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ON SOME RELIABILITY APPROACHES TO HUMAN AGING

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Deceleration in mortality rates for old ages is explained via the concept of population heterogeneity. Two simple probabilistic models of biological aging are considered. The first one assumes that some random resource is acquired by an organism at birth. Death occurs when the accumulated wear exceeds the initial random resource. In the second model death occurs as the consequence of a harmful event. A non-homogeneous Poisson and doubly stochastic Poisson processes of harmful events are considered. These models describe possible causes of population heterogeneity.

Keywords: Random resource; mortality rate; observed hazard rate; doubly stochastic Poisson process; deceleration of mortality; frailty.

1. Introduction

The literature on biological theories of aging is quite extensive. Various stochastic mortality models are reviewed, for instance, in Yashin *et al.*[16] The nature of human aging is in some "biological wearing". As reliability theory possesses the well-developed tools for modeling wear in technical systems, it is natural to apply this technique to biological aging.

There are different probabilistic approaches for modeling wear. The simplest way is just to describe the corresponding lifetime random variable T by its cumulative distribution function (Cdf) $F(t)$ with increasing failure rate. These distributions form the most popular in applications class of aging distributions (Barlow and Proschan).[1] The main demographic model is the Gompertz[8] model for human mortality with exponentially increasing hazard (mortality) rate $\lambda(t)$:

$$F(t) = 1 - \exp\left\{-\frac{\alpha}{\beta}[\exp\{\beta t\} - 1]\right\}, \quad \lambda(t) = \alpha \exp\{\beta t\}, \quad \alpha > 0, \ \beta > 0. \quad (1)$$

The Weibull Cdf with increasing failure rate can be also used for this purpose:

$$F(t) = 1 - \exp\{-(\alpha t)^{\beta}\}, \quad \lambda(t) = \alpha\beta(\alpha t)^{\beta-1}, \quad \alpha > 0, \ \ \beta > 1. \tag{2}$$

Model (2) is also widely used for describing the lifetime of various technical devices that exhibit wear in the process of functioning.

A lifetime model (as all other models, of course) is valid under certain assumptions. One of the important assumptions while describing the lifetime random variables via the conventional distribution functions (e.g., relations (1) and (2)) is the assumption of population homogeneity. But the real world is usually non-homogeneous. In this paper we show that as the result of this heterogeneity the mortality rate is bent down for old ages compared with a classical Gompertz curve (1) and that the failure rate of wearing technical objects, which is often modeled by the power law (2) can even decrease nearly to 0 for large values of time. Therefore, the main goal of this paper is to describe models, which explain deceleration in mortality (failure rate) via the concept of population heterogeneity.

In Sec. 2 some explicit results and corresponding illustrations are presented. In Secs. 3 and 4 theoretical models of mortality, based on wear processes are developed. It should be noted that the wear process of human aging is generally non-observed and there is no real data suitable for the proper statistical analysis so far. However, our models can explain observed facts (e.g., deceleration in mortality), which is very helpful in studies of human aging.

The approach, based on some initial resource of an organism and the remaining resource, which is decreasing in the course life, seems to be rather natural. The death occurs when the monotonically decreasing remaining resource equals 0. The repair and repair capacity, being the main issues in reliability studies, are also important factors in modern theories of aging (Yashin *et al.*).[16] Human mortality is modeled via the Poisson (doubly stochastic Poisson) process of "killing events" (shocks, diseases). We assume that each event with a given probability can be "cured" and with complementary probability can lead to death.

The models to be considered are probably oversimplified from the biological point of view, but they give the overall pattern of human mortality and help to describe and to explain the shape of the real mortality rate function. In what follows we mostly use the conventional reliability terminology: a failure of an object corresponds to the death of an organism and the failure (hazard) rate, as usually, is the synonym for the mortality rate (the force of mortality).

2. Impact of Heterogeneity

It is already a well-established fact in biological and demographic literature (there are numerous publications in the last 10–15 years), that along with mortality increase with age the subsequent mortality leveling-off takes place for old ages. Different explanations of this phenomenon are suggested in the literature (Thatcher).[13] Possible deceleration in mortality rates for the old, as compared with

model (1), was already mentioned by Gompertz[8] and Makeham.[11] In this paper we show analytically and using examples that the main source of this effect is the population heterogeneity. The following introductory example illustrates this effect for the case of constant hazard rates.

Example 1. Let $F(t)$ be a baseline exponential distribution with parameter λ_b and let population heterogeneity be modeled by the multiplicative model $\lambda(t, Z) = Z\lambda_b$, where Z is a random variable with support in $[0, \infty)$. It is well known that the population (mixture) hazard rate $\lambda(t)$ is decreasing (Barlow and Proschan),[1] thus showing the 'deceleration', as compared with a constant hazard rate. For the exponential Z with parameter ϑ, for instance, this function is monotonically decreasing to 0:

$$\lambda(t) = \frac{\lambda_b}{\lambda_b t + \vartheta} \to \frac{1}{t}[1 + o(1)] \to 0 \quad \text{as } t \to \infty.$$

It can be easily shown by formal calculations that the same asymptotic result is valid when $F(t)$ is a gamma distribution (with increasing failure rate).

The mortality data for different historical and contemporary populations fits the Gompertz curve (1) remarkably well for ages beyond 30 (when aging starts) and up to old ages (85–90). For empirical description of the oldest-old mortality the logistic model had been recently used (Thatcher):[13]

$$\lambda(t) = \frac{y}{1 + y}, \tag{3}$$

where

$$y = \alpha \exp\{\beta t\}.$$

When y is small (parameter α is small and t is small), the functions defined by Eqs. (3) and (1) are approximately equal. But for larger values (older ages) mortality rate, defined by Eq. (3) is decelerated (bent down) compared with initial mortality rate (1). This model was also verified on various mortality data sets and had showed a perfect fit (Thatcher).[13]

We will show now that empirical model (3) can be theoretically explained using a concept of heterogeneity. To say more, as human population is heterogeneous (heterogeneous environment, heterogeneous personal biological properties etc.), we believe that this explanation describes the main cause of mortality deceleration at old ages. Consider the following frailty model for the failure rate in a heterogeneous population:

$$\lambda(t, Z) = Z\lambda_b(t),$$

where Z is a random variable with support in $[0, \infty)$ and $\lambda_b(t)$ is a baseline mortality rate given by the Gompertz law (1). Assume also that $E[Z] = 1$, which is necessary for the proper comparison of the baseline failure rate $\lambda_b(t)$ with the observed (mixture) failure rate $\lambda_m(t)$. Let for simplicity of notation $\beta = 1$ and the

distribution of Z is exponential (the case of the gamma distribution can also be considered explicitly). Therefore, the parameter of exponential distribution is also equal to 1. It follows from Finkelstein and Esaulova[4] that the observed (mixture) failure rate for this specific case is given by

$$\lambda_m(t) = \frac{\alpha \exp\{t\}}{\alpha \exp\{t\} - \alpha + 1} = \frac{y}{y - \alpha + 1}. \tag{4}$$

Model (4) explicitly shows the deceleration in mortality for old ages and also results in the Gompertz curve (1) for smaller ages. It turns out that parameter α in the Gompertz model (1) is very small for real populations ($\alpha \sim 10^{-5}$). Therefore, the difference between Eqs. (3) and (4) can be neglected in practice. It is worth mentioning, that as $E[Z] = 1$, the following obvious property for $t = 0$ takes place: $\lambda_m(0) = \lambda_b(0)$.

The deceleration of mortality, due to specific parameters of human populations, occurs only at old ages and therefore this effect, although very important, is not so easily observed, as it needs the sufficient amount of data on, e.g., centurions. On the other hand, technical devices are usually also rather heterogeneous in parameters and should exhibit the similar deceleration in the failure rate or even its bending down practically to 0. In order to support this statement and to show that the effect of heterogeneity is really underestimated by the majority of reliability practitioners the following experiment was conducted at the Max Planck Institute for Demographic research. We recorded the failure times for the population of 750 miniature lamps and constructed the empirical failure rate function (in relative units) for the time interval 250 hrs, which is shown in Fig. 1.

The results were really convincing: the failure rate is initially increasing (a tentative fit showed the Weibull law) and then decreasing to a very low level. The

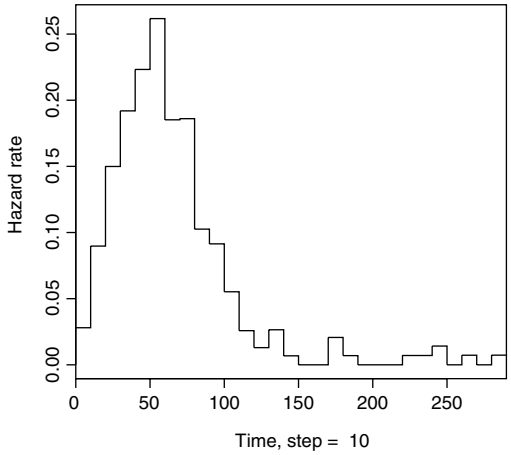

Fig. 1.

pattern of the observed failure rate is exactly the same as predicted in Finkelstein and Esaulova[4] for the Weibull baseline Cdf.

In the following sections we model heterogeneity at a more detailed level. It was already mentioned, that as the wear process in humans is non-observed (so far), these models present a more sophisticated theoretical explanation of the real shape of the failure rate and can be helpful to general analysis of human mortality. We use reliability concepts in developing this approach.

3. Models Based on Initial Resource

Assume that in the process of production (engineering applications) or birth (biological applications) an object at time $t = 0$ had acquired an initial unobserved random resource R with a Cdf $F_0(r) : F_0(r) = P(R \leq r)$. Suppose that for each realization of R the run out resource $W(t)$(deterministic) to be called wear monotonically increases. This means that the remaining resource is decreasing. Thus, the wear increment in $[t, t + dt)$ is defined as $w(t) + o(dt)$. Let additionally $W(0) = 0$ and $W(t) \to \infty$ as $t \to \infty$. Under these assumptions we arrive at the well-known in reliability theory accelerated life model:

$$\begin{gathered} P(T \leq t) \equiv F(t) = F_0(W(t)) \equiv P(R \leq W(t)), \\ W(t) = \int_0^t w(u)\, du; \quad w(t) > 0; \quad t \in [0, \infty). \end{gathered} \tag{5}$$

As follows from (5), the failure (death) occurs when the wear $W(t)$ reaches the random R. This equation describes a *deterministic* diffusion with a random threshold.

It is natural to model a *random* wear, which is the case in reality, by a monotonically increasing stochastic process $W_t, t \geq 0$. Some appropriate models for $W_t, t \geq 0$ can be found in Lemoine and Wenocur,[10] and Singpurwala.[12]

Substituting the deterministic wear $W(t)$ in (5) by the increasing stochastic process $W_t, t \geq 0$ leads to the following relation (Finkelstein):[6]

$$F(t) = P(T \leq t) = P(R \leq W_t) = E[F_0(W_t)], \tag{6}$$

where the expectation is taken with respect to $W_t, t \geq 0$. The Cdf $F_0(W_t)$ should be understood conditionally:

$$F(t|W_t) = P(T \leq t|W_t,\, 0 \leq u \leq t),$$

where $W_t, 0 \leq u \leq t$ is the history of this stochastic process.

Let, as previously, $\lambda(t)$ denotes the hazard rate (the *observed* hazard rate), which corresponds to the Cdf $F(t)$. From relation (6), using results of Yashin and

Manton,[15] the following important relationship between the observed and the conditional hazard rates can be obtained:

$$\lambda(t) = E[w_t \lambda_0(W_t)|T > t], \tag{7}$$

where w_t denotes the stochastic rate of diffusion: $dW_t \equiv w_t dt$ and the hazard rate $\lambda_0(t)$ is defined by the Cdf $F_0(t)$. Equation (7) can be used for analyzing the shape of $\lambda(t)$. Specifically, it can show the deceleration in mortality for sufficiently large t (oldest-old mortality), as opposed to the exponential or power functions defined for $t \in [0, \infty)$ by (1) and (2).

Example 2. Let $\lambda_0 = 1$ and consider a specific case of the process of wear: $W_t = w_t = Z\, k \exp\{t\}$, where $k > 0$ is a constant and Z is an exponential random variable with parameter ϑ (the case of a gamma Cdf is similar). Given the exponential mortality rate (1), it is reasonable to assume that accumulated wear in organisms follows the exponential law as well. Similar to Eq. (4), the mixture (observed) failure rate is:

$$E[w_t|T > t] = \lambda_m(t) = \frac{k\, \exp\{t\}}{k \exp\{t\} - k + \vartheta} = 1 + \frac{k - \vartheta}{k \exp\{t\} - k + \vartheta}. \tag{8}$$

It follows from this equation, that $\lambda_m(0) = k/\vartheta$. For $k < \vartheta$, $\lambda(t)$ is monotonically increasing, asymptotically converging to 1, showing mortality deceleration for sufficiently large t, whereas it approximately follows the exponential law for small t.

The random resource can be a discrete random variable as well, which is illustrated by the following meaningful example, which was used by Gavrilov and Gavrilova,[7] for human life span modeling:

Example 3. Discrete random resource. Let $F_0(n) \equiv P(N \leq n)$ be now a discrete distribution. Consider a specific case when $R = N$ is a random number of initially (at $t = 0$) operable components (in parallel) with a constant hazard rate λ. These components form a system (the generalization on the series-parallel structure is straightforward) which models the lifetime of an organism. The degradation process $W_t, t \geq 0$ for this setting is just a counting process for the corresponding process of pure death: when the number of events (failures of components) reaches N, the death of an organism occurs. Denote by $\lambda_n(t)$ the hazard rate for the time to death random variable for the fixed $N = n, n = 1, 2, \ldots$. ($n = 0$ is excluded, as there should be operable components at $t = 0$.) It can be shown that when N is deterministic the shape of the corresponding hazard rate for the sufficiently small t can be approximately described by the power law (2), and for random N (Poisson and binomial distributions) the observed hazard rate $\lambda(t)$:

$$\lambda(t) = E[\lambda_n(t)|T \geq t] \tag{9}$$

follows for small t the Gompertz model (1). Note that for small t:

$$\lambda(t) \approx E[\lambda_n(t)] = \sum_{n=1}^{\infty} P_n \lambda_n(t).$$

However, as t increases the Gompertz curve is bent down due to conditioning in (9). Eventually, as $t \to \infty$ it asymptotically approaches constant λ from below:

$$\lambda(t) \to \lambda,$$

as conditional probability (on condition that the system is operable) that only one component is operable tends to 1. Note that if the variance of N is sufficiently large $\lambda(t)$ can even initially decrease (Finkelstein).[5]

4. Models Based on Repair Capacity

According to a number of authors (see Yashin *et al.*[16] for references) the DNA repair capacity can be responsible for aging of humans. One can assume that in the absence of the proper repair spontaneous DNA mutation leads to the death of an organism (Yashin *et al.*).[16] Thus, the repair mechanism can constitute the basis for mortality modeling and reliability-related approaches can be quite useful for analyzing repairable biological systems.

Let $P_t, t \geq 0$ denotes the nonhomogeneous Poisson process of harmful events with rate $\mu(t)$, which potentially can lead to death (diseases, infections, shocks etc.). Assume that each event from the process $P_t, t \geq 0$ is minimally repaired with probability $1 - \theta(t)$ and is not repaired (thus resulting in death) with probability $\theta(t); \theta(0) > 0$. Therefore, the function of age of an organism $\theta(t)$ describes the repair capacity of an object. It follows from Block *et al.*, for instance, that the corresponding lifetime Cdf and the hazard (mortality) rate are given in this case by

$$F(t) = 1 - \exp\left\{-\int_0^t \theta(u)\mu(u)\,du\right\}, \quad \lambda(t) = \theta(t)\mu(t), \tag{10}$$

respectively. It is reasonable to assume that, as $\theta(t)$ describes the ability of the organism to perform a proper repair (or equivalently, to resist harmful events from $P_t, t \geq 0$), it should increase with t showing deterioration, which reflects the corresponding aging.

Let $\theta(t) = \theta$ be constant in time for simplicity and assume that it is a random variable (independent of $P_t, t \geq 0$) with support in $[0, 1]$. This is another way of implementing the population heterogeneity into the model. Indeed, for instance, probability of survival after some disease can vary a lot in the population of the same age.

It follows from Yashin and Manton[15] that, as relations (10) are valid conditionally on realizations of θ, the following formulas take place, when θ is a random variable:

$$F(t) = 1 - E\left[\exp\left\{-\theta\int_0^t \mu(u)\,du\right\}\right], \tag{11}$$

$$\lambda(t) = \mu(t)E[\theta|T \geq t]. \tag{12}$$

The shape of $\lambda(t)$ in (12) (for the arbitrary continuous increasing function $\mu(t)$) can be already different from the shape of $\mu(t)$: it can even decrease for sufficiently large t (see Example 4).

Another and maybe much more important source of heterogeneity in harmful events can be modeled by the doubly stochastic Poisson process $\hat{P}_t, t \geq 0$ (instead of the Poisson process of harmful events). Denote a random rate of this process by $\mu(t, \Psi)$ (Cox and Isham),[3] where Ψ is a random variable with support in $[0, \infty)$. For fixed $\Psi = \psi$, similar to relations (10):

$$F(t|\psi) = 1 - \exp\left\{-\int_0^t \theta(u)\mu(u, \psi)\, du\right\}, \quad \lambda(t) = \theta(t)\mu(t, \psi) \tag{13}$$

and similar to (11) and (12):

$$F(t) = 1 - E\left[\exp\left\{-\int_0^t \theta(u)\mu(u, \Psi)\, du\right\}\right], \tag{14}$$

$$\lambda(t) = \theta(t)E[\mu(t, \Psi)|T > t]. \tag{15}$$

There can be different models for $\mu(t, \Psi)$, the multiplicative one being the simplest one:

$$\mu(t, \Psi) = \Psi\mu(t) \tag{16}$$

where $\mu(t)$, as usually in the proportional hazards-type models, plays the role of a baseline (reference) hazard rate. Then Eq. (15) turns into:

$$\lambda(t) = \theta(t)\mu(t)E[\Psi|T > t]. \tag{17}$$

We assume that the baseline function $\mu(t)$ in Eqs. (16) and (17) is increasing. The observed hazard rate, however, can have a different shape due to the fact that conditional expectations in these formulas are decreasing in time (Finkelstein and Esaulova).[4]

Example 4. Consider the linearly increasing with age rate of harmful events: $\mu(t, \Psi) = \Psi t$ and assume that Ψ is gamma distributed with parameters β and ϑ. Then (Finkelstein and Esaulova):[4]

$$\lambda(t) = \frac{\beta\, t}{\vartheta + t^2}.$$

This function is equal to zero at $t = 0$ and tends to zero as $t \to \infty$ with a single maximum at $t = \sqrt{\theta}$. Hence, the mixture of IFR distributions has a decreasing (tending to zero!) failure rate for sufficiently large t and this is rather surprising. Furthermore, the same result asymptotically holds for $\mu(t) = t^\alpha,\ \alpha > 0$. In fact, this example mathematically models the observed failure rate in the light bulbs experiment of Sec. 2.

It is worth noting that the doubly stochastic Poisson process effectively models the diversity among subpopulations (and on the 'individual level' as well) in the rate of harmful events. Lifestyle, external factors, hereditary factors etc are the sources of heterogeneity.

The following example is, in fact, an application of the repair-capacity model to a demogtaphic setting.

Example 5. Let $\mu(t)$ denote now the mortality rate for some baseline, standard level of healthcare. Suppose that the better level of health care had been achieved, which usually results in lifesaving (Vaupel and Yashin):[14] each life, characterized by the initial mortality rate $\mu.(x)$ is saved (cured, or 'repaired') at each event of death with probability $1-\theta(t),\ 0<\theta(t)\leq 1$ (or, equivalently, this proportion of individuals who would have died are now resuscitated and given another chance). Those who are saved, experience a minimal repair. This is what happens in reality when, for instance, new types of surgical operations become available due to advances in medical technology or the output of existing operations is improving. It is clear that this setting is also described by relations (10).

Now we rely on some important demographic results. For instance, Bongaarts and Feeney[2] consider the data for different developed countries. They show with high accuracy that the mortality rate in contemporary populations of Sweden, Germany, USA and UK tend to improve over calendar time by a similar factor *at all ages*, which results in the following Gompertz shift model: (compare with the second equation in (10))

$$\mu(t, y_0)) = a\exp\{bt\}, \qquad a, b > 0, \tag{18}$$

$$\lambda(t, y) = \theta(y)\mu(t, y_0), \quad y > y_0, \tag{19}$$

where y_0 is a baseline calendar time (in Bongaarts and Feeney[2] $y_0 = 1980$) and y is a current calendar time. This means in our notation that probability $\theta(y)$ does not depend on age t and that the repair-capacity model (10) is verified for this setting with high accuracy.

5. Concluding Remarks

Heterogeneity is an important feature of human populations. In Sec. 2 we show that empirical logistic model, which was used by demographers for description of mortality deceleration for old ages can be interpreted in terms of heterogeneous populations. The light bulbs experiment also shows that heterogeneity can result in the dramatic change in the observed failure rate, compared with a homogeneous case, as predicted by the corresponding mathematical model.

The model, based on an initial random resource describes aging as increasing stochastic process of wear accumulation. The death of an organism occurs when this accumulated wear reaches the level of initial resource. Stochastic process of wear accounts for heterogeneity in this model and leads to mortality deceleration. The doubly stochastic Poisson process of harmful events also models heterogeneity and can be considered in combination with random resource. Therefore these models show the possible causes of heterogeneity at a more detailed level.

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