New formulation of the Gompertz equation to describe the kinetics of untreated tumors

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Abstract

Background

Different equations have been used to describe and understand the growth kinetics of undisturbed malignant solid tumors. The aim of this paper is to propose a new formulation of the Gompertz equation in terms of different parameters of a malignant tumor: the intrinsic growth rate, the deceleration factor, the apoptosis rate, the number of cells corresponding to the tumor latency time, and the fractal dimensions of the tumor and its contour.

Methods

Furthermore, different formulations of the Gompertz equation are used to fit experimental data of the Ehrlich and fibrosarcoma Sa-37 tumors that grow in male BALB/c/Cenp mice. The parameters of each equation are obtained from these fittings.

Results

The new formulation of the Gompertz equation reveals that the initial number of cancerous cells in the conventional Gompertz equation is not a constant but a variable that depends nonlinearly on time and the tumor deceleration factor. In turn, this deceleration factor depends on the apoptosis rate of tumor cells and the fractal dimensions of the tumor and its irregular contour.
Conclusions

It is concluded that this new formulation has two parameters that are directly estimated from the experiment, describes well the growth kinetics of unperturbed Ehrlich and fibrosarcoma Sa-37 tumors, and confirms the fractal origin of the Gompertz formulation and the fractal property of tumors.

Introduction

One of the most interesting problems of current oncology is the understanding of the growth kinetics of a malignant tumor, named TGK (TGK), which follows a sigmoidal law. The TGK analysis is equally made by means of graphs of the number of cancer cells (n) versus time t, named n(t); tumor volume (V) versus t, named V(t); and/or the tumor mass (m) versus t, named m(t). This is due to the close relationship between these three physical quantities. Additionally, the sigmoidal form of TGK has been described by different equations, such as Gompertz, Logistics, Bertalanffy-Richards, Kolmogorov-Johnson-Mehl-Avrami modified, being the Gompertz equation (GE) the most used [1–3].

Izquierdo-Kulich et al. [4] report the fractal origin of GE (see appendix A). This fractal origin has also been reported in [5–8] but in terms only of the fractal dimension $D_f$. Here, we have considered the one in [4] because it also takes into account the fractal structure of the boundary of the tumor.

In the different formulations of the GE [1–3] and in the experiment [9, 10] the starting point of TGK is considered when the initial number of tumor cells ($n_0$) and the initial tumor volume ($V_0$) satisfy the conditions $n(t = 0) = n_0$ and $V(t = 0) = V_0$, respectively. In preclinical studies, the researcher chooses $n_0/V_0$ depending on the purpose of the investigation. The time that elapses from the inoculation of the tumor cells in the host until the tumor reaches $n_0/V_0$ is named $t_0$ [1, 3, 9]. Nevertheless, in clinics, $n_0/V_0$ corresponds to the tumor detected for the first time by the doctor by means of clinical and/or imaging methods. For this case, $t_0$ is the time that elapses from the tumor formation in the organism (via chemical, biological and/or physical carcinogens) [10], until its detection for the first time. This supposes $n_0 \geq n_{med}$, where $n_{med}$ is the minimum number of quantifiable cancer cells contained in the smallest measurable tumor volume, named $V_{med}$ ($V_0 \geq V_{med}$). The post-inoculation time that elapses until the tumor reaches $n_{med}/V_{med}$ is named $t_{med}$ ($t_0 \geq t_{med}$) [3].

In [4], it is considered the Gompertz equation given in Eq (1) (named GE$_1$)

$$n(t) = e^{(\frac{a}{b})\left(1-e^{-\beta t}\right)}.$$  

According the considerations in the previous paragraph, GE$_1$ has two limitations: 1) $n_0 = 1$, which means that the tumor has only one cell when it reaches $V_0$, in contradiction with the experiment [9, 10]. 2) The maximum capacity of the tumor ($n_\infty$) depends only on $\alpha$ and $\beta$ and not on $n_0$ ($n(t) = n_\infty = e^{\alpha/\beta}$ when $t \to \infty$). From the mathematical point of view, $n_\infty$ is the upper asymptote of TGK. Nevertheless, in the preclinical, the condition $t \to \infty$ is the post-inoculation time that elapses until the tumor reaches a certain volume, for which animals are sacrificed for ethical reasons [1]. In clinics, this condition means the time that elapses from the tumor formation in the organism until the patient dies.

Each undisturbed solid tumor histological variety, that grows in a type of syngeneic host to it, has its own natural history (only sigmoidal law), which does not depend on the selection of
n_0/V_0, as observed in [3, 10–12]. In the experiment, once the researcher fixes n_0/V_0, t_0 can be estimated \textit{a priori} when the tumor latency time is known, named t_{obs} (t_{obs} < t_0), which is the post-inoculation time that elapses until that the tumor is observed for the first time. In this case, the tumor is observable and palpable but not measurable. However, its size, named V_{obs} (V(t = t_{obs}) = V_{obs}), is estimated following the methodology reported in [1, 3]. When the tumor reaches V_{obs} it contains a number of cells, named n_{obs} (n(t = t_{obs}) = n_{obs}).

The interest of including n_{obs}/V_{obs} (n_{obs}/V_{obs} < n_{med}/V_{med} \leq n_0/V_0) in \textit{GE} is because an important part of vital cycle of a solid tumor occur before it is clinically detected (V_{med}), as reported in [1, 3, 10]. Furthermore, a high cellular viability ($\geq 95\%$) and a correct inoculation of the initial concentration of tumor cells ($c_o$) are guaranteed, t_{obs} can be known \textit{a priori} for a tumor histological variety that grows in a certain type of syngeneic host to it [3, 9–11].

As far as we reviewed, few experimental works report the analysis of TGK from V_{obs} [1, 3] and none of equations used to describe TGK includes n_{obs}/V_{obs}. In addition, in the literature a relationship of $\alpha$ and $\beta$ in terms of $D_f$, $d_f$ and n_{obs}/V_{obs} has not been reported in the literature. Therefore, the aim of this paper is to propose a new formulation of the \textit{GE} that includes n_{obs}/V_{obs}, n_0/V_0, $\alpha$, $\beta$, and to study the relation of these parameters with the fractal dimensions $D_f$ and $d_f$. The validity of this new mathematical formulation and the estimation of its parameters are determined from volumes of the Ehrlich and fibrosarcoma Sa-37 tumors that grow in BALB/c/Cenp mice, previously reported in [9]. Furthermore, the graphs of $\alpha$ versus $d_f$ and $\beta$ versus $d_f/D_f$ for different values of $u_2$ (the constant of the velocity of apoptosis) and n_{obs} are shown.

**Methods**

**Conventional Gompertz equation**

Eq (2), named \textit{GE}_2, is the conventional \textit{GE} and the most used when TGK starts at n_0/V_0, given by

$$n(t) = n_0 \cdot e^{(\beta)(1-e^{-\alpha \beta})}.$$  

Equation (2)

According to \textit{GE}_2, $n_\infty$ depends on n_0, $\alpha$ and $\beta$ ($n(t) = n_\infty = n_0 \cdot e^{\alpha/\beta}$ when $t \to \infty$) and results from solving the ordinary differential Eq (3) with its initial condition, given by

$$\begin{align*} 
\frac{dn}{dt} &= \alpha n - \beta \ln n \cdot \frac{n}{n_0} = \alpha n \left(1 - \frac{\beta}{\alpha} \ln \frac{n}{n_0}\right), \\
\ln(n(t = 0)) &= \ln(n_0).
\end{align*}$$

Equation (3)

\textit{GE}_2 suggests that n_0 (constant in time) has to be included in Eq (A2). Tjørve and Tjørve [2] report that n_0 acts as a parameter of shape ($n_\infty$ changes with n_0) or location ($n_\infty$ remains constant).

**Inclusion of n_0 in Eq (A2)**

In this topic was followed the methodology exposed in [4] and the initial number of tumor cells at $t = 0$, named n_{00}, was included in Eq (A2), resulting the following problem

$$\begin{align*} 
\frac{d\ln(n)}{dt} &= u_2(\theta - 1) \ln \left(\frac{n}{n_n}\right), \\
\ln(n(t = 0)) &= \ln(n_{00}) \quad n(t = 0) = n_{00}.
\end{align*}$$

Equation (4)
The exact solution of Eq (3) was given by

\[ n(t) = (n_{\infty})^{e^{-\beta t}} e^{(\frac{\beta}{\alpha})[1-e^{-\beta t}]}, \]  

with

\[ \left\{ \begin{array}{l}
\alpha = u_2 \left[ \ln \left( \frac{U_1}{U_2} \right) \right] = u_2 \ln \left( \frac{2d_f - 1}{d_f - 1} \right) \\
\beta = u_2(1 - \theta) = u_2 \left( 1 - \frac{d_f}{D_f} \right)
\end{array} \right. \]  

Two inconsistencies were found in [4]: 1) the coefficient 1.5 in the parameter \( \alpha \) of Eq (A3) was not correct but 2/3, as in Eq (6). 2) Different types of experimental tumors with the same starting point of TGK for GE

\[ GE_5 \]  

Eq (5), named GE, agrees with GE when \( n_0 = (n_{\infty})^{e^{-\beta t}} \). In addition, the parameters \( n_{a0} \) and \( n_0 \) coincided exactly at \( t = 0 \). The constant parameter \( n_{a0} (n_{a0} \geq n_{med}) \) constituted the starting point of TGK for GE and reached for \( t = t_0 \). Therefore, it was convenient to

| Parameters | Different formulations of Gompertz equations |
|------------|---------------------------------------------|
| \( \alpha \) (days\(^{-1}\)) | \( \text{GE}_1 \) | \( \text{GE}_2 \) | \( \text{GE}_3 \) | \( \text{GE}_4 \) |
| \( \beta \) (days\(^{-1}\)) | 0.160±0.005 | 0.466±0.012 | 0.285±0.004 | 0.719±0.067 |
| \( V_{obs(\alpha, \beta)} \) (cm\(^3\)) | 0.633±0.066 | 0.391±0.055 | 0.391±0.055 | 0.687±0.131 |
| \( u_2 \) (days\(^{-1}\)) | 0.720±0.061 | 0.768±0.056 | 0.764±0.032 | 0.611±0.052 |
| \( D_f \) | 1.467±0.410 | 1.404±0.346 | 1.583±0.836 | 1.023±0.192 |
| \( V_{obs(\alpha, \beta, \theta, D_f)} \) (cm\(^3\)) | - | - | 0.190±0.041 | - |
| \( \alpha_2 \) (days\(^{-1}\)) | 0.163±0.004 | 0.471±0.009 | 0.286±0.005 | 0.724±0.055 |
| \( \beta_0 \) (days\(^{-1}\)) | 0.134±0.104 | 0.287±0.005 | 0.275±0.009 | 0.261±0.007 |
| \( SE \) | 0.215±0.006 | 0.884±0.021 | 0.088±0.021 | 0.089±0.021 |
| \( PRESS \) | 1.313±0.154 | 0.015±0.012 | 0.015±0.012 | 0.016±0.012 |
| \( MPRESS \) | 1.128±0.144 | 0.015±0.012 | 0.015±0.012 | 0.016±0.012 |
| \( r^2 \) | 0.990±0.006 | 0.998±0.009 | 0.998±0.009 | 0.998±0.001 |
| \( r_2^2 \) | 0.990±0.006 | 0.998±0.009 | 0.998±0.009 | 0.998±0.001 |
| \( RMSE \) (cm\(^3\)) | 0.214±0.006 | 0.088±0.021 | 0.087±0.021 | 0.088±0.022 |
| \( D_{max} \) (cm\(^3\)) | 0.501±0.013 | 0.194±0.050 | 0.194±0.050 | 0.195±0.050 |
| \( e_a \) | 0.042±0.015 | 0.073±0.030 | 0.053±0.021 | 0.095±0.047 |
| \( e_f \) | 0.040±0.018 | 0.046±0.019 | 0.048±0.022 | 0.047±0.020 |
| \( e_{Vobs(\alpha, \beta, \theta, D_f)} \) | - | - | - | 0.033±0.009 |
| \( e_{u2} \) | 0.046±0.007 | 0.052±0.023 | 0.051±0.013 | 0.082±0.025 |
| \( e_{df} \) | 0.071±0.011 | 0.072±0.019 | 0.070±0.021 | 0.073±0.020 |
| \( e_{df} \) | 0.325±0.075 | 0.415±0.068 | 0.761±0.108 | 0.054±0.014 |
| \( e_{Vobs(\alpha, \beta, \theta, D_f)} \) | - | - | - | 0.032±0.008 |

Means ± standard deviation of parameters of the Ehrlich tumor and criteria for model assessment obtained for different formulations of Gompertz equations.

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differentiate $n_0$ and $n_{00}$ to compare $\text{GE}_2$ and $\text{GE}_5$ in order to avoid confusion in the interpretation of these two parameters. $\text{GE}_5$ revealed that $n_\infty$ depends only on $\alpha$ and $\beta$ and not on $n_{00}$ ($n(t) = n_\infty = e^{\alpha/\beta}$ for $t \to \infty$).

**Inclusion of $n_{\text{obs}}$ in $\text{GE}$**

Eq (3) was rewritten as

$$\frac{dn}{dt} = x n \left( 1 - \frac{\beta}{x} \ln \frac{n}{n_{\text{obs}}} \right),$$

$$n(t = 0) = n_{000}$$

where $n_{000}$ was the number of tumor cells that the researcher selected at $t = t_0$. The analytical solution of Eq (7) was given by

$$n(t) = \left[ n_{\text{obs}} \left( \frac{n_{000}}{n_{\text{obs}}} \right)^{e^{\alpha/\beta}} \right] e^{(\frac{x}{2})(1 - e^{-\beta x})}.$$  

Eq (8), named $\text{GE}_{80}$, agreed with $\text{GE}_5$ at $t = 0$ (for all $n_{\text{obs}}$) and when $n_{\text{obs}} = 1$ (for all $t$). The $\text{GE}_8$ coincided with the $\text{GE}_2$ at $t = 0$ (for all $n_{\text{obs}}$) and when $n_0 = n_{\text{obs}} (n_{000}/n_{\text{obs}})^{e^{\beta/\alpha}}$. The parameter $n_{\text{obs}} (n_{\text{obs}} < n_{\text{med}} \leq n_{000})$ was the starting point of TGK. In general, $n_{000}$ did not coincide with $n_0$ (GE$_2$) or $n_{00}$ (GE$_3$). Therefore, it was convenient to differentiate the parameters $n_0$, $n_{00}$ and $n_{000}$. In addition, the $\text{GE}_8$ evidenced that $n_\infty$ depends on $n_{\text{obs}}$, $\alpha$ and $\beta$, but not on $n_{000}$ ($n(t) = n_\infty = n_{\text{obs}} e^{\alpha/\beta}$ for $t \to \infty$). The parameters $\alpha$ and $\beta$ in terms of $u_2$, $U_1$, $\theta$, $d_f$, $D_f$ and $n_{\text{obs}}$ were given by

$$\left\{ \begin{array}{l}
\alpha = u_2 \left[ \ln \frac{U_1}{u_2} \right] - \beta \ln(n_{\text{obs}}) = u_2 \ln \left( \frac{2}{3} \frac{d_f}{D_f} - 1 \right) - \beta \ln(n_{\text{obs}}) \\
\beta = u_2 (1 - \theta) = u_2 \left( 1 - \frac{d_f}{D_f} \right)
\end{array} \right. $$

Eq (9) resulted from assuming that the value of $n$ in the steady state was $n_{ss} = n_{\text{obs}} e^{\alpha/\beta} = (u_2/ U_1)^{1/(\theta - 1)}$ and Eqs (7) and (8) were taken into account.

**Simulations**

**Simulation of Eq (9).** Eq (9) coincided with Eq (6) for $n_{\text{obs}} = 1$. The simulation of $\alpha$ (in days$^{-1}$) versus $d_f$ was shown for $D_f = 5$ and four values for $u_2$ (1, 10, 50 and 100 days$^{-1}$) and $n_{\text{obs}}$ (1, 5, 10 and 20 cells). For this, values of $d_f$ were varied from 0 to 5 with a step of 0.5, taking into account that $d_f < D_f$. The simulation of $\beta$ (in days$^{-1}$) against $d_f/D_f$ was shown for four values of $u_2$ (1, 10, 50 and 100 days$^{-1}$) and the values of $d_f/D_f$ were ranged from 0 to 5 with a step of 0.5.

**Simulations of GE$_2$, GE$_5$ and GE$_8$.** GE$_5$ was used as reference because GE$_5$ and GE$_8$ were reported for the first time in the literature. The simulations of GE$_2$, GE$_5$ and GE$_8$ were shown in a graph of $n(t)$. Simulation of GE$_2$ was made for different values of $n_0$ ($1 \times 10^3, 1 \times 10^4, 1 \times 10^5$ and $1 \times 10^6$ cells). Additionally, GE$_8$ was simulated for three different situations: 1) $n_{\text{obs}} = 1$ cell (GE$_5$ and GE$_8$ coincided) and different values of $n_{00}$ (5, 10, 15, 20 and 25 cells); 2) $n_{\text{obs}} = 1 \times 10^4$ cells and different values of $n_{000}$ ($1 \times 10^4, 5 \times 10^4, 1 \times 10^5$ and $2 \times 10^5$ cells); and 3) $n_{000} = 1 \times 10^5$ cells.
and different values of \( n_{\text{obs}} \) (5x10^3, 1x10^4, 5x10^4 and 1x10^5 cells). In all these simulations, \( \alpha = 1.0 \text{ days}^{-1} \) and \( \beta = 0.3 \text{ days}^{-1} \).

**Experimental groups**

In this study, \( V(t) \) was used by three reasons: 1) \( V(t) \) is related to \( n(t) \) and can be used interchangeably; 2) \( V(t) \) is less cumbersome to estimate than \( n(t) \) and it is frequently used in preclinical [9–11] and clinical [10] studies; and 3) the graphs of \( V(t) \) and \( n(t) \) shown sigmoidal changeably; 2) \( V(t) \) is less cumbersome to estimate than \( n(t) \) and it is frequently used in preclinical studies.

**Criteria for model assessment**

Experimental groups were formed, each consisting of 10 male BALB/c/Cenp mice. The first group corresponded to the Ehrlich tumor, denominated G1, while the second group to the fibrosarcoma Sa-37 tumor, denominated G2. Experimental data of \( V(t) \) for Ehrlich and fibrosarcoma Sa-37 tumors were reported in [9], corresponding to their control groups.

**Interpolation of experimental data**

The Hermite interpolation method [13] was used to interpolate volume data of each individual tumor, in G1 and G2.

**Estimation of values of \( \alpha, \beta, d, D_f \) and \( u_2 \) from experimental data**

Values of \( \alpha \) and \( \beta \) (GE1, GE2, GE3 and GE8) and \( V_{\text{obs}} \) (GE8) were obtained from the individual fitting of each tumor volume (Ehrlich and fibrosarcoma Sa-37). The value of \( V_{\text{obs}} \) estimated directly with GE8 was named \( V_{\text{obs}(\alpha,\beta)} \). The value \( V_0 = V_{90} = V_{000} = 0.5 \text{ cm}^3 \) was the tumor volume chosen to describe TGK. This volume value was reached 15 days after 2x10^6 cells for the Ehrlich tumor and 5x10^4 cells for the fibrosarcoma tumor Sa-37 were inoculated in the BALB/c/Cenp mouse (see details in [9]).

Three equations in terms of \( d_f, D_f \) and \( u_2 \) resulted when Eq (6) was substituted in GE1, GE2 and GE8. The values of these three parameters were determined when each of these equations was used to fit experimental data. Besides, Eq (12) was substituted in GE8 and resulted an equation in terms of \( d_f, D_f \, u_2 \) and \( V_{\text{obs}} \), from which their values were estimated from fitting experimental data. Once known the values of \( d_f, D_f \, u_2 \) and \( V_{\text{obs}} \), they were substituted in their respective Eqs (6) and (9) to calculate their corresponding values of \( \alpha \) and \( \beta \). Values of \( \alpha \), \( \beta \) and \( V_{\text{obs}} \) obtained by this way were denominated \( \alpha_c, \beta_c \) and \( V_{\text{obs}(u_2,d,D_f)} \), respectively, to distinguish these values from those that were directly obtained from fitting of the experimental data with GE1, GE2, GE5 and GE8.

The estimation errors for \( \alpha, \beta, d_f, D_f, u_2, V_{\text{obs}} \) and \( V_{\text{obs}(u_2,d,D_f)} \) were denominated \( e_\alpha, e_\beta, e_d, e_D_f, e_u_2, e_{V_{\text{obs}}} \) and \( e_{V_{\text{obs}(u_2,d,D_f)}} \), respectively. The estimation error for each parameter was reported for each individual tumor of Ehrlich and fibrosarcoma Sa-37.

The difference between \( \alpha \) and \( \alpha_c \), named \( \Delta \alpha (\Delta \alpha = \alpha - \alpha_c) \), was calculated for each equation (GE1, GE2, GE5 and GE8) and experimental group (G1 and G2). In addition, it was computed differences between \( \beta \) and \( \beta_c \), denominated \( \Delta \beta (\Delta \beta = \beta - \beta_c) \), and \( V_{\text{obs}(u_2,d,D_f)} \) and \( V_{\text{obs}(u_2,d,D_f)} \), denominated \( \Delta V_{\text{obs}} (\Delta V_{\text{obs}} = V_{\text{obs}(\alpha,\beta)} - V_{\text{obs}(u_2,d,D_f)}) \).

**Criteria for model assessment**

Five quality-of-fit criteria were used for fitting of experimental data with GE1, GE2, GE5 and GE8: the sum of squares of errors, SSE (Eq (10)); standard error of the estimate, SE (Eq (11)); adjusted goodness-of-fit coefficient of multiple determination, \( r^2_{a} \) (Eq (12)), that depended on
goodness-of-fit coefficient $r^2$ (Eq (14)); predicted residual error sum of squares, PRESS (Eq (14)); and multiple predicted residual sum error of squares, MPRESS (Eq (15)) \[1, 3, 14\], given by

$$\text{SSE} = \sum_{j=1}^{n_1} (\hat{V}'_j - V'_j)^2,$$

$$SE = \sqrt{\frac{\sum_{j=1}^{n_1} (\hat{V}'_j - V'_j)^2}{n_1 - k}},$$

$$r_a^2 = 1 - \frac{n_1 - 1}{n_1 - k} (1 - r^2) = \frac{(n_1 - 1) r^2 - k + 1}{n_1 - k},$$

$$1 - r^2 = \frac{\sum_{j=1}^{n_1} (\hat{V}'_j - V'_j)^2}{\sum_{j=1}^{n_1} (V'_j)^2 - \frac{1}{n_1} \left( \sum_{j=1}^{n_1} V'_j \right)^2},$$

$$\text{PRESS} = \frac{\sum_{j=1}^{n_1} (\hat{V}'_j)^4 - V'_j^4}{n_1 - k},$$

$$\text{MPRESS}(m) = \frac{\sum_{j=m+1}^{n_1} (\hat{V}'_j)^4 - V'_j^4}{n_1 - m},$$

where $V'_j$ was the $j$-th measured tumor volume at discrete time $t_j, j = 1, 2, \ldots, n_1$; $\hat{V}'_j$ was the $j$-th estimated tumor volume by GE$_1$, GE$_2$, GE$_5$ and GE$_8$, $n_1$ the number of experimental points ($n_1 = 10$) and $k$ the number of parameters ($k = 2$ for GE$_1$, GE$_2$ and GE$_5$, and $k = 3$ for GE$_8$). The fitting was considered to be satisfactory when $r_a^2 > 0.98$. Higher $r_a^2$ meant a better fit. $(V'_j)^4$ was the estimated value of $V'_j$ when GE$_1$/GE$_2$/GE$_5$/GE$_8$ was obtained without the $j$-th observation. MPRESS removed the last $n_1 - m$ measurements. Each equation (GE$_1$, GE$_2$, GE$_5$ and GE$_8$) was fitted to the first $m$ measured experimental points ($m = 3, 4$ or $5$) and then from calculated model parameters the error between tumor volume estimated and measured values in the remaining $n_1 - m$ points was calculated. Least Sum of Squares of Errors was obtained when SSE was minimized in the Marquardt-Levenberg optimization algorithm.

The Root Means Square Error, RMSE (Eq (16)) and the maximum distance, $D_{\max}$ (Eq (17)) were also calculated following the methodology suggested in \[1, 3, 14\], given by

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{M} (F_i - G_i)^2}{M}},$$

$$D_{\max} = \max|F_i - G_i|,$$

where $M$ was the number of interpolated data of tumor kinetics (graph of $V(t)$). $F_i$ was the $i$-th
tumor volume of the experimental data, which was chosen as reference. $G_i$ was the $i$-th tumor volume calculated with $GE_1$, $GE_2$, $GE_5$ and $GE_8$.

Each fit with the $GE_1/GE_2/GE_5/GE_8$ was performed for each animal growth curve. A computer program was implemented in the Matlab® software (version R2012b 64-bit, Institute for Research in Mathematics and Applications, University of Zaragoza, Spain) to calculate the tumor volume. In addition, the mean ± standard error of each parameter of the equation ($\alpha$, $\beta$, $V_{\text{obs}(\alpha, \beta)}$, $d_0$, $D_1$, $V_{\text{obs}(u_2, d_1, D_1)}$, $\alpha_c$, $\beta_c$), fit criterion (SE, PRESS, MPRESS, $r^2_a$, RMSE and $D_{\text{max}}$) and estimation error ($e_\alpha$, $e_\beta$, $e_{df}$, $e_{D_1}$, $e_{V_{\text{obs}}}$ and $e_{V_{\text{obs}(u_2, D_1, D_1)}}$) were calculated from their individual values, in each experimental group, following the methodology reported in [1, 3]. These calculations were performed on a PC with an Intel(R) core processor(TM) i7-3770 at 3.40 GHz with a Windows 10 operating system. All calculations took approximately 10 min, for each equation.

**Results**

**Simulation of Eq (6)**

Fig 1 showed the simulations of $\beta$ versus $d/D_f$ (Fig 1A) and $\alpha$ versus $d_f$ (Fig 1B) for different values of $u_2$. The positive values of $\alpha$ (in the interval $0 \leq d_f < 1$) and $\beta$ (in the interval $d_f/D_f < 1$) increased non-linearly with the increase of $d_f$ and decreased linearly with the increase of $d_f/D_f$, respectively. The negative values of $\alpha$ increased non-linearly with the increase in $d_f$ ($d_f > 1.5$). The negative values of $\beta$ decreased linearly with the increase of $d_f/D_f$ ($d_f/D_f > 1$). These behaviors were noticeable for the greater value of $u_2$. Additionally, the parameter $\alpha$ had a discontinuity in the interval $1 < d_f < 1.5$ and $\beta = 0$ when $d_f/D_f = 1$ for all values of $u_2$.

**Simulation of Eq (9)**

Results of the simulation of $\beta$ versus $d_f/D_f$ in Eq (11) coincided with that shown in Fig 1A (see Eqs (6) and (9)). The simulation of $\alpha$ versus $d_f$ for $n_{\text{obs}} = 1$ (Fig 2A) reproduced the same result as in Fig 1B. However, values of $\alpha$ were more negative, in the interval $0 \leq d_f < 1$, when $n_{\text{obs}}$ increased, being noticeable for the higher value of $u_2$ (Fig 2B, 2C and 2D). In Fig 2A, 2B, 2C and 2D, as in Fig 1B, it was observed a discontinuity of $\alpha$ in the interval $1 < d_f < 1.5$.

---

**Fig 1. Simulation of Eq (6).** For different values of $u_2$ (1, 10, 50 and 100 days$^{-1}$) it is plotted (A) Graph of $\alpha$ (in days$^{-1}$) versus $d_f$ and (B) Graph of $\beta$ (in days$^{-1}$) versus $d_f$/D_f.

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Simulations of $GE_2$, $GE_5$ and $GE_8$

Fig 3 showed the behavior of $n(t)$ when $GE_2$ (Fig 3A), $GE_5$ (Fig 3B) and $GE_8$ (Fig 3C and 3D) were used. Fig 3A revealed that the highest value of $n_\infty$ and the fastest TGK occurred for the highest values of $n_0$ and $\alpha$. Fig 3B showed that TGK was faster with the increase of $n_{obs}$ and all TGK tended to the same value of $n_\infty$ for all value of $n_{obs}$, keeping constant values of $\alpha$ and $\beta$. In this case, TGK was faster when the value of $n_{obs}$ increased with respect to $n_{obs}$ (Fig 3B), being noticeable when $n_{obs}$ increased with respect to 1 (Fig 3C). It is important to note that $n_0 = n_{obs}$ (Fig 3B) and $n_0 = n_{obs00}$ (Fig 3C and 3D).

The results of Fig 3D showed that TGK grows slower (when $n < n_{obs00}$) and then faster (when $n > n_{obs00}$) for the greater value of $n_{obs}$; all TGK were cut at $t = 0$ (same value of $n_{obs00}$), for all value of $n_{obs}$ and the value of $n_\infty$ depended on $n_{obs}$ and not $n_{obs00}$ for each TGK. The results shown in Fig 3 were noticeable when the value of $\alpha$ increased with respect to that of $\beta$ (results not shown).

Fig 2. Simulation of Eq (9). For different values of $u_2$ (1, 10, 50 and 100 days$^{-1}$) it is plotted the graph of $\alpha$ (in days$^{-1}$) versus $d_f$ for (A) $n_{obs} = 1$ cell. (B) $n_{obs} = 5$ cells. (C) $n_{obs} = 10$ cells. (D) $n_{obs} = 20$ cells.

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Fitting of experimental data with \( GE_1 \), \( GE_2 \), \( GE_5 \) and \( GE_8 \) and estimation of values of \( \alpha \), \( \beta \), \( d_f \), \( D_f \) and \( u_2 \)

The mean ± standard deviation of each parameter of the equation, fit criterion and estimation error were shown in Tables 1 and 2 of each equation (\( GE_1 \), \( GE_2 \), \( GE_5 \) and \( GE_8 \)) used to fit experimental data of the Ehrlich and fibrosarcoma Sa-37 tumors, respectively. Tables 1 and 2 shown for these two tumor histological varieties: \( 0 < d_f < 1; 1 < D_f < 2; 0 < u_2 < 1 \); the highest values of \( \alpha \), \( u_2 \) and the lowest values of \( d_f \) and \( D_f \) for \( GE_9 \); the lowest SE values for \( GE_5 \) and \( GE_8 \); the lowest values of PRESS, MPRESS, RMSE and \( D_{max} \); the highest values of \( r^2 \) and \( r_a^2 \) for \( GE_2 \), \( GE_5 \) and \( GE_8 \); and values of the parameter \( \alpha \) differed when \( GE_1 \), \( GE_2 \), \( GE_5 \) and \( GE_8 \) were used. Nevertheless, the parameter \( \beta \) was the same when \( GE_2 \), \( GE_5 \) and \( GE_8 \) were used, but not for \( GE_1 \).

For the Ehrlich tumor, \( \Delta \alpha = 0.003, 0.005, 0.001 \) and \( 0.005 \) days\(^{-1} \) for \( GE_1 \), \( GE_2 \), \( GE_5 \) and \( GE_8 \), respectively. The variable \( \Delta \beta = 0.012, 0.026, 0.014 \) and \( 0.000 \) days\(^{-1} \) for these respective equations and \( \Delta V_{obs} = 0.007 \) cm\(^3\). For the tumor fibrosarcoma Sa-37, \( \Delta \alpha = 0.009, 0.003, 0.006 \) and \( 0.019 \) days\(^{-1} \) for \( GE_1 \), \( GE_2 \), \( GE_5 \) and \( GE_8 \), respectively. The variable \( \Delta \beta = 0.025, 0.038, 0.028 \) and \( 0.000 \) days\(^{-1} \) for these respective equations and \( \Delta V_{obs} = 0.006 \) cm\(^3\).
Table 2. Parameters of the models for the fibrosarcoma Sa-37 tumor.

| Parameters | \( \text{GE}_1 \) | \( \text{GE}_2 \) | \( \text{GE}_3 \) | \( \text{GE}_8 \) |
|------------|-----------------|-----------------|-----------------|-----------------|
| \( \alpha \) (days\(^{-1}\)) | 0.188±0.016 | 0.491±0.034 | 0.316±0.018 | 0.833±0.132 |
| \( \beta \) (days\(^{-1}\)) | 0.127±0.017 | 0.252±0.018 | 0.252±0.018 | 0.252±0.018 |
| \( V_{\text{obs}(0)} \) (cm\(^3\)) | - | - | - | - |
| \( u_2 \) (days\(^{-1}\)) | 0.274±0.093 | 0.530±0.152 | 0.471±0.132 | 0.576±0.070 |
| \( d_f \) | 0.759±0.074 | 0.822±0.070 | 0.746±0.058 | 0.688±0.042 |
| \( D_f \) | 1.704±0.672 | 1.810±0.612 | 1.837±0.613 | 1.256±0.191 |
| \( V_{\text{obs}(u_2)}; d_f; D_f \) (cm\(^3\)) | - | - | - | 1.42±0.029 |
| \( \alpha_c \) (days\(^{-1}\)) | 0.197±0.020 | 0.494±0.029 | 0.322±0.011 | 0.814±0.082 |
| \( \beta_c \) (days\(^{-1}\)) | 0.152±0.018 | 0.290±0.020 | 0.280±0.017 | 0.252±0.018 |
| \( \text{SE} \) | 0.162±0.008 | 0.082±0.038 | 0.083±0.038 | 0.083±0.038 |
| \( \text{PRESS} \) | 0.761±0.227 | 0.063±0.059 | 0.063±0.059 | 0.064±0.060 |
| \( MPRESS \) | 0.623±0.203 | 0.063±0.059 | 0.064±0.059 | 0.064±0.060 |
| \( r^2 \) | 0.995±0.004 | 0.998±0.001 | 0.998±0.001 | 0.999±0.001 |
| \( r^2_f \) | 0.996±0.004 | 0.998±0.001 | 0.998±0.001 | 0.999±0.001 |
| \( \text{RMSE (cm}^3\) | 0.161±0.008 | 0.082±0.038 | 0.082±0.038 | 0.082±0.038 |
| \( D_{\text{max}} \) (cm\(^3\)) | 0.499±0.013 | 0.206±0.109 | 0.206±0.100 | 0.207±0.110 |
| \( e_a \) | 0.025±0.011 | 0.046±0.022 | 0.061±0.012 | 0.079±0.035 |
| \( e_\beta \) | 0.034±0.009 | 0.053±0.013 | 0.057±0.029 | 0.055±0.023 |
| \( e_{V_{\text{obs}}} \) | - | - | - | 0.027±0.007 |
| \( e_{u_2} \) | 0.031±0.003 | 0.035±0.013 | 0.039±0.010 | 0.061±0.015 |
| \( e_{d_f} \) | 0.065±0.012 | 0.069±0.014 | 0.067±0.016 | 0.071±0.025 |
| \( e_{D_f} \) | 0.235±0.086 | 0.336±0.045 | 0.679±0.119 | 0.125±0.031 |
| \( e_{V_{\text{obs}}} \) (\( \Delta V_{\text{obs}} \)) | - | - | - | 0.041±0.017 |

Means ± standard deviation of parameters of the fibrosarcoma Sa-37 tumor and criteria for model assessment obtained for different formulations of Gompertz equations.

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Discussion

This study shows that \( \text{GE}_2 \), \( \text{GE}_3 \) and \( \text{GE}_8 \) can be used interchangeably to describe experimental data of Ehrlich and fibrosarcoma Sa-37 tumors, taking into account their higher values of \( r^2 \) and \( r^2_f \), and lower values of each parameter of the equation, fit criterion, estimation error, \( \Delta \alpha \), \( \Delta \beta \) and \( \Delta V_{\text{obs}} \) (\( \Delta V_{\text{obs}} \) is only calculated for \( \text{GE}_8 \)).

The theoretical and experimental results of this work confirm different findings reported previously in the literature, such as: 1) the fractal origin of \( \text{GE}_1 \), \( \text{GE}_2 \), \( \text{GE}_3 \) and \( \text{GE}_8 \), as reported in [4, 15]; 2) the fractal property of tumors once reached \( n_{\text{med}}/V_{\text{med}} \), a matter that agrees with [16, 17]; 3) the role of the fractal dimension for the understanding of TGK, as suggested by Sokolov [18] and Breki et al. [19]; and 4) \( 1 < D_f < 2 \), in agreement with [4, 20, 21] and the preferential growth along the largest diameter of the tumor, despite its ellipsoidal geometry [1, 3, 9, 11]. This fourth finding is in contradiction with \( 2 < D_f < 3 \) reported by Breki et al. [19] in patients with metastatic melanoma; 5) The condition \( 0 < u_2 < 1 \) for both types of tumors is consistent with the Steel equation [12]. If \( u_2 = 0 \), then the tumor growth fraction must be high so that its mean doubling time (TD) is short, in contrast to [10, 12]. If \( u_2 = 1 \text{ day}^{-1} \) (all cancer cells are in apoptosis), TD \( \rightarrow \infty \) and \( \alpha = 0 \) (tumor self-destruction), in contrast to the failure of the apoptosis mechanism in malignant tumors (because of the gene p-53 is repressed) and the existence of other cell loss mechanisms (metastasis, necrosis and exfoliation) [10, 11, 22].
The increase in $u_2$ brings about a decrease in TD and therefore a higher value of $\alpha$ (Figs 1B, 2A, 2B, 2C and 2D).

Other novel findings have been revealed in this investigation that may be of interest for understanding of TGK, such as: 1) TGK sigmoidal form and $n_{\infty}/V_{\infty}$ do not depend on $n_0$ and if on $\alpha$, $\beta$ and $n_{obs}/V_{obs}$ when a given tumor histological variety grows in a certain type of syngeneic host to it. In this way, the action form of parameter $n_0/V_0$ (form or location) is eliminated in GE$_2$, as reported in [2]. 2) The GE$_8$ states that $n_0$ in the GE$_2$ is not a constant parameter but depends non-linearly with $n_{obs}/V_{obs}$ $n_{0000}/n_{obs}$ $(V_{0000}/V_{obs})$, $\beta$ and t. 3) The growth of a malignant tumor occurs for $0 < d_\ell < 1$ and not when $d_\ell = 0$ ($\alpha = 0$: the tumor does not form), $1 < d_\ell < 1.5$ (discontinuity of $\alpha$ due to forbidden conformations or very unlikely tumor) and $d_\ell > 1.5$ ($\alpha < 0$: the tumor self-destructs), in contrast to the values of $d_\ell (1 < d_\ell < 2)$ reported in [4, 14, 23]. The forbidden conformations of the tumor can be explained by its stereochemistry due to the steric collides between all its elements and the tumor-host interaction. 4) The increase of $\alpha$ with the increase of $d_\ell$ at $0 < d_\ell < 1$, confirms that the growth efficiency of a malignant tumor increases with its $d_\ell$ in agreement with [17, 24]. 5) Eq (11) states that this increase of $\alpha$ with $d_\ell$ occurs if $n_{obs}$ satisfies strictly the condition $n_{obs} < [(2/3d_\ell - 1)/(d_\ell - 1)]^{\gamma/\beta}$; otherwise, $\alpha < 0$ for all $\beta$ positive (Fig 2B, 2C and 2D). The case $\alpha < 0$ means that the tumor self-destructs, in contrast to the experiment.

The established condition for $n_{obs}$ suggests that: 1) $n_{obs}/V_{obs}$ depends on $d_\ell$ and the ratio $u_2/\beta$; 2) the fractal property of a malignant tumor also happens before or long before its detection ($n_{med}/V_{med}$), as reported in [1, 25]; 3) the ratio $u_2/\beta$ may be an indirect indicator of the apoptosis-angiogenesis relationship reported in [26, 27]; 4) endogenous anti-angiogenic factors or inhibitors of angiogenesis (endostatin, angiostatin, among others) are present in the tumor before or long before reaching $n_{med}/V_{med}$; 5) the term $e^{-\beta t}$ (see GE$_8$ and the established condition for $n_{obs}$) and the decrease of the parameter $\beta$ with the increase of $d_\ell/D_\ell$ corroborate the essential role of angiogenesis process and the displacement of the balance between endogenous anti-angiogenic factors and endogenous pro-angiogenic factors towards these latter, when the tumor volume grows at time $t$, consistent with [10, 17, 22, 28, 29].

From the biophysical point of view, the condition $0 < d_\ell < 1$ may suggest that the contours of Ehrlich and fibrosarcoma Sa-37 malignant tumors have zero area and/or they are totally disconnected. The first assumption confirms that these two types of tumors can be delimited from their surrounding healthy tissue, as in [9, 11]. The second hypothesis is based on proposition 2.5 [30]: “A set $F \subset \mathbb{R}^n$ with $\dim_H F < 1$ is totally disconnected”. In this proposition, $F$ is any set and $\dim_H$ is the fractal dimension Hausdorff. It is important to note that, although the tumor boundary is wide, $d_\ell < 1$ if its only fractality is given by a totally disconnected line contained in that wide band.

From the biophysical point of view, the tumor contour totally disconnected can indicate the existence in it of pores/channels formed randomly of different sizes and shapes, changing in the time. This porous contour of a tumor may be related to the angiogenesis process (formation of blood vessels), the formation of spicules by fragmentation of the contour into simple forms of molds (for example, triangles), roundness, irregular edge, anisotropy, roughness and compactness, findings reported in [1, 3, 10, 22, 31–34]. We believe that the tumor angiogenesis process can be regulated by the amount of pores/channels existing in its contour to interconnect with the surrounding healthy tissue. This hypothesis can corroborate that the angiogenesis of a malignant tumor is an emergency and regulated by the structural and conformational dynamic transformations that occur during TGK, as reported in [1]. On the contrary, if these pores/channels do not exist, the tumor would behave as an isolated system and would self-destruct, in contrast to the experiment.
Fig 3 deserves a careful interpretation, taking into account experimental results reported in the preclinical [1, 3, 9, 11, 14] and clinical [10] studies. The result of Fig 3A corresponds with the selection of different values of $n_0/V_0$ in the same TGK for different instants $t_0$. For this case, in the experiment is guaranteed fixed $c_0$, cell viability, the tumor histological variety and the type of syngeneic host to it. The higher value of $n_0/V_0$ in the same TGK means a larger tumor size, which is reached at a higher $t_0$.

Results of Fig 3B and 3C are associated to the same tumor histological variety that grows in several types of syngeneic hosts to it. For this case, $c_0$ and cell viability fixed are guaranteed, taking into account the role of the immune system in the delay of TGK, depending on its immunocompetence degree [10, 11, 22, 35]. As a result, tumors reach different values of $n_{obs}/V_{obs} \circ n_{000}/V_{000}$ at the same time $t_0$. The higher value of $n_{000}/V_{000}$ (in Fig 3B) or $n_{000}/V_{000}$ (in Fig 3C) corresponds to the lower immunocompetence degree of the host (e.g., an immunosuppressed host).

Results of Fig 3B refer to two possible situations: 1) different tumor histological varieties that grow in the same type of syngeneic host to them. For this case, $c_0$ is different so that each tumor histological variety reaches the same value of $n_{000}/V_{000}$ at the same time $t_0$. 2) A given tumor histological variety that grows in different types of syngeneic hosts to it. For this case, $c_0$ is the same for each tumor histological variety. For these two cases, $n_{obs}/V_{obs}$ for each tumor histological variety is reached in a different $t_{obs}$, in accordance with the experiment [9, 11]. These two situations become noticeable when $\beta$ approaches $\alpha$ (results not shown). Furthermore, this figure reveals that for the highest value of $n_{obs}/V_{obs}$ (reached in a greater $t_{obs}$) TGK is slower for $n(t) < n_{000}$ ($V(t) < V_{000}$) and then faster for $n(t) > n_{000}$ ($V(t) > V_{000}$). By contrast, the tumor that has the lowest $n_{obs}/V_{obs}$ is the fastest growing for $n(t) < n_{000}$ ($V(t) < V_{000}$) and then its TGK is slower for $n(t) > n_{000}$ ($V(t) > V_{000}$).

The advantages of GE$_\alpha$ over the various formulations of GE [2, 3], the Hahnfeldt model [36–38] and mKJMA equation [1], used to describe undisturbed TGK, are: 1) inclusion of two parameters ($n_{obs}/V_{obs}$ y $n_{000}/V_{000}$) that are measured and estimated from experimental data. 2) TGK and $n_\infty/V_\infty$ can be known a priori if $n_{obs}/V_{obs}$ (starting point of TGK), reached at $t_{obs}$, is estimated for each type of tumor that grows in a syngeneic host to it, as reported in [1, 3, 11].

The relation of the tumor growth with $d_f$ and $D_f$ is previously obtained by using a mesoscopic formalism and fractal dimension [39]. Besides, Izquierdo-Kurlich [39] report the differences between $d_f$ and $D_f$ and propose a relation between $d_f$ and the dynamic quotient on the interface, named $k_\alpha$, (see Eq (48)). This relationship differs from that reported in [4] (see Eq (3)), which is used to obtain Eq (8). If the relation published in [39] is taken into account in this study, Eq (8) is also obtained, except a small change in $\alpha$ numerator (1/2 instead of 1). As a result, 0.75 and 1 are the discontinuities of $\alpha$, instead of 1 and 1.5, respectively. Nevertheless, these change do not affect significantly the results of this manuscript and confirm that tumors exits for $0 < d_f < 1$. It can be verified that $d_f$ for Ehrlich and fibrosarcoma Sa-37 tumors are less than 0.75 and 1 when Eq (48) in [39] and Eq (3) in [4] are used.

In this study, the tumor growth in the time results of the complex interactions that happen in the tumor and between it and the surrounding healthy tissue, as in [3,14]. Nevertheless, in it does not explicitly discuss the interactions among the individuals neither the cooperative capacity of they in a population to explain its growth behavior, as in [25, 5–8]. These works confirm the fractal property of the tumors, as in this study. Therefore, an additional study may include these interactions for Eq (8).

Further studies can be carried out to validate GE$_\alpha$ in TGK of different tumor histological varieties that grow in both immune-competent and immune-deficient organisms. This will allow us to know how $D_f$, $d_f$, $V_2$, $V_{obs}(n, \beta)$ and $V_{obs}(u, d_e, D_f)$ change when using different types of tumors and degrees of immune-competence of several organisms, as well as confirming the
relationship of these five parameters with the aggressiveness [1], angiogenesis [17], coherence [15, 16], anisotropy, heterogeneity, hardness, changes in the mechanical-elastic-electrical properties of a tumor, among others findings [1].

Conclusions
GE8 describes well the growth kinetics of the Ehrlich and fibrosarcoma Sa-37 tumors and includes two parameters that are directly estimated from the experiment that confirm the fractal property of the tumors and the fractal origin of different Gompertz formulations.

Appendix A
In [4] it is assumed that the growth ratio of the number \( n(t) \) of tumor cells obeys to the differential equation

\[
\frac{dn}{dt} = u_1 m - u_2 n, \quad n(0) = n_0,
\]

where \( m \) represents the number of tumor cells at the boundary of the tumor, \( u_1 \) is the constant of the velocity of the mitosis and \( u_2 \) is the constant of the velocity of apoptosis.

Assuming that the boundary has a fractal structure with dimension \( d_f \), then \( m = k_1 r^{d_f} \), \( r \) being the average radius of the tumor. On the other side, \( n \) depends on the morphology of the tumor, described by the fractal dimension \( D_f \) and \( n = k_2 r^{D_f} \). The morphological constants \( k_1 \) and \( k_2 \) are related to the magnification of the image [4].

Substituting these values of \( m \) and \( n \) and eliminating \( r \), Eq (1) can be written as a Bertalanffy-Richards equation.

\[
\frac{dn}{dt} = U_i n^\theta - u_2 n = n u_2 \left( \left( \frac{n}{n_{ss}} \right)^{1-\theta} - 1 \right),
\]

where \( n_{ss} = \left( u_2/U_i \right)^{1/(1-\theta)} \) is the value of \( n \) at the steady state, the dimensionless morphological parameter \( \theta \) is defined by \( \theta = d_f/D_f \) and \( U_i \) is given by \( U_i = u_1 k_1/k_2^\theta \).

Taking into account that

\[
\ln x = \lim_{s \to \infty} s (x^s - 1),
\]

the above equation is approximated in [4] by the Gompertz equation

\[
\begin{align*}
\frac{d\ln(n)}{dt} &= u_2 (\theta - 1) \ln \left( \frac{n}{n_{ss}} \right), \\
\ln(n)_{t=0} &= 0 \quad n(t = 0) = 1
\end{align*}
\]

This approximation is valid when \( \theta \to 1 \) or \( n \to n_{ss} \).

In [36] it is justified that the quotient \( U_i/u_2 \) can be expressed as a function of \( d_f \) and in [4] it is shown that the solution of the differential system (2)

\[
n(t) = e^{-\left( \frac{\ln(U_i/u_2)1-\theta (\theta-1)}{\theta - 1} \right)t}
\]

can be expressed as a Gompertz equation (Eq (1) in this paper)

\[
n(t) = e^{\left( \frac{1}{\theta} \right) (1-e^{-\theta t})}
\]

with the intrinsic growth rate of the undisturbed tumor, named \( \alpha (\alpha > 0) \), and the deceleration...
factor, named $\beta$ ($\beta > 0$), related to the tumor fractal dimensions by

$$
\begin{align*}
\alpha &= u_2 \left( \ln \frac{U_1}{u_2} \right) = u_2 \ln \left( \frac{1.5d_f - 1}{d_f - 1} \right), \\
\beta &= u_2 (1 - \theta) = u_2 \left( 1 - \frac{d_f}{D_f} \right),
\end{align*}
$$

(A3)

Supporting information

S1 Data. Supporting information. (TXT)

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