Modeling of tumor growth incorporating the effect of pegylated liposomal doxorubicin

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***Abstract*— Modeling tumor growth is a fundamental step in the design of automated, optimal, patient specific therapies. We extend our tumor growth model created to describe the effect of an angiogenic inhibitor in order to make it suitable to describe the effect of chemotherapy. By incorporating the dead tumor cell washout into our previous model, we are able to describe the most important phenomena during treatment with chemotherapy. We use measurements from experiments carried out on mice with a chemotherapeutic drug Pegylated Liposomal Doxorubicin, and carry out parametric identification of our model. The results show that the extended model can describe chemotherapy sufficiently.**

I. INTRODUCTION

Modeling the tumor growth dynamics and the effect of different drugs on tumor growth is a fundamental step towards personalized, optimized tumor therapies. The existence of a reliable tumor growth model lets us use control engineering and mathematical methods to optimize the tumor treatment [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]. A good tumor model captures tumor dynamics and drug dynamics as well, with realistic considerations such as the drug has a maximal effect of the tumor growth dynamics.

The most widely used tumor growth model in control applications is the Hahnfeldt model [12], which models the effect of angiogenic inhibitors, but lacks the modeling of pharmacodynamics and dead tumor volume. Experiments showed that in the case of antiangiogenic therapy, the tumor contains dead and living regions, and there is no washout of the dead cells [13]. Moreover, the experiments have also showed that the pharmacodynamics of the drug can not be neglected, since giving one large dose according to the protocol had the same effect as giving 1/180 of the dose each day for an 18 days treatment period. This shows that after a limit, increasing the dose of the drug does not result in linear increase in the effect of the drug, but it has a plateau. This phenomenon is captured by the pharmacodynamics, and is crucial for designing tumor therapies. The Hahnfeldt model has been modified and extended by other authors several times, but they did not incorporate neither pharmacodynamics nor dead regions [14]. A model with pharmacodynamics, dead tumor cell regions and vasculature dynamics has been published recently [15].

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A minimalistic model capturing tumor growth dynamics without dead cell regions and pharmacodynamics has been published in [16], and has been used for controller design in [17], [8], [18], [19], [20], [3]. The model has been extended with pharmacodynamics, mixed-order pharmacokinetics and dead tumor volume dynamics in [21]. Although this model was validated with experimental results from antiangiogenic therapy, the model was formulated to be as general as possible. However, due to the nature of the measurements from antiangiogenic therapy [13], the model does not contain washout of the dead tumor cells, which is an important process in the case of chemotherapy [22]. We extend this model to incorporate dead tumor cell washout [23] and use the extended model to describe a therapy with a chemotherapeutic drug called Pegylated Liposomal Doxorubicin (PLD) [22].

We use experimental data from the Membrane Protein Research Group of the Hungarian Academy of Sciences published in [22]. We use the data acquired from experiments with PLD. In some cases the mice in the experiments became resistant of the chemotherapy, however, our model is not capable to model this effect yet. Thus, we chose the set of measurements where resistance did not seem to be present (except for one case from the chosen measurement set). Our results show that the general model originally created for antiangiogenic therapy can sufficiently model the tumor growth dynamics even in the case of chemotherapy, as long as the tumors do not develop resistance against the drug.

The model extended with the dead tumor cell washout is discussed in Section II, while the methods used for parametric identification are detailed in Section III. The results of the identification are shown in Section IV, while the paper ends with the conclusions in Section V.

II. THE TUMOR GROWTH MODEL

We define the tumor growth model equations with the help of stoichiometric equations using formal reaction kinetics analogy [24]. The fictive species are the X_1 proliferating tumor volume, the species X_2 which represents the dead tumor volume, and the species X_3 that represents the drug level. In the corresponding differential equations the state variables x_1, x_2 and x_3 are the time functions of the proliferating tumor volume, dead tumor volume and drug level, respectively. The stoichiometric equations defining the underlying physiological phenomena are

- $X_1 \xrightarrow{a} 2\,X_1$ that defines that the tumor cells proliferate (divide) with a tumor growth rate a. The correspond-

978-1-7281-1213-8/19/$31.00 ©2019 IEEE

ing term in the differential equation using mass-action kinetics is $\dot{x}_1 = ax_1$;

- $X_1 \xrightarrow{n} X_2$ that defines the necrosis (death) of tumor cells with necrosis rate n, which is the tumor necrosis that is independent of the treatment. Using mass-action kinetics, this equation modifies the dynamics of the proliferating and dead tumor volumes with the terms $\dot{x}_1 = -nx_1$, $\dot{x}_2 = nx_1$;
- $X_2 \xrightarrow{w} O$ that defines the washout of the dead tumor cells with washout rate w. Using mass-action kinetics, this reaction step has the rate wx_2. This extension was not present in our original model [21].
- $X_3 \xrightarrow{c} O$ 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 the approximation of the 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;
- $X_1 + X_3 \xrightarrow{b_2} X_2$ that defines the effect mechanism of the drug in a general way, i.e., if there is living tumor and drug, they turn into dead tumor. The effect of the drug is considered with the approximation of the Michaelis-Menten kinetics with Michaelis-Menten constant ED_{50} resulting in the velocity term $x_1x_3/(ED_{50} + x_3)$. This 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 $\dot{x}_2 = bx_1x_3/(ED_{50} + x_3)$. The dimension of these velocity terms is mm^3/day, thus these terms can not be directly used to modify the dynamics of the drug level, which has the dimension $\text{mg}/(\text{kg} \cdot \text{day})$. Thus, we use the constant b_k with dimension $\text{mg}/(\text{kg} \cdot \text{mm}^3 \cdot \text{day})$ to define the term $\dot{x}_3 = -b_kx_1x_3/(ED_{50} + x_3)$.

The combination of these terms give the differential equation of the system:

$$\dot{x}_1 = (a - n)\, x_1 - b\frac{x_1x_3}{ED_{50} + x_3} \quad (1)$$

$$\dot{x}_2 = nx_1 + b\frac{x_1x_3}{ED_{50} + x_3} - wx_2 \quad (2)$$

$$\dot{x}_3 = -c\frac{x_3}{K_B + x_3} - b_k\frac{x_1x_3}{ED_{50} + x_3} + u, \quad (3)$$

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 mg/kg and u is the input that is the time function of drug injection rate in $\text{mg}/(\text{kg} \cdot \text{day})$.

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.

$$y = x_1 + x_2. \quad (4)$$

The dynamics of the output is described by the differential equation

$$\dot{y} = ax_1 - wx_2 \quad (5)$$

that is the sum of (1) and (2), 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.

III. PARAMETER ESTIMATION

The differential equation system was first converted to a – nonlinear – model where the parameters were assumed to be random effects. In brief, this means that every subject has an own value for each parameter which is assumed to be a random draw from a given (usually normal) distribution, hence the number of estimated parameters is always two – mean and standard deviation – regardless of the number of subjects [25]. The mean measures the overall – population – value, while standard deviation characterizes the between-subject variability. An advantage of this model is that it handles the within-subject correlations, therefore these models are widely used to describe repeated-measures data and are also universally applied in population pharmacokinetics [26], [27].

It was assumed that random effects are all independent from each other. All parameters were estimated on log-scale, which also ensures the positivity of the parameters. Initial values were set to $\ln a = -0.5$, $\ln b = -2$, $\ln ED_{50} = -9.9$, $\ln b_k = -14$, $\ln c = -2$, $\ln n = -2$, $\ln x_1(0) = -4$, $\ln KB = -0.5$ and $\ln w = -1$. Initial value for the standard deviation of the random effect was set to 0.01 for all parameters. Error term was assumed to be additive, with an initial value of 1. Estimation was performed with Stochastic Approximation Expectation-Maximization (SAEM) method which is one of the modern methods to solve the likelihood equations arising from the above-described nonlinear mixed effects models [28], [29]. Calculations were carried out under R statistical program package version 3.5.2 [30] using the library `nlmixr` version 1.0.0-7 [31].

IV. RESULTS

Table I shows the estimated mean (population) parameter values, along with their between-subject variability (measured with coefficient of variation). The between-subject variability of parameters a, b, n, b_k, and w are less than 30 %. However, the pharmacodynamics parameter ED_{50} has large variability (152 %), thus the results show that the effective median dose changes greatly among mice. The initial tumor volume has the largest variability (6050%), however, this is not a model parameter, juts an initial value. Between subject variability is further illustrated in Figure 1 which uses dotplot to visualize the estimated (individual) value for each subject.

Results of the model, shown as the individual predicted tumor volume superimposed on the actual tumor volume are shown in Figure 2. The vertical arrows show the days when the mice got treatments. The dose was 8 mg/kg each time. The model shows good individual fits for the cases 2-6.

For case 1 we can observe from the measurements that the tumor becomes resistant towards the drug during the therapy, which process is not incorporated into the model. The model neglects the initial phase when there is no resistance, and

Parameter	Est.	SE	%RSE	Back-transformed (95%CI)	BSV (CV%)	Shrink (SD)%
Log a	-1.18	0.0744	6.28	0.306 (0.265, 0.354)	6.08%	33.2%>
Log b	-1.79	0.14	7.8	0.166 (0.126, 0.219)	18.2%	11.8%<
Log c	-1.36	0.126	9.29	0.257 (0.2, 0.329)	31.9%	10.4%<
Log n	-1.94	0.0642	3.31	0.144 (0.127, 0.163)	16.3%	22.2%=
Log bk	-14.3	0.0482	0.337	6.12e-007 (5.57e-007, 6.73e-007)	6.60%	85.0%>
Log $x_1\,(0)$	1.94	0.802	41.4	6.94 (1.44, 33.4)	6050.%	-1.74%>
Log KB	-1.02	0.181	17.7	0.36 (0.253, 0.514)	34.5%	33.7%>
Log $ED50$	-9.24	0.764	8.26	9.71e-005 (2.17e-005, 0.000434)	152.%	84.2%>
Log w	-1.08	0.0783	7.26	0.34 (0.292, 0.397)	7.43%	81.6%>
Error	124			124		

TABLE I

ESTIMATED PARAMETERS OF THE NON-LINEAR MIXED EFFECTS MODEL (EST.), SE: STANDARD ERROR, RSE: RELATIVE STANDARD ERROR, CI: CONFIDENCE INTERVAL, BSV: BETWEEN-SUBJECT VARIABILITY, CV: COEFFICIENT OF VARIATION, SD: STANDARD DEVIATION. LOG STANDS FOR NATURAL LOGARITHM.

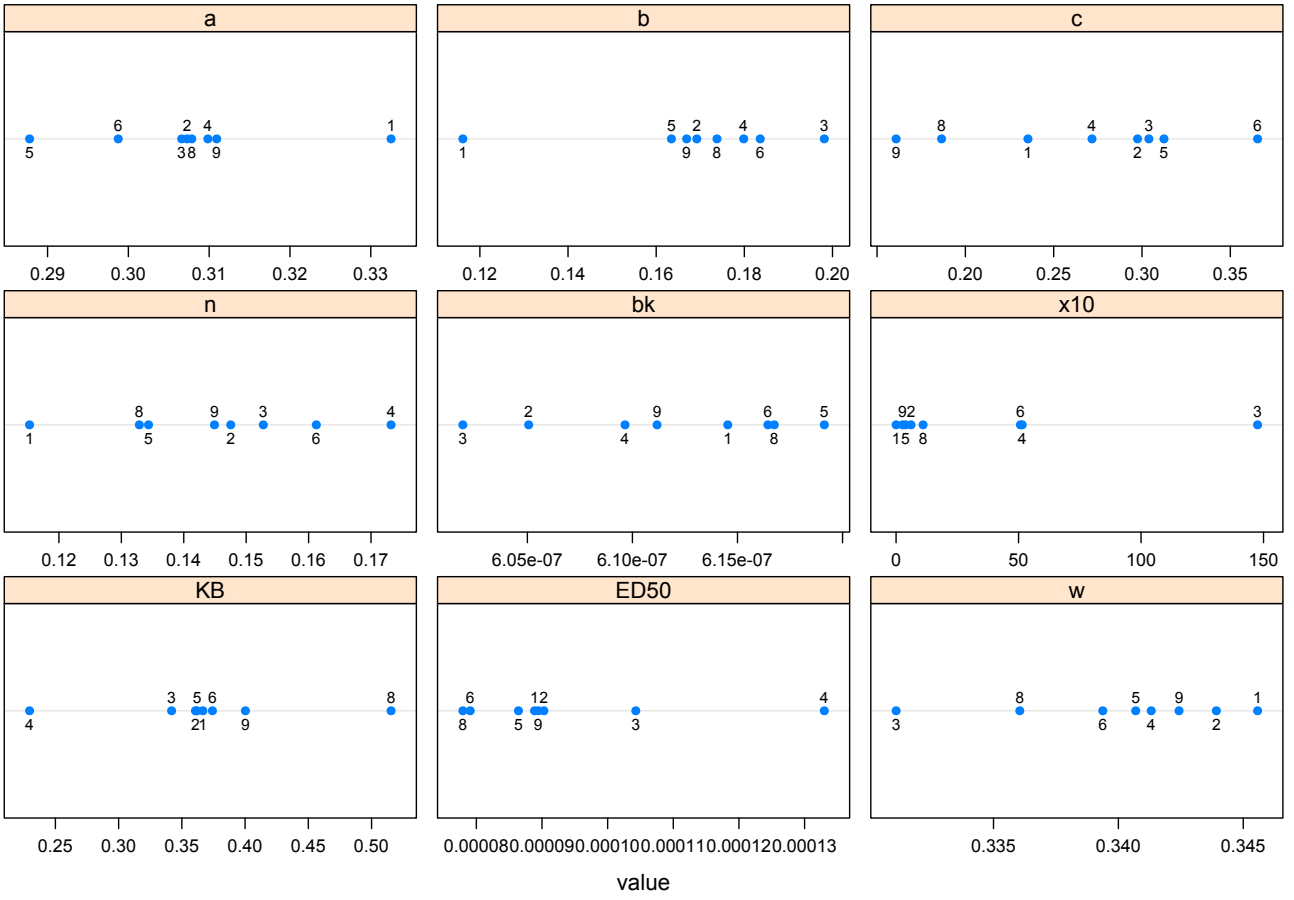

Fig. 1. Estimated individual parameters for each mouse.

learns the curve where the tumor became resistant towards the drug. By looking at Fig. 1, we can conclude that for case 1, the model has the largest tumor growth rate a and smallest necrotic rate n and inhibition rate b, which results in ineffective therapy and uncontrollable tumor growth as it can be seen in Fig. 2. For cases 8 and 9, most of the parameters have average value compared to the other cases, except for the pharmacokinetic parameters c and K_B, where the K_B parameter is larger than for the other cases resulting in faster depletion of the drug. As Fig. 2 shows, for cases 8 and 9 initially there is only one injection with a small effect according to the model, and according to the model the drug only had significant effect when the injections became frequent. Probably, in these cases the problem is not the resistance, but the nature of the measurements, since for most of the time the measured volume is assumed to be zero, but in reality there was some small tumor for both cases, but they were unmeasurable. Note that we do not have case 7,

since the measurement data was not accessible for the case indexed originally with 7 in [22].

V. CONCLUSIONS

The results showed that our general model is suitable for modeling the effect of chemotherapy as well after a modification which incorporates dead tumor cell washout. The parametric identification showed that the pharmacodynamics parameter ED_{50} (the effective median dose of the drug) had the largest interpatient variability, while tumor growth rate a, necrotic washout w and the rate of drug depletion due to the effect b_k had the smallest interpatient variability. These results are important in therapy design, since the dosages must be aligned to the value of effective median dose.

The results showed that the model is not capable of describing the phenomenon when the tumor acquires drug resistance. However, this is not expected, since the model can not handle dynamics changes of the effect of the drug. Incorporating this effect into the model is the subject of further research.

VI. ACKNOWLEDGMENTS

The authors would like to express their thanks to the Membrane Protein Research Group of the Hungarian Academy of Sciences for providing the measurement data. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 679681). Anna Lovrics is supported by the Hungarian National Research, Development and Innovation Office (OTKA PD 124467). The research is partially supported by the Hungarian National Research, Development and Innovation Office (2018-2.1.11-TÉT-SI-2018-00007 and SNN 125739).

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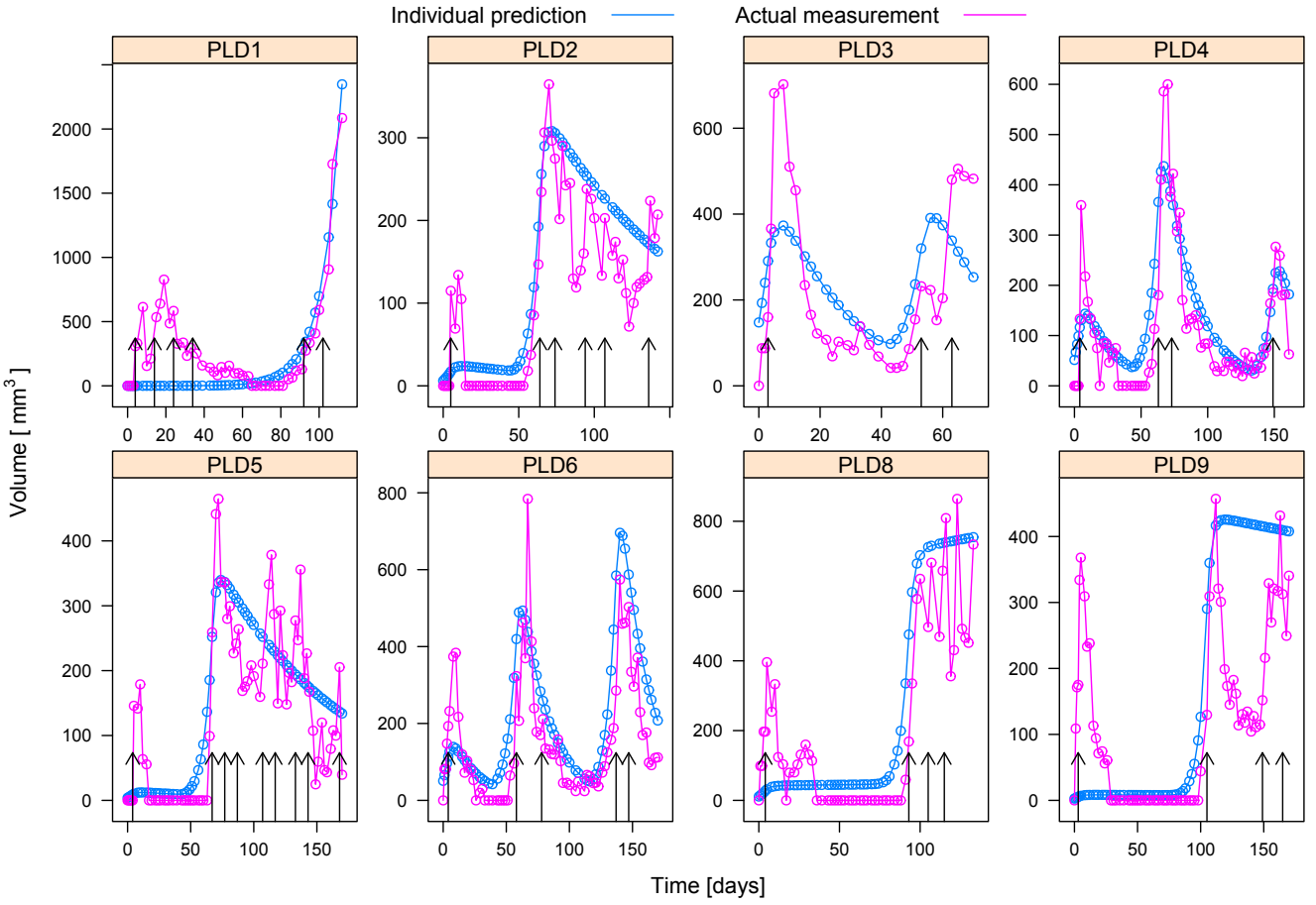

Fig. 2. Actual tumor volumes and (individual) estimations from the model.

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