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THE EVOLUTIONARY ECOLOGY OF SENESCENCE

Evolutionary genetics of ageing in the wild: empirical patterns and future perspectives

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Summary

1. Classical evolutionary theory states that senescence should arise as a consequence of the declining force of selection late in life. Although the quantitative genetic predictions of hypotheses derived from this theory have been extensively tested in laboratory studies of invertebrate systems, relatively little is known about the genetics of ageing in the wild.

2. Data from long-term ecological studies is increasingly allowing quantitative genetic approaches to be used in studies of senescence in free-living populations of vertebrates. We review work to date and argue that the patterns are broadly consistent with theoretical predictions, although there is also a clear need for more empirical work.

3. We argue that further advances in this field of research might be facilitated by increased use of reaction norm models, and a decreased emphasis on attempting to discriminate between mutation accumulation and antagonistic pleiotropy models of senescence. We also suggest a framework for the better integration of environmental and genetic effects on ageing.

4. Finally, we discuss some of the difficulties in applying quantitative genetic models to studies of senescence outside the laboratory. In particular we highlight the problems that viability selection can cause for an accurate estimation of parameters used in the prediction of age-trajectory evolution.

Key-words: ageing, senescence, quantitative genetics

Introduction

The evolutionary theory of ageing provides an explanation for senescent declines in age-specific fitness, a process that appears to be maladaptive. Fundamental to the classic theories of senescence evolution is the idea that the strength of natural selection declines with advancing age. This idea was formalized by Medawar (1952), on the basis of earlier work by Fisher (1930) and Haldane (1941). Medawar's reasoning is that even in a hypothetical organism with indefinite life span, extrinsic mortality diminishes the contribution of late age-classes to subsequent generations, thereby weakening the force of selection acting in old individuals. Stemming from this argument, two genetic mechanisms have been proposed to explain senescent fitness declines. Specifically, senescence might arise either because of the accumulation of late acting deleterious mutations (mutation accumulation, MA; Medawar 1952), or alternatively due to selection favouring genes that improve early-life performance but have adverse effects in later life (antagonistic pleiotropy, AP; Williams 1957; see Monaghan *et al*. 2008 for a broader synopsis on evolutionary theories of ageing).

Extensive theoretical work has led to predictions for detecting these evolutionary mechanisms, and for discriminating between them. For example, age-related increases in dominance and additive genetic variances for fitness-related traits are expected under MA, as well as an increase in inbreeding depression (ID) with age (Rose & Charlesworth 1981; Charlesworth 1990). An increase in additive genetic variance with age may also occur under AP (Charlesworth & Hughes 1996), but only this second mechanism leads to an expectation of negative genetic correlations between early- and late-life fitness (Charlesworth 1990; Rose 1991). The idea of a trade-off between early and late life is therefore integral to AP, as well as to more mechanistic theories of ageing. For example, 'disposable soma' theory (Kirkwood 1977) argues that ageing results from accumulation of damage due to insufficient investment in somatic maintenance and repair. Implicit here is that energetic limitations prevent maintenance of the soma (leading to increased longevity) without incurring a reproductive

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cost. Thus disposable soma can be viewed as a physiological explanation of senescence that is consistent with an AP model of the underlying genetics.

The debate around the relative importance of MA and AP, and our understanding of genetic processes involved in senescence have benefited enormously from quantitative genetic experiments on the fruitfly, *Drosophila melanogaster* and the nematode worm, *Caenorhabditis elegans* (Rose 1991; Hughes & Reynolds 2005; Partridge, Gems & Withers 2005a). In particular, the prediction of an 'early-late' trade-off for fitness has received quite extensive support. For example, elegant artificial selection experiments have been conducted on *Drosophila*, with selection for higher longevity resulting in correlated reductions in early–life fecundity (e.g. Partridge, Prowse & Pignatelli 1999). Predictions from the MA theory also received experimental support, although in a less consistent way (Charlesworth & Hughes 1996; Promislow *et al*. 1996).

While the advantages of experimental studies under laboratory conditions are many (e.g. control of environment, controlled matings, replication of experiments), it is not clear that results can always be generalized to evolutionary processes in nature. For example, several studies on *Drosophila* species have shown that ageing patterns are particularly sensitive to genotype × environment (G × E) interactions (Partridge *et al*. 1999). Furthermore, adaptation to unintended differences in selection regimes might modify the genetic architecture of fitness traits and potentially mask major evolutionary trade-offs such as that between early fecundity and longevity (Leroi, Chippindale & Rose 1994). These observations have raised a series of somewhat thorny questions: What do these laboratory studies tell us about senescence in wild populations? Can we extrapolate their results? Are genetic mechanisms underlying ageing in the wild similar to those measured in the laboratory?

For decades, biologists singularly failed to study senescence in natural populations (Nussey, Coulson & Gaillard 2008a; Ricklefs 2008), believing that it either did not occur (Comfort 1964) or would be impossible to detect due to data limitations (Rose 1991). Only comparatively recently have ecologists begun to gather evidence that both actuarial and reproductive senescence are common in wild populations (e.g. Promislow 1991; Gaillard *et al*. 1994). Although practical challenges remain, for example, in defining fitness and modelling its age trajectories for individual animals (Nussey *et al*. 2008b), considerable progress has been made. Conversely, testing the genetic components of the evolutionary theory has remained an almost exclusively laboratory-based area of research. However, over the last few years, genetic studies of wild-caught individuals have increasingly been combined with ecological work on natural populations to provide novel insights into the ageing process (see, e.g. Brommer, Wilson & Gustafsson 2007). Moreover, long-term longitudinal studies on birds and mammals in wild or semi-wild populations might soon allow the blossoming of a quantitative genetic approach to studying senescence directly in natural systems.

In this paper we review the state of the empirical literature on the evolutionary genetics of ageing in free-living populations. It is our intention to highlight the links that are now being made between genetic and ecological perspectives on ageing, and to suggest avenues of future research that should be interesting to researchers in both fields. Although it seems very likely that molecular and genomic methods will soon provide useful tools for studying ageing processes in the wild, work to date has been largely restricted to pedigree-based quantitative genetic analyses. These techniques consequently form the main focus of our review. We also note that the conditions experienced by many of the populations that have been studied in this way are likely to differ from those experienced over much of their evolutionary history. For example, long-term ecological studies often focus on populations that are artificially predator free (e.g. Clutton-Brock, Guinness & Albon 1982), or subject to sport hunting by humans (Coltman *et al*. 2003). The criticism that such populations are not truly 'natural' is certainly valid but it is also true, to a greater or lesser extent, of all biological systems impacted by human activity.

Empirical studies of ageing outside the laboratory

PHENOTYPIC PATTERNS

Senescence in natural populations has now been documented in a wide range of taxa (e.g. Loison *et al*. 1999; Reznick 2002; Bowen *et al*. 2006), including short-lived organisms (e.g. insects, small birds) where it was long deemed not to occur in the wild (Bennet & Owens 2002; Bonduriansky & Brassil 2002). Although these studies have typically inferred senescent decline from age-related decreases in survival probability or fecundity, we share the view of Bronikowski & Promislow (2005) that studies of additional trait types could increase our understanding of the more proximate mechanisms of ageing. For example, reproductive traits (e.g. laying or parturition date, offspring weight) are frequently under strong selection and can be analysed within the framework of senescence theory as measures of maternal performance (e.g. Nussey *et al*. 2006). Nonetheless, in extending analyses to age trajectories of traits other than direct fitness components, it will be important to adhere to a rigorous definition of senescence. To avoid equating senescence with age-related phenotypic change, we suggest that the former should be inferred only when a trait is moving away from its age-specific optimum. That is the phenotype should be declining with respect to fitness, a condition that will not always be apparent without estimating selection directly. For example, given a trade-off between offspring size and number (Roff 2002), even a decrease in clutch size with age could be adaptive rather than senescent if, for example, accompanied by an increase in egg size.

A slightly different approach to investigating ageing has been to test for early-late trade-offs among life-history traits (see Nussey *et al*. 2008a for an overview). Although convincing where found, a limitation of using phenotypic patterns alone is that negative correlations between early and late-life traits will not always be manifest. Even in the presence of AP, environmental effects can induce positive covariance between

Table 1. Studies testing the quantitative genetic basis of senescence in natural populations

Species	Trait(s)	Effect tested			Reference
		Increased V_A with age	Early-late r_G	Increased ID with age	
Human, *Homo sapiens*	Age of first reproduction, longevity		×		Pettay *et al*. (2005)
Mute swan, *Cygnus olor*	Laying date	×			Charmantier *et al*. (2006a)
	Ages of first and last reproduction		×		Charmantier *et al*. (2006b)
Collared flycatcher, *Ficedula albicollis*	Age specific annual fitness	×	×		Brommer *et al*. (2007)
Red deer, *Cervus elaphus*	Early life fecundity and offspring birth weight	×	×		Nussey *et al*. (2007b)
	Age specific annual fitness (females only)	×	×	×	Wilson *et al*. (2007)
Soay sheep, *Ovis aries*	Age specific annual fitness (females only)	×	×	×	Wilson *et al*. (2007)
Alpine ibex, *Capra ibex*	Horn growth, body mass, faecal egg count			×	von Hardenberg *et al*. (2007)
Song sparrow, *Melospiza melodia*	Annual reproductive success, survival			×	Keller et al. (2008)

traits that mask the phenotypic signature of a genetic correlation (e.g. if individuals occupy territories of differing resource abundance; van Noordwijk & de Jong 1986). Nussey *et al*. (2008a) advocate the use of longitudinal analyses to describe individual patterns of senescence which will not always be apparent from population-level observation. Here we suggest moving one step further by advocating quantitative genetic approaches to explore the genetic basis of among-individual patterns of senescence.

TESTING THE GENETIC MECHANISMS OF SENESCENCE

Individual-level analyses are the necessary starting point for scrutiny of the genetic mechanisms underlying senescent declines *in situ* in natural populations. In one of the first attempts to do this, Hendry *et al*. (2004) found evidence of a trade-off between energy invested in egg production and reproductive life span (defined as the number of days from an individual's start of breeding to death) in sockeye salmon *Oncorhynchus nerka*. In this semelparous species, females that breed earlier were found to invest less in eggs, but survive longer, allowing them to guard their nests against later-breeding individuals. Interpreted as evidence for AP, the authors concluded that the trade-off arises not due to the classically invoked weakening of selection with age (Medawar 1952), but rather due to strong selection on early breeders to stay alive and defend their nests (Hendry *et al*. 2004). Although microsatellite analyses demonstrated that gene flow was restricted between early and late breeders, this study did not yet test directly whether the negative genetic correlation between egg investment and reproductive life span had a genetic component.

In cases where relationships among measured individuals can be recorded, quantitative genetic analyses (Lynch & Walsh 1998) allow explicit scrutiny of the predictions arising from senescence theory. In particular, two expectations have recently proved testable using this framework in free-living populations (Table 1). The first, arising from the MA model of senescence, is that additive genetic variance of fitness-related traits will increase in old age due to the accumulation of late-acting deleterious mutations (Rose & Charlesworth 1981; but see Charlesworth & Hughes 1996 for conditions when this prediction is also compatible with AP). The additive genetic variance V_A, is simply the amount of phenotypic variance (V_P) in a population that is explained by (additive) genetic differences among individuals, and is commonly expressed as a narrow-sense heritability h^2 (defined as the ratio of $V_A : V_P$). A second prediction, which arises under AP, is that negative genetic covariance (i.e. that portion of the phenotypic covariance attributable to additive genetic effects) will be present between early and late fitness traits (Charlesworth 1990).

Tests of these two predictions have been greatly facilitated by evolutionary ecologists adopting mixed-model techniques developed by animal breeders. For example, the so-called 'animal model' has largely superseded more traditional methods (e.g. parent–offspring regression) as a tool for estimating quantitative genetic parameters (Kruuk 2004; Postma & Charmantier 2007). In simple terms, the animal model combines phenotypic and pedigree information to make statistical inferences about the genetic basis of trait (co)variation. Importantly this model is flexible enough to handle the complex pedigrees and missing data typical of data sets from field studies. Coupled with this has been a rapid increase in the use of molecular marker data to infer pedigree information (Wilson & Ferguson 2002; Garant & Kruuk 2005), or to supplement and verify observationally determined relationships.

While the tools are now available to perform quantitative genetic analyses in natural populations, there are plenty of potential pitfalls to avoid when using them. For example, estimates of additive genetic variance can be upwardly biased by common environment effects (e.g. maternal, nest, year; Kruuk & Hadfield 2007). Conversely, pedigree errors arising from extra-pair paternity or from inaccurate molecular parentage assignment will generally cause downward bias in additive variance (Charmantier & Réale 2005). While such issues are not trivial, we have a relatively good understanding of when and where these effects may be important, and have increasingly developed strategies to minimize bias (Kruuk & Hadfield 2007) and to perform appropriate power and sensitivity analyses (Morrissey *et al*. 2007). Nevertheless, for studies of senescence, there are some additional considerations that assume particular importance and we will return to some of these later.

Additive genetic variance, and derived measures such as heritability, are known to change with age in natural populations (Charmantier *et al*. 2006a and references therein). This has been particularly demonstrated in the context of growth by characterization of additive genetic (co)variances for age-specific size traits during ontogeny (e.g. Riska, Atchley & Rutledge 1984; Réale, Festa-Bianchet & Jorgenson 1999; Badyaev & Martin 2000). In the context of testing predictions from models of senescence evolution, data on a population of mute swans (*Cygnus olor)* collected over a 36-year period at Abbotsbury, England showed that laying date, a trait under strong negative selection, senesces. While older birds were shown to lay later in the year, animal model analyses also demonstrated a dramatic increase in V_A for this trait in late life (Charmantier *et al*. 2006a). In the same population, a strong positive genetic correlation r_G (i.e. the genetic covariance expressed on a correlation scale) was found between the heritable traits of age at first reproduction (AFR) and age at last reproduction (ALR) (Charmantier *et al*. 2006b). Taking AFR as a surrogate for early reproductive effort and ALR as indicative of the rate of reproductive senescence, this result supports a genetically based early-late trade-off consistent with an important role for AP (Charmantier *et al*. 2006b). Similarly, analyses of life-history traits in pre-industrial humans (Pettay *et al*. 2005), and red deer (*Cervus elaphus*) on the Scottish island of Rum (Nussey *et al*. 2006, 2008b) are consistent with a role for AP in driving female senescence.

As pointed out earlier, age-related changes in reproductive traits may not always reflect senescence if selection regimes are also changing with age. However, since fitness must be under selection by its very definition, Brommer *et al*. (2007) advocated the use of an annual fitness metric that combines survival and reproductive output for studies of ageing in iteroparous organisms. In a Swedish population of collared flycatchers, *Ficedula albicollis*, annual fitness estimates showed the individuals do senesce (as expected from prior work on the same population; Gustafsson & Pärt 1990), but there was no evidence for age-dependent V_A in either sex (Brommer *et al*. 2007). Furthermore, under the most parsimonious model considered, genetic correlations among fitness measures at all ages were estimated as +1 (Brommer *et al*. 2007). Conversely, a similar methodological approach, (but using annual fitness defined as an individual's contribution to population growth; Coulson *et al*. 2006), revealed late-life increases of V_A in female red deer from Rum, and in Soay sheep (*Ovis aries*) from the Scottish island of Hirta (Wilson *et al*. 2007). Although genetic correlations did decline with the length of time between measurement ages, there was no support for strong negative r_G between early- and late-life annual fitness in either of these populations (Wilson *et al*. 2007).

In addition to additive genetic (co)variances among age-specific fitness traits, patterns of ID can potentially be informative for studies of senescence. Although inbreeding has received considerable attention in natural populations (e.g. Keller & Waller 2002; Coltman & Slate 2003; Pemberton 2004), increasing ID with age as predicted under MA (Charlesworth & Hughes 1996), has only been tested in four wild animal populations (Table 1). In Alpine ibex (*Capra ibex*), use of a marker-based inbreeding estimator (Ritland 1996), showed increasing ID with age for the fitness trait of horn growth, but not for body mass or parasite load (von Hardenberg *et al*. 2007). Pedigree-derived estimates of the inbreeding coefficient (f) have been used to test for MA in the Mandarte island population of song sparrows, *Melospiza melodia*, using annual reproductive success (ARS, the number of offspring raised to independence) and survival as measures of performance (Keller, Reid & Arcese 2008). Senescent declines were observed for both traits and significant ID was also demonstrated. However, increased ID with age was found for the trait of male ARS only (Keller *et al*. 2008). Finally, in the previously cited study of annual fitness, there was statistical support for a late increase of ID in female red deer but not in Soay sheep (Wilson *et al*. 2007).

Perspectives for future research

The studies discussed above clearly demonstrate the utility of quantitative genetic approaches for our understanding of senescence in natural populations. Although the emerging pattern is broadly consistent with expectations from classical senescence theory (Medawar 1952; Williams 1957), the findings of Brommer *et al*. (2007) in particular demonstrate a need to interpret phenotypic patterns cautiously with respect to hypothesized genetic mechanisms. Clearly there is an urgent need for more empirical work, in the absence of which it would seem premature to attempt general conclusions. In the following section we highlight several areas that we feel are of particular relevance to future work in this field of research. First, we suggest the use of a reaction norm approach that may offer practical advantages for future studies of senescence, before addressing several other issues that may be critical for advancing the field. In particular we argue that work to date has rather overemphasized the feasibility (and arguably the importance) of distinguishing between MA and AP. Conversely, although environmental heterogeneity is ubiquitous in nature, the implications of this for the determination and evolution of senescent processes within populations

have rarely been considered. Finally, we highlight the problem of selection bias for studies of senescence and show how selectively missing data presents a major challenge for predicting the evolution of age trajectories for fitness-related traits.

A REACTION NORM APPROACH TO SENESCENCE

Quantitative genetics allows variation among individuals to be partitioned into genetic and environmental components, such that the genetic basis of senescence can be tested. Above, we presented the main theoretical expectations for the different mechanisms underlying senescence and also discussed the empirical support in terms of genetic parameters for (and among) age-specific traits. This view, which can be termed the 'character state approach' is intuitive, but is not the only way to formulate models for exploring the genetic architecture of function-valued traits. The alternative is to model the relationship between the trait and age as a 'reaction norm' (Kirkpatrick, Lofsvold & Bulmer 1990). Although reaction norms are more commonly used in studies of trait plasticity across an environmental gradient (e.g. Nussey, Wilson & Brommer 2007a), by letting age be the 'environmental' variable of interest they are equally applicable to senescence. While the two approaches are mathematically related (and potentially equivalent under some circumstances; Lynch & Walsh 1998), the use of reaction norms may offer some particular advantages for studies of senescence in natural populations.

Under the character state approach, a set of phenotypic records may be divided into sub-traits measured at specific ages (e.g. lay date at successive ages; Charmantier *et al.* 2006a), or developmental stages (e.g. juvenile, prime age, senescent; Wilson *et al.* 2007). The full additive genetic variance–covariance matrix among traits (**G**) may then be estimated (e.g. using a multivariate animal model). In principle, **G** can be estimated even when any given individual's phenotype is measured at a single age (provided that age differs among related individuals) although longitudinal data, with repeated measures on individuals, will afford greater power. Although intuitive, this approach suffers from a lack of power and parsimony that stems from the requirement to sub-divide what may be a continuous process into multiple discrete states. Specifically, increasing the number of defined sub-traits increases the dimensionality of **G** (and hence the number of parameters that need to be estimated), while simultaneously reducing the number of phenotypic records for each defined trait. This presents a challenge to the estimation of genetic (co)variances, particularly in natural populations where incomplete sampling often means that individuals differ both in the number of phenotypic records and in measurement ages (Wilson, Kruuk & Coltman 2005). Furthermore, sample size inevitably decreases with age due to mortality (which can also be non-random with respect to the trait of interest; discussed further below).

The alternative to defining a series of age-specific sub-traits is to model the relationship between an individual's phenotype (or the additive genetic contribution to it) and age as a reaction norm, using 'infinite dimensional' or 'random regression' models (Kirkpatrick *et al.* 1990; Meyer 1998). Widely employed to model trait ontogenies in domestic livestock, this type of mixed-model has also been very recently applied to vertebrate studies in natural environments (e.g. Wilson *et al.* 2005), including analyses of senescence (Brommer *et al.* 2007; Wilson *et al.* 2007). For more detailed information on random regressions, we refer the interested reader to recent reviews of this technique (Schaeffer 2004; Meyer & Kirkpatrick 2005) and some of its applications in the wild (Wilson *et al.* 2005; Nussey *et al.* 2007a). The key premise of random regression for our present interest is that it allows the additive genetic merit, or breeding value, of a trait (a_i) to vary continuously as a function of age. For example, under a simple linear reaction norm model, individual *i*'s breeding value for a trait of interest (e.g. annual fitness) measured at age x might be defined as:

$$a_{ix} = a_{io} + b_i\mathbf{x}$$

where a_{io} is the genetic merit for fitness at $x = 0$ and b_i is the slope of an individual's genetic reaction norm. The covariance structure for a_{io} and b_i can then be estimated as a genetic (co)variance matrix of dimension 2, by including the regression on age as a random effect in an animal model. The estimate of $\mathrm{Var}(a_{io})$ can be interpreted as V_A for fitness at age zero, while $\mathrm{Var}(b_i)$ can be interpreted as genetic variance for ageing, (i.e. a genotype × age interaction, G × A). The significance of $\mathrm{Var}(b_i)$ can be assessed by comparison to a simpler model in which the genetic merit is modelled as constant with age (e.g. using a likelihood ratio test), thereby providing an explicit test for the presence of G × A. Typically the phenotypic mean will also vary with age and random regression animal models should always include a fixed regression of phenotype on age to account for this (Schaeffer 2004). There is no necessary connection between the functional form assumed for the genetic reaction norm (linear in this case), and the relationship between population mean and age (more commonly quadratic, e.g. Nussey *et al.* 2006).

If G × A occurs, then it follows that $V(a_{ix})$, the additive genetic variance for fitness at age x, will change across life stages. Importantly, since data are not subdivided, phenotypic measurements made at any age are informative for parameter estimates across all ages. Thus, for the simple linear reaction norm described above, the **G** matrix for any number (n) of arbitrarily chosen age-specific sub-traits can be inferred from a 2×2 matrix describing the genetic (co)variance structure of the coefficients a_{i0} and b_i (see Kirkpatrick *et al.* 1990). This allows the results of a reaction norm analysis to be interpreted within the character state framework of age-specific traits. **G** obtained using random regression will be a smoothed version of that which would be obtained though multivariate analysis of n age-specific sub-traits (Kirkpatrick *et al.* 1990).

Hence the key benefit of this reaction norm approach is in reducing the dimensionality of the genetic covariance matrix to be estimated. This in turns means a reduction in data requirements and an increase in statistical power which is always likely to be limited in data sets from natural populations.

However, the advantages of random regression models come at the cost of having to assume the functional form of relationship between a_i and age. Ecologists have long used linear reaction norms in studies of phenotypic plasticity (e.g. Scheiner 1993), and this would seem a sensible starting point for testing G × A. Nevertheless, there is no reason to preclude more complex forms being used, and higher order (orthogonal) polynomials have been advocated (Kirkpatrick & Heckman 1989) and used extensively in animal breeding (Schaeffer 2004). Unfortunately, many studies using higher (e.g. third or fourth) order polynomials have found that parameter estimates such as age-specific V_A are erratic at the extremes of the age axis (e.g. Misztal *et al*. 2000). This is particularly true for longitudinal data where most of the measurements relate to early-life phenotype, few records are available at the highest ages, and, a substantial number of individuals have fewer records than the order of polynomial fitted (Meyer 2005; Meyer & Kirkpatrick 2005). These conditions are especially likely in natural systems, meaning that numerical artefacts can potentially cause the very patterns being tested for (e.g. increase in V_A late in life). General and flexible alternatives to polynomials such as spline functions may be less sensitive to these 'edge effects' (Iwaisaki *et al*. 2005; Meyer 2005), and parametric models of genetic covariance functions have also been suggested (e.g. Pletcher & Geyer 1999; Jaffrezic & Pletcher 2000).

ANTAGONISTIC PLEIOTROPY (AP) VS. MUTATION ACCUMULATION (MA)

A major theme of empirical laboratory-based studies of senescence over the past two decades has been an attempt to distinguish between the alternate mechanisms of MA and AP. Work done in natural populations to date has also emphasized the role of both these mechanisms in driving senescent processes as discussed above (see, e.g. Charmantier *et al*. 2006a,b; von Hardenberg *et al*. 2007; Nussey *et al*. 2008b). While it certainly seems appropriate to interpret **G** matrices in light of theses mechanisms (Wilson *et al*. 2007), we do not believe that quantitative genetic approaches will generally be appropriate for conclusively discriminating between them. Furthermore, it is not obvious to us that continued efforts to distinguish MA and AP will add great insight into the causes and consequence of senescence in natural populations, particularly if both mechanisms can (and do) occur.

The first difficulty is that while increasing V_A in old age is expected under MA, it may also occur under AP. Theoretical work has shown that under AP the ratio of dominance variance (V_D) to V_A is expected to decrease with age if the frequency of early-beneficial and late-deleterious alleles is much greater than the frequency of alleles with adverse effects (as expected from the decline in the force of natural selection with age; Charlesworth & Hughes 1996). Thus, perhaps the most readily detected form of age-structure in **G** is not discriminatory. Conversely, while strong negative genetic correlations between early- and late-life performance provide quite compelling evidence for AP, generating precise estimates of genetic correlations requires sample sizes in excess of those generally available from natural populations (Lynch & Walsh 1998). Consequently, even where negative correlations are estimated, statistical support may be difficult to obtain and biological interpretations must therefore proceed with caution.

Predicted increases in V_D and ID under MA but not AP provide additional ways to test the genetic mechanisms of senescence (Charlesworth & Hughes 1996). Although classical approaches to estimating V_D have relied on sib-analysis experiments (Falconer & MacKay 1996) that are difficult to implement in the wild, animal models have been extended to allow estimation of dominance variance in complex pedigrees (e.g. Culbertson *et al*. 1998; Ovaskainen, Cano Arias & Merilä 2008). This involves generating a dominance relationship matrix from a known pedigree which can then be used to estimate V_D in a manner analogous to the estimation of V_A from the additive relationship matrix (Hoeschele & Vanraden 1991). Successfully disentangling dominance from additive (and maternal) effects depends critically on the pedigree structure (and in particular the incidence and distribution of both full and half-sib relationships). To date this approach has not (to our knowledge) been attempted in natural populations.

Tests of age-dependent ID may be more widely applicable, although these have not been extensively employed to date (as noted above). However, there are several important points of caution. First, the correlation between individual measures of genetic diversity (e.g. MLH, f') and the pedigree-based true inbreeding coefficient (f) may be weak at best (Balloux, Amos & Coulson 2004; Slate *et al*. 2004). Furthermore, positive heterozygosity-fitness correlations can arise through associative overdominance as well as ID (David 1998), complicating the interpretation of any significant effects found. Second, even if f can be calculated for each individual from an available pedigree, performing analyses of reasonable power is still contingent on the population containing sufficient variance in inbreeding. This requirement will be met in populations with high numbers of inbred individuals (e.g. in Mandarte's song sparrows, Reid *et al*. 2007; Keller *et al*. 2008), but may be generally restrictive. For example, in a recent analysis of female Soay sheep, just 1% of 1786 individuals had a non-zero inbreeding coefficient (calculated from the pedigree; Wilson *et al*. 2007). Finally, although MA should result in higher ID in late life, it is not the only explanation for this observation. Condition-dependent expression of ID (Armbruster & Reed 2005), coupled with declining condition in old age will generate identical patterns, (even if a mechanism other than MA is responsible for the declining condition).

Perhaps a more fundamental, but less acknowledged, barrier for distinguishing MA and AP is that both mechanisms describe effects at individual loci. In contrast, studies of senescence in the wild usually focus on quantitative traits that are expected to be influenced by many genetic loci. By its very definition, quantitative genetics should not be regarded as an appropriate tool for inferring processes at individual loci. Thus testable predictions regarding the genetic (co)variances will only be clear cut in the situation that all loci contribute to senescent declines via a single mode of action.

This may not be a reasonable starting expectation given that MA and AP are not mutually exclusive and likely to occur simultaneously at different loci (Snoke & Promislow 2003). Simulations to explore how trends in genetic (co)variance are affected by mixtures of genes with different effects might be useful in clarifying when (if ever) locus level mechanisms can be inferred from quantitative genetic studies.

ENVIRONMENTAL HETEROGENEITY AND PLASTICITY OF SENESCENCE

The role of environmental heterogeneity in shaping the evolution of senescence has been of paramount interest to comparative biologists, for example in testing the hypothesis that increased rates of ageing occur in populations with high extrinsic mortality (e.g. Reznick *et al*. 2004; Bronikowski & Promislow 2005). However, environmental conditions experienced by individuals within natural populations will also vary, both in time and space and how this heterogeneity affects the expression of ageing rates has received relatively little attention in theoretical or laboratory studies (but see, e.g. Pletcher & Curtsinger 2000; Service 2000; Partridge, Piper & Mair 2005b; Pijpe, Brakefield & Zwaan 2008). This would seem to be a potentially major omission if we are to extrapolate laboratory results to processes affecting populations in natural conditions.

Phenotypic plasticity, the expression of different phenotypes from a single genotype under different environmental conditions, is ubiquitous in nature (DeWitt & Scheiner 2004). Furthermore, individuals can differ in their plastic responses to an environmental stimulus, with this variation being heritable in the presence of a G × E interaction. G × E is being increasingly scrutinized in natural populations (e.g. Charmantier & Garant 2005) and has been demonstrated for life-history traits in several wild vertebrates (e.g. Nussey *et al*. 2005; Wilson *et al*. 2006). Although comparatively little is known about plasticity of ageing (Brakefield *et al*. 2005), two recent studies have highlighted its potential importance. First, in the red deer population of Rum, females that were born in years of high population density (and hence high resource competition), were found to have accelerated rates of senescence (Nussey *et al*. 2007b). Second, in common guillemots (*Uria aalge*), females that experienced poor climatic conditions in early life showed faster declines in late-life reproductive output (Reed *et al*. 2008). Consequently, harsh conditions experienced in early life were associated with increased rates of ageing in both of these populations. This type of effect may be widespread if individuals compensate for poor conditions early on but suffer costs that only manifest much later in life (e.g. Metcalfe & Monaghan 2001).

If key life-history traits (e.g. litter size) or fitness itself exhibit both genetic variance for ageing (G × A, Fig. 1a) and

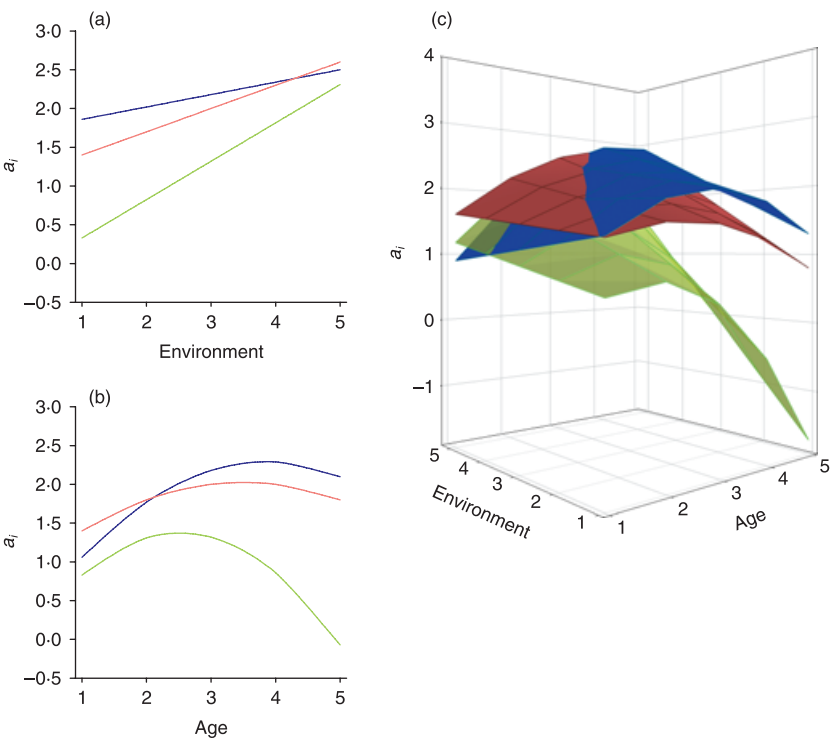

Fig. 1. Hypothetical reaction norms for a fitness trait showing the breeding value (a_i) of three individuals (indicated by colours) as functions of age and an environment parameter E. Panel (a) indicates genotype × environment (G × E) interactions with higher V_A for low values of E (depicted by the wider spaced reaction norms). Panel (b) indicates a genotype × age (G × A) interaction, with increased additive variance (V_A) at later ages. Panel (c) depicts a set of developmental reaction norms in which a_i is a function of age, environment, and the interaction between them (G × A × E). In this hypothetical example V_A for the trait is greatest in old age at low values of E.

for plasticity (G × E, Fig. 1b), then a full understanding of senescence in the wild might need to incorporate the possibility of G × E × A (Fig. 1c). That is to say we may need to consider whether age-specific genetic effects are also environment dependent, and *vice versa*. From an empirical perspective, testing for G × E × A in natural populations represents a somewhat formidable task. Although data will limit statistical power in many cases, extension of models to incorporate both age and environment is conceptually straightforward since similar methods may be utilized for studies of both senescence and plasticity (Nussey *et al*. 2007a). For example, environment specific sub-traits can be defined for studies of G × E, with data partitioned according to explicit environmental parameters (e.g. temperature, food abundance), or biologically-informed measures of environment conditions. In principle G × E × A could therefore be tested by estimating the G matrix for a phenotype partitioned into sub-traits that are both age- and environment-dependent. Alternatively, age and environmental heterogeneity can be incorporated in an extended reaction norm approach termed the 'Developmental Reaction Norm' (Schlichting & Pigliucci 1998). A developmental reaction norm, defined as the set of potential age-dependent trajectories produced by a genotype across all environments, can be represented as a surface (Fig. 1c). By extending random regression animal models to specify a_i as an explicit function of both age and environment, it would be possible to estimate additive genetic variance for the parameters defining that surface, and hence to estimate the **G** matrix at a set of defined combinations of age and environment. This would allow describing how the genetic variance for ageing changes according to environmental conditions, thereby refining general predictions for the direction and strength of senescence evolution.

SELECTION BIAS AND PREDICTING THE EVOLUTION OF AGE-TRAJECTORIES

Quantitative genetic models allow the evolutionary trajectories to be predicted for traits under selection. Thus an obvious objective of future studies might be to predict the further evolution of age-specific traits, and by extension, of senescence itself. However, to do this it is first necessary to tackle a central difficulty in studying senescence, namely that the number of individuals alive declines with age while individuals alive at late ages are unlikely to be a random sample of the initial population. This is a general issue for evolutionary biologists (Grafen 1988), that becomes especially problematic for studies of ageing in the wild. The previously highlighted discrepancy between individual and population level trajectories for age-specific mortality is a case in point (Vaupel, Manton & Stallard 1979; Nussey *et al*. 2008a). For example, imagine a simple scenario where the probability of an individual surviving a time step (S) is constant with age (i.e. there is no survival senescence), but does vary among individuals. The proportion of individuals that die during the first time step will be close to the population average of 1–S. However, later age classes will start to contain more and more individuals that have a lower than average probability of dying, and the proportion of individuals dying between successive time points will start to diminish. In this case, estimating age-specific mortality based only on those individuals that are alive at the beginning of a time step would result in apparent evidence for negative senescence (Vaupel *et al*. 1979).

In quantitative genetics this type of phenomenon is generally termed 'selection bias' (Lush & Shrode 1950). Correctly modelling the evolutionary process requires that a researcher account for the fact that individuals alive at later stages are a non-random sample of those alive at the start (Im, Fernando & Gianola 1989). In simple terms this can be achieved by predicting the age-specific phenotypes for those individuals that actually die before those phenotypes can be expressed (Hadfield 2008), and then averaging over any uncertainty in this prediction. Although this sounds difficult to achieve, there are several sources of information to help with this prediction. First, what an individual did in previous time steps is often a useful predictor of what the phenotype may have been if that individual survived. For example, take the previous scenario but imagine that individuals with a high probability of dying actually produce more offspring in each time step that they are alive. If we estimated the age-specific change in offspring production at the population level a pattern would emerge that may (incorrectly) be interpreted as a senescent decline. However, in this example we have two pieces of information that could be used to help recover the missing phenotypes of individuals that died. Specifically, if repeated measures on each individual's fecundity are correlated across ages then they will be informative for future fecundities (whether they are observed or not). Second, an individual's life span actually provides information on the number of offspring produced. Using this information we can, at least in part, correct for selection bias using multivariate models. Third, by comparison to purely phenotypic models, quantitative genetic analyses have a particular advantage for handling selection bias. This is because they are able to utilize a further source of information to predict phenotypes that are missing due to death, namely phenotypic measurements made on related individuals. For example, in a study of human twins more than 50% of the variance in mortality risk was explained by family effects (including genetic effects; Iachine *et al*. 1998). This demonstrates that family members can be an important source of information for predicting aspects of an individual's phenotype that are difficult, or even impossible, to measure directly (e.g. mortality risk).

Unfortunately, while standard multivariate models may properly account for selection bias under certain conditions, this will not be the case in general. Instead, a general solution for predicting evolution of age-trajectories will require joint modelling of both the selective process and the quantitative genetic parameters, something that is not typically done at present. In the following, we illustrate this inherent problem of selection bias by way of a simple theoretical example. We set the task of predicting evolutionary change in the age trajectory of fecundity, a trait often considered in studies of senescence. Although the biology behind our example is highly contrived, it hopefully serves to illustrate both the

advantages of the quantitative genetic approach, and some of the remaining problems for studying the genetics and evolution of age schedules.

ILLUSTRATING SELECTION BIAS: PREDICTING EVOLUTION OF AGE-SPECIFIC FECUNDITY

The inferential problem we consider is that of predicting the change in age-specific fecundity over a generation. We assume generations are discrete, and each generation has three distinct reproductive age classes. Mortality occurs continuously from birth, with all individuals dying prior to a fourth reproductive age class. The fitness function for individual i is then given by:

$$W_i = S_i(t_1)F_i(t_1) + S_i(t_2)F_i(t_2) + S_i(t_3)F_i(t_3) + \varepsilon_i \qquad \text{eqn 1}$$

where W_i is (absolute) fitness, $S_i(t)$ and $F_i(t)$ are the survivor and fecundity functions evaluated at time t, and ε_i is a residual. Note that $S_i(t)$ is the probability of surviving to time t, and $F_i(t)$ is the number of offspring that would have been produced at time t if the individual was alive. Equation 1 is not deterministic because the survivor functions are probabilities not realizations, and so the residual term is required. If we are interested in the evolution of age-specific fecundities then quantitative genetics proceeds by defining the vector (β) that best predicts fitness

$$W = \beta_1 F(t_1) + \beta_2 F(t_2) + \beta_3 F(t_3) + \varepsilon_F \qquad \text{eqn 2}$$

where β_{1-3} are regression coefficients (often called directional selection gradients) and ε_F are residuals from the regression. Once the vector β is defined, the amount of genetic variance for the three traits along that vector can be measured, and the single generation evolutionary response predicted using the multivariate breeders' equation (Lande 1979):

$$\bar{\boldsymbol{W}}\Delta\bar{\mathbf{z}} = \mathbf{G}\beta \qquad \text{eqn 3}$$

where $\mathbf{G}$ is a 3×3 (co)variance matrix representing the distribution of breeding values for age-specific fecundity in the population in the absence of viability selection, and $\Delta\mathbf{z}$ is the change in age-specific fecundities over a generation. If we assume for now that $\mathbf{G}$ can be measured (as discussed earlier), we are still left with the difficult task of measuring β correctly.

However, one way forward is to use Robertson's (1966) more general expression for evolutionary change to get an insight into what β should look like:

$$\bar{\boldsymbol{W}}\Delta\bar{\mathbf{z}} = \begin{bmatrix} \mathrm{cov}_G(W, F(t_1)) \\ \mathrm{cov}_G(W, F(t_2)) \\ \mathrm{cov}_G(W, F(t_3)) \end{bmatrix} \qquad \text{eqn 4}$$

where $\mathrm{cov}_G(W, F)$ refers to the genetic covariance between absolute fitness and fecundity. A full solution is difficult because the genetic covariance between fecundity and fitness involves the covariance between products of variables. For example, with fitness as specified by eqn (1), expanding the first covariance element of eqn (4) gives:

$$\begin{aligned} \mathrm{cov}_G(W, F(t_1)) &= \mathrm{cov}_G(S(t_1)F(t_1) + S(t_2)F(t_2) \\ &\quad + S(t_3)F(t_3), F(t_1)) \\ &= \mathrm{cov}_G(S(t_1)F(t_1), F(t_1)) \\ &\quad + \mathrm{cov}_G(S(t_2)F(t_2), F(t_1)) \\ &\quad + \mathrm{cov}_G(S(t_3)F(t_3), F(t_1)) \end{aligned} \qquad \text{eqn 5}$$

However, this can be simplified if there is no genetic covariance between survival and fecundity at a time step such that $\mathrm{cov}_G(S(t_1), F(t_1)) = 0$, then:

$$\mathrm{cov}_G(S(t_1)F(t_1), F(t_1)) = E[S(t_1)]\mathrm{var}_G(F(t_1)) \qquad \text{eqn 6}$$

which suggests we can express β in the multivariate breeders equation simply as the mean probability of surviving to each age class and

$$\bar{\boldsymbol{W}}\Delta\bar{\mathbf{z}} = \mathbf{G}\begin{bmatrix} \bar{S}(t_1) \\ \bar{S}(t_2) \\ \bar{S}(t_3) \end{bmatrix} \qquad \text{eqn 7}$$

However, perhaps the most widely used measure of fitness is lifetime reproductive success (LRS), the number of offspring produced over an individual's lifetime. This is simply the sum of the age specific fecundities such that fitness becomes defined as:

$$W_i = F_{i,t_1} + F_{i,t_2} + F_{i,t_3} \qquad \text{eqn 8}$$

Where $F_{i,t}$ are an individual's *observed* fecundities, specified as zero if an individual is dead at time t. Consequently, if LRS is used as the measure of fitness, we would estimate the vector of selection gradients β as:

$$\beta_{\mathrm{LRS}} = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} \text{ rather than } \beta = \begin{bmatrix} \bar{S}(t_1) \\ \bar{S}(t_2) \\ \bar{S}(t_3) \end{bmatrix} \qquad \text{eqn 9}$$

From this observation it follows that combining $\mathbf{G}$ with selection measured through LRS will result in misleading conclusions. This is because we are actually measuring the selection and inheritance of two different quantities: LRS is measuring selection on a compound of survival and fecundity, whereas $\mathbf{G}$ is measuring the inheritance of fecundity alone. The difference in the predicted rate of senescence may be large since:

$$\bar{\boldsymbol{W}}(\Delta\bar{\mathbf{z}}_{\mathrm{LRS}} - \Delta\bar{\mathbf{z}}) = \mathbf{G}\begin{bmatrix} 1 - \bar{S}(t_1) \\ 1 - \bar{S}(t_2) \\ 1 - \bar{S}(t_3) \end{bmatrix} \qquad \text{eqn 10}$$

If we want to measure the selection and inheritance of age trajectories we have to be very careful that they are measured on the same quantities. This may seem trivial but it is not always obvious when the same thing has not been measured.

In the example described, unmeasured fecundity (due to death) was treated as zero when measuring selection through LRS, but treated as missing data when measuring inheritance. This problem could be avoided by either treating unmeasured fecundities as zero when measuring inheritance, or by treating fecundities of dead animals as missing data when measuring selection. We advocate the second approach as it cleanly separates survival from fecundity, and allows for covariances between these two fitness components to be more easily accounted for. In addition, this approach is more consistent with the sampling theory that underlies most statistical models currently used in the field. For example, applying the reaction norm models (as described above) implicitly assumes that the phenotypes of dead individuals are missing data rather than zero (Little 1995). Nevertheless, it is hard to see how this approach can be reconciled with measures of fitness that are actually compounds of survival and fecundity (as used by, e.g. Brommer *et al*. 2007; Wilson *et al*. 2007), suggesting that we will need to build explicit quantitative genetic models of survival and fecundity. Currently these models are in their infancy, in large due to statistical problems arising from the intractability of the likelihood function for non-Gaussian distributions. However, Markov chain Monte Carlo (MCMC) approaches are starting to be developed which break the problem down into much simpler conditional distributions (Sorensen & Gianola 2002). Consequently, practical tools for fitting quantitative genetic models of survival and fecundity should be more widely available in the very near future.

Conclusions

It is now an obvious statement that senescence is widespread in nature. However, longitudinal data within specific populations of several wild vertebrates have shown great variation among individuals in age trajectories for fitness-related traits with, at least in some cases, a genetic component to this variation. Studies testing the evolutionary theories of senescence in the wild are still in their infancy and more empirical work is urgently needed before generalizing the patterns described of genotype × age interaction. In this respect it would be particularly useful to expand the taxonomic range of study systems which has been limited to date (e.g. to include more taxa with indeterminate growth patterns; Vaupel *et al*. 2004). Although empirical findings to date are broadly consistent with a role for both MA and AP, attempts to separate these mechanisms have yielded mixed results, even under laboratory conditions. Consequently, in exploring the genetics of senescence in the wild we share the hope expressed by others (Promislow & Pletcher 2002; Snoke & Promislow 2003) that investigators will broaden the scope of their studies beyond this singular question. In particular, studies of natural populations should allow us to explore the impact of varying environmental conditions on patterns of ageing and senescence. Importantly, MA and AP can both be viewed as forms of G × A interaction that result from mutation selection balance and an expected weakening force of selection in late life. Discerning their relative contributions to senescent processes may well be difficult, but this does not mean that the presence (or absence) of G × A is not of intrinsic interest. In fact, by quantifying G × A (e.g. through determining **G** for age-specific traits), we can begin to model the future evolution of age trajectories, without explicit knowledge of the underlying mechanism.

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