Theory in Biosciences (2021) 140:197–203
https://doi.org/10.1007/s12064-021-00344-8

ORIGINAL ARTICLE

Nutrient supply, cell spatial correlation and Gompertzian tumor growth

P. Castorina[1,2,3] · D. Carco'[1]

Received: 2 March 2021 / Accepted: 3 May 2021 / Published online: 14 May 2021

Abstract
Gompertzian tumor growth can be reproduced by mitosis, related to nutrient supply, with local spatial cell correlations. The global energy constraint alone does not reproduce in vivo data by the observed values of the nutrient expenditure for the cell activities. The depletion of the exponential growth, described by the Gompertz law, is obtained by mean field spatial correlations or by a small word network among cells. The well-known interdependence between the two parameters of the Gompertz growth naturally emerges and depends on the cell volume and on the tumor density.

Keywords Tumor growth · Gompertz law · Tumor cell metabolism · Cell spatial correlation

Introduction

Tumor growth is a complex phenomenon which includes sustaining proliferative signaling, evading growth suppressors, resisting cell death, inducing angiogenesis and activating invasion and metastasis (Hanahan and Weinberg 2011).

The tumor evolution (size, chemotherapy and radiotherapy effects) can be described by macroscopic growth laws, coarse-grain approximations of complex cell dynamics at microscopic level.

In particular, the Gompertz law (GL) has been extensively applied after the seminal paper by Norton (1988) on breast cancer and confirmed by a recent analysis (Vaghi 2020) as a very useful tool for a quantitative understanding of the tumor growth.

The GL, originally formulated as an actuarial curve for the population of England almost two centuries ago (Gompertz 1825), describes the dynamics of a variety of natural phenomena : magnetic hysteresis (Stauffer and Stanley 2017), kinetics of enzymatic reactions (Murray 1989), oxygenation of hemoglobin (Murray 1989), intensity of photosynthesis as a function of CO_2 concentration (Murray 1989), drug dose–response curve, dynamics of growth (e.g., bacteria, normal eukaryotic organisms and cancer) (Laird et al. 1965a, b; Calderon and Kwembe 1991; Waliszewski et al. 1998), spread of COVID-19 (Castorina et al. 2020).

For human mortality, a derivation of the GL can be obtained by the reliability theory designed for man-made machines (Gavrilov and Gavrilova 2001) and by a different model (Shklovskii 2005) which relates the human survival probability with an exponentially rare escape of abnormal cells from immunological response.

Possible theoretical bases of the Gompertz growth for biological systems have been addressed in the literature, since long time and from different points of view (Wheldon 1988; Bajzer and Vuk-Pavlovic 1997; Savageau 1979; Witten 1985; Kendal 1985; Frenzen and Murray 1986; Gyllenberg and Webb 1989; Makany 1991; Ling and He 1993; Qi et al. 1993; Bajzer 1999; Afenya and Calderon 2000; Bajzer and Vuk-Pavlovic 2000; Mombach et al. 2002; Waliszewski and Konarski 2003). More recently, the GL has been discussed by a biochemical approach (Anguelov et al. 2017) and by statistical mechanics methods (Castorina and Zappala 2006), where the energetic balance is considered as the key dynamical ingredient (for a recent review of tumor growth laws, see ref. Jarrett (2018)). Indeed, the idea that the GL dynamics can be considered as an optimization problem, as, for example, an "energy" budget problem (where "energy" can have many different meanings) could explain why it emerges at macroscopic level for so different systems.

✉ P. Castorina
paolo.castorina@ct.infn.it

[1] Istituto Oncologico del Mediterraneo, Viagrande, Italy

[2] Istituto Nazionale Fisica Nucleare, Catania, Italy

[3] Institute of Particle and Nuclear Physics, Charles University, Prague, Czech Republic

In the general classification of growth laws (Castorina et al. 2006), the GL is in the U2 universality class, i.e., it depends on two parameters, with a strong reduction with respect to the large number of dynamical variables of the microscopic models.

A crucial feature of the macroscopic evolution laws is that the feedback effect is global: It depends on the total population N at time t, whereas the microscopic dynamics is local, due, for example, to competition for resource. This aspect becomes more tricky for the GL where the global dependence has the typical nonlinear $ln[N]$ behavior.

In this letter, we study cancer growth by considering mitosis with specific cell local spatial correlations which globally reproduce the GL. The purpose of the analysis is twofold. One shows the crucial role of cell spatial correlations to reproduce in vivo data by GL with realistic values of the growth parameters. Indeed, the model based on the nutrient supply balance, without the local dynamical competition for resources, is not able to describe the tumor progression with the observed cell metabolic activities. Moreover, it is well known that the two GL growth parameters are linearly correlated and this property naturally arises by the link between the spatial correlation effects and cell properties.

Although the language of a biological system is used, the results are more general and can be applied to any local bifurcation process with spatial correlation among participants.

In the next section, we recall the GL, and in Sect. 2, the models are proposed. Section 3 contains our comments and conclusions. "Appendices A and B" are devoted to mathematical details and to the time evolution based on the global nutrient supply constraint only.

Gompertz growth laws

General macroscopic growth laws for a population $N(t)$ are solutions of the differential equation (for a classification see Castorina et al. (2006))

$$\frac{1}{N(t)}\frac{dN(t)}{dt} = f[N(t)], \tag{1}$$

where $f(N)$ is the specific growth rate and its N dependence describes the feedback effects during the time evolution. If $f(N)$ =constant, the growth follows an exponential pattern, with no limit for $t \to \infty$. On the other hand, a saturation is obtained by the Gompertz equation, i.e.,

$$\frac{1}{N(t)}\frac{dN(t)}{dt} = \alpha_g - k_g \ln\frac{N(t)}{N_0} \qquad \text{Gompertz}, \tag{2}$$

where α_g and k_g are constants and N_0 is the initial value. By defining

$$\alpha_g + k_g \ln N_0 = k_g \ln N_\infty, \tag{3}$$

one gets

$$\frac{1}{N(t)}\frac{dN(t)}{dt} = -k_g \ln\frac{N(t)}{N_\infty}, \tag{4}$$

where N_∞ is the carrying capacity, i.e., the steady state is reached for $dN/dt = 0$, when N is equal to N_∞.

A different, equivalent, formulation of the Gompertz equation is

$$\frac{1}{N(t)}\frac{dN(t)}{dt} = \alpha e^{-\beta t}. \tag{5}$$

Indeed, the solution of the previous equation turns out to be

$$ln[N(t)/N_0] = \frac{\alpha}{\beta}(1 - e^{-\beta t}) \tag{6}$$

which gives

$$ln[N_\infty/N_0] = \frac{\alpha}{\beta}. \tag{7}$$

By Eqs. (6, 7), one easily obtains Eq. (2) from Eq. (5) and identifies k_g with β and $\alpha = \alpha_g$.

In the next sections, $n(t)$ refers to the number of cells at time t, since we study the tumor mass progression.

Nutrient supply and cell spatial correlations

A common feature of cancer cell metabolism is the ability to acquire necessary nutrients from a frequently nutrient-poor environment and utilize these nutrients to both maintain viability and build new biomass (Pavlova and Thompson 2016; Fernandez-de-Cossio-Diaz and Vazquez 2017; DeBerardinis et al. 2008).

After the initial phase, the total amount of nutrients is not able to sustain the exponential trend of the complete population of mitotic cells and angiogenic stimulator controls are crucial ingredients to increase the energetic balance. The extremely large nutrient consumption of tumor cells originates a competition for resources which is local and spatially correlated. Different spatial correlations give macroscopic laws with various global and nonlinear feedback effects.

Let us assume, without loss of generality, that $t = 0$ is the end of the exponential phase with n_0 cells and let us call τ_D the average duplication time of the total number of mitotic cells (which is different from the duplication times of a single cell and of the whole tumor). Let us call $t = k\tau_D$ with $k = 1, 2, \ldots$ the time intervals and $n(k)$ the cell population at the beginning of interval k.

After the exponential phase, only a number of cells smaller than $n(k)$ can replicate and, according to the previous definition, $t = 0$ is the time when this condition starts. Apoptosis is initially neglected, and its role in increasing the available nutrients for cell mitosis will be discussed later (see "Appendices A and B").

Since a limited number of mitosis are possible, let us call $n(k)^q$ the number of quiescent cells and $\bar{n}(k)$ the number of duplicating cells during the interval k, that is

$$n(k)^q = n(k) - \bar{n}(k) \tag{8}$$

The average number of cells at the beginning of $k + 1$ interval is therefore:

$$n(k+1) = n(k)^q + 2\bar{n}(k) = n(k) + \bar{n}(k) \tag{9}$$

The local competition for growth implies a spatial correlation, which decreases with the distance between pairs of cells and plays a crucial role. In fact, in Appendices A and B one shows that a model of the tumor evolution, based on the nutrient budget without spatial correlations, is not able to reproduce by GL the, in vivo, breast cancer data with realistic values of the growth parameters. In the next subsections, two different spatial correlation models are discussed from which the GL emerges at global level.

Mean field approximation

According to previous discussion, let us write the number of mitotic cells as a fraction of the total number and a depletion due to spatial correlation effects:

$$\bar{n}(k) = \lambda n(k) - v_0 f_0 \Sigma_{i=1}^{n(k)} \Sigma_{j=1}^{n(k)} (1 - \delta_{ij}) F(d_{ij}) \tag{10}$$

where $\lambda \leq 1$ describes the exponential phase (see "Appendix A"), $F(d_{ij})$ is a function of the distance between cell pairs (i, j),$|\vec{r}_i - \vec{r}_j| = d_{ij}$, δ_{ij} is the Kronecker delta, v_0 is a dimensionfull constant related to cell size, and f_0 is the cell fraction competing for nutrient supply.

A model with competition depending on a power law of the cell distance has been proposed in Ref. Mombach et al. (2002), where different growth laws are determined by the relation between the power δ of spatial correlation, $\simeq 1/d_{i,j}^{\delta}$, and the, assumed, fractal dimension of the cellular structure. Here, we explicitly show the dimensionfull constants in Eq. (10), interpreted in terms of the typical cell size and exponential rate, with a clear understanding of the interrelation among growth parameters that is a crucial aspect of the tumor Gompertzian progression (Vaghi 2020). Moreover, no fractal dimension has been introduced since the GL is obtained, in the mean field approximation, without geometrical self-similar pattern in the branching process.

For a spherical and homogeneous system in 3D, let us assume

$$F(d_{ij}) \simeq \frac{1}{d_{ij}^3} \tag{11}$$

and let us identify v_0 with the cell volume.

For large n, it turns out (Mombach et al. 2002)

$$v_0 f_0 \Sigma_{i=1}^{n(k)} \Sigma_{j=1}^{n(k)} (1 - \delta ij) F(d_{ij}) = 4\pi n(k) f_0 v_0 \rho_0 ln\left(\frac{R}{r_0}\right) \tag{12}$$

where ρ_0 is the constant density, R is the time-dependent maximum size of the system, and r_0 is a minimum characteristic length (of order of cell size, $v_0 = (4/3)\pi r_0^3$).

For the considered system, one has

$$R = \left(\frac{3n(k)}{4\pi\rho_0}\right)^{1/3} \tag{13}$$

and, by Eqs. (9–12), in the mean field approximation (Mombach et al. 2002), one gets

$$\frac{n(k+1) - n(k)}{n(k)} = a_{mf} - b_{mf} ln[n(k)] \tag{14}$$

with

$$a_{mf} = \lambda - \frac{4}{3}\pi f_0 v_0 \rho_0 ln[1/(v_0\rho_0)] \tag{15}$$

and

$$b_{mf} = \frac{4}{3}\pi f_0 v_0 \rho_0, \tag{16}$$

in τ_D time unit.

The comparison with the GL immediately identifies (taking into account the correct time units, τ_D) $b_{mf} = k_g$, $a_{mf} = k_g ln(n_\infty)$. Moreover, by Eq. (14) one gets

$$\ln n_\infty = a_{mf}/b_{mf} = \frac{\lambda - b_{mf} ln[1/(v_0\rho_0)]}{b_{mf}} \tag{17}$$

The consistent identification of the parameters can be checked by in vivo data. Indeed, for breast cancer (Norton 1988) the parameter k_g turns out to follow a log-normal distribution function with average $ln(k_g) = -2.9$ and variance 0.71 (with time in month unit) and then $< k_g > \simeq 0.17$ (month $^{-1}$). Moreover, $n_\infty \simeq 10^{12}$ cells (in 1 liter), corresponding to the density $\rho_0 = 10^6\, mm^{-3}$ cells and the typical average cell radius is $\simeq 7\mu m$. By Eqs. (14–17), one gets ($v_0\rho_0 \simeq 1.43$):

a) linear correlation between a_{mf} and b_{mf}

$$a_{mf} = \lambda - b_{mf} |ln(1/v_0\rho_0)|. \tag{18}$$

This is a crucial aspect of the application of GL to cancer growth: The two parameters turn out to be linearly correlated for different tumor phenotypes (Wheldon 1988; Vaghi 2020);

(b) $f_0 \simeq 3 * 10^{-2}\,(\tau_D/\text{month})$, ranging from 10^{-3} for $\tau_D = 1$ day to $3 * 10^{-3}$ for $\tau_D = 3$ days. For the initial value $n_0 \simeq 10^9$ (Norton 1988), the number of mitosis in τ_D is about 10^6.

Finally, let us notice that the dependence of $F(d_{ij}) \simeq 1/d_{ij}^2$ leads to a generalized logistic growth law.

A small world network correlation

The function and behavior of any given tumor cell are affected by interactions with its neighboring cells which send and receive messages in the form of direct contacts and secreted signaling molecules. This dynamics is limited to small distances from the cell position, and in this sense, a solid tumor can be considered a system of groups of interacting cells with global effects transmitted by cell to cell. According to this point of view, an advanced solid cancer can be qualitatively seen as a cell system with clustering and small correlation length.

In network analysis (Latora 2017), those properties identify the, so called, small world (SM) network (Watts and Strogatz 1998), where the clustering coefficient and the correlation length, L, have a precise quantitative definition in terms of number of nodes and links. In this respect, the suggestion is that, analogously to other biological systems, the cell spatial correlation can be described in terms of small world network, i.e., local connections and a small number of steps to reach distant cells. The average spatial correlation among cells is, accordingly, related to the average geodesic (i.e., shortest path) length L in the SM network, defined by

$$L = \frac{1}{n(k)[n(k)-1]} \Sigma_{i=1}^{n(k)} \Sigma_{j=1}^{n(k)} g_{ij} \tag{19}$$

where g_{ij} is the shortest geodesic distance between nodes (cells) i and j. In SM, for $n > n^* >> 1$, one has (Watts and Strogatz 1998; Latora 2017)

$$L \simeq ln[n(k)/n^*]. \tag{20}$$

By taking into account the maximum volume V for a finite, homogeneous, system, let us write the number of mitotic cells as a fraction of $n(t)$ with a decreasing contribution due to SM network:

$$\bar{n}(k) = n(k)\lambda - \frac{\gamma}{V} \Sigma_{i=1}^{n(k)} \Sigma_{j=1}^{n(k)} g_{ij} \tag{21}$$

where γ is a dimensionfull constant. By Eqs. (19, 20) and $1/V = \rho_0/n(k)$, for large n, one gets

$$\bar{n}(k) \simeq n(k)\lambda - n(k)\gamma\rho_0 ln[n(k)/n^*] \tag{22}$$

and the specific rate turns out to be

$$\frac{n(k+1)-n(k)}{n(k)} = \lambda - \gamma\rho_0 ln[n(k)/n^*]. \tag{23}$$

The comparison with the Gompertz equation gives

$$\alpha_{SM} = \lambda + \gamma\rho_0 ln(n^*), \tag{24}$$

$$\beta_{SM} = \gamma\rho_0, \tag{25}$$

and

$$\alpha_{SM} = \beta_{SM} ln[n_\infty] \tag{26}$$

completely consistent with the condition $\lambda \leq 1$ for $n_\infty \simeq 10^{12}$, $n^* \simeq 10^9$ (Norton 1988) and the previous value of $\beta_g = \beta_{SM}$.

Apoptosis

Cell death, in the form of apoptosis, and cell proliferation are linked by biochemical effects. Moreover, in the energetic balance, apoptosis permits to transfer some nutrient from metabolic activity to mitosis as quantitatively expressed in "Appendices A and B."

However, without spatial correlations, the effect of apoptosis on the global nutrient balance does not solve the problem of the consistency of the GL growth parameters to fit in vivo data with the observed values of the metabolic tumor cell activities (see "Appendices A and B").

Comments and Conclusions

The success of macroscopic growth laws in describing the time evolution of dynamical systems in many different sectors is astonishing. Indeed, with a small number of parameters one can fit large sets of data. Even more surprising is that they contain global and nonlinear feedback effects, although the microscopic dynamics is, in general, local. In other terms, the coarse-grain patterns catch the most important aspects of the underlying phenomena, strongly reducing the large number of parameters typical of the microscopic models.

The proposed results suggest that a branching process with global constraint on the energy budget is not able to reproduce breast cancer in vivo data by GL if the competition for resources is not included: The local spatial correlation among cells is a crucial ingredient to obtain the observed progression.

The linear interdependence of the two GL growth parameters emerges by comparison between the average spatial correlation distances and the typical cell size.

The results are based on a spherical and homogeneous system. On the other hand, heterogeneity is a well-known feature of tumor growth, in particular under radiochemotherapy. This important aspect can be included in the proposed framework by considering different subpopulations with various GL specific rates (Castorina et al. 2009). On the other hand, without spatial correlations, the unique parameter which drives the tumor progression is related to nutrient expenditures for mitosis and for the other metabolic activities (i.e., the parameter δ in Eq. (32), "Appendix A"). Therefore, also if different strains characterize the tumor evolution, it is difficult to obtain a GL description of in vivo data with the observed values of δ.

Appendix A

In this appendix, a model of the time evolution, based on mitosis with a global constraint on the nutrient supply and without cell spatial correlations, is discussed. Apoptosis will be included in "Appendix B."

The exponential phase corresponds to a fixed ratio between total and mitotic cells during any time interval k, i.e., $\bar{n}(k) = n(k)\lambda$ with $0 < \lambda \leq 1$. At each step, the number of quiescent cells is $n(k) - \bar{n}(k)$ and at the end of any single time iteration (in unit τ_D) $n(k+1) = [n(k) - \bar{n}(k)] + 2\bar{n}(k)$. The specific rate turns out to be $[n(k+1) - n(k)]/n(k) = \lambda$.

Let us consider the global constraint by defining the total amount of nutrients, E, and r_M, r_D the resources for the cell metabolic activity and mitosis, respectively (time unit τ_D).

If $r_D n(t) > E$, only a smaller number of cells can replicate. According to the previous definition, $t = 0$ is the time when this condition starts (i.e., after the exponential growth phase) and since a limited number of mitosis are possible, let us call n_0 the cell number and $\bar{n}_0$ the maximum number of duplicating cells. Therefore, $n_0 - \bar{n}_0$ is the initial number of quiescent cells and for the maximum number of mitotic cells, one gets

$$E = r_M(n_0 - \bar{n}_0) + r_D\bar{n}_0 \tag{27}$$

$$\bar{n}_0 = \frac{E - r_M n_0}{r_D - r_M}. \tag{28}$$

Due to biochemical inhibitor factors, the effective number of mitotic cell ν_0 is a fraction $f_0 \leq 1$ of the maximum number $\bar{n}_0$, i.e., $\nu_0 = f_0\bar{n}_0$, and therefore, at the end of the first interval, $k = 1$, the number of cells is given by

$$n_1 = (n_0 - \nu_0) + 2\nu_0 = n_0 + f_0\bar{n}_0. \tag{29}$$

By the "energy" constraint , the maximum number of duplicating cells in the interval $1 \rightarrow 2$ is given by

$$\bar{n}_1 = \frac{E - r_M n_1}{r_D - r_M} \tag{30}$$

which by Eqs. (27–29) turns out to be

$$\bar{n}_1 = \bar{n}_0(1 - f_0\delta) \tag{31}$$

where

$$\delta = \frac{r_M}{r_D - r_M} < 1 \tag{32}$$

since two cells are produced by a single cell, i.e., $r_D = 2r_M + r_R > 2r_M$, where r_R is the nutrient expenditure during the cell cycle. The effective number of mitotic cells is now $\nu_1 = f_1\bar{n}_1$, and when the $k = 2$ interval has been completed, the number of cells is given by

$$n_2 = n_1 + \nu_1 = n_0 + \bar{n}_0[f_0 + f_1(1 - f_0\delta)] \tag{33}$$

By iteration, the final formulas are :

$$\nu_k = f_k\bar{n}_k \tag{34}$$

$$\bar{n}_k = \bar{n}_0\Pi_{i=0}^{k-1}(1 - f_i\delta) \tag{35}$$

$$n_k = n_0 + \bar{n}_0\Sigma_{i=0}^{k-1}f_i\Pi_{j=0}^{i}(1 - f_{j-1}\delta) \tag{36}$$

where $f_{j-1} = 0$ if $j - 1 < 0$.

Let us first consider the case $f_i = f_0 = 1$, $i = 1, 2, \ldots$. Equations (34–36) give

$$\bar{n}_k = \bar{n}_0(1 - \delta)^{k-1} \tag{37}$$

and

$$n_k = n_0 + \bar{n}_0[1 - (1 - \delta)^k]/\delta \tag{38}$$

The specific rate turns out to be

$$\frac{n_{k+1} - n_k}{n_k} = \frac{\bar{n}_0(1 - \delta)^k}{n_0 + \bar{n}_0[1 - (1 - \delta)^k]/\delta} \tag{39}$$

and (by Eq. (38) for $k \rightarrow \infty$)

$$n_\infty = n_0 + \bar{n}_0/\delta. \tag{40}$$

The continuum limit of Eq. (39) is

$$\frac{dn(t)}{n(t)dt} = \frac{1}{\tau_D}\frac{\bar{n}_0 e^{(t/\tau_D)ln(1-\delta)}}{n_0 + (\bar{n}_0/\delta)[1 - e^{(t/\tau_D)ln(1-\delta)}]}, \tag{41}$$

and the comparison with the GL fit for breast cancer data requires a very small value of δ, because the average value $\beta_g \simeq 0.17$ in month $^{-1}$ (Norton 1988).Therefore, $\delta \simeq 0.0057$ for $\tau_D = 1$ day, which is an unrealistic value of the ratio $\delta = r_M/(r_D - r_M)$, with typical range $0.6 - 0.9$ (Fernandez-de-Cossio-Diaz and Vazquez (2017), supplementary materials).

One can easily verify that the condition $f_i = f_0 < 1$, $i = 1, 2, \ldots$, does not solve the previous problem.

Let us now assume $f_{i+1} = cf_i$ with $c \leq 1$. Therefore,

$$\bar{n}_k = \bar{n}_0 \Pi_{i=0}^{k-1}(1 - c^i f_0 \delta) \tag{42}$$

and

$$n_k = n_0 + \bar{n}_0 f_0 \Sigma_{i=0}^{k-1} c^i \Lambda_i \tag{43}$$

where $\Lambda_i = 1$ for $i = 0$ and

$$\Lambda_i = \Pi_{j=1}^{i}(1 - c^{j-1} f_0 \delta) \tag{44}$$

for $i \geq 1$.

However, since $c \leq 1$, the final result is still in disagreement with the GL fit of breast cancer data for realistic values of the parameters.

Appendix B: Including apoptosis

The analysis in "Appendix A" can be generalized by taking into account the number of apoptotic cells. The case $f_i = 1$, $i = 1, 2, \ldots$ is considered.

Let us, respectively, call n_0^A,n_0, $\bar{n}_0$ the number of apoptotic, total and maximum mitotic cells at the time $t = 0$ (end of exponential phase). The number of quiescent cells is therefore $n_0^q = n_0 - n_0^A - \bar{n}_0$, and therefore,

$$r_M(n_0 - n_0^A - \bar{n}_0) + r_D \bar{n}_0 = E, \tag{45}$$

i.e.,

$$\bar{n}_0 = \frac{E + n_0^A r_M - n_0 r_M}{r_D - r_M}. \tag{46}$$

At the end on the first interval, $k = 1$, the total number of cells is

$$n_1 = n_0^q + 2\bar{n}_0 = n_0 - n_0^A + \bar{n}_0. \tag{47}$$

In the interval $k = 1 \rightarrow 2$, only a fraction $\bar{n}_1$ of n_1 can duplicate and by including the corresponding number of apoptotic cells, n_1^A, the number of quiescent cells is

$$n_1^q = n_1 - n_1^A - \bar{n}_1, \tag{48}$$

and

$$\bar{n}_1 = \frac{E + n_1^A r_M - n_1 r_M}{r_D - r_M}. \tag{49}$$

By analogous steps of Appendix A, after simple algebra, one gets

$$\bar{n}_1 = \bar{n}_0(1 - \delta) + \delta n_1^A, \tag{50}$$

with δ in Eq. (32), and the total number of cell at the end of the second interval turns out to be

$$n_2 = n_0 + \bar{n}_0[1 + (1 - \delta)] - n_0^A - (1 - \delta) n_1^A. \tag{51}$$

By interaction, after k intervals,

$$\bar{n}_k = \bar{n}_0(1 - \delta)^k + \Sigma_A, \tag{52}$$

where

$$\Sigma_A(k) = \delta \Sigma_{i=1}^{k}(1 - \delta)^{k-i} n_i^A, \tag{53}$$

and

$$n_k = n_0 + \bar{n}_0 \Sigma_{i=0}^{k-1} - n_0^A - \Sigma_{i=0}^{k} n_i^A (1 - \delta)^{k-i}, \tag{54}$$

$$n_{k+1} - n_k = \bar{n}_0(1 - \delta)^k - n_{k+1}^A + \delta \Sigma_{i=1}^{k} n_i^A (1 - \delta)^{k-i}. \tag{55}$$

The saturation value n_∞ is defined by $n_{k+1} - n_k = 0$, and by Eqs. (52–54), one obtains

$$n_\infty = n_0 + \bar{n}_0/\delta - n_0^A - n_{k+1}^A/\delta \tag{56}$$

The value $n_\infty \simeq 10^{12}$ requires again a very small δ , inconsistent with the observed values of r_D and r_M.

Acknowledgements P.C. thanks Vito Latora for useful suggestions.

Declarations

Funding Work was supported by FERS Sicilia i.n. 08CT8610100110, cup: G89J18000700007

Conflict of interest The authors have no conflicts of interest to declare.

References

Afenya EK, Calderon CP (2000) Diverse ideas on the growth kinetics of disseminated cancer cells. Bull Math Biol 62:427

Anguelov R, Borisov M, Kyurkchiev N, Markov S (2007) On the chemical meaning of some growth models possessing Gompertzian-type property. Math Meth Appl Sci 41:1–12

Bajzer Z (1999) Gompertzian growth as a self-similar and allometric process. Growth Dev Aging 63:3

Bajzer Z, Vuk-Pavlovic S (2000) New dimensions of gompertzian growth. J Theor Med 2:307

Bajzer Z, Vuk-Pavlovic S (1997) Mathematical modeling of tumor growth kinetics. In: Adam J, Bellomo N (eds) A survey of models for tumor-immune system dynamics. Birkenhauser, Boston, p 89

Calderon CP, Kwembe TA (1991) Modeling tumor growth. Math Biosci 103:97

Castorina P, Carco D, Guiot C, Deisboeck TS (2009) Tumor growth instability and its implications for chemotherapy. Cancer Res 69(21):8507. https://doi.org/10.1158/0008-5472.CAN-09-0653

Castorina P, Delsanto PP, Guiot C (2006) Classification scheme for phenomenological universalities in growth problems in physics and other sciences. Phys Rev Lett 96:188701
Castorina P, Zappala D (2006) Tumor Gompertzian growth by cellular energetic balance. Physica A 365(2):473–480
Castorina P, Iorio A, Lanteri D (2020) Data analysis on Coronavirus spreading by macroscopic growth laws. Int J Mod Phys C 31(10):2050135
DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB (2008) The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metab 7:11
Fernandez-de-Cossio-Diaz J, Vazquez A (2017) Limits of aerobic metabolism in cancer cells. Sci Rep 7:13488
Frenzen CL, Murray JD (1986) A cell kinetics justification for Gompertz equation. SIAM J Appl Math 46:614
Gavrilov LA, Gavrilova NS (2001) The reliability theory of aging and longevity. J Theor Biol 213(4):527–545
Gompertz B (1825) On the nature of the function expressive of the law of human mortality and a new mode of determining life contingencies. Philos Trans R Soc 115:513
Gyllenberg M, Webb GF (1989) Quiescence as an explanation of Gompertzian tumor growth. Growth Dev Aging 53:25
Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646
Jarrett AM et al (2018) Mathematical models of tumor cell proliferation: a review of the literature. Expert Rev Anticancer Ther 18(12):1271–1286
Kendal WS (1985) Gompertzian growth as a consequence of tumor heterogeneity. Math Biosci 73:103
Kozusko F, Bajzer Z (2003) Combining Gompertzian growth and cell population dynamics. Math Biosci 185:153–167
Laird AK, Tyler SA, Barton AD (1965) Dynamics of normal growth. Br J Cancer 19:233–248
Laird AK, Tyler SA, Barton AD (1965) Dynamics of tumor growth: comparison of growth rates. Br J Cancer 19:278–291
Latora V, Nicosia V, Russo G (2017) Complex networks—principles, methods and applications. Cambridge University Press, Cambridge
Ling Y, He B (1993) Entropic analysis of biological growth models. IEEE Trans Biomed Eng 40:1193
Makany R (1991) A theoretical basis for GompertzÕs curve. Biometr J 33:121
Mombach JCM, Lemke N, Bodmann BE, Idiart MAP (2002) A mean-field theory of cellular growth. Europhys Lett 59:923
Mombach CM, Lemke N, Bodmann BEJ, Idiart MAP (2002) A mean-field theory of cellular growth. Europhys Lett 59(6):923
Murray JD (1989) Mathematical biology. Springer, Berlin
Norton LA (1988) Gompertzian model of human breast cancer growth. Cancer Res 48:7067–7071
Pavlova NN, Thompson CB (2016) The emerging hallmarks of cancer metabolism. Cell Metab 23:27
Qi A-S, Zheng X, Du C-Y, An B-S (1993) A cellular automaton model of cancerous growth. J Theor Biol 161:1
Savageau MA (1979) Allometric morphogenesis of complex systems: a derivation of the basic equations from first principles. Proc Natl Acad Sci USA 76:6023
Shklovskii BI (2005) A simple derivation of the Gompertz law for human mortality. Theory Biosci 123:431–433
Stauffer D, Stanley HE (2017) From newton to mandelbrot. Theoretical, Mathematical and Computational Physics. Springer ed., Berlin
Vaghi C et al (2020) Population modeling of tumor growth curves and the reduced Gompertz model improve prediction of the age of experimental tumors. PLoS Comput Biol 16(2):e1007178
Waliszewski P, Konarski J (2003) Gompertzian curve reveals fractal properties of tumor growth. Chaos Soliton Fract 16(5):665–674
Waliszewski P, Molski M, Konarski J (1998) On the holistic approach in cellular and cancer biology: nonlinearity, complexity, and quasi-determinism of the dynamic cellular network. J Surg Oncol 68:70–78
Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393:440–442
Wheldon TE (1988) Mathematical models in cancer research. Adam Hilger Publisher, Bristol
Witten M (1985) A return to time, cells, systems, and aging: III. Gompertzian models of biological aging and some possible roles for critical elements. Mech Aging Dev 32:141