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The Quest for the General Theory of Aging and Longevity

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Abstract

Extensive studies of aging phenomenon have produced many important and diverse findings, which require a general theoretical framework for them to be organized into a comprehensive body of knowledge.

As demonstrated by the success of evolutionary theories of aging, based on a general idea of the declining force of natural selection with age, quite general theoretical considerations can in fact be very useful and practical when applied to aging research.

In this study, we attempt to go one step further in the search for a general explanation of aging by applying a general theory of systems failure known as reliability theory.

Considerations of this theory lead to the following conclusions:

(1) *Redundancy* is a key notion for understanding aging and the systemic nature of aging in particular. Systems, which are redundant in numbers of irreplaceable elements, do deteriorate (i.e., age) over time, even if they are built of non-aging elements.

(2) An apparent aging rate or expression of aging (measured as age differences in failure rates, including death rates) is higher for systems with higher redundancy levels.

(3) *Redundancy exhaustion* over the life course explains the observed 'compensation law of mortality' (mortality convergence at later life) as well as the observed late-life mortality deceleration, leveling-off, and mortality plateaus.

(4) Living organisms seem to be formed with a high *load of initial damage*, and therefore their lifespans and aging patterns may be sensitive to *early-life conditions* that determine this initial damage load during early development. The idea of early-life programming of aging and

longevity may have important practical implications for developing early-life interventions promoting health and longevity.

The theory also suggests that aging research should not be limited to the studies of qualitative changes (like age changes in gene expression), because changes in *quantity* (numbers of cells and other functional elements) could be an important driving force of aging process. In other words, aging may be largely driven by a process of redundancy loss.

Finally we suggest adding the reliability theory to the arsenal of methodological approaches applied in aging research.

Keywords: aging theories, longevity, mortality laws, reliability theory, Gompertz law, Weibull law, oldest-old mortality, compensation law of mortality

1. Introduction

There is a growing interest in scientific explanations of aging and in the search for a general theory that can explain what aging is and why and how it happens.

There is also a need for a general theoretical framework that would allow researchers to handle an enormous amount of diverse observations related to aging phenomena. Empirical observations on aging have become so abundant that a special 4-volume encyclopedia, *The Encyclopedia of Aging*, is now required for even partial coverage of the accumulated facts (Ekerdt, 2002). To transform these numerous and diverse observations into a comprehensive body of knowledge, a general theory of species aging and longevity is required.

The prevailing research strategy now is to focus on the molecular level in the hope of understanding the proverbial nuts and bolts of the aging process. In accordance with this approach, many aging theories explain aging of organisms through aging of organisms' components. However, this circular reasoning of assuming aging in order to "explain" aging leads to a logical contradiction, because moving in succession from the aging of organisms to the aging of organs, tissues, and cells, we eventually come to atoms, which are known not to age.

Thus we come to the following basic question on the origin of aging: *How can we explain the aging of a system built of non-aging elements?*

This question invites us to start thinking about the possible systemic nature of aging and to wonder whether aging may be a property of the system as a whole.

In other words, perhaps we need to broaden our vision and be more concerned with the bigger picture of the aging phenomenon rather than its tiny details.

To illustrate the need for a broad vision, consider the following questions:

-- Would it be possible to understand a newspaper article by looking at it through an electronic microscope?

-- Would the perception of a picture in an art gallery be deeper and more comprehensive at the shortest possible distance from it?

Evolutionary perspective on aging and longevity is one way to stay focused on the bigger picture (see reviews in Le Bourg, 2001; Gavrilova and Gavrilov, 2002). Evolutionary explanations of aging and limited longevity of biological species are based on two major evolutionary theories: the mutation accumulation theory (Medawar, 1946) and the antagonistic pleiotropy theory (Williams, 1957). These two theories can be summarized as follows:

(1) Mutation accumulation theory: From the evolutionary perspective, aging is an inevitable result of the declining force of natural selection with age. For example, a mutant gene that kills young children will be strongly selected against (will not be passed to the next generation) while a lethal mutation that affects only people over the age of 80 will experience no selection because people with this mutation will have already passed it to their offspring by that age. Over successive generations, late-acting deleterious mutations will accumulate, leading to an increase in mortality rates late in life.

(2) Antagonistic pleiotropy theory: Late-acting deleterious genes may even be favored by selection and be actively accumulated in populations if they have any beneficial effects early in life.

Note that these two theories of aging are not mutually exclusive, and both evolutionary mechanisms may operate at the same time. The main difference between the two theories is that in the mutation accumulation theory, genes with negative effects at old age accumulate passively from one generation to the next while in the antagonistic pleiotropy theory, these genes are actively kept in the gene pool by selection (Le Bourg, 2001). The actual relative contribution of each evolutionary mechanism to species aging has not yet been determined, and this scientific problem is now the main focus of current research in evolutionary biology.

Evolutionary theories demonstrate that taking a step back from too close consideration of the details over "the nuts and bolts" of the aging process helps to gain a broader vision of the aging problem.

The remaining question is whether the evolutionary perspective represents the ultimate general theoretical framework for explanations of aging. Or perhaps there may be even more general theories of aging, one step further removed from the particular details?

The main limitation of evolutionary theories of aging is that they are most applicable to sexually reproducing organisms, because these theories are based on the idea of natural selection and on the declining force of natural selection with age.

However, aging is a very general phenomenon -- it is also observed in technical devices (like cars), which do not reproduce themselves in a sexual or any other way and which are, therefore, not subject to evolution through natural selection.

Thus, there may exist a more general explanation of aging, beyond mutation accumulation and antagonistic pleiotropy theories.

The quest for a general explanation of aging (age-related increase in failure rates), applicable both to technical devices and biological systems invites us to consider the general theory of systems failure known as reliability theory (Gavrilov and Gavrilova, 2001a).

2. General Overview of Reliability Theory Approach

Reliability theory is a body of ideas, mathematical models, and methods directed to predict, estimate, understand, and optimize the lifespan distribution of systems and their components (Barlow and Proschan, 1975; Gavrilov and Gavrilova, 2001a). The *reliability* of the system (or component) refers to its ability to operate properly according to a specified standard (Crowder et al., 1991). Reliability is described by the *reliability function* S(x), which is the probability that a system (or component) will carry out its mission through time x (Rigdon and Basu, 2000). The reliability function (also called the *survival function*) evaluated at time *x* is simply the probability *P*, that the *failure time X*, is beyond time *x*, designated as *P(X > x)*. Thus, the reliability function is represented in the following way:

$$S(x) = P(X > x) = 1 - P(X \leq x) = 1 - F(x). \qquad (1)$$

where *F(x)* is a standard *cumulative distribution function* from the probability theory (Feller, 1968). The best illustration for the reliability function *S(x)* is a survival curve describing the proportion of those still alive by time *x* (the l_x column in life tables). The *failure rate* $\lambda(x)$, also called the *hazard rate h(x)*, is defined as the relative rate for reliability function decline:

$$\lambda(x) = -\frac{dS(x)}{S(x)dx} = -\frac{d[\log_e S(x)]}{dx} \quad (2)$$

Failure rate is an equivalent to *mortality force, $\mu(x)$,* in demography and gerontology. When the failure rate is constant (i.e., does not increase with age), we have a *non-aging system* (component) that does not deteriorate (does not fail more often) with age. The reliability function of non-aging systems (components) is described by the *exponential distribution*:

$$\lambda(x) = \lambda = const \quad (3a)$$
$$S(x) = S_0 \exp(-\lambda x) \quad (3b)$$

This *failure law* describes the 'lifespan' distribution of atoms of radioactive elements, and it is also observed in many wild populations with high extrinsic mortality (Finch, 1990; Gavrilov and Gavrilova, 1991).

Non-aging behavior of a system can be detected graphically, when the logarithm of the survival function decreases with age in a linear fashion:

$$ln\ S(x) = ln\ S_0 - \lambda x \quad (3c)$$

Interestingly, the survival patterns of humans at extreme old ages (over 100 years old) are rather close to this linear dependence, suggesting that death rates, although very high, do not demonstrate further dramatic deterioration with age (Figure 1).

Figure 1 About Here

The same phenomenon of 'almost non-aging' survival dynamics at extreme old ages is detected in many other biological species including rodents (guinea pigs, rats, and mice) and invertebrates (nematodes, shrimps, bdelloid rotifers, *Drosophila*, *Campanularia Flexuosa*), – a phenomenon well known since the 1970s (Economos, 1979), but still presenting a theoretical challenge to many gerontologists. One interesting corollary from these intriguing observations is that there seems to be no fixed upper limit for individual lifespan (Gavrilov, 1984; Gavrilov and Gavrilova, 1991).

Interestingly, the failure kinetics of manufactured products (steel samples, industrial relays, and motor heat insulators) also demonstrates the same 'non-aging' pattern at the end of their 'lifespan' (Economos, 1979). This observation calls for a very general explanation of this apparently paradoxical 'no aging at extreme ages' phenomenon, which will be suggested in this article.

If failure rate increases with age, we have an *aging system* (component) that deteriorates (fails more often) with age. There are many failure laws for aging systems and the *Gompertz law* with exponential increase of the failure rates with age (Gompertz, 1825) is just one of them (see Gavrilov and Gavrilova, 1991). In reality, system failure rates may contain both non-aging and aging terms as, for example, in the case of the *Gompertz-Makeham law* of mortality (Makeham, 1860; Strehler, 1978; Gavrilov and Gavrilova, 1991):

$$\mu(x) = A + R \cdot \exp(\alpha x), \qquad \text{where parameters } A, R, \alpha > 0 \tag{4}$$

In this formula the first, age-independent term (Makeham parameter, A) designates the constant, 'non-aging' component of the failure rate (presumably due to extrinsic causes of death, such as accidents and acute infections), while the second, age-dependent term (the Gompertz function, $R \cdot e^{\alpha x}$) designates the 'aging' component, presumably due to deaths from age-related degenerative diseases like cancer and heart disease.

The validity of the Gompertz-Makeham law of mortality (4) can be illustrated graphically, when the logarithms of death rates without the Makeham parameter (μ_x - A) are increasing with age in a linear fashion:

$$log\ (\mu_x - A) = log(R) + \alpha x \qquad (5)$$

where log(R) is an intercept coefficient and α is a slope coefficient in this linear relationship.

The log-linear increase in death rates (adjusted for the Makeham term) with age is indeed a very common phenomenon for many human populations at ages 35-70 years (see Figure 2).

Figure 2 About Here

Note that the slope coefficient α characterizes an "apparent aging rate" (how rapid is the age-deterioration in mortality) -- if α is equal to zero, there is no apparent aging (death rates do not increase with age).

At advanced ages (after age 70), the 'old-age mortality deceleration' takes place -- death rates are increasing with age at a slower pace then expected from the Gompertz-Makeham law.

This mortality deceleration eventually produces "late-life mortality leveling-off" and "late-life mortality plateaus" at extreme old ages (Gavrilov and Gavrilova, 1991; 2001a).

The *compensation law of mortality* in its strong form refers to *mortality convergence*, when higher values for the parameter α (in the Gompertz function) are compensated for by lower values of the parameter *R* in different populations of a given species:

$$\ln(R) = \ln(M) - B \cdot \alpha \qquad (6)$$

where B and M are universal species-specific invariants. Sometimes this relationship is also called the Strehler-Mildvan correlation (Strehler and Mildvan, 1960; Strehler, 1978), although that particular correlation was largely an artifact of the opposite biases in parameters' estimation caused by not taking into account the age-independent mortality component, the Makeham term *A* (see Gavrilov and Gavrilova, 1991). Parameter B is called the species-specific lifespan (95 years for humans), and parameter M is called the species-specific mortality rate (0.5 $year^{-1}$ for humans). These parameters are the coordinates for convergence of all the mortality trajectories into one single point (within a given biological species), when extrapolated by the Gompertz function (Figure 2).

In those cases when the compensation law of mortality is not observed in its strong form, it may still be valid in its weak form – i.e., the relative differences in mortality rates of compared populations tend to decrease with age in many species. Explanation of the compensation law of mortality is a great challenge for many theories of aging and longevity (Strehler, 1978; Gavrilov and Gavrilova, 1991; 2001a).

There are some exceptions both from the Gompertz law of mortality and the compensation law of mortality that have to be understood and explained. In some cases the organisms die

according to the *Weibull (power) law* (Hirsch et al., 1994; Eakin et al., 1995; Vanfleteren et al., 1998):

$$\mu(x) = \lambda x^{\alpha} \qquad \text{for } x \geq 0, \text{ where } \lambda, \alpha > 0 \qquad (7)$$

The validity of the Weibull law can be illustrated graphically, when the logarithm of the failure rate increases in a linear fashion as a function of the *logarithm* of age:

$$log\ [\mu(x)] = log(\lambda) + \alpha Z, \qquad \text{where } Z = log\ x \qquad (8)$$

Here $log(\lambda)$ is an intercept coefficient and α a slope coefficient in this linear relationship. Some examples of such linear dependence will be provided later (Figure 3).

Note that the slope coefficient α in the Weibull law characterizes an 'apparent aging rate' (the rapidity of the age-deterioration in mortality), – if α is equal to zero, there is no apparent aging (death rates do not increase with age).

The Weibull law is more commonly applicable to technical devices (Weibull, 1951; Barlow and Proschan, 1975; Rigdon and Basu, 2000), while the Gompertz law is more common to biological systems (Strehler, 1978; Finch, 1990; Gavrilov and Gavrilova, 1991). Possible explanations why organisms prefer to die according to the Gompertz law, while technical devices typically fail according to the Weibull law are provided elsewhere (Gavrilov and Gavrilova, 1991; 2001a) and will be briefly discussed later.

The phenomena of mortality increase with age and the subsequent mortality leveling-off are theoretically predicted to be an inevitable feature of all reliability models that consider aging as

a progressive accumulation of random damage (Gavrilov and Gavrilova, 1991; 2001). Mathematical illustration for this statement is provided in the next section of this paper. In simple words, if the destruction of an organism occurs not in one but in two or more sequential random stages, this is sufficient for the phenomenon of aging (mortality increase) to appear and then to vanish at older ages. Each stage of destruction corresponds to one of the organism's vitally important structures being damaged. In the simplest organisms with unique, critical structures, this damage usually leads to death. Therefore defects in such organisms do not accumulate, and the organisms themselves do not age – they just die when damaged. In more complex organisms with many vital structures and significant redundancy, every occurrence of damage does not lead to death because of this redundancy. Defects do accumulate, therefore, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence (trade-off) of systems' redundancies that ensure increased reliability and increased lifespan of organisms. As defects accumulate, the redundancy in the number of elements finally disappears. As a result of this redundancy exhaustion, the organism degenerates into a system with no redundancy, that is, a system with elements connected in series, with the result being that any new defect leads to death. In such a state, no further accumulation of damage can be achieved, and the mortality rate levels off. The next section provides mathematical illustration for these ideas.

3. Explanations of Aging Phenomena Using Reliability Theory:

An Illustrative Example

Consider a system built of non-aging elements with a constant failure rate k. If these n elements are mutually substitutable, so that the failure of a system occurs only when all the

elements fail (parallel construction in the reliability theory context), the cumulative distribution function for system failure, *F(n,k,x)*, depends on age *x* in the following way:

$$F(n,k,x) = P(X \le x) = \left(1 - e^{-kx}\right)^n \tag{9}$$

Therefore, the reliability function of a system, *S(n,k,x)*, can be represented as:

$$S(n,k,x) = 1 - F(n,k,x) = 1 - \left(1 - e^{-kx}\right)^n \tag{10}$$

Consequently, the failure rate of a system $\mu(n,k,x)$, can be written as follows:

$$\mu(n,k,x) = -\frac{dS(n,k,x)}{S(n,k,x)dx} = \frac{nke^{-kx}\left(1 - e^{-kx}\right)^{n-1}}{1 - \left(1 - e^{-kx}\right)^n} \tag{11}$$

$$\approx nk^n x^{n-1} \tag{11a}$$

when $x << 1/k$ (early-life period approximation, when $1\text{-}e^{-kx} \approx kx$);

$$\approx k \tag{11b}$$

when $x >> 1/k$ (late-life period approximation, when $1\text{-}e^{-kx} \approx 1$)

Thus, the failure rate of a system initially grows as a power function of age (the Weibull law). Then the tempo at which the failure rate grows declines, and the failure rate approaches asymptotically an upper limit equal to *k*. Here we should pay attention to three significant points. First, a system constructed of non-aging elements is now behaving like an aging object: i.e., aging is a direct consequence of the redundancy of the system (redundancy in the number

of elements). Second, at very high ages the phenomenon of aging apparently disappears (failure rate levels-off), as redundancy in the number of elements vanishes. The failure rate approaches an upper limit, which is totally independent of the initial number of elements, but coincides with the rate of their loss (parameter *k*). Third, the systems with different initial levels of redundancy (parameter *n*) will have very different failure rates in early life, but these differences will eventually vanish as failure rates approach the upper limit determined by the rate of elements' loss (parameter *k*). Thus, the compensation law of mortality (in its weak form) is an expected outcome of this illustrative model. These theoretical predictions are supported by experimental studies on *Drosophila melanogaster*, which found no differences in late-life mortality between cohorts of flies having markedly different levels of early robustness (Drapeau et al., 2000).

These theoretical statements, based on general analytical considerations, are also illustrated here with the following particular numerical example. Fig. 3 presents the results of computer simulation of mortality kinetics in systems with different levels of redundancy. Specifically, calculations of failure rates are performed according to formula (11) described earlier, for the numbers of elements, n = 1, 2, 3, 4, and 5. The scales for mortality rates (vertical axis), and for age (horizontal axis) are presented in dimensionless units (μ/k for mortality rates, and kx for age), to ensure the generalizability of the results (invariance of graphs on failure rate of the elements in the system, parameter *k*). Also, the log scale is used to explore the system behavior in a wide range of ages (0.01 - 10 units), and failure rates (0.00000001 - 1.0 units).

Figure 3 About Here

This graph depicts mortality trajectories for five systems with different degrees of redundancy:

(1) System # 1 has only one unique element (no redundancy), and it has the highest failure rate, which does not depend on age (no aging).

(2) System # 2 has two elements connected in parallel (one extra element is redundant), and the failure rate is initially increasing with age (aging appears). The apparent rate of aging can be characterized by a slope coefficient, which is equal to one. Finally the failure rate levels-off at advanced ages.

(3) System # 3 has three elements connected in parallel (two extra elements are redundant), and the failure rate is initially increasing with age (an apparent aging rate, a slope coefficient is equal to two). Then the failure rate levels-off at advanced ages.

(4) System # 4 has four elements connected in parallel (three extra elements are redundant, degree of redundancy = 3), and the failure rate is initially increasing with age with slope coefficient = 3 (apparent relative aging rate). Then again the failure rate levels-off at advanced ages.

(5) System # 5 has five elements connected in parallel (four extra elements are redundant, degree of redundancy = 4), and the failure rate is initially increasing with age with the steepest slope coefficient = 4 (apparent relative aging rate). Finally, the mortality trajectory levels-off at advanced ages.

This computational example illustrates the following statements:

(1) Aging is a direct consequence of a system's redundancy, and the expression of aging is directly related to the degree of a system's redundancy. Specifically, an apparent relative aging rate is just equal to a degree of redundancy in parallel systems.

(2) All mortality trajectories tend to converge with age, so that the compensation law of mortality is observed.

(3) All mortality trajectories level-off at advanced ages, and a mortality plateau is observed.

Thus, the major aging phenomena (aging itself, the compensation law of mortality, late-life mortality deceleration, and late-life mortality plateaus) are already observed in the simplest redundant systems. However, to explain the Gompertz law of mortality, an additional idea should be taken into account (see later).

4. The Idea of High Initial Damage Load

Reliability theory predicts that a failure rate of simple redundant systems increases with age according to the Weibull (power) law (see formula 11a, and Figure 3). This theoretical prediction is consistent with empirical observations that failure kinetics of technical devices follows the Weibull law (Weibull, 1951; Gavrilov and Gavrilova, 1991, 2001a). However, biological systems 'prefer' to fail according to the Gompertz (exponential) law (Gompertz, 1825; Finch, 1990; Gavrilov and Gavrilova, 1991, 2001a), which calls for explanations.

An attempt to explain exponential deterioration of biosystems in terms of the reliability theory had led to a paradoxical conjecture that biological systems start their adult life with high load of initial damage (Gavrilov and Gavrilova, 1991, 2001a).

Although this idea may look like a counter-intuitive assumption, it fits well with many empirical observations on massive cell losses in early development. For example, the female human fetus at age 4-5 months possesses 6-7 million eggs (oocytes). By birth, this number drops to 1-2 million and declines even further. At the start of puberty in normal girls, there are only 0.3-0.5 million eggs – just only 4-8% of initial numbers (Finch and Kirkwood, 2000).

Massive cell losses in early development are creating conditions for Poisson distribution of organisms according to the numbers of remaining cells, which in turn produce the exponential (Gompertzian) law of mortality increase (Gavrilov and Gavrilova, 1991). Because the mathematical proof for this statement is already published elsewhere (Gavrilov and Gavrilova, 1991), we can concentrate here on substantive discussion of the idea of high initial damage load in biological systems.

Biological systems are different from technical devices in two aspects. The first fundamental feature of biosystems is that, in contrast to technical (artificial) devices which are constructed out of previously manufactured and tested components, organisms form themselves in ontogenesis through a process of self-assembly out of de novo forming and externally untested elements (cells). The second property of organisms is the extraordinary degree of miniaturization of their components (the microscopic dimensions of cells, as well as the molecular dimensions of information carriers like DNA and RNA), permitting the creation of a huge redundancy in the number of elements. Thus, we can expect that for living organisms, in distinction to many technical (manufactured) devices, the reliability of the system is achieved not by the high initial quality of all the elements but by their huge numbers (redundancy).

The fundamental difference in the manner in which the system is formed (external assembly in the case of technical devices and self-assembly in the case of biosystems) has two important consequences. First, it leads to the macroscopicity of technical devices in comparison with biosystems, since technical devices are assembled 'top-down' with the participation of a macroscopic system (man) and must be suitable for this macroscopic system to use (i.e., commensurate with man). Organisms, on the other hand, are assembled 'bottom-up' from molecules and cells, resulting in an exceptionally high degree of miniaturization of the

component parts. Second, since technical devices are assembled under the control of man, the opportunities to pretest components (external quality control) are incomparably greater than in the self-assembly of biosystems. The latter inevitably leads to organisms being 'littered' with a great number of defective elements. As a result, the reliability of technical devices is assured by the high quality of elements, with a strict limit on their numbers because of size and cost limitations, while the reliability of biosystems is assured by an exceptionally high degree of redundancy to overcome the poor quality of some elements.

It is interesting to note that the uniqueness of individuals, which delights biologists so much, may be caused by 'littering' the organisms with defects and thus forming a unique pattern of individual damage. Our early experience working with dilapidated computer equipment in Russia in the 1980s gave rise to the same thought: the behavior of this equipment could only be described by resorting to such 'human' concepts as character, freaks, personality, and change of mood.

The idea that living organisms are starting their lives with a large number of defects has deep historical roots. Biological justification for this idea was discussed by Dobzhansky (1962). He noted that, from the biological perspective, Hamlet's *"thousand natural shocks that flesh is heir to"* was an underestimate and that in reality "the shocks are innumerable" (Dobzhansky, 1962, p.126). Recent studies found that the troubles in human life start from the very beginning: the cell-cycle checkpoints (which ensure that cell will not divide until DNA damage is repaired and chromosomal segregation is complete) do not operate properly at early, cleavage stage of human embryo (Handyside and Delhanty, 1997). This produces mosaicism of the preimplantation embryo, where some embryonic cells are genetically abnormal (McLaren, 1998) with potentially devastating consequences in later life. Most of the DNA damage caused

by copy-errors during DNA replication also occurs in early life, because most cell divisions happen in early development. As a result of extensive DNA damage in early development, many apparently normal tissues of young organisms have an unbelievably high load of mutations, including an amazing amount of oncogenic mutations and frequent clones of mutated somatic cells (Cha et. al., 1994; Deng et al., 1996; Johason et al., 1996).

Another potential source of extensive initial damage is the birth process itself. During birth, the future child is first deprived of oxygen by compression of the umbilical cord (Moffett *et al*., 1993), and suffers severe hypoxia (often with ischemia and asphyxia). Then, just after birth, a newborn child is exposed to oxidative stress because of acute reoxygenation while starting breathing. It is known that acute reoxygenation after hypoxia may produce an extensive oxidative damage through the same mechanisms that also produce ishemia-reperfusion injury (IRI) and asphyxia-reventilation injury (Martin et al., 2000). Thus, using Hamlet's metaphor, we may conclude that humans *"suffer the slings and arrows of outrageous fortune"* and have *"a sea of troubles"* from the very beginning of their lives.

It follows from this concept of high initial damage load that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements can potentially result in a remarkable fall in mortality and a significant improvement in lifespan. This optimistic prediction is supported by experimental evidence of increased offspring lifespan in response to protection of parental germ cells against oxidative damage just by feeding the future parents with antioxidants (Harman and Eddy, 1979). Increased lifespan is also observed among the progeny of parents with a low respiration rate (proxy for the rate of oxidative damage to DNA of germ cells, see Gavrilov and Gavrilova, 1991). The concept of high initial damage load also predicts that early life events may affect survival in later adult life

through the level of initial damage. This prediction proved to be correct for such early life indicators as parental age at a person's conception (Gavrilov and Gavrilova, 1997a; 1997b; 2000; 2001b; 2003) and the month of person's birth (Gavrilov and Gavrilova, 1999; 2003; Doblhammer and Vaupel, 2001). There is mounting evidence now in support of the idea of fetal origins of adult degenerative diseases (Barker, 1998; Kuh and Ben-Shlomo, 1997; Leon et al., 1998; Lucas et al., 1999), and early-life programming of aging and longevity (Gavrilov and Gavrilova, 1991; 2001b; 2003).

5. Concluding Remarks

Extensive studies in experimental gerontology have produced many important and diverse findings, which require a general theoretical framework for them to be organized into a comprehensive body of knowledge.

As demonstrated by the success of evolutionary theories of aging, based on a general idea of the declining force of natural selection with age, quite general theoretical considerations can in fact be very useful and practical when applied to aging research (Le Bourg, 2001; Gavrilov and Gavrilova, 2002).

In this study, we attempted to go one step further in the search for a general explanation of aging by applying a general theory of systems failure known as reliability theory.

Considerations of this theory lead to the following conclusions:

(1) *Redundancy* is a key notion for understanding aging and the systemic nature of aging in particular. Systems, which are redundant in numbers of irreplaceable elements, do deteriorate (i.e., age) over time, even if they are built of non-aging elements. The positive effect of systems' redundancy is *damage tolerance*, which decreases mortality and increases lifespan.

However damage tolerance makes it possible for damage to be tolerated and accumulated over time, thus producing aging phenomenon.

(2) An apparent aging rate or expression of aging (measured as age differences in failure rates, including death rates) is higher for systems with higher redundancy levels (all other things being equal). This is an important issue, because it helps to put a correct perspective over fascinating observations of negligible senescence (no apparent aging) observed in the wild and at extreme old ages. Reliability theory explains that some cases of negligible senescence may have a trivial mechanism (lack of redundancies in the system being exposed to challenging environment) and, therefore, will not help to uncover "the secrets of negligible senescence". The studies of negligible senescence make sense however when the total mortality rates are also demonstrated to be negligible.

(3) During the life course the organisms are running out of their cells (Finch and Kirkwood, 2000), and this *redundancy depletion* explains the observed 'compensation law of mortality' (mortality convergence at older ages) as well as the observed late-life mortality deceleration, leveling-off, and mortality plateaus.

(4) Living organisms seem to be formed with a high *load of initial damage*, and therefore their lifespans and aging patterns may be sensitive to *early-life conditions* that determine this initial damage load during early development. The idea of early-life programming of aging and longevity may have important practical implications for developing early-life interventions promoting health and longevity.

The theory also suggests that aging research should not be limited to the studies of qualitative changes (like age changes in gene expression), because changes in *quantity*

(numbers of cells and other functional elements) could be an important driving force of aging process. In other words, aging may be largely driven by a process of redundancy loss.

The reliability theory predicts that a system may deteriorate with age even if it is built from non-aging elements with constant failure rate. The key issue here is the system's redundancy for irreplaceable elements, which is responsible for the aging phenomenon. In other words, each particular step of system destruction/deterioration may seem to be apparently random (no aging, just occasional failure by chance), but if a system failure requires a sequence of several such steps (not just a single step of destruction), then system as a whole may have an aging behavior.

Why is this important? Because the significance of beneficial health-promoting interventions is often undermined by claims that these interventions are not proven to delay the process of aging itself, but instead that they simply delay or "cover-up" some particular manifestations of aging.

In contrast to these pessimistic views, the reliability theory says that there may be no specific underlying elementary "aging process itself" – instead aging may be largely a property of redundant system as a whole, because it has a network of destruction pathways each being associated with particular manifestations of aging (types of failure). Therefore, we should not be discouraged by only partial success of each particular intervention, but instead we can appreciate an idea that we do have so many opportunities to oppose aging in numerous different ways.

Thus, the efforts to understand the routes and the early stages of age-related degenerative diseases should not be discarded as irrelevant to understanding of the "true biological aging". On the contrary, the attempts to build an intellectual firewall between experimental gerontology and clinical medicine are counterproductive. After all, the main reason why people are really

concerned about aging is because it is related to health deterioration and increased morbidity. The most important pathways of age changes are those that make older people sick.

Ageing is a complex phenomenon and a holistic approach using reliability theory may help to analyze, understand and perhaps to control it.

Finally we suggest adding the reliability theory to the arsenal of methodological approaches applied in aging research.

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(1) Annual meeting of the Gerontological Society of America (Boston, November, 2002),

(2) National Institutes of Health Conference "The Dynamic and Energetic Bases of Health and Aging"(NIH, Bethesda, November, 2002), and

(3) Annual Meeting of the Population Association of America (Atlanta, May, 2002).

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Figure Captions

Figure 1.

Survival Patterns After Age 90.

Percent surviving (in log scale) is plotted as a function of age of Swedish women for calendar years 1900, 1980, and 1999 (cross-sectional data). Note that after age 100, the logarithm of survival fraction is decreasing without much further acceleration (aging) in almost a linear fashion. Also note an increasing pace of survival improvement in history: it took less than 20 years (from year 1980 to year 1999) to repeat essentially the same survival improvement that initially took 80 years (from year 1900 to year 1980).

Source: cross-sectional (period) life tables at the Berkeley Mortality Database (BMD):

http://www.demog.berkeley.edu/~bmd/

Figure 2.

Compensation Law of Mortality.

Convergence of Mortality Rates (in different populations) at Advanced Ages.

Death rates (with removed Makeham parameter A, corresponding to age-independent mortality component) are plotted in a log scale as a function of age in the following countries:

1 – India, 1941-1950, males

2 – Turkey, 1950-1951, males

3 – Kenya, 1969, males

4 - Northern Ireland, 1950-1952, males

5 - England and Wales, 1930-1932, females

6 - Austria, 1959-1961, females

7 - Norway, 1956-1960, females

Adapted from (Gavrilov et al., 1978; Gavrilov & Gavrilova, 1991)

Figure 3.

Failure kinetics of systems with different levels of redundancy.

The dependence of the logarithm of mortality force (failure rate) on logarithm of age in five systems with different levels of redundancy (computer simulation experiment). Both the failure rate and the age are presented in dimensionless units as explained in the text.

The dependence 1 is for the system containing only one unique element (no redundancy). The dependence 2 is for the system containing two elements connected in parallel (degree of redundancy = 1). The dependencies 3, 4 and 5 are for systems containing respectively 3, 4 and 5 elements connected in parallel (with increasing levels of redundancy). Note that even in this most simple case the following aging-related phenomena are observed: (1) the emergence of aging as the system becomes redundant; (2) the increase in apparent aging rate with increasing levels of system redundancy; (3) the compensation law of mortality (mortality convergence), and (4) late-life mortality deceleration and levelling-off to mortality plateau. Additional explanations and comments are provided in the text of the paper.

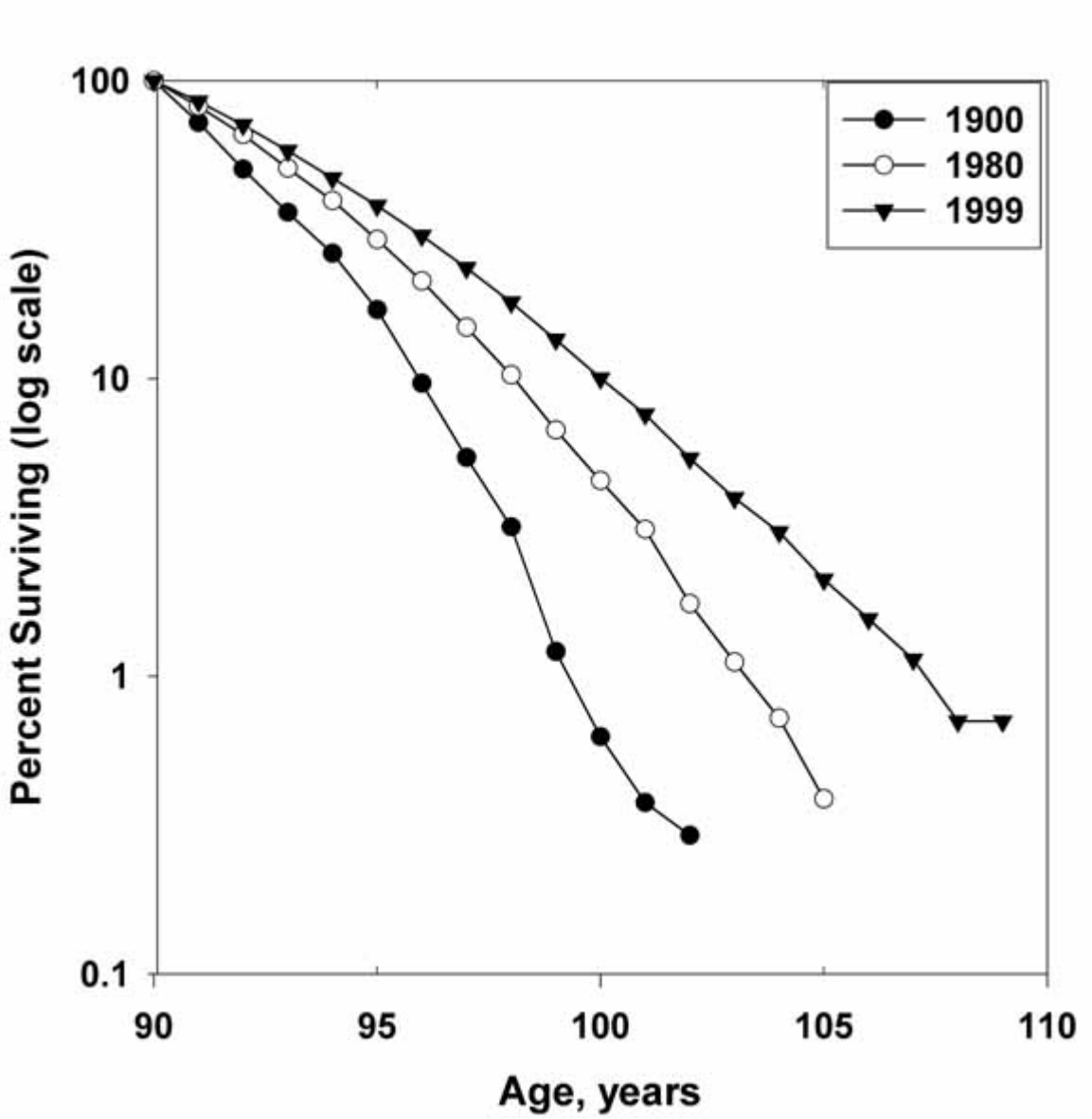
100
10
1
0.1
Percent Surviving (log scale)
90
95
100
105
110
Age, years
1900
1980
1999

Figure 1

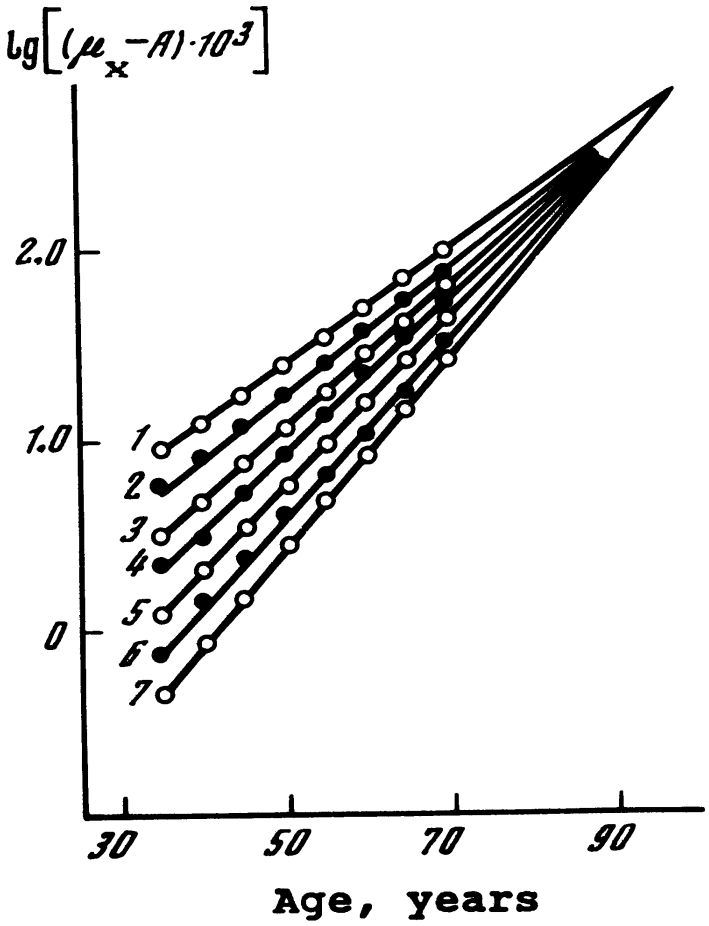

Figure 2

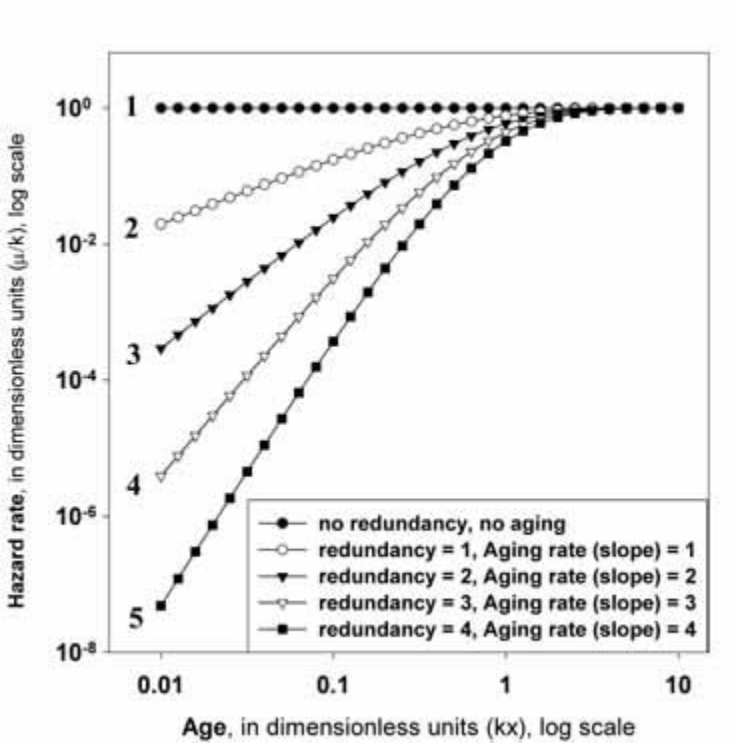
Hazard rate, in dimensionless units (μ/k), log scale
Age, in dimensionless units (kx), log scale
10^0
10^-2
10^-4
10^-6
10^-8
0.01
0.1
1
10
1
2
3
4
5
no redundancy, no aging
redundancy = 1, Aging rate (slope) = 1
redundancy = 2, Aging rate (slope) = 2
redundancy = 3, Aging rate (slope) = 3
redundancy = 4, Aging rate (slope) = 4

Figure 3