

Revisiting the evolutionary origin of allometric metabolic scaling in biology

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Summary

1. In 1997 West, Brown & Enquist published a theoretical explanation for the long-known empirical observation of 3/4-power scaling of organismal metabolic rates with body mass, using an attractive combination of general physical and physiological principles with evolutionary optimization. This model generated hundreds of studies, exploring its implications for physiology, populations, biodiversity, whole-ecosystem functioning, and even medical, engineering and social sciences.
2. However, the evolutionary optimization part of the model has never been carefully scrutinized.
3. In this article we perform the evolutionary optimization as proposed by the authors rigorously and show that it actually leads to a biologically irrelevant network, i.e. a single vessel.
4. Moreover, we find that by relaxing some assumptions in a realistic way we obtain a feasible network but with isometric scaling of metabolism, which is in conflict with Kleiber's empirical law of an allometric exponent of around 3/4.
5. Hence, we conclude that the West-Brown-Enquist model cannot account for the observed universal metabolic scaling relation.
6. As possible solutions to this paradox, we discuss (weak) body-size dependence of capillary properties (leading to different predictions of intra- and inter-specific metabolic scaling), and expanding the West-Brown-Enquist model to an integrated network model (including body shape and oxygen transport to and from the arterial system). Alternatively, the ultimate explanation for the observed allometric patterns may need to be found outside the framework of flow-limited network theory.
7. We conclude that Kleiber's law is still as theoretically unexplained as ecologically important.

Key-words: allometry, metabolism, optimization, pulsatile flow, transport network

Introduction

Kleiber's empirical law, stating that the basal or resting metabolic rate in organisms is approximately a power law of body mass M , i.e. $B = B_0 M^a$ (with $a \approx 0.75$ and B_0 a normalization constant whose units depend on the value of a), is one of the most intriguing and important allometric relations in ecology. It predicts how larger organisms have an increasingly lower rate of energy use per unit of body mass. Kleiber's law has been found to apply across a wide variety of taxa (Peters 1983; Calder 1984; Schmidt-Nielsen 1984; Savage *et al.* 2004 but see Dodds, Rothman & Weitz 2001; White & Seymour 2003; Bokma 2004 for exceptions), and it has far-reaching

consequences at various levels of biological organization, ranging from organismal physiology, life span and evolution, to whole-ecosystem functioning (Brown *et al.* 2004; Whitfield 2006).

In 1997, West, Brown & Enquist (1997) (WBE) presented an appealing mechanistic explanation for the observed value $a = 0.75$. This led to wide-ranging application of Kleiber's empirical law in many fields of biology, as it was now 'upgraded' to a law based on first principles (Brown *et al.* 2004; Martínez del Río 2008). WBE argued that the whole-organism metabolic rate of animals is constrained by the architecture of their internal transport network, which dictates the rate at which nutrients and oxygen are delivered to the cells. They hypothesized that, for species of different size, evolution through natural selection has resulted in an optimized fractal-like network that has minimal transport costs (energy dissipation) for a

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given flow and amount of transport fluid (blood). Assuming further that the network is 'space filling' to optimally service all cells, they arrived at a predicted value of $a = 3/4$ for the pulsatile blood flow that occurs in mammals and birds.

Unfortunately, the WBE article is written in a highly condensed way where not all steps are fully explained. In a previous article (Etienne, Apol & Olf 2006), we have reformulated and explained the basic structure of the original WBE model and demonstrated that 3/4-power scaling is indeed obtained if the transport network possesses the following four main properties: (1) its capillary size is invariant with body mass, (2) it is space filling, (3) its volume scales linearly with body mass and (4) it shows preservation of cross-sectional area upon branching. In other words, the network must have specific values for some internal network scaling exponents. This moves the problem of explaining metabolic 3/4-power scaling to understanding these key network properties. West and co-workers (West *et al.* 1997, 2000; West 1999; West & Brown 2004, 2005) claimed that the last two properties originate from (evolutionary) optimization, that is, minimizing transport costs (dissipation), and as a consequence minimizing wave reflections. That Kleiber's law is the result of evolution through natural selection operating within the context of universal constraints imposed by basic physical laws is probably the most appealing aspect of the WBE theory. However, this evolutionary basis of the theory has never been thoroughly scrutinized (Dodds *et al.* 2001; Kozłowski & Konarzewski 2004, 2005; Etienne *et al.* 2006), probably because of the difficulty of the mathematics involved and the highly condensed way it was presented.

Here we do so by fully reconstructing the WBE model (West *et al.* 1997), including the optimization part. First we briefly develop the relation between metabolic rate and network scaling properties along the lines presented in Etienne *et al.* (2006). Second, we show how the network properties are obtained via optimization. We present the essential logical steps in the model and fully assess all derivations of West *et al.*, for the first time by explicitly providing the pulsatile dissipation function and performing the corresponding optimization of the network. We find that following the logic and assumptions of the WBE model results in a biologically irrelevant network, i.e. a single vessel. We moreover find that at least five points in this derivation are highly questionable from a physical, physiological and/or logical point of view, but which are nonetheless critical to obtaining 3/4-power scaling of basal metabolism. These points concern the incorrect definition and incomplete optimization of the dissipation function by WBE, the assumed fixed vessel wall-thickness to radius ratio, the space-filling network and WBE's derivation of isometric mass scaling of blood volume. We discuss potential modifications of the model (in the spirit of the robustness analysis advocated by Martínez del Río (2008)), which however opens a Pandora's box of possible metabolic exponents. Hence, the current framework of the WBE model cannot account for the observed universal metabolic scaling relation, and at least a more integrated approach including the modelling of oxygen transport from

the capillaries to the cells and from the external environment to the network is needed. Or, explanations for Kleiber's law have to come from entirely different lines of argument.

WBE network model

In a previous article (Etienne *et al.* 2006), we reformulated the WBE model – except for the optimization part – and rederived its predicted 3/4-power metabolic scaling in terms of network scaling properties in a more straightforward way than in the original article (West *et al.* 1997). To also explore the optimization part, we will now summarize and generalize this scheme. It should be noted that we do not develop a new or different model in this and the previous article (as suggested by Martínez del Río (2008)), but follow exactly the line of argument, and optimization procedure that WBE suggested would lead to 3/4-power scaling. Table 1 provides the conversion between our notation and that of West and co-workers.

Consider an organism with a closed branching transport network consisting of C branching levels (e.g. in vertebrates, level 1 is the aorta, level C is the capillaries, but the principle also applies to other taxa with closed vascular networks). At level k , there are N_k vessels of radius r_k , length l_k , wall thickness h_k , and cross-sectional area $A_k = \pi r_k^2$, in which the transport fluid (blood in vertebrates) flows with average velocity u_k due to a pressure gradient ∇p_k (see Fig. 1). We define several scaling ratios that relate these vessel properties across adjacent branching levels: $v_k \equiv N_{k+1}/N_k$ is the branching ratio, $\rho_k \equiv r_{k+1}/r_k$ the radius or diameter ratio, $\lambda_k \equiv l_{k+1}/l_k$ the length ratio and $\eta_k \equiv h_{k+1}/h_k$ the wall-thickness ratio. We now define the internal network scaling exponents c_r , c_l and c_h by expressing the scaling ratios ρ_k , λ_k and η_k in terms of the branching ratio v_k as

$$\rho_k = v_k^{-c_r} \quad \lambda_k = v_k^{-c_l} \quad \eta_k = v_k^{-c_h} \quad (1)$$

These scaling exponents form the critical connection between the topological dimensions of the network and its spatial dimensions (Mandelbrot 1982), in this case, to what extent does branching reduce vessel diameters, lengths and wall radii in the network. The minus signs are included for convenience since in general $0 < \rho_k, \lambda_k, \eta_k < 1$ and $v_k > 1$.

The metabolic rate of the whole organism B is proportional to the total volume flow Q_{tot} through this network,

$$B = f_0 Q_{\text{tot}} \quad (2)$$

which is the so-called Fick equation (Milnor 1990), where f_0 is the concentration difference of metabolites (oxygen) in the blood between the arteries and the veins (arteriovenous difference). In fact, $f_0 Q_{\text{tot}}$ is precisely the amount of oxygen per unit of time that is disappearing from the arterial system, and hence the respiration rate of the organism, which is proportional to its energy use. WBE assume that f_0 , as well as the capillary properties r_C , l_C , h_C and u_C (their radius, length, wall thickness and average fluid velocity) are independent of body mass. Hence, the body-mass dependence of the total flow,

Table 1. Conversion of notation used in this article to that in West, Brown & Enquist (1997) (WBE), West & Brown (2005) (WB) and Womersley (1955, 1958). Symbols that are not listed either have the same meaning in all the articles, or appear only in this article

Property	This article	WBE	WB	Womersley
Level	$k + 1$	k	k	–
Level range	$k = 1 \dots C$	$k = 0 \dots N$	$k = 0 \dots N$	–
Number of levels	C	$N + 1$	$N + 1$	–
Branching number	v_{k+1}	n_k	n	–
Radius ratio	ρ_{k+1}	β_k	–	–
Length ratio	λ_{k+1}	γ_k	–	–
Metabolic exponent	a	a	b	–
Volume flow	Q_{k+1}	\dot{Q}_k	Q_k	Q
Average fluid velocity	u_{k+1}	\bar{u}_k	–	u
Service volume	$V_{s,k+1}$	–	v_k	–
Capillary number, radius, etc.	N_C, r_C, \dots	N_C, r_C, \dots	N_N, r_N, \dots	–
Lagrange multipliers	$\Lambda_b, \Lambda_k, \Lambda_M$	$\lambda, \lambda_k, \lambda_M$	–	–
‘Viscous function’	$\tilde{\Phi}_k$	$-i(J_0(i^{3/2}\alpha_k)/J_2(i^{3/2}\alpha_k))$	$-i(J_0(i^{3/2}\alpha_k)/J_2(i^{3/2}\alpha_k))$	$i/(1 - F_{10}) = i/M'_{10}e^{Re_{10}}$
(Complex) reflection factor	$\tilde{\Gamma}_k$	–	–	$\Lambda = (1 - \lambda)/(1 + \lambda)$
Complex wave velocity	\tilde{c}_k	c	c	c
Moens-Korteweg $a_{inter} = a_{intra} - \delta$ velocity	$c_{0,k}$	c_0	c_0	c_0
Real wave velocity	$c_{1,k}$	–	–	c_1
Mass density fluid (~wall)	ρ_M	ρ	ρ	ρ

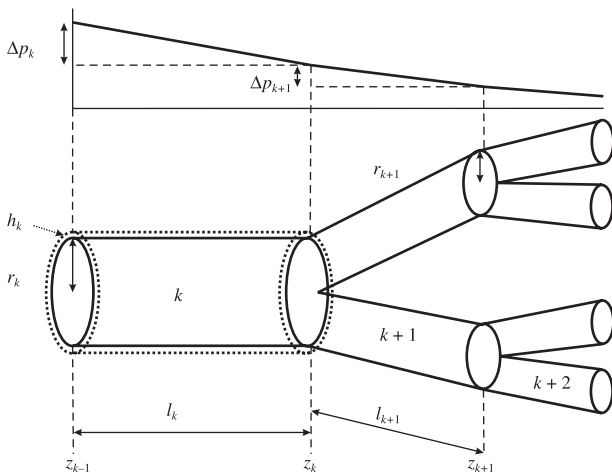


Fig. 1. Schematic representation of a part of the branching transport network (between levels k and $k + 2$), with corresponding notation for a vessel at level k of its radius r_k , length l_k , wall thickness h_k and axial position z_k of the branching point at the end of the vessel.

$$Q_{tot} \equiv N_C \pi r_C^2 u_C \tag{3}$$

and therefore also the body-mass dependence of the metabolic rate, is determined by the body-mass dependence of the number of capillaries N_C . Unfortunately, no straightforward theoretical predictions or good observational data are available for this dependency, as this would directly yield the ‘true’ flow-limited scaling of metabolism with body size. However, because the number of capillaries is subject to topological and geometrical constraints from the network (e.g. every group of capillaries must be supported by a larger vessel, that is again supported by a vessel, etc. up to the aorta), the body-mass dependence of

N_C can be evaluated from some other global property of the network, of which we do know its body-mass dependence experimentally and/or theoretically. In the WBE model, the total blood volume contained in the network $V_b \equiv \pi \sum_{k=1}^C N_k r_k^2 l_k$ is taken for this purpose. With eqn 1 it follows after some straightforward algebra (Appendix S1 in Supporting Information) that the number of capillaries N_C can be expressed in terms of body mass (via the blood volume V_b), the internal scaling exponents (c_r and c_l) and the capillary dimensions as

$$N_C = \left(\frac{V_b}{\pi r_C^2 l_C S_3} \right)^{\frac{1}{2c_r + c_l}} \tag{4}$$

where $S_3 \equiv \sum_{k=1}^C N_k^{-2c_r + c_l - 1}$ is a generalization of the topological S_3 -property (Etienne *et al.* 2006, see Appendix S1), which is just a number in the order of unity that depends on the scaling behaviour of the network (see also Fig. S1). We furthermore assume that blood volume V_b scales allometrically with body mass,

$$V_b = V_{b0} M^b \tag{5}$$

and that the topological property S_3 is approximately independent of body mass (Etienne *et al.* 2006). The latter requires that $2c_r + c_l - 1 > 0$ so that S_3 quickly saturates with increasing number of levels k (Appendix S1). Therefore, the mass dependence of the total volume flow within the network and thus of the metabolic rate is defined through the mass dependence of the blood volume. Hence combining eqns 2, 3 and 4 with the above assumptions, the metabolic rate of the organism is given by

$$B = B_0 M^a \tag{6}$$

where the metabolic scaling exponent a is determined just by two network scaling exponents and by b as

$$a \equiv \frac{b}{2c_r + c_l} \quad (7)$$

The normalization constant (the intercept of Kleiber's law, which was not explored by WBE) depends both on the network scaling exponents and on the properties of the capillaries,

$$B_0 \equiv \pi r_c^2 u_c f_0 \left(\frac{V_{b0}}{\pi r_c^2 l_c S_3} \right)^{\frac{1}{2c_r + c_l}} \quad (8)$$

West *et al.* (1997) assumed $c_l = 1/3$ (space-filling network, based on the argument of spatial efficiency of the network), and argued that optimization of the network leads to $b = 1$ (isometric scaling of blood volume with body mass) and $c_r = 1/2$ (preservation of cross-sectional area). If these values are assumed, $a = 3/4$ is obtained as in Kleiber's law (Etienne *et al.* 2006). However, as we will show next, there are severe problems with deriving these values by optimization of the network.

Network parameters from optimization

WBE assume that the process of evolution via natural selection has resulted in organisms with minimum maintenance costs required for their size thus maximizing energy available for growth and reproduction. To overcome the very slow process of diffusion over distances larger than ~ 1 mm, a convective transport network is an effective solution (Calder 1984). The design of the transport network is likely to be evolutionarily optimal with respect to both costs and efficiency. With regard to the costs, West and co-workers therefore posed the plausible hypothesis that evolution for organisms of different size has resulted in a network that requires minimal transport costs per unit of flow and per unit of body mass to deliver oxygen and metabolites to the cells (West *et al.* 1997, 2000; West 1999; West & Brown 2005). This means that the dimensions of the vessels (all N_k , r_k , l_k and h_k) – or rather, their scaling behavior within the network (the exponents c_r , c_l and c_h) – are assumed to follow from minimizing the energy dissipation during transport. Yet, a network could be optimally designed with a certain internal scaling behavior to minimize transport costs but with an inefficient spatial arrangement of the (terminal) units (capillaries) that must deliver the metabolites to the cells (see Fig. 2a). Therefore, besides transport costs also the spatial efficiency has to be considered: the network has to be optimally embedded within the body volume with the capillaries spanning the whole three-dimensional volume to reduce diffusion distances (see Fig. 2b). To ensure this, WBE hypothesize that an optimal network is 'space filling'. A group of cells that receives oxygen and nutrients from a single capillary is called a 'service volume' $V_{s,c}$ (West *et al.* 1997). If the capillaries are spatially arranged in a specific way to maximize supply efficiency, the vessels at branching level $C - 1$ (one step before the capillaries) must be spatially arranged approximately in the same way, because both levels are

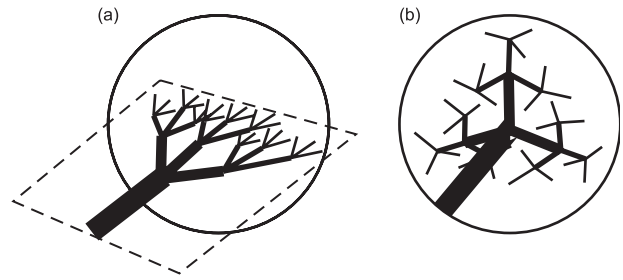


Fig. 2. Schematic view of an optimal network with minimal transport costs but inefficient spatial arrangement (a) and its efficient embedding into the whole body volume (b).

physically connected at the branching points. The same reasoning applies to the arrangement of vessels of levels $C - 2$, $C - 3$, etc. This spatial relation means that the N_{k+1} service volumes of level $k + 1$ occupy approximately the same volume as the N_k service volumes of level k or any other level. Hence, via the argument of spatial efficiency of resource delivery, the properties of the service volume of the capillaries yield a specific relation between the network scaling parameters: the total service volume $X_k \equiv N_k V_{s,k}$ is constant.

WBE argue that because $r_k \ll l_k$, the vessel length is the only length scale relevant for spatial efficiency, so that the volume occupied per vessel should scale as a sphere with vessel length as its diameter, so $V_{s,k} \propto l_k^3$; hence optimal space filling of the network is equivalent to (approximate) preservation of the total 'service volume' per level $X_k = N_k l_k^3$ across all levels. From eqn 1 one can easily see that this implies that $c_l = 1/3$. WBE use this relation as an additional constraint during the cost minimization procedure (West *et al.* 1997, 2000; West 1999).

Apart from the preserved service volume X_k in the network, also some other quantities must be constrained during the optimization. First, the total net volume flow Q_{tot} through the network is assumed fixed so that the goal function (i.e. transport costs or energy dissipation) per unit of flow is optimized. Second, the body volume and mass of the organism are assumed fixed. Third, because we want to find the optimal arrangement of the network within this volume, the total size of the network (which is related to body mass) must be fixed. A suitable proxy of network size is the blood volume V_b . Optimization of the dissipation function with all these constraints is accomplished via the method of Lagrange multipliers (see Appendix S3).

To derive an expression for the energy dissipation function (force \times velocity = pressure difference \times flow), we need a mathematical description of the blood flow through the network. This flow through the cardiovascular system of mammals, birds and other vertebrates is quite complicated, because of the discrete pumping of the heart (Caro *et al.* 1978). Apart from a steady pressure gradient $-\nabla p_k^s = \Delta p_k^s / l_k$ per level k that drives steady Poiseuille flow Q_k^s (Milnor 1989, Nichols & O'Rourke 2005), the pumping of the heart also generates an oscillating (pulsatile) pressure wave, with

accompanying pressure gradient wave $-\nabla p_k^p(t, z)$ and resulting pulsatile flow wave $Q_k^p(t, z)$ that depend on time t and spatial position z (see Fig. 1). The superscripts ‘s’ and ‘p’ denote steady and pulsatile, respectively.

The mathematical solution of pulsatile flow through a blood vessel with elastic walls caused by an applied sinusoidal pressure wave was first solved completely by Womersley (Milnor 1989, Nichols & O’Rourke 2005) by linearizing the Navier-Stokes equations, coupled to the dynamics of the vessel walls (see Appendix S2). The character of the flow is captured by the Womersley number $\alpha_k \equiv r_k \sqrt{\rho_M \omega / \mu}$, where ω is the angular frequency of the heart beat and ρ_M and μ the density and viscosity of the blood (Caro *et al.* 1978; Milnor 1989; Nichols & O’Rourke 2005; see also Appendix S2): for $\alpha_k \gg 1$ (e.g. in the aorta), the flow is strongly pulsatile, and the fluid oscillates more or less like a solid core; for $\alpha_k < 1$ (e.g. in the capillaries), the flow is quasi-steady with a parabolic velocity profile. Because of the wave character of pressure and flow, (partial) reflection of the forward waves may occur at branching points in the network, because in general the characteristic impedances \tilde{Z}_C at both sides of the junction are different (Milnor 1989; Nichols & O’Rourke 2005). A network with an architecture causing strong reflections will be highly inefficient (large dissipation). The degree of reflection is expressed by the reflection factor $\tilde{\Gamma}_k$, the ratio of the backward and the forward pressure wave at the junction (Appendix S2).

Using the linearized Navier-Stokes equations, we find that the total energy dissipation within the network is the sum of the steady and pulsatile components: $W_{tot} = W_{tot}^s + W_{tot}^p$ (Appendix S2). In general, the dissipation per unit length is given by the product of driving force (pressure difference $-\nabla p_k dz$) and flux (volume flow Q_k) per vessel times the number of vessels N_k (Milnor 1989). This must be averaged over one period of oscillation $2\pi/\omega$ (accomplished by multiplying the complex pressure gradient by the complex conjugate of the volume flow and taking one half of the real part), and integrated over the length of each vessel (from z_{k-1} to $z_k = z_{k-1} + l_k$, see Fig. 1):

$$W_{tot} = \sum_{k=1}^C N_k \int_{z_{k-1}}^{z_{k-1}+l_k} \frac{1}{2\pi/\omega} \int_0^{2\pi/\omega} -\nabla p_k(t, z) Q_k(t, z) dt dz \tag{9}$$

$$= \frac{1}{2} \sum_{k=1}^C N_k \int_{z_{k-1}}^{z_{k-1}+l_k} \text{Re}[-\nabla \tilde{p}_k(t, z) \tilde{Q}_k^*(t, z)] dz$$

Complex quantities (Appendix S2) are indicated by a tilde (\sim). For steady flow, where $-\nabla \tilde{p}_k = \Delta p_k / l_k$ and \tilde{Q}_k are both real and independent of time and position in the vessel, eqn 9 correctly reduces to the familiar expression for Poiseuille flow (Fung 1984; Milnor 1989; West *et al.* 1997; Nichols & O’Rourke 2005)

$$W_{tot}^s = \sum_{k=1}^C W_{tot,k}^s = \sum_{k=1}^C N_k \Delta p_k Q_k = \left(\frac{8\mu}{\pi} \right) (Q_{tot})^2 \sum_{k=1}^C \frac{l_k}{N_k r_k^4} \tag{10}$$

The pulsatile component of the dissipation is much more complicated. Evaluating the integral in eqn 9 (Appendix S2), we finally arrive at

$$W_{tot}^p = \sum_{k=1}^C \frac{\pi(1 - \sigma^2)\omega |\tilde{P}_C|^2}{E} \frac{N_k r_k^3 l_k}{h_k} \frac{\text{Re}[\tilde{\Phi}_k]}{|\tilde{\Phi}_k|} \times \Psi_k^{(C)} \tag{11}$$

$$\Psi_k^{(C)} \equiv \frac{1 - 2\cos(\theta_{\Gamma,k}) e^{-2a_k l_k} |\tilde{\Gamma}_k| + e^{-4a_k l_k} |\tilde{\Gamma}_k|^2}{\prod_{m=k}^{C-1} e^{-2a_m l_m} (1 + 2\cos(\theta_{\Gamma,m}) |\tilde{\Gamma}_m| + |\tilde{\Gamma}_m|^2)} \tag{12}$$

In this expression, $|\tilde{\Gamma}_k|$ and $\theta_{\Gamma,k}$ are the absolute value and phase of the reflection factor $\tilde{\Gamma}_k$ and a_k is the damping factor of the attenuated pressure wave; the amplitude of the wave is damped by a factor $e^{-a_k l_k}$ when traveling a distance l_k . Furthermore, $|\tilde{P}_C|$ is the oscillatory pressure amplitude at the beginning of the capillaries (which can also be expressed in terms of the initial pressure amplitude at the beginning of the aorta $|\tilde{P}_1|$ see Appendix S2), and σ and E are the Poisson ratio and Young’s modulus. On the one hand, the energy dissipation depends directly on the vessel dimensions N_k, r_k, l_k and h_k at each level k ; also the damping factors a_k and $\tilde{\Phi}_k \equiv -iJ_0(i^{3/2}\alpha_k) / J_2(i^{3/2}\alpha_k)$ are functions of the Womersley number α_k and hence of r_k (Appendix S2). On the other hand, the reflection factors $\tilde{\Gamma}_k$ of level k are not only functions of the properties N_k, r_k and h_k of the same level, but also of those of the next level, N_{k+1}, r_{k+1} and h_{k+1} , and so they are functions of the scaling ratios v_k, ρ_k and η_k (Appendix S2).

The relative contribution of the steady and pulsatile parts of the energy dissipation per level ($W_{tot,k}^s$ and $W_{tot,k}^p$) changes from the aorta ($k = 1$) via the larger arteries to the microcirculation and finally the capillaries ($k = C$). At the aortic side of the network, the pulsatile contribution dominates, whereas at the capillary side the steady contribution is most important (Lighthill 1975; Fung 1984; West *et al.* 1997). This is partly due to damping of the pressure waves (attenuation) in the vessels, and also due to the change of pulsatility of the oscillating flow (the magnitude of α_k) because the vessel radius decreases in the direction of the capillaries. The part of the network that contributes most to the total blood volume is the aortic side (West *et al.* 1997; Etienne *et al.* 2006); this is linked to the fact that the cumulative S_3 -function quickly saturates with increasing k (eqn 4 and Appendix S1, Fig. S1), meaning that the capillaries contribute relatively little. Hence, the internal network scaling exponents c_s and c_p , that are important for the metabolic scaling a (eqn 7), are virtually only determined by the aortic side of the network. During the optimization procedure, we will therefore consider only the pulsatile part of the dissipation in the limit of large Womersley number, corresponding to the conditions at the aortic side.

We use the analogy with electrical transmission-line theory (Taylor 1957; Milnor 1989; West *et al.* 1997; West 1999; West & Brown 2005) that suggests that elimination of wave reflections is a necessary (but not sufficient) condition to minimize energy loss. We therefore perform the minimization in two stages. In the first stage, we minimize the dissipation with respect to the reflection factor (that is a function of v_k, ρ_k and η_k), both its amplitude and phase. In the second stage, we further optimize the remaining dissipation function with respect to the vessel dimensions N_k, r_k, l_k and h_k , taking into account the constraints that follow from the first stage.

In stage 1, by focussing on the dissipation per level, starting from the capillary side and working backwards to the aorta, we find in general for any α_k and any level k that absence of wave reflections ($|\tilde{\Gamma}_k| = 0$) is the (partial) minimum (see Appendix S5). So indeed we confirm the result of West *et al.* (1997) that, when the network is built in such a way that there are no wave reflections, the pulsatile dissipation function is for a large part minimized. For the aortic side of the network (whose scaling properties predict the metabolic exponent a), it can be shown that the condition of zero wave reflections in the limit $\alpha_k \rightarrow \infty$ gives rise to the additional constraint $v_k \rho_k^{5/2} \eta_k^{-1/2} = 1$, that can be formulated in terms of a new quantity X_k^\dagger that is preserved across all levels of the network,

$$X_k^\dagger \equiv N_k r_k^{5/2} h_k^{-1/2} = \text{constant} \quad (13)$$

By analogy with transmission line theory, the same result can also be obtained by impedance matching (Milnor 1989; Appendix S2), i.e. by equating the total characteristic impedances \tilde{Z}_C at levels k and $k+1$: $\tilde{Z}_{C,k} = \tilde{Z}_{C,k+1}/v_k$ (Milnor 1989, Appendix S5). For large Womersley number α_k these impedances $\tilde{Z}_{C,k} \propto c_{0,k}/N_k r_k^2$ are real, where $c_{0,k}$ is the Moens-Korteweg velocity $c_{0,k} \propto r_k^{-1/2} h_k^{1/2}$ (Milnor 1989; Papageorgiou *et al.* 1990; West *et al.* 1997; Nichols & O'Rourke 2005; Appendix S2). Combining these three relations directly gives eqn 13.

In stage 2 of the optimization process, we minimize the pulsatile energy dissipation function under the condition of zero wave reflections (from the first stage) with the constraints of fixed body mass, fixed blood volume and fixed service volume $X_k = N_k l_k^3$. To account for the extra relation between N_k , r_k and h_k because of the absence of wave reflections as obtained in the first stage, we have to include preservation of X_k^\dagger (eqn 13) as an additional constraint in the second optimization process (see Appendix S5). WBE (1997, 2000) do not take this second step. Instead, they state that the wall thickness is a fixed proportion of the vessel radius, so h_k/r_k is (at least in the aortic side of the network) assumed to be a constant. They provide no theoretical or empirical evidence for this assumption. With their additional assumption, the three internal scaling exponents c_r , c_l and c_h are fully defined by the three network constraints: space filling (so $c_l = 1/3$), zero wave reflections (so $5c_r - c_h = 2$), and a constant ratio h_k/r_k (so $c_r = c_h$). This yields $c_r = 1/2$, which implies that $a = 3/4$ in agreement with Kleiber's law; see case A in Fig. 3.

However, there are several essential steps in this derivation that need further scrutiny. In the following section, we discuss five critical assumptions of the model.

Critical assumptions

NO FULL OPTIMIZATION OF PULSATILE DISSIPATION

As shown earlier (which we shall call case A), the combination of three assumptions: space filling, zero wave reflections, and constant ratio h_k/r_k directly leads to the prediction $a = 3/4$, and WBE end their analysis here. However, only one aspect of

the energy dissipation function (wave reflections) has been taken into account so far, and the dissipation is only partly optimized. This partial optimization merely fixes three out of four internal scaling exponents, so that ρ_k , λ_k and η_k can only be expressed in terms of the unknown branching ratio v_k . The optimal branching ratio can be obtained by further minimizing the remaining dissipation function (already without wave reflections) with respect to all N_k , r_k , l_k and h_k using Lagrange multipliers, which is the second optimization stage.

Performing this further optimization (see Appendix S5), one obtains the remarkable result that the optimal branching ratio is $v_k = 1$, and so in other words, the optimal network is not a network anymore, but simply a single very long vessel that permeates the body (with $N_k = N_C = 1$, $r_k = r_C$, $l_k = l_C$ and $h_k = h_C$ for all k). As this solution has many physiological drawbacks (e.g. bad supply of nutrients because of small concentration gradient across the vessel wall in much of the body, small fluid velocity, sensitivity to damage or obstruction), it constitutes a biologically irrelevant solution that is not observed in real transport systems. Moreover, because the number of capillaries (that is essential for predicting metabolic scaling) is always one, independent of body mass, the metabolic exponent is $a = 0$ (see case B in Fig. 3): all organisms are predicted to have the same metabolic rate. This is in strong contrast to the (incomplete) result of WBE that $a = 3/4$. Although it is tempting to dismiss this second optimization stage because its final outcome does not at all correspond to Kleiber's law, this is not justified within the framework of the WBE model. The single vessel is e.g. still perfectly 'space filling' according to WBE's geometrical definition, does not have wave reflections, is area preserving ($c_r = 1/2$), and has minimal dissipation.

As stated, WBE did not perform this further optimization. However, there is no reason why evolution should stop at a partially optimized network, adjusting only a subset of network dimensions. Only if there are additional constraints making further optimization impossible, minimizing wave reflections may be sufficient. No such additional constraints are offered by WBE.

FORM OF THE PULSATILE DISSIPATION FUNCTION

In our reconstruction of the WBE model, we have used the pulsatile dissipation function defined in eqn 9, i.e. the average product of pressure gradient and flow. This formulation correctly converges in the limit $\alpha_k \rightarrow 0$ (i.e. $\omega \rightarrow 0$) to the expression of steady Poiseuille flow, eqn 10 (see Appendix S2). West and co-workers (West *et al.* 1997, 2000; West 1999; West & Brown 2005) do not provide an explicit expression for their dissipation function, but West & Brown (2005) state that the pulsatile dissipation is proportional to the real part R of the (characteristic) impedance, \tilde{Z}_C . From this we infer that they must have used the average product of pressure and flow,

$$W_{\text{tot}}^p |_{\text{WBE}} = \frac{1}{2} \sum_{k=1}^C N_k \frac{1}{l_k} \int_{z_{k-1}}^{z_{k-1}+l_k} \text{Re}[\tilde{p}_k^p(t, z) \tilde{Q}_k^{p*}(t, z)] dz \quad (14)$$

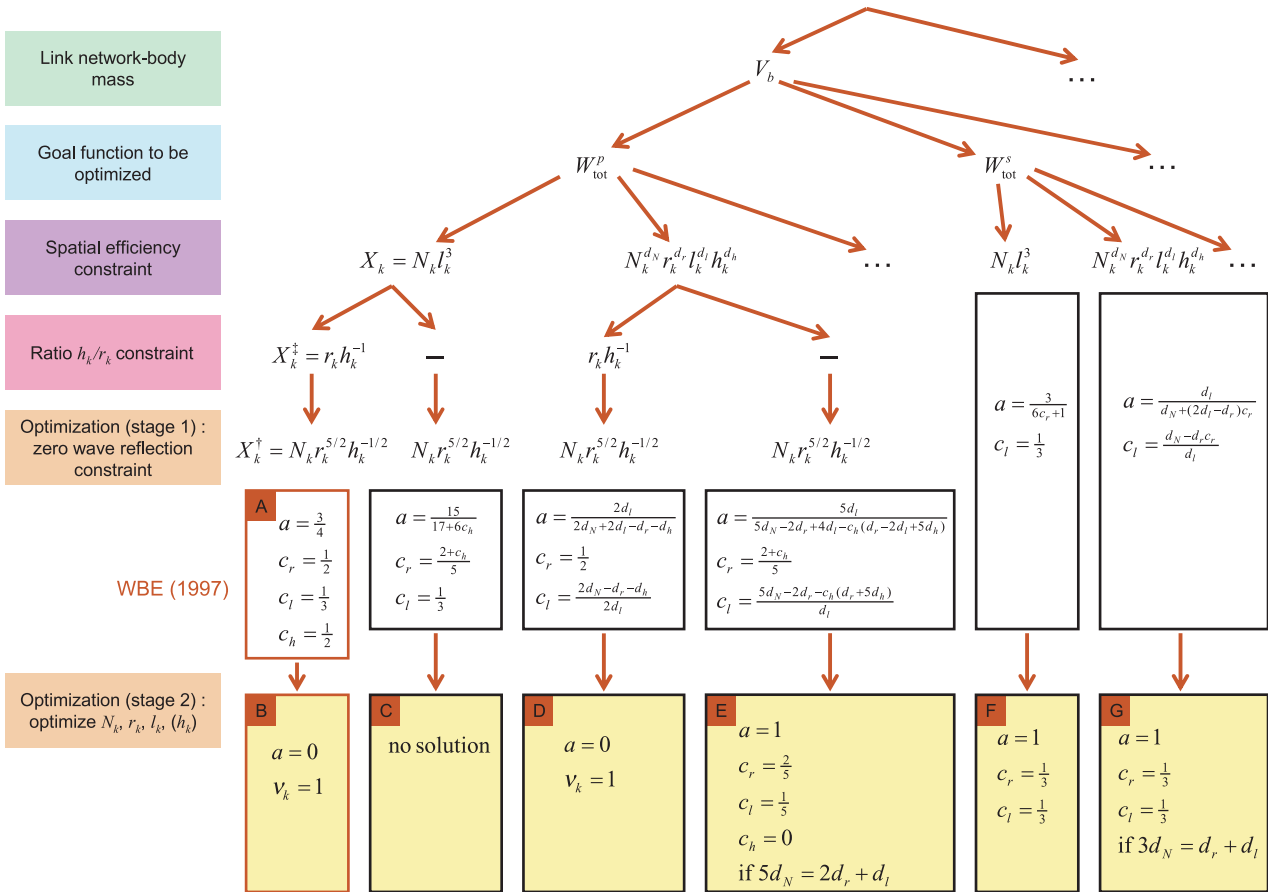


Fig. 3. Flow diagram of possible constraints within the class of network models that includes the WBE model. White boxes represent partial solutions of the internal scaling exponents c_r , c_l , c_h and the prediction of the metabolic exponent a solely based on the constraints; yellow boxes (B–G) represent full solutions. Cases A–E correspond to pulsatile dissipation, whereas cases F and G correspond to steady (Poiseuille) dissipation.

Case A: By not performing the second stage of the optimization of pulsatile dissipation (so only partially optimizing transport costs, but still assuming h_k/r_k constant and geometrical space filling) one arrives at $a = 3/4$ in accordance with experiment. This is the case described by West *et al.* (1997, 2000).

Case B: If one does perform this second stage of optimization, the solution is a biologically irrelevant network with $v_k = 1$ and therefore $a = 0$.

Case C: If one drops the assumption that h_k/r_k is a constant, not all internal scaling exponents are fully defined anymore. Further optimizing all vessel dimensions N_k , r_k , l_k and h_k (stage 2) however yields no optimal solution (Appendix S5). Yet, by only optimizing any three out of four vessel dimensions, e.g. N_k , r_k and h_k , one obtains from minimization a metabolic exponent $a = 15/17 \approx 0.88$ (Appendix S5). Interestingly, this value is very close to the allometric exponent of maximal metabolic rate (Hoppeler & Weibel 2005) and suggests that evolution has aimed to optimize the network for metabolism at its maximum. However, it seems rather arbitrary not to optimize one of the vessel properties.

Case D: If we use the generalized space filling constraint instead of the geometrical one, and assume h_k/r_k to be constant, we again obtain after full minimization of the transport costs an optimal ‘network’ consisting of only a single vessel, leading to $a = 0$.

Case E: By only assuming generalized space fitting, we obtain this interesting alternative solution to the WBE model, that is in fair agreement with anatomical data (Schneck 2000), but predicts $a = 1$.

Cases F and G: Interestingly, for steady Poiseuille dissipation the optimizations with the geometrical and generalized space-filling model yield identical results for c_r , c_l , and a . This follows from the fact that the space-filling exponents are related as $d_r + d_l = 3d_N$, which is indeed compatible with WBE’s space filling definition (Appendix S4).

because this reduces to $W_{tot}^p |_{WBE} \propto (Q_k^{p,rms})^2 \text{Re}[\tilde{Z}_{Ck}]$ in the absence of wave reflections (see Appendix S2), which then corresponds to the expression $Q^2 R$ given by West *et al.* (2000).

There are several problems with eqn 14. First of all, it does not reduce to Poiseuille dissipation when the frequency of the waves ω goes to zero. Second, even if for the sake of argument we would accept eqn 14 as correct, the claim of West *et al.* (1997, 2000) that minimizing this dissipation leads to constant h_k/r_k , is incorrect (Appendix S6, and also see below). Third, WBE merely state that zero impedance matching occurs in

the network (i.e. wave reflections vanish), whereas we show that it follows logically from minimization of the correct dissipation function, eqn 9.

FIXED WALL-THICKNESS TO RADIUS RATIO

West and co-workers (West *et al.* 1997, 2000; West 1999; West & Brown 2005) use the fact that the ratio h_k/r_k is constant (or equivalently, that $c_r = c_h$). Although the authors suggest that this follows directly from the network optimization procedure

(West *et al.* 1997, 2000), this is not the case (see Appendix S6). This assumption is, however, very critical; without it, the desired preservation of cross-sectional area ($c_r = 1/2$) does not follow from minimizing wave reflections (or – equivalently – from impedance matching).

In the hemodynamic literature (see e.g. Brown 1993), a majority of authors (e.g. Karreman 1952; Womersley 1958; Gosling *et al.* 1971) advocate the assumption of constant wall-thickness (i.e. $c_h = 0$), in contrast to the assumption of constant ratio of radius to wall thickness ($c_h = c_r$). The latter model is equivalent to assuming that the complex wave velocities – or for large Womersley number, the Moens-Korteweg velocities – are equal on both sides of a branching point in the network. This could be derived in principle on physical grounds, by assuming that the flow, pressure and pressure gradient are continuous at such branching points (see Appendix S2). Yet, this is a very unusual and strong assumption, as normally only pressure and flow are considered to be continuous (Caro *et al.* 1978; Fung 1984; Milnor 1989; Nichols & O'Rourke 2005). A much more satisfactory way to obtain the relation between vessel radius and wall thickness is as the result of the network optimization procedure (the second stage), not as an independent assumption. And if it has to be assumed then constant h_k/r_k is not supported by the literature on the subject.

SPACE-FILLING NETWORK

The value of the final metabolic exponent $a = 3/4$ also depends critically on setting $c_l = 1/3$, i.e. on the geometric concept of space filling as the best spatial arrangement of the network to service all cells in a three-dimensional shape. However, there are several difficulties with this concept.

First, the validity of the space-filling constraint $X_k \equiv N_k I_k^3 = \text{constant}$ is likely to be not very accurate for small values of k (as also confirmed by West *et al.* 1997), which is exactly the part of the network (the aortic side) that is the focus of the optimization procedure and hence strongly influences the predictions of the metabolic exponent.

Second, as we have discussed previously (Etienne *et al.* 2006), there are various criticisms of this space-filling concept (e.g. Kozłowski & Konarzewski 2004, 2005; Brown, West & Enquist 2005), and we therefore concluded that WBE's definition of service volume must merely be regarded as a geometrical, not a physiological one. In fact, as Kozłowski & Konarzewski (2004, 2005) pointed out, because the capillary properties are assumed to be invariant, the total occupied and serviced volume seems to scale as $N_C \propto M^a$ with $a \approx 3/4$. This would imply that not the whole body volume (that scales as M^1) is serviced, or that service volumes are overlapping for organisms of small body size. West and co-workers (Brown, West & Enquist 2005) countered that the true service volume includes a prefactor $\chi \propto M^{1/4}$ that only depends on the body mass, so that $X_C \equiv N_C V_{s,C} = \chi N_C I_C^3 \propto M^{1/4} M^{3/4} = M^1$. Because M is the same for all levels in the network of a specific organism, this prefactor χ drops out of the space-filling constraint during optimization of an organism of given

mass. This however means that there is no indication that the physiological service volume per capillary should be proportional to I_C^3 (Etienne *et al.* 2006). Therefore, we propose to use a constraint of a more general form: an across-level preserved quantity $X_k \equiv N_k^{d_N} r_k^{d_r} I_k^{d_l} h_k^{d_h}$ that has enough flexibility to mimic a more realistic service volume; the allowed values of the as yet unspecified exponents d_N , d_r , d_l and d_h follow directly from the optimization procedure. Among these allowed preserved quantities X_k (i.e. among the allowed values of d_N , d_r , d_l and d_h), there may be a more physiologically defined and meaningful service volume.

ISOMETRIC SCALING OF BLOOD VOLUME

A final issue concerns the derivation of isometric scaling of blood volume with body mass, or $b = 1$. West *et al.* (1997, 2000) derive this crucial scaling exponent from optimization of the steady (Poiseuille) dissipation W_{tot}^s . Indeed, isometric scaling of blood volume follows from optimizing a network with steady flow at all levels (Appendix S4), but its application to the mammalian system is incorrect. WBE argue that steady dissipation forms the largest contribution to the cardiac output. At the same time, they state that it is dominant only in the capillary part of the network, whereas the largest contribution to the blood volume comes from the aortic side with pulsatile flow and different internal scaling exponents. It is therefore not correct to use the result of steady dissipation also for the pulsatile part of the network, as optimization of pulsatile dissipation does not lead to isometric scaling of blood volume (Appendix S5). This means that the claim that $V_b \propto M$ can be derived theoretically is unjustified.

There is however empirical evidence for this isometric scaling. Experimental data of mammals and birds show that total blood volume V_{blood} within the body scales isometrically with body mass: $V_{\text{blood}} \propto M^{1.0 \pm 0.01}$ (Peters 1983; Calder 1984), blood being roughly 7% of the body mass in mammals and 9% in birds (Calder 1984). Yet, the total blood volume V_{blood} not only includes V_b (the volume of the arterial network between the heart and the capillaries), but also the venal part (capillaries back to the heart) and the pulmonary part of the network (heart to lungs and lungs to heart). Unfortunately, there are virtually no experimental data on the distribution of blood over these four different parts of the circulation as a function of body mass: for a dog about 16% of the blood volume is located between the heart and the capillaries and it is generally assumed that this is the same in man (Milnor 1989). This suggests that this percentage is roughly mass independent, so that indeed $V_b \propto V_{\text{blood}} \propto M^{1.0}$ or $b \approx 1.0$. Still, isometric scaling of blood volume is an additional empirical assumption rather than a property that follows from optimization (or 'first principles').

RELAXING ASSUMPTIONS

In this article, we have discussed several problems with the network model of West *et al.* (1997). We conclude that the procedure advocated but not performed by WBE (fully minimizing pulsatile dissipation with geometric space filling and

h_k/r_k assumed constant) actually leads to a biologically irrelevant network (case A). Here we briefly present the consequences of relaxing some of the constraints; the various possibilities are summarized in Fig. 3 (cases A to E). For completeness, results for steady (Poiseuille) flow optimization are also included (cases F and G), although this is not the dominant component of the energy dissipation at the aortic side of the network.

Of all possibilities, case E is the most interesting one: if we minimize pulsatile dissipation with the generalized space filling constraint outlined above without imposing that h_k/r_k is a constant (for which there is no evidence), we do find an optimal network with $c_r = 2/5$, $c_l = 1/5$ and $c_h = 0$, which implies that $a = 1$. This result is independent of the choice of service volume model (the exponents d_N , d_r , d_l and d_h), as long as $2d_r + d_l = 5d_N$ (for example, when the service volume is given by $X_k = N_k r_k^2 l_k h_k$, $X_k = N_k r_k^3 l_k^3$ or $X_k = N_k r_k^3 l_k^{-1}$). Note that the geometrical space-filling constraint of West *et al.* (1997) is not compatible with such an optimal network for strong pulsatile flow (therefore case C has no solution). It is also worth mentioning that since $a = 1$ (isometric metabolic scaling), there is no inconsistency any more between the body mass scaling of the body volume and the total service volume, so the prefactor of the service volume $\chi \propto M^0$.

Interestingly, the value $c_r = 2/5$ has also been obtained by Bengtsson & Edén (2003) using a different network model, and they show that this value is perfectly compatible with human anatomical data (Schneck 2000). The value of c_l is also in fair agreement with these data. The optimization procedure directly provides the relation between h_k and r_k , i.e. constant wall thickness, i.e. $c_h = 0$ (at least in the aortic part of the network), that is also corroborated by experimental data for the first few levels (Schneck 2000). Furthermore, the predicted mass scaling exponents of the aortic radius and length are also in good agreement with experimental data (see Table 2). For case E and the WBE model, the scaling exponents for the radius are even virtually identical. Another interesting quantity is the total cross-sectional area ratio, $K_{A,k} \equiv N_{k+1} A_{k+1} / N_k A_k = v_k^{1-2c_r}$. WBE obtain with $c_r = 1/2$ an area ratio $K_{A,k} = 1$. Instead, for case E we find $K_{A,k} \approx 1.15$ for a branching ratio $v_k = 2$. This is in close agreement with the data on arteries by Suwa and co-workers ($K_{A,k} \sim 1.19$, Suwa *et al.* 1963; Milnor 1989) and Papageorgiou and co-workers ($K_{A,k} \sim 1.14$, Papageorgiou *et al.* 1990; Brown 1993), all favouring the constant wall-thickness model.

Finally, the minimization procedure for case E predicts isometric scaling of the blood volume with body mass ($b = 1$), if the space-filling exponents d_N , d_r , d_l and d_h satisfy $d_l = d_N - 2d_h - 2$, $d_r = 2d_N + d_h + 1$, $d_N \neq 0$ (see Appendix S5). Clearly, WBE's geometrical space-filling constraint ($N_k l_k^3 = \text{constant}$) does not meet these requirements.

Although various properties of the network are in line with data in case E, it does not yield the observed $a = 3/4$, but instead $a = 1$. This creates a paradox that we will discuss next.

Discussion and conclusions

We have presented theoretical evidence that full optimization along the logic of the WBE model leads to an irrelevant network with $a = 0$. By slightly relaxing assumptions on spatial efficiency and wall thickness, isometric scaling ($a = 1$) of organismal metabolic rate with body mass is predicted (case E), with network scaling parameters that are in agreement with measurements. However, observations on the allometric scaling exponent of basal metabolic rate are centered in the range $a = 0.65 - 0.75$ (Peters 1983; Calder 1984; Schmidt-Nielsen 1984; White & Seymour 2003; Savage *et al.* 2004). This large discrepancy between theoretically predicted and observed values creates a serious paradox. First we assess the possibilities to reconcile our prediction that $a = 1$ with its observed values, while remaining within the WBE framework of network models, i.e. assuming that metabolic rate is limited by resource supply through the internal transport network (supply limitation). Second, we discuss possibilities to generalize the framework. Third, we briefly discuss alternative explanations for allometric scaling of metabolism when this framework would be rejected.

Is it possible to reconcile our prediction that evolutionary optimization leads to $a = 1$ with the apparently conflicting observational evidence that $a = 0.65 - 0.75$, while remaining within the framework of supply-limited network models? This is indeed possible if intra- and inter-specific allometric scaling are different, where the solution may lie in predictable differences between species in the quantity B_0 . Let a_{intra} be the intra-specific scaling exponent, and a_{inter} be the scaling exponent across species. If the evolution optimizes the network only among individuals within species (as this is where natural selection operates), then $a_{\text{intra}} = 1$ is predicted

Property	Mass exponent		Experimental	References
	Case E	WBE		
Radius r_1	2/5 = 0.40	3/8 = 0.38	0.34	(Peters 1983)
			0.36	(Calder 1984)
			0.41 ± 0.01	(Schmidt-Nielsen 1984)
			0.43 ± 0.03	(Milnor 1989)
Length l_1	1/5 = 0.20	1/4 = 0.25	0.28	(Calder 1984)
			0.32	(Calder 1984)
			0.32	(Peters 1983)

Table 2. Body-mass dependence of aortic properties. The predicted mass exponents are $ac_r = bc_r/(2c_r + c_l)$ for radius, and $ac_l = bc_l/(2c_r + c_l)$ for length (see Appendix S1) where we assume $b = 1$. Experimental values of scaling exponents from Schmidt-Nielsen (1984) and Milnor (1989) were obtained by log-log regression

for every species. In that case, average metabolic rates across species can still scale allometrically with body mass ($a_{\text{inter}} < 1$) if the intra-specific prefactor $B_{0\text{intra}} \propto M^{-\delta}$ declines allometrically with average body mass across different species with exponent δ . This means that the metabolic rate across species is $B_{\text{inter}} = B_{00}M^{-\delta}M^{a_{\text{intra}}} = B_{00}M^{a_{\text{inter}}}$ with B_{00} the (mass-independent) prefactor of the inter-specific relation, and the inter-specific exponent thus becomes $a_{\text{inter}} = a_{\text{intra}} - \delta$. This requires that the morphological and physiological parameters that occur in $B_{0\text{intra}}$ (see eqn 8) such as the capillary properties r_c , l_c , h_c and u_c and/or the arteriovenous concentration difference f_0 (a capillary efficiency) depend on the average body mass of a species. In this case, the network model predicts that intra-specific scaling is isometric ($a_{\text{intra}} = 1$) but is silent on inter-specific scaling which can be allometric ($a_{\text{inter}} < 1$). Is there evidence that these properties depend on between-species body mass differences and thus could yield $\delta \approx 0.25$ resulting in $a = a_{\text{inter}} \approx 0.75$?

There is indeed some experimental evidence that r_c and l_c vary with body size across species. Dawson (2001, 2003) claims that for mammals r_c and l_c scale with $M^{0.08}$ and $M^{0.21}$, respectively, which gives for case E in Fig. 3 the value $\delta \approx 0.21$, which leads to $a \approx 0.79$, so much closer to the observed values. Interestingly, since for case E the number of capillaries scales as $N_c \propto M$, the total generalized service volume scales as $X_c \equiv N_c r_c^{d_r} l_c^{d_l} h_c^{d_h} \propto M^{1+0.08(3+d_h)-0.21(1+2d_h)}$, which – for the choice $d_h = 0$ (i.e. setting $X_k \equiv N_k r_k^3 l_k^{-1}$) – yields almost isometric scaling: $X_c \propto M^{1.03}$. The size of red blood cells is fairly constant per vertebrate group (mammals, birds, reptiles, amphibians), suggesting that at least the capillary radii do not change very much with mass (Schmidt-Nielsen 1984). Schmidt-Nielsen also inferred that u_c might even scale as $M^{0.2}$, also affecting the value of a . Hence, dependence on body mass of capillary properties could potentially solve the paradox. Furthermore, if the capillary efficiency f_0 that occurs in the Fick relation (eqn 2) were mass dependent, then the total cardiac output Q_{tot} and metabolic rate B would display a different body-mass scaling (as suggested by Patterson *et al.* 1965; Milnor 1989, 1990), which could also solve the paradox. Spatz (1991) e.g. gives for mammals a mass scaling $\propto M^{0.11}$ because of allometric differences in oxygen unloading (Schmidt-Nielsen 1984). The experimental evidence on intra-specific metabolic scaling is less conclusive. In a recent review, Glazier (2005) showed that mammals display a large variation in exponent: $0.38 < a_{\text{intra}} < 1.11$ with average $a_{\text{intra}} \approx 2/3$, similar to squamate reptiles. On the other hand, varanid lizards as well as juvenile mammals and pelagic invertebrates have a scaling exponent close to one. It should be noted however that this argument leads to a very different mechanistic explanation for the observed 3/4 slope than given by the WBE model. In this case, larger species have a lower per-mass metabolic rate not because of a different optimal network architecture that unavoidably limits supply to the cells, but because of selection during evolution for e.g. different capillary dimensions and/or capillary efficiency (that could even be caused by active down-regulation of metabolism, see Suarez & Darveau 2005). Explaining these body mass dependencies would require a

different class of (diffusion and demand) models, and also a different underlying evolutionary framework (e.g. based on life-history trade-offs).

Another possibility to reconcile the theoretical prediction and experimental value of a is by generalizing the network model, to include the possibility of optimizing a goal function other than dissipation (e.g. the total drag force on the vessel walls), or to use a network property other than blood volume to link body-mass to vessel dimensions (e.g. the total mass of vessel walls, see Fig. 3). This seems a route worthwhile exploring.

A third option, while still remaining within the framework of supply-limiting networks, is to use a more integrated model. The WBE model is, as the authors admit (West *et al.* 2000), a simplified null-model that captures the essential details. Yet, the model seems to be too simple to undisputedly arrive at the seminal result: $a = 3/4$. Therefore we suggest the use of a more integrated model that includes a description of mass transport from the capillaries to the cells. In this way, the spatial efficiency of the network (service volume) can be included mathematically in a more realistic way. The ultimate evolutionary goal of the network is to transport resources in an efficient way to the target cells, not only to the capillaries. Also (part of) the temperature dependence of the metabolic rate (Brown *et al.* 2004) or even stoichiometry might be included in a natural way into such a network framework. A second part of such an integrated model would be the transport of oxygen from the lungs to the blood (lung capillaries, see e.g. Santillan 2003). A third part could consist of constraints that arise from the specific body shape of organisms, which may especially affect the internal network scaling at the aortic side and therefore the metabolic scaling exponent.

If we however fully reject the assumption that metabolism is constrained by the supply through the network, we also have to reject the WBE model as a mechanistic explanation of the between-species metabolic 3/4-power scaling, in favour of alternatives (see e.g. Agutter & Wheatley 2004; Glazier 2005, van der Meer 2006). Even if natural selection optimizes the network architecture to minimize its transport or maintenance costs, the mass-dependence of metabolic rate may be explained by different processes, such as basal transport processes across membranes (Demetrius 2006).

In our view, more anatomical and physiological data are required to solve the paradox between our new predictions and the available observations of allometric scaling. As outlined earlier, predicted and observed differences between intra- and inter-specific scaling of metabolic rate can provide further insight in this discussion. The intercept in allometric scaling relations deserves much more attention from a physiological perspective, besides the role of temperature and stoichiometry (see Brown *et al.* 2004). At the same time, there are interesting new theoretical possibilities left to discover.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

- Appendix S1.** Network model and metabolic rate
- Appendix S2.** Pulsatile flow
- Appendix S3.** Optimization with constraints
- Appendix S4.** Minimization of steady dissipation (Poiseuille flow)
- Appendix S5.** Minimization of pulsatile dissipation (Womersley flow)
- Appendix S6.** Incorrect definition of pulsatile dissipation
- Appendix S7.** References

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