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Review

Metabolic Scaling in Complex Living Systems

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Abstract: In this review I show that four major kinds of theoretical approaches have been used to explain the scaling of metabolic rate in cells, organisms and groups of organisms in relation to system size. They include models focusing on surface-area related fluxes of resources and wastes (including heat), internal resource transport, system composition, and various processes affecting resource demand, all of which have been discussed extensively for nearly a century or more. I argue that, although each of these theoretical approaches has been applied to multiple levels of biological organization, none of them alone can fully explain the rich diversity of metabolic scaling relationships, including scaling exponents (log-log slopes) that vary from ~0 to >1. Furthermore, I demonstrate how a synthetic theory of metabolic scaling can be constructed by including the context-dependent action of each of the above modal effects. This "contextual multimodal theory" (CMT) posits that various modulating factors (including metabolic level, surface permeability, body shape, modes of thermoregulation and resource-transport, and other internal and external influences) affect the mechanistic expression of each theoretical module. By involving the contingent operation of several mechanisms, the "meta-mechanistic" CMT differs from most metabolic scaling theories that are deterministically mechanistic. The CMT embraces a systems view of life, and as such recognizes the open, dynamic nature and complex hierarchical and interactive organization of biological systems, and the importance of multiple (upward, downward and reciprocal) causation, biological regulation of resource supply and demand and their interaction, and contingent internal (system) and external (environmental) influences on metabolic scaling, all of which are discussed. I hope that my heuristic attempt at building a unifying theory of metabolic scaling will not only stimulate further testing of all of the various subtheories composing it, but also foster an appreciation that many current models are, at least in part, complementary or even synergistic, rather than antagonistic. Further exploration about how the scaling of the rates of metabolism

and other biological processes are interrelated should also provide the groundwork for formulating a general metabolic theory of biology.

Keywords: biological regulation; complex living systems; contingent *versus* deterministic mechanisms; ecological adaptation; physical constraints; hierarchical organization; metabolism; networks; resource supply and demand; scaling to system size

1. Introduction

All of life depends on metabolism (biochemical resource use and transformation) to fuel its various vital activities. In addition, since all organisms are products of countless generations of natural selection, one may predict that they should have evolved the highest metabolic rates possible to support competitively superior, maximal rates of resource exploitation and progeny production [1–6]. However, living organisms display a wide variety of metabolic and reproductive rates, a fundamental, but insufficiently understood theoretical problem of much interest to biologists. Both intrinsic and extrinsic factors may influence this variation, including body size, temperature, resource availability and exploitation by other organisms. For example, variation in the rates of metabolism, reproduction and other energy-dependent biological processes is related to body size in remarkably regular ways, often well described by the simple power function:

$$R = aM^b \quad (1)$$

where R is the rate of metabolism, reproduction or some other biological process, a is the scaling coefficient (antilog of the intercept in a log-log plot), M is body mass, and b is the scaling exponent (slope of a log-log plot) (but see Section 10.1). Furthermore, b is often near 3/4, thus inspiring the claim of a universal or near universal 3/4-power law of metabolism [6–14].

Three-quarters-power scaling has fascinated scientists for over 80 years, and many attempts have been made to explain it. The most influential current explanation has been that of West *et al.* [15], which helped to stimulate recent renewed interest in biological scaling [16]. Their general model (hereafter called the WBE model) explains the 3/4-power law as being the result of the physics and geometry of internal resource-transport networks. Although the WBE model is attractive, the claim that it is universally applicable, or nearly so, has generated considerable controversy (reviewed in [17–22]). Three major problems have emerged, related to the assumptions, internal logic, and predictions of the model (also see [18,21]; and Section 6). First, various assumptions of the WBE model have been questioned or shown to be restrictive (not general). Most importantly, only a relatively small proportion of animals (vertebrates) have a closed branching circulatory system powered by a single centrally located heart [23], as specified by the model and later versions of it [15,24,25]. Second, gaps and inconsistencies in the logic of the WBE model have been revealed by several penetrating analyses [26–33]. Third, although the WBE model predicts that the metabolic scaling slope should be 3/4, a diversity of scaling exponents has been found ranging from ~0 to over 1, but mostly between 2/3 and 1 [18,19,34]. Furthermore, many metabolic scaling relationships have been found to be nonlinear with log-log scaling exponents that change gradually or abruptly during ontogeny within

a species or over different body-size intervals within a taxonomic group of species ([18,28,35–42]; also see Section 10.1). Although the geometry and physics of transport networks specified by the WBE model can be modified so as to allow for a diversity of scaling exponents [25,39,43,44], empirical evidence for a match between network geometry and metabolic scaling is still lacking (also see Sections 5.2 and 5.5). Most notably, a modified WBE model and other related resource-transport network models predict that the metabolic scaling exponent should be near 2/3 [24], 5/8 [25] or 1/2 [45] in large (macroscopic) organisms that grow mainly in two dimensions, but by contrast many pelagic animals showing nearly 2D growth actually exhibit scaling exponents closer to 1 ([46]; also see Sections 5.2 and 8.2.1).

Even proponents of the WBE model have acknowledged its limitations; and over time they have increasingly restricted the taxonomic domain of quarter-power scaling. They now claim that 3/4-power scaling only applies to macroscopic, three-dimensional multicellular organisms with specific kinds of internal transport networks and 1/12 power scaling of resource (blood) flow rate, and not to flat, nearly two-dimensional organisms [24,25], animals with body-size independent blood-flow rates [25], organisms without vascular networks [25], small plants [43,47] and mammals [39], and microscopic unicellular and multicellular organisms [48].

As a result of the controversy over the 3/4-power law and the WBE model used to explain it, several other metabolic scaling models have been proposed or have received renewed attention (reviewed in [18–21,49,50]; also see Appendix Table A1). However, at present there is no consensus about which model is most valid. Efforts to test the relative merits of various competing models with new experimental and comparative evidence are only just beginning [46,51–56].

Although I advocate further testing of alternative models (following the method of multiple working hypotheses [57] (also see Section 5), a major aim of this review is to argue that no one existing theoretical approach is likely to be sufficient, but rather a combination of multiple hypothetical models (*cf.* [58])—a "cluster of models" [59] or a "family of subtheories" [60]—is required (also see [20]). In doing so, I evaluate and delineate the apparent domain of applicability of several of the models that have been proposed in light of their match with currently available empirical data. A historical perspective reveals that most of these models can be classified into four major theoretical approaches that have been discussed for nearly a century or more (see Section 3). Using a holistic systems perspective, I further show that the applicability of these theoretical approaches to various hierarchical levels of biological organization (cells, organisms, and groups of organisms) is contingent upon specific internal (system) and external (environmental) conditions. I contend that this perspective shows promise for developing a synthetic theory of metabolic scaling that can largely, if not fully, explain the rich diversity of metabolic scaling that has been observed, by incorporating several features of existing models or subtheories in a contextual way (see Section 8).

2. A Systems View of Metabolic Scaling

One of the leaders in metabolic scaling research during the last century was Bertalanffy [61,62], who was also one of the founders of general systems theory [63]. No doubt his systems thinking influenced his views on the causes of allometric metabolic scaling. As he remarked at the end of a paper on the body-mass scaling of tissue metabolism: "the decline in [mass-specific] basal metabolic

rate [with increasing body size] depends on regulative factors lying in the organism as a whole" ([64], pp. 254–255). Bertalanffy invoked whole-body systemic causes for metabolic scaling, which continues to be the prevailing view [8,65–67]. By contrast, others have emphasized molecular, cellular or other sub-organismal mechanisms ([68–72]; also see Sections 3.4, 4.1 and 5.4). I contend that a resolution to this debate can be facilitated by taking an explicitly hierarchical systems-based view (also see [73,74]; and Section 8.3).

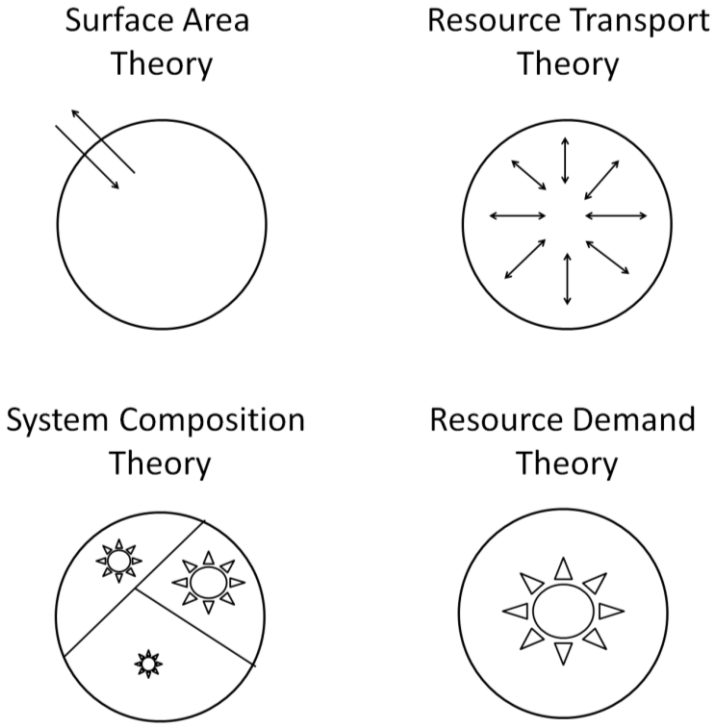
According to Bertalanffy [63] and other systems theorists [60,75–82], living systems have the following properties: (1) they are complex with multiple levels of organization, each with many interacting parts and processes; (2) they are self-regulative with feedback control; (3) they are open, and as such maintain their complex organization by continual interaction with their environment (including resource uptake, waste removal and information reception and transmission); (4) their activities may be influenced by not only upward causation from lower-level (e.g., molecular) properties, but also downward causation from higher-level (e.g., systemic) properties; and (5) their expression of specific properties or processes is context-dependent. According to this systems view, any living phenomenon, including metabolic scaling, emerges from the complex interaction of many parts and processes at multiple hierarchical levels in a way that is sensitive to both the internal state of a living system and its environmental conditions. Therefore, simple reductionist explanations based on molecular or cellular processes or on simple internal physical constraints are not expected to be successful at fully explaining the broad diversity of metabolic scaling. Both downward and upward causation and both internal and external influences are likely to be important.

Following a systems perspective, this review (1) evaluates several important theoretical models of metabolic scaling in terms of their predictive power and applicability to different levels of biological organization; (2) discusses the possible roles of biological regulation and feedback in metabolic scaling; (3) documents the effects of both internal and external factors on metabolic scaling; (4) proposes a synthetic theory of metabolic scaling that includes both upward and downward causation acting contingently according to various context-dependent mechanisms; and (5) explores how metabolic scaling may relate to the scaling of other biological processes, as a step toward building a general metabolic theory of biology. My attempt at building a synthesis is facilitated by classifying the majority of metabolic scaling models into four major types of theoretical approaches ("subtheories").

3. Major Theoretical Approaches: A Historical Perspective

Most theoretical models of metabolic scaling can be classified into four major types: surface area (SA), resource transport (RT), system composition (SC) and resource demand (RD) models (Figure 1). Other kinds of models that receive little or no attention in this review are briefly discussed in the Appendix. In this section, I take a historical perspective with an emphasis on how the above four classes of models (subtheories) have been applied to the organismal level of biological organization. Their application to other hierarchical levels of biological organization is described in Section 4. Evidence for and against these subtheories and their constituent models are discussed somewhat in Sections 3 and 4, but especially in Section 5.

Figure 1. Schematic representations of the four major types of metabolic scaling theory considered in this review: surface area (SA), resource transport (RT), system composition (SC) and resource demand (RD) theory.



All four subtheories have had long bumpy histories marked by varying levels of influence in the scientific community over time. Indeed, over 50 years ago, Kleiber [8] was already able to devote considerable discussion to various versions of all of these theoretical approaches.

3.1. Surface Area (SA) Models

The oldest explanation of metabolic scaling published in 1839 by Sarrus and Remeaux [83] was based on SA theory. They noted that to maintain a constant body temperature, endothermic (warm-blooded) animals must metabolically produce enough heat to exactly offset their heat loss. They reasoned that since heat loss is proportional to body surface area, which scales as $M^{2/3}$, therefore metabolic rate should also scale as $M^{2/3}$. In the late 1800s and early 1900s, this simple SA model was supported by intraspecific data from dogs, rabbits and other birds and mammals of different size, showing that metabolic rate is proportional to body SA or nearly so [84–86]. This "surface law" was prominent until Kleiber [7] and Brody and Proctor [87] showed that the interspecific metabolic scaling exponent (b) for mammals appeared to be closer to 3/4 than 2/3. As the 3/4-power law gained prominence, the influence of the surface law began to wane [7–13]. This decline also resulted from the realization that the thermoregulatory explanation of the surface law does not apply to most organisms, which are ectothermic and have variable body temperatures. The early history of the surface law is discussed by Thompson [88], Brody [89] and Kleiber [7,8].

Nevertheless, many investigators have suggested that resource uptake and gas exchange across surfaces, including internal surfaces of the alimentary and respiratory systems, may be critical for metabolic scaling ([61,90,91] and other references cited in [18]). Increased elaboration of SA (e.g.,

fractal SA of the respiratory organs: [92]), was invoked as a way to explain *b* values >2/3 [18]. The total SA of individual cells was also proposed as accounting for the surface law [93], but this assumes that organisms grow by enlarging their cells and not by increasing their number so as to match the 2/3-power scaling of the external body surface, which is usually not the case, as was frequently pointed out in the early 1900s [8,93–95]. However, this view has morphed into models that consider both cell size and number, thus allowing for an explanation of why *b* may vary between 2/3 and 1 ([68,69]; also see Sections 4.1.1 and 4.3.1).

Although Kleiber [7,8] argued for replacing the expression of metabolic rate as a function of surface area to expressing it as a function of body mass (following Krogh [96]), he did not reject the surface law, as commonly believed. Although he did not believe that surface area or heat loss directly caused metabolic scaling (unlike Rubner [84], who proposed that SA-related neural signals directly stimulated metabolic rate), he did support the view that birds and mammals had evolved metabolic rates that were in balance with heat loss so as to maintain a constant body temperature (a similar view was also expressed more recently by the noted physiological ecologist George Bartholomew [97]).

Contrary to frequent claims [10,12,13,98], SA theory has not been discredited, but continues to attract considerable interest. Several recent models, including dynamic energy budget (DEB) theory [66] and the metabolic-level boundaries hypothesis (MLBH) [19], invoke the importance of SA in metabolic scaling, not only for endothermic birds and mammals [18,19,99–102], but also for various ectothermic organisms [19,46,66,103–105]. As Thompson [88] noted over 70 years ago, scaling effects are commonly due to physical forces acting in proportion to body SA or volume (also see [106,107]). Therefore, SA theory should not be ignored when attempting to develop a comprehensive theory of metabolic scaling.

3.2. Resource Transport (RT) Models

Kleiber [7,8] provides a useful review of the early history of RT theory that, like SA theory, dates back to the 1800s ([8], pp. 186–191). The importance of the blood vascular system for metabolic scaling was recognized in 1839 by Sarrus and Rameaux [83], who proposed that oxygen consumption should be proportional to blood flow. Later workers attempted to relate blood flow to the surface law. In 1888, Hoesslin [108] provided a physical argument (based on principles of geometric similarity) claiming that blood flow should be proportional to the 2/3-power of body weight. Hoesslin [108] assumed that metabolic rate is a function of oxygen supply (as described in [96]). In the 1920s Read [109] and Henderson [110] demonstrated that the rates of circulation and metabolism are directly proportional, which led to heart (pulse) rate being used to estimate metabolic rate [111], a common practice that occurs even today [112,113].

Kleiber ([7], pp. 331–335; [8], pp. 186–191) argued that vascular oxygen transport is related to 3/4-power scaling, rather than to the surface law, thus anticipating some important elements of more recent resource-transport-network (RTN) models, including the influential WBE model [15]. For example, as in the WBE model, he uses the principles of geometric similarity, and assumes that capillary size, blood pressure and blood velocity are independent of body mass, that blood volume and capillary number are directly proportional to body mass, and that the efficiency of oxygen transport is importantly related to metabolic rate. He further points out that the heart rate and metabolic rate of

differently sized mammals are both nearly proportional to $M^{3/4}$, as predicted. Later, arguments were made that the fractal nature of RTNs may help to explain the 3/4-power law [114,115], which were theoretically supported by the WBE model [15]. However, the classic studies of Krogh [116] showed that vertebrate capillaries do not always exhibit fractal branching, as required by the WBE model. In some tissues capillaries do appear to show fractal branching (e.g., in muscle), but in others they may be highly interconnected mesh-like networks (e.g., in intestinal villi) or may consist of simple loops (side branches) occurring periodically along the length of arterioles (e.g., in skin). Other studies have pointed out that RTNs may not be fractal in various other kinds of organisms, as well [27,117]. This problem is avoided by RTN models that do not require fractal networks [6,25,45,117–119].

However, a more serious problem with RT theory (including RTN models) is that, as Kleiber [8] pointed out over 50 years ago, the cardiovascular system and its rate of oxygen supply to metabolizing cells seem to be functions of metabolic rate more than *vice versa* (p. 189), a conclusion also reached by many recent workers [19,27,29,49,120]. Kleiber cites Krogh [116] who showed that the number of open capillaries is a function of metabolic demand (also see [19,27,121,122]). For example, active muscle may have as many as 40 × the number of open capillaries as resting muscle (p. 40). Prolonged exercise may additionally stimulate the biosynthesis of new capillaries in muscle tissues [123,124]. Furthermore, the number of open capillaries varies markedly among different tissues and physiological states (e.g., all or nearly all open in brain, liver and skin, but hardly any open in quiescent stomach, intestines and muscle). In addition, oxygen supply by the tracheal system of insects seems not to "limit metabolic rate, as WBE assume, but adjusts to metabolic needs" ([27], p. 287; also see [125] and Section 5.2).

Kleiber [8] concluded that natural selection has favored a balance between the rates of oxygen supply and metabolism. He writes: "*In natural selection, those animals probably prove to be the fittest whose cells are adapted to a level of oxygen consumption at which the overall metabolic rate is suitable for the maintenance of a constant body temperature and commensurate with an efficient transport of oxygen*" (p. 199). In short, mammalian metabolic rate and its scaling with body size have coevolved with heat exchange and blood circulation, rather than being strictly controlled by them (also see Section 6). The limited taxonomic occurrence of vascular circulatory systems and their metabolically sensitive, phenotypic plasticity suggest that RTN models by themselves cannot provide a generally applicable explanation for metabolic scaling in all of its diverse forms. More general RT theory is needed that applies to organisms that supply oxygen and other resources to their tissues in a variety of ways (not just by vascular circulatory or tracheal systems), and that recognizes that RT systems and metabolic rate are co-adjusted properties. Although the authors of the WBE model recognize that resource supply and metabolic demand have "co-adjusted and co-evolved" ([65], p. 1588), they do not use this knowledge fully to explain why metabolic scaling is so diverse (see Sections 6–9). Their focus on 3/4-power scaling stems from their belief that it is caused by universal RTN supply constraints and that this scaling cannot be derived by focusing only on metabolic demand dictated "by cellular and molecular processes" ([65], p. 1588). Proponents of RTN theory continue to emphasize how resource-supply constraints by RTNs dictate the scaling of metabolic rate, apparently either directly by resource limits or resource-sensitive physiological regulation [65], or indirectly by evolutionary adjustment of metabolic demand to supply, as suggested by Kleiber [8]. By doing so they

neglect to consider the possibility that other systemic effects may also importantly influence metabolic scaling, as discussed throughout this review and summarized in Section 8.

3.3. System Composition (SC) Models

Nearly 100 years ago, Benedict [126] showed that the relative proportions of metabolically active protoplasm *versus* inert fat may affect mass-specific metabolic rate in humans. By the 1930s SC theory was being used to explain allometric metabolic scaling in birds and mammals (as reviewed by Kleiber [7,8], pp. 191–194). For example, Blank [127] and Kestner [128,129] postulated that mass-specific metabolic rate declined with increasing body size because of a decreasing proportion of metabolically active tissues in larger animals. Blank [127] reported that the heart, kidneys, digestive tract and central nervous system (CNS) are relatively larger in small *vs.* larger animals. Kestner [129] similarly reported that small animals have relatively larger brains, hearts, livers, kidneys, and spleens than those of larger animals. Crile [130] and Brody [89] further argued that the similar scaling of brain size and metabolic rate in mammals ($b \sim 0.7$) may not be a coincidence. This finding suggested that smaller species have higher metabolic rates in part because they have relatively large, metabolically active brains. Kestner [129] even claimed that shifts in body composition could completely explain why small animals tend to have higher mass-specific metabolic rates than larger animals.

However, in his influential book *The Fire of Life*, Kleiber [8] argued that changes in body composition could not completely explain allometric metabolic scaling in mammals, and thus he rejected this explanation (for similar arguments, also see [11,64]). As a result, SC theory has been frequently ignored by investigators attempting to construct a general theory of metabolic scaling. However, this outlook has been gradually changing since the 1980s. Some studies have further explored possible connections between brain (CNS) mass and metabolism, but the results have been mixed [131–135]. Even when correlations are found between brain mass and metabolic rate, they may not be due to larger brains causing higher whole body metabolic rates [135], thus following SC theory, but rather due to higher metabolic rates supporting higher brain growth rates [131,136]. Nevertheless, several other investigators have provided evidence that accumulation of metabolically sluggish or inert tissues/materials in larger animals may result in them having lower mass-specific metabolic rates (reviewed in [18]). This work has resulted in a recent upswing of appreciation for SC theory. Notable studies on the intraspecific ontogenetic metabolic scaling of fish [137,138] and on the interspecific metabolic scaling of mammals [139,140] have shown that whole organism metabolic scaling exponents closely match those based on summing the individual metabolic contributions of various organs and tissues. Furthermore, SC theory is an important component of the widely used dynamic energy budget (DEB) theory [66,67,104], and has been the major focus of other recently proposed metabolic scaling models or hypotheses [29,35,40,53,73,140–147], as well. It is difficult to believe that body-size dependent anatomical composition does not contribute at all to metabolic scaling. Even partial effects should not be ignored.

3.4. Resource Demand (RD) Models

The early history of RD theory was reviewed by Kleiber ([8], pp. 194–198). In 1925, Wels [148] promoted the view (attributed to Rubner) that species-specific differences in metabolic rate are

intrinsically set at the tissue level. This hypothesis predicts that similar body-size-related differences in tissue metabolic rate should be observed *in vitro* and *in vivo*. During the 1920s to 1950s, numerous attempts were made to test this hypothesis. Early work showed that *in vitro* tissue metabolism did not vary with donor body size [149,150], but these studies suffered from serious methodological problems [11]. Later, improved studies usually showed that the metabolism of various isolated tissues decreases with increasing body size, but often not to the same degree as whole body metabolic rate ([64,151–153]; and other references cited in [18]). In many cases, tissues respired at different rates *in vitro* than *in vivo* [8]. From these data, Kleiber [8] concluded that tissue metabolic rate is not set by oxygen supply, but is partially genetically determined and partially regulated by various somatic (neuroendocrine) factors (pp. 196–197). Thus, he felt that both systemic and cellular factors played a role in metabolic scaling.

Numerous recent studies have provided further evidence that the metabolic rate of freshly excised cells or tissues show negative allometry with body size ([154–158]; and other references cited in [18]), thus suggesting that metabolic scaling is demand driven by cells that have intrinsically set metabolic rates, at least in part. However, cultured cells show no relationship between metabolic rate and donor body size [159–161]. At first sight, these data appear to support the effect of systemic factors, and not intrinsic cellular factors, on metabolic scaling, but two of the studies have been criticized because they used either heterogenous cell types (including tumor cells with anomalous metabolic properties; [18,159]) or dermal fibroblasts claimed to have unusually low metabolic rates, whose intrinsic differences may have been obscured by rich metabolism-enhancing culture media [160,162]. However, the oxygen consumption rate of cultured mammalian skeletal muscle cells also shows no relationship with body mass, even when the cells are cultured in the serum of their donor species, thus suggesting no hormonal effect, as well [161]. However, this *in vitro* lack of metabolic scaling can be explained as the result of cultured muscle cells being relatively quiescent (e.g., not engaged in routine contractile activity) and thus metabolizing at a uniformly minimal level required for survival, rather than being due to the absence of an *in vivo* systemic effect, such as oxygen limitation ([161]; also see Section 5.2).

RD theory has focused on metabolic demand not only at the tissue level, but also at the whole-body level, including energy-expensive processes such as growth (production), locomotion, and thermoregulation (reviewed in [18,163]). The effect of growth rate on ontogenetic metabolic scaling has been discussed for over 80 years beginning with studies by Teissier [164], Riddle *et al.* [165] and Kibler and Brody [166] showing that the metabolic scaling exponent (b) is positively correlated with growth rate. Although most general metabolic scaling theories have ignored the energetic costs of growth, DEB theory uses this mechanism to explain intraspecific ontogenetic metabolic scaling relationships [66,67]. Marked differences in b between resting and active animals have also sparked interest in how metabolic demand (not just resource supply) can affect metabolic scaling in animals [18,19,99,120,167–169]. In addition, steep metabolic scaling in young growing endotherms has been related to rapid increases in heat production accompanying maturation of the thermoregulatory system [18]. These studies are considered further in Sections 5.4, 6 and 7.

4. Major Theoretical Approaches: Applicability to Different Hierarchical Levels of Biological Organization

Different models of metabolic scaling apply to one or more levels of biological organization (see Appendix Table A1, where relevant sources are listed). These models are discussed in relation to the four major theoretical approaches described in Section 3. As will be seen, all four of these "subtheories" have been applied (or could be potentially applied) at all of the hierarchical levels (cells, organisms, social groups of organisms, populations, communities and ecosystems) considered here.

4.1. Models of Cells or Subcellular Processes

4.1.1. Surface Area (SA) Models

Several investigators have invoked the effects of surface area on metabolic scaling in unicellular organisms [170–173]. According to this view, metabolic scaling is constrained by the fluxes of resources and wastes across cell surfaces, which scale with cell volume to the 2/3 power. According to Phillipson [171], both external and internal cell surfaces should be considered to explain why *b* values different from 2/3 may also occur. Values larger than 2/3 may be the result of changes in cell shape (e.g., increased elongation, flattening or surface folding, thus increasing external SA relative to cell volume) and (or) of increased expansion of the internal metabolically active surfaces of various organelles (e.g., vacuoles and mitochondria) with increasing cell size (also see [48,106,174–176]. However, SA-related resource fluxes in very small cells may not be limiting [177], thus causing metabolic scaling to conform more to volume-related resource demand, as suggested by *b* values ≥ 1 (see Section 5.1).

In addition, it has been claimed that cellular SA can affect the scaling of metabolic rate in multicellular organisms [18,68,69,93,178,179]. When body size increases via cell enlargement, total cellular SA and metabolic rate should scale to the 2/3-power, whereas when body size increases via cell multiplication, total cellular SA and metabolic rate should scale to the 1-power. If body size increases as a result of both cell enlargement and multiplication, *b* should be between 2/3 and 1. Else and Hulbert [180] have also suggested that whole organism metabolic scaling is related to the scaling of mitochondrial SA (also see [120,181,182]).

4.1.2. Resource Transport (RT) Models

Krogh [183] calculated that simple passive diffusion should be sufficient for meeting the maintenance requirements of small organisms (<500 μg). Because of their high surface area to volume ratio, small protozoans can maintain normal aerobic metabolic rates even at very low ambient oxygen levels [184]. However, other active processes, such as cytoplasmic streaming, may be necessary in relatively large cells. West and Brown [65] suggested that fractal resource-transport networks may operate at the intracellular level, thus causing 3/4-power scaling, as reported by Hemmingsen [9]. However, the existence of intracellular hierarchically branching RT networks has yet to be demonstrated [20,21]; and recent studies show that the metabolic rate of unicellular organisms may not scale to the 3/4-power [48,173,185,186], contrary to the WBE model. We still have much to learn about how

metabolites are transported inside cells [187], and whether this transport affects how metabolic rate scales with cell size.

4.1.3. System Composition (SC) Models

Some workers have suggested that changes in cell composition, including the proportions of metabolically active components, with increasing cell size may significantly affect metabolic scaling in unicellular organisms [106,173]. Some studies indicate that relative dry mass or carbon content may decline [188,189], and the relative size of vacuoles increase [106], as cell size increases, both of which could cause negative allometry of metabolic rate (*i.e.*, $b < 1$). Cell-size related changes in the relative density of mitochondria may also affect metabolic scaling in protists [48].

4.1.4. Resource Demand (RD) Models

Some recent models and hypotheses focus on how molecular or subcellular processes may drive the metabolic rates of cells and their scaling with multicellular body size. The mechanisms proposed include thermodynamic processes [190], membrane molecular activity (including proton and ion flux rates) modulated by membrane phospholipid composition [70,191,192], quantum mechanical energy transduction in cellular membranes [21,71,72] and ontogenetic changes in mitochondrial density or protein concentrations [193–195] or in the activity of metabolic enzymes or respiratory electron transport systems [196,197].

4.2. Models of Whole Organisms

Most models of metabolic scaling are focused at this level, as described in Section 3 (also see Appendix Table A1).

4.3. Models of Colonies and Other Social Groups of Organisms

Development of metabolic scaling theory at supra-organismal levels is in its infancy. Nevertheless, all four basic theoretical approaches emphasized in this review (SA, RT, SC and RD theory) have already been applied, or at least considered with respect to colonies and other groups of organisms. Possible applications at still higher levels of biological organization (e.g., populations, communities and ecosystems) are discussed in Section 4.4.

4.3.1. Surface Area (SA) Models

SA theory has been frequently used to explain why the close aggregation or huddling of conspecific organisms often results in a reduction of mass-specific metabolism for each individual or the group as a whole. According to resource-conservation hypotheses, by reducing the exposed surface area to volume ratio, clustered individuals are predicted to reduce rates of heat and (or) water loss, thus causing the total rate of metabolism or resource use of the group to show negative allometry ($b < 1$) with total group mass [198,199]. Huddling is common in small mammals, especially neonates, which have been predicted and often observed to show metabolic scaling to the ~2/3-power in relation to huddle mass ([200–203]; also see Section 5.1). However, this predicted scaling should only occur in

small huddles that have a compact shape. Other *b* values may be seen in large huddles that have formed by expansion largely in two dimensions, *i.e.*, individuals are added to the sides rather than the top of the huddle ([201]; also see Section 5.1). Local heating of the microenvironment by huddled endotherms may also contribute to energy savings, thus further altering the metabolic scaling observed [204].

Rates of metabolism are positively correlated with the surface area to volume ratio of coral species with different growth forms [205]. In social insects, close clumping in nests may also limit respiratory gas exchange, and thus metabolic rates, via reductions in the whole colony surface area to volume ratio [206], though fanning or metabolism-induced increases in air ventilation [207,208] may counteract this effect.

Some colonies may avoid the problem of a decreasing surface area to volume ratio by their modular construction. By adding physiologically and morphologically discrete modules of the same size, a colony can maintain a constant surface area to volume ratio as it grows. If so, SA theory predicts that modular colonies should exhibit isometric metabolic scaling ($b = 1$), which has been observed in some colonial bryozoans ([209,210]; but see [53]), thaliaceans ([211,212]; but see [213]) and ascideans (when in an unconnected state [214]; also see below), but apparently not corals [215,216]. Similarly, some small metazoans, which are essentially modular colonies of cells, show near-isometric metabolic scaling [48,170,171]. Other animals that grow mainly by increasing cell number, rather than cell size, either during early development (as in many fish and invertebrate larvae) or throughout life (as in squid) also exhibit near-isometric metabolic scaling [18]. On the other hand, small eutelic animals, whose postembryonic growth occurs mainly by cell enlargement [217–219], show allometric metabolic scaling (*b* near 2/3 in rotifers [220] and nematodes [18,221]), as predicted by SA theory [18]).

4.3.2. Resource Transport (RT) Models

Hou *et al.* [222] claimed that the WBE model can be applied to social insects. An interspecific analysis of ants, bees, wasps and termites revealed that whole colony metabolic rate scales to the 0.81 power with whole colony mass. This exponent is not significantly different from 3/4, as predicted, but also not from other theoretical values such as 2/3 and 1, either. Furthermore, intraspecific analyses have revealed a wide range of *b* values (0.44–0.94) [222–225], and in some cases aggregation behavior or colonial grouping was observed to have no effect or positive effects on metabolism per individual ([198,226,227]; but see [224]). In addition, although the resource distribution system of colonial insects has been modeled as being hierarchically branched, as specified by the WBE model [228], this has yet to be empirically demonstrated. The properties of ant foraging networks can differ markedly from those of organismal vascular networks, including bidirectional *versus* unidirectional flow, and transport distances that are independent of colony size *versus* dependent on organism size [229,230].

Nevertheless, the metabolic scaling of animal colonies may be influenced by transport networks involving the distribution of resources and information among individuals [231]. For example, when zooids of the colonial ascidean *Botrylloides simodensis* are interconnected, the scaling of metabolic rate is allometric ($b = 0.80$, and not significantly different from 3/4) [214]. By contrast, when the zooids are unconnected, the colony shows near isometric metabolic scaling ($b = 0.95$, and not significantly

different from 1). However, the actual mechanism involved in causing this shift from allometric to isometric metabolic scaling has yet to be identified. The view that fractal resource-transport networks play a role in this shift is weakened by the finding that, when connected, these flat-shaped colonies exhibit a *b* value that is significantly higher than 2/3, which is the predicted value for organisms that grow mainly in two dimensions, according to the WBE model [24,214,232].

4.3.3. System Composition (SC) Models

Changes in the composition of colonies as they grow in size have been invoked to explain allometric metabolic scaling in colonial corals [216] and ants [223–225]. Increasing accumulation of inert materials associated with growth of the coral skeleton appears to be responsible for the low *b* value (0.176) that was found in *Siderastria siderea* [216]. Colony-size-related changes in the proportion of individuals with different body sizes, caste types or levels of activity may also contribute to negatively allometric scaling observed in ant colonies [223–225].

4.3.4. Resource Demand (RD) Models

RD theory has received the least amount of attention in relation to the metabolic scaling of animal colonies. Negatively allometric metabolic scaling may result from an overall decrease in individual activity with increasing colony size. For example, since larger ant colonies tend to have smaller per capita brood production, less metabolically demanding activity would be required for brood care, thus resulting in a decreased per capita metabolic rate, compared to that of smaller colonies [225]. By contrast, positively allometric metabolic scaling could result, if larger groups or colonies promote more frequent or intense individual interactions that stimulate higher metabolic rates directly or indirectly via increased activity rates [198,227].

4.4. Models of Populations, Communities and Ecosystems

Very little attention has been given to the whole-system scaling of metabolic rate or other energy related processes at the population, community or ecosystem levels. Although several studies have scaled energy use or production at these levels to organismal body size (e.g., [233–239]), hardly anything is known about how the "metabolism" of ecological systems scales to their higher-order size (but see [240–243]). Here I suggest that all of the theoretical approaches emphasized in this review could be applied at the level of ecological systems. Hopefully, my speculation in this section will stimulate further, much needed research.

4.4.1. Surface Area (SA) Models

SA theory may provide insight into how rates of light uptake and associated photosynthetic rates by plant populations and communities vary with total biomasses (B) of these entities. Negatively allometric scaling of whole population or community photosynthetic rate ($b < 1$) may result from increased light competition in larger or denser populations and communities, because they have more overlapping foliage, thus causing more interference in light reception by leaf surfaces (see [244]). This effect may be most readily seen in small isolated populations and communities with high ratios of unshaded

peripheral edge (P) to shaded internal canopy area (A). This is because as A increases, P/A decreases, resulting in a lower proportion of edge areas where unshaded leaves could maximize light reception, and thus photosynthesis. Competition for light may not only affect the scaling of tree growth rates in relation to body size, as has been recently demonstrated [245], but also the scaling of whole-system production rates in relation to the sizes (B) of whole tree populations and forest communities.

Surface-area constrained light uptake may also cause negatively allometric scaling of the rates of photosynthesis and associated energy production in ponds, lakes and other aquatic ecosystems in relation to their size. This is because the water-surface area (A) of these ecosystems, through which light enters, should scale to water volume (V) with a power near 2/3, provided that the three-dimensional shapes of the water bodies in question (as specified by area and depth) are relatively isomorphic. If so, rates of photosynthesis and production should also scale with system size (water volume or total biomass, B) with a power between 2/3 and 1, depending on water clarity (and thus depth of light penetration) and how the system morphometry and biomass density actually scale with system size. Negative allometry of whole-system metabolism may also result from other morphometric properties of aquatic systems that affect resource input. In particular, the shoreline (P = perimeter) of aquatic ecosystems can be considered an important contact "surface" with the outside land environment, which supplies many kinds of resources by various physical and biotic processes (e.g., erosion and runoff, animal and plant dispersal, and influxes of terrestrial detritus, including dead leaf material). If the shoreline-related supply of resources is critical, then one can predict that total ecosystem energy use should scale to system size (V or B) with a power as low as 1/2 (depending on the scaling of A and water depth with V or B), because according to Euclidian geometry for isomorphic shapes, P should scale with A to the 1/2 power (*i.e.*, in proportion to the square root of A). Data are needed to test these hypotheses, some of which is presented in Section 5.1.

4.4.2. Resource Transport (RT) Models

RT theory may help explain how rates or patterns of energy flow through food webs vary with community or ecosystem size. Food webs can be modelled as "energy transportation networks" [246–248]. By doing so, it is possible to calculate power functions describing relationships between various energy-flux parameters (e.g., energy-flux variability and energy-storage ability) and the size of the network [248]. As the number of species (S) in a food web increases, the number of interactions between species (energy-flow links, L_i) should also increase, as is often observed [249–251]. Different theoretical models predict that L_i should vary in proportion to S [252] or S^2 [253], with actual webs often showing L_i-S relationships between these predictions [250,251,253]. Food-web theory also predicts that connectance ($C = L_i/S^2$, where L_i = the number of realized interactions between species, and S^2 = the number of possible interactions) should decrease with increasing S, and thus size of a food web [249,250,254,255]. Therefore, further development of food-web theory could provide insight into how the pattern and magnitude of energy flow in ecosystems should scale with number of species and their potential for interaction. In doing so, not only should L_i-S relationships be considered, but also the magnitude and temporal dynamics of energy flowing through each link (see [256]).

4.4.3. System Composition (SC) Models

SC theory may be important in explaining the scaling of whole population or community metabolic rate, if increases in population or community size are accompanied by changes in the relative proportions of low- *versus* high-energy individuals or species. For example, small communities in isolated or resource-poor habitats may have proportionately more low-energy ectotherm *versus* high-energy endotherm species (because ectotherms are able to maintain larger, more extinction-resistant populations in small areas with few resources) than large communities in more expansive or resource-rich habitats. As evidence, on small islands reptiles tend to make up proportionately more of the biomass (B) or species richness (S) of terrestrial nonvolant vertebrate communities than do mammal species, whereas mammals are often more dominant in more expansive continental habitats [257]. As a result, everything else being equal, whole community metabolic rate should scale with positive allometry ($b > 1$) in relation to total community B or S. On the other hand, small communities in isolated or resource-poor habitats may have proportionately more small *versus* large species (because small-bodied species are able to maintain larger, more extinction-resistant populations in small areas with few resources) than large communities in more expansive or resource-rich habitats (see [258–262]). If so, since small species tend to have higher mass-specific metabolic rates than larger species, then whole community metabolism should scale with negative allometry ($b < 1$) in relation to total community B or S. Combining the effects of the relative frequencies of ectotherms *versus* endotherms, of small *versus* large species, and of other lifestyles (e.g., flying *versus* nonflying species) may result in a variety of scaling relationships for community metabolism.

4.4.4. Resource Demand (RD) Models

RD theory may also be useful at the population and community levels. For example, increases in resource abundance or quality may cause increases in both the rates of metabolism of organisms [3,263–265] and their collective biomass (B) in populations and communities, thus potentially resulting in positive allometric scaling of whole population or community metabolic rate with B ($b > 1$). Alternatively, if increased densities of individuals result in lower per capita metabolic rates, as has been recently documented in some protist and animal species [266], then whole population or community metabolic rate may show negatively allometric scaling with B ($b < 1$). The scaling relationship actually observed may depend on a variety of other factors, as well (e.g., the effects of resource abundance and competition on body-size distributions).

5. Major Theoretical Approaches: Evidence For and Against

All four of the major theoretical approaches emphasized in this review have been tested to various degrees at different levels of biological organization. Some of that evidence has already been briefly mentioned in Sections 3 and 4, but here I provide a more general overview of the relevant empirical data that are currently available. By doing so, I show that none of the theoretical approaches are generally applicable, but appear to have restricted domains that depend on specific internal and external factors. This argument is further developed in Section 8.

5.1. Surface Area Theory

SA theory was originally applied to the metabolic scaling of endothermic mammals and birds. Early studies at the intraspecific level revealed that metabolic rate tended to be directly proportional to SA, as predicted (see Section 3.1). Although the classic interspecific analyses of Kleiber [7], Brody [87] and Hemmingsen [9] showed that basal metabolic rate (BMR) tended to scale to a power closer to 3/4 than to 2/3 (but see [89], p. 371), these scaling relationships were based on limited samples, largely composed of domestic or agriculturally important birds and mammals [26,38]. Numerous, more recent interspecific analyses, which have included more extensive, taxonomically representative samples, have revealed that the BMR scaling exponent is closer to 2/3 than 3/4 in both birds [18,99,171,267–273] and mammals ([18,38,99,171,272,274,275]; but see [276]). As a result, several investigators have suggested that SA theory may in fact apply to the interspecific BMR scaling of birds and mammals [18,19,26,38,99,101,104,171,277], contrary to negative claims made by proponents of the 3/4-power law [12,65].

Although almost all recent analyses (including those with phylogenetic corrections) have shown that the BMR scaling exponent of birds is closer to 2/3 than 3/4, thus supporting SA theory, the application of SA theory to the BMR scaling of mammals is complicated by four additional findings. First, some (but not all) phylogenetically informed analyses have shown that mammalian BMR scales with a power between 2/3 and 3/4 and significantly different from both ([278–281]; but see [274] and Section 10.2). Second, several analyses have shown that the BMR scaling of mammals is nonlinear with the log-log scaling slope shifting from near 2/3 for small mammals to ≥3/4 for large mammals [18,26,28,35,38,39,277,282,283]. Third, BMR scaling may vary among mammalian taxa (e.g., orders), with some values being significantly different from both 2/3 and 3/4 [18,28,38,278,280–282]. Fourth, when both SA and BMR are corrected for body-size differences, they are no longer significantly correlated [284].

Some phylogenetically informed analyses may give *b* values >2/3 because they tend to even out the effects of various taxa with different body sizes on the scaling relationship. Standard regressions are more influenced by the relatively large number of small mammal species, which have BMRs that tend to scale closer to 2/3 than do the BMRs of larger mammals. However, in phylogenetically informed analyses, small mammals have a lesser effect on the metabolic scaling relationship because they occur in fewer taxonomic orders (most are rodents, bats and insectivores) than large mammals. This effect also appears to explain why the binning method, which averages BMR estimates for evenly spaced body-size intervals, tends to elevate *b* above 2/3 and closer to 3/4, as well (see [12,18,99]). Both the binning and phylogenetically informed methods actually give more weight to the relatively few species of large, taxonomically disparate mammals, which have BMRs that scale more steeply than that of smaller mammals [18,38,99].

The concave upward curvature of the mammalian BMR scaling relationship has been explained in several different ways. Hypothetical causes of this scaling curvature include size-related changes in: geographic or environmental effects [274], body shape and associated SA scaling [26,277], body composition [35], postural and thermoregulatory costs [101], taxonomic composition ([281]; but see [38,39]), properties of vascular resource-supply networks [6,39], and life-history strategies [285] (also see Section 9.2). In addition, SA-related heat loss may have a greater effect on the BMR scaling

of small mammals ($b \sim 2/3$) because of their high SA/volume (V) ratios [38]. The BMR scaling of larger mammals ($b \geq 3/4$) may be relatively less influenced by SA, while also being relatively more influenced by V-related tissue demand [99,277] or the resource-supply limits of internal transport networks [38]. Reports that b may approach 1 in very large mammals [35,277] appear to be more consistent with the effects of V-related tissue demand than that of resource-transport networks (but see [38,39]). Producing heat to compensate for SA-related heat loss may not be as much of a problem in large mammals, not only because of their lower SA/V ratios, but also because of their ability to grow thicker insulation in cold environments, as compared to small mammals [286]. In addition, in warm environments large mammals have the opposite problem of needing to release (rather than conserve) heat so as to prevent overheating. As a result, the largest terrestrial mammals in the tropics (e.g., elephants and rhinoceroses) have thinly furred skin with expanded surface areas (e.g., large ears and folded skin) (also see [277]).

Some differences in the BMR scaling exponent among mammalian taxa may be related to differences in body size, metabolic level and life style. Small-bodied taxa are more likely to show near 2/3-power scaling than large-bodied taxa (see [18,38,287–289]), possibly for reasons discussed above. The relative effect of SA on b may also vary with metabolic level, as will be explained more fully later in this section and in Section 8. Relationships between ecological lifestyle (life histories) and BMR scaling in mammals are discussed further by Müller *et al.* [285].

The lack of a correlation between body-sized corrected BMR and SA seems to falsify SA theory [50,98,284], but this is not necessarily so. This is because SA may affect metabolic scaling indirectly, rather than directly. That is, BMR may have evolved (especially in small mammals and birds) to compensate indirectly for SA-related heat loss so as to maintain a constant body temperature, as originally proposed by Sarrus & Rameaux [83] and later endorsed by Rubner [84], Kleiber [8], Bartholomew [97] and others [18,19,99,101,104,290] (however, the possibility that heat loss through the skin may also directly affect metabolism, as suggested by Rubner [84], has recently received some support [291]). Furthermore, this compensation may only be readily seen when a large enough body-size range is examined, because then other possible confounding factors will have a minimal effect. This interpretation is consistent with the observation that b is also near 2/3 for cold-induced maximal metabolic rates in both birds and mammals (*i.e.*, when SA-related heat loss is especially critical), but not when maximal metabolic rates are achieved by strenuous exercise (in this case, b approaches 1, presumably because V-related muscular power production now has an observable effect, in addition to that of thermoregulation) [19,99]. A recent analysis has verified that heat loss scales to the 2/3-power in mammals, which must be compensated by similarly scaled heat production to maintain a constant body temperature [292]). The importance of SA-related heat loss on BMR scaling is also shown by the ability of huddling to decrease BMR, apparently by reducing the effective SA/V ratio. Small compact huddles of small mammals often show near 2/3-power BMR scaling with total huddle mass, just like individuals (see below). In addition, the important effect of thermoregulation on mammalian metabolism is indicated by significant interspecific correlations among BMR, body temperature and environmental temperature [38,293]. However, when small species-specific deviations (residuals) of BMR and SA from their respective scaling relationships with body mass are examined, they may not be positively correlated, as predicted by SA theory, because of confounding environmental differences. For example, cold environments may favor both a higher BMR (*i.e.*,

increased heat production) and reduced SA (*i.e.*, reduced heat loss), whereas warm environments may favor a lower BMR (*i.e.*, decreased heat production) and increased SA (*i.e.*, increased heat loss) (see [38,274,294,295]). As a result, across different thermal environments a negative association between the body-size residuals of BMR and SA may be expected that could counter the more general positive association predicted by SA theory. Interestingly, the above mentioned reported relationship between the residuals of BMR and SA is negative, though not significantly so [284]. A better test of SA theory would control for extraneous environmental effects, by comparing residual BMR and SA among mammals living in the same environment or very similar environments.

However, SA theory based on heat flow is probably only applicable to endothermic animals (for a contrasting view, see [296]). SA effects on the metabolic scaling of ectothermic animals may not apply to all species and must involve different mechanisms. The most likely mechanisms are SA-related effects on resource uptake and waste removal. Two major factors may determine when SA effects are important. First, according to the metabolic-level boundaries hypothesis (MLBH), the scaling of basal or resting (inactive) metabolism should be more influenced by SA-related resource or waste fluxes when the metabolic level or intensity (*L*) is high, but should be more influenced by V-related resource demand when *L* is low [18,19,99,107]. As predicted, high-energy animals (e.g., winged insects and endothermic birds and mammals) tend to have interspecific *b* values near 2/3, whereas low-energy ectothermic animals (e.g., scorpions, wingless insects, fish, amphibians and turtles) tend to have significantly higher *b* values approaching 1 [19,107]. Also as predicted by the MLBH, V effects appear to predominate over SA effects, when the *L* of endothermic birds and mammals is substantially lowered during torpor or hibernation (*b* approaches 1) [18,19,99]. During hibernation, endothermic animals essentially become ectothermic (though without entirely losing their power of thermoregulation), and thus not surprisingly both *L* and *b* approach that of many low-energy ectothermic animals [19]. At the intraspecific level, high-energy fish also show significantly lower *b* values (approaching 2/3) than low-energy fish (*b* values approaching 1) [18,297]. Many other lines of evidence support the MLBH, and thus the view that SA effects on metabolic scaling are dependent on *L* [18,19,99,107,169,173,298].

A second factor that may determine whether external SA effects on metabolic scaling are expressed is the permeability of the body's integument. SA theory predicts that the scaling of metabolic rate should be related to the scaling of external SA in animals with permeable integuments that permit significant fluxes of respiratory gases, nutrients and (or) wastes, but not in animals with impervious body coverings (e.g., exoskeletons). A recent analysis of diverse pelagic animals supports this prediction [46]. Skin breathing scyphozoans, ctenophores and salps show parallel scaling of routine metabolic rate and SA (inferred from scaling relationships between body mass and length), whereas arthropods with largely impermeable exoskeletons do not [46]. Early life stages of various invertebrates are also skin breathers, and as predicted, also show correlations between the scaling of SA and metabolic rate ([299,300]; D. S. Glazier, A. G. Hirst and D. Atkinson, unpublished data). In addition, sea anemones routinely alter their SA by periodic contraction and extraction of their tentacles, which significantly changes the scaling of their metabolic rate [301], as predicted by SA theory [18].

In other animals, the SA of special respiratory organs or other internal resource-uptake systems (e.g., the alimentary tract) may also affect metabolic scaling, though relevant data are currently limited. At present, comparative data on the scaling of metabolic rate and the SA of respiratory organs in various animals do not provide a clear picture (reviewed in [18]). However, comparative surveys have

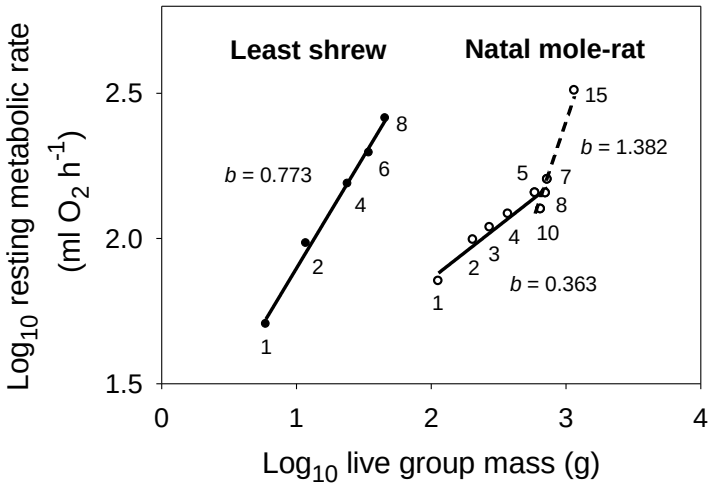
shown that fish and crabs with active, metabolically expensive lifestyles tend to have relatively larger gill SA than those with relatively sedentary lifestyles [302–305]. Ontogenetic shifts in metabolic scaling in fish have also been linked to parallel changes in respiratory SA ([306]; for a contrasting view, see [307]). In addition, experimental manipulations of the functioning of various respiratory surfaces have revealed significant effects on the scaling of metabolic rate in amphibians [308–311] and holothurians [312], as predicted by SA theory [18].

Evidence that SA theory applies to other levels of biological organization also exists. For example, as predicted by the MLBH, high-energy unicells (e.g., fed protozoans) tend to show metabolic scaling exponents near 2/3 (presumably due to SA constraints), whereas low energy unicells (e.g., prokaryotes, unfed protozoans, and algal cells grown at low temperatures) tend to show *b* values closer to 1 (presumably due to greater V effects) [173]. However, additional unicellular studies have yielded what seems to be mixed support for SA theory. Metabolic scaling exponents near 2/3 [171], 3/4 [9,313], 1 [48,185,186,314] and even >1 [48] have been reported. Some of this variation may relate to methodological differences (e.g., use of least squares regression (LSR) *versus* reduced axis analyses (RMA), and the use of heterogeneous data sets containing diverse kinds of unicells in a variety of energy states [313,315]. Some high *b* values that have been reported [48,314] may be at least partly due to the use of RMA, which gives higher estimates of *b* than LSR (also see Section 10.1). In addition, the scaling exponent for metabolism or growth (which is closely linked to metabolism in unicells) depends on energy state (e.g., level of feeding in heterotrophs, and level of irradiance in autotrophs), as predicted by the MLBH [173]. Other reports of isometric metabolic scaling ($b \sim 1$) in prokaryotes and algal cells may also be explained by their low metabolic levels (L). For example, isometric metabolic scaling recently observed in marine phototrophic protists [186] may have resulted from the low experimental temperature (5 ℃) used, thus decreasing mass-specific metabolic rate to a minimal level that was independent of cell size, as predicted by the MLBH ([173]; also see [185,316]. According to the MLBH, SA effects may be seen only at high metabolic levels (*i.e.*, in highly active cells and at high temperatures). An isometric metabolic scaling may have also resulted from a nearly constant ratio between SA and carbon biomass, as observed among the eight species of protists studied, ranging in cell volume by over six orders of magnitude [186]. This occurred despite these species showing a scaling of SA to cell V indistinguishable from 2/3 ($b = 0.675 \pm 0.050$: my analysis of data from [186]). This was because carbon biomass also scaled to cell V with a 2/3 power [186]. In addition, steep scaling of metabolic rate ($b > 2/3$) observed in some unicellular organisms may be the result of disproportionate, cell-size related expansion of external and internal SA [48,106,171], but this remains to be empirically demonstrated.

Further evidence for SA theory can be found in how metabolism scales with total group mass in huddling small mammals. As predicted, small huddles often show near 2/3-power scaling, whereas large huddles that expand largely in two dimensions (by adding individuals horizontally rather than vertically) show steeper scaling [200–203]. Or equivalently for mass-specific metabolic rate, small huddles show near −1/3-power scaling (mean $b \pm 95\%$ confidence intervals $= -0.347 \pm 0.070$, which is not significantly different from −1/3, based on data for 13 small mammal species compiled by Canals *et al.* [202]), whereas large huddles tend to show near 0-power scaling (see [317,318]). Thus, for a wide range of huddle sizes, SA theory predicts that total group metabolic rate should show nonlinear (concave upward) scaling with total group mass. Recent studies on the least shrew and Natal

mole-rat support this prediction [317,318]. As expected, small huddles exhibit negatively allometric scaling, whereas large huddles display near isometric (or perhaps even positively allometric) scaling (Figure 2). However, the scaling slope for small huddles is quite variable (0.36 for the Natal mole-rat, and 0.77 for the least shrew), as also has been reported in other studies (range = 0.41 to 0.87: data calculated from [202]). In addition, SA theory successfully predicts nonlinear scaling of water-loss rates in woodlice (Isopoda) with group size: both individual water-loss rates and SA exposed to air exhibit near −1/3 scaling in small groups, but near 0 scaling in large groups, as predicted [199].

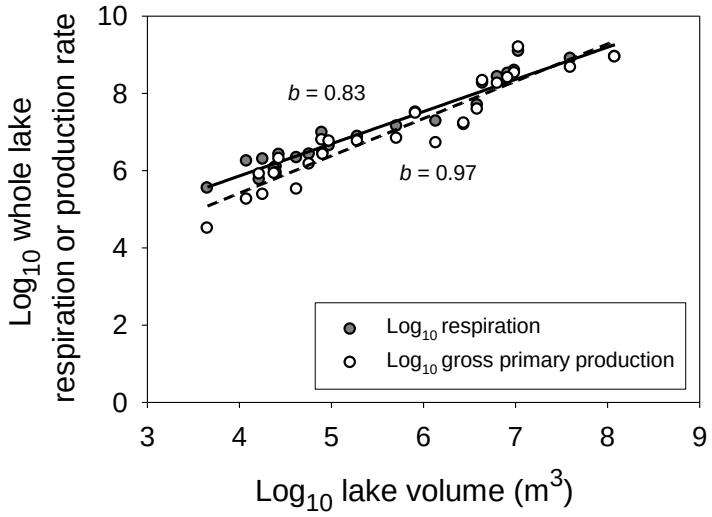
Figure 2. Scaling of group resting metabolic rate (R) with total group mass (M) in the least shrew (*Cryptotis parva*) and Natal mole rat (*Cryptomys hottentotus natalensis*) at 14 ℃ (data from [317,318] and M. Scantelbury, personal communication). The number by each point refers to group size. The *b* values are metabolic scaling exponents (log-log slopes); and the lines refer to least squares regression equations (shrew solid line: $\log_{10}R = 1.124$ (±0.136 95% CI) + $\log_{10}M(0.773$ (±0.103)), $r = 0.997$, $p = 0.00016$; mole rat solid line: $\log_{10}R = 1.134$ (±0.261) + $\log_{10}M(0.363$ (±0.100)), $r = 0.964$, $p = 0.00012$, group sizes = 1–10; mole rat dashed line: $\log_{10}R = -1.745$ (±2.204) + $\log_{10}M(1.382$ (±0.767)), $r = 0.957$, $p = 0.011$, group sizes = 5–15). These scaling relationships confirm the commonly observed pattern that at small group sizes, metabolic rate scales with negative allometry ($b < 1$), whereas at large group sizes it scales with near isometry ($b \sim 1$), probably at least in part, because the growth of group masses changes from being largely 3D to 2D as group size increases, as predicted by surface area (SA) theory (see Sections 3.1 and 5.1). Note that the metabolic scaling slope for large group sizes in the mole rat is not significantly different from 1.



Tests of whether SA theory applies to metabolic scaling at the levels of populations, communities and ecosystems have yet to be undertaken. My analysis of data from Hanson *et al.* [319] shows that the whole system pelagic metabolism (respiration, R) of 25 lakes in Wisconsin and Michigan (USA) scales with negative allometry in relation to their water volume above the thermocline ($b = 0.833 \pm 0.100$; see Figure 3), but with an exponent significantly higher than 2/3. The scaling exponent is closer to, but still significantly different from 2/3 when nutrient levels (total phosphorus concentration) are also included in a multiple regression analysis ($b = 0.796 \pm 0.069$). How important SA/V or P/SA effects (see

Section 4.4.1) are in causing this relationship is unknown. Contrary to expectation, whole system gross primary production (GPP) scaled isometrically with lake volume (b = 0.966 ± 0.136; see Figure 3). By contrast, another recent study on 25 lakes in Denmark reported that pelagic R and GPP per unit water volume both decreased with increasing lake area [241], but it is not known how metabolism scaled with total lake volume or community biomass.

Figure 3. Scaling of total community respiration (R, mmol O_2 d^{-1}) and gross primary production (GPP, mmol O_2 d^{-1}) with total water volume (V, m^3) above the thermocline in 25 lakes from Wisconsin and Michigan (data from [319]). R and GPP were estimated by multiplying measured rates per m^3 times V. The b values are scaling exponents (log-log slopes); and the lines refer to least squares regression equations (solid line: $\log_{10}R = 2.529$ (±0.568 95% CI) + logV(0.833 (±0.99)), r = 0.964, $p < 0.00001$; dashed line: $\log_{10}GPP$ = 1.553 (±0.778) + logV(0.966 (±0.136)), r = 0.951, $p < 0.00001$).



5.2. Resource Transport Theory

The WBE model predicts that metabolic rate should scale with organismal body mass to the 3/4-power. Although the frequent finding of 3/4-power scaling of metabolic rate and other biological processes seems to support this model [12], this interpretation has several problems. First, the WBE model has been shown to be flawed (see Section 1) and many remedial modifications of this model result in predicted slopes (e.g., 2/3, 0.81, 6/7 and 1) different from 3/4 ([26–31,33,44]; but see [25]). Alternative resource-transport network (RTN) models also predict that b should be 2/3, not 3/4 [25,45]. Second, the WBE model only applies to a small subset of existing life: *i.e.*, animals with closed vascular transport systems powered by a single centrally located heart (see Section 1; but note that a modified version of the WBE model has been applied to plants [47,320]). Third, the WBE model assumes that resource (oxygen and nutrient) supply constrains the scaling of metabolic rate with body mass, and therefore cannot explain metabolic scaling when supply limits are not important (e.g., during torpor, diapause or brief episodes of strenuous exercise, and in organisms with low-energy lifestyles [18,19,99,169]). Fourth, in its original form the WBE model predicted universal 3/4-power scaling in three-dimensional organisms, and thus is unable to explain not only extensive taxonomic

variation in the metabolic scaling exponent, but also responses of *b* to changes in physiological state and various environmental conditions ([18,19]; also see Section 7). Fifth, although claims have been made that the WBE model can be modified in ways that permit a diversity of *b* values (0.5 to 1) [25,39,43,44], no direct evidence yet exists that variation in metabolic scaling is mechanistically linked to variation in the geometry or physics of RTNs. Sixth, the WBE model and other RTN models are especially inadequate for explaining cases where metabolic rate shows positive allometry ($b > 1$), as sometimes observed in prokaryotes ([48]; but see [173,185]) and pelagic animals (e.g., salps [18,46,321]), and during the early life-history stages of several other kinds of animals and plants (e.g., fish and invertebrate larvae, neonatal mammals and plant seedlings [18,145,193,321]).

Despite these limitations, is there any strong evidence that RT theory can explain metabolic scaling, at least in some instances? At this time, despite its widespread appeal, the answer appears to be a surprising "no". All current evidence for the WBE model and other RTN models is correlational, and therefore circumstantial. Claiming that RTN models are supported by observations of 3/4-power scaling [12,65,322] is inadequate because this scaling can also be explained by many other theoretical models [18–21,50,67,179,323]. In addition, correlations do not specify cause *versus* effect. RTNs may not necessarily cause variation in metabolism and its scaling with body mass, but rather may secondarily evolve or phenotypically change in a plastic way to match the resource requirements of an organism [8,19,27,29,49,120]. This view is supported by abundant evidence that the anatomy and functioning of RTNs readily respond to changes in metabolic demand (see Sections 3.2 and 6). This demand-related flexibility even includes the ability to alter the permeability of vascular endothelial walls and the density and functioning of oxygen-carrying red blood cells [324].

The most supportive evidence for the WBE model and related RTN models appears to be recent findings that the negative allometry of cellular metabolic rates with organismal body mass disappears when cells are removed from the body and cultured under controlled, resource unlimited conditions [159–161]. Proponents of these models claim that this is because the resource-supply limits of RTNs have been removed, thus causing cells to metabolize at a uniform unconstrained rate [65,159]. However, these findings can be explained in other ways. For example, body-size independent metabolism in cultured cells may reflect an absence of other systemic regulatory factors besides resource-transport supply effects (see Sections 3.4 and 7). Furthermore, although the WBE model predicts elevated metabolic rates in cultured cells, the opposite may happen. Cultured cells may be relatively quiescent because they are no longer engaged in normal *in vivo* physiological activities. As a result, they may exhibit a similar metabolic rate regardless of donor body size because they are metabolizing at a minimal level required for survival [161]. This convergent down-sizing of metabolism may only occur after long-term culturing, which may explain why freshly excised tissues continue to show negative allometry of metabolic rate with donor body size (see Section 3.4).

Furthermore, many tests of the predictions of the WBE model and related RTN models have yielded contrary evidence. For example, the WBE model specifies that the slope of metabolic scaling relationships should be a universal constant for three-dimensional organisms, and should not vary in relation to the elevation (metabolic level) of these relationships, but numerous intra- and interspecific analyses have falsified this prediction [18,19,99,107,169,173,298]. In addition, the WBE model and other RTN models [24,25,45] predict that macroscopic organisms that grow mainly in one or two dimensions should show lower metabolic scaling exponents (*b* varying from 0 to 1/2 for 1D growth

and from 1/2 to 2/3 for 2D growth, depending on specific properties of the RTNs) than those growing in three dimensions (b = 2/3 or 3/4). However, recent studies of diverse pelagic invertebrates that show various degrees of 1D or 2D growth actually show increased scaling exponents (b > 3/4 and often near 1) that are better explained by SA theory ([46]; also see Section 7). Furthermore, the WBE model predicts that small mammals should show steeper metabolic scaling than large mammals [15], but the opposite has been observed [18], and the inflection point occurs at a larger body mass than predicted, as well ([28]; but see [39] for a possible solution to this problem). By contrast, a modified version of the WBE model [47] correctly predicts that small and (or) young plants should show steeper metabolic scaling (b ~ 1) than large and (or) old plants (b ~ 3/4), but this pattern may also be explained by SC or RD theory (see Sections 3.3, 3.4, 5.3 and 5.4). Moreover, large plants (e.g., trees) show metabolic scaling exponents significantly greater than 3/4 [19,40,144,325], contrary to RTN theory. Unfortunately, there is currently no empirically based, experimental evidence supporting a link between variation in RTN properties and organismal metabolic scaling, though a recent computer simulation has shown that WBE plants out-compete other virtual plants with different RTN properties [326].

Similarly, no direct empirical evidence has yet been presented that shows that RT theory can explain metabolic scaling at other levels of biological organization. Intracellular RTNs have been hypothesized to control cellular metabolic scaling [159], but have never been identified [21], and would seem unlikely given that recent analyses show that metabolic scaling exponents are often significantly different from the 3/4 value predicted by the WBE model (b may vary between ~2/3 to ≥1). SA, SC and RD theory appears to have more potential for explaining this variation (see Sections 4.1.1, 4.1.3 and 4.1.4). RTN theory has been invoked to explain negatively allometric metabolic scaling in insect colonies [222], but again other models that also can explain this variation appear to have more empirical support (see Sections 4.3.1, 4.3.3 and 4.3.4). The most promising application of RTN theory to metabolic scaling may be at the level of ecological food webs (see Section 4.4.2), but this remains to be established empirically. Clearly, if RT theory is to survive, it requires further theoretical development, along with direct, mechanistic supporting evidence. Profitable ways by which this may happen include synthesizing RT theory with SA, SC and (or) RD theory, and carrying out experimental manipulations of RTNs to assess their effects on metabolic scaling (also see Sections 3.2 and 8).

5.3. System Composition Theory

SC theory may apply to organismal metabolic scaling whenever the body's tissues have heterogeneous metabolic rates and the masses of these tissues change disproportionately with increasing body size, either through ontogeny or evolution. Negatively allometric scaling of metabolic rate during ontogeny has been attributed, at least partly, to slow relative growth of high-energy tissues (e.g., brain, heart, kidneys and hepatopancreas) and faster relative growth of low-energy tissues (e.g., fat, skeleton and muscle), as has been documented in various fish species [137,138,327]. SC theory also predicts that metabolic scaling should be isometric (b ~ 1) when no changes in the relative proportions of high- *vs.* low energy tissues occur, as has been observed during early growth in fish [137,138,155] and plants ([40]; but see [145]). Similar parallel shifts in the scaling of basal metabolic rate and the masses of metabolically active internal organs (brain, liver, kidneys, lungs and heart) have been observed during early (b = 1.02 and 1.0, respectively) and late ontogeny (b = 0.58 and

0.53) in humans [328]. However, isometric metabolic scaling during early development can also be explained by SA and RD theory (see Sections 3.1, 3.4, 5.1 and 5.4).

In addition, SC theory can explain many cases of highly deviant ontogenetic metabolic scaling, including both very low (<2/3) and high (>1) *b* values, that are not easily explained by SA, RT or RD theory. For example, leptocephalus fish larvae show very low *b* values (−0.05 to 0.47), apparently because they grow largely by accumulating massive amounts of inert storage materials [142]. By contrast, other kinds of newly hatched animal larvae may show positively allometric scaling of metabolic rate ($b > 1$) [329–331] probably because of their depletion of inert storage materials (e.g., yolk), resulting in increasing proportions of actively metabolizing tissues as they grow. Biphasic metabolic scaling observed in growing shrubs and trees, which involves switching from isometric to negatively allometric scaling, has also been attributed to a disproportionate accumulation of metabolically slow or inert tissues (dead wood) after the seedling or sapling stages have been passed [40,144,332]. However, in the freshwater amphipod *Gammarus minus* no relation between ontogenetic changes in the relative proportions of specific low-energy tissues (e.g., fat and exoskeleton) and inter-population variation in the scaling of resting metabolic rate has been observed [52]. Negative allometry of metabolic rate observed during the ontogeny of other arthropods may or may not be related to the accumulation of metabolically inert exoskeletal mass [42,333,334].

Interspecific analyses have also revealed apparent effects of SC changes on metabolic scaling. This has been most notably demonstrated in mammals, where greater proportions of whole body metabolism are affected by high-energy tissues and organs in small *versus* larger species ([70,139,140]; also see Section 3.3). How common these effects are in other taxa remains to be determined. Interspecific scaling analyses of specific tissues or organs have revealed evidence both for and against allometric (disproportionate) mass changes [10,40,70,89,140,141,335–339].

As noted in Sections 4.1.3, 4.3.3 and 4.4.3, SC theory can be applied to other levels of biological organization, as well. For example, it has been suggested that the metabolic scaling of unicellular algae may be affected by the tendency of larger cells to have proportionately larger vacuoles, and thus proportionately less metabolically active cytoplasm than do smaller cells [106,186,340], but this remains to be studied in a rigorous way. However, the finding that dry mass per unit volume decreases with increasing bacterial cell size [188] runs counter to recent observations of isometric or positively allometric scaling of metabolic rate in prokaryotes [48,185].

The negative allometry of metabolic rate of whole colonies of the ant *Pogonomyrmex californicus* ($b = 0.75$) appears to be at least partly attributable to decreases in the relative proportions of active *versus* inactive individuals with increasing colony size [224]. Similarly, the *b* value of some flat bryozoan colonies may be as low as 0.5, because as they grow in size only the actively growing zooids on the periphery (P) have a high metabolic rate, thus resulting in an increasing proportion of metabolically slow, non-growing zooids in the interior of the colony [53]. A *b* value of 0.5 is expected because simple Euclidean geometry for isomorphic shapes dictates that P should vary as a function of $A^{0.5}$, where A is colony area (also see [53] and Section 4.4.1; note that this prediction is not unique to DEB theory, as claimed [53], but can be more generally derived from SC theory). As another example, coral colonies may show negatively allometric metabolic scaling, apparently due to a disproportionate accumulation of inert skeletal materials as they grow in size [216]. However, if colonies grow by simply adding identical individuals (modules) with similar metabolic activity, both SC and SA theory

predicts that the metabolic scaling exponent should be near 1 [209], as has been observed in some colonial bryozoans and thaliaceans (see Section 4.3.1.). This prediction is also upheld by the colonial ascidian *B. simodensis* when its zooids are unconnected (b = 0.95), but not when they are anatomically and functionally linked (b = 0.80) ([214]; also see Section 4.3.2). However, other explanations are possible (see [53]).

5.4. Resource Demand Theory

The body-mass scaling of various energy-demanding processes may affect the scaling of metabolism supporting them. For example, numerous studies have shown that growth rate can affect the scaling of metabolic rate, including several largely forgotten studies published during the early 1900s [164–166] and many more since then (e.g., [341,342] and others reviewed in [18,163]). Rapid growth can explain near isometric metabolic scaling observed during early ontogeny [18,341–344], and progressively slower growth can help explain allometric metabolic scaling later in ontogeny [18,52,332,342] in many kinds of animals and plants, though SA, RT and SC theory can explain these biphasic shifts, as well (see Sections 3.1–3.3 and 5.1–5.3). Some pelagic organisms that show high growth rates throughout their short lives (e.g., salps, which exhibit some of the highest growth rates in the animal kingdom) also show very steep metabolic scaling (b ~ 1 or even >1) [18,321]. In prokaryotes positively allometric scaling of growth expenditure [345] may also help account for positively allometric scaling in metabolic rate [48]. Rare reversals in growth rate during ontogeny (*i.e.*, shifts from slow to rapid growth) are also accompanied by parallel changes in metabolic scaling [18,346]. Various laboratory and natural experiments provide even stronger evidence for the view that the energy demand of growth can affect metabolic scaling. Manipulated increases in growth rates (e.g., via increased food rations [164] or selection [347]) result in significantly higher metabolic scaling exponents (b approaching 1), as predicted. In addition, variation of fish-predation intensity in naturally controlled freshwater spring environments has been shown to cause parallel changes in the scaling of growth and metabolism in various populations of the freshwater amphipod *Gammarus minus*, as predicted by life-history theory [52].

Another energy-demanding activity that strongly affects metabolic scaling is locomotor activity. As locomotor activity increases, the metabolic scaling exponent (b) increases toward 1, as has been observed in several intraspecific [18,36,169,348] and interspecific analyses [18,19,99,120,349–351]. This is most dramatically seen in a classic study by Brett [352], who showed that sockeye salmon (*Oncorhynchus nerka*) progressively increased b, as their swimming speed increased. At rest b was 0.78, whereas at the highest speed b was near 1 (0.97). This effect of locomotor activity does not depend on increasing body temperature (T_b), as has been recently claimed [353], because T_b changes very little during exercise in fish and other ectothermic animals [169]. Rather it appears to be due to an increasing effect of V-related muscular power production, which is most strongly expressed in athletic, ectothermic species, such as winged insects (b ~ 1 [19,349]). In non-athletic species, reduced muscle mass and associated activity has a lesser effect on b [36,120,327,354]. In addition, b is between 2/3 and 1 in active endothermic birds and mammals (b ~ 0.84 to 0.89), apparently because of the opposing effects of thermoregulatory heat production (scaling to the 2/3 power) and muscle power production (scaling to the 1 power) [19].

The MLBH predicts that metabolic scaling should approach isometry ($b \sim 1$) whenever metabolism is largely affected by an energy-demanding process that has pervasive whole-body effects (and thus is V-related) [19]. This effect appears to be true not only for growth and locomotory activity, but also for food processing. The heat increment of feeding or specific dynamic action (SDA), which has metabolic effects throughout the body, has been shown to scale with near isometry in a variety of animals [355].

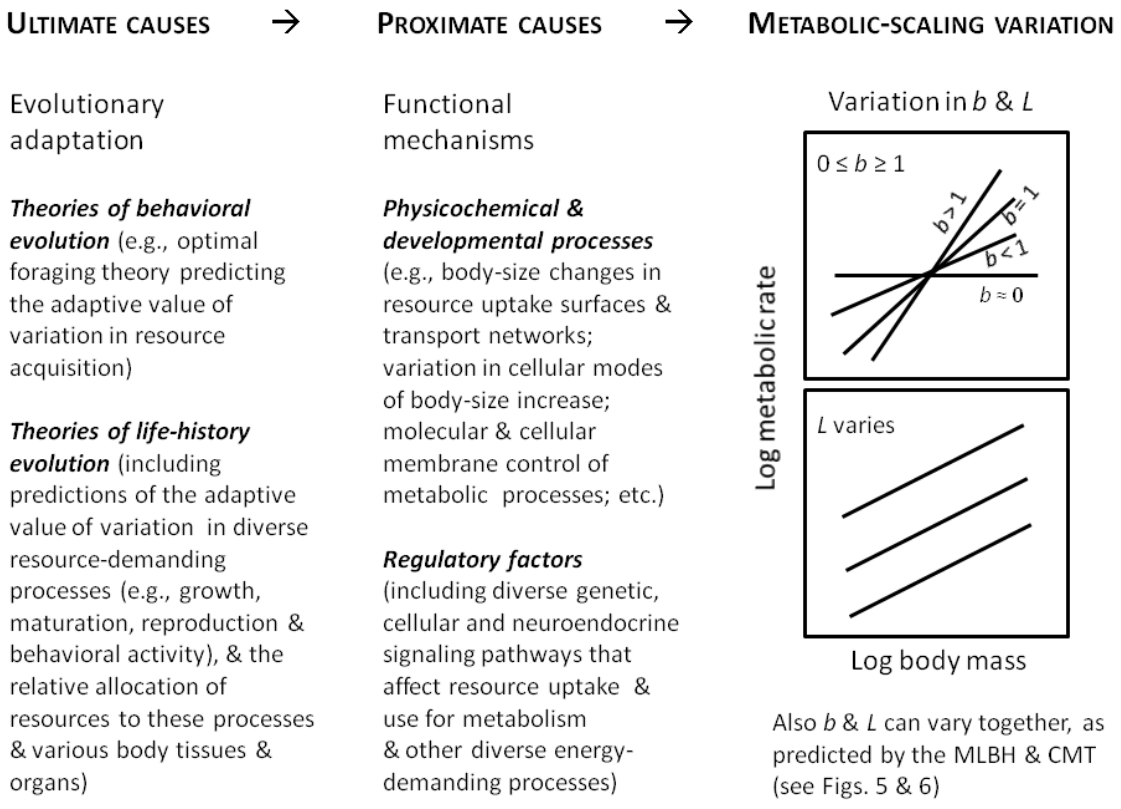
Still other energy-demanding processes, such as reproduction, feeding activity and the development of heat production or other energy-expensive functions, may also affect metabolic scaling [18,19]. For example, the negative allometry of metabolic rate in barnacles ($b < 1$) appears to be linked to decreasing beating of their food-collecting cirri as they grow. As barnacles increase in size, their feeding becomes more efficient, thus decreasing metabolic costs [356]. By contrast, metabolic scaling is often positively allometric ($b > 1$) during the early growth of altricial birds and neonatal mammals [18]. As they develop from being largely ectothermic to endothermic, their metabolic rate (heat production) increases faster than body mass. Accordingly, the age of endothermic maturation tends to coincide with ontogenetic shifts in metabolic scaling from positive to negative allometry [18]. For example, cotton rats (*Sigmodon hispidus*), which show earlier thermoregulatory maturation than wood rats (*Neotoma floridana*), also show earlier inflections in their metabolic scaling [357]. Other supporting evidence is reviewed by Glazier [18]. Steep allometric metabolic scaling ($b \sim 1$ or even >1) often seen in embryonic or larval animals [70,89,193,341,344] may also be influenced by the development of new energy-expensive structures or activities, such as a rapidly metabolizing brain and an actively beating heart [18].

RD theory can be further applied to other levels of biological organization. Several models have been proposed to explain variation in metabolic demand at the cellular level (see Section 4.1.4). The membrane pacemaker hypothesis (MPH) has garnered considerable empirical support [70,191,192,358,359]. It postulates that BMR is increased by enhanced ion and proton fluxes made possible by more fluid membranes with high levels of polyunsaturated fatty acids. As predicted, metabolic rate appears to be correlated with membrane phospholipid content and ion/proton fluxes in various vertebrate animals [358,360,361]. In particular, endothermic mammals tend to have higher sodium and mitochondrial proton flux rates and more polyunsaturated membranes than those of ectothermic reptiles of equivalent size [358,361]. Also like BMR, mitochondrial proton-flux rates and membrane polyunsaturation (MPU) scale allometrically with body mass in both birds and mammals [358,361–363].

However, negative evidence for the MPH has also been found. For example, a recent analysis of 30 mammal species has shown that MPU is not correlated with basal metabolic rate (BMR), contrary to the MPH [364]. Similarly, intraspecific analyses in laboratory mice have revealed no association between BMR and the polyunsaturated fatty acid content of liver cell membranes [365]. Selection for high BMR or maximal metabolic rate in laboratory mice did not result in an increase in MPU [366,367], though significant changes in fatty acid composition were observed [367]. In addition, mitochondrial proton flux rates are not necessarily correlated with BMR [368]. Tests of whether the MPH can be applied to invertebrate animals, as well as plants and unicellular organisms, are also needed [369]. Furthermore, although cellular membranes may be an important proximate (functional) cause of metabolic rates, their properties and associated effects on metabolic rate are likely adaptive (evolutionary) responses to other factors at other levels of biological organization (also see Figure 4;

and Sections 7 and 8.3.3). Like other cellular and subcellular hypotheses, the MPH cannot by itself explain variation in organismal metabolic scaling related to differences in activity level, lifestyle, body shape and composition, and external environmental factors. However, there is some evidence that cellular membrane composition and ion and proton fluxes may change in association with adaptive metabolic depression (e.g., torpor and estivation [361,370–372]).

Figure 4. Ultimate (evolutionary) and proximate (functional) causes of variation in the scaling of metabolic rate with body mass (b = the metabolic scaling slope or exponent; L = the metabolic level or elevation of a scaling relationship; MLBH = the metabolic-level boundaries hypothesis [19,107]; CMT = the contextual multimodal theory, as described in Section 8).



Other cellular models have been proposed [17,71,72,190], but have yet to be tested. The quantum limit version of the quantum metabolism model (QMM) predicts that the metabolic scaling exponent (b) should vary between 1/2 and 1, as a function of the spatial dimensionality of a postulated molecular oscillator network (d), where $b = d/(d + 1)$ [17,72], but direct evidence for this hypothetical mechanism is not yet available. This version of the QMM model is thought to apply to animals with relatively high metabolic rates (rapid nutrient turnover). It has particular difficulty explaining the occurrence of b values >3/4 (requiring $d > 3$), and especially those ≥1 (requiring $d \geq \infty$). It seems unreasonable to suppose that animals with b values ~1 (e.g., many pelagic animals [18,321]) should exhibit an infinite d. Moreover, although b values >1 exist, these are impossible according to the QMM. Furthermore, the QMM seems incapable of explaining why metabolic scaling varies with metabolic level (L) and physiological state [17,19]. As an example, the model requires that d in birds or mammals of differing size should change from being infinite during torpor ($b \sim 1$) down to ~2 at rest ($b \sim 2/3$), and then back

up to almost 7 during strenuous exercise ($b \sim 0.87$). This does not seem possible. A partial solution may be found by also using the classic limit version of the QMM, which predicts that $b = 1$, regardless of the value of d. This model, which may be applied to animals and plants with low metabolic rates (slow nutrient turnover), avoids the problem of $d = \infty$, and also is consistent with observations of $b \sim 1$ in small plants and torpid animals. However, it cannot explain $b < 1$ in large plants (e.g., trees [40,144]). In addition, values of $b \sim 0.87$, as observed in strenuously exercising birds and mammals, still remain problematic, because according to the quantum version of the QMM, which applies to animals with high metabolic levels, d would have to be ~7, which seems unrealistic for 3D organisms.

RD theory may also be applied at supra-organismal levels (see Sections 4.3.4 and 4.4.4), but no empirical evidence supporting such an application is yet available.

5.5. Comparison of Evidence for the Four Theories

Here I recognize three types of supporting evidence: (1) indirect evidence showing a match between predicted metabolic scaling exponents (b) and those actually observed, at least some of the time; (2) direct correlational evidence showing that variation in b is related to variation in the postulated mechanism (*i.e.*, surface area, the geometry or physics of resource-transport networks, system composition, or resource demand); and (3) experimental evidence showing that manipulation of the postulated mechanism alters b as predicted (see Table 1). At the organismal level, only the SA and RD theories are supported by all three kinds of evidence. SC theory is currently supported by indirect and direct correlational evidence, but not experimental evidence. By contrast, RT theory is presently supported only by indirect evidence. Furthermore, RT theory is contradicted by several observations described in Sections 1, 4.2, 5.2, 6 and 7. Therefore, surprisingly RT theory (including the WBE model and other RTN models) has the weakest empirical support, despite being widely regarded as the dominant theory during the last two decades, as indicated by the number of its citations and applications in the literature (e.g., according to Google Scholar, the original WBE model was cited over 2400 times between its publication in 1997 to the end of 2013, by far the most of any current model). Part of the reason for this problematic situation may lie in the difficulty of directly testing the WBE model and other RT theory, which requires detailed measurements of the geometry of RTNs and their rates of resource flow, both in relation to metabolic rate, in multiple organisms or species with different body sizes. Further perspective is provided in Section 8.4.

Table 1. Three kinds of empirical evidence for the four theories emphasized in this review.

	Evidence		
		Direct	
Theory	**Indirect**	**Correlational**	**Experimental**
Surface Area (SA)	X	X	X
Resource Transport (RT)	X		
System Composition (SC)	X	X	
Resource Demand (RD)	X	X	X

Indirect evidence refers to comparative matches between observed and predicted metabolic scaling exponents (b). Direct correlational evidence refers to observed covariation between a postulated mechanism and b. Direct experimental evidence refers to studies showing that manipulation of a postulated mechanism causes variation in b, as predicted. For further details see the text.

6. Resource Supply and Demand and Their Biological Regulation

SA and RT theory focus on how resource supply and the loss of metabolic wastes (including heat) may affect the scaling of metabolic rate. By contrast, SC and RD theory focus on how the resource demand of a living system and its component parts may affect metabolic scaling. Since the metabolism of living systems is affected by both supply and demand, none of these theories can by itself fully explain metabolic scaling. The purpose of this section is to provide supporting evidence for this view (in addition to that presented in Section 5), and to emphasize the important role of biological regulation in achieving an optimal balance between resource supply and demand in living systems. Although not given the attention they deserve, the mechanisms of biological regulation must be considered if we are to achieve a truly comprehensive understanding of metabolic scaling.

Exploring the relative effects of resource supply and demand on metabolic scaling is not "a false dichotomy", as claimed by some proponents of the WBE model ([373], p. 402). They suggest that it is useless to consider metabolic rate as being either supply or demand driven, because natural selection has resulted in a match between supply and demand. However, supply and demand are only matched under chronic steady-state conditions, and may be out of balance, at least temporarily, during periods of torpor or strenuous exercise, thus resulting in a prominent discernable effect of volume-related energy demand on metabolic scaling (b approaching 1 [19]). Maximal supply capacity may also far exceed routine resource demand in many organisms that spend most of their life in a resting state punctuated by brief periods of intense feeding or locomotor activity [19]. Not surprisingly many of these organisms exhibit scaling exponents for resting or routine metabolic rate that exceed that predicted by SA or RTN-related constraints ($b > 2/3$ or 3/4 [19,107]). Even under steady-state conditions, the relative effects of supply and demand on metabolic scaling can be inferred based on incisive experimental and comparative analyses, as described below and in Sections 3.4, 5.4, 7 and 9.3 (also see [19,107,163]).

Traditional metabolic control theory assumes that biochemical reaction rates are controlled mainly by the supply of substrates (starting materials). Although metabolism obviously cannot occur without substrates, recent theory and empirical evidence show that the demand for metabolic products may also play an important role in regulating the rates of various metabolic processes [163,374–376]. Metabolic control by demand is important not only because it prevents the potentially harmful over-accumulation of various metabolites [376], but also because it allows living systems to engage in fitness-promoting activities as they are needed. If metabolism were totally supply driven, living systems would not be able to respond effectively to vital moment by moment demands related to various environmental challenges (e.g., the need to engage in rapid energy-expensive behaviors involving food capture or escape from becoming food). Numerous studies have shown that product demand can control the rates of many major metabolic pathways [70,376,377]. In particular, the metabolic production of adenosine triphosphate (ATP), a major energy currency of living systems, varies in response to ATP demand [377–380], as does photosynthesis in relation to the demand for photosynthetic products [381]. The rates of metabolic production of many other critical metabolites, such as NADPH, acetyl-CoA, amino acids, lipids and sugars also appear to be regulated importantly by demand [376]. Furthermore, many studies are elucidating the various mechanisms (including diverse regulatory factors and signaling pathways) by which demand controls metabolic rates [163,374,375,379,382,383]. Metabolites

themselves can affect various signaling networks involved in the control of resource uptake and use ([384–387]; and other references cited in [163]).

The importance of both resource supply and demand for controlling metabolic rate is seen not only at the biochemical level, but also at the organismal level. As described in Sections 3.4 and 5.4, the resource demand of several biological processes (e.g., growth, locomotion, and heat production) can affect both the magnitude of whole organism metabolic rate and its scaling with body mass (also see [163]). An excellent example is behavioral (locomotor) activity. When an animal engages in intense locomotor activity, the heightened resource demand that results is met by an escalation of metabolic rate and various resource-supply processes (e.g., rates of breathing and blood flow [19,120,163]). The whole body metabolism becomes dominated by volume-related muscular power production, thus causing *b* to approach 1 [19,99,163,169].

Therefore, a complete understanding of the factors determining metabolic rate and its scaling with body size requires increased knowledge about how various regulatory systems control both resource supply and demand, and their coordination. The importance of both resource supply and demand in metabolic scaling has been recognized by many investigators [18,19,70,73,167,379,388], but we are still a long way from fully understanding the mechanisms involved. In addition, although biological regulation has long been thought to be important for metabolic scaling [7,8,64,73,74,389], this perspective has received little theoretical development and few empirical tests. Biological regulation is implicated in SA theories of metabolic scaling based on heat flow in endotherms [8]. According to this theory, metabolic rate (heat production) is regulated to match heat loss, so as to maintain a constant body temperature. However, it is unknown how the actions of various signaling pathways of the thermoregulatory system scale to body size so as to match changes in body surface area relative to volume (but see [390,391] for analyses of how various properties of the thermoregulatory system, such as thermal conductance and the boundaries of the thermal neutral zone, scale with body size in mammals). A similar ignorance pertains to the body-size scaling of the activity of other regulatory systems that control the development of resource-supply networks and the resource demand of various energy consuming tissues, organs and living processes.

A major purpose of the neuroendocrine system is to govern "the body economy" ([89], p. 153), which involves managing the acquisition and use of resources by an organism so that it can effectively cope with environmental challenges (also see [163,392–394]). Other regulatory systems are also important in matching resource supply with demand in an environmentally sensitive way at both the cellular and organismal levels [163]. In particular, our knowledge is rapidly growing on how various regulatory factors can cause resource-supply systems to rapidly adjust to changing resource demands related to high-energy activities, such as locomotion and reproduction. For example, various signaling pathways (including chemo- and mechanoreceptors, neural signals, hormones and other vasoactive agents) increase the supply of resources (oxygen and fuel) to muscle tissues during strenuous exercise by eliciting massive changes in the operation of the circulatory system, including increased heartbeat, blood flow, number of open capillaries, and rates of resource flow across capillary membranes and into muscle cells [324,395–401]. If increases in muscular activity are chronic, additional regulatory factors (e.g., nitric oxide, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2), and oxygen and metabolic sensors, such as the histone deacetylases HADC and SIRT1) will even stimulate the synthesis of new blood vessels (angiogenesis), thus increasing the size of the vascular

network [124,402–405]. Similarly, various regulatory factors help meet the increasing resource demand of mammary glands during energy-expensive lactation by increasing blood flow, which is distributed by an expanded vascular network [406,407]. These examples strengthen the view that it is unlikely that metabolism and its scaling with body size are primarily controlled by resource-supply networks, because these networks and their functioning are highly malleable, and can be readily altered to fit metabolic demand (also see Sections 3.2 and 5.2). As John Hunter astutely declared in 1794, "blood goes where it is needed" [395].

Hormones and other regulatory factors can either stimulate or depress metabolism [408–410]. This is most dramatically seen in heterothermic birds and mammals that rapidly and markedly depress their metabolic rate as an adaptive response to cold, food shortages or other environmental stressors. Daily torpor and seasonal hibernation are achieved by an active down-regulation of metabolism that causes (rather than merely results from) declines in body temperature [295,409,411–415]. When conditions are favorable, torpid birds and mammals can also rapidly up-regulate their metabolism to reestablish high body temperatures and thus normal activities [409,412]. Furthermore, these actively regulated changes in metabolic state markedly affect the body-mass scaling of metabolic rate, which shifts from being allometric ($b \sim 2/3$) during normothermia to isometric ($b \sim 1$) during hypothermia [18,19,99]. Thus during deep torpor the mass-specific metabolic rate becomes independent of body mass (also see [316,416]. In short, biological regulation is so powerful that it can even abolish allometric metabolic scaling! If it can do this, then it seems likely that biological regulation also plays an important role in determining allometric metabolic scaling itself.

If so, we should be able to find evidence that the activity of various regulatory molecules or pathways that control metabolism and other associated biological processes scale allometrically with body mass in a way similar to that of metabolic rate. However, presently there is little evidence to support this prediction. For example, thyroxine (thyroid hormone) is an important regulator of metabolism and its utilization rate varies inversely with body size in mammals, as predicted [417]. However, thyroxine levels are not correlated with body size in mammals [418,419]. Thus the role of thyroxine activity in the scaling of metabolic rate is currently unclear. Other regulatory factors may also be involved. For example, unlike thyroxine, insulin-like growth factor 1 (IGF-1) levels do scale inversely with body size in mammals [420]. Since IGF-1 has important effects on growth and metabolism [163,421], it is possible that this regulatory factor plays a significant role in metabolic scaling. Studies of how the expression of genes involved in controlling resource uptake and use scale with body size could also provide useful insights (e.g., see [422–424]). Elucidation of the regulatory controls of metabolic scaling promises to be an exciting area for future research.

7. Relative Effects of Internal and External Constraints and Processes

Living systems are open, and as such are continually affected by their environment. However, some theoretical models of metabolic scaling focus mainly or entirely on internal physical or chemical constraints (e.g., SA theory based on body-size related patterns of cell size *versus* number, RT theory based on resource-transport networks, and RD theory based on intracellular biophysical or biochemical processes). Therefore, it is not surprising that these models cannot explain why the metabolic scaling exponent (b) varies in response to a variety of environmental factors (reviewed in [18,49]; also see

below). Models that assume that metabolic scaling is purely a matter of "engineering" [295] or internal body design underestimate the power of living systems to actively regulate their metabolism and its scaling with body size in flexible ways that are sensitive to the states of both their internal and external environments (also see Sections 6 and 8). These models (as indicated above) have limited applicability because (1) they are based on only one of the four major kinds of theory that are discussed here, each of which has been shown to have a restricted domain (see Sections 5 and 8); and (2) they focus on only resource acquisition and use, while ignoring another basic requirement of all living systems, the acquisition and use of information. Organisms require both resources and information, and their intimate interaction to effectively perpetuate their own kind [163,425]. Those organisms that most effectively use information about their environments to manage their uptake and use of resources proliferate at the expense of those that are less effective at doing so. Successful organisms are in essence well "informed resource users" [425]. Therefore, many resource-based models of the scaling of metabolism and other biological processes (e.g., growth and reproduction) are incomplete because they ignore the importance of information-based regulatory systems, and thus half of the essence of life ([163]; also see Section 9.3).

Both physical constraints and eco-physiological acclimation or adaptation may importantly affect the scaling of metabolic rate, but their predicted effects differ among different models. For example, RTN theory (including the WBE model) has assumed that physical constraints, associated with the optimally efficient transport of resources to metabolizing cells, cause the presumed central tendency of near 3/4-power metabolic scaling (but see [19,45]), with physiological and ecological effects causing variation only in the elevation of scaling relationships and species-specific deviations from them ([12,43,65,426] and other references cited in [19]). By contrast, the metabolic-level boundaries hypothesis (MLBH) assumes that physical constraints, associated with surface-area related fluxes of resources/wastes and volume-related resource demand, act as boundary limits within which both the scaling slope (b) and elevation (L) can vary in response to various physiological and ecological factors [19,107]. As predicted by the MLBH, evidence is growing that physiological and ecological factors can affect both b and L for both intra and interspecific relationships between metabolic rate and body size [18,19,107,321].

Internal biological processes that strongly affect metabolic scaling include growth, food-processing, heat production and various physiological processes associated with behavioral activity (also see Sections 3.4 and 5.4). Increasing behavioral or physiological activity affects both the slope (b) and elevation or metabolic level (L) of metabolic scaling relationships. L is typically positively correlated with physiological and behavioral activity (also see Section 8.2.2). Furthermore, as predicted by the MLBH, the slope of the interspecific scaling of metabolic rate with body mass shows a U- or V-shaped relationship with L in birds, mammals and winged insects, three independently evolved taxa that are among the most dominant groups of terrestrial animals on earth. At the lowest L (during torpor, hibernation or diapause) $b \sim 1$, at intermediate L (during rest) $b \sim 2/3$, and at the highest L (during strenuous activity) b again approaches 1. A similar U-shaped relationship between b and L has recently been reported for intraspecific metabolic scaling relationships in six chiton species, whose natural lifestyles involve different levels of activity [427]. According to the MLBH, these activity-related changes in b are associated with shifts in the relative importance of SA- and V-related processes on

metabolic rate ([19,107]; also see Section 8). I also suspect that they are mediated by various regulatory factors that govern metabolic level (see Section 6).

In addition, numerous kinds of external environmental factors can affect both *b* and *L*. These include both biotic (e.g., levels of predation [52], parasitism [428] and food availability [164]) and abiotic factors (e.g., temperature [429–433], pH [434], salinity [435] light intensity [172,436], water availability [437] and other habitat factors [438,439]) (also see [18] for many other citations).

The mechanisms by which physiological and ecological factors affect metabolic scaling (especially *b*) are still little understood and represent a major promising area for further research. These mechanisms should be examined at both the proximate (functional) and ultimate (evolutionary) levels (*sensu* [440]). Proximate mechanisms likely involve various physicochemical and regulatory factors, whereas ultimate mechanisms likely involve various fitness-promoting behavioral and life-history strategies (*cf.* [18]). Theories of behavioral and life-history evolution may help us to understand the adaptive (genotypic) causes of metabolic-scaling variation (*cf.* [441,442]), whereas empirical analyses of the underlying physicochemical processes of metabolism and their regulation may elucidate the functional (phenotypic) causes (Figure 4; also see Section 6). For example, Glazier *et al.* [52] have recently shown that the scaling of growth rate with body size in the freshwater amphipod *Gammarus minus* varies significantly among spring-dwelling populations exposed to different levels of size-selective fish predation. As predicted by life-history theory [443–445], amphipods exposed to high levels of predation, which is biased toward large (energy-rich) prey, mature at a relatively small size and show little or no post-maturational growth (*i.e.*, determinate growth), whereas amphipods in fishless springs mature at a larger size and show continual post-maturational growth (*i.e.*, indeterminate growth) as well. Since growth is energetically costly, it is not surprising that amphipods in fishless springs also show steeper metabolic scaling (b = 0.76–0.77) than those in springs with fish (b = 0.54–0.62), and that these differences parallel the inter-population variation in the scaling of growth rate (b = 0.79–0.81, and 0.62–0.72, respectively). Although not yet studied, these inter-population differences in growth and metabolic scaling are probably mediated by variation in the ontogenetic activity of various regulatory factors.

The above example illustrates how an environmental factor (predators) may affect metabolic scaling by its influence on the ontogeny of a resource-demanding (RD) process (in this case growth). Current evidence suggests that this anti-predator response is adaptive (genotypic), but phenotypically plastic responses (acclimation) may also be involved in this case and those involving other ecological effects. For example, the effect of temperature on *b* and *L* of metabolic scaling relationships may be immediate, as observed in various species subjected to short-term temperature changes in the laboratory ([429–431] and other references cited in [18]). Temperature effects on *b* and *L* may also be the result of long-term acclimation or adaptation, as observed in comparisons of fish and crustaceans from habitats with different temperatures [297,446].

Ecological factors may influence metabolic scaling through a variety of mechanisms. Not only RD effects (as appears to be the case for the effect of fish predators on metabolic scaling in freshwater amphipods), but also SA and SC effects may be involved. For example, pelagic environments have apparently favored relatively steep scaling of SA (and thus presumably associated oxygen, nutrient and/or waste fluxes) in many kinds of invertebrates with permeable integuments, which in turn is correlated with relatively steep scaling of metabolic rate (*b* often approaching 1) [46,300]. RD effects

may also be involved in causing this near-isometric metabolic scaling, because natural selection favors high levels of growth, reproduction and (or) anti-sinking locomotor behavior throughout the short lives of many open water invertebrates exposed to high predation [18,321]. In addition, natural selection appears to have favored specific life-history strategies in various fish species that involve either larval depletion or accumulation of inert storage materials, resulting in SC changes that produce either very high or low *b* values, respectively (see Section 5.3).

It is thus becoming increasingly clear that metabolic scaling is not simply a fixed function of internal body design and physical constraints, but is physiologically and ecologically responsive both functionally and evolutionarily. This is especially well illustrated by the strongly divergent metabolic scaling seen between pelagic ($b \sim 1$) and benthic lifestyles ($b < 1$) in four different animal phyla with very different body designs [18,321]. Remarkably, this substantial divergence is also seen within species that have pelagic larval and benthic adult stages [18,321], and may have occurred in extinct pelagic and benthic trilobites, as well [179].

Even the physical constraints specified by prominent models of metabolic scaling are not exempt from the pervasive influence of physiological and ecological factors. As already discussed in Section 6, changes in resource demand by various physiological processes (e.g., lactation and muscular activity) can markedly change the structure and functioning of resource-transport networks, which are thought to physically constrain metabolic rate, according to RTN models. Physiological and ecological effects may also alter the physical boundary limits specified by the MLBH, which predicts that *b* should vary between 2/3 and 1 (also see [107]). For example, if resource demand is not directly proportional to body volume (V) as an organism grows in size, but escalates because of the development of new costly functions or activities, then *b* may exceed the idealized boundary limit of 1 [19]. A good example is the positively allometric metabolic scaling observed in young birds and mammals that are developing increasing powers of endothermy (heat production) ([18]; also see Section 5.4). Another example is the positively allometric scaling of metabolic rate apparently shown by prokaryotes, which has been attributed to increasing metabolic capacity in larger, more DNA-rich cells [48]. Larger prokaryotic cells also appear to have proportionately increased growth demand compared to smaller cells [345]. Conversely, if the resource demand (RD) of some processes (e.g., growth) decreases markedly with increasing size, then *b* may be <2/3, as observed in freshwater amphipods with very slow postmaturational growth [52]. In addition, as already mentioned above, pelagic environments may favor SA scaling with *b* values significantly higher than the idealized value of 2/3. This is because the growth of many pelagic invertebrates does not occur proportionately in three dimensions, but may be biased along one or two dimensions, thus leading to increasing elongation or flattening, respectively. Euclidean geometry shows that 1D or 2D growth results in SA scaling isometrically ($b = 1$), and not allometrically as seen in organisms with 3D growth ($b = 2/3$) [46,447]. Therefore, the prediction that the resting (or routine) metabolic scaling exponent should approach 2/3 in organisms with a high metabolic level (*L*), because of strong SA-related effects of resource supply and (or) waste removal, may not be seen in many pelagic invertebrates whose SA scales more steeply ($b > 2/3$). Conversely, the prediction that the resting (or routine) metabolic scaling exponent should approach 1 in organisms with a low metabolic level (*L*) may not be observed because of significant size-related changes in the relative proportions of high- *versus* low-energy tissues [19]. SC effects may thus help explain why some kinds of organisms with low *L* (e.g., ticks and large trees) show *b* values <1 ([107]; also see

Section 8.2.1). Size-related SC changes may also cause *b* to take on values outside the theoretical range of 2/3 to 1 postulated by the MLBH (see Section 5.3).

8. Toward a Synthetic Theory of Metabolic Scaling

8.1. General Approach and Perspective

A major purpose of this review is to emphasize that no one current model or theoretical approach is sufficient to explain fully the rich diversity of metabolic scaling that has been observed. Metabolic scaling is a "many-splendoured thing" [379], and to fully understand it, we need a comprehensive theory that is sufficiently complex (multi-faceted) to be equal to the task. Complex (but not too complex) theory is needed for complex living systems. To establish such a theory, one first needs to identify the theoretical facets that appear to be most valid (*i.e.*, consistent with empirical evidence). I have focused on four major facets: SA, RT, SC and RD theory, all of which have had a long history of theoretical development and empirical testing (see Section 3). Each of these subtheories is supported by specific models and at least some empirical evidence (see Sections 3–5). Although only two of the subtheories (SA and RD) have experimental support, and one only has indirect support (RT), all four will be considered as components of the synthetic theory presented here.

Before presenting my proposal for a synthetic theory, it is important to note that others have developed models that use two or more of the four featured subtheories. Selected examples of such theoretical syntheses are listed in Table 2 and Appendix Table A2. However, no current theory explicitly incorporates all four subtheories, and only two feature three subtheories (Table 2). DEB theory is based on SA, SC and RD theory [54,66,67], and the MLBH emphasizes SA, RT and RD theory, while also acknowledging possible SC effects [18,19,107]. These two theoretical approaches have important similarities: both invoke SA and RD theory, which have the strongest empirical support of the four subtheories (see Table 1), and both attempt to explain a diversity of metabolic scaling exponents for both intra- and interspecific relationships. Each has advantages and disadvantages, as well.

Although DEB theory includes SC theory, it presently applies this theory to only interspecific and not intraspecific scaling relationships. However, SC theory can also help explain the magnitude of some intraspecific scaling exponents, especially those that are extremely low or high (see Sections 3.3 and 5.3). Furthermore, the DEB application of SC theory to the interspecific body-mass scaling of metabolic rate predicts that the scaling exponent should be steeper for small than large mammals (b = 0.915 and 0.767, respectively [67]), which is the opposite of that observed ($b \sim 2/3$ and $\geq 3/4$, respectively; note that the original WBE model also makes a similarly incorrect prediction; see Section 5.2). DEB theory invokes RD theory to explain intraspecific metabolic scaling, but does so by focusing mainly on the energy cost of growth. Other RD processes (e.g., reproduction, locomotion and heat production) may also significantly affect both intra- and interspecific metabolic scaling (see Sections 3.4 and 5.4). In addition, DEB theory makes no attempt to explain why b varies with activity or physiological state, and in particular metabolic level (L). Lastly, standard DEB theory makes some assumptions that do not appear to be universally applicable (e.g., food consumption rates do not always scale to the 2/3 or 3/4-power for intra- and interspecific relationships, respectively (e.g., [448]; but see [67]); assimilated energy need not always enter into a storage compartment before being used

by other biological activities, such as maintenance, growth and reproduction [449–451]; and the resource-allocation priority rules of organisms may vary in ways not specified by standard DEB theory [425,449–452]. However, standard DEB theory can be modified to take into account changes in these assumptions (e.g., [453]).

Table 2. Selected models of metabolic scaling and their use of the four theories (subtheories) emphasized in this review.

	Subtheories Used			
Model	**SA**	**RT**	**SC**	**RD**
Metabolic-level boundaries hypothesis (MLBH) [19]	**X**	X	x	**X**
Dynamic energy budget (DEB) theory [66]	**X**		**X**	**X**
Resource-transport network (RTN) models [1]	x	**X**	x	
Allometric cascade model [167]			**X**	**X**
Constructal theory [296]	**X**	**X**		
Cell-size model [68,69]	**X**			x
Classic surface law and related heat-loss models [2]	**X**			
Mass-transfer model [103]	**X**			
Membrane pacemaker model [70,191]				**X**
Quantum metabolism model (QMM) [21,71,72]				**X**
Biomechanical support model [454]				**X**

X: Major emphasis; X: Minor emphasis; x: Acknowledged, but not emphasized. [1] Focus here is on the WBE model [15] and its later modifications [24,25,43,47,320]. Banavar *et al.* [388] have also considered how a balance or imbalance between resource (transport) supply (RT theory) and resource demand (RD theory) may affect metabolic scaling. [2] The classic heat loss model devised by Sarrus and Rameaux [83] has been further developed by several workers (e.g., [100–102]).

The MLBH chiefly emphasizes SA and RD theory, whose relative importance is thought to vary with the level of behavioral or physiological activity, and by association metabolic level (L). According to the MLBH, RT effects may also be important at high L, but only for organisms that have resource-transport networks. However, no direct evidence for RT effects yet exists (Table 1). SC theory is not explicitly included in the MLBH, but its potential effects are acknowledged [18,19]. SC effects need to be included in a more comprehensive theory. They may help explain metabolic scaling exponents not predicted by the MLBH, including those that lie outside of the theoretical range of 2/3 to 1 (also see [107] and Section 5.3).

After it was first developed, the WBE model [15] was modified to also include SA theory. This modified model invokes the presumed fractal nature of inner resource-exchange surfaces, which were hypothesized to give life a fourth dimension ([24]; also see Appendix). Deviations from 3/4-power scaling during the early growth of birds were also attributed to changes in relative water content [455], thus invoking SC theory. However, the emphasis of RTN theory has continued to be on the geometry and physics of resource-transport networks [6,25,45].

Other recent models that are based on more than one of the subtheories featured here include constructal theory (SA and RT theory) and the allometric cascade model (SC and RD theory) (see Table 2).

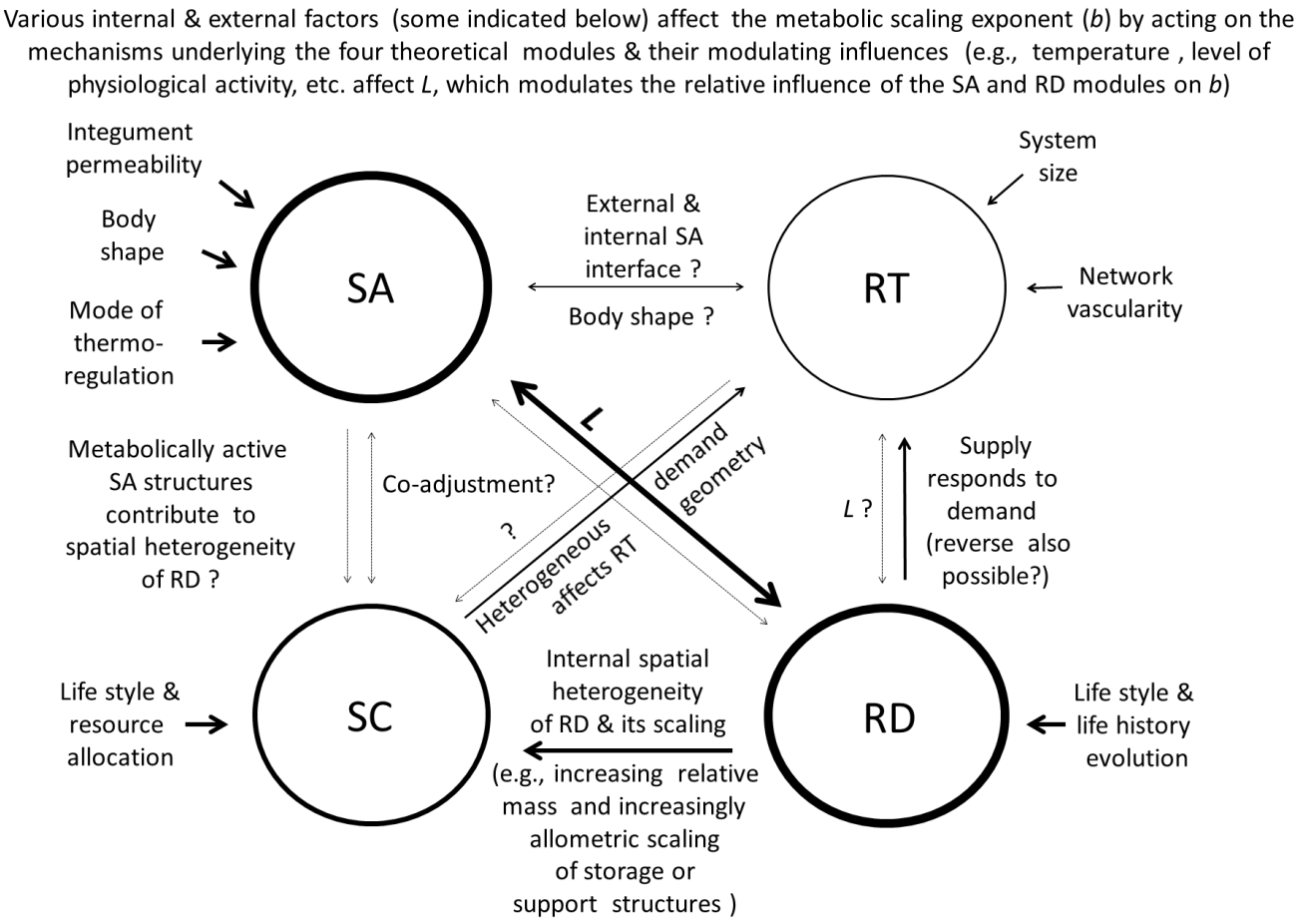
The synthetic theory of metabolic scaling proposed here has three important elements. First, it is modular (multi-modal). Its four modules (or modes of operation) constitute the four subtheories

emphasized in this review (Figure 1). Second, the relative influence of each module on metabolic scaling is governed by several modulating factors (Figure 5). These include (a) metabolic level (*L*), which affects the relative influence of SA-, RD- and possibly RT-related processes, (b) the degree of permeability or insulation of the integument, which determines how much external SA-related resource/waste (including heat) fluxes may affect metabolic scaling, (c) body size and shape, which affect the amount of SA/V available for metabolic resource/waste fluxes, (d) the presence or absence of closed vascular systems, which determines the potential domain of influence of RTNs, (e) thermoregulatory strategy, which affects the importance of SA-related heat loss for metabolic scaling, (f) the degree of heterogeneity of the metabolic rates of different tissues and of the mass scaling of these tissues, which affects the relative influence of SC and RD processes, and (g) type of lifestyle or life-history strategy, which can affect all of the above, as well as the manifestation of specific body-size related SC and RD changes and their influence on metabolic scaling. Third, the expression of all of these modulating effects is contingent, rather than absolutely deterministic. As a result, the influence of each module on metabolic scaling is not universal, but context-dependent. Their relative influence depends on various intrinsic properties of a living system and the state of its internal and external environments.

This multi-faceted synthetic theory, which I call the "contextual multimodal theory" (CMT), is very different from most theories of metabolic scaling that have so far been proposed. It is not deterministic; and it does not depend on a single mechanism. Rather it is based on multiple mechanisms, each of which is expressed only under certain conditions (*cf.* [20]). Therefore, this theory is not mechanistic in the traditional sense, but "meta-mechanistic". Meta-mechanisms are composed of multiple mechanisms whose actions are contingent on specific conditions (this theoretical approach, which can be applied to many areas of biology, as well as other disciplines, will be developed more fully elsewhere). However, meta-mechanistic theories are just as mechanistic as traditional theories based on single mechanisms. Not realizing this has led to some misunderstanding about the mechanistic nature of the MLBH, which is also meta-mechanistic (also see [107]). The CMT and MLBH should not be regarded as being merely descriptive or phenomenological. Although not deterministic, they are contingently mechanistic; and therefore, I would argue more able to explain the diversity of metabolic scaling, and its responsiveness to numerous internal and external factors, than can simple deterministic theories.

During the last two decades, there have been attempts to construct a "Newtonian" view of metabolic scaling based on simple deterministic mechanisms expressed in the form of mathematical laws. This approach is epitomized by the 3/4-power metabolic scaling law and the WBE model supporting it [12,15,65], as well as by the "master equation" of the "metabolic theory of ecology" (MTE), which includes the physical effects of both body size and temperature on metabolic rate [456,457]. However, this approach has been controversial on both theoretical and empirical grounds ([58]; also see Sections 1, 3.2, 5.2, 5.5 and 10.2). Growing evidence indicates that there is no universal 3/4-power law [18,19,34,51,300,458,459], and furthermore the WBE model and the MTE, as originally formulated, cannot explain the extensive diversity of metabolic scaling relationships and their covariation with various physiological and ecological factors ([18,19,52,297,321,427]; also see Section 7).

Figure 5. A schematic depiction of the contextual multimodal theory (CMT) of metabolic scaling as applied to individual organisms. The four focal theoretical modules—surface area (SA), resource transport (RT), system composition (SC) and resource demand (RD) theory—and the various morphological, anatomical, physiological and ecological factors contingently modulating their relative influence on the metabolic scaling exponent (*b*) are shown. Line thickness for the circles and arrows represent the suggested relative importance of each theoretical module and the various modulating factors, respectively, based on current empirical data. For example, the SA and RD modules and their modulation by *L* (metabolic level) are considered to have prominent effects on *b* (also see [107]). Compare to Figures 1, 4 and 6.



Here I argue that a "Darwinian" approach is needed to explain the contingent variability of metabolic scaling. Metabolic scaling is not fixed by physical constraints, but can evolve in response to various ecological factors (e.g., predators: [52]) and the energetic demands of different lifestyles (e.g., pelagic *versus* benthic lifestyles [18,321]). Physical factors, such as SA limits on resource/waste fluxes and V limits on power production, appear to act as broad boundary limits, within which the *b* and *L* of metabolic scaling relationships can vary extensively (*b* usually varying between 2/3 to 1, but also beyond these limits due to extenuating influences), rather than as highly limiting constraints that cause most metabolic scaling patterns to cluster at or near a single centralized relationship (e.g., 3/4-power scaling), as postulated by the WBE model and the MTE [19,107]. Moreover, various physical constraints (including SA and V limits, and the physics and geometry of RTNs) invoked by metabolic

scaling models are not inviolate, but can themselves be altered by various physiological and ecological factors (see Section 7). The theoretical approach that I adopt here is akin to that of other Darwinian approaches, such as various evolutionary optimality models, that recognize that organismal adaptations are contingent on specific ecological circumstances, and are realized within boundary limits set by specific constraints (e.g., see [460–462]).

8.2. Specific Details of the Contextual Multimodal Theory (CMT)

So far, I have given a broad-brushed view of the CMT. In this two-part section, I show how the CMT can explain specific examples of metabolic scaling at the organismal level. In Section 8.2.1, I discuss how various factors may modulate the relative influence of the SA, RT, SC and RD modules on the metabolic scaling exponent (b), causing it to vary between 0 and ≥1. In Section 8.2.2, I show how the CMT can also be used to explain variation in the elevation (or intercept) of metabolic scaling relationships. Although this review focuses on mechanisms affecting the slope (b) of metabolic scaling relationships, it is also important to explain the elevation (L) of these relationships, not only because it is a critical scaling parameter itself, but also because the mechanisms affecting L appear to modulate the effect of mechanisms influencing b.

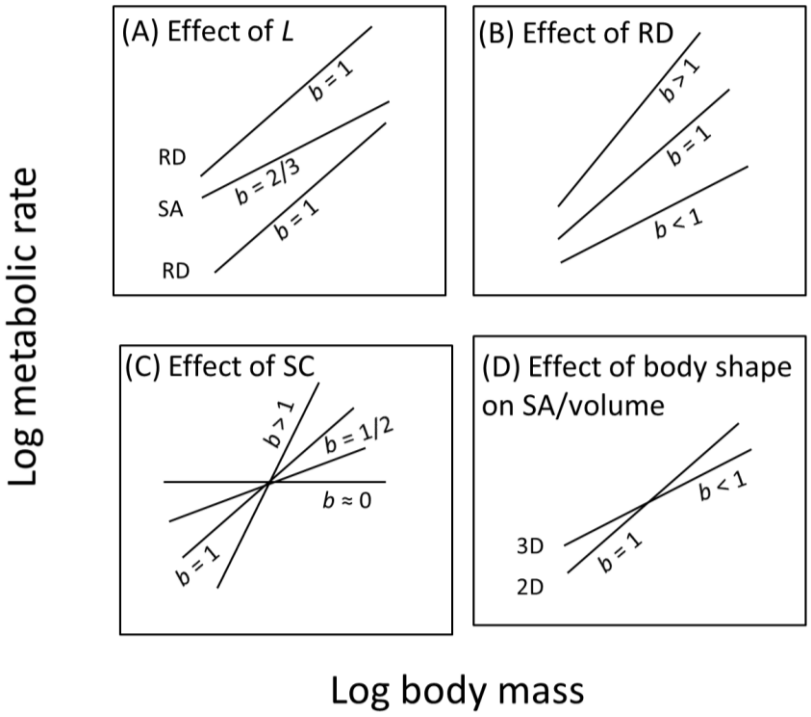
8.2.1. How the Contextual Multimodal Theory (CMT) Can Explain Variation in the Slope (b) of Metabolic Scaling Relationships

Various modulating factors and some of their hypothetical effects on the metabolic scaling slope (b) are depicted in Figures 5 and 6. I first focus on the SA and RD modules and how their relative effects on metabolic scaling (b) are modulated by metabolic level (L), as postulated by the MLBH. This is a good place to start because SA and RD theory has the most empirical support of the four subtheories (see Section 5.5), and b has been shown to be related to L for both intra- and interspecific metabolic scaling relationships in a wide variety of uni- and multicellular organisms [18,19,99,107,169,173,297,298,427]. According to the MLBH, as L increases for inactive metabolic rates, SA effects on b should increase, whereas volume (V)-related RD effects should decrease, thus resulting in b shifting from a potential maximum of 1 to a minimum of 2/3. However, as L increases even further for active metabolic rates, the MLBH predicts that SA effects on b should decrease, whereas V-related RD effects should increase, thus resulting in b shifting from a potential minimum of 2/3 to a maximum of 1 (Figure 6). Over a wide range of L for both active and inactive metabolic rates (ranging from minimal levels during torpor or dormancy to maximal levels during strenuous exercise), b is predicted to show a V- or U-shaped relationship with L, as has been observed in birds, mammals, insects and chitons [19,99,427]. Metabolic level (L) is in turn related to various physiological and ecological factors (see Section 8.2.2).

A modulating effect of L on the relative expression of the SA and RD modules is emphasized over that on the relative expression of the RT and RD modules (Figure 5) for three major reasons. First, no direct evidence for RT effects on metabolic scaling has yet been reported (see Sections 5.2 and 5.5). Second, L effects are observed in organisms (e.g., unicells [173], spiders [298], chitons [427] and many other invertebrates [18,107]) that do not have closed vascular RTNs, as specified by RTN models (e.g., the WBE model). Therefore, RTN theory is not applicable to these cases. Third, L effects

in organisms with RTNs (e.g., vertebrate animals) tend to result in *b* values ranging between ~2/3 and 1 [19,99,297], rather than between ~3/4 and 1, as would be expected if *L* was modulating the relative effects of RT *versus* RD mechanisms, at least according to RTN theory, such as the WBE model, that predicts that *b* should be 3/4. However, since some RTN theory predicts that *b* should be 2/3 rather than 3/4 [25,45], a possible role of RTNs in the modulating effect of *L* on *b* should not be completely discounted at this time, at least for organisms with vascular RTNs.

Figure 6. Quantitative changes in the metabolic scaling exponent (*b*) due to various modulating influences, including the effects of (A) metabolic level (*L*) on the relative influence of surface area (SA) and resource demand (RD), of (B) the scaling of various RD processes (e.g., growth, locomotion, food processing and developmental maturation), of (C) system composition (SC) and mass scaling of various tissues with differing metabolic rates, and of (D) growth-related changes in body shape and associated effects on SA/volume in skin-breathing animals. Compare to Figures 1, 4 and 5.



Thus a second possible modulating factor is the mode of internal resource transport. If this mode involves closed, branching vascular networks, then RT (especially RTN) theory may apply. However, if resource transport occurs by other means, than RT theory may not apply, except perhaps in a fundamentally new form yet to be devised (also see [6]). Recent RTN theory also predicts that the scaling of blood velocity may affect metabolic scaling. If the scaling exponent for blood velocity is 0, *b* for metabolic rate should be 2/3, whereas if it is 1/12, *b* should be 3/4 [25]. Data are needed to test this hypothesis.

A third modulating factor, which acts on the expression of the SA module, is surface permeability to oxygen nutrients, wastes or heat flow (Figure 5). If the body surface of an organism is permeable to fluxes of resources and wastes, then its area relative to body volume may affect the rates at which resources are supplied to and wastes removed from metabolic processes. As a result, the scaling of SA

with respect to body volume or mass may also affect the scaling of metabolic rate. Evidence for this modulating effect includes (1) a significantly positive correlation between the scaling exponents for SA and metabolic rate in soft-bodied pelagic invertebrates with permeable integuments; and (2) the lack of such a correlation in hard-bodied pelagic arthropods with exoskeletons that are largely or wholly impermeable ([46]; also see Section 5.1). The association observed between the scaling of SA and metabolic rate in skin-breathing pelagic animals is apparently mediated by variation in ontogenetic body-shape changes ([46]; Glazier *et al.*, unpublished data), a fourth modulating factor. As growth becomes increasingly biased in one or two length dimensions, resulting in increasing elongation or flattening of body shape, SA theory predicts that *b* should approach 1 (Figure 6), as has been observed in skin-breathing pelagic animals [46]. By contrast, RTN theory predicts that organisms growing chiefly in one or two dimensions should show lower *b* values than those growing in three dimensions [24,45,46], but relevant data contradict this prediction [18,46,214,232,463].

Degree of insulation of the body surface may also modulate the effect of SA heat loss on metabolic scaling in endothermic animals. This may explain why small mammals with relatively thin pelages show *b* values near 2/3 (as predicted by SA theory), whereas large mammals that often have relatively thick insulation, especially in cold environments, show *b* values >2/3 and approaching 1 (as expected if V-related RD effects were relatively more important [99]; for further perspective, also see Section 5.1).

A size-related shift in *b* values in mammals points toward body size being a fifth modulating factor. As mammals get larger, their SA/V ratio becomes smaller, thus perhaps reducing the effect of SA heat loss on metabolic scaling ([38]; also see Section 5.1 for other explanations). Metabolic scaling differs between small and large species of other groups of animals, as well [18,41,170,298], though this was not observed in teleost fishes [297]). Relatively steep metabolic scaling (*b* approaching 1) in some small aquatic, ectothermic invertebrates [170] may be attributed to their high body SA/V ratios, a one to one relationship between cellular SA and body volume, and to the relatively short diffusional distances between their environment and innermost cells (*cf.* [171]; also see Section 4.3.1). By contrast, large species of spiders and snakes tend to show steeper scaling of resting metabolic rate than smaller species, which has been attributed to the lower *L* of larger species, which in turn results in a higher *b*, as predicted by the MLBH [298]. According to RTN theory, small animals and plants should show higher *b* values (near 1) than larger ones (*b* near 3/4) [15,43], but this prediction has mixed support, as indicated by data mentioned above and in Section 5.2.

A sixth modulating factor is thermoregulatory mode (Figure 5). In many endothermic animals, the need to maintain a constant body temperature results in metabolic heat production exactly balancing SA-related heat loss, which scales as $M^{2/3}$ (see Sections 3.1 and 5.1). However, thermoregulatory effects on metabolic scaling may be less important in ectothermic animals with variable body temperatures. Not surprisingly, the interspecific *b* values of homeothermic endotherms (e.g., birds and mammals) tend to be near 2/3, whereas the *b* values of poikilothermic ectotherms (e.g., fishes, amphibians and reptiles) tend to be significantly higher and often approaching 1, as dictated by V-related RD [18,19,171,272,459].

A seventh modulating factor affecting the relative influence of the SC and RD modules is the degree of heterogeneity in the metabolic rate of different somatic tissues and in the scaling of their mass with total body mass. As the scaling of the mass of tissues with different relative metabolic rates becomes more heterogeneous, SC effects should become more dominant over RD effects on the

scaling of whole body metabolism (Figure 5). The scaling exponent for whole body metabolic rate is expected to increase or decrease, as the scaling of high-energy tissue mass becomes steeper or shallower (respectively) compared to that for low-energy tissue mass. These SC effects should be especially prominent in organisms that use or accumulate substantial amounts of metabolically inert storage materials or support structures during their development. At one extreme, as observed during the early development of yolked larval animals, metabolically active tissues rapidly expand by exploiting metabolically inert storage materials that consequently rapidly shrink, thus leading to positive allometry of metabolic rate ($b > 1$) (Figure 6; also see Section 5.3). At the other extreme, as observed in leptocephalus fish larvae, early growth involves the extensive accumulation of metabolically inert storage materials leading to very low b values approaching 0 (Figure 6; also see Section 5.3). In some organisms such as trees, disproportionate increases in metabolically inert support structures during late development may also cause b to decrease relative to that observed during early development (see Section 5.3). On the other hand, volume-related RD effects are expected to be most obvious when the demand of a specific biological process has a largely homogeneous, body-wide effect, as observed for growth, locomotion and food processing. As predicted by RD theory, b approaches 1 under these conditions (Figure 6; also see Section 5.4). However, if the relative resource demand of a process increases during ontogeny (as observed for the maturation of heat production in endotherms), b may exceed 1 (see Section 5.4).

Numerous other internal and external factors may act as modulating factors, as well. For example, natural selection favoring various lifestyles and associated behavioral or life-history strategies may affect not only the expression of all four theoretical modules, but also all of the modulating factors described above (Figures 4 and 5). For example, an active (athletic) lifestyle favors increased muscularity, which results in V-related muscular power production (an RD effect) being a larger proportion of active metabolic rate (AMR), thus causing the scaling of AMR with body mass to be relatively steeper (b approaching 1) compared to that for resting metabolic rate (RMR) [19]. This prediction is supported by observations showing that athletic species of fish show greater differences in b between AMR and SMR than do non-athletic species ([36,327,354]; also see Section 5.4). In addition, selection for different patterns of resource allocation in small *versus* large animals (e.g., high *versus* low reproductive energy expenditure, but low *versus* high fat storage, respectively) may influence metabolic scaling via SC effects (*i.e.*, proportionately more metabolically active tissues in small *versus* large animals).

Furthermore, many interactive effects between various modulating factors likely occur, which require testing. For example, there may be interactions between the modulating effects of L and body size or shape on the relative expression of the SA and RD modules. In particular, since prokaryotic cells have both very small sizes (and thus very high SA/volume ratios and very short diffusion distances between their interior and the environment) and low L (relative to eukaryotic cells of the same size), one can predict that the scaling of their metabolic rates should be more demand-driven (RD-affected) than supply-driven (SA-affected) (*cf.* [173]). The isometric or positively allometric metabolic scaling observed in prokaryotes [48,185] is consistent with this hypothesis. Positive allometry may result from larger prokaryotic cells having proportionately higher growth rates [345] or amounts of genetic material that codes for more metabolic machinery than smaller cells [48]. These explanations fall within the realm of RD theory.

In addition, *L* effects on *b* may not be detectable in some pelagic organisms or larvae, whose SA scales nearly isometrically ($b \sim 1$). In these organisms, both SA-related effects at high *L* and V-related effects at low *L* should result in near-isometric metabolic scaling. SC-related effects may obscure *L* effects, as well (also see [107]). For example, although the MLBH predicts that organisms with a low *L* should exhibit near isometric metabolic scaling ($b \sim 1$), those species or taxa that show a proportionately high amount of metabolically inert support structures at larger sizes may unexpectedly show negatively allometric scaling ($b < 1$). For example, trees have a low *L* and also exhibit near isometric metabolic scaling during their early growth stages, as predicted by the MLBH, but later in their development when "dead wood" accumulates, SC effects result in negatively allometric metabolic scaling. In addition, although ticks have a very low *L* compared to other arthropods, they unexpectedly exhibit a relatively low *b* (0.57 [464]), rather than a higher *b* as predicted by the MLBH. I hypothesize that this low *b* value results from large tick species carrying proportionately more massive, metabolically inert exoskeletons allowing for greater body distension during blood feeding than smaller species, a hypothesis requiring testing (*cf.* [464]).

Many other interactive effects could be described. In the future, it would be useful to contruct mathematical models based on the multiple effects of SA, RT, SC and RD and the various factors modulating their relative influences. In this way, more precise quantitative predictions could be made. For example, a recent analytical model shows how body shape, wind speed and insulation properties may interact to affect the scaling of metabolic rate in endotherms [100].

8.2.2. How the Contextual Multimodal Theory (CMT) Can Explain Variation in the Elevation (L) of Metabolic Scaling Relationships

In this review, I have emphasized the factors that affect the slope (*b*) of metabolic scaling relationships, but the causes of variation in the elevation (*L*) or intercept of these relationships should also be considered, as emphasized by Heusner [465] and others [19,21,28,71,107,295,300,466–469]. Scaling relationships are characterized by both *b* and *L*, and thus a comprehensive theory of metabolic scaling should be able to explain variation in both of these parameters (see Figure 4). Knowledge of the factors affecting *L* is also especially important for the CMT, which posits that *L* modulates the influence of key mechanisms affecting *b* (see Section 8.2.1).

Three of the four modules (subtheories) of the CMT can explain variation in *L*. SA theory can help explain why the elevation of metabolic scaling relationships for multicellular organisms tends to be higher than that for unicellular organisms (as originally reported by Hemmingsen [9]; also see [48,171,469,470]. At the same body mass, multicellular organisms have more cellular SA per body volume than unicellular organisms, thus allowing for larger fluxes of resources and wastes in support of higher metabolic rates [171]. RD theory can also explain why taxonomic groups of organisms with high energy demands, including costly behavioral activity and/or heat production have higher *L* (e.g., endothermic and highly mobile animals) than those with lower energy demands (e.g., ectothermic and relatively sedentary animals and plants) [9,19,428,471–473]. According to SA, SC and RD theory, endothermic vertebrates may also have a higher *L* than ectothermic vertebrates because they have more mitochondria, mitochondrial enzyme activity and mitochondrial membrane SA per unit mass, as well as proportionately more metabolically active visceral tissue mass [474,475]. SA-related heat dissipation

theory further explains why *L* is higher in aquatic *versus* terrestrial endotherms [102]. In addition, as predicted by SC theory, low *L* is associated with low proportions of metabolically active tissues in comparisons of ticks *versus* other arthropods [464], tropical *versus* temperate birds [476] and deep-sea *versus* shallow water fishes ([477]. Note that a decline in *L* of marine fish and other animals with increasing depth of occurrence has been observed even after correcting for both body size and temperature [478], contrary to [479]). Variation in *L* has been linked to other shifts in lifestyle that may be explained by associated changes in SA, RD or SC, as well (see [19,295,297,300,468,480–486]. The only subtheory that cannot explain variation in *L* is RT theory [28]. This is why the WBE model and the associated MTE invoke the effects of additional factors (e.g., temperature) on *L* [456,457,487]. Temperature has a general effect on biochemical reaction rates and thus *L* (e.g., [456,457,479,487]).

8.3. Application of the Contextual Multimodal Theory (CMT) to Various Levels of Biological Organization

The CMT can be applied not only to the organismal level (see Sections 8.1 and 8.2), but also to the cellular and supra-organismal levels, as well.

8.3.1. Application of CMT to Cellular Level

Recent evidence suggests that SA and RD effects on *b* and their modulation by *L* occur in unicellular organisms [173], but more testing of these predictions of the MLBH are needed. It is also reasonable to hypothesize that cell size and shape should modulate SA effects on metabolic scaling ([106,177]; also see Section 4.1.1), as appears to occur for body shape in multicellular animals with permeable integuments [46]. Furthermore, degree of heterogeneity in the metabolic intensity of various components of a cell and their scaling with cell size can be predicted to modulate the relative influence of the SC and RD modules on the metabolic scaling of unicellular organisms (see Section 4.1.1). A major unknown is whether RT theory can be applied at the cellular level (see Sections 4.1.1 and 5.2).

8.3.2. Application of CMT to Groups of Organisms

The shape of groups of huddling small mammals appears to modulate SA effects on the metabolic scaling of these groups in relation to their total mass (see Figure 2 and Sections 4.3.1 and 5.1). Similarly the growth form of bryozoan colonies is related to their metabolic scaling: 2D forms show isometric scaling, whereas 3D forms exhibit allometric scaling [463]. In addition, disconnected colonies of the ascidian *B. simodensis* have a lower *L* and higher *b* than connected colonies [214], as predicted by the MLBH (which involves the modulation of the SA and RD modules by *L*, as portrayed in the CMT model), but these findings can be explained in other ways (see [53]; and Section 4.3.2). Growth rates, which are strongly linked to metabolic rates in algae, also show both lower *L* and higher *b* in colonial than unicellular forms, as predicted by the MLBH [173]. Furthermore, the relative heterogeneity of growth-related RD within bryozoan colonies appears to affect the relative influence of the SC and RD modules on the metabolic scaling of these colonies. When this heterogeneity is great as in fast growing bryozoans, $b < 1$; but when it is minimal as in slowing growing bryozoans, $b \sim 1$ (see [53,463]). It should also be worthwhile to examine how the degree of heterogeneity in the scaling of caste biomass and metabolic rate in insect colonies modulates the relative influence of SC and RD

effects on whole colony metabolic scaling. However, no direct evidence for RT effects on colonial metabolic scaling yet exists (see Section 4.3.2).

Although, it seems likely that many, if not all, of the four theoretical modules of the CMT can be applied to the population, community and ecosystem levels of biological organization (see Section 4.4), whether the effects of these modules are modulated by any of the mechanisms specified by the CMT (as shown in Figure 5) is unknown. Perhaps other modulating effects may also operate at these and other hierarchical levels.

8.3.3. Upward and Downward Causation and Other Hierarchical Effects

Both upward and downward causation likely play a role in influencing metabolic scaling at various hierarchical levels of biological organization. Proximate (functional) explanations of metabolic scaling clearly benefit from employing upward causation from the molecular and cellular levels to higher levels. Subcellular explanations focus on how the rates and machinery of various biochemical and biophysical processes (e.g., specific enzyme activities, rates of cytoplasmic glycolysis and mitochondrial respiration and proton fluxes, the composition of cellular and mitochondrial membranes, and the SA and density of mitochondria) can be translated up to higher levels to explain metabolic scaling (see Sections 3.4, 5.1 and 5.4). Similarly tissue-level explanations are based on summing the different contributions of the metabolic activity of various tissues to estimate whole organism metabolic rate (see Sections 3.3 and 5.3).

However, a comprehensive theory of metabolic scaling requires both proximate and ultimate explanations that also depend on downward causation. Despite their potential usefulness in providing proximate mechanisms, molecular, cellular and tissue based models of metabolic scaling cannot by themselves effectively explain the diversity of metabolic scaling exponents (b) that have been observed (also see Section 5.4). To do so requires that we also examine whole system effects as mediated by biological regulation, ecological factors and evolutionary adaptation. Pioneers in the field of metabolic scaling, including Kleiber [7,8], Brody [89] and Bertalanffy [64] well recognized that system-level effects mediated by downward causation must be invoked to completely explain metabolic scaling (also see Sections 2, 3.4, 5.4 and 6). For example, near 2/3-power scaling of metabolic rate in endotherms can be explained as the result of system-wide thermoregulation resulting in a balance of metabolic heat production with SA-related heat loss so as to maintain a constant body temperature (see Sections 3.1 and 6). This thermoregulatory imperative at the whole body level (or in groups of huddled endotherms) thus dictates the scaling of metabolic processes and structures at the biochemical, cellular and tissue levels. A similar argument has been made with regard to hypothetical systemic effects of RTNs [65]. In addition, diverse ecological lifestyles and physiological demands may favor different levels of metabolism (L), different scaling of various energy-requiring processes (e.g., growth, food processing and behavioral activity), different scaling of various system components with different energy demands, and different internal resource-transport systems, all of which may cause (or be associated with) the diversity of b values that have been observed (as posited by the CMT; see Figure 5), and in turn the scaling of various metabolic processes and properties at the cellular and subcellular levels.

A hierarchical perspective may provide further insight into how the operation of the CMT at one level of biological organization may be translated into different effects at other levels. Consider that variation in the magnitude and body-mass scaling of membrane SA at the cellular and subcellular levels may be linked to variation in *L*, SC or RD effects on metabolic scaling at the organismal level. For example, increases in the SA of mitochondria or other cellular membranes may support increased metabolic activity, thus resulting in increased *L*, which in turn affects *b* (as specified by the MLBH and CMT; also see [107]). Or different levels or scaling of mitochondrial or cellular SA in different tissues may affect the scaling of SC and in turn *b*. Or the scaling of mitochondrial or cellular SA may be linked to the RD of a specific process (e.g., locomotion [120]), that then affects *b*. Many other possible scenarios can be imagined about how the effects of specific CMT modules or modulating influences at the organismal level may be translated into different effects at the group, population, community or ecosystem levels.

In short, metabolic scaling is an emergent property of complex living systems, involving multiple interactions among various component processes and hierarchical levels of organization.

8.4. General Outlook for the Contextual Multimodal Theory (CMT)

It is widely appreciated in science generally [59,488], and sometimes noted in the metabolic scaling literature specifically [43,65], that all theoretical models are caricatures of reality, and thus, although they may be somewhat true, they are also invariably somewhat false. Models focus on specific components of a system, and thus their domain of applicability is limited. Therefore, to better understand complex living systems, Levins [59] advocated that theory should consist of a "cluster of models". By taking into account more system components, a multifaceted theory is more likely to accurately represent how a system works than can a one-facet theory. I would go one step further and suggest that the theory of complex living systems should not only consist of multiple models, but also it should include how the operation of the different mechanisms posited by these models is contingent on specific contexts. Add the effect of context-dependent modulating factors and we now have what I call meta-mechanistic theory. Meta-mechanisms can better explain the diversity of life than can single deterministic mechanisms. Indeed, the most well-known and accepted theory yet offered to explain life's diversity—Charles Darwin's theory of natural selection [489]—is essentially meta-mechanistic, because it invokes the action of multiple, context-specific causes (mechanisms), *i.e.*, various internal and external factors that affect reproductive success and thus evolutionary fitness, each of which can be represented by specific theoretical models (consider the plethora of models on optimal foraging and life-history strategies, not to mention many others). As another example, modern views of the genetic control of organismal development are meta-mechanistic because they recognize the multifactorial and context-dependent nature of gene expression. Various internal and external factors differentially affect the expression of specific genes, thus resulting in various temporal and spatial patterns of growth and differentiation [490]. Thus, both ontogeny and phylogeny are driven by meta-mechanisms. Why not also allometry?

However, one may argue that simple deterministic theory is preferable to complex, multifaceted theory, because it is (1) more parsimonious; (2) more predictive and (3) potentially more general, if it focuses on a general essential property of all systems being studied. All of these attributes have value,

but I would argue that none entitle simple deterministic theory to a higher echelon in science than complex, multi-faceted, context-dependent theory. First, parsimony is merely a pragmatic principle related to the limits of our own minds, rather than a fundamental principle of nature (also see [20]). As Albert Einstein reputedly once said: "Make everything as simple as possible, but not simpler". If a simple theory ignores too much of reality, its usefulness will be severely limited. At the same time, theory is meant to help us understand reality without being overwhelmed by its complexity. An optimal balance between simplicity and realism should be sought. Second, both simple and complex theories can be predictive. Simple, deterministic, mechanistic theories often make precise, quantitative predictions. This property is justifiably highly revered by many scientists, including many who work on metabolic scaling. However, relatively complex, contingent, multi-mechanistic theory can also be quantitatively predictive (see Section 8.2.1; and also [107]). Moreover, it has an advantage over simple deterministic theory because it can predict multiple possible outcomes, thus allowing us to better understand the diversity of nature. Third, both simple and complex theories can be generally applicable (also see [491]). Although some complex models are realistic only for specific systems and thus are not generally applicable, others such as meta-mechanistic theory combine both realism and generality by invoking the context-specific action of multiple mechanisms. In fact, I suggest that meta-mechanistic theory offers a way to maximize all three of the basic properties of theoretical models recognized by Levins [59]: realism, generality and precision. Levins argued that only two of these properties could be maximized simultaneously. For example, some simple deterministic models based on single obligatory mechanisms may maximize both generality and precision, but at the expense of realism. Some complex multi-faceted models tailored to specific systems may maximize both realism and precision, but at the expense of generality. However, meta-mechanistic theory (including the CMT) may maximize all three properties, because it is based on a suite of facultative mechanisms each of which operates in a quantifiable, context-dependent way.

Nevertheless, relatively simple deterministic models, including the WBE and other RTN models, are regarded by many (especially physical and theoretical) scientists as the highest form of theory in science. For them "Science" (with a big "S") is about discovering and explaining universal natural laws based on first principles [13,492,493]. Newtonian-style science is thus seen as the most powerful kind of science. All other science (with a little "s") is considered to be relatively idiosyncratic, and while useful in specific contexts, is not of general importance. The allure of Newtonian-style science may explain why the 3/4-power metabolic scaling law and the simple deterministic theory used to explain it continue to be held in high regard, despite the large body of evidence contradicting the 3/4-power law, and the lack of direct empirical evidence for the RTN theory underpinning it (see Sections 1, 3.2, 5.2, 5.5 and 8.2).

Physical and chemical laws or principles are given priority (hence called "first principles") by Newtonian scientists because they are felt to be more basic in a reductionist sense, and thus more universally applicable than higher-order biological properties and principles that have more restricted domains. However, although complex living systems are affected by numerous physical and chemical laws and principles (they are, of course, physicochemical systems themselves), their behavior is not completely predictable from any one of them taken alone. For example, according to Newton's law of gravity, a bird in the sky should fall to the earth according to the simple equation $v = gt$ (where v is the instantaneous velocity, g is the acceleration of gravity and t is the elapsed time). However, flying birds

can exploit other physical (aerodynamic) principles to decrease their rate of falling or prevent it altogether. Therefore, the behavior of a living system may be contingently, rather than absolutely governed by a specific physical law, because of the variable and conflicting effects of multiple physical, chemical and biological factors.

The contextual operation of physical laws in complex living systems helps explain why the 3/4-power metabolic scaling law, based on the physics and geometry of RTNs, is not universal. Its expression, as a result of physical RTN constraints, may be subverted by many additional factors, including state-dependent variation in the relative control of metabolic rate by supply *versus* demand, presence *versus* absence of anatomical RTNs, malleability of RTNs and their functioning in response to organismal state, and overweighing effects of other physical or biological factors or processes such as heat loss (in endotherms), resource uptake across surfaces, and body-size dependent changes in the metabolic requirements of various tissues, organs and biological activities.

Various attempts have been made to use a Newtonian (universal law) approach in biology, but have failed. For example, Haeckel's Law ("ontogeny recapitulates phylogeny"), which was postulated to be the result of a universal, deterministic, physicochemical mechanism [494,495], was replaced by Gould's [495] meta-mechanistic theory that invokes the contingent operation of two fundamental processes (acceleration and retardation), acting differentially on somatic and reproductive development. Unlike Haeckel's "Newtonian" theory, Gould's now widely accepted "Darwinian" theory helps us to understand why the relative developmental timing of various traits in organisms has evolved in diverse ways, producing not only recapitulation by acceleration, but also progenesis, neoteny and hypermorphosis. Like these examples of "heterochrony", "allometry" is ecologically sensitive and evolutionary malleable [18,496–499], and thus I would argue is also better explained by meta-mechanistic theory such as the CMT, rather than by simple deterministic theory focused on a non-existent universal 3/4-power law. Like Haeckel's Law, Kleiber's Law is too simplistic to account for the adaptive diversity of life.

Therefore, I favor the meta-mechanistic approach as an especially promising way for developing a comprehensive unifying theory that accounts for the broad diversity of metabolic scaling observed in living systems at many hierarchical levels of organization. The CMT is presented as an example of how this may be done, though other theorists may wish to add or subtract modules and modulating influences. Future theoretical and empirical research may produce a general theory of metabolic scaling quite different from what I have proposed, but I predict that it will nevertheless be fundamentally meta-mechanistic. Current debate focuses on what theoretical model best explains metabolic scaling. Here I suggest that it would also be useful to consider an alternative (complementary) question: what components of current models are most valid and how can they be synthesized to produce a comprehensive theory that explains not only specific (idealized) scaling relationships (e.g., 2/3- or 3/4-power scaling), but also the entire diversity that has been observed in nature ($0 \leq b \geq 1$)?

9. General Implications for Biological Scaling and a Metabolic Theory of Biology

Deciphering the causes of metabolic scaling has both fundamental theoretical and significant practical importance for understanding variation in many other vital biological processes requiring metabolic energy. Therefore, in this section I briefly discuss how the rates and body-size scaling of

metabolism and other vital activities, such as growth, reproduction and locomotion, appear to be interrelated. Such knowledge is required if we are to construct a holistic "metabolic theory of biology" (MTB) that comprehensively explains how and why the speed of metabolism and other energy-requiring biological processes varies in response to a variety of internal and external factors. In doing so, I make three major points. First, metabolic rate is not a universal driver of the rates of other biological processes as commonly thought, but rather may also be driven by many of these processes, or even be unrelated to (or dissociated from) some of them. Second, metabolism is not monolithic, but is composed of many different kinds of biochemical pathways, which may proceed at different rates in the same or different tissues. As a result, different components of metabolism may connect to other biological activities in diverse ways. Third, evidence for regulated, mutually co-adjusted associations between metabolism and other living activities reinforce the view advocated here that metabolic scaling is controlled by both supply and demand, and as such appears to be both a cause and a result of the scaling of other biological and ecological processes.

9.1. Metabolic Rate and the Pace of Life

It is a common belief that metabolic rate drives the rates of other biological processes. Or to use the mechanistic metaphor of Needham [500], metabolism is the primary gear (or shaft) in the machinery of biological systems and other vital processes are secondary gears. However, in a recent review, I have shown that, although metabolic rate may be a biological pacemaker in many instances, there are also many exceptions [163]. In some cases, the so-called secondary gears of growth, feeding, reproduction and behavioral activity may drive the so-called primary gear of metabolism, and in still other cases, the gears may be disengaged (e.g., for aging, circadian rhythms, and molecular evolution). The gears of metabolism, growth and development can even be dissociated by experimental manipulation [163,500]. Contrary to the metabolic pacemaker view, recent studies of thermal tolerance have further shown that temperatures at which peak activities of various processes are reached do not necessarily coincide with peaks of metabolism (reviewed in [163]); and various developmental, physiological and behavioral processes and durations may show significantly different scaling relationships among one another and with respect to the scaling of metabolic rate, as well [278,479,501–507].

The above findings indicate that the rates of metabolism and that of other processes are facultatively rather than obligatively linked, and are also involved in reciprocal causation (for a general discussion of the often under-appreciated importance of reciprocal causation in biology, see [508]). Metabolism may not only "push" the rates of other processes (by supplying driving energy and materials), but also be "pulled" by them (by responding to their demand for energy and materials) ([163]; also see Section 6). This two-way connection between the rates of metabolism and other processes making up the pace of life provides a critical key for gaining a comprehensive, mechanistic understanding of the diversity of body-size scaling relationships, not only for metabolism, but also for other biological processes dependent on metabolic energy. In addition, reciprocal causation probably underlies not only the parallelism often seen among the scaling relationships of many different biological processes (*i.e.*, the "principle of similitude": [10], pp. 213–215), but also the temporal harmony often observed among the various processes making up the pace of life [163].

9.2. Metabolism Is Not Monolithic: A Plea for Exploring the Scaling of the Multiple Components of Metabolism and the Various Factors Affecting Them

Typically the scaling of metabolism is studied as a whole, but metabolism is made up of many pathways whose rates may scale differently in response to various internal and external factors (*cf.* [18,167]). These metabolic components can be classified as anaerobic *versus* aerobic, anabolic (biosynthetic and endergonic) *versus* catabolic (biolytic and exergonic), and according to the major substrates or metabolites involved: e.g., carbohydrate, protein and lipid metabolism. Metabolism may be heterogeneous both in rate and type in different parts of an organism at both the cellular (e.g., cytoplasmic glycolysis *vs.* mitochondrial aerobic respiration) and tissue levels (e.g., high rates of lipid metabolism in adipose tissue *vs.* high rates of carbohydrate and protein metabolism in active muscles) (see [11,139,140] and Section 3.3). The various components of metabolism are regulated differently by specific hormones and other regulatory factors [408,410,509–511]. Some hormones (e.g., insulin and growth hormone) may be anabolic, whereas others (e.g., glucagon and epinephrine) may be catabolic or both (e.g., thyroxine) [410]. The same hormone may also have different effects depending on the tissue type (e.g., glucocorticoids, which may stimulate or inhibit the anabolism or catabolism of various macromolecules, such as glycogen and proteins [410]). In addition, some hormones differentially affect carbohydrate, protein and lipid metabolism in species- and tissue-specific ways. For example in fish, growth hormone favors protein and lipid anabolism over catabolism, but carbohydrate catabolism over anabolism [510]. However in mammals, growth hormone preferentially stimulates protein synthesis at the expense of lipid synthesis (so-called "nutrient partitioning") [509], especially during food restriction [511].

These findings raise interesting questions regarding metabolic scaling that are in need of further research. For example, how do the different components of metabolism scale with body size and how can we best estimate this scaling? The growth models of Bertalanffy [61] assume that anabolism scales differently with respect to body size than does catabolism, but this assumption has never been tested, probably because it is difficult to do so. The temperature-size rule (maturation at smaller sizes at higher temperatures) may also be the result of anabolism and catabolism scaling differently with temperature [512], but this hypothesis has never been tested either. One way of estimating the scaling of the different components of metabolism is to measure the body-size dependent activities of specific enzymes involved in different metabolic pathways. This approach has already revealed that in fish and other animals the activities of enzymes involved in aerobic metabolism tend to scale with negative allometry ($b < 1$), whereas those involved in anaerobic metabolism tend to scale with isometry ($b \sim 1$) or positive allometry ($b > 1$) [513–524], though these differences may lessen if metabolic enzyme activity is measured over long time periods [517], or if juveniles are included in the analysis [525]. Furthermore, the wide interspecific variation observed for the scaling of glycolytic (anerobic) and aerobic enzyme activities in fish has been shown to be linked to differences in lifestyle and environmental conditions [516,518,522], thus providing further support for the view promoted in this review that metabolic scaling is ecologically sensitive and evolutionarily malleable. In addition, the intra- and interspecific variability of both aerobic and anaerobic metabolic scaling is revealed by the isometric scaling of aerobic enzyme (citrate synthase) activity in gonatid squids, which also exhibit mixed scaling for anaerobic enzyme (octopine dehydrogenase) activity ($b > 1$ in juveniles, but $b < 1$ in

adults) [481]. In the sea anemone *Metridium senile* the scaling of fluxes through different metabolic pathways was also shown to respond differently to temperature changes [526]. Recent studies on crustaceans have documented that potential aerobic metabolism, as estimated by electron transport system (ETS) activity, scales with a slope near 1 [334,527]; and the scaling of mitochondrial respiration or cellular metabolic rates may vary significantly among different tissues, as well [139,518,528].

It is also possible to estimate rates of various metabolic processes by measuring rates of metabolic waste production. For example, anaerobic metabolism produces lactate as a waste product, and its production scales with positive allometry in the musculature of active animals [517,520,529]. Nearly isometric scaling of methane production in large herbivorous mammals [530] suggests that microbial fermentation may help account for the steeper metabolic scaling observed in large *versus* small mammals (also see [275,531]; and Section 5.1). Relative rates of carbohydrate, protein and lipid metabolism and turnover may also be estimated by isotopic labeling (fluxomic) methods [532–536], but they have yet to be used in body-size scaling analyses.

Another critical question is: how are the various components of metabolism (and its machinery) related to one another and to other biological processes? Some investigators have claimed that various components of maintenance metabolism (including protein turnover, ion pumping, mitochondrial proton leak, and other oxygen-consuming maintenance activities) in mammals tend to vary proportionately in relation to body size [361,537]. The interrelationships among the various components of metabolism may depend on their connectedness [361] and whether they occur in series or as parallel pathways (*cf.* [65]). As for relationships with other biological processes, not surprisingly anabolism is associated with growth and reproduction, whereas catabolism is associated with energizing various behavioral activities. Long-term exercise may also elicit anabolic synthesis of muscle and supporting structures (e.g., increased resource supplying vasculature: see Sections 3.2, 5.2 and 6). Some components of the mitochondrial oxidative system may be related to reactive oxygen species (ROS) production or other processes that cause aging ([538–541]; for a contrasting view, see [542,543]). In addition, multiple components of resting metabolism are related to life-history differences between tropical and temperate birds [544].

The multiplicity of connections between different components of metabolism and other biological processes may help explain why whole body metabolism may not be related to or can be dissociated from other biological processes (see [163]). All biological processes require metabolic energy, and thus cannot be completely dissociated from metabolism. However, the connection may be limited to only one or a few components (pathways) rather than to all of the components of metabolism, which together may vary independently of the process being considered.

In short, we need to go beyond looking at metabolic rate *in toto* (and as a black box) and start to examine the internal dynamics (temporal structure) of its many components to better understand not only the scaling of metabolic rate, but also how metabolic rate is related to the rates of other vital biological processes.

9.3. The Role of Biological Regulation of Supply and Demand in a Metabolic Theory of Biology (MTB)

The metabolic theory of ecology (MTE [456]) presents an incomplete view of the role of metabolism in biology because it emphasizes how metabolic rate drives the rates of other biological and ecological

processes without considering reverse effects. As a result, Glazier *et al.* [52] suggested that the MTE should be complemented with an ecological theory of metabolism (ETM) that specifically examines these reverse effects. Further exploration of reciprocal causation between the rates of metabolism and other biological processes would contribute greatly to a truly comprehensive metabolic theory of biology (MTB).

Another limitation of the MTE and other currently prominent bioenergetic theories (e.g., DEB theory [66]) is that they emphasize only one half of the essence of life—the acquisition and use of energy and other resources—while largely ignoring its other essential half—the acquisition and use of information ([163]; also see Section 7). An increased understanding of regulatory, information-based systems should play a central role in developing a synthetic MTB. Metabolism should not be seen as merely driving the rates of other biological and ecological processes by supplying needed energy and resources (the metabolic pacemaker assumption), nor be seen as merely being driven by the energy and resource demand of other processes (the metabolic enabler assumption), but rather as being co-adjusted with these other processes by means of sophisticated regulatory systems that balance resource supply with demand in ways that are sensitive to both the internal and external states of a living system [163].

9.4. Essential Elements of a Comprehensive Metabolic Theory of Biology (MTB)

In short, I suggest that a truly general and robust MTB should consider (1) the dynamics of both energy and information flow in living systems and their mutual interaction; (2) the central role of biological regulation in mediating multidirectional causality and feedback between the rates of metabolism and that of other resource-dependent biological processes; (3) the effects of both resource supply and demand (and all of the steps of energy flow in living systems from resource acquisition to waste excretion) and their interaction on the rates and system-size scaling of metabolic processes; (4) the hierarchical nature of living systems and the relative effects of upward and downward causation in controlling metabolism; and (5) the open dynamic nature of living systems and thus the sensitivity of the rates and scaling of their energy acquisition and use to both internal (system) and external (environmental) factors. Some of these elements are described in more detail elsewhere in a preliminary Adaptable Informed Resource Use Model [163].

9.5. Practical Applications of the CMT and a Holistic MTB

Developing a contingently mechanistic theory of metabolic scaling (e.g., the CMT) and with it a holistic MTB may not only significantly advance our theoretical understanding of living systems, but also have many practical applications in diverse fields of societal importance, including medicine, pharmacology, nutrition, gerontology, agriculture, forestry and environmental science. As one example, it is becoming increasingly appreciated that like metabolic rate, drug (xenobiotic)-clearance rates (DCR) in mammals do not follow a simple 3/4-power law, as has been commonly thought [545], but show high variability among xenobiotics (b = 0.2 to 1.2, with a mode near 2/3 and a mean near 3/4 [546]). A recent survey of DCRs in humans has also revealed an average b value (0.65) near 2/3, not 3/4 ([547]; but see [548]). Moreover, multiphasic scaling is seen for several kinds of drugs over the entire human lifespan [549–552]. Neonates and infants tend to show significantly steeper DCR scaling exponents ($b \geq 1$) than adolescents and adults ($b < 1$) [549–552]. Therefore, using the 3/4-power law to calculate drug dosages for very young children could have harmful consequences [549]. The nonlinear

scaling of DCR is similar to that seen for the ontogenetic scaling of metabolic rate in humans and many other animals [18]. The parallel shifts in the scaling exponent of metabolic rate and DCR may be related to ontogenetic decreases in the energetic demand of growth and development (see Sections 3.4 and 5.4; and also [18,163]. As highlighted by both the CMT and MTB (as envisioned here) both resource supply and demand and their regulation importantly affect not only the scaling of metabolic rate, but also the rates of other biological processes dependent on metabolic energy.

10. A Methodological Epilogue

10.1. Power Functions and Least-Squares Regression (LSR) Analyses of Log-Transformed Data

Although the purpose of this review is not to describe and evaluate in detail the various methods used to analyze metabolic scaling relationships (for reviews see [50,553–557]), I would like to briefly justify the common use of least-squares regression (LSR) analyses of log-transformed data, which can also be expressed as power functions in arithmetic space. Some workers have suggested that the LSR method should not be used for allometric scaling analyses, because it incorrectly assumes that there is no measurement error in the independent variable (body size) [558]. An alternative method, the reduced major axis (RMA) method has sometimes been used instead, because it allows for measurement error in both the dependent (Y) and independent (X) variables [48,145,466,558]. However, the RMA method assumes that the measurement errors for Y and X are equal, which is often not true, as well [559]. In fact, in most cases, it is likely that metabolic rate, a highly variable trait, is measured with much more error than is body size [556]. Under these conditions, the LSR appears to be the preferred method [556,560]. In any case, even when X is measured with error, the LSR need not underestimate the slope, as often expected [561]. The LSR also has the advantage of permitting not only the prediction of metabolic rate from body size [559,562], but also estimates of the residual variation in actually measured metabolic rates from those predicted by body mass. These residuals can then be compared to other potentially influential (e.g., behavioral and ecological) factors, besides body size (see [49,294,563], and also [564–566] for alternative use of GLM, ANCOVA, and multiple regression analyses).

Other workers have pointed out that metabolic scaling may be nonlinear in log-log space, and thus not adequately represented by a simple power function or loglinear regression analysis (for many examples, see [18,89,170] and other references cited below and in Section 1). Three solutions to this problem have been proposed. A nonlinear scaling relationship may be (1) broken into multiple log-log regression lines, each described by a different power function [18,36,37,170,567]; (2) quantified as a continuous polynomial (quadratic) function in log-log space [28,35,37–39,41,282]; or (3) estimated by nonlinear regression models or mixed power functions in arithmetic space [40,283,555,568]. Some investigators have even suggested that nonlinear regression analyses based on the original arithmetic data are to be preferred over simple power functions or other regression analyses based on log-transformed data, because they believe that log-transformation distorts the original data and thereby produces misleading results [568]. However, these critiques ignore the fundamental importance of proportional comparisons in allometric scaling, which are best represented by log-transformed data [466,567,569–571]. Indeed, all of the empirical scaling slopes discussed in my review are based on proportional (log-log or geometric) changes, which can more readily be compared to the predictions

of various theoretical models than can slopes based on non-proportional arithmetic changes [571]. Log-transformed data also allow correction for multiplicative error, which predominates in scaling analyses involving broad body-size ranges [557,570]. In addition, nonlinear regression of the arithmetic data can lead to large errors in scaling analyses [50,572,573].

10.2. Phylogenetically and Ecologically Informed Analyses

Many interspecific scaling analyses ignore the fact that the metabolic rates and body sizes of various species may covary with other influential factors, including taxonomic affiliation, lifestyle and various ecological conditions. Phylogenetically informed analyses are useful for "correcting" for interspecific differences in evolutionary relatedness [50,574–577]. They may produce significant changes in the estimated slopes and elevations of metabolic scaling relationships, as compared to traditional non-phylogenetic analyses, but these changes are often quite small (e.g., the phylogenetically corrected slopes for birds and mammals with large sample sizes (>100) are usually <0.05 different from traditional estimates based on the same data [271,278–281], but phylogenetic correction produced a somewhat larger change in insects: from 0.82 to 0.75: [323]; also see Section 5.1).

A common method for quantifying environmental effects (as well as the effects of body composition and behavioral activity) in scaling analyses is to include them as multiplicative parameters in power functions or as additive parameters in multiple regression equations. This method has been used for decades in a variety of organisms (e.g., [141,430,470,578–590]), but has only recently received widespread attention as the "master equation" of the metabolic theory of ecology (MTE), which includes multiplicative terms for both body size and temperature [456,457,487]. However, a problem with the MTE is that it assumes that body size and temperature independently affect metabolic rate, each according to a universal constant, which often appears not to be true [18,19,107,297,431]. It also ignores the influence of lifestyle and other ecological factors on the metabolic scaling slope. Interactive effects of body size and other factors on metabolic rate can be examined by analysis of variance and multiple regression techniques [50,566,588,589]. Some investigators have included interactive terms in linear regressions or power functions describing the effects of both temperature and body size on metabolic rate [430,591].

An alternative method is to use analysis of covariance (ANCOVA) to correct body-mass scaling relationships for the influence of other factors. For example, some workers have adjusted the scaling of basal metabolic rate in mammals to differences in body temperature [38,50,275]. McNab [273,276,295] has used both ANCOVA and the multiplicative method described above to show how several behavioral and ecological factors affect the metabolic scaling relationships of birds and mammals. His multivariate method produces "ecologically corrected" slopes and elevations that differ somewhat from those based on traditional analyses (e.g., b = 0.652 and 0.689 for birds, and 0.721 and 0.694 for mammals, for traditional and ecologically corrected slopes, respectively). This approach may also include taxonomic effects, but does not take into account interactive effects among the multiple factors considered.

Confounding effects of phylogeny and ecology can be largely avoided by studying intraspecific scaling relationships, which deserve more investigation [18,52,321,434,458].

10.3. Standard Scaling Analyses are Useful for Constructing General Theory

I have given some attention to statistically based methodological issues, because I believe that it is important that workers should agree on standard methods for determining the parameters of metabolic scaling relationships. Otherwise the discernment of comparable patterns, and thus the construction of general theory will be greatly inhibited. I am not opposed to the use of alternative methods that may provide excellent fits in specific cases, but I recommend that these special methods should be accompanied by a generally applicable method or set of methods (e.g., linear, multiphasic linear or curvilinear LSR based on log-transformed data) that can be used as a standard of reference.

11. Conclusions

Major conclusions of this review are: (1) no one current model is capable of explaining the full diversity of metabolic scaling that has been observed at the organismal and other levels of biological organization; (2) meta-mechanistic theory based on the contextual operation of multiple mechanisms shows the most promise for explaining this diversity; (3) a meta-mechanistic approach may also contribute to the development of a general metabolic theory of biology that recognizes that the rates and system-size scaling of metabolism and other biological processes are mutually interactive, biologically regulated, subject to up- and downward (hierarchical) causation, and sensitive to both internal (system) and external (environmental) factors; and (4) future progress in developing a synthetic understanding of the allometric scaling of various biological processes will be facilitated by continuing the use of standard scaling functions that can be readily compared.

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Conflicts of Interest

The author declares no conflict of interest.

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Appendix

Other Metabolic Scaling Models

My review has focused on four major kinds of metabolic scaling theory that have received the most attention theoretically and empirically: surface area, resource transport, system composition and resource demand theory (see Sections 3, 4, 5 and 8). Other types of theoretical models that have been proposed during the last four decades are briefly mentioned below.

Fourth Dimensional Models

Blum [592] suggested that the 3/4-power law of metabolism results from a four-dimensional version of the surface law, where surface area and volume have three and four dimensions respectively. However, Blum did not identify his hypothetical fourth dimension, nor explain how his model would work in a three-dimensional world [593]. West *et al.* [24] suggested that the fourth dimension may be a manifestation of the fractality of biological surfaces, whereas others have suggested that time may be the fourth dimension [6,337,594,595].

Ginzburg & Damuth [595] regard the time dimension as generation time, and predict that metabolic rate should scale to the 3/4 power in organisms with variable generation times and body dimensions, to the 2/3 power in organisms with similar generation times (one dimension held constant), and to the 1/2 power in organisms with similar generation times and body lengths (two dimensions held constant). They claim support for their model from observations that the metabolic scaling exponent (*b*) averages near 3/4 for interspecific relationships (for a contrasting view, see [19]), near 2/3 for intraspecific relationships (but see [18]) or interspecific relationships with lifepan (a proxy for generation time) held constant, and 1/2 for intraspecific relationships with body length held constant or interspecific relationships with lifepan and body length both held constant. However, the predictions of the model appear to be flawed and (or) of restricted applicability. According to the model, surface area (SA) is 3D (2 spatial dimensions and 1 temporal dimension) and volume (V) is 4D (3 spatial dimensions and 1 temporal dimension). It is then argued that since energy exchange with the environment is SA-dependent and energy expenditure is V-dependent, metabolic rate should scale to the 3/4-power. However, this scaling is considered in relation to the whole 4D system. When metabolic rate is scaled against body mass, which is proportional to spatial volume (3D), *b* should not be 3/4, as claimed, but 3/3 or 1. A *b* value of 1 should also hold, if one or two spatial dimensions are made constant. Therefore, as I interpret it, the four-dimensional model cannot explain *b* values ≠1. Even if the claimed predictions of this model were acceptable, it then would not be able to explain *b* values >3/4. Furthermore, according to Ginzburg & Damuth [595], organisms that show 1D or 2D growth (elongation or flattening, respectively) should display *b* values of 1/2 and 2/3, respectively, but this prediction is contradicted by *b* values approaching or even exceeding 1 in pelagic animals that grow more in one or two dimensions than three [46].

Foraging Models

Witting [441] suggested that the scaling of metabolic rate and other biological processes could be derived from how organisms forage in space. The theory predicts that organisms foraging in 2D and 3D should exhibit *b* values =3/4 and 5/6, respectively. Interestingly, Pawar *et al.* [448] have also predicted that feeding rates should also scale with a higher power in 3D *versus* 2D foragers, as has been observed (*b* = 1.06 and 0.85, respectively). However, available metabolic scaling data are not entirely consistent with Witting's model [18]. Furthermore, it cannot explain *b* values <3/4 and >5/6.

Whole Organism Optimization Models

Although several metabolic scaling models include optimization of a specific function [18], only the model of Kozłowski & Weiner [442] uses whole-organism fitness optimization to predict the scaling of metabolism and other biological processes. This model predicts a range of interspecific scaling exponents depending on size-specific mortality and the scaling parameters of intraspecific relationships. It can explain inter- but not intraspecific allometry of metabolic rate, the latter being an assumed constraint. It assumes that body size and metabolic rate have co-evolved, rather than body size simply acting as a constraint on metabolic rate. This is a point well worth considering (*cf.* [18,497]; for a contrasting view, see [232]).

Statistical Models

Two basic kinds of statistical models for metabolic scaling have been proposed. One kind focuses on the genetic origin of allometric scaling relationships [596]. The other focuses on how stochastic variation in the scaling parameters may affect allometric scaling relationships, including covariation between the slope and intercept [597,598]. Both are phenomenological and not mechanistic in a traditional sense.

Table A1. Theoretical models of metabolic scaling and their application to different hierarchical levels of biological organization (HLBO). Predicted metabolic scaling exponents (*b*) are indicated. SA, RT, SC, RD, V, RTN, MLBH, DEB, SDA, MR and %MSC refer to surface area, resource transport, system composition, resource demand, volume, resource transport network, metabolic-level boundaries hypothesis, dynamic energy budget theory, specific dynamic action, metabolic rate, and percent of system mass that is composed of metabolically slow components (e.g., subcellular structures, somatic tissues, or individuals in a group). (C) and (O) refer to *b* being applicable at cell or whole organism levels, respectively. All O-level models are considered applicable to both C and O because of downward causation (see Section 8.3.3).

HLBO	**Subtheory**	**Model/Hypothesis/Mechanism**	***b***	**Sources**
Cell	SA theory	Cell SA effects	2/3 (C)	[93,171]
		(MLBH)		[173]
		Cell-size and number model	2/3 to 1 (O)	[68,69,178]
		SA elaboration due to cell-shape change	>2/3 (C)	[106,171,173]
		Mitochondrial SA	Variable (C & O)	[120,180–182]
		Photosynthetic pigment light reception	2/3 (C)	[172]
	RT theory	RTN models	3/4 (C)	[159,172]
	SC theory	%MSC (e.g., vacuolar space) increases as cell size increases	<1 (C)	[106,173]
	RD theory	Cell membrane pacemaker model	Variable	[70,191]
		Thermodynamics model	3/4 (O)	[190]
		Amount of metabolic machinery (e.g., number of enzymes or mitochondria)	Variable (C & O) ≥1 (C)	[120,146,181] [48]
		Quantum statistics model (C & O)	2/3, 3/4 1/2 to 1	[71] [72]
		Cell V effects (MLBH)	1 (C)	[173]
Organism	SA theory	Thermoregulatory models: Compensation for heat loss	2/3	[83,84,101,292]
		(MLBH)	2/3	[19]
		Heat dissipation	0.63	[102]
		Resource & waste flux models/hypotheses:	2/3	[61,90,91]
		DEB theory	2/3	[66,104]

Table A1. *Cont.*

HLBO	Subtheory	Model/Hypothesis/Mechanism	*b*	Sources
		Fractal SA of respiratory organs	2/3 to 1 (assumed)	[92]
		Mass-transfer model	1/2 to 5/4	[103]
		MLBH	2/3	[19]
	RT theory	Blood flow models	2/3	[108]
			3/4	[7,8]
		RTN models	3/4	[15,118,119]
			2/3, 3/4	[24,388,602]
			5/6, 1	[26]
			7/9	[117]
			3/5 to 6/7	[594]
			1/2 to 3/4 [1]	[43]
			0.6 to 1 [2]	[43]
			1	[33]
			0.81	[44]
			0 to 2/3	[45]
			1/4 to 3/4	[24,25,46]
		Constructal theory	1/3, 2/3, 3/4	[296]
	SC theory	%MSC increases as body size increases	<1	[18,29,35,40,89, 127,129,137–147, 155,333,599]
		(DEB theory)	<1	[66,104]
		%MSC (inert nutrient reserves) decrease during early development	>1	Present paper
	RD theory	Maintenance demand: Intrinsic cellular/tissue energy costs	Variable	[8,70–72,148,168, 191]
		Body V effects		
		(DEB theory)	1	[66,104]
		(MLBH)	1	[18,19]
		Neuro-endocrine control	Variable	[8,64,84,150]
		Locomotor demand: Support/anti-gravity costs	3/4	[454,600]
		Costs of muscular exertion	>3/4	[167]
		(MLBH)	1	[18,19]
		Growth (production) demand	1	[18,66,67,89,104, 164–166,332,342, 347,601]
			<1	[52]
		Food processing (SDA) demand	1	[19,355]
		Increasing costs of developmental maturation (including thermoregulation)	>1	[18]; Present paper

Table A1 *Cont.*

HLBO	Subtheory	Model/Hypothesis/Mechanism	*b*	Sources
Colony/ other social groups	SA theory	Resource (e.g., energy & water conservation models)	2/3 ≥2/3 0.755 Variable	[200] [199,201,603] [202] [198,203]
	RT theory	RTN models	3/4	[222]
	SC theory	%MSC (e.g., % inert materials or relatively inactive individuals increases as colony size inc.)	<1	[216,223–225]
	RD theory	Additive model (Colony MR = simple sum of individual MRs)	1	[209,214,224]
		Larger individual body sizes in larger colonies	<1	[225]
		Lower activity level of all individuals in colony	<1	[225]
		Neural/chemical stimulation among close individuals	>1	[198]

[1] Large organisms; [2] Small organisms.

Table A2. Selected attempts to link multiple subtheories of metabolic scaling, *i.e.*, surface area (SA), resource transport (RT), system composition (SC) and resource demand (RD) models and theories. RTN = resource transport network; V = volume.

Subtheories Linked	Mechanisms	Sources
SA, RD & RT	Metabolic-level boundaries hypothesis (see text)	[19]
SA, RD & SC	Dynamic energy budget theory (see text)	[66,104]
SA & RT	Matching of scaling of SA & blood circulation	[108]
	Matching of metabolic rate to both SA-related heat loss and internal RT	[8]
	Internal geometry of SA and RT	[24]
	Heat flow across external SA and within body	[296]
	SA and RT effects depend on resource level	[172]
	Relative effects of SA & RT depend on body size	[38]
SA & RD	Cell size & SA/V affect whole organism RD scaling	[68,69,178]
	Variation in relative influence of SA- and V(RD)-related processes	[49]
SC & RD	Allometric cascade model	[73,167,168]
RT & SC	RT theory adjusted to ontogenetic changes in water content (SC)	[455]
	RT predictions adjusted for differences in tissue metabolic rates (SC)	[29]