Universal Relation for Life-span Energy Consumption in Living Organisms: Insights for the origin of ageing.

Andrés Escala

Departamento de Astronomía, Universidad de Chile, Casilla 36-D, Santiago, Chile.

aescala@das.uchile.cl

ABSTRACT

Metabolic energy consumption has long been thought to play a major role in the aging process (1). Across species, a gram of tissue on average expends about the same amount of energy during life-span (2). Energy restriction has also been shown that increases maximum life-span (3) and retards age-associated changes (4). However, there are significant exceptions to a universal energy consumption during life-span, mainly coming from the inter-class comparison (5, 6). Here we present a unique relation for life-span energy consumption, valid for ~300 species representing all classes of living organisms, from unicellular ones to the largest mammals. The relation has an average scatter of only 0.3 dex, with 95% (2 − σ) of the organisms having departures less than a factor of π from the relation, despite the ~20 orders of magnitude difference in body mass, reducing any possible inter-class variation in the relation to only a geometrical factor. This result can be interpreted as supporting evidence for the existence of an approximately constant total number $N_r \sim 10^8$ of respiration cycles per lifetime for all organisms, effectively predetermining the extension of life by the basic energetics of respiration, being an incentive for future studies that investigate the relation of such constant $N_r$ cycles per lifetime with the production rates of free radicals and oxidants, which may give definite constraints on the origin of ageing.

1. Introduction

Ageing seems to be an inherent characteristic of all living organisms, while some inert objects can easily subsist on Earth for many centuries, living systems have a much narrow
existence, typically limited to decades for large animals. Is then somewhat natural trying to associate the process of ageing to metabolism, since all living organisms get the required energy to stay alive from such process. Rubner in 1908 (7), compared energy metabolism and lifespans of five domestic animals (guinea pig, cat, dog, cow and horse) and man, finding that the life-span (total) energy expenditure per gram for the five species is approximately constant, suggesting the total metabolic energy consumption per lifespan is fixed, which later has become known as the ‘rate of living’ theory (1).

Decades later, a mechanism was found in which the idea behind a fixed energy consumption per lifespan might work in the ‘free-radical damage’ hypothesis of aging (8, 9), in which macromolecular components of the cell are under perpetual attack from toxic by-products of metabolism, such as free radicals and oxidants. In addition, energy restriction has been experimentally shown to increase maximum life-span and retard age-associated changes in animals, such as insects, rats, fish, spiders, water fleas and mice (3, 4).

Rubner’s relation was confirmed for around hundred mammals (10) and extended it to birds (11), ectotherms (12) and even unicellular organisms such as protozoa and bacteria (6), totaling almost three hundred different species in a range of 20 orders of magnitude in body mass. Although the total metabolic energy exhausted per lifespan per body mass of given organism appears to be relatively constant parameter, at about the same number determined by Rubner (7) of a million Joule per gram of body weight for mammals, variations over an order of magnitude are found among different animal classes, a result also found by other authors (i.e. 2) and considered the most persuasive evidence against the ‘rate of living’ theory (5).

The origin of such variations in the lifespan energy consumption might come from intrinsic variations in the quantities used to estimate it: lifespans and especially, the metabolic rate relation which universality is still debated (see 13 and references therein). Recently, the empirical metabolic rate relation was corrected in order to fulfill dimensional homogeneity (13), a minimal requirement of any meaningful law of nature (14), proposing a new metabolic rate (B) formula: $B = \epsilon(T) \eta_{O_2} f_H M$, where M is the body mass, $f_H$ is a characteristic (heart) frequency, $\eta_{O_2}$ is a specific O$_2$ absorption factor and $\epsilon(T) = \epsilon_0 e^{-E_a/kT}$ is a temperature correction inspired in the Arrhenius formula, in which $E_a$ is an activation energy and k is the Boltzmann universal constant. Compared to Kleiber’s original formulation (15), $B = B_0 (M/M_0)^{0.75}$, this new metabolic rate relation has the heart frequency $f_H$ as independent controlling variable (a marker of metabolic rate) and the advantage of being an unique metabolic rate equation for different classes of animals and different exercising conditions, valid for both basal and maximal metabolic rates, in agreement with empirical data in the literature (13).
In addition, this new metabolic rate relation can be directly linked to the total energy consumed in a lifespan (13), being a promising way to explain the origin of variations in Rubner’s relation and unify them into a single formulation. In this paper, we will explore the implications of this new metabolic relation for the total energy consumed in a lifespan and the ‘rate of living’ theory, being organized as follows. We start reviewing the results of the new metabolic rate relation found in (13), deriving its prediction for the total energy consumed in a lifespan in §2. Section 3 continues with testing the empirical support of the predicted relation for total energy consumed in a lifespan, with satisfactory results. Finally in §4, we discuss the results and implications of this work.

2. New Metabolic Rate Relation and its Prediction for ‘Rate of Living’ Theory

In the proper mathematical formulation of natural laws, a minimum requirement is to be expressed in a general form that remain true when the size of units is changed, simply because nature cannot fundamentally depend on a human construct such as the definition of units. In mathematical terms, this implies that meaningful laws of nature must be homogeneous equations in their various units of measurement (14). However, most relations in allometry do not satisfy this basic requirement, including Kleiber’s ‘3/4 Law’ (15), that relates the basal metabolic rate and body mass as $B = B_0 (M/M_0)^{3/4} = CM^{3/4}$, being this ‘3/4 Law’ a typical example (14) of a relation where the proportionality factor $C$ has a fractal dimensionality and its value depends on the units chosen for the variables $(B, M)$, therefore, do not fulfill the minimum requirement for being a natural law. Mathematically speaking, to qualify for being a natural law the metabolic rate relation must be first rewritten such the constants with dimensions are universal and restricted to a minimum number, which in no case could exceed the total number of fundamental units of the problem.

To solve this issue, (13) proposed a new unique homogeneous equation for the metabolic rates that includes the heart frequency $f_H$ as independent controlling variable, proposing a the metabolic rate $(B)$ formula: $B = \epsilon(T) \eta_{O_2} f_H M$, where $M$ is the body mass, $f_H$ is a characteristic (heart) frequency, $\eta_{O_2}$ is an specific $O_2$ absorption factor and $\epsilon(T)$ is a temperature-dependent normalization. The new metabolic rate relation is, in addition to be in agreement with the empirical data (13), valid for different classes of animals and for both resting and exercising conditions. Using this formula, it can be shown (13) that most of the differences found in the allometric exponents are due to compare incommensurable quantities, because the variations in the dependence of the metabolic rates on body mass are secondary, coming from variations in the allometric dependence of the heart frequencies $f_H$.
on the body mass \( M \). Therefore, \( f_H \) can be seen as a new independent physiological variable that controls metabolic rates, in addition to the body mass.

One of the advantages of having a metabolic rate relation with the heart frequency \( f_H \) as independent controlling variable, is that it can be straightforwardly linked (13) to the total energy consumed in a lifespan, by the relation of total number \( N_b \) of heartbeats in a lifetime, \( N_b = f_H t_{life} \), which is empirically determined to be constant for mammals and equals to \( 7.3 \times 10^8 \) heartbeats (16). Therefore, for a constant total number of heartbeats in a lifetime, \( t_{life} = N_b / f_H \), the metabolic rate relation (13) can be rewritten as \( B t_{life} = \epsilon(T) \eta_2 N_b M \), giving a straightforward prediction for life-span energy consumption and that can be seen as a test for the ‘rate of living’ theory (1).

However, since the total energy consumed in a lifespan relation is valid even in unicellular organisms without heart (6), in order to find an unique relation for all living organisms the concept of characteristic (heart) frequency must be first generalized. A natural candidate is the respiration frequency, \( f_{resp} \), since this frequency is observed in animals to be strictly proportional to the heart one, \( f_H = a f_{resp} \) (17), and is a still meaningful frequency for organisms without heart. Under this proportionally between frequencies, the empirical relation with lifetime can be rewritten to be also valid for a total number \( N_r \) (= \( N_b / a \)) of ‘respiration cycles’: \( t_{life} = N_b / f_H = N_b / a f_{resp} = N_r / f_{resp} \). This total number of ‘respiration cycles’, \( N_r = f_{resp} t_{life} \), will be assumed from now to be the same number for all living organisms and in §4, we will explore the implications of this conjecture for the origin of aging.

Under the condition of a constant total number \( N_r \) of respiration cycles in a lifetime \( t_{life} \), multiplying the new metabolic rate relation (13) by \( t_{life} / a = N_r / a f_{resp} = N_r / f_H \) is now equivalent to \( B t_{life} / a = \epsilon(T) \eta_2 N_r M \). The factor \( \epsilon(T) \eta_2 = \epsilon_0 \eta_2 e^{-E_a / kT} \) can be rewritten as \( E_{2019} e^{(\frac{1}{T_a} - \frac{1}{T}) E_a} \), where \( T_a \) in a normalizing ‘ambient’ temperature and \( E_{2019} = 10^{-4.313} \text{mlO}_2\text{g}^{-1} \approx 10^{-3} \text{Jg}^{-1} \) (converting 1 ltr \( \text{O}_2 = 20.1 \text{ kJ; } 17 \)) a constant that comes from the best fitted value for the corrected metabolic relation (13). Therefore, for the metabolic rate relation given in (13) and under the condition of fixed respiration cycles in a lifetime, the following relation is predicted to be valid:

\[
\exp\left(\frac{E_a}{kT}\right) \frac{B t_{life}}{a} = E_{2019} \exp\left(\frac{E_a}{kT_a}\right) N_r M. \tag{1}
\]

Eq. (1) is a prediction from the mathematically-corrected metabolic relation (13) under the assumption of constant \( N_r \) respiration cycles in a lifetime, \( t_{life} = N_r / f_{resp} \), which is in principle valid for all living organisms. It is important to emphasize that this relation for lifespan energy consumption is not assumed or hypothesized to be fixed like in the ‘rate of living’ theory; instead is derived directly from the metabolic relation under the conjectured
invariant \( N_r \). Compared to allometric relations, characterized mathematically for having as many dimensional constants \((B_0,M_0,\text{in Kleiber’s case})\) as there are variables \((B,M)\), the relation given by Eq. 1 has (in principle) 7 variables \((t_{\text{life}},B,a,M,E_a,T_a& T)\), one dimensionless number \((N_r)\) and only two constants with units: one universal one (Boltzmann constant \(k\)) and another one coming from best fitting the energetics of respiration \((E_{2019})\), which possible universality will be discussed in §4.

3. Empirical Support for the Corrected Relation of Total Energy Consumed in a Lifespan

In this section we test the validity and accuracy of the derived relation for total energy consumed in a lifespan (Eq. 1), predicted from the new formulation of the metabolic rate relation (13) and the conjectured constant total number \(N_r\) of respiration cycles per lifespan for all living organisms. For that purpose, we use data from 277 species of all classes of living organisms, from unicellular organisms and other ectotherms species, to mammals and birds, listed in Table 1 of (6) with their body mass \(M\), total metabolic energy per lifespan \(B_t_{\text{life}}\) and body temperature \(T\).

Fig 1 shows the relation predicted by Eq. 1 for the 277 living organisms listed in (6), where the activation energy \(E_a\) was chosen to the average value of 0.63 eV, independently determined to temperature-normalize the metabolic rates of unicells and poikilotherms to endotherms (18, 19). The parameter \(a\) was chosen to the empirically determined values of 4.5 for mammals and 9 for birds (17), estimated to be 3 for ectotherms with heart (from the relative size of their hearts; 17) and assumed unity for ectotherms without heart, such as unicellular organisms. The total number \(N_r = N_b/a = 1.62 \times 10^8\) of respiration cycles in a lifetime, was determined from the best fitted values for mammals: \(N_b = 7.3 \times 10^8\) heartbeats in a lifetime (16) and \(a=4.5\) (17).

The data displayed in Fig 1 strongly supports the unique relation predicted by Eq. 1 in a dynamical range of 20 orders of magnitude, for all classes of organisms from \textit{Bacteria} to \textit{Elephas Maximum}. The solid blue curve displays the best fitted value of slope 0.997 and normalization of 1.05, almost undistinguishable from the identity predicted by Eq 1(dashed red curve). The only free parameter (not predetermined by an independent measurement) in Eq 1 is the ‘ambient’ temperature \(T_a = 30^\circ\text{C}\), which was chosen only to match the normalization in the best fitted relation (solid blue) to the identity (dashed red), but is a natural choice for normalization, since ectotherms are typically around 20\(^\circ\text{C}\) and endotherms close to 40\(^\circ\text{C}\) in Table 1 of (6). Moreover, the slope close to unity (0.997) is independent of the \(T_a\) choice and for example, if we instead decide to preset \(T_a\) to the value of mammals
Fig. 1.— Figure shows the relation predicted by Eq. 1 for 277 living organisms, listed in (6). The dashed red curve displays the identity given by Eq 1. The solid blue curve displays the best fitted value of slope 0.997 and normalization of 1.05 for ambient temperature $T_a = 30^\circ C$. The two curves are almost undistinguishable in the dynamical range of 20 orders of magnitude.

(37$^\circ$C), it only changes the best fitted normalization value to 1.81. Therefore, the relation between 5 physiological variables ($t_{\text{life}}, B, a, M, T$) given by Eq 1 is confirmed without the choice of any free parameter.

Fig 2 shows the residuals from the relation predicted by Eq 1 as a function of the organism’s body mass. The relation has only an average scatter of 0.339 dex around the predicted value ($E_{2019} N_r = E_{2019} N_b/a$; dashed line in Fig 2), which impressively small taking into account the 20 orders of magnitude variations in mass and that the values of $E_{2019} = 10^{-3} \text{Jg}^{-1}$ (13), $N_b = 7.3 \times 10^8$ heartbeats in a lifetime (16) and $a=4.5$ (17), comes from three completely independent measurements in mammals. Moreover, around 95% of the points (2 $\sigma$) has departures from the relation less than a factor of $\pi$ ($\approx \pm 0.5$ dex, colored region between the solid curves in Fig 2).

The extremely accurate relation displayed in Fig 2, suggests that the only missing parameters are the ones due to geometrical variations among species, of the order of a
Fig. 2.— Residuals from the relation predicted by Eq. 1 as a function of the organism’s body mass for 277 living organisms, listed in (6). The relation has only an average scatter of 0.339 dex around the predicted value ($E_{2019 N_r}$) denoted by the dashed line. The colored region between the solid curves denotes residuals less than a geometrical factor of $\pi$ from the relation and 95% of the points ($2 - \sigma$) fulfill such criterion.

A dimensionless numerical factor of order unity ($\pi$). If that is indeed the case, this is probably the first relation in life sciences including all the relevant controlling parameters, reaching an accuracy comparable to the ones in exact sciences. Moreover, Fig 2 implies no clear trend (larger than an e-fold $\approx 0.5$ dex) in inter-class comparison from bacteria to the largest mammal.

Inter-class variations was considered the most persuasive evidence against the ‘rate of living’ theory, for example, the inter-class comparison of birds and bats to mammals (2, 5). These exceptions were erased in Fig 2 due to predicted secondary parameters that are not included in the original formulation (mainly the parameter $a = f_H/f_{\text{resp}}$ for the particular case of birds and bats to mammals). Moreover, Eq. 1 implies a dependence of $t_{\text{life}} \propto \frac{M}{B} \exp\left(\frac{E_a}{kT_{\text{a}}}\right)$ that it is in agreement with the three regimens experimentally known to extend life-span (20): lowered ambient temperature $T_{\text{a}}$ in poikilotherms, decrease of physical activity in poikilotherms (lower $B$) and caloric restriction (lower $B$).
4. Discussion

We showed that the new metabolic rate relation (13) can be directly linked to the total energy consumed in a lifespan, if it is conjectured a constant number $N_r$ of respiration cycles per lifespan, finding a corrected relation for the total energy consumed in a lifespan (Eq 1) that can explain the origin of variations in the ‘rate of living’ theory (2, 5) and unify them into a single formulation. We test the validity and accuracy of the predicted relation (Eq 1) for the total energy consumed in a lifespan on $\sim$300 species representing all classes of living organisms, finding that the relation has an average scatter of only 0.3 dex, with 95% of the organisms having departures less than a factor of $\pi$ from the relation, despite the $\sim$20 orders of magnitude difference in body mass. This reduces any possible inter-class variation in the relation to only a geometrical factor and strongly supports the conjectured invariant number of $N_r \sim 10^8$ of respiration cycles per lifespan in all living organisms.

Invariant quantities in physics traditionally reflects fundamental underlying constraints, something also applied recently to life sciences such as Ecology (21, 22). Fig 2 displays the fact that, for a given temperature, the total life-span energy consumption per gram per ‘generalized beat’ ($N_r^G \equiv aN_r = a 1.62 \times 10^8$) is remarkably constant on around $E_{2019}$, supporting that the overall energetics during lifespan is the same for all living organisms, being predetermined by the basic energetics of respiration. Therefore, Rubner’s original picture it is shown to valid without systematic exceptions, but in this more general form. Moreover, since the value determined from Fig 2 is remarkably similar to $E_{2019}$, it can be considered an independent determination for $E_{2019}$, suggesting that $E_{2019}$ is a candidate for being an universal constant and not just a fitting parameter coming from the corrected metabolic relation (13).

In addition, we showed here that the invariant total life-span energy consumption per gram per ‘generalized beat’ comes directly from the existence of another invariant: the approximately constant total number $N_r \sim 10^8$ of respiration cycles per lifetime, effectively converting the ‘generalized beat’ into the characteristic clock during lifespan. Thus, the exact physical relation between (oxidative) free radical damage and the origin of aging, is most probably related to the striking existence such of constant total number of respiration cycles $N_r$ in the lifetime of all organisms, which predetermines the extension of life. Therefore, since all organisms seems to live the same in units of respiration cycles, future theoretical and experimental studies that investigate the exact link between the constant $N_r \sim 10^8$ respiration cycles per lifespan and the production rates of free radicals (and other byproducts of metabolism), should shed light on the origin of ageing and the physical cause of natural mortality.

It have been also suggested that an analogous invariant is originated at the molecular
level \((23)\), the number of ATP turnovers in a lifetime of the molecular respiratory complexes per cell, which from an energy conservation model that extends metabolism to intracellular levels is estimated to be \(\sim 1.5 \times 10^{16} \) \((23)\). Similar number can be determine taking into account that human cells requires synthase approximately 100 moles of ATP daily, equivalent to \(7 \times 10^{20}\) molecules per second. For \(\sim 3 \times 10^{13}\) cells in human body and for a respiration rate of 15 breaths per minute, this gives \(\sim 9 \times 10^7\) ATP molecules synthesized per cell per breath, which for the invariant total number \(N_r\) of respiration cycles per lifetime found in this work, arises to the same number of \(\sim 1.5 \times 10^{16}\) ATP turnovers in a lifetime per cell, showing the equivalence between both invariants, linking \(N_r\) to the energetics of respiratory complexes at cellular level.

The excellent agreement between the predicted relation (Eq 1) and the data across all types of living organisms emphasizes the fact that lifespan indeed depends on multiple factors \((B, a, M, T & T_a)\) and strongly supports the methodology presented in this work of multifactorial testing, as done in Fig 1, since quantities in life sciences generally suffers from a confounding variable problem. An example of this problem, illustrated on individually testing each of the relevant factors is in \((24)\), which for a large (and noisy) sample test for \(t_{\text{life}} \propto 1/B\), finding no clear correlation. From Eq 1, it is clear that in an uncontrolled experiment the dependence on the rest of the parameters \((M, a, T, & T_a)\) might erase the dependence on the metabolic rate \(B\) (in fact, for the same reason Rubner’s work \((7)\) focused on the mass-specific metabolic rate \(B/M\) instead of \(B\)). This work \((24)\) only finds a residual inverse dependence of \(t_{\text{life}}\) on the ambient temperature \(T_a\) for ectotherms, something expected according to Eq 1 \((t_{\text{life}} \propto \exp\left(\frac{E_a}{kT_a}\right))\).

Finally, the empirical support in favor of Eq \(\text{1}\) allow us to compute how much will vary the energy consumption in the biomass doing aerobic respiration, as increases the earth’s temperature, relevant in the current context of possible global warming. This is given by the factor \(\exp\left[\frac{E_a}{k}\left(\frac{1}{T} - \frac{1}{T+1}\right)\right]\) which for an activation energy \(E_a = 0.63\text{eV}\) and temperature of \(30^\circ\text{C}\), implies an increase 8.3% in energy consumption per 1 degree increase on the average Earth temperature. This result can be straightforwardly applied in ectotherm since their body temperatures adapt to the environmental one \((T = T_a)\), but is less clear its implications for the case of endotherms organisms.

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