Red Herrings and Rotten Fish

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A longstanding problem in biology has been the origin of pervasive quarter-power allometric scaling laws that relate many characteristics of organisms to body mass \( M \) across the entire spectrum of life from molecules and microbes to ecosystems and mammals [1] - [3]. In particular, whole-organism metabolic rate, \( B = a M^b \), where \( a \) is a taxon-dependent normalisation constant and \( b \approx \frac{3}{4} \) for both animals and plants. Recently Darveau et al. [4] (hereafter referred to as DSAH) proposed a “multiple-causes model” for \( B \) as “the sum of multiple contributors to metabolism”, \( B_i \), which were assumed to scale as \( B_i = a_i M^{b_i} \). They obtained for average values of \( b \): 0.78 for the basal rate and 0.86 for the maximally active rate. In this note we show that DSAH contains serious technical, theoretical and conceptual errors, including misrepresentations of published data and of our work [5] - [8]. We also show that, within experimental error, there is no empirical evidence for an increase in \( b \) during aerobic activity as suggested by DSAH. Moreover, since DSAH consider only metabolic rates of mammals and make no attempt to explain why metabolic rates for other taxa and many other attributes in diverse organisms also scale with quarter-powers (including most of their input data), their formulation is hardly the “unifying principle” they claim. These problems were not addressed in commentaries by Weibel [9] and Burness [10].

All of the results of DSAH follow from their Eq. (2), \( B = a \sum c_i M^{b_i} \). Since, by definition, the control coefficients [11], \( c_i \), and exponents, \( b_i \), of the \( i \)th process are dimensionless, this equation must be incorrect since it violates the basic dimensional homogeneity constraint required of any physical equation, namely, that all terms must have the same dimensions. Their Eq. (2) is therefore meaningless. For example, it necessarily gives different results when using identical data but with different units for mass. To illustrate: we used their data in their Eq. (2) over the same mass range to obtain \( b \) for the basal rate; with mass in Kg, \( b \approx 0.76 \), when in g, \( b \approx 0.78 \), and when in pg, \( b \approx 1.08 \).

DSAH merely state Eq. (2) without proof, derivation or reference. General considerations from standard control theory [11] expose some of the problems. For a given metabolic state, consider \( B \) as a function of the independent contributions, \( B_i \): \( B = B(B_i) \). By definition, \( c_i \equiv \partial \ln B / \partial \ln B_i \), leading to the well-known sum rule, \( \sum c_i = 1 \), imposed by
Considering $B$ as a function of mass, $B(M) = B[B_i(M)]$, it follows that $b = \sum c_i b_i$, where $b(M) \equiv d\ln B/d\ln M$, is the slope of the allometric plot of $\ln B$ vs. $\ln M$, and $b_i(M) \equiv d\ln B_i/d\ln M$, that of $\ln B_i$ vs. $\ln M$. This is the formula that DSAH should have used to determine $b$. It is equivalent to the standard elasticity sum rule \[\sum c_i \epsilon_i = 0,\] with $\epsilon_i = b - b_i$. These equations are very general, requiring no assumptions about how $B$ and $B_i$ scale or whether the $B_i$ are in parallel or series. In DSAH contributions are added in parallel so $B = \sum B_i$. Thus, $c_i \equiv \partial \ln B / \partial \ln B_i = B_i / B = (a_i/a)M^{-\epsilon_i}$, leading to $B = a \sum (c_i M^{\epsilon_i}) M^{b_i}$, which is the correct, dimensionally homogeneous, version of Eq. (2). If $a$ and $a_i$ are constants, as assumed by DSAH, then, to be consistent, $c_i$ must scale as $M^{-\epsilon_i}$; this $M$ dependence was omitted by DSAH. Moreover, they assume that $c_i$ (and $b_i$) are also independent of $M$, so $b(= \sum c_i b_i)$ must likewise not depend on $M$, in contradiction to their Eq. (2). This inconsistency is concealed in their plots, which cover only 3 orders of magnitude in $M$ over which $b$ is nearly constant ($\sim 0.78$ for the basal case). However, when we extend their plots to the realistic 8 orders of magnitude spanned by mammals, the average value of $b$ for the basal rate increases to $\sim 0.85$ and, for the maximal rate, to $\sim 0.98$; both values are clearly inconsistent with data [1], [3].

Even if DSAH had used correct equations, there are many serious problems with the data and methodology used to estimate the $c_i$, $b_i$ and, in particular, $b$ for maximal activity. Their treatment contains no statistical analysis: they give no confidence intervals for the $c_i$ and $b_i$, nor do they consider how, as data are combined, the errors propagate to determine the confidence intervals for their estimate of $b$. Most $c_i$ quoted in DSAH are derived quantities. Almost none of the references cited actually mention “control coefficients” and DSAH’s Methods section gives insufficient information for how they were derived. For example, $c_i$ should be obtained from infinitesimal responses in $B$ rather than the large finite ones ($\sim 50\%$) used by DSAH. Furthermore, the “data” taken from Wagner [12] for cardiac output, alveolar ventilation and diffusion capacities, are theoretical estimates just for humans, based only on a “very simple model” [12] whose basic assumption is that $\dot{V}_{O_2}^{max}$ is $O_2$ supply-limited” [12], directly contradicting DSAH’s central contention. Several other $c_i$ are literally
guesses (the 0.01 values) and values for the $Ca^{++}$ pump were obtained from scaling of stride frequency of running mammals. In addition, a factor of 0.8 is arbitrarily introduced to rescale some $c_i$ to satisfy the sum rule, $\sum c_i = 1$. The need for such a “fudge” factor is hardly surprising given the empirical uncertainties and theoretical misconceptions.

Also problematic is DSAH’s contention that $b$ for maximal activity is significantly larger than its basal value of $\sim 0.75$. Both DSAH and Burness quote $b = 0.88 \pm 0.02$ from Bishop [13], which is based on the combined data from only 9 mammals (including 2 bats) and 6 birds. Bishop obtained this value as the exponent for $\dot{V}_{O_2}^{max}$ expressed as a power function of heart mass times hemoglobin concentration rather than body mass, $M$. When expressed as a function of $M$ his unadjusted data gives $b = 0.73 \pm 0.04$ for the basal state and $0.78 \pm 0.08$ for $\dot{V}_{O_2}^{max}$ [13], in excellent agreement with previous studies [1], [3]. One of the most quoted of these (though ignored by DSAH) is the comprehensive study by Taylor et al. [14] referred to by Weibel (who was a co-author of the paper) [9]. For 22 wild mammals (which the authors “prefer to use....as the general allometric relationship for $\dot{V}_{O_2}^{max}$” [14] and which are of relevance here), they found $b = 0.79 \pm 0.05$ and concluded that $\dot{V}_{O_2}^{max}$ “is nearly a constant multiple of 10 times resting metabolism $\dot{V}_{O_2}$, and scales approximately proportional to $M^{0.75}$” [14]. In his commentary Weibel cites this paper as giving $b = 0.86$ for $\dot{V}_{O_2}^{max}$ but fails to remark that this is derived from only 8 domestic mammals and has very poor precision: the 95% confidence limits, (0.611, 1.100), obviously include 0.75 [14].

Conservation of energy requires that summing all “ATP-utilising processes” [4] (linked in parallel) must give $B$: $B = \sum B_i$. Consequently, the DSAH “model” is only a consistency check of energy conservation, which must be trivially correct. As such, it cannot be in conflict with our theory. However, in addition to the above problems, the processes that DSAH include in the sum lead to problems of multiple-counting and thereby to a violation of energy conservation. For example, they add together contributions from cardiac output, alveolar ventilation, and pulmonary and capillary-mitochondria diffusion as if they were independent and in parallel. But, as shown in the cartoon in Weibel’s commentary [4], these processes are, in fact, primarily in series. The only reason DSAH obtain a result for $b$ in
reasonable agreement with data is that nearly all the exponents, $b_i$, have similar values.

Since the $b_i$ are simply taken from empirical data, DSAH’s formulation does not provide a fundamental explanation for why $B$ scales non-linearly with body mass. Such an explanation would require models in which the $b_i$ (and $c_i$) are derived from basic principles. It is surely no accident that the $b_i$ cluster around $\frac{3}{4}$; understanding this is the real challenge. Why, for example, should molecular processes like $Na^+$ and $Ca^{++}$ pumps or $ATPase$ activity scale other than linearly with $M$? The simplest expectation, implicit in DSAH, would be that the contributing biomolecular processes, and therefore cellular metabolic rates, do not depend on body size, so that $B$ would scale linearly with $M$. Moreover, nothing in DSAH suggests why cellular level processes scale differently in vivo than in vitro. By contrast our theory, based on scaling constraints inherent in distribution networks and exchange surfaces, correctly predicts that, when these constraints are lifted by removing cells from the body and by culturing these cells for several generations, in vitro cellular metabolic rates converge to a constant value - only in vivo do they scale with body mass, as $M^{-1/4}$.

Finally, we respond to DSAH’s contention that our network theory is supply rate-limiting and cannot accommodate metabolic scope. For a given metabolic state, scaling between organisms of different sizes (varying $M$ with $a$ and $a_i$ fixed) is indeed rate-limited by the network, and this is the origin of quarter-powers. However, within an organism of a given size (fixed $M$), the absolute rate (as distinct from the relative rate) of resource flow and power output (measured by the $a$ and $a_i$, for example) is clearly not rate-limited by the network. Changes in supply and demand cause the flow through the network to change accordingly, as in any transport system. A simplified analogy is the power output of automobile engines: this scales with size, but the power of any given vehicle can be varied on demand by varying fuel supply. Thus, our theory accommodates metabolic scope in a natural and simple way and could be extended to calculate the overall magnitude of increase.

To conclude: DSAH present their “model” as an alternative to our theory for the origin of quarter-power scaling in biology. Unlike their framework, however, our theory offers a comprehensive, quantitative, integrated explanation for allometric scaling, not just of whole-
organism metabolism in mammals, but also of many other characteristics in a wide variety of animals, plants, and microbes. It shows how the geometric, physical, and biological constraints on distribution networks and exchange surfaces with fractal-like designs give the ubiquitous quarter-power scaling laws. Our theory explains why body size has such a powerful influence on biological structure and function at all levels of organization, from the oxygen affinity of hemoglobin molecules and the density of mitochondria, to the rate of fluid flow in the vessels of plants and animals, to ontogenetic and population growth [1]-[3].

By contrast, DSAH present a flawed model that purports to explain only how the scaling of whole-organism metabolic rate in mammals is related to the scaling of some of the underlying processes at molecular, cellular, and organ-system levels. Most importantly it offers no explanation why any of these processes vary with body size, let alone why they should exhibit their observed allometric exponents. Thus, even if the errors were corrected, DSAH’s framework cannot explain the quarter-power scalings of structures, rates, and times that have so fascinated biologists for the last century.
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