THE EXPONENTIAL MODEL OF THE CELL GROWTH: A SIMULATION ERROR

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Mathematical modeling of pathological changes in the body is the means of obtaining information for making decisions about the method of treatment. Numerous studies have shown that the exponential model describes the tumor cells growth, and the time of antigen doubling determines the aggression of cancer cells growth. The present work investigates inaccuracies in determining the antigen doubling time as a function of measurement errors. The study showed that the decision on the method of treatment could be changed by taking into account errors in the prognosis of patient's condition. For patient's stratification in groups of high, medium and low risks, various threshold values corresponding to the antigen level are proposed. The results are presented in the form of a table and graphs.

Key words: mathematical modeling, pathological changes, antigen, simulation error

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Introduction

Cancer is one of the most common fatal diseases. Cancer incidence is on the rise. About six million new cases of malignant tumors are diagnosed every year. Cancer ranks as the third leading cause of death in the world, coming after cardiovascular and respiratory diseases.

Mathematical modeling of pathological changes in the human body is an important tool, providing data for effective decision-making in selecting treatment methods and timing. Either deterministic and stochastic models or those using methods of nonlinear dynamics are commonly chosen as basic models [1 – 11]. Most models rely on experimental data, which entails accounting for errors in setting the problem's parameters. This approach is necessary because a large number of factors affect the course of different diseases.

Prostate cancer is considered the most diagnosed cancer in men and the second (according to statistical data) cause of death from cancer [12]. The level of prostate-specific antigen p (PSA) in serum, measured in ng/ml, is one of the best-studied markers, widely used for early detection of this cancer. The kinetics of the marker may reflect the actual growth rate of the tumor.

The goal of this study has been to analyze the effect of the errors in measuring PSA in serum on the result of determining the antigen's doubling time.

Exponential model

An increase in the number of tumor cells is generally described by an exponential model, and the p level linearly depends on the number of these cells in many cases [12]. The doubling time t_d for p (measured in months in this model) determines the aggressiveness of cancer cell growth. This parameter allows to control the tumor's growth rate, choose the optimal therapeutic approach and assess treatment effectiveness. However, empirical data intrinsically contain errors; for this reason, decision-making based on the predictions of an unstable model should involve error estimation [13].

The given element p is proportional to its increment Δp, leading to an exponential model. In this case, the equality

$$dp = kpdt, \quad (1)$$

holds true, and, consequently,

$$p = \tilde{C}e^{kt}. \quad (2)$$

The law of exponential growth is valid at a certain stage for cell populations in tissue, including tumor cells [1]. The exponential model should be used bearing in mind that the solution of differential equation (2) is Lyapunov-unstable for $k > 0$ [14], i.e., small variations in the initial conditions correspond to significant errors in the final calculations. The exponential model is widespread and appears valid to use provided that its parameters can be adjusted by the observation results or by qualitative study of the system's behavior.

With the known values of p, for example, p_1 and p_2, measured at different times t_1 and t_2, the coefficients of the solution of differential equation (1), written as

$$\ln p = C + kt,$$

have the form

$$C = \frac{t_2 \ln p_1 - t_1 \ln p_2}{t_2 - t_1}; \qquad k = \frac{\ln p_2 - \ln p_1}{t_2 - t_1}. \quad (3)$$

Notably, the coefficient C is a dimensionless quantity, while the coefficient k is measured in (months) $^{-1}$.

The time t_d, elapsed from the time t_2, that it takes for p_2 to double is predicted by the solution of the equation

$$2p_2 = p_2 e^{k \cdot t_d};$$

it follows from here that the following equality should hold true:

$$t_d = \ln 2 \cdot \frac{t_2 - t_1}{\ln p_2 - \ln p_1}. \quad (4)$$

We are going to assume from now on that an absolute measurement error Δp_i $(i = 1, 2)$ can be made in the value of p, with $|\Delta p_i| \le \varepsilon \cdot p_i$. Then the value of p is estimated as

$$p_i \pm \Delta p_i = p_i(1 \pm \varepsilon_i) = q_i \cdot p_i.$$

Here $q_i \cdot 100\%$ is the percentage of relative measurement error for p_i.

In finding the p_1 and p_2 levels with the respective errors q_1 and q_2, the doubling time t_d^{er} for p, taking into account errors, and the relative error δt_d of doubling time prediction are calculated by formulae

$$t_d^{er} = \ln 2 \cdot \frac{t_2 - t_1}{\ln \frac{q_2 p_2}{q_1 p_1}}, \quad (5)$$

$$\delta t_d = \left| \frac{t_d^{er} - t_d}{t_d^{er}} \right| = \left| \frac{\ln q_2 - \ln q_1}{\ln p_2 - \ln p_1} \right|. \quad (6)$$

The relative measurement error for p typically varies from 2 to 20 % [15]. Errors in measuring p lead to large errors in determining t_d. Notably, the projected doubling time is calculated without error even with large but identical relative errors in determining the p levels, which means that it is preferable to measure the p level at the same laboratory with the same equipment.

The denominator in formulae (4), (5) is close to zero for a small time interval $(t_2 - t_1)$ between measurements of p, which significantly increases the error in predicting t_d. To provide the given relative error Q for calculating the doubling time, the time interval between two measurements of p should satisfy the inequality

$$t_2 - t_1 \ge \frac{\left| \ln \frac{q_2}{q_1} \right|}{Q \cdot \ln 2}.$$

For example, with a 5 % error in determining the level of p, the ratio q_2/q_1 can vary from $(100 - 5) / (100 + 5)$ to $(100 + 5)/(100 - 5)$, i.e., from about 0.9 to 1.1, and from 0.82 to 1.22 with a 10% error.

Calculation results and discussion

The data in Table 1 can be used to estimate, for example, the margin of the possible error in predicting t_d^{er} with $p_2/p_1 = 1.51$ and the difference $(t_2 - t_1) = 12$ months. Instead of $t_d = 20$ months, t_d^{er} values range from 17 to 27 months, i.e., include the values below the critical. This means that more intensive treatment should be started at $t_d^{er} = 27$ months taking into

Table

Predicted values for the doubling times t_d^{er} for the cancer marker p depending on the errors q in measuring the marker with different parameters

$q_2/\ q_1$	t_d^{er}, months		
	$p_2 = 1{,}51$ ng/ml, $t_d = 20$ months	$p_2 = 1{,}46$ ng/ml, $t_d = 22$ months	$p_2 = 1{,}56$ ng/ml, $t_d = 19$ months
0.90	27	30	25
0.92	25	28	23
0.94	24	26	22
0.96	22	25	21
0.98	21	23	**20**
1.00	**20**	22	19
1.02	19	21	18
1.04	18	**20**	17
1.06	18	19	17
1.08	17	18	16
1.10	17	18	15

Notations: q_1 and q_2, %, are the errors of measured values of the markers p_1 and p_2, obtained at times t_1 and t_2; t_d is the predicted doubling time without measurement errors.

Notes. 1. t_d^{er} should be calculated by formula (5), assuming that the initial value of the marker p_1 is the same and is 1 ng/ml; the difference $t_2 - t_1 = 12$ months 2. The values of $t_d^{er} = 20$ months are highlighted in bold as critical: the growth rate of cancer cells is regarded as threatening below these values.

account the model's error.

It follows from formulae (4), (5) and Table 1 that the absolute and relative errors of determining t_d increase with smaller values of the p_2/p_1 ratio. Small t_d^{er} values correspond to a large p_2/p_1ratio, while the error in determining the doubling time decreases.

Different threshold values of p were proposed for stratification of patients by groups of high, medium and low risks in accordance with their PSA t_d levels [12]. Let us denote the values corresponding to these risks as p_{top} and p_{low} for further calculations. Patients with $p < p_{low}$ undergo preventive health screenings. Radical treatment is started if $p > p_{top}$. The $[p_{low}; p_{top}]$ interval is commonly referred to as the gray zone [15], as different treatment plans can be chosen for the p values lying in this range. Predicting whether the given p value falls in the gray or critical zone makes it possible to calculate the recommended time for the next measurement of p. If the model for the variation of p corresponds to the exponential one with parameters (3), then the value of p equal to p_b is reached at time t_b, for which one of the following equalities holds true, either

$$t_b = \frac{\ln\left(p_b^{(t_2-t_1)} \cdot \frac{p_2^{t_1}}{p_1^{t_2}}\right)}{\ln\left(\frac{p_2}{p_1}\right)},$$

or

$$t_b - t_2 = (t_2 - t_1) \cdot \frac{\ln \frac{p_b}{p_2}}{\ln \frac{p_2}{p_1}} = \frac{\ln \frac{p_b}{p_2}}{\ln 2} \cdot t_d. \qquad (7)$$

To calculate the t_b prediction taking into account the error in measuring p, q_1p_1 and q_2p_2 should be substituted into formula (7) instead of p_1 and p_2:

$$(t_b^{er} - t_2) = (t_2 - t_1) \cdot \frac{\ln(p_b / q_2p_2)}{\ln(q_2p_2 / q_2p_1)}.$$

Fig. 1,*a* shows how quickly the p value in

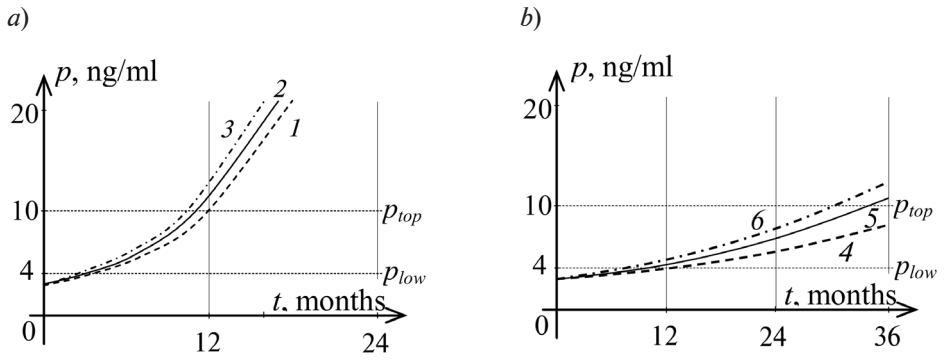

Fig. 1. Growth kinetics for the values of cancer marker p for different values of the t_d parameter, months: 5.61 (*1*), 6.00 (*2*), 6.49 (*3*) (*a*) and 17 (*4*), 20 (*5*) and 27 (*6*) (*b*); p_{top} and p_{low} are the boundaries of the gray zone; $p > p_{top}$ corresponds to the critical zone; p_2= 3 ng/ml; $(t_2 - t_1)$ = month

the gray area is reached and a transition into the critical zone is made with a high PSA growth rate (t_d = 6 months, p_{low} = 4 ng/ml, p_{top} = 10 ng/ml and $(t_2 - t_1)$ = 6 months with p_2= 3 ng/ml). In this case,

$$t_b - t_2 = 6 \cdot \frac{\ln(10 / 3)}{\ln 2} \approx 10,4.$$

This means that the next p measurement should be scheduled in about 10 months, since the level of p is going to fall into the critical zone after 12 months. Taking into account the error in determining p can change this interval by a month. The value of p might fall into the gray zone in 2.5 months; this should be kept in mind when scheduling the p measurement date.

Fig. 1,*b* shows when the gray zone is reached with the same value of p_2 and t_d = 20 months. In this case, the possibility that the lower boundary of the gray zone might be reached should be taken into account and the next p measurement should be scheduled in 8 months. This interval can be varied from 7 to 11 months when accounting for the error in measuring p.

Measuring p at a third time t_3 allows to adjust the values of coefficients (3) provided that the exponential model agrees with the experimental data obtained. The adequacy of the model can be tested in several ways.

If

$$\frac{p_3 - p_2}{t_3 - t_2} \approx \frac{p_2 - p_1}{t_2 - t_1}$$

(or $p_3 + p_1 \approx 2p_2$, provided that the measurements were carried out at equal intervals of time), then p increases linearly and the exponential model should be abandoned. This means that the increase in p is not caused by the growth of the tumor, but by other factors. The date for measuring p was selected with respect to the time when the boundary value p_b might be reached. If the obtained value of p_3 differs little from the predicted one, then the exponential model is chosen correctly. Then, with constant parameters of the model and no error in measuring p, the doubling time is constant, and the results of t_d calculations should be the same for choosing any two measurements taken at different times. The exponential model is adequate given the approximate equality of the value

$$t_d = \ln 2 \cdot \frac{t_2 - t_1}{\ln p_2 - \ln p_1}$$

and the quantities

$$t_{d32} = \ln 2 \cdot \frac{t_3 - t_2}{\ln p_3 - \ln p_2},$$

$$t_{d31} = \ln 2 \cdot \frac{t_3 - t_1}{\ln p_3 - \ln p_1},$$

i.e., with

$$\frac{\ln p_3 - \ln p_2}{t_3 - t_2} \approx \frac{\ln p_2 - \ln p_1}{t_2 - t_1}$$

(or $p_3 \cdot p_1 \approx p_2^2$, if the measurements were carried out at regular time intervals).

The coefficients of the exponent that de-

viates the least from the given three points $(t_1; p_1)$, $(t_2; p_2)$, $(t_3; p_3)$ can be then tailored to estimate the values of the residuals from the experimental points.

In this case, we have an inconsistent system of three equations with two unknowns:

$$\begin{cases} C + kt_1 = \ln p_1; \\ C + kt_2 = \ln p_2; \\ C + kt_3 = \ln p_3. \end{cases} \quad (8)$$

The coefficients C and k, approximately satisfying all the equations of the system, can be found by the least squares method:

$$a = \sum_{i=1}^{3} t_i^2, \quad b = \sum_{i=1}^{3} t_i,$$

$$u = \sum_{i=1}^{3} \ln p_i, \quad v = \sum_{i=1}^{3} t_i \ln p_i,$$

$$\begin{cases} C = \dfrac{a \cdot u - b \cdot v}{3a - b^2}; \\ k = \dfrac{3 \cdot v - b \cdot u}{3a - b^2}. \end{cases} \quad (9)$$

If an exponential model with coefficients (9) is adopted, then the adjusted doubling time for p is calculated by the formula

$$t_d = \frac{(\ln 4)(\tau_{12}\tau_{13} + \tau_{21}\tau_{23} + \tau_{32}\tau_{31})}{\ln\left(\left(\dfrac{p_2}{p_1}\right)^{\tau_{21}} \cdot \left(\dfrac{p_3}{p_2}\right)^{\tau_{32}} \cdot \left(\dfrac{p_3}{p_1}\right)^{\tau_{31}}\right)}, \quad (10)$$

$$\tau_{ij} = t_i - t_j.$$

The error of calculating t_d is found by the formula

$$\delta t_d = \left| \frac{\ln\left(\left(\dfrac{q_2}{q_1}\right)^{\tau_{21}} \left(\dfrac{q_3}{q_2}\right)^{\tau_{32}} \left(\dfrac{q_3}{q_1}\right)^{\tau_{31}}\right)}{\ln\left(\left(\dfrac{p_2}{p_1}\right)^{\tau_{21}} \left(\dfrac{p_3}{p_2}\right)^{\tau_{32}} \left(\dfrac{p_3}{p_1}\right)^{\tau_{31}}\right)} \right|. \quad (11)$$

Formulae (10) and (11) coincide with formulae (4) and (5), provided that the measurements were carried at equal time intervals of time, i.e., with $(t_3 - t_2) = (t_2 - t_1)$:

$$t_{d31} = \ln 2 \frac{t_3 - t_1}{\ln \dfrac{p_3}{p_1}}; \; \delta t_{d31} = \left| \frac{\ln \dfrac{q_3}{q_1}}{\ln \dfrac{p_3}{p_1}} \right|.$$

The error does not depend on the mean measurement error in this case.

Conclusion

Analysis of the growth kinetics of cancer cells [16, 17], established based on an exponential model, is a key step in assessing the effect of the method chosen for patient treatment. Prognosis of the disease outcome in a patient should take into account the total errors of the model, which, as we have established in this study, exceed the error in measuring the characteristics of the patient's condition.

We have obtained the formulae for calculating the relative error of the model, and found potential methods for reducing the effect of this error on the predictive capabilities of the exponential model.

We have confirmed that the decision on choosing a method for treating a patient may change upon taking into account possible errors in predicting the patient's condition.

We have proposed a method for calculating the time interval between patient assessments, necessary for adjusting the parameters of the model describing the patient's condition.

Additional data available on the patient's condition allows to assess the adequacy of the model by the several methods we have described.

Our findings can have beneficial applications not only in medicine, since the the exponential model is effective at some stages of growth rate analysis of consumption, capital, population, etc. [18].

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