

Exercise-induced maximum metabolic rate scaled to body mass by the fractal dimension of the vascular distribution network

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Abstract

The central postulation of the present approach to metabolic rate scaling is that exercise-induced maximum aerobic metabolic rate (MMR) is proportional to the fractal extent (V) of an animal. Total fractal extent can be calculated from the sum of the fractal extents of the capillary service units, as specified by the formula $V \propto N_1 L_1^D$, where \propto means 'proportional to'. Here N_1 is the number of capillaries and L_1 is capillary length, with D the fractal dimension of the vascular distribution network and with L_1^D the fractal extent of a capillary service unit. D can be any real number in the interval $2 \leq D \leq 3$. From dimensional considerations V scales with body mass (M) with power exponent $D/3$, or $V \propto M^{D/3}$. Then $\text{MMR} \propto M^b$ with $b = D/3$ follows from the postulate $\text{MMR} \propto V$. The utility of the relationship $b = D/3$ depends on the feasibility of estimating D . There are two possibilities. The first is to estimate D from the scaling of aorta cross-section area with body mass. The second is from morphometric observations on various body organs. Both give estimates of b in remarkable agreement with estimates obtained by exercise induction or oxygen half-saturation pressure scaling with body mass. The predicted range $2/3 \leq b \leq 1$ is experimentally observed. Likely causes of notable particular instances of the symmorphosis $b = D/3$ with $2 \leq D \leq 3$ include optimal movement requirements, muscle stress limitation, and maximized oxygen delivery and metabolic rates. Lastly, it is shown that the scaling exponent of basal metabolic rate with body mass can be obtained by taking body composition into account in the product of the scaling exponents of MMR and visceral mass.

Key words: basal metabolic rate, fractal dimension, fractal extent, maximum metabolic rate, vascular distribution network

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Introduction

Regularity in the scaling of metabolic rates with body mass is of fundamental importance in biology (Agutter & Tuszynski, 2011). This scaling regularity proved to be difficult to explain, so that the effort by West *et al.* (1997; 1999), based on surface and distribution network fractals, was initially well received. Nonetheless, recently their approach has attracted a wide range of methodological, mathematical and empirical criticisms, not all of which have been answered satisfactorily (Agutter & Tuszynski, 2011). For surface area scaling with body mass (M), Pennycuik (1992) and Weibel & Hoppeler (2005) hypothesized an alternative fractal surface solution in terms of a body mass power (M^b) characterized by an exponent $b = D/3$, with D denoting the fractal dimension of the surface involved in metabolic control. Okie (2013) reformulated and improved this hypothesis by a mathematically rigorous approach in terms of the box counting fractal dimension of rough surfaces, which can be any real number $2 \leq D \leq 3$. Hence, fractal surfaces can explain metabolism scaling exponents of body mass powers with range $2/3 \leq b \leq 1$, instead of the fixed $b = 3/4$ scaling of West *et al.* (1997, 1999) or $2/3 \leq b \leq 3/4$ of Banavar *et al.* (2010).

Okie's (2013) formulation of surface area scaling extends to other cellular and organismal strategies such as geometric dissimilitude and surface internalization, underscoring the importance of surface area in influencing metabolism. Even so, it does not preclude a role for distribution networks in the explanation of metabolic scaling (Okie, 2013). It is the purpose of the present communication to formulate a fractal vascular distribution network approach that complements the previous fractal surface approach by showing that isomorphic body mass scaling exponents of the form $b = D/3$ are applicable to both situations, although possibly different fractal dimensions with $2 \leq D \leq 3$ must be derived or calculated for each situation. Even

though the focus is on the arterial system from the aorta to the capillaries, some of the conclusions and derivations could apply to the corresponding venous system from the capillaries to the venae cavae.

The approach followed here is to derive general algebraic results on metabolic rates (MR) that may be applicable to both basal aerobic metabolic rates (BMR) and maximum aerobic metabolic rates (MMR), and to show from morphometric considerations and measurements of both, that the vascular distribution system is designed for the optimization of MMR during strenuous activity. Furthermore, the self-similarity of the vascular system, together with the observation that BMR is generated mostly by the viscera and MMR by skeletal muscle (Schmidt-Nielsen, 1984; Weibel *et al.*, 2004), allows for the conclusion that the scaling of BMR can be derived from the scaling of exercise-induced MMR by taking body composition into consideration. The derivation of BMR from MMR could be important in delineating the possibility of breeding improvement in the BMR component of the maintenance requirements of farm livestock by body composition manipulation.

Finally, examples from the literature are used to illustrate that the relationship $b = D/3$ could be regarded as a general symmorphosis, with particular instances that may be caused by the advantages of maximum metabolism for snakes, maximum oxygen supply for athletic mammals and lizards, metabolic benefits of optimal movement for nonathletic mammals and rodents, and the limitation of maximum muscle stress for insectivores. The unequal size distribution of the species in the taxa with different instances of the general symmorphosis causes the appearance of non-rectilinearity in the logarithmic relationship between MR and body mass, thus explaining the strongest objection of Agutter & Tuszynski (2011) to fractal network theory.

Cold exposed MMR tends to scale to body mass like surface-dependent processes (Glazier, 2008), while exercise-induced MMR is shown here to scale according to distribution network fractal dimensions. Hence, with a possibly obvious surface area explanatory cause, cold exposed MMR is left aside for present purposes.

Initially developed for water flow description in river basins, network scaling laws date back to the mid-1940s (Horton, 1945) and are brought together in a logical framework by Dodds & Rothman (1999) with extension to biological side branching systems by Turcotte *et al.* (1998). The basic mathematical framework of the present approach is given in these two references, and repetition is limited to the extent necessary for biological understanding. For clarity of and accessibility to the mathematical derivations, the notation of Turcotte *et al.* (1998) is adhered to. It is helpful to know that Hack's exponent (h) in Dodds & Rothman's (1999) two-dimensional coordinate space generalizes to Turcotte *et al.*'s fractal dimension (D) in three-dimensional coordinate space, in such a way that $D = 1/h$ in two-dimensional space. From this key observation it follows that Dodds & Rothman's (1999) mathematical derivations are generally applicable to the situation covered in Turcotte *et al.* (1998). This means that the rules and interpretations of riverine areas generalize to fractal extents in vascular systems. Dodds & Rothman's (1999) two-dimensional illustrations could therefore be used as an aid to understanding the more complex three-dimensional vascular distribution system. Since $h \geq 1/2$ and $D \leq 3$, the riverine $1/2h$ is analogous to the vascular $D/3$. Dodds & Rothman (1999) observe that for a reasonable span of river basin sizes, the inequality $0.57 \leq h \leq 0.60$ holds, so that $0.83 \leq 1/2h \leq 0.88$. These values correspond remarkably with some of the values of $D/3$ that appear in the present approach, suggesting similarities that may reward further exploration.

Newly derived results included here extend the theoretical development of Turcotte *et al.* (1998) to include the scaling of capillary lengths and cross-sections and of capillary numbers inherent in their formulation. Under the assumption of the minimization of transport energy dissipation, these capillary scalings are expressed in terms of the fractal dimension of the vascular distribution network to obtain a simple description and explanation of MMR scaling with body mass.

The fractal dimension of the vascular distribution network can be calculated in two ways. The first is indirectly from aorta cross-section scaling with body mass under various assumptions, and the second more directly from the morphometry of arterial and venous networks. The morphometric measurements for the description of a vascular system by Horton (1945) scaling laws are achieved by casting methods, such as the silicone elastomer-casting method applied to describe pig coronary arterial trees by Kassab *et al.* (1993). Estimates of vascular network fractal dimensions and arterial and venous area preservation scaling exponents for various organs and species have been collated by Huo & Kassab (2012). The statistical methods are presented in Kassab *et al.* (1993) and Turcotte *et al.* (1998).

Results and Discussion

A simple cubic model organism

A simple cubic model organism (SCMO) is designed here to elucidate the difference between smooth geometric shapes that can be handled by standard Euclidian geometry and rough shapes for which fractal geometry should be employed by generalizing shape dimensions from discrete integers to continuous real

numbers. Incidentally, it is shown that the most important results of West *et al.* (1997) and Banavar *et al.* (2010) are consonant with such an SCMO.

An SCMO is served by a vascular system with a central aorta of length proportional to its side length. The starting primal cube is divided into eight subcubes, with side lengths equal to one half of the primal side length. The aorta divides into side branch arteries in such a fashion that each subcube is served by a central artery of length $L_{n-1} = L_n/2$, with the subscript n indicating the aortic level. This process of subdivision of cubes into eight subcubes is continued in a self-similar fashion until the important capillary level of metabolite exchange between the bloodstream and tissue substance is reached. The repeated subdivision is analogous to that portrayed in Figure 7 of Turcotte *et al.* (1998). The subcubes by themselves are not important in the description of a SCMO, but could be regarded merely as an artery placement device.

Each capillary service volume is proportional to L_1^3 and can be associated with a single capillary with length L_1 . Suppose that there are N_1 capillaries so that their total service volume is proportional to $N_1 L_1^3$ and to the SCMO volume V . Assume that there are n levels, each level denoted by k with N_k the number of arterioles or arteries at that level in the SCMO, so that $k = n$ with $N_n = 1$ at the aortic level. Then

$$N_1 L_1^3 = \dots = N_k L_k^3 = \dots = L_n^3 \propto V \tag{1}$$

where the symbol \propto means 'proportional to' with $k = 1, 2, \dots, n$. At each level k denote the vessel cross-section area by A_k , so that the total cross-section area for the level is $N_k A_k$. Furthermore, assume area preserving branching

$$N_1 A_1 = \dots = N_k A_k = \dots = A_n \tag{2}$$

to assure smooth blood flow without reflections at the branch junctions (West *et al.*, 1997). Under the assumption of total body volume (V) proportional to body mass (M) it can be derived from Equations 1 and 2 on assuming $N_1 \propto M^{3/4}$ and $A_n \propto M^{2/3}$ that

$$L_1 \propto M^{1/12} \text{ and } A_1 \propto M^{-1/12}. \tag{3}$$

The conventional assumption of metabolic rate (MR) proportional to blood flow at constant speed (West *et al.*, 1997) gives, from Equation 3

$$MR \propto N_1 A_1 \propto M^{3/4 - 1/12} = M^{2/3} \tag{4}$$

identical to Banavar *et al.* (2010). Banavar *et al.* (2010) provide a derivation that the maximum speed of blood flow in the capillaries (U_1) would be $U_1 \propto L_1 \propto M^{1/12}$. Hence, for blood flow at maximum speed in the capillaries,

$$MR \propto N_1 A_1 L_1 \propto M^{3/4} \tag{5}$$

again identical to Banavar *et al.* (2010).

Real organisms with fractal geometry

The problem with Equations 4 and 5 is that they depend for their validity on Equation 1, which is true only for the smooth shapes of standard geometry, such as cubes, spheres or cylinders. With invariance under contraction or dilation (i.e. self-similarity), the rough shapes of structural forms engendered by vascular transport networks can be described by the fractal geometry developed by Mandelbrot (1989). Hence, for the fractal situation in real organisms Equation 1 generalizes to

$$N_1 L_1^D = \dots = N_k L_k^D = \dots = L_n^D \propto V \tag{6}$$

where V is the fractal extent served by the vascular system. Here the fractal dimension of the vascular system can be any real number subject to the constraint $2 \leq D \leq 3$. In the limit $D = 3$ the fractal extent defined in Equation 6 becomes identical to the conventional volume in Equation 1. The important point is that the fractal extent in Equation 6 is invariant with level k , whereas in a general fractal situation the conventional volume from Equation 1 would depend on the level k . Pennycuik (1992) or Pennycuik & Kline (1986) can be consulted for an explanation of these principles, with reference to similar situations for surfaces or lines.

To obtain a scaling of fractal extent to body mass by multiplication with protoplasm density, a measure of extent of dimension 3 is required. Hence, V , with fractal dimension D , should be adjusted to $V^{3/D}$ for direct proportionality to body mass, so that

$$V \propto M^{D/3}. \tag{7}$$

To quantify the effect of body size on MR, it is the size or extent (proportional to L_1^D) of the capillary service units that must be considered, because it is only at this level that metabolite exchange between tissues and blood takes place. Hence, the postulation from Equation 6 $MR \propto N_1 L_1^D \propto V$, so that it follows from Equation 7 that

$$MR \propto M^{D/3}. \tag{8}$$

The practical utility of Equation 8 depends on the feasibility of estimating the fractal dimension D . There are two possibilities. The first is to estimate it from the scaling of aorta cross-section area with body mass, based on two assumptions, namely i) that the MR estimated from blood flow is proportional to that estimated from fractal extent by Equation 8; and ii) that the vascular system is constructed to minimize

transport energy dissipation. The second way of estimating D is from morphometric observations achieved by casting methods on various body organs. This is covered in the discussion on the construction of Table 1.

Estimating fractal dimension from aorta cross-section area scaling

To estimate D , it is advantageous to generalize Equation 2 to the form

$$N_1 A_1^\alpha = \dots = N_k A_k^\alpha = \dots = A_n^\alpha \quad (9)$$

where the term A_k^α indicates that area to a power with exponent α is preserved from one level to the next. Then, under the assumptions of the Tokunaga side branching condition (Turcotte *et al.*, 1998) and that total blood volume in the body is proportional to body mass (Peters, 1983), it can be derived for the capillary number power scaling with body mass, that

$$N_1 \propto M^{\alpha D / (\alpha + D)}. \quad (10)$$

Equation 10 follows simply from the derivation presented by Turcotte *et al.* (1998) by deleting the basal metabolic terms and their assumed relationship to capillary number and proceeding directly in terms of capillary number N_1 . In a similar fashion to the derivation of Equation 10 it follows that

$$L_1 / L_n \propto M^{-\alpha / (\alpha + D)} \quad (11)$$

$$A_1 / A_n \propto M^{-D / (\alpha + D)}. \quad (12)$$

From Equations 6 and 7 it follows that $L_n \propto M^{1/3}$. This is confirmed from an estimate from Holt *et al.* (1981), to excellent approximation. Furthermore, it could be assumed that $A_n \propto M^w$. Henceforth the following notational conventions are convenient. Denote metabolic rate, capillary number, length and cross-section area as before by MR, N_1 , L_1 and A_1 , respectively, and assume power scalings with body mass (M) with exponents b , x , y and z to avoid the notational inconvenience of superscripts and subscripts in further development. Hence,

$$MR \propto M^b, N_1 \propto M^x, L_1 \propto M^y, \text{ and } A_1 \propto M^z. \quad (13)$$

It follows from the definitions of Equation 13 and Equations 10-12 that the body mass exponents of the capillaries of the whole body fractal system can be described by

$$x = \alpha D / (\alpha + D) \quad (14)$$

$$y = 1/3 - \alpha / (\alpha + D) \quad (15)$$

$$z = w - D / (\alpha + D). \quad (16)$$

Equations 14–15 represent fractal dimension generalizations of the pertinent vascular scaling results of Banavar *et al.* (2010), Barbosa *et al.* (2006) and Bengtsson & Edén (2003). This follows because the assumptions of area preserving branching ($\alpha = 1$ in Equation 9, equivalent to Equation 2) and limit fractal dimensionality ($D = 3$), together with geometrically similar aortic scaling ($w = 2/3$), give $x = 3/4$ and $z = 2/3 - 3/4 = -1/12$ from Equations 14 and 16. This is equivalent to Equations 3 and 4 and in agreement with Banavar *et al.* (2010). An assumption of $w = 3/4$ would give $z = 0$ for Equation (16) and allow the $3/4$ metabolic rate scaling with body mass of West *et al.* (1997) from Equation 14. Furthermore it is possible to derive $\alpha = 5/4$ (α defined in Equation 9) and $w = 12/17$ (w defined in Equation 13) from the model developed by Bengtsson & Edén (2003) so that substitution of the limit $D = 3$ in Equations 14 and 16 gives $x = 15/17$ and $z = 0$. These values of x and z allow the prediction of a metabolic rate exponent of $b = 15/17$, identical to Bengtsson & Edén (2003), from blood flow rate at a speed invariant with body mass.

Transport energy dissipation can be reduced by minimizing network impedance using a Lagrange multiplier method. In predominantly pulsatile flow, it can be derived from Barbosa *et al.* (2006) and Dodds *et al.* (2001) that flow energy dissipation will be minimized by the condition

$$\alpha = 2D / (2D - 1). \quad (17)$$

The limit dimension $D = 3$ then gives $\alpha = 6/5$ in Equation 17, so that substitution of these values in Equation 14 gives $x = 6/7$. The assumption of $w = D / (\alpha + D) = 5/7$ and $z = 0$ (from Equation 16) then allows prediction of a metabolic exponent $b = 6/7$ from $x = 6/7$ and body mass invariant flow speed, identical to Barbosa *et al.* (2006).

In the three foregoing contributions to the scaling of metabolic rate from the vascular transport system, the limit value of $D = 3$ was regarded as a necessary space-filling assumption to ensure adequate blood flow to all parts of an organism. This is erroneous as the maximum value of a fractal dimension is not necessary for a fractal network to be space filling (Dodds & Rothman, 1999). Therefore, it is advantageous to simplify Equations 14–15 by the relationship between α and D of Equation 17 instead of taking the limit value $D = 3$. Substituting Equation 17 in Equations 14–16 then gives

$$x = 2D / (2D + 1) \quad (18)$$

$$y = 1/3 - 2 / (2D + 1) \quad (19)$$

$$z = w - (2D - 1) / (2D + 1). \quad (20)$$

Under the postulate of MR proportional to total capillary service unit fractal extent ($MR \propto N_1 L_1^D$) it follows that

$$b = x + Dy = D/3 \quad (21)$$

from Equations 14 and 15 or 18 and 19, and equivalent to Equation 8. The postulate of MR proportional to blood flow under invariant flow speed in the capillaries with respect to body mass ($MR \propto N_1 A_1$) gives from Equations 18 and 20

$$b = x + z = w + 1/(2D + 1). \quad (22)$$

On assuming that the scaling of metabolic rate estimated from blood flow is proportional to that estimated by fractal volume, Equations 21 and 22 can be equated to give

$$w = D/3 - 1/(2D + 1) \quad (23)$$

or

$$D = [6w - 1 + (36w^2 + 12w + 25)^{1/2}]/4. \quad (24)$$

Maximum aerobic metabolic rate exponents from aorta cross-section scaling

There are two estimates of w in the literature, the first by Clark (1927), and the second by Holt *et al.* (1981). For mature mammals of various species, Clark (1927) found a consistent relationship between A_n and heart mass with exponent of 0.8 in agreement with the 95% confidence interval (CI) 0.80 ± 0.047 , calculated from his appendices II and III. Following Clark's (1927) recommended estimation procedure of multiplying 0.8 with the exponent of 0.9 between heart and body mass, a relationship between A_n and body mass is obtained

$$A_n (cm^2) = 0.130M^{0.72 \pm 0.04} (M \text{ kg}). \quad (25)$$

This is almost identical to the estimate of Holt *et al.* (1981)

$$A_n = 0.132M^{0.72 \pm 0.04} \quad (26)$$

with the same units as in Equation 25.

Combining the estimates of Equations 25 and 26 gives a CI estimate

$$w = 0.72 \pm 0.028. \quad (27)$$

Substitution of Equation 27 in Equation 24 gives $D = 2.638 \pm 0.074$, from which the CI

$$b = 0.879 \pm 0.025 \quad (28)$$

follows from Equation 21. Equation 28 is in substantial agreement with the exercise-elicited MMR scaling exponent of 0.872 ± 0.060 for mammals of Weibel *et al.* (2004) and of 0.879 ± 0.020 for birds and mammals of Bishop (1999), obtained with adjustment to a standard mammalian relative heart size scaling with body mass and haemoglobin concentration.

The exponent of the relationship between heart and body mass of Brody (1945) of 0.98 ± 0.02 , based on more than 100 observations, differs substantially from the 0.9 calculated by Clark (1927) on about 100 observations. Multiplication of Brody's (1945) exponent 0.98 with the CI 0.80 ± 0.047 calculated from Clark (1927) gives an estimate

$$w = 0.784 \pm 0.046. \quad (29)$$

Substitution in Equation 24 gives $D = 2.806 \pm 0.121$, from which

$$b = 0.935 \pm 0.040 \quad (30)$$

follows from Equation 21.

Equation 30 is in substantial agreement with the exercise-elicited exponent CI $b = 0.942 \pm 0.053$ calculated by Weibel *et al.* (2004) for athletic mammals, identified from high observed mass-specific maximum metabolic rates. Weibel *et al.* (2004) noted that athletic species are prevalent in the large size classes. Small mammals tend to have larger heart mass to body ratios than large mammals and Brody's (1945) sample contains relatively fewer small mammals than Clark's (1927), causing the size of constant heart mass to body mass ratios associated with his 0.98 exponent. This exponent therefore correctly predicts the large size prevalent athletic mammal scaling of maximum metabolic rate, in contrast to the better whole sample prediction from Clark's (1927) 0.9 exponent description of the relationship between heart mass and body mass.

A third way of evaluating the validity of Equation 24 for estimating fractal dimensions from aorta cross-section areas is by capitalizing on the eight species' overlap in the aorta measurements of Appendix II of Clark (1927) and the MMR measurements of Table 1 of Weibel *et al.* (2004). These eight species are the mouse, rat, guinea pig, dog, sheep, pig, cattle and horse. The species average observations near maturity from Clark (1927) give a regression coefficient estimate of the aorta cross section area exponent

$$w = 0.8255 \pm 0.0509. \quad (31)$$

From Equation 24

$$D = 2.9157 \pm 0.1353 \quad (32)$$

and from Equation 21

$$b = D/3 = 0.9719 \pm 0.0451. \quad (33)$$

After eliminating the typing errors in Table 1 from a comparison with Table A1, with both tables in Weibel *et al.* (2004), the MMR exponent can be calculated directly by regression analysis on the values nearest to maturity as

$$b = 0.9721 \pm 0.1319 \quad (34)$$

with

$$D = 3b = 2.9163 \pm 0.3957 \quad (35)$$

from Equation 21.

The remarkable agreement between the two sets of estimates of b and D in Equations 32–35 is a strong indication of the validity of the present approach to the between-species scaling of the MRR vascular distribution network complex with body mass in any relevant collection of species.

Morphometric fractal dimension estimates

Estimates for α and D have been achieved from morphometric observations for various combinations of organs and species according to the Horton-Strahler system, which is a special case of the more general Tokunaga taxonomy (Turcotte *et al.*, 1998). Estimates obtained from the literature by Huo & Kassab (2012) for rats, cats, dogs, pigs and humans for pulmonary and heart networks with predominantly pulsatile flow are included in Table 1. Additional estimates of rat kidney arterial and venous networks (Nordsletten *et al.*, 2006) are provided in Table 1, to obtain a total of 14 specie/organ arterial and venous networks. The two estimates of $D > 3$ are included in the weighed estimate of Table 1 as they exceed the limit $D = 3$ probably because of measurement error. If positive measurement errors are excluded from an average, so should negative measurement errors, which are unknown in the present situation. It is therefore best to keep the positive errors.

Table 1 Confidence intervals for averages of estimates of the area preservation exponent (α) and the network system dimension (D) for fractal vascular networks in various organs and species

| Origin | Source* | N | α | D |
|---------------------|---------|----|-----------------|-----------------|
| Huo & Kassab | 1 | 12 | 1.19 ± 0.08 | 2.52 ± 0.32 |
| Rat kidney arteries | 2 | 1 | 1.68 | 3.06 |
| Rat kidney veins | 2 | 1 | 1.34 | 3.31 |
| Average (weighed) | | 14 | 1.24 ± 0.10 | 2.62 ± 0.31 |

*Sources: 1: Huo & Kassab (2012), 2: Nordsletten *et al.* (2006)

Four important aspects can be observed from Table 1. The first is that α , estimated by Equation 17 from $D = 2.62$, is equal to 1.24 and is exactly equal to the average α by direct calculation. Hence, from Barbosa *et al.* (2006) and Dodds *et al.* (2001), energy dissipation is on average a minimum for pulsatile flow in the organs/species under consideration. The second observation is that $D = 2.62 \pm 0.31$ gives from Equation 21 an estimated CI of $b = 0.87 \pm 0.10$, or from Equation 22 and Equation 27 with $w = 0.72$, $b = 0.88 \pm 0.04$. Both are in substantial agreement with the exercise-induced estimates of 0.88 or 0.87 (Bishop, 1999; Weibel *et al.*, 2004). The third observation is that the important postulated equality between the estimates of b from fractal dimensions and from assumed blood flow rates can be confirmed by the strong agreement of estimates obtained directly, without transport energy minimization, from Equations 8, 14 -16, 21 and 27. These estimates give $b = D/3 = x + Dy = 0.840$ in agreement with $b = x + z = 0.849$ from the averages of Huo & Kassab (2012), as well as $D/3 = 0.873$ in agreement with $x + z = 0.883$, from the combined averages, as in Table 1. The fourth observation is that the CI estimates of D in Table 1 indicate significant differences from $D = 3$.

Oxygen delivery from capillaries to mitochondria

The diffusion of oxygen from capillaries to the mitochondria is determined by oxygen partial pressure as a driving force, together with a diffusion conductance (Weibel *et al.*, 1991). The diffusion conductance contains the capillary parameters that affect oxygen diffusion and the characteristic diffusion distance to the vicinity of the mitochondria. It appears that not enough is known for a theoretical estimate of the scaling exponent of diffusion conductance with body mass. As a first approximation, the diffusion conductance scaling exponent with body mass is obtained by the difference between the scaling exponent of oxygen half-

saturation pressure and body mass ($P_{50} \propto M^a$), with $a = -0.054 \pm 0.021$ for eutherian mammals (Lutz *et al.*, 1974), and the mammalian estimate of the MR scaling exponent given by Equation 28 and Bishop (1999). This procedure gives an intercept of $0.879 + 0.054 = 0.933 \pm 0.027$, so that

$$b = 0.933 + a \quad (36)$$

with a the exponent in the scaling of oxygen half-saturation pressure with body mass.

Oxygen partial pressure and maximum aerobic metabolic rate

Estimates of b from oxygen partial pressure (Equation 36), as well as comparisons of such estimates with b estimated directly from exercise induction experiments (E), are given in Table 2. For rodents and birds the agreement between exercise-induced and oxygen partial pressure estimates of MR scaling exponents, is excellent. It is also evident that for athletic mammals the exercise-induced b agrees well with the b predicted from $a = 0$ in Equation 36.

Table 2 The maximum aerobic metabolic rate (MMR) power exponent scaling with body mass (b), estimated from the scaling (a) of oxygen half saturation pressure (P_{50}), compared to the scaling of exercise elicited maximum aerobic metabolic rate (E)

| Taxon | Source* | N | Method | P_{50} -scaling a | MMR b |
|---------------------|---------|----|----------|--------------------------|-----------------|
| Mammals | 1 | 17 | P_{50} | -0.054 ± 0.021 | 0.88 ± 0.02 |
| Mammals/birds | 2 | 15 | E | - | 0.88 ± 0.02 |
| Mammals | 3 | 34 | E | - | 0.87 ± 0.06 |
| Athletic mammals | Eq 36 | - | P_{50} | 0 | 0.93 ± 0.03 |
| Athletic mammals | 3 | 11 | E | - | 0.94 ± 0.06 |
| Nonathletic mammals | 3 | 23 | E | - | 0.85 ± 0.05 |
| Rodents | 4 | 18 | P_{50} | -0.118 ± 0.076 | 0.82 ± 0.08 |
| Rodents | 3 | 10 | E | - | 0.81 ± 0.17 |
| Insectivores | 5 | 17 | P_{50} | -0.303 ± 0.068 | 0.63 ± 0.07 |
| Birds | 1 | 7 | P_{50} | -0.079 ± 0.067 | 0.85 ± 0.07 |
| Birds | 6 | 39 | E | - | 0.84 ± 0.11 |
| Lizards | 7 | 48 | P_{50} | -0.008 ± 0.025 | 0.93 ± 0.07 |
| Snakes | 8 | 34 | P_{50} | 0.077 ± 0.070 | 1.01 ± 0.08 |

*Sources: 1: Lutz *et al.* (1984), 2: Bishop (1999), 3: Weibel *et al.* (2004), 4: Hall (1996), 5: Bartels *et al.* (1969), 6: Norberg (1996), 7: Pough (1977a), and 8: Pough (1977b)

The values for lizards in Table 2 are calculated from the observations for mature animals listed by Pough (1977a), except for the deletion of the extraordinarily low P_{50} value of *Hemidactylus bibroni*, which is about half the value of the next lowest observation. Owing to insufficient information, the P_{50} estimates for insectivores are from two species only, with 11 observations on shrews and six on moles (Bartels *et al.*, 1969). It is included to show that a low P_{50} power index for insectivores is a possibility, though at this stage with no pretence to representativeness.

Significantly different power exponents between mammalian orders for the description of BMR scaling with body mass were obtained by Kozłowski & Konarzewski (2005). This raises the question whether a similar result holds for MMR scaling. The confidence intervals of the P_{50} estimates in Table 2 suggest the possibility of significant differences in MMR between rodents and insectivores similar to the BMR.

From geometric considerations, the fractal dimension of the vascular system is bounded by a surface $D = 2$ and a volume $D = 3$. The relationship $D = 3b$ (Equation 21) indicates that the fractal dimensions of snakes of the two families Colubridae and Boidae (D near to 3) and insectivores (D near to 2) are not significantly different from the limits of D expected on geometrical grounds.

A possible explanation for the snake fractal dimension D near to 3 follows from the proposition that a high metabolic rate, corresponding to a high value of b , may be of selective advantage to the snakes of the families Colubridae and Boidae. For example, Burmese pythons of the family Boidae generally reach their

highest MMR/BMR ratios during digestion owing to their large meal sizes and because the gut atrophy acquired during their long fasts requires high investment in rebuilding it (Secor & Diamond, 1995). The digestion metabolic scope for Burmese pythons on a relatively modest prey mass/body mass ratio of 25% is 17, compared with a locomotion metabolic scope 6, which is comparable to the locomotion scopes of non-athletic mammals. With a realistic 100% prey mass/body mass ratio, pythons achieve a digestion metabolic scope of 45, the same value as the exceptional locomotion scope of race horses (Secor & Diamond, 1995).

The value of 1.01 ± 0.08 for the MMR exponent for snakes from Equation 36 is supported by the conventional BMR power exponent of 1.02 ± 0.08 that can be calculated as a combined value for the Colubridae and Boidae (Galvão *et al.*, 1965).

During heavy exercise about 90 per cent of blood flow is to skeletal muscle (Weibel *et al.*, 2004), which scales isometrically with whole body mass (Peters, 1983). Under the assumption of a fixed maximum stress during muscle exertion, muscle power development will scale proportional to muscle mass with exponent $2/3$ (Pennycuik, 1992) and hence with the same exponent to body mass. This is the likely scaling for insectivores in Table 2, and may be coupled to sudden movement in pursuit of prey or to the burrowing habits of many insectivores.

The scaling predicted for muscle power generation during movement under the combined hypothesis of dynamic and geometric similarity, namely $b = 5/6 = 0.83$ (Pennycuik, 1992), may correspond to a number of important cases in Table 2. This suggests that the value of the fractal dimension $D = 3b = 2.5$ may be owing to modifications by natural selection to allow energetically optimal movement under dynamic similarity.

Weibel *et al.* (2004) found that the exercise-elicited MMR for 34 species of mammals could be naturally separated by substantial differences in mass-specific maximum oxygen consumption into an athletic group and a non-athletic group. Although their separate confidence intervals overlap, their scaling exponents from combined analysis differ according to a probability $P < 10^{-5}$. The scaling exponents of the non-athletic group and the rodents of 0.85 and 0.81, respectively, are consonant with dynamically similar movement. In contrast, the scaling exponent of the athletic group is consonant with the value of b from Equation 36, with $a = 0$, $b = 0.933$. A scaling exponent of a approximately equal to zero could arise if the P_{50} values of the athletic species were all as high as possible, with an upper limit induced by the requirement of a high degree of oxygen saturation of the haemoglobin in alveolar blood. The validity of this argument follows from the sigmoid shape of the oxygen dissociation curve as illustrated in Figure 10.2 of Schmidt-Nielsen (1984), with the asymptote that should be near or to the left of aerial partial oxygen pressure. Here $D = 3b = 2.80$ (Equation 21). Hence the argument for a fractal dimension of $D = 2.80$ would be that it enables movement with a maximum oxygen supply rate.

In summary, the examples in Table 2 seem to indicate that although the fractal nature of the vascular system determines the relationship $b = D/3$, the naturally observed values of b are likely to be evolutionarily established by requirements for optimal movement and metabolism. This can be done by natural selection changing animal transportation network geometry to satisfy equations such as Equations 6 and 24.

The examples in Table 2 indicate that the possibility of the existence of a single fixed body mass exponent for description of MMR is highly unlikely. Instead, they can be understood as particular manifestations of a well-established relationship between MMR and fractal extent in terms of body mass exponents, $b = D/3$, with the symbols defined in Equations 6 and 13. It follows, therefore, that the relationship $b = D/3$ can be regarded as a symmorphosis (defined by Weibel *et al.*, 1991) of a body mass fractal structural design exponent $D/3$ matching the body mass functional demand MMR exponent b . The most notable instance of this symmorphosis is probably the aorta exponential estimate of $w = 0.72 \pm 0.028$ (Equation 27) for mammals from Clark (1927) and Holt *et al.* (1981) predicting $D = 2.638 \pm 0.074$ (Equation 24), giving $b = D/3 = 0.879 \pm 0.025$ in agreement with the exercise-induced $b = 0.872 \pm 0.060$ from Weibel *et al.* (2004) and $b = 0.879 \pm 0.020$ of Bishop (1999).

A schematic listing of the likely causes of notable instances of the $b = D/3$ symmorphosis is given in Table 3. Suarez & Darveau (2005) likewise regard the matching of fractal vascular oxygen supply with capacities of substrate oxidation, aerobic ATP synthesis and utilization as instances of the general principle of symmorphosis.

Two other vascular network approaches (Barbosa *et al.*, 2006; Bengtson & Edén, 2003) to the prediction of MMR assume constant $D = 3$, allowing them to predict $b = 6/7$ or $b = 15/17$, respectively, but clearly $D = 3$ does not allow prediction of the full range of values in Tables 2 and 3. Taking $D = 3$ is regarded as a necessary space-filling assumption to ensure adequate blood flow to all parts of an animal. This is erroneous as the maximum value of a fractal dimension is not necessary for a fractal network to be space filling (Dodds & Rothman, 1999). Furthermore, the CIs of the average values of D in Table 1, calculated from morphometric observations of various organs, indicate estimates of D significantly different from 3 at the 5% level of significance.

The relationship between basal and maximum aerobic metabolic rates

The approaches to MR prediction of Banavar *et al.* (2010) and West *et al.* (1997), both with $\alpha = 1$, and of Barbosa *et al.* (2006) and Bengtson & Edén (2003) with, respectively, $\alpha = 6/5$ and $\alpha = 5/4$, as defined in Equation 9, indicate that different values of α are necessary to predict the scaling exponents of body mass for BMR and MMR. This implies that the mammalian vascular system could be designed primarily for either BMR or MMR optimality, but not both simultaneously. The confidence intervals for α in Table 1 indicate that the mammalian vascular system is designed for MMR optimality. Consequently, it becomes important to know how BMR is accommodated in a fractal system designed for MMR optimality. It can be shown that the scaling exponent of BMR can be derived from MMR scaling by considering the scaling of body composition with body mass.

The principle of self-similarity of the vascular system is consonant with each organ in the body having a major artery supplying it with blood from the heart and a major vein returning it. This means that the whole body fractal vascular dimension scaling exponent $b = D/3$ is applicable to the organ mass of separate organs or their sub-collections such as the viscera and skeletal muscle. The results in Table 1 are in agreement with this statement, because both average estimates of D are based on visceral organs, and these are in accord with the estimate of D obtained from aorta scaling with the whole body. The principal difference between MMR and BMR is that MMR is owing mainly to respiration in skeletal muscle and BMR to respiration in the viscera (Schmidt-Nielsen, 1984; Weibel & Hoppeler, 2005). Hence, it is plausible that identical fractal dimensions of skeletal muscle and visceral vascular systems should give identical power exponent scalings of MMR with skeletal muscle mass (M_m) and of BMR with visceral mass (M_v). It follows from the major muscular localization of MMR that $b = D/3$ gives from Equation 28 and Bishop (1999) $MMR \propto M_m^{0.879} \propto M_w^{0.879}$, where M_w denotes whole body mass, with $M_m \propto M_w$ (Weibel *et al.*, 2004). On the other hand the visceral contribution to BMR would scale as visceral $BMR \propto M_v^{0.879}$. The key to scaling visceral BMR with M_w is that $M_v \propto M_w^{0.871 \pm 0.024}$ (Pace *et al.*, 1979). Hence visceral $BMR \propto M_v^{0.879} \propto (M_w^{0.871})^{0.879} = M_w^{0.766 \pm 0.025}$. The CI 0.766 ± 0.025 covers the generally accepted average 0.75 exponent scaling of BMR with whole body mass.

However, whole body BMR contains a skeletal muscle contribution in addition to the main visceral component (Schmidt-Nielsen, 1984). The scaling of the muscle BMR can be derived from an argument based on shared blood flow from the heart into main arteries connected to both muscle and viscera.

Presumably, this shared cardio-vascular system causes blood flow during rest in skeletal muscle to be proportional to visceral requirements. Locally this can be mediated by capillary closure owing to pre-capillary sphincter muscles or bypass vessels or shunts, causing muscular $BMR \propto N_1(open)A_1$, for open muscle capillaries, similar to the derivation of Equation 22.

Table 3 Likely causes of notable instances of the symmorphosis $b = D/3$ *

| b | D | w | Occurrence | Likely cause |
|--------------|------|---------|--------------------------------|--|
| 2/3 = 0.67 | 2 | 7/15 | Insectivores | Muscle stress limitation |
| 5/6 = 0.83 | 5/2 | 2/3 | Nonathletic mammals Rodents | Optimal movement by geometric and dynamic similarities |
| 7/8 = 0.88 | 21/8 | 143/200 | Mammals | Mixture of athletic and nonathletic mammals |
| 14/15 = 0.93 | 14/5 | 387/495 | Athletic mammals Lizards | Maximum oxygen delivery |
| 1 | 3 | 6/7 | Snakes | Metabolic rate maximized by maximum fractal dimension |

b: body mass exponent of the MMR relationship

D: fractal dimension of the vascular system

w: body mass exponent of the aorta relationship

* Derived from Lutz *et al.* (1984), Bishop (1999), Weibel *et al.* (2004), Hall (1996), Bartels *et al.* (1969), Norberg (1996), Pough (1977a), and Pough (1977b)

The argument on the derivation of BMR scaling from organ metabolism and body composition can be strengthened by considering the evidence on organ metabolism and body composition in the literature. Furthermore, the unequal body mass distribution of the species in taxa with various instances of general symmorphosis in Table 3, together with possible differences in visceral scaling, could plausibly cause the

appearance of non-rectilinearity in the logarithmic relationship between BMR and body mass observed by Clarke *et al.* (2010) and Kolokotronis *et al.* (2010). These matters will be examined in a manuscript on BMR scaling that is under preparation.

List of symbols

| | |
|-----------|---|
| α | blood vessel cross-section area preserving power exponent |
| A_k | blood vessel cross-section area at level k , $k = 1$ capillary level, $k = n$ aorta level |
| a | body mass power exponent for oxygen half-saturation pressure (P_{50}) |
| b | body mass power exponent for metabolic rate (MR) specified by the context in which it appears as maximum aerobic metabolic rate (MMR) or basal metabolic rate (BMR) |
| CI | 95 % confidence interval |
| D | dimension of the fractal surface or fractal volume, specified by the context in which it appears |
| L_k | blood vessel length at level k , $k = 1$ capillary level, $k = n$ aorta level |
| M | body mass, with parts or whole where necessary indicated by subscripts, m , v , and w indicating skeletal muscle, viscera, and whole body, respectively |
| N_k | number of blood vessels at level k , $k = 1$ capillary level, $k = n$ aorta level |
| V | fractal extent of the vascular system |
| w | body mass power exponent for the aorta cross-section area (A_n) |
| x | body mass power exponent for capillary number (N_1) |
| y | body mass power exponent for capillary length (L_1) |
| z | body mass power exponent for capillary cross-section area (A_1) |
| \propto | proportional to |

Conclusion

It is shown that exercise-induced maximum metabolic rate can be scaled to body mass by the fractal dimension of the vascular distribution network in terms of the relationship $b=D/3$, where b is the exponent of the power relationship of MMR with body mass and D is the fractal dimension of the vascular distribution network. The principle of self-similarity of the vascular system allows the prediction of BMR from MMR and body composition.

Authors' Contributions

Only the named author contributed.

Conflict of Interest Declaration

There are no conflicts of interest.

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