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Utility of the coefficient of determination (r^2) in assessing the accuracy of interspecies allometric predictions: Illumination or Illusion?

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Running title: Use of r^2 in allometric scaling

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Abbreviations: PK, pharmacokinetics; CL, clearance; r^2, coefficient of determination

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Abstract

The appropriateness of relying on the coefficient of determination (r^2) as a statistical metric for judging the predictability of human clearance (CL) based on interspecies animal data was assessed. An explicit mathematical expression was derived for r^2 as a function of species body weight and the corresponding measured value of CL. The derived mathematical function demonstrated that r^2 is numerically large in most instances. Simulations using random CL generated from a common combination of species of mouse, rat and monkey resulted in an r^2 of 0.75 as the minimum, and 0.95 and 0.98 at 50^{th} and 75^{th} percentiles, respectively, given that total CL values increase with increasing species body weight. Analysis of literature data also indicated that the prediction accuracy of human CL was not correlated with values of r^2. Therefore, it is concluded that r^2 is a limited statistical measure when assessing allometric scaling for the purpose of predicting human CL.

Introduction

Allometric scaling has been widely used in predicting human pharmacokinetic (PK) parameters, although the allometric approach is empirical and numerous examples of substantial prediction errors have been observed (Boxenbaum 1982; Mahmood and Balian, 1996; Nagilla R and Ward KW, 2004; Tang and Mayersohn, 2006). The allometric relationship for PK parameters across animal species and the confidence in extrapolation of this relationship to humans is often assessed with use of the coefficient of determination (r^2). The latter is obtained from linear regression of log-transformed animal body weights and the corresponding measured values of (log) PK parameters. High r^2 values (ca., greater than 0.90) have been cited for most of the allometric relationships reported in the literature (Mahmood and Balian, 1996; Hu TM and Hayton WL, 2001). By definition r^2 is the fraction of the total squared error explained by the model. It is generally recognized that r^2 is not a good statistical measure for nonlinear models. For example, over-parameterized models could easily lead to high r^2 values, while such models usually have little predictive value. It has also been long recognized that the log-log transformation of the allometric power function ($P = a \cdot W^b$) would minimize deviations from the regression line (Smith, 1984). Therefore, it is reasonable to speculate that r^2 may not offer a good measure for examining the predictive quality of the allometric relationship. We report here an explicit mathematical function of r^2 derived to quantitatively assess the appropriateness of using r^2 as a statistical measure in allometric scaling. Literature data were also evaluated to assess the relationship between r^2 and the prediction performance by allometric scaling.

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Methods

Theory

I. Expression of predicted PK parameters among species

The function relating predicted PK parameters ($\hat{P}$) in humans or animal species to animal body weights (W_i, i = 1 to n, where n is the number of animal species) and observed animal PK parameters (P_i) has been described elsewhere (Tang and Mayersohn, 2005). The following highlights the major mathematical functions needed in the subsequent derivations.

$$P = a \bullet W^b \tag{1}$$

$$a = \prod_{i=1}^{n} P_i^{A_i} \tag{2}$$

$$b = \sum_{i=1}^{n} B_i \bullet \log P_i \tag{3}$$

where,

$$A_i = \frac{1}{n}(1 - B_i \bullet \log \prod_{j=1}^{n} W_j) \tag{4}$$

$$B_i = \frac{1}{n} \bullet \frac{\log\left(\frac{W_i^{n-1}}{\prod_{\substack{k=1 \\ k\neq i}}^{n} W_k}\right)}{\sum_{k=1}^{n}\left(\log W_k - \frac{\log \prod_{l=1}^{n} W_l}{n}\right)^2} \tag{5}$$

The predicted PK parameter value, $\hat{P}$, in the species of interest is obtained from,

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$$\hat{P}_i = a \bullet W_i^{\,b} = \prod_{i=1}^{n} P_i^{[A_i + (\log Wi) \bullet B_i]} \tag{6}$$

II. Expression for r^2

The log-log transformation of, $P = a \bullet W^b$ gives,

$$\log P = \log a + b \bullet \log W \tag{7}$$

Let,

$$Y = \log P;\ X = \log W;\ a = 10^{\alpha};\ b = \beta$$

Then, eq. (7) can be simplified to,

$$Y = \alpha + \beta \bullet X \tag{8}$$

r^2, by definition, is expressed as,

$$r^2 = \frac{\sum_{i=1}^{n} (\hat{Y}_i - \overline{Y})^2}{\sum_{i=1}^{n} (Y_i - \overline{Y})^2} \tag{9}$$

where,

$$\hat{Y}_i = \log \prod_{i=1}^{n} P_i^{[A_i + (\log Wi) \bullet B_i]} \tag{10}$$

$$\overline{Y} = \frac{1}{n} \bullet \log \prod_{i=1}^{n} P_i \tag{11}$$

$$Y_i = \log P_i \tag{12}$$

Although r^2 can be explicitly expressed when eqs. (10) to (12) are placed into eq. (9), a visually clearer form is not readily available. Therefore, a common combination of

animal species (mouse, rat and monkey, with body weights assigned as 0.03, 0.3 and 3 kg, respectively) was used for illustration purposes.

$$\hat{Y}_{mouse} = \log(CL_{mouse}^{0.8333} \bullet CL_{rat}^{0.3333} \bullet CL_{monkey}^{-0.1667}) \quad (13)$$

$$\hat{Y}_{rat} = \log(CL_{mouse}^{0.3333} \bullet CL_{rat}^{0.3333} \bullet CL_{monkey}^{0.3333}) \quad (14)$$

$$\hat{Y}_{monkey} = \log(CL_{mouse}^{-0.1667} \bullet CL_{rat}^{0.3333} \bullet CL_{monkey}^{0.8333}) \quad (15)$$

$$\overline{Y} = \frac{1}{3}\log(CL_{mouse} \bullet CL_{rat} \bullet CL_{monkey}) \quad (16)$$

Substituting eqs. (13) to (16) into eq. (9), results in,

$$\sum_{i=1}^{n}(\hat{Y}_i - \overline{Y})^2 = \frac{1}{2}(\log\frac{CL_{monkey}}{CL_{mouse}})^2 \quad (17)$$

$$\sum_{i=1}^{n}(Y_i - \overline{Y})^2 = \frac{1}{9}[(\log\frac{CL_{mouse}^{\ 2}}{CL_{rat} \bullet CL_{monkey}})^2 + (\log\frac{CL_{rat}^{\ 2}}{CL_{mouse} \bullet CL_{monkey}})^2 + (\log\frac{CL_{monkey}^{\ 2}}{CL_{mouse} \bullet CL_{rat}})^2] \quad (18)$$

Note that, and this is true most of the time, values for total CL in mouse, rat and monkey follow the corresponding order of body weight. Let, $CL_{monkey} = L \cdot CL_{rat}$, $CL_{rat} = M \cdot CL_{mouse}$, where L, M >1, r^2 will be equal to,

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$$r^2 = \frac{3}{4} \bullet \frac{1}{1 - \left(\frac{1}{\sqrt{\frac{\log L}{\log M}} + \sqrt{\frac{\log M}{\log L}}} \right)^2} \qquad (19)$$

III. Simulating r^2 values

Although a wide range of CL values for each species is considered here for simulation purposes, in reality CL values usually do not exceed certain limits in each species. The values ranged from 0.001-times liver blood flow (LBF) at the low end to 5-times LBF at the high end, for each species. A total of 10,000 random values of CL from each species were generated from a uniform distribution of, [0.001xLBF to 5xLBF], in each species, where the LBF for mouse, rat and monkey were, respectively, 5.40, 3.31 and 2.62 L/hr·kg (Davies and Morris, 1993). Thus, 10,000 r^2 values were computed. In reality the magnitude of CL follows the order of species body weight and, therefore, the r^2 values obtained were further constrained under the expected order of CL; $CL_{monkey} > CL_{rat} > CL_{mouse}$. All calculations and simulations were performed using MATLAB (version 6.5; The MathWorks, Inc., Natick, MA).

Literature data evaluation

A large set of allometric data including CL values in rat, monkey, dog and human is available (Jolivette and Ward, 2006). The combination of animal species in this data set was different from the combination of species in the above example developed under Theory. Due to the close body weights of monkey and dog, it is expected that some CL values in those species will not strictly follow the order of body weights. Therefore, lower r^2 values are expected from that combination than from simulations obtained from the combination of mouse, rat and monkey. Nevertheless, the correlation between the prediction performance and the r^2 values can still be assessed.

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Results and Discussion

Values for r^2 obtained from the species combination mouse, rat and monkey are derived from eq. (19). Notice that, $\sqrt{\frac{\log L}{\log M}} + \sqrt{\frac{\log M}{\log L}} \geq 2$, r^2 is, therefore, always greater than 0.75 (when, $\sqrt{\frac{\log L}{\log M}} + \sqrt{\frac{\log M}{\log L}} \to \infty$), and equal to 1 (when, $\sqrt{\frac{\log L}{\log M}} + \sqrt{\frac{\log M}{\log L}} = 2, \text{or}, \log L = \log M$). Furthermore, due to the existence of an approximate allometric relationship, that is,

$$L = \frac{CL_{monkey}}{CL_{rat}} \approx \left(\frac{W_{monkey}}{W_{rat}} \right)^b = 10^b \quad (20)$$

$$M = \frac{CL_{rat}}{CL_{mouse}} \approx \left(\frac{W_{rat}}{W_{mouse}} \right)^b = 10^b \quad (21)$$

the value of m is usually close to that of n. Therefore, one expects that for most of the cases, r^2 is high and close to 1. Even in some extreme situations, for example, when m=10 and n=1000, that is, the CL in rat is 1000-fold higher than that in mouse, while the CL in monkey is only 10-fold higher than that in rat, given the same 10-fold of difference in body weights between rat and mouse, or monkey and rat, the resulting r^2 is still as high as 0.92.

The results from the simulations also indicated that r^2 values were high in the majority of cases based on the random values for CL in each species. The r^2 values were highly right-skewed towards larger values (Figure 1). The r^2 values for the 50th and 75th percentiles are 0.95 and 0.98, respectively. These results clearly demonstrate that the common use of r^2, whose values are often considered to be "good" if they are greater than 0.90 or 0.95, is misleading.

The literature data indicated that there was no correlation between r^2 and prediction performance (Figure 2). This result suggests that r^2 cannot serve as an indicator for predicting human values. This may be the case for several reasons. First, there exists great uncertainty associated with values in humans due to the complexity of biological systems; good r^2 or even a perfect r^2 does not necessarily

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mean that the human value will be on the allometric line of regression. Second, we have shown that r^2 is not an appropriate measure gauging the quality of an allometric relationship; CL randomly sampled from animal species can result in "good" r^2 values. Finally, the change in r^2 is asymmetrical with respect to the values of CL. The procedure of log-log transformation followed by linear regression assumes a log-normal distribution of CL. Differentiating r^2 (eq. 9) with regard to log CL in the monkey, for example, resulted in an asymmetrical function with respect to log CL (the resulting function, $\frac{\partial(r^2)}{\partial(\log CL_{monkey})}$, is not shown here because of its complexity). Assume there is a perfect allometric relationship for mouse, rat and monkey with CL values of 0.130, 0.730 and 4.10 L/hr (r^2=1). Now, changing log CL in monkeys by –0.699 and +0.699 (or 5-fold higher and lower, respectively) results in r^2 values of 0.797 and 0.967, respectively. It is apparent that the same probability for the occurrence of –0.699 and +0.699 log CL resulted in striking differences in r^2 values.

In summary, r^2 has been shown to not be an appropriate statistical measure for allometric scaling. The authors are not aware of another simple statistical measure that would serve in its place. The purpose of this communication was not to discourage reporting of r^2 values for allometric relationships. However, we caution that use of r^2 as a measure for the quality of an allometric relationship is not appropriate. Claiming a "good" allometric relationship based on r^2 values greater than 0.90 or 0.95 is not appropriate, and more practically important is the degree of confidence that one has in the predicted human value.

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Figure Legends

Figure 1. Distribution of r^2 values computed by random CL generated from a uniform distribution of, [0.001 x LBF to 5 x LBF] in mouse, rat and monkey. LBF is liver blood flow.

Figure 2. Correlation between the r^2 values and the prediction fold value for human CL ($CL_{predicted}$ divided by $CL_{observed}$). Based on the allometric data form rat, monkey and dog (n=103; reference 9). Values for r^2 greater than 0.5 (n=94) are shown in (A) and values greater than 0.90 (n=64) are shown in (B).

Fig. 1

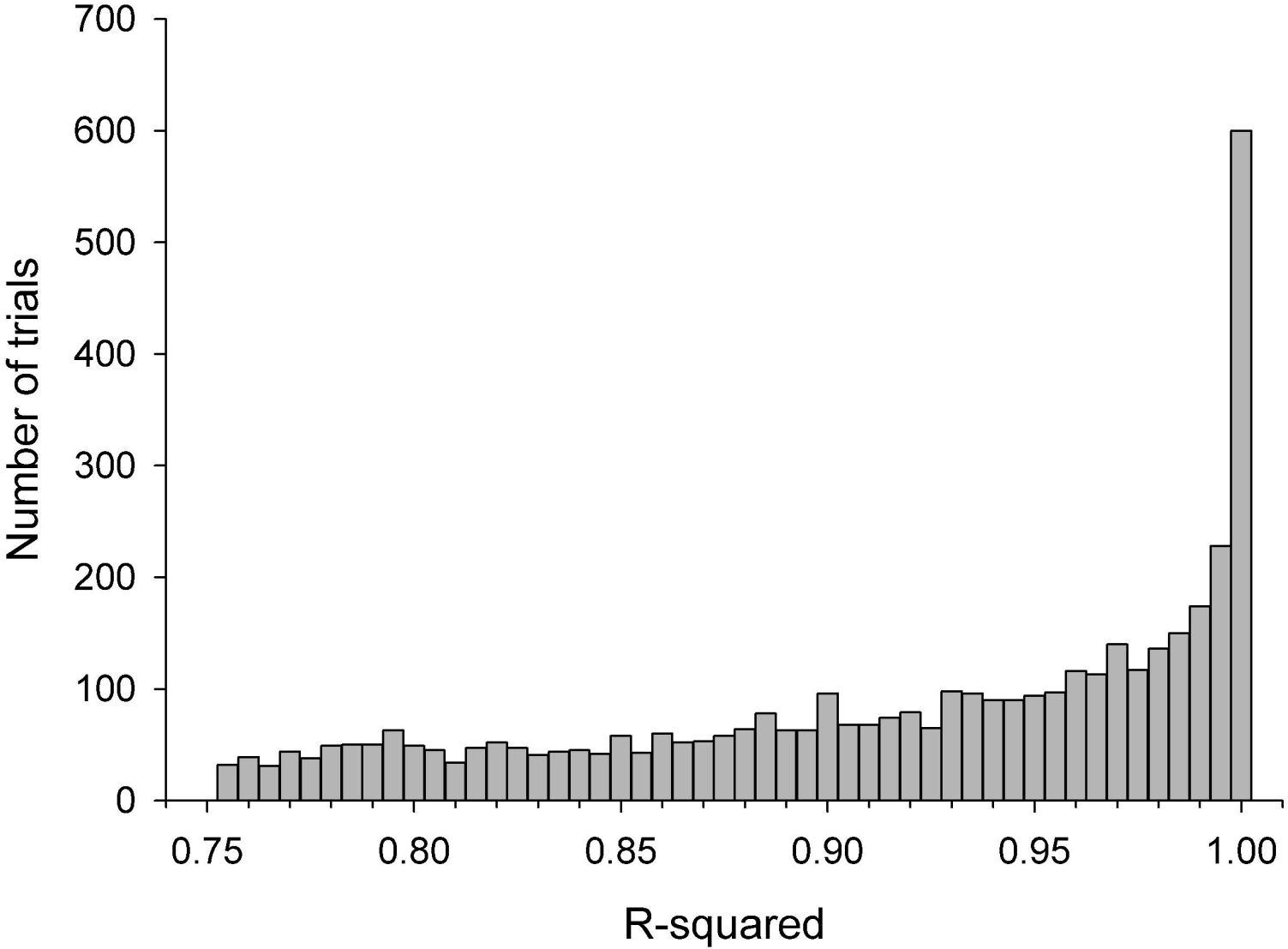


Fig. 2A

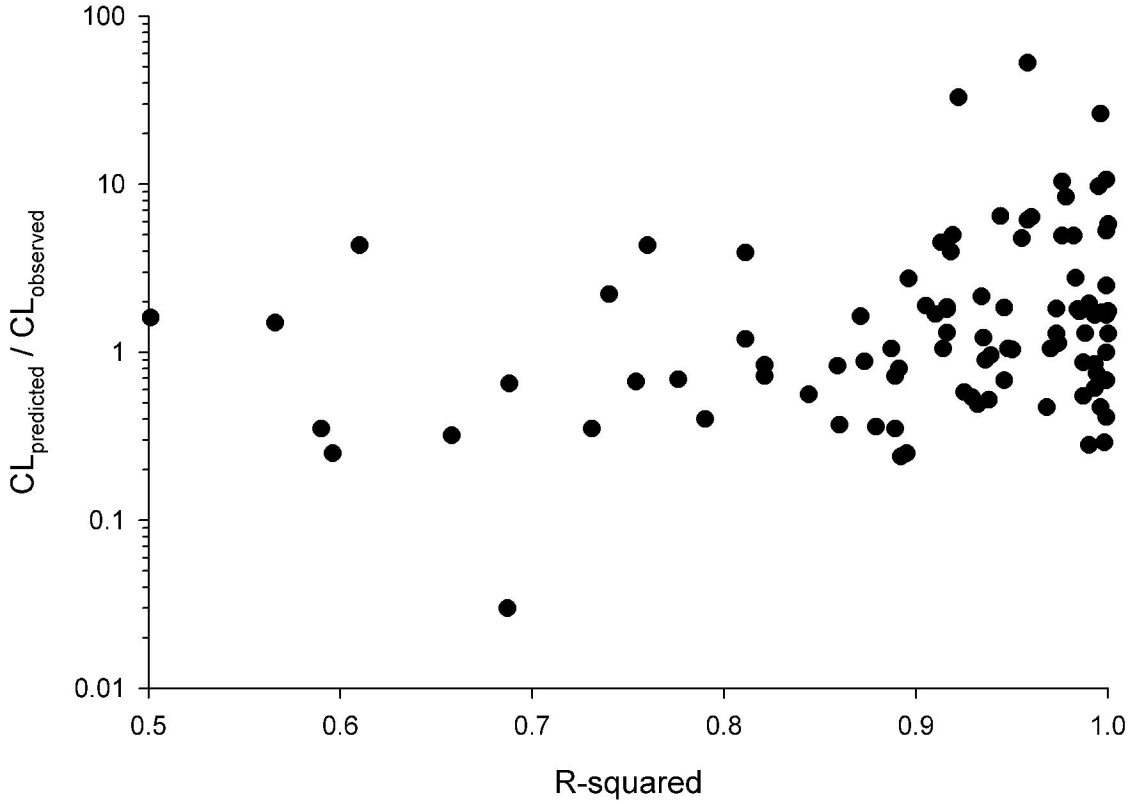
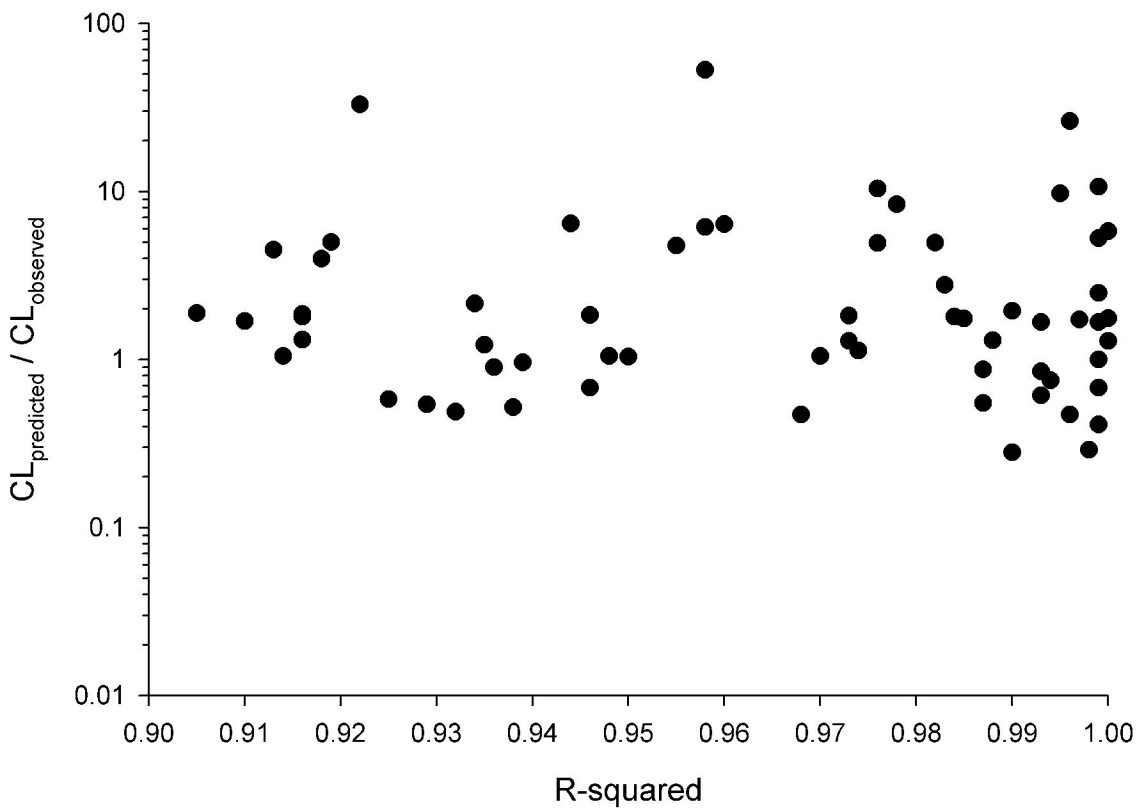

100
10
1
0.1
0.01
$CL_{predicted}$ / $CL_{observed}$
0.5
0.6
0.7
0.8
0.9
1.0
R-squared

Fig. 2B


100
10
1
0.1
0.01
$CL_{predicted}$ / $CL_{observed}$
0.90
0.91
0.92
0.93
0.94
0.95
0.96
0.97
0.98
0.99
1.00
R-squared

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Appendix

Symbols used in derivations in the Method section

a : The coefficient of the allometric power function, $P = a \bullet W^{b}$.

A_i : Equal to $\frac{1}{n}(1 - B_i \bullet \log \prod_{j=1}^{n} W_j)$, and used in $a = \prod_{i=1}^{n} P_i^{A_i}$, which calculates the coefficient (a) of the allometric power function. Note, the PK parameter, P_i, observed in one animal species (i) is raised to its specific exponent, A_i, which is only dependent on the body weights across animal species and bears no relations to observed P_i.

b : The exponent of the allometric power function, $P = a \bullet W^{b}$

B_i : Equal to $\frac{1}{n} \bullet \frac{\log\left(\frac{W_i^{n-1}}{\prod_{\substack{k=1 \\ k \neq i}}^{n} W_k}\right)}{\sum_{k=1}^{n}\left(\log W_k - \frac{\log \prod_{l=1}^{n} W_l}{n}\right)^2}$, and used in $b = \sum_{i=1}^{n} B_i \bullet \log P_i$, which calculates the exponent (b) of the allometric power function. Note, the $\log P_i$ is multiplied by its specific scalar, B_i, which is only dependent on the body weights across animal species and bears no relations to observed P_i.

L : Equal to $\frac{CL_{monkey}}{CL_{rat}}$

M : Equal to $\frac{CL_{rat}}{CL_{mouse}}$

n : The number of animal species

P_i : The PK parameter observed in species i

$\hat{P}_i$: The PK parameter predicted in species i

W_i : The body weight of species i

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X_i : Equal to $\log W_i$, and used to transform the allometric power function, $P = a \bullet W^b$, to linear function, $Y = \alpha + \beta \bullet X$

Y_i : Equal to $\log P_i$, and used to transform the allometric power function, $P = a \bullet W^b$, to linear function, $Y = \alpha + \beta \bullet X$

$\overline{Y}$: Mean of Y_i

$\hat{Y}_i$: Predicted Y_i

α : Equal to $\log a$, and used to transform the allometric power function, $P = a \bullet W^b$, to linear function, $Y = \alpha + \beta \bullet X$

β : Equal to b , and used to transform the allometric power function, $P = a \bullet W^b$, to linear function, $Y = \alpha + \beta \bullet X$