Fractal dimension and universality in avascular tumor growth

Fabiano L. Ribeiro,[*] Renato Vieira dos Santos,[†] and Angélica S. Mata[‡]
Departamento de Física, Universidade Federal de Lavras, 37200-000 Lavras, MG, Brazil
(Received 7 October 2016; revised manuscript received 16 December 2016; published 20 April 2017)

For years, the comprehension of the tumor growth process has been intriguing scientists. New research has been constantly required to better understand the complexity of this phenomenon. In this paper, we propose a mathematical model that describes the properties, already known empirically, of avascular tumor growth. We present, from an individual-level (microscopic) framework, an explanation of some phenomenological (macroscopic) aspects of tumors, such as their spatial form and the way they develop. Our approach is based on competitive interaction between the cells. This simple rule makes the model able to reproduce evidence observed in real tumors, such as exponential growth in their early stage followed by power-law growth. The model also reproduces (i) the fractal-space distribution of tumor cells and (ii) the universal growth behavior observed in both animals and tumors. Our analyses suggest that the universal similarity between tumor and animal growth comes from the fact that both can be described by the same dynamic equation—the Bertalanffy-Richards model—even if they do not necessarily share the same biological properties.

DOI: 10.1103/PhysRevE.95.042406

I. INTRODUCTION

Tumor growth is among the most outstanding issues in the scientific community, from basic science to applied research. This subject began drawing increasing interest from the fields of biology, mathematics, physics, and medicine soon after the relevant increase in diagnosis of tumors in the world population [1–3]. However, in spite of the interdisciplinary research, there is no consensus concerning its causes and development. Empirical observations lead us to believe that tumor growth is ruled by general growth laws which can be represented by differential equations [4]. This approach has many advantages, as, for instance, in estimating the progress of tumors and, consequently, to determine the frequency at which exams such as mammography screening should be performed [5–7]. Furthermore, experimentalists are becoming increasingly convinced that mathematical modeling can clarify and help to interpret a large class of experimental findings.

Even after decades of study and medical breakthroughs, the basic mechanisms underlying tumor growth are still not clear enough and researchers are still attempting to answer the main question regarding this topic: How do tumors grow? From a mathematical point of view, the Gompertz curve, one of the most important current models, has been successful in describing animal and human tumor growth [4,8–10]. On the other hand, the Bertalanffy-Richards model [11–13], which is the general case of the Gompertz, Verhulst, and exponential growth models [4,14–16], provides an accurate description of tumor growth as well [17]. In a brief and simple way, the process of tumor cell growth can be divided into three stages: the avascular phase, the stage where posteriorly new blood vessels form from preexisting vessels (angiogenesis), and, finally, the metastasis stage, when the cancer spreads from one part of the body to another. Within this context, we are interested in characterizing avascular tumor [18] to better understand its development. Although avascular growth corresponds only to the initial stage of tumors, knowledge of this phase is quite important since most experimental data are collected using avascular tumor spheroids *in vitro* [19–21], as they are easier to work with than *in vivo* tumors.

In our current research, supported by previous works such as [22] and [23], we propose a microscopic model to describe tumor growth using two assumptions: self-replication of cells and competition dependent on the distance between them. The model is able to explain the empirical evidence and reproduces the results of some widely known models under certain conditions. Our approach is also able to interpret (at the microscopic level) the phenomenological Bertalanffy-Richards model and, consequently, the Gompertz curve. The model also give an explanation for the fractal distribution of tumor cells, verified in empirical studies [24,25]. Finally, we show that our model is able to explain microscopically the phenomenon responsible for the universal behavior observed in animal and tumor growth (see Figs. 1 and 2), as previously reported in the literature [8]. Our results suggest that the universal similarity between tumor and animal growth comes from the fact that both are described by the same growth equation—the Bertalanffy-Richards model—even if they do not necessarily share the same biological properties. And the universality comes from the fact that the solution of the Bertalanffy-Richards model presents universal mathematical properties. Universality is observed in many physical and biological systems [26–28] and this subject has drawn the attention of theoretical [15,16,29–36] and empirical [8,37–39] studies in the last decades.

The remainder of the paper is organized in the following sections: Section II briefly describes common features in most avascular tumors and some empirical evidence. In Sec. III, we introduce our mathematical model of tumor growth. In Sec. IV we present the concept of optimal fractal dimension and its application to tumor growth. In Sec. V we derive the Bertalanffy-Richards model by a microscopic approach and we also obtain the Gompertz model as a particular case. In Sec. VI we show that our model is able to explain why tumors, as well as animal growth, also follow an universal behavior. Both are described

[*]fribeiro@dfi.ufla.br
[†]renato.santos@dfi.ufla.br
[‡]angelica.mata@dfi.ufla.br

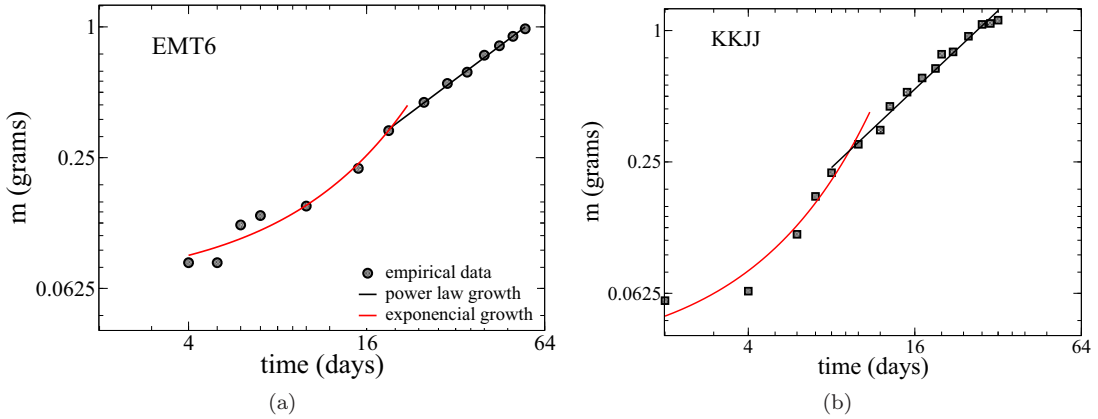

FIG. 1. Growth of two types of tumors, (a) EMT6 and (b) KHJJ, implanted in mice and rats. These data show the usual growth behavior in tumors: an exponential rise in the first stage followed by power-law growth. Source: Ref. [40].

by the same mathematical (Bertalanffy-Richards) model, even though they do not necessarily follow the same biological principles. Finally, in the last section (Sec. VII) we present our conclusions. The Appendix presents a short review of the West, Brown, Enquist (WBE) model [8] for ontogenetic growth.

II. EMPIRICAL EVIDENCE

Many empirical works [17,41–43] suggest that the total mass m of a tumor increases with time t, obeying two regimes: initial exponential growth followed by power-law growth. That is, after the early exponential stage, we have

$$m(t) \sim t^{\alpha}, \tag{1}$$

where α is an exponent which depends on the tumor type and the microenvironment conditions [25,41,44]. The data presented in Fig. 1, reproduced from [41], describe the evolution of the size of a tumor. Moreover, some experiments [41,45] also show that the radius of a solid tumor, $R_{\max}$, grows linearly with time ($R_{\max} \sim t$). Consequently, the spatial size of the tumor scales with its mass as

$$R_{\max} \sim m^{1/\alpha}. \tag{2}$$

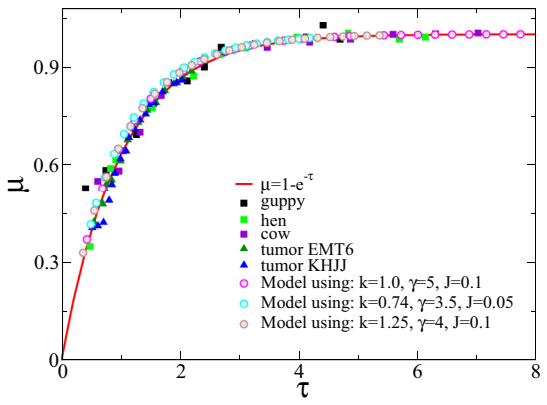

FIG. 2. The universal growth law of the dimensionless mass (μ) as a function of the dimensionless time (τ). Data from completely different organisms collapse in the same universal curve: animals, tumors, and data from the model proposed (see Sec. VI), regardless of the parameter values. The information about tumor and animal growth was extracted from Refs. [40] and [8], respectively.

In earlier studies, tumor growth had been characterized to be chaotic [38,44]. But current researches have adopted fractal geometry to describe this phenomenon, because it is more suitable to quantify the morphological characteristics of solid tumors [25,39,46]. This property is already being taken into account in diagnosing the grade of malignancy of tumors. Some studies suggest that a higher fractal dimension implies greater tumor aggressiveness [24,47–49].

Empirical data on tumors also suggest that their growth seems to follow the same universal pattern observed in animal growth [37,38]. West *et al.* [8] first proposed that the growth of different species (mammals, birds, and fish) follows the same universal curve. The application of the model for tumor growth (*in vivo*, *in vitro*, and in clinical practice) also has yielded successful results [37–39]. Figure 2 summarizes these findings, showing the plot of the dimensionless mass (μ) as a function of the dimensionless time (τ), for completely different kinds of animals (cow, chicken, and guppy) and for two tumors (the same as in Fig. 1). All of them collapse in the same universal curve: $\mu = 1 - e^{-\tau}$ (more details in the Appendix).

The universal behavior of animal growth, according to West *et al.*, is because all species allocate energy in a similar way: to create new cells (growth) and to maintain those that already exist [8,39,40]. However, for tumors, this universal behavior is still not clear enough. In the present work, we show that self-replication and competition among cells, characteristics which seem to be applicable to tumors, can also generate this universal growth pattern.

In order to endorse the empirical evidence previously mentioned in this paper, we propose a simple microscopic model based on the distance-dependent interactions between cells living in a competitive environment. This model explains the following properties of solid-tumor growth:

(a) exponential growth in earlier stages;
(b) power-law growth in later stages;
(c) a diameter following a power law with the number of cells;
(d) fractal-like structures; and
(e) universal behavior.

We present the details of the model in the next section.

III. THE MICROSCOPIC MODEL

We consider three reasonable assumptions from the physical and biological points of view:

(1) The cells compete for resources in their microenvironment, and consequently, they change their position in order to minimize the competition among them.

(2) The replication rate of the cells is affected by this competition.

(3) The intensity of the competition among cells decays as the distance among them increases.

Based on these premises we built a mathematical model that is presented below.

First, let us consider an *interaction function* $f(r)$ which represents the effects—*the field*—that affects a single cell, say i, due to the presence of another cell at distance r. The cells are spatially distributed according to the density function $\rho(\mathbf{r})$, where $\mathbf{r}$ is the *position vector*. Then the total interaction field affecting cell i is

$$I_i = \int_{V_D} \rho(\mathbf{r}) f(r) d^D\mathbf{r}. \tag{3}$$

Here, D (integer) is the Euclidean dimension; V_D is the hypervolume in which the population is immersed; and $d^D\mathbf{r} = r^{D-1} dr\, d\Omega_D$ is the hypervolume element, where $d\Omega_D$ is the solid angle. For more details about this formulation, see Refs. [16,22,50,51].

We consider that the interaction between two cells decays with distance, and therefore, a reasonable choice for the interaction function is

$$f(r) = \begin{cases} \frac{1}{r^\gamma} & \text{if } r > 2r_0, \\ \frac{1}{(2r_0)^\gamma} & \text{otherwise,} \end{cases} \tag{4}$$

where γ is the decay exponent, and r_0 is the diameter of the cell. Hypothesis (4) has been used to describe population cell growth [22,23] and social interaction among individuals in a city [52]. Consider hereafter, for convenience, $r_0 = 1/2$.

Let us suppose that the population grows forming a radially symmetrical structure. We also consider that the number of cells scales as r^{D_f}, where D_f is the dimension of the spacial structure formed by the population, while the hypervolume in which the cells are inserted scales as r^D [53]. Thus, we can write the density of cells as

$$\rho(\mathbf{r}) = \frac{\text{Number of cells}}{\text{Volume}} = \rho_0 \frac{r^{D_f}}{r^D} = \rho_0 r^{D_f - D}, \tag{5}$$

where ρ_0 is a constant and $D_f \leqslant D$.

With these assumptions one can solve Eq. (3) considering *periodic boundary conditions*, following the idea presented in previous works [22,23,54]. At first, this is just a mathematical artifact, but we show that this consideration has physical and biological meaning. The periodic boundary conditions allow us to write the interaction field as (see details in Ref. [22])

$$I_i = I(D_f, N) = \frac{\omega_D}{D_f} \ln_{(\beta-1)}\left(\frac{D_f}{\omega_D} N\right) + \frac{\omega_D}{D_f}, \tag{6}$$

where

$$\beta \equiv 2 - \frac{\gamma}{D_f} \tag{7}$$

and $\ln_{\beta-1}(x) \equiv (x^{\beta-1} - 1)/(\beta - 1)$ is the *generalized logarithm* (see [55]). The particular case $\beta \to 1$ (or $\gamma \to D_f$) leads to the *natural logarithm*. Recent works [16,22,30,51] have suggested that generalized growth models can be written in terms of generalized logarithms, which allows an easier algebraic treatment. In Eq. (6), we also introduced $\omega_D \equiv \rho_0 \int d\Omega_D$, which is a constant that depends only on the dimension D. When $N \to \infty$, the interaction field given by Eq. (6) diverges if $\gamma < D_f$, which implies the existence of long-range interactions between cells. On the other hand, it converges if $\gamma > D_f$; then we have a short-range interaction between them. We restricted our research to the short-range interaction situation, that is, $\gamma > D_f$, which means that the cells interact only with their closer neighbors, and the interaction intensity between them decreases with the distance. It is known from a biological perspective that cells far from each other do not compete for nutrients and, consequently, do not affect each other. This means that the interaction between them is minimal, so short-range interactions is a good assumption. In this case, the periodic boundary conditions, which allow us to get the result given by Eq. (6), simplify the problem and it is good enough to describe realistic situations.

Note that the field given by Eq. (6) does not depend on the index i; that is, it is the same for all individuals in the population. This is a consequence of the periodic boundary conditions [22] and the self-similarity of the mathematical structure that we have proposed to describe the tumors. This means that all cells are subject to the same influence from their neighboring cells. In fact, this influence depends only on the size of the population and the dimension of its structure; that is, $I_i = I(N, D_f)$.

In Sec. IV, we show that the population reaches an optimal space distribution when the cells move in order to minimize the competitive interaction. As we see, this dimension must be fractal when the population is sufficiently large. This means that an optimal fractal dimension appears as a natural consequence of the interaction between cells. So, we can show that the model is able to explain, by a microscopic approach, the spacial distribution observed in real tumors.

As a first application of this model, one can use it to predict how the diameter of the tumor, say $2R_{\max}$, behaves when the number of cells N increases. Considering that $N = \int_{\text{all space}} \rho(\mathbf{r}) d^D\mathbf{r}$ and the density is given by Eq. (5), one has $N = \rho_0 \int d\Omega_D \int_0^{R_{\max}} r^{D_f - 1} dr$ and, consequently,

$$R_{\max} \sim (D_f N)^{\frac{1}{D_f}}. \tag{8}$$

This result is in accordance with the empirical data that the diameter of the tumor follows a power law with the number of cells [41,45].

IV. OPTIMAL FRACTAL DIMENSION

In the growth period, the cells compete for resources in their microenvironment. This means that each cell must to move in order to minimize the competition with the other cells. Figure 3

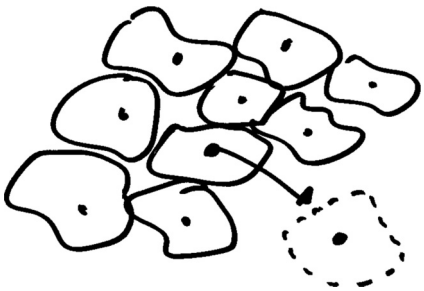

FIG. 3. Schematic of cellular dynamics. In a competitive environment, each cell tries to move in a direction that minimizes the influence (competitive field) of other cells.

shows schematically the movement of a single cell to minimize its competitive field with its neighbors. If all cells perform this movement, the spatial distribution of their population will change adaptively. Consequently, the (fractal) dimension of the structure formed by the population will change over time.

The interaction field generated by the cells presents two extreme values: when $D_f \to 0$ and $D_f \to 3$. When $D_f \to 0$, the population tends to concentrate in a single point [see Eq. (8): $R_{\max} \to 0$ when $D_f \to 0$], creating a high interaction field. On the other hand, when $D_f \approx 3$ and N is sufficiently large, the population is compacted (higher density), which also results in a strong interaction field. However, there is an *optimal dimension* between these two values, that we call D_f^{opt}, which minimizes the competitive field experienced by each cell. One can obtain D_f^{opt} by evaluating

$$\frac{\partial}{\partial D_f} I(N, D_f)\Big|_{D_f = D_f^{\text{opt}}} = 0. \tag{9}$$

Such ideas are illustrated quantitatively in Fig. 4(a), which presents the plot of the interaction field $I(N, D_f)$, given by Eq. (6), as a function of the dimension of the population, with N fixed. It is possible to see that the interaction field always has a minimum ($D_f = D_f^{\text{opt}}$). If N is small, then $D_f^{\text{opt}} = 3$, which means a compacted population; but for a sufficiently large population, the optimal dimension is fractal, which represents a real tumor. Our microscopic model clarifies the role of the fractal geometry of tumor growth since this structure emerges spontaneously as a response of the cells to minimize the competitive field.

In the next section we present the population growth process in this competitive context. We see that the proposed model presents exponential growth in earlier stages, followed by a power-law growth stage, which is in accordance with the empirical evidence.

V. POPULATION GROWTH

Our model presents two time scales. The first one is the time that the cells take to reach the optimal fractal dimension arrangement. The second time scale, represented by t, is measured in generations. The cells reproduce at the end of each generation. We also assume that the time between two consecutive generations is sufficiently large to allow the population to reach an optimal spatial distribution D_f^{opt} before the next procreation. Then, at the moment of reproduction, the field felt by each cell is $I^{\text{opt}}(N) \equiv I(N, D_f = D_f^{\text{opt}})$.

In a *competitive* context, the interaction field exercises inhibitory behavior in the reproduction of the cells [22,23,46]. In this way, it is quite reasonable to consider that the *replication rate* R_i of the i-th cell is given by

$$R_i = k - J I^{\text{opt}}. \tag{10}$$

This equation says that the reproductive capability of the cells depends on both properties: an inherent property—given by the *intrinsic replication rate* k—and an (inhibitory) influence of the other cells in the population, given by $J I^{\text{opt}}$. The parameter k is identical, by definition, for all cells, while $J I^{\text{opt}}$ represents the *rate of competition*. The parameter $J > 0$ measures the intensity of the inhibition. When $J < 0$, we have cooperation among cells. This situation provides a different approach than

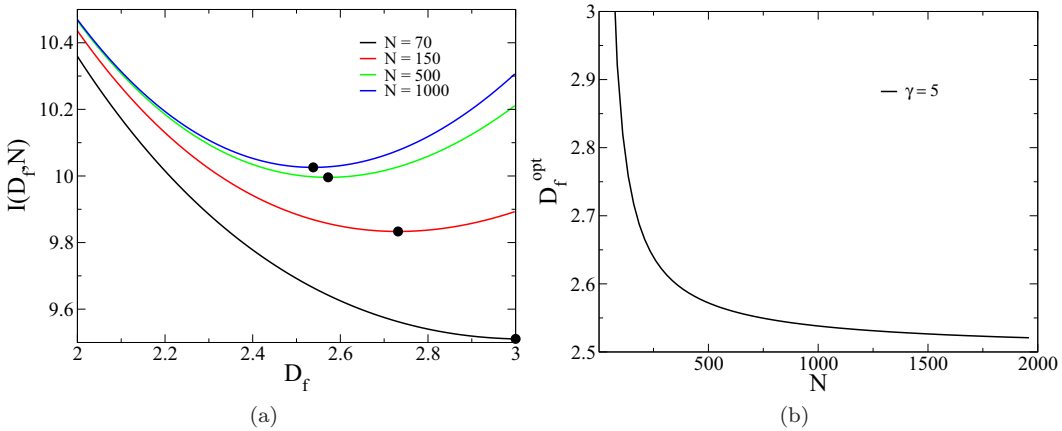

FIG. 4. (a) Plot of the field $I(N, D_f)$, given by Eq. (6), as a function of the fractal dimension. The plot was made for fixed values of population size and using $\gamma = 5$. Black circles represent the minimum value of $I(N, D_f)$ in relation to the fractal dimension, which leads to D_f^{opt}. When the population is small, the plot suggests that the population tends to be compact, that is, $D_f^{\text{opt}} = 3$. However, when the population becomes sufficiently large, the optimal dimension is fractal. (b) Plot of the fractal dimension which minimizes the interaction field (D_f^{opt}) as a function of the population size. The optimal fractal dimension decreases monotonically as the population increases, and it becomes slower for a sufficiently large population.

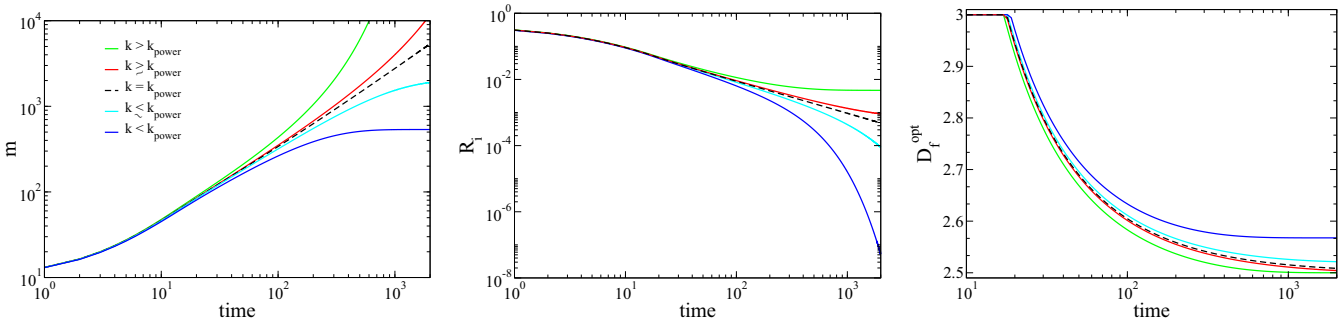

FIG. 5. Temporal evolution for (a) mass, (b) replication rate, and (c) optimal fractal dimension given by our microscopic model. We used different values of the intrinsic replication rate k, and we kept fixed the parameters $J = 0.1$, $\gamma = 5$, and $m_c = 1$. The curves were obtained by Eq. (11). When $k > k_{\text{power}}$ the population (or its mass) diverges, when $k = k_{\text{power}}$ the population grows according to a power law, and when $k < k_{\text{power}}$ the population saturates. If $k \sim k_{\text{power}}$, the population remains in a power-law growth regime for a long period. The population grows in a power-law regime because the replication rate R_i also decreases as a power law. The optimal dimension of the spatial structure formed by the population is 3 (compacted form) in the initial stage, but then it becomes fractal when the population increases. This optimal fractal dimension saturates to what we call D_f^{conv}.

we are interested in and it has been discussed in previous works [16,22,50].

Since $\Delta t R_i$ is the number of daughter cells that cell i generates in a time period Δt, the updated population size in this period is

$$N(t + \Delta t) = N(t) + \Delta t \sum_{i=1}^{N} R_i. \tag{11}$$

In the limit $\Delta t \to 0$, this recurrence equation yields to an *ordinary differential equation*:

$$\frac{dN}{dt} = N(k - JI^{\text{opt}}). \tag{12}$$

Introducing the result given by Eq. (6), we have

$$\frac{dN}{dt} = cN^{\beta^{\text{opt}}} - bN, \tag{13}$$

where

$$b \equiv \frac{J\omega_D\gamma}{D_f^{\text{opt}}\left(\gamma - D_f^{\text{opt}}\right)} - k, \tag{14}$$

$$c \equiv \frac{-J}{\left(1 - \frac{\gamma}{D_f^{\text{opt}}}\right)}\left(\frac{D_f^{\text{opt}}}{\omega_D}\right)^{-\frac{\gamma}{D_f^{\text{opt}}}}, \tag{15}$$

and

$$\beta^{\text{opt}} \equiv 2 - \frac{\gamma}{D_f^{\text{opt}}}. \tag{16}$$

Assuming that each cell has the same mass m_c, the total mass of the tumor at time t can be written as $m(t) = m_c N(t)$. Thus, Eq. (13) becomes

$$\frac{dm}{dt} = am^{\beta^{\text{opt}}} - bm, \tag{17}$$

with

$$a \equiv \frac{-Jm_c^{\frac{\gamma}{D_f^{\text{opt}}}-1}}{1 - \frac{\gamma}{D_f^{\text{opt}}}}\left(\frac{D_f^{\text{opt}}}{\omega_D}\right)^{-\frac{\gamma}{D_f^{\text{opt}}}}. \tag{18}$$

Note that this model reproduces the Bertalanffy-Richards model when the parameter D_f is constant. This particular case is discussed in Sec. V A.

It is difficult to obtain an analytic solution to Eq. (17) since β^{opt} is not fixed (it depends on D_f^{opt}, which, in turn, depends on the population size). However, the dynamics of the model can be investigated by solving numerically the recurrence relation given by Eq. (11). This numerical solution is presented in Fig. 5. The population size (the mass) of the tumor grows exponentially at the beginning and then grows according to a power-law regime before it saturates or blow up. Whether the population saturates or explodes, it depends on the value of the self-replication rate. The value of k that divides these two stages is $k = k_{\text{power}}$, where

$$k_{\text{power}} \equiv \frac{J\omega_D\gamma}{D_f^{\text{opt}}\left(\gamma - D_f^{\text{opt}}\right)} \tag{19}$$

is obtained by assuming $b = 0$ in Eq. (14) (more details in Sec. V A).

When $k = k_{\text{power}}$, the population grows purely in a power-law regime, described by (see Sec. V A)

$$m(t) \sim t^{\frac{D_f}{\gamma - D_f}}. \tag{20}$$

In fact, the power-law growth happens because the replication rate R_i decreases according to a power law [see Fig. 5(b)]. On the other hand, when $k < k_{\text{power}}$, the population saturates because the replication rate tends to 0 as the dynamics evolves. And, finally, the population explodes (exponentially) when $k > k_{\text{power}}$ because the replication rate R_i converges to a constant (greater than 0).[1]

It should be noted that the dynamics of the population always reaches a power-law growth regime regardless of the value of the intrinsic replication rate. This phenomenon has been observed in real tumor growth. According to the numerical results, the period for which the population grows

[1]Malthusian growth happens when the replication rate is constant.

according to this regime depends on the intrinsic replication rate of the cells. If $k \sim k_{\text{power}}$, the population stays for a long period on a power-law growth, but if k is too different from k_{power}, the population stays in this regime for only a short period (see Fig. 5).

The dynamics of the fractal dimension D_f^{opt} are also presented in Fig. 5. Note that small populations have $D_f^{\text{opt}} = 3$ (compacted structure), but for large populations, the dimension becomes fractal. The numeric value of the (fractal) dimension decreases rapidly and then saturates to a value that we call D_f^{conv} (the convergence value). When $k \geqslant k_{\text{power}}$, then $D_f^{\text{conv}} \to \gamma/2$, where γ is the decay exponent of the interaction function.

In a real situation, the condition $k < k_{\text{power}}$ is necessary and the population saturates for longer times; otherwise, the population diverges. However, as discussed in Refs. [37–39], a real tumor does not saturate because, before this happens, either the patient is dead or the tumor cells had already started the vascularization and, consequently, the metastasis. Nevertheless, our microscopic model is good enough to describe the initial stage of real tumors characterized by power-law growth.

The strong point of our model is that it explains, based on few principles, the spatial distribution and growth process of a real tumor. It is also important to emphasize that the model is built using a microscopic (individual-level) approach, and not a phenomenological (macroscopic) perspective, as earlier studies did [1,4,22,44,56].

A. Connection with the Bertalanffy-Richards model

We can obtain an analytical solution to Eq. (17) when the parameter D_f is kept fixed during the growth process, for example, taking $D_f = D_f^{\text{conv}}$. This is reasonable for N sufficiently large. Thus, one can obtain a simpler version of the original approach, that which proves to be the *Bertallanfy-Richards* growth model [12,13,57], whose solution is

$$m(t) = \left[\frac{a}{b} + \left(m_0^{1-\beta} - \frac{a}{b}\right)e^{b(\beta-1)t}\right]^{\frac{1}{1-\beta}}, \qquad (21)$$

where a, b, and β are given by Eqs. (18), (14), and (7), respectively.

In Fig. 6 we show a comparison between the original model (evolving D_f) and its simplified version (keeping $D_f = D_f^{\text{conv}}$ fixed). Note that, despite the differences between the two dynamics during the growth process, they converge to the same saturation mass.

The Bertalanffy-Richards model has been successfully used to describe tumor growth [4,12,37,40]. One of the main points of the model proposed here is that the Bertalanffy-Richards growth model emerges as a consequence of the cellular interaction (microscopic level), and not by a phenomenological (macroscopic) approach.

The solution given by Eq. (21) has two asymptotic behaviors, saturation and divergence, according to the signal of the argument in the exponential of Eq. (21). As $\gamma/D_f > 1$ (short-range interaction regime), then $(\beta - 1)$ is always negative, and consequently the signal of this argument depends only on b.

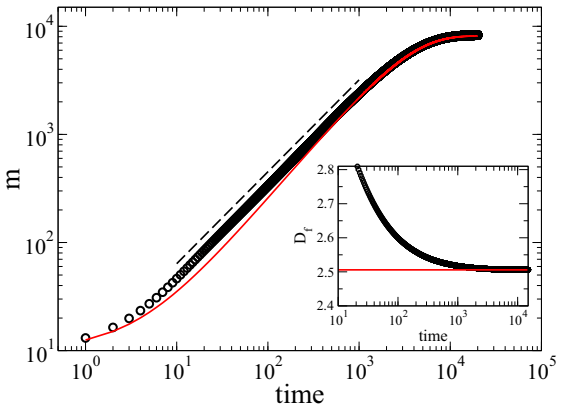

FIG. 6. Predictions of the microscopic model of the population growth (its mass), using two approaches: (i) D_f evolves over time, represented by dots; and (ii) the (fractal) dimension is fixed, represented by the red line (special case of the model, when $D_f = D_f^{\text{conv}}$). In both cases $J = 0.1$ and $\gamma = 5$. The straight dashed line shows a power-law behavior as a guide for the eyes. The red line is slightly different from the dotted curve during the growth process, but they converge to the same saturation value. Inset: Fractal dimension of the population for these two approaches. For the dotted line, the population starts with $D_f^{\text{opt}} = D = 3$ (compacted form) but shortly becomes fractal and converges to a saturation value, $D_f^{\text{opt}} \to D_f^{\text{conv}}$.

In fact, this quantity can be written as $b = k_{\text{power}} - k$, where k_{power} is given by Eq. (19).

If $b < 0$ (that is, $k > k_{\text{power}}$), the population grows exponentially. Then b also plays the role of *growth rate*. Otherwise, if $b > 0$ (that is, $k < k_{\text{power}}$), the population saturates asymptotically. These two accessible regimes are limited by a line characterized by $b = 0$, when the population grows following a power law. In this context, we get Eq. (20).

B. Connection with the Gompertz model

The Bertalanffy-Richards equation represents a generalized growth model since it embraces some phenomenological models as particular cases. We have to analyze the ratio γ/D_f [or the parameter β, by Eq. (7)]. For example, the *Verhulst model* [58] is reached when $\gamma \ll D_f$ (that is, $\beta \to 2$). As proposed in Refs. [22,23,54] this happens when the interaction between cells does not depend on the distance. So, the Verhulst model is some kind of mean-field model.

The *Gompertz model* [59] is also a particular case of the Bertalanffy-Richards model, which is reached when $\gamma \to D_f$ (or $\beta \to 1$). It is easy to see how the Gompertz model emerges from this theoretical framework. Defining $\delta = a - b$ and $\alpha = b(1 - \beta^{\text{opt}})$, Eq. (17) becomes

$$\frac{dm}{dt} = \delta m^{\beta^{\text{opt}}} - \alpha m^{\beta^{\text{opt}}}\left(\frac{m^{1-\beta^{\text{opt}}} - 1}{1 - \beta^{\text{opt}}}\right). \qquad (22)$$

If we take the limit $\beta^{\text{opt}} \to 1^-$,

$$\frac{dm}{dt} = \delta m - \alpha m \ln(m) = -\alpha \ln\left(\frac{m}{K}\right), \qquad (23)$$

which is the *Gompertz equation*, with $K \equiv \exp(\delta/\alpha)$. So the Gompertz model is recovered at the limit of $\beta \to 1$, which

corresponds to the optimal fractal dimension D_f^{opt}'s being numerically equivalent to the decay coefficient γ [see Eqs. (4) and (16)].

We have claimed that there is a relationship between the tumor malignancy and the fractal dimension of the cancerous cell body. The more malignant the tumor, the greater the fractal dimension [25]. If the condition $D_f = \gamma$ is reasonable, the model indicates that malignancy involves cells with shorter-range interaction.

We also noted that, for a large enough population, the replication rate decays exponentially, as shown in Fig. 5. Our model was formulated based on interactions among cells which depend just on the distance that separates them. Even considering just this very simple interaction, our approach is able to explain very well the success of the phenomenological Gompertz model to describe tumor growth.

VI. UNIVERSAL GROWTH BEHAVIOR

In animal growth, West *et al.* (WBE model [8]) suggest that the universal behavior shown in the data in Fig. 2 comes from the fact that species allocate energy in the same way: for growth or for maintenance (see the Appendix). Moreover, to get this universal growth law, it is also necessary to consider that species obey the *allometric law* (also called *Kleiber's law*), which says that the metabolic rate increases sublinearly with the mass of the organism [60]. However, tumors do not necessarily obey the allometric law, and furthermore, they present a fractal form, instead of the space-filling process required by WBE theory [8,38]. Thus, the explanation based on allocation of energy is not necessarily suitable for tumors.

Our model, on the other hand, suggests that this universal growth pattern emerges from first principles, i.e., cell interactions. Specifically, two assumptions at the microscopic level: competition and self-replication. In animal growth, the dimensionless mass μ is related to the ratio between the maintenance energy and the total energy of the organism (details in the Appendix). But in our model this quantity gets another interpretation, although it is still universal. In fact, using the relations given by Eqs. (14), (18), (19), (A6), and (A7), one can show that

$$\mu = \frac{k_{\text{power}} - k}{k_{\text{power}} - J I_i}. \tag{24}$$

This result means that the dimensionless mass is a relationship between the intrinsic replication rate k and the competition rate $J I_i$. While k is constant during the process, the competition rate increases because the population size grows as well.

For a small time frame (i.e., $\tau \approx 0$), the competition rate is lower compared to the intrinsic replication rate, resulting in $\mu \approx 1 - k/k_{\text{power}}$. In this case, the tumor keeps growing. However, for τ sufficiently large, the competition rate reaches the same magnitude as the intrinsic replication rate. In this situation the tumor stops growing (population saturates), which means that $\mu \to 1$. According to the model, as noted for Fig. 2, this happens regardless of the intensity of the competition J, the decay exponent of the competitive interaction γ (and consequently $\beta = 2 - \gamma/D_f$), or the intrinsic replication rate k.

All the settings collapse into a single universal curve, exactly as happens to empirical data on tumor and animal growth. Of course, k has to be less than k_{power} to avoid the unrealistic situation of exploding population size. In other words, no matter what the value of the parameter β, all dynamics collapse in the same universal curve. This means that even if an organism does not follow the allometric law ($\beta = 3/4$), it will still follow the universal curve, as probably happens in the case of tumor growth. Moreover, this approach also explains why as long as the competition among cells increases, due to the population increase, the replication rate decreases.

Finally, our microscopic model suggests that the universal similarity between tumor and animal growth does not necessarily come from common biological properties. The universal behavior that emerges may be because any biological growth (animal, tumor) is in fact described by the same equation, the Bertalanffy-Richards model, (17). Any process (biological or physical) that can be modeled by this equation will also collapse in the same universal curve.

VII. CONCLUSIONS

In this paper, we have presented good reasons to consider that our mathematical model is able to explain empirical evidence of tumor growth. Our microscopic model describe well enough the form and the growth process of avascular tumors, taking into account a few basic principles. In our approach, the competition between cells determines their replication rate, and beyond that the cells can also move in order to minimize this competition among them. Such basic assumptions, at the microscopic level, induce macroscopic properties that can be observed in real tumors.

The model reproduces, for instance, the exponential growth in early stages followed by power-law growth. The fractal structure, observed in many solid tumors [24,25,61], is also described in our model, since the optimal fractal dimension emerges spontaneously, as a consequence of the interaction between the cells.

Moreover, this model shows that the relation between the intrinsic replication rate and the competition rate of the cells plays the same role as energy allocation in growing animals. This leads to the same universal behavior in both animal and tumor growth. In other words, different biological mechanisms can be represented by the same ubiquitous equation, given by the Bertalanffy-Richards model. Besides, the universality found for tumor growth is irrespective of the values of the parameters of the microscopic model.

In short, we have presented a robust model able to describe tumor growth as well as other processes in general. Regardless of the system under discussion, as long as it is described by the Bertalanffy-Richards model, its dynamics will follow universal growth behavior. In conclusion, we believe that our model is able to provide a better comprehension of growth patterns not only in relation to tumors, but also with regard to other biological systems.

ACKNOWLEDGMENTS

We would like to acknowledge the useful and stimulating discussions with Alexandre Souto Martinez, Fernando Fagundes Ferreira, and Camilo Rodrigues Neto. We would also like

to acknowledge the support from CNPq, Fapemig, and CAPES (Process No. 88881.119533/2016-01).

APPENDIX: WBE MODEL FOR ANIMAL GROWTH

In this Appendix we give a short description of the West, Brown, Enquist model [8], which describes animal growth considering Kleiber's law [60] and the principle of conservation of energy. Kleiber's law says that the metabolic rate B of an organism scales sublinearly with its body mass, that is, $B = B_0 m^\beta$, where B_0 is constant for a given taxon and $\beta < 1$ is the allometric constant. According to the WBE model, the total metabolized energy of an organism must be used for maintenance of the already existent cells or to generate new cells. That is,

$$[\text{Total Metabolic Energy}] = [\text{Maintenance}] + [\text{Growth}].$$

It yields the ordinary differential equation,

$$B_0 m^\beta = B_c m + E_c \frac{dm}{dt}, \tag{A1}$$

where B_c is the metabolic rate of a single cell and E_c is the energy necessary to create a new cell. The equation above can be written as

$$\frac{dm}{dt} = a m^\beta - b m, \tag{A2}$$

where

$$a \equiv \frac{B_0 m_c}{E_c} \tag{A3}$$

and

$$b \equiv \frac{B_c}{E_c}. \tag{A4}$$

The constants B_0, m_c, and E_c are scaling invariants and do not depend on the species. That is, these parameters are universal. Then a, given by (A3), which depends only on scale-invariant parameters, is also universal. However, this is not the case for the parameter b, which depends on the biological species.

The solution of Eq. (A2) is

$$m(t) = \left[\frac{a}{b} + \left(m_0^{1-\beta} - \frac{a}{b}\right) e^{b(\beta-1)t}\right]^{\frac{1}{1-\beta}}, \tag{A5}$$

where m_0 is the initial mass of the organism. As $\beta < 1$, the solution of Eq. (A5) converges to

$$M \equiv m(t \to \infty) = \left(\frac{a}{b}\right)^{\frac{1}{1-\beta}}, \tag{A6}$$

which can be interpreted as the maturity mass of the organism.

Consider the quantity

$$\mu \equiv \left(\frac{m}{M}\right)^{1-\beta} = \frac{\text{Maintenance Energy}}{\text{Total Metabolic Energy}}, \tag{A7}$$

a kind of dimensionless mass. Consider also

$$\tau \equiv -\ln\left(1 - \left(\frac{m_0}{M}\right)^{1-\beta}\right) + \frac{a(1-\beta)}{M^{1-\beta}} t, \tag{A8}$$

a kind of dimensionless time. The WBE theory shows that if one plots μ as a function of τ, then many species of animals (birds, mammals, fish) and also tumors collapse in the same universal curve ($\mu = 1 - e^{-\tau}$), as shown in Fig. 2.

[1] S. McElwain and R. Araujo, Bull. Math. Biol. **66**, 1039 (2004).
[2] A. d'Onofrio and A. Gandolfi (eds.), *Mathematical Oncology 2013*, 1st ed. *Modeling and Simulation in Science, Engineering and Technology Series* (Birkhauser, Basel, Switzerland, 2014).
[3] N. L. K. Dominik Wodarz, *Dynamics of Cancer: Mathematical Foundations of Oncology* (World Scientific, Singapore, 2014).
[4] P. Gerlee, Cancer Res. **73**, 2407 (2013).
[5] A. Bernard, H. Kimko, D. Mital, and I. Poggesi, Expert Opin. Drug Metab. Toxicol. **8**, 1057 (2012).
[6] L. Norton, R. Simon, H. D. Brereton, and A. E. Bogden, Nature **264**, 542 (1976).
[7] M. Simeoni, G. De Nicolao, P. Magni, M. Rocchetti, and I. Poggesi, Drug Discovery Today: Technol **10**, e365 (2013).
[8] G. B. West, J. H. Brown, and B. J. Enquist, Nature **413**, 628 (2001).
[9] H. Thames, Int. J. Radiat. Biol. **57**, 1063 (1990).
[10] A. K. Laird, Br. J. Cancer **18**, 490 (1964).
[11] L. Yuancai, C. Marques, and F. Macedo, Forest Ecol. Manage. **96**, 283 (1997).
[12] L. Bertalanffy, Q. Rev. Biol. **32**, 217 (1957).
[13] F. J. Richards, J. Exp. Bot. **10**, 290 (1959).
[14] S. Benzekry, C. Lamont, A. Beheshti, A. Tracz, J. M. Ebos, L. Hlatky, and P. Hahnfeldt, PLoS Comput. Biol. **10**, e1003800 (2014).
[15] A. S. Martinez, R. S. González, and C. A. S. Terçariol, Physica A: Stat. Mech. Appl. **387**, 5679 (2008).
[16] F. L. Ribeiro and K. N. Ribeiro, Physica A: Stat. Mech. Appl. **434**, 201 (2015).
[17] E. A. Sarapata and L. de Pillis, Bull. Math. Biol. **76**, 2010 (2014).
[18] B. Alberts, *Molecular Biology of the Cell* (Garland Science, New York, 2008), p. 2 .
[19] F. Hirschhaeuser, H. Menne, C. Dittfeld, J. West, W. Mueller-Klieser, and L. A. Kunz-Schughart, J. Biotechnol. **148**, 3 (2010).
[20] X. Xu, M. C. Farach-Carson, and X. Jia, Biotechnol. Adv. **32**, 1256 (2014).
[21] C. Wang, Z. Tang, Y. Zhao, R. Yao, L. Li, and W. Sun, Biofabrication **6**, 022001 (2014).
[22] F. L. Ribeiro, Bull. Math. Biol. **77**, 409 (2015).
[23] J. C. M. Mombach, N. Lemke, B. E. J. Bodmann, and M. A. P. Idiart, Europhys. Lett. **59**, 923 (2002).
[24] S. S. Cross, J. Pathol. **182**, 1 (1997).
[25] J. W. Baish and R. K. Jain, Cancer Res. **60**, 3683 (2000).

[26] L. P. Kadanoff, *Statistical Physics: Statics, Dynamics and Remormalization* (World Scientific, Singapore, 2000).
[27] J. M. Yeomans, *Statistical Mechanics of Phase Transitions* (Oxford University Press, Oxford, UK, 1992).
[28] H. E. Stanley, *Introduction to Phase Transitions and Critical Phenomena* (Oxford University Press, Oxford, UK, 1987).
[29] M. Chester, Open J. Ecol. **01**, 77 (2011).
[30] B. C. T. Cabella, A. S. Martinez, and F. Ribeiro, Phys. Rev. E **83**, 061902 (2011).
[31] B. C. T. Cabella, F. Ribeiro, and A. S. Martinez, Physica A: Stat. Mech. Appl. **391**, 1281 (2012).
[32] F. Ribeiro, B. C. T. Cabella, and A. S. Martinez, Theory Biosci. **133**, 135 (2014).
[33] C. Kuehn, S. Siegmund, and T. Gross, IMA J. Appl. Math. **78**, 1051 (2013).
[34] D. Strzalka and F. Grabowski, Physica A: Stat. Mech. Appl. **387**, 2511 (2008).
[35] D. Strzałka, Acta Phys. Pol. B **40**, 41 (2009).
[36] S. Torquato, Phys. Biol. **8**, 015017 (2011).
[37] C. Guiot, P. G. Degiorgis, P. P. Delsanto, P. Gabriele, and T. S. Deisboeck, J. Theor. Biol. **225**, 147 (2003).
[38] C. Guiot, P. P. Delsanto, A. Carpinteri, N. Pugno, Y. Mansury, and T. S. Deisboeck, J. Theor. Biol. **240**, 459 (2006).
[39] V. M. Savage, A. B. Herman, G. B. West, and K. Leu, Discrete Cont. Dynam. Syst. Ser. B **18**, 1077 (2013).
[40] A. B. Herman, V. M. Savage, and G. B. West, PLoS ONE **6**, e22973 (2011).
[41] D. Drasdo, S. Höhme *et al.*, *Individual Based Approaches to Birth and Death in Avascular Tumors* (Max-Planck-Institut für Mathematik in den Naturwissenschaften, Leipzig, 2002).
[42] J. G. Scott, P. Gerlee, D. Basanta, A. G. Fletcher, P. K. Maini, and A. R. Anderson, in *Experimental Metastasis: Modeling and Analysis* (Springer, Berlin, 2013), pp. 189–208.
[43] M. Al-Hajj, M. S. Wicha, A. Benito-Hernandez, S. J. Morrison, and M. F. Clarke, Proc. Natl. Acad. Sci. USA **100**, 3983 (2003).
[44] H. M. Byrne, T. Alarcon, M. R. Owen, S. D. Webb, and P. K. Maini, Philos. Trans. Ser. A Math. Phys. Eng. Sci. **364**, 1563 (2006).
[45] J. P. Freyer and R. M. Sutherland, J. Cell. Physiol. **124**, 516 (1985).
[46] A. DOnofrio, Chaos Solitons Fractals **41**, 875 (2009).
[47] R. Dobrescu, F. Talos, and C. Vasilescu, in *Video/Image Processing and Multimedia Communications 4th EURASIP-IEEE Region 8 International Symposium on VIPromCom* (IEEE, New York, 2002) pp. 173–176.
[48] G. Landini and J. Rippin, J. Pathol. **179**, 210 (1996).
[49] G. A. Losa and C. Castelli, Cell Tissue Res. **322**, 257 (2005).
[50] R. V. Dos Santos, F. L. Ribeiro, and A. S. Martinez, J. Theor. Biol. **385**, 143 (2015).
[51] F. L. Ribeiro, Revista Brasileira de Ensino de Fisica **39**, e1311 (2017).
[52] F. L. Ribeiro, J. Meirelles, F. F. Ferreira, and C. R. Neto, Roy. Soc. Open Sci. **4**, 1 (2017); http://rsos.royalsocietypublishing.org/content/4/3/160926.full.pdf.
[53] K. Falconer, *Fractal Geometry: Mathematical Foundations and Applications* (Wiley, New York, 2004).
[54] A. D'Onofrio, U. Ledzewicz, H. Maurer, and H. Schättler, Math. Biosci. **222**, 13 (2009).
[55] C. Tsallis, *Introduction to Nonextensive Statistical Mechanics: Approaching a Complex World*, 1st ed. (Springer, Berlin, 2009).
[56] A. Swierniak, M. Kimmel, and J. Smieja, Eur. J. Pharmacol. **625**, 108 (2009).
[57] L. Von Bertalanffy, in *Principles and Theory of Growth. Fundamental Aspects of Normal and Malignant Growth*, edited by W. W. Nowinski (Elsevier, Amsterdam, 1960), pp. 137–259.
[58] P. F. Verhulst, Nouveaux mémoires de l'Académie Royale des Sciences et Belles-Lettres de Bruxelles **18**, 14 (1845).
[59] R. Gompertz, Philos. Trans. Roy. Soc. Lond. **115**, 513 (1825).
[60] M. Kleiber, Hilgardia **6**, 315 (1932).
[61] T. F. Nonnenmacher, G. A. Losa, and E. R. Weibel, *Fractals in Biology and Medicine* (Birkhäuser, Basel, Switzerland, 2013).