THE ROYAL SOCIETY

doi 10.1098/rstb.2000.0728

Ageing and immortality

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The concept of the force of natural selection was developed to explain the evolution of ageing. After ageing, however, comes a period in which mortality rates plateau and some individual organisms could, in theory, live forever. This late-life immortality has no presently agreed upon explanation. Two main theories have been offered. The first is heterogeneity within ageing cohorts, such that only extremely robust individuals survive ageing. This theory can be tested by comparisons of more and less robust cohorts. It can also be tested by fitting survival data to its models. The second theory is that late-life plateaus in mortality reflect the inevitable late-life plateau in the force of natural selection. This theory can be tested by changing the force of natural selection in evolving laboratory populations, particularly the age at which the force plateaus. This area of research has great potential for elucidating the overall structure of life-history evolution, particularly the interrelationship between the three life-history phases of development, ageing and immortality.

Keywords: ageing; demography; evolution; mortality; immortality

1. INTRODUCTION

The concept of the force of natural selection was first developed by Haldane (1941), Medawar (1946, 1952) and Hamilton (1966) to explain the evolution of deterioration among adult organisms, otherwise known as ageing. The idea began life as a verbal intuition. Hamilton (1966) formalized the concept and applied it heuristically to life-history data. Charlesworth (e.g. 1980) developed a complete population genetics theory for the evolution of life-history, including ageing. In this type of theory, the terms of the evolutionary equations include the weighting of the force of natural selection explicitly (e.g. Rose 1985).

The most important result involving the force of natural selection is that the impact on fitness of a proportionately uniform change in age-specific survival follows the pattern shown in figure 1. This function is the force of natural selection acting on survival. During development, the force of natural selection is high and constant. During the reproductive period, the force of natural selection steadily falls, converging on zero at the end of reproduction, as shown in figure 1. After the reproductive period, including the period of care for offspring, the force of natural selection remains at zero indefinitely. The falling force of natural selection during the reproductive period was used to explain the evolution of ageing by Hamilton and co-workers. This concept has since stimulated a considerable body of work, both theoretical and experimental (see Rose 1991). However, the force of natural selection was to enjoy a second phase of interest as a theoretical construct in a very different context.

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2. LATE-LIFE MORTALITY PLATEAUS

The finding that undermined the prevailing view of life-history evolution was the demonstration of steady, even declining, mortality rates at very late ages in dipteran species (Carey *et al.* 1992; Curtsinger *et al.* 1992). This finding at first led to a number of criticisms of methodology. We were among those who suggested that a lack of control over density might have produced an artefactual lowering of death rates once most individuals died (Nusbaum *et al.* 1993). This criticism might have had some validity with respect to the study of Carey *et al.* (1992), which involved enormous changes in density. However, such changes in population density were not involved in the studies of Curtsinger *et al.* (1992). Perhaps a more fundamental criticism is that mortality-rate plateaus are a result of reduced reproduction at later ages lessening the physiological burdens imposed on continued survival (Charlesworth & Partridge 1997). This idea has yet to be assessed empirically.

The Curtsinger laboratory, in particular, mounted a considerable programme of repetition and artefact-barring using ageing *Drosophila* cohorts (e.g. Fukui *et al.* 1993, 1996; Khazaeli *et al.* 1995*a*,*b*, 1998). The repeated finding of a deceleration in late-life mortality has produced widespread, if not universal, acceptance of the essential result. These plateaus in late-life mortality have since been found in a number of experimental systems (Vaupel *et al.* 1998), although the *Drosophila* laboratory studies remain better than those with other species.

(a) *Heterogeneity theories for late-life mortality*

The explanation for the apparent termination of ageing favoured by most has been the heterogeneity theory. This theory supposes that all individuals die following a geometrically or exponentially rising probability, as given

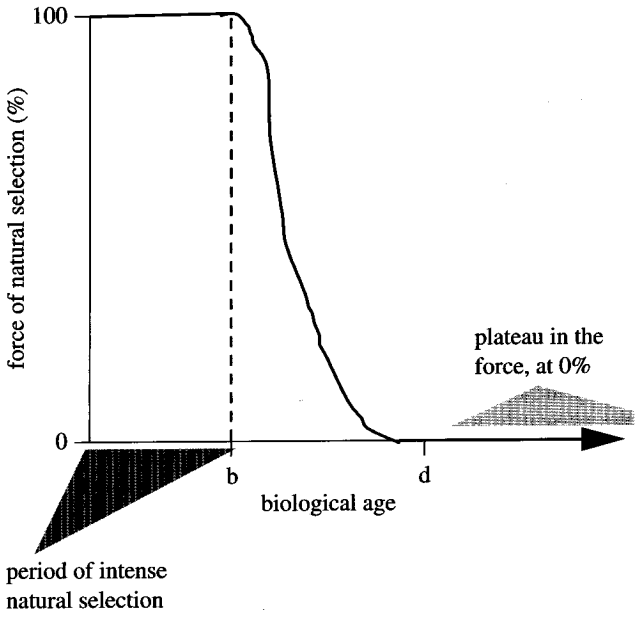

Figure 1. The force of natural selection. The plotted curve indicates the general features of the force of natural selection acting proportionately on age-specific mortality rate. The symbols b and d indicate the start and end of reproduction in the population as a whole. After d, the force of natural selection remains at zero forever, defining a plateau of low, but stable, selection intensity.

by the Gompertz curve (defined formally below) or some related function (cf. Finch 1990). All these functions have in common an unending acceleration toward progressively higher mortality values. These accelerating mortality-rate functions we will refer to collectively as 'Gompertzian'. However, if there is heterogeneity in mortality-rate functions, then the individuals with the greatest propensity to die will be largely absent from a cohort at very late ages. The remaining individuals are thus expected to be so robust that the mortality rate becomes a very shallow function of age, resembling a plateau.

This theory has a number of advantageous features. Since the underlying heterogeneous mortality-rate curves cannot be measured directly, there is considerable opportunity to fit data post hoc by adjusting unknown parameters. Indeed, the fact that there are many unknown parameters that can be tuned to fit any particular set of data gives the theoretician great power to explain observed patterns with no direct risk of experimental falsification. The heterogeneity theory also has the plausibility advantage of assuming nothing more complicated than a large number of Gompertz functions, functions that are so widely used that their epistemological status has passed from data-fitting to ontological certainty. Such functions can be fit to a wide variety of mortality data, with considerable durability of extrapolation and interpolation (Nusbaum *et al.* 1996). This makes the assumption of underlying Gompertzian mortality-rate functions seemingly unchallengeable.

But even in isolation, the heterogeneity theory has some dubious features. The assumption of Gompertzian mortality-rate functions is entirely ad hoc, made acceptable only by familiarity. Furthermore, there are no specific models that limit how many different underlying Gompertzian functions should characterize a heterogeneous cohort. Apparently an arbitrary number can be invoked. Indeed, since highly inbred flies show plateaus in mortality rates (Curtsinger *et al.* 1992; Fukui *et al.* 1996), the heterogeneity in question cannot be genetic. We have no developed theory for environmental variances in quantitative genetics, so it is very difficult to see how an adept theoretician could not fit a heterogeneity model to any particular set of data.

(b) *Testing the heterogeneity theory*

There used to be a number of competing fundamental theories for ageing: somatic mutation theory, error catastrophe theory, force of natural selection and so on. Only one of these general theories retains much credibility today: the evolutionary theory of ageing based on the force of natural selection. The other general theories for ageing have been eliminated by successive rounds of refutation, exception begging, post-hoc modification and so on. Maynard Smith (e.g. 1966) was a leader in this process of selective elimination of ageing theories, particularly his experimental work using *Drosophila subobscura*.

Here we will attempt to emulate Maynard Smith's work by formulating appropriate tests of the contending theories for late-life mortality. We will also indicate studies that we feel come close to providing such tests, although that is not our main objective. We are primarily interested in discussing tests appropriate to each of the theories, tests that could be performed by any laboratory with the required experimental material.

One experimental strategy that tests heterogeneity theory is to change heterogeneity artificially in order to test for the effects that such changes must have on the trajectories of mortality as a function of age. An experiment of this kind was performed by Khaezeli *et al.* (1995*b*) who used a brief heat shock to produce flies with greater heterogeneity in their expected mortality rates. The results were negative, in that no change in later mortality rates was detected as a result of the increased heterogeneity.

Drapeau *et al.* (2000) used a somewhat different design. They studied 15 populations made up of three groups of five replicate *Drosophila* populations. Each group had a distinctive profile with respect to resistance to acute starvation, one group having greatly increased resistance to starvation, one being intermediate. In addition, variation in starvation resistance in these populations had already been shown to correlate with variation in longevity (e.g. Service *et al.* 1985; Rose *et al.* 1992). In such a group of varied populations, where there is a known mortality correlation, cohorts should differentiate from one another as shown in figure 2. That is, more robust cohorts should have lower mortality-rate plateaus, since their most robust members should be more robust than the individuals surviving to the plateau in the less robust cohorts, assuming that there is no initial change in the variance of robustness between individuals.

However, Drapeau *et al.* (2000) did not obtain results of this kind. They found no difference in the mortality rates late in life of cohorts with large differences in robustness. There were, however, significant differences in mortality rates early in life. Robustness can affect early

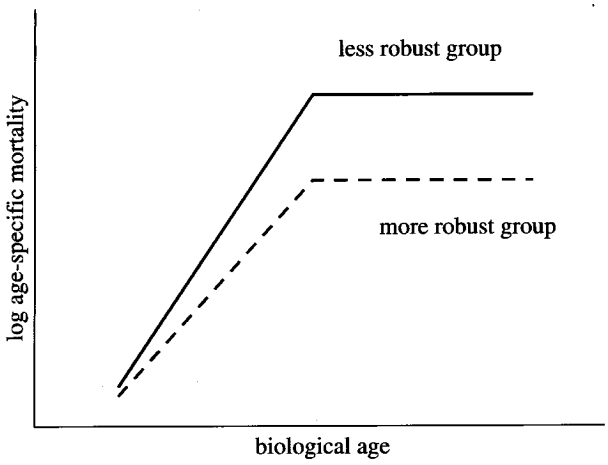

Figure 2. The relationship between robustness and mortality rate assumed by the heterogeneity theory. Highly robust cohorts are expected to live longer, with lower late-life mortality rates, compared with cohorts that are less robust.

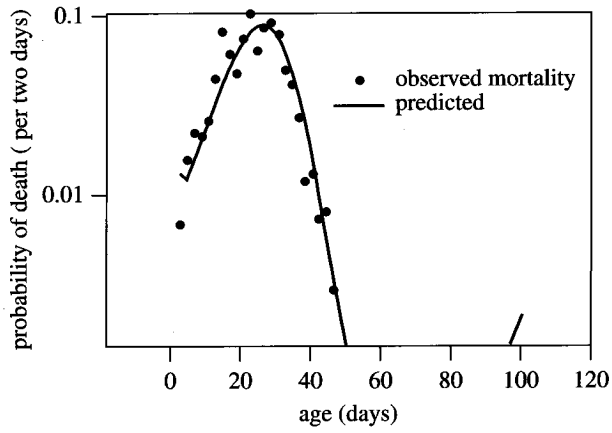

Figure 3. Predicted and observed probabilities of death for the ACO_1 male population. These probabilities are not conditional on the age of the fly. The very first point is for a three-day interval. The heterogeneity model predicts probabilities of death between ages 51 and 100 that are very small and not shown on this graph. There were no observed deaths after age 47. The line at age 100 represents the predicted probability of all deaths at ages 100 or greater. There were no observed deaths in that interval. Predicted mortalities were estimated from 100 computer simulations. In each simulation the times of death for every member of a cohort were determined using the patterns of the ACO data. The size of the cohort was equal to the actual number of ACO flies tested in the experiments. For every member of the cohort a random variable, z, was chosen from a gamma distribution with mean = 1 and variance σ^2. σ^2 was determined from the maximum-likelihood estimates as described in § 2(b). Gamma random variables were generated from the GKM1 algorithm of Fishman (1996) and the RGS algorithm of Best (1983). Mortality for that individual was then determined from equation (1) with $A = zA_0$, where A_0 was determined from the same maximum-likelihood results used to estimate σ^2 and α. A random time of death for this individual was then generated by the inverse transform method (Fishman 1996, p. 149) as $\ln(1-\alpha\ln(1-U)/A)\alpha$, where U is a uniform random number on (0,1). Thus, times of death varied between individuals due to random variation and due to variation in their age-independent mortality parameter. The final estimates of probabilities of death were determined from the average of the 100 simulations.

mortality, but it does not appear to have the expected effect on late-life mortality plateaus.

As mentioned previously, genetically homogeneous populations of *Drosophila* have mortality plateaus. This necessarily implies considerable environmental variation for mortality rates if the heterogeneity theory is to survive. Mortality rates have often been mathematically characterized by the Gompertz equation,

$$u(x) = A\exp(\alpha x), \tag{1}$$

where A is the age-independent mortality parameter and α is the age-dependent parameter. The Gompertz equation is a convenient mathematical component in models that embody heterogeneity theory. A few well-studied environmental factors, such as levels of nutrition and urea, can have significant effects on adult longevity (Nusbaum *et al.* 1996; Joshi *et al.* 1996). However, these changes in longevity arise from changes in the age-independent parameter, A, in the Gompertz equation. These results suggest that a reasonable model of individual heterogeneity would permit the parameter A in the Gompertz equation to vary between individuals. In fact this model has been studied in some detail by Vaupel *et al.* (1979). They showed that the average mortality rate in a cohort aged x time-units is

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

where σ^2 is the variance between individuals. Vaupel *et al.* (1979) suggested that individual variation in sensitivity to the environment, or 'frailty', is determined by a random variable, z, which is gamma distributed with mean = 1 and variance σ^2. The age-independent mortality parameter of any individual is then determined as zA. Equation (2) has been called the 'logistic' model (Promislow *et al.* 1996; Service 2000).

Now we will introduce an alternative model for the purposes of statistical comparison with the heterogeneity theory. (Later we will connect this model to an alternative theory for mortality rates.) Suppose that age-dependent mortality rates of individual genotypes change as

$$u(x) = \begin{cases} A\exp(\alpha x), & \text{if } x < bp \\ \tilde{A}, & \text{if } x \geqslant bp \end{cases}. \tag{3}$$

Model (3) has been called a two-stage Gompertz model. The parameter bp is sometimes called the break-point and represents the age at which mortality rates change from an exponentially increasing Gompertz to a constant plateau.

One test of the heterogeneity theory is to examine the predictions of the distribution function of the underlying statistical model that gives rise to equation (2). To do this requires an estimate of σ^2. One way to get a rough estimate is to treat equation (2) as a density function and use maximum-likelihood techniques to estimate σ^2. Deaths of cohorts of individuals can be simulated with the heterogeneity model of Vaupel *et al.* (1979). We have carried out this type of analysis on five populations called ACO_{1-5}. These populations have been selected for accelerated larval development for more than 200 generations

(Chippindale *et al.* 1997). The results for just the male ACO_1 population are shown in figure 3. While the fit appears to be very good, the heterogeneity model predicts a number of deaths after 100 days, when in fact none was observed. In the case of ACO_1 males the heterogeneity model predicts four deaths out of 2477 at day 100 or later. Repeating this analysis over all five lines, for males and for females, the heterogeneity model predicts a total of 49 deaths over age 100, out of a total of 26 528 deaths over all adult ages. In fact none was observed. The observed number of deaths is consistent with at most three deaths (95% confidence interval). The two-stage Gompertz model (equation (3)), on the other hand, predicts only 0.04 deaths at day 100 or later, out of 26 528. The heterogeneity model used in figure 3 predicts that a small fraction of the population should achieve very extreme ages. With the large number of flies used in these mortality assays we have sufficient evidence to reject this form of the heterogeneity model.

Heterogeneity theory suffers from its strengths. It is very hard to test empirically and its mathematics seem to be infinitely elastic. The few tests it has received have falsified it. This does not mean that variations of this theory cannot be created that would account for data that now seem falsifying. Given the lack of knowledge concerning the parameters that underlie heterogeneity models, theoreticians should always be able to defend heterogeneity theory by post-hoc adjustments.

(c) *The evolutionary theory of late-life mortality*

The main alternative to the heterogeneity theory is the evolutionary theory of late-life mortality. The essential idea is a simple corollary of the evolutionary theory. If the increase in age-specific mortality rates is caused by the fall in the force of natural selection with adult age, then this increase must come to an end once the force of natural selection can no longer fall, to a first approximation. And from that point, the force of natural selection remains stable at zero. This seems, intuitively, as if it could produce late-life mortality-rate plateaus.

We also note that a special variant of evolutionary theory that accounts for late-life mortality plateaus has been proposed. Under the assumption of antagonistic pleiotropy and no recurrent deleterious mutation, optimal life-history models can be constructed that, for some combinations of parameters, lead to approximate plateaus in late-life mortality (Abrams & Ludwig 1995). We do not discuss testing of this type of theory for several reasons. Optimal theories of life-history evolution have a number of general problems, among them their unconstrained hypothesizing of unknown trade-off functions. An additional problem is that there is no universal prediction by Abrams & Ludwig (1995) that late-life mortality-rate plateaus will occur, even though the general assumption is that they are universal. Indeed, this type of theory makes ageing itself a contingent result of model parameters to a degree that is out of conformity with its universality among organisms without fissile reproduction. Finally, as with all such optimality models, and especially those concerning fitness-related characters, there is a demonstrable influx of deleterious mutations that will act to prevent the achievement of optimal evolutionary outcomes. However, none of these points undermine the value of evolutionary genetic models that incorporate many of the model features employed by Abrams & Ludwig (1995).

We simulated explicit evolutionary processes involving both selection and recurrent mutation to check whether the intuitive invocation of the force of natural selection actually corresponds to calculable evolutionary outcomes (Mueller & Rose 1996). Our models explored variations in a number of parameters and structural features, including patterns of pleiotropy, patterns of mutation, population size and so on. It turned out that these did not matter, qualitatively. In every case, evolutionary processes produced late-life mortality plateaus without special choice of parameters and similar devices. In every case, the simulated outcome was qualitatively like the two-stage Gompertz model given above (equation (3)), with an initial period of exponentially rising mortality followed by a second period during which mortality rates seem to conform to a plateau pattern. This finding alone is notable, since heterogeneity theory has to use special, and often extreme, parameters to generate mortality-rate plateaus. With our evolutionary models, all our simulations produced late-life mortality plateaus, without exception.

Our models have some idiosyncratic features that were introduced for ease of calculation. In particular, we studied substitutional evolution only. Stable polymorphism was not allowed. However, these assumptions are not essential to this theory. Further theoretical analysis can test whether the prediction of plateaus is robust as the evolutionary model assumptions are varied.

Charlesworth & Partridge (1997) have pointed out that our work does not constitute an entirely satisfactory theory. One problem is that these simulations do not provide asymptotic results. Therefore, they may still allow that millions of generations of evolution will lead to 100% mortality rates at some age after the cessation of natural selection. This raises the question as to whether such asymptotic states are ever attained by natural populations, which will be subject to environmental variation in both selection coefficients and the timing of reproduction. But Charlesworth & Partridge (1997) also suggest a solution to this problem: generally beneficial alleles, which are favoured at early ages and have the effect of providing some measure of survival at arbitrarily late ages. The theoretical cogency of this idea has not yet been examined formally.

Pletcher & Curtsinger (1998) have also made a number of criticisms of our work. They argue that the appearance of plateaus in our computer simulations are artefacts of the method of generating new mutants. Without these artefacts, they contend, mortality will rise to 100% at advanced ages. Clearly, much more theory exploring additional models of selection and mutation should be explored. However, we disagree with Pletcher & Curtsinger (1998) on at least two counts. First, the alternative methods of generating mutants discussed by them (p. 457) in fact do lead to the evolution of plateaus when these mutations affect multiple age-classes or are antagonistic with fecundity, though neither of these cases was explored by them. Second, the equilibrium mortality derived for our model by Pletcher & Curtsinger (1998) (equation (7)) is incorrect. Their analysis assumes that

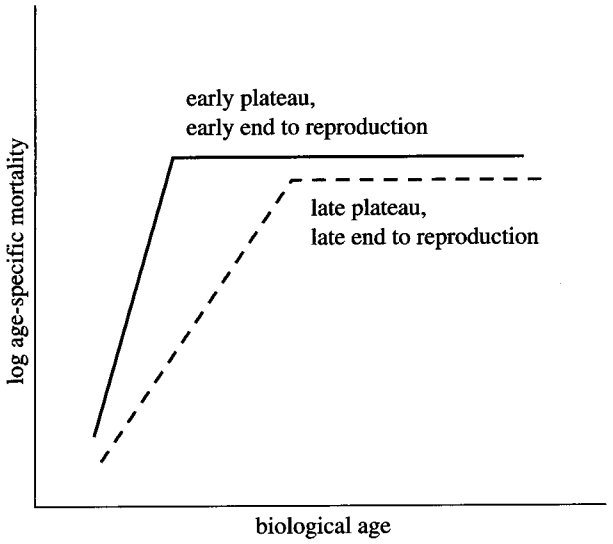

Figure 4. Mortality rates in populations that have had different values for the last age of reproduction for many generations. If a population has an earlier last age of reproduction, then the evolutionary theory for late-life mortality predicts that it will have an earlier mortality-rate plateau. If a population has a later last age of reproduction, then the evolutionary theory for late-life mortality predicts that it will have a later mortality-rate plateau. See § 2(d) for more detail.

there is a constant probability of fixing mutants that increase or decrease survival at a given age. Likewise, they assume there is a constant proportion of deleterious to beneficial mutants over time. These two assumptions cannot be correct simultaneously. Since the fitness of a specific mutant allele depends on the stable age-distribution of the resident population, over evolutionary time the fitness of any given mutant will be different because the resident population is changing. At the beginning of evolutionary time, in our simulations, it is much more likely for a mutant to have net beneficial effects than at the end of the simulation. Thus, the proportion of beneficial to deleterious mutants is changing, contrary to the analysis of Pletcher & Curtsinger (1998).

(d) *Tests of the evolutionary theory of late-life mortality*

It is easier to test the evolutionary theory for late-life mortality than the heterogeneity theory. Since the evolutionary theory is based on the shaping of late-life mortality by the fall in the force of natural selection to zero, and that fall is dependent on a population's reproductive schedule in a well-defined manner, changing the demography of evolving populations must change the plateau pattern over evolutionary time. Specifically, as the last age of reproduction should be relatively close to the age at which the force of natural selection reaches zero, experimental manipulation of that last age of reproduction should lead to the corresponding evolution of the age at which late-life mortality plateaus start. Populations with later last reproduction should have later plateau onset, and conversely. This cannot be an exact prediction because patterns of selection and pleiotropy will obscure this relationship. But populations that differ radically in their last age of reproduction should have qualitatively corresponding differences in plateau positions. This idea is shown in figure 4.

We have made a preliminary start at testing these predictions using the B and O populations that we created earlier (Rose 1984). These have last ages of reproduction of 14 and 70 days, respectively, and they have been evolving separately for hundreds of generations. Therefore, B populations should have late-life mortality-rate plateaus that begin at much earlier ages than those of O populations. This is just one of the explicit predictions of the evolutionary theory that can be tested readily using laboratory evolution.

3. CONCLUSION

Our understanding of life-history evolution has been greatly expanded by the demonstration that mortality rates achieve a stable plateau at very late ages. The conventional explanation for this phenomenon is that it is a product of heterogeneity in robustness, with longer-lived subgroups surviving to later ages, slowing the rate of decline in survival probabilities. An alternative explanation can be derived from the force of natural selection: late-life mortality plateaus because the force of natural selection reaches a plateau after the cessation of reproduction. These theories can both be tested. So far, the heterogeneity theory has not fared well.

Our research has been supported by NIH grant AG11644 and the estate of Robert H. Tyler. We are grateful to M. D. Drapeau for comments on the manuscript.

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