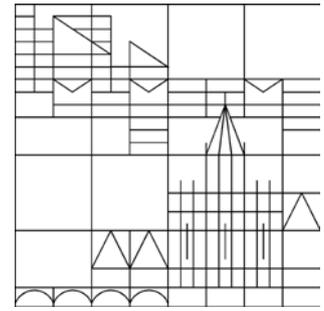


Universität Konstanz



OptiDose : Computing the Individualized Optimal Drug Dosing Regimen Using Optimal Control

Freya Bachmann
Gilbert Koch
Marc Pfister
Gabor Szinnai
Johannes Schropp

Konstanzer Schriften in Mathematik

Nr. 394, September 2020

ISSN 1430-3558

Konstanzer Online-Publikations-System (KOPS)
URL: <http://nbn-resolving.de/urn:nbn:de:bsz:352-2-1ypj4os3d87v2>

OptiDose: Computing the Individualized Optimal Drug Dosing Regimen Using Optimal Control

Freya Bachmann · Gilbert Koch · Marc Pfister · Gabor Szinnai · Johannes Schropp

Received: date / Accepted: date

Abstract Providing the optimal dosing strategy of a drug for an individual patient is an important task in pharmaceutical sciences and daily clinical application. We developed and validated an optimal dosing algorithm (OptiDose) that computes the optimal individualized dosing regimen for pharmacokinetic-pharmacodynamic models in substantially different scenarios with various routes of administration by solving an optimal control problem. The aim is to compute a control that brings the underlying system as closely as possible to a desired reference function by minimizing a cost functional. In pharmacokinetic-pharmacodynamic modeling the controls are the administered doses and the reference function can be the disease progression. Drug administration at certain time points provides a finite number of discrete controls, the drug doses, determining the drug concentration and its effect on the disease progression. Consequently, rewriting the cost functional gives a finite-dimensional optimal control problem depending only on the doses. Adjoint techniques allow to compute the gradient of the cost functional efficiently. This admits to solve the optimal control problem with robust gradient-based descent methods such as quasi-Newton methods from finite-dimensional optimization. OptiDose is applied to three relevant but substantially different pharmacokinetic-pharmacodynamic examples.

Freya Bachmann, corresponding author · Johannes Schropp
Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany
E-mail: freya.bachmann@uni-konstanz.de, johannes.schropp@uni-konstanz.de

Gilbert Koch · Marc Pfister
Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, University of Basel, Basel, Switzerland
E-mail: gilbert.koch@ukbb.ch, marc.pfister@ukbb.ch

Gabor Szinnai
Pediatric Endocrinology and Diabetology, University Children's Hospital Basel, University of Basel, Basel, Switzerland
E-mail: gabor.szinnai@ukbb.ch

Keywords optimal control · model predictive control · quasi-Newton methods · individualized optimal drug dosing · pharmacokinetic-pharmacodynamic models

Mathematics Subject Classification (2000) 49K15 · 65K10 · 92C45 · 92C50

1 Introduction

An optimal drug dosing regimen is a prerequisite to provide the best possible care for every individual patient. However, a diversity of individual factors need to be considered including current disease state, patient characteristics and the clinical goal for this patient. In pediatric patients, developmental changes have to be incorporated additionally. In (preterm) neonates we face even more difficulties because fast maturation processes start immediately after birth which impact the drug effect, see e.g. [1–3]. Therefore, it is essential to support clinicians with sophisticated mathematical methods to compute the optimal dosing regimen for every individual patient.

Mathematical modeling has become an essential tool in drug developing industries and clinical pharmacology departments in hospitals. The U.S. Food and Drug Administration recognized such computational modeling and simulation tools as an improvement of the efficiency for developing safe and effective drugs [4]. Especially, the so-called pharmacokinetics (PK) and pharmacodynamics (PD) models [5–7], a combination of mathematical and statistical methods, incorporate biological, physiological and pharmacological behavior. Roughly speaking, the PK deals with the distribution and elimination of a drug and the PD characterizes the effect of the drug on a specific target. PKPD models are formulated with a system of nonlinear differential equations [7–10].

Up to now the computation of a “good” dosing regimen for an individual patient is a laborious and biased task in clinical pharmacology. Often a large number of simulations for varying dosing regimens is performed with the developed PKPD model and the “best” dosing regimen is selected “by hand”. In contrast, e.g. in the development process of oncology drugs [11], optimal control approaches are already used to increase the probability of successful phase 2 clinical trials [12]. However, the research questions in such clinical trials during drug development may differ from the goals in clinical application and therefore, often the drug concentration of potential drug candidates is optimized and not the doses itself that cause the drug concentration.

In clinics, the goal for the individual patient is usually clearly defined by the physician. For example, in hormonal diseases the aim is not always to return the hormone levels as quickly as possible to the normal range but to follow a moderate disease reduction over several weeks. Another situation is to achieve a specific concentration of a target (e.g. a drug-receptor complex) having the most beneficial impact on the disease [13].

Although control theory is widely applied in many different engineering fields such as aerospace (the field where it was originally developed by Pontr-

jagin [14]) or economics, its application in daily clinical practice is still quite rare. Various reasons are possible, e.g. many drugs are promoted as “one size fits all” and therefore individual patient characteristics are completely ignored. Another reason might be much simpler, currently to our knowledge no software for solving optimal control problems (OCP) is available that is custom-built for PKPD models and addresses the needs in daily clinical application.

In this paper, we develop a mathematical OCP that is especially designed for PKPD models and name the software OptiDose. In contrast to many applications [12, 15, 16] we are not using the time course of the drug as a continuous control. We directly optimize the doses for a given time schedule which is the typical clinical situation for patients treated with oral, subcutaneous or intravenous bolus administration. This allows to construct a finite-dimensional reduced OCP which can be solved using robust gradient-based algorithms such as quasi-Newton methods.

Moreover, we will apply nonlinear model predictive control (NMPC), in engineering also called closed loop strategy, see [17] for theoretical details and [18] for an application to hemodialysis. This meets clinical needs as it allows to adapt patient parameters during the optimization if the covariates change over time e.g. due to maturation processes or sudden changes in the disease characteristics, or if more clinical measurements are available. In addition, this strategy enables to react to unforeseen events such as missed or wrong doses.

Finally, we present three examples of different complexity, a biomarker indirect response model (which can be considered as the test model for OptiDose), a tumor growth inhibition model, and a model characterizing the various binding dynamics of a bispecific monoclonal antibody from immuno-oncology.

2 The Pharmacokinetic-Pharmacodynamic Model

In this section we present the pharmacokinetic-pharmacodynamic (PKPD) model, usually a system of nonlinear ordinary differential equations describing the dynamics of a certain disease and the action of a drug, and discuss its unique solvability.

Let us consider the time interval $[0, T]$ with (possibly large) final time $T > 0$. We assume that the drug doses denoted by the control variable

$$u := (u_1, \dots, u_m) \in \mathbb{R}^m$$

are respectively administered at specific time points

$$0 \leq t_1 \leq \dots \leq t_m < T, \quad m \in \mathbb{N}$$

orally or subcutaneously (SC), as intravenous (IV) bolus or as IV infusion with a constant infusion rate for a certain duration Δt_i , $i = 1, \dots, m$. In accordance with the typical notation in optimal control, we introduce the associated finite-dimensional control space $U = \mathbb{R}^m$. As only nonnegative doses or rates with a

given upper bound $u_{max} \in \mathbb{R}^m$, $u_{max} > 0$ can be administered, we define the convex and compact admissible subset

$$U_{ad} = \{u \in U \mid 0 \leq u \leq u_{max}\} \subset U$$

where ' \leq ' denotes the componentwise comparison. Let $u \in U_{ad}$ be arbitrarily chosen. Then the PKPD model, in the context of optimal control also called the state equation, describes the model state

$$\begin{aligned} y'(t) &= g(t, \theta, u, y(t)), & t \in (0, T] \text{ almost everywhere} \\ y(0) &= y_0(\theta). \end{aligned} \quad (1)$$

Here $g: [0, T] \times \Theta \times U \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ is the PKPD mechanism, θ the model parameter in the set Θ of admissible model parameters, $y_0(\theta) \in \mathbb{R}^n$ the initial value and $u = (u_1, \dots, u_m) \in U_{ad}$ denotes the administered doses. A reliable PKPD model (1) for a population with the same disease has to be validated thoroughly from measured data and the model parameter θ has to be estimated reasonably before addressing the optimal dosing problem. In the optimal dosing step the parameter θ is fixed, i.e. $\theta = \theta_{ind}$ for a certain individual in a population or $\theta = \theta_{av}$ characterizing the average value of a population. Without loss of generality we thus use

$$\begin{aligned} y'(t) &= g(t, u, y(t)), & t \in (0, T] \text{ almost everywhere} \\ y(0) &= y_0 \end{aligned} \quad (2)$$

with $g: [0, T] \times U \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ as PKPD model and initial value y_0 . Moreover, PKPD models inherit an additive structure

$$g(t, u, y) = \tilde{g}(t, y) + r(t, u) \quad (3)$$

between state y and control u from their design principles. In (3) $\tilde{g}: [0, T] \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ describes the pharmacological mechanism and $r: [0, T] \times U \rightarrow \mathbb{R}^n$ the dosing regimen. For the dosing we encounter oral or SC administration into an absorption compartment, or IV bolus injection or IV infusion for a certain duration Δt_i into the central compartment characterizing the blood in the body. This leads to

$$\begin{aligned} r(t, u) &= In(t, u) e^{j_0} \\ &= \begin{cases} \sum_{i=1}^m u_i \delta(t - t_i) e^{j_0} & \text{for oral / SC administration} \\ \sum_{i=1}^m \frac{u_i}{V} \delta(t - t_i) e^{j_0} & \text{for IV bolus} \\ \sum_{i=1}^m \frac{u_i}{V \Delta t_i} \mathbb{1}_{[t_i, t_i + \Delta t_i]}(t) e^{j_0} & \text{for IV infusion} \end{cases} \end{aligned} \quad (4)$$

where $In(t, u)$ denotes the input function depending on the dosing regimen u , δ is the Dirac distribution, j_0 is the component of y to which the dose will be added to and e^{j_0} denotes the j_0 -th unit vector. The parameter V describes the volume of distribution of the body for the specific drug. The difference between oral / SC and IV bolus administration is only the division by V . In the IV bolus and IV infusion case, we divide by the volume of distribution V leading to ‘‘concentration equations’’ in (2). In contrast, oral or SC administration is typically modeled as ‘‘mass equation’’ in (2) where the amount of a drug is added to an absorption compartment.

2.1 Unique Solution of the State Equation

A minimal assumption in PKPD analysis is that for every dosing regimen there is exactly one solution of the state equation which, in addition, has to be sufficiently smooth. To do so, we formally modify our PKPD model (2) by replacing the Dirac distribution $\delta(t - t_i)$ in r by the scaled indicator function $\frac{1}{\epsilon} \mathbf{1}_{[t_i, t_i + \epsilon]}(t)$. So, instead of oral and IV bolus administration we apply a short infusion, e.g. with $\epsilon = 10^{-4}$. This leads to

$$g(t, u, y) = \tilde{g}(t, y) + \tilde{r}(t, u) \quad (5)$$

with

$$\begin{aligned} \tilde{r}(t, u) &= \tilde{I}n(t, u) e^{j_0} \\ &= \begin{cases} \sum_{i=1}^m \frac{u_i}{\epsilon} \mathbf{1}_{[t_i, t_i + \epsilon]}(t) e^{j_0} & \text{for oral / SC administration} \\ \sum_{i=1}^m \frac{u_i}{V\epsilon} \mathbf{1}_{[t_i, t_i + \epsilon]}(t) e^{j_0} & \text{for IV bolus} \\ \sum_{i=1}^m \frac{u_i}{V\Delta t_i} \mathbf{1}_{[t_i, t_i + \Delta t_i]}(t) e^{j_0} & \text{for IV infusion} \end{cases} \quad (6) \end{aligned}$$

For any $u \in U_{ad}$ the function $\tilde{r}(\cdot, u)$ is a step function and $\tilde{r}(t, \cdot)$ is linear in u for $t \in [0, T]$. We assume the pharmacological mechanism \tilde{g} to be continuously differentiable and globally Lipschitz continuous with respect to y . Then iterative application of the Picard-Lindelöf theorem implies that for any u there is a unique solution $y \in C([0, T], \mathbb{R}^n)$ which is continuously differentiable when restricted to any time interval $I \subset [0, T]$ on which $\tilde{r}(t, u)$, $t \in I$ is constant. Due to Example 6.2.5 in [19] the weak derivative of y exists and $y \in Y := H^1(0, T; \mathbb{R}^n) \cap C([0, T], \mathbb{R}^n)$ follows for the modified state equation (2), (5), (6).

3 The Optimal Control Problem

Our goal is to achieve a certain outcome of the disease, e.g. a normal level of a hormone or tumor eradication. This desired disease progression is specified by a reference function $h_{ref}: [0, T] \rightarrow \mathbb{R}$. Then we characterize optimality by minimizing the cost functional $J: Y \times U \rightarrow \mathbb{R}$,

$$J(y, u) = \frac{1}{2} \int_0^T (h(y(t)) - h_{ref}(t))^2 dt + \sum_{i=1}^m \alpha_i u_i \quad (7)$$

with $\alpha = (\alpha_1, \dots, \alpha_m) \geq 0$ and a C^1 -functional $h: \mathbb{R}^n \rightarrow \mathbb{R}$ describing the actual state of the patient resulting from a particular dosing regimen u . In oncology, h could be the sum of proliferating and different stages of apoptotic tumor cells. The standard recommendation is $\alpha = 0$ but for some PKPD models it can be useful to add a small $\alpha > 0$ in favor of a linear dependency [12] to lower drug doses.

To formulate the optimal control problem we rewrite the PKPD model (2) as equality constraint, i.e.:

$$e: Y \times U \rightarrow Z, \quad e(y, u) = \begin{pmatrix} e_1(y, u) \\ e_2(y, u) \end{pmatrix} = \begin{pmatrix} y' - g(\cdot, u, y) \\ y(0) - y_0 \end{pmatrix} = 0 \in Z$$

for $Z := L^2(0, T; \mathbb{R}^n) \times \mathbb{R}^n$. Then, the OCP reads

$$\min J(y, u) \text{ subject to } e(y, u) = 0, y \in Y, u \in U_{ad}. \quad (P)$$

In the sequel, we work with the following set of assumptions:

Assumption Optimal Control Problem

1. $U_{ad} \subset U$ is convex, bounded and closed.
2. $J: Y \times U \rightarrow \mathbb{R}$, $e: Y \times U \rightarrow Z$ are continuously Fréchet differentiable and U, Y, Z are Banach spaces.
3. For all $u \in \tilde{U}$ in a neighborhood $\tilde{U} \subset U$ of U_{ad} , the state equation $e(y, u) = 0$ has a unique solution $y = y(u) \in Y$.
4. $\frac{\partial}{\partial y} e(y(u), u) \in \mathcal{L}(Y, Z)$ has a bounded inverse for all $u \in \tilde{U} \supset U_{ad}$.

The assumptions follow the framework introduced in [20], Ch. 1.7.2 and the additional property $U_{ad} \subset U$ bounded originates from the design of OCPs in PKPD modeling.

Assumption 1) holds by definition of U_{ad} , 2) and 3) are fulfilled due to the smoothness assumptions of \tilde{g} , h and the properties of the step function \tilde{r} . Computing the Fréchet derivative in assumption 4) for arbitrary but fixed $u \in \tilde{U}$ yields the operator:

$$T(u): Y \rightarrow Z, \\ T(u) y_\delta = \left(\frac{\partial}{\partial y} e(y(u), u) \right) y_\delta = \begin{pmatrix} y'_\delta - \frac{\partial}{\partial y} g(\cdot, u, y(u)) y_\delta \\ y_\delta(0) \end{pmatrix} \in Z$$

Obviously, $T(u)$ is a linear operator which is bijective due to the Picard-Lindelöf theorem and the approximation of L^2 -functions by continuous functions. Moreover, the Lipschitz continuity of g yields that $\|\frac{\partial}{\partial y} g(\cdot, u, y(u))\|$ is bounded and therefore $T(u)$ is continuous. Then assumption 4) follows by the bounded inverse theorem, cf. [21].

3.1 Existence of Optimal Controls

Definition 3.1 A control $\bar{u} \in U_{ad}$ is called optimal for (P) and $\bar{y} = y(\bar{u}) \in Y$ is called the associated optimal state if

$$J(\bar{y}, \bar{u}) \leq J(y(u), u) \text{ for all } u \in U_{ad}.$$

The assumptions of the OCP admit to introduce the reduced cost functional

$$\hat{J}(u) := J(y(u), u)$$

and the reduced optimal control problem

$$\min \hat{J}(u) \quad \text{s.t.} \quad u \in U_{ad}. \quad (\hat{P})$$

The existence of an optimal control \bar{u} then follows from the compactness of $U_{ad} \subset \mathbb{R}^m$ and the Weierstraß theorem, since the map $\hat{J}: U_{ad} \rightarrow \mathbb{R}$ is continuously differentiable as the solution operator of the state equation $u \in \tilde{U} \mapsto y(u) \in Y$ is continuously differentiable by the implicit function theorem and the assumptions of the OCP.

Remark 3.1 Due to the nonlinearity of the PKPD model and the lacking strictness of the convexity of J we cannot guarantee uniqueness of the optimal control.

Theorem 5.2.2 in [22] ensures that if $\bar{u} \in U_{ad}$ is a local solution of the reduced problem (\hat{P}) then \bar{u} satisfies the variational inequality

$$\langle \nabla \hat{J}(\bar{u}), u - \bar{u} \rangle_U \geq 0 \quad \text{for all } u \in U_{ad}. \quad (8)$$

Now, we will derive necessary optimality conditions for a local solution $\bar{u} \in U_{ad}$.

3.2 Necessary First-Order Optimality Conditions

Following the notation in [20, Ch. 1.6.4] we define the Lagrange function associated with (P) :

$$L: Y \times U \times Z \rightarrow \mathbb{R}, \quad L(y, u, p) = J(y, u) + \langle p, e(y, u) \rangle_Z$$

Here, we identified Z with its dual space Z^* and $p = (\tilde{p}, \tilde{p}_0)$ is the so-called adjoint state. Moreover, as $\tilde{p}_0 = \tilde{p}(0)$ holds we write $p =: \tilde{p}$. The inner product $\langle \cdot, \cdot \rangle_Z$ is given by

$$\langle \tilde{p}, e(y, u) \rangle_Z = \langle \tilde{p}, e_1(y, u) \rangle_{L^2(0, T; \mathbb{R}^n)} + \langle \tilde{p}(0), e_2(y, u) \rangle_{\mathbb{R}^n}.$$

If (\bar{y}, \bar{u}) is an optimal solution to the problem (P) , then there exists a Lagrange multiplier $\bar{p} \in Z$ such that the following optimality conditions hold, also called the KKT conditions after Karush, Kuhn and Tucker [20, Ch. 1.7.2]:

$$\begin{aligned} \forall u \in U_{ad} : \langle \frac{\partial}{\partial u} L(\bar{y}, \bar{u}, \bar{p}), u - \bar{u} \rangle_U &\geq 0 \\ \frac{\partial}{\partial y} L(\bar{y}, \bar{u}, \bar{p}) &= 0 \\ \frac{\partial}{\partial p} L(\bar{y}, \bar{u}, \bar{p}) &= e(\bar{y}, \bar{u}) = 0 \end{aligned}$$

For arbitrary $u_\delta \in \mathbb{R}^m$ we compute the Fréchet derivative

$$\begin{aligned} \frac{\partial}{\partial u} L(y, u, p) u_\delta &= \left\langle \frac{\partial}{\partial u} J(y, u), u_\delta \right\rangle_{\mathbb{R}^m} + \left\langle \frac{\partial}{\partial u} \langle p, e(y, u) \rangle_Z, u_\delta \right\rangle_{\mathbb{R}^m} \\ &= \langle \alpha, u_\delta \rangle_{\mathbb{R}^m} - \left\langle \int_0^T p(t)^\top \frac{\partial}{\partial u} g(t, u, y(t)) dt, u_\delta \right\rangle_{\mathbb{R}^m} \end{aligned} \quad (9)$$

and analogously for arbitrary $y_\delta \in Y$ we have

$$\begin{aligned} \frac{\partial}{\partial y} L(y, u, p) y_\delta &= \frac{\partial}{\partial y} J(y, u) y_\delta + \left(\frac{\partial}{\partial y} \langle p, e(y, u) \rangle_Z \right) y_\delta \\ &= \int_0^T \langle (h(y(t)) - h_{ref}(t)) \frac{\partial}{\partial y} h(y(t)), y_\delta \rangle_{\mathbb{R}^n} dt + p(0)^\top y_\delta(0) \\ &\quad + \int_0^T \langle p(t), y'_\delta(t) \rangle_{\mathbb{R}^n} - \langle p(t), \left(\frac{\partial}{\partial y} g(t, u, y(t)) \right) y_\delta(t) \rangle_{\mathbb{R}^n} dt. \end{aligned}$$

From the second KKT condition we can derive the adjoint equation for $t \in (0, T]$ almost everywhere:

$$\begin{aligned} p'(t) &= - \left(\frac{\partial}{\partial y} g(t, u, y(t)) \right)^\top p(t) + (h(y(t)) - h_{ref}(t)) \frac{\partial}{\partial y} h(y(t)), \\ p(T) &= 0 \end{aligned}$$

Using adjoint techniques and (5) it can be shown [20, Ch. 1.6.4] that

$$\begin{aligned} \langle \nabla \hat{J}(u), u_\delta \rangle_{\mathbb{R}^m} &= \frac{\partial}{\partial u} L(y(u), u, p(u)) u_\delta \\ &= \langle \alpha, u_\delta \rangle_{\mathbb{R}^m} - \left\langle \int_0^T p(t)^\top \frac{\partial}{\partial u} \tilde{r}(t, u) dt, u_\delta \right\rangle_{\mathbb{R}^m} \end{aligned} \quad (10)$$

for all $u_\delta \in \mathbb{R}^m$ and therefore, the variational inequality (8) is the first KKT condition with the derivative computed in (9). Having a formula for $\nabla \hat{J}(u)$ we can now solve (\hat{P}) numerically using gradient-based descent algorithms.

Remark 3.2 In contrast to the general, infinite-dimensional setting discussed in [20] we construct a finite-dimensional OCP by exploiting the design of PKPD models, see (5), (6). Therefore, the evaluation of $\nabla \hat{J}(u)$ comes at very low computational cost.

3.3 Open Loop Problems and Convergence Properties

Assuming that all model parameters are known prior to the optimization we can solve (\hat{P}) in a so-called open loop process in which the controls are computed iteratively until a certain stopping criterion is satisfied. We will use a quasi-Newton method with Armijo step size control where the Hessian $\nabla^2 \hat{J}(u)$ is approximated by projected BFGS updates named after Broyden, Fletcher,

Goldfarb and Shanno. For more details on the step size strategy, the algorithm, local and global convergence results we refer the reader to [22, Ch. 5]. It should be noted that during the iteration process there is no option to update parameters or react to external perturbations.

3.4 The Nonlinear Model Predictive Control Method

In this section, we will focus on the nonlinear model predictive control (NMPC) method, in engineering mainly called closed loop strategy. The idea is to optimize the control u on a sequence of overlapping open loop problems with short time horizon $I_i \subset [0, T]$ covering the time interval instead of solving one open loop problem on the full time interval. This approach allows parameter adaptations due to changes in the patient data between consecutive open-loop problems. The time intervals I_i should be chosen in a way such that one dose gets applied and then the time horizon is shifted to start just before the next dosing time point, therefore it is sometimes also called moving horizon method. For the dosing time points $M := \{t_1, \dots, t_m\}$ choose a suitable prediction horizon length Δt_M with

$$\max_{i=2, \dots, m} (t_i - t_{i-1}) \leq \Delta t_M \ll T$$

to cover the full time interval $[0, T]$ with short prediction horizons. Independently of the value Δt_M we have to solve m open loop problems to find an optimal control u_i for each dosing time point t_i , $i \in \{1, \dots, m\}$.

Suppose we are at time $t_{0,i} \in [0, T - \Delta t_M]$ and consider the horizon $I_i = [t_{0,i}, t_{f,i}]$ with $t_{f,i} = t_{0,i} + \Delta t_M$. By

$$M_i := M \cap I_i = \{t_i, \dots, t_{i+\ell_i}\}, \quad \ell_i = \#M_i$$

we denote the dosing time points that belong to the current time interval I_i . We previously computed the optimal doses u_1, \dots, u_{i-1} and the associated optimal state trajectory y^{i-1} from the last iteration. Therefore, we set $y_0^i := y^{i-1}(t_{0,i})$ as an initial value for the state equation on I_i

$$\begin{aligned} (y^i)'(t) &= g(t, u^{(i)}, y^i(t)), & \text{for } t \in I_i \text{ a.e.} \\ y^i(t_{0,i}) &= y_0^i \end{aligned}$$

where the control $u^{(i)}$ denotes $u^{(i)} = (u_i, \dots, u_{i+\ell_i}) \in U_{ad}^{(i)}$ and

$$U_{ad}^{(i)} := \{u^{(i)} \in \mathbb{R}^{\ell_i} \mid 0 \leq u^{(i)} \leq u_{max}^{(i)}\}$$

with $u_{max}^{(i)} = ((u_{max})_i, \dots, (u_{max})_{i+\ell_i})$ is the corresponding admissible set. In the i -th step on the prediction horizon I_i we use the cost functional

$$J_i(y^i, u^{(i)}) = \frac{1}{2} \int_{t_{0,i}}^{t_{f,i}} (h(y^i(t)) - h_{ref}(t))^2 dt + \sum_{k=i}^{i+\ell_i} \alpha_k u_k \quad (11)$$

One can also add stabilizing terminal conditions to (11) penalizing the deviation of the state to the reference state at the end of the moving horizon $t_{f,i}$ if necessary. As before, we introduce the reduced cost functional

$$\hat{J}_i(u^{(i)}) := J_i(y^i(u^{(i)}), u^{(i)})$$

with the unique solution to the state equation $y^i(u^{(i)})$. The open loop problem

$$\min \hat{J}_i(u^{(i)}), \quad \text{s.t. } u^{(i)} \in U_{ad}^{(i)} \quad (\hat{P}_i)$$

is solved as in section 3.3 computing an optimal control vector and predicting the dynamics on the time horizon $[t_{0,i}, t_{f,i}]$. Now, only the first component of the optimal control vector $u_i = (u^{(i)})_1$ is applied and the time horizon is shifted to the next interval $I_{i+1} = [t_{0,i+1}, t_{0,i+1} + \Delta t_M]$ with initial condition $y_0^{i+1} := y^i(t_{0,i+1})$. Before solving (\hat{P}_{i+1}) it is possible to update parameters or react to unforeseen perturbations such as dosing errors or missed doses.

In Algorithm 1 we display a pseudocode for the described closed loop technique.

Algorithm 1 (The NMPC method)

Require: Initial state y_0 , initial guess for control u_0

- 1: Set $u = []$;
 - 2: Set $y_0^1 := y_0$;
 - 3: **for** $i = 1, \dots, m$ **do**
 - 4: Set current observation horizon $I_i := [t_{0,i}, t_{0,i} + \Delta t_M]$;
 - 5: Compute $M_i := M \cap I_i$;
 - 6: Compute a (numerical) solution $\bar{u}^{(i)}$ and the associated state \bar{y}^i to the open loop problem (\hat{P}_i) with initial condition y_0^i and initial guess $u_0^{(i)}$
 - 7: Save all state values \bar{y}^i belonging to $[t_{0,i}, t_{0,i+1})$
 - 8: Save $y_0^{i+1} := \bar{y}^i(t_{0,i+1})$ as new initial condition
 - 9: Save u_i , i.e. set $u = [u; (\bar{u}^{(i)})_1]$;
 - 10: Update parameters if necessary
 - 11: **end for**
-

Remark 3.3 On one hand, the NMPC approach allows adaptations due to changes in the patient data between consecutive open loop problems which makes it extremely flexible and thus, is the method of choice in most real world applications. On the other hand, please keep in mind the computed controls in the i -th step are optimal only on the shorter time horizon $I_i \subset [0, T]$ according to problem (\hat{P}_i) , $i = 1, \dots, m$. Therefore, in the case of no data changes the NMPC method leads to a “nearly optimal” solution.

4 Application of OptiDose to Relevant Examples of Pharmacokinetic-Pharmacodynamic Models and Presentation of Numerical Results

We present three relevant examples of PKPD models used in drug development and clinical pharmacology and apply the developed OptiDose algorithm to compute the optimal dosing regimen. In contrast to the theoretical part where a short infusion was necessary to guarantee the existence of the solution, in application the OptiDose code will use the numerically more efficient representation (4) instead of (6) whenever possible. As in the standard PKPD software NONMEM [23] and Monolix [24] the integration process is stopped at every dosing time point, the dose is then added to the corresponding state (e.g. an absorption or central compartment) and integration is continued to the next dosing time point.

4.1 The OptiDose Software

For the software OptiDose the presented open and closed loop algorithms were implemented in Matlab [25] using the built-in solver ode15s to solve the arising initial value problems. The open loop problems were solved with the damped BFGS method. All computations were performed on an ASUSTek computer with Intel(R) Core(TM) i7-7700HQ CPU processor with 2.80GHz and 16GB RAM.

4.2 Biomarker Indirect Response Models: a Test Model for OptiDose

In Fig. 1 a) we display the model schematic for a test example where a biomarker B is elevated and a drug is administered to return those high biomarker levels to the normal range. We further assume that the disease cannot be cured, i.e. in absence of the drug the biomarker will return to its initial state B^0 at diagnosis. The test model is a so-called indirect response model (IDR) which is a fundamental tool in PKPD modeling, cf. e.g. [26, 27]. IDR models consist of a zero-order production rate k_{in} and a first-order elimination rate k_{out} and the drug stimulates or inhibits these rates usually with Michaelis-Menten type of terms [28]. Here the drug will be administered via IV bolus into the central compartment according to (4). The drug concentration C is described by a linear one-compartment model with drug elimination rate k_{el} . Maximal stimulating effect of the drug is E_{max} and the drug concentration to produce the half-maximal effect is EC_{50} . The PKPD model reads

$$\begin{aligned} \frac{d}{dt}C &= In(t, u) - k_{el}C, & C(0) &= 0, \\ \frac{d}{dt}B &= k_{in} - k_{out} \left(1 + \frac{E_{max}C}{EC_{50} + C} \right) B, & B(0) &= B^0 = \frac{k_{in}}{k_{out}}. \end{aligned}$$

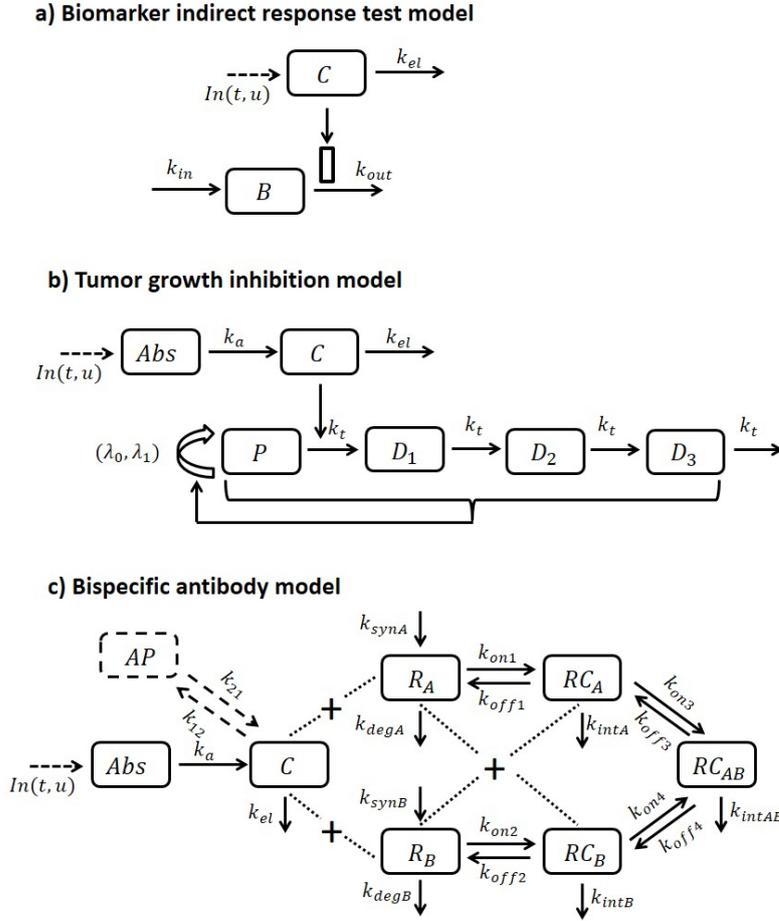


Fig. 1 Model schematics for the three examples

A clinically realistic dosing scenario for non-hospitalized patients is that the doses are administered daily but they change only every week. The aim is to control the biomarker B to follow a predefined reference function characterized by

$$B_{ref}(t) = \begin{cases} \frac{1}{(7m_1)^2} (B^0 - B_{tar}) t^2 - \frac{2}{7m_1} (B^0 - B_{tar}) t + B^0, & t \leq 7m_1 \\ B_{tar}, & t > 7m_1 \end{cases}$$

providing a slow quadratic approach towards the target biomarker level B_{tar} . We choose $\alpha = 0$ in the cost functional, a target value of $B_{tar} = 10$, a loading phase of $m_1 = 2$ weeks and $m = 6$ weeks in total. Fig. 2 shows the optimal solution, on the left the actual and desired biomarker levels and on the right the optimal doses and the resulting drug concentration.

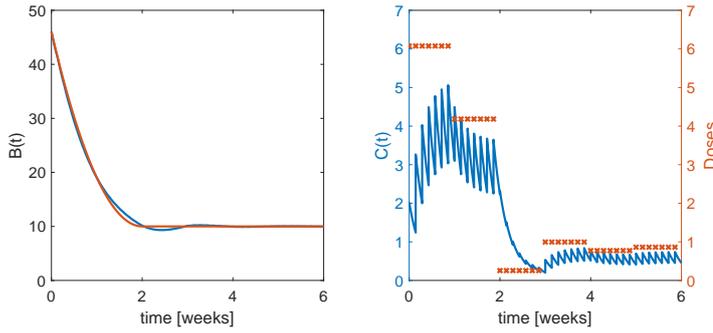


Fig. 2 Left: Pharmacodynamics of optimal solution in blue and reference function in red. Right: Drug concentration for optimal dosing in blue and doses administered at dosing time points (red crosses)

Starting from an initial guess of $u_0 = 1$ for all doses the optimal open loop solution u^* was computed within 85 seconds and a cost functional value of $\hat{J}(u^*) = 3.89$. The closed loop with an observation horizon of e.g. three weeks reproduces the open loop solution up to neglectable differences.

Individual parameter values used are $\theta_{ind} = (V, B^0, k_{out}, k_{in}, k_{el}, E_{max}, EC_{50}) = (3, 46, 0.02, 0.92, 0.49, 8.8, 0.81)$.

4.3 Tumor Growth Inhibition Model

Proliferating tumor cells usually grow exponentially in the beginning and transition later to a linear growth, cf. [29,30]. Depending on the tumor type, size and environment, a saturation of the growth can be observed, however, this is neglected in the following example. Many drugs act in a cytotoxic manner, meaning that the tumor cells are attacked by the drug. Attacked cells then undergo apoptosis until they eventually die. The presented example is based on preclinical oncology drug development in mice, see [30] for details and Fig. 1 b) for the model schematic. The structure of the model is widely applied in industry and academia for these type of experiments.

Let P be the proliferating tumor cells with an exponential growth rate λ_0 and a linear growth rate λ_1 [30]. The drug C , orally administered into an absorption compartment Abs with absorption rate k_a , acts on the proliferating cells with a linear drug effect term with potency k_{pot} . The apoptotic cell population is described with three transit compartments D_1, D_2, D_3 [31], each reflecting a certain age stage of the apoptotic cells with transit rate k_t . The sum of the proliferating and apoptotic cells is the total tumor weight

$W = P + D_1 + D_2 + D_3$. The PKPD model (2) reads

$$\begin{aligned} \frac{d}{dt}Abs &= In(t, u) - k_a Abs, & Abs(0) &= 0, \\ \frac{d}{dt}C &= k_a \frac{Abs}{V} - k_{el}C, & C(0) &= 0, \\ \frac{d}{dt}P &= \frac{2\lambda_0\lambda_1 P^2}{(\lambda_1 + 2\lambda_0 P)W} - k_{pot}C \cdot P, & P(0) &= P^0, \\ \frac{d}{dt}D_1 &= k_{pot}C \cdot P - k_t D_1, & D_1(0) &= 0, \\ \frac{d}{dt}D_i &= k_t(D_{i-1} - D_i), & D_i(0) &= 0, \quad i = 2, 3. \end{aligned}$$

First the tumor is grown to a specific size, then the drug is administered daily from day 12 to 28. The aim is to decrease the tumor weight W towards zero. For the reference function we choose a sigmoid shape starting at 0.5 on day 12 and tending to zero:

$$W_{ref}(t) = \frac{0.25 (\exp(2) - \exp(-2))}{0.5 (\exp(2) - 3 \exp(-2)) + \exp(0.5t - 8)}, \quad t \geq 12$$

As the drug is acting on the proliferating tumor cells via $k_{pot}C \cdot P$ in the third equation in the PKPD model, its impact decreases as the tumor size shrinks towards 0. In fact, the problem loses its controllability meaning significantly different doses, e.g. 10, 100, 1000, achieve nearly the same pharmacodynamic behavior. Naturally, small doses are preferred which is why we choose $\alpha = 10^{-7} > 0$ in the cost functional in favor of lower doses.

The initial guess for each dose is $u_0 = 0$. We solve the OPC with the NMPC (i.e. closed loop) method as described in Algorithm 1 with an observation horizon of $\Delta t_M = 7$ days. This means, we consider a moving time horizon of 7 days, i.e. make predictions for one week. Starting with days 12 to 18 we compute the optimal doses for these 7 days of which we administer only the first one on day 12. If necessary we now have the option to update parameters. Then we shift the time horizon to cover the days 13 to 19, compute the optimal dosing regimen and apply the dose for day 13. Repeatedly, we move the time horizon further and solve the open loop problems on the short time horizons until we have computed the final dose for day 28. Altogether, we find the closed loop solution \hat{u} , see Fig. 3 within 49.2 seconds with cost functional value $\hat{J}(\hat{u}) = 2.22 \cdot 10^{-3}$ and its norm of the gradient $2.2 \cdot 10^{-6}$.

We compare this solution to the open loop solution u^* , i.e. computing the optimal dosing regimen for days 12 to 28 at once to see how the strategy performs. The open loop yields slightly different results within 108.7 seconds we get $\hat{J}(u^*) = 2.08 \cdot 10^{-3}$ with norm of gradient $2.0 \cdot 10^{-7}$, see Fig. 4 and Fig. 5 for comparison. The open loop solution provides higher doses on days 16 to 18 whose necessity the shorter horizon does not see, but the closed loop then

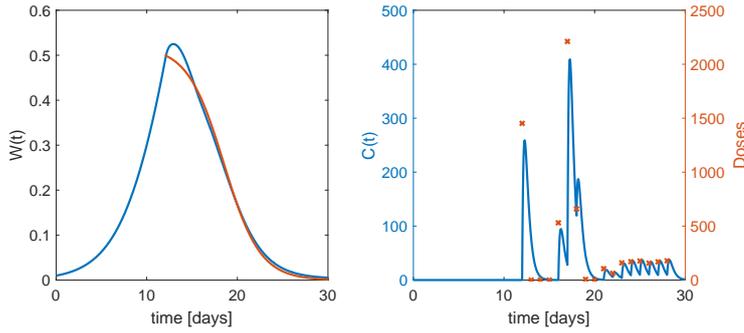


Fig. 3 Left: optimal closed loop solution for an observation horizon of 7 days in blue and the sigmoid reference function in red. Right: drug concentration for optimal dosing in blue (computed for an observation horizon of 7 days) and administered drug doses \hat{u} (red crosses)

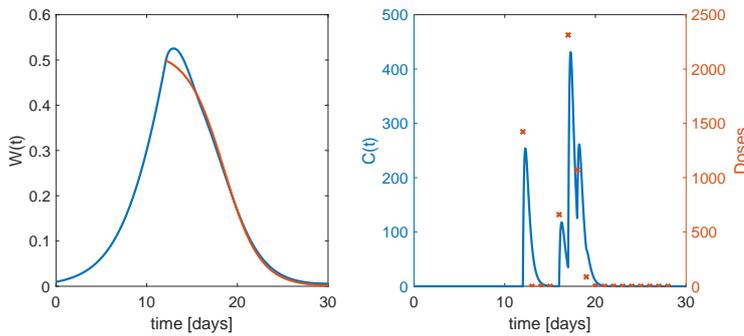


Fig. 4 Left: optimal solution from open loop in blue and the sigmoid reference function in red. Right: drug concentration for optimal dosing in blue (computed with open loop) and administered drug doses u^* (red crosses)

compensates this with larger doses in the following days. The difference in the cost functional is neglectable.

The parameter values $\theta = (V, k_a, k_{el}, \lambda_0, \lambda_1, k_t, k_{pot}, P^0)$ taken from [30] are $V = 2.79, k_a = 5, k_{el} = 2.53, \lambda_0 = 0.194, \lambda_1 = 0.246, k_t = 0.666, k_{pot} = 0.0077$ and the initial state $P^0 = 0.0098$.

4.4 Binding Kinetics of a Bispecific Antibody and Formation of the Drug-Receptor Complex

Bispecific antibodies (BsAbs) are promising drug candidates in immuno-oncology [32] and currently extensive research is performed by both academia and pharmaceutical companies. A BsAb is an artificial protein and exerts the effect e.g. by bridging effector T cells and cancer cells. The idea of BsAbs is to use

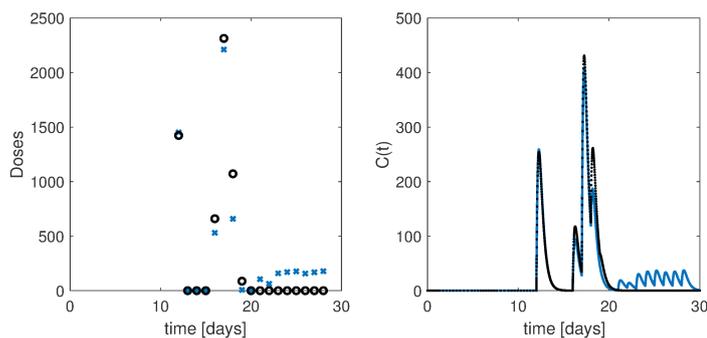


Fig. 5 Left: Optimal doses u^* from the open loop (black circles) and optimal doses \hat{u} from the closed loop with observation horizon 7 (blue crosses). Right: Drug concentration for optimal dosing in black (computed with open loop) and for optimal dosing computed with closed loop (blue)

the own human immune system to attack tumor cells instead of administering cytotoxic drugs as in the previous example.

Mechanistic modeling of a BsAb is a sophisticated task and includes characterization of many different binding kinetics [33, 34]. A BsAb C binds to two different receptors R_A and R_B forming the two binary drug-receptor complexes RC_A and RC_B . Both of these complexes further cross-bind to the other receptors to form the ternary complex RC_{AB} which finally drives the drug effect. The absorption process of the BsAb is described by Abs . The full BsAb

model is schematically displayed in Fig. 1 c) and reads (see [13] for details):

$$\begin{aligned}
\frac{d}{dt}C &= -k_{el}C - k_{on1}C \cdot R_A + k_{off1}RC_A - k_{on2}C \cdot R_B + k_{off2}RC_B \\
&\quad - k_{12}C + k_{21}\frac{AP}{V} + k_a\frac{Abs}{V}, \\
\frac{d}{dt}R_A &= k_{synA} - k_{degA}R_A - k_{on1}C \cdot R_A + k_{off1}RC_A - k_{on4}R_A \cdot RC_B \\
&\quad + k_{off4}RC_{AB}, \\
\frac{d}{dt}R_B &= k_{synB} - k_{degB}R_B - k_{on2}C \cdot R_B + k_{off2}RC_B - k_{on3}R_B \cdot RC_A \\
&\quad + k_{off3}RC_{AB}, \\
\frac{d}{dt}RC_A &= k_{on1}C \cdot R_A - (k_{off1} + k_{intA})RC_A - k_{on3}R_B \cdot RC_A + k_{off3}RC_{AB}, \\
\frac{d}{dt}RC_B &= k_{on2}C \cdot R_B - (k_{off2} + k_{intB})RC_B - k_{on4}R_A \cdot RC_B + k_{off4}RC_{AB}, \\
\frac{d}{dt}RC_{AB} &= k_{on4}R_A \cdot RC_B + k_{on3}R_B \cdot RC_A - (k_{off3} + k_{off4} + k_{intAB})RC_{AB}, \\
\frac{d}{dt}AP &= k_{12}C \cdot V - k_{21}AP, \\
\frac{d}{dt}Abs &= -k_aAbs + In(t, u).
\end{aligned}$$

Briefly, the k_{on} and k_{off} are binding rates, k_{syn} and k_{deg} production resp. degradation rates, k_{int} internalization rates, k_{el} is the elimination rate of the BsAb and k_{12} , k_{21} describe the transfer to a peripheral compartment AP .

Antibody drugs have a very long half-life and are often administered via SC injection, cf. (4). Therefore, we consider the time interval $[0, 140]$ days with administration of the same dose into the absorption compartment Abs at days 0, 48, 96. Initially, we assume the system to be at baseline, i.e. $R_A(0) = k_{synA}/k_{degA}$ and $R_B(0) = k_{synB}/k_{degB}$ and all others are 0. Throughout the whole interval our goal is to keep the ternary complex RC_{AB} at the best possible reference value $\min(k_{synA}/k_{degA}, k_{synB}/k_{degB})$. In the cost functional we choose $\alpha = 0$.

Starting from an initial guess for the dose of 800, we find the optimal solution $u^* = 663.78$ within 8 iterations of damped BFGS method and 28 seconds. The optimal doses and resulting ternary complex can be seen in Fig. 6. As we need to compute only one dose we used the open loop method. The cost functional value at the optimal solution is $\hat{J}(u^*) = 5.0$ and the norm of its gradient is $5.8 \cdot 10^{-8}$. Starting from an initial guess far from the optimal solution resulting in a large cost functional value, e.g. $u_0 = 0$ with $\hat{J}(u_0) = 7000$ yields the same optimal solution within 22 iterations and 32 seconds, i.e. the algorithm shows numerical robustness.

The parameter values taken from a simulation study [13] are $k_{el} = 0.1$, $k_{on1} = 10$, $k_{off1} = 0.01$, $k_{on2} = 1$, $k_{off2} = 0.01$, $k_{on3} = 1$, $k_{off3} = 0.01$, $k_{on4} = 10$, $k_{off4} =$

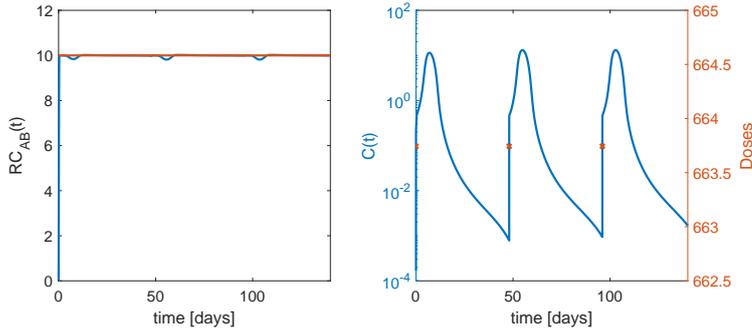


Fig. 6 Left: Ternary complex RC_{AB} for the optimal solution in blue and reference value 10 in red. Right: Concentration level C as semilogarithmic plot for the optimal solution in blue and administered dose u^* at dosing time points (red crosses)

$0.01, k_{synA} = 1, k_{degA} = 0.1, k_{synB} = 10, k_{degB} = 0.1, k_{intA} = 0.05, k_{intB} = 0.05, k_{intAB} = 0.1, k_{12} = 0, k_{21} = 0.03, k_a = 0.2$ and $V = 3$.

5 Conclusion

We have set up an OCP which is especially designed for PKPD models using the doses as finite-dimensional control variables (instead of optimizing the drug concentration). Therefore, the reduced OCP can be solved by robust gradient-based descent algorithms from finite-dimensional optimization. An efficient calculation of the required derivatives is ensured by the use of adjoint techniques. In addition, we incorporated closed loop (NMPC) algorithms which provide the potential to guide patients safely along a desired reference function h_{ref} , in particular in case of long-term treatments. Application to a variety of PKPD models shows the robustness and efficiency of the software. Thus, the presented OptiDose code is a widely usable tool for computing the individualized optimal drug dosing regimen in PKPD and, to our knowledge, the first calculating the doses directly.

On the other hand, we still need to address some PKPD issues, e.g. a rigorous sensitivity analysis of the computed optimal doses with respect to uncertainty in the estimation of the parameter values. Suitable measures to identify sensitive parameters should be discussed.

Another important issue will be how to handle negative side effects from drug treatment such as myelosuppression in oncology: The administration of cytotoxic drugs to attack a tumor also suppresses the production of new blood cells in the bone marrow leading to low levels of circulating blood cells. As white blood cells play an important role in the immune system they need to stay above a certain threshold in order to not risk the life of the patient. Mathematically this means to include so-called state constraints in the OCP making it usually much harder to solve numerically. A promising way is to

apply augmented Lagrangian techniques using an additional penalization term in the cost functional.

Furthermore, in daily clinical routine the available oral doses are typically restricted to certain sizes which mathematically leads to discrete ODE-constrained OCPs. The presented open issues are both mathematically challenging and of huge interest in applications and provide a wide field for future research.

Acknowledgements This work has been supported by the DFG, project no. SCHR 692/3-1 (Germany). This study was supported by a grant awarded to GK from the Swiss National Science Foundation; Grant Number: 179510.

References

1. Van Donge, T., Evers, K., Koch, G., van den Anker, J., Pfister, M.: Clinical Pharmacology and Pharmacometrics to Better Understand Physiological Changes During Pregnancy and Neonatal Life. Handbook of Experimental Pharmacology. Springer (2019)
2. Kearns, G.L., Abdel-Rahman, S.M., Alander, S.W., Blowey, D.L., Leeder, J.S., Kauffman, R.E.: Developmental pharmacology - drug disposition, action, and therapy in infants and children. *N Engl J Med* **349**, 1157–1167 (2003)
3. Koch, G., Datta, D.N., Jost, K., Schulze, S.M., van den Anker, J., Pfister, M.: Caffeine citrate dosing adjustments to assure stable caffeine concentrations in preterm neonates. *J Pediatr* **191**, 50–56 (2017)
4. Gobburu, J.V.S., Marroum, P.J.: Utilisation of pharmacokinetic-pharmacodynamic modeling and simulation in regulatory decision making. *Clin Pharmacokinet* **40**, 883–892 (2001)
5. Gibaldi, M., Perrier, S.: Pharmacokinetics. CRC Press Taylor & Francis Group, Boca Raton (1982)
6. Mager, D., Wyska, E., Jusko, W.: Diversity of mechanism-based pharmacodynamics. *Drug Metab Dispos* **31**, 510–519 (2003)
7. Koch, G., Schropp, J.: Mathematical concepts in pharmacokinetics and pharmacodynamics with application to tumor growth. In: P. Kloeden, C. Pötzsche (eds.) *Nonautonomous dynamical systems in the life sciences*, pp. 225–250. Springer, New York (2013)
8. Bonate, P.: Pharmacokinetic-Pharmacodynamic Modeling and Simulation, second edition. Springer US (2011)
9. Gabrielsson, M., Weiner, D.: Pharmacokinetic and Pharmacodynamic Data Analysis, fifth edition. Swedish Pharmaceutical Press (2017)
10. Pfister, M., D’Argenio, D.Z.: The emerging scientific discipline of pharmacometrics, special issue. *Clin Pharmacol* **50**, 1–6 (2010)
11. Schättler, H., Ledzewicz, U.: Optimal control for mathematical models of cancer therapies. Springer, New York (2015)
12. Moore, H.: How to mathematically optimize drug regimens using optimal control. *J Pharmacokinet Pharmacodyn* **45**, 127–137 (2018)
13. Schropp, J., Khot, A., Dhaval, S.K., Koch, G.: Target-mediated drug disposition model for bispecific antibodies: properties, approximation, and optimal dosing strategy. *CPT Pharmacometrics Syst. Pharmacol* **8**(3), 177–187 (2019)
14. Pontrjagin, L.S.: *Mathematische Theorie optimaler Prozesse*, 2-te Auflage. R. Oldenbourg, München, Wien (1967)
15. Irurzun-Arana, I., Janda, A., Ardanza-Trevijano, S., Troconiz, I.F.: Optimal dynamic control approach in a multiobjective therapeutic scenario: Application to drug delivery in the treatment of prostate cancer. *PLoS Comput Biol* **14**(4), e1006087 (2018)
16. Abboubakar, H., Kamgang, J.C., Nkague Nkamba, L., Tieudjo, D.: Bifurcation thresholds and optimal control in transmission dynamics of arboviral diseases. *J Math Biol* **76**, 379–427 (2018)

17. Grüne, L., Pannek, J.: Nonlinear model predictive control. Springer (2011)
18. Rogg, S., Fuerstinger, D.H., Volkwein, S., Kappel, F., Kotanko, P.: Optimal EPO dosing in hemodialysis patients using a non-linear model predictive control approach. *Konstanzer Schriften in Mathematik* **372** (2018)
19. Hackbusch, W.: Elliptic Differential Equations, Theory and Numerical Treatment. *Computational Mathematics* 18, second edition. Springer (2003)
20. Hinze, M., Pinnau, R., Ulbrich, M., Ulbrich, S.: Optimization with PDE Constraints. *Mathematical Modelling: Theory and Applications*. Springer (2009)
21. Renardy, M., Rogers, R.C.: An introduction to partial differential equations. *Texts in Applied Mathematics* 13 (Second ed.). Springer, New York (2004)
22. Kelley, C.: Iterative Methods for Optimization. *Frontiers in Applied Mathematics*. SIAM, Philadelphia, PA (1999)
23. Beal, S., Sheiner, L.B., Boeckmann, A., Bauer, R.J.: NONMEM user's guides. *ICON Development Solutions*, Ellicott City (2009)
24. Lavielle, M., Meza, H., Chatel, K.: The Monolix software 4.3. Lixoft, Orsay (2014)
25. The Math Works, I.: MATLAB Release (2018a). MathWorks, Natick, MA (2018)
26. Dayneka, N.L., Garg, V., Jusko, W.J.: Comparison of four basic models of indirect pharmacodynamic responses. *J Pharmacokinet Biopharm* **21**(4), 457–478 (1993)
27. Koch, G., Schropp, J.: Delayed logistic indirect response models: realization of oscillating behavior. *J Pharmacokinet Pharmacodyn* **45**(1), 49–58 (2018)
28. Koch, G., Schropp, J., Jusko, W.J.: Assessment of non-linear combination effect terms for drug-drug interactions. *J Pharmacokinet Pharmacodyn* **43**(5), 461–479 (2016)
29. Simeoni, M., Magni, P., Cammia, C., De Nicolao, G., Croci, V., Pesenti, E., Germani, M., Poggesi, I., Rocchetti, M.: Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. *Cancer Res* **64**, 1094–1101 (2004)
30. Koch, G., Walz, A., Lahu, G., Schropp, J.: Modeling of tumor growth and anticancer effects of combination therapy. *J Pharmacokinet Pharmacodyn* **36**(2), 179–197 (2009)
31. Koch, G., Krzyzanski, W., Perez-Ruixo, J.J., Schropp, J.: Modeling of delays in PKPD: classical approaches and a tutorial for delay differential equations. *J Pharmacokinet Pharmacodyn* **41**(4), 291–318 (2014)
32. Jiang, X., Chen, X., Carpenter, T.J., Wang, J., Zhou, R., Davis, H.M., Heald, D.L., Wang, W.: Development of a target cell-biologics-effector cell (TBE) complex-based cell killing model to characterize target cell depletion by T cell redirecting bispecific agents. *MAbs* **10**(6), 876–889 (2018)
33. Doldan-Martelli, V., Guantes, R., Miguez, D.G.: A mathematical model for the rational design of chimeric ligands in selective drug therapies. *CPT Pharmacometrics Syst. Pharmacol* **2**(2), 26–33 (2013)
34. Rhoden, J.J., Dyas, G.L., Wroblewski, V.J.: A modeling and experimental investigation of the effects of antigen density, binding affinity, and antigen expression ratio on bispecific antibody binding to cell surface targets. *J Biol Chem* **291**, 11,337–11,347 (2016)