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Review

The evolution of late life

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Abstract

Late life is a distinct phase of life characterized by a cessation in the deterioration of survivorship and fecundity characteristic of normal aging. Several theories have been proposed to explain non-aging at late ages, specifically with regards to late-life mortality-rate plateaus. All such theories must be compatible with formal evolutionary theory and experimental findings. Here, we develop a critique of theories of late life based on evolutionary biology.

Keywords: Aging; Fecundity; Force of natural selection; Late life; Mortality; Plateaus

1. Introduction: the third phase of life

Gerontologists and demographers have long described the aging process in terms of the equation for mortality rates proposed by Benjamin Gompertz:

$$\mu(x) = A\,\mathrm{e}^{\alpha x} \tag{1}$$

where x is age, $\mu(x)$ is the age-specific mortality rate, A an age-independent parameter that gives the baseline mortality rate of the population, and α an age-dependent parameter or the rate of aging. This equation predicts an exponential increase in mortality rates with age as individuals within a population deteriorate over time (Finch, 1990). There was never any specific biological reasoning behind the Gompertz equation, although evolutionary biologists attributed such mortality patterns to the decline in the age-specific force of natural selection during the reproductive period (e.g. Hamilton, 1966). But late-life

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human data do not conform to Eq. (1) (e.g. Greenwood and Irwin, 1939; Comfort, 1964; Gavrilov and Gavrilova, 1991), showing a stabilization of age-specific mortality rates at very late ages. However, these observations were often dismissed, because scientists thought they could be explained away by the advent of modern medicine and public health measures.

It was not until the 1990s that ''late life'' was first definitively observed in two dipteran species (Carey et al., 1992; Curtsinger et al., 1992) (Fig. 1). In these studies, late ages were characterized by an apparent cessation of age-related deterioration. That

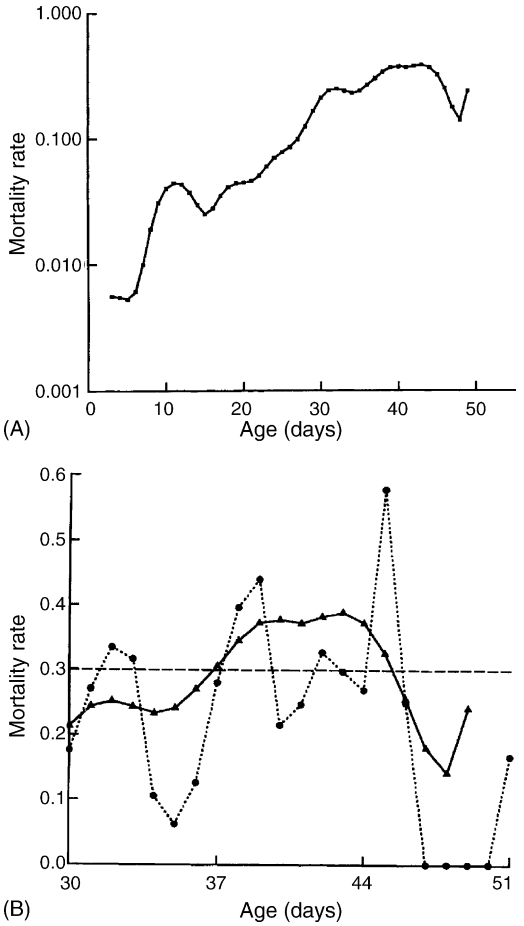

Fig. 1. (A) Age-specific semilog mortality rates from an inbred line of male *Drosophila melanogaster*, demonstrating the plateauing of mortality rates in late life. The cohort started with 5751 individuals. (B) Detailed look at the last 1906 deaths (arithmetic scale) from the initial inbred cohort. The dotted line represents the daily probabilities of death, the sold line represents the smoothed mortality-rate estimates, and the horizontal dashed line represents the maximum likelihood estimate of mortality rates from a two-stage Gompertz model. The fitted Gompertz model in this cohort estimated a slowing of mortality rates, or a plateau, at age 30 days. Excerpted with permission from Curtsinger et al. (1992). Copyright 1992 AAAS.

is, mortality rates increased exponentially during mid-life in these populations, as expected in aging organisms, but stopped increasing and ''plateaued'' at later ages. At first, the cessation of aging at late ages seemed paradoxical because the accumulation of damage with age was expected to increase until mortality rates reached 100%, especially given the Gompertz equation. However, since the discovery of this post-aging period of life, data from a variety of laboratories have suggested that late life occurs generally among aging organisms (Fukui et al., 1993; Tatar et al., 1993; Brooks et al., 1994; Kannisto et al., 1994; Charlesworth and Partridge, 1997; Vaupel et al., 1998). Without question, mortality patterns in very old organisms do not generally follow the Gompertz pattern. Late-life mortality rates vary widely among species, but a reliable attribute of late life is the switch from accelerating mortality to a relatively stable mortality, on average.

Late life is not only characterized by a deceleration in age-specific mortality rates, but recently has also been characterized by the cessation of age-specific reproductive aging (Rauser et al., 2003, in press). Together these observations of mortality and fecundity patterns strongly suggest that late life is as distinct a phase of life history as either development or aging, and thus in principle deserves as much experimental and theoretical attention. In this paper, we review the theoretical and experimental work performed on late-life mortality and fecundity, analyzing the successes and failures of this body of work from the standpoint of evolutionary biology.

2. Theories that might explain late life

2.1. Various minor theories

Although the deceleration of mortality rates at late ages has been explained by two main kinds of theory, evolutionary theory based on the force of natural selection and lifelong heterogeneity theory, several other theories have been proposed (reviewed by Olshansky and Carnes, 1997). These theories are generally not biologically motivated and lack the necessitous features of the two main theories we will discuss below. Therefore, we will only discuss two of these other theories, and those briefly.

One such theory attempts to explain late-life mortality patterns in terms of optimal life-history theory (e.g. Abrams and Ludwig, 1995). This theory attributes the decline in mortality rates at late ages to the cessation of reproduction. It depends critically on the existence of particular trade-offs between reproduction and mortality. Such trade-offs are both variable in their occurrence and their form (cf. Rose et al., 1996). It is implausible that the proposed trade-offs would ubiquitously generate late-life plateaus in the manner predicted by Abrams and Ludwig (1995).

Gavrilov and Gavrilova (2001) proposed a theory of organismal mortality that assumes that mortality is a result of the failure of multiply redundant physiological components, with death occurring once the last of these redundant components fails. However, the features of the components assumed by this theory are surely under the control of natural selection, which ultimately leaves us with mortality patterns that are shaped by evolution.

2.2. Hamilton's forces of natural selection

2.2.1. The force of natural selection acting on mortality

Haldane (1941) and Medawar (1946, 1952) were the first to describe aging as a consequence of the weakening force of natural selection with age. However, it was Hamilton (1966) who actually derived a quantitative formula for this force for the first time. According to Hamilton, the force of natural selection acting on mortality is given by $s(x)/T$, where x is chronological age and T is a measure of generation length. The function s at age x is given by

$$s(x) = \sum_{y=x+1} \mathrm{e}^{-ry} l(y) m(y) \tag{2}$$

where r is the Malthusian parameter or the growth rate of the population, associated with the specified $l(y)$ survivorship and $m(y)$ are fecundity functions. The variable y is used to sum up the net expected reproduction over all ages after age x. Ultimately, the $s(x)$ function represents the immediate fitness impact of an individual's future reproduction. Note that, before the first age of reproduction, s is always equal to 1, once reproduction has ended, s is equal to 0, and during the reproductive period, $s(x)$ progressively falls. Fig. 2 shows an example of an $s(x)$ function that depicts how the force of natural selection acting on mortality declines with adult age, throughout the reproductive phase, and converges on zero at very late ages.

Implicit within Hamilton's (1966) original theory for the force of natural selection is an evolutionary theory of late life. Recall that s is equal to zero for all ages after reproduction has ceased. Therefore, age-specific mortality rates should mimic the plateau in the force of natural selection, because natural selection is unable to distinguish fitness differences in survival at different ages after the cessation of reproduction in the course of a population's evolution (Mueller and Rose, 1996). Mortality rates do not necessarily have to reach zero as soon as reproduction ceases, because beneficial effects

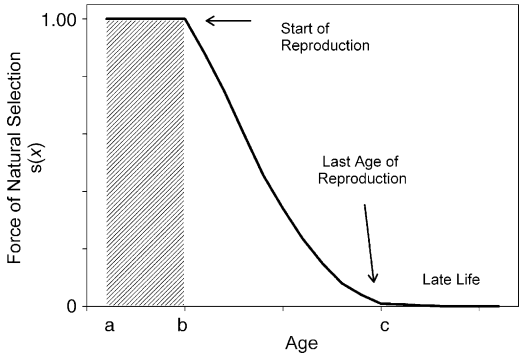

Fig. 2. The age-specific forces of natural selection acting on mortality. Natural selection is intense at early ages, until the first age of reproduction (from ages a to b), and then begins to decline rapidly until the last age of reproduction, after which it converges on, and remains at zero. The onset of late-life mortality-rate plateaus occurs sometime after age c.

that are not age-dependent will continue to benefit individuals who remain alive after the force of natural selection has converged on zero. Any age-independent genetic benefits will be favored by natural selection acting at early ages and will have positive pleiotropic benefits at all later ages.

Mueller and Rose (1996) numerically demonstrated that mortality plateaus can arise as a consequence of the force of natural selection in age-structured populations. Their simulations showed that mortality plateaus evolve because of two genetic mechanisms: mutation accumulation and antagonistic pleiotropy (Fig. 3). [Mutation accumulation in aging is defined as the increase in frequency of deleterious mutations at later ages due to the weak force of natural selection at those ages, while antagonistic pleiotropy occurs in aging when multiple effects of a genetic change are opposed in their impact on early fitness and later survival or fecundity, resulting in active selection for aging (vid. Rose, 1991).] In addition to demonstrating leveling of mortality rates at late ages, these models also showed an exponential increase in mortality rates at earlier ages, the pattern that is merely assumed by the Gompertz model. However, there have been critiques of this theory (Partridge and Charlesworth, 1997; Pletcher and Curtsinger, 1998; Wachter, 1999). It has been suggested that mortality rates must eventually rise to 100% under mutation accumulation and antagonistic pleiotropy because of selection's inability to eliminate deleterious mutations at later ages. Charlesworth (2001) solved the problem of why plateaus are not necessarily confined to 100% mortality by showing theoretically that age-independent beneficial effects can forestall the evolution of 100% mortality before late life starts.

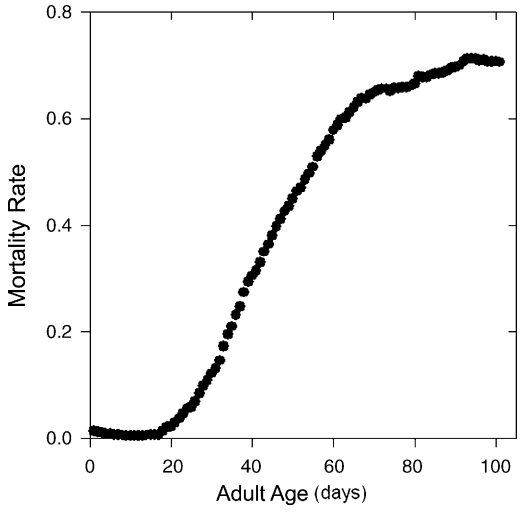

Fig. 3. Age-specific mortality rates arising from long-term evolution involving antagonistic pleiotropy. These evolved patterns are the results of computer simulations that are described in Mueller and Rose (1996). Initially, mortality was constant over all ages and equal to 10%. Simulated mutations had broad pleiotropic effects over 40 adjacent days (age classes). Natural selection results in an exponential (Gompertzian) increase in mortality rates at early ages and a plateau at late life.

2.2.2. The force of natural selection acting on fecundity

The evolutionary theory of late life based on the force of natural selection can also be applied to the evolution of age-specific fecundity. Like mortality, the age-specific force of natural selection acting on fecundity, $s'(x)$, has a scaling effect

$$s'(x) = \mathrm{e}^{-rx} l(x). \tag{3}$$

All the variables in Eq. (3) have the same definitions as those in Eq. (2). The force of natural selection acting on fecundity declines with age if population growth is not negative (cf. Hamilton, 1966; Charlesworth, 1980, 1994). The probability of survival to age x directly affects the force of natural selection on fecundity at that age. According to this theory, $s'(x)$ will converge on zero after the last age of survival in the population's evolutionary history.

Hamilton's forces of natural selection acting on mortality and fecundity are similar in their effects, and thus will shape both age-specific mortality and fecundity within populations in a comparable manner. Therefore, the evolutionary theory of late life also predicts that late-life fecundity will roughly plateau at ages greater than the age at which $s'(x)$ declines to zero.

We can illustrate this evolutionary inference using numerical simulations based on conventional age-structured population genetics. Our computer simulations had populations evolving with recurrent mutations to explore how age-specific fecundity is molded by natural selection. We assumed that survival from age class-i to age class-$i + 1$, p_i, was constant. The chance of surviving to age class-j, l_j, would then be $p^{(j-1)}$. We assumed environmental variation affected female fecundity such that a female age-i would have fecundity equal to, $F_i = f_i + cf_iZ$, where $Z \sim N(0, 1)$. In a constant environment, fitness in an age-structured population is found from the solution, r_0, to the Lotka equation, $1 = \sum_{i=1}^{d} \mathrm{e}^{-r_0 i} l_i f_i$, where d is the total number of age classes (Charlesworth, 1994). Fitness of new mutant genotypes in a variable environment were determined from a stochastic growth rate parameter, $w = r_0 - \frac{c^2}{2T_0^2}$, where T_0 is the mean generation time (Tuljapurkar, 1990, Eq. (15.2.1)).

Random genetic drift could affect the fate of weakly beneficial or deleterious mutants. We modeled this by using the fitness of the resident and mutant genotype to determine the probability of fixation from Ewens (1979, Eq. (3.28)). A uniform random number would then be chosen to simulate this fixation event.

We assumed a life history of nine juvenile, pre-reproductive age classes and a maximum of 100 post-reproductive age classes, and set initial fecundity to 10 for each age class. Age-specific survival was assumed constant and equal to 0.999. The random variation parameter, c^2, was set to 0.5 and the effective population size was 10,000.

In this example, the mutant fecundity schedules all exhibit antagonistic pleiotropy. Thus, a mutant consisted of a stretch of 5 consecutive days of elevated fecundity and 5 consecutive days of depressed fecundity, relative to the resident. The onset of elevated fecundity was chosen at random from the 100 possible age classes, and similarly, but independently, for depressed fecundity. If the current resident's fecundity at day-i was f_i, then a mutants fecundity would be elevated to $f_i + (f_{\max} - f_i)U$, where $f_{\max}$ is the maximum allowable fecundity set to 100 in these simulations and U is a uniform random

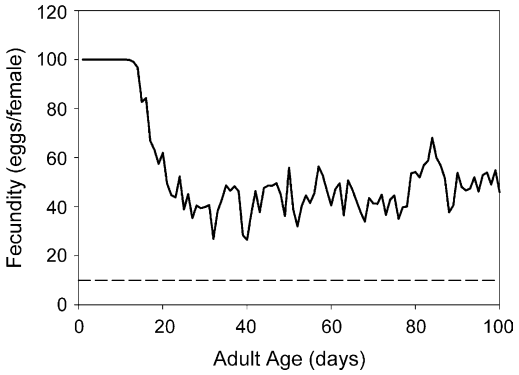

Fig. 4. Simulation results for the evolution of fecundity with recurrent mutations in a population of 10,000 individuals. The solid line represents the average age-specific population fecundity from 20 such simulations. Fecundity is high at early ages, declines rapidly, and plateaus at later ages, just as evolutionary theory based on the force of natural selection predicts. Starting fecundity for each simulation was 10 eggs/female over all age classes (represented by the horizontal dashed line).

number between 0 and 1. Fecundity was depressed by, $f_i - f_i U$. One simulation consisted of generating 100,000 mutants.

The average results of 20 simulations show that fecundity evolves to its maximum level at young ages (Fig. 4), but then declines rapidly and reaches a more or less constant value at about age 25–30 and thereafter. Thus, the force of natural selection becomes so weak at later ages that these ages eventually evolve an absence of differences making fecundity plateau.

The expansion of evolutionary theory to include late life is fundamental to our understanding of both aging and late life. More analytical mathematical derivation of evolutionary late-life theory is undoubtedly necessary. However, as it stands, this theory readily allows for testable predictions regarding age-specific mortality and age-specific fecundity at late ages. Unlike the theories described in the previous section, the evolutionary theory based on the force of natural selection is much more general. It allows us to explain the evolution of aging and late life without resort to specific demographies or specific physiological trade-offs.

2.3. Lifelong heterogeneity theories

The other main set of theories proposed to explain the leveling of mortality rates at late ages are demographic theories based on lifelong differences in individual robustness. These theories suppose that there is sufficient heterogeneity in lifelong robustness within a population to cause the slowing of mortality rates at late ages. That is, mortality rates will start to slow at later ages, after the less robust individuals in the population have died. Note that demographic heterogeneity should not be confused with mere genetic or environmental variation within a population (cf. Carnes and Olshansky, 2001). The assumption of consistent lifelong differences between individuals is more exigent.

The idea of demographic heterogeneity predates the definitive discovery of late-life mortality-rate plateaus. Beard (1959) derived mathematical models for mortality that accounted for heterogeneity in mortality. He was an actuary who primarily analyzed human data and was concerned about the way late-age human data did not conform to the Gompertz family of mortality models. His mortality models included variables that accounted for individual differences in ''vitality'' (Beard, 1964). He even suggested that these differences in vitality may be the underlying cause of the slowing in late-age human mortality rates (Beard, 1971).

Vaupel et al. (1979) developed the first complete *lifelong demographic heterogeneity* theory to explain late life. This theory leads to a robust prediction of decelerating age-specific mortality late in life, granting only a few, seemingly natural, assumptions. The heterogeneity theory assumes that aging cohorts are comprised of a collection of secondary groups, with each subgroup having its own characteristic Gompertz function that defines its mortality pattern. Thus, one subgroup might have a relatively low baseline mortality rate (A from Eq. (1)) compared to other subgroups that will reduce its age-specific mortality rates throughout life, but the same rate of aging (α from Eq. (1)). With this version of Vaupel's heterogeneity model the average age-specific mortality rate is,

$$\bar{\mu}(x) = \frac{A\, e^{\alpha x}}{1 + [\sigma^2 A(e^{\alpha x} - 1)]\alpha^{-1}} \tag{4}$$

where σ^2 is proportional to the variance in A. At advanced ages, once most individuals in the less robust subgroups have died, the average mortality rate of Eq. (4) approaches a mortality-rate plateau equal to $\alpha\sigma^{-2}$.

On the other hand, the rate of aging, i.e. the value of α, may be the parameter that varies among subgroups, resulting in some groups having a significantly higher rate of aging than others (Pletcher and Curtsinger, 2000). Although allowing the rate of aging to vary among subgroups is much more difficult to analyze, Pletcher and Curtsinger (2000) and Service (2000) have examined the age-dependent changes in the variance of mortality rates. Mueller et al. (2003) used this model to develop predictions regarding the number of individuals that should be alive at late ages in populations of *Drosophila*. They supposed that individuals with lower values of baseline mortality (A) and lower rates of aging (α) would be the individuals to survive to late ages. Note that the main premise of the demographic heterogeneity theory, and the distinction among groups within cohorts, is based on the idea that these subsidiary groups have inherent *lifelong* differences in mortality patterns. Therefore, whenever either type of lifelong heterogeneity arises, one can expect a deceleration in mortality at late ages once the individuals with high values of A and/or α die off.

There is no equally natural explanation of late-life plateaus in fecundity from the heterogeneity theory, but post hoc explanations are possible. One such explanation could be the differential loss of more fecund individuals. That is, it is conceivable that some females lay a lot of eggs at early ages, but die prematurely, leaving only those individual females that always laid a low number of eggs preponderant among later ages. This explanation assumes there is a trade-off between mortality and reproduction, and couples high mortality with high fecundity, and conversely. Another possible heterogeneity

explanation for the existence of late-life fecundity plateaus is based on some sort of highly generalized robustness, whereby some females both survive better and are more fecund. In addition to these two possible explanations, any number of variations based on heterogeneity in fecundity can be imagined.

3. Evolutionary problems facing late-life theories

3.1. Forces of natural selection

One of the most obvious evolutionary challenges facing the evolutionary theory of late life based on the force of natural selection is the empirical finding that late-age mortality rates do not reach 100%, nor does late-age fecundity decline to zero. Charlesworth (2001) has addressed this concern mathematically in age-structured populations subject to mutation accumulation, considering cases in which beneficial gene effects are age-independent. These genes will be selected to remain in the population because of their beneficial effect at earlier ages, and will continue to have a beneficial effect during late life as well. The pleiotropic ''echo'' from these age-independent beneficial genes will hold mortality rates below 100% and fecundity above zero at late ages. This idea is exactly the opposite of antagonistic pleiotropy (cf. Rose, 1991).

Because the late-life force-of-natural-selection theory is an evolutionary theory, late life should evolve in ways predictable from the forces of natural selection, given enough genetic variation and an ample number of generations. Rose et al. (2002) used computer simulations of life-history evolution in which late-life mortality plateaus evolved with recurrent mutations. The key point was the manipulation of the last age of reproduction. Recall that the force of natural selection acting on mortality converges on zero sometime after the last age of reproduction (and after the last age of survival for fecundity). Therefore, Rose et al. (2002) predicted that late-life mortality plateaus should evolve accordingly. Their simulation results demonstrated that the start of mortality-rate plateaus is positively correlated with the last age of reproduction (Fig. 5). Similarly, the last age of survival should determine the start of late-life plateaus in fecundity. The evolutionary theory of late life based on the force of natural selection predicts that late life should evolve according to the timing of the convergence of the forces of natural selection on zero.

3.2. Lifelong heterogeneity

Some variability in robustness, the underlying controller of mortality rates in cohorts free of exogenous mortality, undoubtedly exists within natural populations due to genetic and environmental variation. There is a substantial amount of literature showing that life-history characters vary (reviewed in Finch, 1990; Rose, 1991; Roff, 1992; Stearns, 1992), which might be taken to mean that the heterogeneity model is well founded. In fact, heterogeneity can arise when evolution by natural selection maintains genetic variation, which means that the two main theories of late life are not necessarily entirely incompatible. However, what the heterogeneity theory requires is that there are great enough lifelong differences in individual mortality rates to result in the observed slowing of

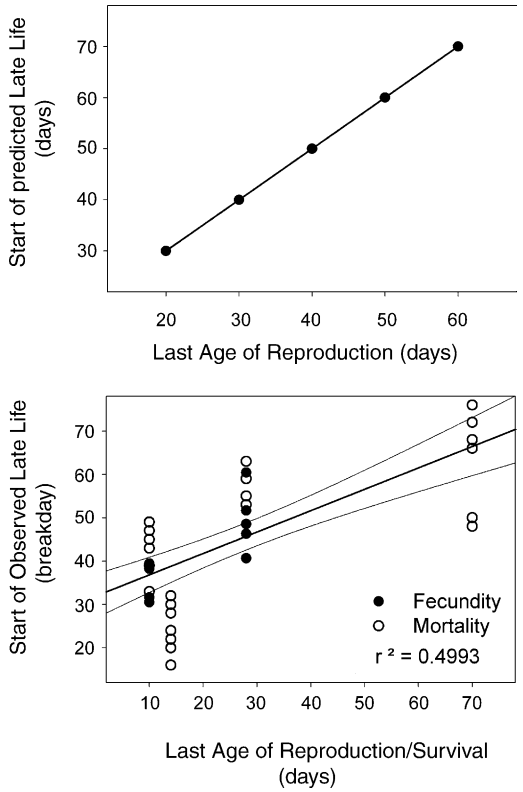

Fig. 5. Predictions from the evolutionary theory of late life based on the force of natural selection. The top figure shows the basic results of computer simulations for the evolution of mortality-rate plateaus in response to changes in the age of reproduction. As the last age of reproduction increases, so does the onset of late-life mortality-rate plateaus. The bottom figure shows the breakdays for mortality (open circles) and fecundity (solid circles) compared to the age of reproduction for each population. A linear regression was performed on the data that corroborates the results of the computer simulations: as the last age of reproduction increases, so does the onset of late life (breakday) ($P < 0.0001$). All data are from the studies of Rose et al. (2002) and Rauser et al. (in press).

mortality rates at late ages. Mueller et al. (2003) demonstrated that the heterogeneity theory requires either too much variation, or it predicts that a greater number of individuals will live to very late ages than has been empirically observed in Drosophila cohorts.

The heterogeneity theory of late life faces major difficulties. Evolutionary theory predicts that natural selection will tend to decrease genetic variation in fitness-related traits like early adult mortality (Nagylaki, 1992). However, the lifelong heterogeneity theory requires a large amount of sustained lifelong heterogeneity for mortality, either genetic or environmental. If the genetic heterogeneity for mortality rates, both early and late, is heritable, it is going to be strongly subject to natural selection. Natural selection will, of course, reduce the amount of genetic heterogeneity in a population over time, unless there is some form of balancing selection, which is not that common. Without balancing selection, or some other mechanism constantly introducing genetic variation into the

population, natural selection will purge most genetic variation for lifelong robustness from the population.

The lifelong heterogeneity required by the late-life heterogeneity theory can also be environmental, or even merely developmental. If there is a substantial amount of variation arising from the environment, whether it is spatial, temporal, or both, then the measure of fitness is given by the average effect of an allele minus a term giving the variation in fitness. Thus, the equation $\mu - \frac{1}{2}\sigma^2$ determines the evolutionary outcome, or fitness, of a genotype (Gillespie, 1973), where μ is the measure of average fitness and σ^2 is the measure of environmental variance in fitness. Therefore, evolution by natural selection will also tend to reduce environmental sources of lifelong heterogeneity. Because fecundity is also a major fitness component, we expect the same reduction in genetic and environmental variation from natural selection on fecundity as with mortality.

Despite these points, lifelong heterogeneity can be expected to produce some effects on mortality rates, when it arises. One candidate mechanism that could produce such an effect would be size variation in organisms that grow a fixed adult structure, a group that includes most terrestrial animal species, though not most trees or marine organisms. In such cases, a particular animal within a cohort may have a characteristic underlying mortality rate throughout its adult life. However, superimposed on this effect of lifelong heterogeneity will be the universal plateauing of the forces of natural selection.

4. Comparative tests of late-life theories

4.1. Existence of late life

The evolutionary theory of aging and late life based on the forces of natural selection, which we might call Hamiltonian theory, requires that late life should always exist, at least potentially. This, of course, is not true for most organisms in the wild because they will almost never live long enough to express late-life patterns because of the very way in which Hamiltonian theory works. These organisms may show late life under protected laboratory conditions, as has been observed in the medfly (Carey, 2003). However, late-life patterns might not be observed in some organisms even under laboratory conditions because of gene $\times$ environment interactions, since the phenotype may not be exhibited in an evolutionarily novel environment. Even under protected laboratory conditions, semelparous organisms will not show late life because these are organisms in which antagonistic pleiotropy apparently overwhelms the effects of age-independent beneficial effects (cf. Charlesworth, 2001). However, semelparous life histories are already considered a special case from the standpoint of aging research generally, so this particular case is not inherently confusing for any type of theory for late life. Semelparity is thus easily excluded as a context for the application of late-life theories. Fissile organisms also should not show late life because they only have one-phase life cycles and never show aging, either.

Thus far, we are not aware of any instances in which late life clearly does not exist in iteroparous organisms, at least with respect to mortality rates. Research from various laboratories has shown that late-life mortality plateaus occur in medflies, *Drosophila*, wasps, beetles, nematodes, yeast, and humans (Vaupel et al., 1998). In addition, Rauser

et al. (2003, in press) demonstrated that population fecundity also plateaus at late ages as predicted by Hamiltonian theory. The plateauing of late-life fecundity should occur under the same criteria as those set forth for the existence of late life in general, described above.

In contrast to Hamiltonian theory, the lifelong heterogeneity theory, or ''Vaupelian theory,'' does not require that late life should *always* exist in iteroparous organisms. In fact, Vaupelian theory makes late life more of a slowing in the rate of aging, rather than the plateau which is expected at evolutionary equilibrium under Hamiltonian theory. Vaupelian theory framed so as to take into account the action of natural selection in minimizing lifelong heterogeneity implies that late life should be characteristically a minor inflection in the overall aging pattern. Most importantly, Vaupelian theory does not make late life fundamentally distinct from aging, but rather a mere cohort-sampling effect, with aging proceeding at all ages. By contrast, Hamiltonian theory predicts the cessation of aging at late ages regardless of cohort constitution.

4.2. Quantitative variation in late life

According to Hamiltonian theory, the timing of late life depends on the last age of reproduction for mortality, and the last age of survival for fecundity, in the evolutionary history of the organism. The exact timing is subject to complications from pleiotropy and gene × environment interactions. Therefore, at a gross qualitative level, the comparative biology of quantitative variation in late life should be analogous to that of aging: late life should generally start later in organisms with later last ages of reproduction and survival. That is, species like elephants and bristlecone pines should have a much later onset of late life than shorter lived species like mice, flies, and weeds. As of now, there is not enough data on different species to test these qualitative predictions.

Vaupelian theory predicts that the distinctness of late life should depend on the amount of variation in the A and α parameters of the Gompertz model (or cognate parameters from cognate models). This variation can be genetic and/or environmental in nature. Therefore, clonal non-fissile organisms that have low environmental variation (V_E) should exhibit almost no late-life plateaus, while genetically variable and environmentally sensitive organisms should exhibit strong mortality-rate deceleration in comparison. But do insects, mice, and weeds exhibit a more distinct late-life plateau? Again there is a dearth of data available to test these predictions among species.

5. Experimental evolution of late life

5.1. The experimental demonstration of plateaus for life-history characters

In late-life evolutionary theory, the predicted pattern of late life is that the declines of survival probabilities and fecundity values which characterize aging will eventually stop, resulting in an absolute cessation of aging in iteroparous organisms. Thus, we use models that have actual plateaus in the statistical models fitting our data, even though the attainment of an *exact* plateau is not going to be observed in a finite amount of time with finite data.

Instead, actual mortality and fecundity data will have gradual approaches to plateaus, with a great deal of experimental error in the estimation of the plateau level. In addition, the sampling variance of the estimated mortality and fecundity rates will increase at later and later ages, in a real-world experiment, because the sample sizes diminish due to deaths. We simply have too few data at much later ages to estimate the plateau properties precisely. This gives rise to increasing diversity of individual mortality and fecundity trajectories with age, some continuing to rise, other trajectories actually falling, etc. All of these effects are predictable a priori. We have both simulated these effects numerically and assayed 25 simultaneous Drosophila cohorts (recording mortality rates on about 60,000 flies—data not shown) that show these effects dramatically. With an *expectation* of eventual convergence to a plateau on average, the individual *sample paths* will frequently show continued aging OR reversed aging. Thus, finite sets of data will often feature cohorts which show continuing rises or falls in late-life life-history characters.

Another problem facing the use of evolutionary theory for *any* phase of life history is that the predictions of evolutionary theory usually refer to the phenotypes that can be observed in populations that have evolved for some time in the same habitat as the habitat in which the population has evolved for some time, preferably hundreds of generations. Otherwise gene × environment interaction effects can obscure the evolutionarily relevant life-history pattern. To test evolutionary theories of late life requires a long period of antecedent selection in the environment in which data are being collected. Few observable populations meet this criterion, although laboratory evolved Drosophila populations often will.

5.2. Late-life mortality rates

Hamiltonian theory predicts that late-life mortality rates should plateau and evolve according to the last age of reproduction in a population's evolutionary history (Hamilton, 1966; Mueller and Rose, 1996; Rose et al., 2002). Several studies have established the plateauing of late-life mortality rates. However, it was not until 10 years after Carey and Curstinger's groups published their late-life mortality papers that Rose et al. (2002) published their tests of the evolvability of late-life mortality in *Drosophila*. They compared the onset of late-life mortality-rate plateaus in three independent pairwise comparisons, employing 25 genetically distinct populations that had long been selected for different last ages of reproduction. As predicted, mortality plateaus started later in late-reproducing populations compared to early-reproducing populations (see Fig. 5). They also demonstrated that late-life mortality is affected by the genetic mechanism of antagonistic pleiotropy. The onset of mortality plateaus from populations long having late ages of reproduction responded quickly to selection for earlier reproduction (Fig. 6).

5.3. Late-life fecundity

Late-life fecundity should also plateau and evolve according to the last age of survival in a population's evolutionary history (Hamilton, 1966; Rauser et al., 2003). Rauser et al. (2003) was the first group to test whether fecundity plateaus at late ages, analogous to the plateauing of mortality rates, using large cohorts of *Drosophila*. They found that average population fecundity declines during mid-life, then it stops declining and plateaus at late

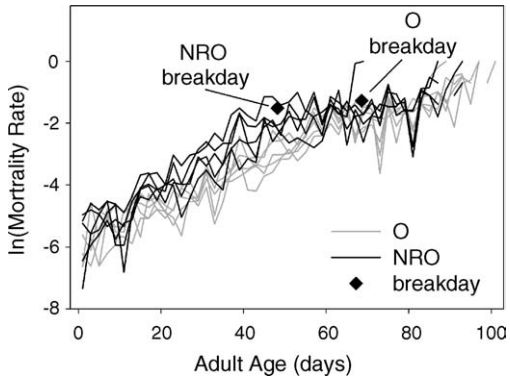

Fig. 6. Two-day log mortality rates for males from five replicate O populations, cultured with late last ages of reproduction for more than 100 generations, and 5 replicate NRO populations, cultured with early ages of reproduction. The NRO populations were derived from the corresponding O populations and selected for early ages of reproduction for only 25 generations prior to the start of the assays. Late-life plateaus in mortality start significantly later in the O populations compared to the NRO populations, which is predicted by the evolutionary theory of late life based on the declining force of natural selection. The quick response of late-life mortality to selection for earlier reproduction in the NRO populations indicates that antagonistic pleiotropy is a genetic mechanism shaping late-life mortality patterns. These were among the first results corroborating any theory proposed to explain mortality patterns in late life (Rose et al., 2002).

ages in three independent populations. The plateau in fecundity is not exact because populations may not be in evolutionary equilibrium, but the rate of decline in fecundity definitely slows and remains at some number of eggs greater than zero (Fig. 7). Rauser et al. (in press) also tested whether fecundity, like mortality, evolves according to Hamiltonian theory and found that the last age of survival predicts the timing of the onset of late-life

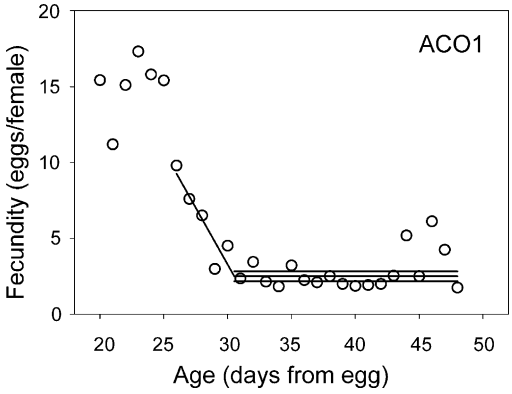

Fig. 7. Average mid- and late-life fecundity from a population of *Drosophila melanogaster* selected for early reproduction (open circles). A two-stage linear model, having a second-stage plateau, was fit to the data to test for the presence of late-life plateaus in fecundity. This model was chosen a priori because it is the simplest model that captures the predictions of the evolutionary theory of late life based on the force of natural selection. The 95% confidence intervals around the second stage of the model suggest that fecundity stops declining at late ages and plateaus at some number of eggs greater than zero (Rauser et al., 2003).

fecundity plateaus. They found in two independent comparisons that late-life fecundity plateaus start later in populations with later last ages of survival (see Fig. 5). In addition, antagonistic pleiotropy was also implicated as a genetic mechanism shaping late-life fecundity patterns, as the onset of fecundity plateaus rapidly evolved according to changes in the last age of survival.

6. Experimental tests of lifelong heterogeneity

6.1. Late-life morality rates

Vaupelian theory requires a large amount of variance in A or α values between subgroups of individuals comprising a cohort. Although lifelong heterogeneity this extreme has yet to be shown experimentally for any organism, a theoretical analysis of the Carey et al. (1992) mortality data for medflies demonstrated that their data could be fitted post hoc to a Vaupelian demographic heterogeneity model (Kowald and Kirkwood, 1993), using entirely hypothetical high levels of lifelong heterogeneity.

Lifelong heterogeneity in mortality could be genetic or environmental in origin. An important empirical corollary is that genetically homogenous populations should show a less distinct mortality-rate plateau than genetically heterogeneous populations. Brooks et al. (1994) compared an isogenic population of *Caenorhabditis elegans* with a genetically heterogeneous population and found a more distinct plateau in the heterogeneous population. However, Vaupel et al. (1994) pointed out that the isogenic line was grown under different environmental conditions than the heterogeneous line, complicating the interpretation of these results. In addition, isogenic lines do not always show a less distinct plateau compared to heterogeneous populations in cohorts of *Drosophila* (Curtsinger et al., 1992; Fukui et al., 1996). Lastly, Fukui et al. (1993) found clear mortality plateaus with highly inbred *Drosophila* lines (inbreeding coefficient > 0.99), suggesting that genetic variation is not required for mortality plateaus.

If lifelong heterogeneity in mortality does not arise from genetic heterogeneity, then it must come from heterogeneity in the environment, or from accidents of development. However, Khazaeli et al. (1998) found that environmentally induced heterogeneity in flies is not a primary factor in determining late-life mortality rates.

The lifelong heterogeneity theory also patently requires variation in robustness between individuals in a population. Drapeau et al. (2000) compared the late-life mortality patterns of populations of files having markedly different levels of robustness, arising from selection on resistance to starvation. They found no significant differences in late-life mortality patterns between populations with widely varying levels of robustness, when the data were fit to Gompertz models using maximum likelihood. However, Steinsaltz (2005) has argued that fitting other mortality models to the same data gives results that support the heterogeneity model. Note however that Steinsaltz (2005) omitted mortality data from earlier ages post hoc when fitting the data to his models.

Mueller et al. (2003) tested Vaupelian theory by fitting heterogeneity models to mortality data from populations of *Drosophila melanogaster*, specifically choosing parameter values for these models that fit the observed data as closely as possible. The

heterogeneity models that best fit the overall mortality were, however, quite poor at predicting the late-life mortality pattern, especially the age at death of the last fly to die. The heterogeneity models predicted that more flies would be alive at late ages than actually were. Mueller et al. (2003) also showed that the variance in the natural log of mortality rates changed little with age in genetically variable laboratory populations of *Drosophila*, leaving aside very early and late ages. According to the heterogeneity model, variance in mortality should consistently change with age over the lifetime of a cohort (cf. Service, 2004).

Collectively, these experimental results do not support a role of demographic heterogeneity in late-life mortality. But they do not exclude a contribution of lifelong heterogeneity to some of the slowing in mortality rates at late ages. However, it is unlikely that this theory can explain late-life patterns entirely on its own.

6.2. *Late-life fecundity*

Vaupelian theory has not been extended to include fecundity, but as we outlined above, several post hoc explanations that are based on demographic heterogeneity might explain the existence of late-life plateaus in fecundity. Fecundity models analogous to the Vaupelian model for mortality could be based on lifelong differences in individual fecundity. Unlike the case of robustness, lifelong fecundity patterns can easily be measured in females. One possibility is that females that lay a high number of eggs die prematurely, leaving only the females that always laid a low number of eggs preponderant among late ages. Another possibility is that some females both live longer and sustain fecundity better. In either case, if fecundity plateaus are a consequence of lifelong differences in egg laying, then measuring individual fecundity patterns for females comprising a large cohort, and comparing the fecundity of individuals that live to lay eggs in late life with those that do not, would test either possibility. We have preliminary results from our laboratory that suggest that such lifelong heterogeneity in fecundity and survival does not explain late-life fecundity patterns.

7. Conclusion: only one dog barks

In this paper, we have contrasted the problems, successes, and failures of the two main theoretical approaches to late life: Hamiltonian and Vaupelian. In virtually every respect, the Hamiltonian approach to late-life works, both theoretically and experimentally. More work could be done on the comparative biology of late life, as this is an area of late-life research that is largely unexplored. While Vaupelian late life is a possibility, there is no consistent empirical evidence that it is quantitatively significant. As is the case with aging, we conclude that the foundations of late life are best understood from the perspective of evolution, specifically Hamilton's twin forces of natural selection.

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References

Abrams, P.A., Ludwig, D., 1995. Optimality theory, Gompertz' law, and the disposable soma theory of senescence. Evolution 49, 1055–1066.

Beard, R.E., 1959. Note on some mathematical mortality models. In: Wolstenholme, G.E.W., O'Connor, M. (Eds.), The Lifespan of Animals. Ciba Foundation Colloquium on Ageing, Little, Brown, Boston, pp. 302–311.

Beard, R.E., 1964. Some observations on stochastic processes with particular reference to mortality studies. Int. Congress Actuaries 3, 463–477.

Beard, R.E., 1971. Some aspects of theories of mortality, cause of death analysis, forecasting and stochastic processes. In: Brass, W. (Ed.), Biological Aspects of Demography. Taylor and Francis, London, pp. 57–69.

Brooks, A., Lithgow, G.J., Johnson, T.E., 1994. Mortality-rates in a genetically heterogeneous population of *Caenorhabditis elegans*. Science 263, 668–671.

Carnes, B.A., Olshansky, S.J., 2001. Heterogeneity and its biodemographic implications for longevity and mortality. Exp. Gerontol. 36, 419–430.

Carey, J.R., 2003. Longevity: The Biology and Demography of Life Span. Princeton University Press, Princeton.

Carey, J.R., Liedo, P., Orozco, D., Vaupel, J.W., 1992. Slowing of mortality rates at older ages in large medfly cohorts. Science 258, 457–461.

Charlesworth, B., 1980. Evolution in Age-Structured Populations. Cambridge University Press, London.

Charlesworth, B., 1994. Evolution in Age-Structured Populations, second ed. Cambridge University Press, London.

Charlesworth, B., 2001. Patterns of age-specific means and genetic variances of morality rates predicted by the mutation-accumulation theory of ageing. J. Theor. Biol. 210, 47–65.

Charlesworth, B., Partridge, L., 1997. Ageing: leveling of the grim reaper. Curr. Biol. 7, R440–R442.

Comfort, A., 1964. Ageing: The Biology of Senescence. Routledge and Kegan Paul, London, p. 90 (Fig. 18).

Curtsinger, J.W., Fukui, H.H., Townsend, D.R., Vaupel, J.W., 1992. Demography of genotypes: failure of the limited life span paradigm in *Drosophila melanogaster.* Science 258, 461–463.

Drapeau, M.D., Gass, E.K., Simison, M.D., Mueller, L.D., Rose, M.R., 2000. Testing the heterogeneity theory of late-life mortality plateaus by using cohorts of *Drosophila melanogaster.* Exp. Gerontol. 35, 71–84.

Ewens, W.J., 1979. Mathematical Population Genetics. Springer-Verlag, New York.

Finch, C.E., 1990. Longevity, Senescence, and the Genome. University of Chicago Press, Chicago.

Fukui, H.H., Xiu, L., Curtsinger, J.W., 1993. Slowing of age-specific mortality rates in *Drosophila melanogaster.* Exp. Gerontol. 28, 585–599.

Fukui, H.H., Ackart, L., Curtsinger, J.W., 1996. Deceleration of age-specific mortality rates in chromosomal homozygotes and heterozygotes of *Drosophila melanogaster.* Exp. Gerontol. 31, 517–531.

Gavrilov, L.A., Gavrilova, N.S., 1991. The Biology of Lifespan: A Quantitative Approach. Harwood Academic Publishers, New York.

Gavrilov, L.A., Gavrilova, N.S., 2001. The reliability theory of aging and longevity. J. Theor. Biol. 213, 527–545.

Gillespie, J.H., 1973. Natural selection with varying selection coefficients—a haploid model. Genet. Res. 21, 115–120.

Greenwood, M., Irwin, J.O., 1939. Biostatistics of senility. Hum. Biol. 11, 1–23.

Haldane, J.B.S., 1941. New Paths in Genetics. George Allen and Unwin, London.

Hamilton, W.D., 1966. The moulding of senescence by natural selection. J. Theor. Biol. 12, 12–45.

Kannisto, V., Lauristen, J., Vaupel, J.W., 1994. Reduction in mortality at advanced ages: several decades of evidence from 27 countries. Popul. Dev. Rev. 20, 793–810.

Khazaeli, A.A., Pletcher, S.D., Curtsinger, J.W., 1998. The fractionation experiment: reducing heterogeneity to investigate age-specific mortality in *Drosophila*. Mech. Ageing Dev. 105, 301–317.

Kowald, A., Kirkwood, T.B.L., 1993. Explaining fruit fly longevity. Science 260, 1664–1665.
Medawar, P.B., 1946. Old age and natural death. Mod. Q. 1, 30–56.
Medawar, P.B., 1952. An Unsolved Problem of Biology. H.K. Lewis, London.
Mueller, L.D., Rose, M.R., 1996. Evolutionary theory predicts late-life mortality plateaus. Proc. Natl. Acad. Sci. U.S.A. 93, 15249–15253.
Mueller, L.D., Drapeau, M.D., Adams, C.S., Hammerle, C.W., Doyal, K.M., Jazayeri, A.J., Ly, T., Beguwala, S.A., Mamidi, A.R., Rose, M.R., 2003. Statistical tests of demographic heterogeneity theories. Exp. Gerontol. 38, 373–386.
Nagylaki, T., 1992. Introduction to Theoretical Population Genetics. Springer-Verlag, Berlin.
Olshansky, S.J., Carnes, B.A., 1997. Ever since Gompertz. Demography 34, 1–15.
Partridge, L., Charlesworth, B., 1997. Ageing: levelling of the grim reaper. Curr. Biol. 7, R440–R442.
Pletcher, S.D., Curtsinger, J.W., 1998. Mortality plateaus and the evolution of senescence: why are old-age mortality rates so low? Evolution 52, 454–464.
Pletcher, S.D., Curtsinger, J.W., 2000. The influence of environmentally induced heterogeneity on age-specific genetic variance for mortality rates. Genet. Res. 75, 321–329.
Rauser, C.L., Mueller, L.D., Rose, M.R., 2003. Aging, fertility and immortality. Exp. Gerontol. 38, 27–33.
Rauser, C.L., Tierney, J.J., Gunion, S.M., Covarrubias, G.M., Mueller, L.D., Rose, M.R. Evolution of late-life fecundity in *Drosophila melanogaster*. J. Evol. Biol., in press.
Roff, D.A., 1992. The Evolution of Life Histories: Theory and Analysis. Chapman and Hall, New York.
Rose, M.R., 1991. Evolutionary Biology of Aging. Oxford University Press, New York.
Rose, M.R., Chippindale, A.K., Nusbaum, T.J., 1996. Laboratory evolution: the experimental wonderland and the Cheshire Cat Syndrome. In: Rose, M.R., Lauder, G.V. (Eds.), Adaptation. Academic Press, New York.
Rose, M.R., Drapeau, M.D., Yazdi, P.G., Shah, K.H., Moise, D.B., Thakar, R.R., Rauser, C.L., Mueller, L.D., 2002. Evolution of late-life mortality in *Drosophila melanogaster*. Evolution 56, 1982–1991.
Service, P.M., 2000. Heterogeneity in individual morality risk and its importance for evolutionary studies of senescence. Am. Nat. 156, 1–13.
Service, P.M., 2004. Demographic heterogeneity explains age-specific patterns of genetic variance in mortality rates. Exp. Gerontol. 39, 25–30.
Stearns, S.C., 1992. The Evolution of Life Histories. Oxford University Press, Oxford.
Steinsaltz, D., 2005. Re-evaluating a test of the heterogeneity explanation for mortality plateaus. Exp. Gerontol. 40, 101–113.
Tatar, M., Carey, J.R., Vaupel, J.W., 1993. Long-term cost of reproduction with and without accelerated senescence in *Callosobruchus maculates*: analysis of age-specific mortality. Evolution 47, 1302–1312.
Tuljapurkar, S., 1990. Population Dynamics in Variable Environments. Springer-Verlag, New York.
Vaupel, J.W., Manton, K., Stallard, E., 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography 16, 439–454.
Vaupel, J.W., Johnson, T.E., Lithgow, G.J., 1994. Rates of mortality in populations of *Caenorhabditis elegans*. Science 266, 826.
Vaupel, J.W., Carey, J.R., Christensen, K., Johnson, T.E., Yashin, A.I., Holm, N.V., Iachine, I.A., Kannisto, V., Khazaeli, A.A., Liedo, P., Longo, V.D., Zeng, Y., Manton, K.G., Curtsinger, J.W., 1998. Biodemographic trajectories of longevity. Science 280, 855–860.
Wachter, K.W., 1999. Evolutionary demographic models for mortality plateaus. Proc. Natl. Acad. Sci. U.S.A. 96, 10544–10547.

Glossary

A: an age-independent parameter from the Gompertz equation that defines the baseline mortality rate for a population.
Age class: the individuals within one range of ages, or the number of such individuals.
Age-specific fecundity: the number of offspring produced by members of one age class.
Age-specific mortality rates: the number of individuals within one age class who die within one time period.
Aging: increasing rates of death or decreasing fecundity as chronological age increases.

Alpha (α): an age-dependent parameter from the Gompertz equation that defines the rate of aging for a population.

Antagonistic pleiotropy: when genes have beneficial effects on some ages, and deleterious effects upon other ages.

Comparative biology: the comparison of multiple species to reveal patterns of evolution.

Demography: the study of the growth and age-class composition of populations.

Development: the growth and differentiation of cells and tissues to produce reproductively mature organisms.

Fecundity: the production of offspring by individuals within an age class; the number of such offspring.

Fitness: the net reproductive output of an individual or genotype.

Force of natural selection: the effect on fitness of an age-specific change in survival probability or fecundity.

Genetic mechanisms of aging: how specific types of genes cause aging.

Gompertz functions: linear regressions of the logarithm of the mortality rate on adult age.

Hamiltonian theory: an evolutionary theory that explains late-life mortality and fecundity patterns by the age-specific force of natural selection.

Immortality, biological: the absence of aging during reproductive maturity.

Late life: a distinct phase of life characterized by a strong deceleration in the decline of age-specific survivorship and fecundity.

Malthusian parameter: the rate of growth of a population with a stable distribution of age classes, equal to the average fitness of members of such populations.

Mortality rate: the number of deaths in a fixed period of time.

Mutation accumulation: when deleterious genes increase in frequency at late ages because of the weak force of natural selection at those ages.

Semelparous organisms: organisms in which reproduction occurs in a single burst.

Senescence: a synonym for aging, except in plants, where it may refer to the loss of leaves or flowers.

Survivorship: the probability of survival to a particular age.

Vaupelian theory: a demographic heterogeneity theory that explains late-life mortality patterns by lifelong differences in robustness.