Mathematical models of tumor growth*

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

Key words: *mathematical modeling, tumor growth, multicellular tumor spheroids*

Sažetak. **Matematički modeli rasta tumora.** *U predavanju su opisani neki dijelovi matematičkog modeliranja rasta tumora. Prikazani su matematički modeli koji su najčešće korišteni za opis rasta tumora. Također opisan je i razvoj jednog modela na osnovi bioloških pretpostavki. Prikazano je testiranje i usporedba modela na eksperimentalnim podacima.*

Ključne riječi: *matematičko modeliranje, rast tumora, višestanični tumorski sferoidi*

1. Introduction

A mathematical model of tumor growth is a mathematical expression of the dependence of tumor size on time. In the lecture 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 experimental data.

*The lecture presented at the Mathematical Colloquium in Osijek organized by Croatian Mathematical Society - Division Osijek, June 7, 1996.

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3. Acceptance of model or its rejection and change of assumptions.

It is important to note that a model may be rejected due to wrong assumption(s) or inadequate number of assumptions.

A particularly convenient experimental tumor paradigm is provided by the multicellular tumor spheroids (MTS) culture system [3, 27]. Spheroids provide a system for the study of 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 interactions. In MTS oxygen and nutrition come through the surface of spheroids and necrotic cells lay in the center of tumor.

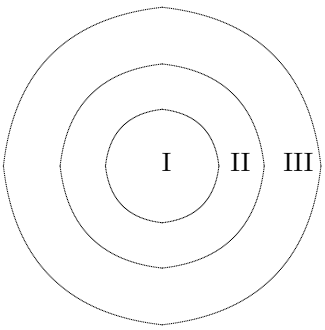

Figure 1. *Three layers in idealized scheme of MTS*

Figure 1 shows three layers in idealized scheme of MTS: necrotic core (I), quiescent (nonproliferating) cells (II) and proliferating cells (III). Moreover, the growth curve for tumor spheroids can conveniently be determined with uniquely dense measurements and high precision [10].

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 models that reflect the sigmoid nature of growth. The models are divided into three groups: empirical models, functional models (based on cell kinetics), and structural models (developed specifically for spheroid growth).

2.1. Empirical models

These models are based on the fundamental empirical insight that growth results from the increase in size concomitant with processes that limit the size of the system. We consider two sets of empirical models developed for growth of biological systems.

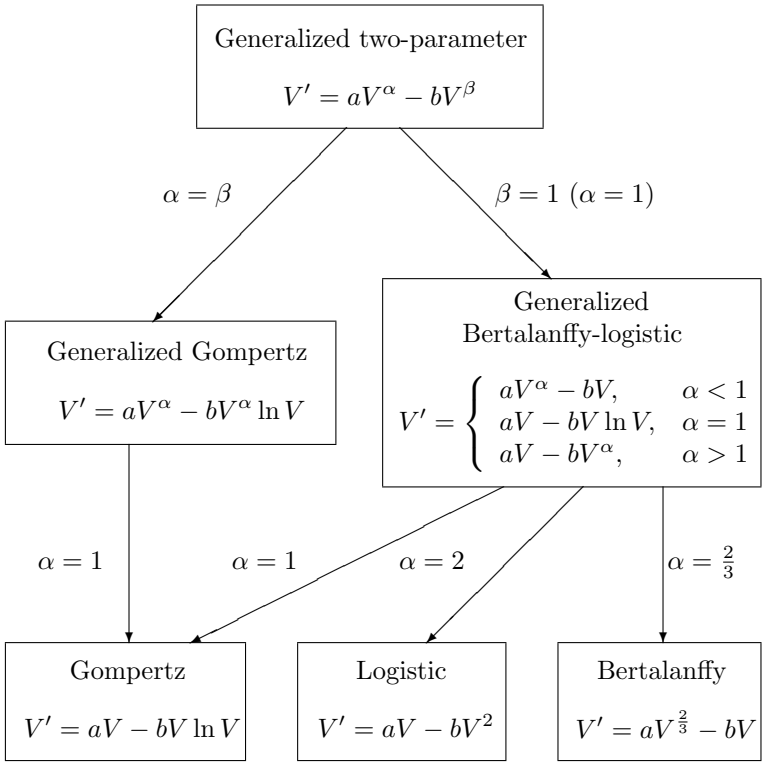

Figure 2. *Nesting scheme for models originating from the generalized two-parameter model of growth*

One set of models is based on the principle that for tumor size V, the rate of change in size V' 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

$$V' = aV^\alpha - bV^\beta. \tag{1}$$

(Starting from different assumptions, Savageau [23] later derived the same equation.) This model is named the "generalized two-parameter model" [15].

As the special cases, equation (1) includes the well known logistic growth equation ($\alpha = 1,\ \beta = 2$) [20, 30] and the von Bertalanffy growth equation ($\alpha = 2/3,\ \beta = 1$) [1]. Both models have been used for description of tumor growth [29].

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

$$V' = aV - bV \ln V. \tag{2}$$

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. *Figure 2* 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.* [28], is given in *Figure 3*. It is assumed there that the rate of change in size is proportional to the product of one function increasing with size and the other function decreasing with size. The corresponding equation reads

$$V' = \frac{\beta}{k^n} V^{1-np} \left(k^n - V^n\right)^{1+p}, \tag{3}$$

where $-1 < p < \frac{1}{n}$, $n > 0$, and the solution is designated as the "generic growth curve". Turner *et al.* [28] derived the special cases of equation (3). One is the "hyper-Gompertz" model and the other is the "hyper-logistic" model.

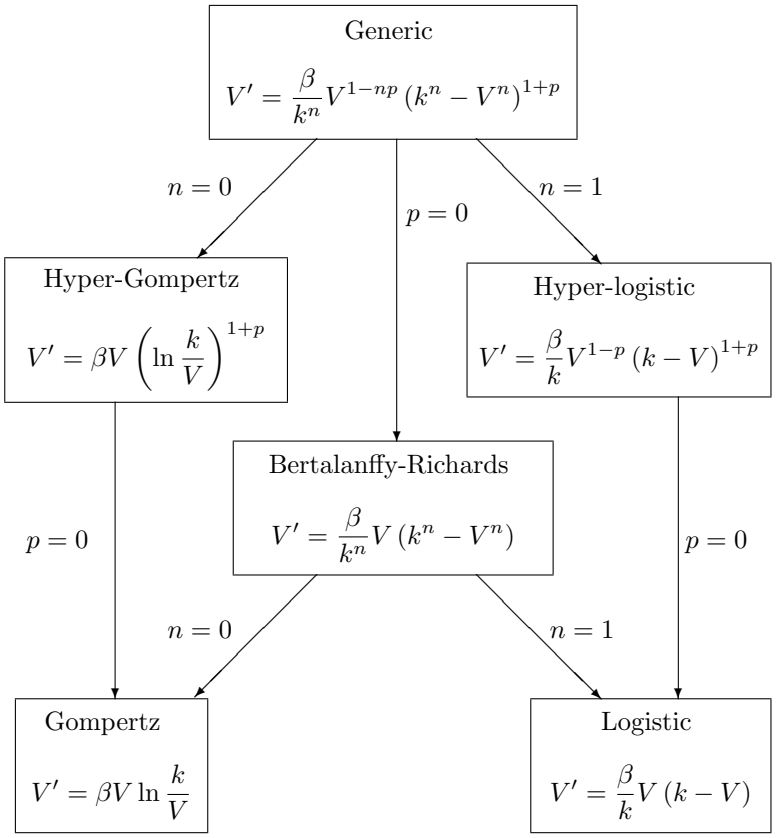

Figure 3. *Nesting scheme for models originating from the generic model*

For $p = 0$ the generic equation reduces to the Bertalanffy-Richards equation [28] 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 [31]. It is a combination of the often used exponential model and the Gompertz model. The differential equation for this model is

$$V' = \begin{cases} \alpha V, & V < V_c, \\ \alpha V - \beta \ln \frac{V}{V_c}, & V \geq V_c, \end{cases} \qquad V(0) = V_0. \tag{4}$$

This model describes explicitly the initial exponential spheroid growth. For $V_c = V_0$, the Gomp-ex equation reduces to the simpler Gompertz equation.

2.2. Functional models

From the fertile field of functional models based on cell kinetics, we selected some with few parameters. Thus, we considered the model by Piantadosi [21]:

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

the inhibition model formulated on the basis of work by Wheldon *et al.* [32] and Cox *et al.* [6]:

$$\frac{V'}{V} = \alpha \frac{1}{1+\beta V} - \omega,$$

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

$$\frac{V'}{V} = \alpha \frac{1+S}{1+\beta V} - \omega, \qquad S' = aV - bS^2.$$

These models are characterized by the cellular doubling time, the fraction of actively dividing cells (growth fraction), and the random loss of cells 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, 21, 32]. 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 functional 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 equations 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 spheroid (layer III in *Figure 1*); the rim is of constant thickness, k [13]. This model was modified by Wheldon adding initial exponential growth [31]:

$$R' = \begin{cases} \frac{1}{3}\alpha R, & R \le k, \\ \alpha R\left[\frac{k}{R} - \left(\frac{k}{R}\right)^2 + \frac{1}{3}\left(\frac{k}{R}\right)^3\right], & R > k, \end{cases} \qquad R(0) = R_0. \tag{5}$$

The model describes 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 analogy to the previous models:

$$R' = \begin{cases} \left(\frac{1}{3}\alpha - \omega\right) R, & R \le k, \\ \alpha R \left[\frac{k}{R} - \left(\frac{k}{R}\right)^2 + \frac{1}{3}\left(\frac{k}{R}\right)^3\right] - \omega R, & R > k, \end{cases} \qquad R(0) = R_0. \tag{6}$$

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

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

3. An example of model development

Here we present a model with assumptions of fundamental mechanisms of growth. To develop a model, one must assume the level of elementariness and to impose necessary abstractions and idealizations. We assume that cells are elementary units in MTS and abstract from any mechanistic details involved in cell division and in cell death. In addition, we impose the following idealizations:

1. The number of cells is large enough to be represented by a smooth function of time.
2. Spheroid volume is directly proportional to the number of cells.
3. Spheroids are ideal spheres.
4. Proliferating cells are strictly contained within the outer rim which is an ideal spherical annulus.

Now we can formulate the model by five postulates:

1. *A cell population of the size $N = N(t)$ consists only of reproducing subpopulation of the size $P = P(t)$ and the quiescent subpopulation of the size $Q = Q(t)$.*
2. *Each cell divides into exactly two cells. The growth rate is characterized by the rate constant α and is proportional to the size of the reproducing subpopulation.*
3. *Cells in quiescent subpopulation reenter the reproducing subpopulation at the time-dependent rate $g = g(t)$.*

4. *Dying of cells in both subpopulations ia a first order process characterized by the same rate* ω.

5. *Thickness of viable rim is constant during the MTS growth.*

Postulate 1 can be expressed by equation

$$N = P + Q, \tag{7}$$

while postulates 2–4 can be expressed by

$$\begin{aligned} P' &= g\,Q + \alpha P - \omega\,P, & (8)\\ Q' &= -g\,Q - \omega\,Q. & (9) \end{aligned}$$

Equations (7–9) can be combined into one differential equation

$$N' = \alpha F N - \omega N \tag{10}$$

where

$$F = \frac{P}{N} \leq 1 \tag{11}$$

is the growth fraction. According to the second idealization and discussion in 2.3. we substitute number of cells N in (10) by volume V, and obtain

$$V' = \alpha F V - \omega V.$$

From the fifth postulate the growth fraction is

$$F = \frac{R^3 - (R-k)^3}{R^3}, \tag{12}$$

where R is the radius of MST and k is thickness of viable rim (layer III in *Figure 1*). In the initial phase of growth ($R \leq k$) all cells are in the reproducing subpopulation, so the growth fraction is equal to one:

$$F = 1. \tag{13}$$

This model is named the *simple spheroid model* [17].

The first four postulates specify the simplified cell cycle as presented by Piantadosi [21]. Different choice of postulates leads to different equations for the growth fraction. In the Piantadosi model

$$F = \frac{1}{(1+\beta V^\gamma)^{1/\gamma}}, \tag{14}$$

in the inhibition model [6, 32]

$$F = \frac{1}{1+\beta V}, \tag{15}$$

and in the autostimulation model [16]

$$\begin{aligned} F &= \frac{1+S}{1+\beta V}, & (16)\\ S' &= aV - bS^2. & (17) \end{aligned}$$

4. 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 squares method. The best-fit curve for the model was obtained by minimization of the function

$$\chi^2 = \sum_{i=1}^{n} \left(\frac{V_i - V(t_i)}{\sigma_i} \right)^2 \tag{18}$$

over the model parameters. Here, V_i stands for the measured volume at time t_i, $V(t_i)$ for the corresponding volume computed from the model and σ_i for the standard deviation of V_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

$$\chi^2 = \sum_{i=1}^{n} \left(\ln V_i - \ln V(t_i) \right)^2 .$$

The use of the unweighted least squares method ($\sigma_i = 1$ in (18)) does not give a satisfactory fit. More details on the choice of minimization criterion can be find in [18].

To obtain volumes $V(t_i)$ in (18), some considered differential equations were solved analytically and some numerically by the use of the computer code ODEN [25]. For nonlinear minimization of the χ^2 function (18), we combined the Nelder-Mead simplex [22] and the Levenberg-Marquardt minimization procedures [19]. To satisfy the nonnegativity constraints on parameters mandated by the models, we used the penalty functions.

We exemplify results on one data set only (V79 fibroblast cell line). The same analysis is done in [17] on 15 data sets. A typical spheroid growth curve is shown in *Figure 4*. The curve is obtained from 45 measurements of volumes during the time period of 60 days. It demonstrates the three phases of spheroid development: exponential growth, linear growth and plateau. Further, *Figure 4* shows the best-fit curves for Gompertz and logistic model on this data set obtained by minimization of (18). It is clear that the Gompertz model describes data much better than the logistic model.

To quantify the quality of the fits we analyzed normality of residuals (*Figure 5*)

$$r_i = \frac{V_i - V(t_i)}{\sigma_i},$$

using the χ^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 and by the runs test [26].

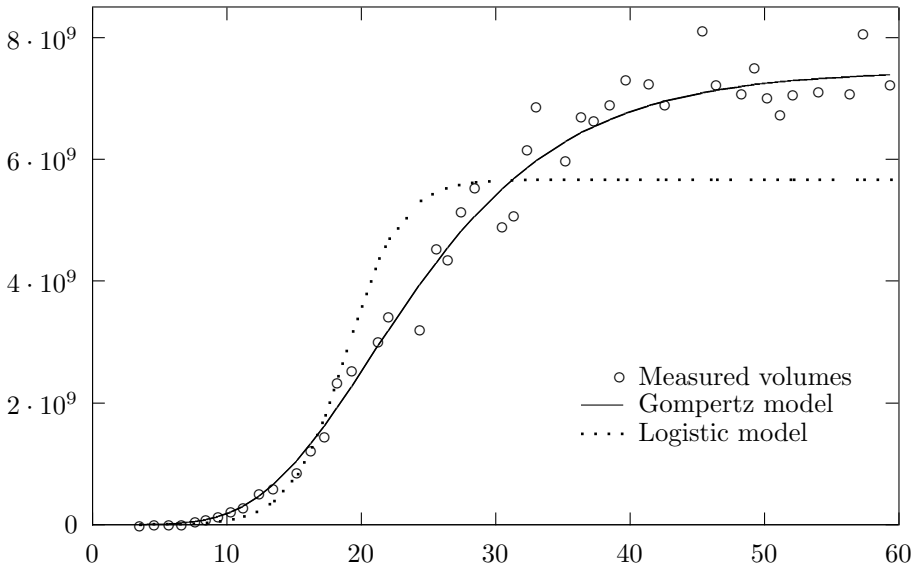

Figure 4. *Best-fit curves by Gompertz and logistic models (volumes in μm^3 vs. time in days)*

Table 1 summarizes results of analysis of considered models. Gomp-ex model (4) and Bertalanffy-Richardson model (*Figure 3*) yielded fits identical to fit by Gompertz model, so they are not listed in the table. Most of the models resulted with comparable χ^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 [17] approved this conclusion.

All fits yielded the χ^2 values which were too large in comparison to the expected value of $n - m$ (n - number of data points, m - number of model parameters). So, we used the polynomial function, because it is likely to provide reliable description of data. Procedure for determination of its degree is described in the next section. For the exemplary data set the fit by polynomials yielded the χ^2 value of 1731, while expected value was $n - m = 38$. However, the residuals were distributed normally and were not correlated. These findings imply the high likelihood that the models did provide an adequate description of the data and that the large χ^2 values resulted from the underestimated standard deviations in measurements of spheroid volume.

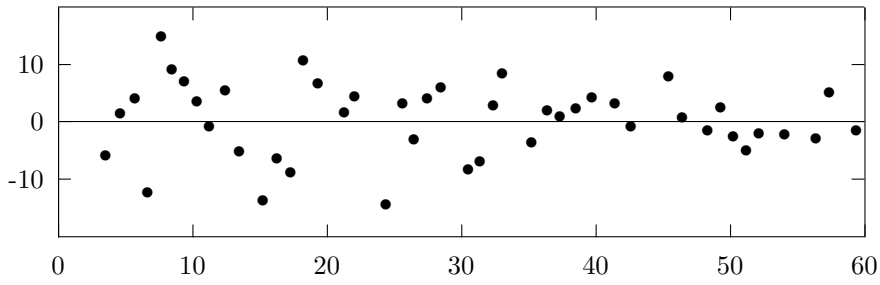

Figure 5. *Plot of residuals for Gompertz model*

5. Comparison of the models

In the previous section we saw that almost all considered models describe data well. The nesting of some models (*Figures 2–3*) allowed the selection of the most applicable model(s) by the F-test [5]. The F-test is based on the statistic

$$f = \frac{(n - m_2)\left[\chi^2(m_1) - \chi^2(m_2)\right]}{(m_2 - m_1)\chi^2(m_2)}, \tag{19}$$

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

The fits by models not related by nesting can be compared by the Bayes information criterion (BIC) according to Schwarz [24]:

$$\mathrm{BIC} = \chi^2(m) + \frac{m}{2}\ln n,$$

where m is the number of free parameters and $\chi^2(m)$ corresponds to the least χ^2 value. The test is applicable when $\chi^2(m)$ is distributed by χ^2-distribution with the expected value $n - m$. In our case the value of $\chi^2(m)$ is larger due to underestimated measurement errors σ_i estimated by, say $\bar{\sigma}_i$. Then, the standard deviation can be estimated from the fit to a flexible function which is likely to yield low χ^2 value (say $\chi_1^2(m_1)$) and the fit is characterized by m_1 free parameters and by the normally distributed residuals. Namely, we can assume that standard deviations are given by $\sigma_i = \rho\bar{\sigma}_i$ and determine the factor ρ by imposing $\chi_1^2(m_1) = n - m_1$. This procedure implies that BIC takes the form used in this paper:

$$\mathrm{BIC} = (n - m_1)\frac{\chi^2(m)}{\chi_1^2(m_1)} + \frac{m}{2}\ln n. \tag{20}$$

The value of $\chi_1^2(m_1)$ was obtained by fitting polynomials to data. We calculated the χ^2 values for polynomials of increasing order and chose the lowest order for which changes in χ^2 were no longer significant ($P \leq 0.05$ by F-test). According to the above criterion, the preferred fit is characterized by a smaller BIC (20).

All empirical models (except logistic and von Bertalanffy) described the data similarly well. On the base of F-test the fits for the generalized two-parameter, generalized Gompertz, generalized logistic-Bertalanffy and Gompertz models were equally good. Further, comparison by the F-test showed that the Gompertz, hyper-Gompertz and Bertalanffy-Richards models fitted data equally well as the generic model. As among equivalent models the Gompertz model is characterized in both groups by the least number of parameters. Therefore, this comparison indicated that the Gompertz model was the most applicable among those nested within the generalized two-parameter model (*Figure 2*), as well as

those nested within the generic model (*Figure 3*). In [17] where 15 data sets are used, the Gompertz model was also the most preferable model on all but two data sets, where the Bertalanffy-Richards model and the hyper-Gompertz model were better. The hyper-logistic model resulted in significantly worse fits in ten data sets. In conclusion, this analysis of empirical models showed that the Gompertz model was preferable for description of spheroid growth curves.

The comparison of the fits by the inhibition model and the autostimulation model (F-test) shows that the difference in χ^2 values is significant. This difference is significant also for the fits by the inhibition model and the Piantadosi model. Importantly, the residuals in fit by the inhibition model are significantly serially correlated. Thus, the inhibition model appears inadequate for description of these data. The comparison of fits by the autostimulation model and the Piantadosi model by BIC shows preference for the autostimulation model. But, in [17], for the former model, BIC was larger for eight data sets, whereas the BIC calculated for the Piantadosi model was larger for seven data sets. So, there was no preference for any of those two models. It is noteworthy that the autostimulation model yielded the least χ^2 value for seven data sets and the Piantadosi model for only one data set.

The χ^2 value and BIC for the simple spheroid model are notably larger than for other models, but the residuals for this fit are still distributed normally and are not correlated. In [17] the simple spheroid model resulted in notably larger χ^2 values for six data sets (in three data sets residuals were distributed normally and not correlated and in three data sets distribution of residuals differed significantly from the normal distribution). In the comparison of the fits by the BIC, the simple spheroid model was preferred over the Gompertz model in three data sets.

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 curves. 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 [18] and estimation of some biological parameters (*e.g.* doubling time and viable rim thickness [17]) may be used for the selection of an appropriate model.

Acknowledgment. In the lecture are presented results of author's collaboration with Drs. Željko Bajzer and Stanimir Vuk-Pavlović from Mayo Clinic and Foundation, Rochester, MN, U.S.A. and James P. Freyer from Los Alamos National Laboratory, Los Alamos, NM, U.S.A. [15]–[18]

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Table 1: *The χ^2 values for different models and p-values for tests used in analysis of residuals (χ^2: χ^2-goodnes-of-fit, KS: Kolmogorov-Smirnov, DW: Durbin-Watson)*

Model	G (3)	GG (4)	L (3)	B (3)	GBL (4)	GTP (5)	HG (4)
χ^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
χ^2 test	0.68	0.46			0.46	0.68	0.10
KS test	>0.20	>0.20	0.02	>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

Model	HL (4)	Ge (5)	AS (6)	P (5)	I (4)	SS (4)	Pol. (7)
χ^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	
χ^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

Abbreviation: G: Gompertz, GG: generalized 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 designation stands for the number of free parameters.