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Review

The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization

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Summary

Life is the most complex physical phenomenon in the Universe, manifesting an extraordinary diversity of form and function over an enormous scale from the largest animals and plants to the smallest microbes and subcellular units. Despite this many of its most fundamental and complex phenomena scale with size in a surprisingly simple fashion. For example, metabolic rate scales as the 3/4-power of mass over 27 orders of magnitude, from molecular and intracellular levels up to the largest organisms. Similarly, time-scales (such as lifespans and growth rates) and sizes (such as bacterial genome lengths, tree heights and mitochondrial densities) scale with exponents that are typically simple powers of 1/4. The universality and simplicity of these relationships suggest that fundamental universal principles underly much of the coarse-grained generic structure and organisation of living systems. We have proposed a set of principles based on the observation that almost all life is sustained by hierarchical branching networks, which we assume have invariant terminal units, are space-filling and are optimised by the process of natural selection. We show how these general constraints explain quarter power scaling and lead to a quantitative, predictive theory that captures many of the essential features of diverse biological systems. Examples considered include animal circulatory systems, plant vascular systems, growth, mitochondrial densities, and the concept of a universal molecular clock. Temperature considerations, dimensionality and the role of invariants are discussed. Criticisms and controversies associated with this approach are also addressed.

Key words: allometry, quarter-power scaling, laws of life, circulatory system, ontogenetic growth.

Introduction

Life is almost certainly the most complex and diverse physical system in the universe, covering more than 27 orders of magnitude in mass, from the molecules of the genetic code and metabolic process up to whales and sequoias. Organisms themselves span a mass range of over 21 orders of magnitude, ranging from the smallest microbes (10^{-13} g) to the largest mammals and plants (10^{8} g). This vast range exceeds that of the Earth's mass relative to that of the galaxy (which is 'only' 18 orders of magnitude) and is comparable to the mass of an electron relative to that of a cat. Similarly, the metabolic power required to support life over this immense range spans more than 21 orders of magnitude. Despite this amazing diversity and complexity, many of the most fundamental biological processes manifest an extraordinary simplicity when viewed as a function of size, *regardless of the class or taxonomic group being considered*. Indeed, we shall argue that mass, and to a lesser extent temperature, is the prime determinant of variation in physiological behaviour when different organisms are compared over many orders of magnitude.

Scaling with size typically follows a simple power law behaviour of the form:

$$Y = Y_0 M_{\mathrm{b}}^{\,b}\,, \qquad (1)$$

where Y is some observable biological quantity, Y_0 is a normalization constant, and M_{b} is the mass of the organism (Calder, 1984; McMahon and Bonner, 1983; Niklas, 1994; Peters, 1986; Schmidt-Nielsen, 1984). An additional simplification is that the exponent, b, takes on a limited set of values, which are typically simple multiples of 1/4. Among the many variables that obey these simple quarter-power allometric scaling laws are nearly all biological rates, times, and dimensions; they include metabolic rate ($b\approx3/4$), lifespan ($b\approx1/4$), growth rate ($b\approx-1/4$), heart rate ($b\approx-1/4$), DNA nucleotide substitution rate ($b\approx-1/4$), lengths of aortas and heights of trees ($b\approx1/4$), radii of aortas and tree trunks

($b\approx3/8$), cerebral gray matter ($b\approx5/4$), densities of mitochondria, chloroplasts and ribosomes ($b=-1/4$), and concentrations of ribosomal RNA and metabolic enzymes ($b\approx-1/4$); for examples, see Figs 1–4. The best-known of these scaling laws is for basal metabolic rate, which was first shown by Kleiber (Brody, 1945; Kleiber, 1932, 1975) to scale approximately as $M_b^{3/4}$ for mammals and birds (Fig. 1). Subsequent researchers showed that whole-organism metabolic rates also scale as $M_b^{3/4}$ in nearly all organisms, including animals (endotherms and ectotherms, vertebrates and invertebrates; Peters, 1986), plants (Niklas, 1994), and unicellular microbes (see also Fig. 7). This simple 3/4 power scaling has now been observed at intracellular levels from isolated mammalian cells down through mitochondria to the oxidase molecules of the respiratory complex, thereby covering fully 27 orders of magnitude (Fig. 2; West et al., 2002b). In the early 1980s, several independent investigators (Calder, 1984; McMahon and Bonner, 1983; Peters, 1986; Schmidt-Nielsen, 1984) compiled, analyzed and synthesized the extensive literature on allometry, and unanimously concluded that quarter-power exponents were a pervasive feature of biological scaling across nearly all biological variables and life-forms.

Another simple characteristic of these scaling laws is the emergence of *invariant* quantities (Charnov, 1993). For example, mammalian lifespan increases approximately as $M_b^{1/4}$, whereas heart-rate decreases as $M_b^{-1/4}$, so the number of heart-beats per lifetime is approximately invariant ($\sim1.5\times10^9$), independent of size. A related, and perhaps more fundamental, invariance occurs at the molecular level, where the number of turnovers of the respiratory complex in the lifetime of a mammal is also essentially constant ($\sim10^{16}$). Understanding the origin of these dimensionless numbers should eventually lead to important fundamental insights into the processes of aging and mortality. Still another invariance occurs in ecology, where population density decreases with individual body size as $M_b^{-3/4}$ whereas individual power use increases as $M_b^{3/4}$, so the energy used by all individuals in any size class is an invariant (Enquist and Niklas, 2001).

It seems impossible that these 'universal' quarter-power scaling laws and the invariant quantities associated with them could be coincidental, independent phenomena, each a 'special' case reflecting its own unique independent dynamics and organisation. Of course every individual organism, biological species and ecological assemblage is unique, reflecting differences in genetic make-up, ontogenetic pathways, environmental conditions and evolutionary history. So, in the absence of any additional physical constraints, one might have expected that different organisms, or at least each groups of related organisms inhabiting similar environments, might exhibit different size-related patterns of variation in structure and function. The fact that they do not – that the data almost always closely approximate a power law, emblematic of self-similarity, across a broad range of size and diversity – raises challenging questions. The fact that the exponents of these power laws are nearly always simple multiples of 1/4 poses an even greater challenge. It suggests the operation of general underlying mechanisms that are independent of the specific nature of individual organisms.

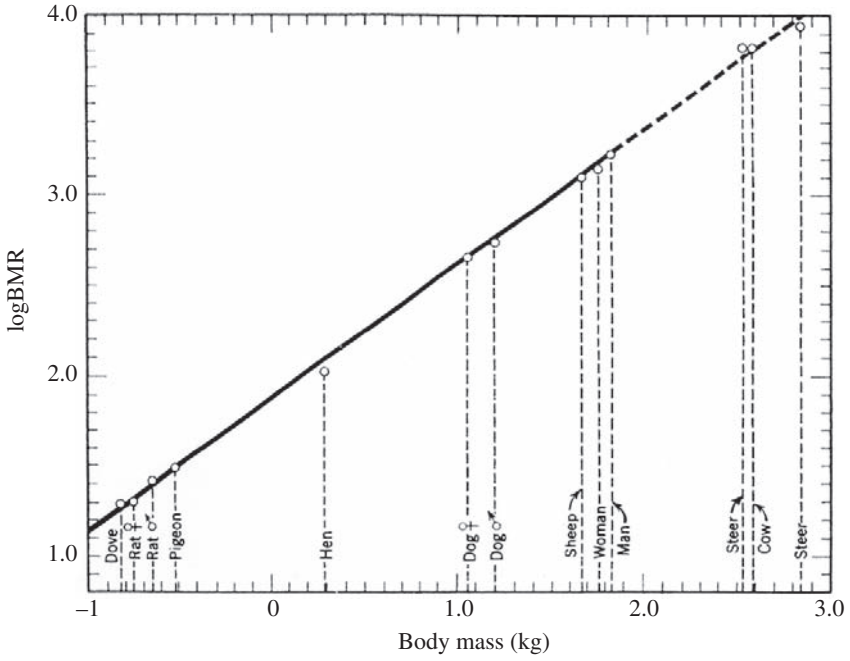

Fig. 1. Kleiber's original 1932 plot of the basal metabolic rate of mammals and birds (in kcal/day) plotted against mass (M_b in kg) on a log–log scale (Kleiber, 1975). The slope of the best straight-line fit is 0.74, illustrating the scaling of metabolic rate as $M_b^{3/4}$. The diameters of the circles represent his estimated errors of 10% in the data.

We argue that the very existence of such ubiquitous power laws implies the existence of powerful constraints at every level of biological organization. The self-similar power law scaling implies the existence of average, idealized biological systems, which represent a '0th order' baseline or point of departure for understanding the variation among real biological systems. Real organisms can be viewed as variations on, or perturbations from, these idealized norms due to influences of stochastic factors, environmental conditions or evolutionary histories. Comparing organisms over large ranges of body size effectively averages over environments and phylogenetic histories. Sweeping comparisons, incorporating organisms of different taxonomic and functional groups and spanning many orders of magnitude in body mass, reveal the more universal features of life, lead to coarse-grained descriptions, and motivate the search for general, quantitative, predictive theories of biological structures and dynamics.

Such an approach has been very successful in other branches of science. For example,

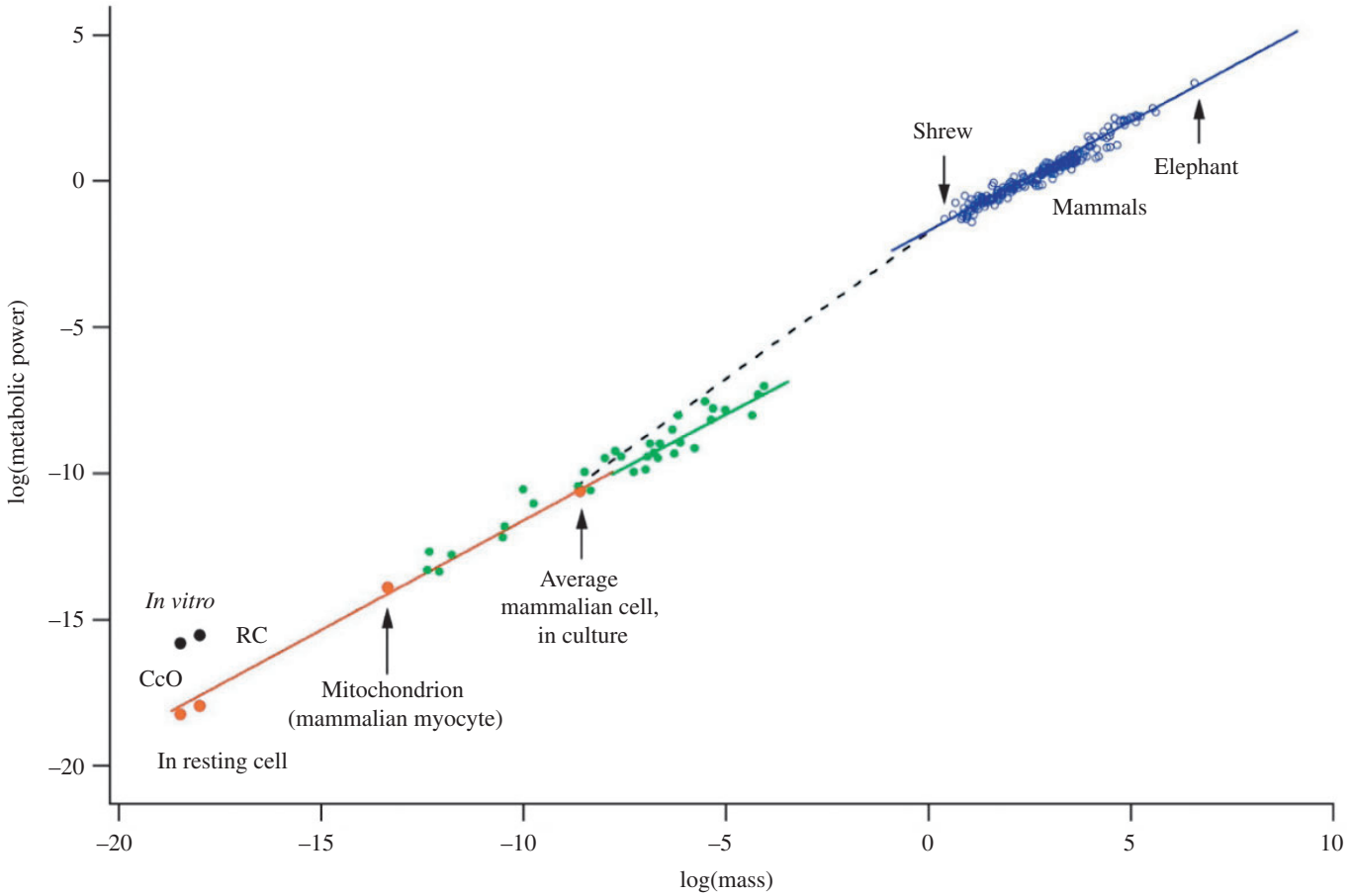

Fig. 2. Extension of Kleiber's 3/4-power law for the metabolic rate of mammals to over 27 orders of magnitude from individuals (blue circles) to uncoupled mammalian cells, mitochondria and terminal oxidase molecules, CcO of the respiratory complex, RC (red circles). Also shown are data for unicellular organisms (green circles). In the region below the smallest mammal (the shrew), scaling is predicted to extrapolate linearly to an isolated cell *in vitro*, as shown by the dotted line. The 3/4-power re-emerges at the cellular and intracellular levels. Figure taken from West et al. (2002b) with permission.

classic kinetic theory is based on the idea that generic features of gases, such as the ideal gas law, can be understood by assuming atoms to be structureless 'billiard balls' undergoing elastic collisions. Despite these simplifications, the theory captures many essential features of gases and spectacularly predicts many of their coarse-grained properties. The original theory acted as a starting point for more sophisticated treatments incorporating detailed structure, inelasticity, quantum mechanical effects, etc, which allow more detailed calculations. Other examples include the quark model of elementary particles and the theories describing the evolution of the universe from the big bang. This approach has also been successful in biology, perhaps most notably in genetics. Again, the original Mendelian theory made simplifying assumptions, portraying each phenotypic trait as the expression of pairs of particles, each derived from a different parent, which assorted and combined at random in offspring. Nevertheless, this theory captured enough of the coarse-grained essence of the phenomena so that it not only provided the basis for the applied sciences of human genetics and plant and animal breeding, but also guided the successful search for the molecular genetic code and supplied the mechanistic underpinnings for the modern evolutionary synthesis. Although the shortcomings of these theories are well-recognized, they quantitatively explain an extraordinary body of data because they do indeed capture much of the essential behavior.

Scaling as a manifestation of underlying dynamics has been instrumental in gaining deeper insights into problems across the entire spectrum of science and technology, because scaling laws typically reflect underlying general features and principles that are independent of detailed structure, dynamics or other specific characteristics of the system, or of the particular models used to describe it. So, a challenge in biology is to understand the ubiquity of quarter-powers – to explain them in terms of unifying principles that determine how life is organized and the constraints under which it has evolved. Over the immense spectrum of life the same chemical constituents and reactions generate an enormous variety of forms, functions, and dynamical behaviors. All life functions by transforming energy from physical or chemical sources into organic molecules that are metabolized to build, maintain and reproduce complex, highly organized systems. We conjecture

that metabolism and the consequent distribution of energy and resources play a central, *universal* role in constraining the structure and organization of all life at all scales, and that the principles governing this are manifested in the pervasive quarter-power scaling laws.

Within this paradigm, the precise value of the exponent, whether it is exactly 3/4, for example, is less important than the fact that it approximates such an ideal value over a substantial range of mass, despite variation due to secondary factors. Indeed, a quantitative theory for the dominant behaviour (the 3/4 exponent, for example) provides information about the residual variation that it cannot explain. If a general theory with well-defined assumptions predicts 3/4 for average idealized organisms, then it is possible to erect and test hypotheses about other factors, not included in the theory, which may cause real organisms to deviate from this value. On the other hand, without such a theory it is not possible to give a specific meaning to any scaling exponent, but only to describe the relationship statistically. This latter strategy has usually been employed in analyzing allometric data and has fueled controversy ever since Kleiber's original study (Kleiber, 1932, 1975). Kleiber's contemporary Brody independently measured basal metabolic rates of birds and mammals, obtained a statistically fitted exponent of 0.73, and simply took this as the 'true' value (Brody, 1945). Subsequently a great deal of ink has been spilled debating whether the exponent is 'exactly' 3/4. Although this controversy appeared to be settled more than 20 years ago (Calder, 1984; McMahon and Bonner, 1983; Peters, 1986; Schmidt-Nielsen, 1984), it was recently resurrected by several researchers (Dodds et al., 2001; Savage et al., 2004b; White and Seymour, 2003).

A deep understanding of quarter-power scaling based on a set of underlying principles can provide, in principle, a general framework for making quantitative dynamical calculations of many more detailed quantities beyond just the allometric exponents of the phenomena under study. It can raise and address many additional questions, such as: How many oxidase molecules and mitochondria are there in an average cell and in an entire organism? How many ribosomal RNA molecules? Why do we stop growing and what adult weight do we attain? Why do we live on the order of 100 years – and not a million or a few weeks – and how is this related to molecular scales? What are the flow rate, pulse rate, pressure and dimensions in any vessel in the circulatory system of any mammal? Why do we sleep eight hours a day, a mouse eighteen and an elephant three? How many trees of a given size are there in a forest, how far apart are they, how many leaves does each have and how much energy flows in each or their branches? What are the limits on the sizes of organisms with different body plans?

Basic principles

All organisms, from the smallest, simplest bacterium to the largest plants and animals, depend for their maintenance and reproduction on the close integration of numerous subunits: molecules, organelles and cells. These components need to be serviced in a relatively 'democratic' and efficient fashion to supply metabolic substrates, remove waste products and regulate activity. We conjecture that natural selection solved this problem by evolving hierarchical fractal-like branching networks, which distribute energy and materials between macroscopic reservoirs and microscopic sites (West et al., 1997). Examples include animal circulatory, respiratory, renal, and neural systems, plant vascular systems, intracellular networks, and the systems that supply food, water, power and information to human societies. We have proposed that the quarter-power allometric scaling laws and other features of the dynamical behaviour of biological systems reflect the constraints inherent in the generic properties of these networks. These were postulated to be: (i) networks are space-filling in order to service all local biologically active subunits; (ii) the terminal units of the network are invariants; and (iii) performance of the network is maximized by minimizing the energy and other quantities required for resource distribution.

These properties of the 'average idealised organism' are presumed to be consequences of natural selection. Thus, the terminal units of the network where energy and resources are exchanged (e.g. leaves, capillaries, cells, mitochondria or chloroplasts), are not reconfigured or rescaled as individuals grow from newborn to adult or as new species evolve. In an analogous fashion, buildings are supplied by branching networks that terminate in invariant terminal units, such as electrical outlets or water faucets. The third postulate assumes that the continuous feedback and fine-tuning implicit in natural selection led to 'optimized' systems. For example, of the infinitude of space-filling circulatory systems with invariant terminal units that could have evolved, those that have survived the process of natural selection, minimize cardiac output. Such minimization principles are very powerful, because they lead to 'equations of motion' for network dynamics.

Using these basic postulates, which are quite general and independent of the details of any particular system, we have derived analytic models for mammalian circulatory and respiratory systems (West et al., 1997) and plant vascular systems (West et al., 1999b). The theory predicts scaling relations for many structural and functional components of these systems. These scaling laws have the characteristic quarter-power exponents, even though the anatomy and physiology of the pumps and plumbing are very different. Furthermore, our models derive scaling laws that account for observed variation between organisms (individuals and species of varying size), within individual organisms (e.g. from aorta to capillaries of a mammal or from trunk to leaves of a tree), and during ontogeny (e.g. from a seedling to a giant sequoia). The models can be used to understand the values not only for allometric exponents, but also for normalization constants and certain invariant quantities. The theory makes quantitative predictions that are generally supported when relevant data are available, and – when they are not – that stand as *a priori* hypotheses to be tested by collection and analysis of new data (Enquist et al., 1999; Savage et al., 2004a; West et al., 1997, 1999a,b, 2001, 2002a,b).

Metabolic rate and the vascular network

Metabolic rate, the rate of transformation of energy and materials within an organism, literally sets the pace of life. Consequently it is central in determining the scale of biological phenomena, including the sizes and dimensions of structures and the rates and times of activities, at levels of organization from molecules to ecosystems. Aerobic metabolism in mammals is fueled by oxygen whose concentration in blood is invariant, so cardiac output or blood volume flow rate through the cardiovascular system is a proxy for metabolic rate. Thus, characteristics of the circulatory network constrain the scaling of metabolic rate. We shall show how the body-size dependence for basal and field metabolic rates, $B \propto M_b^{3/4}$, where B is total metabolic rate, can be derived by modeling the hemodynamics of the cardiovascular system based on the above general assumptions. In addition, and just as importantly, this whole-system model also leads to analytic solutions for many other features of the blood supply network. These results are derived by solving the hydrodynamic and elasticity equations for blood flow and vessel dynamics subject to space-filling and the minimization of cardiac output (West et al., 1997). We make certain simplifying assumptions, such as cylindrical vessels, a symmetric network, and the absence of significant turbulence. Here, we present a condensed version of the model that contains the important features pertinent to the scaling problem.

In order to describe the network we need to determine how the radii, r_k, and lengths, l_k, of vessels change throughout the network; k denotes the level of the branching, beginning with the aorta at $k=0$ and terminating at the capillaries where $k=N$. The average number of branches per node (the branching ratio), n, is assumed to be constant throughout the network.

Space-filling (Mandelbrot, 1982) ensures that every local volume of tissue is serviced by the network on all spatial scales, including during growth from embryo to adult. The capillaries are taken to be invariant terminal units, but each capillary supplies a group of cells, referred to as a 'service volume', v_N, which can scale with body mass. The total volume to be serviced, or filled, is therefore given by $V_S=N_N v_N$, where N_N is the total number of capillaries. For a network with many levels, N, space-filling at all scales requires that this same volume, V_S, be serviced by an aggregate of the volumes, v_k, at each level k. Since $r_k \ll l_k$, $v_k \propto l_k^3$, so $V_S \approx N_k v_k \propto N_k l_k^3$ for every level, k. Thus $l_{k+1}/l_k \approx n^{-1/3}$, so space-filling constrains only branch lengths, l_k.

The equation of motion governing fluid flow in any single tube is the Navier–Stokes equation (Landau and Lifshitz, 1978). If non-linear terms responsible for turbulence are neglected, this reads:

$$\rho \frac{\partial \mathbf{v}}{\partial t} = \mu \nabla^2 \mathbf{v} - \nabla \mathbf{p} , \qquad (2)$$

where $\mathbf{v}$ is the local fluid velocity at some time t, $\mathbf{p}$ the local pressure, ρ, blood density and μ, blood viscosity. Assuming blood is incompressible, then local conservation of fluid requires $\nabla \bullet \mathbf{v}=0$. When combined with Eq. 2, this gives:

$$\nabla^2 \mathbf{p} = 0 . \qquad (3)$$

The beating heart generates a pulse wave that propagates down the arterial system causing expansion and contraction of vessels as described by the Navier equation, which governs the elastic motion of the tube. This is given by:

$$\rho_w \frac{\partial^2 \xi}{\partial t^2} = E \nabla^2 \xi - \nabla \mathbf{p} , \qquad (4)$$

where ξ is the local displacement of the tube wall, ρ_w its density, and E its modulus of elasticity. These three coupled equations, Eq. 2–4, must be solved subject to boundary conditions that require the continuity of velocity and force at the tube wall interfaces. In the approximation where the vessel wall thickness, h, is small compared to the static equilibrium value of the vessel radius, r, i.e. $h \ll r$, the problem can be solved analytically, as first shown by Womersley (Caro et al., 1978; Fung, 1984), to give:

$$\left(\frac{c}{c_0}\right)^2 \sim -\frac{J_2(i^{3/2}\alpha)}{J_0(i^{3/2}\alpha)} \quad \text{and} \quad Z \sim \frac{c_o^2 \rho}{\pi r^2 c} , \qquad (5)$$

where J_n denotes the Bessel function of order n. Here, ω is the angular frequency of the wave, $\alpha \equiv (\omega\rho/\mu)^{1/2} r$ is a dimensionless parameter known as the Womersley number, $c_0 \equiv (Eh/2\rho r)^{1/2}$ is the classic Korteweg–Moens velocity, and Z is the vessel impedance. Both Z and the wave velocity, c, are complex functions of ω so, in general, the wave is attenuated and dispersed as it propagates along the tubes. The character of the wave depends critically on whether $|\alpha|$ is less than or greater than 1. This can be seen explicitly in Eq. 5, where the behavior of the Bessel functions changes from a power-series expansion for small $|\alpha|$ to an expansion with oscillatory behavior when $|\alpha|$ is large. In humans, $|\alpha|$ has a value of around 15 in the aorta, 5 in the arteries, 0.04 in the arterioles, and 0.005 in the capillaries. When $|\alpha|$ is large ($\gg 1$), Eq. 5 gives $c \sim c_0$, which is a purely real quantity, so the wave suffers neither attenuation nor dispersion. Consequently, in these large vessels viscosity plays almost no role and virtually no energy is dissipated. In an arbitrary unconstrained network, however, energy must be expended to overcome possible reflections at branch junctions, which would require increased cardiac power output. Minimization of energy expenditure is therefore achieved by eliminating such reflections, a phenomenon known as impedance matching. From Eq. 5, $Z \sim \rho c_0/\pi r^2$ for large vessels, and impedance matching leads to area-preserving branching: $\pi r_k^2 = n \pi r_{k+1}^2$, so that $r_{k+1}/r_k = n^{-1/2}$. For small vessels, however, where $|\alpha| \ll 1$, the role of viscosity and the subsequent dissipation of energy become increasingly important until they eventually dominate the flow. Eq. 5 then gives $c \sim (1/4) i^{1/2} \alpha c_0 \rightarrow 0$, in quantitative agreement with observation (Caro et al., 1978; Fung, 1984). Because c now has a dominant imaginary part, the traveling wave is heavily damped, leaving an almost steady oscillatory flow whose impedance is, from Eq. 5, just the classic Poiseuille formula, $Z_k = 8\mu l_k/\pi r_k^4$. Unlike energy loss due to reflections at branch points, energy loss due to viscous dissipative forces cannot be

entirely eliminated. It can be minimized, however, using the classic method of Lagrange multipliers to enforce the appropriate constraints (Marion and Thornton, 1988; West et al., 1997). To sustain a given metabolic rate in an organism of fixed mass with a given volume of blood, V_b, the cardiac output must be minimized subject to a space-filling geometry. The calculation shows that area-*preserving* branching is thereby replaced by area-*increasing* branching in small vessels, so blood slows down allowing efficient diffusion of oxygen from the capillaries to the cells. Branching, therefore, changes continuously down through the network, so that the ratio r_{k+1}/r_k is not independent of k but changes continuously from $n^{-1/2}$ at the aorta to $n^{-1/3}$ at the capillaries. Consequently, the network is not strictly self-similar, but within each region (pulsatile in large vessels and Poiseuille in small ones), self-similarity is a reasonable approximation that is well supported by empirical data (Caro et al., 1978; Fung, 1984; Zamir, 1999).

In order to derive allometric relations between animals of different sizes we need to relate the scaling of vessel dimensions within an organism to its body mass, M_b. A natural vehicle for this is the total volume of blood in the network, V_b, which can be shown to depend linearly on M_b if cardiac output is minimized, i.e. $V_b \propto M_b$, in agreement with data (Caro et al., 1978; Fung, 1984). This is straightforwardly given by $V_b=\Sigma N_k V_k=\Sigma n^k \pi r_k^2 l_k$, where $N_k=n^k$ is the number of vessels at level k. Provided there are sufficiently large vessels in the network with $|\alpha|>1$ so that pulsatile flow dominates, the leading-order behavior for the blood volume is $V_b \propto n^{4N/3} V_N$. Conservation of blood requires that the flow rate in the aorta, $Q_0= N_N Q_N$, where Q_N is the flow rate in a capillary and $N_N \approx n^N$, the total number of capillaries. But $Q_0 \propto B$, the total metabolic rate, so putting these together we obtain $B \propto (V_b/V_N)^{3/4} Q_N$. However, capillaries are invariant units, so V_N and Q_N are both independent of M_b, whereas from minimization of energy loss, $V_b \propto M_b$, so we immediately obtain the seminal result $B \propto M_b^{3/4}$.

The allometric scaling of radii, lengths and many other physiological characteristics, such as the flow, pulse and dimensions in any branch of a mammal of any size, can be derived from this whole-system model and shown to have quarter-power exponents. Quantitative predictions for all these characteristics of the cardiovascular system are in good agreement with data (West et al., 1997). For example, even the residual pulse wave component in capillaries is determined: it is predicted to be attenuated to 0.1% with its velocity being ~10 cm s^{-1}, compared to ~580 cm s^{-1} for the unattenuated wave in the aorta, both numbers being invariant with respect to body size.

To summarise: there are two independent contributions to energy expenditure: viscous energy dissipation, which is important only in smaller vessels, and energy reflected at branch points, which is important only in larger vessels and is eliminated by impedance matchings In large vessels (arteries), pulse-waves suffer little attenuation or dissipation, and impedance matching leads to area-preserving branching, such that the cross-sectional area of daughter branches equals that of the parent; so radii scale as $r_{k+1}/r_k=n^{-1/2}$ with the blood velocity remaining constant. In small vessels (capillaries and arterioles) the pulse is strongly damped since Poiseuille flow dominates and substantial energy is dissipated. Here minimization of energy dissipation leads to area-increasing branching with $r_{k+1}/r_k=n^{-1/3}$, so blood slows down, almost ceasing to flow in the capillaries. Consequently, the ratio of vessel radii between adjacent levels, r_{k+1}/r_k, changes continuously from $n^{-1/2}$ to $n^{-1/3}$ down through the network, which is, therefore, *not* strictly self-similar. Nevertheless, since the length ratio l_{k+1}/l_k remains constant throughout the network because of space-filling, branch-lengths are self-similar and the network has some fractal-like properties. Quarter-power allometric relations then follow from the invariance of capillaries and the prediction from energy optimization that total blood volume scales linearly with body mass.

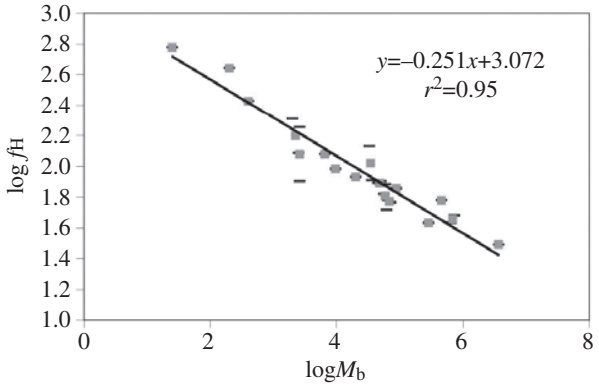

Fig. 3. Plot of heart rates (f_H) of mammals at rest *vs* body mass M_b (data taken from Brody, 1945). The regression lines are fitted to the average of the logarithms for every 0.1 log unit interval of mass, but both the average (squares) and raw data (bars) are shown in the plots. The slope is –0.251 (P<0.0001, N=17, 95% CI: –0.221, –0.281), which clearly includes –1/4 but excludes –1/3. Figure taken from Savage et al. (2004b) with permission.

The dominance of pulsatile flow, and consequently of area-preserving branching, is crucial for deriving power laws, including the 3/4 exponent for metabolic rate, B. However, as body size decreases, narrow tubes predominate and viscosity plays an ever-increasing role. Eventually even the major arteries would become too constricted to support wave propagation, blood flow would become steady and branching exclusively area-increasing, leading to a linear dependence on mass. Since energy would be dissipated in *all* branches of the network, the system is now highly inefficient; such an impossibly small mammal would have a beating heart (with a resting heart-rate in excess of approximately 1000 beats min^{-1}) but no pulse! This provides a framework to estimate the size of the smallest mammal in terms of fundamental cardiovascular parameters. This gives a minimum mass M_{min}~1 g, close to that of a shrew, which is indeed the smallest mammal (Fig. 3; West et al., 2002b). Furthermore, the predicted linear extrapolation of B below this mass to the mass of a single cell should, and does, give the correct value for the

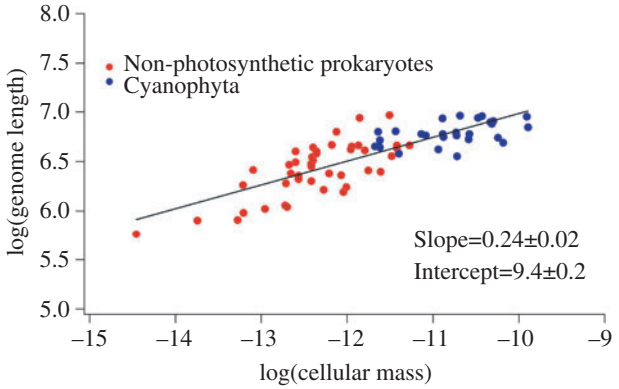

Fig. 4. Plot of genome length (number of base pairs) *vs* mass (in g) for a sequence of unicells on a log–log scale. The best straight-line fit has a slope very close to 1/4.

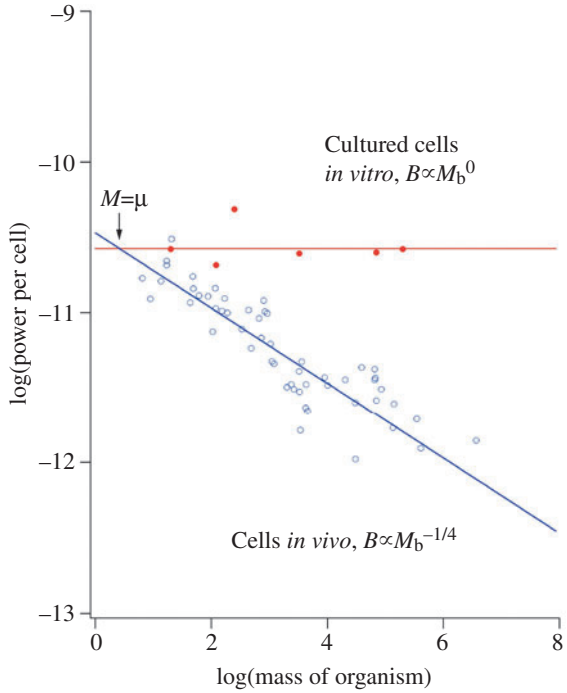

Fig. 5. Metabolic rates (in W) of mammalian cells *in vivo* (blue line) and cultured *in vitro* (red line) plotted as a function of organism mass (M_b in g) on a log–log scale. While still in the body and constrained by vascular supply networks cellular metabolic rates scale as $M_b^{-1/4}$. When cells are removed from the body and cultured *in vitro*, their metabolic rates converge to a constant value predicted by theory (West et al., 2002b). The two lines meet at the mass of the smallest mammal (the shrew with mass ~1 g, as predicted). Figure taken from West et al. (2002b) with permission.

metabolic rate of mammalian cells growing in culture isolated from the vascular network (Fig. 2).

The derivation that gives the 3/4 exponent is only an approximation, because of the changing roles of pulsatile and Poiseuille flow with body size. Strictly speaking, the theory predicts that the exponent for B is exactly 3/4 only where pulsatile flow completely dominates. In general, the exponent is predicted to depend weakly on M, manifesting significant deviations from 3/4 only in small mammals, where only the first few branches of the arterial system can support a pulse wave (West et al., 1997, 2002b). Since small mammals dissipate relatively more energy in their networks, they require elevated metabolic rates to generate the increased energy expenditure to circulate the blood. This leads to the prediction that the allometric exponent for B should decrease below 3/4 as M_b decreases to the smallest mammal, as observed (Dodds et al., 2001; Savage et al., 2004b).

If the total number of cells, N_c, increases linearly with M_b, then both cellular metabolic rate, $B_c(\approx B/N_c)$, and specific metabolic rate, B/M_b, decrease as $M_b^{-1/4}$. In this sense, therefore, larger animals are more efficient than smaller ones, because they require less power to support unit body mass and their cells do less work than smaller animals. In terms of our theory this is because the total hydrodynamic resistance of the network decreases with size as $M_b^{-3/4}$. This has a further interesting consequence that, since the 'current' or volume rate of flow of blood in the network, Q_0, increases as $M_b^{3/4}$, whereas the resistance decreases as $M_b^{-3/4}$, the analog to Ohm's law (pressure=current×resistance) predicts that blood pressure must be an invariant, as observed (Caro et al., 1978; Fung, 1984). This may seem counterintuitive, since the radius of the aorta varies from approximately 0.2 mm in a shrew up to approximately 30 cm in a whale!

Scaling up the hierarchy: from molecules to mammals

At each organisational level within an organism, beginning with molecules and continuing up through organelles, cells, tissues and organs, new structures emerge, each with different physical characteristics, functional parameters, and resource and energy network systems, thereby constituting a hierarchy of hierarchies. Metabolic energy is conserved as it flows through this hierarchy of sequential networks. We assume that each network operates subject to the same general principles and therefore exhibits quarter-power scaling (West et al., 2002b). From the molecules of the respiratory complex up to intact cells, metabolic rate obeys 3/4-power scaling. Continuity of flow imposes boundary conditions between adjacent levels, leading to constraints on the densities of invariant terminal units, such as respiratory complexes and mitochondria, and on the networks of flows that connect them (West et al., 2002b). The total mitochondrial mass relative to body mass is correctly predicted to be $(M_{min}m_m/m_cM_b)^{1/4} \approx 0.06M_b^{-1/4}$, where m_m is the mass of a mitochondrion, M_{min} is minimum mass, m_c is average cell mass and M_b is expressed in g. Since mitochondria are assumed to be approximately invariant, the total number in the body is determined in a similar fashion. This shows why there are typically only a few hundred per human cell, whereas there are several thousand in a shrew cell of the same type.

As already stressed, a central premise of the theory is that general properties of supply networks constrain the coarse-grained, and therefore the scaling properties, of biological

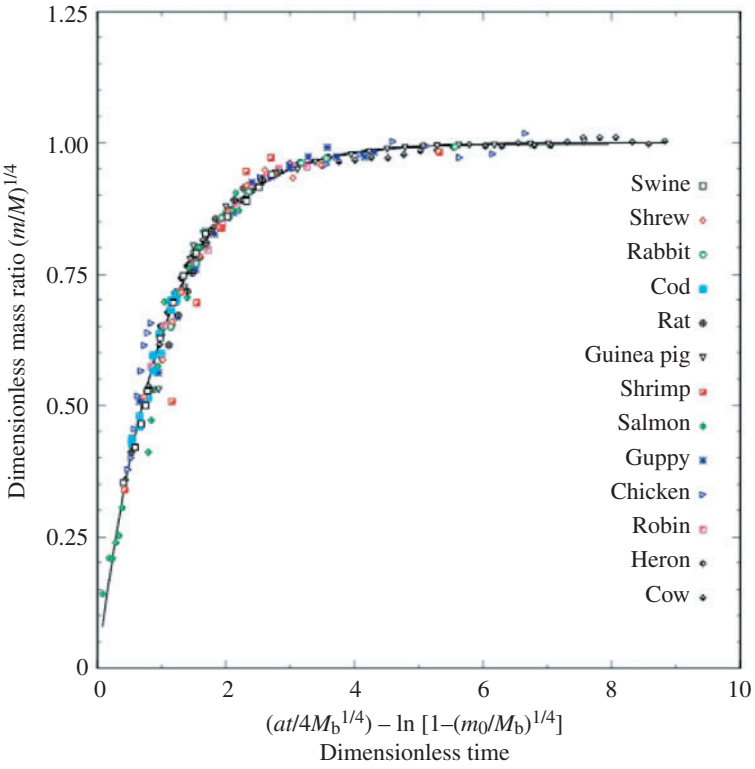

Fig. 6. The universality of growth is illustrated by plotting the dimensionless mass ratio $(m/M)^{1/4}$ against a dimensionless time variable, as shown. When data for mammals, birds, fish and crustacea are plotted this way, they are predicted to lie on a single universal curve; m is the mass of the organism at age t, m_0 its birth mass, M_b its mature mass, and a a parameter determined by theory in terms of basic cellular properties that can be measured independently of growth data. Figure taken from West et al. (2001) with permission.

systems. An immediate qualitative consequence of this idea is that, if cells are liberated from the network hegemony by culturing them *in vitro*, they are likely to behave differently from cells *in vivo*. An alternative possibility is that cellular metabolic rates are relatively inflexible. This, however, would be a poor design, because it would prevent facultative adjustment in response to variation in body size over ontogeny and in response to the varying metabolic demands of tissues. If the metabolic rate and number of mitochondria per cell are indeed tuned facultatively in response to variations in supply and demand, the theory makes an explicit quantitative prediction: cells isolated from different mammals and cultured *in vitro* under conditions of unlimited resource supply should converge toward the *same* metabolic rate (predicted to be ~6×10^{-11} W), rather than scaling as $M^{-1/4}$ as they do *in vivo* (Fig. 5); cells *in vitro* should also converge toward identical numbers of mitochondria, losing the $M^{-1/4}$ scaling that they exhibit *in vivo*. The *in vivo* and *in vitro* values are predicted to coincide at M_{min}, which we estimated above to be approximately 1 g. So cells in shrews work at almost maximal output, which, no doubt, is reflected in their high levels of activity and the shortness of their lives. By contrast cells in larger mammals are constrained by the properties of vascular supply networks and normally work at lower rates.

All of these results depend only on generic network properties, independent of details of anatomy and physiology, including differences in the size, shape and number of mitochondria among different tissues within a mammal. Since quarter-power scaling is observed at intracellular, as well as whole-organism and cellular levels, this suggests that metabolic processes at subcellular levels are also constrained by optimized space-filling, hierarchical networks, which have similar properties to the more macroscopic ones. A major challenge, both theoretically and experimentally, is to understand quantitatively the mechanisms of intracellular transport, about which surprisingly little is known.

Extensions

Ontogenetic growth

The theory developed above naturally leads to a general growth equation applicable to all multicellular animals (West et al., 2001, 2002a). Metabolic energy transported through the network fuels cells where it is used either for maintenance, including the replacement of cells, or for the production of additional biomass and new cells. This can be expressed as:

$$B = N_c B_c + E_c \left(\frac{dN_c}{dt} \right), \qquad (6)$$

where N_c is the total number of cells in the organism at time t after birth and E_c the energy needed to create a new cell. Since $N_c=m/m_c$, where m is the ontogenetic mass and m_c the average cell mass, this leads to an equation for the growth rate of an organism:

$$\frac{dm}{dt} = \left(\frac{B_0 m_c}{E_c} \right) m^{3/4} - \left(\frac{B_c}{E_c} \right) m , \qquad (7)$$

where B_0 is the taxon-dependent normalization constant for the scaling of metabolic rate: $B \equiv B_0 m^{3/4}$. The parameters of the resulting growth equation are therefore determined solely by fundamental properties of cells, such as their metabolic rates and the energy required to produce new ones, which can be measured independently of growth. The model gives a natural explanation for why animals stop growing: the number of cells supplied ($N_c \propto m$) scales faster than the number of supply units (since $B \propto N_N \propto m^{3/4}$), and leads to an expression for the asymptotic mass of the organism: $M_b=(B_0 m_c/B_c)^4$. Eq. 7 can be solved analytically to determine m as a function of t, leading to a classic sigmoidal growth curve. By appropriately rescaling m and t as prescribed by the theory, the solution can be recast as a universal scaling curve for growth. When rescaled in this way, growth data from many different animals (including endotherms and ectotherms, vertebrates and invertebrates) all

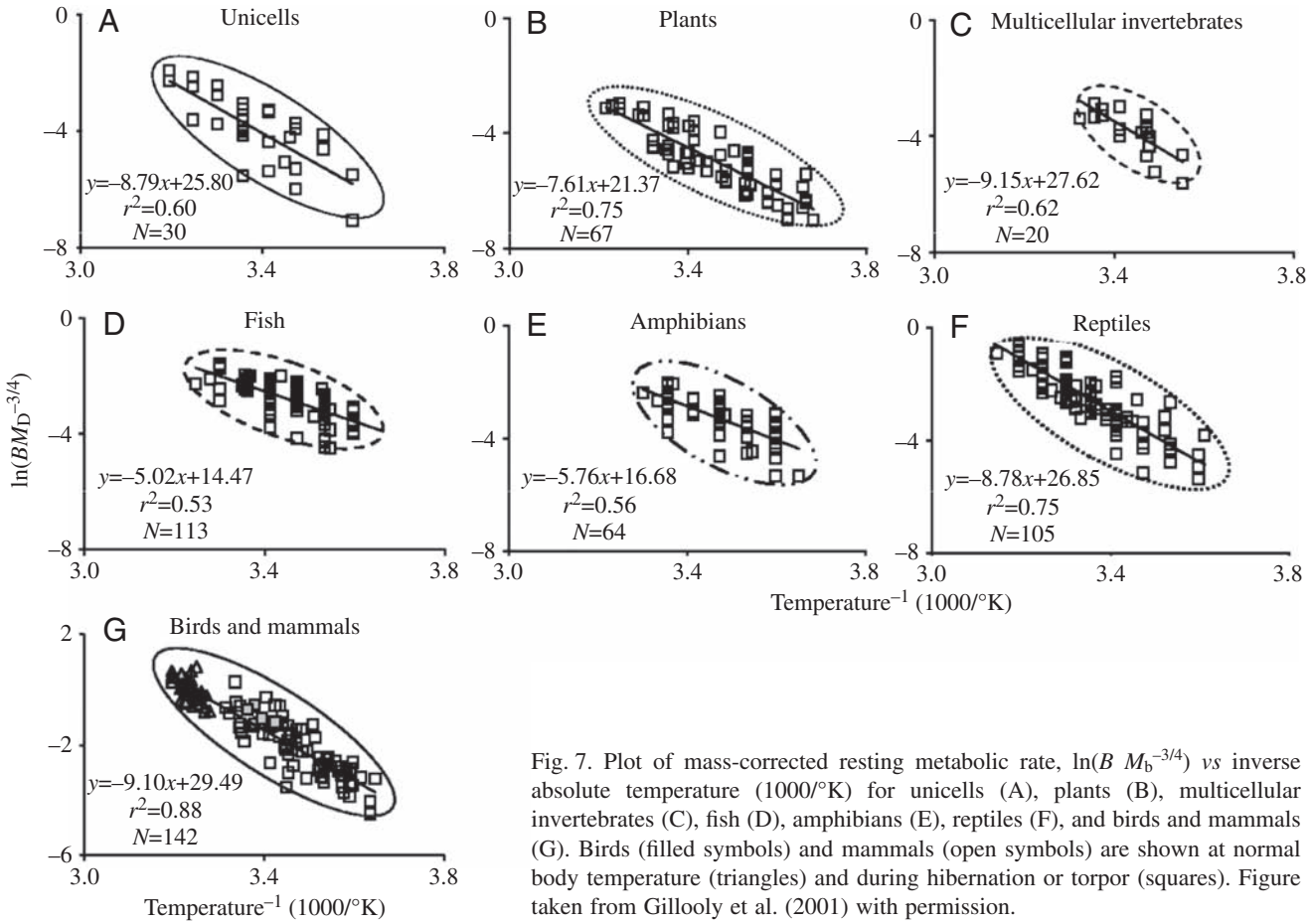

Fig. 7. Plot of mass-corrected resting metabolic rate, $\ln(B\ M_b^{-3/4})$ *vs* inverse absolute temperature (1000/°K) for unicells (A), plants (B), multicellular invertebrates (C), fish (D), amphibians (E), reptiles (F), and birds and mammals (G). Birds (filled symbols) and mammals (open symbols) are shown at normal body temperature (triangles) and during hibernation or torpor (squares). Figure taken from Gillooly et al. (2001) with permission.

closely fit a single universal curve (Fig. 6). Ontogenetic growth is therefore a universal phenomenon determined by the interaction of basic metabolic properties at cellular and whole-organism levels. Furthermore, this model leads to scaling laws for other growth characteristics, such as doubling times for body mass and cell number, and the relative energy devoted to production *vs* maintenance. Recently, Guiot et al. (2003) applied this model to growth of solid tumors in rats and humans. They showed that the growth curve derived from Eq. 7 gave very good fits, even though the parameters they used were derived from statistical fitting rather than determined from first principles, as in ontogenetic growth. This is just one example of the exciting potential applications of metabolic scaling theory to important biomedical problems.

Temperature and universal biological clocks

Temperature has a powerful effect on all biological systems because of the exponential sensitivity of the Boltzmann factor, $e^{-E/kT}$, which controls the temperature dependence of biochemical reaction rates; here, E is a chemical activation energy, T absolute temperature, and k Boltzmann's constant. Combined with network constraints that govern the fluxes of energy and materials, this predicts a joint universal mass and temperature scaling law for *all* rates and times connected with metabolism, including growth, embryonic development, longevity and DNA nucleotide substitution in genomes. All such rates are predicted to scale as:

$$R \propto M_b^{-1/4} e^{-E/kT} , \quad (8)$$

and all times as:

$$t \propto M_b^{1/4} e^{E/kT} . \quad (9)$$

The critical points here are the separable multiplicative nature of the mass and temperature dependences and the relatively invariant value of E, reflecting the average activation energy for the rate-limiting biochemical reactions (Gillooly et al., 2001). Data covering a broad range of organisms (fish, amphibians, aquatic insects and zooplankton) confirm these predictions with E~0.65 eV (Fig. 7). These results suggest a general definition of biological time that is approximately invariant and common to all organisms: *when adjusted for size and temperature, determined by just two numbers (*1/4 *and E*~0.65 *eV), all organisms to a good approximation run by the same universal clock with similar metabolic, growth, and evolutionary rates!* (Gillooly et al., 2005).

Metabolic scaling in plants: independent evolution of $M^{3/4}$

One of the most challenging facts about quarter-power scaling relations is that they are observed in both animals and plants. Our theory offers an explanation: both use fractal-like

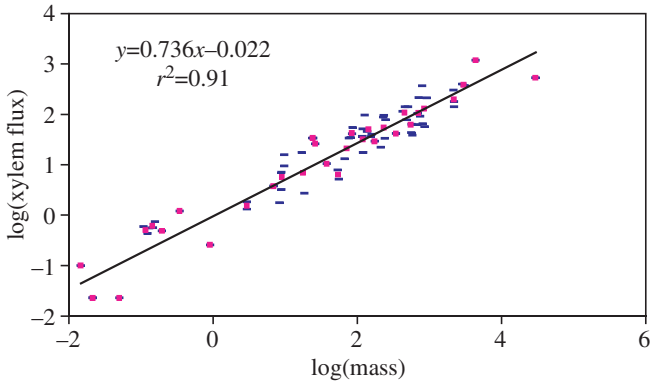

Fig. 8. Plot of maximum reported xylem flux rates (liters of fluid transported vertically through a plant stem per day) for plants (Enquist and Niklas, 2001). The RMA regression line is fitted to the average of the logarithm for every 0.1 log unit interval of plant biomass, but both the average (circles) and raw data (bars) are shown in the plot. The slope is 0.736 (P<0.0001, N=31, 95%CI: 0.647, 0.825). The regression fitted to the entire unbinned data set gives a similar exponent of 0.735 (P<0.0001, N=69, 95% CI: 0.682, 0.788). Figure taken from Enquist and Niklas (2001) with permission.

branching structures to distribute resources, so both obey the same basic principles despite the large differences in anatomy and physiology. For example, in marked contrast to the mammalian circulatory system, plant vascular systems are effectively fiber bundles of long micro-capillary tubes (xylem and phloem), which transport resources from trunk to leaves, driven by a non-pulsatile pump (Niklas, 1994). If the microcapillary vessels were of uniform radius, as is often assumed in models of plants, a serious paradox results: the supply to the tallest branches, where most light is collected, suffers the greatest resistance. This problem had to be circumvented in order for the vertical architecture of higher plants to have evolved. Furthermore, the branches that distribute resources also contain substantial quantities of dead wood which provide biomechanical support, so the model must integrate classic bending moment equations with the hydrodynamics of fluid flow in the active tubes.

Assuming a space-filling branching network geometry with invariant terminal units (petioles or leaves) and minimization of energy use as in the cardiovascular system, the theory predicts that tubes must have just enough taper so that the hydrodynamic

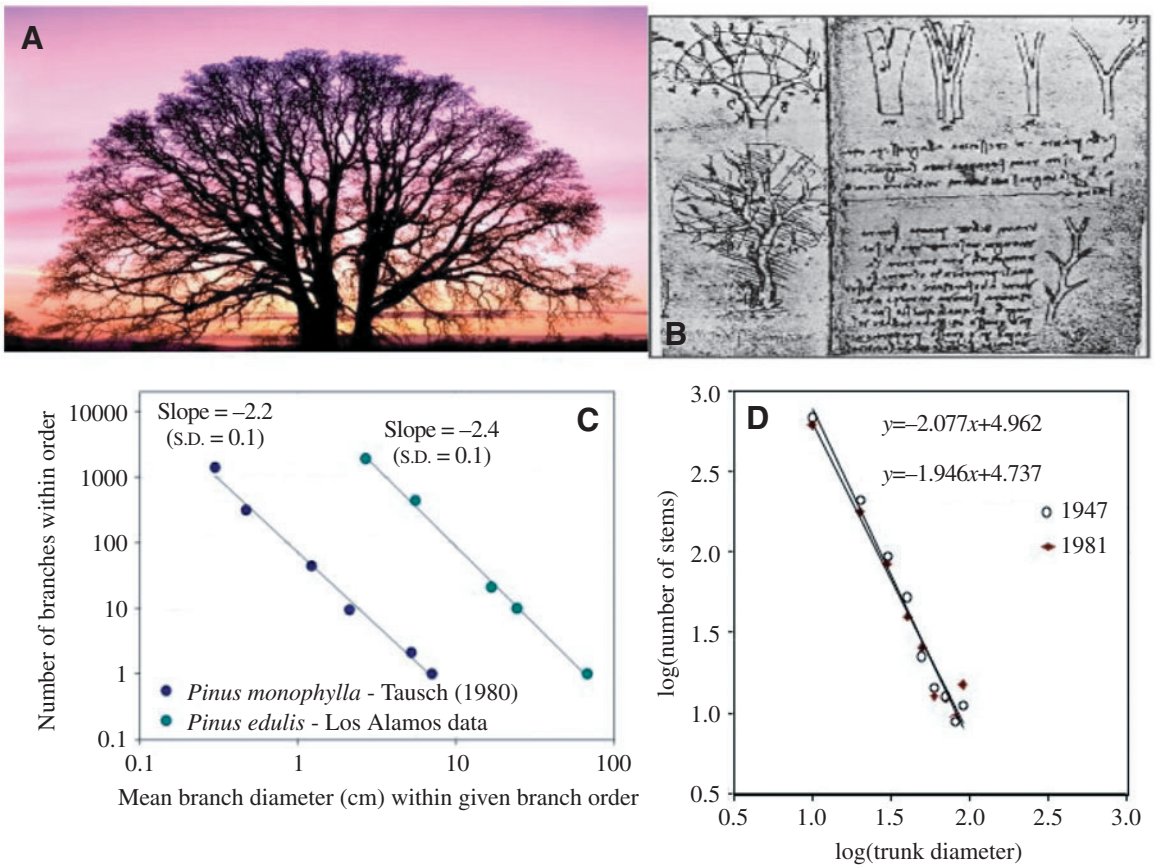

Fig. 9. (A) A typical tree. (B) A page from Leonardo's notebooks illustrating his discovery of area-preserving branching for trees. (C) A plot of the number of branches of a given size in an individual tree versus their diameter (in cm) showing the predicted inverse square law behaviour. (D) A plot of the number of trees of a given size *vs* their trunk diameter (in cm) showing the predicted inverse square law behaviour. The data are from a forest in Malaysia taken at times separated by 34 years, illustrating the robustness of the result. Even though the individual composition of the forest has changed over this period the inverse square law has persisted. Figure taken from West and Brown (2004), with permission.

resistance of each tube is independent of path length. This therefore 'democratises' all tubes in all branches, thereby allowing a vertical architecture. As in the mammalian system, many scaling relations can be derived both within and between plants, and these make quantitative testable predictions for metabolic rate (the 3/4 exponent), area-preserving branching, xylem vessel tapering and conductivity, pressure gradients, fluid velocity, and the relative amount of non-conducting wood to provide biomechanical support (Figs 8, 9).

Of particular relevance here is the fact that these two systems, in plants and mammals, which have evolved independently by natural selection to solve the problem of efficient distribution of resources from a central 'trunk' to terminal 'capillaries' and which have such fundamentally different anatomical and physiological features, nevertheless show identical $M_b^{3/4}$ scaling of whole-organism metabolic rate, and comparable quarter-power scaling of many structures and functions. Our model accurately predicts scaling exponents for 17 parameters of trees (West et al., 1999b). These sets of comparable quarter-power scaling laws reflect convergent solutions of trees and mammals to the common problems of vascular network design satisfying the same set of basic principles.

The fourth dimension

We have shown that power law scaling reflects generic properties of energy and resource distribution networks: space-filling, invariant terminal units and minimization of energy expenditure are sufficient to determine scaling properties, regardless of the detailed architecture of the network. For example, area-preserving branching and the linearity of the network volume with body mass both follow from optimising the solution to the dynamical equations for network flow and are sufficient to derive quarter-powers in both mammals and plants. Nevertheless, one can ask why it is that exponents are destined to be quarter-powers in all cases, rather than some other power, and why should this be a universal behaviour extending even to unicellular organisms with no obvious branching network. Is there a more general argument, independent of dynamics and hierarchical branching that determines the 'magic' number 4? This question was addressed by Banavar et al. (1999) who, following our work, also assumed that allometric relations reflect network constraints. They proposed that quarter-powers arise from a more general class of directed networks that do not necessarily have fractal-like hierarchical branching. They assumed that the network volume scales linearly with body mass M_b and claimed on general grounds that a lower bound on the overall network flow rate scales as $M_b^{3/4}$. Although intriguing, the biological significance of this result is unclear, not only because it is a lower bound rather than an optimization, but more importantly, because it was derived assuming that the flow is *sequential* between the invariant terminal units being supplied (e.g. from cell to cell, or from leaf to leaf) rather than hierarchically *terminating* on such units, as in most real biological networks. Whether their result can be generalized to general networks of more relevance in biology is unclear.

A general argument (West et al., 1999a) can be motivated from the observation that in d dimensions our derivations of the metabolic exponent obtained from solving the dynamical equations leads to $d/(d+1)$, which in three dimensions reduces to the canonical 3/4. Thus, the ubiquitous '4' is actually the dimensionality of space ('3') plus '1'. In our derivations this can be traced partially to the space-filling constraint, which typically leads to an increase in effective scaling dimensionality (Mandelbrot, 1982). For example, the total area of two-dimensional sheets filling three-dimensional washing machines clearly scales like a volume rather than an area. In this scaling sense, organisms effectively function as if in four spatial dimensions. Natural selection has taken advantage of the generalised fractality of space-filling networks to maximise the effective network surface area, A, of the terminal units interfacing with their resource environments. This can be expressed heuristically in the following way: if terminal units are invariant and the network space-filling, then metabolic rate, $B \propto A$, which scales like a volume, rather than an area; that is, $B \propto A \propto L^3$ (rather than $\propto L^2$), where L is some characteristic length of the network, such as the length of the aorta in the circulatory system of mammals or the length of the stem in plants. However, the volume of the network, $V_{net} \propto AL \propto L^4$. So, if we assume that $V_{net} \propto M$ (proven from energy minimisation in our theory), we then obtain $V_{net} \propto M \propto L^4$. Thus, $L \propto M^{1/4}$ leading to $B \propto A \propto L^3 \propto M^{3/4}$. This therefore provides a geometrical interpretation of the quarter-powers, and, in particular, a geometrical 'derivation' of the 3/4 exponent for basal metabolic rate (West et al., 1999a).

Criticisms and controversies

Since our original paper was published (West et al., 1997), there have been several criticisms (Darveau et al., 2002; Dodds et al., 2001; White and Seymour, 2003). Some of these revolve around matters of fact and interpretation that still need to be resolved – such as the scaling of maximal metabolic rates in mammals or the precise value of the exponent. Others claim to provide empirical information or theoretical calculations that refute our models. We have not found any of these latter criticisms convincing for two reasons. First, most of them rest on single technical issues, for which there are at least equally supportable alternative explanations, and some that are simply incorrect. Furthermore, most of these have been concerned solely with mammalian metabolic rate, so they fail to appreciate that our theory offers a single parsimonious explanation, rooted in basic principles of biology, physics and geometry, for an enormous variety of empirical scaling relations. None of the criticisms offer alternative models for the complete design of vascular networks or for the $M_b^{3/4}$ scaling of whole-organism metabolic rate. Here, we address some of the more salient issues.

Scaling of metabolic rate: is it 3/4, 2/3 or some other number?

Some of the recent criticisms have centered around whether

whole-organism metabolic rate really does scale as $M_b^{3/4}$ (Dodds et al., 2001; White and Seymour, 2003). Indeed, Kleiber himself (Kleiber, 1932, 1975) and many others (Brody, 1945; Calder, 1984; McMahon and Bonner, 1983; Niklas, 1994; Peters, 1986; Schmidt-Nielsen, 1984) had expected that basal mammalian metabolic rates (BMR) should scale as $M_b^{2/3}$, reflecting the role of body surface area in heat dissipation. Heusner (1982) presented a statistical analysis focusing on intra-specific comparisons and suggested that the exponent was indeed 2/3 rather than 3/4, indicative of a simple Euclidean surface rule. The statistical argument was strongly countered by Feldman and McMahon (1983), and by Bartels (1982), after which the debate subsided and the ubiquity of quarter powers was widely accepted (Calder, 1984; McMahon and Bonner, 1983; Peters, 1986; Schmidt-Nielsen, 1984). In his synthetic book on biological scaling, Schmidt-Nielsen seemed to have settled the argument when he declared that '*the slope of the metabolic regression line for mammals is 0.75 or very close to it, and most definitely not 0.67*' (Schmidt-Nielsen, 1984).

Arguments that the scaling of whole-organism metabolic rate is effectively a Euclidean surface phenomenon were overshadowed by two lines of opposing evidence. First, metabolic rates of many groups of ectothermic organisms, whose body temperatures fluctuate closely with environmental temperatures, so that control of heat dissipation is not an issue, were also shown to scale as $M_b^{3/4}$. Second, extensive work on temperature regulation in endotherms elucidated powerful mechanisms for heat dissipation, in which body surface area *per se* played an insignificant role (Schmidt-Nielsen, 1984).

Recently, however, this controversy was resurrected by Dodds (2001) and by White and Seymour (2003), who concluded that a reanalysis of data supported 2/3, especially for smaller mammals (<10 kg). These and earlier authors (Heusner, 1982) argued for an empirical exponent of 2/3 based on their reanalyses of large data sets, using various criteria for excluding certain taxa and data, and employing non-standard statistical procedures. For every such example, however, it is possible to generate a counter-example using at least equally valid data and statistical methods (Bartels, 1982; Feldman and McMahon, 1983; Savage et al., 2004b). Observed deviations from perfect $M_b^{3/4}$ seems attributable to some combination of elevated rates for the smallest mammals, as first observed empirically by Calder (1984) and predicted theoretically by our model (see above; West et al., 1997), and statistical artefacts due to small errors in precisely estimating the characteristic body masses of species. Ironically, one might argue that deviations from the 3/4 exponent for small mammals is another of the successful predictions of our theory.

More telling than repeated reanalyses of the largely overlapping data on basal metabolic rates of mammals would be a reanalysis of all of the multiple studies of scaling of whole-organism metabolic rate in different groups of organisms. Peters (1986) published such a meta-analysis of the large number of studies available at the time of his synthetic monograph. He obtained an approximately normal-shaped frequency distribution of exponents, with a sharp peak at almost exactly 3/4. Savage et al. (2004b) recently performed a similar analysis, incorporating data from additional studies,

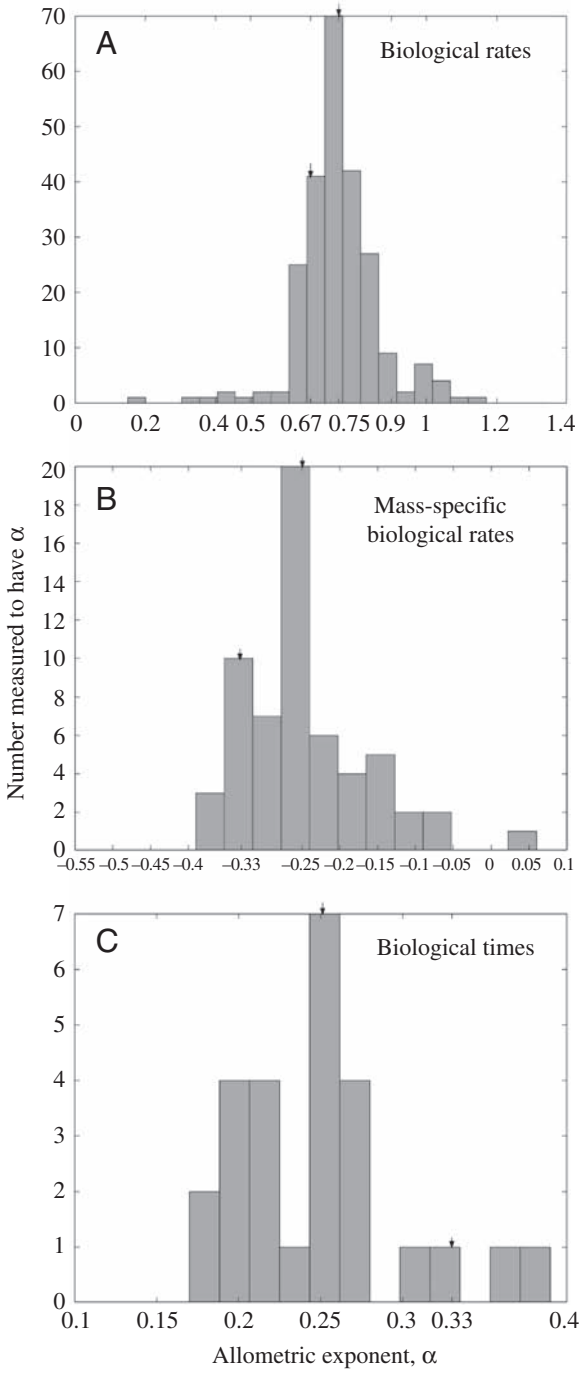

Fig. 10. Histograms of the exponents of (A) biological rates, (B) mass-specific biological rates (Peters, 1986) and (C) biological times (Calder, 1984). Note that the peak of the histogram for biological rates is very close to 0.75 (0.749±0.007) but not close to 0.67. Moreover, the histogram for mass-specific rates peaks near –0.25 (–0.247±0.011) but not –0.33, and the histogram for biological times peaks at 0.25 (0.250±0.011) and not 0.33. All errors quoted here are the standard error from the mean for the distribution. In all cases, the majority of biological rates and times exhibit quarter-power, not third-power, scaling. Figure taken from Savage et al. (2004b) with permission.

and obtained virtually identical results: the mean value of the exponent is 0.749±0.007, so the 95% confidence intervals include 3/4 but exclude 2/3 (Fig. 10). This analysis was extended to a variety of other rates and times leading to similar results: the mean value of the exponent for mass-specific rates was found to be –0.247±0.011 and for times, 0.250±0.011, so both of these clearly exclude a 1/3 exponent. It is worth emphasizing that these meta-analyses include studies of a wide variety of processes in a broad range of taxa (including ectotherms, invertebrates, and plants, as well as birds and mammals) measured in a very large number of independent studies by many different investigators working over more than 50 years. This kind of evidence had earlier led Calder (1984) to conclude that '*Despite shortcomings and criticisms [including the lack of a theoretical model], empirically most of the scaling does seem to fit* $M^{1/4}$ *scaling*.....', and Peters (1986) to remark that *'.....one cannot but wonder why the power formula, in general, and the mass exponents of 3/4, 1/4, and –1/4, in particular, are so effective in describing biological phenomena.*' We see no reason to change this assessment in the light of the very few recent studies that have once again argued for $M_b^{2/3}$ scaling.

Ours are whole-system models: how do other parameters scale?

Many critics lose sight of the fact that our theory generates a complete, whole-system model for the structure and function of the mammalian arterial system as well as quantitatively predicting many other unrelated biological phenomena. The model quantifies the flow of blood from the heart to the capillaries. It predicts the scaling exponents for 16 variables, including blood volume, heart rate, stroke volume, blood pressure, radius of the aorta, volume of tissue served by a capillary, number and density of capillaries, dimensions of capillaries and oxygen affinity of hemoglobin (Fig. 3; West et al., 1997). No alternative whole-system model has been developed that makes different predictions.

The most serious theoretical criticism, by Dodds et al. (2001), took issue with our derivation of the 3/4 exponent for mammals based on an analysis of the pulsatile circulatory systems Their calculation, however, naively minimized the total complex impedance of the network, which includes analogs to capacitance and inductance effects not directly associated with energy dissipation. This is a subtle, but important, point. The meaningful, physical quantity associated with energy dissipation due to viscous forces is the real part of the impedance, and it is only this that must be minimized in order to minimize the total energy dissipated. In addition, and as already emphasized above, the total energy expended in a pulsatile system is the sum of two contributions: the viscous energy dissipated (determined from the real part of the impedance) and the loss due to reflections at branch points. Dodds et al. neglected, however, to consider this critical latter effect and so failed to impose impedance matching, thereby allowing arbitrary reflections at all branch points, so the total energy expended is no longer minimised. Consequently, they did not obtain area-preserving branching in large vessels nor, therefore, a 3/4 exponent nor a realistic description of the flow. Put simply, their criticism is invalid because they failed to correctly minimize the total energy expended in the network.

For those who would have mammalian BMR scale as $M^{2/3}$, the onus is on them to explain the scaling of other components of the metabolic resource supply systems In particular, they need to explain why cardiac output and pulmonary exchange also scale as $M^{3/4}$ in mammals (Schmidt-Nielsen, 1984). Heart rate (f_H), stroke volume (V_S), respiration rate (R_l) and tidal volume (V_T) can all be measured with at least as much precision and standardization as metabolic rates It is well established that $f_H \propto R_l \propto M^{-1/4}$, and $V_S \propto V_T \propto M$, so the cardiac output, $f_H \times V_S$, scales as $M^{-1/4}M = M^{3/4}$, and similarly for the rate of respiratory ventilation, $R_l\, V_T$, again scaling as $M^{3/4}$. Of course this is not surprising if metabolic rate scales as $M^{3/4}$, because the rate of respiratory gas exchange in the lungs and the rate of blood flow from the heart with its contained oxygen and fuel must match the rate of metabolism of the tissues. There is, however, a serious unexplained inconsistency in the quarter-power scalings of these components of the circulatory and respiratory systems if metabolic rate scales as $M^{2/3}$.

Supply and demand at the cellular level: why do the cells care about the size of the body?

Darveau et al. (2002) and Suarez et al. (2004) criticized our theory as being 'flawed' for implying that '*there is a single rate-limiting step or process that accounts for the* b *value in equation (1)*' (i.e. the allometric exponent for metabolic rate). As an alternative, they suggested a much more complicated, multiple-causes, allometric cascade model, in which metabolic rate is the sum of all 'ATP-utilising processes', $B_i{:}B = \Sigma B_i$. This sum simply represents overall conservation of energy, so it must be correct if it is carried out consistently. Therefore, it cannot be in conflict with our theory. Darveau et al. incorporated many details of metabolic processes both at whole-organism and at cellular–molecular levels in their sum: from pulmonary capacity, alveolar ventilation and cardiac output to Na^+,K^+-ATPase activity, protein synthesis and capillary–mitochondria diffusion. All were added as if they were independent and in parallel. However, many of these processes are primarily in series, thereby leading to multiple-counting and therefore to a violation of energy conservation. Each B_i was assumed to scale allometrically as $B_i = a_i M^{b_i}$ so $B = a\Sigma c_i M^{b_i} \equiv aM^b$, where the $c_i (= a_i/a)$ were identified with conventional control coefficients defined as '*the fractional change in organismal flux divided by the fractional change in capacity*' of the *i*th contributing process. As such, the c_i are dimensionless. Unfortunately, however, it is obvious that the c_i as used by Darveau et al. in the above equations cannot be dimensionless since the b_i that were used all have different values. Consequently, their results are inconsistent and incorrect (West et al., 2003).

Even without this fatal flaw, their model makes no *a priori* predictions about the scaling of metabolic rate, since no explanation is offered for the origin or values of the scaling

exponents for the contributing processes, b_i. If the sum is carried out correctly, it simply verifies the conservation of metabolic energy. From the Darveau et al. point of view the b_i are simply inputs; from ours, they are potentially outputs determined from network constraints. It is surely no accident that almost all of the b_i cluster around 0.75.

Although we take issue with the characterization of our theory as 'single-cause' – and point out that it predicts the scaling of 16 variables for the mammalian cardiovascular system in addition to metabolic rate and, in addition, makes similar predictions for plants – we regard its relative simplicity as a strength rather than a weakness. We contend that for a given metabolic state, scaling of metabolic rate between different-sized organisms (that is, its relative value: M varying, but with a and a_i fixed) is indeed constrained by the network and this is the origin of quarter-powers. However, the absolute rate of resource flow and power output (given by a and a_i) within an individual organism (that is, with fixed M) is not rate-limited by the network: as in any transport system, changes in supply and demand cause the network flow to change accordingly. The concept of an absolute 'single-cause' as used by Darveau et al. simply does not arise. Because of this, our model deliberately leaves out much of what is known about the biochemistry and physiology of metabolism at cellular-molecular levels.

More generally, analytic models are typically deliberate oversimplifications of more complex realities. They are intended to ignore many details, to capture just the most fundamental essence of a phenomenon, to provide a useful conceptual framework, and to make robust testable predictions. To make an analogy, the basic theory of Mendelian genetics still provides the conceptual foundation for most of modern population and evolutionary genetics, even though it does not incorporate much of what is known about genetics at the cellular (chromosomal) and molecular level. Indeed, for at least a century Mendel's laws have helped to guide the research into the structure and function of the genetic material. Mendel's laws ignore linkage, epistasis and crossing over, not to mention such features of genomic architecture as regulatory regions, introns and transposons. They can now be amended or extended to account for these phenomena if and when it is important to incorporate such details into a conceptual framework or an empirical analysis.

We therefore find it surprising that certain features of metabolic processes at molecular and cellular levels (Darveau et al., 2002) are viewed as irreconcilable alternatives to our model. We view them as generally consistent and complementary. So, for example, cellular–molecular processes related to BMR generally scale close to $M^{3/4}$ (but with higher exponents for some processes linked more directly to maximal metabolic rate (Weibel et al., 2004). This is used as input to the 'allometric cascade model' of Darveau et al. (2002), who claim that the $M^{3/4}$ scaling of metabolic rate is determined by demand-generated processes at the cellular–molecular level rather than by supply-generated processes at the whole-organism level. We fail to see the logic of this argument, which makes an explicit distinction between supply- and demand-driven processes. We conjecture that metabolic systems at the molecular, organelle and cellular levels, and the circulatory, respiratory, and other network systems that supply metabolic requirements at the whole-organism level, are co-adjusted and co-evolved so as to match supply to demand and *vice versa*. More importantly, if whole-organism metabolic rate is determined entirely by cellular and molecular processes, why should it scale at all and why should it scale as $M^{3/4}$? The simplest design would be to make the cells and molecules in mammals of different sizes identical building blocks so that cellular metabolic performance is invariant. Whole-organism metabolic rate would then simply be the sum of the rates of all the identical cells, and so would scale linearly with mass. Our theory shows, however, that the constraints on blood volume, cardiac output, etc resulting from generic properties of network design naturally lead to $M^{3/4}$ scaling. But given this scaling of whole-organism metabolic rate, it is completely consistent – indeed it is predicted by our theory – that *in vivo* the cellular and molecular processes of metabolism also scale as $M^{3/4}$ (West et al., 2002b).

Although we disagree with the dichotomous supply- and demand-driven views of metabolic regulation, our model does make predictions about the consequences of altering the relationship between the cells that perform the work of metabolism and the vascular networks that supply the resources. Specifically, it predicts that since the cellular metabolic rates of large mammals are downregulated to obey the constraints of reduced resource supply, their rates should increase and converge on the cellular rates of small mammals when they are grown in culture with abundant resources. This is indeed observed (Fig. 5). Metabolic rates of cells derived from different species and body sizes of mammals converge to near maximal rates after being grown for multiple generations in tissue culture under conditions of abundant resource supply (West et al., 2002b). A complementary result consistent with this is reported by Else et al. (2004), who found that when avian liver cells were disassociated and maintained in culture for short periods, the allometric exponent decreased: from approximately –1/3 *in vivo* (the exact value is complicated by the fact that the study used both passerine and non-passerine birds, which likely have different normalization constants) to approximately –0.1 *in vitro*. Although Else et al. state that this result '*undoubtedly supports the allometric cascade model*,' it ironically is exactly what would be expected in our theory if the cells have only partially compensated for isolation from the vascular supply network, because they had been maintained in culture without division for only a few hours. We conjecture that, if they had been cultured for many days and had the opportunity to divide and adjust the numbers of mitochondria, the exponent would continue to decrease and eventually asymptote near zero.

Scaling of other biological rates and times: are quarter powers universal?

Nearly all biological rates scale as $M^{-1/4}$, although these vary from milliseconds for twitch frequencies of skeletal muscle

to decades for periods of population cycles (Calder, 1984; Lindstedt and Calder, 1981). Similarly, biological times tend to scale as $M^{1/4}$, although these again vary from milliseconds for turnover times of ATP to decades for lifespans of individuals. Recently, we (Savage et al., 2004b) collected data and performed a meta-analysis of many of these rates and times. The results were very clear: average exponents for rates and times showed clear peaks very close to 1/4 and –1/4, respectively, and the 95% confidence intervals excluded the values of –1/3 and 1/3 that would be predicted on the basis of Euclidean geometric scaling (Fig. 10). So, the scaling of these many other attributes contributes to a synthetic body of evidence providing overwhelming support for quarter-power allometric scaling. This is a pervasive feature of biology across an enormous range of mass, time and space.

Our recent work has involved extensions of metabolic theory to explain scaling of other attributes of biological structure and function at the levels of individuals, populations and ecosystems. Beyond ontogenetic growth and development of individuals discussed above (Gillooly et al., 2001; West et al., 2002a), these have focused on individual-level production of biomass in animals and plants (Gillooly et al., 2001, 2002), population growth rates and related life history attributes (Savage et al., 2004a), rates of carbon flux and storage and flux in ecosystems (Allen et al., 2005), and rates of molecular evolution (Gillooly et al., 2005).

BMR, FMR and $\dot{V}_{O2max}$: what is optimized by natural selection?

Most of the historical and recent discussion about the allometric scaling of metabolic rate, especially when applied to mammals, has focused on basal metabolic rate (BMR). BMR is used as a standardized measure of physiological performance because it can be rigorously defined and quite accurately measured as the metabolic rate of a resting, fasting, post-absorbtive mammal within its thermoneutral zone. However, since the animal is not in an energetic steady-state, let alone at a normal level of activity, BMR is of questionable biological significance.

Of much more biological relevance is the field metabolic rate (FMR), which is the rate of energy expenditure of an animal during 'normal' activity in nature (Nagy et al., 1999). This immediately raises the question of standardization. What does normal activity mean? FMR is typically determined using doubly-labeled water or a similar technique to obtain an integrated measure of metabolic rate over a period of several days. So it includes the costs of locomotion, grooming, foraging and other 'maintenance' activities, but usually not the greater costs of reproduction or of thermoregulation to counteract severe cold or heat stress, and not the energetic savings accrued by entering hibernation, aestivation or torpor. Natural selection has presumably operated to maximize the performance of the mammalian metabolic processes – and of the cardiovascular system that supplies resources for metabolism – over the entire life history, thereby incorporating the costs of reproduction, thermoregulation, hibernation, migration, and other such activities throughout an annual cycle. There are few studies on such a scale, however, so FMRs probably provide the most relevant measures of metabolic performance.

Some physiologists (Taylor et al., 1988; Weibel et al., 2004, 1991) have emphasized the maximal sustained aerobic metabolic rate (MMR) or $\dot{V}_{O2max}$. Such levels of performance are typically measured in non-volant mammals as rates of energy utilization or oxygen consumption while running at high speed. They are undoubtedly of great adaptive significance, especially during predator avoidance, prey capture and reproductive activity. There are, however, some problems of standardization. One concerns how long and at what speed the mammals are run. Since both maximal speed and endurance scale positively with body size (Calder, 1984; Schmidt-Nielsen, 1984), there is the issue of how this should be incorporated into experimental protocols. Additionally, there is substantial variation in performance among species, even those of the same body size. 'Athletic' mammals such as cheetahs, dogs, horses, antelopes and hares, which have evolved to run at high speeds, have several-fold higher $\dot{V}_{O2max}$ and factorial aerobic scope than 'sedentary' species of similar size.

Nevertheless, we are convinced, especially by the recent work of Weibel et al. (2004), that the athletic species define an upper boundary for the scaling of $\dot{V}_{O2max}$, which has an exponent significantly greater than 3/4 and perhaps even approaching 1. We are quick to point out, however, that while this raises important questions, it does not invalidate our theory. There are several issues. First, the high metabolic rates of these athletic mammals are still supplied by the hierarchically branching arterial network, so many of the principles embodied in our model must still apply. Second, there is a reallocation of blood flow during exercise. Heart rate increases and blood flow is shunted to the metabolically active tissues, chiefly cardiac and skeletal muscle, to supply the increased oxygen demand. But since total blood volume remains virtually unchanged, blood is diverted from other tissues, such as digestive organs, and they are temporarily oxygen-deprived. Third, it is unlikely that the steep scaling of MMR can hold over the entire mammalian size range, including the great whales. Simple extrapolation of two allometric relationships, one with an exponent of 3/4 for BMR and FMR, and the other with a much higher exponent for MMR, would require a very large factorial aerobic scope and prevent any of the largest mammals from being athletic.

Lastly, our theory predicts that the allometric exponent should change between BMR and MMR because of the sensitivity of impedance matching to heart beat frequency. Recall that an important ingredient to our derivation of the 3/4 was that reflections be eliminated at branch junctions, leading to area-preserving branching. However, all the important physiological variables, including heart-rate, are 'tuned' to body size. If heart rate is increased because of increased activity, but the dimensions of the large vessels are kept fixed, there is a mis-match and reflections result. We speculate that

while the scalings of BMR and FMR reflect minimization of energy loss (thereby requiring impedance matching), scaling of MMR reflects maximization of power output, which is achieved by several changes in the cardiovascular system, including giving up impedance matching. Such an effect would indeed drive the exponent larger, but it is difficult to calculate the exact value without a formal model.

We suggest that what is needed is an effort to model the performance of the cardiovascular and skeleton–muscular systems of athletic mammals performing under standardized conditions of $\dot{V}_{O_2max}$. Such a model would retain many features of our model for the arterial system, but would also incorporate what is known about changes in heart rate, blood flow and tissue metabolism. To the extent that not all of the data desired may be available, such a model would help to motivate empirical studies by comparative physiologists to better understand how the mammalian cardiovascular system adjusts dynamically to the shifting demands imposed by different levels of activity. Some features of our original model may need to be changed. For example, natural selection has likely maximized blood flow to certain tissues so as to maximize power output for speed or endurance rather than to minimize expenditure of energy within the arterial network. Nevertheless, such a whole-system model would demand basic constraints, such as conservation of blood volume within the network and sufficient oxygen supply to meet aerobic metabolic demand. Ultimately this could lead to a complete model that would quantitatively predict the scaling exponents and normalizations for many relevant parameters of the system, including how they deviate from quarter-powers in the active state.

Concluding remarks

We are very much aware that the philosophy of our theoretical research program on biological scaling runs counter to recent trends in comparative and mammalian physiology. Although not a major theme of current research, analytical mathematical models and general theory based on first principles have in the past played an important role in physiology. As examples, we cite applications of thermodynamics to body temperature regulation (Scholander et al., 1950), electrical and chemical potentials to nerve conduction (Hodgkin and Huxley, 1952), countercurrent exchange principles to thermoregulation (Scholander and Schevill, 1955), aerodynamic theory to flying animals (Greenwalt, 1975), and hydrodynamic principles to aquatic organisms (Vogel, 1981).

Recently, however, most research programs have had a strong empirical emphasis. They have sought to explain variation in performance of organisms from different environments and phylogenetic lineages in terms of details of structure and function at cellular and molecular levels. They have accumulated and organized a vast store of information. A powerful theme in basic and comparative physiology has been to understand the molecular basis, including characterizing enzyme kinetics and identifying genes, for variation in whole-organism function. This trend mirrors similar reductionist themes in many branches of science, from atomic physics to human psychology, during the last few decades.

While we recognize the scientific merit and importance of this approach, we also believe that general theory and mathematical models can play an important role. Sciences typically cycle between periods of empiricism and theory, reductionism and holism. Empirical advances are typically unified and synthesized by theoretical contributions that use basic principles and idealized, simplified models to obtain generalized insights. Reductionist studies that discover components and processes at microscopic levels are given additional meaning by holistic studies that show how these phenomena contribute to structure and function of large, complex systems at higher levels of organization. Theoretical and empirical, reductionist and holistic studies are typically conducted by different individuals, motivated by different questions and predilections. Both are equally necessary for scientific progress.

We believe that new theories of biology can play a major role in synthesizing recent empirical advances and elucidating universal features of life. We see the prospects for the emergence of a general theory of metabolism that will play a role in biology similar to the theory of genetics. Genetic theory is increasingly successful in explaining the development of the phenotype and the dynamics of evolutionary change in terms of the heritable traits of individual organisms, and in understanding how those individual-level traits are coded and regulated by the molecular structure and function of the genome. Genetic theory is successful in part because there is a universal molecular genetic code. The code operates according to certain basic principles of structure and function to direct the ontogeny and determine the phenotype of individual organisms, and these individuals live, die, and leave offspring according to additional rules of population genetics and ecology to determine the evolutionary dynamics of populations and lineages.

Similarly, all organisms share a common structural and functional basis of metabolism at the molecular level. The basic enzymes and reactions are universal, at least across the aerobic eukaryotes. Additional general rules based on first principles determine how this molecular-level metabolism is supplied and regulated at higher levels of organization: from organelles, to cells, to organisms, to ecosystems. The most important of these rules are those relating to the size of the systems, including the body size of the individual organisms, and the temperature at which they operate. Our theory of quarter-power scaling offers a unified conceptual explanation, based on first principles of geometry, biology, physics and chemistry for the size-dependence of the metabolic process. The theory is based on generic properties of the metabolic distribution networks in simplified, idealized organisms. It provides a 0th order quantitative explanation for many observed phenomena at all of the hierarchical levels of organization.

Quarter-power scaling theory is not the only ingredient of a general theory of metabolisms Thermodynamics and, in particular, temperature are clearly another critical ingredient. As already emphasised, quarter-power allometry and simple Boltzmann kinetics together account for the body size and temperature dependence of metabolic rates and other related biological structures, rates, and times across all levels of organization from molecules to ecosystems (Gillooly et al., 2001, 2002; Savage et al., 2004a). For example, these two basic components of metabolic theory account for more than 99% of the variation in rates of whole-organism biomass production across an enormous diversity of organisms spanning 16 orders of magnitude in body mass from unicellular algae and protists to trees and mammals (Ernest et al., 2003).

There is much work still to be done, but we look forward to the development of universal theories of biology that integrate across levels of organization from molecules to populations and ecosystems and across the diverse taxonomic and functional groups of organisms. Such theories will incorporate recent empirical discoveries, especially the recent advances at cellular to molecular levels of organization. Ultimately they may provide for biology the kinds of unifying conceptual frameworks, based on first principles and expressed quantitatively in the language of mathematics, that similar theories do for physics and chemistry. This is a bold but exciting vision for the 21st Century, which many are calling the Century of Biology.

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