Tumor dynamics modeling based on formal reaction kinetics

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Abstract: Modeling the effect of therapeutic drugs on tumor dynamics is a fundamental step that leads to the optimization of cancer therapy using mathematical tools. We discuss three tumor dynamics models starting from a minimalist model describing the effect of bevacizumab based on experiments where the measurements can be defined with one parameter exponential curves, and finally discussing a more complex model that describes the effect of pegylated liposomal doxorubicin (PLD) based on measurements with richer dynamics. The differential equations are created with the analogy of formal reaction kinetics, enabling universal interpretation of the modeled phenomena. Parametric identification is carried out based on measurements to prove the efficacy of the models. The results of the parametric identification show that the discussed models can sufficiently describe the experimental results. The between-subject variability of the model parameters is given which highlights the parameters that may change the most in a virtual patient set.

Keywords: antiangiogenic therapy; chemotherapy; pegylated liposomal doxorubicin; stochastic approximation expectation maximization

1 Introduction

Model-based optimization and personalization of tumor therapies require tumor growth models which reliably describe the effect of the drug used during the therapy [1]. Creation and validation of tumor models can be carried out using time series measurements in mice experiments involving drugs for cancer treatment [2]. Mathematical models, i.e, differential equations, however, can be hard to interpret by clinical experts, thus we use formal reaction kinetics analogy [3] to create the tumor models, similar to the work of Kuznetsov et al [4].

The most common tumor growth models assume Gompertzian growth function [1, 5], which introduces a nonlinear term in the differential equation. Although,

Gompertzian growth function expresses the fact that the tumor volume (or cell number) has an upper limit, we do not use Gompertzian function in our model. Since our modeling is driven by mice experiments, and during the experiments, the tumor never reaches its upper limit, but operated on the linear dynamics range (i.e., tumor growth is exponential), we use linear dynamics to describe the tumor growth.

The tumor modeling is built up starting from a simple model ending with complex one incorporating nonlinear pharmacokinetics and pharmacodynamics. Section 2 covers the simplest model incorporating the effect of tumor proliferation, drug clearance and drug effects [6], resulting in a planar system with one bilinear term in the differential equations and two linear terms. The solution of the differential equation can be written symbolically if the input is one single injection, which was used for least squares parameter estimation in [6]. This model is also referred to as the minimal model some papers related to tumor control [7–10].

The minimal model is extended with dead tumor volume dynamics, nonlinear pharmacokinetics and pharmacodynamics in Section 3. The model is validated using measurements with angiogenic inhibitor bevacizumab [11]. The extension of the model with dead tumor volume enables more realistic identification, since in the experiment, the sum of the volume of the dead and living tumor volume is measured [12]. The mixed-order pharmacokinetics and nonlinear pharmacodynamics makes the model even more realistic, with the latter incorporating the effective median dose (ED_{50}) parameter, which introduces an input saturation. The qualitative analysis of the extended model is carried in [13].

The extended model is used to model the effect of chemotherapeutic agent pegylated liposomal doxorubicin (PLD) in Section 4, where the dead tumor volume washout is also added to the model. The results show that the model can sufficiently describe the effect of chemotherapeutic agent applied to mice with breast cancer [2], which has been used for therapy optimization in [14] with a modified optimization algorithm of [15].

2 Minimal Tumor Model

The first version of the tumor model based on formal reaction kinetics was published in 2017 [6]. The tumor growth model is given by the planar system

$$\dot{x} = ax - bxy \tag{1}$$
$$\dot{y} = -cy \tag{2}$$

where x is the time function of tumor volume given in mm^3, y is the time function of the level of drug in the patient given in $\mathrm{mg/kg}$ (i.e., mg of inhibitor per body mass kg of the host). The parameters of the model are

- a : the tumor growth rate $[1/\mathrm{day}]$;
- b : the drug efficiency rate $[\mathrm{kg}/(\mathrm{mg}\cdot\mathrm{day})]$;

- c : the clearance of the drug $[1/\text{day}]$.

The drug depletion is defined with linear pharmacokinetics in (2). Thus, the depletion of the drug is governed by a linear differential equation, yielding that the time function of drug level is given by

$$y(t) = y(0)e^{-ct} \tag{3}$$

with $y(0)$ being the initial condition. Suppose, that we give $y(0)$ amount of the drug to the patient at time $t = 0$. If there are no more injections, the level of the drug in the patient is described by (3) if there was no drug present in the patient before the injection.

The parameter c used in (3) is the clearance of the drug. The clearance and half-life of drug are both used in medical practice. The clearance parameter can be acquired from the half-life of the drug denoted by $T_{1/2}$ using

$$c = \frac{\ln 2}{T_{1/2}}. \tag{4}$$

The tumor growth dynamics is described by (1), where the first term on the right-hand side characterizes exponential growth of tumor volume with growth parameter a. This term defines an unstable system if a is positive, i.e., the tumor grows uncontrollably (described by an exponential function with positive exponent), and there is no upper bound for the tumor volume. Tumor growth dynamics is typically described as a Gompertzian growth function [5], i.e., the tumor volume has an upper bound, however, we found that this model without upper bound fits the measurements adequately and we were not able to observe the saturation process of the tumor volume throughout many experiments [12].

The effect of the drug is described by the second term on the right-hand side of (1). This bilinear term is the product of the tumor volume and the drug level, thus if there is no tumor, then there is no therapeutic effect regardless of the amount of drug present in the host. This bilinear term is the most simple term that can describe this phenomenon. The rate of drug efficiency is the constant b, and since the sign of the second term is negative, b is positive if the drug acts against the growth process (thus inhibits tumor growth).

The solution to the differential equation (1) is

$$x(t) = x(0)exp\left(at - \frac{by_0}{c}\left(e^{-ct} - 1\right)\right), \tag{5}$$

with $x(0)$ being the initial tumor volume and $y(0)$ being the amount of drug injected at time 0, provided that there was no drug present in the host before injection and there are no other injections during the therapy.

The minimal model given by (1)-(2) which describes unstable tumor growth, effect of the drug and linear pharmacokinetics can be formulated as a fictive chem-

ical reaction given by the following reaction steps with species X representing the tumor volume and the species Y representing the drug level:

- $X \xrightarrow{a} 2X$ that defines that tumor cells divide with rate a, i.e. species X doubles its volume with a reaction rate coefficient a. Considering mass action kinetics, the corresponding differential equation is $\dot{x} = ax$;
- $Y \xrightarrow{c} O$ that defines that there is an outflow of the species Y with a reaction rate coefficient c, i.e., the drug is cleared from the body of the host, considering mass action kinetics, the corresponding differential equation is $\dot{y} = -cy$;
- $X + Y \xrightarrow{b} Y$ that defines that the species X and Y react and after the reaction the species X disappears with a reaction rate coefficient b, i.e., the drug destroys tumor volume; considering mass action kinetics, the corresponding differential equation is $\dot{x} = -bxy$.

The connection of formal reaction steps and the corresponding differential equations (1)-(2) can be described by the methods that can be found e.g., in [3, 16, 17].

The minimal model can not capture the following phenomena that are physiologically important:

- giving an upper bound for the tumor growth, typically described by Gompertzian functions in the literature [5];
- describing the indirect effect of the inhibitor on tumor growth through modeling the dynamics of the supporting vasculature, if the model is used to describe antiangiogenic therapy;
- modeling the dynamics of dead tumor volume (this will be incorporated into the models in Sections 3 and 4);
- modeling the pharmacodynamics of the drug, i.e., the increase of the drug dose does not yield linear increase in the effect, but the effect has a saturation (this will be incorporated into the models in Sections 3 and 4 as well).

The minimal model has only one equilibrium point specified by (1)-(2), which is the trivial equilibrium, i.e., the equations

$$0 = ax_\infty - bx_\infty y_\infty \tag{6}$$
$$0 = -cy_\infty \tag{7}$$

are satisfied only at $x_\infty = 0$ and $y_\infty = 0$. This equilibrium is unstable, since the Jacobian of the system of differential equations (1)-(2) at the equilibrium point is

$$\left(\begin{array}{c} ax - bxy \\ -cy \end{array} \right)' \Big|_{x=0,y=0} = \left(\begin{array}{cc} a - by & -bx \\ 0 & -c \end{array} \right) \Big|_{x=0,y=0} = \left(\begin{array}{cc} a & 0 \\ 0 & -c \end{array} \right) \tag{8}$$

which is a saddle if $a > 0$ (i.e., it implies unstable tumor growth without drug). Thus, if we give only one injection at the beginning of the treatment, the tumor volume will not be stabilized in an equilibrium, but it will grow with growth rate a after the drug is depleted.

However, if we extend the inhibitor dynamics by adding drug inflow rate I (e.g., to model further injections or infusion), i.e., (2) becomes

$$\dot{y} = -cy + I, \tag{9}$$

then the equilibria of the model are the solutions to

$$0 = ax_\infty - bx_\infty y_\infty \tag{10}$$
$$0 = -cy_\infty + I_\infty \tag{11}$$

that are

$$y_\infty = \frac{a}{b} \tag{12}$$
$$I_\infty = c\frac{a}{b} \tag{13}$$

with $x_\infty \in \mathbb{R}^+$. This implies that if there is an exogenous drug dosage, then the equilibrium is independent of the tumor volume, and only depends on the parameters of the model, thus after we drive the tumor volume in the given state, we give the amount drug described by (12)-(13) to keep the tumor in that state.

Parametric identification of the tumor model based on mice experiments [12] was carried out using mixed-effect model with Stochastic Approximation Expectation-Maximization detailed in [18, 19]. The results of parametric identification fit for each mouse in the experiment is shown in Figure 1. The individual parameter sets show good fit for the measurements.

The identified values of the parameters with 95% confidence intervals and between-subject variability are shown in Table 1. In the identification process, the initial volume appears as an identified parameter. The between-subject variabilities of the parameters are relatively small, the only parameter in the identification with large between-subject variability of the initial tumor volume, which is not a real parameter of the model.

In conclusion, although the model given by (1)-(2) is relatively simple and models only a few physiological phenomena and some critical processes are not modeled, the results in Figure 1 show that the model can describe the measurements. In the next section, the model is extended to incorporate the missing, critical physiological phenomena; the extended model will have similar fit results as the minimal model discussed in this section.

Parameter	Identified value (95%CI)	BSV(CV%)
a	0.206 (0.179, 0.238)	15.4<
b	0.117 (0.00163, 8.47)	23.9>
c	0.0709 (6.35e-005, 79.1)	4.01>
x_{10}	76.4 (47.5, 123)	84.9<

Table 1
Estimated parameters of the non-linear mixed effects model for the tumor model given by the differential equations (1)-(2)., CI: confidence interval, BSV: between-subject variability, CV: coefficient of variation

3 Tumor Model for Antiangiogenic Therapy

The minimal model was extended to incorporate the dynamics of the dead tumor volume, the pharmacodynamics of the drug and mixed-order pharmacokinetics of the drug in [11] and used to explain the effect of the angiogenic inhibitor bevacizumab [12]. The model was also described using formal reaction kinetics analogy as follows: the species X_1 represents the proliferating tumor volume, the species X_2 represents the dead tumor volume and the species X_3 represents the inhibitor serum level. The equations of the model are:

- $X_1 \xrightarrow{a} 2X_1$ that defines that the tumor cells proliferate (divide) with a tumor growth rate a. Using mass-action kinetics, this equation results in the term $\dot{x}_1 = ax_1$;

- $X_1 \xrightarrow{n} X_2$ that defines the necrosis of tumor cells with necrosis rate n. Note that this necrosis is independent of the treatment. Using mass-action kinetics, this equation modifies the dynamics of the proliferating and dead tumor volumes with the terms $\dot{x}_1 = -nx_1$, $\dot{x}_2 = nx_1$;

- $X_3 \xrightarrow{c} O$ that defines that there is an outflow of the drug with a reaction rate coefficient c, i.e. the clearance of the drug. We use Michaelis-Menten kinetics in order to have a mixed-order model for the pharmacokinetics, so this equations results in the term $\dot{x}_3 = -cx_3/(K_B + x_3)$, where the parameter K_B is the Michaelis-Menten constant of the drug;

- $X_1 + X_3 \xrightarrow{b} X_2$ that defines that if the drug meets living tumor cells, the result is dead tumor cells, i.e., the effect of the drug in a general way. This equation is considered with Michaelis-Menten kinetics with Michaelis-Menten constant ED_{50} (called the median effective dose [20]) resulting in the velocity term $x_1x_3/(ED_{50} + x_3)$. The drug effect on the volumes is considered with reaction rate coefficient b. The effect of this equation on the dynamics of the proliferating and dead tumor volumes is expressed by the terms $\dot{x}_1 = -bx_1x_3/(ED_{50} + x_3)$ and $\dot{x}_2 = bx_1x_3/(ED_{50} + x_3)$. Since these terms have the dimension mm^3/day, these terms can not be directly used to modify the dynamics of the drug level, since that has the dimension $mg/(ml \cdot day)$. Thus, we use the constant κ with dimension $mg/(ml \cdot mm^3)$ to define the term $\dot{x}_3 = -\kappa bx_1x_3/(ED_{50} + x_3)$. However, for simplicity, in-

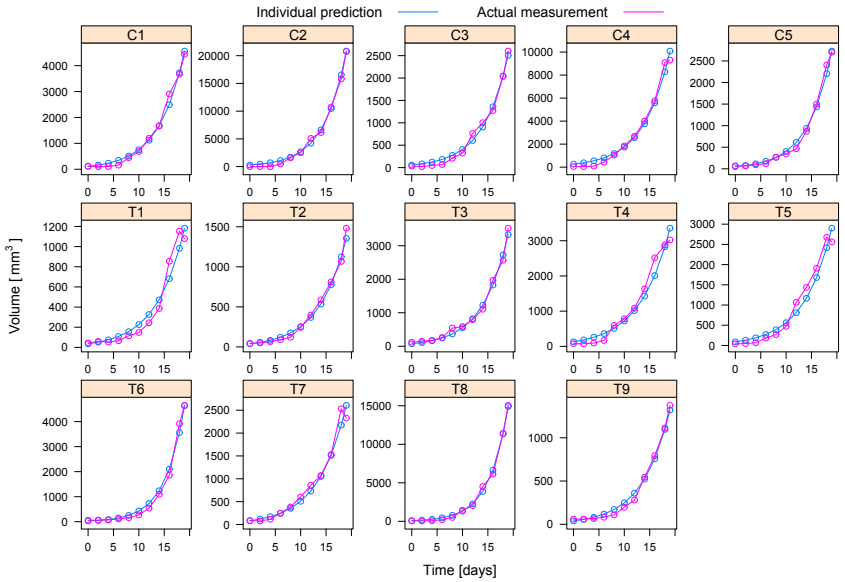

Figure 1
Actual tumor volumes (magenta) from the experiments in [12] and (individual) estimations (blue) from the model described by (1)-(2). The mice got one large dose of bevacizumab at the first day for the cases C1–C5 and one small dose each day for the cases T1–T9.

stead of κ, we introduce the constant $b_\kappa = \kappa b$.

The combination of these terms give the differential equation of the extended tumor growth model:

$$\dot{x}_1 = (a-n)x_1 - b\frac{x_1 x_3}{ED_{50}+x_3} \tag{14}$$

$$\dot{x}_2 = nx_1 + b\frac{x_1 x_3}{ED_{50}+x_3} \tag{15}$$

$$\dot{x}_3 = -c\frac{x_3}{K_B+x_3} - b_\kappa\frac{x_1 x_3}{ED_{50}+x_3} + u, \tag{16}$$

where x_1 is the time function of proliferating tumor volume in mm^3, x_2 is the time function of the dead tumor volume in mm^3, x_3 is the time function of drug serum level in $\mathrm{mg/ml}$, u is the input that is the time function of drug injection rate in $\mathrm{mg/(ml \cdot day)}$.

The output y of the system is the measured tumor volume in mm^3 that is the sum of the proliferating (x_1) and dead (x_2) tumor volumes, i.e.

$$y = x_1 + x_2. \tag{17}$$

The dynamics of the output is described by the differential equation

$$\dot{y} = ax_1 \tag{18}$$

that is the sum of (14) and (15), thus the change of the measured tumor volume depends only on the tumor growth rate constant a and the actual volume of the proliferating tumor volume.

The trivial equilibrium of the model is

$$x_1^* = 0 \tag{19}$$
$$x_3^* = 0 \tag{20}$$

with $x_2^* \in \mathbb{R}^+$. This equilibrium is a stable node if $a-n<0$, i.e., the tumor is defeated by the host, and a saddle, if $a-n>0$. In the latter case, the tumor grows without therapy. Qualitative analysis of the model extended with a linear state feedback control law was carried out in [13], and it has been shown that the therapy can be efficient (i.e., there is a positive equilibrium achieved during the therapy) if and only if $a-n-b<0$. This inequality is also the sufficient and necessary condition to achieve decreasing proliferating tumor volume as it has been shown in [11].

Parametric identification of the tumor model based on mice experiments [12] was carried out using mixed-effect model with Stochastic Approximation Expectation-Maximization detailed in [18, 19]. The identified values of the parameters with 95% confidence intervals and between-subject variability are shown in Table 2. In the identification process, the initial volume appears as an identified parameter, and shows the largest between-subject variability, while the real model parameters have small BSV.

The results of parametric identification fit for each mouse in the experiment is shown in Figure 2. The individual parameter sets show good fit for the measurements, similar to the results in Section 2.

The model described by (14)-(16) has similar modeling power as the model given by (1)-(2) based on the identification using the measurements from [12]. However, the model discussed in this section is more complex, and the equations of the model are physiologically more feasible, the measurements suggest that the complexity of the model is not required. However, in the next section, we modify the model given by (14)-(16) to describe measurements from chemotherapy where the measurement results show much richer dynamics than the simple exponential growth that can be observed on the measurements with bevacizumab [12] in Figures 1 and 2.

Parameter	Identified value (95%CI)	BSV (CV%)
a	0.373 (0.349, 0.399)	7.56%
b	0.124 (0.116, 0.132)	1.55%
c	0.132 (0.124, 0.14)	4.30%
n	0.176 (0.154, 0.202)	16.2%
b_k	7.25e-7 (6.43e-7, 8.16e-7)	8.01%
$x_1(0)$	46.5 (30, 71.9)	80.6%
K_B	0.591 (0.497, 0.703)	8.80%
ED_{50}	4.63e-005 (2.48e-005, 8.63e-005)	17.1%

Table 2
Estimated parameters of the non-linear mixed effects model for the tumor model for antiangiogenic therapy described by (14)-(16), CI: confidence interval, BSV: between-subject variability, CV: coefficient of variation

4 Tumor Model for Chemotherapy

The model given in [11] was further modified to add the effect of dead tumor cell washout in [18] in order to make it able to describe the dynamics of chemotherapy using PLD [2]. Since the effect of the drug was specified with a general mechanism (i.e., meeting of the proliferating tumor cell and drug results in dead tumor cell), it was unnecessary to modify the corresponding stoichiometric equation to make it mores suitable to describe chemotherapy. The dynamics of dead tumor cell washout is given by the stoichiometric equation

$$\mathrm{X}_2 \xrightarrow{\mathrm{w}} \mathrm{O}$$

which describes the washout of the dead tumor cells with washout rate w. Using mass-action kinetics, this reaction step has the rate $-wx_2$, which modifies the dynamics of the dead tumor cell volume. Thus, the modified differential equations of the model are

$$\dot{x}_1 = (a-n)x_1 - b\frac{x_1x_3}{ED_{50}+x_3} \tag{21}$$

$$\dot{x}_2 = nx_1 + b\frac{x_1x_3}{ED_{50}+x_3} - wx_2 \tag{22}$$

$$\dot{x}_3 = -c\frac{x_3}{K_B+x_3} - b_k\frac{x_1x_3}{ED_{50}+x_3} + u, \tag{23}$$

where x_1 is the time function of proliferating tumor volume in mm^3, x_2 is the time function of dead tumor volume in mm^3, x_3 is the time function of drug level in $\mathrm{mg/kg}$ and u is the input that is the time function of drug injection rate in $\mathrm{mg/(kg \cdot day)}$. Since the injection doses were provided in $\mathrm{mg/kg}$ [2], the units of x_3, u, ED_{50}, and K_B differ from the units of the corresponding variables and parameters in the model (14)-(16) where the basic unit was $\mathrm{mg/ml}$.

The output y of the system is the measured tumor volume in mm^3 that is the sum

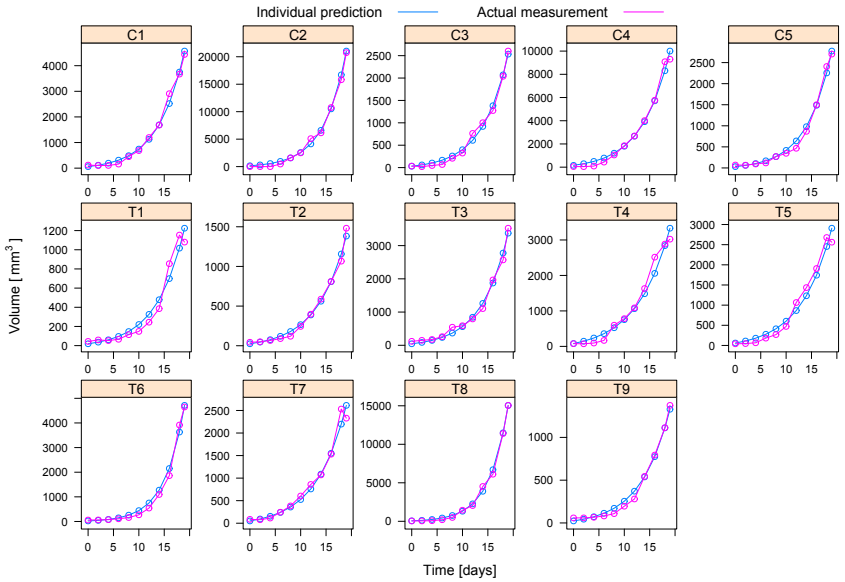

Figure 2
Actual tumor volumes (magenta) from the experiments in [12] and (individual) estimations (blue) from the model described by (14)-(16). The mice got one large dose of bevacizumab at the first day for the cases C1–C5 and one small dose each day for the cases T1–T9.

of the proliferating (x_1) and dead (x_2) tumor volumes, i.e.

$$y = x_1 + x_2. \tag{24}$$

The dynamics of the output is described by the differential equation

$$\dot{y} = ax_1 - wx_2 \tag{25}$$

that is the sum of (21) and (22), thus the change of the measured tumor volume depends directly only on the tumor growth rate constant a, the necrotic washout w and the actual volume of the proliferating tumor volume and the dead tumor volume.

The output dynamics (25) effectively describes a behaviour that seems like the drug has delayed effect on the tumor volume. The delayed effect is produced by the fact that initially the living tumor cells die (and become dead tumor cells), thus the output (the sum of living and dead tumor cell volume) does not change, and the remaining living tumor cells proliferate, resulting in increasing output, and the dead tumor cells start to be cleared during the washout process, which decreases the output. However, as long as the living tumor cells dominate (25), i.e., the ratio of x_1 and x_2 is such that (25) is positive, the output is increasing, and will only start to decrease when the ratio of the dead and living tumor cells

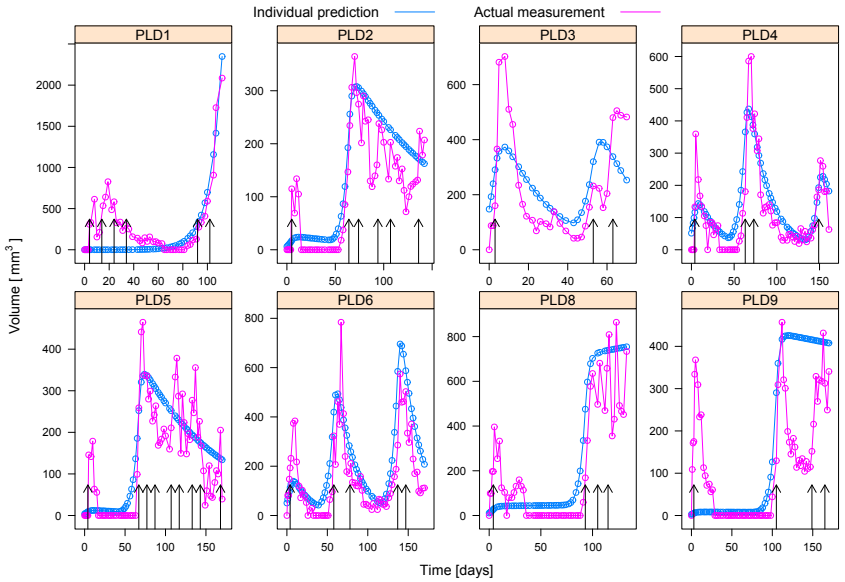

Figure 3
Actual tumor volumes (magenta) from the experiments in [2] and (individual) estimations (blue) from the model described by (21)-(23). The black arrows indicate 8 mg/kg injections of PLD in the experiments.

reach a value when (25) becomes negative. This effect can be observed in the measurements as well in Figure 3, where the measurements are indicated by magenta diamonds, while the injections are indicated as arrows on the horizontal axis. The injections were 8 mg/kg of PLD, a cytotoxic agent injected to mice with breast cancer [2].

Parametric identification of the tumor model based on mice experiments [2] was carried out using mixed-effect model with Stochastic Approximation Expectation-Maximization detailed in [18, 19]. The identified values of the parameters with 95% confidence intervals and between-subject variability are shown in Table 3. In the identification process, the initial volume appears as an identified parameter, and shows the largest between-subject variability, while the real model parameters have small BSV. The only exception is the effective median dose parameter (ED_{50}), which shows large between-subject variability.

The results of parametric identification fit for each mouse in the experiment are shown in Figure 3. The individual parameter sets show good fit for the measurements, except for the cases PLD1, PLD8 and PLD9. The most possible explanation of the bad fit for these cases maybe that the tumor acquired resistance for PLD1, PLD8 and PLD9, and the model is not able to describe this phenomenon.

[t!]

Parameter	Identified value (95%CI)	BSV (CV%)
a	0.306 (0.265, 0.354)	6.08%
b	0.166 (0.126, 0.219)	18.2%
c	0.257 (0.2, 0.329)	31.9%
n	0.144 (0.127, 0.163)	16.3%
bk	6.12e-7 (5.57e-7, 6.73e-7)	6.60%
$x_1(0)$	6.94 (1.44, 33.4)	6050%
KB	0.36 (0.253, 0.514)	34.5%
$ED50$	9.71e-5 (2.17e-5, 0.000434)	152%
w	0.34 (0.292, 0.397)	7.43%

Table 3
Estimated parameters of the non-linear mixed effects model for describing the effect of PLD with the equations (21)-(23), CI: confidence interval, BSV: between-subject variability, CV: coefficient of variation.

Conclusions

The tumor models based on formal reaction kinetics analogy demonstrate that the modeling approach can be beneficial for the modeling of physiological systems. The reaction kinetics analogy makes the differential equations interpretable for experts not familiar with the theory of differential equations (e.g., clinical experts), while the different modeling alternatives (e.g., mass-action kinetics or Michaelis-Menten kinetics) can be used to find the optimal choice between model complexity and modeling power.

The simple model, also called the minimal model, has good modeling power in a small "operative" range only, however, if the tumor is controlled, the states of the system can be kept in that range, where the model is realistic. The simplicity of the model is advantageous for model-based controller design, and allows the use of numerous sophisticated control design techniques.

More complex models have the power to describe physiological processes in more detail, however, the complexity makes controller design more difficult. As the results showed with chemotherapy, the complex models can be used to describe the effect of therapy on a larger scale on both time and state space, thus more complex models are more beneficial for designing impulsive therapies.

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