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Allometric Scaling by the Length of the Circulatory Network

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Abstract

Background: Allometric scaling is a well-known research tool used for the metabolic rates of organisms. It measures the living systems with fractal physiology. The metabolic rate versus the mass of the living species has a definite scaling and behaves like a four-dimensional phenomenon. The extended investigations focus on the mass-dependence of the various physiological parameters. **Objective:** Proving the length of vascularization is the scaling parameter instead of mass in allometric relation. **Method:** The description of the energy balance of the ontogenic growth of the tumor is an extended cell-death parameter for studying the mass balance at the cellular level. **Results:** It is shown that when a malignant cellular cluster tries to maximize its metabolic rate, it changes its allometric scaling exponent. A growth description could follow the heterogenic development of the tumor. The mass in the allometric scaling could be replaced by the average length of the circulatory system in each case. **Conclusion**: According to this concept, the dependence of the mass in allometric scaling is replaced with a more fundamental parameter, the length character of the circulatory system. The introduced scaling parameter has primary importance in cancer development, where the elongation of the circulatory length by angiogenesis is in significant demand.

Keywords

Allometry, Metabolism, Four-Dimension, Optimization, Cancer, Circulatory System, Characteristic Length

1. Introduction

The spatiotemporal organization of biosystems is complex. The complexity is driven by self-organization ([1] [2] [3]), and validated by new science: fractal physiology ([4] [5]), including the bioscaling processes ([6] [7]). Understanding

the challenges of the complexity of human medicine requires the development of a new paradigm [8].

The Basal Metabolic Rate (BMR) shows allometric scaling of the mass of the organism [9], describes as the power function of the mass ($\mathcal{M}$) [10]:

$$BMR \propto \mathcal{M}^{\alpha} \tag{1}$$

The allometric relation connects the surface-controlled metabolic processes with the geometry of the given material, which uses the available energy. In the simple formulation, metabolic processes are surface-dependent, while the mass is proportional to the volume. Therefore, the exponent of their ratio mirrors the dimensionality, and consequently, the exponent is $\alpha = 2/3$. On the other hand, the complex living allometry shows the exponent as $\alpha = 3/4$ instead of $\alpha = 2/3$ [11], explaining the relationship between the three-dimensional surface and the four-dimensional volume. Metabolic scaling in solid tumors is significant, but its heterogeneity and its rapid development by intensive proliferation and the supporting vascularity [12] change the scaling behavior [13], and this is described as dynamic evolution [14].

Life in this context is "four-dimensional" based on its metabolic exchange processes [15]. The self-organized multicellular structure creates fractal arrangements, and their metabolic energy-exchange proceeds on fractal surfaces, maximizing the available energy-consumption, scaling the fluctuation of the metabolic power by the universal scaling law [16]. This optimization of energy consumption was rigorously tested in the context of the scaling idea and can be extended to broader mechanisms [17], such as the energy-consumption's subcellular level, including the mitochondria and respiratory complexes [17].

The scaling model has been shown to be valid in a broad category of living structures and processes. The primary physiological parameters exponentially depend on the mass of the body [18]. The allometry shows a structural, geometrical constraint for living organisms. Nevertheless, life is more complex than what can be determined by its geometrical structure. A self-similar spatial-temporal-fractal structure defines the self-organizing procedure both in space and time [19]. A particular noise (temporal fractal noise)—like a fingerprint of the self-organizing [20]—is a typical and general behavior of the living biomaterial [21]. The stochastic fluctuations have a characteristic effect on malignant development [22], acting in the apoptotic threshold of cancer [23], and is well observable in the growth process [24].

The measured structural patterns could be applied to evaluate the cancer development [25] [26], an example of this is the use of image analysis is done by a pathologist. The metabolic power not only depends on the size of the surface involved in active transport, but also on the flow-rate of the same active surface size. This dependence could modify the transport. In the case of Benthic invertebrates (n = 215), they have the lowest average scaling exponent because they metabolize in an anaerobic way. This can be written as: ($\alpha_{mean} = 0.63$, [near to 2/3], $CI_{mean} = 0.18$), where α is the scaling exponent, and CI is the Confidence

Interval [27]. However, the other studied animals (n = 496) have ($\alpha_{mean} = 0.74$, [near to $\alpha_{mean} = 3/4$], $CI_{mean} = 0.18$) [28]. The scaling of the metabolic activity is also different in mitochondrial and non-mitochondrial processes [29]. Mitochondrial metabolism is always aerobic, and its scaling exponent is nearly $\alpha = 3/4$ [30] [31]. When the oxygen supply is limited, the cell extends its ATP production to fermentation by non-mitochondrial respiration, where the allometric scaling exponent lowers to nearly $\alpha = 2/3$.

Based on the scaling theory, a general model for ontogenic growth has been proposed [32] [33] [34]. Allometry is a consequence of the evolution process [35]. The variation of the personal sizes of the organs and the whole body of the individuals can be addressed in the frame of the power-law. The high fractal dimension could be used as a significant prognostic factor in diseased tissues [36]. There is research on tumor growth evaluated from an ontogenic basis [14] [37] [38] in which the tumor is successfully described, despite the substantial heterogeneity of the blood-supply [39] and the cellular structures differing from their regular counterparts. If the whole tumor mass differs from the mass of the viable part of the tumor, and the viable part has a scaling by the complete tumor mass with a high confidence scaling exponent $\alpha = 0.78$ then the inadequate metabolic supply causes an extension of the nectrotic tissue inside advanced tumors [40].

2. Method

The general model for ontogenic growth described tumor-cell growth needs to calculate the cell-production considering also the vanished cells in the energy balance [40]. We learned, however, how vital programmed cell-death (apoptosis) is in the development of the fetus of mammals [41], and we considered it as a basic biological phenomenon [42]. The concept of cell-death is crucial in cancer development, considering one of the hallmarks of the malignancy is its escape from apoptosis [43], and is instead more susceptible to a more drastic kind of death: necrosis [44]. Following the line and extensive discussion of numerous other authors [28] [30] [32] [33] [34], who adapted the death-free energy balance from the original [45] publication, we extended this view with the changes caused by the perished cells. This approach became even more relevant with the study of malignancies, where a large mass of the tumor could well involve non-living necrotic tissue, so the ontogenic calculations [37] [40] need modification based on their energy-balance.

The number of cancerous cells (N_c) is the difference between the newly produced cells (P), and the perished (due to apoptosis or necrosis) drop off cells (D) at the unit time, basically follow the method of [40]:

$$\frac{\mathrm{d}N_c}{\mathrm{d}t} = P - D \tag{2}$$

The value of the changing cells is zero, while production just equal to the perished cells ($P = D$). It is a realistic assumption that the perished cells are pro-

portional to the complete cell number in unit time:

$$D = \lambda N_c \tag{3}$$

where λ is the cell death-rate in a tumor. Note, at the beginning of the tumor-growth the P is also proportional with N_c, ($P = \xi N_c$) and in this case, the tumor growth exponentially: $N_{c(0)}(t) = \exp(\xi - \lambda)t$. When P is constant during the development, the balance of the cell number by the time:

$$\frac{\mathrm{d}N_c}{\mathrm{d}t} = P - \lambda N_c \tag{4}$$

The $P = const$ deviates from the assumption of [40]. Our consideration concentrates on the fact that the cellular production after the initial period of growth became constant due to the stabilized balance of the resources and the autonomic growth of cells in a supporting healthy host environment by resources. The situation in this phase is well similar to the *in-vitro* experiments of the monoculture system when the allometric exponent is zero [31]. The energy balance is determined by the transported energy-flux delivered by the bloodstream. The energy-transport current intensity, the metabolic rate (B), is divided into two parts: one produces new cells, while the other keeps the living set alive. Hence:

$$\begin{aligned} B &= N_c B_c + E_c P = N_c B_c + E_c \left(\frac{\mathrm{d}N_c}{\mathrm{d}t} + \lambda N_c \right) \\ &= N_c B_c + E_c \left(\frac{\mathrm{d}N_c}{\mathrm{d}t} + \frac{N_c}{T_c} \right) \end{aligned} \tag{5}$$

where B_c is the metabolic rate of a cell, and E_c is the necessary metabolic energy to create a new cell and $\lambda^{-1} = T_c$ is the average lifespan of a cell in the tumor. Consequently:

$$E_c \frac{\mathrm{d}N_c}{\mathrm{d}t} = B - N_c (B_c + \lambda E_c) \tag{6}$$

Metabolic energy can be scaled by exponent a,

$$B = B_0 N_c^{\alpha} \tag{7}$$

where B_0 is a normalizing factor that shows the metabolic rate in the unity of N_c. Therefore, we obtain:

$$E_c \frac{\mathrm{d}N_c}{\mathrm{d}t} = B_0 N_c^{\alpha} - N_c (B_c + \lambda E_c) \tag{8}$$

Hence:

$$\begin{aligned} &\frac{\mathrm{d}N_c}{\mathrm{d}t} = a_c N_c^{\alpha} - b_c N_c \\ &a_c = \frac{B_0}{E_c};\ b_c = \frac{B_c}{E_c} + \lambda \end{aligned} \tag{9}$$

By multiplying N_c by the average mass of a single cell (m_c) we now obtain the energy-balance for the full tumor-mass (m):

$$\frac{\mathrm{d}m}{\mathrm{d}t} = am^{\alpha} - bm \tag{10}$$

where:

$$a = \frac{B_0 m_c^{1-\alpha}}{E_c} \quad \text{and} \quad b = \frac{B_c}{E_c} + \lambda = \frac{B_c}{E_c} + \frac{1}{T_c} \tag{11}$$

This balance was previously similarly formulated [46]. The mass has a maximum limit M, asymptotic value, a saturation when no more real changes of the mass can be observed, so:

$$0 = \frac{\mathrm{d}M}{\mathrm{d}t} = aM^{\alpha} - bM \tag{12}$$

Consequently:

$$M = \left(\frac{a}{b}\right)^{\frac{1}{1-\alpha}} = \left(\frac{B_0 m_c^{1-\alpha}}{B_c + \lambda E_c}\right)^{\frac{1}{1-\alpha}} \tag{13}$$

3. Results

A death parameter of the single-cell characteristically appears in the energy-balance of the ontogenic growth of the tumor. The nutrients supply profoundly determines the death of cancer-cells. At least at larger tumor sizes, the cell growth never happens with optimal nutrition supply; the cells intensively compete for the available energy sources.

The exponent α is located in the interval $2/3 \le \alpha \le 1$, and it is $\alpha = 3/4$ at ideal basal conditions [15] [45]. The ideal nutrition supply supports ontogenic growth. The "ideal" asymptotic mass (M_{id}) from (13) is: $M_{id} = \left(\frac{a}{b}\right)^4$, hence the BMR^* in non-ideal conditions:

$$M = \left(\frac{a}{b}\right)^{\frac{1}{1-\alpha}} = \left(M_{id}\right)^{\frac{1}{4(1-\alpha)}} \Rightarrow BMR^* = M^{\alpha} = \left(M_{id}\right)^{\frac{\alpha}{4(1-\alpha)}} \tag{14}$$

Substituting (14) into (10):

$$\frac{\mathrm{d}m}{\mathrm{d}t} = am^{\alpha}\left(1 - \left(\frac{m}{M}\right)^{1-\alpha}\right) \tag{15}$$

So:

$$\frac{\mathrm{d}\left(\frac{m}{M}\right)^{1-\alpha}}{\mathrm{d}t} = \frac{a(1-\alpha)}{M^{1-\alpha}}\left(1 - \left(\frac{m}{M}\right)^{1-\alpha}\right) \tag{16}$$

which has a sigmoidal solution:

$$\begin{aligned} \left(\frac{m}{M}\right)^{1-\alpha} &= 1 - \left(1 - \left(\frac{m_0}{M}\right)^{1-\alpha}\right)\mathrm{e}^{-\frac{a(1-\alpha)t}{M^{1-\alpha}}} \\ &= 1 - \exp\left(-\frac{at(1-\alpha)}{M^{1-\alpha}} + \ln\left(1 - \left(\frac{m_0}{M}\right)^{1-\alpha}\right)\right) \\ &= 1 - \mathrm{e}^{-\tau} \end{aligned} \tag{17}$$

where

$$\tau = \frac{at(1-\alpha)}{M^{1-\alpha}} - \ln\left(1-\left(\frac{m_0}{M}\right)^{1-\alpha}\right) \tag{18}$$

and m_0 is the mass at the start of a tumor (probably a few times m_c), the initial (just born) mass. The ratio (r) of the energy spent on keeping cells alive ($\lambda = 0$) from (13) is:

$$r(\tau) = \frac{N_c B_c}{B} = \frac{B_c m}{m_c B_0 m^{\alpha}} = \frac{b}{a} m^{1-\alpha} = \left(\frac{m}{M}\right)^{1-\alpha} = 1 - \mathrm{e}^{-\tau} \tag{19}$$

Using $\alpha = 3/4$ for the ideal four-dimensional case, the solution is:

$$\left(\frac{m}{M}\right)^{1/4} = 1 - \mathrm{e}^{-\tau}, \quad \tau = \frac{at}{4M^{1/4}} - \ln\left(1-\left(\frac{m_0}{M}\right)^{1/4}\right) \tag{20}$$

This is formally the universal growth law [45], but has a difference in the values of b (see (11)) and M (see (13)), including the average life-time of the malignant cells (death rate λ) in ontology description. The M value became smaller by shortening the average life-time of the cells and elongating τ time approaching the saturatin of the mass.

4. Discussion

The four-dimensionality and the allometry with evolutional optimization require different approaches: as the evolutionary conditions have a higher than a four-dimensional allometric scaling. The tumor mass is a somewhat indefinite parameter because the whole environment of the tumor suffers from sub-optimal alimentation. Consequently, the mass does not describe the allometry well. A more fundamental parameter of the networking conditions is requested.

From the original "four-dimensional life" fractal concept, we get scaling of the characteristic volume (v) with a characteristic length (l) [15] [45]:

$$v = kl^4 \tag{21}$$

where k is a constant.

When the mass density of the tumor is relatively homogeneous, we assume proportional relation between the mass and volume:

$$m \propto v \tag{22}$$

When l_0 is the average asymptotic length of the circulatory network of the organ, and M is the asymptotic mass, from (21) and (22) with other K constant:

$$M = Kl_0^4 \tag{23}$$

Consequently, from (23) and (21), we obtain:

$$r = \left(\frac{m}{M}\right)^{1/4} = \left(\frac{Kl^4}{Kl_0^4}\right)^{1/4} = \frac{l}{l_0} \tag{24}$$

The fourths-root of the relative mass growth to the asymptotic value (the relative basal metabolic rate) corresponds to the relative ratio of the length of the circulatory network. The geometrical parameter of the vascularity offers a more

evident intrinsic factor than the mass. The length looks essential in the allometric relations.

From (20) and (24) the geometric growth rate is obtained, where a universal law can describe the average relative length of the circulatory network:

$$r(\tau)=1-\mathrm{e}^{-\tau},\ \ \tau=\frac{at}{4M^{1/4}}-\ln(1-r_0) \tag{25}$$

where $r_0=\left(\frac{m_0}{M}\right)^{1/4}$. The ratio of the energy maintaining new cells is $R(\tau)=(1-r(\tau))=\mathrm{e}^{\tau}$. Assuming the average density of the cancerous cell colony in the experiments of Bru *et al.* [47], the scaling law could be determined by the characteristic lengths, which are (at $\alpha=3/4$ [45]), $m\propto L^4$ in ideal cases, consequently:

$$r(\tau)=\left(\frac{m}{M}\right)^{1-\alpha}=\left(\frac{L^4}{L_0^4}\right)^{1/4}=\frac{L}{L_0}=1-\mathrm{e}^{-\tau} \tag{26}$$

where L_0 is the asymptotic size of the cancer-cell cluster. It is naturally assumed that $L_0\gg L$, then from equation (17) the Taylor expansion of τ could be truncated at its second term, so (26) will be the linear dependence as measured:

$$L(t)\cong\frac{a}{4K}t-L_0\ln\left(1-\frac{L(\tau=0)}{L_0}\right) \tag{27}$$

However, if the energy supply is not ideal (which is the case in almost all the developed tumors *in-vivo*), the results do not support the ideal scaling by $\alpha=3/4$ [38]. It is shown in a generalized model that the fractal surface and the covered volume are scaled rigorously [48].

In cases of sub-optimal alimentation (there is an energy-deficiency for optimal growth), the scaling-exponent changes, and it depends on the fractal dimension of the vascular network (D_v) [48]. The shortage of energy for adequate alimentation is a usual condition for the rapidly proliferating structures. Two strategies can be followed to distribute the available (sub-optimal) energy resources: maximizing the metabolism on the surface of the cells. The elongation of the vascular network (angiogenesis) is the optimal strategy in this growing phase of the tumor ($\alpha_1=\frac{3}{3+D_{v1}}$) [49]. The optimizing strategy could change in the advanced stages when the blood volume is limited despite the elongated vascular possibilities. In the advanced cases, the energy-distribution request a $\alpha_2=\frac{4-D_{v2}}{4}$ exponent ($\alpha_2<\alpha_1, D_v>1$) [49]. The growth of the mass would be in these cases (as described by (16)):

$$\frac{\mathrm{d}m_{\max}^{(1)}}{\mathrm{d}t}=\frac{aD_{v1}}{(3+D_{v1})M^{\frac{D_{v1}}{3+D_{v1}}}}\left(1-\left(\frac{m}{M}\right)^{\frac{D_{v1}}{3+D_{v1}}}\right) \tag{28}$$

and

$$\frac{\mathrm{d}m_{\max}^{(2)}}{\mathrm{d}t} = \frac{aD_{v2}}{4M^{\frac{4-D_{v2}}{4}}}\left(1-\left(\frac{m}{M}\right)^{\frac{4-D_{v2}}{4}}\right) \tag{29}$$

The generalized form of relation (25) could be used in $\alpha_2 < \alpha_1$, ($D_{v1}, D_{v2} > 1$) exponents, when the allometry exponent is α. The phase 1 and phase 2 stages of tumors had been studied by various publications [49] [50] [51]. We choose two characteristic values to demonstrate the differences, $D_{v1} = 1.28$ and $D_{v2} = 1.52$.

The time development well shows the different saturation time of the processes with various exponents (**Figure 1**).

The mass and the characteristic length are strictly connected:

$$m_{\max}^{(1)} = Kl^{\frac{3+D_v}{D_v}} \quad \text{and} \quad m_{\max}^{(2)} = Kl^{\frac{4-D_v}{4}} \tag{30}$$

In general:

$$M = Kl_0^{\frac{1}{1-\alpha}} \tag{31}$$

and therefore:

$$r = \left(\frac{m_{\max}}{M}\right)^{1-\alpha} = \frac{l}{l_0} \tag{32}$$

For optimal distribution, we get the exact same result:

$$r = \left(\frac{m_{opt}}{M}\right)^{1-\alpha} = \frac{l}{l_0} \tag{33}$$

The limited nutrition, the energetic control of the tumor could be considered as a part of the controlled therapy [52]. If the cell culture were to be placed on the tumour region, and the cell culture had the same or higher demands as the

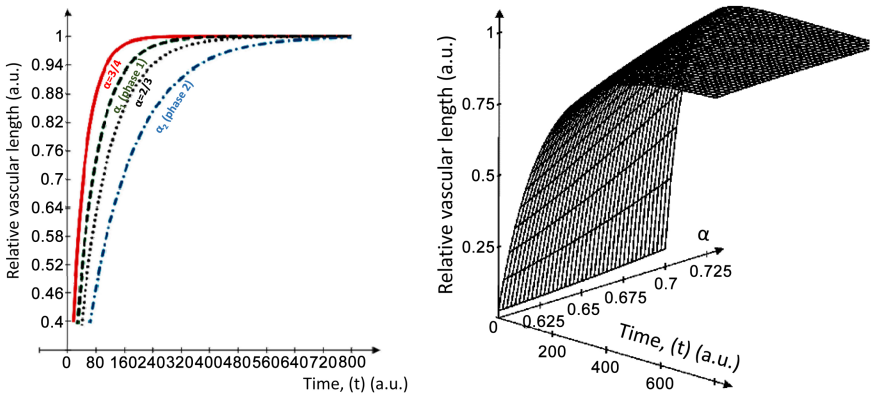

Figure 1. Development of the relative length in time of vascular structure in a tumor at various allometric exponents: the normal, tumor-free tissue $\alpha = 3/4$ (solid line) and in the Euclidean geometrical construction $\alpha = 2/3$ (dotted line). The saturation time to reach the final length increases by the decreasing of the vascular fractal-dimension, ($\alpha_1 = 0.701$, dashed line; and $\alpha_2 = 0.62$, dash-dotted line). The chosen sample parameters: $m_0 = 1$ a.u. and $M = 1000$ a.u. .

tumour tissue, then it could successfully compete against the cancer cells supplied from the same sources of energy. These in-silico results have not yet been verified experimentally, they are expected in the future.

5. Conclusions

The mass change to the more fundamental length of the vascular network in allometric scaling is generally proven in optimal metabolic conditions. We had shown the application in two basic kinds of non-optimal alimentation processes, too.

We proved that allometric scaling could eliminate the mass and an entirely intrinsic parameter, the average relative length of the circulatory network. The allometric model by the length directly connects the metabolic energy intake of the tumor with the length of the vascular system, as a supplier of energy. The derivation of the equations is rather general because the obtained fractal dimensions are model-independent. We regard the vascular length as more fundamental than the mass because the tumor volume is usually indefinitely smeared out, having a gradient formed by the mix of the precancerous and host cells. Hence, the fractal determination of the vascular network gives a more precise solution for allometric relations.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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