Modeling of Antitumor Drug Pharmacodynamics Using Genetic algorithm

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Abstract— *Available mathematical models of tumor growth and the effect of anticancer treatments in animals are still of limited practical use within the drug industry because of complex and contradictory aspects. A simple and effective model would facilitate the preclinical development of oncology drugs owing to prediction capabilities. Another challenge of this field is to estimate the model parameters according to laboratory experimental data. Simplicity of mathematical models often causes a major impediment in fitting the models to experimental data. In this paper, a minimal Pharmacokinetic-Pharmacodynamic (PK-PD) model is studied to analyze the effects of antitumor drugs using empirical data obtained from the experimentations on 5 groups of laboratory mice: one group untreated and 4 groups treated with four different antitumor drugs which are intravenously administered. Tumor growth and process of cell death are here modeled by three differential equations obtained from a compartmental model. The related compartmental model is then applied to experimental data supposing an exponential decaying model for drug concentration. Using Genetic algorithms, the parameters of model have been optimally estimated. According to simulations, the proposed model copes with the interpretation of contradictory effects of CpG drug. Besides, the parameters of immunological system are uniquely obtained in the presence of different anticancer drugs. Proposed model parameters may be used in the prediction of an eventual treatment of mixing profile.*

Keywords: drug, tumor growth, model; mice, genetic algorithm.

I. Introduction

To understand and predict the pharmacological behavior of anticancer drugs, it is crucial to quantify the time course of pharmacodynamic responses in relation to the plasma concentration. The response of anticancer drugs is delayed relative to the time course of drug exposure.

A fundamental step of the preclinical development of oncology drugs is the in vivo evaluation of the antitumor effect. For this purpose, a series of experiments are performed, in which tumor cells from immortalized cell lines are inoculated into athymic mice. Tumor volumes are measured at different times throughout the experiment in all of the animals, treated either with a vehicle (control) or with an active drug. The effect of the active molecule is then measured by comparing the average tumor weights in treated and control animals at the end of the experiment, or by recording the animals surviving their disease [1-3]. This approach can be used to select the most potent candidate within a series using the same dosing regimen, or the most appropriate dosing regimen among those tested for a specific compound. However, in this way, the time course of the tumor growth is often neglected, so that only partial use of the information available from the experiment is made.

Empirical models use mathematical equations (e.g., sigmoid functions, such as logistic, Verhulst, Gompertz, and von Bertalanffy [4,5]) to describe the tumor growth process, without an in-depth mechanistic description of the underlying physiological processes. In this context, the effect of a drug can be evaluated only in terms of changes of the parameter values describing the tumor growth. These changes depend on the dose level as well as the administration schedule, so that those approaches can be applied only retrospectively and not as predictive tools when used outside the tested regimens.

Functional models, conversely, are based on mechanistic, physiology-based hypotheses. They suppose a set of assumptions about the tumor growth, including cell-cycle kinetics and biochemical processes, such as those related to anti-angiogenetic and/or immunological responses [5,6]. Such models usually represent the cell population in its heterogeneity, splitting it into at least two subpopulations: the proliferating and the quiescent cells. More complex models describe the cell population as age-structured and take into account subpopulations related to specific phases of the cell cycle. These models have a much larger number of parameters compared with the empirical ones. Their development is time consuming and a number of quantitative observations (e.g., flow cytometry analyses, biochemical and immunological marker measurements, and so forth) are required to avoid the identifiability problems due to the over-parameterization [7]. The situation becomes even more complex when the effect of the treatment with an anticancer drug is considered [8-11], also because of the incomplete knowledge of the mode of action in vivo. As a consequence, these models are rarely used in industrial drug research.

In conclusion, despite the existence of several tumor growth models, a practical tool that supports oncology drug development is still missing. In this respect, the only metrics of success are its application to the experimental data and the savings of experiments, time, costs, resources, and animal requirements. In this article, the described model is an effective compromise between empirical and mechanism-based approaches. It relies on a few identifiable and biologically relevant parameters, the estimation of which requires only the data typically available in the preclinical setting: the pharmacokinetics of the anticancer agents and the tumor growth curves in vivo. According to the large uncertainty about the parameter space, the model parameters have been estimated using Genetic algorithm in this paper.

II. PK-PD Model of Tumor Growth

A. Introduction

A Pharmacokinetic-Pharmacodynamic (PK-PD) model would greatly improve the preclinical development of oncology drugs linking the administration regimen of an agent to tumor growth dynamics. To achieve this property, it is firstly necessary to have a mathematical model governing on the progression of disease in the absence of any treating agent [12].

Empirical models can use mathematical differential equations to describe the tumor growth curve, without an in-depth mechanistic description of the underlying physiological processes. However, the modeling equations should already be extracted from the physio-pathological phenomena and reactions. In first dilemma, the effect of a drug can be evaluated only in terms of changes of the parameter values describing the tumor growth. These changes depend mostly on the dose level and the administration schedule. So, the related approaches can be applied only retrospectively and may not be used as predictive tools out of the tested regimens. The predicting capability relies on the basic PK-PD model comprising the relevant chemical reaction chains [13].

The availability of mathematical models being able to predict the dynamics of tumor growth as a function of the drug concentration would result in several advantages such as saving time and cost of experimentation and validation of immunotherapeutic theories. The mathematical modeling of tumor growth dynamics has been under extensive investigations [14]. All proposed models generally involve a dozen of parameters that can be hardly identified from the experimental data. In this paper, a PK-PD model is used with four parameters [15,16]. The parameters of the pharmacodynamic model are related to the growth characteristics of tumor, drug potency, and the kinetics of the tumor cell death. The model parameters are then optimally estimated according to the experimental data applying genetic algorithms as optimization tools. Finally, the model can be used to describe or predict the tumor growth rate considering different vaccination profiles. Also, it may be used to propose new mixing profiles of vaccination as a prospective drug.

This paper has been organized as follows. The next section describes a PK-PD model for tumor growth. In the third section, the experimentation procedures have been explained. Also, the result simulation results are discussed. Finally, the results are summarized in the conclusion section.

B. PK-PD Model

In untreated mice, experimental data demonstrate that tumor growth follows two distinctive and different phases: first, an initial phase with exponential growth, secondly a linear growth phase and a smooth transition between two phases. In treated animals, the tumor growth rate is proportionally decreased in terms of both drug concentration and the concentration of proliferating tumor cells. Anticancer treatment influences basic growth dynamics of tumor so that proliferating cells become non-proliferating with a rate depending on the drug concentration in plasma. Invoking immunological principles, the tumor growth in the presence of antitumor drug may be modeled by a compartment model as shown in Fig.1. [17]:

$$x_1' = \frac{2\lambda_0\lambda_1 x_1^2(t)}{(\lambda_1 + 2\lambda_0 x_1(t))w(t)} - k_2 C(t) x_1(t)\ , x_1(0) = w_0 \quad (1)$$

$$x_2' = k_2 C(t) x_1(t) - k_1 x_2(t)\ , \qquad x_2(0) = 0 \quad (2)$$

$$x_i' = k_1 (x_{i-1}(t) - x_i(t))\ , \qquad x_i(0) = 0\ , i = 3,...,N \quad (3)$$

$$w(t) = \sum_{i=1}^{N} x_i(t) \quad (4)$$

In this model, all tumor cells are assumed to be proliferating. The model assumes that the anticancer treatment makes some cells nonproliferating as well (Fig.1), eventually bringing them to death. For a given time t, $x_1(t)$ indicates the portion of proliferating cells within the total tumor weight w(t) and c(t) indicates the plasma concentration of the anticancer agent respectively. $x_1(t)$ represents the portion of w(t) that is actually proliferating. The model assumes that the drug elicits its effect decreasing the tumor growth rate by a factor proportional to $c(t).x_1(t)$ through the constant parameter k_2, which is, thus, an index of drug efficacy [17].

It is assumed that the cells affected by drug action stop proliferating and pass through *n* different stages (namely $x_2,\ldots, x_n$), characterized by progressive degrees of damage, and, eventually, they die. The dynamics by which the cells proceed through progressive degrees of damage is modulated via a rate constant k_1 that can be interpreted in terms of the kinetics of cell death.

In practice, the drug absorption function can be replaced as following [17]:

$$C(t) = \frac{\beta\gamma}{\beta - \alpha}\left(e^{-\alpha t} - e^{-\beta t}\right) \quad (5)$$

That C(t), β, α and γ stand for the mean plasma concentration of drug, absorption and elimination rates and the volume of distribution respectively.

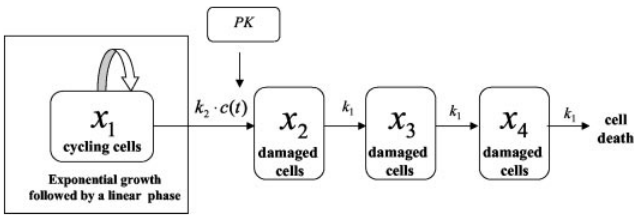

Figure 1. Scheme of PK-PD model of cell death. k_1 : first order rate constant of transit; k_2 :measure of drug potency; C(t): the plasma concentration of anticancer agent.

In the experimental study of this paper, the parameters $(\lambda_0, \lambda_1, k_1, k_2)$ are supposed to be constant through different vaccination profiles (model parameters). The model

parameters are to be optimally estimated by genetic algorithms invoking the experimental data. Contradictory effects of different vaccins (CpG versus Listeria for example) renders the optimization problem tough.

III. Experimentations and Simulation Results

In the experiments, tumor cells were subcutaneously inoculated to mice. With a palpable tumor after one week, they are randomly divided into 5 groups: one untreated and 4 others treated by 4 different drugs of Lps, CpG, Tumor Lysate and Listeria monocytogenes. Each drug is administered in 3 classes: once, twice and triple injection on 7^{th}, 10^{th} and 13^{th} day respectively. Then, the tumor size is tracked every two days for all groups. The parameters of PK-PD model are estimated invoking experimentation data. Using experimentation data, the PK-PD model is simulated for different groups of mice. Genetic algorithm toolbox of Matlab is used to optimize the model parameters so that the total error tends to minimum. Simulations took about 30 minutes for each run of optimization toolbox (P4 dual core, RAM 4GB). In the simulations, four stages of damage (n=4) for cells are considered and the model is a four compartment model.

Once the optimization toolbox with seven parameters to be estimated $(\lambda_0, \lambda_1, k_1, k_2, \alpha, \beta, \gamma)$ is executed, a limit range for variation of drug parameters is obtained. The drug parameters for those mice in CpG group and Listeria group are reported in table I.

TABLE I: Drug parameters of CpG and Listeria for distribution in plasma.

	α	β	γ
CpG	0.252	0.651	1.53
Listeria	0.151	0.21	0.82

The drug concentration for CpG group with triple injection on 7^{th}, 10^{th} and 13^{th} day is shown in Fig. 2. It can be seen that after first, second and third injections, the plasma concentration of the drug goes up and eventually decreases exponentially being consistent with the physiology.

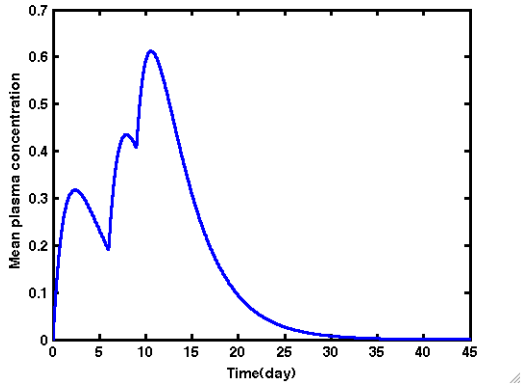

Figure 2. Mean plasma concentration of CpG with triple injections.

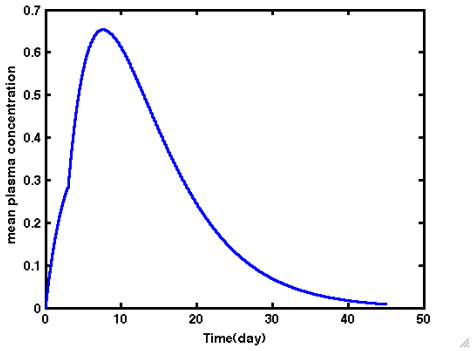

Figure 3. Mean plasma concentration of Listeria with double injections.

The drug concentration for Listeria group with twice injection on 7^{th} and 10^{th} days is shown in Fig. 3.

Now, the optimization toolbox for each group of mice with different drug administration is invoked and accordingly the model parameters for each group is obtained (see table I). It can be seen from estimated parameters for each group that the range of their variation is the same. In the next stage, the mean estimated value for each estimated parameter is used. It may be seen from the results that the result parameters have been estimated with a good accuracy. The model parameters are finally obtained as shown in table III invoking different vaccination profiles and agents.

Then, using the proposed dynamic parameters (Table III), the optimization toolbox is run invoking each group of experimentation mice and considering the related vaccination *C(t)*. Simulation results have been shown in Figure 4.

TABLE II: Proposed Model parameters using experimental trials for different vaccines types.

	λ_0	λ_1	k_1	k_2
Lps	1.019	5.56	0.1038	0.199
CpG	1.0136	6.5	0.3999	0.1118
Lysate	0.8	5.5	0.1969	0.2
Listeria	1.158	6.13	0.148	0.63

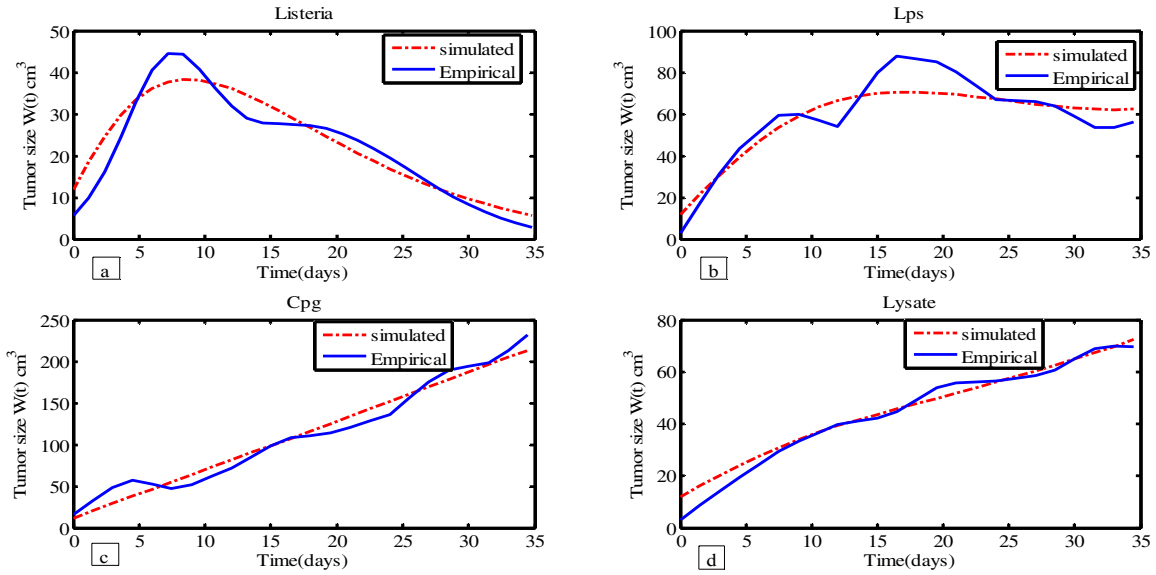

Figure 4. Average tumor growth: empirical (in blue) and simulated (in red) values. The curves are associated with the different vaccination trials of: (a) Listeria group (top left); (b) Lps group (top right); (c) CpG group (bottom left) and (d) Lysate group 9bottom right).

TABLE III: Optimized model parameters for fifferent vaccination groups

λ_0	λ_1	k_1	k_2
0.9995	5.9225	0.2121	0.285

As it may be seen in Figure 4, the model curves can properly follow up the empirical data in spite of contradictory behavior of CpG agent versus other vaccination agents.

In the next step of research, this model will be used to predict the performance of immunology system and the tumor size using different profiles of vaccination.

IV. Conclusion

In this paper, a novel PK-PD model was presented for predicting and describing the tumor growth and the effect of anticancer agents in animal models. The pharmacodynamic part of the model was based on four physiological parameters. These parameters are identifiable without additional efforts, using the typical experiments performed in nude mice as part of the drug research and development process. Three parameters (w_0, λ_0, and λ_1) describe the features of the tumor kinetics in control animals, characterized by an exponential growth followed by a linear growth. Despite contradictory behavior of experimented drugs, the optimization process resulted in a series of optimum parameters for model. It exhibits the compatibility of the PK-PD model with experimentations data. Thus, the mentioned PK-PD model may be used to predict the tumor growth in the presence of different dosage of drugs. Besides, the model may be used to predict the tumor growth invoking combinational vaccinations.

V. Acknowledgment

The experimentation data used in this paper have been provided by the Immunology Department of Tehran University of Medical Sciences. Many Thanks to Dr Jamshid Hajati and Mr Pourgholami.

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