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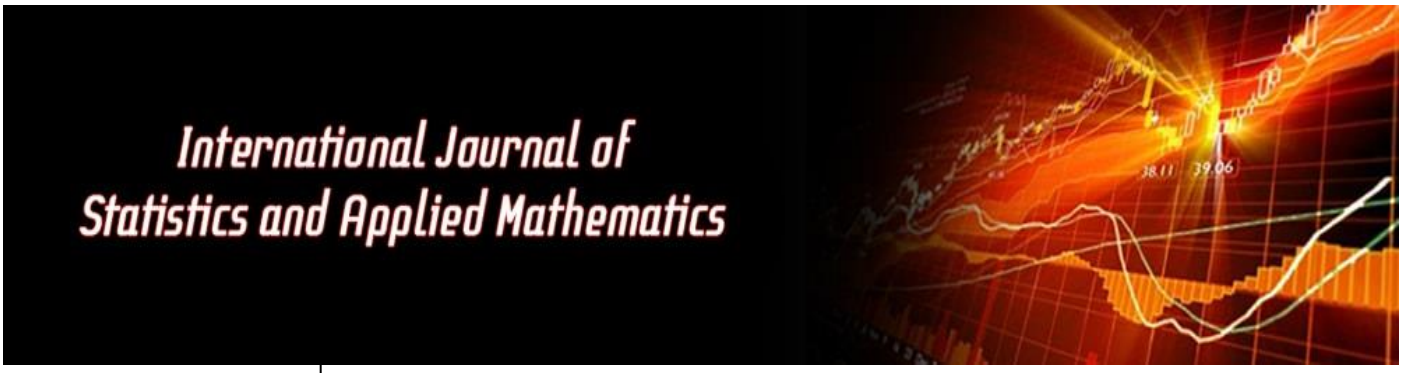

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A study of mathematical model of tumor growth by multicellular tumor spheroids

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Abstract
In this paper we describe some elements of mathematical modeling of tumor growth by multicellular tumor spheroids. We present deterministic mathematical model most often used for description of tumor growth. Development of a model, based on some biological assumption, is also illustrated by one example. Discribed model are tested and compared by ability to describe experimental data.

Keywords: Mathematical model, tumor growth, multicellular tumor spheroids

1. Introduction
A mathematical model of tumor growth is a mathematical expression of the dependence of tumor size on time. In the paper we present some results in the field of deterministic mathematical modeling of tumor growth. There are three main steps in the process of mathematical modeling:

1. Definition of model based on biological assumptions.
2. Testing the model against experiment data.
3. Acceptance of model or its rejected and change of assumptions.

It is important to note that a model may be rejected due to wrong assumptions or inadequate number of assumptions.
A particularly convenient experimental tumor paradigm is provided by the multicellular tumor spheroids (MTS) culture system [3]. Spheroids provide a system for the prevascular phase of tumor growth in the absence of tumor-host interactions, and for investigating the regulation of growth by three- dimensional cell-cell interaction. In MTS oxygen and nutrition come through the surface of spheroids and necrotic cell lay in the center of tumor.

2. Mathematical models
In the case of multicellular spheroids, growth follows the sigmoid curve with the three distinct phases : the initial exponential phase, the linear phase and the plateau[13].For this study, we selected mathematical model of that reflect the sigmoid nature of growth. The models are divided into three groups: empirical models, functional models and structural models.

2.1 Empirical models
These model are based on the fundamental empirical insight that growth results from the increase in size concomitant with processes that limit the size the system. we consider two sets of empirical model developed for growth of biological system.
One set of models is based on the principle that for tumor size B, the rate of change in size $B^{`}$, is a difference between the rate of growth and the rate of degradation. According to von Bertalanffy [2], both rates follow the law of allometry, i.e., they are proportional to the power of tumor volume, so the growth equation is of the form

$$B^{`}=cB^{\alpha}-dB^{\beta} \quad \ldots\ldots\ldots\ldots\ldots\ldots(1)$$

(Starting from different assumptions, Savageau [22] later derived the same equation.) This model is named the "generalized two-parameter model" [15].

As the special cases, equation (1) includes the well know logistic growth (α = 1,β = 2) [20, 30] and the von Bertalanffy growth equation (α = 2/3, β = 1) [1]. Both models have been used for description of tumor growth.

It is interesting that a particular limiting case of equation (1) is the most often used Gompertz equation [11]

$B' = cB - dB \ln B$ …… (2)

When parameters α and β approach 1, the growth curve represented by Eq. 1 does not necessarily approach an exponential curve, but it may also approach the Gompertz growth curve. Furthermore, equation (1) contains the more general equations as special cases: "generalized Gompertz equation" [15] and "generalized Bertalanffy-logistic equation".

The above models are special cases of the model described by equation (1) and are nested within this model. In this paper we illustrates the nesting relationships. These relationships make it possible to compare the models by well defined statistical criteria.

Another set of nested empirical models, proposed by Turner *et al*. [25], is given. It is assumed there that the rate of change in size is proportional to the product of one function increasing with size and other function decreasing with size. The corresponding equation reads

$$B' = \frac{\beta}{k^n} B^{1-np}(k^n - B^n)^{1+p} \quad \text{……(3)}$$

Where -1 < p<, 1/ n > o, and the solution is designed as the "generic growth curve". Turner *et al*. [25] derived the special cases of equation (3). One is the "hyper-Gompertz" model and the other is the "hyper-logistic" model.

For p= 0 the generic equation reduces to the Bertalanffy-logistic equation [25] which is a special case of the generalized Bertalanffy-logistic equation. The Gompertz model and the logistic model are nested in the hyper- Gompertz and the hyper-logistic models, respectively.

Another empirical model is the "Gomp-ex" model [26]. It is a combination of the often used exponential model and the Gompertz model. The differential equation for this model is

$$B' = \{^{\alpha B,}_{\alpha B - \beta \ln \frac{B}{B_c},}{}^{B<Bc,}_{B\geq Bc,} \quad B(0) = B_0 \quad \text{……..(4)}$$

This model describes explicity the initial exponential spheroid growth. For $B_c = B_0$, the Gomp-ex equation reduces to the simpler Gompertz equation reduces to the simpler Gompertz equation.

2.2 Functional models

From the fertile field of functional modal based on cell kinetics we selected some with few parameters. Thus we considered the model by Piantadosi [20]:

$$\frac{B'}{B} = \alpha \frac{1}{(1+\beta B\gamma)^{1/\gamma}} - \omega,$$

The inhibition model formulated on the basis of work by wheldon *et al*. [27] and Cox *et al*. [6]:

$$\frac{B'}{B} = \alpha \frac{1}{(1+\beta B)} - \omega,$$

As well as the autostimulation model [16] based on the autocrine hypothesis:

$$\frac{B'}{B} = \alpha \frac{1+A}{(1+\beta B)} - \omega, \; A' = aB - bA^2.$$

These models are characterized by the cellular doubling time, the fraction of activity dividing cells and the random loss of cell from population. The magnitude of the growth fraction depends on the population size.

The models account for volumes, though originally they were developed for cell numbers [6, 16, 20, 27]. Although the total spheroid volume is not directly proportional to the number of living cells due to changes in cell size and central necrosis during growth [9, 10], these changes do not alter the overall size of the spheroid. Consequently, the spheroid volume can be substituted for the cell number in these models. This substitution makes it possible to apply the function models to the measurements of spheroid volumes.

2.3 Structural models

Several mathematical models have been developed for description of spheroid growth in structural terms. All such models assume that the spheroid is a perfect sphere and that processes such as proliferation, necrosis, diffusion, shedding, inhibition, etc, obey spherical symmetry. Thus the growth of a spheroid can be conveniently described by its radius, R(t). However, the corresponding equation can be obtained in terms of volume by substitutions $V = 4/3\pi R^3$.

Conger and Ziskin [4] based their "constant crust" model on the observation that cells proliferate at a constant rate α within the proliferating cell rim of the spheroids, the rim is of constant thickness, k [13]. This model was modified by Wheldon adding initial exponential growth [26]:

$$R' = \{^{\frac{1}{3}\alpha R, R\leq k}_{\alpha R[\frac{k}{R}-(\frac{k}{R})^2+(\frac{k}{R})^3], R>k,} \quad R(0) = R_0 \quad \text{……(5)}$$

The models described the exponential and the linear phases of spheroid growth. The solution of equation (5) is unbounded. Consequently, it does not describe the final plateau phase, and we exclude it from further analysis.

To include the loss of cells, we modified equation (5) in analog to the previous models:

$$R' = \begin{matrix} (\frac{1}{3}\alpha-\omega)R, R\leq k, \\ \alpha R[\frac{k}{R}-(\frac{k}{R})^2+\frac{1}{3}(\frac{k}{R})^3]-\omega R, R>k, \end{matrix} \quad R(0) = R_0 \quad \text{……..(6)}$$

Again, the loss is assumed to be proportional to spheroid volume, with the rate of loss characterized by the rate constant $3w$. Due to simplicity of assumptions, we named this model the "simple spheroid model".

Structural models also include more complex model development for growth of tumor spheroids by Landry *et al*. [13] and the diffusion model of spheroid growth by Maggelakis and Adam [14].

3. Testing the model

To test the adequacy of the model we fit curve generated by the model to the tumor data using the weighted least obtained by minimization of the function

$$\chi^2 = \sum_{i=1}^{n} (\frac{B_i - B(t_i)}{\sigma_i})^2 \quad \text{……(7)}$$

over the model parameters. Here, B_i stands for the measured volume at time t_i, $B(t_i)$ for the correspounding volume computed from the model and σ_i for the standard deviation of

B_i. The least squares method can be meaningfully applied when errors in measurement are distributed normally. Measurements used in this paper were obtained as means of 50 volumes and, consequently, the error distribution can be expected to approach the normal distribution, what is testified by analysis of residuals. Since standard deviation of measurements is approximately proportional to the measured volumes, we may apply minimization of

$$\chi^2 = \sum_{i=1}^{n} (\text{In } B_i - \text{In } B(t_i))^2$$

The use of the unweighted least squares method ($\sigma_i = 1\ in\ (7)$) does not give a satisfactory fit. More details on the choice of minimized criterion can be find in [16]. To obtain volumes $B(t_i)$ in (7), some considered differential equation were solved analytically and some numerically by the use of the computer code ODEN [23]. For nonlinear minimaization of the X^2 funtion(18), we combined the Nelder-Mead simplex [21] and the Levenberg-Marquardt minimaization procedures [18]. To satisfy the nonnegativity constraints on parameters mandated by the models, we used the penalty functions. To quantify the quality of the fits we analyzed normality of residuals

$$r_i = \frac{B_i - B(t_i)}{\sigma_i},$$

using the X^2 goodness-of-fit test and the Kolmogorov-Smirnov goodness-of-fit test [12]. Further, we tested the serial correlation of residuals r_i by use of the Durbin-Watson test [7, 8] and randomness of residuals by the sign test by the runs test [24].

Table 1 summarizes results of analysis of considered models. Gomp-ex model (4) and Bertalanfly-Richardson model yielded fits identical to fit by gompertz model, so they are not listed in table. Most of the model resulted with comparable X^2 values. Exceptions are logistic and von Bertalanffy models. They are obviously incapable to describe the data. The same is true for the inhibition model by Wheldon and Cox. Analysis of residuals supports this conclusion. Simple spheroid model is somehow worse than other models but much better than previously mentioned three models. Fits to other data sets [16] approved this conclusion.

Comparison of the models

In the previous section we saw that almost all considered models describe data well. The nesting of some models allowed the section of the most applicable models by the F-test is based on the statistics

$$F = \frac{(n-m_2)[X^2(m_1) - X^2(m_2)]}{(m_2-m_1)X^2(m_2)} \qquad \ldots\ldots\ldots\ldots\ldots\ldots(8)$$

which follows approximately the F-distribution with m_2- m_1 and n-m_2 degrees of freedom. Here the values of $X^2(m_1)$ and $X^2(m_2)$ corresponds to the least X^2 values obtained for the nested model defined by m_1 and m_2 free parameters, respectively ($m_2 > m_1$).

The fits by model not related by nesting can be compared by the Bayes information criterion (BIC) according to Schwarz:

$$BIC = X^2(m) + \frac{m}{2} \text{ In } n,$$

Where m is the number of free parameter and $X^2(m)$ corresponds to the least x^2 value. The test is applicable when $X^2(m)$ is distributed by X^2- distribution with the expected value n - m. In our case the value o$X^2(m)$ is larger due to underestimated measurement errors e_1 estimated by, $\bar{e}_i$. Then the standard deviation can be estimated from the fit to flexible function which is likely to yield low X^2 value (say $X_1^2(m_1)$) and the fit is characterized by m_1 free parameters and by the normally distributed residuals. Namely we can assume that standard deviation are given $e_i = \rho \bar{e}_i$ and determine the fector ρ by imposing $X_1^2(m_1) = n - m_1$. This procedure implies that BIC takes the form used in this paper:

$$BIC = (n - m_1)\frac{X^2(m)}{X_1^2(m_1)} + \frac{m}{2} \text{ In } n \qquad \ldots\ldots\ldots\ldots\ldots\ldots..(9)$$

The value of $X_1^2(m_1)$ was obtained by fitting polynomials to data. We calculated the x^2 values for polynomials of increasing order and chose the lowest order for which changes in x^2 were no longer significanct

($P \leq 0.05$ by F- test). According to the above criterian, the preferred fit is characterized by a smaller BIC (9).

In conclusion, we may recapitulate that the Gompertz model, the autostimulation model and the Piantadosi model are models of choice for the description of the MTS growth curve. It is noteworthy to mention that capability of models to describe growth curve data is not the only criterion for its evaluation. Some other criteria, such as prediction of growth curve [17] and estimation of some biological parameters (*e.g.* doubling time and viable rim thickness [16]) may be used for the section of an appropriate model.

Table 1: The X^2 values for different models and p-values for test used in analysis of residuals (x^2: X^2 –goodnes-of-fit KS: Kolmogorov-Smirnov, D W: Durbin-Watson)

Model	**G (3)**	**GG (4)**	**L (3)**	**B (3)**	**GBL (4)**	**GTP (5)**	**HG (4)**
X^2-value	1796.9	1708.6	21903.6	13101.0	1708.6	1682.6	1750.1
BIC	45.15	45.12	486.52	293.29	45.12	46.45	47.93
X^2 test	0.68	0.46			0.46	0.68	0.10
KS test	>0.20	>0.20	0.20	>0.20	>0.20	>0.20	>0.20
DW test	>0.05	>0.05	0.025	0.025	>0.05	>0.05	>0.05
Sign test	0.55	0.55	0.02	0.23	0.55	0.37	0.55
Runs test	0.92	0.92	0.00	0.00	0.92	0.68	0.92

Abbreviation: G: Gompertz, GG: generized Gompertz, L: logistic, B: Bertalanffy, GBL: generalized Bertalanffy-logistic, GTP: generalized two- parameter, HG: hyper-Gompertz, HL: hyper-logistic, Ge: generic, AS: autostimulation, P: Piantadosi, I: inhibition, SS: simple spheroid, Pol Polynomials. IC: inconclusive. The number associated with each designed stands for the number of free parameters.

Model	HL	Ge	AS	P	I	SS	POl.
	(4)	(5)	(6)	(5)	(4)	(4)	(7)
X^2-value	1850.5	1750.1	1526.8	1708.6	4594.3	2440.9	1731.1
BIC	48.23	47.93	44.93	47.02	108.46	61.19	
X^2 test	0.58	0.10	0.61	0.46	0.27	0.78	0.38

KS test	>0.20	>0.20	>0.20	>0.20	>0.20	>0.20	>0.20
DW test	>0.05	>0.05	>0.05	>0.05	0.025	IC	>0.05
Sign test	0.55	0.55	0.77	0.55	0.07	0.77	1.00
Runs test	0.16	0.92	0.86	0.92	0.00	0.30	0.83

Table 2: The X^2 values for different models and p-values for test used in analysis of residuals(x^2: X^2 –goodnes-of-fit KS: Kolmogorov-Smirnov, D W:Durbin-Watson)

Model	G	GG	L	B	GBL	GTP	HG
	(3)	(4)	(3)	(3)	(4)	(5)	(4)
X^2-value	1796.9	1708.6	21903.6	13101.0	1708.6	1682.6	1750.1
BIC	45.15	45.12	486.52	293.29	45.12	46.45	47.93
X^2 test	0.68	0.46			0.46	0.68	0.10
KS test	>0.20	>0.20	0.20	>0.20	>0.20	>0.20	>0.20
DW test	>0.05	>0.05	0.025	0.025	>0.05	>0.05	>0.05
Sign test	0.55	0.55	0.02	0.23	0.55	0.37	0.55
Runs test	0.92	0.92	0.00	0.00	0.92	0.68	0.92

Abbreviation: G: Gompertz, GG: generized Gompertz, L: logistic, B: Bertalanffy, GBL: generalized Bertalanffy-logistic, GTP: generalized two- parameter, HG: hyper-Gompertz, HL: hyper-logistic, Ge: generic, AS: autostimulation, P: Piantadosi, I: inhibition, SS: simple spheroid, Pol Polynomials. IC: inconclusive. The number associated with each designed stands for the number of free parameters.

Model	HL	Ge	AS	P	I	SS	POl.
	(4)	(5)	(6)	(5)	(4)	(4)	(7)
X^2-value	1850.5	1750.1	1526.8	1708.6	4594.3	2440.9	1731.1
BIC	48.23	47.93	44.93	47.02	108.46	61.19	
X^2 test	0.58	0.10	0.61	0.46	0.27	0.78	0.38
KS test	>0.20	>0.20	>0.20	>0.20	>0.20	>0.20	>0.20
DW test	>0.05	>0.05	>0.05	>0.05	0.025	IC	>0.05
Sign test	0.55	0.55	0.77	0.55	0.07	0.77	1.00
Runs test	0.16	0.92	0.86	0.92	0.00	0.30	0.83

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