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A typical interdisciplinary topic: questions of the mortality dynamics

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Abstract

Dynamic characteristics of mortality experience are intensely studied in demography and in experimental gerontology. The classic Gompertz-Makeham function is also a significant starting point of numerous investigations in this topic. By comparative analysis of human vital statistics, one can observe characteristic secular and topological variations of the Gompertz parameters. Some of these findings are reviewed briefly in the article. Some other related questions are also touched upon. For example, the concept of the maximum life span is criticised. A thorough overview of literature data makes it clear that the general male mortality excess is by far not so unambiguous as is widely supposed. Surprisingly simple stochastic models, published by one of us in the recent past, can serve as theoretical background for the Gompertz law. Further studies would be necessary to check the biological relevance of these models.

Keywords: Mortality; Gompertz parameters; Maximum life span; Models of ageing

1. Introduction

The theme of biological life span research is clear. At the same time, from the point of view of concrete investigations, the field is by far not homogeneous. Its components can be considered as parts of very different research fields. This makes it more difficult to gain a general overview of results of really remote topics, such as

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human vital statistics and gerontology, demography, life insurance or survival questions in medicine or age distribution and competition of specific causes of death. Other aspects are those of experimental gerontology or the questions of zoological and plant demography. Considering the altered mortality experience, some issues of pharmacology and toxicology must not remain also unreported.

The multitude of complexities of components is usual in all biological disciplines. However, the historical preliminaries and the motivations are, with the biological life span problems, completely different. This makes it necessary, from time to time, to renew some classic and modern results in this discipline. In the present article some quantitative regularity and new modelling results are also mentioned. These are treated in more detail in a book by Gavrilov and Gavrilova (1991). This book will be quoted repeatedly hereafter.

2. The force of mortality

Denote with T, the random variable relating to the life span of an individual. For the sake of simplicity the existence of the density function is assumed. It is easy to realise that the dynamics of mortality experience is locally characterizable by the function

$$\mu(x) = \lim_{\Delta x \to 0+} \frac{P(x \leq T < x + \Delta x \mid T \geq x)}{\Delta x} = \lim_{\Delta x \to 0+} \frac{F(x + \Delta x) - F(x)}{\Delta x(1 - F(x))}$$

$$= \frac{f(x)}{1 - F(x)} \tag{1}$$

$\mu(x)$ is known in biology as the force of mortality (hazard rate, intensity of risk of death) and, in context with technical problems, as the failure rate. Its use is indispensable and very effective when treating mortality dynamics. It was introduced already by Bernoulli (1766). Later on, Benjamin Gompertz (1825) postulated a basic law in respect to this function. Namely, he came to the conclusion that the force of mortality is approximable in a broad age interval by an exponential function. The starting point of Gompertz's reasoning was that the rate of resistivity decline of an organism is a linearly decreasing function of the resistivity itself. The solution of the corresponding differential equation is indeed the $R \cdot \exp(\alpha x)$ exponential function with parameters R and α. The corresponding lifetime distribution function is

$$F(x) = 1 - \exp\left(\frac{R}{\alpha}(1 - \exp(\alpha x)\right) \qquad (x > 0) \tag{2}$$

This probability shows that a given individual will die before age x. As we can see, the mortality experience can be described more suitably by the intensity function rather than by the life span distribution function. Gompertz assumed that μ has also

another term, which is independent from age. This question was analysed in more detail by Makeham (1860). The so called Gompertz-Makeham function with the formula

$$\mu(x) = A + R \exp(\alpha x) \tag{3}$$

makes possible a good approximation of the parameters A, R and α. The approximation is good (one can say, very good) in the broad life interval which is 35–85 years of life with human populations. Similar good results can be achieved for a number of other species. Taking into consideration the vast number of factors influencing the mortality experience, it is amazing that one can characterise this dynamic by only three parameters from *Drosophila* to man. Naturally, by increasing the number of model parameters, one can achieve a better approximation. However, it is hard to speak about an essential gain, as the interpretation of the new parameters difficult. Although the Gompertz law is a part of the classical biological intelligence, a lot of interesting details are unsolved as of yet. It is worth mentioning that, in a considerable age interval, there are not systematic departures from the exponential law, despite the evident age dependency of some causes of death. This indicates that a single cause of death can play a secondary role in the formation of mortality dynamics. When the organism, due to the general ageing process, becomes protected against a sort of fatal disease, the manifestation of a similar disease will increase greatly. On the other hand, we can conclude that the diversity of the causes of death (Izsák, 1988; Gavrilov and Gavrilova, 1991, Chap. 6.9) do not influence the basic mortality dynamics.

Naturally, there exist a number of further biological or formal concepts regarding the law of mortality. A detailed review can be found in Economos (1982). For example, another basic concept of aging dynamics is formulated by the so-called Weibull equation (Weibull 1951)

$$\mu(x) = Bx^c \text{ or } \mu(x) = A + Bx^c \tag{4}$$

where B, c and A are model parameters. The Weibull function seems to be applicable in a narrower circle in biological ageing processes than the Gompertz function. This also holds for other species, although some counter examples are known as well (Slob and Janse, 1988).

The exponential and the power function law of mortality are not really antagonistic. Such models are known (see below), which, constrained on appropriate age intervals, make possible the simultaneous good fitting of both functions. It is also probable that both the Gompertz and Weibull functions play an important role in modelling of mortality and failure dynamics. In infancy for man, until about the 12th year of life, when the mortality rate is declining, other functions are used for the approximation. This question is much less revealed. What is sure is that the delayed effect of genetic defects dominates in this age. A decreasing exponential function, or among others, the function $a/(b + cx)$ is in use here to approximate the force of mortality. The very high mortality in the case of very young individuals is

of importance on the population dynamics of many animal species. The early age period characterised by very high mortality and a steep mortality decline starts just with the formation of the zygote. This period, including the infancy, resembles the burning out period known in the quality control of new technical devices. However, it is worth mentioning that both the Gompertz and Weibull functions are good applications to modelling the life span of complicated technical and other inanimate systems. As the application of very complicated technical systems is widening, the parallelism between the failure dynamics of those and mortality dynamics of individuals will be more and more exciting.

In very old age (with man above the 100–150th years) the applicability of the Gompertz function is limited, because the increase of μ is conspicuously low. It is probable that in these years of life the functional redundancy practically vanishes and the mortality dynamics follow a first order process, similar to the atomic decay. A possible explanation is detailed below. A number of other models, also capable of fitting to experimental data at very advanced ages, are reviewed by Economos (1982). More recently Piantanelli published a similar model, fitting well to survival data (Piantanelli et al., 1992). For recent experimental findings on slowing of mortality rates at older ages, see Carey and co-workers (1992).

3. Some new results with regard to the Gompertz function

3.1. On a noted invariance of populations

There exists an interesting correlation between parameters R and α. Studying a number of human populations, Strehler and Mildvan (1960) found a negative linear correlation between $\ln R$ and α. According to this, taking the logarithm form of the Gompertz function

$$\ln \mu(x) = \ln R + \alpha x, \tag{5}$$

this negative correlation involves a compensation effect. Namely, an enhanced α would produce an essential increase in $\mu(x)$, but this is, at least, largely compensated for by the decrease of the R value. At the same time Gavrilov and Gavrilova (1991, Chap. 4) have shown recently that the statistical method and reasoning failed in this study, in as much as Strehler and Mildvan did not take into account the A parameter in the Gompertz-Makeham equation. This is not negligible in the studied age interval. After all, the corrected analysis gives a similar result, that is the regression equation

$$\ln R = D - C\alpha \tag{6}$$

between R and α proved to be true (C is a positive constant here). A number of human populations served as a basis for this study. For the i-th population the regression equation prescribes the relation

$$\mu^{(i)}(x) = A^{(i)} + \exp(D - C\,\alpha^{(i)} \cdot \exp(\alpha^{(i)}x) = A^{(i)} + \exp(D + \alpha^{(i)}(x - C)), \tag{7}$$

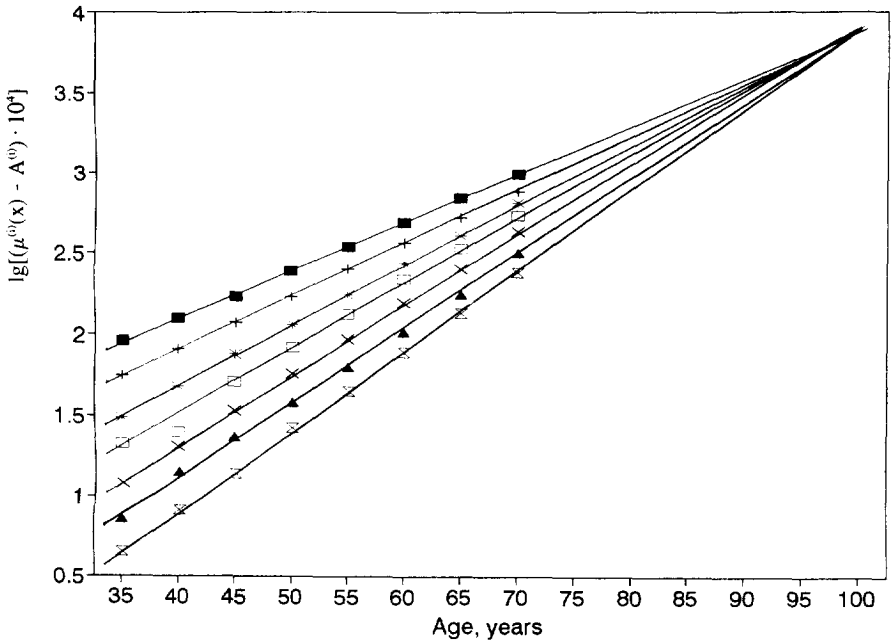

Fig. 1. Plotting the logarithm of age-dependent components against age for certain countries. Symbols: (■) India, men, 1941–1950; (+) Turkey, men, 1950–1951; (*) Kenya, men, 1969; (□) Northern Ireland, men, 1950–1952; (×) England and Wales, women, 1930–1932; (▲) Austria, women, 1959–1961; (▮) Norway, women, 1956–1960.

that is the logarithm of the $R\exp(\alpha x)$ component is such a linear function of age that the substitution value in $x = C$ is D. As follows, delineating the quantity $\ln(\mu^{(i)}(x) - A^{(i)})$ in a coordinate system with the age on the x-axis, we obtain a set of straight lines with the common point (C,D) for the ensemble of populations (Fig. 1).

When the age-dependent component $R\exp(\alpha x)$ dominates and A is negligible (from the 50th year of life on), then the same can be said for the only delineation of $\mu^{(i)}(x)$. This special case was treated recently by Riggs (1993). It is of importance that similar observations can be made also for other species, although there are exceptions. Assume now that the above regularity is true for the populations of a given species. Establishing the intersection of the mentioned straight lines using the data of two populations, one can determine the age-dependent component of force of mortality for the populations in an arbitrary age, when the intensity belonging to a single age is known. These results are known in a relatively narrow circle of researchers. It would be desirable to validate this interesting biological phenomenon by further investigations in the future. Of course, a lot of data is needed for this promising and interesting work. The mostly under-utilised vital statistics offer a good opportunity for such analyses. It would be desirable on behalf of biologists to hold a

greater interest in the mathematical basis of life span. Unfortunately, it is a worldwide phenomenon that many interdisciplinary topics are only on the periphery of classical fields.

3.2. On the maximum life span

According to the above, the intensity function is, without any doubt, a basic tool for treating the mathematics of life span. There are some characteristics of mortality dynamics, however, which are based on other demographical functions. For example, the mode of life span is linked to the life span density function. We should call attention to an expression which is to be avoided, namely, to the *maximum life span* (Gavrilov and Gavrilova, 1991; 1993). In the case of finite populations one can speak on the experimental value of life span, or, in other words, on the recorded life span. But with infinite populations the one probability value of death is reached on the age scale only asymptotically.

Consequently, life span limit and 'impossible' age do not exist and the (potential) maximal life length is not an appropriate concept. Illustrating this issue, observing a very great human population, one could almost certainly find a 300-year-old person. Despite this, numerous publications appear on the 'maximal life span'. Life span data based on small populations of wild animals are extraordinarily vague. In addition, predation and other factors have practically a trimming effect on populations of some species. It must be mentioned here that in special cases, for example in the case of vegetative reproduction, the exact definition of the life span is difficult. With animals this way of reproduction is not frequent, although it occurs even with the Prochordata. With plants the formation of propagulates is widespread and the question of life span gets a new dimension. Plant demography is, anyway, quite an autonomous topic (Silvertown, 1982). For example, the annual and biennial plants finish their life according to a biological program. Another problematic issue is the distinction between living and lifeless state with trees.

3.3. Historical and biological component of mortality

Despite the mentioned problems it can be said that the Gompertz law is valid in a wide range. As a remarkable fact, the dramatically changing sociological and environmental circumstances and health care conditions do not affect essentially the goodness of fit; only the fitting parameters change. Interesting observations have been made relating this issue in the recent past. Fig. 2. shows the secular decline of the A constant in the last decades, while the term $R \exp(\alpha x)$ remains practically unchanged. So it is logical to call A and $R \exp(\alpha x)$ the historical and the biological components of the force of mortality. According to Fig. 2, in Sweden the socio-economical and public health limits of life span were reached in some decades, that is in a relatively short time interval. One can not hope for further rapid improvement. Similar can be said of a number of other developed countries, such as other Scandinavian states, Denmark, Italy and Japan. Considering the historically much more stable biological component, further instructive observations can be made in European countries. The variation of this component is remarkable. However, this 'hard core' changes slowly. Presumably the natural environment, the traditional diet and

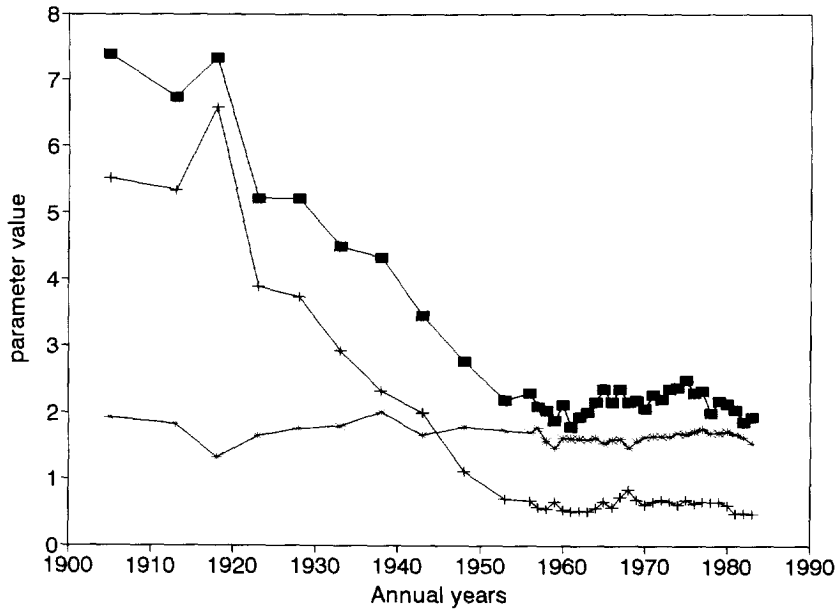

Fig. 2. Secular changes of mortality parameters for Swedish males at age 40. (■) total mortality, (+) historical component, (*) biological component. Original values are multiplied by 10^3.

the way of life stay in the background of its variability. On the other hand, a male excess in the biological component is observable in all of these countries. As it is widely known, such a case is frequent with a number of animal species as well. At the same time, analyses of the recent past and some earlier studies point out that this excess is not so general as was thought. Fig. 3 visualises observations on different *Drosophila melanogaster* populations. We can establish the balance of populations with male and female mortality excess.

Estimation of Gompertz parameters is sometimes inappropriate when analysing changes in mortality experience. This is the case, for example, with pharmacological and toxicological analyses, where the studied populations are often relatively small and the hypothesis on the unaltered mortality experience of a treated group of animals is only studied. The Kaplan-Meier method (Kaplan and Meier, 1958) is a well-known statistical tool in this case. It is a frequently used non-parametric method also in ecological demography, when mortality experiences of animal populations are to be compared.

4. Models (or allegories?)

4.1. Relationship between the Gompertz function and the extreme value theory

Life length is a probability variable also in such cases, when the variability of environmental factors is excluded. Two profoundly different things stay in the

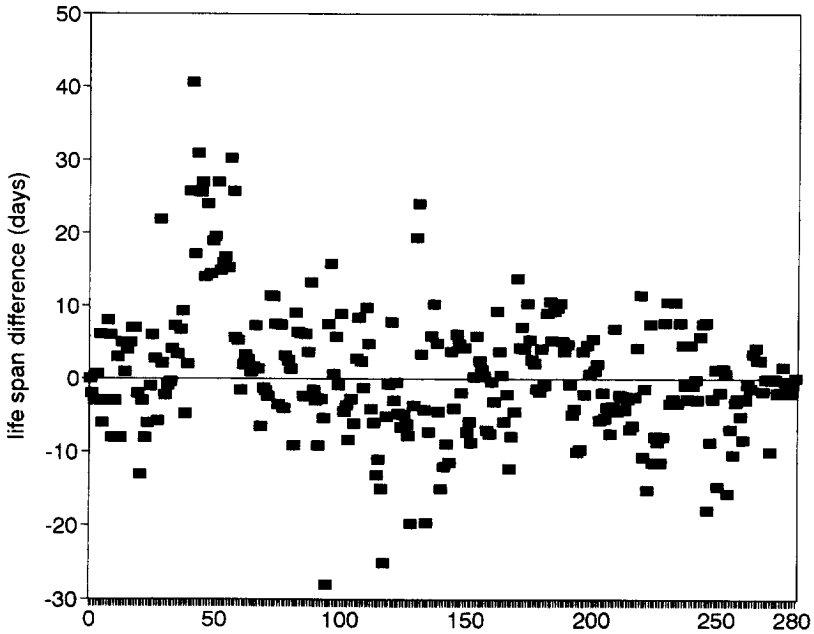

Fig. 3. Differences between the mean life span of *Drosophila melanogaster* male and female study groups. Positive values indicate a male excess of mean life span. Abscissa: the serial numbers of data sources collected by Gavrilov, L.A.

background. On the one side, the genetical constitution varies from individual to individual in human and also in most other populations. Thus the life span would vary also if the genetical background would have a deterministic role, but the latter assumption is not valid. The situation is similar to that of identical radioactive atoms, the decay of which is undeterministic, despite their identical structure. As it follows, by modelling the dynamics of mortality, we can start with the construction of life span distribution models of practically identical individuals. Omitting details, we mention that one can derive both the Gompertz and Weibull functions from such a purely stochastic situation. The second step can be the introduction of inherent individual differences. For suggesting the spirit of relating models, we mention below the mathematical concept, where both functions play a central role; this is the extreme value theory. The basic subject here is the maximum or minimum of independent observations on a real valued random variable. According to the series of observations, a series of E_n ($n = 1,2, \ldots$) extreme values arises, the members of which are sample elements from an F_n ($n = 1,2, \ldots$) distribution function. In some cases F_n converges to a limiting distribution. As an interesting fact, in 'regular' cases there exist only three limiting distributions. Two of the related intensity functions are just the exponential and the power function, i.e. the Gompertz and Weibull functions. There exists more than only a formal connection between life span studies

and extreme values. Plotting the processes in a coordinate system with the time on the x-axis, the physiological parameters must remain in a band. The probability of extreme values which exceed the limits is directly connected with the mortality dynamics. The scenario is similar to complicated technical systems and with some natural inanimate systems. Gumbel, the founder of the extreme value theory was the first to call attention to such analogies (Gumbel, 1954). Despite numerous thoughts on the applicability of these extreme crossing processes in life span models (Leadbetter et al., 1983), the question is not properly detailed.

Combinatorial models of mortality dynamics are of a very different nature. A number of these are published in the above quoted book of Gavrilov and Gavrilova. The combinatorial models are in a sense more concrete than those based on distribution functions. Naturally, a great simplification is needed to treat ageing processes by combinatorial ideas. Surprisingly, despite this, these models also lead to the well-known mortality intensity functions.

4.2. Mortality increase as a cascade process

Let s_0 be the number of individuals in a population without any defect. In the following, these individuals get $n = 0,1,2, \ldots$ defects. Denote these individuals with t_n and their number with s_n ($n = 1,2, \ldots$). The μ_0 additive component of force of mortality is by definition independent from the individual status. The total force of mortality of t_n type individuals is then $\mu_0 + n\mu$, where μ is a status independent factor. The $t_n \to t_{n+1}$ transition probability is postulated as $\lambda_0 + n\lambda$; λ here is a constant, i.e. the transition probability is a linearly increasing function of the number of existing defects. This explains why we speak here of a cascade process. All these assumptions lead to the linear differential equation

$$s'_n(x) = (\lambda_0 + (n-1)\lambda)s_{n-1}(x) - (\lambda_0 + \mu_0 + n(\lambda + \mu))s_n(x) \qquad (n = 0,1,2,\ldots) \tag{8}$$

Solving the initial value problem $s_0(0) = s_0$, $s_n(0) = 0$ ($n = 1,2, \ldots$), we get the $s_n(x)$ ($n = 0,1,2, \ldots$) functions. The number of individuals living in age x is

$$l(x) = \sum_{n=0}^{\infty} s_n(x) = \left(\frac{\lambda + \mu}{\mu + \lambda \exp[-(\lambda + \mu)x]}\right)^{\lambda_0/\lambda} \exp(-\lambda_0 + \mu_0)x) \tag{9}$$

The relating force of mortality is

$$\mu(x) = -\frac{l'(x)}{l(x)} = \mu_0 + \frac{\mu\lambda_0(1 - \exp(-(\lambda + \mu)x)}{\mu + \lambda \exp(-(\lambda + \mu)x)} \tag{10}$$

In the case $\lambda >> \mu$ the approximation $\mu(x) \approx A + R \exp(\alpha x)$ can be applied with

$$A = \mu_0 - \mu\lambda_0/\lambda, \qquad R = \mu\lambda_0/\lambda \qquad \text{and} \qquad \alpha = \lambda + \mu \tag{11}$$

If x is very large, then on the basis of formula (10) the $\mu(x)$ value is approximately $\mu_0 + \lambda_0$. Thus the model explains the observation, that at extreme ages the increase of force of mortality is minimal and does not follow either the Gompertz or the Weibull laws.

4.3. Binomial model

Let m be the number of identical blocks, and n the number of elements in each of them. A failure in the system occurs when any of the blocks fails. The latter occurs when all elements of the block fail. (These conditions resemble those with a serial and parallel connection in electrical networks.) On the other hand, defects in the system are assumed from the onset and an element of the system is functional only with a q probability. The failure rate of an element is k (constant), similar to the decay rate of atoms. Under these conditions the failure intensity in a block, with i originally functioning elements, is approximately $ik\ (kx)^{i-1}$ ($i = 0,1,2, \ldots$), when $x \ll 1/k$. Single combinatorial reasoning shows that failure rate intensity of the whole system is approximately

$$\mu(x) \approx cm(qk)^n\ (x_0 + x)^{n-1}. \tag{12}$$

Here is $c = (1 - (1 - q)^{n-1})$ and $x_0 = (1 - q)/qk$. If q equals to 1, then $\mu(x)$ is essentially a power function. That is, if all elements are functioning at the start, so in a certain age interval the failure intensity of the system is well approximated by the Weibull function. As an instructive parallelism, with technical systems, where the elements are really working at the start, the Weibull function fits well to the failure intensity function. If $q < 1$, then for a positive x_0 always exists such a $(0, x_0)$ interval, for which one can approximate $\mu(x)$ by

$$cmn(qk)^n x_0^{n-1} \exp((n - 1)x/x_0) \tag{13}$$

That is, the failure intensity increases in this case nearly exponentially and the Gompertz law is valid.

Omitting the recital of further models, it must be clear that quite simple assumptions lead to the Gompertz and Weibull laws, establishing also a transition between them. In some respects, more realistic ones are models where individuals are assumed to be burdened by defects already at the start of life. In this case the application of mixed distributions leads also to the Gompertz function.

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