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A New Model of Aging: Specific Versions and Their Application

ANDREJ YU. YAKOVLEV[1], ALEXANDR D. TSODIKOV[1] and VLADIMIR N. ANISIMOV[2]

[1] Curie Institute, Paris, France, and St. Petersburg Technical University, Russia
[2] N. N. Petrov Institute of Oncology, St. Petersburg, Russia

Summary

This paper is concerned with some versions of a stochastic model of aging proposed recently by TYURIN et al. (1993). In contrast to the commonly used Gompertz-Makeham approach, the model yields a bounded hazard rate, thereby providing a better description of survival of old individuals in a population. Depending on plausible biological assumptions to be tested, only a few special cases of the basic model appear to be useful in experimental data analysis. We report the results of their application to experimental data on animal longevity obtained in a follow-up study. When interpreted in terms of the model parameters, the data suggest drastically dissimilar patterns of aging for female versus male rats.

Key words: Aging; Life-time distribution; Random minima; Bounded hazard; ML estimates; Goodness of fit testing.

1. Introduction

Over a long time, the Gompertz-Makeham formula has been practised as a common, if not unique, means of survival data analysis in gerontological studies (GOMPERTZ, 1825; SACHER, 1956; 1977; SACHER and TRUCCO, 1962a; 1962b; HIRSCH, 1982; BOXENBAUM et al. 1986; ANISIMOV, 1987; HONDA et al., 1993, to name a few). Much like the Gompertz model of tumor growth (QI et al., 1993), the Gompertz-Makeham lifetime distribution is purely phenomenological and its parameters are not related to any specific mechanisms of aging. To the best of our knowledge the only attempt that have been made to justify the distribution theoretically was due to BASS et al. (1989). Proceeding from hypothetical life-prolonging and life-shortening cells in every organism and describing their interaction by a generalized Volterra-type competitive exclusion, Bass et al. gave a deterministic substantiation of the Gompertz distribution for the life length of aging individuals.

A new stochastic model of aging was recently developed by TYURIN et al. (1994) within the random minima framework. The model offers interpretation of experimental or epidemiological observations in terms of accumulation and expression of intracellular lesions caused by environment or intrinsic genetic

program. For testing the goodness of fit, a Kolmogorov-type statistical test for composite hypotheses was introduced by Tyurin et al. (1994) with special reference to the proposed family of lifetime distributions. The main line of reasoning in this work was similar to that in the earlier proposed model of carcinogenesis (Klebanov et al., 1993), which seems to be quite natural in view of a profound connection between aging and cancer (Dilman, 1981; Anisimov, 1987). Along the same lines a model of hormesis in relation to longevity was developed by Yakovlev et al. (1993). It is the processes of lesion repair, operating at the molecular and cellular levels, that were assumed to be responsible for the life-prolonging effect of some agents which are harmful at higher doses. It transpired that the model could be instrumental in giving further insight into the hormesis phenomenon as evidenced by its application to the analysis of some published data on the effect of prolonged irradiation and of procaine on animal longevity (Yakovlev et al., 1993).

In Section 3 of this paper, we consider some simplified versions of the model by Tyurin et al. (1994) which are feasible for application to experimental data analysis. For completeness sake a description of the basic model is given in the next section. Sections 4 and 5 deal with problems of the model application.

2. The Model

The model is based on the following substantive assumptions:

(i) The primary event in the process of aging is the formation of an intracellular lesion which is potentially lethal, i.e., in the long run it is capable of resulting in death of the organism. Such primary events occur at random time instants and their sequence in time may be thought of as a point stochastic process. We specify this process by a Poisson one with intensity $\lambda_0(t)$, so that the number of lesions $\nu_0(T)$ accumulated by time T is a Poisson random variable with expectation $\int_0^T \lambda_0(t)\,dt$. The rationale of the Poisson character of the process of lesion formation lies in the well-known asymptotic properties of the superposition of a large number of independent point processes (Cox and Isham, 1980, p. 109).

(ii) At present there is hardly a shadow of doubt that cells are endowed with a capacity to repair radiation and chemical injury, including injuries that result in cancer induction (Ainsworth, 1982; Raaphorst et al., 1990; Zhu and Hill, 1991). A potentially transforming damage repair is taken into consideration within the framework of a Markovian-type model of carcinogenesis developed by Kopp-Schneider and Portier (1991). It is natural to assume participation of the same repair mechanisms in the elimination of background lesions as well. All primary lesions are subject to repair processes but some of them remain unrecognized by the repair system and, consequently, unrepaired. Some of the

lesions happen to be misrepaired due to errors in the functioning of repair mechanisms (TOBIAS et al., 1980; ALBRIGHT, 1989; SACHS et al., 1990). We do not distinguish between unrecognized and misrepaired lesions but consider them as a single pool of misrepaired lesions. The existing experimental evidence on the temporal characteristics of enzymatic repair of lesions (TOBIAS et al., 1980; YAKOVLEV and ZORIN, 1988; FRANKENBERG-SCHWAGER, 1989) in particular indicates that this process can be considered to be effectively instantaneous as compared with the typical life lengths measured in mortality studies. Therefore, we assume that, unless there is exogeneous stimulation of repair systems, each lesion is repaired or misrepaired immediately after its origination. The repair effect is modeled as the specific thinning operation (see COX and ISHAM, 1980, p. 98) on the original Poisson process: with probability $1-p$ each point (lesion) is deleted independently of the others and of the whole point process. The probability p, in a general case, is allowed to be time dependent, i.e. $p=p(t)$. As a result we have a thinned Poisson process of intensity $\lambda(t)=p(t)\,\lambda_0(t)$ to represent the misrepaired lesion formation.

Remark 1. More generally, the misrepair probability is expected to be a nondecreasing function of the rate λ_0. One way to specify this function is to consider the functioning of the repair system as the $M/M/n$ queue with losses (TAYLOR and KARLIN, 1984). If λ_0 is constant in time, the stationary probability for the lesion not to be served by the repair system (the probability of "losing a customer") is given by the well-known formula

$$p=\frac{(\lambda_0/\mu_0)^n/n!}{\sum\limits_{k=0}^{n}(\lambda_0/\mu_0)^k/k!},$$

where μ_0 is the service rate, and n is the number of servers or repair units. This parametrization is of more direct interest in studies on radiation carcinogenesis, especially in a quantitative description of the dose-rate effects (KLEBANOV and YAKOVLEV, 1993); it is of little consequence for our further considerations.

(iii) The time from the i-th lesion formation to death of the organism eventually caused by this lesion is a random variable X_i. We call X_i the *potential progression time.* The nonnegative random variables X_i, $i=1, 2, \ldots$, are assumed to be independent and identically distributed with the common cumulative distribution function $F(x)$. Denote $v(t)$ the number of misrepaired lesions accumulated in the organism by the time t, and assume that the random variable $v(t)$ is independent of the sequence $X_1\ X_2, \ldots$ The latent period is defined as

$$U=\bigwedge_{i=0}^{v(t)}(E_i+X_i), \tag{1}$$

where E_i is the time of i-th lesion formation given that this time is less than t, $\wedge$ is the minimum symbol, E_i and X_i are mutually independent and $E_0 + X_0 = +\infty$ (no lesion) with probability one.

Remark 2. The notion of the potential progression time should not be taken too literally. It does not refer to the duration of any specific lethal disease but serves to model the temporal organization of lesion expression in a relatively facile way. The assumption on the identical distribution of X_i can be weakened by considering more than one cause of death within the competing risks framework. This extension, however, requires an additional information on causes of death which is not always available in the survival data.

The above assumptions enable us to derive the distribution function G for the random variable U given by (1). Indeed, the corresponding survival function, $\bar{G} = 1 - G$, can be expressed by the formula of total probability as follows

$$\bar{G}(t) = \Pr\{U \geqq t\} = \sum_{k=0}^{\infty} \bar{R}^k(t) \frac{\left(\int_0^t \lambda(x)\, dx\right)^k}{k!} e^{-\int_0^t \lambda(x)\, dx}, \tag{2}$$

where $\bar{R}$ is the conditional survival function for the sum $E_i + X_i$ given $\nu(t) = k$. Now we can use the following property of the Poisson process (see, COX and ISHAM , 1980, p. 46): given that there are exactly k points in the interval $(0, t]$, these points are independent and identically distributed with density $\lambda(x) / \int_0^t \lambda(u)\, du$, $x \in (0, t)$. Then, for the distribution $R = 1 - \bar{R}$ we have

$$R(t) = \frac{\int_0^t F(t-x)\, \lambda(x)\, dx}{\int_0^t \lambda(x)\, dx}.$$

Substituting this expression for R in (2), we finally obtain

$$\bar{G}(t) = \exp\left\{-\int_0^t \lambda(x)\, F(t-x)\, dx\right\}. \tag{3}$$

This formula describes the survival of individuals in a follow-up study starting from the date of birth. Its key advantage is to show explicitly the contribution of the two distinct characteristics of the process of aging: the rate of formation of intracellular lesions, λ, and the rate of their subsequent progression described by the function F.

Consider the hazard function, $h(t)$, defined for the survival function given by (3),

$$h(t) = \int_0^t \lambda(t-x)\, dF(x). \tag{4}$$

Assuming $F(0)=0$, it is easy to verify that $h(t)$ is a bounded (from above) function of time if the rate λ is bounded, the latter assumption being natural from the biological standpoint. This restriction excludes, amongst others, the Gompertz hazard function which is unlimited at large t. Assuming that $\lambda(t)$ has a finite limit and applying the simplest Tauberian theorem (Cox, 1962), one can see that the survival function $\bar{G}(t)$, given by (3), is asymptotically (as $t \to +\infty$) exponential. Therefore, this function is expected to provide a better description of the survival of old individuals in a population than the Gompertz-Makeham distribution (see Gavrilov et al., 1983; Gavrilov, 1984; Gavrilov, Parkin and Hrisanov, 1984; for discussion). This property will hold true for all the versions of model (3) considered in the next section.

Using standard probabilistic argument, it is easy to show that the conditional survival function $\bar{H}(t, a)$ for the random variable U given $U > a$, $a > 0$, can be expressed as follows

$$\bar{H}(t, a) = \exp\left\{-\int_a^t \lambda(x)\, F(t-x)\, dx\right\}. \tag{5}$$

The last expression for $\bar{H}(t, a)$ describes survival of the animals sampled at a prescribed age a. This experimental design is fairly typical for the studies on animal longevity.

3. Special Cases

In order for the model of aging to be applied to real data, it is necessary to specify the function $\lambda(t)$ in expression (3). Since there is no way to measure the quantity $\lambda(t)$ by an experimental approach or to specify its general parametric form on independent theoretical grounds, we will consider some special cases in which the estimation problems appear to be feasible.

Model 1

If $\lambda(t)$ is constant in time, we have the following special case of formula (3)

$$\bar{G}(t) = \exp\left\{-\lambda \int_0^t F(x)\, dx\right\}. \tag{6}$$

The corresponding hazard rate,

$$h(t) = \lambda F(t),$$

is a nondecreasing function bounded from above.

Remark 3. To describe populations, which are nonhomogeneous with respect to the parameter λ, a randomized version of model (6) can be constructed by specifying a pertinent prior distribution. Most convenient for this purpose are the gamma distribution and $\frac{\alpha}{2}$-stable distributions (Klebanov et al., 1993).

Model 2

The structure of Model 1 is amenable to the incorporation of competing risks. In particular, if there are two major causes of death in a given population, e.g. pyelonephritis and cancer as was documented for mice (Lorenz et al., 1954), then, proceeding from the independent competing risks model (David and Moeschberger, 1978), one may write

$$\bar{G}(t) = \exp\left\{-\lambda_1 \int_0^t F_1(x)\,dx - \lambda_2 \int_0^t F_2(x)\,dx\right\}. \tag{7}$$

In this model, the potential progression time distribution is represented as a two-component mixture of the distributions F_1 and F_2. Clearly, it is advisable to apply model (7) when the components F_1 and F_2 are sufficiently distinct from one another. Further detailing of model (7) by introducing an additional competing risks tends to render it impractical for estimation purposes.

Model 3

The assumption on the constancy of the rate $\lambda(t)$ for the entire lifetime may appear to be rather restrictive. Tyurin et al. (1994) presented some evidence against this assumption. As follows from their analysis of published data on longevity of mice and rats, the rate of lesion formation is not sustained at a constant level throughout life, though in some cases its variations with age can be considered negligible. In consonance with this conclusion are some independent indications in the literature on an age-related decline of the activity of repair enzymes (Anisimov, 1987). Yakovlev et al. (1993) proposed a parsimonious model allowing for that regularity in the context of modeling the hormesis effect. In like manner, a stepwise increase of the rate λ at some nonrandom time instant $t_0 > 0$ can be introduced in formula (6). As a result, we have one more version of the basic model under consideration

$$\bar{G}(t) = \exp\left\{-\lambda_1 \int_0^t F(x)\,dx\right\}, \quad t \leqq t_0,$$

$$\bar{G}(t) = \exp\left\{-\lambda_1 \int_0^{t_0} F(t-x)\,dx - \lambda_2 \int_{t_0}^t F(t-x)\,dx\right\}, \quad t > t_0,$$

where $\lambda_1 \leqq \lambda_2$.

Model 4

The model structure will retain sufficient simplicity if we introduce an age-varying rate of lesion formation by specifying the function $\lambda(t)$ in the form

$$\lambda(t) = c(1 - e^{-\gamma t}),$$

where c and γ are positive constants. In this case

$$\bar{G}(t) = \exp\left\{-c \int_0^t (1 - e^{-\gamma x})\, F(t-x)\,dx\right\}. \tag{8}$$

Formula (8) reduces to Model 1 if $\gamma \to +\infty$. This fact is useful in evaluating the evidence in favor of Model 1.

4. Estimation Procedure

The method of maximum likelihood provides a pertinent procedure for obtaining estimates of unknown parameters in the above considered parametric models. The method is of particular assistance in the accomodation of censored data in modern survival analysis (KALBFLEISCH and PRENTICE, 1980). In an illustration that follows, we will be concerned only with complete samples, and the classical chi-square test will be used for testing the goodness of fit. Therefore, the estimation procedure will be based essentially on the multinomial form of the likelihood function.

To put the model to practical use, it remains to specify the potential progression time distribution. In this work, preference is given to the two-parameter gamma distribution by virtue of its flexibility and clear meaning of shape and scale parameters, hereafter denoted by α and β, respectively. These parameters are related to the mean, τ, and the variance, σ^2, of the potential progession time as follows: $\tau = \alpha/\beta$, $\sigma^2 = \alpha/\beta^2$. The gamma distribution density is of the form

$$f(x)=\begin{cases}\dfrac{\beta^{\alpha}}{\Gamma(\alpha)}\,x^{\alpha-1}\,e^{-\beta x}, & \alpha\geqq 1,\ x>0,\\[2ex] 0\quad , & x\leqq 0.\end{cases}$$

Another reason for such a choice is that finite mixtures of gamma distributions are identifiable (Teicher, 1961; Yakowitz and Spragins, 1968), and so are the competing risks models of type (7).

To maximize the log-likelihood with respect to the model parameters, we use the following 3-step nonlinear programming procedure:

- Step 1: apply the random search algorithm (Zhigljavsky, 1992) that requires the specification of a domain A containing the overall maximum but not a starting point for the optimization.
- Step 2: apply the Davidon-Fletcher-Powell algorithm (Himmelblau, 1972) with the initial points provided by step 1. If the boundary of the set A is attained then go to step 3, otherwise step 2 gives the final solution.
- Step 3: apply the Zoutendijk algorithm (Himmelblau, 1972) allowing for constraints which specify A.

To avoid computational difficulties, the search for the estimate of α can be limited to the set of positive integers. The procedure is described at length in the work by Hoang et al. (1995).

5. Application

We apply the model to analyze data on lifetimes of white outbred LIO rats (bred in the N.N. Petrov Research Institute of Oncology, St. Petersburg) followed from an age of 100 days up to natural death. Some animals were sacrificed by ether in agonal condition. 7 groups of females (573 rats in total) and 4 groups of males (462 rats) were under observation. After weaning, male and female rats were kept separately in standard polypropylene cages (5 per cage). They were given natural meal, standard lab chow and tap water *ad libitum*. Light regime was 14 h light/10 h dark, room temperature $+22\pm 2\,^{\circ}$C.

The results of the goodness of fit testing for female rats are shown in Table 1. Obviously, these results favor Model 1 much more than the other models. In all cases the parameter γ formula (8) tends to take very high values, thereby showing that Model 4 reduces to Model 1. This may be considered as an additional evidence in favor of Model 1. Hence, one may conclude that the hypothesis on constancy of the rate λ is consistent with the data for female rats. The estimated values of the model parameters are given in Table 2. As evident from this table, the parameter values vary widely with different samples of female rats.

Table 1
Goodness of fit for different versions of the model. Female rats.
Sample sizes and significance level values are given in parentheses.

Group of animals	Model			
	1	2	3	4
1 ($n=68$)	+ ($p>0.05$)	−	−	−
2 ($n=86$)	+ ($p>0.3$)	−	+ ($p>0.05$)	+ ($p>0.05$)
3 ($n=75$)	+ ($p>0.1$)	−	−	−
4 ($n=76$)	+ ($p>0.05$)	−	−	−
5 ($n=85$)	+ ($p>0.3$)	−	+ ($p>0.1$)	+ ($p>0.2$)
6 ($n=66$)	+ ($p>0.05$)	−	−	−
7 ($n=117$)	+ ($p>0.05$)	−	−	−

In contrast to the results obtained for female animals, it is Model 3 that provides a better description of the data for male rats (Table 3). For one example, the estimated survival functions for Group 4 of male rats corresponding to Model 1 and Model 3 are depicted in Fig. 1. There is a marked discrepancy between the two estimates. Hence, the most likely speculation is that a sharp increase in the rate of lesion formation occurs at some age t_0 in male rats. Note

Table 2
The model parameters for female rats.

Group of animals	Estimates of parameters		
	λ	τ	σ
1	27	4214	2980
2	37	704	497
3	50	1555	1100
4	4	347	142
5	6	378	154
6	19	1428	824
7	25	1592	919

Table 3

Goodness of fit. Male rats.
Sample sizes and significance level values are given in parentheses.

Group of animals	Model			
	1	2	3	4
1 ($n=218$)	+ ($p>0.2$)	+ ($p>0.2$)	+ ($p>0.2$)	+ ($p>0.1$)
2 ($n=71$)	−	−	−	−
3 ($n=86$)	−	−	+ ($p>0.3$)	−
4 ($n=87$)	−	−	+ ($p>0.3$)	−

Table 4

The model parameters for male rats.

Group of animals	Estimates of parameters				
	λ_1	$\lambda_2-\lambda_1$	t_1 (weeks)	τ	σ
1	0.091	0.335	75	194	112
2	0.022	0.575	94	61	35
3	0.025	2.235	91	83	34
4	0.021	1.518	87	76	29

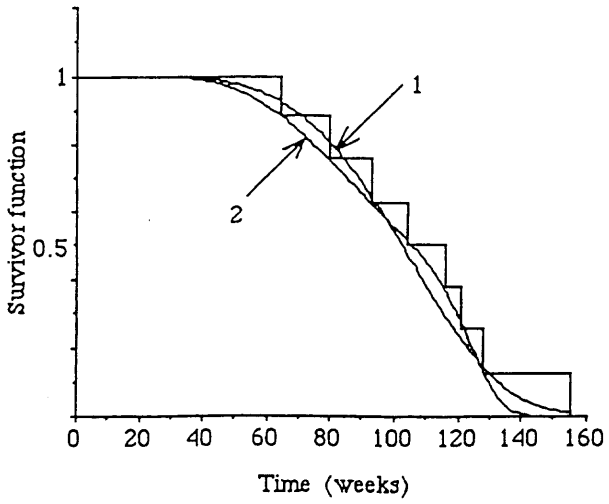

Fig. 1. Parametric estimation of the survival function based on Model 1 (curve 1) and Model 3 (curve 2). Male rats of Group 4.
Stepwise curve represents the nonparametric (life-table) estimate.

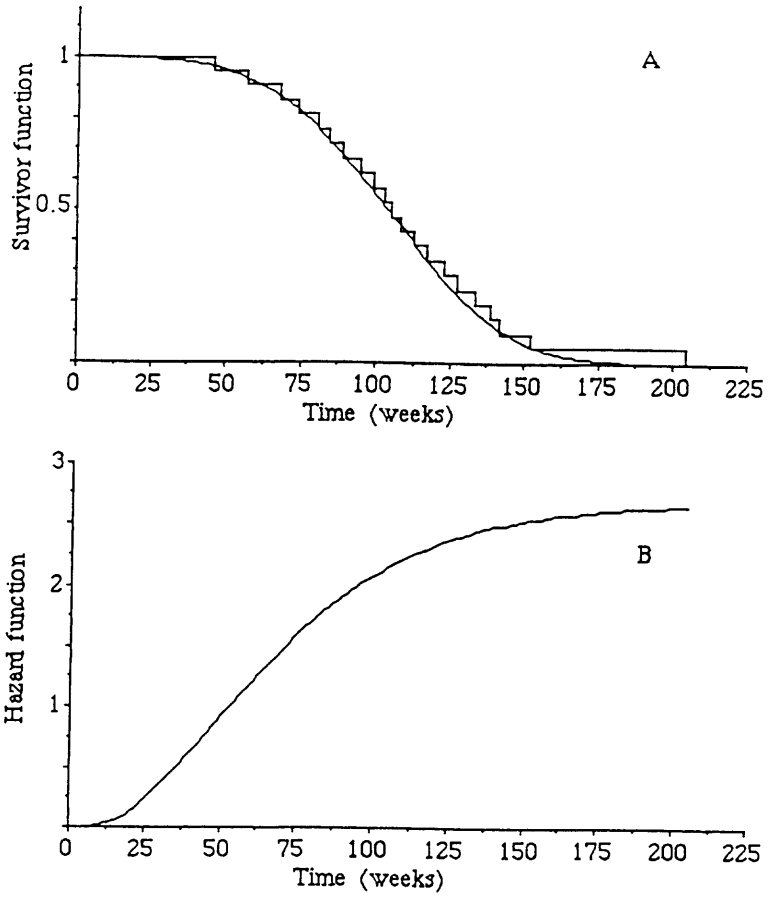

Fig. 2. Parametric estimation (Model 1) of the survival function (A) and the hazard rate (B) for male rats of Group 1.

that the estimated values of t_0 are virtually the same for the four groups of male animals (Table 4). On the other hand, none of the models is consistent with the observations for Group 2, but all of them are in good agreement with the data for Group 1 of male rats. Since the latter group is the most numerous one, it may well be heterogeneous and this is in line with a high significance level provided by the competing risks model (Model 2). The estimated survival and hazard functions for Group 1 are shown in Fig. 2. Although the chi-square test rejects Model 3 for Group 2 of male rats, this model parameters appear to be fairly close to those for the other groups (Table 4). As follows from Table 4 the parameter estimates for males vary but slightly as compared with their variations observed for female rats (Table 2). Besides, male rats tend to have much lower rates of lesion formation (higher efficiency of the repair system?) and yet much shorter potential progression times than is the case for females. In this connection it is worth noting that the life-prolonging effect of chronic irradiation and of procaine was documented for male but not for female animals (LORENTZ et al., 1954; ASLAN et al., 1965). This analysis, tentative as it is, indicates that the distinction between principal characteristics of the aging process in males and females is by no means sharp and may be attributed to dissimilar values of the model parameters.

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Andrej Yu. Yakovlev
Alexandr D. Tsodikov
Biostatistical Unit
Curie Institute
26, Rue D'Ulm
75231 Paris, France
and
Department of Applied Mathematics
St. Petersburg Technical University
St. Petersburg 195251, Russia

Vladimir N. Anisimov
Laboratory of Experimental Tumors
N. N. Petrov Institute of Oncology
St. Petersburg, Russia