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THE EVOLUTIONARY ECOLOGY OF SENESCENCE

Environment, damage and senescence: modelling the life-history consequences of variable stress and caloric intake

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Summary

1. Senescence is intimately connected with physiological state, which is affected by the environment. Two aspects of the environment – stress and caloric intake – are investigated in the context of senescence, particularly in the context of repair of damage caused by endogenous and exogenous stressors.

2. In a simple life-history model, the organism is characterized by size (affecting reproductive success) and accumulated damage (affecting survival) at age. The modelled organism experiences an imprinting period, at the end of which it estimates the level of food and damaging sources in the environment. From those, an optimal life history is determined, assuming that reproduction is an allometric function of size.

3. The optimal life history involves a behavioural trait (intensity of foraging) and an allocation process (amount of energy allocated to repair of damage). Subsequent to the imprinting period, the organism lives experiencing levels of stress or caloric intake that differ from those during the imprinting period. The mismatch is such that either the caloric intake is greater post-imprinting than during imprinting or environmental stress is smaller post-imprinting that during imprinting.

4. Since reproduction is given allometrically and the organism cannot shrink, there is no reproductive senescence. In all cases, mortality increases with age. Senescence is caused by accumulated damage and we focus on the allocation of potential growth to repair and environmental mismatch.

5. In the case of stress mismatch, the general qualitative result is that both the optimal level of activity and the allocation to repair are greater than their values in the case of no mismatch and they are positively correlated. For caloric mismatch, during the post-imprinting period the intensity of foraging is greater than that predicted if there were no mismatches. However, we predict either a negative correlation between genes characterizing activity and repair (for small mismatch), no correlation (for moderate mismatch) or positive correlation (for large mismatch). Furthermore, caloric mismatch is predicted to lead to a considerable reduction in lifetime reproduction, but stress mismatch is predicted to induce an increase in stress resistance throughout life with little cost to lifetime reproduction.

Key-words: life-history theory, hormesis, foetal programming, metabolic syndrome, damage, foraging

Introduction

More than 70 years ago, Raymond Pearl and John Miner (Pearl & Miner 1935, p. 78) wrote that 'for it appears clear that there is no one universal "law" of mortality ... different species may differ in the age distribution of their dying just as characteristically as they differ in their morphology'. They drew this conclusion through the comparative study of life tables, survivorship curves and death rates of a variety of organisms (*Drosophila*, hydra, roach, slug and rotifer). The challenge that arises from a lack of a single, universal law of mortality is that one needs a means of characterizing the different kinds of trajectories of mortality. Pearl and Miner thought through this too: 'but what is wanted is a measure of the individual's *total* activities of all sorts, over its *whole* life; and also a numerical expression that will serve as a measure of

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net integrated effectiveness of *all* the environmental forces that have acted upon the individual throughout its life' (p. 77).

At first blush, it may appear that Pearl and Miner's vision is answered through the Euler–Lotka equation, which connects survival to age t, $l(t)$, fecundity at age t, $b(t)$, and the growth rate, r, of a genotype with those schedules of survival and fecundity according to $1 = \sum_t e^{-rt} l(t)b(t)$. That is, this equation is solved for r, which depends upon the functions of age $\{l(t), b(t)\}$. It is this equation that Hamilton (1966) used to make more precise the arguments of Medawar (1952) and Williams (1957) on mutation accumulation and antagonistic pleiotropy, respectively, as mechanisms of ageing (also see Rose *et al*. 2007).

As powerful and deep as that theory is, the Euler–Lotka equation cannot be the entire story. Treating fecundity and survival as simple schedules of age, for example, ignores the major features that often make biology most interesting: density-dependence, physiological state and individual variation. Pearl and Miner clearly saw that these were important and if one reads the classic works of Brody (1945) and Comfort (1956), it is clear that they too saw the importance of these factors. Two recent developments should give optimism concerning our ability to ultimately carry out the program that Pearl and Miner called for. The first is the development of state-dependent life-history theory (e.g. Mangel & Ludwig 1992; Houston & McNamara 1999; Clark & Mangel 2000; Mangel 2006) and its application to problems of the evolutionary ecology of ageing (e.g. Mangel 2001; McNamara *et al*. 2004; Mangel & Munch 2005). The second factor is the formalization of evolutionary biodemography (reviewed in Carey 2001; Carey & Judge 2001), which can be understood as the merging of demography (traditionally a statistical science of the size, density, distribution and vital statistics of populations) with evolutionary thinking (Charlesworth 1994). The goals of evolutionary biodemography are broad and deep: to use the comparative method to explore similarities and differences in patterns of mortality across species (much as Pearl and Miner did) and to understand these patterns as the result of evolution by natural selection (which is a key mechanism for generation of such patterns). Carey (2001) and Carey & Judge (2001) identify the following biodemographic principles concerning longevity: (i) longevity is adaptive; (ii) life span is indeterminate; (iii) reproduction is a fundamental longevity determinant; and (iv) the heritability of individual life span is small. They identify the following concerning mortality: (i) although mortality rate generally increases with age, it is possible for mortality to slow at oldest ages; (ii) female mortality advantage is not universal; (iii) mortality trajectories are facultative; and (iv) selection shapes mortality trajectories. The challenge is how to make these principles operational. For example, a biodemographic theory should predict the structure of mortality trajectories as a result of life-history adaptation. In this paper, I show that two apparently disparate life-history phenomena, when considered from the proper perspective, can be seen as two sides of the same coin.

HORMESIS AND FOETAL PROGRAMMING LEADING TO METABOLIC SYNDROME

Hormesis is defined differently in different sub-disciplines of biology (Calabrese 2006; Calabrese & Baldwin 2003; Mattson 2008a) In toxicology, hormesis refers to a biphasic dose–response curve but in population biology or medicine hormesis is said to occur when exposure of an individual to a mild stress at a young age leads to increases in components of fitness (e.g. longevity, reproductive output, resistance to stronger stresses) at middle age or beyond. [For reviews see Minois & Rattan (2003), Rattan (2004), Calabrese & Blain (2005) or Arumugam *et al*. (2006). A spate of review articles appeared at the start of 2008, just as this paper was being completed: Calabrese (2008), Rattan (2008), Gomez-Cabrera, Domenech & Viña (2008), Gomez-Pinilla (2008), Marini *et al*. (2008), Mattson (2008a,b), Radak, Chung & Goto (2008a), Radak *et al*. (2008b) and Sachdev & Davies (2008). They make good reading.] The fundamental scientific discovery concerning hormesis was made by Hugo Schulz in 1888 (Calabrese 2005a,b) who showed that although disinfectants at high doses inhibited the metabolism of yeast, at low doses the same chemicals enhanced the metabolism. Similarly, it has long been known (Luckey 1982) that very small doses of ionizing radiation provide benefits to growth, fecundity, health and longevity, and that the mechanisms of such benefits are multi-faceted. The notion is that the young animal experiences a non-fatal stress of relatively short duration [because prolonged exposure to stress has many harmful effects (Hadnay *et al*. 2006)] that induces an adaptive response which carries on throughout its life. Calabrese (2005a) suggests that the long and bitter feud between traditional and homeopathic medicines (which has a close historical association with hormesis) lead to the rejection of hormesis when trying to understand dose–response relationships.

Examples of hormesis abound. It can be induced by hydrogen peroxide (Le Bourg 2007a), temperature (Le Bourg 2007b; Scannapieco *et al*. 2007); dietary restriction (Cypser, Tedesco & Johnson 2006); a variety of drugs and pathogens (Murado & Váquez 2007) or ionizing radiation (Parsons 2000; Moskalev 2007). Recent work (Brunk 2007) shows that growing cells in 40% ambient oxygen (an extremely high level of oxygen) conditions them to resist subsequent oxidative stress.

Hormesis is now recognized as an important manipulation in the study of ageing and hormesis has been proposed (with associated controversy) as the mechanism for longevity extension by dietary restriction (Masoro 1998, 2006; Minois 2000; Le Bourg 2003). For example, the life span of *Caenorhabditis elegans* is extended following mild treatments of heat early in life, with the greatest increase in life span correlated with treatments earlier rather than later. Olsen, Vantipalli & Lithgow (2006) hypothesize that the magnitude of the hormetic effect is related to the level of expression of certain heat shock proteins. In some senses, hormesis induces anti-senescence.

The notion of foetal origins of adult diseases began with observations that areas of the UK with high rates of neonatal

mortality (and thus presumably impaired foetal growth) were also ones with high levels of heart and kidney disease for the surviving adults (Barker 1998, 2004; Gluckman & Hanson 2005). The key is longitudinal studies (e.g. Barker *et al*. 2002; Robinson & Barker 2002; Nussey *et al*. 2008; Wilson, Charmantier & Hadfield 2008) and many of them have suggested that rapid postnatal or childhood growth, which is likely to cause stress to the organism, is associated with a variety of adult onset diseases. Indeed, Kermack, McKendrick & McKinlay (1934) noted this pattern through their analysis of mortality at age across different decades 'it is clear that the regularities in the relative mortality-rates described in detail above imply a very remarkable statistical relationship. The figures behave as if the expectation of life was determined by conditions which existed during the child's earlier years' (p. 700). This is now generally known as foetal programming leading to metabolic syndrome, which is characterized by the early onset and increased risk of coronary heart disease and other diseases related to plaque buildups in artery walls (e.g. stroke and peripheral vascular disease) and type 2 diabetes. The risk factors of metabolic syndrome include abdominal obesity, disorders of the blood fat (high triglycerides, low HDL cholesterol and high LDL cholesterol), elevated blood pressure, insulin resistance or glucose intolerance, and pro-thrombotic and pro-inflammatory states (see Finch 2007 for review). These issues are exceptionally important for the policy implications of health care in the 21st century (Fogel 2004).

At the molecular level, our understanding of obesity, cardiometabolic syndrome and type 2 diabetes continues to grow. In particular, oxidative stress that causes cellular and tissue damage is clearly implicated in these diseases (Finch 2007; Lastra & Manrique 2007), although whether it is the early or late in life oxidative stress that leads to senescence is still uncertain. At the whole organism level, patterns of foetal origins continue to be confirmed and poor foetal growth followed by rapid postnatal growth often leads to disease and death (Hales & Ozanne 2003; Ozanne & Hales 2005). For example, a recent meta-analysis (Huxley, Shiell & Law 2000) confirms an association of accelerated postnatal growth with elevated blood pressure at subsequent ages but the matter is not at all clearly resolved (Huxley, Neil & Collins 2002; Brakefield *et al*. 2005). However, as Adair & Prentice (2004) note '... few would doubt the basic conclusion that an organism's nutritional experience during critical periods of ontogeny can have permanent effects on how it later responds to its environment. In short, the backbone of the theory has graduated from hypothesis to accepted biology even though the details remain controversial' (p. 191).

The objective of this work is twofold. First, I will show how it is possible to bring a quantitative evolutionary framework to assess the benefits and costs (*sensu* Korte *et al*. 2005) of a low level of stress early in life as occurs in hormesis. Second, we will use a very simple life-history model to investigate the effects of developmental programming (Gluckman & Hanson 2004a,b; Levin 2006) on life-history decisions and senescence. The model suggests that hormesis and the developmental origins of health and disease (Gluckman & Hanson 2006) can be understood as life-history phenomena associated with a mismatch between the information received during imprinting and the experienced world during the rest of life. Kermack *et al*. (1934) also saw this: '... these results are consistent with the hypothesis that the important factor from the point of view of the individual during his whole life is his environment up to the age of say 15 years' (p. 703), but we now are able to turn these statistical observations into a process-based predictive framework.

Methods

To illustrate the ideas, we use a simple life-history model, which is very much in the spirit of the model of Yearsley *et al*. (2005), although they do not have an imprinting period. More complicated ones could clearly be developed (see Discussion), but none of the principles would change. The simplest division of a life history is into an imprinting period and the rest of life (Fig. 1). During the imprinting period, the organism experiences a certain level of caloric intake and damage-generating stress. At the end of the imprinting period, certain life-history decisions are made and fixed for the rest of life. The best evidence of this imprinting period comes from rat studies that show that the administration of a false development cue changes the foetal programming (Vickers *et al*. 2005) and recent data suggest that this change in the development programming is due to epigenetic factors (Gluckman *et al*. 2007; Wells 2007).

Most often, decisions at the end of an imprinting period are considered to be structural decisions (e.g. organ size); McMillen & Robinson (2005) provide a superb review of 'tissue programming' at the end of the imprinting period. However, at the end of the imprinting period an organism could also set behavioural or allocation programmes. For example, Vickers *et al*. (2000) demonstrate that profound adult hyperphagia is a consequence of foetal programming

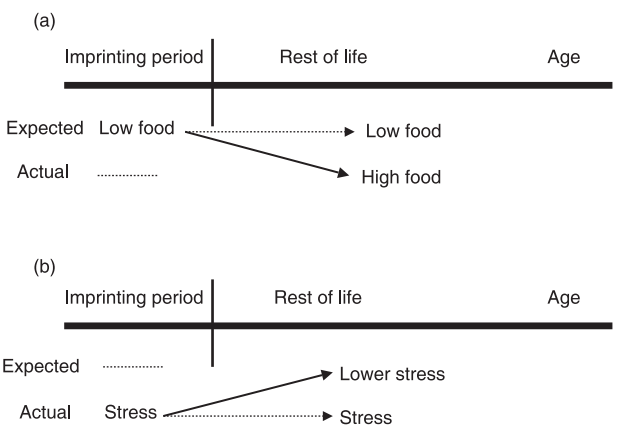

Fig. 1. The simplest life-history model for the phenomena considered here involves an imprinting period, at the end of which certain life-history patterns are set (here they are the intensity of foraging and the allocation to repair of damage) and the rest of life, however long that may be. In foetal programming leading to metabolic syndrome (panel a) low food is experienced during the imprinting period and life-history parameters are set with that expectation but high food is experienced during the rest of life. In hormesis (panel b) a stress leading to molecular, cellular or organ damage is experienced during the imprinting period but a lower stress is experienced during the rest of life. See text for more details.

(also see Simmons 2005 for a review) and Langley-Evans & Sculley (2005) show how antioxidant levels (and thus apoptosis and loss of tissue function) may be programmed during foetal life. We thus focus on the level of foraging effort (a behavioural decision and assuming that there is a risk associated with foraging) and the fraction of energy intake allocated to repair of damage (an allocation decision). To capture the life history requires characterization of growth in size (which is related to fecundity) and the accumulation of damage (which is related to the rate of mortality). A complication would be inclusion of an allocation decision related to reproduction; here reproduction is more simply treated as an allometric function of size. Metabolic syndrome (Fig. 1a) corresponds to a situation in which low food during the imprinting period is followed by high food during the rest of life. Hormesis (Fig. 1b) corresponds to a situation in which high stress during the imprinting period is followed by lower stress during the rest of life.

Hormetic treatments may alter the expression of hundreds or even thousands of genes (Scannapieco *et al*. 2007 and references therein) and this suggests a natural role for phenotypic modelling using life-history optimization (the alternative would be a model based on quantitative genetics) in which internal state plays a key role (cf. Williams & Day 2003). The theory developed here is in many ways a quantitative version of the 'ecological stress theory' of Parsons (2007a,b).

We assume that the environment provides a source of energy and a variety of sources of damage. One may most simply envision them as either free radicals or agents that create free radicals, so that the damage model here is consistent with the free radical theory of ageing (Harman 1998; Mangel & Munch 2005), Yin & Chen's (2005) notion of irreparable damage from biochemical side reactions, Finch's (2007) notions of 'bystander damage', as well as the idea that reactive oxygen and reactive nitrogen species play key signalling roles but that their regulation is not 100% effective (Linnane, Kios & Vietta 2007) so that they can also play key roles in metabolic syndrome and diabetes (Lastra & Manrique 2007). In particular, the effect of hormesis may be to increase the abilities of cells to withstand oxidative stress (e.g. Alonso-Alvarez *et al*. 2006; Arumugam *et al*. 2006).

Thus, we characterize the environment by the energy available (E_i, E_f) either in the imprinting period (i) or during post-imprinting when the animal is living forward (f) and by the rate at which damage is produced (υ_i, υ_f). In addition to external sources of damage, metabolism and somatic growth are associated with accumulation of damage; there is ample evidence for this (Rollo, Carlson & Sawada 1996; Rollo 2002; Alonso-Alvarez *et al*. 2007).

DYNAMICS OF SIZE AND DAMAGE DURING THE IMPRINTING PERIOD

We begin with the growth in size, which is assumed to follow von Bertalanffy-like dynamics. We let $L(t)$ denote length at age t (Table 1), k the von Bertalanffy growth rate parameter, and E_i the energy delivered to the organism during the imprinting period, then the potential increment in size in a single unit of time is (Mangel 2006)

$$dL = \frac{E_i}{k}(1 - e^{-k}) - L(t)(1 - e^{-k}) \qquad \text{eqn 1}$$

and asymptotic size is predicted to be $L_\infty = (E_i/k)$ A fraction ρ of the potential growth is used to repair damage. Maximum growth rate occurs when $\rho = 0$. However, in general we expect some amount of incoming energy to be allocated to repair, with $\rho > 0$. No growth corresponds to $\rho = 1$, so that values $\rho < 1$ give us some sense of the cost of growth (in terms of accumulated damage and implicated mortality, see below).

Thus, given a value of allocation to repair, the change in length from one age to the next is

$$L(t + 1) = L(t) + (1 - \rho)dL \qquad \text{eqn 2}$$

For simplicity, we assume that ρ is fixed during the imprinting period by factors outside the life-history optimization, but this is not required.

We assume that damage is repaired at a rate $\upsilon_r\rho dL$ and accumulates from external sources (at rate υ_e), from metabolism (assumed to be proportional to the cube of length) and from growth (measured by specific growth rate). Thus damage follows the dynamics

$$D(t+1) = D(t)\exp[-\upsilon_r\rho dL] + \upsilon_i + \upsilon_L L(t)^3 + \upsilon_g\frac{L(t+1) - L(t)}{L(t)} \qquad \text{eqn 3}$$

Table 1. Parameters and their values used in the numerical example

Interpretation	Notation	Value
von Bertlanffy growth rate	k	0·05
Energy in the environment when living life forward	E_f	10
Rate of damage production from the environment	υ_f	0·1
Multiplier on energy for the case of metabolic syndrome	κ_E	Varies
Multiplier on damage for the case of hormesis	κ_d	Varies
Maximum age	T	50
Length of the imprinting period	T_i	6
Initial size	$L(0)$	1
Initial amount of damage	$D(0)$	0·01
Size and damage-independent rate of mortality	m_0	0·01
Damage dependent rate of mortality	m_d	0·04
Foraging dependent rate of mortality	m_f	0·15
Size dependent rate of mortality	m_L	0·1
Maximum rate of repair	υ_r	5
Rate of accumulation of damage due to metabolism	υ_L	$6{\cdot}25 \times 10^{-9}$
Rate of accumulation of damage due to growth	υ_g	$6{\cdot}25 \times 10^{-9}$
Exponent relating size and reproduction	B	3
Allocation to repair during the imprinting period	ρ_i	0·35

where υ_L converts from metabolism to damage and υ_g converts from growth to damage (see Table 1).

The rate of mortality $M(t)$ has a variety of components. First, there is damage-, state- and behaviour-independent mortality, characterized by rate m_0. Second, there are components of mortality that depend upon foraging activity $\gamma(t)$, damage $D(t)$ and size $L(t)$ at age t, characterized by rates m_f, m_d, m_L, respectively. We thus write

$$M(t) = m_0 + m_f\gamma(t) + m_d D(t) + \frac{m_L}{L(t)} \qquad \text{eqn 4}$$

The classical theory of senescence (e.g. Charlesworth 1994) focuses on the role of m_0 in shaping patterns of senescence. The work here provides a connection between environment and the shape of mortality, through behaviour and physiological states. That damage increases the instantaneous rate of mortality is consistent with the experimental work of Mair *et al.* (2003). The form of size dependence of mortality rate implies that being larger is safer (as often happens in the marine and fresh water environments). Clearly, as the individual's size increases, this component of mortality will decline. Alternatives to the form of size dependent mortality are clearly possible (e.g. Carlson, Kottas & Mangel 2008). We will assume that during the imprinting period the organism does not forage ($\gamma = 0$) as would occur were a parent delivering food to an offspring.

Thus survival to age $t = 1$ is calculated from

$$S(t+1) = \exp(-M(t))S(t) \qquad \text{eqn 5}$$

with $S(0) = 1$. The use of deterministic difference equations (or deterministic differential equations) implies that the accumulation of damage (and thus ageing) are time, rather than event-related, although Finch (2007) compellingly argues for the latter. To do so requires the use of stochastic methods that would blur the fundamental ideas of this paper and so we will stick with the deterministic models.

AN INFORMATIONAL STATE AT THE END OF THE IMPRINTING PERIOD

At the end of the imprinting period, the organism is required to estimate the energy flow from the environment, which we denote by $\hat{E}$, and the rate of damage production from the environment, which we denote by $\hat{\upsilon}$. In most cases one would expect that only noisy information will be available to the organism, because either E_i and v_i fluctuate in a stochastic fashion or have fundamental uncertainty to them (Mangel 1990). In the simplest case, which we choose to follow here to illustrate the key ideas, the information is perfect. Then the organism estimates $\hat{E} = E_i$ and $\hat{\upsilon} = \upsilon_i$.

THE OPTIMAL LIFE-HISTORY POST-IMPRINTING

Given the values of $\hat{E}$ and $\hat{\upsilon}$, the organism must determine how hard to forage and how much energy to allocate to repair in the future. To do this, we project forward in time allowing the individual to choose how hard to forage (γ) and the fraction of potential growth to be allocated to repair (ρ). In this projection, eqn 1 is replaced by

$$dL = \frac{\gamma\hat{E}}{k}(1 - e^{-k}) - L(t)(1 - e^{-k}) \qquad \text{eqn 6}$$

We may describe γ as the temperament of the organism (*sensu* Darlington & Wright 2006), since it will relate to behavioural characteristics of the foraging organism. Equations 2–5 do not change except in the obvious ways to account for the appropriate information about the environment.

If we assume that the imprinting period lasts until age T_i and that reproduction at size $L(t)$ is an allometric function of the form $AL(t)^B$ starting after the imprinting period, then lifetime reproductive success is a function of γ and ρ given by

$$R_0(\gamma, \rho) = \sum_{t=T_i+1}^{T} S(t)AL(t) \qquad \text{eqn 7}$$

(There is actually a very thorny question, reserved for the discussion, about whether one should use $R_0(\gamma, \rho)$ or the solution $r(\gamma, \rho)$ of the Euler–Lotka equation $1 = \sum_{t=T_i+1}^{T} e^{-r(\gamma,\rho)}S(t)AL(t)^B$ or something else). In order to do a numerical computation, one must choose a value of T, which is an ad-hoc maximum life span. However, it is unreasonable to assume that an organism can survive to age T but not to age $T + \varepsilon$, where $\varepsilon \ll 1$. Thus, one should understand that it is the mortality rate in eqn 4 that determines appropriate measures of life span (e.g. mean life span, age at which survival drops to 10% or 1% or 0·1%) and that the parameters in eqn 4 and T need to be chosen appropriately.

Using eqn 7 as a measure of fitness also means that the optimal life-history parameters are insensitive to the value of A, although clearly the value of $R_0(\gamma, \rho)$ will not be. The optimal life-history parameters γ^* and ρ^* maximize $R_0(\gamma, \rho)$, given the information obtained during the imprinting period. However, the actual environment that is experienced may be different subsequent to the imprinting period may be different.

POST-IMPRINTING: LIVING LIFE FORWARD

Once γ^* and ρ^* are determined, the organism lives its post-imprinting life forward in an environment in which the energy available is E_f and the environmental source of damage is υ_f. These may match those experienced during the imprinting period (no mismatch), or it may be that the environment is calorically richer post-imprinting than it was during imprinting (caloric mismatch), or the environment may be less stressful post-imprinting than it was during imprinting (stress mismatch). The other cases (a calorically poorer or more highly stressed environment post-imprinting) are less interesting for the points discussed here and are not investigated.

Regardless of the level of match between imprinting and post-imprinting periods, the dynamics of size and survival are determined by modifications of eqns 1–6, using foraging effort and allocation to repair determined with parameters that need not match those from the imprinting period.

In particular, metabolic syndrome is most simply represented as a post-imprinting environment that is calorically richer than the imprinting environment. That is, metabolic syndrome is captured by $E_i = \kappa_E E_f$ with $\kappa_E < 1$ and $\upsilon_i = \upsilon_f$. Hormesis is most easily represented as a post-imprinting environment that is less stressful than the imprinting environment: $E_i = E_f$ and $\upsilon_i = \kappa_d\upsilon_f$ with $\kappa_d > 1$.

Results

The parameter space for this model is very rich and in principle one should conduct an analysis similar to the ones done by Mangel & Munch (2005) and Munch & Mangel (2006) in which we sweep over all of the parameter space to determine the qualitative behaviour of the model in response to variation in all of the parameters. That is beyond the scope

of this paper. Rather we present results for a particular case (Table 1) to illustrate some of the main points of the theory.

Because of the structure of eqns 1 and 2, in all cases (perfect matching of imprinting and post-imprinting periods, caloric mismatch or stress mismatch), growth in size is von Bertalanffy-like, growing from a size of about 45 at the end of the imprinting period to more than 250 at the end of life. The trajectory of mortality increases with age. This trajectory is not an input to the model as it would have to be in the classical theory, but is an output of the optimal life history. The rise in mortality rate in time is due to the increase in damage in time, which could not *a priori* be predicted. The efficiency of repair, measured by υ_r is high (Table 1) and since potential growth dL is of the order of 1–5 (or even larger early in life), relatively high values of ρ could effectively control the growth of damage. That control, however, would come at a cost of growth for the organism and it is not optimal to pay that cost. For a wide range of parameter values, the optimal allocations to repair never rise to more than a few percent of the potential growth – selection is for reproduction (through size) and not longevity.

In the case of stress mismatch, the general qualitative property to emerge from the theory both the optimal level of activity (γ^*) and the allocation to repair (ρ^*) are greater than their values in the case of no mismatch. In addition, as κ_d increases both of them increase. This means, for example, that if one were to study the expression of genes associated with activity and allocation to repair, then we predict a positive correlation in the expression of these genes.

In the case of caloric mismatch, the qualitative properties are more complicated. During the post-imprinting period, the intensity of foraging is greater than that predicted if there were no mismatch and the allocation to repair may be larger or smaller than that if there were no mismatch. An example is shown in Fig. 2. In consequence, when studying gene expression as a result of caloric mismatch, we predict either a negative correlation between genes characterizing activity and repair (for small mismatch), no correlation (corresponding to the neighbourhood of the minimum of ρ^* when there is moderate mismatch), or positive correlation (for large mismatch). Not shown in Fig. 2 is the relative reproductive success (normalized to the case of no mismatch). In the case of caloric mismatch, the relative reproductive success drops from 1·0 (no mismatch) to slightly more than 50% at $\kappa_E = 0{\cdot}3$. For the case of stress mismatch, relative reproductive success drops from 1·0 (no mismatch) to about 92% (at $\kappa_d = 4{\cdot}0$).

We thus see the effect of hormesis inducing an increase in repair throughout life with little cost to lifetime reproduction.

The intuition emerging from these results is that in the case of hormesis, the organism anticipates a more stressful environment and forages with greater intensity in order to obtain energy that will be used to repair damage. Following caloric restriction, the organism forages more intensely in order to make up an anticipated deficiency in caloric intake and forgoes some repair of damage under cases of small mismatch.

Clearly, the picture would become muddled very rapidly if one simultaneously caused mismatch of stress and caloric intake, but that surely happens in nature. Furthermore, we need not expect the same biochemical mechanisms to be in action in caloric mismatch and stress mismatch, even if the life-history mechanism were the same.

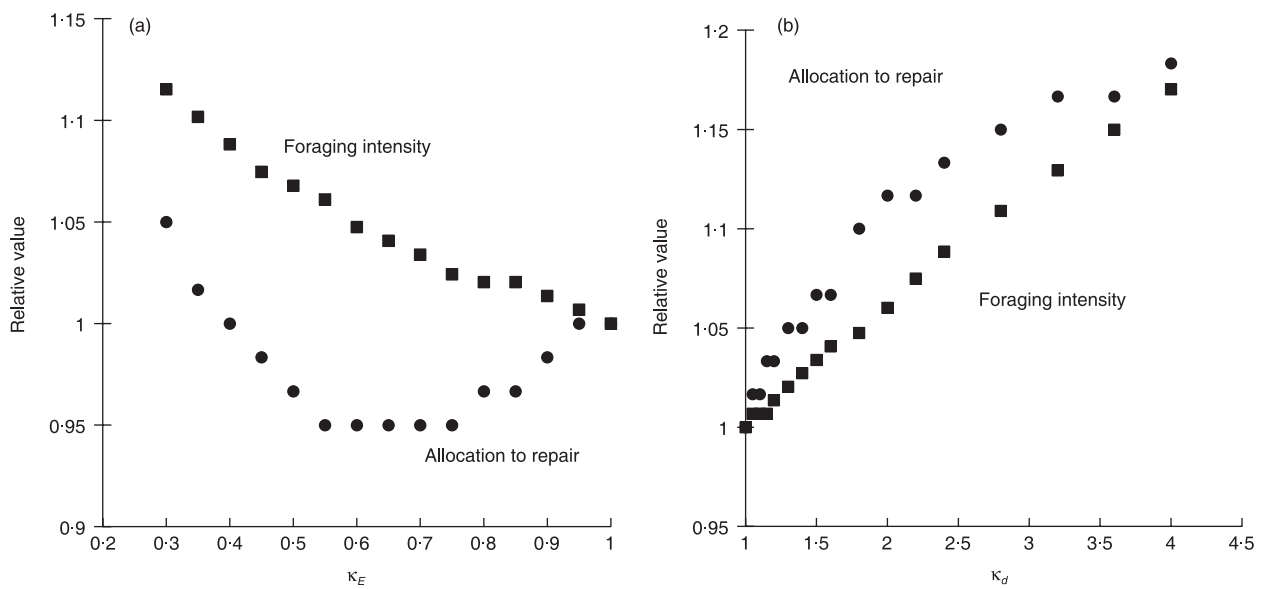

Fig. 2. An example of the consequences of mismatch. For ease of presentation, we present the relative intensity of foraging and the relative allocation to repair, normalized to the case of no mismatch. In the case of caloric mismatch (measured by $\kappa_E < 1$, panel a) caloric intake during the imprinting period is less than post-imprinting. We predict that foraging intensity increases as the mismatch increases, but that the allocation to repair during post-imprinting may decline, be relatively independent, or increase with the mismatch. In the case of stress mismatch (panel b, $\kappa_d < 1$), both foraging intensity and allocation to repair (and thus stress resistance) are predicted to increase as the mismatch increases.

Discussion

Our results point towards another way of viewing the individual variation in basal metabolic rate (cf Speakman, Krol & Johnson 2004) – that metabolic rate (for which γ^* is a proxy) may be set early in life through a series of imprinting events and that variation in energy delivered by a parent during the imprinting phase will be reflected by variation in offspring metabolic rates and activity. Our results also show an interaction between the intensity of foraging and the allocation to repair; more intense foraging – with the associated higher risk of mortality during foraging – allows greater allocations to repair, which reduces long-term mortality risk. Thus, an organism is predicted to simultaneously manage short- and long-term risks of mortality.

As with every model (or empirical study, for that matter), things could be made more complicated. We could, for example, consider multiple imprinting periods for the organism, which would allow readjustment of either behaviour or repair to allocation. Were there multiple imprinting periods, one might envision that the efficiency of repair would vary across life, for example, being greater in early life than later. Multiple imprinting periods might occur, for example, when environmental mismatch is on a time scale that is short relative to generation time (cf. de Jong 1995). The information received during imprinting could be noisy, so that the organism used Bayesian updating following the imprinting period (for example, see Mangel 1990), with associated complexity in the life-history calculation because then information becomes a state. With noisy information, there will be a level of uncertainty at which any time of matching becomes problematic and allocation to repair and activity might be selected to be not-too-bad regardless of the environment. Alternatively, the environment (e.g. caloric intake) could be stochastic, in which case great care is needed in the formation of the life-history optimization problem (McNamara 2000). The situation of both mismatch and stochasticity also begs the question of how the future is discounted if the solution of the Euler–Lotka equation instead of lifetime reproductive success is used as the measure of fitness (Souza & Seymour 2003; Schuck-Palm, Pompilio & Kacelnik 2004).

We have only allowed one allocation decision – the fraction of potential growth shunted from growth to repair. A more sophisticated treatment could allow two allocation decisions: a fraction of the potential growth allocated to repair, and a fraction of potential growth allocated to reproduction. Such a model would be best operationalized used state dependent life-history theory and stochastic dynamic programming (Mangel & Clark 1988; Houston & McNamara 1999; Clark & Mangel 2000). A model with a second allocation decision would likely show an age at which growth stops and all potential growth is allocated to either repair or reproduction. However, none of this would change the fundamental insight – that hormesis and metabolic syndrome can be understood as life-history phenomena associated with a mismatch between the expected and experienced worlds. We have also ignored the potential of reinforcement of damage on itself (cf Mangel & Munch 2005); this would change some of our quantitative results but not likely the qualitative ones.

As soon as one allows a combination of behaviour (how intensely to forage) and allocation (repair to damage), one is lead to rethink and reconsider what qualitative predictions might emerge from life-history theory. For example, Johnston *et al*. (2006) discuss challenges to the notion that organisms cannot 'have it all' ['it all' in this case being high rates of fecundity and extended life spans]. However, even without additional calculation intuition from the modelling framework suggests that if an animal were in an environment in which the risk associated with foraging were small then it would be possible to have it – by foraging hard and allocating a higher amount of energy to repair.

Our results also shed light on compensatory growth or catch-up growth (CG), which is the ability of an organism to grow at an accelerated rate following a period of food shortage (see Metcalfe & Monaghan 2001; Barker 2004; Yearsley, Kyriazakis & Gordon 2004; Mangel & Munch 2005 for a more complete discussion). CG has been observed for many years in plants, invertebrates and vertebrates, both in the laboratory and in the wild and both in juveniles and adults. It occurs following conditions of under nutrition rather than malnutrition. In a classic paper, Pitts (1986) offered the following classification for CG. Following a period of food deprivation, an organism may fully catch up to the control or normal trajectory ('successful catch up'), or it may fail to catch up in two ways. In 'parallel failure of catch up' the organism partially catches up but then sets itself on a new growth trajectory in which rates of change in mass are identical for the treatment and control organisms. In 'diverging failure of catch up', the organism sets itself on a new growth trajectory in which the rate of change of mass of the treatment animals is lower than that of the control animals. The arguments presented here suggest that whether the organism has successful, parallel failure, or diverging failure of catch up growth may depend upon the relationship between the period of dietary perturbation and the periods of imprinting. Clearly the theory presented here is only a starting point much remains to be done.

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