A General Model for Scaling Basal Metabolic Rate, Glomerular Filtration Rate and Drug Clearance from Birth to Adulthood

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Abstract

A generic quantitative equation for describing the ontogeny of human metabolic processes from infancy to adulthood has broad implications in biology, clinical medicine and drug discovery. In this paper, we infer quantitative knowledge of human ontogeny from a systematic analysis of diverse datasets related to basal metabolic rate (*BMR*), glomerular filtration rate (*GFR*) and drug clearance (*CL*). The datasets contain bodyweight-specific values of the three physiological quantities spanning neonates and adults. Ontogenetic data were either directly taken from the literature or generated from existing models, which universally show biphasic curves of bodyweight scaling on log-log coordinates. Accordingly, a biphasic-allometry equation was proposed and evaluated as a general model using nonlinear regression. The proposed equation consists of two allometric terms in the form of reciprocals that asymptotically determine the overall curvature. Specifically, the biphasic curve is characterized by superlinear (slope >1) and sublinear (slope <1) phases of bodyweight scaling. Phase transition occurs at a critical bodyweight, which could be estimated from fitted model parameters. Overall, the proposed model is versatile in the sense that it fits satisfactorily to all datasets. Moreover, through further derivation and generalization, the model reveals the similarities and differences among ontogenetic processes. In conclusion, the ontogenetic development of important human functions can be modeled by a novel mixed-allometry equation.

1. Introduction

Ontogeny, the developmental history of a living organism, has been considered as one of the major problems in biology (1). Most organisms undergo continuous changes in their size, shape and function during the developmental process. Human ontogeny, a subject of extensive interests and implications (2, 3), is a process that involves growth of body size and maturation of physiological functions. It is generally accepted that body functions do not scale linearly with bodyweight, but with a power-law relation

(i.e. in the form of $Y = aX^b$). This simple allometric equation has been used to describe physiological and pharmacological parameters such as glomerular filtration rate (*GFR*) and drug clearance (*CL*) for neonates, children and adults. However, ontogenetic data usually are not a simple straight line in a double logarithmic plot. In fact, different allometric types have been reported in biological studies, from simple log-log linear scaling with a fixed exponent to more complex scaling patterns with multiple log-log linear phases connected at one or more transitional points (4-6). Although this shifting (or transition) phenomenon has been recognized in metabolic scaling (7, 8), there is a lack of systematic analysis regarding the search for a quantitative model that best describes human ontogenetic data.

The basal metabolic rate (*BMR*), i.e. the rate of energy transformation within the body at rest, is perhaps the most fundamental biological rate. *BMR* is considered as a universal 'pacemaker' for biological processes (6). Therefore, allometric scaling of *BMR* has gained much attention and been hotly debated for over a century. In biology, the discussion has been shifted from whether there is a universal scaling law to how intra- and interspecific scaling vary beyond the '3/4-power' law (5). In medicine, human energy requirements are important considerations in clinical and public-health nutrition (9-13). Thus, the WHO issues sex- and age-specific recommendations on human energy requirements (14). The WHO recommendations consist, for each sex, of 3 bodyweight-based linear equations for estimating *BMR*. The equations have different constant values for separate age groups (0-3 yr, 4-10 yr and 11-18 yr), suggesting that *BMR* varies with bodyweight in a nonlinear manner during the growth period. To date, the inherent nonlinearity in human metabolic scaling remains to be addressed by a unified quantitative model.

Glomerular filtration rate (*GFR*) is an important parameter of renal function. In pharmacology and toxicology, *GFR* determines the renal elimination capacity for xenobiotics and environmental toxicants. The information of *GFR* is particularly useful for dosing renally cleared drugs, especially for pediatric patients, because dosing information for children is often limited by ethical and clinical considerations in clinical trials. Accordingly, attempts have been made to predict pediatric *GFR* values from adult's value using quantitative models. Existing data show that *GFR* undergoes continuous change after birth and reaches adult's level in the early childhood (15, 16). Several models have been proposed to model the growth and maturation of *GFR*, with a focus on predicting *GFR* for neonates or children from adults (15-17). The previous models have different levels of complexity. The simplest model has the form of simple allometry, where *GFR* scales with bodyweight in a single power-law function, with

either fixed or variable exponents. More complicated models include both age and bodyweight as the input variables (15, 16). Studies have shown that all models encounter the same uncertainty problem in prospective prediction (17). Since available data reveal significant curvature on the log-*GFR* vs. log-bodyweight plot (15), in this paper, we proceed to quantify this curvature using a mixed-allometry equation.

Drug clearance (*CL*) is an essential pharmacokinetic parameter that offers direct estimation of drug dose. The magnitude of *CL* is determined by body size and the function of drug elimination organs (i.e. the kidneys and liver). Therefore, *CL* values are subjected to ontogenetic changes of renal and hepatic functions. The *CL* values of many drugs have been compiled from both population pharmacokinetic studies and physiologically-based pharmacokinetic (PBPK) modeling (18-23). Besides, several growth and maturation models have been evaluated for their predictive performance (24-27). Overall, the previous findings are highlighted as follows: First, *CL* scales with bodyweight raised to a power that is variable with age or body weight (18, 20, 28). Second, more profound changes were observed in earlier life than in later life (e.g. neonates to toddlers vs. toddlers to adolescents or adults) (18, 20). Finally, a good ontogenetic model usually takes age and bodyweight into consideration (21, 29-31). In fact, the same features apply for *GFR*. However, *CL* is highly drug-specific and heterogenous, rendering generalization difficult, if not impossible. In this paper, following the analysis of *BMR* and *GFR* data, the proposed mixed-allometry model was extended to diverse *CL* datasets.

In summary, a mixed-allometric equation is proposed here to model the ontogenetic data of *BMR*, *GFR* and drug *CL*. The equation consists of two allometric terms in their reciprocals, where bodyweight is the only independent variable. All the data were directly retrieved or generated from existing ontogenetic models. The datasets thus represent the mean tendency of various human functions. Accordingly, the overall goal is not to predict the unknown, but to infer common ontogenetic features from systematic analysis of diverse datasets. The proposed mixed-allometry equation allows for quantitative description of the universal phase-transition phenomenon in the development of common physiological and metabolic functions. Such phase transformation in growing humans might be the result of the trade-off between two limiting forces—growth and maturation.

2. Methods

2.1 *BMR* data

The basal metabolic rate (*BMR*) data, in kcal/day, for males and females from birth to adulthood were generated from the age- and sex-specific equations, according to the WHO recommendations on human energy requirements (14). The recommendations divide the preadult population into three age groups, where male and female individuals are separately considered. All the equations are linear functions of bodyweight (*W*, kg), which have a general form of $BMR = aW + b$, where, for males, (a, b) = (59.512, –30.4), (22.706, 504.3), and (17.686, 658.2) for ages 0-3 yr, 4-10 yr and 11-18 yr, respectively; for females, (a, b) = (58.317, –31.1), (20.315, 485.9), and (13.384, 692.6) for ages 0-3 yr, 4-10 yr and 11-18 yr, respectively. The *BMR* data were generated by first predetermining a group of subjects with ages of 0 to 18 yr, at an interval of 0.25-1 yr. Then, the corresponding age- and sex-specific median bodyweights were adopted from the WHO report on energy and protein requirements (32). The bodyweight range is 3.3-62.6 kg and 3.2 to 58 kg, for males and females, respectively. Finally, *BMR* values were obtained by plugging bodyweight into the WHO equations.

2.2 *GFR* data

The glomerular filtration rate (*GFR*) data, in mL/min, were generated using the general equation proposed by Anderson et al. (16) for hypothetical human subjects.

$$P = P_{adult} \cdot F_{age} \cdot F_{size} \qquad \textbf{[1]}$$

Where here P is *GFR* and P_{adult} is the adult *GFR* value (136 mL/min (15)); F_{age} is the age function (maturation function), and F_{size} is the body size function (allometric function):

$$F_{age} = \frac{PMA^{\theta}}{(TM_{50})^{\theta} + PMA^{\theta}} \qquad \textbf{[2]}$$

$$F_{size} = \left(\frac{W}{W_{adult}}\right)^{\mu} \qquad \textbf{[3]}$$

The variables and parameters are defined as: *PMA*, postmenstrual age (weeks); θ, the Hill coefficient; TM_{50}, maturation half-life; *W*, bodyweight of the individual; W_{adult}, adult bodyweight (70 kg); μ, allometric, bodyweight exponent.

A set of *GFR* vs. *W* data was generated using Equations 1-3. The *PMA* data was transformed from pre-determined postnatal ages (*PNA*, 0.049 to 240 months), assuming a gestational age of 40 weeks (16). The age-specific body weight, ranging from 3.17 to 70 kg, was taken from the literature (15). The parameter values used for generating the *GFR* dataset are from the literature (16): $\theta = 3.4$, $TM_{50} = 47.7$ weeks, $\mu = 0.75$.

2.3 Drug *CL* data

The first *CL* datasets were retrieved from Björkman's work (19) on physiologically based pharmacokinetic (PBPK) modeling of two model drugs, theophylline and midazolam. The *CL* and bodyweight values of both sexes are directly available for neonates, children ages 0.5, 1, 2, 5, 10 and 15 yr, and adults. The total *CL* values were estimated from PBPK-modeled hepatic *CL*, and/or renal *CL* (if applicable). These *CL* datasets were evaluated in the initial modeling trial for drug *CL*.

Next, extended modeling was applied to *CL* datasets of 17 drugs. The *CL* values were generated using the same general models of Anderson et al. (30, 31) described in Equation 1 (where P and P_{adult} are replaced by CL and CL_{adult}). All the drug-specific parameters in the age function (Equation 2) and size function (Equation 3) were taken from the literature (31). The age and corresponding bodyweight ranges are the same as those for the *GFR* data described above.

2.4 Modeling and simulation

In this study, the following mixed-power equation was proposed to model the datasets mentioned above.

$$\frac{1}{P} = \frac{1}{A \cdot W^{\alpha}} + \frac{1}{B \cdot W^{\beta}} \qquad \textbf{[4]}$$

or

$$P = \left(\frac{1}{A \cdot W^{\alpha}} + \frac{1}{B \cdot W^{\beta}}\right)^{-1} \qquad \textbf{[5]}$$

, where P is the metabolic or physiological quantity of interest, viz. *BMR*, *GFR* or drug *CL*. The equation consists of two allometric coefficients ($0<A<B$) and two allometric exponents ($\alpha>\beta>0$). For model comparison, the simple allometric model was also included for analysis:

$$P = GW^{\gamma} \qquad \textbf{[6]}$$

, where G and γ are the allometric coefficient and exponent, respectively.

Model fitting was performed using Mathematica® (Wolfram). The model parameters were obtained by fitting the model equations to all available datasets (with $1/y^2$ weighting) using the nonlinear regression functions of Mathematica®. The comparison of models was based on the corrected Akaike's Information Criterion, AIC_c (33).

A simulation was conducted to characterize the mixed-power function. The following hypothetical parameters were used: A = 0.1, B = 10, α= 2.5, β= 0.5. By plugging the

parameter values into Equation 4, a set of hypothetical (P, W) data was generated for a simulated body-weight range of 3-70 kg (at a 1-kg interval).

3. Results

3.1 Characteristics of the biphasic model

In this study, we propose a mixed-power function (the biphasic allometry model; Equation 4) to scale human *BMR*, *GFR* and drug *CL* from neonates to adults. In fact, this study was inspired by allometric scaling of whole-plant respiration from small seedlings to giant trees (7). Equation 4 states that the reciprocal of a physiological or metabolic parameter (P) is equal to the sum of reciprocals of each of two individual power-law bodyweight functions (i.e. allometric functions). Here, we first present the key features of the model using simulation ($\alpha = 2.5$, $\beta = 0.5$, $A = 0.1$, $B = 10$). Figure 1A shows the simulated data and two asymptotic lines on log-log coordinates. Let P_1 and P_2 be the first and second asymptotic functions, respectively, then the asymptotic bodyweight functions are:

$$P_1 = AW^{\alpha} \quad \textbf{[7]}$$

$$P_2 = BW^{\beta} \quad \textbf{[8]}$$

, and Equation 4 can be expressed as:

$$\frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2} \quad \textbf{[9]}$$

When $P_1 \ll P_2$, $P \approx P_1$, which is the first asymptote near the low bodyweight region of $W \ll (B/A)^{1/(\alpha-\beta)}$ (by solving the inequality relationship). In contrast, when $P_1 \gg P_2$, $P \approx P_2$, and the second asymptote occurs at $W \gg (B/A)^{1/(\alpha-\beta)}$. Thus, the characteristic bodyweight ($\widetilde{w}$) is revealed as:

$$\widetilde{w} = (B/A)^{1/(\alpha-\beta)} \quad \textbf{[10]}$$

Mathematically, $\widetilde{w}$ is exactly the bodyweight at which the two asymptotic lines intersect ($P_1 = P_2$ and $A\widetilde{w}^{\alpha} = B\widetilde{w}^{\beta}$). Biologically, it is the critical bodyweight at which ontogeny undergoes transition from one phase to another phase (i.e. the phase-transition bodyweight). By taking the derivative of Equation 4, the following expression for the slope (S) of the biphasic curve is obtained:

$$S = \frac{d\log P}{d\log W} = \beta\left(\frac{P_1}{P_1+P_2}\right) + \alpha\left(\frac{P_2}{P_1+P_2}\right) \quad \textbf{[11]}$$

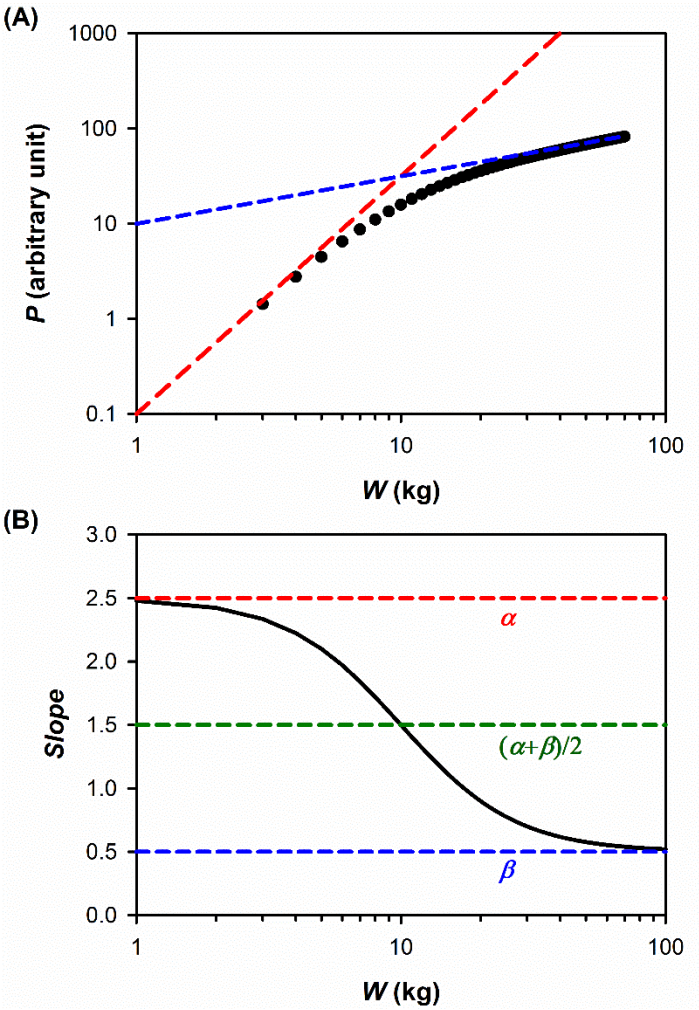

Figure 1. Characteristics of the mixed-power function. (A) Simulated data of physiological quantity (P) vs. bodyweight (W). The lines represent the two asymptotic power-law functions with respective y-intercepts (i.e., 0.1 and 10, at $W = 1$ kg) and an interception point which defines the critical point of phase transition (at $W = 10$ kg). (B) Slope as a function of bodyweight. The plot highlights the two allometric exponents (α and β) and the corresponding mean value at the point of phase transition.

Therefore, according to Equation 11, the slope of the biphasic model can be estimated at any given bodyweight. Figure 1B shows that the slope decreases with increasing bodyweight. The slope curve is indeed flanked by two asymptotic lines: slope ≈ α, at the low body weight region where $W \ll \tilde{w}$ or when $P_1 \ll P_2$; whereas slope ≈ β, at $W \gg \tilde{w}$ or when $P_1 \gg P_2$. Note that the characteristic slope (S^*) at the phase-transition bodyweight is exactly the mean of the two asymptotic exponents, since at $W = \tilde{w}$, $P_1 = P_2$, Equation 11 is reduced to:

$$S^* = (\alpha + \beta)/2 \qquad \textbf{[12]}$$

In sum, Figure 1 captures the essence of the proposed mixed-allometry model by revealing all the parameter values used for the simulation: two asymptotic exponents of 2.5 and 0.5 (exactly α and β), two asymptotic allometric coefficients (A = 0.1, B = 10), a critical bodyweight of 10 kg (i.e. $\widetilde{w} = (B/A)^{1/(\alpha-\beta)} = (10/0.1)^{1/2}$) where the slope of the biphasic curve at this critical point is exactly the mean of the two exponents (i.e. 1.5).

3.2 Scaling basal metabolic rate

In this study, various neonate-to-adult datasets were acquired to test the generalizability of the biphasic allometry model. The data will be presented and discussed in the following order: *BMR*, *GFR* and *CL*. The *BMR* data were generated using the WHO equations described in 2.1. Figure 2A shows biphasic curves in a log-log plot for the male and female *BMR*. The mixed-power equation offers the best fits and clearly discriminates from the simple allometry (*SA*) equation (AIC_c: −149 vs. >190; Table 1). The slope of the biphasic curve varies with bodyweight, with two asymptotic allometric exponents at extreme body sizes (Figure 2B). The first exponent is >1 (viz. 1.72 and 1.62), whereas the second exponent is <1 (viz. 0.36 and 0.22), with the transition occurring at 7.13 kg and 9.32 kg (and mean slope of 1.04 and 0.92), for males and females, respectively (Table 1).

Table 1. Model fitting results for *BMR* and *GFR**

	A	α	B	β	$\widetilde{w}^{\dagger}$	S^*	AIC_c (*BA*)	AIC_c (*SA*)
BMR								
M	28.2±4.5	1.72±0.17	403±119	0.36±0.07	7.13	1.04	-149	192
F	28.1±3.8	1.62±0.13	645±211	0.21±0.08	9.32	0.92	-149	199
GFR	0.48±0.08	2.15±0.16	11.9±3.3	0.57±0.07	7.70	1.36	-129	65.7

* Fitted parameters are mean±SE; male (*M*); female (*F*); bodyweight at phase transition (kg), $\widetilde{w} = (B/A)^{1/(\alpha-\beta)}$; the slope at transition, $S^* = (\alpha+\beta)/2$; corrected Akaike's Information Criterion (AIC_c); biphasic allometry model (*BA*); simple allometry model (*SA*).

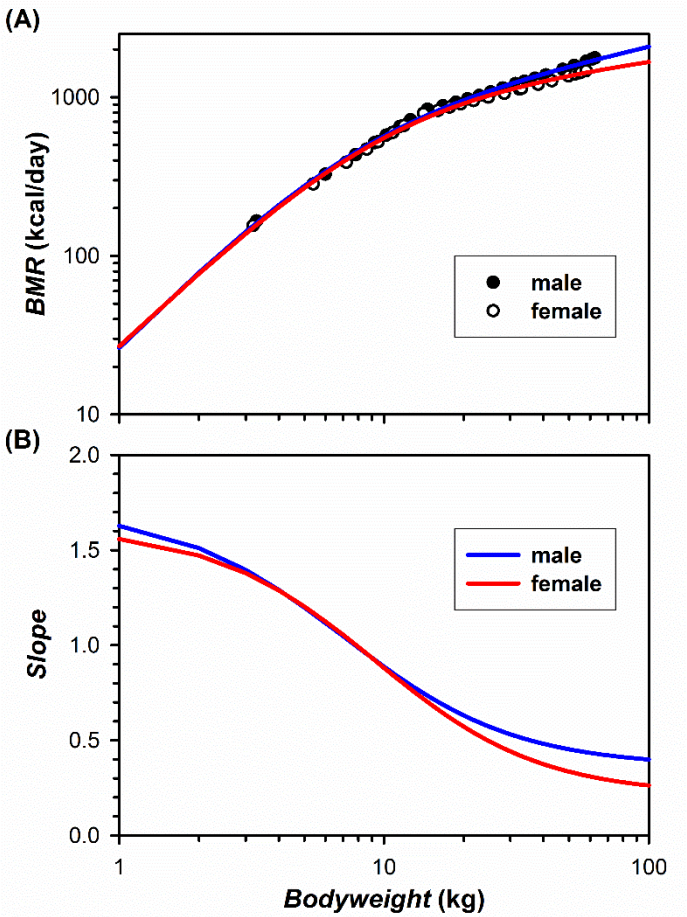

Figure 2. Ontogenetic scaling of *BMR*. (A) Continuous *BMR* vs. bodyweight data generated from WHO-recommended, age-specific equations for males and females. Nonlinear regression was used to fit the data to the mixed-power model (Equation 4; lines). (B) The corresponding bodyweight-dependent slope estimated from Equation 11.

3.3. Scaling renal function

Ontogenetic scaling of renal function has great implications in medicine. Particularly, accurate estimation of *GFR* for pediatric patients helps better predict drug dosages. We first generated bodyweight-vs.-*GFR* data according to Equations 1-3 (16). The data were then fitted to the mixed-power equation. Figure 3 again shows a biphasic curve consisting of a superlinear scaling phase (slope >1) and a sublinear scaling phase (slope <1). Besides, the corresponding slope of the biphasic curve decreases with increasing bodyweight. The two asymptotic allometric exponents are 2.15 and 0.57, respectively; and the phase transition occurs at 7.7 kg (Table 1). The slope at the phase-transition bodyweight is 1.36 (Table 1).

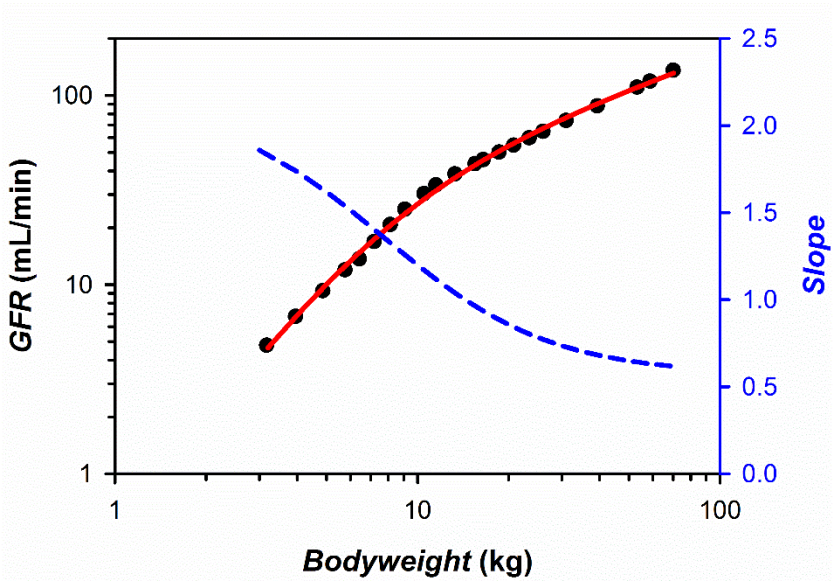

Figure 3. Ontogenetic scaling of *GFR*. Equations 1-3 were used to generate mean *GFR* values as input datapoints (symbol). The solid line represents the nonlinear-regression best-fit for the mixed-power function (Equation 4). The dashed line is weight-dependent slope of the fitted curve (Equation 11).

3.4 Scaling drug clearance

The acquisition of accurate *CL* information is critical in drug development and in clinical use of drugs. The *CL* data for children are often unattainable, because of the limitation of conducting clinical trials in very young subjects. Thus, various prediction models have been proposed to draw quantitative relationship between *CL* and age and/or bodyweight. Our analysis divides into two parts. First, the proposed model was fitted to the ontogenetic *CL* data taken directly from the literature (19). Figure 4 shows that the datapoints are scarcely distributed in the bodyweight range spanning neonates and adults. Nevertheless, compared with simple allometry (based on AIC_c) the biphasic allometry model provides the best fits. (Table 2 and Table 3). Again, the features of the model (i.e. 2 phases with defined phase transition) were clearly illustrated in this analysis. The two drugs have high first-phase exponents (ca. 2.6 to 3) and comparable, but less than unity, second-phase exponents (ca. 0.5 to 0.6). The results also show superlinear allometry in the early childhood and sublinear allometry in the later life. The transition occurs at 8.6 to 9.5 kg, with the corresponding ontogenetic slopes (S^*) being close to 1.6 and 1.8, for theophylline and midazolam, respectively (Tables 2 & 3).

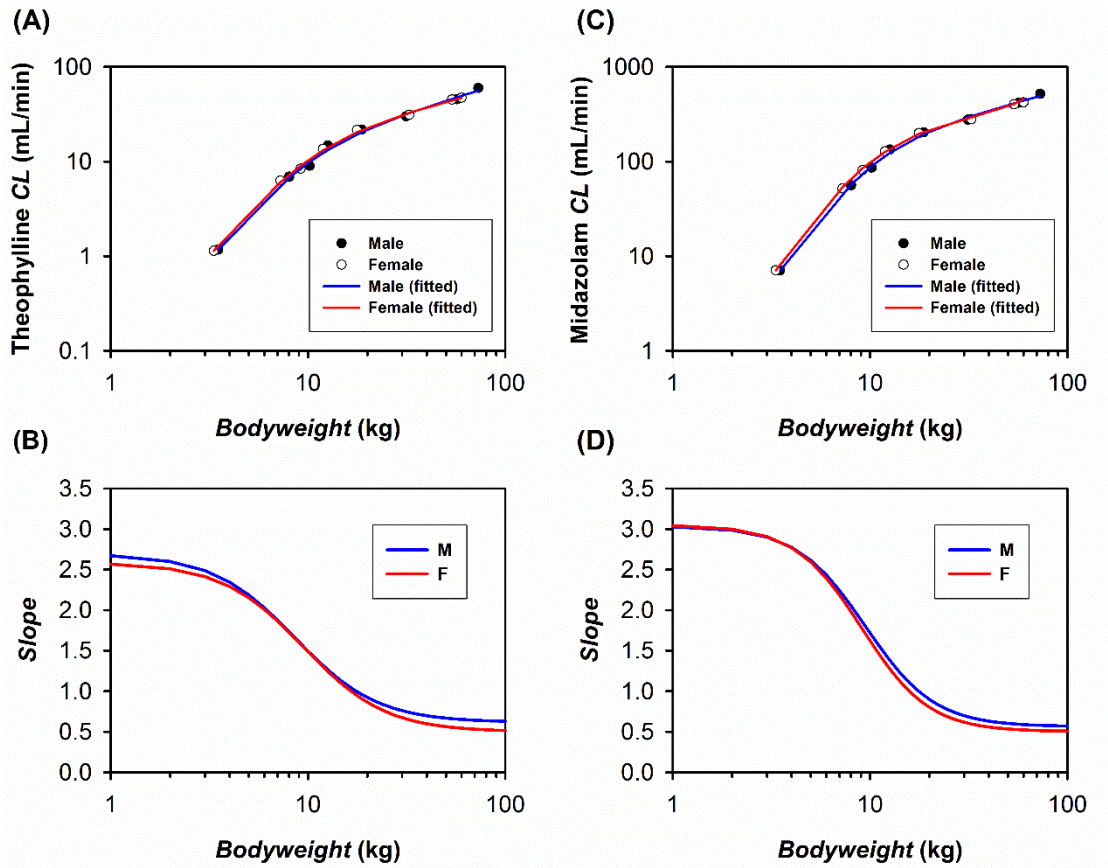

Figure 4. Ontogenetic scaling of drug clearance. An initial trial on sparse data of theophylline *CL* (A and B) and midazolam *CL* (C and D). Symbols are PBPK-modeled *CL* values directly taken from the literature (19). Lines are the best nonlinear-regression fits and estimation for the biphasic model.

Secondly, the analysis was extended to model-generated *CL* for 17 drugs. Figure 5 shows all *CL* data and fitting lines. The results demonstrate unequivocally that the biphasic allometry model prevails. Table 4 summarizes all fitted parameters. The allometric coefficients (*A* & *B*) are highly variable among drugs, because the absolute *CL* values span ~4 orders of magnitude. However, the allometric exponents have a narrow distribution: the first exponent (α) ranges from 1.62 to 3.81 (mean = 2.46 and CV of 27.1%), whereas the second exponent (β) are in the range of 0.25 to 0.72 (mean = 0.52, CV = 28%). The mean weight transition is 10.2 ± 5.2 kg (range = 2.9 to 18 kg, CV = 51%). The mean transitional slope (S^*) is 1.49 ± 0.35 (range = 1.0 to 2.3; CV = 23.7%). Together, biphasic ontogenetic scaling with superlinear-to-sublinear phase transition appears to be universal.

Table 2. Model fitting results for theophylline clearance*

Model	Model equation	Fitted parameters	$\tilde{w}$ and S^*	AIC_c
Biphasic model (biphasic allometry)	$CL = \left(\frac{1}{AW^{\alpha}} + \frac{1}{BW^{\beta}}\right)^{-1}$	A: 0.05±0.02 (M) 0.06±0.02 (F) α: 2.70±0.39 (M) 2.59±0.22 (F) B: 4.03±2.69 (M) 6.18±3.16 (F) β: 0.62±0.16 (M) 0.50±0.13 (F)	$\tilde{w}$: 8.6 kg (M) 9.5 kg (F) S^*: 1.66 (M) 1.55 (F)	−3.95 (M) −10.7 (F)
Simple allometry	$CL = GW^{\gamma}$	G: 1.50±0.33 (M) 1.68±0.42 (F) γ: 0.86±0.06 (M) 0.82±0.06 (F)	NA	24.5 (M) 24.9 (F)

* Fitted parameters are mean±SE; male (*M*); female (*F*); body weight at phase transition, $\tilde{w} = (B/A)^{1/(\alpha-\beta)}$; the slope at transition, $S^* = (\alpha + \beta)/2$; corrected Akaike's Information Criterion (AIC_c).

Table 3. Model fitting results for midazolam clearance*

Model	Model equation	Fitted parameters	$\tilde{w}$ and S^*	AIC_c
Biphasic model (biphasic allometry)	$CL = \left(\frac{1}{AW^{\alpha}} + \frac{1}{BW^{\beta}}\right)^{-1}$	A: 0.17±0.05 (M) 0.19±0.04 (F) α: 3.04±0.21 (M) 3.05±0.14 (F) B: 44.3±17.1 (M) 53.8±14.8 (F) β: 0.56±0.10 (M) 0.50±0.07 (F)	9.5 kg (M) 9.1 kg (F) S^*: 1.80 (M) 1.78 (F)	−9.27 (M) −15.5 (F)
Simple allometry	$CL = GW^{\gamma}$	G: 14.9±3.6 (M) 15.9±4.3 (F) γ: 0.83±0.06 (M) 0.81±0.07 (F)	NA	61.5 (M) 61.8 (F)

* Fitted parameters are mean±SE; male (*M*); female (*F*); body weight at phase transition, $\tilde{w} = (B/A)^{1/(\alpha-\beta)}$; the slope at transition, $S^* = (\alpha + \beta)/2$; corrected Akaike's Information Criterion (AIC_c).

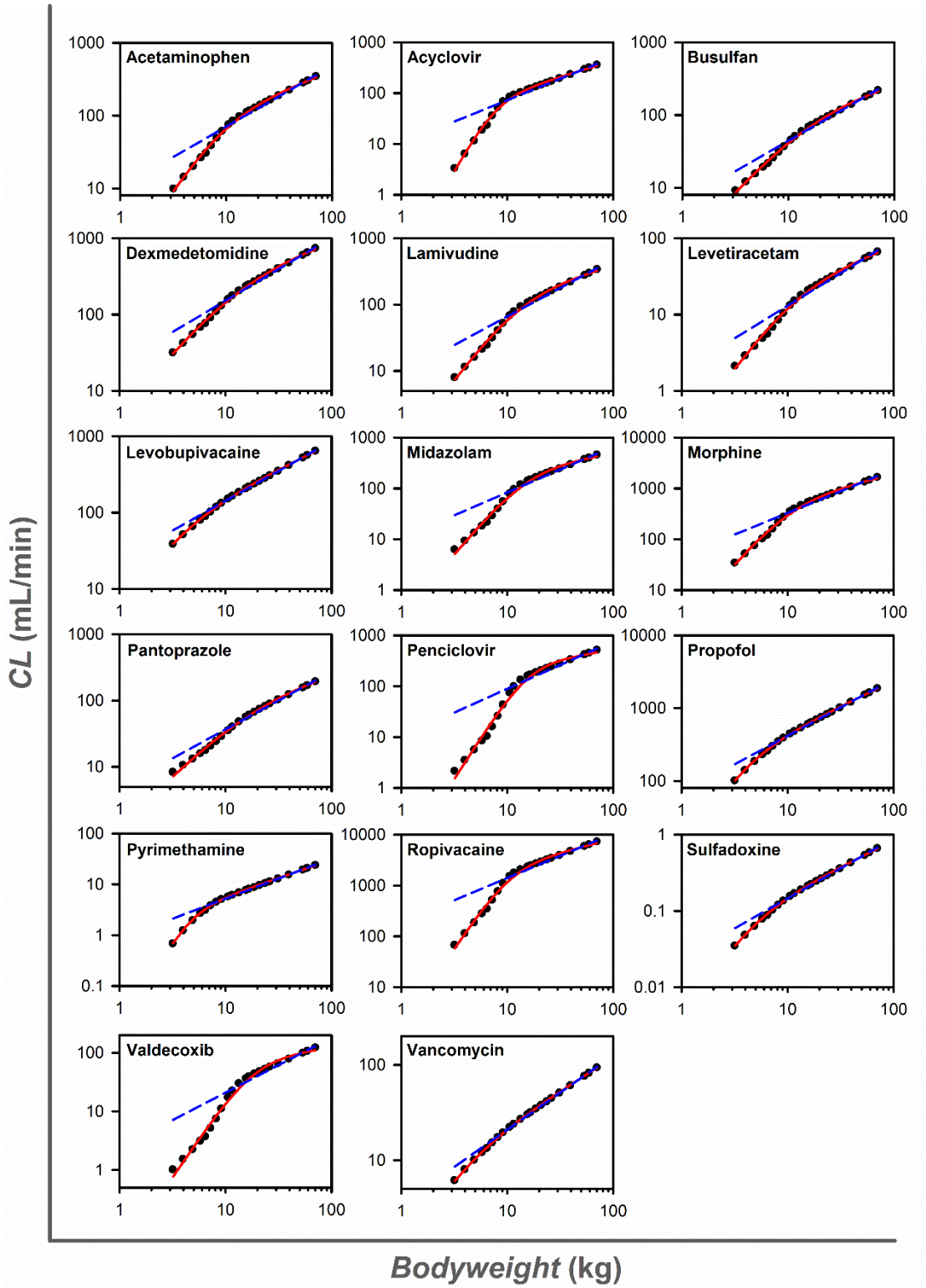

Figure 5. Ontogenetic scaling of *CL* (extended analysis of 17 drugs). *CL* values were generated according to the sigmoidal maturation model described in Method. Each dataset (symbol) was fitted to the biphasic model (solid line) and to simple allometry (dashed line).

Table 4. Fitted and estimated parameters for drug *CL* datasets

Drug	A	α	B	β	$\tilde{w}$	S^*
Acetaminophen	0.776	2.27	34.5	0.54	8.97	1.41
Acyclovir	0.042	3.74	23.5	0.63	7.68	2.19
Busulfan	1.44	1.66	41.1	0.42	14.8	1.04
Dexmedetomidine	5.05	1.71	111	0.46	12.1	1.09
Lamivudine	0.652	2.16	54.8	0.43	12.9	1.30
Levetiracetam	0.227	1.98	8.62	0.49	11.5	1.24
Levobupivacaine	6.42	2.15	35.0	0.69	3.19	1.42
Midazolam	0.306	2.46	102	0.35	15.6	1.41
Morphine	2.12	2.43	193	0.50	10.4	1.47
Pantoprazole	1.25	1.62	32.7	0.46	16.4	1.04
Penciclovir	0.035	3.26	117	0.33	15.8	1.80
Propofol	10.4	2.52	94.6	0.70	3.37	1.61
Pyrimethamine	0.011	3.81	1.12	0.72	4.41	2.27
Ropivacaine	1.65	3.10	795	0.51	10.8	1.81
Sulfadoxine	0.004	2.31	0.036	0.68	3.75	1.50
Valdecoxib	0.035	2.67	40.3	0.25	18.2	1.46
Vancomycin	1.26	2.01	5.05	0.69	2.86	1.35
Mean		2.46		0.52	10.2	1.49
SD		0.67		0.15	5.2	0.35
CV (%)		27.1		28.0	51.0	23.7

$\tilde{w} = (\mathrm{B}/\mathrm{A})^{1/(\alpha-\beta)}$; $S^* = (\alpha+\beta)/2$

3.5 Unifying all the datasets

In this study, human ontogenetic datasets vary significantly, with the exact values spanning >4 orders of magnitude; however, our initial analysis reveals their common features. To further elucidate the similarities and differences among datasets, a dimensionless analysis was conducted.

First, let $X = W/\tilde{w}$, where W is the exact bodyweight, and $\tilde{w}$ is the critical bodyweight (i.e. at phase transition). Thus, X is the dimensionless, fractional number associated with bodyweight. Similarly, let $Y = P/\tilde{p}$, where P is physiological parameters such as *BMR* and *GFR*, or *CL*, and $\tilde{p}$ is the corresponding P value at W =$\tilde{w}$, and according to Equation 4,

$$\frac{1}{\tilde{p}} = \frac{1}{A\tilde{w}^{\alpha}} + \frac{1}{B\tilde{w}^{\beta}} \qquad \textbf{[13]}$$

Accordingly, Y is defined as the fractional value of *BMR*, *GFR* or *CL* (relative to their critical value at phase transition). Then, the original Equation 4 can be expressed and rearranged as follows:

$$\frac{1}{\tilde{p}Y} = \frac{1}{A(\tilde{w}X)^{\alpha}} + \frac{1}{B(\tilde{w}X)^{\beta}} \qquad \textbf{[14]}$$

$$\frac{1}{Y} = \tilde{p}\left(\frac{1}{A(\tilde{w}X)^{\alpha}} + \frac{1}{B(\tilde{w}X)^{\beta}}\right) \qquad \textbf{[15]}$$

By substituting $\tilde{p}$ in the last equation from Equation 13, and after further rearrangement, the final equation is obtained:

$$\frac{1}{Y} = f_1\left(\frac{1}{X^{\alpha}}\right) + f_2\left(\frac{1}{X^{\beta}}\right) \qquad \textbf{[16]}$$

Where

$$f_1 = \frac{B\tilde{w}^{\beta}}{A\tilde{w}^{\alpha}+B\tilde{w}^{\beta}} = \frac{1}{2} \qquad \textbf{[17]}$$

$$f_2 = \frac{A\tilde{w}^{\alpha}}{A\tilde{w}^{\alpha}+B\tilde{w}^{\beta}} = \frac{1}{2} \qquad \textbf{[18]}$$

According to Equation 16, all unitless data will converge at (X, Y) = (1, 1), which is also the transition point of the biphasic curve. The equation indicates that metabolic parameters scale with bodyweight superlinearly at X<1 (i.e. bodyweight < critical weight) and sublinearly at X>1 (i.e. body weight > critical weight).

To compare all datasets in the same plot, the original data were further converted to unitless numbers, according to the definition of X and Y. Figure 6 compares all the datasets, where *CL* data are deliberately shown in dim color to contrast and highlight the *BMR* and *GFR* data. This composite plot clearly divides the biphasic curves into two segments at the reference point of (X, Y) = (1, 1), which was considered as a maturation point. The two variables are fractions or multiples of the two characteristic values ($\tilde{w}$ and $\tilde{p}$). The first segment is within the region where both X and Y are below the unity, whereas the second segment locates at (X, Y) above unity. All the data in the first region show steeper slopes than those in the second region. Notably, the segments are not evenly distributed. For example, some *CL* datasets show longer first segment, while the others show the opposite. The *BMR* and *GFR* datasets, however, have universally shorter first-portion than second-portion. The segment length may manifest the maturation rate of the physiological and metabolic parameters. In fact, large critical weight leads to longer first-phase and shorter second-phase. Apparently, the elimination of some drugs takes a longer time to reach the maturation point. As shown in Table 4, the mean maturation rate (critical weight) is about 10 kg; however, some drugs exhibit maturation of *CL* at W >10 kg. In contrast, *BMR* and *GFR* mature almost at the same

pace (i.e. showing comparable starting points and similar first-segment length in Figure 6) with critical bodyweights of 7 to 9 kg (Table 1). Another important observation from Figure 6 is that the lines of *BMR* locates at the extreme boundaries of both regions. Thus, the maturation of *BMR* seems to have the lowest exponents in both early and later childhood. This finding suggests that *BMR* sets the basal maturation process. Interestingly, the biphasic curve of *GFR* locates about the center of the grey regions composed of *CL* data, which coincides with the fact that the exponent values for *GFR* data ($\alpha = 2.15$, $\beta = 0.57$, Table 1) are very close to the mean exponent values of all the *CL* data ($\alpha = 2.46$, $\beta = 0.52$, Table 4).

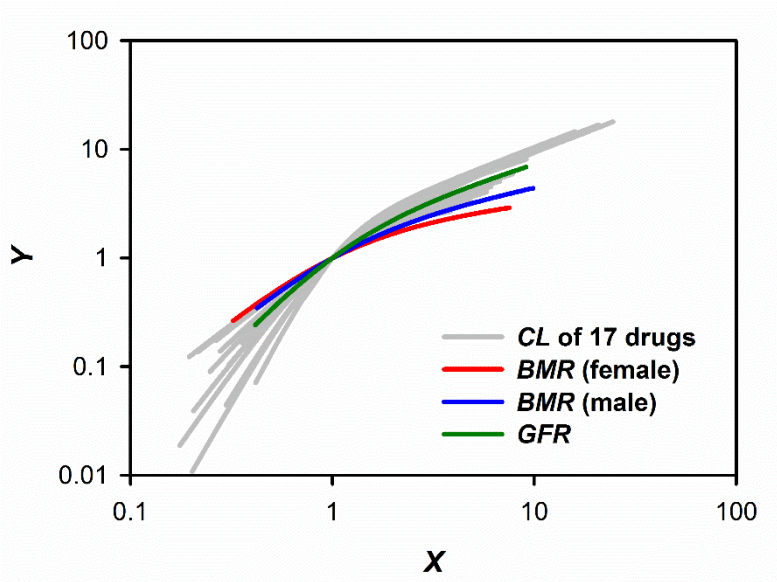

Figure 6. Finding similarities and differences in ontogeny among datasets using dimensionless analysis. The raw *BMR*, *GFR* and *CL* data were transformed into dimensionless variables, *X* (fractional *W*) and *Y* (fractional *P*) according to the definitions of *X* and *Y* mentioned in the text. All transformed unitless data merges at (*X*, *Y*) = (1, 1), at which the scaling curve universally divides into two phases whose slopes and lengths, however, are highly data-specific.

4. Discussion

The long-held belief that body functions develop at distinct pace in different stages of human development is well supported by extensive empirical evidence. For example, a study dated back to 1949 has shown that renal function matures with the most rapid rate in the first 6 months, followed by slower rates to reach adult values around the second year of life (34). Numerous empirical models have been proposed to scale the ontogenetic processes of body functions. These quantitative equations are frequently developed for practical considerations, e.g., estimating children's values. The equations

are usually data-specific and age-categorized. Most equations contain bodyweight as an input variable; meanwhile, age was often included as an additional variable. The equations are either separate, discontinuous linear equations with cut-points at certain age thresholds, or continuous nonlinear equations integrated with age and bodyweight terms. Since body sizes and organ functions evolve simultaneously with age, here we hypothesize that ontogenetic scaling of human functions can be modeled by bodyweight-based equations.

The present study shows that a mixed-allometry equation with bodyweight as the only independent variable successfully models diverse ontogenetic datasets, including those for *BMR*, *GFR* and drug *CL*. Our systematic quantitative analysis leads to 3 major findings. First, a mixed-power allometric equation is a generic equation for describing the development of important human functions from birth to adulthood. Second, all the ontogenetic processes undergo continuous, dynamical changes with a clear phase transition occurring at a critical point. Third, the entire process is characterized by two limiting allometric conditions, which will be further elaborated below.

A previous study has shown that brain's metabolic requirement starts to accelerate after the first 6-month of life and reaches a lifetime peak at about 5 years of age (2). During this particular period, the increasing demand of energy in human brain development was compensated by slow rate of body growth (2). Our analysis seems to coincide with this finding, given that biphasic scaling relations described here shift at bodyweights of 7-18 kg (corresponding to 0.5 to 5 years of age). Since other important organs, such as the liver and the kidneys, may develop similar ontogenetic dynamics in energy demands, the biphasic ontogeny may be associated with the trade-off between maturation (functional development) and growth (body-size development). In the first phase of development, high blood-perfusion organs (e.g., brain, liver, kidney) take up more metabolic substrate (e.g., glucose) to allow fast development of organ functions (fast maturation), which results in less energy available for the building of body mass (slow growth). Therefore, this phase is characterized by accelerated energy needs for the maturation of vital organs, leading to the superlinear bodyweight scaling relations (exponent >1). In the second phase, the metabolic demands for the matured organs start to decrease from the peak, which allows reshuffling of energy to other organs, e.g. muscle. Together, energy re-allocation between high and low energy-demanding organs may attribute to biphasic ontogeny. This view is consistent with the general model of West et al. (35) which suggests that the growth of body size is limited by the capacity of resource allocation networks.

We therefore argue that biphasic ontogeny is governed by two extreme allometric conditions: one is maturation-dominant (maturation without growth), the other is growth-dominant (growth without maturation) — i.e. the two hypothetical states of purely maturation without the influence of growth and vice versa. They reflect the intrinsic difference in energy consumption between the two major events of human development. Each of the two extreme states is represented by a single allometric function of bodyweight raised to a constant power (α or β). The magnitude of the two exponents shape the entire curve: for example, higher α together with lower β produces greater curvature and more obvious phase transitions, as indicated in the modeling of the *CL* values for 17 drugs (Table 4 and Figure 5). Moreover, the biphasic model shows that the slope of the scaling curve continuously changes during the developmental period, which agrees with previous observations (18, 20, 28). Nevertheless, our biphasic model offers a mechanistic understanding of the change.

Besides the common features mentioned above, the present study also highlights the differences among all 3 types of functional data. Our analysis shows that *BMR* scales with minimal characteristic exponents (Table 1 and Figure 6), whereas the scaling of *CL* is highly drug-specific, with the highest exponent value of >3.8 (Table 4 and Figure 6). The disparities may be explained by the fact that *BMR* is measured at a completely resting state of healthy individuals. However, the data of *GFR* and *CL* were usually measured in less restricted or even stressed patients (e.g. non-resting or disease states or under the influence of drugs).

Finally, some caveats and future perspectives are noted here. As mentioned initially, the datasets are not from direct measurement, but are mean values generated from existing models. Therefore, the implications of this study, particularly in clinical decision making, remains to be determined. Nevertheless, the current findings may be applied in future studies of population pharmacokinetics and PBPK modeling. Moreover, this paper may inspire future attempts in finding a theoretical framework and derivation of the equation based on first principles.

5. Conclusion

In this paper, a general equation is proposed to model the ontogeny of diverse human functions, including *BMR*, *GFR* and drug *CL*. The equation (Equation 4) is expressed in reciprocal terms of mixed allometric functions where bodyweight is the only independent variable. All the ontogenetic curves are biphasic with a transitional bodyweight on log-log coordinates. The biphasic curvature is determined by two asymptotic allometric functions, representing the maturation and growth functions,

respectively. The first phase occurs when bodyweight is below the critical bodyweight, which is universally characterized by much steeper slopes (superlinear scaling with slope >1). The second phase, however, exhibits sublinear scaling (slope <1). The proposed equation can be further expressed in a unitless form, where the relationship between the fractional physiological/metabolic quantity (Y) and the fractional bodyweight (X) can be described by a general equation with two allometric exponents, α and β.

$$\frac{1}{Y} = \frac{1}{2}\left(\frac{1}{X^{\alpha}}\right) + \frac{1}{2}\left(\frac{1}{X^{\beta}}\right) \qquad \textbf{[19]}$$

The corresponding slope of the dimensionless curve on a log-log plot has the following symmetrical form:

$$Slope = \frac{\beta X^{\alpha} + \alpha X^{\beta}}{X^{\alpha} + X^{\beta}} \qquad \textbf{[20]}$$

The unified equations fully characterize biphasic ontogeny for 3 different types of human functional data, with two characteristic parameters. In conclusion, the proposed mixed-allometry model enables a systematic analysis that offers a quantitative understanding of human development from birth to adulthood.

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There is no competing interest to declare.

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