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Why organisms show late-life mortality plateaus: a null model for comparing patterns of mortality

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ABSTRACT

We show that deceleration in hazard functions (mortality curves) and the resulting mortality plateaus are an intrinsic property of time-to-event traits that are affected by many underlying genetic and environmental factors. We argue that just demonstrating that a mortality curve decelerates with age and reaches a plateau provides little information about the underlying biology associated with lifespan and mortality. To test hypotheses about the rate of deceleration of mortality curves and the level of mortality plateaus, observed curves must be compared with mortality curves expected under a null model – that is, the deceleration of a mortality curve and the mortality plateau generated from a normally distributed trait of the same mean and variance. Comparisons between the observed data and the null models can be achieved with simple statistical tests. The results of these comparisons can be very informative regarding which questions about the shapes of mortality curves will be most meaningful.

Keywords: Gompertz mortality curve, hazard function, lifespan, longevity, mortality rate.

INTRODUCTION

Senescence is a gradual deterioration of physiological function with increasing age and is generally associated with decreasing performance, decreasing fecundity or an increasing probability of mortality with increasing age (Partridge and Mangel, 1999). In humans and many other organisms, the mortality rate [$u(t)$] increases approximately exponentially with age (Finch, 1990; Rose, 1991; Bronikowski *et al.*, 2002; Ricklefs and Scheuerlein, 2002) and can be explained by a variety of mathematical functions, the most common of which is the Gompertz equation in which $u(t) = ae^{bt}$ (Pletcher, 1999a,b). This model has the nice property that $\ln[u(t)] = \ln(a) + bt$ describes a straight line. Differences in mortality rates among organisms, whether different species or groups exposed to different experimental treatments within a species, can be compared by simply comparing the parameters of the Gompertz model, in which a higher b implies a more rapid increase in the mortality rate with age and a higher a indicates a higher intercept (baseline mortality rate).

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However, recent studies on mortality rates of old-age individuals have shown that the rate of increase in the mortality rate slows down at older ages, often leading to a mortality plateau (Carey *et al.*, 1992; Curtsinger *et al.*, 1992; Fukui *et al.*, 1993; Brooks *et al.*, 1994; Kannisto *et al.*, 1994; Vaupel *et al.*, 1994; Pletcher *et al.*, 1998; see reviews by Pletcher and Curtsinger, 1998; Partridge and Mangel, 1999; Carey, 2001). The deceleration of mortality rates and the presence of mortality plateaus have been argued to be inconsistent with evolutionary theories of ageing (e.g. Demetrius, 2001; but see Partridge and Mangel, 1999). Substantial debate has since arisen over the explanation for mortality plateaus (Vaupel, 1990; Gavrilov and Gavrilova, 1991, 2001; Vaupel and Carey, 1993; Mueller and Rose, 1996; Horiuchi and Wilmorth, 1998; Pletcher and Curtsinger, 1998; Partridge and Mangel, 1999; Wachter, 1999; Bains, 2000; Drapeau *et al.*, 2000; Rose and Mueller, 2000; Service, 2000) and their evolutionary consequences (Demetrius, 2001). However, much of this debate is based on the assumption that the accumulation of alleles with negative effects late in life should generate mortality rates that increase monotonically with increasing age. We show that deceleration in mortality rates and the resulting mortality plateaus are an intrinsic property of time-to-event traits (such as lifespan and development time) that are affected by many underlying genetic and environmental factors. Thus, Gompertz-type mortality functions are the inappropriate null model against which to compare shapes of mortality curves. The question researchers should be asking is not 'Why do mortality rates decelerate at older ages?', but 'Do mortality rates decelerate in a manner inconsistent with the degree of deceleration expected for quantitative traits and, if so, why?'

MORTALITY PLATEAUS ARE AN INTRINSIC PROPERTY OF NORMALLY DISTRIBUTED LIFESPANS

First, consider the properties of traits that are affected by multiple genes. Imagine a set of genes that affect how long an organism lives. Each gene has multiple alleles, and thus the effect of the gene on the organism's lifespan may be large or small, positive or negative, depending on which combination of alleles that organism carries. For our purposes here, all that matters is that we can describe the distribution of effects of a gene (g_i) as having some probability distribution that has mean μ_i and variance σ_i^2 (the shape of the distribution is unimportant). Of course, lifespan is affected by many genes, each of which has a different distribution of effects on lifespan. The total lifespan of an organism is the sum of the effects of all these separate genes; the expected lifespan of an individual (T; age at death) can thus be described as

$$T = \sum_{i}^{n} g_i \tag{1}$$

where g_i is the effect of gene i on the lifespan of the individual and n is the number of genes affecting lifespan. Important to our discussion here is that as n approaches infinity, the distribution of T converges on a *normal* distribution (i.e. a bell curve) of form

$$f(T) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(T-\mu)^2}{2\sigma^2}\right] \tag{2}$$

regardless of the distributions of the individual genetic effects underlying T as long as the underlying effects have non-zero σ_i^2 (the Central Limit Theorem; Yule, 1902). This model

can be expanded to include environmental variables that affect age at death, with each environmental effect e_j having some distribution with non-zero σ_{j2}. This simply expands the model to

$$T = \sum_{i}^{n_i} g_i + \sum_{j}^{n_e} e_j \tag{3}$$

where e_j is the effect of environmental factor j on lifespan. The distribution of T still converges on a normal distribution regardless of the distributions of the genetic or environmental effects underlying T. Thus, even in a population of genetically identical individuals, lifespan can be normally distributed due to environmental differences between those individuals. It is this general statistical result that underlies the field of quantitative genetics (e.g. Roff, 1997) and, more generally, the statistical fields of linear regression, analysis of variance and analysis of covariance (Neter *et al.*, 1985).

This observation can be carried one step further. The hazard function, or mortality rate [$u(T)$], is the instantaneous risk of death which, for a normal distribution, is

$$u(T) = \frac{\dfrac{1}{\sigma\sqrt{2\pi}} \exp\left[-\dfrac{(T-\mu)^2}{2\sigma^2}\right]}{\displaystyle\int_T^{\infty} \frac{1}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(t-\mu)^2}{2\sigma^2}\right]} \tag{4}$$

This function has a shape as shown in Fig. 1B. Deceleration in mortality rates and mortality plateaus are thus properties of traits that have an underlying normal distribution. One need not assume any evolutionary or physiological mechanism, or anything at all about why individuals die, to explain the presence of mortality plateaus. One need only assume that there are many genetic and environmental factors that affect an individual's lifespan, and that these factors are variable among individuals.

Note that this curve has a shape similar to the logistic function, which is often used to describe deceleration in mortality curves:

$$u(T) = \frac{a\mathrm{e}^{bT}}{\left[1 + \left(\dfrac{as}{b}\right)(\mathrm{e}^{bT} - 1)\right]} \tag{5}$$

where a is the intercept, b is the rate of exponential increase in mortality at young ages and s describes the deceleration in mortality with increasing age (Pletcher, 1999a). However, this logistic model and variations of this model, such as the Gompertz-Makeham and logistic-Makeham (Pletcher, 1999b) models, describe the shape of the mortality curve but have no underlying mechanistic interpretation. In contrast, the mortality curve predicted by this normal distribution is a property of traits affected by a large number of genetic and environmental factors. Note that the Weibull mortality function, which is often used to describe mortality rates, is also derived from an assumed underlying distribution of lifespans (a Weibull distribution) that is a special type of 'extreme value distribution' governing the time to failure of the weakest link of many competing failure processes. However, the parameters of the Weibull distribution and thus the underlying failure times that generate the Weibull mortality curve have no direct biological interpretation (Fox, 1993).

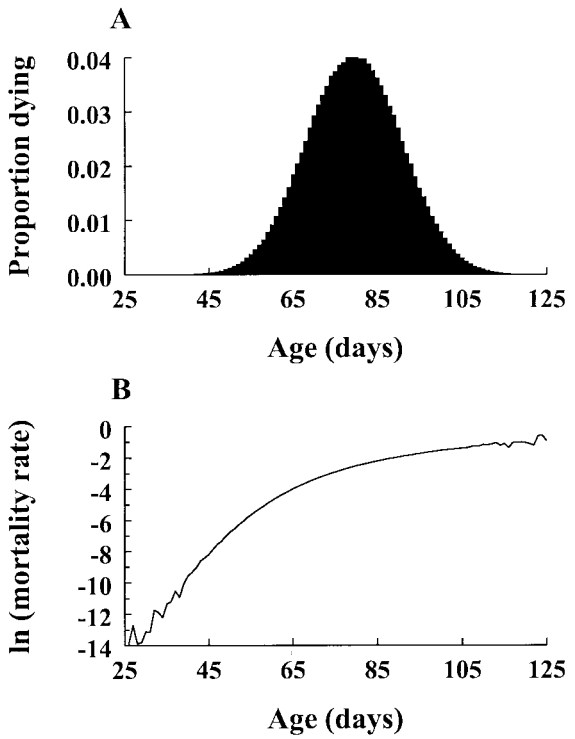

Fig. 1. Distribution of lifespans (A) and the expected mortality curve (B: ln[$u(T)$] versus T) for a randomly generated, normally distributed lifespan data set of 1 million random data points ($\mu = 79$ days, $\sigma^2 = 117$ days; values from Hughes, 1995) sampled at 1 day intervals.

'NORMAL' MORTALITY CURVES AS A NULL MODEL

Normally distributed lifespan data, regardless of the mean or variance, necessarily produce logistically shaped mortality curves – that is, the rate of increase in the mortality rate necessarily decelerates and reaches a mortality plateau. Thus, the null hypotheses of 'no deceleration in mortality rate with age' and 'no mortality plateau' are the wrong null hypotheses against which to compare mortality curves; that is, Gompertz and other monotonically increasing mortality functions are inappropriate null hypotheses against which to compare shapes of mortality curves. Instead, lifespan distributions should first be examined to determine whether they deviate from normality and, if they do, mortality curves should then be examined to determine how they deviate from the expected shape of the mortality curve generated by a normally distributed trait, the expected distribution for any trait affected by multiple genetic or environmental factors. This requires calculation of parameter values for the logistic mortality model under the null model. These parameters for the null model can be calculated in two ways. First, since we have two different equations for $u(T)$ (equations 4 and 5), we can solve for the parameter values a, b and s in terms of the mean and variance of the underlying distribution (with the mean and variance estimated from the real data). However, the integral in the denominator of equation (4) has no analytical solution and would thus need to be solved numerically. Alternatively, we can

compare observed mortality patterns with mortality curves generated from random normal data sets with mean (μ) and variance (σ^2) equal to the mean and variance of the real data set. This latter technique may be preferable because parameter estimates are sensitive to the interval at which death is scored and thus the number of intervals sampled (Pletcher, 1999a). The use of random data sets allows death of individuals to be scored at identical intervals to the real data, and thus can be compared directly with the real data.

We have used this technique to examine whether mortality curves for a variety of organisms differ from the expected curves for a normally distributed trait. We calculated the expected parameters of the logistic mortality curve (*a, b* and *s*) under the null model by generating random data sets with 1 million data points having identical mean and variance to the real data and sampled at the same interval. This procedure assumes that the mean and variance estimated from the data closely approximate the true mean and variance of the population, which is a reasonable assumption given the large data sets used (see legend to Fig. 2). Figure 2 shows the results of this analysis for two different populations of the seed beetle, *Callosobruchus maculatus*. For the *C. maculatus* population presented in Fig. 2A, the shape of the female mortality curve is almost exactly as predicted from the null model, but the male mortality curve differs significantly from expected (higher *b* and higher *s*; $P < 0.05$ for both parameters). Interestingly, the results of Tatar and Carey (1994) for a

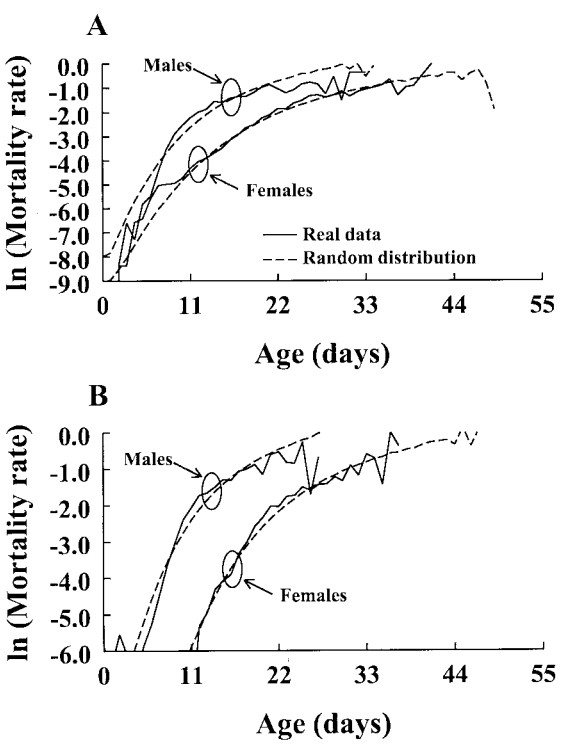

Fig. 2. Actual and predicted mortality curves for two populations of *Callosobruchus maculatus*. (A) Data from C.W. Fox (unpublished) (males: mean = 15.48, variance = 17.84, $n = 4395$; females: mean = 22.80, variance = 34.92, $n = 4299$). (B) Data from Tatar and Carey (1994) (males: mean = 24.40, variance = 24.66, $n = 1840$; females: mean = 14.77, variance = 14.48, $n = 1789$).

different population of *C. maculatus* (Fig. 2B) show exactly the same result; parameter values for females are not different from the null model, but males have higher *b* and *s* than expected from the null model. This raises the really interesting question of why one sex (females) fits the null hypothesis and the other does not. Thus, rather than asking 'why do males and females differ in the shapes of their mortality curves?' and even 'why do organisms show mortality plateaus?', we can now refine our question to 'why do some curves differ from that expected for a quantitative trait, while others do not?' This question could not previously be asked without a definition of a null model. For *C. maculatus*, we can specifically ask 'why do male mortality rates accelerate faster than expected for a quantitative trait, whereas female mortality rates do not?'

Other organisms deviate even more substantially from the null model than do male *C. maculatus*. For example, mortality rates of the seed beetle *Stator limbatus* show higher acceleration (*b*) than expected for a normally distributed trait with the same mean and variance (Fig. 3A), and medflies have both higher acceleration and a *very* long mortality plateau relative to the expected curve (Fig. 3B). Many mammals, including humans, show substantially less deceleration (lower *s*) than predicted from the null model (e.g. re-analysis of data from Bronikowski *et al.*, 2002). We argue that it is the reduced deceleration in mortality observed in humans and some other mammals (see references in Bains,

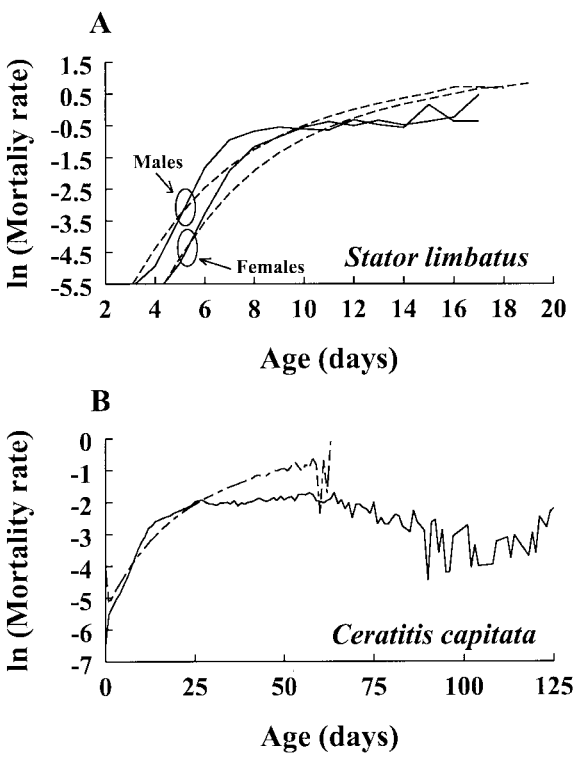

Fig. 3. Actual and predicted mortality curves for (A) four seed beetle, *Stator limbatus* (data from Fox *et al.*, in press) (males: mean = 9.26, variance = 4.05, $n = 1401$; females: mean = 10.48, variance = 3.99, $n = 1411$) and (B) the medfly, *Ceratitis capitata* (data from Carey *et al.*, 1992) (mean = 20.3, variance = 85.6, $n = 1{,}203{,}646$).

2000) that is in need of explanation, not the presence of mortality plateaus in other organisms. The Gompertz and Weibull mortality models, which do not include a deceleration term, do not describe the shape of mortality curves expected for a trait affected by many underlying factors.

HOW DOES THIS MODEL DIFFER FROM PREVIOUSLY PUBLISHED 'HETEROGENEITY' MODELS?

The above discussion shows that logistic mortality curves are an intrinsic property of traits affected by many genetic or environmental factors. However, this result relies on one important assumption – individuals are variable at either multiple loci or in multiple environmental experiences that affect longevity (i.e. the σ_i^2 are non-zero). That mortality plateaus may be a consequence of heterogeneity among individuals or cohorts of individuals has been suggested by many authors (e.g. Vaupel and Yashin, 1985; Vaupel, 1990; Kowald and Kirkwood, 1993; Vaupel and Carey, 1993; Brooks *et al.*, 1994; Horiuchi and Wilmorth, 1998; Pletcher and Curtsinger, 1998, 2000; Partridge and Mangel, 1999; Drapeau *et al.*, 2000; Service, 2000). These authors have shown that heterogeneity can generate plateaus even when age-specific mortality rates increase exponentially within cohorts or genotypes (i.e. fit a Gompertz mortality model) – variation in the parameters of the Gompertz curve among cohorts or genotypes within a population can generate mortality deceleration at the population level (Pletcher and Curtsinger, 1998; but see Bains, 2000, who shows that heterogeneity within populations is not a prerequisite for generating mortality plateaus). Genotypes or cohorts with either steeper individual mortality curves or higher initial mortality rates will die sooner, leaving less frail individuals in the population at advanced ages (Vaupel and Yashin, 1985; Vaupel, 1990; Horiuchi and Wilmorth, 1998).

However, our quantitative genetic explanation for deceleration of mortality rates and the presence of mortality plateaus differs from prior heterogeneity explanations in two important respects. First, we make no assumptions about how mortality curves vary among individuals. In fact, no assumption about the underlying shapes of mortality curves of individuals or cohorts of individuals is required to generate logistic mortality curves. We assume only that the lifespan of individuals is a complex trait affected by many underlying factors, and deceleration of mortality rates is a necessary consequence. Second, our explanation provides a defined null model against which to compare shapes of mortality curves – the expected mortality curve for any organism is as defined by equation (4) and is dependent only on the mean and variance of the distribution of lifespans in the population, and the interval at which death is scored.

DEVIATIONS FROM NORMALITY

Although the shapes of lifespan distributions will converge on normality when the number of genetic and environmental factors affecting lifespan is large, most real distributions deviate from normality, probably because the number of independently segregating factors affecting traits is finite and some genes or environmental effects may have disproportionately large effects (Lynch and Walsh, 1998). In general, factors that increase the right skew or kurtosis of the distribution will increase the slope of the increase in mortality rate (b), whereas left skew will decrease the deceleration parameter (s) so that the mortality curve flattens and looks more like a Gompertz when skew is high. The question thus becomes,

'how do specific biological factors change the shape of lifespan distributions and thus the shape of mortality curves?' For example, a few genes with large effects on lifespan have been identified in organisms as diverse as mice (Holzenberger *et al.*, 2003) and *Drosophila* (Tatar *et al.*, 2001); such genes lead to lifespan distributions that deviate from normality (generally by increasing the skew of the distribution; Lynch and Walsh, 1998). In Fig. 4 we show the effect of a single gene of large effect on the shape of $u(T)$. Changing the frequency of an allele with large effect substantially changes the shape of the mortality curve. For example, imagine a population initially fixed for allele A_1 into which allele A_2, which increases lifespan by 20%, invades (each copy of A_2 increases lifespan by 20%; mean lifespan: $A_1A_1 = 100$ days, $A_1A_2 = 120$ days, $A_2A_2 = 140$ days). As A_2 increases above 0, the lifespan distribution becomes right-skewed and produces a mortality curve with a steeper increase in mortality with age (higher b), faster deceleration (higher s; Fig. 4B) and longer plateau than expected by the null model (Fig. 4), whereas at high frequencies the lifespan distribution becomes left-skewed and the mortality curve is much flatter than expected from the null model. Increasing the effect size of the allele to 40% results in a bimodal distribution of lifespans and a humped-shaped mortality curve (kurtosis < -1.2; Wyszomirski, 1992). Modelling how other patterns of inheritance affect the shape of $u(T)$ is beyond the scope of this paper, but should be easily accomplished now that a suitable null model has been established with which to compare alternative distributions.

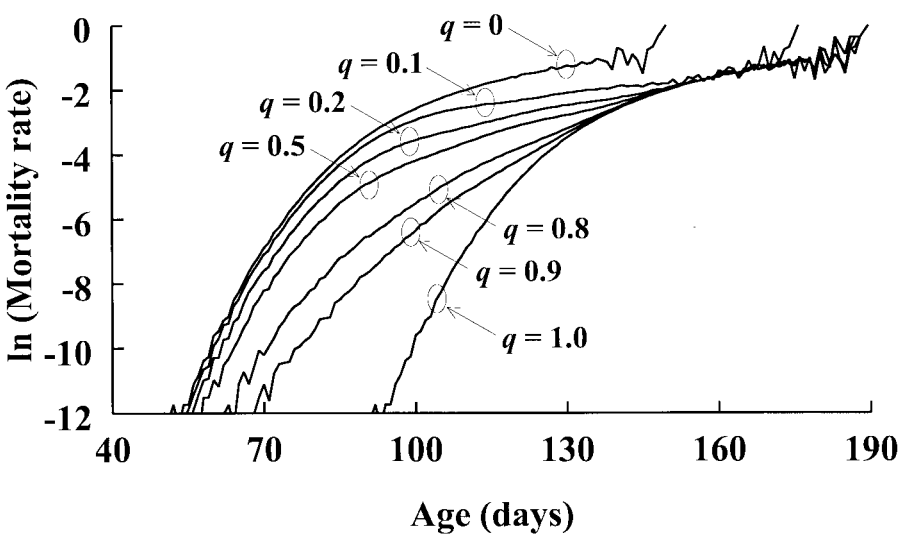

Fig. 4. The predicted change in shape of $u(T)$ when a single allele of large effect invades a population. q is the frequency of A_2, the invading allele. When $q = 0$, the lifespan distribution is normally distributed with $\mu = 100$ days and $\sigma^2 = 120$ days. As A_2 invades, the mortality curve shifts to the right because the mean lifespan in the population shifts (because A_2 has a positive effect on lifespan). Note, however, the substantial shift in the shape of $u(T)$ as the frequency of A_2 increases. Note also that all mortality curves deviate from the expected curve for a normally distributed set of lifespans, except when $q = 0$ and $q = 1$. Each curve was generated using 1 million data points. [See chapter 13 and Figure 13.1 in Lynch and Walsh (1998) for examples of how genes of major effect affect the shape of lifespan distributions.]

CONCLUSION

The lifespan of an individual is a quantitative trait, simultaneously affected by many genes and environmental factors. The simultaneous effects of many genetic and environmental factors generate normally distributed times-to-death in the population, which, when translated into mortality curves, show the mortality deceleration and mortality plateaus similar to the deceleration and plateaus observed in numerous organisms. Therefore, questions about the shape of mortality curves must be reframed in terms of deviations from null models (i.e. the mortality curves expected for quantitative traits). We show how comparisons between the observed data and the null models can be achieved with simple statistical tests, and that the results of these comparisons can be very informative regarding which questions about the shapes of mortality curves will be most meaningful.

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