Prediction of tumor parameters based on regression models for rats for combined treatment with hyperthermia and chemotherapy

Evgeny Kostyuchenko[1], Elena Kataeva[2], Denis Pakhmurin[3], Polina Shelupanova[4]

[1]Associate Professor & HOL, Laboratory of Collection, Analysis and Control of Biological Signals, Tomsk State University of Control Systems and Radioelectronics (TUSUR), 634050, Tomsk, Russian Federation
[2] Assistant Professor, Security Department, Tomsk State University of Control Systems and Radioelectronics (TUSUR), 634050, Tomsk, Russian Federation
3 Associate Professor, Laboratory of Collection, Analysis and Control of Biological Signals, Tomsk State University of Control Systems and Radioelectronics (TUSUR), 634050, Tomsk, Russian Federation
Siberian State Medical University, 634055 Tomsk, Russian Federation
4 Associate Professor, Laboratory of Collection, Analysis and Control of Biological Signals, Tomsk State University of Control Systems and Radioelectronics (TUSUR), 634050, Tomsk, Russian Federation
Emal: [1]key@fb.tusur.ru, [2]kes@fb.tusur.ru,
3pdo@ie.tusur.ru, 4pi6i-mne@yandex.ru

Abstract- The paper considers the possibility of predicting tumor parameters (weight, volume) depending on the method of treatment and doses of drugs used. A comparison is made of the applicability of several regression models, taking into account the limited amount of data. Brown's adaptive model, paired regression, multiple regression are compared. Previously, all constructed regression models were tested for adequacy by assessing the significance of the coefficient of determination according to Fisher's criterion, and only the models that were recognized as adequate were used for further predictions. The advantage of Brown's model on the considered limited data set is shown experimentally and recommendations are given on the choice of the method parameters.

Keywords: tumor size, prediction, regression models, Brown's model

1. INTRODUCTION

The problem of studying various methods of treating tumors is urgent. Despite the large variety of approaches to treatment, such as chemotherapy [1-6], hyperthermia [7-9], radiation therapy [10-12], immune therapy [13-14] and other, universal treatment methods that do not depend on the type the tumor, the patient's condition and other factors do not exist. When

forming a treatment, there is a need to take into account the parameters of a particular patient, and on their basis to form one or another combination of treatment methods. One of the methods of treatment that reduces the negative effect on the body is hyperthermia. The basic principle of this approach is based on the fact that tumor cells are much more susceptible to the temperature rise factor than healthy cells [15, 16]. For this reason, the application of a local increase in temperature in the area of the tumor can lead to a positive effect in the treatment of tumors. This work examines the use of local hyperthermia using the Phoenix-2 complex [17, 18]. The experimental data were obtained on the basis of its application.
However, the question arises: how the tumor (its parameters) will behave when treatment is stopped or when combined treatment with different parameters is used. This work is devoted to the possibilities of using regression mechanisms for constructing such predictions based on biological models (rats).

2. LITERATURE REVIEW

The conducted literature review revealed the following methods for predicting tumor development. The work [19] shows the possibility of using statistical methods to predict survival in the treatment of breast cancer. In [20], correlation exponential models are used to assess the survival rate and the problematicness of using such methods for constructing a prediction is shown. Within the framework of work [21], a study is carried out of the applicability of differential models for choosing the time between injections of the drug that provides the greatest effect within the framework of the prediction. The model is based on biological objects (mice). However, despite the similar nature of the study, it uses values for a longer period (49 days, of which 12 days of treatment) as input, due to the difference between biological models and types of tumors.

In addition, based on the analysis of the issuance of a query within the SCOPUS indexing system, a total of more than 40 works were identified on the query "predicting AND dynamics AND tumor AND size", most of which were based on the use of the simplest statistical mechanisms to predict various tumor parameters and survival. The data in [22-21] confirm the applicability of basic statistical methods in making predictions, depending on the problem being solved.

The analysis shows that there are no general recommendations on the applicability of various statistical models. In the context of limited amounts of input data, the same models can be effective when constructing a prediction, and vice versa. This confirms the possibility of studying certain general statistical methods (in particular, based on regression mechanisms), along with the use of machine learning methods, to solve certain particular problems of predicting the dynamics of tumor development, as well as the occurrence of relapses. This fact confirms the relevance of the study.

Problem Statement

This work addresses the problem of predicting tumor (carcinoma) parameters in biological models (rats) using combined treatment based on hyperthermia and chemotherapy after

cessation of speech. The main problem of this study is the limited set of input data. When observing 37 rats during the experiment, the geometric parameters of the tumor size were taken, on the basis of which its volume was calculated, in addition, according to the results of the experiment, the tumor mass was directly measured. At the same time, in the course of the experiment, observation was initially carried out for 9 days, within which the input parameters of the model were measured. After that, an attempt was made to predict the behavior of the tumor after the end of treatment, within which an additional 12 values were measured. The individuals were grouped according to the method of treatment used in 4 groups, in which hyperthermia was used for treatment in combination with various doses of cyclophosphamide (0, 5, 8 and 10 mg / kg). The main problem being solved is the prediction of the measured parameters of the tumor after the termination of treatment based on similar parameters during the treatment process and before it starts.

Solutions: in this paper, taking into account the small number of values in the time series used in the construction of the model, it is proposed to compare several regression methods (Brown's model, pairwise regression and multiple regression [32]), as well as to give recommendations on the choice of their parameters and assess the quality obtained prediction values.

Proposed work

The article considers the time series compiled as a result of daily measurements of tumor volume in 37 rats for 21 days. As a result of the experiment, the rows can be divided into 4 groups:

1) 10 rows obtained from the observation of rats that were treated based on hyperthermia and were given cyclophosphamide at a dosage of 10 mg / kg;

2) 10 rows obtained from observation of rats treated with hyperthermia and given cyclophosphamide at a dosage of 8 mg / kg;

3) 10 rows obtained from observation of rats treated with hyperthermia and given cyclophosphamide at a dosage of 5 mg / kg;

4) 7 rows obtained from the observation of rats treated with hyperthermia and given cyclophosphamide at a dosage of 0 mg / kg (no chemotherapy).

For each level of any time series from the specified set, we introduce the notation:

$$y_t^{(s)},\ s=\overline{1,\ 37},\ t=\overline{1,\ n}$$

where s is the row number,

t is the moment in time corresponding to the value of the series,

n is the number of counts in a row (generally n = 21).

Each row consists of a training part (the first 9 values) and a test part (the remaining 12 values). The training part is used to build a model, the test part is used to check the prediction quality using the resulting model.

The training part of the considered time series is not large, therefore, to construct the prediction, we used Brown's adaptive model, which is often used to extrapolate short time series. She presents the development process as a linear trend of the form

$$f(t)=a_k+b_k t \qquad (1)$$

where a_k, b_k are constantly changing parameters that adjust the model to the dynamics of the

series on a small interval near the moment in time and contain information about the behavior of the series at the moment. Prediction is performed according to the formula:

$$f(k+\tau) = a_k + b_k\tau \qquad (2)$$

Where τ is the prediction step,

k is the number of series values used to build the model (that is, determine the parameters a_k, b_k).

Let's briefly describe the process of building a model. First, you need to estimate the initial values of the parameters a_0 and b_0 model (1) using the first five values of the time series using the least squares method. Next, consider some k -th iteration:

1) using the previously obtained parameters a_{k-1} and b_{k-1} build a one-step prediction (that is $\tau = 1$) according to the formula (2):
$$f(k-1+\tau) = f(k) = a_{k-1} + b_{k-1}\tau = a_{k-1} + b_{k-1};$$
2) compare the prediction $f(k)$ with the value of the series y_k and calculate the deviation value e_k :
$$e_k = y_k - f(k);$$
3) calculate the new values of the model parameters a_k and b_k using the formulas:
$$a_k = a_{k-1} + b_{k-1} + (1-\beta^2)e_k,$$
$$b_k = b_{k-1} + \alpha^2 e_k,$$

where β is the data discounting factor, reflecting the degree of confidence in later observations;

$\alpha = 1-\beta$ - smoothing factor.

The optimal value β is usually found iteratively: Brown's model is built for different β and its value is chosen at which the model prediction error is minimal.

4) if $k < n$, go to step 1; if $k = n$, then the constructed model is ready for further prediction by the formula (2), where $k = n$.

where β is the data discounting factor, reflecting the degree of confidence in later observations.

Also, for each investigated time series, the following external factors are known: the body weight of the rat, the dose of the administered drug, time (this factor was introduced additionally). The factors are time series of the same length as a series of measurements of tumor volume. In this regard, the following regression models were built for prediction:

- pair regression

$$f(x_i) = a + bx_i,$$

where is the moment of time or the dosage of the drug, $i = \overline{1,n}$.

The body weight was not taken into account, since the tumor is in the body of the rat, accordingly, it is part of the weight of the rat, and it is incorrect to use only the statistical relationship between these parameters to predict the tumor volume.

- multiple regression

$$f\left(x_i^{(1)},...,x_i^{(m)}\right)=a_0+a_1x_i^{(1)}+...+a_mx_i^{(m)},$$

where $x_i^{(p)}$ are the values of body weight, drug dose or time point, $i=\overline{1,n}$, $p=\overline{1,m}$, $m=2,3$ (that is, the factors are combined in the model in pairs or all three are included).

The coefficients of the regression models are determined using the least squares method.

Each specified model was built for the same row twice:

only for the teaching part of the series (that is $n=9$);

on the training part with the addition of the first nine test observations (that is $n=18$) - this is necessary to determine the behavior of the model with an increase in the amount of information.

Then, using each constructed model for all series, three predicted values $\hat{y}_{n+\tau}^{(s)}$ were calculated as follows:

1) according to Brown's model, the prediction is equal to $\hat{y}_{n+\tau}=f(n+\tau)$ for $\tau=1,2,3$, where $f(n+\tau)$ is calculated by formula (2);

2) according to the paired regression model, the prediction is built according to the formula:

$\hat{y}_{n+\tau}=f(x_{n+\tau})=a+bx_{n+\tau}$,

Where n takes the above values, the prediction step $\tau=1,2,3$;

3) according to the multiple regression model, the prediction is built according to the formula:

$$f\left(x_{n+\tau}^{(1)},...,x_{n+\tau}^{(m)}\right)=a_0+a_1x_{n+\tau}^{(1)}+...+a_mx_{n+\tau}^{(m)}$$

where n takes the previously indicated values, the prediction step $\tau=1,2,3$, and the number of factors m is determined for each model.

Previously, all constructed regression models were tested for adequacy by assessing the significance of the coefficient of determination R^2 according to Fisher's criterion, and only the models that were recognized as adequate were used for further prediction.

3. RESULTS

The difference between the known value of the time series $y_{n+\tau}$ and the value $\hat{y}_{n+\tau}$ that was calculated using one of the selected models was used for assess the prediction accuracy:

$e_{n+\tau}=y_{n+\tau}-\hat{y}_{n+\tau}$.

This value was calculated for each predicted value $\hat{y}_{n+\tau}$, and with its help you can enter the relative error δ, calculated by the formula:

$$\delta=\frac{\sum_{j=1}^{\tau}\left|e_{n+j}\right|}{\tau\cdot\bar{y}}\cdot100\% \qquad (3)$$

where $\bar{y} = \frac{1}{n}\sum_{t=1}^{n} y_i$ – the average value of the levels of the series on which this model was built.

This error is measured as a percentage of the average value of the series and allows you to estimate the average behavior of the predicted value.

Tables 1-4 below show the results of assessing the prediction quality using all constructed models for $\tau = 1$ and $\tau = 3$ for each group of series separately. The tables show the values of the relative error δ for each model and each series of the group at the specified values of the prediction step (for Brown's model, the minimum error values are given). The first column indicates the factors used in the model (for regression models) and the length of the series used to build the model.

Brief designations of factors:

"Time" is a moment in time $t = \overline{1, n}$;

"Dose" - the dose of the administered drug to rats in the study group;

"Weight" is the body weight of the rat whose tumor volume is being investigated.

The second column of the table shows the size of the prediction step τ. Further, each column corresponds to a time series from the group.

Lines for Brown's model have been added. They indicate the parameter β value at which the corresponding minimum values of the relative error δ were obtained.

Table 1. Results for patients without medication

Model characteristics	Prediction step		1	2	3	4	5	6	7
Pairwise regression									
time, $n = 9$	$\tau = 1$		25.02	–	51.03	27.1	63.2	54.8	47.4
	$\tau = 3$		58.8	–	59.4	25.4	48	64.6	71.4
time, $n = 18$	$\tau = 1$		–	48.7	27.03	–	**1.6**	–	93.6
	$\tau = 3$		–	53.4	28.5	–	**0.9**	–	126.3
Multiple regression (2 factors)									
time, weight, $n = 9$	$\tau = 1$		–	–	50.4	25.7	62.6	52.5	–
	$\tau = 3$		–	–	59.3	24.3	48.2	62.7	–
time, weight, $n = 18$	$\tau = 1$		62.8	9.97	34.8	–	**1.9**	–	–
	$\tau = 3$		31.7	16.3	49.7	–	**1.4**	–	–
Brown's model									
$n = 9$	$\tau = 1$	$\delta, \%$	**3.7**	**1.6**	32.97	**5.38**	63.3	**1.1**	**0.2**
		β	0.1	0.4	0.4	0.1	0.6	0.1	0.2
	$\tau = 3$	$\delta, \%$	16.99	37.7	36.4	21.8	48.6	**9.9**	14.8
		β	0.8	0.8	0.4	0.9	0.6	0.2	0.2
$n = 18$	$\tau = 1$	$\delta, \%$	**0.04**	**6.3**	13.7	**1.74**	**0.7**	**1.3**	**8.6**
		β	0.4	0.1	0.8	0.7	0.7	0.1	0.6
	$\tau = 3$	$\delta, \%$	**7.5**	10.3	**0.8**	**7.99**	**6.6**	**8.7**	57.5

		β	0.8	0.6	0.7	0.8	0.8	0.5	0.3

As can be seen from the table, Brown's method is expected to show the best prediction quality. For example, when predicting series no. 7, despite the linearity of its dynamics, the prediction errors by regression with one factor “time” are an order of magnitude larger than the errors for Brown's model. This is due to the fact that in the test part there is a change in the trend of the series in comparison with the training part (Figure 1).

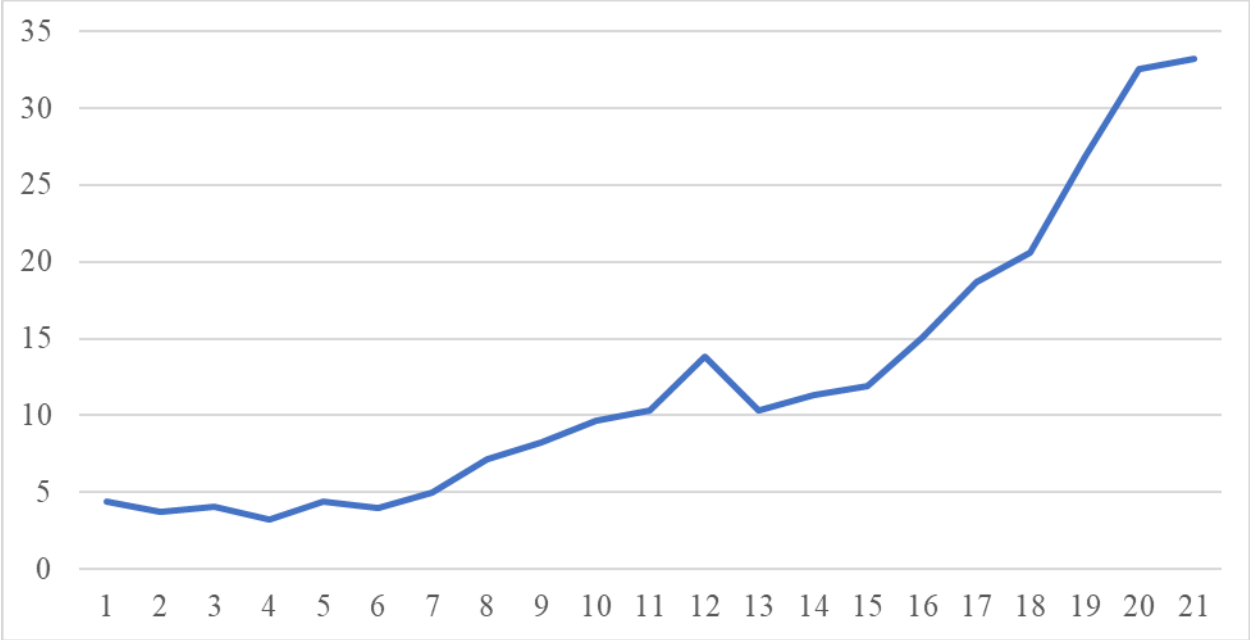


Figure 1. Graph of changes in the tumor volume of rat №7 (from the control group).

One of the drawbacks of Brown's model is the strong dependence of the prediction quality on the behavior of the series under study. In particular, the prediction by this model for 1 step for series No. 3 gives a worse result than for the other series. This is due to the fact that the direction of dynamics changes abruptly at the last value (Fig. 1) and the model does not have time to adjust. Such moments are observed in other groups as well.

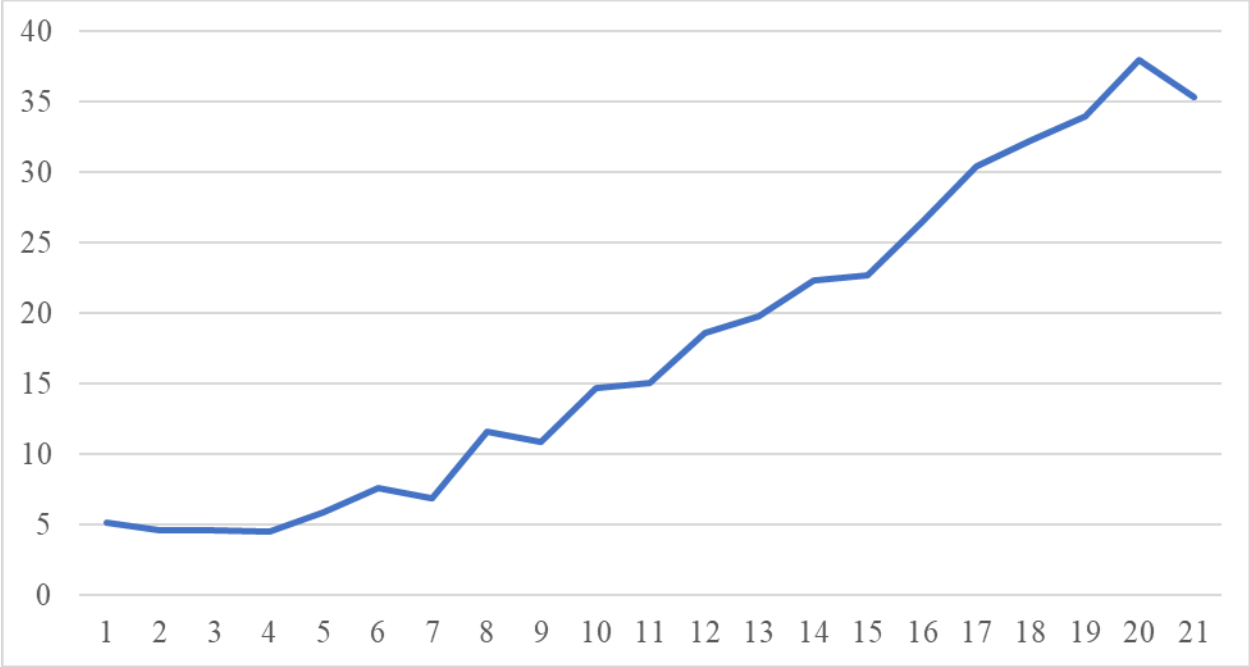


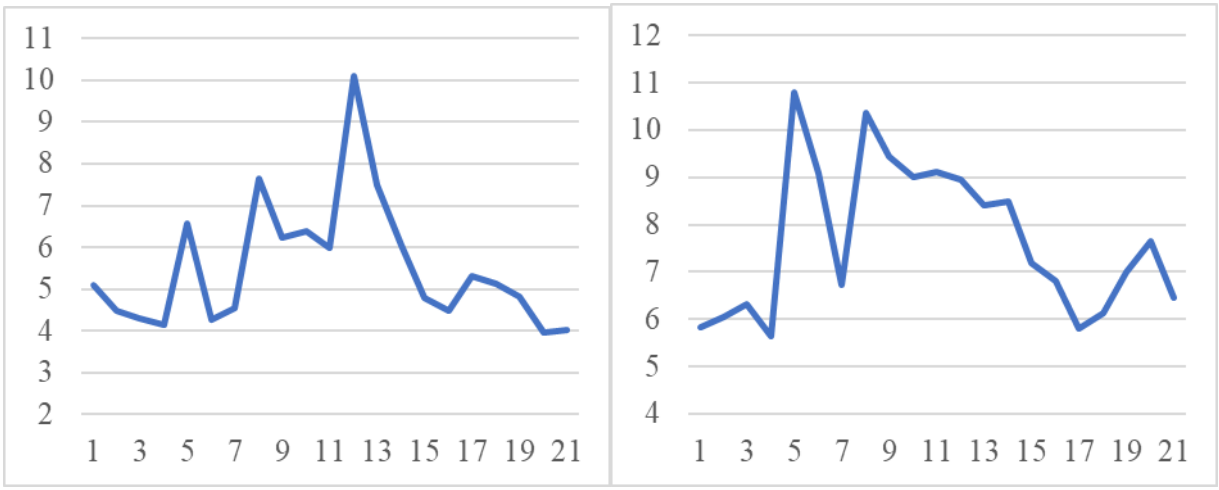
Figure 2. Graph of changes in the tumor volume of rat №3 (from the control group).

Table 2. Prediction errors for patients with dosage 5 mg/kg.

Model characteristics	Prediction step	1	2	3	4	5	6	7	8	9	10
Pairwise regression											
time, $n=9$	$\tau=1$	15	21.7	**4.3**	24.3	21.5	–	18.3	48.4	18.4	**9.2**
	$\tau=3$	11.3	17.9	12.0	11.2	35.1	–	12.3	37.8	24.9	14.3
time, $n=18$	$\tau=1$	23.2	–	–	–	–	–	91.8	106.5	–	20.7
	$\tau=3$	47.4	–	–	–	–	–	93.5	129.6	–	33.0
dose, $n=9$	$\tau=1$	–	–	–	–	–	–	13.3	–	–	–
	$\tau=3$	–	–	–	–	–	–	65.5	–	–	–
dose, $n=18$	$\tau=1$	–	35.3	–	87.6	–	**9.0**	–	–	**4.6**	–
	$\tau=3$	–	25.2	–	64.8	–	18.5	–	–	**6.7**	–
Multiple regression (2 factors)											
time, weight, $n=9$	$\tau=1$	17.5	–	**4.9**	24.4	–	–	–	–	–	10.5
	$\tau=3$	12.8	–	12.3	29.3	–	–	–	–	–	13.9
time, weight, $n=18$	$\tau=1$	21.8	–	–	59.3	17.5	–	–	106.0	–	18.1
	$\tau=3$	47.1	–	–	39.1	25.0	–	–	128.8	–	29.0
time, dose, $n=9$	$\tau=1$	–	–	–	–	–	–	–	–	–	–
	$\tau=3$	–	–	–	–	–	–	–	–	–	–
time, dose, $n=18$	$\tau=1$	16.4		–	–	27.7	–	–	111.3	–	–
	$\tau=3$	40.8		–	–	38.5	–	–	134.2	–	–
weight, dose, $n=9$	$\tau=1$	–	–	–	–	–	–	–	–	–	–
	$\tau=3$	–	–	–	–	–	–	–	–	–	–
weight,	$\tau=1$	–	42.9	–	23.7	17.6	–	–	–	–	–

dose, $n=18$	$\tau=3$		–	33.5	–	20.5	26.0	–	–	–	–	–
Multiple regression (3 factors)												
time, weight, dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
time, weight, dose, $n=18$	$\tau=1$		15.6	–	–	–	–	–	–	–	–	–
	$\tau=3$		41.0	–	–	–	–	–	–	–	–	–
Brown's model												
$n=9$	$\tau=1$	$\delta,\%$	**4.2**	17.3	**3.9**	26.6	**5.2**	**3.1**	**1.3**	27.5	**3.4**	**3.3**
		β	0.1	0.5	0.8	0.6	0.8	0.9	0.3	0.1	0.1	0.7
	$\tau=3$	$\delta,\%$	**5.4**	16.1	10.8	20.0	10.6	25.6	**6.6**	30.8	**1.8**	14.3
		β	0.4	0.5	0.8	0.9	0.8	0.9	0.6	0.8	0.1	0.8
$n=18$	$\tau=1$	$\delta,\%$	**1.8**	10.7	**0.9**	**8.8**	**6.5**	**0.9**	**0.3**	**8.7**	**5.5**	**2.9**
		β	0.4	0.9	0.2	0.3	0.3	0.7	0.2	0.7	0.7	0.7
	$\tau=3$	$\delta,\%$	**8.6**	14.7	30.7	**4.7**	38.5	**5.0**	36.8	130.2	**5.0**	**9.2**
		β	0.2	0.8	0.1	0.8	0.9	0.6	0.1	0.4	0.8	0.1

In this table, the factor of the effect of cyclophosphamide on rats is added, which in general does not affect the quality of the prediction, but two series with a good prognosis can be distinguished according to the model with one factor "dose" - rows No. 6 and No. 9 (Figure 3).



a) b)

Figure 3. Graph of changes in the tumor volume of rat No. 6 (a) and rat No. 9 (b) (from the group with a dosage of 5 mg/kg).

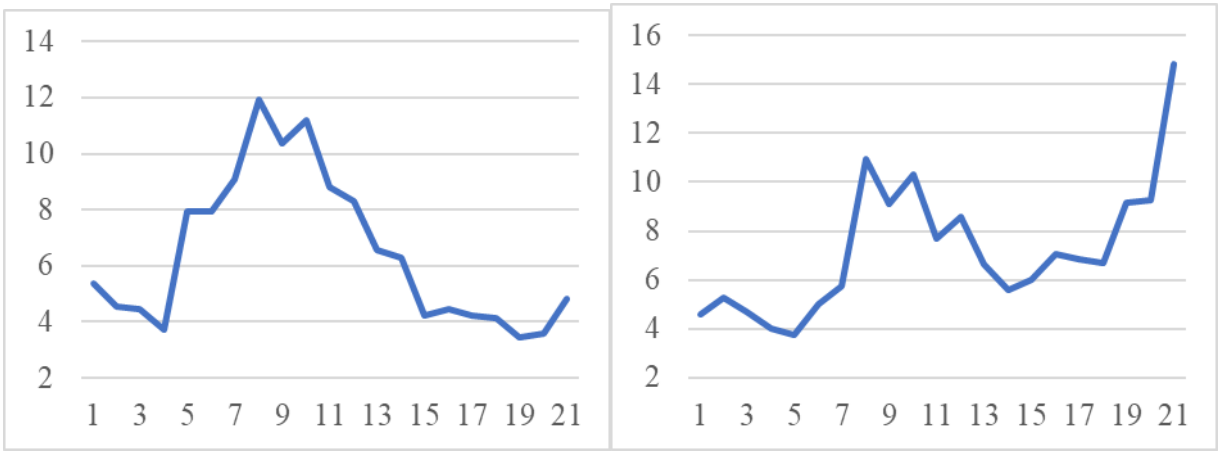
The graphs show that after receiving the next dose of the drug, the tumor volume temporarily decreases against the background of the absence of an increasing or decreasing trend. In addition to the indicated effect, this behavior of the series explains the low quality of the prediction by regression with one factor “time”.

Table 3. Results for patients with dosage 8 mg/kg

Model characteristics	Prediction step		1	2	3	4	5	6	7	8	9	10
Pairwise regression												
time, $n=9$	$\tau=1$		18.3	**1.3**	53.6	36.4	20.2	10.8	10.6	**9.4**	160.9	**6.0**
	$\tau=3$		28.5	22.3	83.3	60.9	59.4	46.8	37.6	46.2	94.4	48.6
time, $n=18$	$\tau=1$		40.6	–	–	**5.3**	–	36.4	23.5	–	–	–
	$\tau=3$		61.8	–	–	12.2	–	17.4	44.3	–	–	–
dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
dose, $n=18$	$\tau=1$		–	–	28.5	71.0	65.2	82.0	–	37.2	15.2	48.7
	$\tau=3$		–	–	51.4	95.7	45.9	89.9	–	30.0	39.2	77.9
Multiple regression (2 factors)												
time, weight, $n=9$	$\tau=1$		–	–	–	–	–	–	10.4	**8.0**	–	–
	$\tau=3$		–	–	–	–	–	–	37.4	44.4	–	–
time, weight, $n=18$	$\tau=1$		16.6	–	–	**6.2**	–	–	–	16.7	–	–
	$\tau=3$		36.5	–	–	10.9	–	–	–	52.5	–	–
time, dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
time, dose, $n=18$	$\tau=1$		–	–	–	**5.0**	–	45.3	28.0	–	–	25.8
	$\tau=3$		–	–	–	18.8	–	49.3	48.7	–	–	52.5
weight, dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
weight, dose, $n=18$	$\tau=1$		–	–	16.1	56.9	17.8	–	–	35.5	–	43.9
	$\tau=3$		–	–	37.8	74.2	49.4	–	–	31.3	–	72.8
Multiple regression (3 factors)												
time, weight, dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
time, weight, dose, $n=18$	$\tau=1$		–	–	–	**4.0**	–	–	–	–	–	–
	$\tau=3$		–	–	–	17	–	–	–	–	–	–
Brown's model												
$n=9$	$\tau=1$	$\delta,\%$	**3.6**	**5**	**6.1**	25.3	**1.4**	**4.2**	**0.4**	**8.3**	149.9	**0.2**
		β	0.9	0.8	0.9	0.5	0.7	0.5	0.9	0.1	0.1	0.6
	$\tau=3$	$\delta,\%$	10.6	24.0	**6.3**	38.7	15.8	21.8	14.9	**0.6**	79.7	18.1
		β	0.9	0.8	0.1	0.9	0.2	0.2	0.1	0.8	0.1	0.8
$n=18$	$\tau=1$	$\delta,\%$	**3.8**	**0.0**	**4.2**	**1.8**	**5.0**	**0.1**	**3.0**	18.9	**3.5**	69.3
		β	0.7	0.4	0.7	0.3	0.5	0.4	0.6	0.1	0.6	0.3
	$\tau=3$	$\delta,\%$	**9.3**	**5.6**	24.3	19.3	24.2	46.8	29.5	**8.9**	18.2	66
		β	0.5	0.3	0.9	0.9	0.9	0.9	0.9	0.3	0.1	0.4

In this group, the dosage of cyclophosphamide is increased, but at the same time the quality of

prediction deteriorates according to the model with one factor "dose". This may be due to the fact that locally after drug administration the tumor volume decreases, but on average there is an increasing trend along the entire length of the row. Perhaps this is caused by a general decrease in immunity from a higher dose of cyclophosphamide, but not sufficient for strong destruction of the tumor. Brown's model still shows good prediction results, which is explained by the absence of sharp breaks in the behavior of the series. The exceptions are rows No. 8 and No. 10 (Figure 4).



a) b)

Figure 4. Graph of changes in the tumor volume of rat No. 8 (a) and rat No. 10 (b) (from the group with dosage 8 mg/kg).

As you can see from the graphs, the last value shows a change in trend, which significantly spoils the quality of the prediction.

Table 4. Results for patients with dosage 10 mg/kg

Model characteristics	Prediction step	1	2	3	4	5	6	7	8	9	10
Pairwise regression											
time, $n=9$	$\tau=1$	32.6	41.4	45.9	25.3	13.3	55.2	54.9	96.7	6.0	35.6
	$\tau=3$	20.7	27.3	19.9	60.5	20.0	81.4	80.0	44.2	32.8	64.5
time, $n=18$	$\tau=1$	10.4	–	**0.6**	40.7	30.7	40.6	**9.2**	41.5	26.0	28.2
	$\tau=3$	28.9	–	7.6	78.0	21.6	47.3	11.7	26.2	65.1	70.2
dose, $n=9$	$\tau=1$	–	–	–	–	–	–	–	–	–	–
	$\tau=3$	–	–	–	–	–	–	–	–	–	–
dose, $n=18$	$\tau=1$	50.8	–	41.6	–	–	–	–	–	–	69.9
	$\tau=3$	72.6	–	51.9	–	–	–	–	–	–	115.5
Multiple regression (2 factors)											
time, weight, $n=9$	$\tau=1$	34.2	–	45.4	–	–	–	–	96.9	–	–
	$\tau=3$	21.5	–	20.0	–	–	–	–	44.8	–	–
time, weight, $n=18$	$\tau=1$	**5.1**	–	–	–	30.8	–	–	40.4	–	–
	$\tau=3$	22.5	–	–	–	21.6	–	–	27.1	–	–
time, dose, $n=9$	$\tau=1$	–	–	–	–	–	–	–	–	–	–
	$\tau=3$	–	–	–	–	–	–	–	–	–	–

time, dose, $n=18$	$\tau=1$		18.7	–	**8.4**	49.1	25.7	–	–	34.5	32.5	35.6
	$\tau=3$		37.1	–	15.2	86.2	21.4	–	–	19.3	71.4	77.4
weight, dose, $n=9$	$\tau=1$		–	–	–	**4.2**	–	–	–	–	–	–
	$\tau=3$		–	–	–	28	–	–	–	–	–	–
weight, dose, $n=18$	$\tau=1$		6.1	–	–	24.9	–	–	–	–	–	36.6
	$\tau=3$		9.8	–	–	61.6	–	–	–	–	–	61.9
Multiple regression (3 factors)												
time, weight, dose, $n=9$	$\tau=1$		–	–	–	–	–	–	–	–	–	–
	$\tau=3$		–	–	–	–	–	–	–	–	–	–
time, weight, dose, $n=18$	$\tau=1$		14.4	–	–	–	–	–	–	34.0	32.2	–
	$\tau=3$		31.8	–	–	–	–	–	–	20.6	69.7	–
Brawn model												
$n=9$	$\tau=1$	$\delta,\%$	21.4	**1.3**	48.1	**0.03**	**9.9**	14.3	14.1	80.9	13	**1**
		β	0.1	0.2	0.7	0.3	0.7	0.9	0.1	0.4	0.8	0.1
	$\tau=3$	$\delta,\%$	18.6	13.5	22.8	14.9	32.1	22.1	11.6	38.9	19.6	10.8
		β	0.5	0.6	0.7	0.1	0.7	0.1	0.9	0.4	0.4	0.1
$n=18$	$\tau=1$	$\delta,\%$	**4.4**	**2.5**	11.3	14.3	14.4	**1.2**	14.4	**0.1**	63.5	34
		β	0.1	0.6	0.9	0.1	0.1	0.5	0.4	0.6	0.3	0.1
	$\tau=3$	$\delta,\%$	19.3	**4.9**	**9.1**	58.7	18.1	32.5	13	13.2	23.9	55.9
		β	0.2	0.6	0.9	0.4	0.3	0.9	0.1	0.8	0.4	0.9

In this group, there is a deterioration in the prediction quality by the Brown model. This is due to the fact that in all rows of the group, except for №2, from the moment of time there is a sharp increase in the tumor volume (Figure 5) - perhaps a withdrawal syndrome occurs due to the rat receiving large doses of cyclophosphamide for a week and further discontinuation of the drug administration.

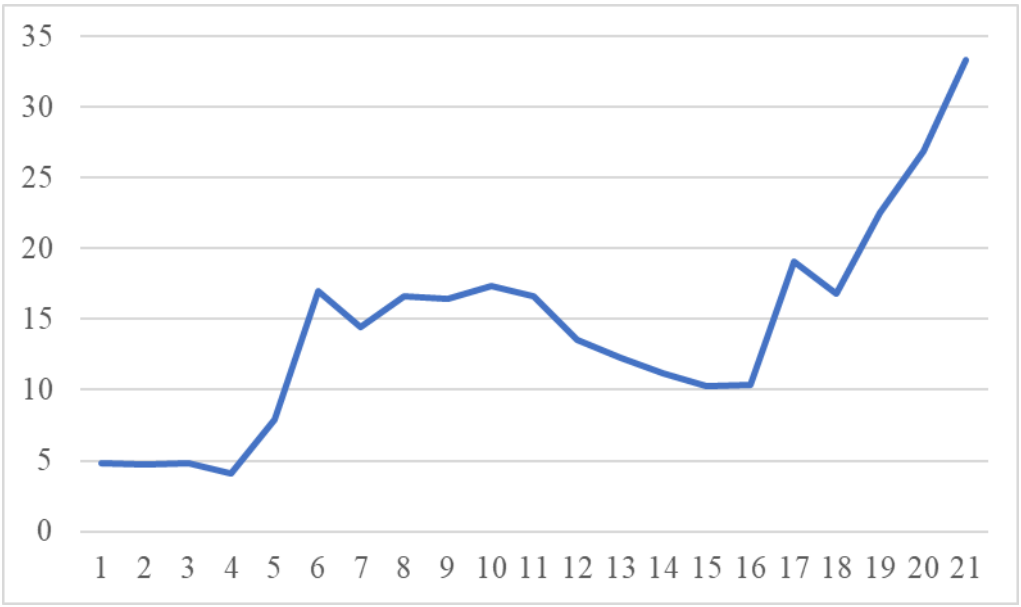


Figure 5. Graph of changes in the tumor volume of rat No. 4 (from the group with a dosage of

10 mg/kg).

The deterioration of the prediction quality is caused by the peculiarity of the selected tool for assessing the prediction quality - the error, measured as a percentage of the mean. In particular, the average value of series no. 4 for $n=18$ is 13.4, and the gain on the last and predicted value of the series is 6.4. The model does not have time to adapt to such growth and leads to a large prediction error, since the average value of the series is too far from the last value.

4. CONCLUSION

From these tables for all groups it can be seen that the influence of the factor "dose" is not significant in the training sample. This is due to the fact that in the first 9 days the medicine was given only 2 times, and this amount of information is not enough to draw statistical conclusions. When a part of the test sample is added up to 9 elements, the effect of the drug becomes much more noticeable, but not yet sufficient for a qualitative prediction. It should be noted that these parameters (the dose of a chemotherapy drug) do not have an effect precisely when trying to build models of tumor development after stopping treatment based on the considered regression methods. This fact in no way speaks of the general insignificance of the chemotherapy procedure in combination treatment.

It can also be seen for all groups that multiple regression, built only on the training part, is mostly insignificant. This is because its length $n=9$ is too short to introduce more than one factor into the model. This once again shows the correctness and the need for repeated calculations with the addition of a test part.

In the process of studying the values of the parameter β of the Brown model, at which the prediction error is minimal, no recommendations were made on the choice of its value for further prediction, since the process of adjusting to the series, which is controlled by the parameter β, very much depends on the dynamics of a particular time series on a single segment. Only with an approximate statistical estimate based on the data in the table, it can be assumed that it is better to choose a value $\beta \approx 0.4$ to build a one-step prediction.

As a conclusion, we can conclude that to predict tumor volume for a short period, Brown's model with a parameter $\beta \approx 0.4$ can be chosen, and that to take into account the effect of the drug, a larger volume of the training part is required.

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