Accuracy of allometrically-predicted pharmacokinetic parameters in humans- Role of species selection

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Abbreviations: PK, pharmacokinetics; CL, clearance; CV, coefficient of variation; PE, percentage error; PC, percentage change

Abstract

A general equation was derived, which directly describes the mathematical relationship between the allometrically-predicted pharmacokinetic (PK) parameters in humans and the body weights of animal species (along with their corresponding measured PK parameters). It was shown, with use of the derived equation, that the predicted values in humans, based on combinations of animal species commonly used in allometry, are heavily dependent on certain species, for example, the dog. In contrast, parameter values from the rat made no contribution to the predicted human values, as long as the rat was not the smallest species used. Monte Carlo simulations were further performed to examine the species or weight dependency. The cost-effective combinations of animal species, in term of number and species type, were theoretically examined through simulations. Finally, literature data demonstrated the species or weight dependency predicted from the equation and as illustrated through the Monte Carlo simulations. Appreciation of this species or weight dependency should guide researchers in selecting animal species and designing optimal experiments in the application of allometric scaling.

Introduction

Allometric scaling is one of the most widely used approaches in predicting human pharmacokinetic (PK) parameters (e.g., CL, V_d, $T_{1/2}$) based on values in animals, The basic allometric relationship has been observed to follow the power function: parameter = a (body weight) ^{b}, where a and b are a coefficient and an exponent, respectively. The observed power function is empirical, although there is some possible underlying physiological rationale (Boxenbaum, 1982;Mordenti, 1986). For example, the "¾ power law" of metabolic rate was theoretically derived from the hydrodynamics and fractal geometry of nutrition-supply network of the organisms (West, et al., 1997). However, there are numerous examples of substantial differences between predicted and observed values in humans. Great effort has been focused on how to improve the accuracy of allometric scaling. There various modifications include: *in vitro* correction (Lave, et al., 1997); a two-term power function approach (Boxenbaum and Fertig, 1984); maximum life-span potential (MLP) or brain weight (BrW) correction (Mahmood and Balian, 1996b); "rule of exponents" (Mahmood and Balian, 1996a); unbound CL approach (Feng, et al., 2000).   Unfortunately, none of these modifications is completely satisfactory since there are always deviations from prediction. Basically there are two reasons leading to such deviations. One is the deviations of the values of PK parameters in certain species (animal or human) from the assumed power function. The other is the measurement errors in the reported PK parameters. The former one could be considered as a "position error" (though it is not an error) and such error is fixed for each species. The latter measurement error is a random one.

Power functions are well known for creating substantial errors in data fitting. The log-log transformation of the data will visually minimize the deviations from a regression line. A high R^2, greater than 0.90 or even 0.95, does not guarantee that all the data points will be close to the regression line. The extrapolation of this regression line to obtain a predicted human value, which is obtained from fitting data based on a limited number of animal species, may have great uncertainty associated with it. It is also well known that the regression process does not treat the weight of each animal species comparably. The measurement errors in a given parameter from an animal species could lead to significant prediction error in humans as a result of fitting this power function. Therefore, it is necessary and desirable to know how quantitatively a measurement error or a "position error" in a given parameter in animals affects the regression analysis and the ultimate quantitative prediction in humans.

In this report, we have derived a general equation, which describes the mathematical relationship between predicted PK parameters in humans and the body weights of selected animal species and the values of the corresponding measured PK parameters. Using clearance (CL) as an example, simulations were performed to examine the dependency of the variability of predicted human CL on the variability of animal CL. Finally, data from the literature were examined to demonstrate the species dependency as derived from theory. Based on these results, some suggestions are proposed for the optimal selection of animal species and the application of animal data in allometric scaling.

Methods

Theory

The function relating predicted PK parameters in humans ($P_{predicted}$) to animal body weights (W) and observed animal PK parameters (P_i) is derived in the following sections.

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

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

Let

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

Then, Equation (1) can be simplified to,

$$Y = \alpha + \beta \bullet X \tag{2}$$

Suppose *n* different animal species are used for allometric scaling. Therefore, there are *n* sets of (*X*, *Y*) data to fit using linear regression. Based on the method of least square for linear regression, α and β can be calculated as,

$$\beta = \frac{\sum_{i=1}^{n}(X_i - \overline{X})(Y_i - \overline{Y})}{\sum_{i=1}^{n}(X_i - \overline{X})^2} \tag{3}$$

$$\alpha = \overline{Y} - \beta \bullet \overline{X} \tag{4}$$

Substituting, $Y = \log P$; $X = \log W$ into Equation (3) and (4), and further substituting α

and β into $a = 10^{\alpha}$; $b = \beta$, expressions of a and b are obtained as,

$$a = \prod_{i=1}^{n} P_i^{A_i} \tag{5}$$

$$b = \sum_{i=1}^{n} B_i \bullet \log P_i \tag{6}$$

where,

$$A_i = \frac{1}{n}(1 - B_i \bullet \log \prod_{j=1}^{n} W_j) \tag{7}$$

$$B_i = \frac{1}{n} \bullet \frac{\log \dfrac{W_i^{n-1}}{\displaystyle\prod_{\substack{k=1 \\ k \neq i}}^{n} W_k}}{\displaystyle\sum_{k=1}^{n}(\log W_k - \dfrac{\log \displaystyle\prod_{l=1}^{n} W_l}{n})^2} \tag{8}$$

By assuming a human body weight of 70 Kg, the predicted P in humans is obtained from,

$$P_{predicted} = a \bullet 70^b = \prod_{i=1}^{n} P_i^{(A_i + 1.845 B_i)} \tag{9}$$

Direct fitting of power functions with incorporation of a weighting strategy has been

shown to not improve the prediction performance by allometric scaling (work not

shown). The above log-log transformation and linear regression appears to be the best

approach in allometry. In reality, this method is inevitably applied in allometric scaling.

Monte Carlo simulations

CL was used as an illustrative example of a PK parameter. Typical body weights

of animals commonly used in allometry are listed in Table 1. Assuming that there is a

perfect allometric relationship, $CL = a \bullet W^b$, between *CL* and *W* and setting $a = 30$ ml/min,

$b = 0.75$, the *CL* value for each species "seed values" for Monte Carlo simulations can be

obtained (Table 1). Log-normal distribution, $N(\ln CL_{seed} + CV)$, is assumed for CL, where

the coefficient of variation (CV) is 30% or 100%. Thirty percent and one-hundred percent

CV are employed in order to assess the effect of the experimental measurement errors

and the overall "errors" (including both measurement errors and "position errors") on the

prediction performance, respectively. The magnitude of the "position errors" is

considered to be much greater than that of the measurement errors. The arithmetic mean

and median values of $CL_{predicted}$ in humans from these simulations are listed for

comparison with the theoretically perfect value (726.0 ml/min) predicted from the power

function. For some combinations of commonly used animal species, in addition to the

simulations where all the *Pi* values were variables, simulations were also performed by

assuming that only one *Pi* was variable, whereas the others were held constant (at the

"seed values"). This was done in order to assess the contribution of each species to the

prediction performance. Different combinations of animal species from five species to

two species were used for simulation purposes in order to select optimal combinations of

animal species. Percentage errors (PE), which are, $\frac{CL_{predicted} - CL_{observed}}{CL_{observed}} \times 100\%$, for over-

prediction and, $\frac{CL_{observed} - CL_{predicted}}{CL_{predicted}} \times 100\%$, for under-prediction, were used to assess the

prediction performance. All the calculations and simulations were performed with

MATLAB 6.5 (The MathWorks, Inc., MI).

Literature data experimentation

Twenty-six sets of allometric scaling data for *CL* from at least three species

including mouse, rat and dog, were randomly collected from the literature. *CL* in humans

was predicted by allometry. Percentage change (PC) is defined as:

$\frac{CL_{remove-ith-species} - CL_{all}}{CL_{all}} \times 100\%$ for an increase and, $\frac{CL_{all} - CL_{remove-ith-species}}{CL_{all}} \times 100\%$ for a

decrease, where CL_{all} is the *CL* predicted using all animal species and $CL_{remove-ith-species}$ is

the CL predicted by removing the ith species.

Results

Theoretical experimentation

The equation,

$$P_{predicted} = a \bullet 70^b = \prod_{i=1}^{n} P_i^{(A_i + 1.845 B_i)} \tag{9}$$

not only directly depicts the relationship between the predicted PK values in humans to those observed in animals, but more importantly it indicates the dependency of the prediction variability on animal body weights, which determine the value noted in the exponent of Pi. Each animal Pi is raised to a specific power, $A_i + 1.845 B_i$. Prediction of CL is used as an example of a parameter, P, in the following discussion, though the principle can be applied to any PK parameter such as volume of distribution and half-life. A typical example of an animal species combination, mouse, rat, rabbit and dog, was used to illustrate the body weight dependency suggested by Equation (9). Substituting body weights from these species into, $A_i + 1.845 B_i$, gives the equation;

$$CL_{predicted} = CL_{mouse}^{-0.3631} \bullet CL_{rat}^{-0.005357} \bullet CL_{rabbit}^{0.5596} \bullet CL_{dog}^{0.8089} \tag{10}$$

The exponent (-0.005357) for rat CL is close to 0, indicating that the CL in the rat would have little effect on the prediction of human CL when this specific set of animals is chosen. In contrast, the CL in the dog would be expected to have a large effect on the predicted CL in humans. For example, a doubling of the values of dog CL results in a 0.75-fold increase in the predicted CL in humans; whereas, there is little prediction effect on the predicted value in humans even with a 100-fold change in rat CL (Figure 1).

The roles that different species play in their contribution to the prediction accuracy and variability, were also examined by simulations allowing only one Pi to vary at a time. Commonly used species combinations were examined: mouse, rat, rabbit, monkey, dog; mouse, rat, monkey, dog; and mouse, rat, dog (Table 2). The results demonstrate that the prediction of a value in humans is most sensitive to the value in dogs values; whereas, the rat made essentially no contribution to the prediction. For example, the 30% CV random error in rat CL only generates a mean of 0.01% PE. The mouse also showed a small contribution to the prediction variability. These results are consistent with the results derived from the model equation, which shows that rat CL has a trivial effect on the variability in predicted human CL; whereas, a significant effect is observed using the value of CL from the dog.

Literature data experimentation

The mouse, rat, rabbit or dog was individually removed from allometric scaling in order to examine the effect of deleting one species on the prediction in humans (by using the log-log transformation and linear regression method), since the majority of the 26 allometry data sets used these four species. The rat contributed virtually nothing to the prediction, because all the values of percentage change were very close to 0 after removal of the rat. In contrast, removal of the dog from the allometry resulted in a significant change in predicted CL values in humans (Table 3, Figure 2).

Discussion

The equation that has been derived here offers insight into allometric analysis in that it describes quantitatively the dependency of prediction variability on each animal species (*i.e.,* species weight). An immediate practical significance of these findings will allow investigators to recognize such animal species or body weight dependency, on the predicted human value, and permit design of better or more optimal experiments. For example, large variability in the data for dog PK parameters would have a high potential risk for producing large deviations in predicted human values, whereas, variability in rat data can essentially be ignored. Having such a quantitative equation available and realizing the magnitude of the species weight dependency, investigators may increase sample size for the species having the most significant effect on the predicted value in order to improve its accuracy, and appropriately reduce or eliminate completely the sample size for the species with the least effect. As demonstrated by both theoretical and literature experimentation, rats had no significance in predicting human PK parameters as long as the body weight of the rat is not the smallest in the species used in the allometric relationship. Why then have rats been widely, almost inevitably, included in allometric scaling? One reason is that the rat is relatively inexpensive and readily available. The other reason may be that investigators rely on the concept "the more, the better", without recognizing the magnitude of improvement in prediction brought by adding more species, the rat, in this discussion. In fairness, however, the role of species weight in allometric prediction has not been recognized until now.

It is apparent and not surprising that the more species used in establishing an allometric relationship, the better the human prediction will be. However, it is costly, time-consuming and not realistic to design allometric experimentation to include five or more species. A practical and economical approach to minimize the number of animal species is to recognize the role of species weight; while still achieving the desired prediction goal. Monte Carlo simulations using different combinations of animal species were performed to select the "best" or optimal combination of animal species. The results showed not surprisingly, that, in general, the more species used, the better becomes prediction performance (Tables 4 and 5). By comparing the percentage errors among different combinations of animal species, the following observations, in terms of prediction performance, could be obtained:

1) The five-species combination is the best having the smallest PE mean, however, it offers no significant improvement over the four-species combinations.

2) Certain three-species combinations, such as mouse/rat, monkey and dog, showed a similar prediction performance to that of the four species combinations; while some three-species combinations, such as rabbit, monkey and dog, showed a significantly worse prediction performance.

3) The two-species combination showed the worst prediction performance, especially for the combinations of mouse and rat, rabbit and monkey, or monkey and dog, which should be forbidden combinations in allometric scaling.

4) Comparison of any combination having more than three species including mouse and rat showed that removal of the rat has little effect on the prediction performance, which is consistent with the previous findings.

5) A three-species combination, mouse/rat, rabbit and dog, or mouse/rat, monkey and dog, may be economically desirable without scarifying the predictability compared to a five-species combination.

However, investigators should keep in mind that all of the above observations are purely mathematical. The differences or similarities between animal species and humans in terms of anatomy, physiology, biochemistry, *etc.* are not considered. These differences or similarities would account for different CVs used the above analyses. Unfortunately, there are still no significant findings, or agreement, for what animal species regarding these differences/similarities should be used to provide the best prediction in humans.

To summarize, an equation has been derived that relates the accuracy of predicted PK parameters in humans to species weight used in allometric scaling and the Monte Carlo simulations provided a quantitative approach to appreciate the prediction variability in a species-dependent way (or more general, body weight-dependent). The awareness that such dependency exists may be helpful in selecting animal species and designing experiments, such as increasing the sample size for species having the greatest effect on the prediction, and reducing or even deleting the species having the smallest effect on the prediction. It is especially noted that rats were found to have no significance in predicting human PK parameters as long as the body weight of rats is not the smallest among the species used in the allometric experimentation. In addition, some economical

combinations of three animal species, mouse/rat, rabbit and dog, or mouse/rat, monkey

and dog, which allow a theoretically reasonable predictability, are proposed.

Acknowledgement

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Footnotes

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Legends to Figures

Figure 1. Fold-range in predicted human clearance as a function of the fold-range in clearance in selected animal species. A hypothetical combination of animal species was considered: mouse (long-dashed line), rat (dotted line), rabbit (short-dashed line) and dog (black line). Note that log-scales are used.

Figure 2. Percentage difference in the predicted human value for clearance ('Box and whisker' plots) when one individual species is removed from a combination of three or more species. The in-set graph illustrates a limited, but the major range of percentage difference. Analysis is based on real data taken from the literature (Table 3).

Table 1. Animal body weights and the "seed values" of CLi used for Monte Carlo simulations. CLi is the clearance in the ith species.

Species	Body weights (Kg)	"Seeds" of CLi (ml/min)
Mouse (m)	0.03	2.2
Rat (r)	0.2	9.0
Rabbit (b)	4	84.9
Monkey (k)	8	142.7
Dog (d)	15	228.7
Human (h)	70	726.0

Table 2. The effects of variability of species on the prediction performance in humans based on Monte Carlo simulations with 30%CV as input random error and 100 trials.

Species combinations[*]	Variables [#]	$CL_{predicted}$ mean	$CL_{predicted}$ median	PE mean
m, r, b, k, d	all	705.0	702.5	20.1
	m	734.9	729.5	6.9
	r	727.2	726.3	1.2
	b	722.8	730.4	8.8
	k	705.9	697.7	12.1
	d	703.4	719.1	13.3
m, r, k, d	all	758.8	758.4	21.8
	m	732.9	718.7	7.0
	r	725.9	725.9	0.01
	k	729.8	741.6	14.1
	d	724.7	727.4	17.1
m, r, d	all	706.8	695.7	34.6
	m	739.8	722.9	8.0
	r	724.3	725.3	2.5
	d	718.5	732.2	29.2

* m: mouse; r: rat; b: rabbit; k: monkey; d: dog

All indicates all animal species whose clearance values were variables. The single letters indicate only that species whose values were variables and the others were constants at the "seed values".

Table 3. The effect of removing one species from the combination of animal species on the prediction in humans based on real data.

Drug	Percent change by removing:			
	Mouse	Rat	Rabbit	Dog
Acivicin[(McGovren, et al., 1988)]	23.2	3.1	NA*	17.5
5-FU[(Khor, et al., 1997)]	-43.	-9.5	NA	691.6
Amphotericin B[(Robbie and Chiou, 1998;Hutchaleelaha, et al., 1997)]	-38.5	-6.2	17.0	5.2
Amsacrine[(Paxton, et al., 1990)]	12.2	-1.0	100.5	-169.1
CI-921[(Paxton, et al., 1990)]	-239.3	-21.1	77.2	0.1
AZT[(Hussey, et al., 1994;Patel, et al., 1990)]	-93.7	-7.0	NA	91.3
Bosentan[(Lave, et al., 1996;Ubeaud, et al., 1995)]	-169.7	0.1	-251.8	3698.0
Candoxatrilat[(Kaye, et al., 1997)]	17.2	0.1	28.7	-89.7
DA-1131[(Kim, et al., 1998a;Kim, et al., 1998b)]	3.8	0.9	-28.4	46.3
Enprofylline[(Tsunekawa, et al., 1992)]	59.2	-1.8	17.0	-206.8
Interferon [(Lave, et al., 1995)]	30.4	-1.8	-10.0	12.5
Meloxicam[(Busch, et al., 1998)]	164.7	12.2	NA	50.7
Moxifloxacin[(Siefert, et al., 1999)]	-11.4	1.4	NA	64.8
Phencyclidine [(Owens, et al., 1987)]	26.2	2.4	NA	-113.5
Propafenone[(Puigdemont, et al., 1991)]	0.5	1.6	-2.6	11.4
Sch34343[(Lin, et al., 1987;Chung, et al., 1985)]	65.8	3.8	-26.6	-33.5
Sildenafil[(Walker, et al., 1999)]	-5.2	-1.5	NA	36.0
Cefotetan[(Sawada, et al., 1984;Komiya, et al., 1981;Matsushita, et al., 1990)]	-7.8	0.5	-27.9	-43.2

Cefmetazole[(Sawada, et al., 1984;Murakawa, et al., 1980)]	-91.4	2.8	-17.9	-0.8
Cefoperazone[(Sawada, et al., 1984)]	-31.8	2.7	-5.8	-147.4
Moxalactam[(Sawada, et al., 1984;Mahmood, 1999)]	-22.6	0.9	-7.1	-0.7
Cefpiramide[(Sawada, et al., 1984;Ohshima, et al., 1991;Mahmood and Sahajwalla, 2002)]	58.7	-0.3	34.7	-422.2
Cefazolin[(Sawada, et al., 1984;Lee, et al., 1980)]	1.1	-0.1	-4.2	-34.7
Erythromycin[(Duthu, 1985)]	-8.0	-0.7	-21.4	-6.2
Oleandomycin[(Duthu, 1985)]	-25.3	-7.1	NA	145.0
rt-PA[(Mordenti, et al., 1991)]	-7.3	-0.3	14.7	-77.8

* NA: Data not available for rabbit

Table 4. Comparison of the prediction performance in humans obtained from different combinations of animal species based on Monte Carlo simulations with 30% CV random error and 100 trials.

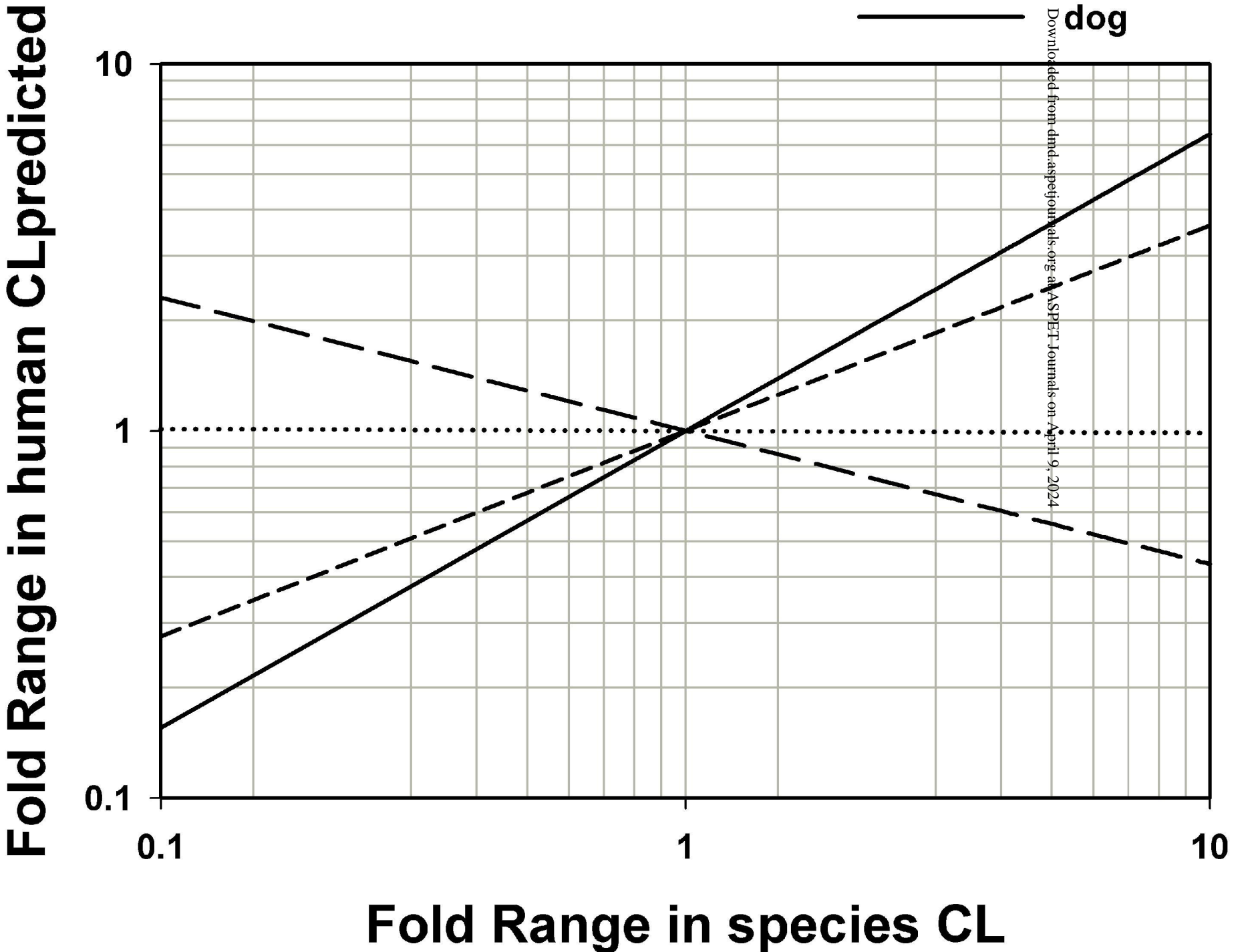| Species	$CL_{predicted}$ mean	$CL_{predicted}$ median	PE mean
m, r, b, k, d	755.2	751.8	25.4
m, r, b, k	797.7	768.9	38.3
m, r, b, d	765.7	718.5	31.6
m, b, k, d	754.6	719.8	23.5
m, r, k, d	760.1	753.5	25.3
r, b, k, d	780.0	702.7	32.4
m, r, b	908.2	741.9	56.6
m, r, k	836.4	769.8	51.1
m, r, d	772.7	729.3	33.8
m, b, k	771.9	706.7	34.8
m, b, d	753.6	749.1	30.6
m, k, d	784.1	732.7	28.1
r, b, k	797.2	739.5	48.0
r, b, d	777.2	769.5	46.1
r, k, d	1826	785.6	35.7
b, k, d	941.9	638.0	98.1
m, r	2052	661.5	445.7
m, b	868.6	787.8	64.6
m, k	804.1	742.9	40.9
m, d	766.6	692.9	41.7
r, b	886.9	726.9	81.9
r, k	810.2	742.0	57.8
r, d	768.0	704.3	45.2
b, k	1758	625.4	501.9
b, d	1161	841.5	133.5
k, d	1601	761.7	250.9

*m: mouse; r: rat; b: rabbit; k: monkey; d: dog

Table 5. Comparison of the prediction performance in humans obtained from different combinations of animal species based on Monte Carlo simulations with 100% CV random error and 100 trials.

Species	$CL_{predicted}$ mean	$CL_{predicted}$ median	PE mean
m, r, b, k, d	957	736	131
m, r, b, k	1200	771	207
m, r, b, d	1145	663	191
m, b, k, d	1162	766	150
m, r, k, d	1082	680	175
r, b, k, d	1706	791	243
m, r, b	3298	810	821
m, r, k	1811	595	413
m, r, d	1983	803	339
m, b, k	1229	632	204
m, b, d	1122	732	152
m, k, d	1231	865	157
r, b, k	2922	864	536
r, b, d	1292	735	215
r, k, d	1831	826	269
b, k, d	9002	558	1987
m, r	6×10^5	547	7×10^5
m, b	2009	833	362
m, k	1908	646	392
m, d	1819	889	282
r, b	13677	907	2463
r, k	2355	944	543
r, d	2067	641	370
b, k	9×10^5	791	2×10^5
b, d	20233	722	5213
k, d	4×10^6	590	3×10^6

*m: mouse; r: rat; b: rabbit; k: monkey; d: dog

Fig. 1

Fig. 2