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WHY GROWTH OF CANCEROUS TUMORS IS GOMPERTZIAN: A SYMMETRY-BASED EXPLANATION

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Abstract

It is known that the growth of a cancerous tumor is well described by the Gompertz's equation. The existing explanations for this equation rely on specifics of cell dynamics. However, the fact that for many different types of tumors, with different cell dynamics, we observe the same growth pattern, make us believe that there should be a more fundamental explanation for this equation. In this paper, we show that a symmetry-based approach indeed leads to such an explanation: indeed, out of all scale-invariant growth dynamics, the Gompertzian growth is the closest to the linear-approximation exponential growth model.

Key words

Gompertzian growth, tumor growth, cancer, symmetry approach, scale-invariance.

1 Introduction

Cancer growth is Gompertzian: an empirical fact. It is known that the dependence of the size $n(t)$ of the growing cancer tumor on time t is well described by the Gompertzian equation

$$\frac{dn}{dt} = a \cdot n - b \cdot n \cdot \ln(n); \qquad (1)$$

see, e.g., [Frenzen and Murray, 1986; Kendal, 1985; Kozusco and Baizer, 2003; Norton, 1988; Tracqui, 2009; West et al., 2016], and references therein.

How Gompertzian groth is explained now. At present, the Gompertzian character of the cancerous tumor growth is explained by the specific features of cell dynamics; see [Frenzen and Murray, 1986; Kendal, 1985; Kozusco and Baizer, 2003; Norton, 1988; Tracqui, 2009; West et al., 2016].

Need for a more general explanation. Cancer is a general name for many very different diseases, with different cell dynamics. The fact that the same Gompertzian growth is observed in all kinds of cancers make us believe that there is a more fundamental explanation for the ubiquity of equation (1), an explanation that does not depend on the specifics of cell dynamics.

What we do in this paper. In this paper, we show that natural symmetry ideas can indeed provide the desired general explanation for the Gompertzian growth.

2 Growth: A General Idea

Our goal is to find the right-hand side $f(n)$ of the general equation

$$\frac{dn}{dt} = f(n) \qquad (2)$$

that describes the corresponding growth.

We consider *growth*, not the emergence of a tumor. This means that if originally, we had no tumor ($n = 0$), there is nothing to grow, so we should have $f(n) = 0$. In other words, the desired function $f(n)$ should have the property $f(0) = 0$.

3 First Approximation Model: Description and Limitations

Growth: first approximation leads to the exponential growth. From the practical viewpoint, the earlier we diagnose the cancer, the better our chances of curing it. Thus, it is very important to emphasize the initial stages of the growth, when the size n of the tumor is still small.

When n is small, a reasonable idea is to expand the function $f(n)$ in Taylor series and keep only the first terms in this expansion. Since $f(0) = 0$, the first nonlinear term in the Taylor expansion of this function is a linear term $f(n) = c \cdot n$. The resulting equation

$$\frac{dn}{dt} = c \cdot n \qquad (3)$$

leads to the known exponential solution

$$n(t) = n(0) \cdot \exp(c \cdot t).$$

Need to go beyond a simple exponential growth model. The exponential growth model well describes the initial growth stage, when the tumor is still small. However, it cannot describe all the stages, since:

- in the exponential growth model, the size of the tumor tends to infinity, while
- in real life, this size is limited – e.g., by the size of the corresponding organ.

It is therefore reasonable to modify the simple exponential growth model, to get a more realistic description of the tumor growth.

4 How Can We Generalize? Enter Symmetries

How can we go beyond the simple exponential growth model? To generalize the exponential growth model, a natural idea is:

- to select important features of this model, and then
- to see which more general models are possible that preserve these important features.

Why symmetries. Which features should we select? To make this decision, let us recall that one of the main objectives of science in general is to predict what will happen:

- what will happen if we do not interfere, and
- what will happen if we perform a certain interfering action.

How can we predict? There are many prediction methods, but the main idea behind these methods is the same: to predict what will happen in a given situation:

- we search for similar situations in the past, and
- we predict that in the current situation, the outcome will be similar to what we have observed in similar situations in the past.

In particular, if a certain equation was valid in all previous similar situations, we expect this equation to be valid in the current situation as well.

From this viewpoint, the most fundamental notion is the notion of similarity between objects and/or situations. In mathematical terms, this corresponds to *symmetries* – transformations that preserve important features and thus, keep the situation similar.

For example, if we repeat the same experiment at a later time, we expect the same results – why? Because we believe that the future situation is similar to the past one, i.e., that a simple shift in time, from the original time t to the new time $t + t_0$, does not change the situation and is, thus, a symmetry.

With this in mind, let us look for the natural symmetries in our growth situation.

Scaling as a natural symmetry. In principle, the size of the tumor can be described by the number of cancerous cells. However, in practice, even a small tumor, of size smaller than 1 mm^3, contains thousands and millions of cells. We do not actually count these cells, we measure the tumor size by its mass or by its volume.

The numerical value of the size therefore depends on what measuring unit we use. For example, if we replace cubic millimeters with cubic microns, the numerical size will increase by a factor of 10^9. In general, if we use a different unit, then the original numerical value n is replaced by a new unit $n \to n' = \lambda \cdot n$ for some $\lambda > 0$.

From the physical viewpoint, whatever units we use, the tumor remains the same. It is therefore reasonable to require that the equations that describe the tumor growth also do not depend on the choice of the measuring unit, i.e., that they are, in some reasonable sense, invariant under the corresponding scaling transformation $n \to \lambda \cdot n$.

Linear model is indeed scale-invariant. The linear model (3) is indeed scale-invariant: if we re-scale the size n, i.e., replace n with $\lambda \cdot n$, then we get the exact same growth rate $r = f(n)$, provided, of course, that we accordingly change the unit for the growth rate (i.e., equivalently, the unit for time).

In precise terms, if we replace n by $n' = \lambda \cdot n$, then we get $f(n') = \text{const} \cdot f(n)$. In other words, while the actual function $f(n)$ changes when we re-scale n, the corresponding 1-parametric family of functions $\{C \cdot f(n)\}_C$ remains unchanged.

Let us use this as a way to generalize the exponential growth model.

5 1-Parametric Scale-Invariant Growth Models: Idea, Description, and Limitations

Natural idea. As we discussed earlier, let us consider 1-parametric scale-invariant growth models, i.e., growth models $f(n)$ for which the family

$$\{C \cdot f(n)\}_C$$

is scale-invariant.

Let us describe all such growth models. Invariance means that for every λ, the function $f(\lambda \cdot n)$ belongs to the family $\{C \cdot f(n)\}_C$, i.e., that for every λ, there exists a value $C(\lambda)$ for which

$$f(\lambda \cdot n) = C(\lambda) \cdot f(n). \quad (4)$$

To solve this functional equation, let us take into account physical features of this situation.

It is reasonable to require that the growth rate be a differentiable function of the tumor size n. In the physical world, most processes are continuous. In particular, we expect that small changes in n lead to small changes in $f(n)$. It is therefore reasonable to require that the function $f(n)$ be differentiable – at least, for the case $n > 0$.

Let us use this assumption to solve the above equation. From the equation (4), we conclude that

$$C(\lambda) = \frac{f(\lambda \cdot n)}{f(n)}.$$

Since the function $f(n)$ is differentiable, we conclude that the function $C(\lambda)$ is differentiable as well, as a ratio of two differentiable functions.

Thus, we can differentiate both sides of the equation (4) with respect to λ and take $\lambda = 1$. As a result, we get the following formula:

$$n \cdot \frac{df(n)}{dn} = c \cdot f(n), \quad (5)$$

where we denoted $c \stackrel{\text{def}}{=} \frac{dC(\lambda)}{d\lambda}_{|\lambda=1}$. In the equation (5), we can separate the variables by moving all the terms containing n to the right side and all the terms containing f to another. Thus, we get:

$$\frac{dn}{n} = c \cdot \frac{df}{f}.$$

Integrating both sides, we get $\ln(n) = c \cdot \ln(f) + \text{const}$, hence

$$\ln(f) = c^{-1} \cdot \ln(n) + \text{const}.$$

Thus, we get the following formula for $f(n) = \exp(\ln(f(n))$:

$$f(n) = A \cdot n^{\alpha}, \quad (6)$$

where $\alpha \stackrel{\text{def}}{=} c^{-1}$.

Limitations of the resulting equation. For the growth rate (5), the corresponding dynamic equation has the form

$$\frac{dn}{dt} = A \cdot n^{\alpha}.$$

Separating variables in this equation, we get

$$\frac{dn}{n^{\alpha}} = A \cdot t.$$

Integrating both sides, we get

$$\frac{n^{1-\alpha}}{1-\alpha} = A \cdot t + C,$$

hence $n^{1-\alpha} = (1-\alpha) \cdot (A \cdot t + C)$, and $n = (a \cdot t + b)^{\alpha}$.

This function has the same limitation as the exponential growth model: it tends to infinity as t grows, it does not have any bounds.

Natural idea. Since we did not get a good solution by considering *1-parametric* scale-invariant families of functions, a natural idea is to consider *2-parametric* families of functions. Let us describe this idea in precise terms.

6 2-Parametric Scale-Invariant Growth Models: Idea, Description, and Analysis

Idea. Let us consider 2-parametric scale-invariant growth models, i.e., functions $f(n)$ that belong to a 2-parametric scale-invariant family

$$\{C_1 \cdot f_1(n) + C_2 \cdot f_2(n)\}_{C_1, C_2}.$$

The fact that we only consider differentiable functions means that both basis functions $f_1(n)$ and $f_2(n)$ are differentiable.

Let us describe all such growth models. Invariance means that for every λ and for every i, the function $f_i(\lambda \cdot n)$ belongs to the above family, i.e., that for every λ, there exists values $C_{ij}(\lambda)$ for which

$$f_1(\lambda \cdot n) = C_{11}(\lambda) \cdot f_1(n) + C_{12}(\lambda) \cdot f_2(n), \quad (7)$$

$$f_2(\lambda \cdot n) = C_{21}(\lambda) \cdot f_1(n) + C_{22}(\lambda) \cdot f_2(n). \quad (8)$$

Let us prove that the functions $C_{ij}(\lambda)$ are differentiable. For each i, we can consider two different values $n_1 \neq n_2$. Thus, we get a system of two linear equations for the two unknowns $C_{i1}(\lambda)$ and $C_{i2}(\lambda)$:

$$f_i(\lambda \cdot n_1) = C_{i1}(\lambda) \cdot f_1(n_1) + C_{i2}(\lambda) \cdot f_2(n_1), \quad (9)$$

$$f_i(\lambda \cdot n_2) = C_{i1}(\lambda) \cdot f_1(n_2) + C_{i2}(\lambda) \cdot f_2(n_2). \quad (10)$$

The solution to this system of linear equations can be described by using the Cramer's rule:

$$C_{i1}(\lambda) = \frac{f_i(\lambda \cdot n_1) \cdot f_2(n_2) - f_i(\lambda \cdot n_2) \cdot f_2(n_1)}{f_1(n_1) \cdot f_2(n_2) - f_2(n_1) \cdot f_1(n_2)}$$

and

$$C_{i2}(\lambda) = \frac{f_i(\lambda \cdot n_1) \cdot f_1(n_2) - f_i(\lambda \cdot n_2) \cdot f_1(n_1)}{f_2(n_1) \cdot f_1(n_2) - f_1(n_1) \cdot f_2(n_2)}.$$

Since the functions $f_i(n)$ are differentiable, we conclude that the functions $C_{ij}(\lambda)$ are differentiable as well.

Let us now differentiate. Since all the functions $f_1(n)$, $f_2(n)$, and $C_{ij}(\lambda)$ are differentiable, let us differentiate both sides of the equations (7) and (8) with respect to λ and take $\lambda = 1$. As a result, we get the following system of equations:

$$n \cdot \frac{df_1}{dn} = c_{11} \cdot f_1(n) + c_{12} \cdot f_2(n),$$

$$n \cdot \frac{df_2}{dn} = c_{21} \cdot f_1(n) + c_{22} \cdot f_2(n),$$

where we denoted $c_{ij} \stackrel{\text{def}}{=} \frac{dC_{ij}(\lambda)}{d\lambda}_{|\lambda=1}$.

This system of equations can be further simplified if we introduce a new variable $x = \ln(n)$ for which $dx = \frac{dn}{n}$, and $n = \exp(x)$. In terms of this new variable, we have

$$f_i(n) = F_i(x) = F_i(\ln(n)),$$

where $F_i(x) \stackrel{\text{def}}{=} f_i(\exp(n))$. Then, the above equations take the form

$$\frac{dF_1}{dx} = c_{11} \cdot F_1 + c_{12} \cdot F_2,$$

$$\frac{dF_2}{dx} = c_{21} \cdot F_1 + c_{22} \cdot F_2.$$

This is a system of linear differential equations with constant coefficients.

Solutions to this system of equations are well known (see, e.g., [Robinson, 2004]): the functions $F_i(x)$ are linear combinations of functions of the type $\exp(\alpha_1 \cdot x)$ and $\exp(\alpha_2 \cdot x)$, where $\alpha_1 \neq \alpha_2$ are the eigenvalues (in general, complex) of the matrix c_{ij}. In situations in which we have a double eigenvalue $\alpha_1 = \alpha_2$, each of the functions $F_i(x)$ is a linear combination of the terms $\exp(\alpha_1 \cdot x)$ and $x \cdot \exp(\alpha \cdot x)$.

Thus, the growth function $F(x) = f(\exp(n))$ (for which $f(n) = F(\ln(n))$) – and which is itself a linear combination of the functions $F_1(x)$ and $F_2(x)$ – is also a linear combination of the corresponding functions:

- either a linear combination of the functions $\exp(\alpha_1 \cdot x)$ and $\exp(\alpha_2 \cdot x)$ corresponding to $\alpha_1 \neq \alpha_2$,
- or a linear combination of functions $\exp(\alpha_1 \cdot x)$ and $x \cdot \exp(\alpha_1 \cdot x)$ (corresponding to the case when $\alpha_1 = \alpha_2$).

Substituting $x = \ln(n)$ into these formulas, we conclude that the growth functions $f(n) = F(\ln(n))$ is:

- either a linear combination of the functions n^{α_1} and n^{α_2} for some $\alpha_1 \neq \alpha_2$,
- or a linear combination of the functions n^{α_1} and $n^{\alpha_1} \cdot \ln(n)$.

Comments.

- The formula corresponding to $\alpha_2 = \alpha_1$ can be viewed as a limit case of the general formula with $\alpha_2 \neq \alpha_1$ when we take $\alpha_2 \to \alpha_1$, i.e., when $\alpha_1 = \alpha_1 + \varepsilon$ for $\varepsilon \to 0$. Indeed, in this case,

  $$n^{\alpha_2} = n^{\alpha_1+\varepsilon} = n^{\alpha_1} \cdot n^{\varepsilon}.$$

  Here,

  $$n^{\varepsilon} = (\exp(\ln(n))^{\varepsilon} = \exp(\varepsilon \cdot \ln(n)) =$$

  $$1 + \varepsilon \cdot \ln(n) + o(\varepsilon),$$

  thus

  $$n^{\alpha_2} = n^{\alpha_1} \cdot n^{\varepsilon} = n^{\alpha_1} + \varepsilon \cdot n^{\alpha_1} \cdot \ln(n) + o(\varepsilon).$$

  So, in the limit $\varepsilon \to 0$, linear combinations

  $$C_1 \cdot n^{\alpha_1} + C_1 \cdot n^{\alpha_2}$$

  indeed become linear combinations of functions n^{α_1} and $n^{\alpha_1} \cdot \ln(n)$.
- The main ideas behind this analysis of growth models first appeared in [Nguyen and Kreinovich, 1997], where we analyzed possible scale-invariant growth models.

7 Which of the 2-Parametric Scale-Invariant Growth Models Is the Closest to the Exponential Growth Model?

It is reasonable to select a growth model which is the closest to the exponential one. In the previous section, we described all possible 2-parametric scale-invariant growth models. Which of these models should we choose?

In the first approximation, tumor growth is described by the exponential growth model. It is therefore reasonable, as the next approximation, to select a model which is – in some reasonable sense – the closest to the exponential growth model.

How to describe closeness. As we have shown, each 2-parametric scale-invariant family F has either the form

$$F(\alpha_1, \alpha_2) \stackrel{\text{def}}{=} \{C_1 \cdot n^{\alpha_1} + C_2 \cdot n^{\alpha_2}\}_{C_1,C_2}$$

for some α_1 and α_2 or the form

$$\{C_1 \cdot n^{\alpha_1} + C_2 \cdot n^{\alpha_1} \cdot \ln(n)\}_{C_1,C_2}$$

that corresponds to the limit case when $\alpha_2 \to \alpha_1$, i.e., when α_2 is "infinitely close" to α_1. We will denote the limit-type family by $F(\alpha_1, \alpha_1 + \varepsilon)$, where ε denoted a number that tends to 0.

From this viewpoint, each scale-invariant family can be characterized by a pair $\alpha = (\alpha_1, \alpha_2)$ of numbers or number-like expressions:

- in the non-degenerate case, when the eigenvalues α_1 and α_2 are different, we can simply take

$$\alpha = (\alpha_1, \alpha_2);$$

- in the degenerate case, when we have the same eigenvalue α_1, we take $\alpha = (\alpha_1, \alpha_1 + \varepsilon)$.

Thus, as a measure of closeness between the two families $F(\alpha)$ and $F(\alpha')$, it is reasonable to take the distance between the corresponding pairs α and α':

$$f(F(\alpha), F(\alpha')) = D(\alpha, \alpha'),$$

for some reasonable distance function $D(\alpha, \alpha')$.

As $D(\alpha, \alpha')$, for numerical pairs, we can take, e.g., the Euclidean distance. For pairs including the infinitesimal distance ε, the Euclidean formula leads to the distance in terms of ε: e.g.,

$$D((\alpha_1, \alpha_1), (\alpha_1, \alpha_1 + \varepsilon)) = \varepsilon$$

is an infinitesimal distance (still different from 0).

In this sense, the Gompertzian model is indeed the closest. The exponential model can be viewed as a particular case of the general 2-parametric family corresponding to $\alpha_1 = \alpha_2 = 1$, i.e., as a family $F(1, 1)$.

One can easily see that the closest truly 2-parametric scale-invariant model is the one that corresponds to the infinitesimally close pair $(1, 1 + \varepsilon)$, i.e., to the family $F(1, 1 + \varepsilon)$ that consists of linear combinations of the functions $n^1 = n$ and $n^1 \cdot \ln(n) = n \cdot \ln(n)$, i.e., of functions of the type $f(n) = a \cdot n - b \cdot n \cdot \ln(n)$. This is exactly the Gompertz growth function.

So, the symmetry-based approach indeed explains the ubiquity of Gompertzian growth functions.

Gomperzian model beyond tumors. Gompertzian model also provides a reasonable description of growth in different application areas ranging:

- from bacterial growth in biology (see, e.g., [Zweitenberg, 1990])
- to mobile network growth (see, e.g., [Islam, Fiebig, and Meade, 2002])
- to growth of financial markets (see, e.g., [Caravelli et al., 2016]).

The fact that the Gompertzian models provides a good description of growth in many application areas led to general physical explanations for this model; see, e.g., [Yamano, 2009]. However, this explanation is somewhat too specific and too complex to be a convincing explanation for this general phenomenon. We believe that our symmetry-based explanation is more adequate – and we hope that it will lead to a better understanding of the Gompertzian growth phenomenon.

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