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Allomeric Scaling: Theory and Applications

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ABSTRACT

The history and bases for selectedallometric energy relationships are reviewed in this article, specifically those related to quarter-power scaling as described by M. Kleiber, i.e. interspecies metabolic rates scaleas a function of mass to the three-quarters power (metabolic body size). Interspecies requirements for essential factors are also noted (e.g., vitamins and minerals). A case is made thatinterspecies vitamin and mineral requirements are similar when expressed per unit of metabolizable energy consumed or metabolic body size. Furthermore, it is emphasized that: 1) these relationships may be applied broadly and allow for the scaling of energy-related and nutrient needs in animals as small as screws to as large as elephants, and 2) application of appropriate allometric scaling methods to nutritional questions allows one to make stronger inferences when extrapolating results derived from experimental animal models to humans.

Key words: Nutrient requirements, basal metabolism, metabolic body size, allometric scaling

INTRODUCTION:

Allometry is an approach used to examine non-isometric relationships of body size to various functional limits necessary for growth, aspects of behavior, and energy utilization [1]. The earliest roots of allometry stem in part from the observations of Leonardo Bonacci, known as Fibonacci; a Western mathematician of the Middle Ages. Although a significant aspect of Fibonacci's work focused on replacing the Roman numerical system that dominated Southern Europe in the 11th and 12th centuries, he also developed numerical sequence strategies to describe how rapidly certain animals could breed in ideal circumstances. What evolved was the Fibonacci series, often described as Nature's numbering system [2], which may be used to describe geometric patterns of growth. Another important contributor was François Édouard Anatole Lucas, a French mathematician, who expanded upon the concepts developed by Fibonacci (Fig. 1).

However, in the context of intraand interspecies comparisons, our current appreciation for and understanding of allometry did not begin until the 1800's. In 1883, Rubner [3] introduced what he described as the "surface hypothesis" from observations that the metabolic rates for many homeothermic birds and mammals appeared to be proportional to their body surface area.

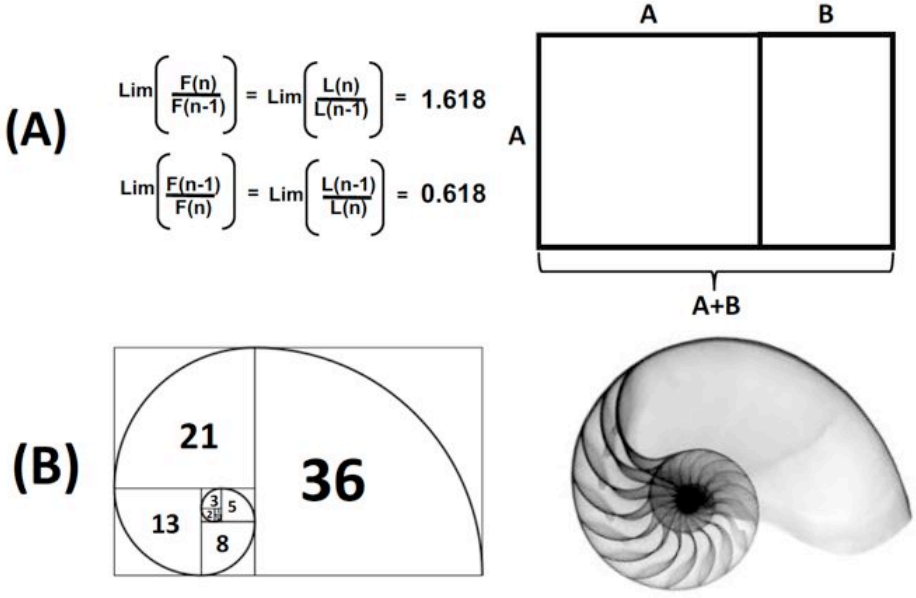

Figure 1. Fibonacci and Lucas number sequences. Fibonacci and Lucas sequences are used in biological settings to describe phenomena ranging from branching in trees and flowering patterns in fruits and vegetables to inheritance patterns involving the X-chromosome at a given ancestral depth. In the Fibonacci sequence, every number after the first two is the sum of the two preceding ones: 1,1,2,3,5,8,13,21,34,55,89, etc. Like the Fibonacci sequence, a Lucas numbering sequence is the sum of the two immediately previous terms. The first two Lucas numbers, however, are L0 = 2 and L1 = 1 in contrast to the first two Fibonacci numbers F0 = 0 and F1 = 1. Although similar, Lucas and Fibonacci numbers exhibit distinct properties, both lead to the golden ratio or mean (1.618, **A**) that has been used to describe spirals, and self-similar curves often observed in nature (e.g. from helical structures to the branching of capillaries to shell patterns in the mollusk, **B**). [Persaud, D and O'Leary, JP., "Fibonacci Series, Golden Proportions, and the Human Biology" (2015). HWCOM Faculty Publications.27 http://digitalcommons.fiu.edu/com_facpub/27] for additional examples.

Others who advocated allometric approaches include D'Arcy Thompson, a mathematical biologist, whose book in 1917, "On Growth and Form," was one of first that focused on physical laws and the mechanics of growth and development [4]. Over the following twenty-five years, Julian Huxley, among others, refined some of the mathematical approaches, emphasizing that allometric relationships could be expressed linearly following logarithmic transformations [cf. ref. 5]. Huxley with Georges Teissier also coined the term allometry in a classic 1936 paper that described the potential importance of statistical shape analysis [6]. Next, was the suggestion of a 'quarter power' relationship offered by Kleiber [7], i.e. the observation that for most animals, metabolic rate scales to the ¾ power of the animal's mass.

EMPIRICAL VERSUS MATHEMATICAL APPROACHES TO QUARTER POWER SCALING

The Kleiber scaling relationship, however, often provokes controversywhen stated as a principle or law. A common argument is that although useful, quarter power scaling is merely empirical and statistical, and the values are possibly artifacts arising from data selection [8-16]. For example, in many studies the exponential function for the allometric scaling of the log of body mass to the log of energy-related requirementstoggles between ~2/3^{rds}to~1.0. That is the values for '*b'* in the equation: $Y = aM^b$or in logarithm form, log $Y = a$•log$M$+log$b$, with'*Y'*representing metabolic rate and '*M'*representing body mass. In this regard, a part of the controversy arises, because the statistical observations of basal energy needs versus body weight often suggest for animals below 10 Kg, an exponent nearer to 2/3^{rds} power gives the best fit for $Y = aM^b$. In contrast, for large animals, an exponent nearer to 3/4^{rds} power gave the best fit [13].

Nevertheless, quarter power scaling has now taken on more the status of a principle or law, particularly due to mathematical proofs arising in part from fractal geometry, constructal theory, and mathematical approaches that are independent of geometric form or size.

Afractal is a mathematical set of well-defined and distinct objects that exhibit a repeating pattern displayed at every scale. Geoffrey West and his colleagues provided what is considered the first well-defined proof for the origin of the Kleiber-related allometric scaling laws [17, 18]. Their proof was derived using a model built on three assumptions:

1) that fractal networks in biological systems are tubes that branch in fractal-like patterns;
2) that such networks minimize the amount of energy needed to transport materials to given targets;
3) that size of the terminal units at the ends of the networks do not vary with body size.

The use of fractals extended the view that body size and energy relationships were more than a function of surface area in that the flow of nutrients and fuels in fractal networks adds in effect an additional or "4th" dimension with temporal characteristics. At about the same time as the efforts of West and colleagues, Bejan and his colleagues came to similar conclusions based on what they designated as constructal design principles [19-22]. An underlying premise of this system is that constructal systems provide easier access to nutrients and fuels, i.e. "for a finite-size system to persist in time, it must evolve in such a way that it provides easier access to the imposed currents that flow through it" [22]. In constructal systems, the least accessible components constitute the constructal's smallest "unit," somewhat analogous to a fractal. Another assumption is that resistance cannot be minimized indiscriminately, due to the limitations of space and the necessity of flow systems to connect with all components within the system.A fourth dimension again arises from the network for distributing nutrients (e.g., in endothermic animals, a system of capillaries) with sites for the assimilation of fuels and other nutrients.As a delivery system, such networks also take on a temporal character, i.e. a measure of "biological time."If the effective density of the system is constant, then the mass or volume of a constructal system is proportional to its spatial dimensions (height width, depth), L_hX L_wX L_d or L^3 times L_n, the network dimension. Therefore, as a general statement L is $\propto M^{1/4}$. Moreover, if

the total metabolic rate is a function of the number of sites served within the volume of a constructal system, the metabolic rate can be stated be proportional to L^3 or $M^{3/4}$. Recently, a more mathematically oriented proof that is independent of either an expansive network (a constructal system) or hierarchical system branched model (a fractal-based system) has been presented by Banavar and her colleagues [23, 24]. Several theoretical approaches have now been presented to justify the use of quarter power scaling principles.

But why are quarter-power relationships subject to so much controversy? One or more of the following have been stated to contribute the controversy:

1) Deviations or differences in body temperature regulation. A wide range of species are used in allometric studies that differentially display ectothermic/poikilothermic, cold-blooded vs. endothermic/homeothermic, warm-blooded, characteristics. Homeotherms have adaptive heat generating systems that can increase metabolic rates in response to changes in environments, which this is not the case for poikilotherms. Furthermore, each of the 21 orders of mammals have different strategies for heat partitioning when needed. Calculation of heat transfer, even in well-defined systems, usually requires the use of partial differential equations containing multivariable functions and related partial derivatives. Consequently, it is argued that 'like it or not,' the nature of the exponent for $Y = aM^b$ is variable due to the complexity of the various metabolic strategies involved in heat transfer [25].
2) Deviations in body shape, composition, organ shapes, sizes, and heat production. Body organs can vary widely in their energy demands and heat production; as a result, not correcting for interspecies differences in organ shape and size, or body composition, has been suggested to cause wide variations in the 'a' coefficient for the relationship, $Y = aM^b$ [26, 27]. For example, comparisons of organ weights in animals of differing size result in allometric scaling exponents for organ weight versus body weight plots that range from 0.5 to greater than 1.0 [26], i.e. a doubling of body size does not necessarily result in a doubling of organ size. Consideration of body shape or composition, however, is usually ignored or not addressed, leading to the assumption that because the statistical derivation of the mass exponent *'b'* assumes that '*a'* is relatively constant any variation most likely influences '*b.'* Several investigators have pointed out that when covariant analysis approaches are used to adjust '*a'* relative to body mass, the mass exponent '*b*' centers closer to 2/3rds and not 3/4ths [13, 15]. Stated another way, in the Kleiber equation, the ¾ power rule is a statistical artifact caused by holding or treating the factors associated with '*a'*as a constant.
3) Deviations in the exponential component of $Y = aM^b$ for interspecies comparisons are like those observed for interspecies comparisons. This observation gives rise to the argument that if quarter power scaling is a law, it would be expected that within a specific phylum less variation in the 'b' exponent would occur [10-16].
4) Deviations due to factors that may influence what is defined as basal conditions. Such factors include the degree of maturation of the organism used for estimates, growth, residual components resulting from activity or work, differential responses to environment, contribution to heat production from the microbiome, i.e., more attention needs to be given to what is operationally defined as a basal condition.

Eachof the concerns summarized above has potential merit. Accordingly, it is not unreasonable to ask whether nutrient supply network models consistently and unequivocally predict thatmetabolic rate scales as $M^{3/4}$at all hierarchical levels. However, numerous attemptsare being made to reconcile such concerns.

As examples, Gillooly et al. [28] have provided approaches that address normalization of differences in body temperature. They have provided perspectives on temperature-compensated resting metabolic rates for microbes, ectotherms, endotherms (including those in hibernation), and plants in temperatures ranging from 0^o to 40^o C (Fig. 2). The data supports that time-scales and sizes (e.g., bacterial genome lengths, tree heights, and mitochondrial densities) scale with exponents that are often simple powers of 1/4. Variations in cell size and cellular transport costs have also been studied related to their potential to influence the allometric exponent *'b'*. Corrections and suggestions are offered by Yuri Shestopaloff [29] to reconcile anomalies in experimental results across different taxa. Accordingly, it may be possible to eventually resolve many of the criticisms and concerns surrounding whether quarter power relationships are physical laws or principles. Suffice to say, whether a general principle or law or not, extrapolations and comparisons based on quarter power scaling have served us well in making predictions and estimates when data are limited or only available experimental models.

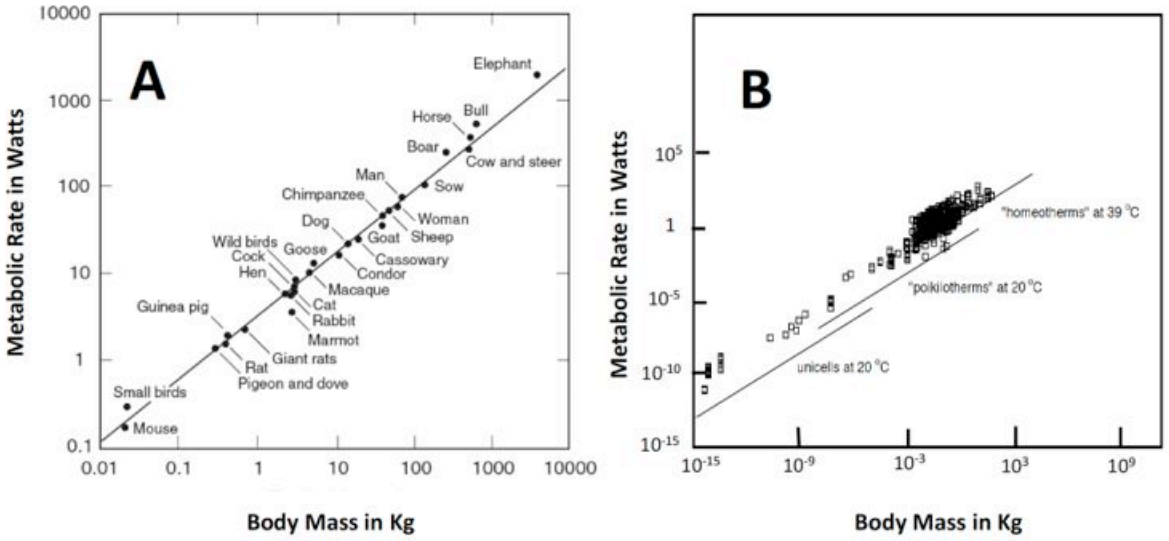

Figure 2. Graphical expressions of Kleiber's Law. For most homeothermic animals, metabolic rate scales to the ¾ power of the animal's mass (**A**). With temperature standardization ($Y \sim aM^{3/4}e^{-EikT}$, where E_i represents activation energy and T represents temperature, cf. [28]), it is possible to extend the relationship to poikilotherms and single cell organisms.

IMPLICATIONS THAT ARE LINKED TO THE ALLOMETRY OF SHAPE AND FORM:

From an evolutionary and genetic perspective, the ability to scale energy needs across a diverse array of animal implies that an interspecies comparison of genes directed at energy metabolism should also share or have a high degree of similarity. For example, in general terms, human genes show over 95% similarity with chimpanzees, about 90% with cats and, depending on calculation methodology, over 60-70% similarity with many rodents and some avian species [30]. Indeed, much of what we know about receptors, transport systems, and cell signaling have

come from studies of genes in single cell organisms (e.g., yeast) that serve homologs for those in humans. For example, it is possible to express human proteins in yeast that can function as components of metabolic pathways [31-33]. The point emphasized here is that as it relates to energy utilization and quarter power relationships, similarities at genetic and evolutionary levels, make it less surprising that one can scale from single cell organisms to large mammals.

Along these lines, recent work by Bolstad et al. [34] provides an additional nuance. They tested the evolutionary potential of an allometric scaling relationship in Drosophila (wing shape, which is nearly invariant across 111 species and separated by millions of years of evolution). After 26 generations of artificial selection, however, they could increase the allometric slope to the outer range of those found among the sampled species. Nevertheless, this response was rapidly lost when selection was suspended, which is consistent with a role for pleiotropic constraints and suggests a potential for remarkable evolutionary stability in measures that allometrically scale.

As another extension, Riedel et al. [35] have recently shown that ¾ power scaling also relates to bacteria when measurements are made in the stationary phase under nutrient-limited conditions. Under such conditions, Kleiber's law appears to extend down to the mass of a bacterium (i.e. in 100-fg range, Fig. 2). This is important in that significant body heat can be produced from microbial metabolism.

Rosenberg and Rosenberg [36] have estimated that the human colon's resident bacteria can produce as much as 40 kcal of heat per hour or about 70% of body heat at rest. The actual value, however, is substantially less when appropriately scaled. The 70% value is based on scaling of the heat produced by one gram of bacteria to 300 grams of bacteria on a dry weight basis (a typical dried fecal content for a 70 Kg person). Three quarter-power scaling from one gram to 300 grams, however, lowers this value to ~14 percent. Given the obvious importance of the metabolometo metabolism, this is a question that should be addressed and resolved. What is currently known is that the diversity and volume of the microbiome does increase in vertebrates in an allometric fashion. Godon et al. [37] observed that vertebrate bacterial gut diversity (assessed by the Simpson diversity index using 16S rDNA gene fingerprinting patterns) scales with a slope of 0.34 ± 0.03 in animals ranging in weight from ~10 g (Finch) to 3500 Kg (Asian elephant). The Simpson's index measures the probability that two constituents randomly selected from a sample will belong to the same species (or some category other than species).

Despite the diversity of themicrobiomes and feedstuffs consumed by animals, however, there is less diversity or variance when the requirements of individual dietary essential factors are compared relative to dietary energy needs. For example, when expressed on an energy basis, dietary requirements are often similar for deferent species, specifically within the same phyla. In this regard, Lucky, Maynard, and others [38, 39] were among the first to recognize that most, if not all animals share a common set of requirements for those nutrients that are deemednutritionally essential or important. As an extension, a case may also be that for animals

capable of synthesis of otherwise nutritionally essential substances, their daily production of the nutrient can be shown to be equivalent to the amounts needed in the diets of animals that require a dietary supply (see NUTRITIONAL APPLICATIONS SECTION). Metabolic pathways have evolved in a homologous fashion in many organisms to utilize fuels and disperse energy and heat. Consequently, a common set essential factors (e.g. vitamins, minerals, signaling molecules and accessory factors) would also need to evolve to facilitate the reactions or act as catalysts.

NUTRITIONAL APPLICATIONS:

As emphasized above, within certain parameters, allometric approaches are well suited to aid in making heuristic estimates of nutrient requirements. Examples may be found in previous publications [40-46] by my colleagues and myself, i.e. as with energy, most vitamin and mineral dietary requirements appear to scale in a three-quarter power fashion across a wide range of species.

An excellent example is ascorbic acid owing to the ability to compare the dietary requirements for those animals that require ascorbic acid to those that produce it from the oxidation of L-gulono-1,4–lactone by L-gulonolactone oxidase. The US Dietary Reference Intake for ascorbic acid is 90 milligrams per day for adult men and 75 mg/day for adult women; values are very close to what might be inferred from animal allometric scaling data [44].

Regarding synthesis, an examination of two rodent genetic models, the gulonolactone oxidase null mouse and the ODS (osteogenic disorder Shionogi) rat suggests the dietary requirement for such animals corresponds to what mice and rats typically produce [44, 46 and references cited therein], i.e. on the order of 80-160 mg L-ascorbic acid/1000 Kcal of diet consumed. Moreover, expressed per unit of food energy intake for humans, this amounts to ~200 mg per day, which is near the requirement for humans and the ascorbic acid content typically present in human milk (~ 3-4 mg/dl or about 50 mg/1000kcal, assuming 60--75 kcal/100 ml [44].

When these relationships were first presented [41], criticism was made that the daily turnover of ascorbic acid in the species compared was not considered [43, 47]. However, addressing this question provided a form of validation for quarter-power scaling. For example, if nutrient transfer rates are proportional to metabolic needs for interspecies comparisons, the nutrient turnover should be a function of $(M)^{¼}$. This is derived by assuming the body pool size of the substance (total content) is proportional to mass. Consequently, as an extension, turnover should be a function of the transfer rate (proportional to $M^{¾}$) divided into the pool size (proportional to M) or $M/M^{3/4}$, i.e. $M^{1/4}$. As shown in Fig.3, turnover can be estimated for the guinea pig and human from the values for experimental animals that make ascorbic acid.

$$\text{turnover} \sim \frac{k_{ps}(Wt_{Kg})^1}{k_{tr}(Wt_{Kg})^{3/4}} \sim k_{tu}(Wt_{Kg})^{1/4}.$$

Animal	$(Wt_{Kg})^{1/4}$	Half-life	Guinea pig	Human
		Days	*Days*	*Days*
Mouse	0.414	1–2	~3.5	9.8
Hamster	0.569	2.5–3.0	4.7	13.7
Rat	0.669–0.775	2.3–2.6	3.6–3.7	10.4–10.8
Rabbit	1.41	4–5	2.8 –3.5	8.0–10
Guinea pig	1.0	3.5	3.5	10
Human	2.89	10–11	~3.7	10–11

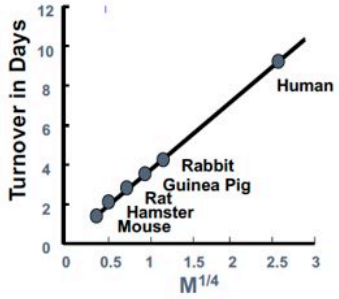

Figure 3. Allometric estimates for ascorbic turnover in the guinea pig and human. Values for the guinea pig and man were computed by dividing the $(Wt_{kg})^{¼}$ for the guinea pig (i.e. ~1 Kg) or man (i.e.~70 Kg) by the values in the column labeled $(Wt_{kg})^{¼}$ and then multiplying by the appropriate values for ascorbate half-life. The values for half-lives were taken from Ginter [47 and references cited therein]. The body weights which were used to calculate the given animal values for $(Wt_{kg})^{¼}$ were also derived from the data provided by Ginter [47]. The value of 3.6 days for the guinea pig and 10-11 for humans correspond to the values estimated in vivo for ascorbic acid turnover [46 and references cited therein].

CONCLUSIONS:

An appreciation of allometric scaling encourages thoughtful thinking as it relates to nutrient and energy flux, rather than merely thinking in terms of given amounts per day to elicit a given response. The design of nutrition experiments clearly benefits from allometric algorisms and approaches, particularly those using experimental animal models as precursors to human studies. Although it is appreciated that for specific compounds of nutritional interest, differences in secondary metabolism can influence a given outcome or response, when the secondary metabolism between species is similar, there is usually a high probability that the amounts of tested compounds will scale allometrically [46]. Expressing drug dosages and nutrients needs directly to mass, which is often done, is also conceptually short sited. It may lead to several orders of magnitude over-dosing in a moderately large animal (e.g., a human) compared to a small animal (e.g., a mouse) and vis-a-versa. Like the golden mean and patterns in nature that reflect the Fibonacciand Lucas series, allometric scaling principles extend deeply into geologic and evolutionary time. Indeed, given the extent to which allometric scaling occurs, there is usually a good biological question to be asked (and answered), when a phenomenon deviates markedly froma known allometric relationship.

Abbreviations: Symbols used in scaling equations: Y = metabolic rate, M = mass or body weight in Kg, a is the equation coefficient that includes constants used to define Y, b is the scaling exponent;16S ribosomal RNA (or 16S rRNA) is the 30S small subunit of a prokaryotic ribosome that binds to the Shine-Dalgarno, a ribosomal binding site in bacterial and archaeal messenger RNA, generally located around 8 bases upstream of the start codon AUG; ODS rat (osteogenic disorder Shionogi) rat.

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REFERENCES:

1. Reiss MJ.The Allometry of Growth and Reproduction. Cambridge University Press. 1991, New York City, NY, pp. 1-174.
2. Vajda V. Fibonacci and Lucas Numbers, and the Golden Section: Theory and Applications. 1989, Dover Publications Inc., Mineola, NY, 11501, pp. 1-189.
3. Chambers WH.Max Rubner: June 2, 1854-April 27, 1932. J Nutr. 1952, 48:3-12.
4. Thompson, DW. On Growth and Form. Cambridge University Press. 1917, New York City, NY, pp. 1-793.
5. Gayon J., History of the Concept of Allometry. Amer. Zool., 2000, 40:748–758.
6. Huxley, JS. &Teissier G. Terminology of relative growth. 1936, Nature 137:780–781.
7. Kleiber M. The Fire of Life: An introduction to animal energetics. 1969, Wiley, New York, pp. 1- 454.
8. Glazier DS. Body-Mass Scaling of Metabolic Rate: What are the Relative Roles of Cellular versus Systemic Effects? Biology (Basel). 2015, 4:187-99.
9. Glazier DS.Beyond the '3/4-power law': variation in the intra- and interspecific scaling of metabolic rate in animals. Biol Rev Camb Philos Soc.2005, 80:611-62.
10. Heusner AA.Size and power in mammals. J Exp Biol. 1991, 160:25-54.
11. Heusner AA., What does the power function reveal about structure and function in animals of different size? Annu Rev Physiol.1987, 49:121-33.
12. Heusner AA., Body size and energy metabolism. Annu Rev Nutr. 1985, 5:267-93.
13. Heusner AA., Energy metabolism and body size. I. Is the 0.75 mass exponent of Kleiber's equation a statistical artifact? Respir Physiol. 1982, 48:1-12.
14. Dodds PS., Rothman DH., &Weitz JS. Re-examination of the "3/4-law" of metabolism. J Theor Biol. 2001, 209:9-27.
15. Hulbert AJ., A Sceptics View: “Kleiber’s Law” or the “3/4 Rule” is neither a Law nor a Rule but Rather an Empirical Approximation. Systems, 2014, 2:186-202.
16. Mahmood I. Theoretical versus empirical allometry: Facts behind theories and application to pharmacokinetics. J Pharm Sci. 2010, 99:2927-33.
17. West GB., Woodruff WH., Brown JH. Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals. Proc Natl Acad Sci U S A 2002,99: Suppl 1, 2473-2478.

18. West, GB. &Brown JH., The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization. J Exp Biol 2005,208:1575-1592.
19. Bejan A. The constructal law of organization in nature: tree-shaped flows and body size. Journal of Experimental Biology. 2005, 208: 1677–86.
20. Bejan A., Lorente S. The constructal law of design and evolution in nature. Philos Trans R Soc Lond B Biol Sci. 2010, 365:1335-47.
21. Bejan A.&Zane JP. Design in nature. How the constructal law governs evolution in biology, physics, technology and social organization. 2012, New York: Doubleday.
22. Bejan A., Lorente S. The constructal law and the evolution of design in nature. Phy Life Rev. 2011, 8:209–240.
23. Banavar JR, Cooke TJ, Rinaldo A, &Maritan A. Form, function, and evolution of living organisms. Proc Natl Acad Sci USA. 2014, 111:3332-7.
24. Anfodillo T, Carrer M, Simini F, Popa I, Banavar JR, Maritan A. An allometry-based approach for understanding forest structure, predicting tree-size distribution and assessing the degree of disturbance. Proc Biol Sci. 2013, 280:20122375.
25. Speakman JR., Król E. The heat dissipation limit theory and evolution of life histories in endotherms--time to dispose of the disposable soma theory? Integr Comp Biol. 2010. 50:793-807.
26. Müller MJ., Langemann D., Gehrke I., Later W., Heller M., Glüer CC., Heymsfield SB., Bosy-Westphal A. Effect of constitution on mass of individual organs and their association with metabolic rate in humans--a detailed view on allometric scaling. PLoS One. 2011, 6:e22732.
27. Lindstedt SL, Schaeffer PJ. Use of allometry in predicting anatomical and physiological parameters of mammals. Lab Anim. 2002, 36:1-19.
28. Gillooly JF., Brown JH., West GB., Savage VM., Charnov EL. Effects of size and temperature on metabolic rate. Science. 2001, 293:2248-51.
29. Shestopaloff YK. Metabolic allometric scaling model: combining cellular transportation and heat dissipation constraints. J Exp Biol. 2016, 219(Pt16):2481-9.
30. Loomis WF.Similarities in eukaryotic genomes. Comp BiochemPhysiol B.1990, 95:21-7.
31. Wells L. &Fridovich-Keil JL. The yeast, Saccharomyces cerevisiae, as a model system for the study of human genetic disease. SAAS Bull BiochemBiotechnol. 1996, 9:83-8.
32. Khan AH., Bayat H., Rajabibazl M., Sabri S.&Rahimpour A. Humanizing glycosylationpathways in eukaryotic expression systems. World J MicrobiolBiotechnol. 2017, 33:4.
33. Wells E.&Robinson AS. Cellular engineering for therapeutic protein production:product quality, host modification, and process improvement. Biotechnol J. 2017, 12doi: 10.1002/biot.201600105.
34. Bolstad GH., Cassara JA., Márquez E., Hansen TF., van der Linde K., Houle D. & Pélabon C. Complex constraints on allometry revealed by artificial selection on the wing of Drosophila melanogaster. Proc Natl Acad Sci U S A. 2015, 112:13284-9
35. Riedel TE., Berelson WM., Nealson KH. &Finkel SE. Oxygen consumption rates of bacteria under nutrient-limited conditions. Appl Environ Microbiol. 2013, 79:4921-31.

36. Rosenberg E. &Zilber-Rosenberg I. Do microbiotas warm their hosts? Gut Microbes. 2016, 7:283-285.
37. Godon JJ., Arulazhagan P., Steyer JP. &Hamelin J. Vertebrate bacterial gut diversity: size also matters. BMC Ecol. 2016, 16:12. doi:10.1186/s12898-016-0071-2.
38. Lucky TD. A single diet for all living organisms. Science. 1954, 120:396-8.
39. Maynard LA. &Loosli JK. Animal nutrition (7th ed.). 1969, McGraw-Hill, New York pp. 1-602.
40. Rucker RB. Elevated metabolic rates in obesity. Lancet. 1978, 2:106-7.
41. Rucker RB., Dubick MA. &Mouritsen J. Hypothetical calculations of ascorbic acid synthesis based on estimates in vitro. Am J ClinNutr. 1980, 33:961-4.
42. Dubick MA., Critchfield JW., Last JA., Cross CE. &Rucker RB. Ascorbic acid turnover in the mouse following acute ozone exposure. Toxicology 1983, 27:301-13.
43. Rucker, RB. &Dubick M. Reply to letter by Ginter. Am JClinNutr. 1981, 34: 1450-1451.
44. Rucker RB. &Steinberg FM. Vitamin Requirements: Relationship to Basal Metabolic Need and Functions. Biochemistry and Molecular Biology Education, 2002, 30: 86-89.
45. Rucker RB. &Storms D. Interspecies comparisons of micronutrient requirements: metabolic vs. absolute body size. J Nutr. 2002, 132:2999-3000.
46. Rucker, R.B. Allometric scaling, metabolic body size and interspecies comparisons of basal nutritional requirements. JAn Phys An Nutri, Berlin 2007, 91:148-56.
47. Ginter E. Endogenous ascorbic acid and recommended daily allowances for vitamin C. Am.J. Clin. Nutrition. 1981, 34:1448-1451.