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The Intrinsic Self-Time of Biosystems

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Abstract

In biological systems, self-time differs from the physical time scale. Biological self-time is the characteristic of individual biosystems and invariantly describes the various dynamic processes in organisms. This biological invariance is introduced by using 2 basic theorems: Allometric scaling and the Weibull psychometric function. Our objective was to precisely describe the timing phenomenon in biosystems and provide a framework to further develop this analogy for other fields.

Keywords

Psychometric Function, Allometry, Scaling, Bio-Invariance, Survival

1. Introduction

The lifetime of biological objects is measured by their dynamical development. Studies have a surprising universality by the self-organizing [1] [2] and consequently, self-similarity. A further consequence of this self-managed process is the spatiotemporal fractal structure [3] [4], and the bioscaling behavior, [5]. These ideas are forming the similarities of the species [6], which directly leads to an expected lifetime universality of well-selected cohorts. Heart rates are well scaled by the $\alpha = 1/4$ power-law by the body-mass in mammals [7] from the smallest to the largest. The allometry is generally applicable description from respiratory complexes, through the mitochondria, to the largest mass animals [8]. The heartbeat and the metabolic rate have the same mass-scaling dependence. The statistical value of the heart-beat in their lifetime does not change by the life-expectancy or by the mass of the organism and pretty stable for mammals around $n_{hb/lt} \approx (7.3 \pm 5.6) \times 10^8$ heartbeat/lifetime [9] which supports the unified delivery of the nutrition, but many other factors could modify this picture. Based on the universality, it is estimated, that all biological species have the

same basal oxygen consumption, $\approx 10^{-8}$ oxygen molecules per heartbeat [10]; this measurement defines the actual self-time. In consequence, the full lifetime (T_{lt}) is also scaled by the $\alpha = 1/4$ power-law, using the heartbeat (f_h) [9]:

$$T_{lt} = n_{hb/lt} / f_h \propto M^{1/4} \tag{1}$$

Self-time can be introduced on a thermodynamic optimizing basis when entropy production is constant over time [11]. Self-time is connected to allometry [12], and it scales with the allometric factor *a*. This power rule is strongly supported by various physiological times [13]. In a broader context, the intrinsic time could be explained similarly to the special relativity; time is not independent of space (only the space-time is invariant), and in biosystems, time is an integrative parameter of complex conditions [14].

Our objective is to study the self-time of biological objects in comparison to the coordinate time (clock time) measured by the observervations outside the studied bio-system, to develop an analogy for brittle materials by introducing the Weibull function (cumulative form of two-parametric Weibull distribution) for survival times. We transform time-scales and show the accuracy of the fit of Weibull based calculation to standard allometric scaling.

2. Weibull Statistics of Brittle Materials

The generalized cumulative Weibull distribution [15] is:

$$W(x) = \exp\left(-\left(\frac{x}{x_0}\right)^n\right), \tag{2}$$

where *n* is the shape factor, or form parameter, and x_0 is the scale parameter. This function is widely used in physiology and psychometry [16].

Weibull's statistics was originally developed to describe the fracture of brittle materials [15], and it provides the probability of a damage-free survival of a given material. The Weibull investigated brittle materials, such as ceramics, to describe the probability of breaks due to mechanical stress [15] [17]. Using the notation from [18], the "survival" of the material's integrity (P_S) and the survival rate probability define the percentage of sample breaks when multiple probes are tested. When processing the statistical data, the cumulative probability of survival at a homogeneous σ stress on a sample with *V* volume is:

$$P_S(\sigma, V) = \exp\left(-\frac{V}{V_0}\left(\frac{\sigma}{\sigma_0}\right)^n\right), \tag{3}$$

where V_0 is the reference volume, σ_0 is the reference stress, and *n* is the Weibull's form factor of the function. When experimenting with *N* samples, NP_S pieces of this count will not fail even under the maximum stress of *σ*. The reference stress and volume should be introduced into the exponent for dimensional reasons. When we have a sample where $V = V_0$ and $\sigma = \sigma_0$, and these are both independent from the form factor *n*, by solving the Equation (3) we obtain:

$$P_{S0} = \exp\left(-\frac{V_0}{V_0}\left(\frac{\sigma_0}{\sigma_0}\right)^n\right) \cong 0.3678. \tag{4}$$

Therefore, the survival probability of such a sample is 36.78%.

The above Weibull function (3) can be rewritten by using the familiar 2-parametric shape:

$$P_S(\sigma, V) = \exp\left(-V^{1/n}\left(\frac{V_0^{1/n}}{\sigma_0}\right)\left(\frac{\sigma}{x_0}\right)^n\right). \tag{5}$$

The relationship between the individual scale parameter characteristics can be readily associated with the Weibull statistics (2) used in the strength theory:

$$x = \sigma V^{1/n} \quad \text{and} \quad x_0 = \sigma_0 V_0^{1/n}. \tag{6}$$

It is possible to determine the survival probability of the same stress and volume relationship, *i.e.*, the scaling law from the Weibull distribution in (3), when we have the same survival probability:

$$\sigma = \frac{const}{V^{1/n}}, \tag{7}$$

which means a smaller sample is stronger and stabler than a larger one.

The Weibull function is based on 2 primary properties: volume dependence and self-similarity. To formulate the above equations in another way, imagine, that a sample is composed of 2 parts (**Figure 1**), and we want to express the likelihood of failure of the complete, complex system using the failure probability for each individual part.

By applying the Weibull Function (3) to the scenario shown in **Figure 1**, the likelihood of σ stress failure of the $V_1 + V_2$ sample volume is:

$$P_S(\sigma, V) = \exp\left(-\frac{V_1+V_2}{V_0}\left(\frac{\sigma}{\sigma_0}\right)^n\right) = P_S(\sigma, V_1)P_S(\sigma, V_2). \tag{8}$$

From (7), sample failure occurs at the weakest location (the structural fault location). In the Weibull theory, the structural failure probability is proportional to the sample volume. The effect of the form factor is shown in **Figure 2**.

Step-function occurs at large form factors. In other words, if $\sigma \leq \sigma_0$, each sample component survives, however, when $\sigma > \sigma_0$, the entire sample fails. Materials composed of links with equal strength, that is, homogeneous chains like metals, show such behavior.

3. Links to Survival Characteristics of Patients

A recent study attempted to describe the connection between fractal geometry and the circulatory system with Weibull's survival function by using the age of the patient and body weight as its parameters [18]. Specifically, this study examined the link between brittle material fracture survival and cancer patient survival [18]. This allometric approach links geometric and life parameters
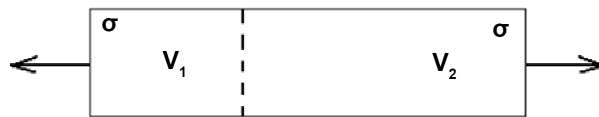
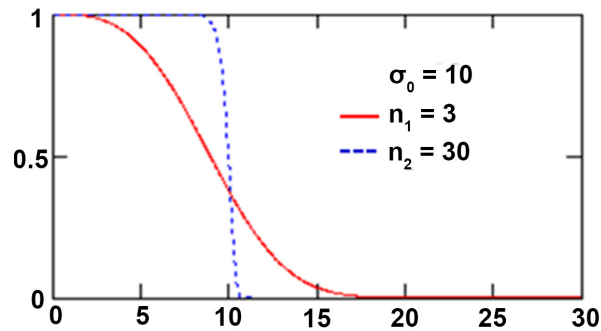**Figure 1.** Two-part system for Weibull analysis.

Figure 2. Form factor impact on the probability of survival.

(ontogenetic growth [19]), to survival probability described by the cumulative Weibull parametric distribution function [15]. The resulting function was used to assess the cancer patients' survival statistics. Since this approach utilized body mass, it did not examine the links between other patient details, including cancer type, vascularization or tumor size, on fractal geometry and actual survival statistics. Individuals are exposed to a variety of complex stresses—environmental, nutritional, physical, lifestyle-related and spiritual—that are not equivalent to the mechanical strength of inanimate material. There is no doubt, however, that in a cohort of healthy individuals with similar life stresses, the best single parameter may be their collected experiences.

The above assumption is not far from strength theory, where repetitive stress would likely be the best parameter to statistically investigate and characterize failure. This characterization is called the fatigue test. When each stress cycle takes a nearly identical course, the measurement can be reduced to a single parameter, and the load is characterized by the spending time. Statistical functions can describe both inanimate objects and organisms; although living organisms are far more complex than objects described with mechanical rheology. Indeed, we found many similarities between machine parts and the organs of a living body by using lifespan approximations with the Weibull function [15]. For example, one can compare machine part wear with the wear that results from mechanical friction and stress at joints. Both processes cause damage to the materials and influence lifespan. Additionally, heart diseases may be caused by increased electrical conductivity in specific heart regions that alters the initial sinus node electrical signal propagation and thus modifies heart function. Similarly, parts of a printed circuit board unit located in a wet and/or dusty environment would likely stop functioning appropriately. The actual size of the malfunctioning areas does not matter (as long as they are small), but over time the collective malfunctioning could cause failure, or disease in a biological system.

Malignant tumors are the result of altered biological activity in an organ. Tumor dynamism overloads normal systemic functions by their aggressive demands for nutrients and thus alters organ function. Hence, in addition to the tumor's metastasis, there are 3 direct reasons why organ failure may occur due to this malignant process:

- the cancerous metabolism overwhelms normal physiological consumption;
- tumor metabolism becomes comparable to the host organ metabolism;
- the geometric scale of the tumor makes normal organ function impossible.

Consequently, tumor size influences the individual's lifespan. Tumor volume is related to the structural failure probability. This parameter is constant over time for healthy individuals; however, the tumor size is time dependent. Therefore, there is a qualitative difference between the volumetric parameters of the Weibull law and the so-called "faulty volume" of the disease. Naturally, the growing cancerous tumor reduces survival probability. The increased, faulty tissue volume increases the probability of structural incompatibility problems and stress caused by the growing tumor increases the probability of failure. Thus, the analogy between mechanical failure and survival is as follows:

- mechanical stress, σ, is analogous to survival time t (or observation time during treatment);
- the reference stress, σ_0, is analogous to the scale parameter t_0 (the reference time in the therapy, when the survival probability is 36.8%);
- the volume, V, is analogous to the actual size (volume) or the actual metabolic activity (energy consumption rate) of the tumor, G(t). This function is additive and could be the volume or the metabolic rate. Both parameters are additive in the destructive process;
- the reference volume, V_0, is analogous with the reference size (volume) or the reference metabolic activity (energy consumption rate) of the tumor (G_0).

Hence, the Weibull law (as in (3) and (2)), which corresponds to survival by time (t) distribution is:

$$W(t) = \exp\left(-\left(\frac{t}{t_0}\right)^n\right);$$ (9)

alternatively, when considered in the context of an administered therapy, it is analogous with (3):

$$P_S(t) = \exp\left(-\frac{G(t)}{G_0}\left(\frac{t}{t_0}\right)^n\right).$$ (10)

4. Metabolic Considerations

As discussed above, tumor size could be geometric (volume) or metabolic (energy consumption). Extra energy demands are due to the high proliferative and metabolic processes of cancer cells. Indeed, tumor energy consumption may be several times higher than the metabolism of healthy cells, and energy is supplied by intensive glucose production from non-oxidative glycolysis [20].

The size of the host organism and its net metabolic rate (basal metabolic rate, R_0) can be expressed by the actual body mass (m) of the healthy adult individual, as introduced by the allometric considerations (allometric law [21]):

$$R_0 \propto m^\alpha. \tag{11}$$

In case of satisfactory nourishment, $\alpha = \alpha_0 = 3/4$ [22]. If one considers adult individuals, who would exhibit a stable mass (M), the mass-specific basal metabolic rate function would be:

$$\frac{R_0}{M} \propto M^{\alpha-1}. \tag{12}$$

These allometric considerations could be applied for organs, where M is the final, stable organ mass, and R_0 is the organ's basal metabolic rate.

Tumor growth satisfies the allometric metabolic rule; that exhibits universal growth dynamics [23] [24]. The approximate change in the number of tumor cells (n_c) depends on production (proliferation, P) and cell death (annihilation, A); A is proportional to n_c as shown below:

$$\frac{dn_c}{dt} = P - A \quad \text{and} \quad A = \lambda n_c, \tag{13}$$

where $\lambda^{-1} = T$ is the average life of the cell.

Energy balance has 3 components: energy to support current cells (the metabolic rate of a single cell, R_c), energy to produce new cells (E_c) and external work (W_e) on the system. All of these factors originate from the energy flux of blood flow (I) through capillary terminals:

$$I = R_c n_c + PE_c + W_e = R_c n_c + \left(\frac{dn_c}{dt} + \lambda n_c\right)E_c + W_e. \tag{14}$$

Due to allometric considerations [8] [19]:

$$I = R_0 n_c^\alpha \quad \text{and} \quad W_e = C_0 n_c^\alpha, \tag{15}$$

where $\alpha \leq 1$ [25] [26]. Substitute these terms into (14):

$$E_c \frac{dn_c}{dt} = (R_0 - C_0) n_c^\alpha - n_c (R_c + \lambda E_c). \tag{16}$$

Multiply by the mass of an individual cell (m_c):

$$\frac{dm}{dt} = am^\alpha - bm \tag{17}$$

$$a = \frac{(R_0 - C_0) m_c^{(1-\alpha)}}{E_c}, \quad b = \frac{R_c}{E_c} + \lambda.$$

Due to energy flux changes by the α power of the mass during metabolism to maintain homeostasis, (dm/dt) is positive, and thus the maximum mass (M) is limited and can be expressed by the mass of a cell (m_c):

$$aM^\alpha - bM = 0 \rightarrow M = \left(\frac{a}{b}\right)^{\frac{1}{(1-\alpha)}} = \left(\frac{R_0 m_c^{(1-\alpha)}}{R_C + \lambda E_C}\right)^{\frac{1}{(1-\alpha)}} \tag{18}$$

When substituting b from (18) into (17), we get the Verhulst-Pearl differential equation [27], similar to the results of [18]:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = am^{\alpha}\left(1 - \left(\frac{m}{M}\right)^{(1-\alpha)}\right). \tag{19}$$

The solution of this differential equation describes a sigmoid curve:

$$\left(\frac{m}{M}\right)^{1-\alpha} = 1 - \mathrm{e}^{-\tau}, \tag{20}$$

where

$$\tau = \frac{a(1-\alpha)t}{M^{(1-\alpha)}} - \ln\left(1 - \left(\frac{m_0}{M}\right)^{(1-\alpha)}\right); \tag{21}$$

moreover, m_0 is the initial (birth) mass.

The ratio of energy flux for stationery stabilization and metabolism is:

$$r(t) = \frac{n_c R_c}{I} = \frac{m R_c}{m_c R_0 m^{\alpha}} = \frac{b}{a}m^{1-\alpha}. \tag{22}$$

Using (18) and (20), the relative metabolic rate for maintaining stationary equilibrium is:

$$r_m(t) = \left(\frac{m}{M}\right)^{1-\alpha} = 1 - \mathrm{e}^{-\tau}; \tag{23}$$

moreover, the universal energy-function used for growth is:

$$R_m(t) = 1 - r(t) = \mathrm{e}^{-\tau}. \tag{24}$$

$r(t)$ and $R(t)$ are the same functions of τ for all organs with m mass; the time-scale τ may be regarded as a biological self-time. τ is invariant for the organ or organism; it is a time scale that is determined wholly by the biological system and not by any outside processes. The existence of physiologic time, which is different from clock time, was previously hypothesized [28].

Equation (20) is a universal function, and so the above considerations are well suited to living organisms [8] [19] and tumor growth [23] [24], when self-time is defined as above. Maximum mass growth occurs at the inflection point, where:

$$\frac{\mathrm{d}^2 m}{\mathrm{d}t^2} = 0. \tag{25}$$

Here, mass and growth rate are:

$$m = \left(\frac{3}{4}\right)^4 M \cong \frac{M}{3}; \tag{26}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{27a}{256}M^{2/3} \cong 0.1aM^{2/3},$$

when $\alpha = \alpha_0 = 3/4$. Thus, relative metabolic rate (r_m) and the part of metabolism related to growth ($R_m = 1 - r_m$) are:

$$r_m = \frac{3}{4} \quad \text{and} \quad R_m = \frac{1}{4}. \tag{27}$$

Several investigations have estimated that $2/3 \leq \alpha \leq 1$ depends on the fractal geometry of the nutrient supply of the tumor [25]. In the case of volumetric supply, $\alpha \approx 1$, while for surface supply, $\alpha \approx 2/3$ [29]. Consequently, it is necessary to examine the possibility of the above analogies with strength theory in the self-time (biological time) scale, τ (observation of biological self-time during therapy).

5. The Relationship between the Variants of Time Scales

Identical tumor size ($G(\tau) = G_0$) and biological self-time ($\tau = \tau_0$) could differ from the physical time (t) periods, and the survival probability (P_s) in this situation would be approximately 36.8%. However, the connection between the two-time scales, according to (20), is:

$$t = \frac{M^{(1-\alpha)}}{a(1-\alpha)}\left[\tau + \ln\left(1 - \left(\frac{m_0}{M}\right)^{(1-\alpha)}\right)\right]. \tag{28}$$

The difference depends on the metabolic rate per unit volume, the initial size of the tumor and actual vascularization. Generally, scaling biological self-time shows the same survival probability of lifespan from (10) to any actual probability:

$$\frac{G(\tau)}{G_0}\left(\frac{\tau}{\tau_0}\right)^n \cong const. \tag{29}$$

Hence,

$$\tau \cong const \frac{\tau_0}{\left(\frac{G(\tau)}{G_0}\right)^{\frac{1}{n}}}. \tag{30}$$

Thus, survival time decreases as tumor size increases. The higher the value of m, the more it reduces the dependency rate. The physical timescale using (30) is:

$$t \cong const \frac{M^{(1-\alpha)}}{a(1-\alpha)}\left[\frac{\tau_0}{\left(\frac{G(\tau)}{G_0}\right)^{\frac{1}{n}}} + \ln\left(1 - \left(\frac{m_0}{M}\right)^{(1-\alpha)}\right)\right]. \tag{31}$$

If we substitute (18) into (31) we get:

$$t \cong const \frac{1}{b(1-\alpha)}\left[\frac{\tau_0}{\left(\frac{G(\tau)}{G_0}\right)^{\frac{1}{n}}} + \ln\left(1 - \left(\frac{m_0}{M}\right)^{(1-\alpha)}\right)\right]. \tag{32}$$

Consequently, if the enlarged initial mass decreases, the surface supply increases the physical lifetime. It is also clear from (32) that individuals with high-

er $G(\tau)$ would exhibit a reduced survival, especially when n is relatively small.

6. The Scaling Law and the Physical Timescale

From above, the Weibull law is applicable to biological self-time and also correlates with physical time. Lifespans connected to the same survival probability have a dependence as shown in (10) and similarly to (29):

$$\frac{G(\tau)}{G_0}\left(\frac{t}{t_0}\right)^n \cong const,$$ (33)

from which we conclude, that survival time decreases as tumor size increases:

$$t \cong const \frac{t_0}{\left(\dfrac{G(t)}{G_0}\right)^{\frac{1}{n}}}.$$ (34)

The greater the value of n, the more independent t is of G.

We know from [19] that the metabolic flux is:

$$\Phi = cm^\alpha,$$ (35)

where c is a constant with a peculiar dimension, that is, the nutrient flux per unit weight of the system. This is not a good measure since it is not additive. The additive rate is:

$$G(t) := \Phi^{\frac{1}{\alpha}} = c^{\frac{1}{\alpha}} m(t) \text{ and } G(\tau) := \Phi^{\frac{1}{\alpha}} = c^{\frac{1}{\alpha}} m(\tau);$$ (36)

alternatively, any of its homogeneous linear function.

From a mathematical point of view, 2 cases will produce a biparametric Weibull function:

$$G(\tau) \cong const = K \text{ or } G(\tau) \cong \tau^\delta .?$$ (37)

The $G(\tau) \approx$ const case occurs when the tumor has almost reached its final size. This scenario may occur if tumor vascularization cannot sufficiently supply the required nutritional demand and/or due to interventional therapy. However, here $\alpha \approx 1$, denoting conformity with surrounding surface supply. This case is termed as a stagnant cancer. The second case is equivalent to the long physical time related to short biological time. This phenomenon could occur with a large M (matured tumor mass) or when the tumor supply is volumetric. τ could be $m_0 \approx 1$ and $\alpha \approx 1$; hence, the observed real-time survival would be accompanied with a very short biological self-time. This case represents a rapidly growing tumor.

When τ is small, the Equation (20) is well approximated by the linear function $1 - e^{-\tau} \cong \tau$. Comparing this biological self-time scale set to the allometric law, the rate of weight is:

$$G(\tau) = m(\tau) = M\left(\left(\frac{m}{M}\right)^{1-\alpha}\right)^{\frac{1}{1-\alpha}} \cong M\tau^{\frac{1}{1-\alpha}}.$$ (38)

Substituting (37) for the Weibull function using the analogy of biological self-time, we get:

$$P_S = \exp\left(-\frac{M}{M_0}\left(\frac{\tau}{\tau_0^{n/q}}\right)^q\right) = \exp\left(-\left(\frac{\tau}{\tau_0^{n/q}\left(\frac{M}{M_0}\right)^{1/q}}\right)^q\right) \tag{39}$$

$$q = n + \frac{1}{1-\alpha},$$

where the selected reference is the metabolic flux of the tumor with the power α, and M_0 corresponds to the healthy reference G_0. If the tumor is near to the entirely surface-determined supply ($\alpha \approx 1$), the exponent will be large, the phenomenon will become digital (1 or 0, e.g., all or none) and the deviation of survival times will be low. The scaling law in this case would be:

$$\tau \cong const \cdot \tau_0^{1-\alpha}\left(\frac{M_0}{M}\right)^{\frac{1}{q}}. \tag{40}$$

This equation again shows that in the case of tumor surface feeding, survival time becomes independent of the parameters.

When the first condition of (37) is valid, then:

$$\tau \cong const \cdot \tau_0\left(\frac{M_0}{M}\right)^{\frac{1}{n}}. \tag{41}$$

When the second condition of (37) is valid (metabolic rate is high), then:

$$G(\tau) = a^{1/\alpha} m(\tau) = a^{1/\alpha} M\left(\left(\frac{m}{M}\right)^{1-\alpha}\right)^{\frac{1}{1-\alpha}} \cong a^{\frac{1}{\alpha}} M \tau^{\frac{1}{1-\alpha}}. \tag{42}$$

When we substitute (41) into the Weibull function obtained by using the biological self-time analogy, we get:

$$P_S = \exp\left(-\frac{a^{1/\alpha}M}{a_0^{4/3}M_0}\left(\frac{\tau}{\tau_0^{n/q}}\right)^q\right) = \exp\left(-\left(\frac{\tau}{\tau_0^{n/q}\left(\frac{a_0^{4/3}M_0}{a^{1/\alpha}M}\right)^{1/q}}\right)^q\right). \tag{43}$$

Concerning the metabolic flux of the reference tumor with allometric exponent α, we used $\alpha_0 = 3/4$ for the healthy (τ_0, reference) exponent.

It again appears that at a near surface supply condition, the exponent will be large and a digital behavior will occur. From this point of view, the scaling law is:

$$\tau \cong const \cdot \tau_0^{1-\alpha}\left(\frac{a_0^{\frac{4}{3}}M_0}{a^{\frac{1}{\alpha}}M}\right)^{\frac{1}{q}} \tag{44}$$

Again, the above equation describes universal behavior, namely, that survival time increasingly becomes independent in the case of surface supply. According to the second equation of (42), a simple deduction to the real physical time scale from the above equation to describe biological self-time leads to:

$$\tau \cong \frac{a(1-\alpha)t}{M^{1-\alpha}} = b(1-\alpha)t. \tag{45}$$

Substituting (44) into (43), we get the Weibull law associated with the physical time scale:

$$P_S = \exp\left(-\frac{a^{1/\alpha}M}{a_0^{4/3}M_0}\left(\frac{\tau}{\tau_0^{1-\alpha}}\right)^q\right) = \exp\left(-\left(\frac{t}{\frac{\tau_0^{1-\alpha}}{b(1-\alpha)}\left(\frac{a_0^{4/3}M_0}{a^{1/\alpha}M}\right)^{1/q}}\right)^q\right). \tag{46}$$

Consequently:

$$t \cong const \cdot \frac{\tau_0^{1-\alpha}}{b(1-\alpha)}\left(\frac{a_0^{\frac{4}{3}}M_0}{a^{\frac{1}{\alpha}}M}\right)^{\frac{1}{q}}. \tag{47}$$

We again see that the supply tends to become localized at the surface when $\alpha \to 1$, and so the growth of the tumor becomes independent of the survival parameters.

7. Allometry Scaling and Weibull Function

Several theories describe the growth of cell populations (including tumors). The time dependence of tumor size has several competing theories, but recently hyperbolic growth models have been proposed [30]. Weibull's law provides a simplified version of the general hyperbolic fit. The tumor size (e.g., the mass) satisfies the following equation in the hyperbolic model:

$$\frac{d\left(\frac{m}{M}\right)}{dt} = \left(1-\frac{m}{M}\right)\frac{\lambda}{\beta^\lambda}t^{\lambda-1}, \tag{48}$$

where M is the final tumor size. This equation is actually the Weibull equation. The solution is:

$$\frac{m}{M} = 1-\left(1-\frac{m}{M}\right)\exp\left(-\left(\frac{t}{\beta}\right)^\lambda\right); \tag{49}$$

or slightly modified:

$$\frac{m}{M} = 1-e^{-\tau}; \tag{50}$$

$$\tau := \left(\frac{t}{\beta}\right)^\lambda - \ln\left(1-\frac{m_0}{M}\right).$$

If $m_0 \ll M$, then:

$$\frac{m}{M} = 1 - e^{-\left(\frac{t}{\beta}\right)^{\lambda}}, \tag{51}$$

and the equation is returned to the well-known Weibull law. Considering (20), the allometric law could be formulated as:

$$\frac{m}{M} = \left(1 - e^{-\tau}\right)^{1/(1-\alpha)}. \tag{52}$$

A simple comparison shows the validity of the approximation of the allometric law using the Weibull's function (Figure 3).

The Shannon entropy of the Weibull functions for fits to $\alpha = \frac{2}{3}$ and $\alpha = \frac{3}{4}$ are $s_{2/3} \cong 1.403$, and $s_{2/3} \cong 1.452$; respectively. This $\cong 3.5\%$ difference shows a more certain death (less lifetime) in the $\alpha = \frac{2}{3}$ case than in $\alpha = \frac{3}{4}$, because the growing entropy shows a growing uncertainty.

This observation reveals a more profound relationship and can be proven by rigorous mathematical calculation. If α and β are large values in (50), then the following linear approximation is valid:

$$\frac{m}{M} \approx \left(\frac{t}{\beta}\right)^{\lambda}. \tag{53}$$

Thus, rapidly growing tumors could also be described by the Weibull evolutive equation. Note, that the probability of cumulative survival covariates with the normalized tumor size, *i.e.*:

$$\frac{m}{M} = 1 - e^{-\left(\frac{t}{\beta}\right)^{\lambda}} \cong F_S(t). \tag{54}$$
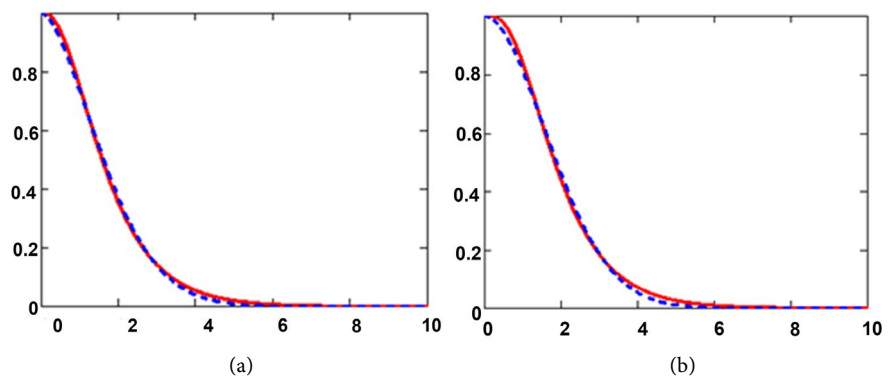

Figure 3. The allometric law (solid line) of survival could be well approximated by the Weibull function (dashed line). (a) $\alpha = \frac{2}{3}; n \cong 1.698, t_0 \cong 2.005; error < 2 \times 10^{-3}$ (b) $\alpha = \frac{3}{4}; n \cong 1.917, t_0 \cong 2.286; error < 2 \times 10^{-3}$. (The error is defined by the integral of the square of the differences of the functions in the [0, 10] interval.)

The same can also be formulated in a more approximate version. The cumulative survival probability is the self-similar function of $(1 - m/M)$. In other words, the slopes of Equations (55) and (56) are equal, and the straight lines are parallel.

$$\ln(t) \mapsto \ln\left(\ln\left(F_S(t)\right)\right); \tag{55}$$

$$\ln(t) \mapsto -\ln\left(\ln\left(1 - \frac{m}{M}\right)\right). \tag{56}$$

This formulation allows the fitting of the β scale parameter of survival to the final mass of the tumor (or to fit other tumor characteristics). In other words, $\ln\left(F_S(t)\right)$ is a self-similar function of $\ln(1 - m/M)$, so:

$$\ln\left(\ln\left(F_S(t)\right)\right) = K_1 \ln\left(K_2\right) \ln\left(1 - \frac{m}{M}\right), \tag{57}$$

where K_1 and K_2 are constants.

8. Conclusion

We proposed an intrinsic time model that differs from clock time. We analyzed the self-time for tumor growth and showed its scaling based on allometric scaling as well as compared it to the Weibull physiologic function. The allometric function could be well approached by the Weibull function which highlights the intrinsic values of both the bioscaling and the Weibull physiologic function for living objects.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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