On the Gompertzian growth in the fractal space–time

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Abstract

An analytical approach to determination of time-dependent temporal fractal dimension \( b_t(t) \) and scaling factor \( a_t(t) \) for the Gompertzian growth in the fractal space–time is presented. The derived formulae take into account the proper boundary conditions and permit a calculation of the mean values \( \langle b_t(t) \rangle \) and \( \langle a_t(t) \rangle \) at any period of time. The formulae derived have been tested on experimental data obtained by Schrek for the Brown-Pearce rabbit’s tumor growth. The results obtained confirm a possibility of successful mapping of the experimental Gompertz curve onto the fractal power-law scaling function \( y(t) = a_t b^t \) and support a thesis that Gompertzian growth is a self-similar and allometric process of a holistic nature.

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1. Introduction

In 1825 Benjamin Gompertz (1825) introduced an actuarial function for investigation of the aging process. The slope of this function characterizes the rate of actuarial aging, while the differences in longevity between species are mainly a result of differences in the rate of aging. Nowadays the Gompertz function is widely applied to fit the demographic (Bongaards, 2005), biological (Wheldon, 1988) and medical (Bajzer and Vuk-Pavlovic, 2000) data, in particular the growth of organisms, organs, tissues and tumors (Wheldon, 1988; Bajzer and Vuk-Pavlovic, 2000; Laird, 1964). The Gompertz function can be specified in the form (Gompertz, 1825):

\[
G(t) = G_0 e^{(b/a)(1-e^{-at})}
\]

in which \( G_0 \) stands for the initial mass, volume or number of proliferating cells, \( a \) is the retardation constant, whereas \( b \) denotes the initial growth or regression rate constant.

Recently, an idea has been developed that the Gompertz function (1) representing, for example, the growth curve for neuron-like differentiating cells (Waliszewski and Konarski, 2002) or malignant tumors (Waliszewski and Konarski, 2003) can be successfully fitted by the power-low fractal function (Waliszewski and Konarski, 2002, 2003)

\[
y(t) = a_t b^t, \quad t > 0
\]

in which \( y(t) \) characterizes the time-evolution of the system, \( b_t \) is its temporal fractal dimension and \( a_t \) is a scaling factor. The mean values of \( b_t \) and \( a_t \) can be determined by the fit of the experimental Gompertz curves in the three intervals (Waliszewski and Konarski, 2002, 2003): (i) from zero to the inflection time \( t_i \), in which a number of cells reaches the 37% of the final cell number, (ii) from the inflection time to the time-point at which the process of differentiation reaches a plateau and (iii) at which the number of cells remains constant. In particular for the Brown-Pearce rabbit’s tumor growth, the following mean values have been obtained (Waliszewski and Konarski, 2002, 2003): \( \langle b_t \rangle = 2.081, \langle a_t \rangle = 3.529 \) for \( t = (0, 15.9) \) [day], \( \langle b_t \rangle = 0.345, \langle a_t \rangle = 492.290 \) for \( t = (15.9, 46.3) \) [day] and \( \langle b_t \rangle = 0.007, \langle a_t \rangle = 1698.240 \) for \( t = (46.3, 100) \) [day].

An attempt has been made to generalize this approach and derive an analytical formulae describing the time-dependence of the fractal dimension (Waliszewski, 2005):

\[
b_t(t) = b_t e^{-at}, \quad \lim_{t \to 0} b_t(t) = 0
\]

and scaling factor \( a_t(t) \) using the relationship

\[
a_t b_t = e^{(b/a)(1-e^{-at})}, \quad t > 0
\]

and its first derivative. A look into (4) reveals that this equation does not take into account a suitable boundary condition for
It is easy to verify (using, e.g. Maple processor for symbolic calculations) that the correct formulae (9) for $b(t)$ takes the limiting values

$$\lim_{t \to 0} b(t) = 1, \quad \lim_{t \to \infty} b(t) = 0$$

in accordance to the second boundary condition (8) specified above.

The model proposed can be experimentally verified as it predicts in an early stage of the Gompertzian growth a linear growth according to the equation

$$y(t \to 0) = a t, \quad b t = 1$$

with the fractal dimension equal to one, whereas the previous model (Waliszewski, 2005) predicts a plateau at this stage as

$$y(t \to 0) = a t, \quad b t = 0$$

On the other hand, for $t \to \infty$ the fractal dimension (9) tends to zero. Hence, the two relationships

$$\lim_{t \to 0} \left[ \frac{1}{G_0} \frac{dG(t)}{dt} \right] = b = a t (t \to 0),$$

$$\lim_{t \to \infty} \left[ \frac{G(t) - G_0}{G_0} \right] = e^{b a} - 1 = a t (t \to \infty)$$

should be rigorously satisfied. It should be pointed out here that the limit $a t (t \to 0)$ is undefined due to the fundamental requirement $t \neq 0$ in (1). Hence, we determine it in the vicinity of $t = 0$, applying the value $t = 0.000001$ [day].

It can be proved that the analytical expression derived for $b(t)$ is independent of whether the Gompertz function (1) or its normalized form

$$g(t) = \frac{G(t)}{G_0} e^{b a} = e^{(-b a) e^{-a t}}$$

are taken into considerations. Simple mathematical operations prove that

$$b(t) = b t e^{-a t} \left[ \frac{e^{b a (1-e^{-a t})}}{e^{b a (1-e^{-a t})} - 1} \right] = b t e^{-a t} \frac{G_0 e^{b a (1-e^{-a t})} - G_0}{G_0 e^{b a (1-e^{-a t})} - G_0} = b t e^{-a t} \frac{e^{(-b a) e^{-a t}} - e^{-b a}}{e^{(-b a) e^{-a t}} - e^{b a}}$$

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Hence, instead of relationship (6), it is possible to use its normalized version
\[ a_t b_t = e^{-a b t} - e^{-b t} \]
which satisfies the boundary condition for \( t \to 0 \). The matter is important as only the normalized Gompertz function represents a fractal (Waliszewski and Konarski, 2003), i.e. an object endowed with self-similarity and temporal fractal dimension. Eq. (15) demonstrates that the temporal fractal dimension can be determined either from the original Gompertz function (1) or its normalized form (14). The final result will be the same provided that the suitable boundary condition for \( t \to 0 \) is taken into account.

A detailed analysis of the previous approach (Waliszewski, 2005) reveals that it gives also an erroneous relationship between the Gompertz function (1) and the spatial Morse potential
\[ U(x(t)) = D_e (1 - e^{-a x(t)})^2 \]
describing the growth of a supramolecular cellular system in the fractal space. Here, \( D_e \) and \( a \) denote the dissociation energy and the range parameter, respectively. To obtain the correct formulae we have to employ a spatial counterpart of the relation (4)
\[ a_t x(t)^{b_t} = e^{b_t \alpha (1 - e^{-a t})} - 1, \quad x(t \to 0) \to 0 \]
which satisfies first of the boundary conditions (8) adopted for spatial coordinate \( x(t) \). In Eq. (18) \( a_t \) and \( b_t \) stand for the scaling factor and the spatial fractal dimension, respectively; \( x(t) \) denotes the radius of a family of the concentric spheres or circles covering the entire cellular spheroid at the time \( t \). Eq. (18) permits the calculation of \( x(t) \)
\[ x(t) = \left( \frac{1}{a_t} \right)^{1/b_t} \left[ e^{b_t \alpha (1 - e^{-a t})} - 1 \right]^{1/b_t} \]
which, introduced to the Morse function (17), yields
\[ U(t) = D_e \left\{ 1 - \exp \left[ a_t \left( \frac{1}{a_t} \right)^{1/b_t} \left[ e^{b_t \alpha (1 - e^{-a t})} - 1 \right]^{1/b_t} \right] \right\}^2 \]
the correct form of the anharmonic potential energy function for interacting supramolecular cellular systems growing in the fractal space. The specified above equation differs from that obtained previously (Waliszewski, 2005).

### 3. Results and discussion

In order to confirm the correctness of the derived formulae (9), test calculations were performed using the experimental data obtained by Schrek (1936) for Brown-Pearce rabbit’s tumor. They were analyzed by Laird (1964) to yield the Gompertzian parameters: \( a = 0.1690 \pm 0.0168 \) [day], \( b = 1.262 \pm 0.270 \) [day] and \( G_0 = 18 \) mm³. They were used to calculate the values of Gompertz function (1) and its derivative employed to determine the limiting values according to Eq. (13). All calculations were performed using Maple ver. 7.0 processor for symbolic calculations. The results obtained for the time-points \( t = 0, t = 0.000001, t = 5.76 \) and \( t = \infty \) are presented in Table 1.

A look into Table 1 reveals that formulae (9) representing the temporal fractal dimension \( b_t(t) \) and the scaling factor \( a_t(t) \) satisfactory describe their time-dependence in the period (0, \( \infty \)). In particular, relations (13) are perfectly satisfied. Since the previous approach (Waliszewski, 2005) for \( t = 0 \) predicts incorrect value of \( b_t(t = 0) = 0 \), the improvement of this model is apparent.

The possibility of mapping the experimental Gompertz curve, characterizing the Brown-Pearce tumor growth, onto the fractal power-law scaling function confirms that Gompertzian growth is a self-similar and allometric process (Bajzer, 1999) of a holistic nature (Waliszewski et al., 1998; Molski and Konarski, 2003). It means that all spatially separated subelements (cells) of the whole system (tumor) are interrelated via long-range (slowly decaying) interactions, which seem to be an essential ingredient of the self-organized Gompertzian growth (Mombach et al., 2002). Such interactions can be mediated, e.g. through diffusive substances (growth factors), which interact with specific receptors on the surface of the cells, affecting proliferation (Mombach et al., 2002). The long-range interactions are indispensable in coherent formation of the specific growth patterns, cooperative phenomena, self-organization, positive and negative feedbacks on (between) all hierarchical structures of life. They play also an important role in formation of architecture of the tumor tissue in the fractal space–time and specific changes in the temporal fractal dimension and the scaling factor during tumorigenesis. In the case of the Brown-Pearce rabbit’s tumor the temporal fractal dimension increases from 1 for \( t = 0 \) to a maximal value 2.77 for \( t = 5.76 \) [day] and then decreases to zero (see Fig. 1). As to the scaling factor \( a_t(t) \) its value for \( t = 0 \) is equal to \( b = 1.262 \) and increases to value of 2.19 for \( t = 1 \) [day], then it decreases to a minimal value of 0.80 for \( t = 5.76 \) [day] and increases again to a maximal constant value of 1749.1480. These results indicate that formation of the specific growth pattern during the Brown-Pearce tumor growth is a result of the interplay between the temporal fractal dimension and the scaling factor, which mutually accelerate and decelerate tumor growth in two periods of the tumorigenesis: before and after the inflection time

\[ t_i \text{ (day)} = \frac{1}{a} \ln \left( \frac{b}{a} \right) = 11.90 \]
Hence, the Gompertzian growth is usually interpreted as a result of two classes of competitive processes: the first one which stimulates the growth, and the second, which constrains the growth at saturation stage. Then, the temporal fractal dimension of two classes of competitive processes: the first one which stimulates the growth, and the second, which constrains the growth at saturation stage. Then, the temporal fractal dimension attains zero as $b(t \to \infty) = 0$ and not one $b(t \to \infty) = 1$ as it has been stated previously (Waliszewski and Konarski, 2002, 2003). This result indicates that at a plateau of the Gompertz curve the dynamics of the tumorigenesis is slow down to zero and cells become non-interactive (Waliszewski and Konarski, 2002, 2003).

The results obtained permit a verification of an interesting hypothesis (Waliszewski and Konarski, 2003) that the fractal structure of space–time in which tumorigenesis occurs, is lost during tumor progression. The results obtained for Brown-Pearce tumor reveal that in the period $t = (0, 5.76)$ [day] the fractal dimension increases from 1 to the maximal value 2.77 and only then it decreases to 0. In view of this the fractal structure of space–time is lost in the period $(5.76, \infty)$ [day] and not $(0, \infty)$ [day] as it has been concluded previously (Waliszewski and Konarski, 2003). On the basis of the results reported in Table 2, one may formulate a thesis that only the mean value of the temporal fractal dimension is lost during progression. The obtained results indicates that the temporal fractal dimension can be applied as a numerical measure of the tumor complexity emerging in the process of differentiation, which is correlated with the morphofunctional cell organization (Molski and Konarski, 2006). In particular, the change from the maximal value of the fractal dimension $b(t = 5.76) = 2.77$ to the zero attained at the plateau, reflects the creation of the tumor in its highly organized form.

The formulae (9) permit the calculation of the temporal fractal dimension and scaling factor for evolving Gompertzian systems at an arbitrary moment of time and not evaluate their mean values in the characteristic periods of growth (Waliszewski and Konarski, 2002, 2003). It is interesting to compare the mean values of $b(t)$ and $a(t)$ for Brown-Pearce rabbit’s tumor, calculated by taking advantage of (9) and the equation

$$
\langle f_t(t) \rangle = \frac{1}{N} \sum_{t=t_0}^{t_e} f_t(t), \quad N = \frac{t_e - t_0}{s}
$$

with those obtained previously (Waliszewski and Konarski, 2003). Here, $t_0$ and $t_e$ denote the beginning and the end of the period under consideration; $N$ is the number of the time-points in the period $(t_0, t_e)$ whereas $s$ is an interval (step) between two neighbouring time-points used in calculations.

The results specified in Table 2 indicate that the mean fractal dimensions of the space–time in which Brown-Pearce tumor grows, are consistent with those obtained previously (Waliszewski and Konarski, 2003), whereas the mean values of the scaling factor calculated in the period $t = (15.9, 46.3)$ [day] significantly differ.

The model proposed can be extended to other exponential and S-shape growth functions (Chapman, Hill, Logistic, Sigmoid, etc.). Having determined an appropriate function of growth, one may calculate both $b(t)$ and $a(t)$ in the scheme proposed in this work.

To summarize, a few important results have been obtained in the present study. Firstly, the results of the test calculations indicate that the formulae derived for the time-dependent temporal fractal dimension and the scaling factor satisfactory describe the Brown-Pearce tumor growth in the fractal space–time. They take into account the proper boundary conditions and permit a calculation of the temporal fractal dimension and scaling factors at any moment of time. Secondly, we proved that the temporal fractal dimension at saturation stage attains zero $b(t \to \infty) = 0$ and not one $b(t \to \infty) = 1$ as it has been stated previously (Waliszewski and Konarski, 2002, 2003). Thirdly, the hypothesis that the fractal structure of space–time in which tumorigenesis occurs is lost during tumor progression has been verified and modified. Fourthly, the possibility of mapping the Gompertz function of tumor growth, onto the fractal power-law scaling function confirms that Gompertzian growth is a self-similar and allometric process of a holistic nature.

### References


(In this work not only the analytical expression for $b(t)$ but also for $a(t)$ are calculated incorrectly (compare Eq. (B.6) with Eq. (9) here). Other errors appearing in this work are discussed in arXiv:0706.3676 q-bio.OT).


### Table 2

Comparison of the mean values of the temporal fractal dimension ($b(t)$) and scaling factor $a(t)$ calculated in the period ($t_0$, $t_e$) using Eq. (18) with the values of $b(t)^{W\cdot K}$ and $a(t)^{W\cdot K}$ obtained by Waliszewski and Konarski (2003)

<table>
<thead>
<tr>
<th>$b(t)$</th>
<th>$b(t)^{W\cdot K}$</th>
<th>$a(t)$</th>
<th>$a(t)^{W\cdot K}$</th>
<th>$t_0$</th>
<th>$t_e$</th>
<th>$s$</th>
<th>$N$</th>
</tr>
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<td>3.529</td>
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<td>15.9</td>
<td>0.01</td>
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