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A general model for ontogenetic growth under food restriction

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Food restriction (FR) retards animals' growth. Understanding the underlying mechanisms of this phenomenon is important to conceptual problems in life-history theory, as well as to applied problems in animal husbandry and biomedicine. Despite a considerable amount of empirical data published since the 1930s, there is no relevant general theoretical framework that predicts how animals vary their energy budgets and life-history traits under FR. In this paper, we develop such a general quantitative model based on fundamental principles of metabolic energy allocation during ontogeny. This model predicts growth curves under varying conditions of FR, such as the compensatory growth, different age at which FR begins, its degree and its duration. Our model gives a quantitative explanation for the counter-intuitive phenomenon that under FR, lower body temperature and lower metabolism lead to faster growth and larger adult size. This model also predicts that the animals experiencing FR reach the same fraction of their adult mass at the same age as their ad libitum counterparts. All predictions are well supported by empirical data from mammals and birds of varying body size, under different conditions of FR.

Keywords: energy allocation; food restriction; growth; metabolism

1. INTRODUCTION

Animals often face food scarcity and must vary their life-history characteristics in response. These responses can include foraging behaviours, the ages at which a certain developmental stage is reached, or reproductive efforts and so on [1–4]. Perhaps the most profound and direct life-history changes associated with low food availability or food restriction (FR) are retarded growth and reduced adult body size. Understanding the effects of FR on animals' energy budgets during growth is not only important to conceptual problems in life-history theory, but also to many applied problems. For example, in animal husbandry it has been suggested that appropriate FR on domestic birds can lighten body mass and improve total egg production (e.g. [5,6]). In biomedicine, it has been shown that FR (also known as caloric restriction) extends animals' lifespans and enhances their somatic maintenance functions (e.g. [7–9]). Despite the wealth and significance of empirical data derived from FR studies since the era of McCay in the 1930s [10], there has been no relevant theoretical framework that predicts how FR affects energy budgets and growth characteristics. Here, we present a general quantitative model based on fundamental principles of metabolic energy allocation during ontogeny, which provides a deeper understanding of the changes in life-history traits associated with the growth of mammals and birds under different conditions of FR.

We build on two ontogenetic growth models that together specify the complete metabolic energy allocation for animals fed ad libitum. The first model provides quantification of the fact that energy from food fuels growth [11]. When an animal is growing, a fraction of the energy assimilated from food is synthesized and stored as new biomass. The remaining fraction is used to fuel the total metabolic rate, B_{tot}, which is dissipated as heat and not conserved in stored biomass [11]. This is described by

$$A = B_{\mathrm{tot}} + S = B_{\mathrm{tot}} + E_{\mathrm{C}}\frac{\mathrm{d}m}{\mathrm{d}t}, \tag{1.1}$$

where A is the rate of intake of metabolizable energy from food, S $(=E_{\mathrm{C}}(\mathrm{d}m/\mathrm{d}t))$ is the rate of energy stored as new biomass, E_{C} is the combustion energy content of one unit biomass and $\mathrm{d}m/\mathrm{d}t$ is the rate of change in body mass, m, at time, t. The total metabolic rate, B_{tot}, is the sum of the resting metabolic rate, B_{rest}, and the rate of energy expenditure for locomotion, feeding and other activities, B_{act}. B_{tot} can be expressed as $B_{\mathrm{tot}} = B_{\mathrm{rest}} + B_{\mathrm{act}} = fB_{\mathrm{rest}}$, where f is a dimensionless parameter that reflects the activity level of the organism [11]. For wild mammals and birds, the value of f ranges from 2 to 3 with an average of 2.7. For caged animals, f is usually below 2 [11]. This relationship between total and resting metabolic rate is strongly supported by empirical data [11–13].

In the second model [14], the resting metabolic rate, B_{rest}, is further partitioned into the rate of energy allocated to synthesizing new biomass, B_{syn}, and the rate of energy allocated to maintenance of existing biomass B_{maint}. Hence, we write: $B_{\mathrm{rest}} = B_{\mathrm{syn}} + B_{\mathrm{maint}}$ [14]. The term B_{syn} is expressed as $B_{\mathrm{syn}} = E_{\mathrm{m}}(\mathrm{d}m/\mathrm{d}t)$, where E_{m} is the amount of metabolic energy required to synthesize one unit of biomass. E_{m} differs from E_{C} in equation (1.1) in that E_{C} is the amount of energy *stored* in one unit of biomass. Likewise, B_{syn} differs from S in equation (1.1) in that S is the rate at which energy is accumulated as new biomass; the maintenance of existing biomass is expressed as $B_{\mathrm{maint}} = B_{\mathrm{m}}m$, where B_{m} is the mass-specific maintenance metabolic rate. Empirical measurements

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and theoretical predictions provide evidence that resting metabolic rate $B_{\mathrm{rest}}(m)$ is roughly equal to $B_0 m^{3/4}$ [15–17], where B_0 is a normalization constant for a given taxon and exponentially increases with body temperature as $B_0 = b_0 \mathrm{e}^{-E_0/(KT)}$. The exponential factor $\mathrm{e}^{-E_0/(KT)}$ is called Boltzmann–Arrhenius (B–A) factor, where E_0 is the average activation energy of metabolism (*ca* 0.65 eV), K is Boltzmann's constant ($8.62 \times 10^{-5}\,\mathrm{eV\,K^{-1}}$) and T is body temperature in Kelvin [18]. The coefficient b_0 is a constant within a taxon, and independent of body mass and temperature. Taken together, this gives a growth equation of the form:

$$E_{\mathrm{m}} \frac{\mathrm{d}m}{\mathrm{d}t} = B_0 m^{3/4} - B_{\mathrm{m}} m. \tag{1.2}$$

When growth stops, that is, $\mathrm{d}m/\mathrm{d}t = 0$, and an animal reaches its adult mass, M, equation (1.2) gives $B_0 M^{3/4} = B_{\mathrm{m}} M$, and $B_{\mathrm{m}} = B_0 M^{-1/4}$.

A combination of equations (1.1) and (1.2) allows the food assimilation rate, A, to be expressed as a function of body mass during growth;

$$\begin{aligned} A[m(t)] &= B_{\mathrm{tot}} + S = B_{\mathrm{maint}} + B_{\mathrm{act}} + B_{\mathrm{syn}} + S \\ &= \left(f + \frac{E_{\mathrm{C}}}{E_{\mathrm{m}}} \right) B_0 m(t)^{3/4} - \frac{E_{\mathrm{C}}}{E_{\mathrm{m}}} B_0 M^{-1/4} m(t), \end{aligned} \tag{1.3}$$

with four parameters, B_0, f, E_{C} and E_{m}. Data for mammals and birds of diverse body sizes and taxa support the predictions of equation (1.3) [11].

When animals are under FR, their metabolic energy intake from food is lowered to a fraction, β, of that received by ad libitum animals, so that the assimilation rate of FR animals becomes $A_{\mathrm{FR}}(t) = \beta \times A(t)$. Under laboratory conditions, β ranges from 30 to 80 per cent and is usually set as a constant or a segment function of time [7]. In the field, β is a result of seasonally determined variations in abundance [1,2]. To derive the growth equation for animals under FR from equation (1.3), we assume that parameters, E_{C}, E_{m} and f, do not change under FR. E_{C} and E_{m} represent the combustion energy content of one unit biomass and the energy required to synthesize one unit of biomass, respectively. Their values correspond to the energetics of basic physico-chemical processes, quantified by heats of reaction, energies of formation and degradation, bond energies, etc. These values are elemental and do not vary. Empirical data also support our assumption that f will not change under FR. Activity levels are typically measured by motion/activity counts per unit time, and studies have shown that FR elicits no change in this value (see review of empirical evidence in appendix A and table 1). FR animals expend the same multiple of their resting metabolic rate on activities as do their ad libitum counterparts, and f does not change under FR. In other words, if B_{rest} is reduced by FR, B_{act} is also reduced, but the ratio of these two is assumed to remain constant.

However, there are some cases in which FR does slightly reduce animals' mass-corrected resting metabolic rates, expressed as either B_{rest}/M or $B_{\mathrm{rest}}/M^{3/4}$. In cases of severe restriction, FR animals can respond with mass-corrected metabolic rates that are as much as 15–20% lower than those of their ad libitum counterparts. As is often the case in biology, evidence to the contrary exists, and shows that the mass-corrected metabolic rates of FR animals do *not* differ from those of their ad libitum counterparts (appendix A and table 1). We take this drop in resting metabolic rate as evidence that the FR animals have a smaller normalization coefficient, $B_{0,\mathrm{FR}}(=B/M^{3/4})$. Some empirical studies have also reported body temperature drops in FR cohorts, e.g. 1–2°C in mice, approximately 1°C in rats and 0.5°C in Rhesus monkeys (appendix A and table 1). Since $B_0 = b_0\, \mathrm{e}^{-E_0/(KT)}$ and b_0 is a fixed constant, independent of body mass and temperature, the drops in body temperature ($T_{\mathrm{FR}} - T$) and the reduction in mass-corrected metabolic rate ($B_{0,\mathrm{FR}}/B_0$) can be reconciled by the B–A factor, $B_{0,\mathrm{FR}}/B_0 = \mathrm{e}^{-E_0 K/(T_{\mathrm{FR}} - T)}$. For example, if B_0 decreases by 15 per cent, the B–A factor predicts that the drop in body temperature is approximately 2°C, in agreement with most empirical observations. Our model will draw from multiple sources of empirical data, some of which report their results as changes in mass-corrected basal metabolic rates, and others report resultant data in terms of body temperature changes. Only B_0 is used to account for metabolic rate in our model, so where source data are presented in terms of body temperature, we use the B–A factor to convert the value of temperature change to B_0. Among 32 studies that reported the effect of long-term FR on metabolic rate or body temperature, the mean value of B_0 reduction is 9.6 per cent (s.d. = 7.7%). The drop in B_0 (ΔB_0) is not correlated to the degree of FR (β), $\Delta B_0 = 0.08 - 0.02\beta$ ($n = 32$, $r^2 = 0.03$, $p = 0.86$; data listed in table 1).

Accounting for altered ($B_{0,\mathrm{FR}}$) and unaltered (f, E_{C}, E_{m}) parameters, equation (1.1) for an FR animal becomes:

$$\begin{aligned} \beta A(t) &= A_{\mathrm{FR}}(t) \\ &= B_{\mathrm{tot,FR}} + E_{\mathrm{C}} \frac{\mathrm{d}m_{\mathrm{FR}}(t)}{\mathrm{d}t} \\ &= f B_{0,\mathrm{FR}} m_{\mathrm{FR}}^{3/4}(t) + E_{\mathrm{C}} \frac{\mathrm{d}m_{\mathrm{FR}}(t)}{\mathrm{d}t}, \end{aligned} \tag{1.4}$$

where $m_{\mathrm{FR}}(t)$ is the body mass of FR animals during growth. Recalling that the assimilation rate of ad libitum animals, $A(t)$, is determined by its growth via equation (1.3), we can substitute equation (1.3) into equation (1.4) to yield:

$$\begin{aligned} &\beta \left[\left(f + \frac{E_{\mathrm{C}}}{E_{\mathrm{m}}} \right) B_0 m(t)^{3/4} - \frac{E_{\mathrm{C}}}{E_{\mathrm{m}}} B_0 M^{-1/4} m(t) \right] \\ &\quad = f B_{0,\mathrm{FR}} m_{\mathrm{FR}}^{3/4}(t) + E_{\mathrm{C}} \frac{\mathrm{d}m_{\mathrm{FR}}(t)}{\mathrm{d}t}. \end{aligned} \tag{1.5}$$

Equation (1.5) is the major result of this model. We now make several predictions based on equation (1.5).

Prediction 1: the adult mass of FR animals, M_{FR}. When both FR and ad libitum animals stop growing, i.e. $m(t) = M$, $\mathrm{d}m_{\mathrm{FR}}/\mathrm{d}t = 0$, and $m_{\mathrm{FR}}(t) = M_{\mathrm{FR}}$, equation (1.5) reduces to $M_{\mathrm{FR}} = M \times (\beta \times B_0/B_{0,\mathrm{FR}})^{4/3}$.

Prediction 2: the growth curve of FR animals, $m_{\mathrm{FR}}(t)$. Equation (1.5) establishes the relationship between $m(t)$ and $m_{\mathrm{FR}}(t)$. If the species-specific growth parameters of the ad libitum animals are known empirically, namely: initial mass, m_0; adult mass, M; and energy required to synthesize biomass, E_{m}; then the growth curve of the ad libitum animal, $m(t)$, can be expressed by the solution of equation (1.1), $m(t) = (1 - [1 - (m_0/M)^{1/4}]\, \mathrm{e}^{-B_0 t/4E_{\mathrm{m}}M^{1/4}})^4 M$ [14]. Since we assume that f, E_{m} and

Table 1. Changes in mass-specific metabolic rate (B/M or $B/M^{3/4}$), body temperature (T_b) and activity level in different species and strains under FR. (B is the resting or starving metabolic rate (unless noted otherwise); M is the adult body mass. The percentages in the columns of B/M and $B/M^{3/4}$ are relative to data for ad libitum animals. The symbols =, ⇑ and ⇓ denote same as, higher than and lower than the ad libitum, respectively.)

species	strain	FR level (%)	B/M	$B/M^{3/4}$	T_b drop (°C)	activity	source
chronic effects (*stabilized*)							
mice	B10C3F1	50			2		[19]
mice	C57BL/6 (B6)	90			1.2		[20]
mouse	SHN/C3HF1	50			2.2		[21]
mice	CD2F1	75			1.5		[22]
mouse	B6	40			1		[23]
mouse	DBA/2				1.5		[23]
mice	B6C3F1	60			1.2	73% ⇑	[24]
mice	QS		⇑			=	[25]
mice	golden spiny	70			1.2–1.5	slight⇑	[26]
rat	Fishcher 344	50			1		[27]
rat	Sprague-Dawley (S-D)	moderate		10%			[28]
rat	S-D	severe		17%			[28]
rat	F344	60		=		=	[29]
rat	F344	60		=			[30]
rat	Wistar	50		=			[31]
rat	FBNF1	60–70		slightly⇓		=	[32]
rat	F344	60			0.8	slight⇑	[24]
rat	S-D	80	= [a]			slight⇑	[33]
rat	S-D	70	= [a]			= or⇓	[33]
rat	S-D	60	25%[a]			⇑or⇓	[33]
rat				14%[a]			[34]
rat	F344	60	12%	9–10%			[35]
rat		60	slightly⇑	=			[36]
rat	F344	60			0.9	slight⇑	[37]
Rhesus monkey			11–16%			=	[38]
Rhesus monkey		70				slight⇓	[39]
Rhesus monkey		70		1.3%			[40]
Rhesus monkey		70			0.5		[41]
Rhesus monkey		70				=	[42]
dog		75		=			[43]
ewe[c]		50		=			[44]
broiler chicken		50	10% and = [b]				[45]
hen	Babcock B300	80		12%			[46]
hen	Warren SSL	80		12%			[46]
hen		80		10%			[47]
cockerels		80		22%			[47]
short-term effects							
mouse	B6 male	50			4.5		[21]
mouse	B6 female	50			4.4		[21]
mouse	SHN/C3HF1	50			3.3		[21]
mice	B6C3F1	60	62%		3.2	50% ⇑	[24]
rat	F344	60		39%		=	[29]
rat	Wistar	70	6%				[48]
rat	Wistar	16	5%				[48]
rat	S-D	60		8%[d]			[49]
rat	Long-Evans	60		15%[d]			[49]
rat	S-D	50		8.20%		15% ⇓	[50]
rat	S-D	35		18%		20% ⇑	[50]
rat	S-D	65		3%[e]			[51]
rat	S-D	moderate		6%			[28]
rat	S-D	severe		13%			[28]
Rhesus monkey		70			1		[41]

[a]Total energy expenditure rate.
[b]10% lower on day of age 10 (d_{10}) but no change on d_{18}, expressed as $B/M^{0.67}$.
[c]Non-catheterized ewes; the mass-corrected metabolic rate, $B/M^{3/4}$, drops 22% in catheterized ewes.
[d]Averaged over values during light and dark periods.
[e]Averaged over values on d_{10}, d_{11} and d_{12}.

E_C should not change between FR and ad libitum animals, substituting $m(t)$ into equation (1.5) and numerically solving it will produce the growth curve of an FR animal, $m_{FR}(t)$, without any extra free-adjusting parameters. The only empirical inputs required to solve equation (1.5) for $m_{FR}(t)$ are the degree of FR, β and

$B_{0,FR}$; the latter of which can be calculated, if necessary, from the reduction in body temperature using the B–A factor as discussed.

Prediction 3: we predict that FR and ad libitum animals reach the same fraction of their adult mass at the same age, $m(\tau)/M = m_{FR}(\tau)/M_{FR}$, where τ is the age of the animals after a transient period. It is commonly thought that FR slows growth rate and delays the age associated with certain development stages, such as certain fraction of adult mass and puberty (e.g. [52,53]). However, theoretical consideration of our model and analyses of empirical data suggest that this is only true under certain FR conditions. If FR starts early in life and β, the fraction of ad libitum food given to FR animals, is kept constant, then equation (1.5) predicts that after the transient period, during which FR causes negative growth, the FR and ad libitum animals will reach the same percentage of their adult mass at the same age, i.e. $m(\tau)/M = m_{FR}(\tau)/M_{FR}$.We present the detailed proof below.

During the transient period FR animals experience negative growth; they lose body mass immediately following the initiation of FR. The negative growth is predicted by equation (1.5) based on the same assumption introduced in predictions 1 and 2, i.e. parameters f, E_m and E_C are the same for FR animals and for ad libitum animals; and changes in body temperature (and therefore B_0) are constant during entire period of FR. After the transient period, growth rates can be expressed as $dm_{FR}(t)/dt = B_{0,FR}\, m_{FR}(t)^{3/4} - B_{m,FR} m_{FR}(t)$, which is the analogue of equation (1.1) for FR animals. When growth stops, this yields $B_{m,FR} = B_{0,FR} M_{FR}^{-1/4}$. Substituting both equations into equation (1.5) gives:

$$\beta\left[\left(f+\frac{E_C}{E_m}\right)B_0 m(t)^{3/4} - \frac{E_C}{E_m} B_0 M^{-1/4} m(t)\right] = \left(f+\frac{E_C}{E_m}\right)B_{0,FR} m_{FR}^{3/4}(t) - \frac{E_C}{E_m} B_{0,FR} M_{FR}^{-1/4} m_{FR}(t).$$

Letting $f + E_C/E_m = a$ and $E_C/E_m = b$, yields $\beta B_0 M^{3/4}[a\mu(t)^{3/4} - b\mu(t)] = B_{0,FR} M_{FR}^{3/4}[a\mu_{FR}^{3/4}(t) - b\mu_{FR}(t)]$, where $\mu(t) = m(t)/M$ is the relative mass of ad libitum animals, and $\mu_{FR}(t) = m_{FR}(t)/M_{FR}$ is the relative mass for FR animals. Using $M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{4/3}$ we have:

$$a\mu(t)^{3/4} - b\mu(t) = a\mu_{FR}^{3/4}(t) - b\mu_{FR}(t). \qquad (1.6)$$

Now, let us assume that there exists a time T, such that $\mu(T) \neq \mu_{FR}(T)$. Since both $\mu(t)$ and $\mu_{FR}(t)$ monotonically increase from 0 to 1, $\mu^{3/4}(T) \neq \mu_{FR}^{3/4}(T)$, and therefore, $a\mu(T)^{3/4} - b\mu(T) \neq a\mu_{FR}^{3/4}(T) - b\mu_{FR}(T)$. This is in contradiction to equation (1.6), which holds for all times, t, after the transient period. So, for any time, t, after the transient period, it will be true that $\mu(t) = \mu_{FR}(t)$, regardless of the degree of FR or the age at which FR initiates. In figure 1, we illustrate this relationship.

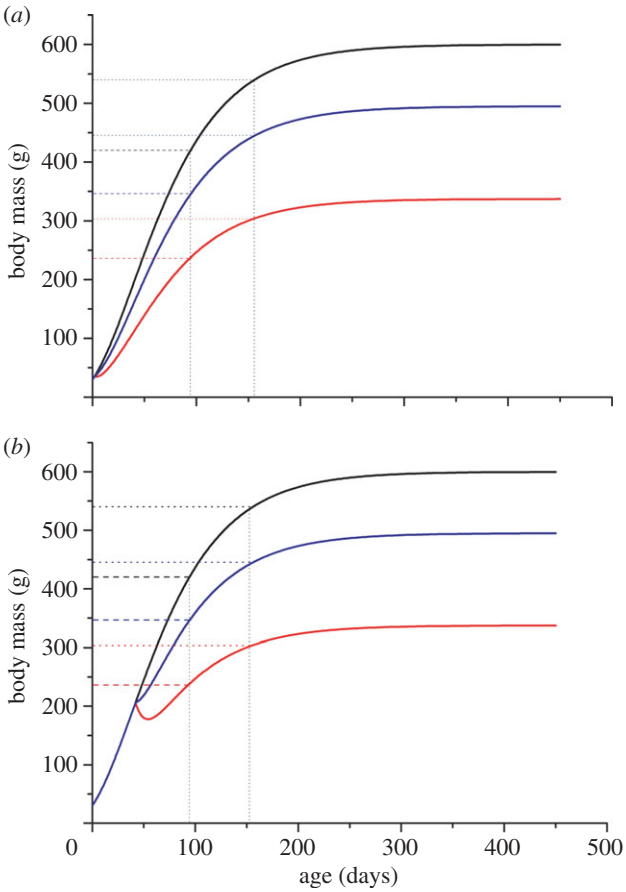

Figure 1. Theoretically, FR and ad libitum animals reach the same fraction of adult mass at the same age. (*a*) FR starts on day 2 of age; (*b*) FR starts on day 42 of age. Dotted lines, 90% of adult body mass; dashed lines, 70% of adult body mass; black line, ad libitum fed; blue line, 80% FR; red line, 60% FR.

2. RESULTS AND DISCUSSION

We evaluate predictions using laboratory and field data for the growth of FR and ad libitum animals.

In figure 2, we plot predicted values (black squares) against empirical values of adult mass for FR animals, M_{FR}, derived from 62 studies of mammals and birds across a broad range of body sizes and taxa, including rodents, monkeys, dogs, chickens and quails. Empirical data strongly support our first prediction $M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{4/3}$; predictions plotted against empirical data have a line of best fit (solid black) with a slope of 0.98 and include the predicted value of 1. Our predictions are based on the scaling power of resting metabolic rate over ontogeny, 3/4, which has been used in allometric theories and supported by data on a diverse set of animals, including mammals, birds and fishes [15–17,54]. In figure 2, we also show that if the scaling power is taken to be 2/3 instead of 3/4, our predictions of M_{FR} (red circles) would deviate only slightly from the empirical values. The slope of the line (red dashed) is 0.94, which indicates that a 2/3 scaling power underestimates the adult mass of FR animals. The confidence interval for this slope does not include the predicted value of 1. In appendix B, we show that the prediction of M_{FR} is not very sensitive to the scaling power; varying scaling power from 0.65 to 0.85 generates 0.7–9% variation in M_{FR} from this prediction.

In figure 3, we plot predicted and empirical growth curves for the FR animals, $m_{FR}(t)$. We first fit the empirical growth curves of ad libitum animals to the solution of equation (1.2), in order to obtain the species-specific growth parameters; m_0, M and E_m; and the analytic expression of $m(t)$. The values of fitted parameters and statistics are listed in the electronic supplementary material,

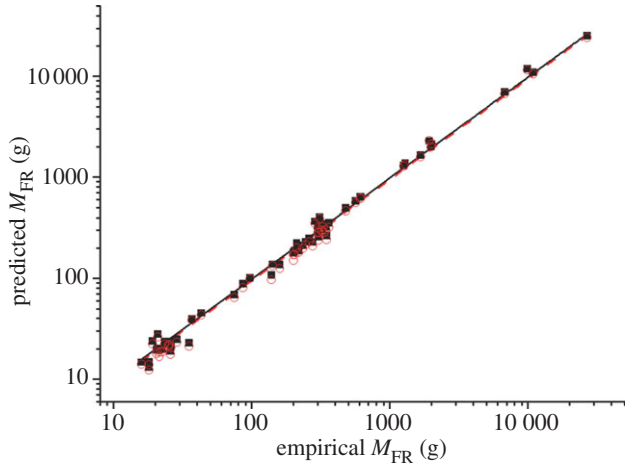

Figure 2. Predicted values of ultimate body mass of FR animals, $M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{4/3}$, against the empirical values. (Empirical data are in table S1 of the electronic supplementary material.) Black filled squares, predictions based on scaling power = 3/4; solid line, $y = 0.98x$ (fixed intercept = 0; $r^2 = 0.99$; 95% CI: 0.96, 1); red open circles, predictions based on scaling power = 2/3; dashed line, $y = 0.94x$ (fixed intercept = 0; $r^2 = 0.99$; 95% CI: 0.92, 0.97).

table S2. We then substituted $m(t)$ into equation (1.5), assuming that the combustion energy in one unit of biomass, E_C, is constant within an individual and across mammalian and bird species with a value of roughly 7000 J g^{-1} [55,56]. Solving equation (1.5) numerically with a defined level of FR, β and known values of B_0, we determine the growth curves of FR animals, $m_{FR}(t)$. So, the predicted $m_{FR}(t)$ in figure 3 were not obtained by fitting the empirical FR data. The model successfully predicts how FR affects growth for different mammals and birds of diverse body sizes. Predicted and empirical data have strong linear relationships; the slopes and r^2 values are nearly identical to 1, and $p < 10^{-5}$ (detailed statistics are shown in the electronic supplementary material, table S3). More importantly, our model predicts growth curves under different FR conditions, e.g. different ages at which FR starts (figure 3*a*,*e*); different levels of FR, β (figure 3*c*,*d*); and alternations between FR and ad libitum (figure 3*d*–*f*).

Body temperature plays an important role throughout ontogenesis. The effects of variable body temperature on growth have been studied extensively in ectotherms (e.g. [57]). However, mammals, especially small rodents, also vary their body temperatures over ontogeny in response to FR (e.g. [58] and review in appendix A and table 1). Figure 3 shows predictions based on constant body temperature throughout the entire period of FR. Empirical evidence has shown that in many cases, body temperature drops severely after implementation of FR, and after a transient period it increases to a stabilized level (e.g. [29]). One study on two strains of mice [21] reported growth curves and temperature drops at different ages under FR. We take the reported, variable temperature drops to predict the growth curves of FR mice (figure 4). Our model predicts that under FR, lower body temperature, meaning lower $B_{0,FR}$ by virtue of the B–A factor, $B_0 = b_0\ e^{-E_0/KT}$, leads to a relatively larger body size ($M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{4/3}$ and figure 4). Equation (1.1) gives a quantitative explanation. The rate of new biomass storage (growth) is the difference between food intake rate, A, and metabolic rate, B, which increases with body temperature. When A is restricted during FR, lower temperatures lead to lowered metabolic rates, therefore, leaving a relatively larger amount of energy to be allocated to growth.

To test our third prediction, we plotted in figure 5 the ages of 11 FR animals against those of their ad libitum counterparts, at which 70 per cent (figure 5*a*) and 90 per cent (figure 5*b*) of the adult body masses were reached. Our model's prediction is well supported by empirical data. Life-history theories suggest that mammals and birds need to reach a critical fraction of adult mass for sexual maturity [59–61]. So, minimizing the time to reach the fraction of adult mass associated with reproductive maturity will maximize the animals' fitness. Theoretical predictions by our model and empirical data shown in figure 5 illustrate the finding that, despite the stress of FR, FR animals with a constant β reach the same fraction of adult mass at the same age as their ad libitum counterparts. Many studies reported that FR delays puberty (e.g. [62,63]), but in most of those studies FR was not set as a constant fraction of the amount of food that ad libitum animals obtain, which is the condition of our prediction. By contrast, empirical evidence shows that rats [64] and quails [65] under FR with constant β reach puberty at the same age as their ad libitum fed counterparts, in agreement with our theoretical prediction.

One of the fundamental issues in ontogenetic growth is whether growth is constrained by food intake or metabolism [66]. Together with previous ontogenetic growth models [11,14], the model presented here illustrates that both provide constraints on growth. When available food is unlimited, metabolic rate is the dominant influence on growth, and is positively correlated with the growth rate. Under FR, however, food intake has more influence on growth, and is positively correlated to growth. More importantly, under FR, owing to the trade-off between metabolism and new biomass storage, higher metabolism leads to slower growth. This negative correlation has been reported in experiments on rats, in which food was restricted and elevated metabolic rates were found to be associated with severely reduced growth [67].

In summary, we have derived a general quantitative model for understanding growth under FR, which is based on the first principles of energy balance and allometries of metabolism. This model predicts growth curves under different conditions of FR (figures 2 and 3), and explores the effects of body temperature and metabolic rate on growth (figure 4). The model also predicts that animals reach the same fraction of their adult mass at the same age, regardless of whether they endure FR or are allowed to eat ad libitum (figures 1 and 5). In its general form, this model contributes to our current understanding of the pattern of energy budgeting under FR. In addition, it presents a conceptual framework from which more detailed, species- or strain-specific studies may be possible. The model partitions the metabolic rate between the rate of energy allocated to growth and the rate of energy allocated to maintenance of the existing biomass (equations (1.2) and (1.5)). Since FR greatly suppresses growth but only slightly reduces

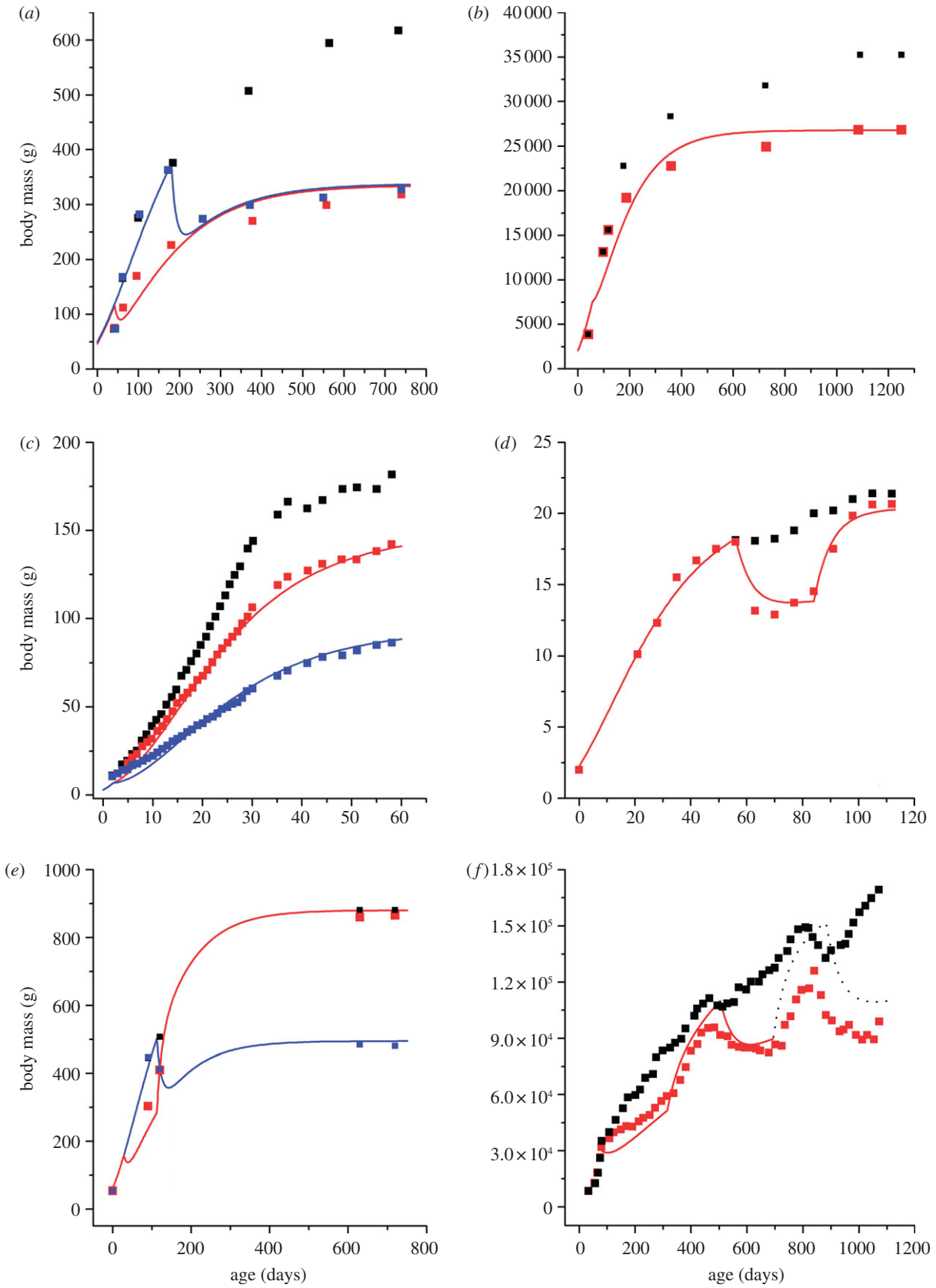

Figure 3. Empirical (dots) and predicted (solid lines) growth curves of ad libitum and FR animals. In (*f*), the accuracy of the prediction is lost after day *ca* 700 of age. This is because both ad libitum and FR deer stags had the rut, which causes irregular food intake and body mass change (empirical data and statistics are in table S2, electronic supplementary material). (*a*) Rat: black squares, ad libitum fed; red squares, 60% FR from day 42; blue squares, 60% FR from day 180; (*b*) dog: black squares, ad libitum fed; red squares, 75% FR from day 56; (*c*) quail: black squares, ad libitum fed; red squares, 70% FR from day 2; blue squares, 40% FR from day 2; (*d*) mouse: black squares, ad libitum fed; red squares, 67% FR from day 56 then switched to 95% FR from day 84; (*e*) rat: black squares, ad libitum fed; blue squares, ad libitum fed for 12 week after weaning then 60% FR; red squares, 60% FR for 12 week after weaning then ad libitum; (*f*) red deer: black squares, ad libitum fed; red squares, 70% FR and refeeding; dotted line, accuracy lost due to rut.

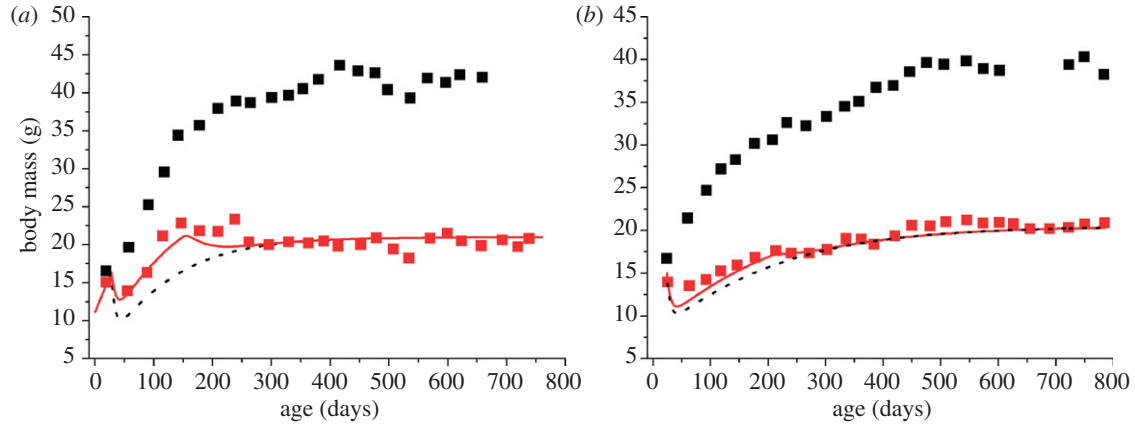

Figure 4. Predicted growth curves with accurate variable temperature (solid lines) drops during whole periods of FR. (*a*) B6 mice; (*b*) SHN/C3H mice. Dashed lines indicate the predictions with constant, stabilized temperature drops. For FR mice in this study [21], the body temperature changed from T_1 at age d_1 to T_2 at age d_2 ($T_1 < T_2$ and $d_1 < d_2$). The body temperature of ad libitum mice is roughly a constant, T_{AL}. We assume that the temperature of FR mice is a function of time, and increases smoothly from T_1 at age d_m, which is between d_1 and d_2, to reachT_2 at age d_2. The function we took for the calculation has the form $(T_2 - T_1) \times [1 - e^{-a(t-d_m)}]$, where a is a dimensionless constant that controls the rate of increase. Note: any function that smoothly increases from T_1 to T_2 would give a similar result. The values of T_1, T_2, d_1, d_2, d_m and a are listed in table 2. The growth curves of FR animals are obtained by numerically solving equation (1.5). This was completed using the B–A factor to determine B_0 from temperature data.

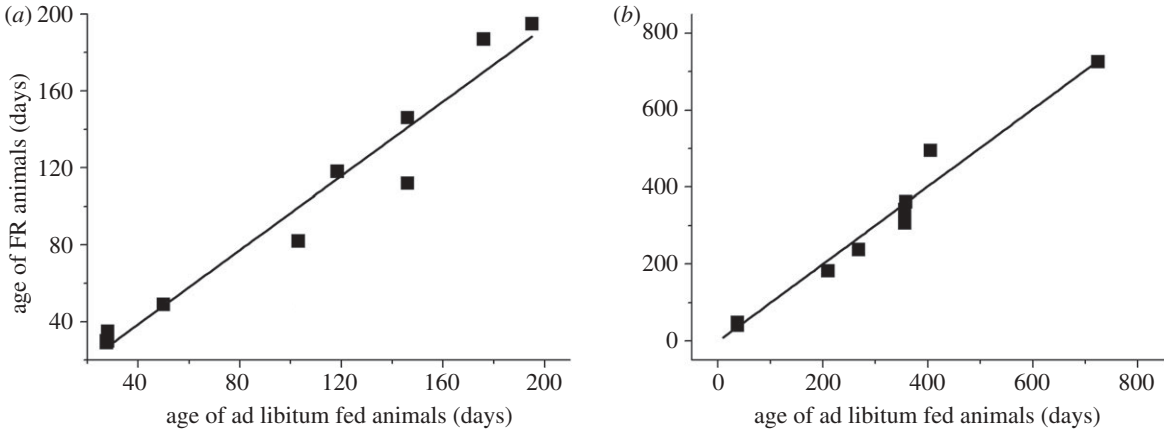

Figure 5. The age of FR animals against the age of ad libitum counterparts at which they reach to the same percentage of the adult masses, M and M_{FR}. (*a*) Age at 70% of adult body mass (solid line, $y = 0.97x$ (fixed intercept = 0; $r^2 = 0.99$ 95% CI: 0.89, 1.04)); (*b*) age at 90% of adult body mass (solid line, $y = 1.00x$ (fixed intercept = 0; $r^2 = 0.99$ 95% CI: 0.93, 1.08)). The points are derived from empirical studies instead of predictive curves (empirical data are in tables S4 and S5, electronic supplementary material). Where the exact value, i.e. exact 70 or 90% of M or M_{FR} was not available, we used the closest value having error less than 4%. Dashed line, $y = 0.97x$ (fixed intercept = 0; $r^2 = 0.99$% CI: 0.89, 1.04).

Table 2. Parameters for predicting growth curves in figure 3.

strain	T_1 (°C)	T_2 (°C)	d_1	d_2	d_m	a[b]
B6 (FR)	33.2	35.3[a]	day 90	day 390	day 150	0.025
B6 ad libitum	37.7	37.7				
SHN/C3H (FR)	34.1	34.8	day 90	day 390	day 210	0.025
SHN/C3H ad libitum	37.2	37.2				

[a]At d_2 (day 390), the body temperature drop in SHN/C3H mice is 2.4°C. The authors did not report T_2 at d_2 for B6 mice. We assume the same drop (2.4°C) for B6 mice at age d_2.
[b]We set the value of a to be 0.025 so that the temperature smoothly increases from T_m to T_2 at an appropriate rate. A too large/small a will make the temperature increase too fast/slow and reach to T_2 too much before/after age d_2.

mass-specific metabolism, it channels extra energy for mass-specific maintenance. Therefore, this model offers a departure point for quantitatively understanding how FR enhances organisms' maintenance functions. From an energetic point of view, this enhancement in maintenance provides a feasible and quantifiable explanation for the phenomenon of lifespan extension that has been observed in food-restricted animals [7,8].

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APPENDIX A. BODY TEMPERATURE, METABOLIC RATE AND ACTIVITY LEVEL UNDER FOOD RESTRICTION

Numerous empirical studies of FR in mammals, such as rodents, ewes, dogs, and primates; and on birds, such as quail and chicken; have shown that the mass-specific metabolic rates of FR animals, expressed per gram of body mass or per gram of body mass to 3/4 power (metabolic mass), either decreases slightly or sometimes remains roughly the same as those of their ad libitum fed counterparts [25,26,28,29–31,33,36,37,43,44,46,47,68–69]. Under severe FR (50 or 60%), the mass-specific metabolic rates may drop up to 15–20% in some cases [28,33–35,40], although in one case, rates showed an increase in severely FR animals [25]. Studies have also shown that animals under FR keep the same or even slightly increased activity levels [25,26,33,38,42,70,71]. Only one study reports increased activity levels as pronounced as 50–70% above normal [24].

Some empirical studies have reported slight body temperature drops, e.g. approximately 1°C for rats [24,27,37], 1–2°C for mice [19,22–24,26,58,72] (but up to 4°C for a few strains [58]), and 0.5–1°C for Rhesus monkeys [41]. Studies have also reported that drops in body temperatures and metabolic rates are more severe immediately after FR starts [21,24,29,41], but one study showed the opposite result [28]. We summarize the reported changes in mass-specific metabolic rates, body temperatures and activity levels of different species and strains under FR in table 1.

APPENDIX B. SENSITIVITY OF M_{FR} ESTIMATES TO THE VALUE OF METABOLIC RATE SCALING POWER

Our estimate of M_{FR} depends on the value of the scaling power of the metabolic rate. In general, if the power is α, the predicted value of M_{FR} from equation (1.5) would be $M_{FR} = M(\beta \times B_0/B_{FR})^{1/\alpha}$, where M, β, B_0 and B_{FR} are empirically determined. We now show how deviation from $\alpha = 3/4$ affect our prediction of M_{FR}.

First, we take the natural logarithm of both sides of the prediction of M_{FR}, giving $\ln M_{FR} = \ln M + 1/\alpha \ln(\beta \times B_0/B_{FR})$. Then, we take the derivative of $\ln(M_{FR})$ with respect to α, and get $\mathrm{d}\ln M_{FR}/\mathrm{d}\alpha = -\ln(\beta \times B_0/B_{0,FR})/\alpha^2$. Since $\mathrm{d}\ln M_{FR} = \mathrm{d}M_{FR}/M_{FR} = \Delta M_{FR}/M_{FR}$, then $\Delta M_{FR}/M_{FR} = -\Delta\alpha \times \ln(\beta \times B_0/B_{0,FR})/\alpha^2$. The value of β ranges from 0.6 to 0.8, and the ratio of $B_0/B_{0,FR}$ ranges from 1 to 1.2, so the value of $\ln(\beta \times B_0/B_{FR})$ varies from -0.5 to -0.04. In the main text, we assume $\alpha = 3/4$. If for some particular species the empirical value of $\alpha = 0.65$ or 0.85, i.e. $\Delta\alpha = -0.1$ or 0.1, then $\Delta M_{FR}/M_{FR} = \mp$ (0.007–0.089), so the value of M_{FR} will be 0.7–9% lower or greater than our estimate based on the 3/4 power.

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