Increasing Energetic Cost of Biosynthesis during Growth Makes Refeeding Deleterious

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abstract: Diet restriction (DR) enhances animals' health maintenance, but refeeding reverses its beneficial effects. However, to what degree refeeding reverses the beneficial effects of DR remains controversial. Here, I develop a theoretical model for reconciling the results of refeeding studies and understanding the dynamic and reversible mechanism underlying the effects of diet on health from the energetic viewpoint. By illustrating the negative correlation between health maintenance and the energetic cost of growth in animals under different diet regimes, the model explains why, in some cases, refed animals have better health and live longer than freely fed controls. More importantly, the model reveals that, in some species, the energetic cost of synthesizing biomass increases during growth, so the expensive compensatory growth induced by refeeding later in life offsets the benefits of the inexpensive retarded growth induced by diet restriction early in life. Thus, in these species, refeeding drives animals to allocate more energy to growth and less to maintenance and therefore leads to poor health status and shorter life span compared to freely fed controls.

Keywords: diet restriction, refeeding, compensatory growth, oxidative damage, metabolism.

Introduction

Diet restriction (DR) extends the life spans of a broad variety of species (Weindruch and Walford 1988; Masoro 2005, 2009; Sinclair 2005; Mair and Dillin 2008). It also keeps animals in a relatively youthful and healthy state, indicating that DR enhances somatic maintenance functions in animals (Holehan and Merry 1986; Yu 1994; Merry 1995; Heilbronn and Ravussin 2003; Sinclair 2005; Mair and Dillin 2008; Masoro 2009). The effects of DR on health maintenance and life-span extension have merited it as a public tool to test aging hypotheses (Yu 1996). However, several long-standing questions in this field remain. One of the most significant unanswered questions involves the effects of refeeding after a period of diet restriction (Merry 1995, 2002; Metcalfe and Monaghan 2001, 2003; Mangel and Munch 2005; Stoks et al. 2006; Campero et al. 2008; De Block and Stoks 2008*a*; Dmitriew 2011). Numerous empirical studies have led to the consensus that rapidly refeeding reverses the effects of DR on health maintenance and aging (Merry 2002; Mair et al. 2003; Dhahbi et al. 2004; Spindler 2005). But to what degree refeeding reverses DR's effects remains controversial. Several studies on small rodents have shown that although refed animals had shorter life spans than those under continuous DR, they still lived longer than their counterparts that were fed ad lib. (AL; Cheney et al. 1983; Kubo et al. 1984; Yu et al. 1985; Beauchene et al. 1986). However, in a few exceptions, refeeding rats after 1, 5, or 8 months of DR shortened their life spans compared to the AL control (Merry 1987, 1995). The mortality rate of fruit flies decreases during DR, but when refeeding starts after 14 or 22 days of DR, it increases rapidly to the same level as that of the AL controls (Mair et al. 2003). Refeeding previously diet-restricted animals is also detrimental to subsequent survival in fish (Inness and Metcalfe 2008) and parasites (Hakalahti et al. 2005). Compared to continuous ad lib. feeding, refeeding after a period of diet restriction increases protein oxidative damage in mice (Forster et al. 2000), reduces adult immune functions and increases oxidative stress in insects (De Block and Stoks 2008*b*), decreases red blood cell resistance to free radical attacks in birds (Alonso-Alvarez et al. 2007), and leads to poor performance in fish (Morgan and Metcalfe 2001). In an extreme type of refeeding, human and other mammalian individuals who experience poor prenatal but enriched postnatal nutritional environments have higher chances for adult diseases and shortened life spans (Eriksson et al. 1999; Jennings et al. 1999; Lucas et al. 1999; Ong et al. 2000; Aihie Sayer et al. 2001; Poore et al. 2002; Ozanne and Hales 2004; Langleyevans and Sculley 2006). In summary, all of the studies have shown that compared to animals under continuous DR, refed animals are less healthy and have shorter lives. However, some studies have shown

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better health and longer life spans in refed animals compared to freely fed controls, some have shown the opposite, and some have shown no difference. The effect of refeeding is complex, and "the mechanism through which diet acts to retard aging is both dynamic and reversible" (Merry 1995, p. 248). The purpose of this article is to develop a theoretical model for reconciling the results of these refeeding experiments and understanding the dynamic and reversible mechanism underlying these effects.

Many researchers have attributed the effects of diet restriction and refeeding to the life-history trade-off between somatic maintenance and growth induced by the diet supply (Mangel and Stamps 2001; Metcalfe and Monaghan 2001, 2003; Mangel 2003; Mangel and Munch 2005; Stoks et al. 2006; De Block and Stoks 2008*a*; Monaghan et al. 2009; Dmitriew 2011; Hou et al. 2011*a*, 2011*b*; Hou 2013). These studies suggest that the diet per se does not have a direct effect on life-span extension but that it is merely a way to manipulate growth. So, to understand the "dynamic and reversible" mechanism through which diet acts on life span and health maintenance, we should first analyze how diet acts on growth and then analyze how growth trades off with health and longevity.

In a previous study (Hou et al. 2011*b*), my colleagues and I studied how changes in nutritional environments before and after birth would affect organisms' health maintenance and life span. We developed a model illustrating that since the indirect energy cost of postnatal growth is more expensive than that of prenatal growth, individuals with small birth weight due to prenatal malnutrition but experience "catch-up" growth after birth would invest less energy in health maintenance and therefore have increased chances for adult diseases and shortened life spans (Hou et al. 2011*b*). In this study, I extend the model and analyze the dynamic postnatal growth process responding to DR and refeeding and its effects on health maintenance. The model predicts the reversal effects of diet on health maintenance and explains why refed animals live longer than the controls in some cases but not in others. More importantly, the model reveals that in some species, the indirect energy cost of growth increases during postnatal growth, so the expensive growth induced by refeeding later in life offsets the benefits of retarding cheap growth induced by diet restriction early in life, and therefore, in these species, refeeding leads to deleterious effects on health maintenance and life span.

Compensatory Growth Induced by Refeeding

Diet restriction retards growth. Refeeding previously restricted animals usually leads to compensatory growth (CG), which refers to a phase of accelerated growth (Williams 1981; Broekhuizen et al. 1994; Ali et al. 2003; Mangel and Munch 2005; Dmitriew 2011). In most species, CG has three patterns, namely, partial compensation, full compensation, and overcompensation, depending on the relationship between the ultimate sizes of the refed and continuously freely fed animals (Ali et al. 2003; Mangel and Munch 2005). Under certain circumstances, few fish species fail to compensate growth after refeeding starts (Ali et al. 2003). Since "no compensation" is rare and has only been observed in fish, in this article I will focus on the three common patterns listed above.

Several theoretical efforts have been made to understand the mechanism of CG (Williams 1981; Broekhuizen et al. 1994; Mangel and Munch 2005; Lee et al. 2011). These models successfully describe the trajectories of CG in different diet regimes (e.g., Broekhuizen et al. 1994) and explain how physiological and life-history characteristics determine the pattern of compensation (e.g., Mangel and Munch 2005). However, for the purpose of this study—that is, to analyze the energy trade-off between growth and health maintenance—many detailed parameterizations and complex mathematical expressions used in those growth models are not necessary. Here, I build on a simple energy model with five empirical parameters that accurately predicts the growth trajectories under DR and refeeding (Hou et al. 2011*c*). During growth, a fraction of the energy assimilated from food is synthesized and stored as new biomass, and the remaining fraction is used to fuel the total metabolic rate, B_{tot},

$$\begin{aligned} A &= B_{\text{tot}} + S \\ &= B_{\text{tot}} + E_{\text{c}}\frac{dm}{dt}, \end{aligned} \tag{1}$$

where A is the rate of intake of metabolizable energy from food, S ($= E_{\text{C}}[dm/dt]$) is the rate of energy stored as new biomass, E_{c} is the combustion energy content of a unit of bio-tissue, and dm/dt is the growth rate, that is, body mass (m) gain per unit time (t). If both rates of food assimilation and metabolism, A and B_{tot}, are known, growth curve, $m(t)$, can be obtained by solving equation (1) (see details in app. A; apps. A–D are available online). During refeeding, the different combinations of A and B_{tot} lead to different patterns of CG (fig. A1; app. A; figs. A1, B1, D1–D4 are available online). For example, if food assimilation rate, A, is higher and metabolic rate, B, is lower in refed animals than in controls, then growth ($\propto A - B$) will be overcompensated; in contrast, if A is lower, but B is higher, then growth will be partially compensated; meanwhile, if both A and B increase or decrease with the same degree in the refed animals, then the final body mass will be the same in the refed and control animals (full compensation). Considering the importance of food assimilation and metabolic rates for growth, I briefly review in appendix B the

theoretical hypotheses and empirical evidence regarding how animals with different life histories alter these rates as adaptive responses to the changes in diet regimes.

Different CG patterns are determined by the combinations of different food assimilation and metabolic rates. Unlike the life-history models developed by Mangel and Munch (2005) and Lee et al. (2011), the physiological model developed in this study does not include reproductive success, which interacts with foraging activity and oxidative damage. So, this model does not address the evolutionary mechanisms underlying the variation in the rates of food assimilation and metabolism, but its simplicity and accuracy will enable us to reveal the salient features of the trade-offs between growth and longevity induced by DR and refeeding. In the following sections, I will discuss how variations in these rates affect the production and repairing of oxidative cellular damage and how cellular damage is linked to longevity, one of the most important fitness components. I will also compare the life-history and physiological models of CG after the issue of damage and repair are discussed within the framework of the physiological model.

Energy Trade-Off between Growth and Longevity

I previously developed a model to quantitatively estimate the trade-off between growth and longevity (Hou et al. 2011*a*, 2011*b*; Hou 2013). Here, I extend this model and illustrate in detail the effects of food assimilation rate, activity level, metabolic rate, and biosynthesis on oxidative damage in animals experiencing CG. The model is based on three assumptions, the first two made for estimating the accumulation of oxidative damage and the third to link the damage level to longevity (life span). (1) The deleterious products of oxidative metabolism, such as reactive oxygen species (ROS), cause molecular and cellular damage (Barja 2004; Bokov et al. 2004; Balaban et al. 2005). Within a species, the relationship between the rates of oxygen consumption (metabolic rate) and ROS generation are proportional to each other (see review in Hou 2013). So, I assume that the rate of damage, H (damaged mass/time), is proportional to the total metabolic rate, B_{tot}; that is, $H = \delta B_{\text{tot}}$, where δ is a constant within a species, indicating the amount of damaged mass associated with one unit of metabolic energy. Here, the damaged mass can be cell membrane, protein, DNA, or other macromolecules (Mangel and Munch 2005). (2) Repairing the damage requires metabolic energy. The rate of repair, R (repaired mass/time), is proportional to the energy available for maintenance (repairing damage), B_{maint}, with a coefficient η; that is, $R = \eta B_{\text{maint}}$, where η is also a constant, indicating the amount of mass that can be repaired by one unit of metabolic energy. During growth, the energy for maintenance, B_{maint}, is the difference between resting metabolic rate, $B_{\text{rest}} = B_0 m^{\alpha}$, and energy allocated to biosynthesis (indirect cost of growth), $B_{\text{syn}} = E_{\text{m}}(dm/dt)$ (app. A; West et al. 2001; Hou 2013), where B_0 is the normalization coefficient; α is the scaling power, averaging about three-quarters; E_{m} is the energy required to synthesize one unit of bio-tissue; and dm/dt is the growth rate (body mass gain per unit time). The total metabolic rate, B_{tot}, is a multiple of the resting metabolic rate (Nagy et al. 1999; Hou et al. 2008); that is, $B_{\text{tot}} = f \times B_{\text{rest}} = f \times B_0 m(t)^{3/4}$, where f is a dimensionless constant, indicating the activity level of the animal (app. A). The net damage, $H - R$, accumulates. The mass-specific accumulated damage can be integrated as a function of time,

$$D(t) = \frac{1}{m(t)} \int_0^t (B_{\text{rest}} - \varepsilon \times B_{\text{maint}}) d\tau, \tag{2}$$

where $\varepsilon = \eta/(\delta f)$ is the effective maintenance efficiency. Substituting these relationships into equation (2), we have

$$D(t) = \frac{1}{m(t)} \left[\int_0^t (1 - \varepsilon) B_0 m(\tau)^{3/4} d\tau + \varepsilon \int_0^t E_{\text{m}} \frac{dm(\tau)}{d\tau} d\tau \right]. \tag{3}$$

Equation (3) estimates the accumulation of mass-specific molecular and cellular damage levels as a function of age, t. But why should the level of damage matter? How is it related to organisms' fitness? To quantitatively link damage level to life-history trait, here I introduce assumption 3 (Hou et al. 2011*b*; Hou 2013): When a critical fraction of body mass, C, is damaged, the animal reaches its life span; that is, $D(\text{LS}) = C$, where LS is life span. The threshold mass-specific damage, C, is assumed to be a constant within a taxon. It is difficult, if not impossible, to estimate the value of C. But a series of quantitative predictions can be derived from equation (3) and assumption 3 without knowing the value of C. These predictions agree well with empirical data from inter- and intraspecific studies (Hou et al. 2011*b*; Hou 2013). Interspecifically, equation (3) and assumption 3 offer a theoretical foundation for the long-standing "rate of living theory" for free-living animals (Pearl 1928; McCoy and Gillooly 2008); that is, lifetime mass-specific energy usage is roughly a constant cross species within a taxon. They also predict—and empirical data on mammals, birds, and invertebrates confirm—that the life span of animals within a taxon scales with body mass to a one-quarter power law (app. C; McCoy and Gillooly 2008; Hou et al. 2011*b*). Intraspecifically, equation (3) and assumption 3 establish a quantitative relationship between growth suppression

and life-span extension, which is strongly supported by empirical data from almost 200 studies of diet restriction on small rodents (app. C; Hou 2013). In appendix C, I give detailed derivation of these predictions from equation (3) and assumption 3 and discuss empirical tests of them. With assumption 3, the rate of damage accumulation, $D(t)$, estimated by equation (3) can be considered the rate of aging; that is, faster $D(t)$ means the animal reaches its life span sooner. Thus, it can also be used as a proxy of health maintenance.

Equation (3) has two terms. The first term, $D_B(t)$, integrates the damage caused by metabolism (B); the second term, $D_G(t)$, is the contribution of growth to the damage. If we assume that the energy for biosynthesis, E_m, is a constant during growth, then the growth term becomes

$$D_G(t) = \frac{\varepsilon E_m[m(t) - m(0)]}{m(t)} = \frac{\varepsilon E_m \Delta m(t)}{m(t)}, \quad (4)$$

where $\Delta m(t) = m(t) - m(0)$ is the body mass gain from birth to age t. Overall, the mass-specific accumulated damage can be expressed as

$$D(t) = D_B(t) + D_G(t) = \frac{1-\varepsilon}{m(t)} \int_0^t B_0 m(\tau)^{3/4} d\tau + \frac{\varepsilon E_m \Delta m(t)}{m(t)}. \quad (5a)$$

It has the dimension of energy/mass.

Equation (5a) attributes cellular damage to metabolism, D_B, and growth, D_G. Taking freely fed rats as an example, we can qualitatively estimate and compare the contributions of these two terms. Based on the parameters in table 1, the total mass-specific metabolic energy spent by a rat from birth to 200 days old is about $\int_0^{200\ \text{days}} B_0 m(t)^{3/4} dt / m(200\ \text{days}) =$ 67,800 J/g. The energy spent on bio-tissue synthesis from birth to 200 days old is $E_m \Delta m(200\ \text{days})/m(200\ \text{days}) =$ 6,000 J/g. The total metabolic energy is about 10 times larger than the energy for biosynthesis. However, D_B and D_G have different coefficients, $(1 - \varepsilon)$ and ε. Based on the first principle of biochemistry (Hou et al. 2011*b*) and data fitting (Hou 2013), the effective maintenance efficiency, ε, has been estimated to be very close to 1. For rats, previous calculation shows that the lower limit of ε is about 0.999 (Hou 2013). This means that $1 - \varepsilon$ is at least 1,000 times smaller than ε, and therefore, the metabolic term D_B is roughly 100 times smaller than the growth term D_G. Figure 1*A* illustrates the contributions of D_B and D_G to the overall damage level. During growth, the total damage level (fig. 1*A*, solid line) increases quickly, because body mass gain $\Delta m(t)$ increases quickly so that D_G (dashed line) increases quickly, whereas D_B (dotted line) remains small. After adult mass is reached, D_G stops increasing, and the overall damage increases slowly due to the slow increase of D_B. It is straightforward to calculate the slope of D_B after the adult mass is reached at large time t. Integrating the D_B term in equation (5a) for large t yields $D_B(t) \cong (1 - \varepsilon) B_0 M^{-1/4} t$. So, the slope of the damage curve in adulthood depends on the effective maintenance efficiency, ε, the metabolic normalization coefficient, B_0, and the adult body mass, M.

For DR and refed animals, if the growth curve, $m_{DR}(t)$, is obtained (app. A), then the model predicts the damage curve $D_{DR}(t)$ as a function of $m_{DR}(t)$,

$$D_{DR}(t) = D_{B,DR}(t) + D_{G,DR}(t) = \frac{1-\varepsilon}{m_{DR}(t)} \int_0^t B_{0,DR} m_{DR}(\tau)^{3/4} d\tau + \frac{\varepsilon E_m \Delta m_{DR}(t)}{m_{DR}(t)}. \quad (5b)$$

Table 1: Parameters required to produce figures 1, 3, A1, and D1–D4

Symbol	Biological meaning	Values	Source
m_0	Birth mass	5 g	Mass of an average rat
M	Adult mass	600 g	Mass of an average rat
β	Degree of diet restriction	60%	
τ	Age at which diet restriction starts	Day 42	
T	Age at which diet restriction stops	Day 126	
B_0	Metabolic normalization constant	.0223 W/g$^{0.75}$	Peters 1986
ε	Effective maintenance efficiency, $\varepsilon = \rho/(f\eta)$	.999	Hou 2013; Hou et al. 2011*b*
E_m	Energy required to synthesize one unit of biomass during postnatal growth	6,000 J/g	Table 2
E_0	Maximum energy required to synthesize one unit of biomass during growth	10,000 J/g	
a	Constant that controls the shape of $E_m(t)$	Dimensionless; $a = 0.5$	
E_C	Combustion energy of one unit of body mass	7,000 J/g	Cummins and Wuycheck 1971

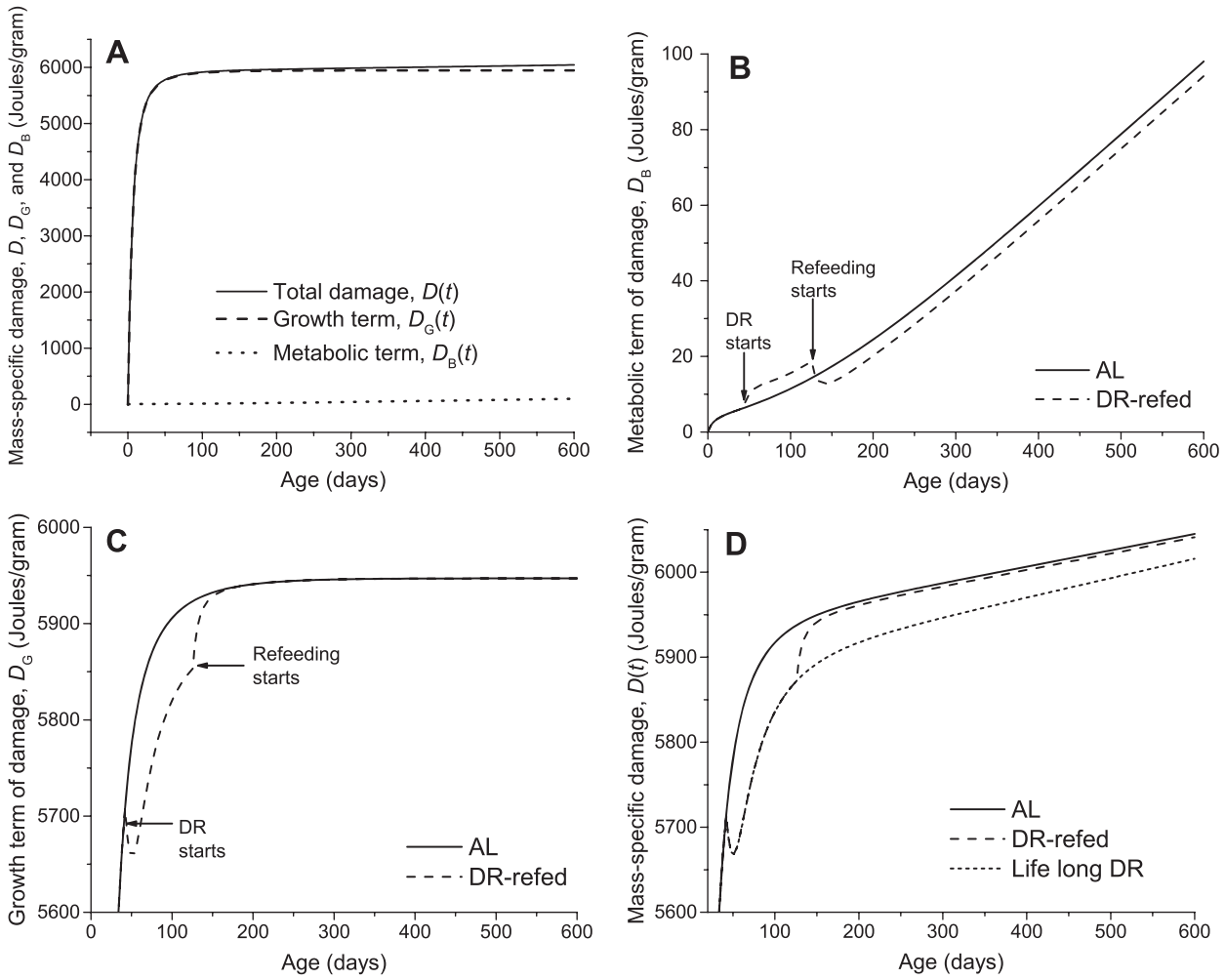

Figure 1: Mass-specific cellular damage levels as functions of age. *A*, Total damage ($D(t)$) and contribution from the growth ($D_G(t)$) and metabolic ($D_B(t)$) terms in animals fed ad lib. (AL). Compared to the growth term, the contribution from the metabolic term is small. *B*, Metabolic term of the damage in AL animals and animals refed after a period of diet restriction (DR). The difference in this term induced by refeeding is small. *C*, Growth term of damage in AL and refed animals. When growth is suppressed by DR and compensated with refeeding, the damage level changes accordingly. *D*, Total damage in AL, refed, and lifelong DR animals. *B–D* were produced based on the assumption of full compensatory growth.

Note, the metabolic scaling normalization coefficient of the refed animals, $B_{0,\mathrm{DR}}$, may be different than that of the controls. The change in $B_{0,\mathrm{DR}}$ can be caused by changes in body temperature (Gillooly et al. 2001; Hou et al. 2011*c*) or activity levels (Nagy et al. 1999; Hou et al. 2008). Using equations (5a), (5b), we can compare the damage levels in animals that are fed ad lib. (AL), in those on restricted diets (DR), and in refed animals. Figure 1*B* shows the contribution of the metabolic term in animals under different diet regimes. After DR has begun, since growth is retarded and body mass, $m_{\mathrm{DR}}(t)$, is smaller compared to AL animals, the mass-specific metabolic term, $[1/m_{\mathrm{DR}}(t)] \times \int_0^t B_{0,\mathrm{DR}} m_{\mathrm{DR}}(\tau)^{3/4} d\tau$, is higher than that of AL animals. After refeeding starts, the body mass of the refed animals increases quickly during CG, so their mass-specific metabolic term is lower than that of AL animals. Nonetheless, the difference in D_B induced by DR and refeeding is very small (fig. 1*B*), because the term D_B itself is small, as discussed above. Figure 1*C* shows how the growth term, D_G, contributes to the overall damage level in AL, DR, and refed animals. The extent of D_G is proportional to $E_m \Delta m(t)/m(t) = E_m[1 - m(0)/m(t)]$ (eq. [5a]), which is the mass-specific energy spent on synthesizing biomass $\Delta m(t) = m(t) - m(0)$, where $m(0)$ is mass at birth. When DR starts, growth is suppressed, that is, $1 - m(0)/m_{\mathrm{DR}}(t) < 1 - m(0)/m_{\mathrm{AL}}(t)$, so the damage level of DR animals is lower than that of AL animals. When refeeding initiates, animals

Table 2: List of studies, where refed animals live longer than ad lib. (AL) controls

Species	Strain	τ (days)	T (days)	M_{AL} (g)	M_{refed} (g)	β (%)	LS_{AL} (days)	LS_{refed} (days)	Source
Mouse	MRL/1	42	84	43.8	40.6	50	218	247	Kubo et al. 1984
Mouse	B10C3F1	21	448	32.9	28.4	50	1,094	1,251	Cheney et al. 1983
Mouse	B10C3F1	7	434	32.9	28.0	50	1,094	1,229	Cheney et al. 1983
Rat	S-D female	21	105	600	585	80	756	788	Nolen 1972
Rat*	S-D female	21	105	600	635	60	756	805	Nolen 1972
Rat	S-D male	21	105	881	848	80	706	723	Nolen 1972
Rat	S-D male	21	105	881	860	60	706	782	Nolen 1972
Rat	Wistar	30	395	557	489	60	931	1,043	Beauchene et al. 1986
Rat	F344	42	186	617	532	60	701	808	Yu et al. 1985

Note: In these studies, the adult body mass of refed animals is smaller than that of the AL controls. The Sprague-Dawley (S-D) female rat under 60% diet restriction (DR; indicated by an asterisk) is the only exception, where refed rats are heavier than the AL controls but also live longer. Variables τ and T are the ages at which diet restriction starts and stops; β is the degree of diet restriction; and LS_{AL} and LS_{refed} are the life spans of AL and refed animals, respectively.

experience CG, that is, $\Delta m_{refed}(t)$ increases, so the damage level of refed animals increases accordingly. Figure 1*D* compares the total damage levels in AL, DR, and refed animals. As discussed above, the contribution to total damage from the growth term, D_G, is much larger than that from the metabolic term, D_B, so the difference in the total damage between AL, DR, and refed animals is mainly attributed to the difference in their growths.

This model explains two phenomena observed in the diet restriction and refeeding studies. First, it predicts the reversible effects of DR (Dhahbi et al. 2004; Spindler 2005). Many studies have found that the effects of DR on health maintenance and aging dissipate shortly after refeeding (Merry 2002; Spindler 2005). In this model, as soon as DR stops and refeeding initiates, animals resume growth (fig. A1), which in turn causes the increase of molecular and cellular damage, as seen in figure 1. Second, the model also explains why, in some studies, refed animals still live longer than AL controls, although the damage level in refed animals increases quickly and the effects of DR are reversed after DR stops. In this model, DR suppresses growth by $\Delta m_{AL}(t) - \Delta m_{DR}(t)$ and channels energy that would be spent on biosynthesis to health maintenance; the amount of this energy equals

$$E_m\left(\frac{\Delta m_{AL}(t)}{m_{AL}(t)} - \frac{\Delta m_{DR}(t)}{m_{DR}(t)}\right) = E_m \times m(0) \times \left[\frac{1}{m_{DR}(t)} - \frac{1}{m_{AL}(t)}\right].$$

Refeeding counteracts the effect of DR on growth. But it may not fully compensate growth. If the final body mass of refed animals is smaller than that of the AL controls, that is, if $1/m_{refed}(t) > 1/m_{AL}(t)$, then the energy spent on health maintenance in refed animals is still larger than that of AL animals, $E_m \times m(0) \times [1/m_{refed}(t) - 1/m_{AL}(t)] > 0$. This means that the refed animals still have a longer life span than the controls. The empirical data support this prediction. In the refeeding studies that show that refed animals live longer than AL controls, the final body mass of the refed animals is always smaller than that of the AL controls (table 2).

However, the model cannot explain why full compensatory growth (full CG) often leads to worse health maintenance and a shorter life span. According to the model, if refeeding completely counteracts the effect of DR on growth so that the final body mass of refed animals reaches that of AL animals, that is, if $1/m_{AL}(t) = 1/m_{refed}(t)$, and if E_m is a constant during growth, then no energy would be channeled to health maintenance because $E_m \times m(0) \times [1/m_{refed}(t) - 1/m_{AL}(t)] = 0$. This means that in the case of full CG, the effects of DR on health maintenance would be completely offset by refeeding, and therefore, there would not be any difference in health status and life span between refed and AL animals. This prediction is contradictory to the empirical observations reviewed above. In the following section, I discuss four hypotheses that aim to explain why full CG can be deleterious in some species.

Why Full Compensatory Growth Is Deleterious in Some Cases

Full compensatory growth can be achieved if both rates of food assimilation and metabolism are higher in the refed animals than in the continuously AL-fed controls (app. A; fig. A1). Given assumption 1 that oxidative damage production rate is proportional to metabolic rate, it is possible that the deleterious effects of full CG originate from high damage production resulting from high metabolism. To test this hypothesis, I use equations (5a), (5b) to calculate the net damage level of refed CG animals with higher food assimilation and metabolic rates than the controls. The results show that with a certain assimilation rate, increasing B_0 (fig. D1) can result in full CG, but the final damage level in full-CG animals is the same as in the controls (see

details in app. D). This is because the damage contributed by metabolism is negligible compared to that contributed by growth, as shown in the previous section (fig. 1*A*–1*C*), so that the same amount of body mass gain in full-CG and control animals results in the same amount of damage accumulation, regardless of whether their metabolic rates are the same.

The second hypothesis is that refed animals allocate less energy to maintenance (repairing damages) so that the animals with full CG end up with the higher damage level. The available energy spent on maintenance, B_{maint}, is the difference between metabolic energy, B, and the indirect cost of growth, B_{syn}; that is, $B_{\text{maint}} = B - B_{\text{syn}}$, where B_{syn} is proportional to growth rate (app. A). In the case of full CG, the indirect cost of growth, B_{syn}, is the same in the refed animals as in the AL controls, so the only way for B_{maint} to decrease is to decrease the metabolic rate, B. In figure D2, I show that a decreased metabolic rate, together with a decreased food assimilation rate, can result in full CG but does not lead to a lower damage level in refed animals (app. D). The reason is the same as in the previous case, where metabolic rate increases in refed animals; that is, the metabolic contribution to damage is negligible compared to growth.

Metabolic rate in refed animals may increase or decrease for two reasons. First, basal metabolic rate may change, which can be reflected in changes in the scaling normalization coefficient, B_0. Second, the activity level, which is the multiple of basal metabolic rate (Mangel and Munch 2005; Hou et al. 2008), can also alter the coefficient, B_0, in equations (5). As shown above and in appendix B, the damage level is mainly determined by growth (body mass gain), so changes in either basal metabolic rate or activity level do not have a large impact on damage level directly. However, changes in metabolism (either basal rate or activity level) may alter the energy allocated to growth and therefore have influence on damage level indirectly. During refeeding, both food assimilation rate, A, and metabolic rate, B, can vary at the same time, and growth is determined by the difference between A and B ($\propto A - B$). So, a higher B may lead to higher, lower, or the same final body mass in refed animals compared to the controls (app. A), depending on the food assimilation rate. Thus, in the case of refeeding, it is difficult to predict without knowledge of the food assimilation rate how metabolic rate affects growth and, in turn, damage level. In the case of DR, however, the food assimilation rate, A, is more or less fixed. The fixed food assimilation rate imposes a trade-off between metabolism and growth (Derting 1989; Hayes et al. 2014); that is, high metabolic rate (either basal or activity) suppresses growth ($\propto A - B$), which in turn will lead to a lower damage level. So, under DR, changes in metabolic rate do have an impact on damage, but this impact is exerted through the effect of that damage on growth. In appendix B, I review empirical data on how species with different life histories alter their metabolic rates as adaptive responses to diet restriction. Here, I predict that under the same level of food restriction, species that prioritize growth and lower metabolic rate will benefit less in terms of health maintenance than those that keep their metabolic rate the same, or even increase it, at the cost of growth. I call for dedicated manipulative experiments to test this prediction.

The third hypothesis is that the effective maintenance efficiency, ε, may be smaller in refed animals. This efficiency reflects animals' capability of repairing damages, which was estimated to be very close to 1 (Hou et al. 2011*b*; Hou 2013). However, if the refed animals are relatively inefficient at repairing damage, then even full-CG animals may have higher damage levels than the controls. In figure D3, I show that lower ε does lead to higher damage level. But, it must be pointed out that this is an ad hoc hypothesis. There is no empirical evidence or theoretical foundation showing that the efficiency of maintenance is actually lower in the refed individuals of any species.

Now I discuss the fourth hypothesis, which, I will show, has both empirical and theoretical support and is able to explain why full CG can be deleterious. When deriving equations (5), I assumed that the energy required to synthesize a unit of bio-tissue, E_{m}, is a constant during growth. Previous studies have shown that the growth trajectories of AL animals (West et al. 2001) and DR animals in some species (Hou et al. 2011*c*) can be accurately predicted from equations (A2)–(A4) in appendix A with constant values of E_{m}. However, in principle, the value of E_{m} may vary during growth (Sears et al. 2012). This is because body compositions, such as the percentages of protein, fat, and water, vary during ontogeny (Eisen 1976; Robbins 1983; Oltjen et al. 1986). Since synthesizing different components requires different amounts of energy, changes in the compositions will cause changes in E_{m}. To be rigorous, instead of a constant E_{m}, equations (5) (and eqq. [A2]–[A4]) should have a function of age, $\sum_i m_i(t) \times E_{\text{m},i} / \sum_i m_i(t)$, where $m_i(t)$ is the ith body component as a function of age, and $E_{\text{m},i}$ is the energy required to synthesize one unit of the ith component. It would be difficult, if even possible, to derive the exact expression of $E_{\text{m}}(t)$ as a function of age from the first principles (Eisen 1976; Parry 1983), because it requires data on body composition changes during growth and calculation of the energy cost on synthesizing each component. However, we can assume an expression of $E_{\text{m}}(t)$ with a few free parameters and obtain the values of the free parameters from the fitting of empirical growth data.

Empirical evidence indicates that in some species, especially in small rodents, $E_{\text{m}}(t)$ has a sigmoidal shape. It

Table 3: Results of fitting the empirical growth data of species that have a constant or nearly constant energy cost of biosynthesis, E_m

Species	Constant E_m (J/g)	R^2 for constant E_m	E_0 (J/g)	a	R^2 for varying $E_m(t)$	Source
Guinea pig	11,097	.983	10,900	0	.982	West et al. 2001
Pig	5,878	.956	5,694	0	.951	West et al. 2001
Rabbit	5,365	.993	5,281	0	.992	West et al. 2001
Shrew	1,739	.974	1,739	0	.972	West et al. 2001
Quail	2,429	.968	2,366	0	.966	van der Ziel and Visser 2001
Robin	1,310	.965	1,307	0	.961	West et al. 2001
Dog	5,027	.96	6,495	.325	.958	Kealy et al. 2002

Note: Parameters are defined in table 1.

has been known for several decades (Bailey et al. 1960; Sutherland et al. 1974; Eisen 1976) that in mice and rats, protein, ash, and fat percentages increase and water percentage decreases from birth to weaning; after weaning, protein and ash percentages remain stable, fat percentage increases, and water percentage decreases. Since the ratio of protein and water increases with age at a decreasing rate until it becomes a constant at the age of "chemical maturity" (Eisen 1976), Bailey et al. (1960) have recommended the protein : water ratio as an index of "physiological age." The energetic cost of synthesizing protein is high, whereas that of synthesizing water is almost zero. So the variation of the protein : water ratio during growth leads to an increasing $E_m(t)$, which reaches a constant at maturity. Similarly, the ratio of fat content to water also increases over ontogeny (Bailey et al. 1960; Sutherland et al. 1974; Eisen 1976). Since fat is also more energetically expensive to synthesize than water, the increase of this ratio enhances the increase in E_m. Based on this evidence, I assume that $E_m(t)$ has the format

$$E_m(t) = E_0\left(1 - a \times e^{-B_0 t/4E_0M^{1/4}}\right),$$

where E_0 and a are two parameters controlling the magnitude and shape of the curve, which is sigmoidal, just like the ratio of protein : water over ontogeny. In principle, the format can be any function with similar shape. But this particular function has two advantages. First, it has exactly the desired shape, that is, increasing quickly at the beginning of growth and leveling off after adult mass is reached. Second, it shares some parameters with the growth curve (B_0 and M, which affect the shape of the curve), so that the number of extra parameters that need to be introduced is minimal. Parameter E_0 sets the maximum value of the function. At large age t, $E_m(t)$ reaches E_0. Parameter a ranges between 0 and 1. When $a = 0$, the function reduces to a constant E_0; when $a = 1$, the function has the largest variation during growth. Figure D4 shows a few curves with different values of parameter a.

Substituting $E_m(t)$ into the growth equation, equation A2, we have the growth curve,

$$m(t) = M \times \left[1 - \frac{(1-a)\left(1 - [m_0/M]\right)^{1/4}}{e^{B_0 t/(4E_0M^{1/4})} - a}\right]^4,$$

where m_0 is mass at birth. When $a = 0$, this growth curve reduces to the original form, which assumes a constant E_m. The parameters in the curve, a and E_0, can be obtained by fitting the empirical growth data. I fit the empirical growth data from 19 species/strains using two theoretical growth curves with a constant E_m and a varying $E_m(t)$. The results are shown in tables 3 and 4. For the species listed in table 3, the values of parameter a are either 0 or small, and a constant E_m accurately describes the growth curve, because the R^2 value of the fitting with a constant E_m is close to 1. So, there is no difference in the fittings with a constant or varying E_m in these species. In most mouse and rat strains as well as a cow listed in table 4, however, the values of parameter a are large and close to 1, which indicates that $E_m(t)$ increases substantially during growth. For these species, I used Akaike Information Criterion (AIC) to compare the quality of the two theoretical curves with a constant and varying E_m. The AIC values of the curves with a varying $E_m(t)$ are significantly smaller than those with a constant E_m, and the AIC weight is nearly 0 (table 4), so varying $E_m(t)$ describes the growth better than constant E_m in these species. Figure 2 illustrates the differences in the shapes of growth and the fittings of a few species. The species in figure 2*A* grow quickly at the beginning, and after a turning point, the body mass quickly reaches the adult level. The theoretical curves with a varying $E_m(t)$ (fig. 2*A*, solid line) completely overlap with the curves with a constant or nearly constant E_m ($a \approx 0$; fig. 2, dashed curves), indicating that in these species, a constant E_m is sufficient to describe the growth curves accurately. In contrast, the species in figure 2*B* grow quickly at the beginning but slow down for a considerably long period before the body mass reaches its ultimate level.

Table 4: Results of fittings the empirical growth data of species that have a varying energy cost of biosynthesis, $E_m(t)$

Species	Strain	Constant E_m (J/g)	AIC_{const}	E_0 (J/g)	a	AIC_{var}	AIC weight	Source
Cow		5,012	434	12,866	.792	389	2.0×10^{-10}	West et al. 2001
Mouse female*	DBA/2N	8,337	−62	9,074	.156	−60.5	2.04	Sprott 1997
Mouse male	DBA/2N	9,326	8.5	17,269	.667	−34.7	4.0×10^{-12}	Sprott 1997
Mouse female	CD2F1	1,381	25.8	15,701	.967	−26.2	5.1×10^{-12}	Nelson and Halberg 1986
Mouse female	C57BL/6N	12,855	65.4	98,733	.935	−7.4	1.6×10^{-16}	Sprott 1997
Mouse male	B6/D2F1	14,258	75.5	71,460	.908	26.6	2.4×10^{-11}	Sprott 1997
Mouse male	B6/C3F1	10,320	65.7	78,302	.935	15.7	1.4×10^{-11}	Sprott 1997
Mouse female	SHN/C3H	17,452	60.8	73,968	.901	31.9	5.2×10^{-7}	Koizumi et al. 1992
Rat male	F344	7,262	159.0	24,630	.873	121.7	8.0×10^{-9}	Frame et al. 1998
Rat female	F344	7,127	69.0	81,364	.961	13.1	7.2×10^{-13}	Sprott 1997
Rat male	S-D	5,868	813.7	17,734	.853	611.5	1.2×10^{-44}	Hubert et al. 2000
Rat female	S-D	5,956	252.2	29,471	.926	161.8	2.3×10^{-20}	McShane and Wise 1996

Note: S-D = Sprague-Dawley. AIC_{const} and AIC_{var} are Akaike Information Criterion values for models with constant and varying E_m, respectively, calculated as $AIC = N \times \ln(RSS/N) + 2K + [2K(K + 1)/N - K - 1]$, where N is the sample size, K is the number of parameters in the model, and RSS is the residual sum of square. The AIC weight is calculated as $e^{0.5(AIC_{var}-AIC_{const})}$. In these species, except for the female DBA/2N mouse (indicated by an asterisk), a varying $E_m(t)$ greatly improves the fitting, because AIC_{var} values are smaller, and AIC weight is almost 0, indicating that the model with constant E_m is zero times as probable as the model with varying $E_m(t)$ to minimize the information loss.

Growth rate is negatively correlated to the energetic cost of growth. When synthesizing a unit of biomass becomes more energetically expensive, growth slows down accordingly. This is what is shown in figure 2*B*; that is, the transition between fast and slow growth before adult mass is reached reflects the increase in the energetic costs of biosynthesis, E_m.

An increasing $E_m(t)$ explains why full compensatory growth is deleterious in some species, such as rats and mice. As analyzed in the previous section, DR retards growth, and refeeding offsets this effect by CG. If E_m increases during growth, then gaining a unit of body mass early in life is energetically cheaper than gaining it later. Thus, although the body mass reduction induced by DR is equal to the body mass gain induced by refeeding, the energy spent on CG is larger than the energy saved by retarded growth. Overall, the animals that experience retarded and then full compensatory growth allocate more energy to growth and less to health maintenance than the ones with normal growth. Figure 3 shows that growth suppressed by DR is fully compensated with refeeding, but the total damage level in the refed animal is higher than in the AL control.

Comparison between the Physiological and Life-History Models of Compensatory Growth

Based on the conservation of energy, I have used a series of physiological characteristics of animals over ontogeny to illustrate the trade-offs between growth and damage accumulation. Two previously proposed life-history models have also taken growth-dependent physiological damage into account for understanding the evolutionary mechanisms underlying compensatory growth and its impact on animal behaviors, such as foraging activity and other life-history traits, including reproduction and life span (Mangel and Munch 2005; Lee et al. 2011). Here, I briefly review these models and compare them with the model developed for this study.

Mangel and Munch (2005) aimed to understand what causes different patterns of CG by considering CG as adaptive and measuring its fitness consequences. The authors assumed that the rate of net damage accumulation is the sum of a catabolic term, which is proportional to the product of body mass and activity level, and a self-reinforcement term, which is proportional to the current damage level, minus a term of repair effort, which is determined by body mass and damage level. Repair is modeled as the amount of energy allocated to the reduction of damage. In this model, growth is described in terms of the rates of energy acquired and lost through metabolism, both of which are governed by animals' activity level. The authors modeled survival during a nonreproductive period as a function of body mass, activity, and damage and then assumed that fitness is determined by the survival rate and the reproductive values associated with the size and damage attained by the end of the nonreproductive period. They then used the optimal activity schedule to conduct virtual compensatory growth experiments and used the results to determine which physiological and life-history parameters are associated with which type of CG.

The purpose of Mangel and Munch (2005) is to understand, from the viewpoint of adaptation, why and how CG evolves different patterns. In contrast, my model aims

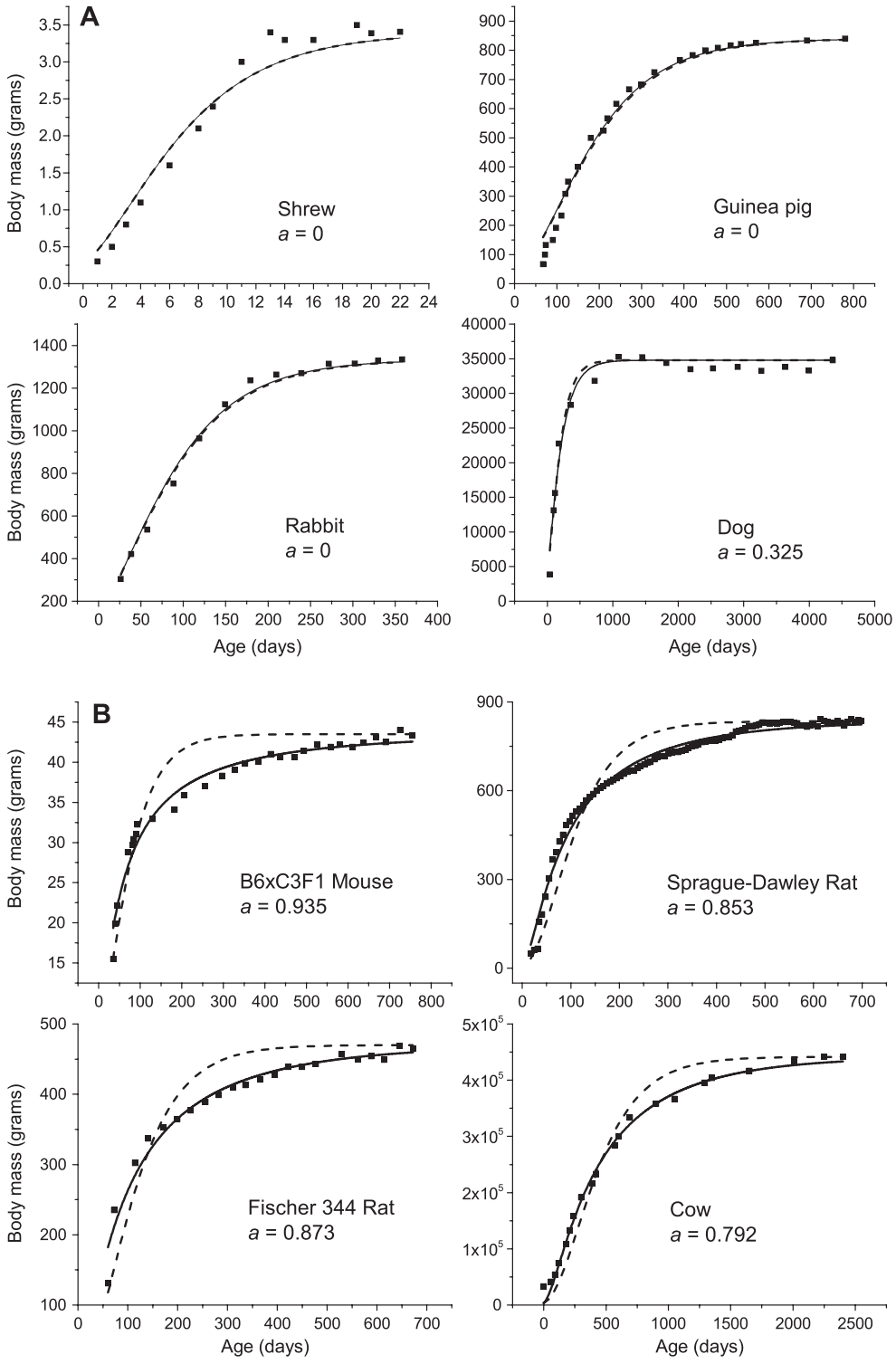

Figure 2: Fittings of empirical growth curves (squares) with varying total energy required to synthesize one unit of bio-tissue ($E_m(t)$; solid lines) and constant energy cost of biosynthesis (E_m; dashed lines). *A*, Species that have constant or nearly constant E_m during growth. In these species, the solid lines (varying $E_m(t)$) and dashed lines (constant E_m) of the fittings overlap, and the dashed lines are invisible. *B*, Species that have increasing E_m during growth. Varying $E_m(t)$ greatly improves the goodness of fit in these species. Detailed Akaike Information Criterion (AIC) values, AIC weights, and sources of empirical data are listed in tables 3 and 4. The curves show average growth in a certain species. Most of the curves come from studies investigating the effect of diet restriction on growth, in which animals were not allowed to reproduce. Some studies did not give error bars, so error bars are not included here.

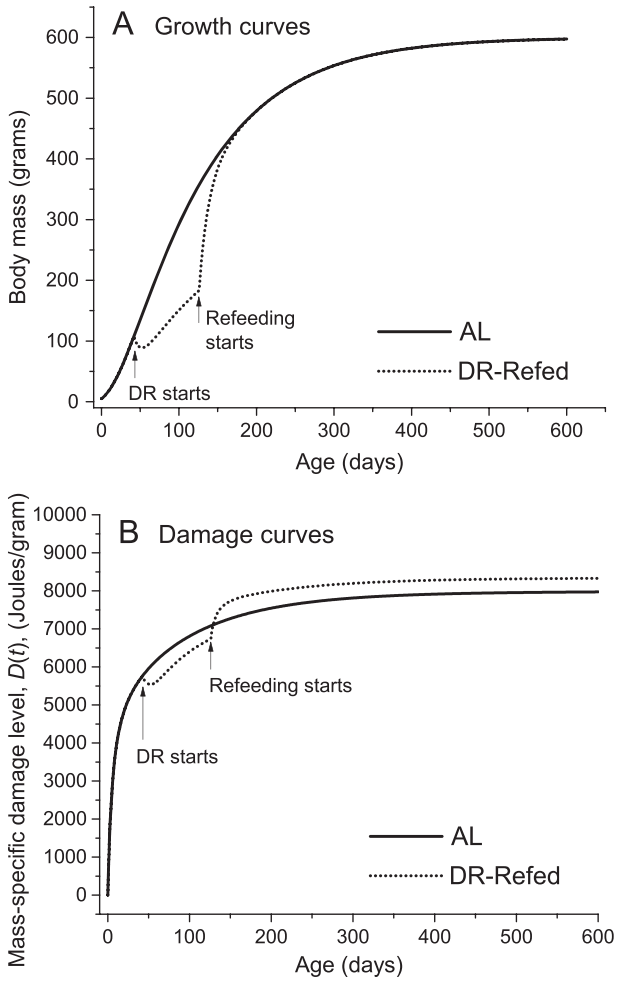

Figure 3: Growth curves (*A*) and damage curves (*B*) of animals fed ad lib. (AL) and animals refed after a period of diet restriction (DR-refed) with increasing energy cost of biosynthesis, E_m. Although retarded growth induced by diet restriction (DR) is completely compensated by refeeding, and the AL and refed animals have the same ultimate body mass, the damage level is higher in refed animals due to the increasing energy cost of growth. The parameters used to produce figure 3 are listed in table 1.

to estimate the effects of a given pattern of CG on longevity and health maintenance, using damage level as a proxy. In my model, the different patterns of CG are the results of different rates of food assimilation and metabolism during refeeding (app. A). Similar to Mangel and Munch (2005), these rates vary in my model. However, since my model includes only one life-history trait—longevity—and does not consider reproductive success, it does not address the evolutionary mechanisms for the variations in these rates. Instead, my model treats them as given empirical inputs for estimating growth curves and associated damage level.

Mangel and Munch (2005) concluded that compensatory growth would not occur in the absence of damage. The authors also predicted how each type of CG depends on the damage parameters. In brief, short-term CG (referring to individuals exhibiting faster-than-normal growth immediately after food restriction is lifted) is associated with low damage-dependent mortality; long-term CG (referring to faster-than-normal growth at some later time) occurs when damage-dependent mortality is high; overshooting CG (full or overcompensatory growth) requires high repair capacity. Here, I compare the results from this life-history model with the results from my physiological model. In both models, damage accumulation is an inevitable physiological result of growth and dissipative oxidative metabolisms. However, these two models have different emphases. Mangel and Munch (2005) were more interested in how CG evolves and suggested that damage parameters are the key to understanding CG. By considering survival rate and reproductive values and applying optimal activity schedule, they showed from evolutionary viewpoints that different types of CG are associated with different damage-dependent mortalities and repairing abilities. This study, on the other hand, is more interested in the physiological consequences of CG on damage accumulation and, therefore, its effects on longevity. By applying the principle of energy conservation and allometric scaling laws, my model establishes quantitative relationships between damage accumulation rate and growth rate and explains the effects of diet restriction (growth suppression) and refeeding (compensatory growth) on an animal's life span. The results from these two models can be reconciled. My model predicts that damage level is positively correlated to growth rate. Compared to the long-term CG, the short-term CG has a higher growth rate, which in turn leads to a higher damage level. If damage-dependent mortality is high, then damage associated with this type of CG will result in low survival and, therefore, low overall fitness. So, from the viewpoint of adaptation, if short-term CG can happen, damage-dependent mortality must be low, which is predicted by Mangel and Munch (2005). Moreover, my model predicts that full and overcompensatory growth ("overshooting" in Mangel and Munch's model) cause more damage than partial CG. Again, if CG is adaptive, then the repair capacity must be high in the case of overshooting, so that the high damage associated with this type of CG can be offset for overall fitness, as predicted by Mangel and Munch (2005).

Building on Mangel and Munch's work (2005), Lee et al. (2011) developed and compared four life-history models to understand the consequences of CG on reproduction. The authors studied "the trade-offs faced by vertebrate ectotherms between early growth and damage in relation to both temperature and food supply, taking into

account the level of activity required to obtain a given amount of food and the resulting pattern of energy allocation" (Lee et al. 2011, p. 775). The authors tested the predictions of four models on growth curves, activity levels, reproductive output, and damage level against the empirical data from three-spined sticklebacks whose growth had been manipulated by ambient temperatures. Fish were divided into three cohorts. The first cohort was reared at 6°C for 4 weeks and then switched to 10°C until the breeding season (cohort 6°–10°C); the second cohort was reared at 14°C for 4 weeks and then switched to 10°C (cohort 14°–10°C); and the third cohort was reared at 10°C throughout the experiment (cohort 10°–10°C). The authors found that the most accurate predictions were made by the model that considers the relationship between activity and mortality risk, the response of growth to physiological damage, and the energy partition between somatic growth, gonadal growth, and damage repairing. The model predicts that the damage level was highest in cohort 6°–10°C and lowest in cohort 14°–10°C. The growth rate of fish is positively correlated with ambient temperature. So after the temperature change, cohort 6°–10°C experienced an accelerated growth, whereas the growth of cohort 14°–10°C was decelerated. The authors concluded that "decelerated growth" has positive effects; that is, fish with fast growth earlier but suppressed growth later perform better than animals that grow steadily at a constant temperature.

The focus of Lee et al. (2011) was to understand the consequences of CG on reproduction. But to compare the results from their study and this one, we will focus on the relationship between growth rate and damage level. It is not surprising that animals with decelerated growth accumulate less damage than those with steady growth. After all, numerous diet restriction studies have shown that accumulation of damage was suppressed, while growth was decelerated. What we are interested in here is that fish experiencing compensatory growth (cohort 6°–10°C) had the highest damage level. Both Lee et al.'s (2011) model and my model consider the trade-off between growth and health maintenance (damage repairing), so both models attribute the high damage level in this cohort partially to compensatory growth. However, Lee et al.'s model assumes that damage level is proportional to activity level (multiples of basal metabolism), and the cohort 6°–10°C had the highest activity, so the high damage level in this cohort is also partially due to high activity. In contrast, my model, based on the physiological parameters, predicts that compared to the growth term in equations (5), the metabolic contribution (including activity) to damage is negligible (fig. 1). My model also predicts that the increasing cost of growth (E_m) enhances damage accumulation, even if the net body mass gain is the same in the treatment and control animals (fig. 3). From the empirical data on three-spined sticklebacks, it is impossible to tell whether activity (and metabolic rate) is a major influence on damage and whether the cost of biosynthesis, E_m, increases over ontogeny. I call for more manipulative experiments that measure cellular damage and biosynthesis cost with activity (and metabolism) being controlled to further test the theoretical models.

Conclusion

Body mass and age at a certain development stage, for example, the first reproduction, are important life-history traits that fundamentally affect organisms' fitness (Stearns 1992; Gotthard 2001; Roff 2001). However, it is not sufficient to understand the life-history links between age and body mass if only the "two dimensions of age and size" are considered (Gotthard et al. 1994). Gotthard et al. (1994) argued that "for understanding the life-history variation, it is necessary... to take into full account the triangular nature of the relationship between size, time and growth rate" (p. 281). The model presented here, as well as the other life-history models discussed above (Mangel and Munch 2005; Lee et al. 2011), echo Gotthard et al. (1994) from the energetic viewpoint. Growth rate is under selection, even if age and body mass at a certain developmental stage are fixed. This is because growth rate may vary in different ways to reach a desired body mass within a certain development time, and different energetic costs of growth lead to different levels of cellular damage, mortality, and reproductive success (Mangel and Munch 2005; Lee et al. 2011). Nonetheless, if the energy required to synthesize one unit of the biomass, E_m, is a constant, then it would not matter how growth rate varies, because as long as the total body mass gain and the development time are fixed, the total amount of energy spent on growth (and, therefore, the associated cellular damage) is fixed. The model suggests that a varying growth rate will not make a difference in damage level and mortality unless the energy cost of growth varies at different ages. In other words, although animals with full compensatory growth and normal growth achieve the same body mass within the same development time, fast growth later in life with a higher cost leads to higher total energy on growth and, therefore, a higher damage level in the animals with compensatory growth.

In summary, the model presented here associates cellular damage and health maintenance to the energetic cost of growth and explains the dynamic and reversible effects of diet on health. More importantly, the model reveals that variation in growth rate during ontogeny makes a difference in the health maintenance and overall fitness of an-

imals, if the energetic cost of growth varies during ontogeny.

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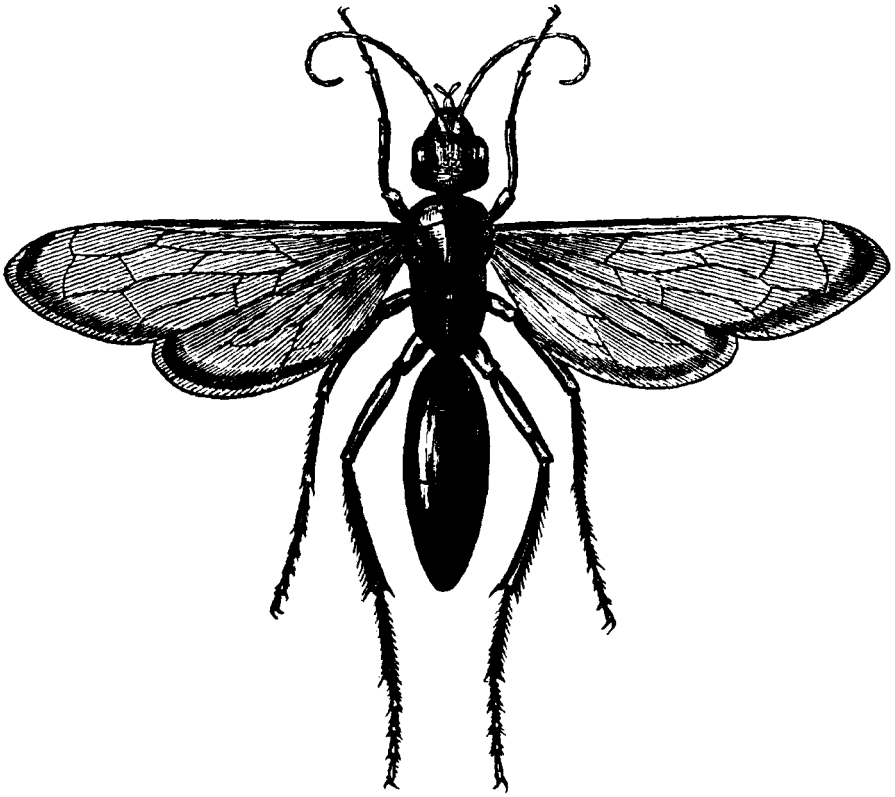

"The large, red-winged 'Tarantula Killer' (the *Pompilus formosus* of Say) [...] takes its prey by stinging, thus instantly paralyzing every limb of its victim. The effects of the introduction of its venom [are] as sudden as the snap of the electric spark." From "The Tarantula Killers of Texas" by G. Lincecum (*The American Naturalist*, 1867, 1:137–141).