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The influence of environmentally induced heterogeneity on age-specific genetic variance for mortality rates

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Summary

Using parametric models that describe the increase in mortality rates with age, we demonstrate that environmentally induced heterogeneity among genetically identical individuals is sufficient to generate biased estimates of age-specific genetic variance. Although the magnitude of the bias may change with age, one general trend emerges: the true genetic variance at the oldest ages is likely to be dramatically underestimated. Our results are robust to different manifestations of heterogeneity and suggest that such a bias is a general feature of these models. We note that age-dependent estimates of genetic variance for characters that are correlated with mortality (either genetically or environmentally) can be expected to be similarly affected. The results are independent of sample size and suggest that the bias may be more widespread in the literature than is currently appreciated. Our results are discussed with reference to existing data on mortality variance in *Drosophila melanogaster*.

1. Introduction

The two predominant evolutionary theories of senescence – mutation accumulation and antagonistic pleiotropy – predict that genetic variance for fitness characters should increase with age for populations in mutation–selection–drift equilibrium (Charlesworth, 1990, 1994; Partridge & Barton, 1993; Charlesworth & Hughes, 1996). Two large demographic experiments were undertaken to test this prediction using age-specific mortality rates in *Drosophila melanogaster*. Hughes & Charlesworth (1994) reported that additive genetic variance for mortality rates increased monotonically with age, while Promislow *et al.* (1996) provide evidence for an initial increase and subsequent decrease in genetic variance.

A reanalysis of both data sets by Shaw *et al.* (1999) suggests an explanation for the contradictory observations. If small sample sizes are used, then a model that describes an exponential increase in mortality rates throughout life (the Gompertz model: see below) often provides a good fit to the observed mortality data. More complicated dynamics at older ages, such as levelling-off of mortality, are often undetected (Pletcher, 1999). On the other hand, if large samples are employed then levelling-off is observed, and the mortality trajectories tend to be logistic rather than Gompertzian (Carey *et al.*, 1992; Curtsinger *et al.*, 1992; Vaupel *et al.*, 1998). Shaw *et al.* (1999) show that there is an intimate connection between the detection of levelling-off and the behaviour of the genetic variance at advanced ages; in particular, with smaller sample sizes and Gompertz dynamics, genetic variance increases at advanced ages, while larger samples and logistic behaviour produce declining genetic variance later in life. The relatively small samples per cohort in the Hughes and Charlesworth experiment provide little statistical power for detecting non-Gompertzian mortality dynamics and therefore (under the model of Shaw *et al.*) little power for detecting a decline in genetic variance at older ages (Shaw *et al.*, 1999).

A second type of experiment that is relevant to understanding age-dependent patterns of genetic variance involves the measurement of the effects of

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new mutations on age-specific mortality rates. Nonelinear age-trajectories of mortality variance in *Drosophila* are reported by Pletcher *et al.* (1998, 1999) for genetic variation resulting directly from spontaneous mutations and from *P*-element-induced mutations (S. D. Pletcher, unpublished data). Mutational variance is high for mortality early in life and essentially zero at the oldest age. The lack of observed genetic variation at older ages is puzzling. Mechanistic and/or evolutionary explanations for why new mutations have relatively little influence on old-age mortality rates are not obvious (Pletcher *et al.*, 1998; Promislow & Tatar, 1998).

Age-related declines in genetic variance for mortality rates seem to pose interesting challenges to evolutionary theory (Promislow & Tatar, 1998). However, whether the trends in the observed data accurately represent underlying patterns is still open to debate. Because individuals are either alive or dead, mortality rates are measured on populations, and individual death rates are assumed to reflect the population measure. If all individuals in the population are identical, then this assumption is justified. In many cases, however, individuals may vary in their mortality characteristics and such a simplification may be misleading (Vaupel & Yashin, 1985). It is possible, for example, to develop a model in which individual mortality rates increase exponentially with age but population mortality rates decelerate and even level off (Vaupel *et al.*, 1979; Vaupel, 1990*b*). Such models have been termed *heterogeneity* models because they assume that individuals in the population are heterogeneous – either genetically or as a result of environmental influences – for mortality characteristics. Several authors have suggested heterogeneity as an explanation for observing reduced genetic and mutational variance at older ages (Promislow *et al.*, 1996; Pletcher *et al.*, 1998; Service, 1999), but a rigorous justification of this assertion has not been presented. Heterogeneity is also the most popular explanation for the levelling-off of mortality rates at advanced ages (Kol'tower *et al.*, 1993; Vaupel & Carey, 1993; Jazwinski, 1996), and so it is natural to invoke that same explanation for the second-order behaviour.

Here we investigate the impact of environmentally induced heterogeneity among individuals on the estimated age patterns of genetically based variance among groups of individuals. To this end we extend the extensive work that has been carried out on fixed-frailty models of heterogeneity (Vaupel, 1990*a*, and references therein), and we develop a new model, termed the accelerated-aging model, which assumes heterogeneity influences the rate of change in mortality rates with age rather than the baseline probability of death. Relationships among the actual and estimated age patterns of genetic variance are described for several specific situations, and results are discussed with reference to existing data on mortality variance in *Drosophila melanogaster*.

2. Models of heterogeneity

(i) *General considerations*

Heterogeneity models strive to describe the observed rate of death, over time, for a cohort of individuals when age-specific death rates for individuals within that cohort show significant variation. In such cases, observed cohort mortality rates are not necessarily reflective of mortality rates in the individual organism (Beard, 1953; Vaupel *et al.*, 1979; Vaupel & Yashin, 1985). As mentioned above, this poses a problem when we are ultimately interested in individual, rather than population, behaviour.

Heterogeneity within cohorts is quantified by the random variable z. For clarity, z will be referred to as the *individual risk*, and we use $\mu(x, z)$ to denote the mortality rate of individuals with individual risk z at age x. Vaupel *et al.* (1979) showed that the observed death rate of the cohort, $\bar{\mu}(x)$, is the weighted average of the death rates of the individuals in the population:

$$\bar{\mu}(x) = \int_0^\infty \mu(x, z) f_x(z)\, dz, \tag{1}$$

where $f_x(z)$ is the conditional probability density function of individual risk from the survivors to age x; $f_x(z)$ can be derived given the distribution of individual risk at birth (see Appendix). Thus, given information about the shape of individual mortality trajectories, $\mu(x, z)$, and about the distribution of heterogeneity at birth, cohort level mortality rates can be calculated for any age.

(ii) *Relative risk model*

In this paper, the relative risk model refers to a model of individual risk originally presented by Vaupel *et al.* (1979) and further developed by Vaupel & Yashin (1985). In this model, the mortality rate of individuals with individual risk z can be written

$$\mu(x, z) = z\mu(x), \tag{2}$$

where $\mu(x)$ is interpreted as a 'baseline' or 'standard' mortality rate for all individuals in the population. The standard death rate, $\mu(x)$, also represents the mortality rates for the class of individuals with a relative risk of unity (Vaupel & Yashin, 1985).

Assuming that individual risk is gamma distributed with mean 1 and variance σ^2, the observed cohort level mortality trajectory is

$$\bar{\mu}(x) = \frac{\mu(x)}{1 + \sigma^2 H(x)}, \tag{3}$$

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where $H(x)$ is the cumulative hazard (see Appendix) (Vaupel & Yashin, 1985).

The relative risk model that has clearly received the most attention in the evolutionary and genetic literature assumes that the standard mortality function follows the Gompertz model:

$$\mu(x) = ae^{bx}, \tag{4}$$

where a is termed the baseline mortality parameter and b is the rate parameter (Gompertz, 1825). In this case, the cohort level mortality function is

$$\bar{\mu}(x) = \frac{ae^{bx}}{1+[\sigma^2 a(e^{bx}-1)]/b}. \tag{5}$$

This is the well-known logistic (or frailty) mortality model (Vaupel & Yashin, 1985; Pletcher *et al.*, 1998; Service *et al.*, 1999). The logistic model predicts cohort-level mortality rates that increase exponentially early in life and then decelerate and level off at advanced ages. This is despite the fact (see equation 4) that individual mortality rates continue to increase exponentially.

(iii) *Accelerated-aging model*

In a model we call the accelerated-aging (AA) model, individual risk affects the rate of increase in mortality with age, rather than modifying mortality by an equal proportion at all ages. This model is analogous to the accelerated-failure models that are commonly used in reliability engineering (Gertsbakh, 1989). Thus, the AA model differs from the relative risk model of Vaupel *et al.* (1979) in its most basic assumption about the mortality effects of heterogeneity. For the models discussed in this paper, the mortality rate of individuals with individual risk z is assumed to follow

$$\mu(x,z) = ae^{bzx}. \tag{6}$$

The model is similar to the relative risk model in that it assumes a Gompertzian baseline mortality, but in this case z can not be interpreted as a relative risk, as it influences mortality rates by different amounts at different ages.

Unfortunately, the simple change in the placement of the risk variable, z, greatly complicates subsequent calculations of the cohort-level mortality trajectory. Following the procedure outlined in the Appendix, and assuming a gamma distribution of individual risk at birth with mean 1 and variance $\sigma^2 = 1/k$, the cohort mortality trajectory resulting from the AA model can be expressed as

$$\bar{\mu}(x) = \frac{a\int_0^\infty z^{k-1}\exp\{bzx-\phi(x,z)\}\,dz}{\int_0^\infty z^{k-1}\exp\{-\phi(x,z)\}\,dz}, \tag{7}$$

where $\phi(x,z) = kz-[a(e^{bzx}-1)]/bz$. Although this function is quite complicated, it can be evaluated numerically for specific values of a, b and σ^2 and for all ages x.

3. Heterogeneity and genetic variance

(i) *Genetic effects on mortality rates*

Fitness sensitivities for survival probabilities and mortality rates decline with age. Thus, an age-dependent increase in genetic variance in these traits for populations in mutation–selection balance is expected (Charlesworth, 1990; Charlesworth & Hughes, 1996). The rate of increase, however, depends on the scale of analysis and on the mode of gene action. The classical evolutionary models of senescence assume that genes act multiplicatively on age-specific survival probabilities, $P(x)$ (therefore additively on $\mu(x) = -\ln P(x)$) (Hamilton, 1966; Charlesworth, 1994; Charlesworth & Hughes, 1996). In this case, the genetic variance for mortality, $\mu(x)$, is expected to increase with age at about the same rate as the mean mortality rate (Charlesworth & Hughes, 1996), which results in a decline in the genetic variance for $\ln\mu(x)$ with age.

Recent evidence suggests, however, that genes act multiplicatively on $\mu(x)$; thereby additively on the logarithm of age-specific mortality rate, $\ln\mu(x)$ (reviewed in Promislow & Tatar, 1998). Evidence for this idea is provided by the proportional effects of phenotypic manipulations on mortality rates at all ages and the log-normal distribution of the effects of mutations on mortality (Promislow & Tatar, 1998). In this situation, genetic variance for log-mortality is expected to increase slightly faster than linearly with age for populations with age-specific alleles in mutation–selection balance (S. Pletcher, unpublished results). Such patterns have been observed for laboratory populations of *Drosophila*, where the genetic variance of log-mortality increases markedly with age early in life (Hughes & Charlesworth, 1994; Promislow *et al.*, 1996; Shaw *et al.*, 1999).

To correspond with empirical results, we assume that mutations act additively on $\ln\mu(x)$. Although we do not explicitly present them here, qualitatively similar results are obtained if mortality rates are treated on their natural scale (S. Pletcher, unpublished data). Log-mortality rates are estimated from cohorts that are composed of genetically identical individuals (e.g. Hughes & Charlesworth, 1994; Promislow *et al.*, 1996; Pletcher *et al.*, 1998; Shaw *et al.*, 1999). Mortality rates obtained from such cohorts can be considered characteristic of a particular genotype, and genetic variance is obtained by estimating the variance in log-mortality among genotypes. Heterogeneity occurs *within* genotypes as a result of micro-

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environmental differences among individuals during development. Effects of heterogeneity on estimations of genetic variance are examined in detail for two simple cases: (i) the true genetic variance among cohorts is constant across ages, and (ii) the true genetic variance is increasing with age. For each case the relative risk and AA models will be examined in turn.

(ii) *Case i: Constant genetic variance at all ages*

Assume the following:

1. All individuals in all cohorts follow the Gompertz mortality model (4).
2. Genotypes differ only with respect to the parameter a in the Gompertz model. If alleles from different loci act additively on log-mortality, then age-specific mortality rates are normally distributed on the log scale (Promislow *et al*., 1996; Pletcher *et al*., 1998; Promislow & Tatar, 1998). Thus, we assume that the random variable $a^* = \ln(a)$ is normally distributed with variance $\sigma^2_{a^*}$.
3. Individuals within each genetic line are heterogeneous for individual risk, with individual z values chosen from the gamma distribution with mean 1 and variance σ^2. The distribution of individual risk is identical for all genotypes.

Ignoring heterogeneity for the moment, assumptions 1 and 2 imply that the genotypic mortality rate at age x for genetic line i follows.

$$\mu_i(x) = a_i e^{bx} \tag{8a}$$

and

$$\ln(\mu_i(x)) = a_i^* + bx, \tag{8b}$$

where a_i^* is normally distributed among genotypes (see assumption 2). Thus, if the log-mortality rates of *individuals* could be measured, the mortality trajectory for each genetic line, i, would follow (8b), and a constant genetic variance at all ages would result as, $\mathrm{Var}[\ln(\mu(x))] = \mathrm{Var}[a^* + bx] = \mathrm{Var}[a^*] = \sigma^2_{a^*}$, which is invariant over all ages.

(*a*) *Relative risk model*. Under the relative risk model, the mortality rate for individual j of genetic line i will follow

$$\mu_{i,j}(x) = z_j a_i e^{bx}, \tag{9}$$

where z is a random variable drawn from the distribution of individual risk (see assumption 3).

Although the mortality trajectory for individuals of each genotype is Gompertz with parameters (a_i, b), heterogeneity causes the observed cohort-level mortality trajectory for genetic line i to take the form

$$\bar{\mu}_i(x) = \frac{a_i e^{bx}}{1 + [\sigma^2 a_i (e^{bx} - 1)]/b} \tag{10}$$

(see equation 5).

Transforming (10) to the log scale and adjusting for the mean genotype value,

$$\bar{g}_i(x) = \pi_{a^*} + a_i^* + bx - \ln[1 + \frac{\sigma^2}{b}(e^{\pi_a + a_i^*})(e^{bx} - 1)], \tag{11}$$

where $\bar{g}_i(x)$ now represents the observed genotypic value of the log-mortality rate in line i at age x, π_{a^*} is the average (over all genetic lines) baseline log-mortality parameter, a_i^* is normally distributed among genetic lines with mean 0 and variance $\sigma^2_{a^*}$, and σ^2 is the variance of individual risk at birth.

To determine the age-specific genetic variance in the presence of variation in individual risk, we require a general expression for $\mathrm{Var}[\bar{g}(x)]$. Using the delta method (Lynch & Walsh, 1998), and noting that

$$\frac{\partial \bar{g}}{\partial a^*} = \left(1 + \frac{\sigma^2}{b} e^{\pi_{a^*} + a^*}(e^{bx} - 1)\right)^{-1}, \tag{12}$$

results in

$$\mathrm{Var}[\bar{g}(x)] = \sigma^2_{a^*}\left(1 + \frac{\sigma^2}{b} e^{\pi_{a^*}}(e^{bx} - 1)\right)^{-2}. \tag{13}$$

This function is monotonic decreasing in x and

$$\lim_{x \to 0} \mathrm{Var}\,[\bar{g}(x)] = \sigma^2_{a^*} \tag{14a}$$

and

$$\lim_{x \to \infty} \mathrm{Var}\,[\bar{g}(x)] = 0. \tag{14b}$$

Equations (13) and (14) show that the true genetic variance is observed only at age 0, after which the observed variance declines monotonically to zero. Thus, under the relative risk model, the selective death of the most frail individuals *within* cohorts has the effect of causing mortality curves *among* cohorts to converge at older ages. This can be explained intuitively by noting that genotypic mortality curves differ only by the baseline mortality parameter, a, of the Gompertz model. Since all genotypes share the same rate parameter and the same distribution of individual risk, all lines plateau at the same level ($= b/\sigma^2$) and genetic variance is reduced to zero at very old ages. This is despite the fact that the true genetic variance is constant throughout life.

(*b*) *Accelerated-aging model*. For the AA model, patterns of age-specific genetic variance must be examined using numerical techniques. For each of 1000 genotypes, baseline mortality parameters $a^* = \ln(a)$ were drawn from the normal distribution with a mean of $\ln(0{\cdot}001)$ and variance of 0·6. For each genotype, log-mortality trajectories were calculated by numerically integrating (7), and among-line variance was calculated at each age. This process was repeated for many different parameter values (a, b, and σ^2), but the patterns were absolutely consistent –

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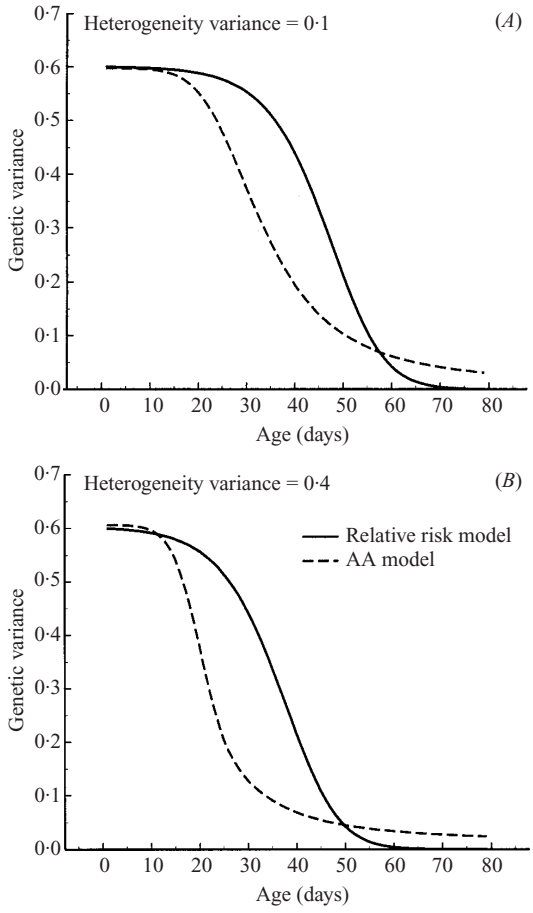

Fig. 1. Observed age-specific genetic variance for log-mortality rates generated under the relative risk and accelerated-aging (AA) models. Actual genetic variation is constant (= 0·6) across all ages. Individuals age according to the Gompertz mortality model. Genotypic baseline mortality (a) parameters are normally distributed with mean log(0·001) and variance 0·6. Rate (b) parameters are 0·14. Variance among genotypes was determined using numerical methods. (A) Variance in individual risk is 0·1; (B) variance in individual risk is 0·4.

although the true genetic variance is constant, the estimated genetic variance declines monotonically with age. At older ages, however, an asymptote of low variance is apparently approached.

Fig. 1 shows predicted variance patterns (for two different degrees of heterogeneity) for the AA model and the relative risk model. For both models the true genetic variance (= 0·6) is observed only at age 0, after which the measured variance declines monotonically. For a given amount of heterogeneity, the decline in variance is more rapid in the AA model. For both models, greater amounts of heterogeneity produce a more rapid decline in variance (Fig. 1).

(iii) *Case ii: Increasing genetic variance with age*

Assume the following:

1. All individuals in all cohorts follow the Gompertz mortality model (4).
2. Genotypes differ only with respect to the parameter b in the Gompertz model, and b is normally distributed with variance σ_b^2.
3. Individuals within each genetic line are heterogeneous for individual risk, with individual z values chosen from the gamma distribution with mean 1 and variance σ^2. The distribution of individual risk is identical for all genotypes.

In the absence of heterogeneity, the mortality rate of genotype i is

$$\mu_i(x) = ae^{b_i x} \tag{15a}$$

and

$$\ln(\mu_i(x)) = a^* + b_i x, \tag{15b}$$

where $a^* = \ln(a)$ and b_i is a random variable described in assumption 2. If we could accurately determine the log-mortality rates of individuals, the genetic variance would increase with the square of age, as $\mathrm{Var}[\ln(\mu(x))] = \mathrm{Var}[a+bx] = x^2\sigma_b^2$.

(a) *Relative risk model.* Although the genetic variance is present in the rate parameter b, the mortality rate for individual j in genetic line i is

$$\mu_{i,j} = az_j e^{b_i x}. \tag{16}$$

Thus, the observed cohort-level mortality trajectory is

$$\bar{g}_i(x) = a^* + (\pi_b + b_i)x - \ln\left[1 + \frac{\sigma^2}{(\pi_b + b_i)} \times (e^{a^*})(e^{(\pi_b+b_i)x} - 1)\right], \tag{17}$$

where $\bar{g}_i(x)$ is the observed genotypic log-mortality rate of line i at age x, a^* is the baseline log-mortality parameter, π_b is the average (over all genetic lines) rate parameter, b_i is distributed normally among genetic lines with mean 0 and variance σ_b^2, and σ^2 is the variance of the risk distribution.

Applying the delta model we obtain

$$\mathrm{Var}[\bar{g}(x)] = \left(\frac{\pi_b^2 x + e^{a^*}\sigma^2(e^{\pi_b x} - 1 - \pi_b x)}{\pi_b[\pi_b + \sigma^2 e^{a^*}(e^{\pi_b x} - 1)]}\right)^2 \sigma_b^2. \tag{18}$$

For a broad range of parameter values (including those observed for *Drosophila*), this function is 0 at birth, reaches a maximum at some intermediate age, and asymptotes at large x at a level equal to the squared coefficient of genetic variance of the slope parameter.

$$\lim_{x\to 0} \mathrm{Var}[\bar{g}(x)] = 0 \tag{19a}$$

and

$$\lim_{x\to\infty} \mathrm{Var}[\bar{g}(x)] = \frac{1}{\pi_b^2}\sigma_b^2. \tag{19b}$$

While the true genetic variance is increasing monotonically with age as a result of variation in the slope parameter of the Gompertz model, variation in relative

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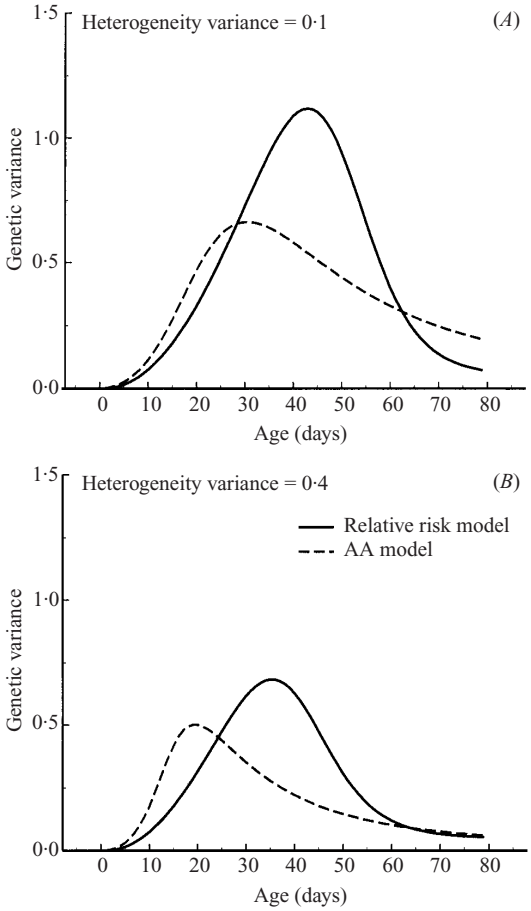

Fig. 2. Observed age-specific genetic variance for log-mortality rates generated under the relative risk and accelerated-aging (AA) models. Actual genetic variation increases with the square of age, x, such that $V_G = x^2(0{\cdot}000\,92)$. Individuals age according to the Gompertz mortality model. Genotypic baseline mortality (a) parameters are 0·001, while rate parameters (b) are normally distributed with mean 0·14 and variance 0·000 92. Variance among genotypes was determined using numerical methods. (*A*) Variance in individual risk is 0·1; (*B*) variance in individual risk is 0·4.

risk can cause the observed genetic variance to show more complicated dynamics, in which variance increases, reaches a maximum and subsequently decreases to a relatively low level at the oldest ages (Fig. 2). For very low π_b (*e.g.* $< 0{\cdot}009$), the approach to the asymptote may be gradual and monotonic (results not presented).

(*b*) *Accelerated-aging model.* As before, patterns of age-specific genetic variance predicted by the AA model were determined numerically. One thousand random genotypic values for the b_i were drawn from the normal distribution with mean 0·14 and variance 0·000 92. The variance was chosen to produce levels of genetic variance comparable to those for the constant variance situation examined above. For each genotype, log-mortality trajectories were calculated by numerically integrating (7), and among-line variance was determine for each age. We investigated variance trajectories for several sets of average parameter values, which varied over the range reported for *Drosophila*, mice, and other laboratory populations (Finch, 1990). The absolute level of variance at each age was strongly influenced by the amount of variance in the rate parameter. The overall shape of the variance trajectories, however, was insensitive to the degree of rate variance – genetic variance increases, reaches a maximum at intermediate ages, and declines to low levels late in life. As with the relative risk model, very low levels of π_b result in gradual, monotonic approach to an apparent asymptote (results not presented).

In comparison with the relative risk model, for a given amount of variance in the distribution of individual risk, the age trajectory of genetic variance increases more rapidly, reaches a lower peak, and is more right skewed (Fig. 2). Even when the variance in b is increased to equalize the observed variances, the age-dependent patterns produced by the two models remain different.

(ii) *Summary*

The effects of the relative risk and AA models on the observed age-trajectories of genetic variance can be summarized as follows:

- Both models predict that the estimated genetic variance at older ages will be substantially less than the true genetic variance.
- When genetic variance is constant across ages, the true variance is observed only at age 0, after which the observed variance declines monotonically with age. The decline is more rapid under the AA model compared with the relative risk model (Fig. 1).
- More complicated dynamics are observed when the true genetic variance increases with age as a result of genetic variance in the slope parameter of the Gompertz model. For a broad range of parameter values, both models predict genetic variance to increase from zero, reach a maximum at an intermediate age, and then decline to relatively low levels late in life. The AA model shows a more rapid increase in genetic variance and a slower decline within the likely range of observed data (Fig. 2).

More complicated dynamics of the estimated genetic variance as a function of age occur when both the baseline mortality and rate parameters of the Gompertz model are allowed to exhibit genetic variation. For these cases, reasonably useful equations relating the variance at each age as a function of variance in the mortality parameters could not be obtained. Such equations were even more involved

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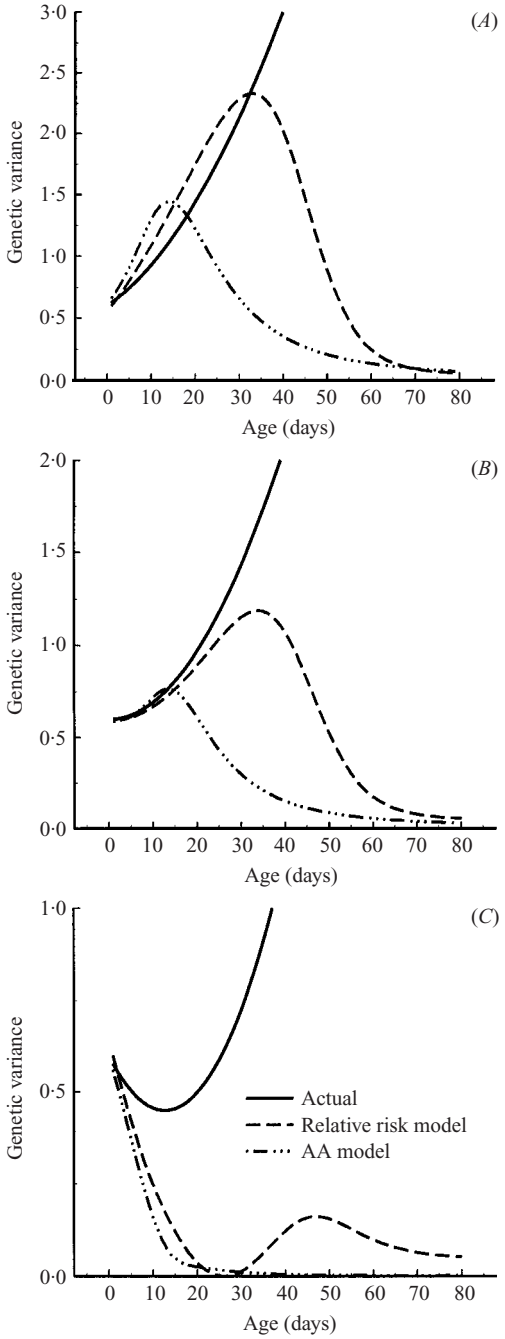

Fig. 3. Actual age-specific trajectories of genetic variance for log-mortality rates, and observed variance resulting from heterogeneity among individuals. Individuals age according to the Gompertz mortality model. For all three panels, genotypic baseline mortality (a) and rate (b) parameters are distributed as multivariate normal with mean vector {log(0·001), 0·14} and variance vector {0·6, 0·000 92}. Variance among genotypes was determined using numerical methods. The actual genetic variance depends on the correlation between the two parameters. (A) correlation is 1·0 and $V_G = 0{\cdot}6 + x + 0{\cdot}000\,92x^2$ (x is age in days); (B) correlation is 0 and $V_G = 0{\cdot}6 + 0{\cdot}000\,92x^2$; ($C$) correlation is $-1{\cdot}0$ and $V_G = 0{\cdot}6 - x + 0{\cdot}000\,92x^2$. The variance of the heterogeneity distribution (σ^2) is 0·2.

when we considered the possibility of genetic covariance between parameters. Nevertheless the equations could be evaluated numerically, and Fig. 3 provides useful examples of the range of behaviours from the models.

When the genetic correlation between baseline mortality (a) and rate parameters (b) of the Gompertz model is near 1·0, the actual genetic variance grows quite rapidly from birth. Rather surprisingly, heterogeneity causes an overestimate of the genetic variance at younger ages and an underestimate later in life (Fig. 3*A*). When a and b are uncorrelated the pattern is similar to that produced by variance in b alone (Fig. 3*B*) – variance is underestimated at the oldest ages. In cases where the baseline mortality and rate parameters are highly negatively correlated, the pattern of observed variance can be quite complex. In our example, the relative risk model reveals variance that declines early in life, increases through middle age, and decreases again very late in life (Fig. 3*C*).

4. Discussion

We have shown that environmentally induced heterogeneity among genetically identical individuals is sufficient to generate biased estimates of age-specific genetic variance for log-mortality rates. In the presence of heterogeneity, the shape of the estimated age-trajectory of genetic variance may deviate significantly from the true underlying function (Figs 1–3). When individual, non-genetic variation is taken into account, situations where (i) the actual genetic variance is constant across ages or (ii) the actual genetic variance increases with age can result in a variety of estimated patterns of variance. Observed variance can decrease monotonically with age (Fig. 1); increases early, reach a maximum and decrease at older ages (Fig. 2); or decrease at very early ages, increase and then decrease again (Fig. 3). In certain situations the estimated age pattern of genetic variance among cohorts only weakly reflects the actual genetic variation among individuals of different genotypes.

These results are robust to different manifestations of heterogeneity and to different mortality patterns. They suggest that such observations may be general features of these models. Moreover, age-dependent measures of variance for any character that is genetically or environmentally correlated with mortality can be expected to be influenced by this phenomenon. Variation in the quality of the environment experienced by different individuals might be expected to induce positively correlated effects on many life-history characters (De Jong & van Noordwijk, 1992; Stearns, 1992), suggesting this bias may be more widespread than is currently appreciated. We point out that such a bias is inevitable and is not alleviated with increased sample size. The results

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presented in Figs. 1–3 assume that cohorts are composed of essentially infinite numbers of individuals. To the extent that small samples result in the extinction of high-mortality cohorts, the bias will be even greater.

Based on estimates of weekly log-mortality rates, Promislow *et al.* (1996) suggest that genetic variance increases and subsequently decreases with age in experimental populations of *Drosophila melanogaster*. They argue that such an observation is inconsistent with predictions of current evolutionary models of senescence, which seem to predict a monotonic increase in genetic variance with age (Charlesworth, 1990, 1994; Charlesworth & Hughes, 1996). It is clear from our analysis, however, that in the presence of heterogeneity, an *observed* decrease in genetic variance among cohorts is not inconsistent with an *actual* genetic variance that increases monotonically with age. Shaw *et al.* (1999) were able to estimate genetic variance in the parameters of the logistic mortality model (5), which incorporates the assumptions of the relative risk models of heterogeneity. They found significant genetic variance in all three parameters of the model (a, b and σ^2). If the relative risk model is assumed to be true, the negative genetic correlation between a and b implies that the actual genetic variance is high at birth, decreases until approximately age 15 days post-eclosion, and subsequently increases indefinitely with age. A decline in the estimated genetic variance is a result of significant variance in frailty (i.e. a significant average σ^2). Thus, if environmentally induced heterogeneity is the sole cause of the reduction in observed genetic variance at advanced ages, the Promislow *et al.* (1996) results are not at odds with current evolutionary theory.

The same argument can be applied to the data of Pletcher *et al.* (1998, 1999), who observed relatively high mutational variance (genetic variance generated by spontaneous mutations) early in life and little or no variance at older ages. A lack of mutational effects on old-age mortality rates is suggested and, if true, the results are intriguing (Pletcer *et al.*, 1999). Unfortunately, heterogeneity among individuals could not be estimated, leaving open the possibility that the actual genetic variance in these studies is constant or increasing with age – an alternative that leads to different conclusions about mutational effects.

5. Conclusions

If individuals are heterogeneous for mortality characteristics, the estimated genetic variance may decline substantially with age even when the actual genetic variance is rapidly increasing. Therefore, the precise role of non-genetic heterogeneity in influencing the observed decline in genetic variance is an important and open question. We have not provided any evidence in favour of heterogeneity as an explanation for the observations; rather we establish this as a valid hypothesis. Given the current data, it is equally possible that the reduction of variance at older ages reflects some biological constraint on the expression of age-dependent characters. A needed empirical approach is to directly measure or manipulate the amount of heterogeneity in a cohort of organisms to test the influence of non-genetic variation on observed mortality rates. Khazaeli *et al.* (1999) attempted such an experiment using *Drosophila* by manipulating larval development to reduce the chances for environmentally induced variation in experimental cohorts. They report no significant effect of heterogeneity (as described by the parameter σ^2 in the relative risk model) on the mortality differences between homogeneous and control cohorts (Khazaeli *et al.*, 1999).

Distinguishing individual from cohort behaviour is fundamental to the interpretation of age-specific data, and it remains to be seen whether non-genetic, cohort heterogeneity figures prominently in the explanation of age-specific changes in genetic variance. Irrespective of the ultimate outcome, there are certain requirements in the short term. Experimental procedures for measuring and manipulating environmentally induced heterogeneity are needed, as are improved statistical techniques for quantifying age-dependent environmental variation among individuals. Biological models of aging that *predict* mortality deceleration and/or variance reduction with age are vital for providing alternative models to describe data and for directing further research into potential genetic mechanisms of life-history variation.

Appendix

The conditional density of individual risk given survival to age x is

$$f_x(z) = \frac{f_0(z)\,\mathrm{e}^{-H(x,z)}}{\int_0^\infty f_0(z)\,\mathrm{e}^{-H(x,z)}\,dz}, \qquad \text{(A 1)}$$

where $\mu(x,z)$ is the mortality rate for an individual with risk z, $f_0(z)$ is the distribution of individual risk in the population at birth and $H(x,z)$ is the cumulative hazard from birth to age x for an individual with risk z

$$H(x,z) = \int_0^x \mu(x,z)\,dz \qquad \text{(A 2)}$$

(Vaupel & Yashin, 1985).

Equations (1), (A 1) and (A 2) allow us to derive the expected cohort-level mortality rate based on a model describing how individual mortality rates change with age. Given a functional form for $\mu(x,z)$ we use (A 2) to calculate $H(x,z)$. Assuming a certain distribution

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of individual risk in newborn individuals (e.g. a normal or gamma distribution), (A 1) is used to obtain the age-specific conditional distribution of risk among survivors to age x. Given this distribution, (1) is used to calculate the expected cohort mortality rate at age x. Performing this series of calculations for each age in the lifespan generates an observed cohort-level mortality trajectory based on individual mortality trajectories of the form given by $\mu(x, z)$.

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