the effect of “fast” acting drugs (see Fig. 2) and sigmoidal functions that also capture the behavior at lower concentrations (see Fig. 3). Mathematically, these models are given by the equations
\[ s(c) = \frac{E_{\text{max}} c}{EC_{50} + c}, \] respectively, \[ s(c) = \frac{E_{\text{max}} c^n}{EC_{50}^{n} + c^n}, \] \( n > 0 \), (5)
where \( EC_{50} \) denotes the concentration at which half of the maximum effect \( E_{\text{max}} \) is realized. Both \( EC_{50} \) and \( E_{\text{max}} \) are well established parameters in pharmacology. Thus the \( E_{\text{max}} \)-model is described by a Michaelis-Menten (MM) type equation while generalised Hill-type functions are used in sigmoidal models. We remark that, although this often is the case, \( n \) need not be an integer. In practice, drugs are typically administered in the upper range of the dose level-concentration curves and then the \( E_{\text{max}} \)-model seems to be most adequate.

3. A general model for chemotherapy with pharmacometrics. We formulate an abstract mathematical model for chemotherapy with a single pharmaceutical agent. We consider a general dynamics of the form
\[ \dot{x} = f(x) + s(c)g(x), \quad x(0) = x_0. \] (6)
The variable \( c \in [0, \infty) \) is a non-negative scalar which represents the concentration of the chemotherapeutic agent and the state \( x \in D \subset \mathbb{R}^n_+ \) is a column vector of non-negative numbers which represents cells in various compartments that are included in the modeling. These may be cancer cells, but also could include other cell types related to the vasculature or elements of the immune system that interact with the
The dynamics is described by smooth vector fields $f$ and $g$ defined on $D$. The drift vector field $f$ describes the evolution of the (mathematically) uncontrolled system when no drugs are given. The control vector field $g$ models the effects which the drug has on the system at concentration $c$ under the pharmacodynamic model $s = s(c)$. We always assume that the function $s : [0, \infty) \to [0, \infty)$, $c \mapsto s(c)$, is strictly monotonically increasing and satisfies $s(0) = 0$.

Pharmacokinetics is modelled through the bilinear system introduced earlier. We denote the dose rate of the drug by $u$ and this is the control of the system. We thus have that

$$\dot{c} = -(\rho + \eta c) c + u = -\rho c + (1 - \eta c)u, \quad c(0) = 0,$$

with $\rho$ the clearance rate of the drug. Formally, admissible controls are Lebesgue measurable functions with values in a compact interval, $u : [0, T] \to [0, u_{\text{max}}]$. It is easy to see [22] that the concentration $c$ is well defined over $[0, T]$ for any admissible control and that $0 \leq c(t) < \frac{u_{\text{max}}}{\rho + \eta u_{\text{max}}}$ holds for all times. In particular, $\eta c(t) < 1$.

The variables $x$ and $c$ together describe the state of the system and are functions of time $t$. Generally, however, in order not to burden the notation, we drop the argument $t$. As a generic convention, Greek letters denote parameters/constants. Naturally, the existence of solutions for the dynamics over an a priori prescribed interval $[0, T]$ depends on properties of the drift and control vector fields. We merely remark that it can always be guaranteed that the solution exists on $[0, T]$ if these vector fields are linearly bounded (e.g., see [8]), i.e., if there exist non-negative constants $a$ and $b$ such that

$$\|f(x)\| \leq a\|x\| + b, \quad \|g(x)\| \leq a\|x\| + b.$$

In any medical treatment side-effects need to be taken into account. One possible approach—and this is the one we consider here—is to take the point of view that an acceptable amount of drugs has been determined a priori based on the toxicity of the agent and/or other medically relevant aspects which are not included in the modeling. Mathematically, this is described by an isoperimetric constraint of the form $\int_0^T u(t) \, dt \leq A$. We emphasize that an $L_1$-integral of the dose rate, respectively, the concentration in simplified models which identify dosage with concentration, is used to model the total amount of drugs used. This agrees with standard practice in the pharmaceutical industry of using AUC (area under the curve) as one of the
main indicators for the effects (and thus also the side-effects) of treatment. The total amount of drugs given then is incorporated into the dynamics by adding the trivial equation
\[ \dot{y} = u, \quad y(0) = 0, \]
which tracks the amount of agents administered to the system and the terminal constraint \( y(T) \leq A \).

Using \( \dagger \) to denote the transpose, we define a new and extended state variable \( z \) as the column vector \( z = (x, c, y) \dagger \subset \mathbb{R}_{+}^{n+2} \) and define the augmented drift and control vector fields \( F \) and \( G \) as
\[ F(z) = \begin{pmatrix} f(x) + s(c)g(x) \\ -\rho c \\ 0 \end{pmatrix} \quad \text{and} \quad G(z) = \begin{pmatrix} 0 \\ 1 - \eta c \\ 1 \end{pmatrix}. \]

The dynamics can then be expressed as a control-affine system in the concise form
\[ \dot{z} = F(z) + G(z)u \quad z(0) = z_0 = (x_0, 0, 0) \dagger. \]

The natural question thus is how to use the given amount of therapeutic agents in a “best possible” way. Obviously, what exactly is meant by this is up to interpretation. It is generally accepted that some compromise needs to be made between minimizing the tumor cells (i.e., kill as much of the cancer as possible) and side-effects. In the approach taken here side-effects have already been limited through the total amount \( A \) of agents to be administered and therefore one may aim to maximize the tumor kill or, equivalently, minimize the tumor cells. We therefore take the objective in the form
\[ J(u) = \langle \alpha, x(T) \rangle + \int_0^T \langle \beta, x(s) \rangle \, ds \]
where \( \alpha \) and \( \beta \) are \( n \)-dimensional row vectors of non-negative weights and \( \langle \cdot, \cdot \rangle \) represents the inner product. By writing the vector of weights as a row vector, we also have the simple matrix product \( \langle \alpha, x \rangle = \alpha x \) and henceforth we also use this simpler notation. The weights in the objective will generally be taken positive for components of \( x \) that correspond to tumor cells, but they may be taken as zero for other compartments. Indeed, if one would want to up-regulate certain cell populations, then even negative values could be allowed. In this paper, however, we do not consider this case. We thus arrive at the following optimal control problem:

**[CC1]**: Minimize the functional \( J \) over all admissible controls \( u : [0, T] \rightarrow [0, u_{\text{max}}] \) subject to the dynamics described by the equations
\[ \begin{align*}
\dot{x} &= f(x) + s(c)g(x), \quad x(0) = x_0, \\
\dot{c} &= -(\rho + \eta u)c + u, \quad c(0) = 0, \\
\dot{y} &= u, \quad y(0) = 0,
\end{align*} \]
and the terminal constraint \( y(T) \leq A \). The terminal time \( T \) is free.

If the time under consideration is large relative to the half-life of the drug (e.g., months or weeks versus hours or minutes), then pharmacokinetics can be considered instantaneously. In such a case, it is appropriate/reasonable to drop the model for PK and identify the dose rate \( u \) with the concentration \( c \). Hence we also consider the following simplified version \([CC0]\) of model \([CC1]\). Mathematically, the model \([CC0]\) also is a useful stepping stone to be analyzed first before considering the full problem \([CC1]\).
[CC0]: Minimize the functional $J$ over all admissible controls $u : [0,T] \rightarrow [0,u_{\text{max}}]$ subject to the dynamics described by the equations

$$
\begin{align*}
\dot{x} &= f(x) + s(u)g(x), \quad x(0) = x_0, \\
\dot{y} &= u, \quad y(0) = 0,
\end{align*}
$$

and the terminal constraint $y(T) \leq A$.

We merely remark that it would not be difficult to extend the model structure to multi-input systems if there are no strong interactions between the drugs, i.e., if in some sense these drugs have different activation mechanisms. In this case, the concentration $c$ is a vector and the dynamics takes the form

$$
\dot{x} = f(x) + \sum_{i=1}^{m} s_i(c)g_i(x).
$$

If synergistic or antagonistic effects need to be taken into account, however, the dynamics will become fully non-linear and quite often the specifics of these interactions are only poorly understood. We therefore restrict our discussions to the single-input case.

4. **Necessary conditions for optimality.** Necessary conditions for optimality for the optimal control problems [CC] are given by the Pontryagin maximum principle [28]. (For some more recent references on the topic, see [1, 2, 30].) For problem [CC1] the (control) Hamiltonian is the function given by the formula

$$
H : (R^{n+3})^* \times R^{n+2} \times R, \quad (\lambda_0, \lambda, \mu, \nu; x, c, y, u) \mapsto H(\lambda_0, \lambda, \mu, \nu, x, c, y, u),
$$

$$
H(\lambda_0, \lambda, \mu, \nu, x, c, y, u) = \lambda_0 \langle \beta, x \rangle + \langle \lambda, f(x) + s(c)g(x) \rangle + \mu(-\rho + u\eta)c + u + \nu u,
$$

(12)

where $\lambda_0 \in R_+^*$, $\lambda \in (R^n)^*$, $\mu \in R^*$ and $\nu \in R^*$ are multipliers associated with the objective and the dynamics. According to an interpretation of multipliers as linear functionals, we consequently write them as row vectors. Combining the multipliers into one covector $\Lambda = (\lambda, \mu, \nu) \in (R^{n+2})^*$ and using the state $z$ and the augmented vector fields $F$ and $G$, the Hamiltonian simply is the inner product of the multipliers with the objective and the dynamics:

$$
H(\lambda_0, \Lambda, z, u) = \lambda_0 \langle \beta, x \rangle + \langle \Lambda, F(z) + G(z)u \rangle.
$$

(13)

If $u_*$ is an optimal control with corresponding trajectory $z_* = (x_*, c_*, y_*)$, then there exists an absolutely continuous co-vector $\Lambda_* : [0,T] \rightarrow (R^{n+2})^*$ and a constant $\lambda_0 \geq 0$ such that the following conditions are satisfied:

(i) [non-triviality condition] the multipliers $\lambda_0$ and $\Lambda(t)$ do not vanish simultaneously: $\langle \lambda_0, \Lambda(t) \rangle \neq 0$ for a.e. $t \in [0,T]$,

(ii) [adjoint equations]

$$
\dot{\lambda} = -\frac{\partial H}{\partial x} = -\lambda(Df(x) + s(c)Dg(x)) - \lambda_0\beta,
$$

(14)

$$
\dot{\mu} = -\frac{\partial H}{\partial c} = -s'(c)\lambda g(x) + \mu(\rho + u\eta),
$$

(15)

$$
\dot{\nu} = -\frac{\partial H}{\partial y} = 0;
$$

(16)

here $D$ denotes the Jacobian matrix of the partial derivatives with respect to the state $x$. 

(iii) [transversality conditions] \( \lambda(T) = \lambda_0 \alpha, \mu(T) = 0 \) and \( \nu(T) \geq 0 \).
(iv) [minimization condition] the Hamiltonian function \( H \) is minimized point-wise over the control set a.e. by the optimal control along the covector \( \Lambda \) and the optimal trajectory \( z^* \). That is,
\[
H(\lambda_0, \Lambda(t), z^*(t), u^*(t)) = \min_{0 \leq v \leq u_{\text{max}}} H(\lambda_0, \Lambda(t), z^*(t), v) \quad \text{for a.e. } t \in [0, T].
\]
(v) the function \( t \mapsto H(\lambda_0, \Lambda(t), z^*(t), u^*(t)) \) vanishes identically on \([0, T]\),
(vi) the complementary slackness condition \( \nu(y_*(T) - A) = 0 \) holds. In particular, by equation (16), the multiplier \( \nu \) is a non-negative constant.

Triples \( \Gamma = ((\lambda_0, \Lambda), z_*, u_*) \) consisting of a controlled trajectory \((z_*, u_*)\) and a multiplier \( \Lambda \) for which all the conditions (i)-(vi) of the Pontryagin maximum principle stated above are satisfied are called extremals. They are called normal if the multiplier \( \lambda_0 \) corresponding to the objective is positive and abnormal if this multiplier is zero.

It is not difficult to see that extremals are normal unless the optimal control \( u_* \) vanishes identically [22]. We ignore this degenerate case and only consider normal extremals. We thus normalize the multiplier \( \lambda_0 \) to be \( \lambda_0 = 1 \) and henceforth drop it in the notation.

As the Hamiltonian \( H \) is linear in the control, the minimization condition implies that optimal controls satisfy the following condition:
\[
u^*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0, \\ 1 & \text{if } \Phi(t) < 0, \end{cases} \quad \text{where } \Phi(t) = \langle \Lambda(t), G(z_*(t)) \rangle. \tag{18}
\]
The function \( \Phi = \Phi(t) \) is the term multiplying the control in the definition of the Hamiltonian \( H \) and is called the switching function of the optimal control problem. Clearly, whenever \( \Phi(\tau) = 0 \) and \( \Phi(\tau) \neq 0 \), then optimal controls switch at time \( \tau \) between the extreme points 0 and \( u_{\text{max}} \) of the control set. Corresponding controls are called bang-bang controls. If the switching function vanishes identically over some non-empty open interval \( J \), then the minimization property by itself does not give any information about the control. In this case, however, also all derivatives of \( \Phi(t) \) vanish identically on \( J \) and this typically determines the corresponding controls. Such controls are called singular.

In the biomedical scenario, bang-bang controls correspond to protocols with switchings between maximal dose, often called MTD (maximum tolerated dose), segments and rest periods. Singular controls, on the other hand, represent time-varying administrations of a drug using lower doses. Thus, the question whether optimal controls are bang-bang or singular is of immediate practical interest.

**Definition 4.1.** Let \( \Gamma = (\Lambda, z_*, u_*) \) be an extremal lift for the optimal control problem \([CC0]\) or \([CC1]\) which is singular on an open interval \( I \subset [0, T] \), i.e., the switching function \( \Phi \) vanishes identically on \( I \). The corresponding control \( u_* \) is said to be singular on \( I \) and the response of the system \( z_* \) is called a singular arc. The singular control is said to be of order \( k \) over \( I \) if the first \( 2k - 1 \) derivatives of the switching function do not depend on the control \( u \) while the coefficient at the control \( u \) in the derivative of order \( 2k \) of the switching function does not vanish.

Although more general structures cannot be excluded a priori, for a typical situation optimal controls will be concatenations of bang and singular controls. The
following result, the generalized Legendre-Clebsch Condition (e.g., see [1, 30]) gives a higher order necessary condition for optimality of singular controls.

**Theorem 4.2.** Let $u_*$ be an optimal control for problem $[CC]$ which is singular of order $k$ over an open interval $I \subset [0, T]$ with corresponding extremal lift $\Gamma = (\Lambda, z_*, u_*)$. It then holds that

$$(-1)^k \frac{\partial^{2k}}{\partial u \partial t^{2k}} \frac{\partial H}{\partial u}(\Lambda(t), z_*(t), u_*(t)) = (-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \Phi(t) \geq 0 \quad \text{for all } t \in I.$$  \hspace{1cm} (19)

The Legendre-Clebsch condition for singular controls for problem $[CC1]$ has been analyzed in [22]. It follows from the necessary conditions for optimality that the multiplier $\nu$ is constant and non-negative. If it is positive—and this is the generic situation—we have the following result:

**Proposition 1.** [22] Assuming $\nu > 0$, an extremal singular control $u_*$ defined on an open interval $I$ is of order $1$ if and only if

$$\frac{1}{2} s''(c) \frac{s'(c)}{s'(c)} \neq \eta - \eta c.$$  \hspace{1cm} (20)

The strengthened Legendre-Clebsch condition for minimality is satisfied if and only if

$$\frac{1}{2} s''(c) \frac{s'(c)}{s'(c)} < \eta - \eta c.$$  \hspace{1cm} (21)

We recall from above that $1 > \eta c(t)$ for all times.

**Corollary 1.** [22] Recall that the function $s$ modeling pharmacodynamics is non-negative and monotonically strictly increasing.

(a) If $\eta \geq 0$ and $s$ is a strictly concave function, then singular controls are of order one and the strengthened Legendre-Clebsch condition for minimizing the objective $J$ is satisfied.

(b) If $\eta > 0$ and $s$ is concave, then singular controls are of order one and the strengthened Legendre-Clebsch condition for minimizing the objective $J$ is satisfied.

(c) If $\eta = 0$, i.e., for the standard linear model of PK, the strengthened Legendre-Clebsch condition for minimizing the objective $J$ is satisfied where $s$ is strictly concave and it is violated where $s$ is strictly convex.

The situation is more complicated for a Hill-type sigmoidal function, $s(c) = \frac{E_{\text{max}} c^n}{EC_{50} + c^n}$, which has an inflexion point.

**Corollary 2.** [22] Suppose $\eta = 0$, i.e., a linear pharmacokinetic model is used. With a Hill-type pharmacodynamic model $s(c) = \frac{E_{\text{max}} c^n}{EC_{50} + c^n}$, the strengthened Legendre-Clebsch condition for minimizing $J$ is satisfied where

$$\left(\frac{c}{EC_{50}}\right)^n > \frac{n-1}{n+1}$$

and it is violated where

$$\left(\frac{c}{EC_{50}}\right)^n < \frac{n-1}{n+1}.$$  \hspace{1cm} (22)

In general, for both the model formulations $[CC0]$ and $[CC1]$, the problem then becomes to synthesize the optimal solutions from bang and singular control pieces which satisfy the strengthened Legendre-Clebsch condition. In the rest of the paper, we discuss at the hand of various examples how these optimal structures can change as one passes from one model formulation to another and as the models for pharmacodynamic effects are changed.
5. Comparison of optimal controlled trajectories for the models [CC0] and [CC1]: An example for anti-angiogenic therapy. We discuss the general changes that arise in optimal controls as the model formulation is changed from [CC0] which does not include pharmacokinetics to [CC1] where a linear pharmacokinetic model is incorporated. We use a well-studied mathematical model for tumor development under angiogenic signaling formulated by Hahnfeldt, Panigrahy, Folkman and Hlatky [6] to illustrate the results. Our discussion is based on mathematically proven results from [19, 31].

We briefly describe the model by Hahnfeldt et al. [6], but refer the reader to the literature for a thorough discussion of the model. Here the vector fields $f$ and $g$ are given by

$$f(x) = \left( -\xi_p \ln \left( \frac{p}{q} \right) \frac{bp}{bp - (\mu + dp^2)q} \right) \quad \text{and} \quad g(x) = \left( \begin{array}{c} 0 \\ -q \end{array} \right), \quad x = \left( \begin{array}{c} p \\ q \end{array} \right),$$

and the pharmacodynamic model is the linear Skipper model $s(u) = E_{\text{max}} u$. As concentration and dose rate are identified in the model, we use the letter $u$ to represent the control. The state $x$ consists of the primary tumor volume $p$ and the carrying capacity $q$ of the vasculature. This quantity is not considered constant, but becomes a state variable whose evolution is governed by a balance of stimulatory and inhibitory effects. The term $bp$ represents the stimulation of the vasculature by the tumor and is taken proportional to the tumor volume. The term $dp^2 q$ models the inhibition which is represented as an interaction term between the tumor surface and the vasculature. The coefficients $b$ and $d$ are mnemonically labelled for birth and death of cells in the vasculature, respectively.

In [17, 30] we analyzed the problem formulation [CC0] with the objective $J(u) = p(T)$, i.e., with $x = (p, q)^T$ we have $\alpha = (1, 0)$ and $\beta = (0, 0)$ in equation (24), and have given a complete global solution to this problem in terms of a regular synthesis of optimal controlled trajectories. For a medically realistic initial condition, and large enough supply of anti-angiogenic inhibitors, (the precise conditions are given in [17]), optimal solutions are concatenations of a short full dose segment followed by a long piece where the control is singular and then end with another short period when no drugs are given. On this interval, after-effects of the previous administration still reduce the tumor volume. The most important structural element in this solution is the singular arc and the corresponding optimal singular control is of order 1. Figure 4 gives the time-evolution of a typical solution. The control is discontinuous at the junction times between the bang and singular arcs and thus, from an interpretational point of view, resembles the dose rate of the drug. On the other hand, in the modeling clearly $u$ represents the concentration. This kind of discrepancy will always be present in the model formulations [CC0] and, in fact, assigning units to the control $u \sim c$ is somewhat arbitrary and may lead to wrong interpretations.

Yet, there are good reasons for using the mathematical approximation [CC0] over the more realistic model [CC1]. When a linear model for PK is incorporated—and this is the standard approach, for example done in [6]—the order of the singular control increases from 1 to 2 [19, 31]. This, however, significantly changes the structure of optimal solutions. It is well-known in the control literature that such controls cannot be concatenated optimally with a constant bang control [30], but that these connections are made by chattering arcs (Fuller phenomenon), i.e., by
controls that switch infinitely many times near the switching point (and thus are merely Lebesgue-measurable functions). Clearly, such solutions are not practicable and thus the relevant question becomes how close to optimal can one be with a reasonable realistic control. Knowing the structure of the optimal solution simply allows us to judge such approximations and, indeed, for this particular model, and also in general, excellent approximations of the optimal tumor volume can be achieved with even the simplest piecewise constant approximations [10, 18].

Overall, while the model formulation [CC0] has some obvious deficiencies with its interpretation (as dose rates which typically are discontinuous are identified with concentrations which are continuous), it nevertheless provides a better approach towards solving the problem as it avoids the difficulties related to having optimal singular arcs of higher order—a non-generic, but real phenomenon. Based on the solution for problem [CC0], it is rather straightforward to obtain reasonably structured and close to optimal solutions for the more realistic modeling formulation [CC1]. This applies not only to the particular model referenced here, but is generally valid if the optimal solution includes singular arcs. If optimal solutions are bang-bang, like, for example, for cell-cycle specific models for cancer chemotherapy (e.g., [15, 39]), such difficulties do not exist and the procedures to go from model [CC0] to model [CC1] are straightforward.

6. Optimal control problems with Michaelis-Menten type pharmacodynamics. Still keeping as objective the minimization of the tumor volume, i.e., $J(u) = p(T) \rightarrow \min$, the situation is different if we change the pharmacodynamic
model from the Skipper linear term $s(u) = E_{\text{max}}u$ to a saturating Michaelis-Menten functional form $s(u) = \frac{E_{\text{max}}u}{EC_{50} + u}$. Mathematically, obviously it is possible to normalize $EC_{50}$ to $EC_{50} = 1$ by scaling the concentration $c$ in units of $EC_{50}$, but this is not done in pharmacology because of the practical importance of this parameter and so we retain this parameter. This makes for easier interpretations of the formulas. For such a model, it follows from Theorem 3.1 in [20] that optimal controls for the model [CC0] are always continuous in agreement with an interpretation of the controls as concentrations. In this case, optimal controls change continuously between the upper and lower values of the control set along segments when the control takes values in the interior of the control set and is differentiable. The controls along these interior segments are easily computed by solving the equation

$$0 \equiv \frac{\partial H}{\partial u}(\lambda, \nu, x, u) = \nu + \frac{E_{\text{max}}EC_{50}}{(EC_{50} + u)^2} \langle \lambda, g(x) \rangle$$

for $\tilde{u} = \tilde{u}(t)$ as a function of the time-dependent multiplier $\lambda$ and state $x$. If the solution $\tilde{u}$ to this equation lies outside of the admissible control interval $[0, u_{\text{max}}]$, then the control is simply capped at the respective limit. This leads to the following simple formula for the optimal controls $u^\ast$ from which continuity is immediate:

$$u^\ast = u^\ast(t) = \max\{0, \min\{\tilde{u}(t), u_{\text{max}}\}\}.$$  

In [21] this version [CC0] of the Hahnfeldt-model for anti-angiogenic treatment was considered with the $E_{\text{max}}$-model for PD and again, and depending on initial data and the amount of available agents, optimal controls consist of an initial full dose segment followed by an interior control and ending with a brief no dose segment when after-effects still take place. Qualitatively this structure resembles the one for the case of a linear PD, but with continuous transitions. Clearly, for this model therefore there is a direct and clean interpretation of the control as the concentration and, in principle, the question of realizing the optimal concentration through the dose rate could be treated separately. We only remark on the side that for the Hahnfeldt-model the formula for the interior control $\tilde{u}$ has a removable singularity on the diagonal (which is caused by the term $\ln\left(\frac{p}{q}\right)$ in the dynamics) and numerically it actually becomes much more difficult to compute this interior control than it is to compute the singular control for a linear PD-model. Thus, from a mathematical point of view, there seems to be no clear argument that would favor one or the other model.

If a standard linear model for PK is incorporated into the dynamics, then the optimal control problem [CC1] once more is control affine and optimal controls (which now represent the dose rates) are again concatenations of bang and singular controls [22]. It is shown in that paper that the singular control is given as a feedback function of the state variables $(p, q, c)^T$ in the form

$$u_{\text{sing}} = \rho c + \frac{1}{2}(EC_{50} + c) \left( \frac{b \ln\left(\frac{p}{q}\right) - 1 + \mu + dp^2 + E_{\text{max}} \left(\frac{c}{EC_{50} + c}\right)^2}{\ln\left(\frac{p}{q}\right)} \right).$$

We note that this formula also exhibits the removable singularity on the diagonal $(p = q)$ alluded to above. As expected, it is shown in [22] that the dynamics of the system [CC1] along the singular control agrees with the dynamics of the model [CC0] along the interior control. This confirms that it is possible to consider the
7. Comments on robustness properties of solutions. We close with brief comments about the robustness of optimal controls for a model for long-term drug administration (on the scale of several years) for CML (chronic myeloid leukemia) which are based on the papers [12, 13, 23] by U. Ledzewicz and H. Moore. This model does not fall into the class of problems defined in [CC0] and [CC1], but is a multi-drug optimization problem over an a priori prescribed therapy horizon (on the order of 5 years). The dynamics is a 3-compartment model with the compartments representing proliferating leukemic cells $P$, quiescent leukemic cells $Q$ and effector cells $E$ taken as a representation of the effects of the immune system. CML is treated by a cocktail of drugs and in this model a general BCR-ABL1 inhibitor $u_1$, a BCR-ABL1 inhibitor $u_2$ which also has immune effects, and the action of an immunomodulatory compound $u_3$ are considered. The PK of the drugs is short compared with the time-horizon for the therapy and therefore PK is neglected. Michaelis-Menten terms are used for PD which leads to an interpretation of the controls as concentrations.

After suitable mathematical scalings of variables and parameters which is indicated by tildes on the respective quantities [12], and only to give an impression of the complexity of the nonlinear structure of the model, the dynamics can be represented in the following form:

$$\frac{dQ}{dt} = r_Q \tilde{Q} - \delta_Q \left[ 1 + \left( 1 + \frac{U_{2,\text{max},1} \bar{u}_2}{1 + \bar{u}_2} \right) \left( 1 + \frac{U_{3,\text{max},1} \bar{u}_3}{1 + \bar{u}_3} \right) \frac{E_{\text{max},1} \bar{E}}{1 + \bar{E}} \right] \tilde{Q},$$

$$\frac{d\tilde{P}}{dt} = \left( 1 - \frac{U_{1,\text{max},1}}{1 + \bar{u}_1} \right) \left( 1 - \frac{U_{2,\text{max},2} \bar{u}_2}{1 + \bar{u}_2} \right) \left[ \left( k_p \frac{Q_{\text{ref}}}{PC_{50}} \right) \tilde{Q} + r_P \tilde{P} \ln \left( \frac{P_{50}}{P \cdot PC_{50}} \right) \right] - \delta_P \left( 1 + \frac{U_{1,\text{max},2} \bar{u}_1}{1 + \bar{u}_1} \right) \left( 1 + \frac{U_{2,\text{max},3} \bar{u}_2}{1 + \bar{u}_2} \right) \tilde{P}$$

$$- \delta_P \left( 1 + \frac{U_{2,\text{max},1} \bar{u}_2}{1 + \bar{u}_2} \right) \left( 1 + \frac{U_{3,\text{max},1} \bar{u}_3}{1 + \bar{u}_3} \right) \frac{E_{\text{max},2} \bar{E}}{1 + \bar{E}} \tilde{P},$$

and

$$\frac{d\tilde{E}}{dt} = s_E \left[ 1 + \left( 1 + \frac{U_{2,\text{max},4} \bar{u}_2}{1 + \bar{u}_2} \right) \left( 1 + \frac{U_{3,\text{max},2} \bar{u}_3}{1 + \bar{u}_3} \right) \frac{P_{\text{max},1} \bar{P}}{1 + \bar{P}} \right] \tilde{E} \ln \left( \frac{E_{\text{ss}}}{E \cdot EC_{50}} \right)$$

$$- \delta_E \left[ 1 + \left( 1 - \frac{U_{2,\text{max},5} \bar{u}_2}{1 + \bar{u}_2} \right) \left( 1 - \frac{U_{3,\text{max},3} \bar{u}_3}{1 + \bar{u}_3} \right) \frac{P_{\text{max},2} \bar{P}}{1 + \bar{P}} \right] \tilde{E}.$$

With a suitable re-scaling of the parameters all $C_{50}$-values (i.e., the concentrations when drugs show half of their effect) in the Michaelis-Menten expressions have been normalized to 1. We refer the reader to the papers [12] and [13] for detailed explanations of the modeling and the parameters.
The objective $J$ to be minimized is taken as a weighted average of the leukemia cells during and at the end of therapy and of the total doses of the drugs given in the form

$$J(u) = \alpha_1 Q(\tau) + \alpha_2 P(\tau) + \int_0^\tau [\beta_1 Q(t) + \beta_2 P(t) + \gamma_1 u_1(t) + \gamma_2 u_2(t) + \gamma_3 u_3(t)] \, dt.$$  

(24)

Here $\alpha_1, \alpha_2, \beta_1, \beta_2, \gamma_1, \gamma_2, \gamma_3$ are constant weights and the treatment period $[0, \tau]$ is fixed.

In the paper [23], an extensive comparison is given between numerically computed optimal controls and controls which are optimal for a constrained drug regimen when the doses are restricted to be piecewise constant with values that are only allowed to change every three months. Figure 5 gives a comparison of the optimal piecewise constant controls with a numerically computed optimal control for year 3 of such a regimen. As is clear from the figure, the piecewise constant controls provide an excellent approximation of the numerically computed optimal control. Similar extremely strong robustness properties of the controls have been seen over a wide range of numerical simulations. The initial condition for the state, however, was always chosen according to the steady-state proportions of the corresponding uncontrolled dynamics (see [12, 23]).

These simulations therefore strongly suggest—at least for the treatment of CML—that the value function is truly flat around an optimal solution and thus many simple and realistic dosing schedules close to the optimal one exist which, for all practical intents and purposes, replicate optimal responses.

8. **Conclusion.** In this paper, we reviewed and discussed various results that compare the structure of optimal chemotherapy protocols depending on the pharmacometric modeling used. There exist good heuristic reasons for a modeling approach that simplifies the system by ignoring selective, so-to-speak, higher order effects and then incorporate them later on as needed. For medical problem formulations this approach is clearly taken in the approach to PK and PD in the literature. Naturally, any change, be it in the mathematical modeling for PK and/or PD, or simply changes in the parameter values for a given model, will cause quantitative changes which can reasonably well be investigated numerically. Conceptually, however, it is more significant whether qualitative changes arise as these may alter the overall approach to treatment.

Using a model for anti-angiogenic therapy as illustration, we have shown [20, 21] that this indeed is the case if a model for PK is not included initially. In this case, optimal controls more closely represent dose rates of the agent if a linear log-kill model is used for PD while they resemble concentrations if an $E_{\text{max}}$-model is used. In the later case, incorporating a linear PK-model into the modeling then restores the more typical interpretation of optimal controls as dose rates and the structure of optimal controls as discontinuous concatenations of bang and singular arcs. While there exist theoretically significant differences (such as in continuity properties of the optimal controls or in the order of optimal singular controls), from a practical perspective these do not seem to contribute to large differences in the optimal values.

Another practically relevant question is the robustness of optimal therapies. In the model for CML given in the paper, the value function is extremely flat near the
Figure 5. Comparison of the solution to the restricted optimization problem where controls are kept constant for 3 months for year 3 (top row; controls shown on the left and the corresponding states are given on the right) with the solutions to the optimal control problem for year 3 (shown in the bottom row).
optimum which implies great robustness properties of the solutions. Almost any reasonable approximate dosing strategy based on the optimal structure comes very close to the optimal one in its effects. Obviously, this does not mean that just any dosing stratagem would work equally. But, and this also has been seen in other models [18], sensitivities of the optimal solutions with respect to pharmacometric data generally seem to be low. This probably is also the reason for the effectiveness of most drug treatments as the PK of a drug must be very well researched, generally is known and published, but data about the PD of specific drugs are either unknown or well guarded by the industry as it is almost impossible to get such data from the pharmaceutical literature.

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