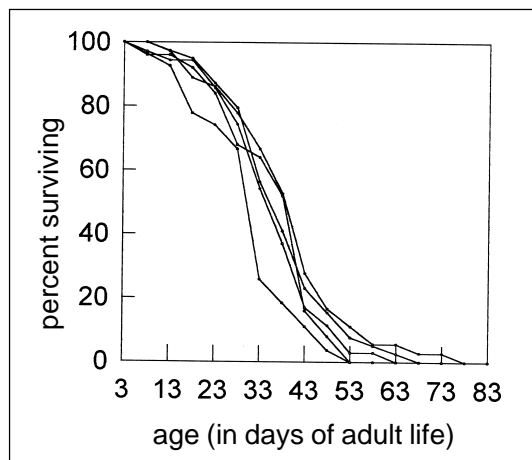


Modelling the Evolution of Rates of Ageing

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The study of ageing has traditionally been independently approached at two levels of biological organisation: at the individual and sub-individual level by gerontologists interested in the physiology of human ageing, and at the populational level by demographers primarily interested in patterns of mortality in human populations. Early on in their study of patterns of mortality, demographers used simple mathematical models that could provide a good fit to observed survivorship curves (*Figure 1*). These models were not

Figure 1. Typical survivorship curves of five populations of the fruit fly *Drosophila melanogaster*. The sharp decline between days 23 and 43 in the fraction of the population still alive corresponds to rapid increases in the age-specific mortality rates. Many other species, including humans, show this type of age-specific survivorship pattern.



based on any particular biological principles; their test was simply that they should fit the observed data well. Subsequently, these models were widely used in demography and some of the parameters of these models were given biological interpretations in terms of the 'rate of ageing', as we shall see. More recently, evolutionary biologists have also been studying ageing and their studies have begun to lead to a synthesis that brings together the divergent findings from demography and gerontology into a more coherent and unified picture of ageing, and how it has evolved (see *Resonance* Nov. 1996, 51–63). One recent advance in this synthesis, which is the focus of this article, has been an attempt to reconcile the demographic models with biological reality, by deriving models of the evolution of mortality rates from first principles of population genetics, a branch of genetics that provides the theoretical underpinnings of evolutionary biology.

One of the most popular demographic models used in studies of ageing is the Gompertz equation, proposed in 1825 by Benjamin Gompertz who observed from census records of human populations in England that 'the number of living corresponding to ages increasing in arithmetical progression decreased in geometrical progression', a pattern similar to that depicted in *Figure 1*. Gompertz found that a simple non-linear equation depicting the mortality rate at any age x , $\mu(x)$, as a function of x could provide close fits to data on human mortality from various parts of England. The Gompertz

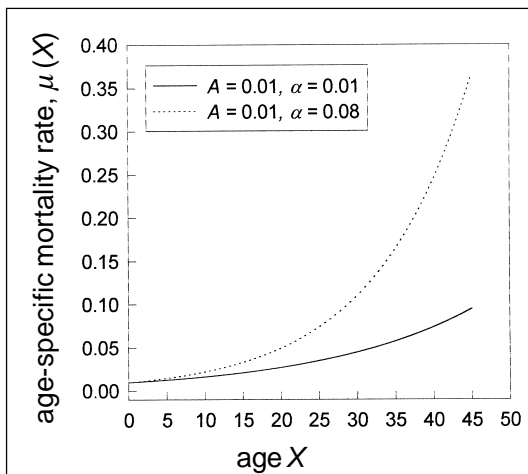
Equation relates age-specific mortality rates to two parameters A and α , as follows:

$$\mu(x) = Ae^{\alpha x}.$$

In this formulation, A represents a constant (age-independent) level of mortality, whereas α is analogous to acceleration, in that it represents the rate at which the rate of change of mortality rates with age is itself changing (Figure 2). The parameter α in this model has, therefore, been widely interpreted as being the 'rate of ageing', since, in demography, ageing is typically defined as the progressive increase in mortality rate with age.

In the past half-century or so, the Gompertzian parameter α has been extensively used as a convenient comparative measure of the rate of ageing, enabling

Figure 2. Age-specific mortality rates predicted by the Gompertz model for two different values of the 'rate of ageing' α . It is clear that as α increases, the rate at which mortality rates increase with age is itself speeded up.



biologists interested in studying ageing to make comparisons of ageing rates across different experimental treatments, or among species with different types of life-histories. However, in the early 1990s, a number of large scale studies of insects and mammals showed that mortality rates did not appear to exponentially increase throughout the life of individuals, as one would expect based on the Gompertz model. In these studies, mortality rates were typically seen to increase exponentially during early life, with a rapid increase in mortality shortly after the attainment of reproductive maturity, as predicted by the Gompertz model. At very advanced ages, however, mortality rates either levelled off, or, in some cases, actually decreased over time. This phenomenon was seen only in studies with very large sample sizes (on the order of 10^4 – 10^6 individuals), because at the very advanced ages that the levelling off or decline in mortality rates was seen, less than 2% of the population would still be living. Nevertheless, this observation sparked off a major controversy as some scientists claimed that the levelling off or decline of mortality rates with age called into question the validity of the Gompertz model as a description of the ageing process. Moreover, because the increase in mortality rates with age is also a qualitative prediction that can be made from evolutionary biology theory, many scientists felt that if the Gompertz model was not a valid descriptor of the ageing process, then the evolutionary theories about ageing may also be incorrect. On the other hand, evolutionary biologists

pointed out that a phenomenon affecting only a miniscule fraction of the population, and that too at an age to which hardly any individuals in nature could be expected to survive, could hardly be used to invalidate theories that had firm empirical evidence supporting them. Nevertheless, this controversy continued in the pages of the evolutionary and demographical literature, partly because it was difficult to resolve the issue conclusively in the absence of any general theory predicting, on the basis of first principles of population genetics, what the shape of the graph of mortality rates over age should be expected to look like.

In 1996, in a paper published in the *Proceedings of the National Academy of Sciences USA*, Laurence D Mueller and Michael R Rose, evolutionary biologists at the University of California, Irvine, reported results from a computer simulation study in which they examined how the relationship of mortality rate and age might be expected to evolve under a number of plausible genetic scenarios. This is the first attempt made to derive demographic models directly from population genetics theory.

Mueller and Rose built their models around two genetic theories regarding the evolution of ageing that have been empirically verified and are now generally accepted (these theories and their experimental verification were described in detail in *Resonance* Nov. 1996, 51–63). Both theories are based on the fact that the force of natural selection acting on a gene decreases with the age at which the

phenotypic effects of the gene are expressed. The antagonistic pleiotropy theory predicts that genes with beneficial effects early on in life will be favoured by natural selection, even if the same genes have harmful effects late in life. Thus, ageing is seen as the consequence of the harmful effects of these genes late in the life of an individual. In the mutation accumulation theory, ageing is seen to be the consequence of the expression of genes that have no effects early in life, but have harmful effects late in life. These genes can become quite common in populations through random genetic drift, because they escape natural selection as they do not have adverse effects early in life, when natural selection against harmful genes would be at its strongest. In general, the declining power of natural selection during middle to late life would suggest that mortality rates during this period should increase as more and more harmful genes that escaped selection will get expressed at increasing ages. The issue that Mueller and Rose addressed in their study was to determine what would be the form of the increase in mortality rates with age, given various genetic assumptions within the framework of these two theories.

To answer this question, Mueller and Rose simulated the evolution of mortality rates under several different scenarios incorporating antagonistic pleiotropy and mutation accumulation. They assumed they were dealing with a *Drosophila* like organism and fixed the life cycle as having a 9 day juvenile period and a maximum lifespan of 110 days.



The initial life history was assumed to be a survivorship probability of 90% each day (i.e. a constant mortality rate) and a fecundity of 1 egg per day of adult life. Next they generated random mutations with some effects on the life history (different models varied with regard to the exact nature of these effects), and for each such mutant calculated the probability that such mutation would get fixed in the population, assuming that both natural selection and random genetic drift were operating on the mutation. If the simulation resulted in a mutation being fixed (i.e. all individuals in the population possess the mutant gene), the life history parameters (i.e. the daily survivorship probability and fecundity) were reset to new values based upon the effects of that particular mutation. This process was then repeated for the next mutation, and so on, for between 40,000 to 400,000 mutations. At the end of this process, the pattern of how mortality rate changed with increasing age was examined.

Several models based on the antagonistic pleiotropy theory were studied in this manner. In some models, it was assumed that the mutations affected only age-specific survivorship probabilities, whereas in other models the mutations were assumed to affect both fecundity and survivorship. Within each type of model, several different assumptions were made regarding the details of how the antagonistic pleiotropic effects of the mutations were expressed. Thus, the period in days over which the mutations expressed their beneficial and harmful effects was

varied: some simulations assumed a narrow 'window' of 1 day for the effects, other assumed a broad 'window' of 40 days, and in yet other simulations the 'windows' were set at random. When exactly in the life-cycle the beneficial and harmful effects were expressed was also varied randomly from one mutation to the next. Thus, for example, in a particular simulation, the first mutation to occur could have a beneficial effect on survival (i.e. it would increase the age-specific survivorship probability) during days 9–15 of adult life, and a harmful effect on fecundity during days 27–38 of adult life. In another case, the beneficial effect could be on fecundity during days 19–26 and the harmful effect on survivorship during days 70–80. In this manner, numerous simulations were carried out by Mueller and Rose, and in each case the qualitative nature of the relationship between mortality rates and age was similar. Most simulations resulted in a pattern wherein mortality rates remained very low early in life and then showed a period of Gompertzian increase, followed by a plateau at advanced ages (*Figure 3*). Thus, the patterns of mortality that evolved in these simulations were consistent with the Gompertz and other such models, at least for a major part of the life span. The results also indicated that there is nothing particularly odd about the observed levelling off or decline in mortality rates at very advanced ages: indeed, this is also predicted by these simulations. Basically, what is happening is that early in life (before the bulk of reproductive activity has occurred) natural selection against harmful mutations



is very strong, keeping such mutations at very low frequencies in the population. Then comes a period where the force of natural selection rapidly declines, resulting in an exponential increase in age-specific mortality rates due to the accumulation of late acting harmful mutations that have become common in the population by escaping selection. Eventually, at fairly advanced ages, the power of natural selection against harmful mutations is essentially zero. At this point, the frequencies of harmful genes giving rise to increased mortality rates are governed entirely by random forces such as genetic drift, and, therefore, we see a plateau in mortality rates. It should be noted that the plateau is level only in the average sense: in any individual simulation, mortality rates at very advanced ages may decline, increase, remain relatively steady, or even fluctuate with age (Figure 3), thus explaining why a decline in mortality rate is seen in some experiments and a levelling off of mortality rate in others.

In addition to the models described above, Mueller and Rose also studied several models with very different assumptions, in order to test the robustness of their conclusions. In some models, rather than determining a fixed 'window' of time during which the mutations expressed their harmful and beneficial effects, these effects were assumed to be scattered at random among various days in the life-cycle. In other models, population sizes were assumed to be small and demographic stochasticity was included in the simulations. In yet other models, mutations were assumed

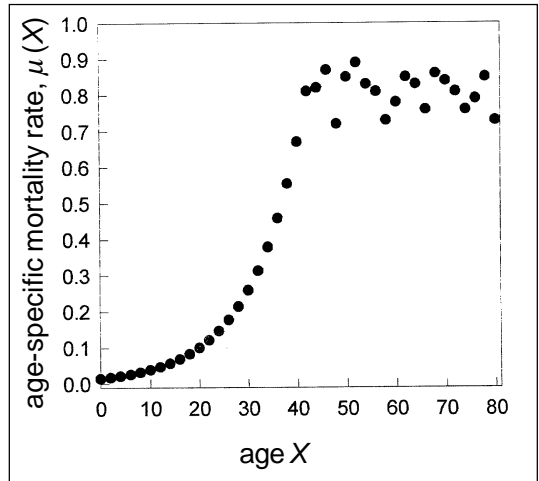


Figure 3. An example of the kind of mortality rate curves that were seen to evolve in the simulation studies of Mueller and Rose. Although the age at which mortality rates began to steeply increase and level off varied across models and simulations, the overall nature of the relationship between mortality rate and age was as shown here.

to have no pleiotropic effects, but only beneficial or harmful effects expressed at different ages and for different durations of time. In all cases, the results were in agreement with those obtained from the models incorporating antagonistic pleiotropy: mortality rates showed an exponential increase followed by a levelling off at advanced ages.

Overall, from this study it is clear that evolutionary theory, under a fairly wide variety of assumptions and models, does predict late life plateaus in age-specific mortality rates. It is also clear, that under most biologically plausible scenarios, the

Gompertz model, and others similar to it, adequately describe the behaviour of mortality rate with age, at least upto ages at which the vast majority of any population would already have died. Thus, in a sense, this study answers a somewhat philosophical question that Gompertz himself posed, namely, why should populations of organisms appear to obey a 'law of mortality'? More importantly, this study roots demography more firmly in a foundation of biology, by deriving demographic models directly from first principles of population genetics. This is a very welcome, and long overdue, development and it will hopefully lead to a deeper merger of the demographic and evolutionary genetic viewpoints on ageing.

Suggested Reading

- [1] J R Carey and P Liedo. Sex-specific life table ageing rates in large medfly cohorts. *Exp. Gerontol.* 30 (3/4). 315, 1995.
- [2] A Joshi, Evolution, Fruit Flies and Gerontology, *Resonance.* 1(11). 51, 1996.
- [3] L D Mueller and M R Rose, Evolutionary theory predicts late-life mortality plateaus. *Proc. Natl. Acad. Sci. USA.* 93. 15249, 1996.

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