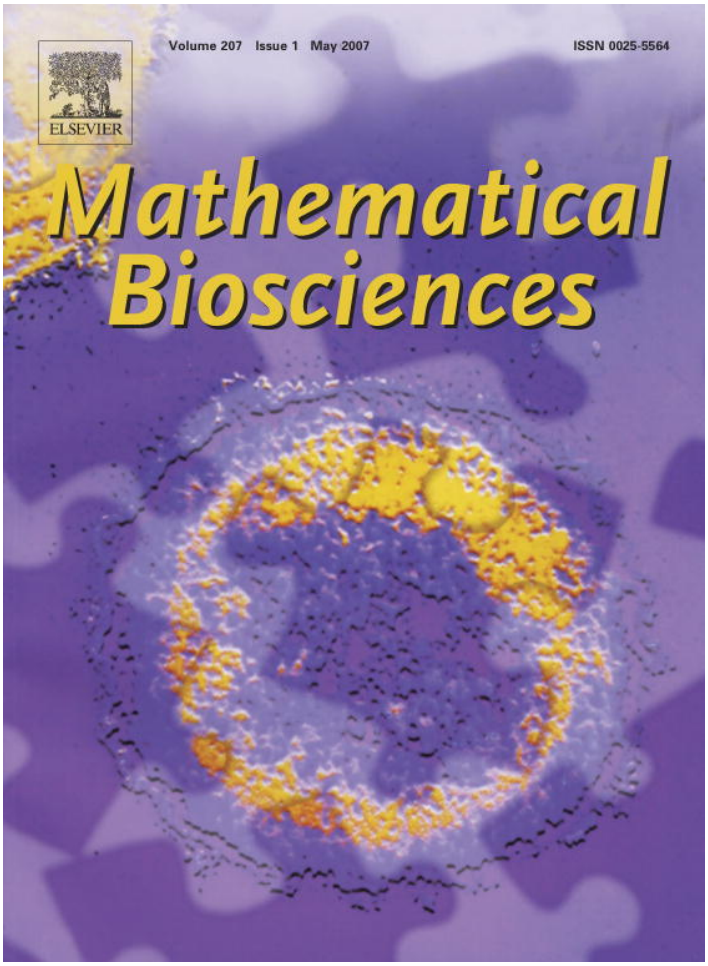

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Aging: Damage accumulation versus increasing mortality rate

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Abstract

If aging is understood as some process of damage accumulation, it does not necessarily lead to increasing mortality rate. Within the framework of a suggested generalization of the Strehler–Mildwan (1960) [B.L. Strehler, A.S. Mildvan (1960). General theory of mortality and aging, Science, 132, 14] model, we show that even for models with monotonically increasing degradation, the mortality rate can still decrease. The decline in vitality and functions, as manifestation of aging, is modeled by the monotonically decreasing quality of life function. Using this function, the initial lifetime random variable with ultimately decreasing mortality rate is 'weighted' to result in a new random variable, which is already characterized by the increasing mortality rate.

Keywords: Aging; Mortality; Accumulated damage; Quality of life function

1. Introduction

Mortality rates of most species increase with time at least in the post-reproductive period. For advanced ages they sometimes also tend to level off or even to decrease, which among other reasons, can result due to population heterogeneity [22]. In this note, however, we will focus only on a homogeneous case. Does a possible deceleration in mortality mean a

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deceleration in aging? This certainly depends on a definition of aging and we show under certain assumptions that when overall aging of an organism is understood as some accumulation of damage (additive degradation, which models age related dynamics of bio-markers of aging), and this is our assumption, it does not always lead to increasing mortality rates. Therefore, we distinguish between the deterioration per se and its manifestation in the form of the increasing mortality rate, which is likely but not always to occur. In this way we partially argue with Finch [8], where he defines senescence as 'age-related changes in an organism that adversely affect its vitality and functions, but most important increase the mortality rate etc.' (see also Vaupel et al. [23] for the corresponding discussion). We, on the contrary, emphasize the fact that accumulation of damage of some kind, e.g., deleterious mutation accumulation ([18,14]) eventually defines these age related changes in an organism and, combined with other factors, determines the shape of the mortality rate. This approach is definitely not a new one, and was recently supported in a rather general setting by Aalen and Gjessing [3] in their path breaking paper with a speaking for itself title: understanding the shape of the hazard rate: a process point of view.

Consider an organism in a post-reproductive phase of life, when the accumulated damage already noticeably results in negative age related changes. On the other hand, assume that the mortality rate is leveling off or even decreasing at sufficiently advanced age, which is observed in humans and some other species. How can these, at first sight, contradictory properties coexist? Firstly, we show that under certain assumptions this can still be the case, and, secondly, we suggest how, at least formally, to deal with and to interpret the stated contradiction.

Apart from a shape of the mortality rate, the following question can be asked: is the 'value' of a unit of a lifetime of humans at sufficiently advanced ages the same as at previous phases of life? Humans at advanced ages usually have restrictions of various kinds, showing a substantial decrease in vitality and functions, which obviously results in a deterioration of a quality of life at this stage. On the other hand, it is clear that this decline should be somehow reflected in the shape of the mortality rate or in some similar characteristic even in the case when formally the mortality rate is leveling off or declining.

In Section 2, using our random vitality model and a generalization of the Strehler–Mildwan (1960) model [21], we show that even for models with monotonically increasing degradation the mortality rate can still decrease. In Section 3 we suggest a weighting of a lifetime random variable based on a quality of life index.

2. Degradation and mortality rate

Let T denote a lifetime random variable with the cumulative distribution function (Cdf) $F(t)$ and the corresponding mortality rate $\mu(t)$. Does increasing mortality rate $\mu(t)$ really describe aging? In fact, this is a matter of definition: in reliability theory, e.g., the simplest and the most popular class of aging distributions is the class of distributions with increasing failure rate (IFR) ([4]). The increasing mortality rate shows that probability of death of organisms increases with age. This is a rather natural definition, which certainly can be applied to human mortality at adult ages. Another wider class of aging distributions is a class of distributions with decreasing $m(t)$ – life expectancy at age t, which is defined via $\mu(t)$ as

$$m(t) = \int_0^\infty \exp\left(-\int_t^{x+t} \mu(u)\mathrm{d}u\right)\mathrm{d}x. \tag{1}$$

It follows from (1), that $m(t)$ is decreasing when $\mu(u)$ is increasing. The inverse is generally not true [10]. Therefore, the decreasing in t life expectancy at age t may be, in fact, the weaker and, in some sense, the better characteristic of aging.

The foregoing expresses a statistical (black box) point of view, when the only information at hand is the mortality data. When we speak about biological aging, an underlying biological process (processes) of aging should be taken into account. Most researchers agree that aging can be described by accumulation of some kind of damage, which leads to 'age-related changes in an organism that adversely affect its vitality and functions', and in the current note we shall follow this interpretation.

Does damage accumulation (e.g., of deleterious mutations) lead to increasing mortality rates? General progressive models of aging [3], described by underlying monotonically increasing stochastic processes of wear or degradation, often result in increasing mortality rates. But this is not always the case, which will be illustrated by the following two meaningful models.

3. Model 1. A random vitality model

Assume that at birth ($t = 0$) an organism acquires an initial unobserved random resource or vitality R with the Cdf $F_0(r)$. Suppose that for each realization of R the deterministic (for simplicity) run out resource $W(t)$ ($W(0) = 0$) to be called wear (or degradation) monotonically increases. Death occurs when the wear reaches R, which means that $W(T) = R$, therefore

$$F(t) \equiv \Pr(T \leqslant t) = \Pr(W(T) \leqslant W(t)) = \Pr(R \leqslant W(t)). \tag{2}$$

As $F_0(r) \equiv \Pr(R \leqslant r)$, substituting $W(t)$ instead of r and taking into account Eq. (2)

$$F_0(W(t)) = \Pr(R \leqslant W(t)) = F(t). \tag{3}$$

Thus the lifetime Cdf $F(t)$ is defined in terms of the resource Cdf. $F_0(r)$ and the wear $W(t)$. The mortality rate $\mu(t)$ can be also defined via Eq. (3) [9]

$$\mu(t) = \frac{f(t)}{1 - F(t)} = W'(t)\lambda_0(W(t)), \tag{4}$$

where $\lambda_0(t)$ is the failure rate, which corresponds to the Cdf $F_0(t)$ and $f(t) = F'(t)$ is the corresponding probability density function.

Eq. (4) can be used for analyzing a shape of the mortality rate in this model. Assume, at first, for simplicity that $\lambda_0(t) = \text{const}$, and that $W(t)$ is increasing as a power function t^α, $0 < \alpha < 1$. It is easy to see from (4) that the mortality rate $\mu(t)$ is decreasing. Another example is the Weibull distribution with a linear failure rate: $\lambda_0(t) = \beta t$; $\beta > 0$. Then $\mu(t)$ is decreasing, when $0 < \alpha < 0.5$. The linear failure rate is a good approximation for the failure rate of the truncated Normal distribution, which can be used for $F_0(r)$ modeling. Thus, these examples show that although degradation takes place since the wear function $W(t)$ is increasing, the mortality rate is still decreasing.

In what follows in this section we will present and justify mathematically a model, which is, in fact a generalization of the Strehler–Mildwan (1960) model of human mortality.

4. Model 2. Generalization of the Strehler–Mildwan model

As in the previous model, consider a first passage-type setting but with an additional feature of killing events [20,2,11]: let W_t, $t \geqslant 0$ denote an increasing stochastic process of damage accumulation and let $B(t)$ be a function that defines the corresponding boundary. Death occurs when W_t exceeds $B(t)$ for the first time. Let $W(t)$ denote the increasing realization of this process. Usually it is reasonable to assume that $B(t)$ does not change with time: $B(t) = B$, but for the sake of model generality we will keep the time dependent notation.

Let P_t, $t \geqslant 0$ be a point process of external instantaneous harmful events (external stresses or demands for energy) with rate $\lambda(t)$. Following reliability terminology, we will call these events 'shocks'. Assume, that each shock, independently from the previous ones, results in death with probability $\theta(t)$ and is 'survived' with the complementary probability $1 - \theta(t)$. This can be interpreted in the following way: each shock has a random magnitude $Y_i = Y$, $i = 1,2,\ldots$ with a common distribution function $\Psi(y)$. The death at age t occurs when this magnitude exceeds $B(t) - W(t)$. Therefore

$$\theta(t) = \Pr(Y > B(t) - W(t)) = 1 - \Psi(B(t) - W(t)). \tag{5}$$

In the original Strehler–Mildwan (1960) model, which was widely applied to human mortality data (see [16,17], among others), our $B(t) - W(t)$ had a meaning of remaining at time t vitality. It was also supposed in this model that this function linearly decreases with age, which can be a reasonable assumption as some biological markers of human aging can behave linearly [15]. But the crucial unjustified assumption was that the distribution function $\Psi(y)$ is exponential [26]. The combination of linearity of $B(t) - W(t)$ and of exponentiality of $\Psi(y)$ results in the exponential form of the mortality rate and therefore can not be considered as a justification of the empirical Gompertz law of human mortality. Arbeev et al. [1] consider modification of this model and apply it to modeling human cancer incidence rates. They assume that $B(t) - W(t)$ is decreasing exponentially. Our forthcoming approach does not need additional assumptions on $\Psi(y)$ and $B(t) - W(t)$.

It is well known [19] that the rate (intensity) $\lambda(t)$ does not define an arbitrary point process. However, it can be defined via its complete intensity function $\lambda(t; H_t)$ [6], which takes into account the history ('locations' of all points) up to time t. Thus, $\lambda(t; H_t)\mathrm{d}t$ can be interpreted as a probability of a shock occurrence in $[t, t + \mathrm{d}t)$, given the process history up to t. Therefore, the conditional mortality rate in our model is

$$\mu_c(t, H_t)\,\mathrm{d}t = \Pr\{T \in [t, t + \mathrm{d}t) | H_t, T(H_t) \geqslant t\} = \theta(t)\lambda(t, H_t)\,\mathrm{d}t, \tag{6}$$

where condition $T(H_t) \geqslant t$ means that all shocks in $[0, t)$ were survived (for the specific configuration of shocks given by the history H_t). However, Eq. (6) reduces to the conventional, not history-dependent mortality rate $\mu(t)$ only for the specific case of the Poisson process

$$\mu_c(t, H_t) = \theta(t)\lambda(t) = \mu(t). \tag{7}$$

Therefore, the corresponding survival function is

$$\overline{F}(t) \equiv 1 - F(t) = \exp\left\{-\int_0^t \theta(u)\lambda(u)\,\mathrm{d}u\right\} \tag{8}$$

and this completes the proof for the specific case of the Poisson process of shocks. Unfortunately, Strehler–Mildwan (1960) did not make this crucial assumption, without which their approach is not mathematically valid.

Remark 1. Taking into account that death can also occur when vitality reaches 0, Eq. (8) can be obviously modified to

$$\overline{F}(t) = \begin{cases} \exp\left\{-\int_0^t \theta(u)\lambda(u)\,\mathrm{d}u\right\}, & t \leqslant t_r, \\ 0, & t > t_r, \end{cases}$$

where t_r is defined as the minimal solution of equation $B(t) = W(t)$. If the curves $B(t)$ and $W(t)$ do not cross, then $t_r = \infty$. Humans and other organisms do not usually dye directly from accumulated damage, which is a slowly increasing process. Therefore, we can assume that formally $t_r = \infty$ and relations (7) and (8) hold.

Remark 2. We have derived Eqs. (7) and (8) for a sample path $W(t)$. A general case of the increasing stochastic process W_t, $t \geqslant 0$ can be also considered by obtaining the corresponding expectations (with respect to W_t, $t \geqslant 0$) [25,11]. This conditioning can only result in additional deceleration (decrease) in the observed mortality rate.

Eq. (7) states that the resulting mortality rate is just a simple product of the rate of the Poisson process and of the probability $\theta(t)$. Therefore, its shape can be easily analyzed. When $B(t) - W(t)$ is decreasing, the probability $\theta(t)$ is increasing with age, which goes in line with the accumulation of degradation reasoning. If, additionally, the rate of harmful events $\lambda(t)$ is not decreasing, or decreasing not faster than $\theta(t)$ is increasing, the resulting mortality rate $\mu(t)$ is also increasing. The following possible scenarios can result in the decreasing mortality rate $\mu(t)$:

a. $\theta(t)$ is decreasing, as the boundary function $B(t)$ is increasing faster than $W(t)$: additional vitality is additively 'earned' by an organism with age (some relevant general models for this case can be considered, which is a topic for a special study). Let, for instance, $W(t) = wt$, $B(t) = bt$; $0 < w < b$. Then

$$\theta(t) = \Pr(Y > B(t) - W(t)) = 1 - \Psi((b-w)t)$$

is decreasing in t.

b. Lifesaving [24,13]: assume that each life, characterized by the initial mortality rate $\mu(t)$, is saved (cured) with probability $1 - l(t)$, $0 < l(t) < 1$. Equivalently, a proportion of individuals who would have died are now resuscitated and given another chance due to improvements in healthcare. Then in accordance with the foregoing considerations, the resulting mortality rate is $l(t)\mu(t)$ and it can decrease at advanced ages due to decreasing $l(t)$.

c. The rate of harmful events $\lambda(t)$ is decreasing. This assumption can be quite realistic, e.g., for human populations in developed countries when the exposure to stresses of different kinds decreases at advanced ages.

Thus, the case of negative aging can still occur within the framework of the suggested generalized Streller–Mildwan model. This supports our claim that in general the shape of the mortality rate alone is not sufficient for defining aging properties, whereas the accumulated damage, which is responsible for age related changes in an organism, combined with other factors, eventually determines the shape of the mortality rate. On the other hand, it seems *intuitively* unnatural that a degradable object is characterized by the decreasing mortality rate. Therefore, in the next section a regularization procedure will be suggested which can eventually boil down in the increasing 'mortality' rate for a supplementary lifetime random variable.

5. Quality of life function

Denote by $q(t) \leqslant 1$ – a quality of life index at age t. The function $q(t)$ defines a weight which is given to a unit increment of life at age t. As it was stated in the Introduction, humans at advanced ages usually have restrictions of various kinds, showing a substantial deterioration in vitality and functions, which decrease a quality of life at this stage. Although formally vitality and functions decrease at all adult ages, the noticeable decline in the corresponding quality of life due to these processes occurs usually only at relatively advanced ages.

These considerations are somehow similar to the starting point of the Quality Adjusted Life Years (QALYs) approach (see, e.g., [7]), but the goal is different. This approach is focused on solving individual health care decision problems, when, for instance, an operation with probability p can add a number of quality years ($q = 1$), but can result in death ($q = 0$) with probability $1 - p$. Without an operation a patient lives with a lower quality of life: $q < 1$. Our interest is not in a specific decrease in abilities of individuals with concrete health problems, but rather in modeling a general trend, which shows the decline in quality of life as a manifestation of senescence. Therefore, we will assume that $q(t) = 1$, $t \in [0, t_s)$ and that this function monotonically decreases for $t \geqslant t_s$, where t_s is the starting point of senescence: a noticeable decline in 'abilities and possibilities'.

Let, as previously, T be a lifetime random variable with the Cdf $F(t)$ and the mortality rate $\mu(t)$. Denote by $Q(T)$ a 'weighted lifetime': a random variable weighted in accordance with the quality of life function $q(t)$

$$Q(T) = \int_0^T q(u)\,\mathrm{d}u, \tag{9}$$

where the function $q(t)$ should be such that $Q(\infty) = \infty$.

It is clear that, when $q(t) \equiv 1$, the lifetimes are equal: $Q(T) = T$. Thus, $Q(T)$ already reflects in an 'integrated way' not only the length of life but its quality as well. The distribution function of $Q(T)$ is easily derived via the generic Cdf $F(t)$

$$G(t) = \Pr(Q(T) \leqslant t) = \Pr(T \leqslant Q^{-1}(t)) = F(Q^{-1}(t)), \tag{10}$$

where $Q^{-1}(t)$ is the inverse function to $Q(t)$, which exists and increases, as the function $Q(t)$ increases. In accordance with the definition, the mortality rate $\mu_q(t)$, which corresponds to $G(t)$ is

$$\mu_q(t) = \frac{\mathrm{d}(G(t))}{\mathrm{d}t(1-G(t))} = \frac{\mathrm{d}(F(Q^{-1}(t))}{\mathrm{d}t(1-F(Q^{-1}(t))} = \frac{\mathrm{d}(F(Q^{-1}(t)))\mathrm{d}(Q^{-1}(t))}{\mathrm{d}(Q^{-1}(t))\mathrm{d}t} = \frac{\mathrm{d}(Q^{-1}(t))}{\mathrm{d}t}\mu(Q^{-1}(t)). \tag{11}$$

Our intention is to show that, for instance, in the case of the ultimately decreasing mortality rate $\mu(t)$, which is usually qualified as negative senescence, the function $\mu_q(t)$ can still increase, which is somehow more intuitively acceptable for models with degradation. It is natural to model $q(t)$ as a decreasing power function for large t. A generalization to the regularly varying functions [5] is rather straightforward. Let: $q(t) \propto t^{-\alpha}$, $0 < \alpha < 1$. By this notation we mean proportionality. The case: $\alpha = 1$ will be considered separately, whereas the range $\alpha > 1$ is not allowed, as $Q(\infty) = \infty$. Then

$$Q(t) \propto t^{-\alpha+1} = t^{\frac{k}{n}}; \quad k < n, \qquad Q^{-1}(t) \propto t^{\frac{n}{k}}.$$

Therefore, as follows from definition (11), e.g, for a constant mortality rate $\mu(t)$, the rate $\mu_q(t)$ is already increasing and $\mu_q(t) \propto t^{\frac{n}{k}-1}$. It is easy to see that it will be still increasing even for decreasing mortality rates: $\mu(t) \propto t^{-\beta}$, if $0 < \beta < 1 - \frac{k}{n}$. Thus, under some reasonable assumptions a 'regularization' procedure has been performed resulting in the increasing rate $\mu_q(t)$. The following example deals with the case: $\alpha = 1$.

Example. Let $F(t) = 1 - \exp\{-\mu t\}$ and

$$q(t) = \begin{cases} 1, & t \leqslant t_s, \\ \frac{k}{(t-t_s)+k}, & t > t_s, \end{cases}$$

where $k > 0$, which means that for sufficiently large t: $q(t) \propto k/t$. Then

$$Q(t) = \begin{cases} t, & t \leqslant t_s, \\ t_s + k\left[\ln\left(\frac{t-t_s}{k} + 1\right)\right], & t > t_s. \end{cases} \tag{12}$$

It is easy to see that the inverse function $Q^{-1}(t)$ is linear in $[0, t_s]$ and is exponentially increasing for $t > t_s$. It follows from Eqs. (11) and (12) that $\mu_q(t)$ is also increasing for $t > t_s$ and is constant in $[0, t_s]$. This shape already reflects degradation in the model. The same, in accordance with Eq. (12), is true for the case when $\mu(t)$ is decreasing but slower than $(Q^{-1}(t))'$ is increasing.

The quality of life approach is probably more natural to be used for considering the corresponding life expectancy at time t than for the mortality rate itself. Similar to definition (1)

$$m_q(t) = \int_0^\infty \exp\left(-\int_t^{x+t} \mu_q(u)\,\mathrm{d}u\right)\mathrm{d}x,$$

which means that $m_q(t)$ can decrease when $m(t)$ is constant or increasing.

6. Concluding remarks

Usually mortality rates increase with age as the consequence of age-related changes in an organism that adversely affect its vitality and functions. Within the framework of the generalized

Strehler–Mildwan model, we show that theoretically different shapes of mortality rate functions are possible even with degradation. Modeling of probability $\theta(t)$ is crucial for this approach. The assumption that the process of shocks is the Poisson one is important for obtaining the mortality rate in the closed simple form (7). We can generalize the approach to the renewal process of shocks [12] and also can incorporate in the model the fact that after the successfully survived shock the level of accumulated damage increases on a random amount, but the corresponding technical derivations are rather cumbersome.

The suggested change of variables defined by relation (9), captures a natural degradation at advance ages, which is crudely characterized by the decreasing function $q(t)$.

A general approach developed in this paper can be applied to overall bio-markers of organism's aging. However, models of degradation on lower levels (organs, cells) can be also considered, and these are the topics for future applications.

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References

[1] K. Arbeev, S. Ukraintseva, L. Arbeeva, A. Yashin, Mathematical models for human cancer incidents rates, Demogr. Res. 12, 237, <http://www.demographic-research.org/volumes/vol12/default.htm>.
[2] T. Aven, U. Jensen, Stochastic Models in Reliability, Springer, Berlin, 1999.
[3] O.O. Aalen, H.K. Gjessing, Understanding the shape of the hazard rate: a process point of view, Stat. Sci. 16 (2001) 1.
[4] R. Barlow, F. Proschan, Statistical Theory of Reliability and Life Testing. Probability Models, Rinehart and Winston, New-York, Holt, 1975.
[5] N.H. Bingham, C.M. Goldie, J.L. Teugels, Regular Variation, University, Cambridge, 1987.
[6] D.R. Cox, V. Isham, Point Processes, Chapman and Hall, London, 1980.
[7] M. Hunink, P. Glaszion, J. Siegel, J. Piskin, A. Elstein, M. Weinstein, Decision Making in Health and Medicine: Integrating Evidence and Values, Cambridge University, Cambridge, 2001.
[8] C. Finch, Longevity, Senescence, and the Genome, University of Chicago, Chicago, 1990.
[9] M.S. Finkelstein, Wearing-out components in variable environment (1999), Reliability Eng. Sys. Saf. 66 (N3) (1999) 235.
[10] M.S. Finkelstein, On the shape of the mean residual life function, Appl. Stochastic Models Bus. Ind. 18 (2002) 135.
[11] M.S. Finkelstein, A model of biological aging and the shape of the observed hazard rate, Lifetime Data Anal. 9 (2003) 93.
[12] M.S. Finkelstein, Simple bounds for terminating Poisson and renewal processes, J. Stat. Plann. Inference 113 (2003) 541.
[13] M.S. Finkelstein, Lifesaving explains mortality decline with time, Math. Biosci. 196/2 (2005) 187.
[14] L.D. Mueller, M.R. Rose, Evolutionary theory predicts late life mortality plateaus, PNAS 93 (1996) 15249.
[15] E. Nakamura, M. Lane, G. Roth, D. Ingram, A strategy for identifying biomarkers of aging, Exp. Gerontol. 33 (1998) 4.
[16] J.E. Riggs, R.J. Millecchia, Using the Gompertz–Strehler model of aging and mortality to explain mortality trends in industrialized countries, Mech. Aging Dev. 65 (1992) 217.

[17] J.E. Riggs, G.R. Hobbs, Nonrandom sequence of slope-intercept estimates in longitudinal Gompertzian analysis suggests biological relevance, Mech. Aging Dev. 100 (1998) 269.
[18] M.R. Rose, Evolutionary Biology of Aging, Oxford University, Oxford, 1994.
[19] S.M. Ross, Stochastic Processes, John Wiley and Sons, New York, 1996.
[20] N.D. Singpurwalla, Survival in dynamic environment, Stat. Sci. 10 (1995) 86.
[21] B.L. Strehler, A.S. Mildvan, General theory of mortality and aging, Science 132 (1960) 14.
[22] J.W. Vaupel, K.G. Manton, E. Stallard, The impact of heterogeneity in individual frailty on the dynamics of mortality, Demography 16 (1979) 439.
[23] J.W. Vaupel, A. Baudisch, M. Dolling, D.A. Roach, J. Gampe, The case of negative senescence, Theor. Popul. Biol. 65 (2004) 339.
[24] J.W. Vaupel, A.I. Yashin, Repeated resuscitation: how life saving alters life tables, Demography 4 (1987) 123.
[25] A.I. Yashin, K.G. Manton, Effects of unobserved and partially observed covariate processes on system failure: a review of models and estimation strategies, Stat. Sci. 12 (1997) 20.
[26] A.I. Yashin, I.A. Iachine, A.S. Begun, Mortality modeling: a review, Math. Popul. Stud. 8 (2000) 305.