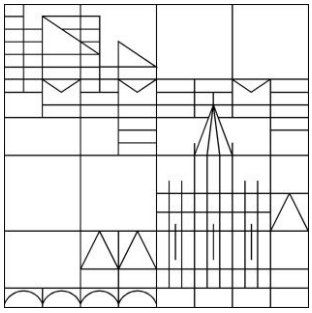

Universität Konstanz

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Freya Bachmann
Gilbert Koch
Marc Pfister
Gabor Szinnai
Johannes Schropp

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A SENSITIVITY ANALYSIS OF THE OPTIMAL DRUG DOSING ALGORITHM OPTIDOSE

FREYA BACHMANN, GILBERT KOCH, MARC PFISTER, GABOR SZINNAI, AND JOHANNES SCHROPP

Abstract. OptiDose is a drug dosing algorithm that computes the optimal doses for a given patient and dosing schedule based on control theory. Here, a sensitivity analysis for OptiDose using derivative based and regression methods is performed. Two sensitivity measures with respect to the model parameters are presented, the sensitivity of the optimal doses and the sensitivity of the minimized cost functional. Further, the sensitivity analysis is applied to typical pharmacokinetic-pharmacodynamic examples.

1. Introduction

One of the most important tasks in pharmaceutical sciences is to find the optimal drug dosing strategy for an individual or a group of patients. For that purpose an optimal dosing algorithm (OptiDose) using control theory was developed and validated [1]. OptiDose is especially designed to solve optimal dosing problems where the state equation is governed by a pharmacokinetic-pharmacodynamic (PKPD) model. PKPD models are parameter- and covariate-dependent differential equations based on the underlying pharmacological mechanism. Typical parameters of a PKPD model are clearance, elimination or absorption rates, or initial baseline values whereas patient data like weight or sex denote standard covariates. The parameters in the PKPD model are estimated with nonlinear mixed effects methods [16, 2] and contain uncertainty or measurement errors.

In the present paper, a sensitivity analysis particularly well-suited for OptiDose is performed (see, e.g., [4, 5, 9] for an overview of sensitivity analysis methods). Local sensitivity methods are applied, since the range of the model parameters is a-priori determined by nonlinear mixed effects modeling [15]. Two different measures of sensitivity both with respect to the PKPD model parameters are presented, the sensitivity of the optimal doses and the sensitivity of the minimized cost functional. Such quantification of uncertainty is essential in pharmacological applications to identify the model parameters for which a small parameter change leads to a large change in

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the corresponding optimal doses, i.e., to quantify the propagation of uncertainty or input errors to the optimal doses.

Section 2 gives a short summary on the OptiDose algorithm, in section 3 the two sensitivity measures are derived, followed by numerical experiments in section 4. Finally, a conclusion is drawn in section 5.

2. Summary on OptiDose

In this section, we briefly summarize the properties of the dosing algorithm OptiDose. For further explanations and details see [1].

A drug gets administered at time points $t_1 < \ldots < t_m$, $m \in \mathbb{N}$ within the observation interval $[0, T]$ with corresponding dose amounts $u := (u_1, \ldots, u_m) \in \mathbb{R}^m$ called the control variable. Defining the admissible set as convex subset of $\mathbb{R}^m$ via

$$U_{ad} = \{u \in \mathbb{R}^m \,|\, 0 \leq u_a \leq u \leq u_b\}$$

allows to include boxed control constraints with lower and upper bounds on the doses with componentwise comparison.

Let the model parameter $\theta \in \Theta \subset \mathbb{R}^q$, $q \in \mathbb{N}$ describe, e.g., the individual characteristic of a patient within a set Θ of reasonable model parameters. Then, the state variable y denotes the solution of a PKPD model which is described by an initial value problem

$$\begin{aligned} \frac{\partial}{\partial t} y(t) &= g(t, u, y(t), \theta) = \tilde{g}(t, y(t), \theta) + In(t, u)\, e^{j_0}, \\ y(0) &= y_0(\theta) \end{aligned} \tag{2.1}$$

for $t \in (0, T]$ almost everywhere (a.e.). Here, $g\colon [0, T] \times U_{ad} \times \mathbb{R}^n \times \Theta \to \mathbb{R}^n$ describes the PKPD mechanism where $\tilde{g}\colon [0, T] \times \mathbb{R}^n \times \Theta \to \mathbb{R}^n$ is continuously differentiable. The inflow $In\colon [0, T] \times U_{ad} \to \mathbb{R}$ depends on the drug administration and dosing schedule where j_0 is indicating the dosing compartment of the state variable and e^{j_0} is the corresponding unit vector. The initial value $y_0\colon \Theta \to \mathbb{R}^n$ denotes the initial condition of the patient at time $t = 0$. The additive structure between the state variable y and the control variable u in the right hand side of (2.1) is inherited from basic PKPD design principles of drug action [3, 7].

A clinically relevant dosing scenario is that the doses are given multiple times, e.g., the doses are administered daily but the amount of dose changes only every week. Suppose for $i = 1, \ldots, m$ each dose u_i will be administered n_i times at time points $t_{i,j}$ with $j = 1, \ldots, n_i$. Then, the inflow in (2.1) is given by

$$In(t, u) = \sum_{i=1}^{m} u_i \sum_{j=1}^{n_i} \delta(t - t_{i,j}) \tag{2.2}$$

where δ denotes the Dirac distribution leading to impulse ordinary differential equations, i.e., equations of the form (2.1) for $t \in (0,T]$, $t \neq t_{i,j}$ with jump conditions

$$y_{j_0}(t_{i,j}^+) - y_{j_0}(t_{i,j}^-) = u_i, \quad j = 1, \dots, n_i,\ i = 1, \dots, m$$

at the dosing time points $t_{i,j}$. Here, $t_{i,j}^+$, $t_{i,j}^-$ denote the limits at the dosing point $t_{i,j}$ from above and below, respectively. The standard approach in PKPD modeling is to stop the numerical integration at each dosing time point and add the dose to the dosing compartment.

Moreover, the actual disease progression is described by a C^1-functional $h\colon \mathbb{R}^n \to \mathbb{R}$ and the desired disease progression by $h_{ref}\colon [0,T] \times \Theta \to \mathbb{R}$. Then, optimality is characterized with respect to minimizing the cost functional

$$J(y,u,\theta) := \frac{1}{2}\int_0^T \left(h(y(t)) - h_{ref}(t,\theta)\right)^2 \, dt + \sum_{i=1}^m \alpha_i n_i u_i \tag{2.3}$$

for $y \in Y, u \in U_{ad}$, $\theta \in \Theta$ and a weight parameter $\alpha = (\alpha_1, \dots, \alpha_m) \geq 0$.

In order to treat the problem as optimization problem in Banach spaces, the solution y of (2.1) needs more regularity. Thus, one chooses $\gamma\colon \mathbb{R} \to \mathbb{R}$ integrable, $\gamma \geq 0$, $\gamma \equiv 0$ on $\mathbb{R} \setminus [0,1]$ with $\int_0^1 \gamma(t)\, dt = 1$ and replaces the Dirac distributions $\delta(t - t_{i,j})$ by $\frac{1}{\epsilon}\gamma(\frac{t-t_{i,j}}{\epsilon})$, i.e., the regularized inflow is given by

$$\tilde{In}(t,u) := \sum_{i=1}^m u_i \sum_{j=1}^{n_i} \frac{1}{\epsilon}\,\gamma\left(\frac{t - t_{i,j}}{\epsilon}\right). \tag{2.4}$$

Using the indicator function $\gamma = \mathbb{1}_{[0,1]}$ as in [1] corresponds to a short infusion of length ϵ and ensures $y \in Y := H^1(0,T;\mathbb{R}^n) \cap C([0,T];\mathbb{R}^n)$ with H^1 denoting the Sobolev Hilbert space of once-weakly differentiable functions. For higher regularity, one approximates the Dirac distributions by smoother functions γ.

For each fixed $u \in U_{ad}$ and $\theta \in \Theta$ the solution to (2.1) is unique [1] and we write $y = y(u,\theta) \in Y$ describing the state of the patient with parameter θ resulting from the treatment u. This property allows to introduce the reduced cost functional

$$\hat{J}(u,\theta) := J(y(u,\theta),u,\theta) \tag{2.5}$$

and the reduced optimal control problem

$$\min\ \hat{J}(u,\theta) \quad \text{subject to} \quad u \in U_{ad}. \tag{2.6}$$

Reformulating (2.1) as equality constraint yields

$$e(y,u,\theta) = \begin{pmatrix} y' - g(\cdot,u,y,\theta) \\ y(0) - y_0(\theta) \end{pmatrix} = 0 \in Z := L^2(0,T;\mathbb{R}^n) \times \mathbb{R}^n \tag{2.7}$$

where Z is equipped with the inner product $\langle .,. \rangle_Z$ given by the sum of the inner products on $L^2(0,T;\mathbb{R}^n)$ and $\mathbb{R}^n$. Then, following [8] the Lagrange function

$$L(y,u,\theta,p) = J(y,u,\theta) + \langle p, e(y,u,\theta) \rangle_Z$$

is defined which provides the existence of a Lagrange multiplier $(\bar{p}, \bar{p}(0)) \in Z$ such that at an optimal solution $(\bar{y}, \bar{u})$ with $\bar{y} = y(\bar{u},\theta)$ the necessary first-order optimality conditions hold, also named the KKT conditions after Karush, Kuhn and Tucker [8]. From these, one can derive the adjoint equation for p as

$$\begin{aligned} \frac{\partial}{\partial t} p(t) &= -\left(\frac{\partial}{\partial y} g(t,u,y(t),\theta) \right)^\top p(t) + (h(y(t)) - h_{ref}(t,\theta)) \frac{\partial}{\partial y} h(y(t)), \\ p(T) &= 0 \end{aligned}$$

for $t \in [0,T)$ a.e. where $y = y(u,\theta)$ and $p = p(u,\theta)$ both depend on u and θ which are, however, fixed while solving the state and adjoint equation, respectively. Consequently, the gradient with respect to u can be computed (see [8]) via

$$\begin{aligned} \nabla_u \hat{J}(u,\theta) &= \frac{\partial}{\partial u} L(y,u,\theta,p) \\ &= \alpha^\top N - \int_0^T p(t)^\top \frac{\partial}{\partial u} g(t,u,y(t),\theta)\, dt \end{aligned} \tag{2.8}$$

with $N = \operatorname{diag}(n_1,\ldots,n_m)$.

Remark 1. a) In contrast to [8] the finite number of doses provides a finite-dimensional optimal control problem (2.6) which allows to apply fast and robust quasi-Newton methods using the efficient computation of the gradient (2.8).
b) In application the OptiDose code will use the numerically more efficient representation (2.2) instead of (smooth) approximations of the Dirac distributions, i.e., the integration process is stopped at each dosing point, the dose added to the corresponding state and the integration is continued. This is the standard approach in applied pharmacology and works well for the computation of the derivatives of $\hat{J}$ since (2.8) implies

$$\nabla_{u_i} \hat{J}(u,\theta) = \begin{cases} \alpha_i n_i - \sum_{j=1}^{n_i} p_{j_0}(t_{i,j}), & \text{for (2.2)} \\ \alpha_i n_i - \sum_{j=1}^{n_i} \frac{1}{\epsilon} \int_{t_{i,j}}^{t_{i,j}+\epsilon} p_{j_0}(t)\, \gamma(\frac{t-t_{i,j}}{\epsilon})\, dt, & \text{for (2.4)} \end{cases}$$

for $i = 1,\ldots,m$. Consequently, the gradient of the regularized problem converges for $\epsilon \to 0$ towards the gradient of the original problem by the mean value theorem of integration. $\lozenge$

The OptiDose algorithm applied to a PKPD problem characterized by a parameter θ terminates at a stationary point $\bar{u} = \bar{u}(\theta)$ of the cost functional $\hat{J}(\cdot, \theta)$ in (2.5). Due to [10] this means that $\bar{u}$ satisfies

$$u - P(u - \nabla_u \hat{J}(u, \theta)) = 0$$

where $P\colon \mathbb{R}^m \to U_{ad}$ denotes the canonical projection, i.e., the projection to the closest point in U_{ad} with respect to the Euclidean norm.

3. Sensitivity measures with respect to the model parameters

In order to investigate the changes of the doses u with respect to changes in the parameter θ we assume the cost functional J and the constraint map e (see (2.3), (2.7)) to be twice continuously differentiable. This means the functions $\tilde{g}$ in (2.1), h and h_{ref} in (2.3) to be two times continuously differentiable and requires a continuously differentiable function γ in (2.4) to approximate the Dirac distributions.
Then, consider the function

$$F(u, \theta) := u - P(u - \nabla_u \hat{J}(u, \theta)).$$

Let $\hat{\theta} \in \Theta$ be a particular parameter and let $\hat{u} \in U_{ad}$ denote the corresponding optimal doses, i.e.,

$$F(\hat{u}, \hat{\theta}) = \hat{u} - P(\hat{u} - \nabla_u \hat{J}(\hat{u}, \hat{\theta})) = 0. \tag{3.1}$$

Further, assume $(\hat{u}, \hat{\theta})$ to be a regular solution, i.e.,

$$\frac{\partial}{\partial u} F(\hat{u}, \hat{\theta}) = I - P'(\hat{u} - \nabla_u \hat{J}(\hat{u}, \hat{\theta}))(I - \nabla_u^2 \hat{J}(\hat{u}, \hat{\theta})) \tag{3.2}$$

is invertible where I denotes the identity matrix. By the implicit function theorem a branch $u = u(\theta)$ exists for θ in an open neighbourhood $V(\hat{\theta}) \subset \Theta$ of $\hat{\theta}$ with $u(\hat{\theta}) = \hat{u}$ and

$$F(u(\theta), \theta) = 0 \ \text{ for } \theta \in V(\hat{\theta}). \tag{3.3}$$

Using derivative based methods the sensitivity of the solution $(\hat{u}, \hat{\theta})$ satisfying (3.1) with respect to θ is defined by the linearization $u'(\hat{\theta}) \in \mathbb{R}^{m \times q}$. Differentiating (3.3) yields

$$\frac{\partial}{\partial u} F(u(\theta), \theta)\, u'(\theta) + \frac{\partial}{\partial \theta} F(u(\theta), \theta)\, I = 0,$$

and we obtain the local sensitivity $u'(\hat{\theta})$ of the doses with respect to the PKPD model parameters as

$$u'(\hat{\theta}) = -\left(\frac{\partial}{\partial u} F(\hat{u}, \hat{\theta})\right)^{-1} \frac{\partial}{\partial \theta} F(\hat{u}, \hat{\theta}). \tag{3.4}$$

The derivatives in (3.4) are given by (3.2) and

$$\frac{\partial}{\partial \theta} F(\hat{u}, \hat{\theta}) = P'(\hat{u} - \nabla_u \hat{J}(\hat{u}, \hat{\theta}))(\nabla_\theta(\nabla_u \hat{J}(\hat{u}, \hat{\theta}))). \tag{3.5}$$

Remark 2. The second derivatives $\nabla_u^2 \hat{J}(\hat{u}, \hat{\theta})$ and $\nabla_\theta \nabla_u \hat{J}(\hat{u}, \hat{\theta})$ are approximated by central difference quotients of the gradients $\nabla_u \hat{J}(u, \theta)$ which itself are computed using the representation (2.8). Therefore, $2(m+q)$-evaluations of the gradient $\nabla_u \hat{J}$ are necessary which make the computation of the local sensitivity $u'(\hat{\theta})$ according to (3.4) costly. $\lozenge$

Consequently, indicators for sensitivity at a lower computational cost might be of interest, such as the sensitivity of the cost functional $\hat{J}$ with respect to the model parameter θ. Namely, the gradient of $\hat{J}$ with respect to θ can be calculated by

$$\begin{aligned}\nabla_\theta \hat{J}(u,\theta) &= \frac{\partial}{\partial \theta} L(y,u,\theta,p) \\ &= -\int_0^T (h(y(t)) - h_{ref}(t,\theta)) \left(\frac{\partial}{\partial \theta} h_{ref}(t,\theta)\right) \, dt \\ &\quad - \int_0^T \left(\frac{\partial}{\partial \theta} g(t,u,y(t),\theta)\right)^\top p(t) \, dt \; - \; \left(\frac{\partial}{\partial \theta} y_0(\theta)\right)^\top p(0)\end{aligned}$$

using adjoint techniques (see [8]) again.

4. Sensitivity Analysis applied to PKPD Examples: Numerical Results

4.1. **Indirect response model.** An essential class in PKPD modeling are indirect response models, cf., e.g., [6, 12]. These 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 [6, 13]. We consider an example where a biomarker B is elevated and a drug is administered to return those high biomarker levels to the normal range. In absence of the drug the biomarker returns to its initial state B^0 at diagnosis, i.e., the disease cannot be cured but requires persistent treatment.

The time course of the drug concentration C is described by a linear one-compartment model with drug elimination rate k_{el}. The drug is administered daily via an intravenous bolus and the amount of dose changes only every week, i.e., $n_i = 7$ in (2.2) for $i = 1, \ldots, m$. The parameter V describes the volume of distribution in the body for the specific drug. 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

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

The aim is to control the biomarker B to follow a predefined reference function characterized by

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

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.

The sensitivity analysis is performed for the parameters

$$\hat{\theta} = (\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3) = (B^0, k_{out}, EC_{50}) = (46, 0.02, 0.81).$$

Moreover, $V = 3, k_{el} = 0.49, E_{max} = 8.8$ and $k_{in} = B^0 \cdot k_{out} = 0.92$ are fixed.

The optimization terminates if the norm of the gradient is smaller than 10^{-5} or the relative change in the cost functional is smaller than 10^{-7}. Starting from an initial guess of $u^0 = 1$ for all doses the optimal solution

$$\hat{u} = \begin{pmatrix} 6.08 \\ 4.18 \\ 0.26 \\ 0.99 \\ 0.77 \\ 0.86 \end{pmatrix}$$

depicted in Figure 1 was computed within 85 seconds[1] providing a cost functional value of $\hat{J}(\hat{u}, \hat{\theta}) = 3.89$ with norm of the gradient $3 \cdot 10^{-4}$.

For the sensitivity analysis, the second order derivatives in (3.2) and (3.5) were approximated by central differences with step size 10^{-4}. The tolerances for the ODE solver were tightened to 10^{-10} for computing the sensitivities compared to the default for the optimization of 10^{-7}.

Computing the sensitivity of the cost functional with respect to the parameter $\hat{\theta}$ required 12.8 seconds whereas computing the sensitivity of the doses took 122 seconds. The results can be seen in Table 1 and Table 2. The sensitivity of all parameters is higher during the loading phase (first two weeks) than during the maintenance phase (week 3 to 6) according to Table 1 which coincides with medical expectation. This information cannot be obtained from the cost functional sensitivity measure, since it computes values for the whole observation interval. But comparison of Table 1 and Table 2 shows that both sensitivity measures identify k_{out} to be the most sensitive parameter and the remaining parameters to be less sensitive. On

[1]All computations were performed on an ASUSTek computer with Intel(R) Core(TM) i7-7700HQ CPU processor with 2.80GHz and 16GB RAM.

the other hand the sensitivity of B^0 and EC_{50} is ranked differently.

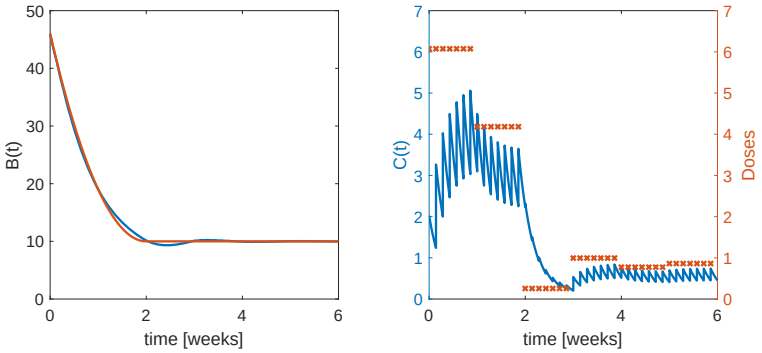

FIGURE 1. Indirect response model. In the left panel the optimal solution is depicted in blue and the reference function in red. The right panel shows the optimal doses administered at dosing time points (red crosses) and the resulting drug concentration in blue.

	$\frac{\partial u}{\partial B^0}$	$\frac{\partial u}{\partial k_{out}}$	$\frac{\partial u}{\partial EC_{50}}$
$u_1'(\hat{\theta})$	0.2383	-1318.2803	7.5010
$u_2'(\hat{\theta})$	0.4952	-354.3865	5.1672
$u_3'(\hat{\theta})$	-0.0154	38.6880	0.3154
$u_4'(\hat{\theta})$	0.0524	-7.8997	1.2288
$u_5'(\hat{\theta})$	0.0347	2.8630	0.9541
$u_6'(\hat{\theta})$	0.0416	-1.5320	1.0635

TABLE 1. Sensitivity of the doses for each parameter.

	$\frac{\partial \hat{J}}{\partial B^0}$	$\frac{\partial \hat{J}}{\partial k_{out}}$	$\frac{\partial \hat{J}}{\partial EC_{50}}$
$\nabla_\theta \hat{J}(\hat{u}, \hat{\theta})$	0.2535	390.7027	0.0222

TABLE 2. Sensitivity of the cost functional for each parameter.

To verify the results in Table 1 we applied the linear regression method for computing the sensitivity. We simulated 40 patients with varying k_{out} values in the interval $[0.019, 0.021]$, computed their optimal doses respectively and performed a linear regression with the doses as dependent variable. The results are displayed in the first column of Table 3. The second column shows a linear regression, but only for k_{out} values closer to 0.02, namely in the interval $(0.0197, 0.0203)$. The corresponding optimal doses for the varying k_{out}

values are shown in Figure 2 as well as the regression line for the second case.

The values of Table 3 have to be compared with those of Table 1, column 2 computed by derivative based methods. The values computed with linear regression analysis match those computed by derivative based methods within reasonable accuracy. Both of them contain approximation errors due to the central difference quotients, the choice of the regression interval as well as the stopping criteria in the optimization. Figure 2 illustrates as well that the sensitivity is a local sensitivity, e.g., for the first dose the regression line will be steeper for smaller k_{out} and flatter for larger k_{out}.

	regression slope for $k_{out} \in$	
	$[0.019, 0.021]$	$[0.0197, 0.0203]$
u_1	-1362.6789	-1324.8979
u_2	-363.106	-364.7559
u_3	39.5272	39.7425
u_4	-8.0872	-8.1721
u_5	2.8379	2.8407
u_6	-1.5361	-1.4791

TABLE 3. Sensitivity of k_{out} based on linear regression for $k_{out} \in [0.019, 0.021]$ in the first column and for $k_{out} \in [0.0197, 0.0203]$ in the second column.

4.2. **Tumor growth inhibition model.** Typically, proliferating tumor cells follow an exponential growth in the beginning and transition later to a linear growth, cf. [17, 14]. A saturation of the growth is possible depending on the tumor type, size and environment, however, this is neglected in the following example. Many so-called cytotoxic drugs attack the tumor cells which then undergo apoptosis until they eventually die. The presented example is based on preclinical oncology drug development, see [14] for details.

Let P be the proliferating tumor cells with an exponential growth rate λ_0 and a linear growth rate λ_1 [14]. The drug C, 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 by three transit compartments D_1, D_2, D_3 [11], each reflecting a certain age stage of the apoptotic cells with transit rate k_t. The total tumor weight $W = P + D_1 + D_2 + D_3$ is the sum of the proliferating and apoptotic cells.

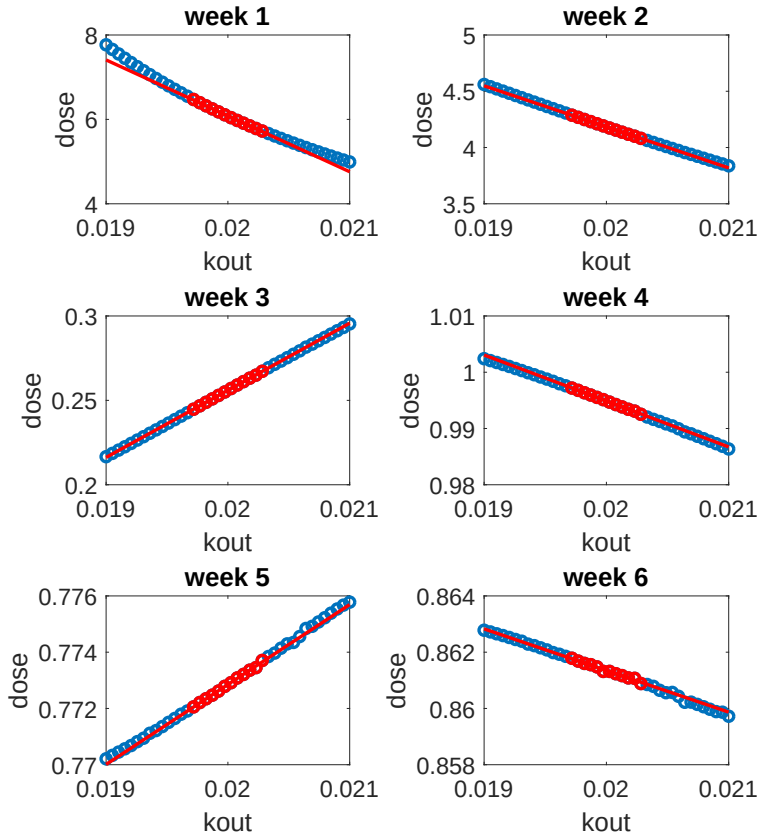

FIGURE 2. Linear regression for computed optimal doses for varying parameter k_{out}. Blue circles are the computed doses for $k_{out} \in [0.019, 0.021]$, the regression line was computed using the red circles, i.e., only $k_{out} \in [0.0197, 0.0203]$, corresponding to Table 3, column 2.

The PKPD model (2.1) reads

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

First the tumor is grown to a specific size. Then the drug is administered daily from day 12 to 27 where the amount changes only every four days, i.e., $m = 4$, $n_i = 4$, $i = 1, \dots, 4$ in (2.2). The aim is to decrease the tumor weight W towards zero. For the reference function we choose a sigmoid shape starting on day 12 at 0.5 (which is roughly the weight the tumor has reached by then) 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. If we choose $\alpha = 0$ in the cost functional the optimal control problem loses its controllability meaning significantly different doses, e.g., 10, 100, 1000 achieve nearly the same pharmacodynamic behavior. Thus, and in favor to lower doses we set $\alpha = 2.5 \cdot 10^{-6} > 0$ in the cost functional.

The parameter values taken from [14] 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 $P^0 = 0.0098$. The sensitivity analysis is performed for the parameters

$$\hat{\theta} = (\hat{\theta}_1, \dots, \hat{\theta}_4) = (\lambda_0, \lambda_1, k_t, k_{pot}).$$

The initial guess for each dose is $u^0 = 300$ and the iteration terminates if the norm of the projected gradient is smaller than 10^{-7} or if the relative change in the cost functional is smaller than 10^{-10} (stricter tolerances than in the indirect response model example). We compute the optimal solution

$$\hat{u} = \begin{pmatrix} 728.4 \\ 83.5 \\ 405.7 \\ 0 \end{pmatrix}$$

displayed in Figure 3 within 66 seconds with $\hat{J}(\hat{u}, \hat{\theta}) = 2.23 \cdot 10^{-2}$ with norm of the gradient $7.2 \cdot 10^{-8}$.

The sensitivity analysis based on derivative methods (again with step size 10^{-4} in the central difference quotients) yields the results for the sensitivity of the doses with respect to each parameter shown in Table 4 within 365 seconds. The computation of the sensitivity of the cost functional displayed in Table 5 required 25 seconds.
The values in Table 4 show the change of the sensitivity along the dosing schedule. Since $\hat{u}_4 = 0$ (i.e., the boxed constraint u_a is active) the fourth row in Table 4 is zero. The most sensitive parameters are k_{pot} and λ_0, whereas the parameters λ_1 and k_t are less sensitive. For the tumor growth inhibition model the sensitivity of the cost functional (see Table 5) also determines

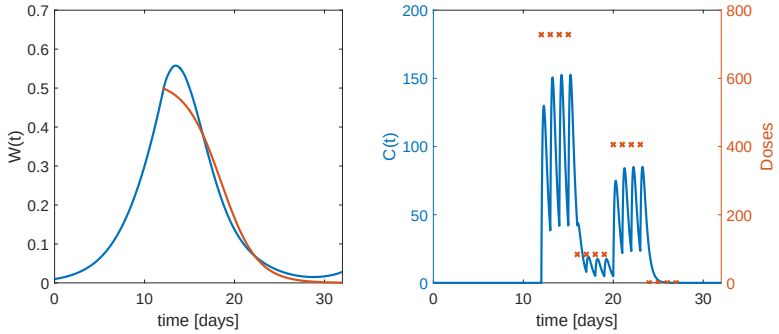

FIGURE 3. Tumor growth inhibition model. The left panel shows the optimal solution in blue and the sigmoid reference function in red. In the right panel the drug concentration for optimal dosing is shown in blue and the administered drug doses $\hat{u}$ (red crosses).

	$\frac{\partial u}{\partial \lambda_0}$	$\frac{\partial u}{\partial \lambda_1}$	$\frac{\partial u}{\partial k_t}$	$\frac{\partial u}{\partial k_{pot}}$
$u_1'(\hat{\theta})$	0.1975	0.0334	-0.0182	-0.9451
$u_2'(\hat{\theta})$	-0.3312	-0.0561	0.0069	-0.1299
$u_3'(\hat{\theta})$	0.1737	0.0273	0.0176	-0.4253
$u_4'(\hat{\theta})$	0	0	0	0

TABLE 4. Sensitivity (in $[10^5]$) of the doses for each parameter.

	$\frac{\partial \hat{J}}{\partial \lambda_0}$	$\frac{\partial \hat{J}}{\partial \lambda_1}$	$\frac{\partial \hat{J}}{\partial k_t}$	$\frac{\partial \hat{J}}{\partial k_{pot}}$
$\nabla_\theta \hat{J}(\hat{u}, \hat{\theta})$	-1.0315	-0.1684	-0.0366	1.5803

TABLE 5. Sensitivity of the cost functional for each parameter.

k_{pot}, λ_0 to be sensitive and λ_1, k_t to be less sensitive and, thus, matches the sensitivity relations between the parameters calculated by derivative based methods.

5. Discussion and Conclusion

OptiDose is an optimal control algorithm designed to compute optimal doses for a given dosing schedule for PKPD models. Typically, the parameters in these models contain uncertainty. We have presented a sensitivity analysis to quantify how input errors in the model parameters propagate to the optimal doses. With respect to the model parameters both the classical sensitivity of the doses and the sensitivity of the minimized cost functional have been considered. The computation of the second measure is significantly less costly and might yield first insights on sensitive parameters though one cannot hope

for a strong mathematical relation between both measures. Nevertheless, if a small parameter change provides a large change in the cost functional it might as well lead to a large change in the corresponding optimal doses. Clearly, the two methods will not produce the same sensitivity values but they should be able to rank the model input parameters similarly according to their sensitivity, or at least group them similarly into sensitive and less sensitive parameters.

We applied these measures to two relevant PKPD examples of different complexity and investigated whether the sensitivity of the cost functional can be used to identify the sensitive model parameters. In both examples we observed an approximate speedup of factor 10 and the most sensitive parameter was identified properly. However, if a full sensitivity ranking of the model parameters is desired we recommend to perform a sensitivity analysis using derivative based or linear regression methods instead of relying on the sensitivity of the cost functional only.

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(F. Bachmann) Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany
E-mail address: freya.bachmann@uni-konstanz.de

(G. Koch) Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, University of Basel, Basel, Switzerland
E-mail address: gilbert.koch@ukbb.ch

(M. Pfister) Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, University of Basel, Basel, Switzerland
E-mail address: marc.pfister@ukbb.ch

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

(J. Schropp) Department of Mathematics and Statistics, University of Konstanz, Konstanz, Germany
E-mail address: johannes.schropp@uni-konstanz.de