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, \( B_{\text{tot}} \), which is dissipated as heat and not conserved in stored biomass [11]. This is described by

\[
A = B_{\text{tot}} + S = B_{\text{tot}} + E_C \frac{dm}{dt}, \tag{1.1}
\]

where \( A \) is the rate of intake of metabolizable energy from food, \( S = E_C(dm/dt) \) is the rate of energy stored as new biomass, \( E_C \) is the combustion energy content of one unit biomass and \( dm/dt \) is the rate of change in body mass, \( m \), at time, \( t \). The total metabolic rate, \( B_{\text{tot}} \), is the sum of the resting metabolic rate, \( B_{\text{rest}} \), and the rate of energy expenditure for locomotion, feeding and other activities, \( B_{\text{act}} \). \( B_{\text{tot}} \) can be expressed as \( B_{\text{tot}} = B_{\text{rest}} + B_{\text{act}} = fB_{\text{rest}} \), 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, \( B_{\text{rest}} \), is further partitioned into the rate of energy allocated to synthesizing new biomass, \( B_{\text{syn}} \), and the rate of energy allocated to maintenance of existing biomass \( B_{\text{maint}} \). Hence, we write: \( B_{\text{rest}} = B_{\text{syn}} + B_{\text{maint}} \) [14]. The term \( B_{\text{syn}} \) is expressed as \( B_{\text{syn}} = E_m(dm/dt) \), 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, \( B_{\text{syn}} \) 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 \( B_{\text{maint}} = B_{\text{act}}/f \), where \( B_{\text{act}} \) is the mass-specific maintenance metabolic rate. Empirical measurements

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and theoretical predictions provide evidence that resting metabolic rate $B_{0m0}(m)$ is roughly equal to $B_0m^{3/4}$ [15–17], where $B_0$ is a normalization constant for a given taxon and exponentially increases with body temperature as $B_0 = b_0e^{-E_b/RT}$. The exponential factor $e^{-E_b/RT}$ is called Boltzmann–Arrhenius (B-A) factor, where $E_b$ is the average activation energy of metabolism (ca 0.65 eV), $K$ is Boltzmann’s constant (8.62 × 10$^{-5}$ 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.

When growth stops, that is, $dm/dt = 0$, and an animal reaches its adult mass, $M_t$, equation (1.2) gives $B_0M^{3/4} = B_{0m}M_t$, and $B_{0m} = B_0M^{-1/4}$.

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

$$A[m(t)] = B_{tot} + S = B_{maint} + B_{act} + B_{syn} + S,$$

with four parameters, $B_{0m}, f_0, E_c$ 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, $\beta$, of that received by ad libitum animals, so that the assimilation rate of FR animals becomes $A_{FR}(t) = \beta \times A(t)$. Under laboratory conditions, $\beta$ ranges from 30 to 80 per cent and is usually set as a constant or a segment function of time [7]. In the field, $\beta$ 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 $f_0$ 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, energy 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 $B_{rest0}M$ or $B_{rest}M^{3/4}$. 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, $B_{0FR}(= B_0M^{3/4})$. 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 $B_0 = b_0e^{-E_b/RT}$ and $b_0$ is a fixed constant, independent of body mass and temperature, the drops in body temperature ($T_{FR} - T$) and the reduction in mass-corrected metabolic rate ($B_{0FR}/B_0$) can be reconciled by the B–A factor, $B_{0FR}/B_0 = e^{-E_b/RT}$ [17]. 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 $B_0$ ($\Delta B_0$) is not correlated to the degree of FR ($\beta$), $\Delta B_0 = 0.08 - 0.02\beta$ ($n = 32$, $r^2 = 0.03$, $\rho = 0.86$; data listed in table 1).

Accounting for altered ($B_{0FR}$) and unaltered ($f_0, E_c, E_m$) parameters, equation (1.1) for an FR animal becomes:

$$\beta A(t) = A_{FR}(t) = B_{tot,FR} + EC \frac{dm_{FR}(t)}{dt} = J • B_{0FR}M^{3/4}(t) + E_c \frac{dm_{FR}(t)}{dt},$$

where $m_{FR}(t)$ 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:

$$\beta \left[ \left( f + \frac{E_c}{E_m} \right) B_0m(t)^{3/4} - \frac{E_c}{E_m} B_0M^{3/4}m(t) \right] = J • B_{0FR}M^{3/4}(t) + E_c \frac{dm_{FR}(t)}{dt}.$$

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. $m(t) = M_t$, $dm_{FR}/dt = 0$, and $m_{FR}(t) = M_{FR}$, equation (1.5) reduces to $M_{FR} = M \times (\beta \times B_0/B_{0FR})^{3/4}$.

**Prediction 2:** the growth curve of FR animals, $m_{FR}(t)$. Equation (1.5) establishes the relationship between $m(t)$ and $m_{FR}(t)$. If the species-specific growth parameters of the ad libitum animals are known empirically, namely: initial mass, $m_0$; adult mass, $M_t$; 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), $m(t) = (1 - (m_0/M)^{3/4}) e^{-B_0d_{4d}m(t)^{3/4}M}$ [14]. Since we assume that $f_0$, $E_m$ and...
EC should not change between FR and ad libitum animals, substituting \( m \) 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, \( \beta \) and 

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

<table>
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<th>species</th>
<th>strain</th>
<th>FR level (%)</th>
<th>( B/M )</th>
<th>( B/M^{3/4} )</th>
<th>( T_b ) drop (°C)</th>
<th>activity source</th>
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<td>= ( \uparrow )</td>
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<td>slight ( \uparrow )</td>
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<td>= ( \downarrow )</td>
<td></td>
<td>or ( \downarrow )</td>
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<td>25% ( \uparrow )</td>
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<td>or ( \downarrow )</td>
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<td>0.5</td>
<td>= ( \uparrow )</td>
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<tr>
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<td>6%</td>
<td>= ( \downarrow )</td>
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<tr>
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<tr>
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<td>= ( \downarrow )</td>
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<td></td>
<td>70</td>
<td>1</td>
<td></td>
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<td>[55]</td>
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\( ^{a} \)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 \(d_{12}\).
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 \( \tau \) 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 \( \beta \), 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 \( E_m \) and \( E_C \)) are constant during entire period of FR. After growth stops, this yields \( B_{0,FR} = B_{0,FR}M_{FR}^{-1/4} \). Substituting both equations into equation (1.5) gives:

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

Letting \( f + E_C/E_m = a \) and \( E_C/E_m = b \), yields \( \beta B_{0,FR} M_{FR}^{1/4} [a \mu(t)]^{3/4} - b \mu(t) = B_0 M_{FR}^{1/4} [a \mu_{FR}(t)]^{3/4} - b \mu_{FR}(t) \), 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 \( M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{3/4} \) we have:

\[
a \mu(t)^{3/4} - b \mu(t) = a \mu_{FR}(t)^{3/4} - b \mu_{FR}(t).
\]

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, \( a \mu(T)^{3/4} - b \mu(T) \neq a \mu_{FR}(T)^{3/4} - b \mu_{FR}(T) \). 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.

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 plotted 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 \( M_{FR} = M \times (\beta \times B_0/B_{0,FR})^{3/4} \); 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 plotted 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 \( E_{in} \), and the analytic expression of \( m(t) \). The values of fitted parameters and statistics are listed in the electronic supplementary material,
assuming that the combustion energy in one unit of bio-
data have strong linear relationships; the slopes and
predicts how FR affects growth for different mammals
by fitting the empirical FR data. The model successfully
B
body temperature, meaning lower
drops severely after implementation of FR, and after a
drop in body temperature. Solving equation (1.5) numerically
with a defined level of FR,
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 con-
dition of our prediction. By contrast, empirical evidence
shows that rats [64] and quails [65] under FR with con-
stant β reach puberty at the same age as their ad
libitum counterparts, in agreement with our theoretical

table S2. We then substituted $m(t)$ into equation (1.5),
assuming that the combustion energy in one unit of bio-
mass, $E_C$, 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. differ-
ent ages at which FR starts (figure 3a,c); different levels of
FR, β (figure 3c,d); and alternations between FR and
ad libitum (figure 3d–f).

Body temperature plays an important role throughout
ontogeny. 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 ($M_{FR} = M \times (β \times B_0/B_{0,FR})^{k/3}$ 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 5a) and 90
per cent (figure 5b) of the adult body masses were
reached. Our model’s prediction is well supported by
empirical data. Life-history theories suggest that mam-
mals 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
is greatly suppresses growth but only slightly reduces

One of the fundamental issues in onontogenetic growth is
whether growth is constrained by food intake or metab-
olism [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 influ-
ence 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 allome-
tries 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 meta-
Bolic 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 2. Predicted values of ultimate body mass of FR ani-
mals, $M_{FR} = M \times (β \times B_0/B_{0,FR})^{k/3}$, against the empirical
values. (Empirical data are in table S1 of the electronic sup-
plementary 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).
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.
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].

![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 \(d_0\), to reach \(T_2\) 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; \(r^2 = 0.99\) 95% CI: 0.89, 1.04).

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

<table>
<thead>
<tr>
<th>strain</th>
<th>(T_1) (°C)</th>
<th>(T_2) (°C)</th>
<th>(d_1)</th>
<th>(d_2)</th>
<th>(d_{m})</th>
<th>(a)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6 (FR)</td>
<td>33.2</td>
<td>35.3^a</td>
<td>day 90</td>
<td>day 390</td>
<td>day 150</td>
<td>0.025</td>
</tr>
<tr>
<td>B6 ad libitum</td>
<td>37.7</td>
<td>37.7</td>
<td>day 90</td>
<td>day 390</td>
<td>day 210</td>
<td>0.025</td>
</tr>
<tr>
<td>SHN/C3H (FR)</td>
<td>34.1</td>
<td>34.8</td>
<td>day 90</td>
<td>day 390</td>
<td>day 210</td>
<td>0.025</td>
</tr>
<tr>
<td>SHN/C3H ad libitum</td>
<td>37.2</td>
<td>37.2</td>
<td>day 90</td>
<td>day 390</td>
<td>day 210</td>
<td>0.025</td>
</tr>
</tbody>
</table>

^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 \(d_2\).

^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 \(d_2\).
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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 $M_{FR} = M(β \times B_{0}/B_{FR})^{1/α}$, where $M$, $β$, $B_{0}$ and $B_{FR}$ are empirically determined. We now show how deviation from α = 3/4 affect our prediction of $M_{FR}$.

First, we take the natural logarithm of both sides of the prediction of $M_{FR}$, giving $\ln M_{FR} = \ln M + 1/α \ln (β \times B_{0}/B_{FR})$. Then, we take the derivative of $\ln M_{FR}$ with respect to α, and get $d \ln M_{FR}/dα = - \ln(β \times B_{0}/B_{FR})/α^2$. Since $d \ln M_{FR}/dM_{FR} = M_{FR}/M_{FR}$, then $\Delta M_{FR}/M_{FR} = - \Delta α \times \ln(β \times B_{0}/B_{FR})/α^2$. The value of β ranges from 0.6 to 0.8, and the ratio of $B_{0}/B_{FR}$ ranges from 1 to 1.2, so the value of $\ln(β \times B_{0}/B_{FR})$ varies from −0.5 to −0.04. In the main text, we assume α = 3/4. If for some particular species the empirical value of α = 0.65 or 0.85, i.e. $\Delta α = 0.1$ or 0.1, then $\Delta M_{FR}/M_{FR} = \pm (0.007–0.089)$, 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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