Evolutionary demography and quantitative genetics: age-specific survival as a threshold trait

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Researchers must understand how mutations affect survival at various ages to understand how ageing evolves. Many models linking mutation to age-specific survival have been proposed but there is little evidence to indicate which model is most appropriate. This is a serious problem because the predicted evolutionary endpoints of ageing depend upon the details of the specific model. We apply an explicitly quantitative genetic perspective to the problem. To determine the inheritance of dichotomous traits (such as survival), quantitative genetics has long employed a threshold model. Beginning from first principles, we show how this is the most defensible mutational model for age-specific survival and how this, relative to the standard model, predicts delayed senescence and mortality deceleration at late age. These are commonly observed patterns of ageing that heretofore have required more complicated survival models. We also show how this model can be developed further to unify quantitative genetics and evolutionary demography into a more complete conceptual framework for understanding the evolution of ageing.

Keywords: senescence; liability; G-matrix

1. INTRODUCTION

Life-history theory argues that senescence and, in particular, age-related increases in mortality rates, will evolve as an inevitable consequence of the declining force of selection with age. However, evolutionary models of age-specific mortality differ in how they view the relationships between mutations and survival, leading to qualitatively different predictions of how mortality rates will evolve. The nature of the relationship between mutation and survival is largely unknown but investigators have assumed that mutations act additively either on the scale of survival, mortality (the negative natural logarithm of survival), or the natural logarithm of mortality. Promislow & Tatar [1] suggest that environmental and genetic manipulations usually act additively on the scale of log-transformed mortality, though when it comes to the effect of de novo mutations on mortality, there is no clear empirical evidence for what is the most appropriate choice of mutational model for ageing. There is little theory to guide this decision, although some have argued that it should not matter when selection is weak [2]. In general, however, changing the scale of additive gene action may change predicted evolutionary patterns because additivity on one scale implies epistasis on others, especially under strong selection [3]. These scaling-type interactions can manifest as diminishing epistasis, where each newly accumulated mutation has less of an effect than the last, or synergistic epistasis, where the marginal effect of a new mutation increases with mutational load.

Because purifying selection against mutational load decreases with age [4], deleterious mutations can accumulate and epistatic effects can strengthen. This

may have profound implications for models of ageing. Most frequently and most notably by Hamilton [5], mutations have been modelled to act additively on the scale of mortality (i.e. the negative logarithm of survival probability, $\mu_x = -\ln(p_x)$, where p_x is the frequency of survival at age x). Under this assumption, we expect Gompertz mortality, or a log-linear increase in mortality with age [2]. Alternatively, when mutations act additively on the scales p_x or $\ln(\mu_x)$, selection can change non-linearly with age on the $\ln(\mu_x)$ scale, causing mortality rates to accelerate or decelerate with age relative to the classical predictions [6]. Mortality deceleration is of particular interest to demographers because it predicts larger proportions of elderly individuals than are predicted by the classical model [7].

We argue that the most realistic model can be identified from first principles. To that end, we recognize two indisputable points and one reasonable assumption relating to the effects of mutations. First, the death of individuals at some age is entirely determined by the collective influence of the individuals' genes and their environments. Second, these genetic and environmental factors are manifold. If we assume that these effects are relatively small, random and independent of one another, then the central limit theorem predicts that the collective influence of all these factors is Gaussian on some scale. These principles correspond to the basic tenets of the threshold model of quantitative genetics.

The threshold model explains how large numbers of genes and environmental factors can influence the expression of dichotomous traits and how these traits are inherited from one generation to the next. It assumes that there is some latent and continuous Gaussian phenotype, often called 'liability' [8], that wholly determines whether the dichotomous trait is expressed as one state

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Figure 1. Selection on liability is negative frequency dependent. Selection is the difference between the phenotypic mean of a population (unweighted by fitness) and the mean weighted by fitness. (a) Illustrates this difference for the case where incidence is 50% (half the population has the character state associated with positive liability) and fitness is solely determined by the character state. The two phenotypic means are indicated by the broken vertical lines. Selection is the difference between these two lines. Figure 2 shows the case where incidence is 90%. These two cases demonstrate how selection becomes weaker as the more fit character state becomes more common.

or the other depending upon whether or not it exceeds the value of some threshold (arbitrarily defined to be at zero). The mean of the population (the variance is arbitrarily defined as one) determines the proportion of the population with positive liability, all of which exhibit some shared phenotypic character. Individuals with negative liability share the alternative character. It has been argued that the model is appropriate so long as normality can be assured by 'any reasonable transformation' [9]. This would include log transformations, meaning that the model is appropriate even if genetic and environmental contributions have multiplicative effects. Note that it is sufficient that normalizing functions exist—not that they actually be performed on real data. The strength of selection on liability is proportional to the difference between mean liability of the more fit outward phenotype (e.g. alive) and the population mean liability before selection (alive and dead). Because this difference increases as the proportion of the more fit state decreases (figure 1), threshold traits can be said to be under negative frequency-dependent selection [10,11]. This may increase the equilibrium frequency of rare, deleterious alleles to levels that are much greater than one would expect from a simple, Mendelian trait [12].

Here, we consider the evolution of age-specific survival genes using the threshold model. We investigate the consequence of age-specific mutation accumulation when these mutations act additively on the scale of liability. We show that the negative frequency-dependent selection that is inherent in the threshold model increases early-age mortality but mitigates the increase in death rates with age. At equilibrium, this model predicts more realistic mortality trajectories than other simple models, and offers a more parsimonious explanation than more complex models for features such as apparent age-independent mortality early in life and late-age mortality deceleration.

2. MATERIAL AND METHODS

Hamilton [5] provided the standard quantitative model for how the strength of selection on allele frequencies changes

with age and how this modifies selection on age-specific survival. His model makes explicit the relationship between fitness and vital rates (age-specific survival and reproduction). Here, we only consider age-specific survival. To begin, we first need to explicitly describe in the most general way possible, selection on the frequencies of alleles that have age-specific effects on survival. Second, we must show how changing the scaling relationship between allele frequency and age-specific survival affects selection. In this way, we clarify how changes in these survival functions propagate through these relationships and alter selection away from Hamilton's predictions [5], which are based, in part, upon his assumptions regarding the scaling of mutational effects. This recapitulates results from Baudisch [6] while placing it in a form more recognizable to evolutionary biologists and quantitative geneticists. Finally, we apply this approach to the threshold model and show how this function predicts negative frequency-dependent selection that, when compared with Hamilton's predictions, reduces selection against early-acting mortality mutations but increases selection against mutations with late-age deleterious effects. Compared with Hamilton's predictions, there should be smaller differences in the frequency of age-specific mortality alleles between early and late ages.

First, we invoke the Robertson–Price identity [13–15]. This is a general definition of selection which states that the change in a trait mean owing to selection in one generation is equal to the covariance between the trait and relative fitness. Fitness can be a difficult property to describe when generations overlap. However, when populations are at demographic equilibria with respect to their age distributions, it is generally accepted that the long-term growth rate of the population is an appropriate measure for population mean fitness [2,5,16,17]. This is equal to the dominant eigenvalue of the population projection matrix (i.e. the 'Leslie' matrix), and because it describes the population mean, we will call it $\bar{\lambda}$ [18]. Absolute fitness of an individual or trait value i is described by the dominant eigenvalue of the population projection matrix with elements conforming to vital rates associated with i . Relative fitness λ_i is the ratio of the individual value to the population mean $\bar{\lambda}$.

Let there be an allele with an effect on fitness at some age x . Its frequency in the population is q_x . Following the Robertson–Price identity, selection is the covariance between relative fitness and the trait of interest, which, in this case, is an allele frequency. Expressed in terms of a regression, the change in q_x over one generation owing to selection is

$$\Delta q_x = \frac{d\tilde{\lambda}}{dq_x} \sigma_{q_x}^2, \quad (2.1)$$

or the product of a selection gradient and the variance in allele frequencies. If the sign of the derivative is positive, selection will increase the frequency of q_x , but mutations, being deleterious on average to survival, will act in the opposite direction. At mutation–selection equilibrium, the magnitudes of the two forces are equal. Incidentally, genetic equilibria for relevant allele frequencies at all ages are necessary in order to define fitness using a scalar (such as λ , or its natural logarithm r).

Let us imagine that q_x contributes to fitness by acting only upon the probability of survival at age x . In principle, fitness can scale to the frequency of survival genes in any way, but recall that Hamilton [5] assumed that mutations acted additively on the log-survival scale. Using the chain rule, let us redefine equation (2.1) to reflect this perspective:

$$\Delta q_x = \frac{d\tilde{\lambda}}{d(-\ln(p_x))} \frac{d(-\ln(p_x))}{dq_x} \sigma_{q_x}^2, \quad (2.2)$$

which is always correct given that the standard assumptions of genetic and demographic stability hold (and λ is, indeed, absolute fitness). However, Hamilton’s model is specific in that it requires that $d(-\ln(p_x))/dq_x$ be constant (note that p_x refers to survival rate, not $1 - q_x$). Despite arguments to the contrary [19], this is only an assumption and it is not an incontrovertible fact (unlike the Robertson–Price identity, for example). In any case, this ratio is equivalent to the quantitative genetic concept of the average effect of a gene substitution α [20] on mortality at age x . In the absence of epistasis and dominance, the locus-specific average effect α is defined by the difference in phenotypic values between genotypes irrespective of the frequency of alleles. In the presence of these interaction effects, however, the average effect of a gene substitution changes with allele frequency. It is worth noting that if Hamilton’s assumptions hold true and mutations act additively on the scale of mortality, then non-additive effects such as dominance and epistasis will exist on other scales. Alternatively, if mutations act additively on another scale, then non-additive effects will manifest on the log mortality scale and Hamilton’s assumptions cannot hold true.

To examine the evolutionary ramifications of the different mutational models, Baudisch [6] investigated how selection for age-specific mortality changes when mutations are additive on scales of survival other than mortality. Her main results, put into the context of the Robertson–Price identity, can be summarized as follows for survival, mortality and $\ln(\text{mortality})$, respectively:

$$\Delta q_x \left| \left(\frac{d\alpha_{p_x}}{dq_x} = 0 \right) = \frac{H_x^+}{p_x} \alpha_{p_x} \sigma_{q_x}^2, \quad (2.3a)$$

$$\Delta q_x \left| \left(\frac{d\alpha_{-\ln(p_x)}}{dq_x} = 0 \right) = H_x^+ \alpha_{-\ln(p_x)} \sigma_{q_x}^2, \quad (2.3b)$$

and

$$\Delta q_x \left| \left(\frac{d\alpha_{\ln(-\ln(p_x))}}{dq_x} = 0 \right) = \ln(p_x) H_x^+ \alpha_{\ln(-\ln(p_x))} \sigma_{q_x}^2, \quad (2.3c)$$

where $H_x^+ = d\tilde{\lambda}/d(-\ln(p_x))$ and mortality is the negative natural log of survival. The term α_f is the constant average effect of a gene substitution on the scale f that satisfies $d\alpha_f/dq_x = 0$. If, for example, mutations act additively on the scale of age-specific survival, then $d\alpha_{p_x}/dq_x = 0$.

All these models assume that survival or mortality are continuously distributed traits, with mutations acting directly on these rates (i.e. each individual has some intrinsic ‘rate’ specific to its genotype and age). Let us instead ask how selection works if age-specific liability, z_x , is a linear function of allele frequencies, with survival at a given age-class limited to those individuals whose liability falls above some threshold. In other words, let us assume that $d\alpha_{z_x}/dq_x = 0$. Following the chain rule, selection changes allele frequencies as follows:

$$\Delta q_x = \frac{d\tilde{\lambda}}{dp_x} \frac{dp_x}{dz_x} \frac{dz_x}{dq_x} \sigma_{q_x}^2, \quad (2.4a)$$

or, in terms of the average effect of a gene substitution when mutations act additively on the liability scale,

$$\Delta q_x \left| \left(\frac{d\alpha_{z_x}}{dq_x} = 0 \right) = \frac{d\tilde{\lambda}}{dp_x} \frac{dp_x}{dz_x} \alpha_{z_x} \sigma_{q_x}^2. \quad (2.4b)$$

We can use this relationship to compare the strength of selection on genes that act additively on liability compared with genes that act additively on mortality, as assumed by Hamilton. First, we note from Baudisch [6] that $d\tilde{\lambda}/dp_x = H_x^+/p_x$. Next, survival for threshold traits is defined as the unit normal cumulative distribution function (*cdf*) at the population mean liability; this is indicated by $p_x = \Phi(\bar{z}_x)$ when liability is applied to age-specific survival. Furthermore, the first derivative of the *cdf* with respect to liability is its probability density function, which, in this case, is the height of the standard unit Gaussian curve at the population mean liability, $P(\bar{z}_x)$. Substituting these identities into equation (2.4b), we find

$$\Delta q_x \left| \left(\frac{d\alpha_{z_x}}{dq_x} = 0 \right) = H_x^+ \frac{P(\bar{z}_x)}{\Phi(\bar{z}_x)} \alpha_{z_x} \sigma_{q_x}^2. \quad (2.5)$$

Finally, we recognize that because the unit normal distribution is symmetrical about zero, $P(\bar{z}_x) = P(-\bar{z}_x)$ and $\Phi(\bar{z}_x) = 1 - \Phi(-\bar{z}_x)$. We can express equation (2.5) more succinctly as

$$\Delta q_x \left| \left(\frac{d\alpha_{z_x}}{dq_x} = 0 \right) = H_x^+ T(-\bar{z}_x) \alpha_{z_x} \sigma_{q_x}^2, \quad (2.6)$$

where $T(y)$ is the normal distribution hazard function, $p(y)/(1 - \Phi(y))$. The T function is illustrated in figure 2 and is proportional to the strength of selection acting on liability. It is clearly negative frequency dependent, making selection for survival strongest when liability is lowest. Referencing equation (2.6) to the scale of mortality (while still assuming that z_x is a linear function of q_x) gives us

$$\Delta q_x \left| \left(\frac{d\alpha_{z_x}}{dq_x} = 0 \right) = H_x^+ T(-\Phi^{-1}(\exp(\ln(p_x)))) \alpha_{z_x} \sigma_{q_x}^2, \quad (2.7)$$

which is illustrated in figure 3. This relationship shows that, all else equal, selection for survival is greatest when mortality is highest.

Figure 2. Effect of mean liability on selection for liability. The normal distribution hazard function T on the scale of liability. Increasing liability decreases mortality. If mutations act linearly on the liability scale, then the figure also illustrates the relative strength of selection against the build-up of mutational load (liability z decreases with increased load). Selection is clearly directional against deleterious mutations (it is positive) and negative frequency dependent (it decreases with increasing z).

3. RESULTS

We compare results from our threshold model (equation 2.7) with that from Hamilton's model (equation 2.3b), where it is assumed that mutations act additively on the mortality scale. For our comparative purposes, we can assume that α is equivalent for both models. Under these conditions, figure 3 shows how the relative strength of selection on age-specific survival in the two models changes with age-specific mortality. The strength of selection on liability alleles is negatively frequency dependent (figures 2 and 3), whereas Hamilton's scaling assumptions do not produce any direct relationship between allele frequency and the strength of selection. Hamilton's model does predict an indirect relationship, of course, by showing that ageing reduces the strength of age-specific selection. Although Hamilton shows us that H_x^+ decreases with age, we see that T increases with age as result of increased mortality. Because these two factors have opposite relationships with age, we can say that the threshold model partially mitigates the loss of selection with age predicted by Hamilton [5]. The threshold model predicts a nonlinear relationship between allele frequency and fitness (figure 2), despite the linear relationship between allele frequency and liability, suggesting that the threshold model generates both directional selection (favouring alleles that increase age-specific survival) and negative frequency-dependent selection (selection for survival alleles decreases as survival increases).

In figure 4, we use an example from a human life-history table to show how our model can predict very different relationships between selection and age (here it shows that selection is shifted away from early to later life survival). Although this example does not show it because mortality is relatively low throughout the age range, the threshold model clearly predicts rapidly increasing selection as survival declines (e.g. less than 0.5, or about what we see per year in very old humans). If we look over a very wide range of ages, mortality will appear to begin low, accelerate at early age and decelerate at

Figure 3. Effect of mortality on selection gradients under the threshold model. The strength of selection on survival alleles is the product of the normal distribution hazard function T and Hamilton's sensitivity (dotted line). This function is illustrated here on the $\ln(\text{mortality})$ scale. Compared with Hamilton's model, the threshold model predicts weaker selection against the build-up of deleterious mutations when mutational load is low but stronger selection when load is high.

later age. This is the logistic-Makeham pattern of ageing that is frequently observed in real populations [7,21,22].

In general, selection can increase with age provided that survival allele frequencies drop rapidly enough. At equilibrium, however, selection for age-specific survival alleles must decline with age. The reason for this can be appreciated if we imagine that age-specific allele frequencies are equal at two different ages. Hamilton's sensitivity will promote stronger selection on survival alleles at the early age but our term $T(-z_x)$ will not distinguish between the two age classes. Selection, or the product of the two terms, $H_x^+ T(-z_x)$, will necessarily decline with age. If survival rates were higher later in life than early in life, then both H_x^+ and $T(-z_x)$ would decline with age. Our qualitative results agree with Hamilton's most important point: selection cannot increase with age at evolutionary equilibria. However, different from Hamilton's, our model predicts much less of a distinction between early- and late-age mortality in terms of the strength of selection.

4. DISCUSSION

We have argued from the central limit theorem that the threshold model is the most appropriate model for conceptualizing selection and inheritance for mortality. While we are certainly not the first to argue this (e.g. [23]), we are, to our knowledge, the first to apply the model to age-specific mortality and, by obvious extension, to the evolution of ageing. We show that when compared with Hamilton's predictions, this model will generate negative frequency-dependent selection that will (i) relax purifying selection at early age and (ii) intensify purifying selection at late age. This will both increase early-age mortality and mitigate senescence. It will also appear to dampen changes in early-age mortality, causing evolved mortality curves to conform to Makeham mortality. Differently put, they will appear more S-shaped

Figure 4. Example of how the threshold model predicts different changes in selection intensity with increased age. Using United States life-history tables [44,45] and the ‘demogR’ package in R 2.9.1 [46,47], we plotted mortality rates to age 40 in (a). Using the same software and data, we calculated sensitivities of fitness on age-specific survival. These are divided by survival rates to find Hamilton’s indicators (following Baudisch [6]) and standardized by the value at the first age to show the proportional decline in the strength of selection with age as predicted by Hamilton and applied to the human data (illustrated by the dashed curve in (b)). Using equation (2.7), we calculated the strength of selection on liability if mutation acts additively on this scale. This is also standardized by the first value and illustrated in (b) (solid line).

than Gompertz mortality. Such departures from Gompertz mortality have been explained by a diversity of factors, including social effects [5], age-specific mutational effects [24] and positive covariance between frailty factors across ages [25,26]. While these mechanisms are plausible and probably important, we show that a relative simple and biologically reasonable genetic model of survival will also contribute to these observed patterns.

Some well-known population genetic models of ageing (e.g. [2]) consider dominance interactions but ensure linearity of the mortality function α by assuming that the alleles that increase mortality are very rare at all ages. By the same logic, we could do the same, and so relax our assumption of strict additivity without altering the conclusions of our model. It is not clear yet, however, whether this assumption is necessary because we do not know yet if dominance for age-specific survival liability exists. While inbreeding depression for age-specific survival does provide evidence for directional dominance on the mortality scale [27–29], the relationship between dominance, liability and survival is less obvious because inbreeding causes an expansion of genetic variance, which will tend to increase the frequency of rare types even in the absence of dominance interactions [20]. Thus, changes in incidence with inbreeding do not necessarily imply directional dominance for liability. Conversely, inbreeding depression on the scale of liability need not be manifested on the scale of incidence (e.g. age-specific survival). For this reason, a purely additive model of liability can be justified on the basis of parsimony. If new evidence comes to light that indicates dominance for liability, then our model still stands under the rare-allele conditions assumed by the standard population genetic models.

Although the threshold model has heretofore been ignored by demographers, it is an important component of quantitative genetics, dating back at least to the origins of the field [30]. One advantage of using a quantitative genetic perspective is that it allows us to predict short-term evolutionary change, which requires an integrated

statistical understanding of how selection acts on phenotypes and how phenotypes are inherited from one generation to the next [31,32]. Accordingly, evolutionary biologists have used these approaches for the past 30 years to understand the evolution of multivariate phenotypes. Since the age-specific probability of death is a profoundly important multivariate character, it makes sense to use a quantitative genetic perspective to study the evolution of senescence.

To our knowledge, Falconer [8] created the only other model of a threshold trait with age-specific liability values. However, he implicitly assumed perfect genetic correlations between age-specific liability values (his model essentially considers a single-threshold trait). A general model of age-specific survival must relax this assumption. One way to do this is to imagine that thresholds are age-specific and allow age-specific liability values to covary freely between ages. Multivariate liability phenotypic distributions are the summation of two multivariate Gaussian distributions, one determined by additive genetic effects and the other determined by the effects of non-additive gene action and the environment. Variation is described by two liability variance–covariance matrices: the first is an additive genetic variance–covariance matrix (a liability **G**-matrix) that governs the rate and direction of multivariate phenotypic evolution [18,32]. This quantity is required to predict the joint effect of selection on survival at all ages. The second is a phenotypic variance–covariance matrix (a liability **Z**-matrix) that includes both the **G**-matrix and an analogous environmental variance–covariance matrix (an **E**-matrix). Superimposing orthogonal, age-specific thresholds onto the **Z**-matrix defines the distribution of observable longevity for the population (figure 5).

Methods for inferring heritability and genetic variance components for liability have been well developed for the univariate case [8,20,33,34], but new statistical methods will need to be developed to estimate liability **Z**- and **G**-matrices for survival at many ages. Animal breeders have developed promising statistical approaches to

Figure 5. Illustration of a quantitative genetic perspective on demographic heterogeneity. Bottom and right univariate probability density functions illustrate a population's liability distributions for survival at ages 1 and 2. These distributions are drawn to represent the latent distributions *before* survival is determined. Only those individuals with liability $z_1 > 0$ survive to age 2. Only those individuals with liability $z_1, z_2 > 0$ survive to age 3. The plot in the centre illustrates some arbitrary confidence contour for the bivariate distribution of age-specific liability. In this case, liability values are highly correlated and the variance along the principle component axis (thick grey line) defines the frailty variance. The minor axis (thin grey line) defines variation for a trade-off.

describing **G**-matrices involving one or more threshold traits [35–37] and to describe the inheritance of age-specific survival insofar as it affects reproductive ability [38,39]. We are hopeful that approaches such as these can lend themselves to effective analyses of age-specific survival **Z**- and **G**-matrices.

Correlations across ages will greatly complicate the estimation of these matrices. In these situations, death at one age will change liability values, and, thus, survival rates at later ages. If correlations between early- and late-age liabilities are negative, then early death will increase rates of death later in excess of what we might expect from the late-age liability mean. On the other hand, positive between-age correlations will mean that early deaths increase liability at late age, causing death rates to decline. Qualitatively, the latter case is similar to the demographic concept of heterogeneity that posits the existence of frailty factors, or those that increase the likelihood of survival at all ages [7,40]. In fact, a multivariate threshold model of age-specific survival fully incorporates both demographic heterogeneity and genetic trade-offs into quantitative genetic theory by providing an explicit definition in terms of the **Z**-matrix. Phenotypic frailty variation is equivalent to the eigenvalue corresponding to the eigenvector of **Z** with all positive elements. Phenotypic trade-offs are indicated by any eigenvector of **Z** with at least one negative and one non-negative value. Genetic frailty and trade-offs follow the same rules applied to the **G**-matrix.

Finally, a properly scaled quantitative genetic analysis of age-specific survival provides for the most appropriate tests of previous ageing theory. Charlesworth [2] reasoned that the age-related decline in selection on age-specific mortality will allow for more segregating variation at late age compared with early in life. He demonstrated this by using population genetic models which assumed that mutations act additively on the mortality scale. Because our model agrees with Hamilton's basic prediction that age must diminish selection, it stands to reason that genetic variation for liability must also increase with age. This may be detected as increasing narrow-sense heritability in liability with age. However, just as negative frequency-dependent selection on liability reduces the effects of age on the means of mortality (i.e. less senescence), it should also mitigate changes in heritable genetic variation. Compared with the standard model [2], our model predicts smaller increases in the heritability of age-specific mortality with age.

Evolutionary biologists have frequently employed other quantitative genetics approaches to test hypotheses for the evolution of ageing ([27–29,41], but see [42]). However, these studies follow demographic convention by considering inheritance of survival on the scale of mortality. Quantitative genetics can be applied to any scale given certain caveats [43], but its capacity to provide the most powerful insights into the evolutionary process require two assumptions that are usually ignored by

evolutionary demographers. First, the regression of offspring on parent phenotypes must be linear. It is the failure of dichotomous traits to satisfy this requirement that motivates the threshold model [8–10,20]. Second, the phenotypes must be multivariate normal. Lande [18] makes it clear that this assumption applies to life-history characters that are expressed at different ages. Age-specific survival is a conspicuous example of a trait that cannot satisfy this assumption by its very nature (individuals do not have measureable mortality rates—they simply live until they die). Some have argued that age-specific mortality or log mortality may be multivariate normal [1], but this evidence follows from distributions of line means (derived from highly inbred populations) that may poorly reflect distributions in more natural, random-mated populations. Furthermore, they say nothing about the interplay between genes and environment and how both of these contribute to the phenotypes that are directly exposed to natural selection. The multivariate threshold model described here takes a more inclusive phenotype perspective of evolution. For this reason, and thanks to its solid theoretical foundation (the central limit theorem), the threshold model provides the soundest conceptual framework for a quantitative genetic theory of ageing.

For nearly a half century, evolutionary demography has used population genetic models to explain how senescence evolves. Understanding how mutations cause death at specific ages is necessary to explain the shapes of mortality functions and to understand demographic structure itself. Various models make different quantitative assumptions about how the accumulation of mutations scales to survival, but these scaling models are steeped in demographic tradition and ignore important quantitative genetic concepts. In this paper, we argue that ageing theory requires the application of one particular quantitative genetic model. Applying the same simplifying assumptions made by Hamilton's foundational model to an age-structured threshold model of survival, we show that under a threshold model, selection on survival is negative frequency dependent. As a consequence, ageing will depart from simple Gompertz mortality and take on attributes of frequently observed logistic-Makeham mortality, with its characteristic age-independent mortality at early ages and reduced senescence late in life.

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