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REVIEW

Exploring Patterns of Human Mortality and Aging: A Reliability Theory Viewpoint

Leonid A. Gavrilov[1,2,a]* and Natalia S. Gavrilova[1,2]

[1]*NORC at the University of Chicago, 60637 Chicago, IL, USA*

[2]*Institute for Demographic Research, Federal Center of Theoretical and Applied Sociology, Russian Academy of Sciences, 109028 Moscow, Russia*

[a]*e-mail: lagavril@yahoo.com*

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Abstract—The most important manifestation of aging is an increased risk of death with advancing age, a mortality pattern characterized by empirical regularities known as mortality laws. We highlight three significant ones: the Gompertz law, compensation effect of mortality (CEM), and late-life mortality deceleration and describe new developments in this area. It is predicted that CEM should result in declining relative variability of mortality at older ages. The quiescent phase hypothesis of negligible actuarial aging at younger adult ages is tested and refuted by analyzing mortality of the most recent birth cohorts. To comprehend the aging mechanisms, it is crucial to explain the observed empirical mortality patterns. As an illustrative example of data-directed modeling and the insights it provides, we briefly describe two different reliability models applied to human mortality patterns. The explanation of aging using a reliability theory approach aligns with evolutionary theories of aging, including idea of chronic phenoptosis. This alignment stems from their focus on elucidating the process of organismal deterioration itself, rather than addressing the reasons why organisms are not designed for perpetual existence. This article is a part of a special issue of the journal that commemorates the legacy of the eminent Russian scientist Vladimir Petrovich Skulachev (1935-2023) and his bold ideas about evolution of biological aging and phenoptosis.

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INTRODUCTION

The increasing interest in unraveling the intricacies of aging underscores the necessity for a comprehensive theoretical framework. There has been a significant surge in the volume of empirical data on aging, reflecting a substantial expansion in our understanding of the aging processes. The exploration of individual genes, pathways, and molecules in understanding the mechanisms that modulate aging has indeed seen significant progress. Researchers have made strides in identifying the components involved in the aging process. However, the challenge lies in comprehending how these various factors interact on a larger scale to influence the aging processes. While we can pinpoint specific genes, pathways, and molecules, the integration of these elements into a comprehensive understanding of aging, including the emergence of functional phenotypes like mortality laws, remains a complex puzzle [1].

Evolutionary theories can provide a broader understanding of the aging phenomenon. Until recently, there was a consensus among gerontologists that there is no specific program of aging, because such program could not appear when overwhelming majority of animals in the wild and humans in the past did not survive to advanced ages [2-4]. However, this view was revised in the last decade and there are more arguments now in favor of aging as a program. Vladimir P. Skulachev was among the researchers who promoted an

* To whom correspondence should be addressed.

idea of programmed aging. He attempted to resurrect Weismann's theory of programmed death by proposing the existence of a distinct self-destruction program for entire organisms, termed "phenoptosis" [5-7]. This program is believed to serve "crucial functions, cleansing communities of organisms from undesirable individuals" [7]. As such, Weismann's evolutionary theory of programmed death continues to be a subject of scientific debate and inquiry. Moreover, the ideas of harmful role that older individuals play in population by accumulating infections gain popularity among gerontologists [6, 8]. Nevertheless, theories and hypotheses about programmed aging primarily elucidate the reasons organisms are not inherently designed to be flawless and fall short in explaining the actual process of age-related deterioration itself.

The primary limitation of evolutionary theories of aging is that they rely on the concept of natural selection and the diminishing impact of natural selection with age. However, aging is observed in non-replicating technical systems like automobiles, which lack the capacity for procreation and are therefore unaffected by evolution driven by natural selection.

Recognizing this broader context prompts the exploration of more universal explanations for aging that transcend the constraints of evolutionary theories. Beyond overarching concepts, there is a crucial need to explore empirical regularities in aging and mortality, often referred to as mortality laws. This pursuit aims to provide a comprehensive understanding of aging phenomena that goes beyond the scope of traditional evolutionary frameworks.

In this context, we examine the established mortality laws and regularities alongside recent advancements in the field of biodemography of aging. The existing patterns of mortality and aging are scrutinized through the lens of reliability theory. Additionally, this discussion encompasses the presentation of further developments in reliability models of aging, contributing to an enhanced understanding of the underlying mechanisms shaping the aging process.

MORTALITY LAWS IN THE BIOLOGY OF AGING AND LIFESPAN

To gain a more precise understanding of the mechanisms behind an organism's decline, we can explore mortality patterns frequently referred to as mortality laws. Here we assume definition of aging applied in reliability theory, which considers aging as a process leading to increasing risk of death with age [9]. In ecology this process is also called an actuarial senescence [10].

The Gompertz–Makeham law. In 1825, the British actuary Benjamin Gompertz unveiled a principle of mortality, now recognized as the Gompertz law [2, 11-13]. According to the Gompertz law, human mortality rates double approximately every 8 years of adult age:

$$\mu(x) = Re^{\alpha x}, \quad (1)$$

where x is age, R and α are parameters (Gompertz intercept and Gompertz slope, since Gompertz law represents a straight line in semi-log coordinates).

An exponential (Gompertzian) increase of mortality rates with advancing age is observed across various biological species, encompassing fruit flies [2, 14], flour beetles like Tribolium confusum [2], mice [14, 15], baboons [16, 17], and others. Most importantly, this law describes mortality of humans [2, 11-14, 18, 19].

In reality, organisms' hazard rates can encompass both non-aging and aging components, as seen in the Gompertz–Makeham law of mortality [2, 11, 13, 19, 20]:

$$\mu(x) = A + Re^{\alpha x}. \quad (2)$$

Within this equation, the initial, age-independent term (known as the Makeham parameter, "A") signifies the constant, "non-aging" facet of the hazard rate, presumably stemming from external causes of death, such as accidents and acute infections. In biodemography this constant term is called background mortality [2]. The subsequent, age-dependent term (the Gompertz function, $Re^{\alpha x}$) represents the "aging" component, presumably arising from age-related degenerative diseases like cancer and heart disease. This aging-related term received the name of senescent mortality [21]. Carnes and Olshansky proposed another way to classify total mortality using causes of death. Mortality from external causes of death and infections they called an extrinsic mortality while mortality from aging-related causes they called an intrinsic mortality [22]. Thus, extrinsic and intrinsic types of mortality may both depend on age. It is important to note that the slope coefficient α characterizes an "apparent aging rate," indicating the speed of age-related deterioration in mortality. If α equals zero, there is no apparent aging, which means that death rates remain constant with age.

Some authors have proposed a generalized form of the Gompertz–Makeham law (GGM) [23]. In this alternative perspective, the exponent, indicative of stress resistance, is considered to be a function beyond a linear form. The Makeham term, traditionally treated as a constant, is redefined to be associated with mortality resulting from inherently irresistible stresses and depends on age. This departure from the standard Gompertz–Makeham law introduces a more flexible approach to modeling mortality [23].

For technical systems one of the most popular models for failure rate of aging systems is a Weibull

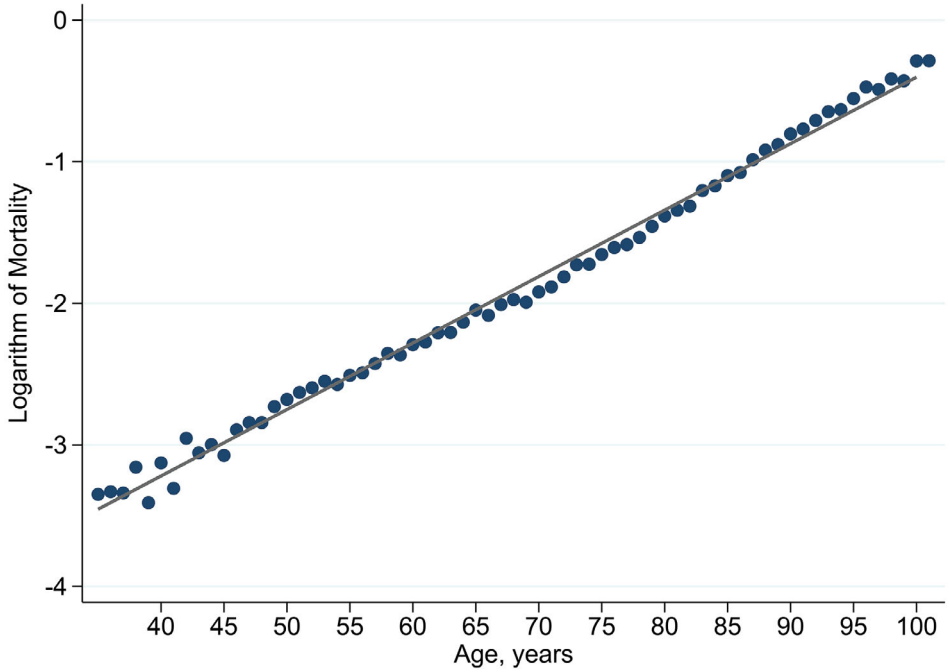

Fig. 1. Mortality of Norwegian women in 2010 in semi-log scale and its linear fit according to the Gompertz law. Data source: Human Mortality Database (www.mortality.org).

model, the power-function increase in failure rates with age [2]:

$$\mu(x) = \alpha x^{\beta} \text{ for } x \geq 0, \text{ where } \alpha, \beta > 0. \quad (3)$$

The Weibull law, proposed by Swedish engineer and mathematician W. Weibull in 1939 to describe the strength of materials, is widely employed in characterizing the aging and failure of technical devices [9]. It has also found occasional application in the study of a limited number of biological species including nematodes *C. elegans* [24-26]. According to the Weibull law, the logarithm of failure rates exhibits a linear increase with the logarithm of age.

A comparative meta-analysis of 129 life tables for fruit flies and 285 life tables for humans demonstrated that the Gompertz law of mortality offers a more accurate fit to the data for each of these two biological species compared to the Weibull law [2].

While working with human data it was found that mortality of women in semi-log scale demonstrated slightly more concave trajectory than predicted by the Gompertz model and mortality of men was somewhat more convex [2]. Similar deviations from the Gompertz law were observed by other researchers [27]. Further analyses of local estimates of the Gompertz slope using life table aging rate (LAR) found increase of LAR after age 60 mostly among women [28, 29]. Recently acceleration of LAR after age 60 was found for both men and women and for period and cohort mortality using contemporary data [30]. Despite these small deviations Gompertz law describes mortality remarkably well (see Fig. 1). There are indeed small fluctuations of mortality around the main Gompertz trajectory whereas the general direction of mortality line remains stable. In humans the Gompertz model fits both period and cohort data [31, 32].

In addition to the commonly used Gompertz and standard two-parameter Weibull laws, another mortality law known as the binomial law of mortality has been proposed and theoretically justified through the lens of system reliability theory [2, 9]. This particular law is considered a special case of the three-parameter Weibull function. Notably, it incorporates a negative location parameter, offering a nuanced perspective on the dynamics of mortality and aging within the framework of reliability theory:

$$\mu(x) = \alpha (x_0 + x)^{\beta}. \quad (4)$$

In this equation, the parameter x_0 is referred to as the initial virtual age of the system [2, 9, 33]. This parameter, measured in units of time, represents the age at which an initially ideal system would accumulate damage equal to those of a real system at the starting age ($x = 0$).

When a system is in its undamaged state with an initial virtual age of zero, the mortality rate adheres to a power function of age, consistent with the characteristics outlined in the Weibull law. However, as the initial damage load accumulates, there is a deviation from the Weibull law. This departure becomes more

pronounced with increasing levels of initial damage load, eventually leading to a transition where the failure dynamics align with the quasi-Gompertz mortality law [9].

Compensation law or compensation effect of mortality. Another empirical finding, known as the compensation law or compensation effect of mortality (CEM), in its strong form pertains to mortality convergence at older ages. This is when higher values for the slope parameter α (in the Gompertz function) are offset (compensated) by lower values of the intercept parameter R in different populations of a specific species:

$$\ln(R) = \ln(M) - B\alpha, \quad (5)$$

where B and M represent species-specific constants.

This relationship is occasionally referred to as the Strehler–Mildvan correlation [13, 34], although this correlation was significantly affected by biases in parameter estimation arising from neglecting the age-independent mortality component, the Makeham term A [2, 20]. Parameter B is called the species-specific lifespan, and parameter M is called the species-specific mortality rate [2, 9, 35]. Recent estimates of parameters B and M using data for contemporary human populations showed that these estimates remain rather stable over time [31, 32]. These parameters represent the coordinates where all mortality trajectories converge into a single point when extrapolated using the Gompertz function [2]. This signifies that in disadvantaged populations within a specific species, high mortality rates are compensated for by a slower apparent "aging rate" (resulting in a longer mortality doubling period). As a consequence of this compensation, relative differences in mortality rates have a tendency to decrease with age within a given biological species.

The term "Compensation Effect of Mortality" was introduced in 1978 when incorporating the Makeham parameter yielded substantially different parameter estimates for the Strehler–Mildvan correlation [35]. This effect is defined by the convergence of senescent (age-dependent) mortality patterns at advanced ages [2, 35]. CEM is observed not only for humans but for some other species [2, 36, 37].

There were assertions that the Strehler–Mildvan correlation arises as a statistical artifact of spurious correlation between the estimates of the Gompertz parameters and does not exist in reality [38]. Nevertheless, even when controlling for collinearity, the correlation coefficients between the Gompertz parameters experience only a modest reduction, yet the core correlation remains intact [31]. Furthermore, it is worth noting that the convergence of mortality trajectories in a semi-logarithmic scale (CEM) at older ages can be observed independently of the estimation of the Gompertz parameters [31, 32]. Also, in human populations CEM is observed for both period and cohort data on mortality [31, 32].

As mortality convergence is approached, a decrease in the relative variation of mortality is expected. Consequently, we anticipate a decline in the relative variation of mortality, assessed through metrics like the coefficient of variation and the standard deviation of the log of mortality, as the convergence point corresponding to the species-specific lifespan is reached. This theoretical prediction will be subject to validation in upcoming studies.

Late-life mortality deceleration. At more advanced ages (beyond age 70 in humans), sometimes a phenomenon known as "old-age mortality deceleration" occurs, wherein death rates increase with age at a slower pace than expected based on the Gompertz law [2, 21, 39-41]. Some biologists called this cessation of mortality growth (non-aging state) "a revolution for aging research" [42], although for humans it was known by actuaries since the Gompertz times. This deceleration in mortality ultimately leads to "late-life mortality leveling-off" and "late-life mortality plateaus" at extremely old ages [2, 43, 44].

Actuaries, including Gompertz himself, were among the first to observe this phenomenon. They proposed a logistic formula to model the age-related increase in mortality, aiming to address the decrease in mortality growth at advanced ages.

Figure 2 illustrates mortality deceleration at older ages using an example of mortality for cohort of U. S. women born in 1886. Note that after age 90 years the observed mortality deviates from the Gompertz law in this particular case.

In humans mortality deceleration is almost always observed for cross-sectional data. In the case of cohort data, there is no consensus on the pattern of late-life mortality trajectories. Earlier studies suggested that mortality after age 80 displayed a slower increase with age compared to the exponential Gompertz law. This deceleration in mortality at advanced ages was observed in both cohort and period data for various countries [21]. However, for U. S. cohort data, it was revealed that mortality adheres to the Gompertz law within wide age range of 80-106 years [45, 46]. Similar results were recently obtained using French cohort data [47]. Other scholars have found that the extent of mortality deceleration varies among different countries [48, 49]. The primary issue with these studies was the attempt to deduce the existence of only one conceivable mortality trajectory shape. Recently the existing controversy about the shape of mortality at advanced ages was resolved by studying long series of U. S. cohort data. It turns out that mortality of earlier birth cohorts (born before 1887) always demonstrates mortality deceleration. On the other hand, later birth cohorts follow the Gompertz law up to ages 105-106 years [50].

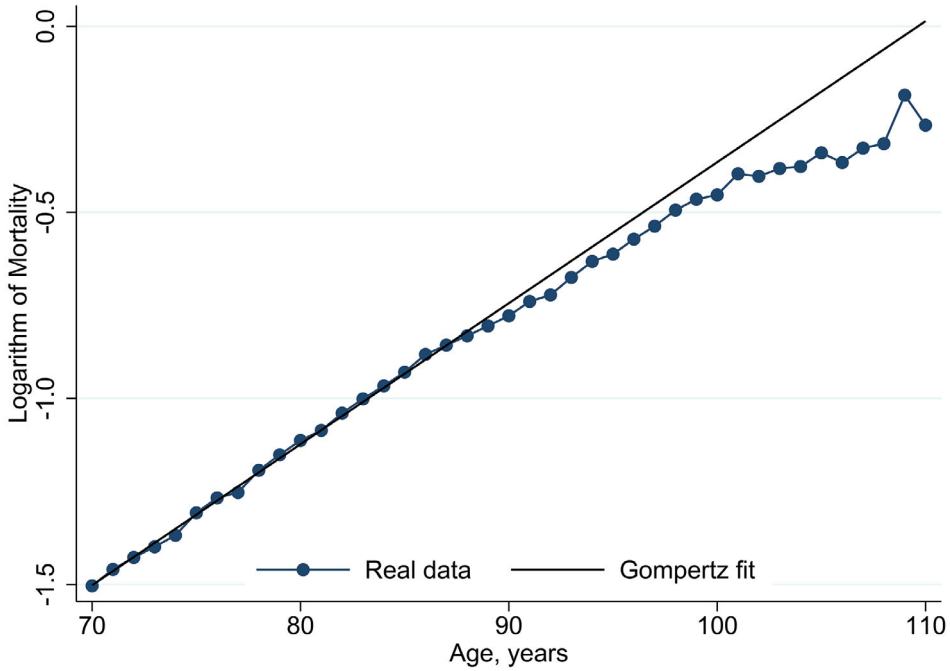

Fig. 2. Mortality deceleration for cohort of U. S. women born in 1886. Data source: Human Mortality Database (www. mortality.org).

This trend called gompertzialization of mortality trajectory is observed in other countries as well, although with slower pace [51].

EXPLORING FURTHER ASPECTS OF AGING

As widely recognized, the aging phase constitutes a substantial portion of the lifespan of many species, necessitating that any mortality model offer an explanation for this extended period of life. For modeling the aging process, it is important to take into account some additional age-related phenomena.

Similarity between mortality of biological and technical systems. A notable parallel exists between living organisms and technical devices in their age-related mortality patterns, often following what's known as the "bathtub curve". [9]. This curve comprises three distinct periods. Initially, mortality rates are high and gradually decline with age, referred to as the "working-in" period or the phase of "burning-out" defective components. A similar early period, known as "infant mortality," can be observed in most living organisms, including humans. Following this, there is the "normal working period," characterized by relatively low and stable failure rates. While this period exists in humans as well, it tends to be relatively short, lasting approximately 10-15 years before transitioning to the third period known as "the aging period." During this phase, mortality rates increase inexorably with age, following an explosive exponential trajectory, akin to the Gompertz curve. For humans, this aging period typically spans from around 20 to 100 years. This similarity in mortality patterns between technical and biological systems is further emphasized by the presence of a fourth common period at extremely advanced ages. This phase is recognized in biology as "late-life mortality leveling-off" and is also observed in technical systems [52].

Keeping in mind this similarity in the phases of age-specific mortality between biological and technical systems, Siler suggested an empirical equation that described mortality of biological organisms during the entire life period [53]. This equation considers three mortality terms. The first term describes mortality decline with age after birth and can be described by declining exponential function. Two other terms are represented by already known background and senescent mortality. The minimum of mortality around age 10 received lately an attention from researchers. It turns out that the minimum of mortality measured in period data looks very narrow while for cohort data mortality may be flat for much longer period. This long period of almost flat mortality was called a "quiescent phase" [54] and was observed for cohorts born around the 1920s (Fig. 3).

This phenomenon serves as a clear example of an almost zero apparent (actuarial) aging rate, arising from the counteracting influences of two opposing forces that offset one another: the mitigating effect of mortality reduction (attributable to advancements in healthcare and improved living conditions) and the inexorable force of aging [32]. Figure 3 shows that mortality at age 10 for 1920th cohort is almost the same as at ages

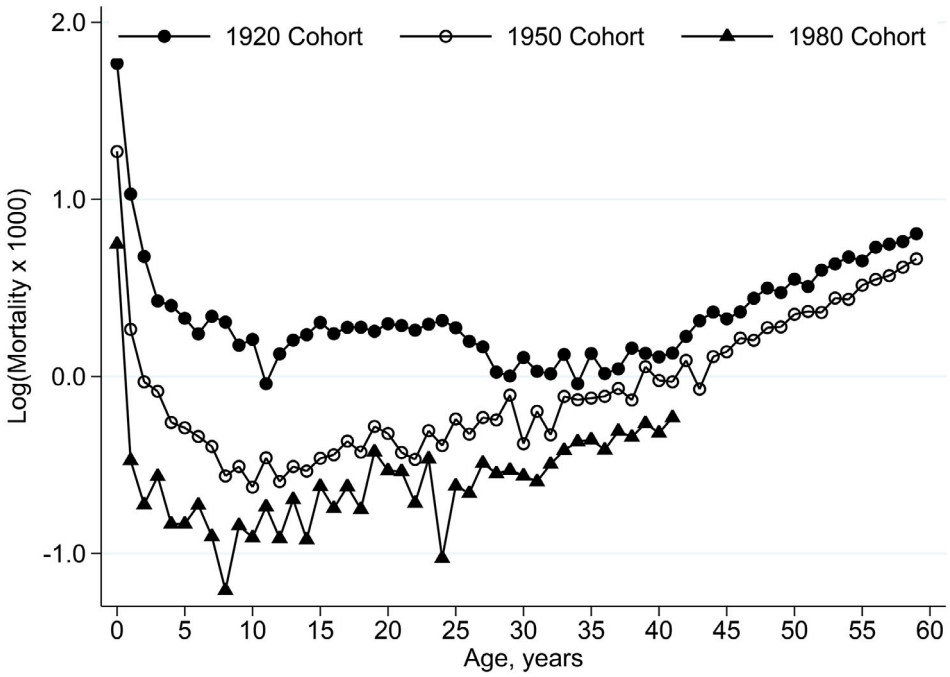

Fig. 3. Mortality for selected Swedish female birth cohorts. Data source: Human Mortality Database (www.mortality.org).

30-40 years, so that there is no clear minimum of mortality around ages 10-40 years. This phase looks like rather long "normal working period" in technical systems, but is rather a result of declining mortality due to healthcare achievements and improvement of living conditions [51].

The authors of the original study of quiescent phase limited their analysis by extinct cohorts only [54]. However, mortality at younger ages can be studied for more recent birth cohorts. Figure 3 shows that for 1950 and 1980 birth cohorts mortality is not flat and slowly increases with age. It also looks like the position of mortality minimum is shifting to younger ages over time. When mortality from infectious diseases was mostly eradicated and historical mortality decline slowed down, the quiescent phase practically disappeared and mortality started to grow from very young ages (8-12 years) without visible hump. It should be noted that we use here data for women in order to avoid substantial external mortality due to social factors, which is common for men at ages 18-25 years. Figure 3 shows that mortality for more recent birth cohorts can be described by two rather than three phases with disappearing the "normal working period" or quiescent phase.

The concept of high initial damage load. In 1991 it was suggested that early developmental processes in living organisms generate an exceptionally high load of initial damage, comparable in magnitude to the subsequent accumulation of age-related deterioration throughout the entire adult lifespan [2]. While this concept, known as the High Initial Damage Load (HIDL) hypothesis [55], may appear counterintuitive, it aligns with empirical observations of developmental noise and substantial cell losses during early development [56]. Recent advancements in molecular developmental biology have recognized the stochastic nature of development, often referred to as "developmental noise." This phenomenon has the potential to induce phenotypic heterogeneity even in the absence of any other alterations in genes or the environment [57]. In a human body, approximately a hundred thousand cells are generated every second through mitosis, and a comparable number undergo a physiological suicide process known as apoptosis. A significant portion of cells produced during mammalian embryonic development experiences physiological cell death before the conclusion of the perinatal period [58]. Significant cell losses during early development create conditions for the uneven distribution of organisms based on the number of remaining cells, which can be modeled using the binomial or even the Poisson distribution. [2].

The idea of high initial damage of biological systems recently received a further development. It was found that the mortality and incidence of age-related diseases exhibit a U-shaped curve, with the minimum occurring before puberty. However, quantitative biomarkers of aging, such as somatic mutations and DNA methylation, do not follow this pattern and continue to increase starting from birth or even before birth [59]. It was suggested that aging initiates early but is concealed by early-life mortality decline. According to this idea aging may be represented by the growth of the sum of deleterious changes, the deleteriome [59, 60].

The concept of a high initial damage load also suggests that events occurring early in life can impact survival in later adulthood through the level of initial damage. This prediction has been substantiated for early-life indicators like parental age at a person's conception and the month of a person's birth [61-66]. There is an increasing body of evidence supporting the notion of fetal origins of adult degenerative diseases [67, 68] and the early-life programming of aging and longevity [55, 69-71].

Loss of functional elements in an organism over its lifespan. Aging is characterized by a progressive loss of functional tissue influenced by a combination of genetic and environmental factors, nutrition, and lifestyle choices [72, 73].

The accumulation of damage in various cellular structures, coupled with the loss of fully differentiated and irreplaceable cells like neurons and cardiomyocytes, should be considered as irreversible. If these irreplaceable components of an organism age and eventually perish, it follows that the organism as a whole will experience aging as well. This emphasizes the critical role of cellular damage and the loss of vital components in the overall aging of organisms [74].

Cell death mechanisms have traditionally been categorized into two types: programmed cell death (PCD) mechanisms, which require energy, and necrotic cell death mechanisms, which do not [73, 75]. The increased occurrence of PCD during aging is implicated in the decline of the immune system, skeletal muscle wasting (sarcopenia), loss of cells in the heart, and neurodegenerative diseases. Throughout the aging process, several tissues experience cell loss attributed to either PCD or PCD-like processes. In mammals, there is an aging-associated skeletal muscle atrophy known as sarcopenia, characterized by reductions in muscle fiber size and fiber loss [73]. Necroptosis, a regulated form of cell death, plays a role in the genesis and progression of various life-threatening diseases, including cancer, neurological disorders, cardiac myopathy, and diabetes [73].

Research indicates a decline in the numbers of specialized cells with age, including a significant reduction in nephrons in healthy human kidneys with aging. Comparing the youngest (18-29 years) and oldest (70-75 years) age groups, there was a 48% decrease in the number of nonsclerotic glomeruli, while cortical volume only decreased by 16% [76].

While there is substantial knowledge about specific molecular mechanisms of cell death [77], the age-specific loss of cell numbers is less explored and is presented in a limited number of publications [78-80]. Existing studies have uncovered the possibility that some cells within the aging organism may exhibit nonaging characteristics. Notably, in a diverse spectrum of aging-related neurodegenerative conditions (18 diverse examples of inherited and acquired neurodegeneration including Parkinson's disease), the rate of neuronal death does not increase with age [79, 81, 82]. Neurons in different parts of brain of cognitively healthy humans show constant rate of atrophy with age [83]. These findings align with the observation that "an impressive range of cell functions in most organs remain unimpaired throughout the life span" [11], p. 425. Therefore, the current understanding of the kinetics of cell loss with age indicates that an exponential distribution (with constant mortality) is a plausible approximation for the mechanism of loss in vital elements, such as functional cells or telomeres.

EXPLAINING MORTALITY LAWS THROUGH THE LENS OF RELIABILITY THEORY

There is a whole spectrum of models attempting to explain the observed mortality phenomena. Heterogeneity models were among the first models attempting to explain human aging and mortality and became popular after the pioneer publication by Beard in 1959 [84]. These models assume exponential increase for baseline risk of death. Heterogeneity in these models is introduced usually by postulating gamma distribution of individual risks [85-87]. Heterogeneity models are famous for explaining late-life mortality deceleration and mortality plateau as a result of mortality selection. However, the exponential growth of mortality risk with age is postulated in these models in advance. Thus, it would be more interesting to consider a model, which can use organism's structure and properties to derive the observed empirical mortality regularities.

It is noteworthy that the phenomena of increasing mortality with age, followed by a plateauing of mortality rates, are inherently anticipated features of reliability models that conceptualize aging as the progressive accumulation of damage or loss of vital elements with age [2, 9, 33]. Reliability models of aging presented in more detail earlier [2, 33] consider living organism as a system with series-parallel reliability structure. In a system of n independent components connected in series, the entire system fails if any one of the components fails. This means that the reliability of the system is contingent on the reliability of each individual component in series. It is clear that human organs like heart, brain or liver can be considered as vital components connected in series because failure of any of these organs leads to organism's death. On the other hand, in a parallel system of n independent components, the system fails only when all the components simultaneously fail. In this configuration, the system remains operational as long as at least one of the parallel components continues to function, providing a redundancy that enhances overall system reliability.

It is also clear that functional cells in each vital organ can be considered as components connected in parallel, although in real organs the threshold for normal functioning may be higher than one element (cell). Thus, reliability models in the context of living organisms consider the inherent functional structure and dynamics of biological systems. These models acknowledge and incorporate observed processes, such as the loss of functional cells with age. This approach helps in understanding the intricate relationships between different elements within biological systems and their impact on overall mortality.

Consider a parallel system comprising n non-aging elements, each characterized by a constant failure rate denoted as μ and a reliability (survival) function expressed as $e^{-\mu x}$ [9]. In such a scenario, the reliability function for the entire parallel system can be described as:

$$S(x) = 1 - (1 - p)^n = 1 - (1 - e^{-\mu x})^n. \quad (6)$$

This equation applies to the most straightforward scenario where the failures of individual elements are statistically independent. As a result, the failure rate of the entire system, denoted as $\mu_s(x)$, can be expressed in the following manner:

$$\mu_s(x) = -\frac{dS(x)}{S(x)dx} = \frac{n\mu e^{-\mu x}(1 - e^{-\mu x})^{n-1}}{1 - (1 - e^{-\mu x})^n}, \quad (7)$$

$\approx n\mu^n x^{n-1}$ when $x \ll 1/\mu$ (early-life period approximation, when $1 - e^{-\mu x} \approx \mu x$);
$\approx \mu$ when $x \gg 1/\mu$ (late-life period approximation, when $1 - e^{-\mu x} \approx 1$).

Hence, the system's failure rate initially exhibits growth in accordance with an age-dependent power function (following the Weibull law). According to this model, systems with varying initial redundancy levels (parameter *n*) will display distinct failure rates in early stages, but these differences will diminish over time as the rates converge toward the upper limit determined by the rate of elements' loss (parameter μ). Consequently, the expected outcome of this model aligns with the compensation law of mortality (in its weak form).

The failure rate of a simple parallel system composed of non-aging elements exhibits an increase with age, contrary to the Gompertz law, with the initial failure kinetics following the Weibull law. This deviation from the Gompertz law arises from the model's assumption that the system is constructed with initially ideal structures, where all elements are functional from the outset. This limitation highlights the importance of considering real-world scenarios where components may not be flawless initially and may experience variations in functionality over time, influencing the overall failure kinetics of the system. In order to obtain the quasi-Gompertz mortality growth we need to consider models with distributed redundancy.

It is important to highlight that reliability models align seamlessly with evolutionary models, including the concept of programmed death. The accrual of damage might follow a stochastic process, whereas the parameters governing this damage, such as the initial redundancy level and the rate of damage, could be preprogrammed. Evolutionary models elucidate why organisms are constructed with distinct properties, while reliability models specifically elucidate the process of deterioration itself, which may be considered as slow or chronic phenoptosis [71, 88].

Reliability model of initially homogeneous population. The model, which was published earlier [33] examined a scenario where blocks (e.g., specific organs) within each organism exhibit varying degrees of redundancy, while the organisms themselves are initially considered initially identical to each other and share an equal risk of death. This assumption can be justified in the following cases [2]:

1. Population homogeneity may occur when a rigid genetic program determines the initial degree of redundancy for each block (organ) in the organism. This situation may occur in the course of programmed cell death during early development. In this case, the variability in block redundancy is not entirely random, and the homogeneous models are applicable because the genetically programmed distribution of blocks according to their redundancy can be approximated by the Poisson or binomial distribution.

2. Organisms may have nearly identical initial distributions of the number of blocks with different redundancy levels, even when the redundancy formation mechanism is random. This occurs when the number of irreplaceable (vital) blocks is very large. Consequently, the population is practically homogeneous in terms of the risk of each organism dying, despite potential heterogeneity in the risk of failure of individual blocks.

The simplest model within this family of reliability models is the series-parallel structure with distributed redundancy within the organism. This model as outlined in [33] considers the distribution of subsystems based on initially functional elements, described by the Poisson law due to a high initial damage load. In such systems, the failure rate can be initially approximated by the exponential (Gompertz) law, with subsequent mortality leveling-off [33]. In systems with lower damage levels, where initially functional elements follow a binomial distribution, the failure rate experiences initial growth in line with the binomial law [2].

It is worth noting that there have been allegations of errors in this straightforward model [89]. However, it is important to point out that the authors failed to acknowledge that this model was designed for a homo-

geneous population and improperly recommended the use of a formula tailored to a heterogeneous population [89].

One interesting conclusion from the model of initially homogeneous population is related to the opportunity of estimating the rate of vital elements loss in human organism or true aging rate. This rate is approximately equal to the inverse of the species-specific lifespan [1/B, B comes from equation (5)]. It was found that the estimated species-specific lifespan is stable over time and is equal to 95-97 years [2, 31]. Thus, the estimated rate of loss of vital elements is approximately equal to 1% per year. It is interesting that this rate is consistent with the empirical estimates of annual cell loss in several neural tissues – 0.6-1.6% [78]. Empirically estimated rate of telomere loss in peripheral blood mononuclear cells in humans is somewhat lower – 0.5% base pairs per year [90], but still is of similar magnitude. It was found that the rate of telomere loss is a species-specific trait and is proportional to the lifespan of animal species [90].

Reliability model of heterogeneous population. Accounting for population heterogeneity leads us to another model, which provides an explanation for all the basic mortality laws, even in the simplest case where the organism comprises a single vital block with n elements.

The model considers the simplest case when the organism consists of a single vital block with n elements connected in parallel with q being the probability that an element is initially functional. Then the probability of encountering an organism with i initially functional elements out of a total number n of elements is given by the binomial distribution law.

The final formula for failure rate in heterogeneous population, $\mu_p(x)$, is (see [2] for more detail):

$$\mu_p(x) = -\frac{F'(x)}{1 - F(x)} = \frac{nq\mu e^{-\mu x}(1 - qe^{-\mu x})^{n-1}}{1 - (1 - qe^{-\mu x})^n}, \quad (8)$$

$\approx Cnq\mu\,(1 - q + q\mu x)^{n-1}$ for $x \ll 1/\mu$;
$\approx \mu$ for $x \gg 1/\mu$,
where C is a normalizing factor.

Thus, the hazard rate of a heterogeneous population at first grows with age according to the binomial law of mortality, then asymptotically approaches an upper limit μ:

$$\mu_p(x) \approx Cn(q\mu)^n \left[\frac{1 - q}{q\mu} + x\right]^{n-1} = Cn(q\mu)^n (x_0 + x)^{n-1}, \quad (9)$$

for $x \ll 1 / \mu$
$\mu_p(x) \approx \mu$ for $x \gg 1 / \mu$
where $x_0 = (1 - q) / q\mu$, a parameter which is called the initial virtual age of the population. This parameter has the dimension of time, and corresponds to the age by which an initially homogeneous population would have accumulated as much damage as a real population actually possesses at the initial moment in time (at x = 0). In particular, when q = 1, i.e., when all the elements in each organism are functional at the outset, the initial virtual age of the population is zero and the hazard rate of population grows as a power function of age (the Weibull law). However, when the population is not initially homogeneous (q < 1), we arrive at the already mentioned binomial law of mortality. Thus, the heterogeneous population model described here can also provide a theoretical justification for the binomial law of mortality.

Heterogeneity model also addresses the compensation effect of mortality. The compensation effect of mortality is evident when variations in mortality result from differences in the number of elements in the organism (n) between populations, while other parameters, including the true aging rate (μ), remain nearly identical for all populations of the same species [2, 9].

Figure 4 illustrates Gompertz, binomial and Weibull models fitting mortality of Norwegian women born in 1920. In the case of binomial model, it is assumed that every block (e.g., vital organ) has on average 50 vital elements and the initial virtual age (indicator of initial damage load) estimated using nonlinear regression method is equal to 370 years. Note that binomial model fits mortality data almost as well as the Gompertz model with similar values of Akaike Information Criterion of goodness of fit (-466 and -462 respectively) while Weibull model significantly underestimates mortality at younger ages (see Fig. 4). It is important to note that extrinsic mortality below the age of 60 years is significant. However, adjusting for extrinsic mortality using the Gompertz–Makeham model becomes challenging due to the variation of Makeham term over time in cohort data. Thus, even this simplified heterogeneity model is able to fit aging-related mortality of humans.

In summary, the model of a heterogeneous population provides an explanation for the regularities of organism mortality: the initial quasi-exponential growth in the hazard rate, followed by mortality deceleration, along with the compensation effect of mortality as follows from the model formulas [2].

The heterogeneous population model shares basic conclusions with the initially homogeneous model of series-connected blocks with varying degrees of redundancy [33]. However, these are two distinct models. In the first model, individual mortality risk is uniform across all organisms and grows exponentially with age. In the second model, there initially exist n subpopulations of living organisms with differing death risks that increase as a power function rather than exponentially with age.

The fact that these two different models yield nearly identical interpretations of certain mortality phenomena offers some reason for optimism. For instance,

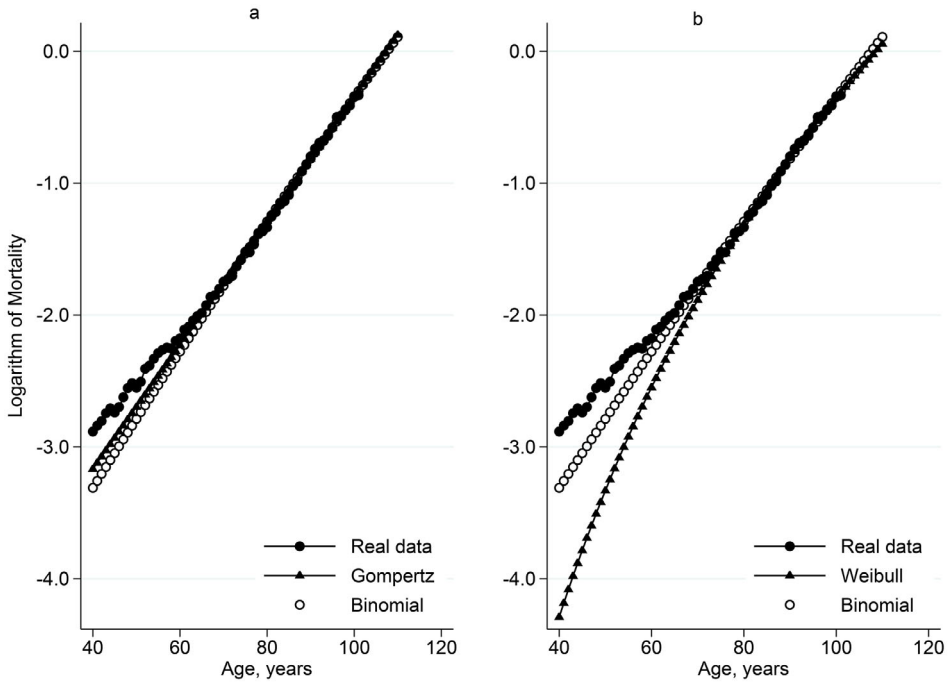

Fig. 4. Fitting mortality of Norwegian women born in 1920 by binomial law and competing Gompertz (a) and Weibull (b) laws. Data source: Human Mortality Database (www.mortality.org).

the compensation effect of mortality is a common feature of all these models, occurring only when the rate of irreversible age changes (true aging rate) remains constant within a species. This treatment of the compensation effect of mortality is not unique to the models discussed here, as it is consistent with other models as well [34, 35, 91, 92]. The existence of various competing models does not hinder the reliable and meaningful interpretation of many mortality phenomena, as multiple models can reach agreement on several aspects.

Further developments of reliability models. We would like to mention here several studies developing reliability models further. One of the first reliability models of aging was suggested in 1978 and was based on the phenomenon of linear decline in the function or cells over time [91]. This simple model could explain the Gompertz law, CEM and late-life mortality plateau. This approach was developed further by Milne who created "nested binomial" model also explaining existing mortality regularities [93]. These models explained mortality in terms of probability of dying and did not consider organism's structure.

Laird and Sherrat extended the approach of applying reliability theory to aging of biological systems described above by considering three alternative types of element/genetic architecture [94]. In addition to the "Parallel" model, they also presented a "Series" model and a third type of model – a "Cascade" model, analogous to the multi-stage model of disease progression in which irreparable damage occurs in a strict sequence. They showed that redundancy leads to actuarial senescence in the Parallel and Cascade models but not in the Series model. Finally, the authors attempted to add evolutionary dynamics to their reliability model and found that a population's equilibrium redundancy is sensitive to the environmental conditions that prevailed during its evolution, such as the rate of extrinsic mortality [94]. For some reason, the authors did not consider a series-parallel reliability model while only this model is close to the real organism's structure where vital organs are connected in series and specialized cells in each organ are connected in parallel. The authors do not attempt to fit their models to real data, so it is difficult to check the model value.

Another model is able to explain all three mortality regularities mentioned above. This is a simple mathematical model combining the heterogeneity of populations with an assumption that the mortality in each subpopulation grows exponentially with age [95]. It has been proven that this model is capable of reproducing the entire mortality pattern in a human population including the observed peculiarities at early- and late-life intervals. The authors found that the evolution of the model parameters validates the applicability of the compensation law of mortality to each subpopulation separately. This study has indicated that the population structure changes so that the population tends to become more homogeneous over time [95].

In a separate study, the authors systematically examined the practical utility of redundancy models for investigating the mechanisms of aging in a quanti-

tative manner [96]. The authors analyzed predictions of the reliability model of homogeneous population described in the previous section [33]. They showed that redundancy models fit the data well and argue that this is a strength of redundancy models over non-mechanistic models because (i) when contrasting aging patterns can be understood within the framework of a single mechanistic model this indicates that the model may capture the essence of the aging process, and (ii) redundancy parameter inference may teach us something about the underlying mechanisms and can as such be used to develop new hypotheses [96].

In summarizing it can be concluded that reliability models of aging continue to be developed further and are able to explain existing mortality regularities outlined earlier.

CONCLUDING REMARKS

In this article, we examined various empirical phenomena associated with the aging process and introduced new insights into describing patterns of mortality using reliability theory concept.

A substantial body of research on aging has yielded a multitude of important and varied discoveries, prompting the need for a unified theoretical framework to consolidate this wealth of knowledge. Evolution-based theories of aging, grounded in the concept of diminishing natural selection with advancing age, demonstrate the practical applicability of broad theoretical principles in the field of aging research [97-99]. V. P. Skulachev has played a significant role in advancing evolutionary concepts. His contributions have been instrumental in shaping contemporary perspectives on aging, suggesting the presence of a specific program or mechanism that influences the aging process. Skulachev's work has added depth to the exploration of evolutionary theories, challenging traditional views and paving the way for further investigations into the molecular and genetic aspects of aging. He posited that if aging is indeed programmed, it could be delayed, prevented, or potentially reversed through interventions that disrupt the execution of this program, similar to our ability to intervene in cell death programs [5, 100]. His perspectives have generated numerous hypotheses characterizing aging as a programmed process.

In this article, our aim was to offer a more comprehensive explanation of aging as a process of deterioration, extending beyond reproductive species, through the application of the general systems failure theory known as reliability theory. This approach aligns seamlessly with evolutionary theories, including those related to programmed aging, when considering aging as a chronic phenoptosis. It became evident that redundancy plays a central role in understanding aging, particularly within a systemic framework. Systems that incorporate redundancy in essential components inevitably undergo degradation (i.e., aging) over time, even if constructed from elements that do not age. Redundancy has a dual impact, enhancing damage tolerance to reduce mortality and extend lifespan, while also allowing the accumulation of damage, thus giving rise to the aging phenomenon.

Systems with higher redundancy levels exhibit a higher apparent aging rate or expression of aging, all else being equal. This insight offers valuable perspective on the observation of negligible senescence in certain environments, revealing that some cases of negligible senescence may be attributed to a lack of system redundancies. For example, birds exhibit long lifespans compared to their weight and low actuarial aging rate (negligible senescence). However, they have relatively high mortality at younger ages suggesting low level of redundancy (cell reserves) [9]. On the other hand, complex, redundant systems designed for greater durability may exhibit more pronounced expressions of aging.

Throughout their lifespans, organisms deplete their cells and reserve capacity, providing a potential explanation for phenomena such as the CEM, mortality convergence in older ages, late-life mortality deceleration, leveling-off, and mortality plateaus. Organisms appear to start their lives with an initial load of damage [55, 59], and their lifespan and aging patterns can be sensitive to early-life conditions that determine this initial damage load during development. This concept of early-life programming has potential implications for interventions aimed at promoting health and longevity.

Aging is an intricate phenomenon, and adopting a holistic approach, incorporating reliability theory, may assist in analyzing, comprehending, and potentially managing it. Today, gerontologists realize that a top-down systemic approach is necessary to fully understand and explain the phenomenon of aging [1].

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Contributions. Leonid A. Gavrilov designed the study, analyzed and interpreted results, and edited the manuscript. Natalia S. Gavrilova conducted statistical analyses and prepared the manuscript.

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