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Analysis of cancerous tumor growth by the competitive model based on the evolutionary game theory

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Abstract

The behavior and growth of cancerous tumor is an interesting research subject and it has been widely analyzed from theoretical and empirical aspects. Various models have been applied to determine the growth pattern of cancerous tumor . In one of the current models, which we refer to as the competitive model, the tumor growth rate is determined based on the competition between the healthy and cancer cells. In this model, the competition matrix between the healthy and cancer cells is a type of prisoner's dilemma game matrix, so the growth curve of tumor has a sigmoid or S shape. According to the effective application of this model in determining the tumor growth rate, some methods to get rid of the model restrictions are presented so that it can be used for tumor progression pattern. Finally, in order to evaluate the efficiency of the developed model, it has been implemented in some empirical examples.

Keywords: Cancerous tumor, Curve fitting, Evolutionary game theory, Fitness, Growth rate, Prisoner's dilemma game
2020 MSC: 91A80, 92C37, 91A22

1 Introduction

Cancer is a complex disease which begins with the abnormal cell proliferation of the body's cells. The abnormal growth of these cells will lead to the formation of big masses called tumor. The behavior and the growth of these tumors have been widely explored and analyzed from the biological and empirical points of view. Understanding the patterns of tumor growth is one of the important fields of study about the cancerous tumor . Different mathematical models have been introduced to explore these patterns. One of the simplest growth rules is the exponential growth model which indicates that the number of tumor cells doubles by a constant rate, meaning that the growth rate will always be constant, and thus its plot will be like a straight line in the semi-log plot [6, 11]. The exponential growth model was challenged by Gompertz in 1825, who stated that the doubling time of the tumor volume is not constant and the growth rate will decrease as the tumor volume increases. The Gompertz's growth curve is like sigmoid or S shape. The other model is the logistic growth which states that the growth rate reduces and finally reaches zero, when the population tends to the maximum carrying capacity [4]. Both models are sigmoid but Gompertz model indicates an exponentially decreasing growth rate, while in the logistic model, the growth rate decreases linearly proportional to the size of tumor.

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Karl Ludwig Von Bertalanffy, an Austrian biologist, has developed a model for the description of tumor growth [2]. At first, this model was suggested for the organism growth, which was then used for the exploration of the tumor growth. This model indicates that the tumor birth rate (cell) is proportional to its surface, while the death rate is proportional to the tumor's mass volume. The other tumor regression models can be found in references [1, 8].

Despite the introduction of different and relatively successful models for the tumor regression, these models are not sufficient to deal with the perturbed tumors (under treatment). Therefore, it is necessary to provide the biological interpretations of tumor growth mechanism with new approaches, so that it can be used in perturbed tumors regression. One of the models which has been recently introduced in this regard, and it will be referred to as the competitive model is designed based on the competition between the healthy and cancer cells [14, 13]. In this paper, we intend to expand and develop the usage of the competitive model by providing some methods.

In the competitive model, the healthy and cancer cells compete with each other in order to obtain the nutrients and duplicate their own type. As the duplication control tools are damaged or demolished in the cancer cells, in the competition between the healthy and cancer cells, the latter cells have growth advantage and consequently more fitness. Through this, the number of cancer cells increases in the first stage, but as the number of cancer cells increases, they also have to compete with one another over time. These changes in the competition reduce the fitness of cancer cells, and consequently, decreases the tumor growth.

Such a competition leads us to the famous prisoner's dilemma game. The theoretical foundations of this model as a competitive model have been examined in details in the references mentioned above. It is worth noting that the tumor growth decrement and the saturation reached after a period of fast growth are considered as the basic assumptions in the Gompertz model as well. West and colleagues introduced the following game matrix for the healthy and cancer cells competition

$$B = \begin{bmatrix} 3 & 0 \\ 5 & 1 \end{bmatrix}. \tag{1.1}$$

Using this matrix, they computed the payoff of each cell from the interaction with the cell population.

In the competitive model, the fitness of each cell is achieved by applying the intensity of selection, and then the growth of cancer cells is simulated using the Moran process. It should be noted that a matrix with constants elements cannot be used for all tumors. Tumor regression by the competitive model requires a specific prisoner's dilemma matrix for each tumor. In other words, the game matrix cannot be formed independent of tumors. In this paper, we will consider the prisoner's dilemma game matrix elements as parametric, and determine their values according to the data obtained in the clinical observations. An advantage of this technique is to eliminate the ambiguity from the appropriate value of the intensity of selection in tumor regression.

In addition, the time variable in tumor regression is noted under the competitive model. Normally, tumor regression in other models is performed in terms of time (day, week, etc.). But in the model introduced by West and colleagues, tumor regression is done based on the cell division. A tumor with the volume of $10mm^3$ to $10cm^3$ has 10^7 to 10^{10} cells (each $1mm^3$ of tumor is considered equivalent to 10^6 cell number). In order to simulate the regression of this tumor using the Moran birth-death process in the competitive model, 10^9 to 10^{12} cell division is needed, which requires a lot of calculations. Therefore, we are interested in providing the regression of the tumor in terms of time (day, week, etc) by applying the appropriate changes. This reduces the desired calculation significantly. In fact, our changes will reduce the number of iterations to the number of days or weeks used in the tumor regression examination, which is a major benefit.

2 Motivation and significance

Some of the used drugs in chemotherapy are cell-cycle non-specific drugs. The loss rate of cancer cells by the mentioned drugs has a relationship with the size of tumors, and this means that a constant ratio of tumor cells will be destructed in each use of these drugs. But some other drugs in chemotherapy are specific for cell-cycle. These drugs will affect the cells in a specific stage of their proliferation, thus it is expected that there is a relationship between the loss rate of tumor cells and the growth rate of tumors (and not their size). One of these drugs is Fluorouracil, for example, which is effective in the phase S of the cell-cycle [5].

Based on the clinical observations and mathematical modeling, Norton and Simon have presented their hypothesis, indicating that the reduction of the cancer cells is proportional to the growth rate of tumors, and thus when the growth rate of tumors is higher, the depletion of cancer cells will be faster in response to the treatment period [9, 10]. The loss function of Norton-Simon hypothesis in the following equation is an example of the specific model for the

cell-cycle.

$$\dot{n} = f(n_t)(1 - L_t), \tag{2.1}$$

where n_t is the model growth rate of tumor at time t, $f(n_t)$ is the growth dynamics associated with the unperturbed tumor, and L_t is the loss function of cells resulting from the treatment. The reduction of the cancer cells which is proportional to the tumor growth rate, indicates the importance of instantaneous growth rate of tumors (in both unperturbed and perturbed tumors).

The competitive model can determine the tumor instantaneous growth rate with a rational interpretation from the interaction of the cancerous and healthy cells, that is, not only in the unperturbed tumors, but also in the tumors which are under treatment. Some application of competitive model in adaptive therapy can be found in [14, 15, 16, 17].

The effective usage of the competitive model provides an incentive for its development which includes two topics: Determination of the matrix elements in the prisoner's dilemma in accordance with the tumor's behavior, and the decrease in computations for tumor regression.

3 The competitive model development for tumor progression pattern

In the competitive model, the growth rate of tumor will be determined based on the competition result of the healthy and cancer cells. The healthy cells of a tissue or organism cooperate with the other cells, while the cancer cells defect the cooperation process with other cells, and each cell will receive an utility for its selected strategy. Assume that the following matrix is the game matrix of the healthy and cancer cells

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}. \tag{3.1}$$

A cancer cell will receive a utility c against a healthy cells, which is higher than the utility of the competition of a healthy cell with the other healthy cells, thus $c > a$. On the other hand, the healthy cells cooperate with each other unlike the cancer cells, therefore their utility will be more than the cancer cells in comparison, thus $a > d$. Because the healthy cells have less utility in contrast with the cancer cells, thus $d > b$. The inequalities $c > a > d > b$ recall that the matrix A is a prisoner's dilemma game matrix.

West et al. introduced the amounts of $a = 3, b = 0, c = 5, d = 1$, and then simulated the tumor growth process (by considering the selection probability of each cell for the proliferation equal to the fitness of that cell). In order to develop the competitive model, two limitations are needed to be fixed. The first limitation is that the payoff matrix of each tumor is a function of that tumor's characteristics and the default values cannot be used.

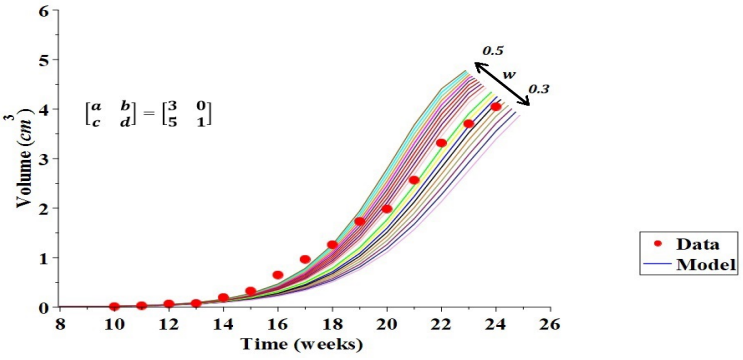
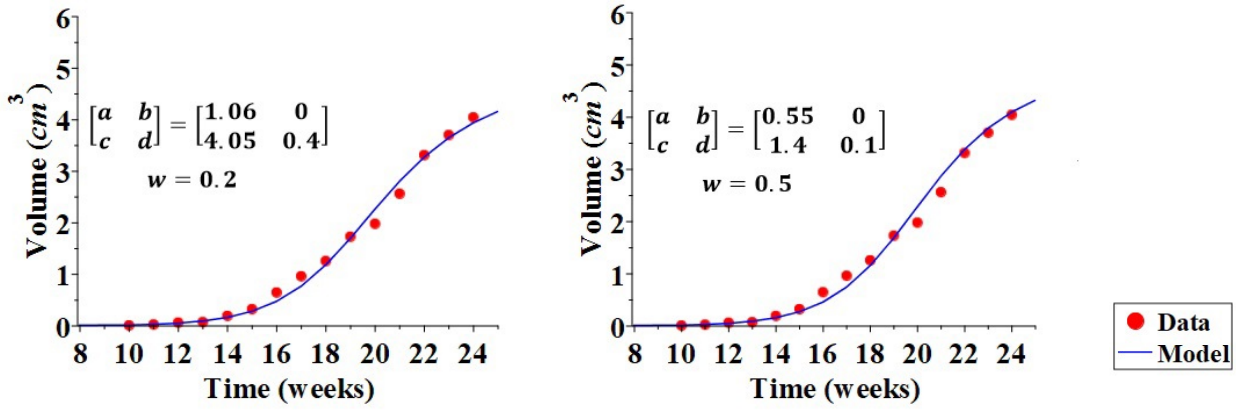


Figure 1: A tumor data and its simulation in the competetive model with respect to the constant elements of prisoner's dilemma matrix and different values of selection intensities.

To explain further, the real data of mammary tumor extracted from reference [3] were used. In Fig. 1, we have illustrated the expected growth curve of cancer cells by using the constant elements and different selection intensities in the competitive model. The used selection intensities in Fig. 1 have different values ranging between 0.3 and 0.5 with a distance of 0.01. Fig. 1 clearly shows that the competitive model cannot simulate correctly the cancer cells' growth by considering the mentioned constant elements and any selection intensity. In Fig. 2, the previous data and two different selection intensities of 0.2 and 0.5 have been considered, but we have changed the elements of prisoner's dilemma matrix. As it can be seen in Fig. 2, the growth rate of cancer cells has been approximated more accurately.



(a) (b)

Figure 2: The previous tumor data (given in Fig. 1) and its simulation in the competitive model with appropriate elements of prisoner's dilemma matrix and two different values of selection intensities.

Fig. 1 and 2 indicate that the matrix of prisoner's dilemma with the constant elements cannot be used for all tumors, and these elements should be selected based on the tumor behaviors. Below, we will explain a method to find the elements of prisoner's dilemma matrix. The other limitation is that the simulation of tumor growth with the volume of $10mm^3$ to $10cm^3$ cells will require 10^9 to 10^{12} iterations in Moran's process (we have approximately considered $1mm^3$ of cells equal to 10^6 cells and the required cell divisions for simulation is about $25 \times N$, where N is the number of cells exposed to cancer); therefore, a technique must be put forth in which the calculations are reduced sufficiently. To fix these limitations, we will use the cell masses (typically 10^6 or $1mm^3$ or 1 milligram cells) interaction, instead of considering the cells interaction. Suppose that the matrix A in (3.1) is the competition matrix of the healthy and cancer masses (with a volume of constant v) per unit of time (day, week, etc.). We consider the matrix elements as parametric and let their values be determined according to the tumor characteristics that were observed in the clinical trials. Therefore, if V is the population volume of N cells (i.e. tumor carrying capacity) and v_t is the volume of tumor at time t, then the fitness of healthy and cancer cell mass with constant volume v at time t are determined by the following formulas

$$f_t = 1 - w + wF_t \tag{3.2}$$
$$g_t = 1 - w + wG_t, \tag{3.3}$$

where,

$$F_t = \frac{a(V - v_t - 1) + b(v_t)}{V - 1} \tag{3.4}$$
$$G_t = \frac{c(V - v_t) + d(v_t - 1)}{V - 1}, \tag{3.5}$$

and w is the intensity of selection which is a number in the interval $[0, 1]$, and it shows the effect of competition in the evolution process. Usually, w is considered as a small number, so that some properties such as the one-third law will be held. Our empirical computations show that the numbers between 0.05 and 0.5 for the selection intensity will lead to better results in order to calculate the growth rate and simulate the growth process in the competitive model. Considering the main idea of evolutionary game theory that considers the growth rate of species proportional to their fitness, the expected tumor volume in the next time is obtained by the following formula

$$v_{t+1} = \frac{V \cdot g_t \cdot v_t}{g_t \cdot v_t + (V - v_t) \cdot f_t}. \tag{3.6}$$

Note that v_{t+1} is obtained according to the parameters a, b, c, d. Similarly, tumor volume can be obtained at the later times.
It is interesting to see that

$$\Delta v_t\big|_{t \to 0} \approx k v_t, \tag{3.7}$$

where $k = \dfrac{w(V(c-a)+(a-d))}{(V-1)(1-w+wa)}$. Based on the relationship between the matrix elements of the prisoner's dilemma problem, if $a > \dfrac{1-w}{w}$, then $k > 0$, which results an exponential growth of tumor in the initial stages of cancer cell growth process. In the following parts, we will let $b = 0$ and the condition $k > 0$ be provided.

To obtain the value of parameters a, b, c, and d, we use the clinical observations and solve a problem in order to implement the curve fitting process. Suppose that $(t_1, u_1), (t_2, u_2), \ldots, (t_k, u_k)$ are the clinical observations of tumor, where, u_j is the tumor volume observed at time t_j $(j = 1, \ldots, k)$. Each time starting from (t_j, u_j), we obtain $v_{t_{(j+1)}}$ parametrically for $j = 1, \cdots, k-1$. Then, under the curve fitting process, we compute the parameters a, b, c, and d by solving the following problem

$$\min \sum_j (v_{t_j} - u_j)^2 \quad s.t \quad c > a > d > b. \tag{3.8}$$

If the number of clinical observations is sufficient, there is no need to constraints $c > a > d > b$ and the optimal solution of the unconstrained minimization problem will be satisfied these constrains.

As the variables of the non-linear programming problem (3.8) are limited only to 4 variables a, b, c and d, it can be solved by the standard mathematical softwares (especially because of the existence of appropriate initial solution such as $a = 3, b = 0, c = 5$, and $d = 1$ as well).

Remark 3.1. The values of parameters a, b, c, and d are not unique and depend on the selected value for the intensity of selection. Therefore, we do not worry about the value of intensity of selection, because the parameters a, b, c, and d are obtained proportional to the intensity of the selection.

Remark 3.2. Since the distance between the matrix elements plays an essential role in the prisoner's dilemma matrix, we can let $b = 0$ in order to reduce the size of the problem of the curve fitting.

Remark 3.3. Once the values of the prisoner's dilemma matrix are determined, the tumor regression could be obtained in the pre-clinical phase if it is taken to consideration; If t_0 is the time before the clinical observations, its related value v_{t_0} which is in the interval $[0, v_{t_1}]$ can be found, simply, with the bisection search such that the tumor volume at the time t_1 is equal to the volume observed at that time in the competitive model.

4 Experimental examination of the developed competitive model

In this section, we implement the developed competitive model presented in the previous section on the tumors data of 10 types of male mice with the lung cancer extracted from [1, 12]. Some experiments were conducted on ten mice, therefore, the data of each type of mouse is the average of the data belonging to the same type of mouse. The tumors data are measured in a period of 4 to 22 days on the mice with 6 to 8 weeks age. These data set display the volume range of 3 to $1449mm^3$ (we consider 10^6 cells as $1mm^3$ cells).

In the study mentioned above, the tumors volume was not measured in day 0, and thus we measured v_0 as described in Remark 3.3. As it was mentioned in Remark 3.1, there is no concern in choosing the value of intensity of selection w, because the matrix elements of the prisoner's dilemma will be obtained proportional to the parameter w, but the tumor carrying capacity V should be a reasonable amount compared to the clinical observations. In order to obtain the elements of prisoner's dilemma matrix, we used $w = 0.5$ and $V = 2500mm^3$, and then we drew the tumor growth regression using the developed competitive model. The value of parameters has been given in Table 1 (In some cases, the solution of the problem (3.8) is four-digit or five-digit numbers, so we limited the range of parameter a, without making a significant change in the optimal value of the problem. That is why the value of 1 is repeated several times for parameter a).

The results of the tumor regression has been illustrated in Fig. 3. The circle dots and the continuous curves display the clinical observations and tumor regression respectively. Note that the obtained regression is pointwise and we have drawn it as a continuous curve in order to distinguish it visually.

Fig. 3 shows that our model is successful in explaining lung tumor growth and it is fairly adjusted with the tumor growth data except in one case. As it can be seen in Fig. 3-f, there is a abnormal distance with two observations in the regression corresponding to the mouse 6. The reason of this difference may be due to the stochastic growth process of cancer cells (which, does not necessarily follow the expected growth pattern) or a measurement error.

In order to show the capability of the competitive model to interpret and simulate the growth process of cancerous tumor , we have used the coefficient of determination (R^2) index to measure the accuracy of the model. We have calculated this index for each regression, and we have given the obtained values in the last row of Table 1.

Mouse No.	1	2	3	4	5	6	7	8	9	10
a	1	0.5	1	1.2	1	3.2	1	1	1	6
b	0	0	0	0	0	0	0	0	0	0
c	1.72	1.06	1.6	1.8	1.65	5	1.8	1.65	1.58	8.3
d	0.24	0.1	0.87	0.7	0.5	0.5	0.5	0.5	0.8	0.4
v_0	10	10	15	9	10	6	10	10	10	7
R^2	0.994	0.993	0.987	0.992	0.987	0.855	0.977	0.993	0.996	0.995

Table 1: The obtained values for the elements of prisoner's dilemma matrix, the initial volume of tumors and the values of coefficient of determination (R^2) for each regression

Model	Exponential-linear	Gompertz	Generalized logistic	Power law	Exponential V_0	Von Bertalanffy	Dynamic CC	Logistic	Exponential 1	Competitive model
R^2	0.96	0.97	0.98	0.96	0.93	0.97	0.97	0.96	0.64	0.98

Table 2: The mean value (among all mice) of coefficient of determination (R^2) for different growth models.

In [1], for the same dataset, the mean value (for all mice) of R^2 index has been calculated in different models, which have been presented in Table 2 along with the related value in the competitive model. As it can be seen, the competitive model and the generalized logistic model have the best performance in simulating the cancerous tumor growth.

These results indicate the good structure flexibility, which have provided the adaptation of competitive model with the real data.

5 Conclusion

The competitive model is a model in which the growth rate of the cancerous tumor is determined by the outcome of the competition of cancer and healthy cells. In this paper, some methods have been presented to fix the limitations of the model in order to develop its usage. The model examination on the experimental data shows the model's success in tumor regression. The application of this model in prediction of chemotherapy treatment and dose schedule optimization are the subjects of future studies.

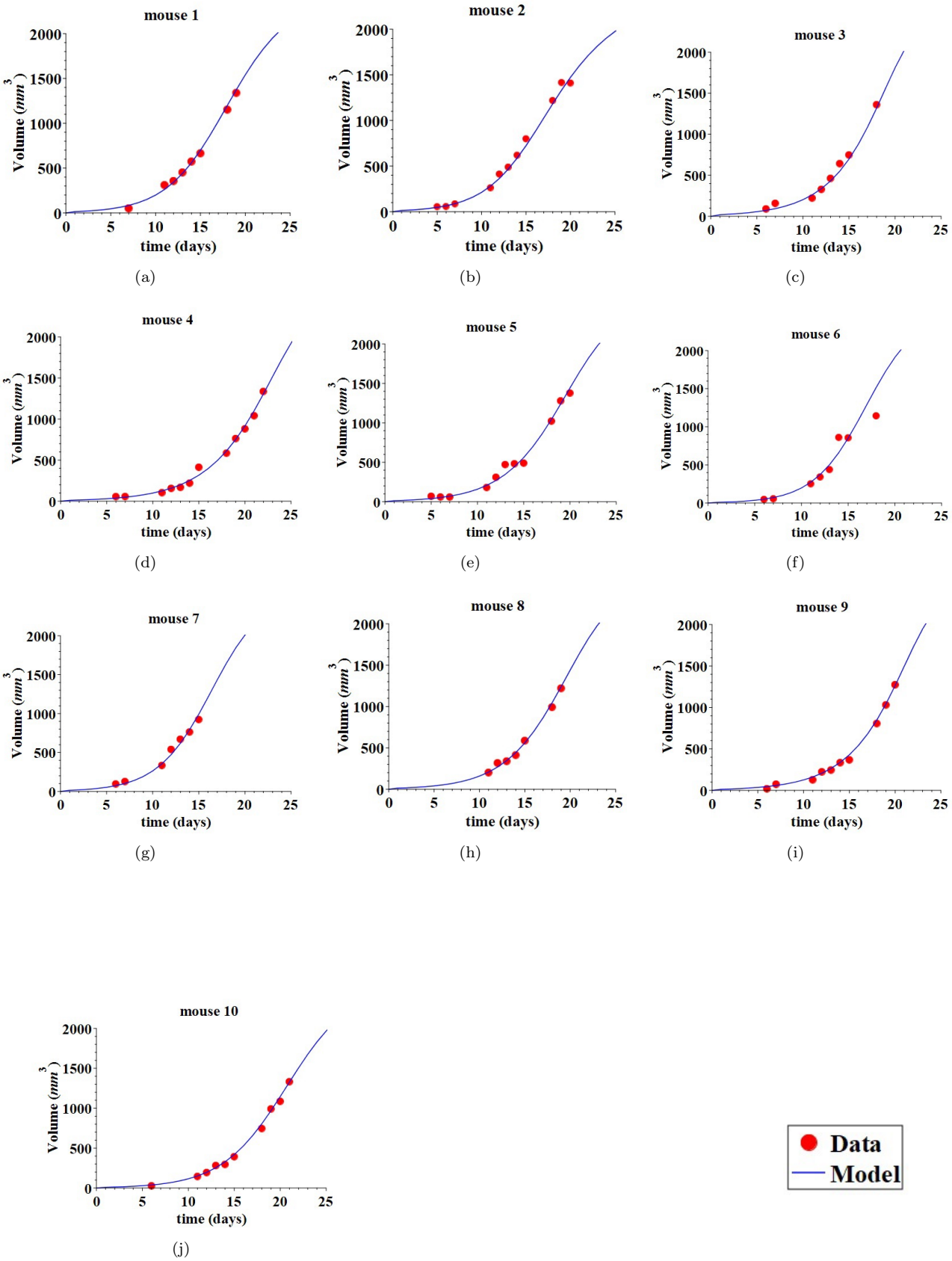


Figure 3: Tumors data and their regressions

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