The Journal of Experimental Biology 214, 1055-1062

doi:10.1242/jeb.054502

REVIEW

Analytic theories of allometric scaling

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Accepted 14 December 2010

Summary

During the 13 years since it was first advanced, the fractal network theory (FNT), an analytic theory of allometric scaling, has been subjected to a wide range of methodological, mathematical and empirical criticisms, not all of which have been answered satisfactorily. FNT presumes a two-variable power-law relationship between metabolic rate and body mass. This assumption has been widely accepted in the past, but a growing body of evidence during the past quarter century has raised questions about its general validity. There is now a need for alternative theories of metabolic scaling that are consistent with empirical observations over a broad range of biological applications. In this article, we briefly review the limitations of FNT, examine the evidence that the two-variable power-law assumption is invalid, and outline alternative perspectives. In particular, we discuss quantum metabolism (QM), an analytic theory based on molecular–cellular processes. QM predicts the large variations in scaling exponent that are found empirically and also predicts the temperature dependence of the proportionality constant, issues that have eluded models such as FNT that are based on macroscopic and network properties of organisms.

Key words: fractal network theory, two-variable power law, allometric cascade model, metabolic limit boundaries hypothesis, quantum metabolism.

Introduction

The dependence of metabolic rate on body mass is a fundamental problem in bioenergetics. It has implications for many aspects of biology including species variations in body size, the evolution of life history, the structure and function of ecological communities, pharmacokinetics, and the origins of cancer and other age-related diseases (e.g. Ings, 1990; Nagy, 2005; Speakman, 2005; Bangert et al., 2008; Ramanujan and Herman, 2008). For almost a century, this dependence has been assumed to obey a two-variable power law ($B=\alpha M^{\beta}$, where B is metabolic rate, M is body mass, α is a proportionality constant and β is the scaling exponent). This proposal was first articulated by Krogh in the context of respiration, the usual surrogate for mammalian metabolic rate (Krogh, 1916). Kleiber, like others, claimed that β is ~¾ in mammals, and Hemmingsen extended that claim to unicellular organisms and ectotherms (Kleiber, 1947; Hemmingsen, 1960). Since then, it has been widely assumed that the '¾-power law' is universal. Numerous attempts have been made to explain it, usually ignoring the proportionality constant α. Most such attempts have been framed largely in terms of macroscopic organismic properties: elastic similarity (McMahon, 1973) or the geometry of transport pathways (West et al., 1997; Banavar et al., 2002). However, recent investigations of unicellular organisms, plants and animals (reviewed by Glazier, 2005) indicate that the scaling exponent can assume values mostly between ½ and 1, depending on taxon and body mass, and that α is also described by a large range of values.

These recent findings are difficult to reconcile with the presently dominant account of allometric scaling, the fractal network theory (FNT) proposed approximately 13 years ago (West et al., 1997; West et al., 1999; West et al., 2002). In this review we evaluate FNT on the basis of current perspectives and we consider the potential of alternative models of allometric scaling, emphasizing a recent theory, quantum metabolism (QM), which adopts a molecular–cellular perspective.

Our analysis focuses on the empirical observations that (1) β can assume a large range of values and (2) α is temperature dependent and varies within and among taxa. We will give particular attention to FNT because of the interest it has generated, but we will also discuss other macroscopic models. Our argument for QM, the only current theory that analyzes metabolic regulation from a molecular–cellular perspective, is based partly on the fundamental mechanism it invokes, and partly on its ability to explain the variations in both scaling exponent and proportionality constant.

FNT and QM are both mechanistic in that they aim to derive the empirical allometric rules by mathematical analysis of certain biological processes. FNT acts at the macroscopic level and is based on the flow of fluids in a branching network; this analysis is achieved by appealing to fluid mechanics in complex geometries. QM acts at the molecular–cellular level and is based on the process of energy transduction within cellular organelles; this analysis is achieved by appealing to the formalism of quantum mechanics as adapted to the flow of energy in biological systems.

Mechanistic models are valuable because of their predictive scope and explanatory power based on fundamental processes. Qualitative perspectives based on hypotheses consistent with empirical observation are also valuable in identifying relationships that mechanistic analysis must explore, and will be considered in our discussion.

FNT

FNT is a macroscopic theory of metabolic activity. It assumes that the resource distribution system in an organism is fractal-like or

self-similar, i.e. if a small part of the system were magnified it would resemble the whole. In a true fractal this branching would continue indefinitely and the finest branches would be infinitesimal; however, FNT contends that finest branches are capillaries with dimensions that are identical irrespective of animal size.

The analysis rests on several assumptions, of which the following are crucial: (1) the relationship between B and M satisfies the rule $B \propto M^a$ where a is some numerical constant; (2) blood systems of differently sized animals occupy equal fractions of their body volume; and (3) at every level of the distribution system each daughter branch has half the length, one-eighth the cross-sectional area and one-sixteenth the volume of the parent branch.

Exploiting the physical processes describing fluid flow within this geometrical network, FNT predicts $a=¾$, using these assumptions.

FNT was subsequently applied to other aspects of physiology, e.g. growth (of organisms with vascular supply networks) and carcinogenesis (Moses et al., 2008), and to aspects of evolutionary theory (Gillooly et al., 2005) and ecology (Brown et al., 2004). An alternative model predicting ¾-power scaling on the basis of distribution networks, but without assuming a fractal-like branching resource supply system, was published more or less concurrently (Banavar et al., 1999; Banavar et al., 2002). Recently, a close relationship between this alternative model and FNT has been proposed (Banavar et al., 2010).

Critiques of FNT

Any scientific theory may be evaluated in at least three ways. First, its assumptions may be challenged on the grounds of completeness, reasonableness and consistency with reality. Second, its predictions may be compared with empirical data. Third, its internal logic may be scrutinized to determine whether the predictions follow from the assumptions. Many studies during the past 10 years have revealed problems with FNT in respect of one or more of these three criteria (e.g. Alexander, 1999; Dodds et al., 2001; Chen and Li, 2003; Dawson, 2003; Makarieva et al., 2003; Makarieva et al., 2005a; Makarieva et al., 2005b; Kozłowski and Konarzewski, 2004; Agutter and Wheatley, 2004; Painter, 2005a; Hoppeler and Weibel, 2005; Glazier, 2005; Glazier, 2006; da Silva et al., 2006; Etienne et al., 2006; Chaui-Berlinck, 2006; Chaui-Berlinck, 2007; Clemente, 2007; O'Connor et al., 2007; Apol et al., 2008; Petit and Anfodillo, 2009; Mahmood, 2009). Some, but not all, of these criticisms have been answered (West and Brown, 2005), leading to debates [e.g. Kozłowski and Konarzewski (Kozłowski and Konarzewski, 2004; Kozłowski and Konarzewski, 2005) *versus* Brown et al. (Brown et al., 2005); Savage (Savage et al., 2007) *versus* Chaui-Berlinck (Chaui-Berlinck, 2006; Chaui-Berlinck, 2007)]. Some have questioned whether any universal theory of metabolic allometry is possible (Feldman, 1995; Riisgärd, 1998; Bokma, 2004).

The main criticisms fall under the following headings.

Range of value of scaling exponent

The scaling exponent $a=¾$ is inconsistent with a large body of empirical data. Collectively, these data show that the scaling exponent can assume values mostly in the range $½<\beta<1$ (e.g. Hayssen and Lacy, 1985; Dodds et al., 2001; White and Seymour, 2003; Makarieva et al., 2005c; Glazier, 2005; Farrell-Gray and Gotelli, 2005; White et al., 2007; Mahmood, 2009).

Range of applicability

The supply network, a crucial component of FNT, exists in vertebrates and invertebrates such as squids but not in animals such as crustaceans and snails with open blood systems, or lower invertebrates and unicellular organisms that lack anatomical circulatory systems (e.g. Alexander, 1999; Kooijman, 2000; Dawson, 2003; Kozłowski and Konarzewski, 2004; Painter, 2005a; Painter et al., 2006). In answer to this criticism, West et al. wrote: "We emphasize that the network can be 'virtual'; it need not be a physical system of branching tubes, so long as it exhibits hierarchical pathways of material flow" (West et al., 1999). However, although the assumption that intracellular solute transport depends (almost) exclusively on diffusion is naïve, no study of intracellular transport to our knowledge demonstrates hierarchical distribution networks within cells.

The proportionality constant

The assumptions of FNT overlook the fact that organisms with similar scaling exponent and similar mass may have different metabolic rates. The temperature dependence of metabolic rate is not a consequence of supply network geometry; it had to be accommodated into FNT by introducing kinetic principles extrinsic to the original theory (Gillooly et al., 2001; Downs et al., 2008).

Dependence of scaling exponent on environmental factors

Nakaya et al. showed empirically that the scaling exponent in the same organism can change from ¾ to 1 when the environmental constraints are altered (Nakaya et al., 2003). This is incompatible with FNT, which predicts a *unique* value of ¾, and with the amended network model by Banavar et al., which predicts a *maximum* value of ¾ and invariance within the same organism (Banavar et al., 2010).

In addition, some commentators have drawn attention to inaccuracies in the mathematical argument of FNT (e.g. Kozłowski and Konarzewski, 2004; Kozłowski and Konarzewski, 2005; Painter, 2005b; da Silva et al., 2006), which have been debated by the proponents of the theory. Readers who are interested in the mathematical details are referred to the original papers. Brown et al. (Brown et al., 2004) sought to extrapolate FNT to a 'metabolic theory of ecology', but many ecologists consider this attempt dubious because (1) the minimization of resource–supply cost is not a plausible criterion for evolutionary optimization and (2) there are numerous exceptions to ¾ scaling (e.g. Chen and Li, 2003; van der Meer, 2006; O'Connor et al., 2007).

In view of these criticisms, the current consensus is that FNT fails to meet the three broad criteria for theory evaluation: assumptions, agreement with observations and internal logic. One line of criticism, however, is especially problematical.

Metabolic rate is not related to body mass by a two-variable power law

The belief that metabolic rate and other physiological variables are related to body mass by a two-variable power law is assumed *a priori* in FNT. Yet it is not deducible from any principles of physics, geometry or biology, so it must be considered an unacknowledged *ad hoc* assumption.

Several reports during the past two decades have shown that log–log plots of metabolic rate and other physiological variables against body mass are not rectilinear, as the power-law assumption requires; they are either multilinear or curved (e.g. Hayssen and Lacy, 1985; Chappell, 1989; Jolicoeur, 1989; Knoops and Grossman, 1993; Batterham and George, 1997; Dodds et al., 2001;

Glazier, 2005; Painter, 2005b; Makarieva et al., 2009). These reports cast doubt on the two-variable power-law assumption. A recent paper by Fontana and colleagues (Kolokotrones et al., 2010) corroborates this conclusion: the numerous empirical data available for mammals are approximately consistent with a ¾ scaling exponent only over a limited body mass range, even for this restricted group of organisms. The authors were able to fit phenomenological equations to the mammalian data, notably quadratic equations, confirming that the log–log plots have a convex curvature. Data for other taxa are likely to give similarly non-linear log–log plots (e.g. Glazier, 2005), so any future theory of metabolic scaling must be required to predict such curvature.

Kolokotrones et al. suggest modifications of FNT that could meet this requirement (Kolokotrones et al., 2010). These *ad hoc* devices seem unlikely to apply throughout the biosphere because they suppose that metabolic rate is always determined by a resource supply network, and many organisms lack such networks (Alexander, 1999). More importantly, they further vitiate the claim that FNT rests on fundamental principles of geometry, physics and biology, and they appear not to be amenable to refutation by critical experimentation. The amendments proposed by Banavar et al. do rely on fundamental principles, but they too seem difficult to test critically (except for the prediction that blood velocity scales as the 1/12 power of body mass) (Banavar et al., 2010). A particular difficulty with this amendment is whether each of the service volumes (into which they divide the organism functionally) receives an equal share of the resource supply (Banavar et al., 2010). No matter whether this is assumed or denied, the consistency of the argument is questionable.

Alternative macroscopic perspectives

Analytic models with restricted applicability

Many of the alternative attempts to explain allometric scaling have been reviewed elsewhere, so they may be treated briefly here. For example, the biophysical model of McMahon (McMahon, 1975) applies only to animals with endoskeletons and skeletal muscles, and like FNT it fails to distinguish between standard and maximum metabolic rates (Agutter and Wheatley, 2004). Another biophysical model (Patterson, 1992) applies only to small aquatic organisms, and again it presupposes that metabolic rate is supply limited. Notwithstanding their restricted scope, both these models are mechanistic: they show that power law or other relationships between metabolic rate and body mass can be deduced mathematically from basic principles of physics and biology.

In addition to Kolokotrones et al. and Banavar et al. (Kolokotrones et al., 2010; Banavar et al., 2010), several other authors have suggested amendments of FNT. The most sophisticated of these accounts (da Silva et al., 2006) presents a mathematical analysis of the original theory and reviews alternative models; it concludes that a universal analytic theory is possible, based on a generalization of FNT (Barbosa et al., 2006), and predicts both standard and maximal metabolic rates in mammals and birds that are consistent with empirical data. However, it is not clear whether it applies to other taxa. Moreover, it still relies on the notion that (fractal-like) resource supply networks determine metabolic rate, so it is subject to the general criticisms discussed above.

The allometric cascade model

The allometric cascade model (Darveau et al., 2002; Hochachka et al., 2003) is phenomenological rather than mechanistic, but its underlying principles are important for any attempt to account for metabolic scaling. Its authors emphasize that different tissues (e.g. in mammals) metabolize at different rates and whole-body metabolic rate is a weighted sum or average of these rates, and they distinguish the scaling exponents associated with standard and maximal metabolic rates, which are known to be different (Weibel et al., 2004; Weibel and Hoppeler, 2005; White and Seymour, 2005; Glazier, 2008; Glazier, 2009). They exploit the apparatus of metabolic control analysis to develop their idea, emphasizing that it is simplistic to assume that a single constraint (e.g. resource supply) determines metabolic rate; rates are regulated at multiple levels of biological organization (Hochachka et al., 2003; Suarez and Darveau, 2005). In principle, the allometric cascade model could apply to all taxa, though it is explicitly aimed at metazoans. There is supporting evidence, e.g. from exercise physiology (Batterham and Jackson, 2003), and organ scaling involves a range of scaling exponents (Gutierrez, 2002).

The three-compartment model proposed by Painter does not derive from the allometric cascade concept, but exploits a similar idea (Painter, 2005b). It assumes a two-variable power law, but with a different scaling exponent in each compartment. The three compartments are: (1) allometric scaling of metabolic rate per unit cell mass, (2) tissues such as skin in which the scaling exponent may be expected to be ⅔ and (3) tissues such as skeletal muscle in which the scaling exponent may be expected to be 1. Painter's model predicts the convex curvature of the log–log plot of metabolic rate against mass, and the prediction is quantitatively close to the curve obtained from more than 600 standard metabolic rate measurements in mammals. In contrast, Wang et al. used a five-compartment model for mammals and showed that a weighted sum of the components generated a whole-body metabolic rate that scaled as the ¾ power of body mass, apparently supporting the two-variable power-law concept (Wang et al., 2001).

The metabolic level boundaries hypothesis

Glazier and his colleagues have advanced a metabolic level boundaries (MLB) hypothesis, inspired partly by the work of Kooijman and partly by the consideration that ecological factors impinge significantly on an organism's energy demands (Glazier, 2005; Glazier, 2008; Glazier, 2009; Glazier, 2010; Killen et al., 2010; Kooijman, 2000). The two-variable power law $B=\alpha M^{\beta}$ is assumed. The scaling exponent β is limited by two boundary constraints: (1) limitations on the fluxes of resources, heat and wastes imposed by exchange surface; (2) limitations on maintenance energy costs or (during periods of high activity) power production by body mass. The authors infer that β-values predominantly range between ⅔ and 1. According to the MLB hypothesis, β and α (which Glazier and colleagues call the 'metabolic level') are not independent: they correlate negatively when organisms are dormant or inactive and positively when they are active, so an overall plot of β against α should be U-shaped. Empirical evidence, for example from studies on teleost fish, supports this (Killen et al., 2010). A three-way link is suggested among ecological selection pressures, 'metabolic level' and the scaling of metabolic rate with body mass (Glazier, 2005; Glazier, 2009).

The MLB hypothesis forges a link between ecology and physiology and it seems to apply to all taxa. It is not a mechanistic theory in the sense of FNT or the McMahon and Patterson models; it does not purport to rely on mathematical reasoning from physical or geometrical principles. Nevertheless, it places constraints on any future analytic theory, which must be able to predict the U-shaped relationship between β and α.

QM

Harold, Hochachka et al., Darveau et al. and Painter observed that the relationship between metabolic rate and mass pertains to single cells as well as multicellular organisms and *ipso facto* requires explanation at the cellular level (Harold, 1986; Hochachka et al., 2003; Darveau et al., 2002; Painter, 2005b). The presumption underlying QM, i.e. metabolic scaling results from subcellular processes rather than the geometry of a resource supply system, has significant support (Benedict, 1938; Krebs, 1950; Altman and Dittmer, 1968; Rolf and Brown, 1997; Hochachka and Somero, 2000; Kozłowski et al., 2003).

The quantum theory of solids

The methodology of QM derives from the Einstein–Debye model (Kittel, 1995) that explains the relationship between specific heat and temperature. This model, the quantum theory of solids, assumes that the atoms in a crystalline solid are fixed in a lattice and undergo coupled vibrations because of the thermal energy of the system. The central assumption in the model is that these oscillations are quantized. This can be formally expressed in terms of Planck's quantization principle: the energy (E) that can be stored in a material oscillator with frequency ω can only be integral multiples of a basic energy unit that is proportional to the characteristic frequency of the oscillator according to:

$$E_n = nh\omega,\ n=1,2,\ldots, \quad (1)$$

where h is Planck's constant. The fundamental unit of energy in Einstein–Debye theory, the typical energy per molecule, is:

$$E(T) = k_B T, \quad (2)$$

where k_B is Boltzmann's constant and T is the absolute temperature.

The atoms in a crystal lattice undergo oscillations about the equilibrium with a simple harmonic dynamical process. The quantization of the material oscillators (θ) ensures that the mean energy per atom will be determined by the ratio of the vibrational energy spacing of the harmonic oscillator ($h\omega$) to the typical thermal energy per atom:

$$\theta = \frac{h\omega}{k_B T}\ . \quad (3)$$

This circle of ideas provided the analytical basis for explaining the empirical laws relating specific heat and temperature. QM exploits this methodology.

Arnold et al. exploited the ergodic theory of dynamical systems to derive a formal set of relationships between the macroscopic variables in statistical thermodynamics and the macroscopic parameters that describe the large-scale behaviour of birth and death processes in population dynamics (Arnold et al., 1994). These analytical methods were subsequently developed (Demetrius, 2003; Demetrius, 2006, Demetrius, 2008; Demetrius et al., 2009) to establish a formal set of correspondences between various concepts in thermal physics and concepts in bioenergetics:

Temperature ↔ cycle time
Specific heat ↔ metabolic rate
Gibbs–Boltzmann entropy ↔ evolutionary entropy.

These formal equivalences have a rigorous mathematical basis, provided by the framework, for applying the methodology of the quantum theory of solids to the study of energy transduction processes in cells; these energy transduction processes are determined by differences in the rates of metabolic reactions and are therefore mediated by differences in cycle time (see below).

Quantum theory of living matter: metabolism in unicellular organisms

QM studies the relationship between metabolic energy and the cycle time of the processes that transform external resources into biological work. The model assumes that energy transduction within cells can be understood in terms of the coupling of two molecular mechanisms: a redox or electron transport chain, and an ATPase motor that drives ADP phosphorylation. In aerobes, these processes are embedded in biomembranes, such as the inner membranes of the mitochondria present in almost all eukaryotic cells. The enzymes occupy fixed, localized positions within such membranes and are assumed to undergo coupled oscillations. A crucial element of this model is that the continuous supply of energy, derived from external substrates, into metabolic work will result in elastic vibrations of the embedded enzymes. These oscillations were predicted to be highly coherent in view of the strong coupling between the molecular groups involved (Fröhlich, 1968), though experimental confirmation of these predictions is still lacking.

QM rests on the postulate that Planck's quantization principle, a cornerstone of the Einstein–Debye quantum theory of solids, has an analogue in the oscillations of embedded enzymes. In this context, the quantization principle again asserts that the energy that can be stored in an enzymatic oscillator with frequency ω can only be integral multiples of a basic energy unit that is proportional to the characteristic frequency of the oscillator. Analytically, this means that:

$$E_n = n\eta\omega,\ n=1, 2, \ldots, \quad (4)$$

where the characteristic quantity η is an analogue of Planck's constant. The fundamental unit of energy in the quantum theory of cells is:

$$\tilde{E}(\tau) = g\tau, \quad (5)$$

where τ is the cycle time, the mean turnover time of the metabolic reactions in the cellular organelles, and g is the metabolic energy generated per unit time. It depends on the mode of coupling between the two molecular mechanisms of energy transduction, the redox chain and the ADP phosphorylation process.

The quantization of the enzymatic oscillators ensures that the mean energy per oscillator, θ, is given by the ratio of the vibrational spacing of $h\omega$ to the metabolic energy per enzyme:

$$\tilde{\theta} = \frac{\eta\omega}{g\tau}\ . \quad (6)$$

These ideas were applied (Demetrius, 2003; Demetrius, 2006) to derive (1) an expression for the mean metabolic energy generated by the cell and (2) the total metabolic energy u. u can be expressed as a function of τ and a dimensionality parameter, d:

$$u = \alpha\tau^{d+1}\ . \quad (7)$$

The quantity d is the number of independent degrees of freedom of the enzymes embedded in the cellular matrix. It describes the dimensionality of the molecular network. The metabolic rate is given by:

$$B = u / \tau\ . \quad (8)$$

By appealing to the relationship between metabolic energy and cell mass, namely, $u \propto M$, it can be shown that:

$$B = \alpha M^{\frac{d}{d+1}}\ . \quad (9)$$

The proportionality constant α is given by the Arrhenius equation:

$$\alpha = \rho\left[-\frac{\Delta E}{RT}\right]. \quad (10)$$

The constant ρ will depend on whether the coupling between reductant transfer and ADP phosphorylation is electrical (Mitchell, 1966) or chemical (R is the gas constant).

Electrical coupling

This is typical of aerobic metabolism. In this case $\rho \propto \Delta p$, where Δp is the proton-motive force across the membrane.

Chemical coupling

This characterizes anaerobic metabolism. In this case $\rho \propto J$, where the flux J depends on the kinetic parameters of the glycolytic enzymes.

These qualitative differences between different modes of metabolic energy generation are ascribed to events at the molecular and subcellular levels and offer a new angle on biological energy production. What is still lacking in QM is an examination of specific quantitative biological examples, especially in regard to different dimensionalities and the predicted variations in the scaling exponent.

Metabolism in multicellular organisms

A large body of empirical data reveals metabolic allometry at several levels of biological organization: tissues, organs, organisms and perhaps populations, as well as single cells. According to these studies, the scaling exponent remains approximately invariant as we move from lower to higher organizational levels, but the proportionality constant changes. This is consistent with the view that fundamental laws in science remain substantially the same at smaller and larger scales. (Thus, the neo-Darwinian theory of evolution explains diversity within and among populations in terms of mutation and natural selection; it is now generally accepted that diversity within species and within clades can be explained in terms of the same fundamental principle.) The relationship between lower and higher level processes relating to the allometric scaling of metabolic rate has been discussed previously (Hochachka et al., 2003; Suarez and Darveau, 2005). Table 1, adapted from Wang et al., shows that the proportionality constants differ markedly among mammalian organs but the scaling exponents are much the same (Wang et al., 2001).

The formalism of QM allows this kind of variation to be explained, at present only qualitatively, but a direct derivation involving an organizational hierarchy of an organism is still needed. Nonetheless, denoting the metabolic rate and the mass of a single cell, respectively, by B_c and M_c, QM obtains the scaling law in the form:

$$B_c = \alpha_c M_c^{\beta}, \quad (11)$$

Table 1. Proportionality constants and scaling exponents in different mammalian tissues

Organ	Proportionality constant	Scaling exponent
Liver	0.033	0.87
Brain	0.011	0.76
Kidney	0.007	0.85
Heart	0.006	0.98

where $\beta = d/d+1$. Considering an organ as an aggregate of cells, using N_c to denote the number of cells in the organ and letting $\tilde{B}$ and $\tilde{M}$ denote the metabolic rate and the mass of the organ, respectively, yields:

$$\tilde{B} = N_c B_c, \quad (12)$$

$$\tilde{M} = N_c M_c. \quad (13)$$

Neglecting the effects on organ metabolic rate of organ geometry and the mode of interaction among the constituent cells, then leads to:

$$\tilde{B} = \tilde{\alpha}\tilde{M}^{\beta}, \quad (14)$$

where:

$$\tilde{\alpha} = \alpha_c N_c^{\frac{1}{d+1}}. \quad (15)$$

Hence, under highly simplified assumptions, the scaling exponent appears to be invariant, but the proportionality constant changes according to cell mass and the scaling exponent. These qualitative observations support the validity of the rule derived from QM, though further factors are likely to be involved in the variability of the scaling exponent. Again, applying these general principles to a range of specific biological examples is, in our opinion, crucial for the wider acceptability of QM as a competitor to FNT.

The argument that QM may apply to higher levels of biological organization suggests that it could form a basis for a metabolic theory of ecology. However, at higher levels of organization, important caveats would have to be accommodated: (1) the organism in the ecosystem may have different scaling exponents [in plants we have $\beta=1$, in small mammals β is ~⅔ and in large mammals it is ~¾ (see earlier discussion about variations in β)] and (2) the proportionality constant need not depend only on the number of organisms in the ecosystem.

A coherent metabolic theory of ecology would need to integrate QM with the multilevel scaling model explored by Suarez and Darveau that takes into account the dynamic interaction among components of the biological network, and with principles arising from ecological studies such as those of Glazier and his colleagues (see earlier) (Suarez and Darveau, 2005).

Predictions of QM

(1) Scaling exponent: $\beta = d/d+1$ ($1 \leq d \leq \infty$), hence $½ < \beta < 1$, in accordance with many empirical data (see above).
(2) Because d, and therefore β, is not independent of body mass, plots of log$B$ against log$M$ are curved, in accordance with empirical findings.
(3) Proportionality constant: α is inherently temperature dependent.
(4) Range of applicability: QM applies to unicellular organisms, plants and animals, aerobes and anaerobes.

Support and current limitations of the QM theory

The findings of Nakaya et al. showed that d is not just geometrical but functional (Nakaya et al., 2003). When the cells in the colonial organism functioned individually, d was determined locally by each cell. When they cooperated to form a colony, d changed accordingly; empirically, the scaling exponent changed from 1 to ¾, consistent with the QM theory. QM predicts that slime mould metabolism should behave similarly. This prediction is testable.

The opposite obtains in cancers, where individual cells become de-synchronized so the dimensionality of the network changes its

meaning from that of the tissue to that of each individual cell. Recently, there has been renewed interest in the Warburg hypothesis that cancer cells differ from normal differentiated cells in their modes of energy production and conversion. According to QM, cancer cells and normal cells are characterized by different scaling exponents and different proportionality constants (Demetrius et al., 2010). Because the proton current is altered by changes in the phospholipid content of an energy-transducing membrane (Brookes et al., 1998; Brand et al., 2003; Demetrius and Tuszynski, 2010), α is susceptible to alteration by diet, exercise and drugs that regulate enzyme activity, suggesting a new adjunctive approach to cancer therapy that may have fewer side effects than current regimes.

In contrast to FNT, QM claims to account for (1) metabolic rate differences between cancer and normal cells, (2) large variations in metabolic rate within taxa and (3) the dependence of metabolic rate on temperature and biomembrane composition. Table 2 summarizes the contrasts between QM and FNT. It remains to be seen whether QM can be made compatible with the constraints of the allometric cascade model (Hochachka et al., 2003) and can predict the U-shaped relationship between β and α (Killen et al., 2010; Glazier, 2010) and the phenomenological equations of Kolokotrones et al. (Kolokotrones et al., 2010). As it stands, it shows that β and α are related but in its present form it does not characterize the relationship precisely. The key presumption of the theory, that there are coherent vibrations among the enzymes embedded in the energy-transducing biomembrane in response to energy input, has not been corroborated experimentally; it is based on the early suggestive work of Frölich, which is still largely unproven (Frölich, 1968). Direct experimental corroboration of this assumption is therefore required. In addition, one of the key variables used in the development of QM, cycle time (a quantity analogous to temperature in thermodynamics), requires more rigorous definition that will allow experimental data to be accommodated. It also needs to be established whether cycle time remains an invariant parameter at higher levels of biological organization, as the theory in its current form supposes.

In its current form, QM comes close to meeting the challenges that may be levelled at scientific theories, but it remains incomplete. Its assumptions are reasonable, and consistent with reality as far as they have been tested, but they might not be complete. So far, its predictions are consistent with empirical data, but further critical testing is required. The internal logic seems robust (the predictions follow rigorously from the assumptions), but application of QM to higher levels of biological organization will require additional assumptions and the internal logic will then have to be reconsidered.

QM in the context of present-day biology

QM exploits the formalism of quantum mechanics but it is not an application of quantum mechanics per se. In QM, the cycle time is the organizing variable. Hence, the analysis given in QM is different from traditional quantum effects in biology, where temperature, not cycle time, is the organizing variable. To refer the reader to relevant biological examples, below we enumerate several cases to illustrate the difference between quantum phenomena where metabolic energy is quantized and phenomena where thermal energy is quantized.

Quantum mechanical effects entail the length and time scales over which the wave properties of constituent particles preserve phase coherence (Nagy et al., 2006; Abbott et al., 2008). Some primary events in biological processes occur on time scales commensurate with quantum coherence phenomena (Nagy et al., 2006). Biologically important quantum processes (Davydov, 1982) include proton tunnelling in hydrogen bond dynamics, absorbance of frequency-specific radiation (e.g. photosynthesis and vision), conversion of chemical energy into mechanical motion (ATP hydrolysis by motor proteins) and single electron transfer along biological polymers (e.g. DNA or protein chains). Quantum mechanics explains energetics in plants (Fleming and Scholes, 2004; Sension, 2007). Recent advances in femtosecond laser-based two-dimensional spectroscopy have enabled the relevant time scales of quantum coherence in biological systems to be determined directly. The intracellular and intercellular synchronization of metabolism through gene and enzyme regulation involves collective and coordinated transcriptional cycles in cultured yeast and mammalian cells (Bianchi, 2008). Evidence is mounting that a living cell is an oscillator exhibiting collective behaviour in gene regulation, coordinating mitochondrial and metabolic functions (Klevecs et al., 2008; Palumbo et al., 2008), a view that could be consistent with QM.

Conclusions

FNT has dominated the allometric scaling field for 13 years. Not all of the mathematical and methodological criticisms of it have been satisfactorily resolved. The paper by Kolokotrones et al. implies that they cannot be resolved in principle (Kolokotrones et al., 2010). Admittedly, FNT has renewed interest in allometric scaling and has stimulated investigations in many areas of biology. Some of these investigations have given rise to different theories of allometric scaling, at least one of which – QM – claims to involve fundamental principles of biology and physics, and is distinctive in operating at the molecular–cellular level. These theories now merit greater attention.

To find common patterns among diverse phenomena, and to explain them all in the same simple manner, seems at first sight the highest attainment of science. In practice, however, such ‘grand theories’ in biology often evaporate under the heat of critical scrutiny. There is a striking similarity between the history of FNT and that of ‘scale-free network theory’ (Albert et al., 1999; Barabási and Albert, 1999), the shortcomings of which were exposed by

Table 2. The contrasts between fractal network theory and quantum metabolism

	FNT	QM
Mechanism	Macroscopic: resource supply network with fractal-like geometry	Microscopic: energy transduction in biomembranes
Scaling exponent	3/4	$d/(d+1)$, $1 \leq d \leq \infty$
Proportionality constant	Not described	Function of proton conductance and proton motive force
Temperature dependence	Added as a consideration from biochemical kinetics	Inherent in the proportionality constant
Explanatory power	Animal growth rates (?)	Origin of cancer (Warburg effect)
	‘Metabolic theory of ecology’ (?)	Species diversity in metabolic rate and body size
Range of application	Organisms with a vascular supply network	All aerobic organisms, with possible extension to anaerobes

FNT, fractal network theory; QM, quantum metabolism.

Keller (Keller, 2005). Both FNT and scale-free network theory first appeared in leading journals and initiated a flood of publications; both were lauded as major scientific advances (e.g. Whitfield, 2006); both were based on power law assumptions; and neither could withstand subsequent empirical, theoretical, mathematical and philosophical criticism. All theories in biology and related sciences that claim universality of scope are vulnerable to a comparable fate. Time will tell whether QM, or any alternative theory of allometric scaling, can avoid that fate. In the meantime, we hope for more research to test these new ideas on a growing number of concrete examples from a wide range of biological systems.

List of symbols and abbreviations

B	metabolic rate
E	energy
FNT	fractal network theory
M	body mass
MLB	metabolic level boundaries
QM	quantum metabolism
α	proportionality constant
β	scaling exponent

Acknowledgements

J.A.T. acknowledges generous support for this research provided by NSERC, Alberta Cancer Foundation, the Allard Foundation, the Canadian Breast Cancer Foundation and the Alberta Advanced Education and Technology. The authors thank Dr L. Demetrius and Dr J. Turner for useful discussions, and the anonymous referees and the editor for their valuable comments.

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