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Reliability Theory of Aging and Longevity

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I. Introduction

In this paper we discuss theoretical models of systems failure in aging. Mathematical models of systems failure are important for the studying of human aging, because aging is associated with increased risk of failure in human physiological systems. Theoretical analysis of systems failure in aging invites us to consider the general theory of systems failure known as reliability theory (Barlow & Proshan, 1975; Barlow et al., 1965; Gavrilov,1978; Gavrilov & Gavrilova, 1991, 2001, 2003a, 2004a, 2005; Gavrilov et al.,1978).

Reliability theory was historically developed to describe failure and aging of complex electronic (military) equipment, but the theory itself is a very general theory based on mathematics (probability theory) and systems approach (Barlow & Proschan, 1975; Barlow et al., 1965). It may therefore be useful to describe and understand the aging and failure of biological systems too. Reliability theory may be useful in several ways: first, by providing a kind of scientific language (definitions and cross-cutting principles), which helps to create a logical framework for organizing numerous and diverse observations on aging into a coherent picture. Second, it helps researchers to develop an intuition and an understanding of the main principles of the aging process through consideration of simple mathematical models, having some features of a real world. Third, reliability theory is useful for generating and testing specific predictions, as well as deeper analyses of already collected data. The purpose of this paper is to review the theoretical reliability models and approaches, which help to understand the mechanisms and dynamics of systems failure in aging.

II. Reliability approach to system's failure in aging

Reliability theory is a body of ideas, mathematical models, and methods directed to predict, estimate, understand, and optimize the lifespan and failure distributions of systems and their components (adapted from Barlow & Proschan, 1975). Reliability theory allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components.

A. Definitions of system's failure and aging

The concept of failure is important to the analysis of system's reliability. In reliability theory failure is defined as the *event* when a required function is terminated (Rausand, Houland, 2003). In other words, failure is such an outcome when the system deviates from optimistically anticipated and desired behavior ("fails"). Failures are often classified into two groups:

(1) degradation failures, where the system or component no longer functions properly, and

(2) catastrophic or fatal failures – the end of system's or component's life.

Good examples of degradation failures in humans would be an onset of different types of health impairments, diseases, or disabilities, while catastrophic or fatal failures obviously correspond to death. The notions of aging and failure are related to each other in the following way: when the risk of failure outcomes increases with age ('old is not as good as new') – this is aging by definition. Note that according to reliability theory aging is not just growing old, instead aging is a degradation leading to failure (adverse health outcomes) -- becoming sick, disabled, frail and dead. Therefore, from a reliability-theory perspective the notion of 'healthy aging' is an oxymoron like a healthy dying, or a healthy disease. More appropriate terms instead of 'healthy aging' or 'aging well' would be a delayed aging, postponed aging, slow aging, arrested aging, or negligible aging (senescence).

Because the reliability definition of biological aging is linked to health failures (adverse health outcomes, including death), aging without diseases is just as inconceivable as dying without death. Diseases and disabilities are an integral part (outcomes) of the aging process. Not every disease is related to aging, but every progression of disease with age has some relevance to aging: aging is a "maturation" of diseases with age.

Note that a system may have an aging behavior for one particular type of failure, but it may remain to be as good as new for some other type of failure. Thus the notion of aging is outcome-specific – it requires specifying for which particular type of failure (or group of failures) the system deteriorates. Consequently, the legitimate anti-aging interventions may be outcome-specific too, and limited to postponing some specific adverse health outcomes. Aging is likely to be a summary term for many

different processes leading to various types of degradation failures, and each of these processes deserves to be studied and prevented.

B. Basic failure models

Reliability of the system (or its 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 & Basu, 2000). The reliability function (also called the *survival function*) evaluated at time *x* is just the probability *P*, that the *failure time X*, is beyond time *x*. Thus, the reliability function is defined in the following way:

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

where F(x) is a standard *cumulative distribution function* in 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).

Failure rate, $\mu(x)$, or instantaneous risk of failure*,* also called the *hazard rate, h(x),* or mortality force is defined as the relative rate for reliability function decline:

$$\mu(x) = -\frac{dS_x}{S_x dx} = -\frac{d\,lnS_x}{dx}$$

In those cases when the failure rate is constant (does not increase with age), we have *non-aging system* (component) that does not deteriorate (does not fail more often) with age:

$$\mu(x) = \mu = \text{const}$$

The reliability function of non-aging systems (components) is described by the *exponential distribution*:

$$S(x) = S_0 e^{-\mu x}$$

This *failure law* describes 'lifespan' distribution of atoms of radioactive elements and, therefore, it is often called an exponential decay law. Interestingly, this failure law is observed in many wild populations with high extrinsic mortality (Finch, 1990; Gavrilov & Gavrilova, 1991). This kind of distribution is observed if failure (death) occurs entirely by chance, and it is also called a 'one-hit model', or a 'first order kinetics'. The nonaging behavior of a system can be detected graphically when the logarithm of the survival function decreases with age in a linear fashion.

Recent studies found that at least some cells in the aging organism might demonstrate nonaging behavior. Specifically, the rate of neuronal death does not increase with age in a broad spectrum of aging-related neurodegenerative conditions (Heintz, 2000). These include 12 different models of photoreceptor degeneration, "excitotoxic" cell death in vitro, loss of cerebellar granule cells in a mouse model, and Parkinson's and Huntington's diseases (Clarke et al., 2000). In this range of diseases, five different neuronal types are affected. In each of these cases, the rate of cell death is best fit by an exponential decay law with constant risk of death independent of age (death by chance only), arguing against models of progressive cell deterioration and aging (Clarke et al., 2000, 2001a). An apparent lack of cell aging is also observed in the case of amyotrophic lateral sclerosis (Clarke et al., 2001a), retinitis pigmentosa (Burns, 2002; Clarke et al., 2000, 2001a; Massof, 1990) and idiopathic Parkinsonism (Calne, 1994; Clarke et al., 2001b; Schulzer et al., 1994). These observations correspond well with another observation that "an impressive range of cell functions in most organs remain unimpaired throughout the life span" (Finch, 1990, p. 425), and these unimpaired functions might reflect the "no-aging" property known as "old as good as new" property in survival analysis (Klein & Moerschberger, 1997, p. 38). Thus we come to the following fundamental question about the origin

of aging: How can we explain the aging of a system built of nonaging elements? This question invites us to think about the possible systemic nature of aging and to wonder whether aging may be a property of the system as a whole. We would like to emphasize the importance of looking at the bigger picture of the aging phenomenon in addition to its tiny details, and we will suggest a possible answer to the posed question in this paper.

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 most famous one in biology is the *Gompertz law* with exponential increase of the failure rates with age (Finch, 1990; Gavrilov & Gavrilova, 1991; Gompertz, 1825; Makeham, 1860; Strehler, 1978):

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

An exponential (Gompertzian) increase in death rates with age is observed for many biological species including fruit flies *Drosophila melanogaster* (Gavrilov & Gavrilova, 1991), nematodes (Brooks et al., 1994; Johnson, 1987, 1990), mosquitoes (Gavrilov, 1980), human lice *Pediculus humanus* (Gavrilov & Gavrilova, 1991), flour beetles *Tribolium confusum* (Gavrilov & Gavrilova, 1991), mice (Kunstyr & Leuenberger, 1975; Sacher, 1977), rats (Gavrilov & Gavrilova, 1991), dogs (Sacher, 1977), horses (Strehler, 1978), mountain sheep (Gavrilov, 1980), baboons (Bronikowski et al., 2002) and, perhaps most important, humans (Finch, 1990; Gavrilov & Gavrilova, 1991; Gompertz, 1825; Makeham, 1860; Strehler, 1978). According to the Gompertz law, the logarithm of failure rates increases linearly with age. This is often used in order to illustrate graphically the validity of the Gompertz law – the data are plotted in the semi-log scale (known as the Gompertz plot) to check whether the logarithm of the failure rate is indeed increasing with age in a linear fashion.

For technical systems one of the most popular models for failure rate of aging systems is the Weibull model, the power-function increase in failure rates with age (Weibull, 1939):

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

This law was suggested by Swedish engineer and mathematician W. Weibull in 1939 to describe the strength of materials (Weibull, 1939). It is widely used to describe aging and failure of technical devices (Barlow & Proschan, 1975; Rigdon & Basu, 2000; Weibull, 1951), and occasionally it was also applied to a limited number of biological species (Eakin et al., 1995; Hirsch & Peretz, 1984; Hirsch et al., 1994; Janse *et al*., 1988; Ricklefs & Scheuerlein, 2002; Vanfleteren et al., 1998). According to the Weibull law, the logarithm of failure rate increases linearly with the *logarithm* of age with a slope coefficient equal to parameter β. This is often used in order to illustrate graphically the validity of the Weibull law – the data are plotted in the log-log scale (known as the Weibull plot) to check whether the logarithm of the failure rate is indeed increasing with the *logarithm* of age in a linear fashion.

We will show later that both the Gompertz and the Weibull failure laws have a fundamental explanation rooted in reliability theory. Therefore it may be interesting and useful to compare these two failure laws and their behavior.

Figure 1a presents the dependence of the logarithm of the failure rate on age (Gompertz plot) for the Gompertz and the Weibull functions.

Note that this dependence is strictly linear for the Gompertz function (as expected), and a concave-down for the Weibull function. So the Weibull function looks like decelerating with age if compared to the Gompertz function.

Figure 1b presents the dependence of the logarithm of the failure rate on the *logarithm* of age (Weibull plot) for the Gompertz and the Weibull functions.

Note that this dependence is strictly linear for the Weibull function (as expected), and a concave-up for the Gompertz function. So the Gompertz function looks like accelerating one with the *logarithm* of age if compared to the Weibull function.

There are two fundamental differences between the Weibull and the Gompertz functions.

First, the Weibull function states that the system is immortal at starting age -- when the age X is equal to zero, the failure rate is equal to zero too, according to the Weibull formula. This means that the system should be initially ideal (immortal) in order the Weibull law be applicable to it. On the

contrary, the Gompertz function states that the system is already vulnerable to failure at starting age -- when the age X is equal to zero, the failure rate is already above zero, equal to parameter R in the Gompertz formula. This means that the partially damaged systems having some initial damage load are more likely to follow the Gompertz failure law, while the initially perfect systems are more likely to follow the Weibull law.

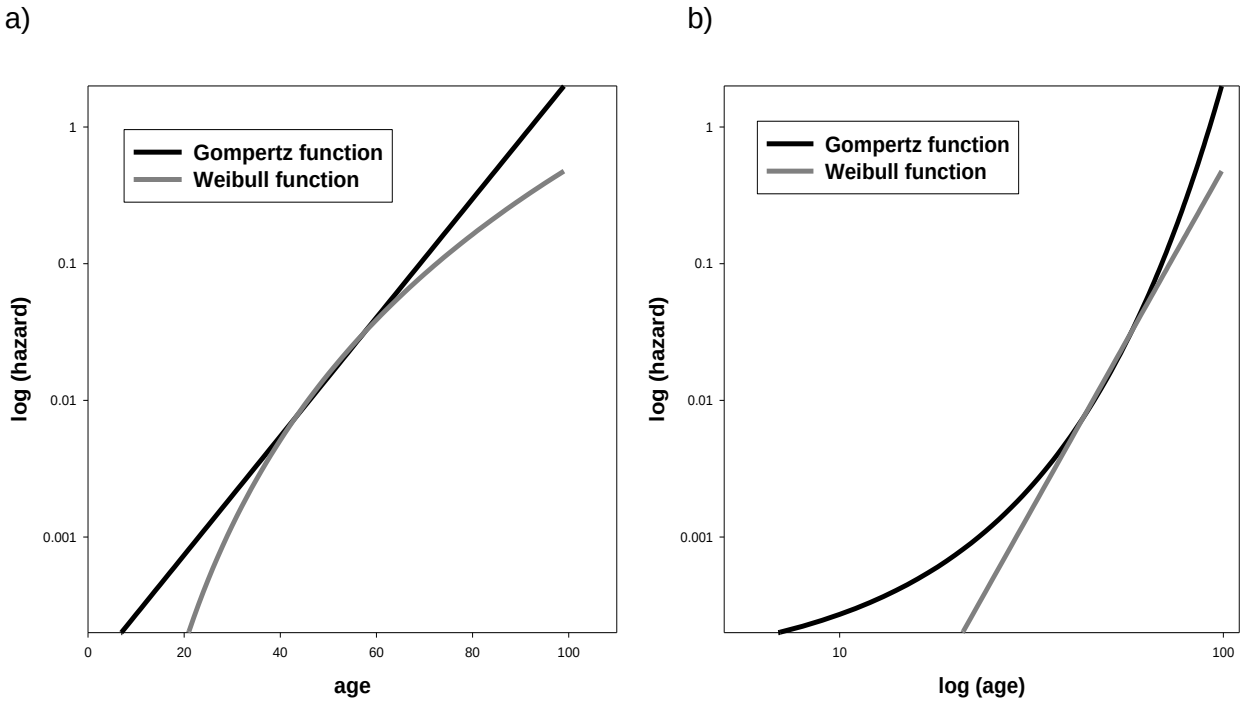

Figure 1. Plots of Gompertz and Weibull functions in different coordinates.
a) semi-log (Gompertz) coordinates. **b)** log-log (Weibull) coordinates. Source: Gavrilov & Gavrilova, 2005.

Second, there is a fundamental difference between the Gompertz and the Weibull functions regarding their response to misspecification of the starting age ('age zero'). This is an important issue, because in biology there is an ambiguity regarding the choice of a 'true' age, when aging starts. Legally, it is the moment of birth, which serves as a starting moment for age calculation. However, from a biological perspective there are reasons to consider a starting age as a date either well before the birth date (the moment of conception in genetics, or a critical month of pregnancy in embryology), or long after the birth date (the moment of maturity, when the formation of a body is finally completed). This uncertainty in starting age has very different implications for data analysis with the Gompertz or the Weibull functions. For the Gompertz function a misspecification of a starting age is not as important, because the shift in the age scale will still produce the same Gompertz function with the same slope parameter α. The data generated by the Gompertz function with different age shifts will all be linear and parallel to each other in the Gompertz plot. The situation is very different for the Weibull function -- it is linear in the Weibull plot for only one particular starting age, and any shifts in a starting age produce a different function. Specifically, if a 'true' starting age is larger than assumed, then the resulting function will be a non-linear concave-up curve in the Weibull plot indicating model misspecification and leading to a bias in estimated parameters. Thus, researchers choosing the Weibull function for data analysis have first to resolve an uneasy biological problem – at what age does aging start?

An alternative graceful mathematical solution of this problem would be to move from a standard two-parameter Weibull function to a more general three-parameter Weibull function, which has an additional 'location parameter' γ (Clark, 1975):

$\mu(x) = \alpha(x - \gamma)^{\beta}$, for x>γ, and equal to zero otherwise

Parameters of this formula, including the location parameter γ could be estimated from the data through standard fitting procedures, thus providing a computational answer to a question "when does aging start?" However, this computational answer might be shocking to researchers, unless they are familiar with the concept of initial damage load, which is discussed elsewhere (Gavrilov & Gavrilova, 1991; 2001; 2004b; 2005).

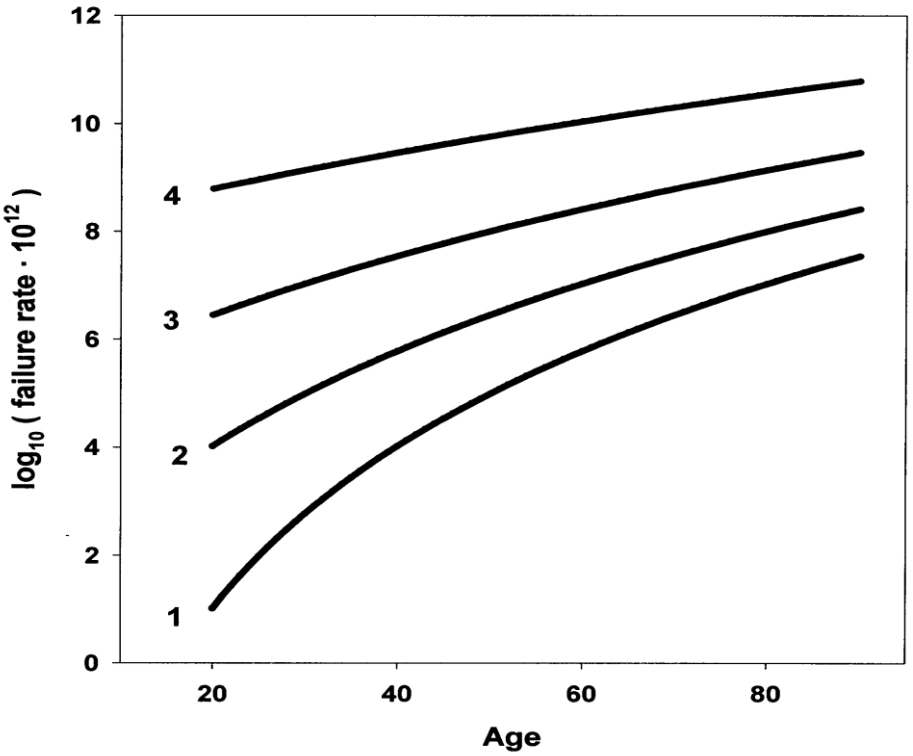

Figure 2. Failure kinetics of systems with different levels of initial damage.
Dependence 1 is for initially ideal system (with no damage load). Dependence 2 is for system with initial damage load equivalent to damage accumulated by 20-year old system. Dependencies 3 and 4 are for systems with initial damage load equivalent to damage accumulated respectively by 50-year old and 100-year old system. Source: Gavrilov & Gavrilova, 2006.

In addition to the Gompertz and the standard two-parameter Weibull laws, a more general failure law was also suggested and theoretically justified using the systems reliability theory. This law is known as the *binomial failure law* (Gavrilov & Gavrilova, 1991; 2001; 2005), and it represents a special case of the three-parameter Weibull function with a negative location parameter:

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

The parameter x_0 in this formula is called the *initial virtual age of the system, IVAS* (Gavrilov & Gavrilova, 1991; 2001; 2005). This parameter has the dimension of time, and corresponds to the age by which an initially ideal system would have accumulated as many defects as a real system already has at the starting age (at $x = 0$). In particular, when the system is initially undamaged, the initial virtual age of the system is zero and the failure rate grows as a power function of age (the Weibull law). However, as the initial damage load is increasing, the failure kinetics starts to deviate from the Weibull law, and eventually it evolves to the Gompertz failure law at high levels of initial damage load. This is illustrated at Figure 2, which represents the Gompertz plot for the data generated by the binomial failure law with different levels of initial damage load (expressed in the units of initial virtual age).

Note that as the initial damage load increases the failure kinetics evolves from the concave-down curves typical to the Weibull function, to an almost linear dependence between the logarithm of failure rate and age (the Gompertz function). Thus, biological species dying according to the Gompertz law may have a high initial damage load, presumably because of developmental noise, and a clonal

expansion of mutations occurred in the early development (Gavrilov & Gavrilova, 1991; 2001; 2003a; 2004b).

C. System's failure and reliability structure

A branch of reliability theory, which studies reliability of an entire system given reliability of its components and components' arrangement (reliability structure) is called system reliability theory (Rausand & Hoyland, 2003). System reliability involves the study of the overall performance of systems of interconnected components. The main objective of system reliability is the construction of a model that represents the times-to-failure of the entire system based on the life distributions of the components, from which it is composed. Consideration of some basic ideas and models of the system reliability theory is important because living organisms may be represented as structured systems comprised of organs, tissues and cells.

System reliability theory tells us that the way of components arrangement strongly affects the reliability of the whole system. The arrangement of components that are important for system reliability is also called reliability structure and is graphically represented by a schema of logical connectivity. It is important to understand that the model of logical connectivity is focused only on those components that are relevant for the functioning ability of the system. If the components do not play direct role in system's reliability they usually are not included in the analyzed reliability structure (Rausand & Hoyland, 2003). For example, organs of vision are not included in the reliability structure of living organism if only death is the type of failure to be analyzed (complete failure of vision does not cause an immediate death of the organism). On the other hand, if disability is the type of failure under consideration, then organs of vision should be included in the schema of reliability structure. Therefore, reliability structure does not necessarily reflect a physical structure of the object.

There are two major types of components arrangement (connection) in the system: components connected in series and components connected in parallel (Rausand & Hoyland, 2003). Here we consider a simple system of n statistically independent components, where failure of one component does not affect the failure rate of other components of the system.

Components connected in series

For a system of *n* independent components connected in series, the system fails if any one of the components fails like in electrical circuits connected in series. Thus, the failure of any one component results in failure of the whole system like in the Christmas tree lighting chains. Figure 3a shows a schema of the logical connectivity of the system in series.

This type of system is also called a weakest-link system (Ayyub & McCuen, 2003). In living organisms many organs and tissues (heart, lung, liver, brain) are vital for organism's survival being a good example of series-connected components. Thus, the series connection means a logical connectivity, but not necessarily a physical or anatomical one.

The reliability of a system in series (with independent failure events of the components), P_s, is a product of reliabilities of its components:

$$P_s = p_1 p_2 \ldots p_n$$

where $p_1 \ldots p_n$ are reliabilities of system's components. This formula explains why complex systems with many critical components are so sensitive to early failures of their components.
For example, for a system built of 458 critical components, the initial period of components life when their cumulative risk of failure is only 1% corresponds to the end of systems life when 99% of systems have already failed. This discrepancy between the lifetimes of systems and the lifetimes of their components is increasing further with systems complexity (numbers of critical components). Therefore, the early failure kinetics of components is so important in determining the failure kinetics of a complex system for its entire life.

The failure rate of a system connected in series is a sum of failure rates of its components (Barlow et al., 1965):

$$\mu_s = \mu_1 + \mu_2 + \mu_i \ldots + \mu_n$$

If failure rates of all components are equal, then the failure rate of the system with n components is $n\mu$. It follows from this formula that if system's components do not age (μ_i = const), then the entire system connected in series does not age either.

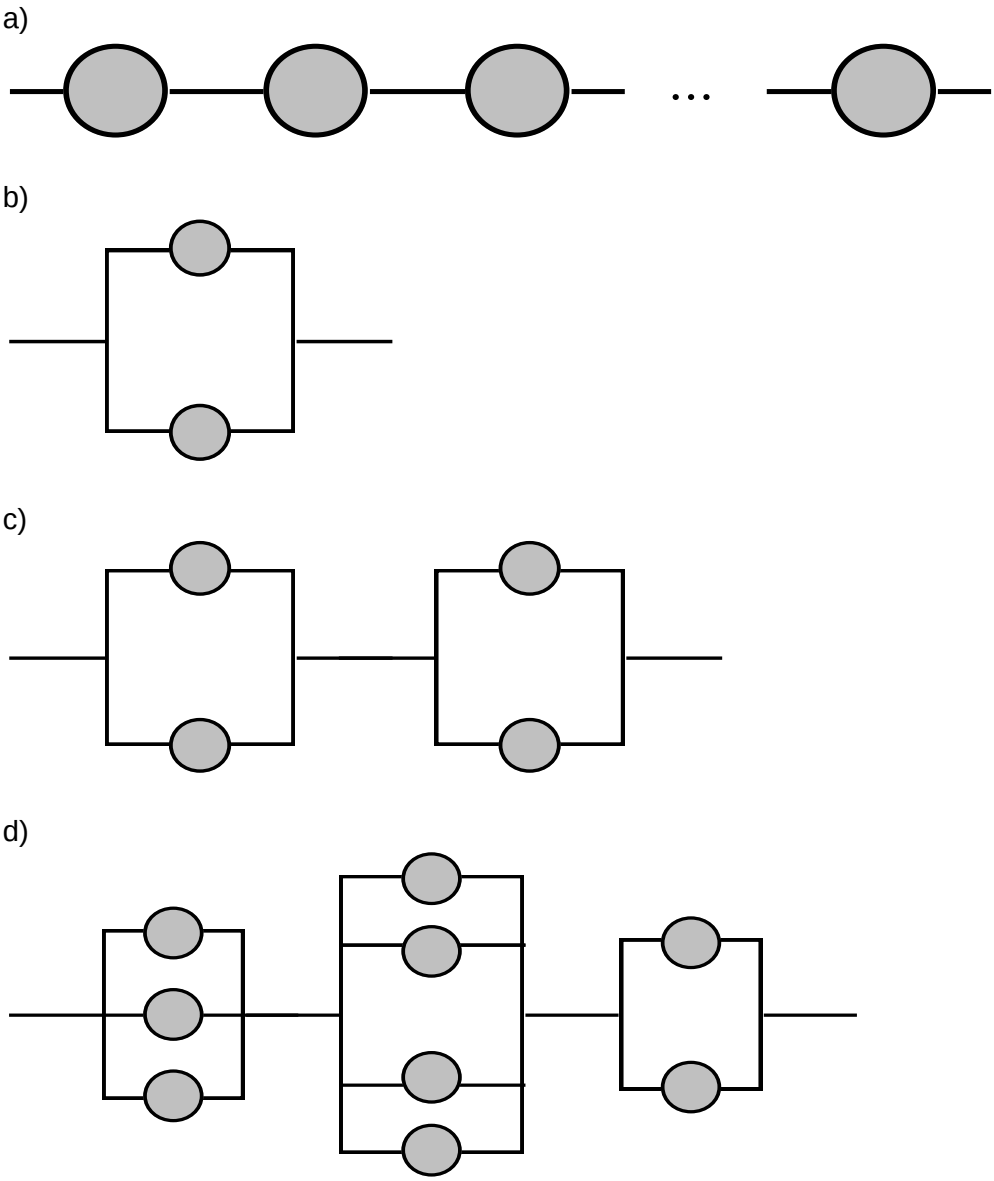

Figure 3. Logical schemas of systems with different types of elements connectivity
a) system connected in series. **b)** system connected in parallel. **c)** series-parallel system.
d) series-parallel system with distributed redundancy. Source: Gavrilov & Gavrilova, 2006.

Components connected in parallel

A parallel system of n independent components fails only when all the components fail (like in electrical circuits connected in parallel). The logical structure of parallel system is presented in Figure 3b.

An example of parallel system is a system with components performing identical function. This function will be destroyed only in the case when all the components fail. Number of additional components in parallel structure with one and the same function is called redundancy or reserve of the system. In living organisms vital organs and tissues (such as liver, kidney or pancreas) consist of many cells performing one and the same specialized function.

For parallel system with *n* independent components probability of system's failure, Q, is a product of probabilities of failure for its components, q:

$$Q_s = q_1 q_2 ... q_n$$

Hence the reliability of parallel system, P_s, is related to reliabilities of its components in the following way:

$$P_s = 1 - Q_s = 1 - (1 - p_1)(1 - p_2)...(1 - p_n)$$

Reliability of parallel system with components of equal reliability, *p*, is:

$$P_s = 1 - (1 - p)^n$$

What is very important is the emergence of aging in parallel systems - a parallel system is aging even if it is built of non-aging components with a constant failure rate (see more details in section IV).

In a real world most systems are more complex than simply a series and parallel structures, but in many cases they can be represented as combinations of these structures.

More complex types of reliability structure

The simplest combination of the two reliability structures is a series-parallel system with equal redundancy shown in Figure 3c.

A general series-parallel system is a system of *m* sub-systems (blocks) connected in series, where each block is a set of n components connected in parallel. It turns out that even if the components themselves are not aging, the system as a whole has an aging behavior – its failure rate grows with age according to the Weibull law and then levels-off at advanced ages (Gavrilov & Gavrilova, 1991; 2001, 2003a). This type of a system is important to consider, because a living organism can be presented as a system of critical organs and tissues connected in series, while each organ consists of specialized cells connected in parallel. Reliability model for this type of system is described in more detail in section IV.

Another type of reliability structure, a series-parallel system with distributed redundancy, was introduced by Gavrilov and Gavrilova in 1991 (Gavrilov & Gavrilova, 1991; 2001). The series connected blocks of this system have non-equal redundancy (different numbers of elements connected in parallel) and the elements are distributed between the system's blocks according to some particular distribution law (see schema in Figure 3d).

Gavrilov and Gavrilova (1991; 2001) studied the reliability and failure rate of series-parallel systems with distributed redundancy for two special cases: (1) the redundancy distributed within an organism according to the Poisson law or (2) according to the binomial law. They found that the failure rate of such systems initially grows according to the Gompertz law (in the case of the Poisson distributed redundancy) or binomial failure law in the case of the binomially distributed redundancy (Gavrilov & Gavrilova, 1991; 2001). At advanced ages the failure rate for both systems asymptotically approaches an upper limit (mortality plateau). Reliability models for this type of system are described in more detail in section V.

Now when the basic concepts of reliability theory are discussed, we may proceed to linking them to empirical observations on aging and mortality.

III. Empirical observations on systems failure in aging

A. General overview of failure kinetics

There is a striking similarity between living organisms and technical devices in the general age pattern of their failures - in both cases the failure rate usually follows the so-called "bathtub curve" (Figure 4).

The bathtub curve of failure rate is a classic concept presented in all textbooks on reliability theory (Ayyub & McCuen, 2003; Barlow & Proshan, 1975; Rausand & Hoyland, 2003).

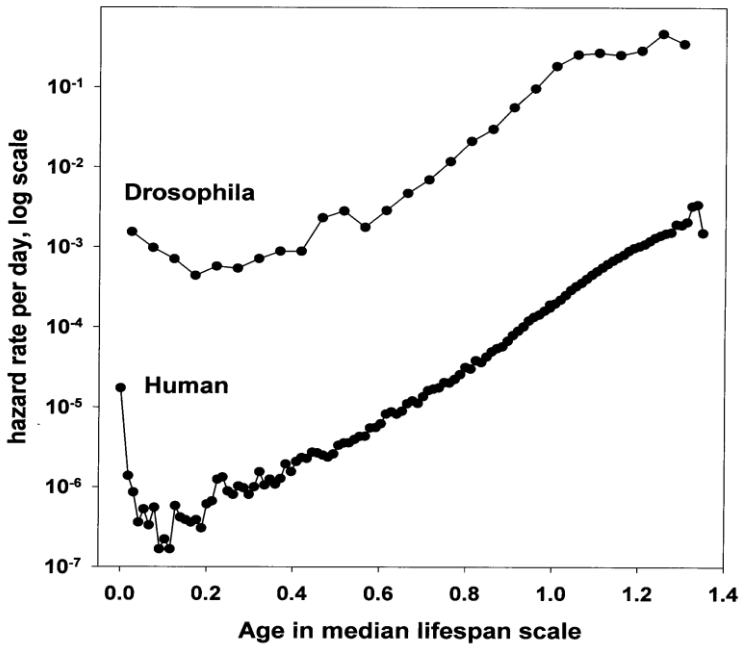

Figure 4. Bathtub mortality curves for humans and fruit flies.
Mortality is estimated on a daily basis, age is expressed in a median lifespan scale (a similar approach was used by Pearl & Miner, 1935 and Carnes et al., 1998). Mortality for *Drosophila melanogaster* was calculated using data published by Hall (1969). Mortality for humans was calculated using the official Swedish female life table for 1985 (ages 0-80 years), and the 1980-90 decennial life table for Swedish females available in the Kannisto-Thatcher Database on Old Age Mortality, http://www.demogr.mpg.de/databases/ktdb (ages over 80 years).
Source: Gavrilov & Gavrilova, 2005.

The bathtub curve consists of three periods. Initially the failure rates are high and decrease with age. This period is called the "working-in" period, and the period of "burning-out" of defective components. For example, the risk for a new computer to fail is often higher at the very start, but then those computers, which did not fail initially, work normally afterwards. The same period exists early in life for most living organisms, including humans, and it is called “infant mortality” period. Then follows the second period called “the normal working period”, corresponding to an age of low and approximately constant failure rates. This period also exists in humans, but unfortunately it is rather short (10-15 years) and ends too soon. Then the third period, “the aging period” starts, which involves an inexorable rise in the failure rate with age. In most living organisms, including humans, this rise in failure rates follows an explosive exponential trajectory (the Gompertz curve). For humans, the aging period lies approximately within the interval 20-100 years. Thus there is a remarkable similarity in the failure patterns of technical and biological systems. This similarity is reinforced further by the fact that at extreme old ages there is one more, the forth period common to both technical devices and living organisms (Economos, 1979). This period is known in biology as a period of late-life mortality leveling-off (Carey & Liedo, 1995; Clark & Guadalupe, 1995; Economos, 1979; Fukui *et al*., 1993; 1996; Vaupel *et al*., 1998), and also as the late-life mortality deceleration law (Fukui *et al*., 1993; 1996; Khazaeli *et al*., 1996; Partridge & Mangel, 1999).

B. Failure laws in survival studies

B.1 The Gompertz-Makeham law

Attempts to develop a fundamental quantitative theory of aging, mortality, and lifespan have deep historical roots. In 1825, the British actuary Benjamin Gompertz discovered a law of mortality (Gompertz, 1825), known today as the Gompertz law (Finch, 1990; Gavrilov & Gavrilova, 1991; Olshansky & Carnes, 1997; Strehler, 1978). Specifically, he found that the force of mortality increases in geometrical progression with the age of adult humans. According to the Gompertz law, human mortality rates double over about every 8 years of adult age.

Gompertz also proposed the first mathematical model to explain the exponential increase in mortality rate with age (Gompertz, 1825). 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 (Finch, 1990; Gavrilov, Gavrilova, 1991; Makeham, 1860; Strehler, 1978):

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

In this formula the first, age-independent term (Makeham parameter, *A*) designates the constant, 'non-aging' component of the failure rate (presumably due to external causes of death, such as accidents and acute infections), while the second, age-dependent term (the Gompertz function, $R\,e^{\alpha x}$) 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 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. 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 (Gavrilov & Gavrilova, 1991). 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).

The Gompertz-Makeham formula describes the life span distributions of a wide variety of biological species (drosophila, mosquitoes, flour beetles, mice, rats, horses and mountain sheep), including humans (Gavrilov and Gavrilova 1991). There are some reports that the competing Weibull formula (power law) fits data better than the Gompertz formula. These reports are usually based on analysis of a few life tables for populations of small size (often less than 100 animals). Our comparative study of Weibull and Gompertz models using data for 260 human life tables and 129 life tables for fruit flies (with large initial population size) demonstrated that on average the Gompertz-Makeham law fits mortality at adult ages better than the Weibull-Makeham law (Gavrilov and Gavrilova 1991) although in some rare cases Weibull formula shows better fit of mortality data.

Subsequently, there were many attempts to modify the Gompertz law. The most common way of modifying the Gompertz function is to use what are called logistic equations. The earliest such formula was proposed by Perks and the latest and the most widely used one was proposed by Kannisto and is called a Kannisto formula (Kannisto 1994):

$$\mu_x = \frac{B\exp(\alpha x)}{1 + B\exp(\alpha x)}$$

The formulas listed above are applicable to mortality of adult population (usually above age 20 years). There were also attempts to describe mortality in the entire age interval, such as Heligman-Pollard (Heligman and Pollard 1980) and Siler (Siler 1979) formulas.

Parametric formulas can be used in population projections by analyzing historical trends of their parameters. For example, in 1979, during an analysis of the historical changes in the mortality of the Swedish male population, it was found that the age-dependent component of mortality in the Gompertz-Makeham formula demonstrates surprising historical stability despite rapid decline in age-independent mortality (Makeham term) (Gavrilov and Gavrilova 1979). Further more careful investigation confirmed the validity of this phenomenon (Gavrilov and Gavrilova 1991; Gavrilov, Gavrilova and Nosov 1983) and the study of historical time series of mortality for 17 countries permitted the conclusion that it was quite general in character (Gavrilov and Gavrilova 1991). Figure 1 shows changes in total, background and senescent mortality for Swedish males. It can be seen that the background component of mortality is the only mortality component, which has significantly changed over the studied period (1900-1970). The senescent mortality (and two Gompertz parameters), turn out to be practically unchanged, despite the sharp fall in total mortality in the 20th century. We observe that the substantial decline in mortality rates in Sweden at the beginning of the 20th century can be explained by a decrease in the Makeham component while the Gompertz component remained virtually constant during the same period. In the 1960s, as the Makeham component had almost reached zero, it became foreseeable that the rapid decline in mortality rates would come to an end. And this is what happened in fact in the 1960s (Gavrilov et al. 1983). Thus, based on the observation of

the mortality tables for the first half of the 20th century, it was possible to predict a "biological limit" to the force of mortality. For example, at the beginning of the 20th century, total mortality was substantially higher in Norway than in Denmark. However, based on the observation that the Gompertz component was considerably lower in Norway, we were able to predict a reversal in the trend as the Makeham component declines. This is exactly what happened (Gavrilov and Gavrilova 1991). Similarly, in Italy, the mortality rates of men and women were virtually identical at the beginning of the 20th century but the biological limit for women was lower due to the lower corresponding Gompertz component. Based on data from the beginning of the 20th century, we were able to predict that eventually, women's mortality would become lower than male mortality (Gavrilov and Gavrilova 1991). However after the 1960s, new unexpected trends in mortality have started. These trends were not well visible at the time of this study, although some indications of further mortality decline have been already noticed (Gavrilov and Gavrilova 1991; Gavrilov and Nosov 1985).

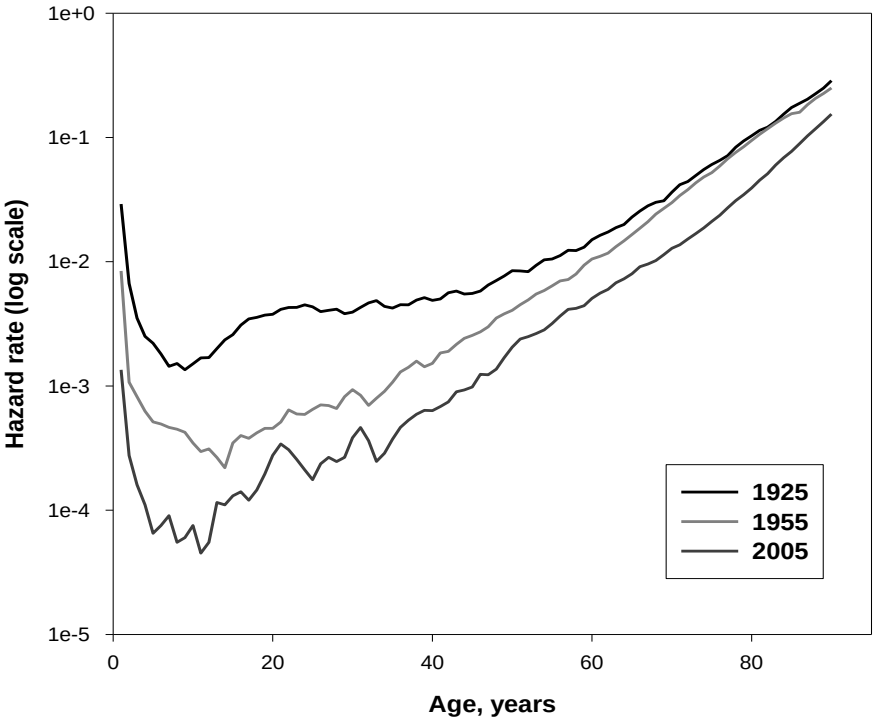

Figure 5. Changing patterns of mortality decline for Swedish females.

Recently Bongaarts developed further the method based on studying historical trends of Gompertz-Makeham parameters suggesting use of logistic formula for mortality forecasting (Bongaarts 2005). This modification was reasonable because mortality rates for period life tables in Human Mortality Database used in his study were fitted by logistic formula after age of 85 years (Wilmoth et al. 2007). His study analyzed historical trends in the interval 1950-2000 years for 14 countries and confirmed decline of the background mortality and stability of the slope parameter in the Gompertz term found in the previous studies. Due to the limited number of life tables (no life tables before 1950 were used) this study could not demonstrate the full scale of decline in background mortality during the first half of the 20th century. However this study revealed another interesting regularity that could not be fully analyzed in the past: decline in the pre-exponential multiplier of senescent mortality. Decline of this parameter (called the level parameter by Bongaarts) in conjunction with stability of the slope parameter in the Gompertz term means that the senescent component of mortality in developed countries undergoes parallel shift in semi-log coordinates over time. This pattern of mortality change was called a shifting logistic model (Bongaarts 2005). Based on this mortality pattern, Bongaarts suggested a new approach to mortality projections. This approach is based on estimating parameters of the logistic formula for a number of years and extrapolating the values of three parameters (background mortality and two parameters of senescent mortality) to the future (Bongaarts 2005, 2009).

Figure 5 illustrates the two phases of mortality decline in the 20th century. When we analyze mortality data on a larger time scale, we observe a decline of mortality in all age groups between 1925 and 1955 except for the elderly where death rates remained relatively constant. Note that mortality trajectories for 1925 and 1955 are close to each other at older ages, which corresponds to the stability of the senescent mortality during the first half of the 20th century. After the 1950s, the parallel shift of mortality has been observed, which corresponds to the model proposed by Bongaarts (for example, compare mortality trajectories for 1955 and 2005).

B.2. Late-life mortality deceleration

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 (Curtsinger et al., 1992; Economos, 1979; 1983; Gavrilov & Gavrilova, 1991; Greenwood and Irwin, 1939; Vaupel et al., 1998). Actuaries (including Gompertz himself) first noted this phenomenon and proposed a logistic formula for mortality growth with age in order to account for mortality fall off at advanced ages (Perks, 1932; Beard, 1959; 1971). Greenwood and Irwin (1939) provided a detailed description of this phenomenon in humans and even made the first estimates for the asymptotic value of human mortality (see also review by Olshansky, 1998). According to their estimates, the mortality kinetics of long-lived individuals is close to the law of radioactive decay with half-time approximately equal to 1 year.

The same phenomenon of 'almost non-aging' survival dynamics at extreme old ages is detected in many other biological species. In some species mortality plateau can occupy a sizable part of their life (see Figure 6).

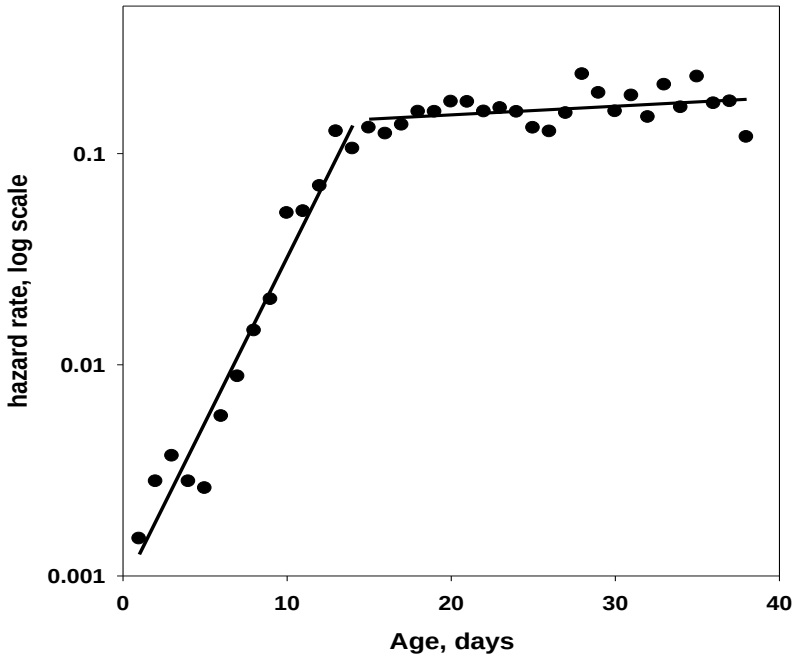

Figure 6. Mortality leveling-off in a population of 4,650 male house flies.
Hazard rates were computed using life table of house fly, *Musca domestica*, published by Rockstein and Lieberman (1959). Source: Gavrilov & Gavrilova, 2006.

Biologists were well aware about mortality leveling-off since the 1960s. For example, Lindop (1961) and Sacher (1966) discussed mortality deceleration in mice. Strehler and Mildvan (1960) considered mortality deceleration at advanced ages as a prerequisite for all mathematical models of aging to explain. Later A. Economos published a series of articles claiming a priority in the discovery of a “non-Gompertzian paradigm of mortality” (Economos, 1979; 1980; 1983; 1985). He reported that mortality leveling-off is observed in rodents (guinea pigs, rats, mice) and invertebrates (nematodes, shrimps, bdelloid rotifers, fruit flies, degenerate medusae *Campanularia Flexuosa*). In the 1990s the phenomenon of mortality deceleration and leveling-off became widely known after publications, which demonstrated mortality leveling-off in large samples of *Drosophila melanogaster* (Curtsinger et al.,

1992) and medflies *Ceratitis capitata* (Carey et al., 1992), including isogenic strains of Drosophila (Curtsinger et al., 1992; Fukui et al., 1993; 1996). Mortality plateaus at advanced ages are observed for some other insects: house fly *Musca vicina* and blowfly *Calliphora erythrocephala* (Gavrilov, 1980), bruchid beetle *Callosobruchus maculates* (Tatar et al., 1993), fruit flies *Anastrepha ludens*, *Anastrepha obliqua*, *Anastrepha serpentine* and a parasitoid wasp *Diachasmimorpha longiacaudtis* (Vaupel et al., 1998).

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 phenomenon is presenting a theoretical challenge to many models and theories of aging. One interesting corollary from these intriguing observations is that there seems to be no fixed upper limit for individual lifespan (Gavrilov, 1984; Gavrilov & Gavrilova, 1991; Wilmoth, 1997).

This observation calls for a very general explanation of this apparently paradoxical 'no aging at extreme ages' phenomenon.

B.3. Late-life mortality deceleration: Further developments

Mortality deceleration and subsequent mortality plateau (logistic formula) is now presented as universal mortality law. Indeed, the existence of mortality plateaus is well established for a number of lower organisms, mostly insects, including fruit flies, medflies and house flies (Carey et al. 1992; Curtsinger et al. 1992; Curtsinger, Gavrilova and Gavrilov 2006; Gavrilov and Gavrilova 2006; Vaupel et al. 1998). In the case of mammals, however, data are much more controversial. Although Lindop and Sacher reported short-term periods of mortality deceleration in mice at advanced ages (Lindop 1961; Sacher 1966) Austad later argued that rodents do not demonstrate mortality deceleration even in the case of large samples (Austad 2001). Study of baboons found no mortality deceleration at advanced ages (Bronikowski et al. 2002). Recent study of mortality in primates also failed to find mortality deceleration at older ages (Bronikowski et al. 2011). In the case of humans, this problem is not yet resolved, because of scarceness of data and/or their low reliability. Thus, more studies on larger human birth cohorts are required to establish with certainty the true mortality trajectory at advanced ages.

We have carried out a study based on the analyses of data taken from the U.S. Social Security Administration Death Master File (SSA DMF). Social Security Administration Death Master File (DMF) is a publicly available data source that allows a search for deceased individuals in the United States using various search criteria: birth date, death date, first and last names, social security number, place of last residence, etc. This resource covers deaths that occurred in the period 1937-2010 and captures about 95% of deaths recorded by the National Death Index (Sesso, Paffenbarger and Lee 2000). According to other estimates, DMF covers about 92-96 percent of deaths for persons older than 65 years (Hill, Rosenwaike, 2001).

We obtained data for persons who died before 2011 and were born in 1875-1895. Assuming that the number of living persons belonging to these birth cohorts in 2010 is close to zero, it is possible to construct a cohort life table using the method of extinct generations, which is considered to be the most accurate method to study old-age mortality (Kannisto 1994). In the first stage of our analyses we calculated an individual life span in completed months. Having this information it is possible to estimate hazard rates at each month of age by standard methods of survival analysis. All calculations were done using the Stata statistical software, release 11 (StataCorp 2009). This software calculates nonparametric estimates of major survival functions including the Nelson-Aalen estimator of hazard rate (force of mortality). In this study, survival times were measured in months, so the estimates of hazard rates initially had a dimension of $month^{-1}$. For the purpose of comparability with other published studies, which typically use the $year^{-1}$ time scale, we transformed the monthly hazard rates to the more conventional units of $year^{-1}$, by multiplying these estimates by a factor of 12 (one month in the denominator of hazard rate formula is equal to 1/12 year). It should be noted that hazard rate, in contrast to probability of death, can be greater than 1, and therefore its logarithm can be greater than 0 (and we indeed observed these values at extreme old ages in some cases). In this paper we focus our analyses on 1886-1895 birth cohorts, because we found that data quality for earlier cohorts is not particularly good.

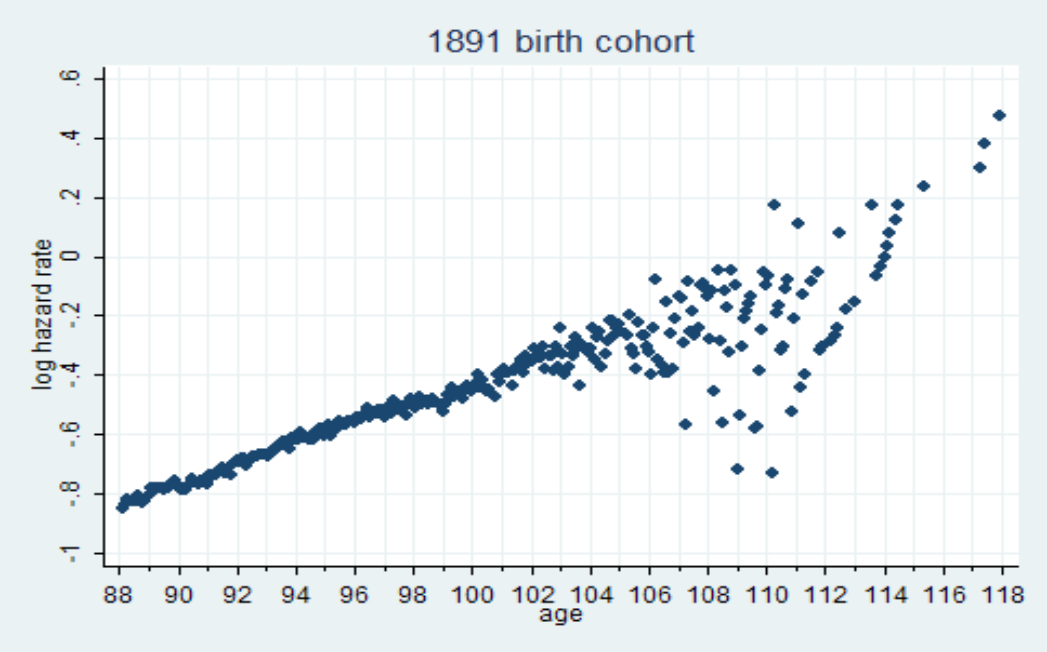

Figure 7. Age-specific hazard rates (log scale) for U.S. population born in 1891. Data from the Social Security Administration Death Master File.

Results of the hazard rate estimates for 1891 birth cohort are presented in Figure 7. Note that mortality trajectory in semi-log scale is linear up to the age 105-106 years. After age 106 years data points show very high variation suggesting declining data quality (possible age misreporting). One approach to evaluate data quality at advanced ages is to calculate female to male ratio at advanced ages. Taking into account that female mortality is always lower than male mortality it is reasonable to expect that the female-to-male ratio should continuously increase with age. On the other hand, old men have a tendency for age exaggeration and in populations with poor age registration there is a relative excess of men at very advanced ages (Caselli et al. 2006; Willcox et al. 2008). We calculated female-to-male ratio after age 95 years for 1887-1892 U.S. birth cohorts from the SSA DMF and found out that the female to male ratio is growing steadily with age up to ages 106-107 years. After this age the female-to-male ratio starts to decrease indicating declining quality of age reporting. This result agrees well with recent study that shows that invalid age clains in SSA DMF increase from 65% at age 110-111 to 98% by age 115 to 100% for 120+ years (Young et al., 2010). Thus, the estimates of hazard rates obtained from the SSA DMF are of acceptable quality up to the age of 106 years. For this reason we used age interval 88-106 years for mortality modeling.

Next step of our study was to compare two competing models of mortality at advanced ages - the Gompertz and the logistic models - using data of reasonably good quality. Study of data quality of at advanced ages described above suggests that age reporting among the oldest-old in the United States is good until the age of 106 years. It means that comparing mortality models beyond this age is not feasible because of poor quality of mortality data. It was shown that age reporting for persons applied to Social Security Numbers in the Southern states of the U.S. is significantly less accurate compared to persons applied in the Northern states regardless of race. (Rosenwaike and Stone 2003). For this reason, we used a subsample of deaths for persons applied to SSNs in the 'Northern' states and born in 1886-1895, because these data have reasonably good quality. We applied the Gompertz and logistic (Kannisto) models (Thatcher, Kannisto and Vaupel 1998) to mortality modeling in the age interval 88-106 years using nonlinear regression method for parameter estimation. Calculations were performed using Stata statistical software, release 11 (StataCorp 2009). Bayesian information criterion (BIC) was used as a goodness-of-fit measure and in 8 out of 10 cases (studied birth cohorts), the Gompertz model demonstrated better fit (lower BIC) than the logistic model for age interval 88-106 years. Our study of late-life mortality based on the data from the U.S. SSA Death Master File suggests that for rather homogeneous single-year birth cohorts mortality at advance ages does not decelerate up to very advanced ages.

Few people survive to advanced ages and, in standard mortality tables, it is frequently necessary to compile data over an entire decade to obtain a sufficiently large sample. Our work shows that the

observed deceleration in measured mortality rates could result in part from the heterogeneity of the data. There consequently remains a great deal of research to carry out if we are to improve our understanding of mortality at advanced ages. The second problem we examined is frequently overlooked by demographers and actuaries: the problem of correct estimation of the instantaneous mortality rate (hazard rate). At the most advanced ages, the rates of death are so high that it is impossible to assume that the number of dying is distributed uniformly within the studied one-year intervals. As a result, the estimates of mortality rates (or central death rates) are biased downwards at advanced ages. And finally, the third problem is related to the fact that elderly people tend to round their ages up, thereby exaggerating their true age. In the United States, this may have made impaired the accuracy of mortality rate estimates in the past.

These results of more careful study of mortality at advanced ages for humans as well as some recent data on mammals require additional explanations of why more complex biological systems (mammalian species) apparently lack mortality deceleration at advanced ages.

B.4. The Strehler-Mildvan correlation

In 1960, Bernard L.Strehler and Albert S.Mildvan published an article entitled "General Theory of Mortality and Aging" in the leading scientific journal Science (Strehler and Mildvan, 1960). In this article, it was noted in particular that there is an inverse relationship between the parameters of the Gompertz law: in those countries where the values of the pre-exponential multiplier (designated as R_0) were high, the values of the exponential index (α) were reduced. If these values, obtained for a number of countries, are plotted on a single graph, a near-linear inverse relationship is observed between α and the logarithm of R_0 (Strehler and Mildvan, 1960). Subsequently, this observation became known as the Strehler-Mildvan correlation, and it acquired the status of a fundamental law describing the survivorship of organisms (Strehler, 1977).

Strehler and Mildvan (1960) describe their research method as follows: "The age specific mortality rates of all countries in the UN Demographic Yearbook 1955 were plotted on semi-log paper. The curves were smooth for nearly all countries. However, in those few instances where great scatter was exhibited, the data were not further analyzed. the best straight lines through points from age 50 to 70 and, in most cases, from age 35 to 80 were drawn visually, and the values of R_0 and α were extracted by graphical extrapolation and measurement, respectively" (Strehler and Mildvan, 1960, p.21).

Three comments arise in relation to the above-mentioned methodology. First of all, the authors have analyzed not the force of mortality, but the probability of death. However, as has already been noted, exponential growth is characteristic of the hazard rate rather than the probability of death. Nevertheless, this limitation is not very important, since for ages 35-80 the numerical values of the hazard rate and the probability of death (for one-year age interval) practically coincide.

The second limitation concerns the quality of the statistical processing of the data. In fact, the data were analyzed by subjective methods ("straight lines ... were drawn visually"), for different age intervals (sometimes for ages 50-70, sometimes for ages 35-80), and with no estimate of the accuracy of the determined quantities (absence of confidence intervals). This method of data analysis is without doubt not the best method available even at that time. However, this limitation also can be considered unimportant in comparison with the third and final limitation.

In their study, Strehler and Mildvan have completely ignored the existence of the background component of mortality, although this quantity should not have been neglected, especially in the case of the following tables used by the authors: Algeria (1948), Argentina (1947), Brazil (1950), Costa Rica (1950), Egypt (1947), etc. Of course, when the background component of mortality is zero, the analysis of the data is greatly simplified, reducing to the determination of the parameters of the linear dependency between the logarithm of the force of mortality and age. However, in this particular case, this simplification is completely unfounded, as can be seen even in the graphs presented by the authors. For example, Fig.1 of the article in question contains a graph of the logarithm of the mortality rate against age for Egyptian men in 1947. This graph, which has a pronounced concave shape bearing witness to a high background mortality, cannot, even with a feat of the imagination, be called linear (see Strehler and Mildvan, 1960). Despite the fact that the authors cite the Gompertz-Makeham formula at the beginning of the article, their subsequent analysis is based on the Gompertz

formula. As will be demonstrated below, this "simplification" alone is sufficient to generate a spurious correlation which coincides with the Strehler-Mildvan correlation.

Figure.8 shows, in semi-logarithmic coordinates, the graph of the logarithm of the hazard rate as a function of age for the same values of parameters R_0 and α, but different values of parameter A. It can be observed that, as the background component of mortality (A) is reduced, the graph becomes steeper and steeper, corresponding to an increased estimate for parameter à as determined graphically from a measurement of the slope. It can also be seen that at the same time there is a reduction in the value of the point at which the straight line drawn by Strehler and Mildvan intersects the y-axis. This corresponds to a reduction in the estimate for parameter RÂ, likewise determined graphically. Consequently, the method used by Strehler and Mildvan to determine the parameters leads to biased estimates for R_0 and α, and what is more, when the background component of mortality (A) is altered, these estimates are biased in opposite directions, generating a false correlation.

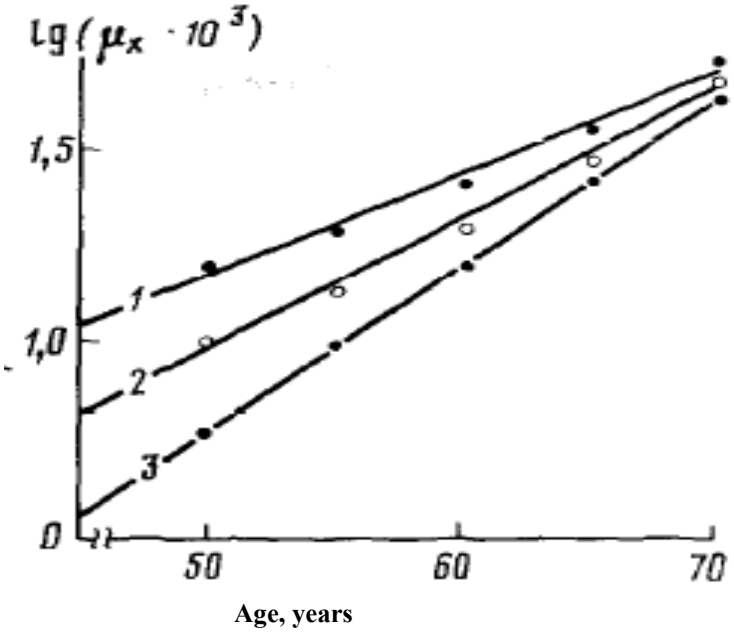

Figure 8. Modeling mortality at different levels of Makeham parameter but constant Gompertz parameters. 1 – A=0.01 year^{-1}; 2 – A=0.004 year^{-1}; 3 – A=0 year^{-1}.

Naturally, the question which arises is whether this spurious correlation, related to the incorrect data treatment, coincides with the Strehler-Mildvan correlation. In order to answer this question, we carried out a numerical experiment using typical values for the parameters of the Gompertz-Makeham formula: α = 0.1 year-1, $R_0 = 4\times10^{-5}$ year^{-1}, A = 0.0-0.01 year^{-1}. With these constant values of parameters R_0 and α, dependencies between the hazard rate and age were modeled for a whole range of values of parameter A. Then the data were analyzed in accordance with the methodology used by Strehler and Mildvan. Since these authors did not indicate the cases in which they used the age interval 35-80 for the linearization, and the cases in which they used 50-70, one and the same interval (50-70 years) was used for the analysis of the data. In conformity with the methodology used by Strehler and Mildvan, the intervals between the points were 5 years, so that each dependency contained 5 points corresponding to ages 50, 55, 60, 65 and 70. The only essential difference from the methodology of Strehler and Mildvan was that the "linear" dependency was determined not visually, but by the least squares method, in order to eliminate any subjectivity in estimating the parameters of the "straight" line, and in order to determine their accuracy. The results of these calculations showed that depending on the level of the background component of mortality, a significant bias was observed in estimates of the parameters R_0 and α (Gavrilov, Gavrilova, 1991). If these results were compared with Strehler and Mildvan's data, there was a striking coincidence (see Figure 9). Thus, the Strehler-Mildvan correlation is not different from the spurious correlation created by the incorrect method used by Strehler and Mildvan.

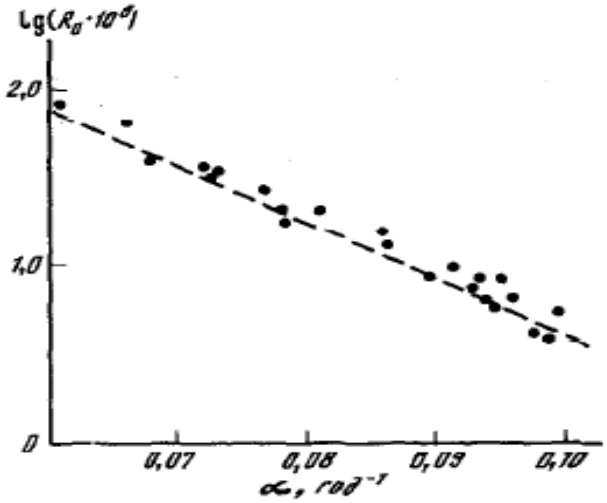

Figure 9. Coincidence of the spurious inverse correlation between the Gompertz parameters and the Strehler-Mildvan correlation. Dotted line – spurious inverse correlation between the Gompertz parameters. Data points for the Strehler-Mildvan correlation were obtained from the data published by Strehler-Mildvan (1960).

This example shows that a discussion of what appear to be purely methodological questions can lead to exceptionally important conclusions. Indeed, the correlation claimed by Strehler and Mildvan is widely cited without any serious critical analysis (Strehler, 1978; Doubal, 1982; Yashin et al., 2002; Bebbington et al., 2011; Zheng et al., 2011), and is even considered to be a fundamental law which every theory of aging, mortality and life span must obey (Strehler and Mildvan, 1960; Strehler, 1978). However, attempts to use the Strehler and Mildvan correlation in constructing mathematical models of aging lead to absurd results. Indeed, from the data presented in the article by Strehler and Mildvan (1960), it follows that the slope coefficient of the linear regression of $\ln R_0$ with α is only 68.5 years. However, in the framework of the "General theory of mortality and aging" by Strehler and Mildvan (1960), this quantity ought to correspond to the age at which so-called vitality, "the capacity of an individual organism to stay alive" (p.15), becomes zero! The absurd result that this parameter, equal to 68.5 years, corresponds to an absolute limit to the human life span, follows from another mathematical model of aging and mortality (Koltover, 1983). The incongruity of these consequences of the Strehler-Mildvan correlation was pointed out by the French demographer Herve Le Bras (Le Bras, 1976). Indeed, the magnitude of the species-specific limit to the human life span turns out to be significantly less than average life span of the population of many developed countries! It would seem that this artefact alone ought to have put researchers working in this area on their guard. However, unfortunately, this did not happen (Strehler, 1978; Doubal, 1982; Koltover, 1983; Yashin et al., 2002; Bebbington et al., 2011; Zheng et al., 2011), although the existence of a contradiction is obvious and has been pointed out on several occasions (Le Bras, 1976; Gavrilov et al., 1978; Gavrilov, 1984).

Since the data in Strehler and Mildvan's article are processed using the subjective visual method, we attempted in 1978 to arrive at a new estimate of the slope coefficient of the given dependency, in order to exclude the possibility of error at this point also (Gavrilov et al., 1978). The values of the parameters R_0 and α were taken from the same article by Strehler and Mildvan (from the table which presents 32 paired values of the parameters for the male population of different countries in the world), and the least square method was used to determine the value of the slope coefficient of the linear regression of $\ln R_0$ with α. The value of this coefficient and the corresponding standard deviation turned out to be 74±3 years (Gavrilov et al., 1978). Although the calculated value is somewhat larger than the estimate obtained by Strehler and Mildvan (68.5 years), it is nevertheless significantly lower than the required value for a species-specific limit to the human life span.

Of course, the contradiction which has been exposed may be related to a whole range of causes: the artefactual nature of the Strehler-Mildvan correlation, the incorrectness of the proposed mathematical models of mortality, and the erroneous nature of the very notion of an absolute species-specific life span limit. It is possible that all three of these factors are present in this case. Naturally, the authors themselves (B.L.Strehler and A.S.Mildvan) could not help but notice the lack of consistency between their theory of mortality and the estimate of the species-specific life span limit which

follows from the correlation they discovered. However, they did not place any emphasis on this disagreement, and quickly turned to other methods of estimating the magnitude of the species-specific limit which are based on additional assumptions (Strehler and Mildvan, 1960). For instance, on the assumption that the life span limit corresponds to the age at which the exponentially increasing mortality rate becomes unity, it was calculated that this limit is 103 years (Strehler and Mildvan, 1960). It can be seen that even this estimate is significantly lower than the vast number of documented cases of exceptional longevity. In addition, as can be calculated from Strehler and Mildvan's (1960) data, this value is not a species-specific invariant and varies widely from population to population, oscillating within the range 90-116 years. Nevertheless, in their subsequent publications, the authors did not return to check the reliability of the described correlation, referring to it as to an established fact (Strehler, 1978). Their example was followed by other investigators (Doubal, 1982; Koltover, 1983; Yashin et al., 2002; Bebbington et al., 2011; Zheng et al., 2011). This situation may seem rather strange, but it has to be admitted that the canonization of artefacts through long-term uncritical citation is often happened in modern science.

Thus, although the Strehler and Mildvan correlation is widely cited in the scientific literature, it cannot be considered a proven scientific fact. What is more, the failure of Strehler and Mildvan to take into account the background component of mortality inevitably generates an artefactual dependency which, as we have shown, coincides with the dependency described by Strehler and Mildvan. Nevertheless, this does not mean that the very idea of comparing the parameters of the Gompertz-Makeham formula is flawed. On the contrary, as will be shown below, this idea can be brought to fruition if only we correctly estimate the parameters of the Gompertz-Makeham formula.

B.2 Compensation law of mortality

In 1978, the so-called compensation effect of mortality was discovered (Gavrilov et al., 1978), and its existence was confirmed in subsequent research (Gavrilov, 1984; Gavrilov and Gavrilova, 1979). It turns out that, within the limits of a single species, the values of the age-dependent component of mortality are correlated in such a way that, when extrapolated, they meet at a single point. This surprising phenomenon is not only observed in man, but also in the fruit fly Drosophila melanogaster (Gavrilov, Gavrilova, 1991; 2006). It can be seen that this intersection at a single point is related to the fact that the reduction in the level of the age-dependent component of mortality in the transition to more fortunate populations is compensated by an increase in the relative rates at which it grows with age, hence the name compensation effect or compensation law of mortality (Gavrilov et al., 1978; Gavrilov, 1984).

This empirical observation, 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 by lower values of the parameter *R* in different populations of a given species:

$$\ln(R) = \ln(M) - B\alpha$$

where B and M are universal species-specific invariants. Sometimes this relationship is also called the Strehler-Mildvan correlation (Strehler, 1978; Strehler & Mildvan, 1960), although (as it was shown earlier) 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 & Gavrilova, 1991; Golubev, 2004). 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 (Gavrilov & Gavrilova, 1979; 1991). This means that high mortality rates in disadvantaged populations (within a given species) are *compensated* for by a low apparent 'aging rate' (longer mortality doubling period). As a result of this compensation, the relative differences in mortality rates tend to decrease with age within a given biological species (Figure 10).

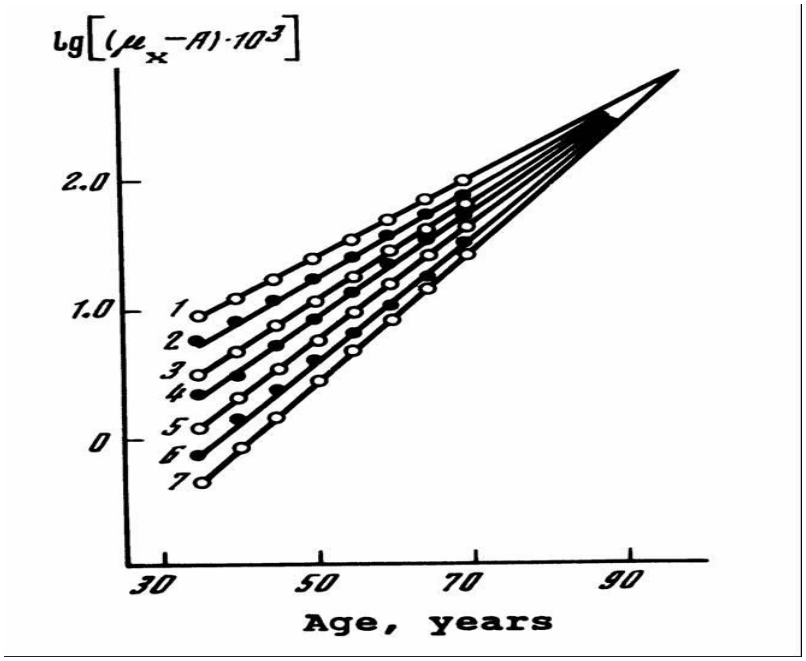

Figure 10. Compensation Law of Mortality.
Convergence of mortality rates in different populations at advanced ages.
Death rates (with removed age-independent external mortality component) are plotted in a log scale as a function of age in the following countries: 1 – India, 1941-1950, males; 2 – Turkey, 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 & Gavrilova, "The Biology of Life Span," 1991.

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 (Gavrilov & Gavrilova, 1991; Strehler, 1978).

There are some exceptions both from the Gompertz law of mortality and the compensation law of mortality that have to be understood and explained. There were reports that in some cases the organisms die according to the Weibull (power) law (see section II.B). The Weibull law is more commonly applicable to technical devices (Barlow & Proschan, 1975; Rigdon & Basu, 2000; Weibull, 1951), while the Gompertz law is more common in biological systems (Finch, 1990; Gavrilov & Gavrilova, 1991; Strehler, 1978). As was already noted, the exponential Gompertzian increase in age-specific mortality is observed for many biological species including fruit flies *Drosophila melanogaster*, nematodes, mosquitoes, human lice, flour beetles, mice, rats, dogs, horses, mountain sheep, baboons and humans. Comparative meta-analysis of 129 life tables for fruit flies as well as 285 life tables for humans demonstrates that the Gompertz law of mortality provides a much better data fit for each of these two biological species, compared to the Weibull law (Gavrilov & Gavrilova, 1991, pp. 55-56, 68-72). 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 & Gavrilova, 1991, 2001; 2005) and will be discussed later in this paper (see section V).

Both the Gompertz and the Weibull failure laws have fundamental explanation rooted in reliability theory (Barlow & Proschan, 1975) and are the only two theoretically possible *limiting extreme value distributions* for systems whose lifespans are determined by the first failed component (Gumbel, 1958; Galambos, 1978). In other words, as the system becomes more and more complex (contains more vital components, each being critical for survival), its lifespan distribution may asymptotically approach one of the only two theoretically possible limiting distributions - either Gompertz or Weibull (depending on the early kinetics of failure of system components). The two limit theorems in the statistics of extremes (Gumbel, 1958; Galambos, 1978) make the Gompertz and the Weibull failure laws as fundamental as are some other famous limiting distributions known in regular statistics, e.g., the normal distribution and

the Poisson distribution. It is puzzling, however, why organisms prefer to die according to the Gompertz law, while technical devices typically fail according to the Weibull law. One possible explanation of this mystery is suggested later in this paper.

Thus, a comprehensive theory of species aging and longevity should provide answers to the following questions:

(1) Why do most biological species deteriorate with age (i.e., die more often as they grow older) while some primitive organisms do not demonstrate such a clear mortality growth with age (Austad, 2001; Finch, 1990; Haranghy & Balázs, 1980; Martinez, 1998)?

(2) Specifically, why do mortality rates increase exponentially with age in many adult species (Gompertz law)? How should we handle cases when the Gompertzian mortality law is not applicable?

(3) Why does the age-related increase in mortality rates vanish at older ages? Why do mortality rates eventually decelerate compared to predictions of the Gompertz law and occasionally demonstrate leveling-off (late-life mortality plateau)? Why does mortality deceleration look not so strong in mammalian species including humans?

(4) How do we explain the so-called compensation law of mortality (Gavrilov & Gavrilova, 1991)?

Any theory of human aging has to explain these last three rules, known collectively as mortality, or failure, laws. And reliability theory, by way of a clutch of equations, covers all of them (see section V, and Gavrilov & Gavrilova, 1991, 2001; 2005).

C. Decline in systems' redundancy with age

Many age changes in living organisms can be explained by cumulative effects of cell loss over time. For example, such very common phenomenon as hair graying with age is caused by depletion of hair follicle melanocytes (Commo et al., 2004). Melanocyte density in human epidermis declines gradually with age at a rate approximately 0.8% per year (Gilchrest et al., 1979). Hair graying is a relatively benign phenomenon, but cell loss can also lead to more serious consequences.

Recent studies found that such conditions as atherosclerosis, atherosclerotic inflammation and consequent thromboembolic complications could be linked to age-related exhaustion of progenitor cells responsible for arterial repair (Goldschmidt-Clermont, 2003; Libby, 2003; Rauscher et al., 2003). Taking these progenitor cells from young mice and adding them to experimental animals prevents atherosclerosis progression and atherosclerotic inflammation (Goldschmidt-Clermont, 2003; Rauscher et al., 2003).

Age-dependent decline in cardiac function is also linked to the failure of cardiac stem cells to replace dying myocytes with new functioning cells (Capogrossi, 2004). It was found that aging-impaired cardiac angiogenic function could be restored by adding endothelial precursor cells derived from the young bone marrow (Edelberg et al., 2002).

Chronic renal failure is known to be associated with decreased number of endothelial progenitor cells (Choi, 2004). People with diminished numbers of nephrons in their kidneys are more likely to suffer from hypertension (Keller et al., 2003), and the number of glomeruli decreases with human age (Nyengaard & Bendtsen, 1992).

Humans generally loose 30-40% of their skeletal muscle fibers by age 80 (Leeuwenburgh, 2003), which contributes to such adverse health outcomes as sarcopenia and frailty. Loss of striated muscle cells in such places as rhabdosphincter from 87.6% in 5-week-old child to only 34.2% in 91-year-old has obvious implications for urological failure – incontinence (Strasser, 2000).

A progressive loss of dopaminergic neurons in substantia nigra results in Parkinson's disease, loss of GABAergic neurons in striatum produces Huntington's disease, loss of motor neurons is responsible for amyotrophic lateral sclerosis, and loss of neurons in cortex is causing the Alzheimer's disease over time (Baizabal et al., 2003). A study of cerebella from normal males aged 19-84 years revealed that the global white matter was reduced by 26% with age, and a selective 40% loss of both Purkinje and granule cells was observed in the anterior lobe. Furthermore a 30% loss of volume, mostly due to a cortical volume loss, was found in the anterior lobe, which is predominantly involved in motor control (Andersen et al., 2003).

Such phenomenon of human aging as menopause also is caused by loss of ovarian cells. 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 (Gosden, 1985; Finch & Kirkwood,

2000; Wallace & Kelsey, 2004). It is now well established that the exhaustion of the ovarian follicle numbers over time is responsible for menopause (reproductive aging and failure), and women having higher ovarian reserve have longer reproductive lifespan (Wallace & Kelsey, 2004). When young ovaries were transplanted to old post-reproductive mice, their reproductive function was restored for a while (Cargill et al., 2003). This example illustrates a general idea that aging largely occurs because of cell loss, which starts early in life.

Loss of cells with age is not limited to the human species and is observed in other animals as well. For example, a nematode *C. elegans* demonstrates a gradual, progressive deterioration of muscle, resembling human sarcopenia (Herndon et al., 2002). The authors of this study also found that the behavioral ability of nematode was a better predictor of life expectancy than chronological age.

Interestingly, caloric restriction can prevent cell loss (Cohen et al., 2004; McKiernan et al., 2004), which may explain why caloric restriction delays the onset of numerous age-associated diseases and can significantly increase life-span in mammals (Masoro, 2003).

In terms of reliability theory the loss of cells with age is a loss of system redundancy, and therefore this paper will focus further on the effects of redundancy loss on systems aging and failure.

IV. Causes of failure rate increase with age

A. The origin of age-related increase in failure rates

Aging period for most species occupies the greater part of their lifespan, therefore any model of mortality must explain the existence of this period. It turns out that 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 & Gavrilova, 1991). The detailed mathematical proof of this prediction for some particular models is provided elsewhere (Gavrilov & Gavrilova, 1991; 2001) and is briefly described in the next sections of this paper.

The simplest schema, which demonstrates an emergence of aging in a redundant system is presented in Figure 11.

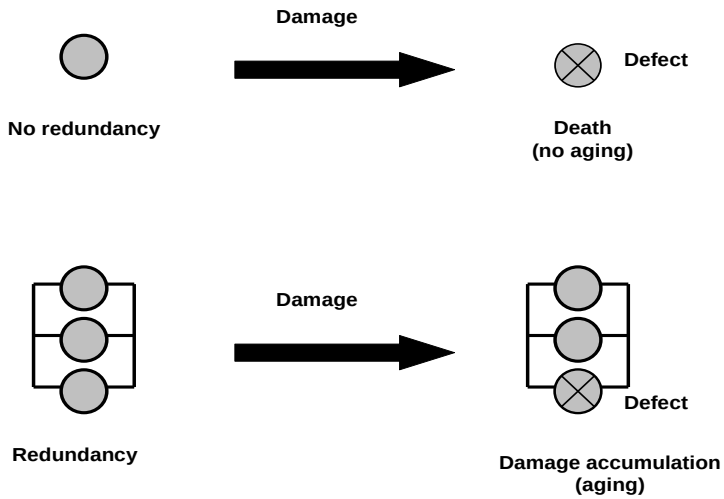

Figure 7. Redundancy creates both damage tolerance and damage accumulation (aging). Systems without redundancy (on the top) fail every time when they are damaged, and therefore damage is not accumulated among survivors (no aging). Redundant systems (on the bottom) can sustain damage because of their redundancy, but this damage tolerance leads to damage accumulation (aging).

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. For example, the inactivation of microbial cells and spores exposed to a hostile environment (such as heat) follows approximately a nonaging mortality kinetics; their semi-logarithmic survival curves are almost linear (Peleg et al., 2003). This observation of nonaging survival dynamics is extensively used in the calculation of the efficacy of sterilization processes in medicine and food preservation (Brock et al., 1994; Davis et al., 1990; Jay, 1996). A similar nonaging pattern of inactivation kinetics is often observed for viruses (Andreadis & Pallson, 1997; Kundi, 1999) and enzymes (Kurganov, 2002; Gouda et al., 2003).

In more complex systems with many vital structures and significant redundancy, every occurrence of damage does not lead to death (unless the environment is particularly hostile) because of their redundancy. Defects accumulate, therefore, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence (trade-off) of a system's redundancies, which ensure increased reliability and an increased life span of more complex 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, in which 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 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.

The positive effect of systems' redundancy is *damage tolerance*, which decreases the risk of failure (mortality) and increases lifespan. However damage tolerance makes it possible for damage to be tolerated and accumulated over time, thus producing the aging phenomenon.

The next section provides a mathematical illustration for these ideas.

B. The simplest reliability model of aging

In this section we show that a system built of non-aging components demonstrates an aging behavior (mortality growth with age) and subsequent mortality leveling-off.

Consider a parallel system built of n non-aging elements with a constant failure rate μ and reliability (survival) function $e^{-\mu x}$ (see also figure 3b). We already showed (see section II.C) that in this case the reliability function of the entire parallel system is:

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

This formula corresponds to the simplest case when the failure of elements is statistically independent. More complex models would require specific assumptions or prior knowledge on the exact type of the interdependence in elements failure. One of such models known as "the model of the avalanche-like destruction" is described elsewhere (see pp. 246-251 in Gavrilov, Gavrilova, 1991) and is briefly summarized in section V.

Consequently, the failure rate of the entire system $\mu_s(x)$, can be written as follows:

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

$$\approx n\mu^n x^{n-1}$$

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

$$\approx \mu$$

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

Thus, the failure rate of a system initially grows as a power function *n* 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 μ.

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 μ). 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 μ). Thus, the compensation law of mortality (in its weak form) is an expected outcome of this illustrative model.

Note also that the identical parallel systems in this example do not die simultaneously when their elements fail by chance. A common view in biology is the idea that all the members of homogeneous population in a hypothetical constant environment should die simultaneously so that the survival curve of such population would look like a rectangle. This idea stems from the basic principles of quantitative genetics, which assume implicitly that every animal of a given genotype has the same genetically determined lifespan so that all variation of survival time around a genotype mean results from the environmental variance. George Sacher (1977) pointed out that this concept is not applicable to longevity and used an analogy with radioactive decay in his arguments.

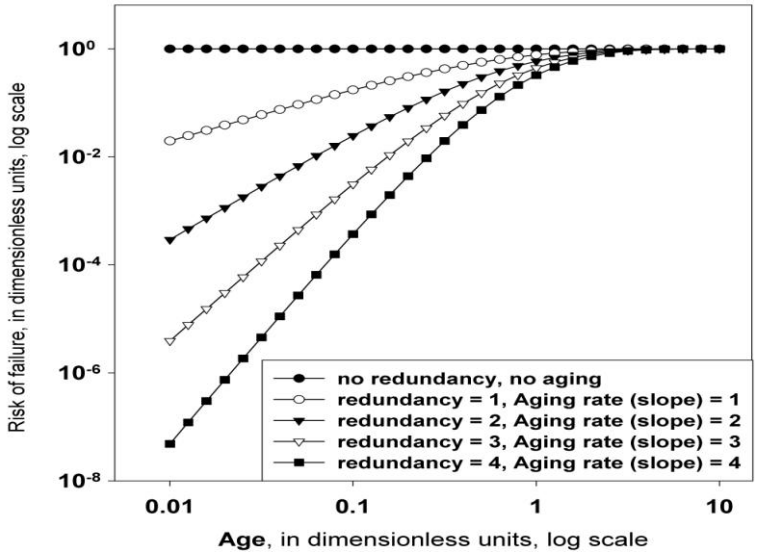

Figure 12. Failure kinetics of systems with different levels of redundancy.
The dependence of the logarithm of mortality force (failure rate) on the logarithm of age in five systems with different levels of redundancy (computer simulation experiment). The scales for mortality rates (vertical axis), and for age (horizontal axis) are presented in dimensionless units (μ_s/μ) for mortality rates, and μx for age), to ensure the generalizability of the results (invariance of graphs on failure rate of the elements in the system, parameter μ). 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).

Dependence 1 is for the system containing only one unique element (no redundancy). Dependence 2 is for the system containing two elements connected in parallel (degree of redundancy = 1). Dependencies 3, 4 and 5 are for systems containing, respectively, 3, 4 and 5 elements connected in parallel (with increasing levels of redundancy). Source: Gavrilov & Gavrilova, 2006.

Even the simplest parallel system has a specific lifespan distribution determined entirely by a stochastic nature of the aging process. In order to account for this stochasticity it was proposed to use a stochastic variance component of lifespan in addition to genetic and environmental components of phenotypic lifespan variance (Gavrilov & Gavrilova, 1991). Stochastic nature of system's destruction

also produces heterogeneity in an initially homogeneous population. This kind of induced heterogeneity was observed in isogenic strains of nematodes, in which aging resulted in substantial heterogeneity in behavioral capacity among initially homogeneous worms kept in controlled environmental conditions (Herndon et al., 2002).

The graph shown in Figure 12 depicts mortality trajectories for five systems with different degrees of redundancy. System 1 has only one unique element (no redundancy), and it has the highest failure rate, which does not depend on age (no aging). System 2 has two elements connected in parallel (one extra element is redundant), and the failure rate initially increases with age (aging appears). The apparent rate of aging can be characterized by a slope coefficient that is equal to 1. Finally, the failure rate levels off at advanced ages. Systems 3, 4, and 5 have, respectively, three, four, and five elements connected in parallel (two, three, and four extra elements are redundant), and the failure rate initially increases with age at an apparent aging rate (slope coefficient) of 2, 3, and 4, respectively. Finally, the mortality trajectories of each system level off at advanced ages at exactly the same upper limit to the mortality rate.

This computational example illustrates the following statements: (i) 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 equal to the degree of redundancy in parallel systems. (ii) All mortality trajectories tend to converge with age, so that the compensation law of mortality is observed. (iii) 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 of initial damage load should be taken into account (see next section).

V. Theoretical models of systems failure in aging

A. Highly redundant system replete with defects

It was demonstrated in section IV that failure rate of a simple parallel system grows with age according to the Weibull law. This model analyzed initially ideal structures in which all the elements are functional from the outset. This standard assumption may be justified for technical devices manufactured from pretested components, but it is not justified for living organisms, replete with initial defects (see Gavrilov & Gavrilova, 1991; 2001; 2004b; 2005).

Following the tradition of the reliability theory, we start our analysis with reliability of an individual system (or homogeneous population). This model of series-parallel structure with distributed redundancy was suggested by Gavrilov and Gavrilova in 1991 and described in more detail in 2001.

Consider first a series-parallel model in which initially functional elements occur very rarely with low probability q, so that the distribution of the organism's subsystems (blocks) according to the initial functioning elements they contain is described by the Poisson law with parameter $\lambda = nq$. Parameter λ corresponds to the mean number of initially functional elements in a block.

As has already been noted, the failure rate of a system constructed out of m blocks connected in series is equal to the sum of the failure rates of these blocks, μ_b (Barlow et al., 1965):

$$\mu_s = \sum \mu_b = \sum_{i=1}^{n} m P_i \mu_b(i) = mCe^{-\lambda} \sum_{i=1}^{n} \frac{\lambda^i \mu_b(i)}{i!}$$

where P_i is a probability of block to have i initially functioning elements. Parameter C is a normalizing factor that ensures the sum of the probabilities of all possible outcomes being equal to unity (see Gavrilov, Gavrilova, 1991; 2001). For sufficiently high values of n and λ, the normalizing factor turns out to be hardly greater than unity.

Using formula for failure rate of block of elements connected in parallel (see section IV.B), we obtain the final expression for the series-parallel system with distributed redundancy:

$$\mu_s = \mu\lambda mCe^{-\lambda}\sum_{i=1}^{n}\frac{(\lambda\mu x)^{i-1}}{(i-1)!} \approx R(e^{\alpha x} - \varepsilon(x)) \approx Re^{\alpha x}$$

where $R = Cm\lambda\mu e^{-\lambda}$, $\alpha = \lambda\mu$

$\varepsilon(x)$ is close to zero for large n and small x (initial period of life, see Gavrilov, Gavrilova, 1991; 2001 for more detail).

In the early-life period (when $x << 1/\mu$) the mortality kinetics of this system follows the exponential Gompertzian law.

In the late-life period (when $x >> 1/\mu$), the failure rate levels-off and the mortality plateau is observed:

$$\mu_s(x) \approx m\mu$$

If the age-independent mortality (*A*) also exists in addition to the Gompertz function, we obtain the well-known Gompertz-Makeham law described earlier. At advanced ages the rate of mortality decelerates and approaches asymptotically an upper limit equal to $m\mu$.

The model explains not only the exponential increase in mortality rate with age and the subsequent leveling off, but also the compensation law of mortality:

$$\ln(R) = \ln(Cm\alpha) - \frac{\alpha}{\mu} = \ln(M) - B\alpha$$

where $M = Cm\alpha$, $B = 1/\mu$.

According to this model, the compensation law is inevitable whenever differences in mortality arise from differences in the parameter λ (the mean number of initially functional elements in the block), while the 'true aging rate' (rate of elements' loss, μ) is similar in different populations of a given species (presumably because of homeostasis). In this case, the species-specific lifespan estimated from the compensation law as an expected age at mortality convergence (95 years for humans, see Gavrilov & Gavrilova, 1991) characterizes the mean lifetime of the elements ($1/\mu$).

The model also predicts certain deviations from the exact mortality convergence in a specific direction because the parameter *M* proved to be a function of the parameter α according to this model (see earlier). This prediction could be tested in future studies.

It also follows from this model that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements (λ) can potentially result in a remarkable fall in mortality and a significant improvement in lifespan.

The model assumes that most of the elements in the system are initially non-functional. *This interpretation of the assumption can be relaxed, however, because most non-functional elements (e.g., cells) may have already died and eliminated by the time the adult organism is formed*. In fact, the model is based on the hypothesis that the number of *functional* elements in the blocks is described by the Poisson distribution, and the fate of defective elements and their death in no way affects the conclusions of the model. Therefore, the model may be reformulated in such a way that stochastic events in early development determine later-life aging and survival through variation in initial redundancy of organs and tissues (see, for example, Finch & Kirkwood, 2000). Note that this model does not require an assumption of initial population heterogeneity in failure risks. Instead the model is focused on distributed redundancy of physiological systems within a given organism, or a group of initially identical organisms.

B. Partially damaged redundant system

In the preceding section, we examined a reliability model for a system consisting of *m* series-connected blocks with numbers of elements distributed according to the Poisson law. In this section, we consider a more general case in which the probability of an element being initially functional can take any possible value: $0 < q \leq 1$ (see Gavrilov & Gavrilova, 1991; 2001 for more detail).

In the general case, the distribution of blocks in the organism according to the number of initially functional elements is described by the binomial rather than Poisson distribution.

If an organism can be presented as a system constructed of *m* series-connected blocks with binomially distributed elements, its failure rate is given by the following formula:

$$\mu_s \approx Cmn(q\mu)^n \left(\frac{1-q}{q\mu} + x \right)^{n-1} = Cmn(q\mu)^n (x_0 + x)^{n-1}$$

where $x_0 = \frac{1-q}{q\mu}$

It is proposed to call a parameter x_0 the *initial virtual age of the system, IVAS* (Gavrilov & Gavrilova, 1991; 2001). Indeed, this parameter has the dimension of time, and corresponds to the age by which an initially ideal system would have accumulated as many defects as a real system already has at the initial moment in time (at $x = 0$). In particular, when $q = 1$, i.e., when all the elements are functional at the beginning, the initial virtual age of the system is zero and the failure rate grows as a power function of age (the Weibull law), as described in the section IV. However, when the system is not initially ideal ($q < 1$), we obtain the *binomial law of mortality* (see section II.B).

In the case when $x_0 > 0$, there is always an initial period of time, such that $x << x_0$ and the following approximation to the binomial law is valid:

$$\mu_s \approx Cmn(q\mu)^n x_0^{n-1} \left(1 + \frac{x}{x_0} \right)^{n-1} \approx Cmn\ (q\mu)^n x_0^{n-1} \exp\left[\frac{n-1}{x_0}\ x \right]$$

Hence, for any value of $q < 1$ there always exists a period of time x when the number of newly formed defects is much less than the original number, and the failure rate grows exponentially with age.

So, if the system is not initially ideal *(q<1)*, the failure rate in the initial period of time grows exponentially with age according to the Gompertz law. A numerical example provided in Figure 2 (section II) shows that increase in the initial system's damage load (initial virtual age) converts the observed mortality trajectory from the Weibull to the Gompertz one.

The model discussed here not only provides an explanation for the exponential increase in the failure rate with age, but it also explains the compensation law of mortality (see Gavrilov & Gavrilova, 1991; 2001).

The compensation law of mortality is observed whenever differences in mortality are caused by differences in initial redundancy (the number of elements in a block, *n*), while the other parameters, including the 'true aging rate' (rate of elements' loss μ) are similar in populations of a given species (presumably because of homeostasis - stable body temperature, glucose concentration, etc.). For lower organisms with poor homeostasis there may be deviations from this law. Our analysis of data published by Pletcher et al. (2000) revealed that in Drosophila this law holds true for male-female comparisons (keeping temperature the same), but not for experiments conducted at different temperatures, presumably because temperature may influence the rate of element loss.

The failure rate of the blocks asymptotically approaches an upper limit which is independent on the number of initially functional elements and is equal to μ. Therefore the failure rate of a system consisting of *m* blocks in series tends asymptotically with increased age to an upper limit $m\mu$, independently of the values of *n* and *q*.

Thus the reliability model described here provides an explanation for a general pattern of aging and mortality in biological species: the exponential growth of failure rate in the initial period, with the subsequent mortality deceleration and leveling-off, as well as the compensation law of mortality.

This model might also be called the model of series-connected blocks with varying degrees of redundancy or distributed redundancy. The basic conclusion of the model might be reformulated as follows: *if vital components of a system differ in their degree of redundancy, the mortality rate initially grows exponentially with age (according to the Gompertz law) with subsequent leveling-off in later life*.

C. Heterogeneous population of redundant organisms

In the previous sections, we examined a situation in which series-connected blocks have varying degrees of redundancy within each organism, while the organisms themselves were considered to be

initially identical to each other and to have the same risk of death. This latter assumption can be justified in some special cases (see Gavrilov & Gavrilova, 1991) and also when the focus is on the analysis of the individual risks of failure. In a more general case the population heterogeneity needs to be taken into account, because there is a large variation in the numbers of cells for the organisms of the same species (Kirkwood & Finch, 2001).

In this section, we demonstrate that taking into account the heterogeneity of the population provides an explanation for all the basic laws of mortality. This model of heterogeneous redundant systems was proposed by Gavrilov and Gavrilova in 1991 (pp. 264-272).

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 Gavrilov & Gavrilova, 1991 for more details):

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

$$\approx Cnq\mu(1 - q + q\mu x)^{n-1} \quad \text{for } x << 1/\mu$$

$$\approx \mu \quad \text{for } x >> 1/\mu$$

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:

$$\mu_p(x) \approx Cn(q\mu)^n\left(\frac{1-q}{q\mu} + x\right)^{n-1} = Cn(q\mu)^n(x_0 + x)^{n-1} \quad \text{for } x << \frac{1}{\mu}$$

$$\mu_p(x) \approx \mu \quad \text{for } x >> \frac{1}{\mu}$$

where $x_0 = \frac{1-q}{q\mu}$, a parameter which we propose to call 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 many damaged organisms 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), this being the case described in section IV. 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 proposed here can also provide a theoretical justification for the binomial law of mortality.

If a population is initially heterogeneous (q < 1), the hazard rate in the initial period of time grows exponentially with age (according to the Gompertz law).

The heterogeneous population model not only provides an explanation for the exponential growth in the failure rate with age, but also the compensation law of mortality (Gavrilov & Gavrilova, 1991). The compensation effect of mortality is observed whenever differences in mortality are brought about by interpopulation differences in the number of elements in the organism (n), while the other parameters, including the rate of aging (the rate of irreversible elements failure μ) are similar for all compared populations of a particular species (presumably because of homeostasis in physiological parameters). It is not difficult to see the similarity between this explanation for the compensation effect of mortality and the explanations which emerge from the models of individual system described in preceding sections (V.A-B).

Figure 13 presents the age kinetics of failure rate in heterogeneous population where redundancy is distributed by the Poisson law (a special case of binomial distribution) with different mean number of functional elements (λ = 1, 5, 10, 15 and 20).

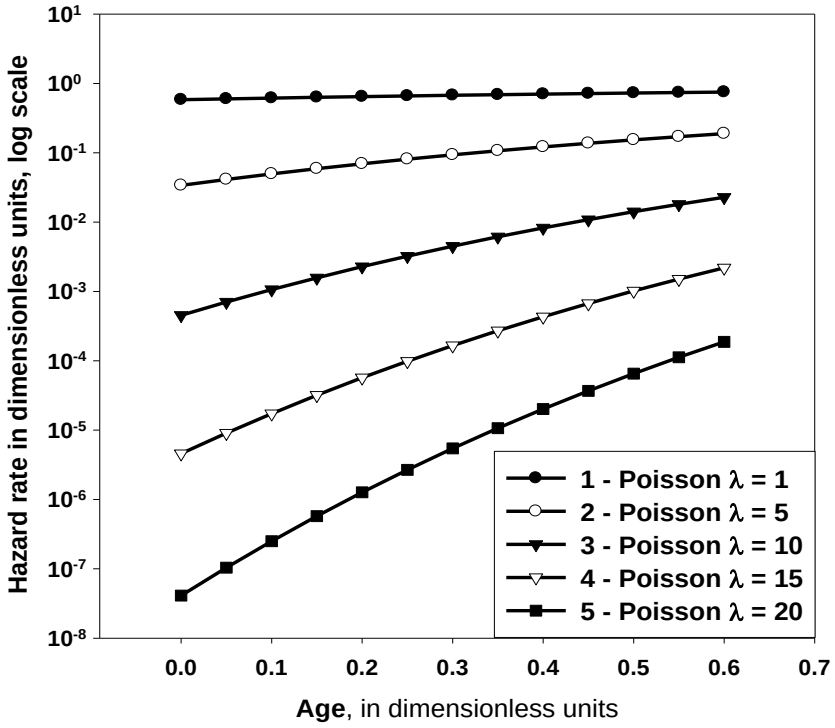

Figure 13. Failure kinetics in mixtures of systems with different redundancy levels. Initial period. The dependence of failure rate as a function of age in mixtures of parallel redundant systems having Poisson distribution by initial numbers of functional elements (mean number of elements, λ = 1, 5, 10, 15, 20). Source: Gavrilov & Gavrilova, 2006.

Note that that the logarithm of the failure rate is increasing with age in almost a linear fashion, indicating a reasonable applicability of the Gompertz law in this case. Also note that the slope of the lines is increasing with higher mean redundancy levels (λ), and the lines have a tendency for convergence (compensation law of mortality).

The heterogeneous population model leads in principle to the same conclusions as the previously discussed model of series-connected blocks with varying degrees of redundancy. However, we are dealing with two fundamentally different models: whereas in the first model the individual risk of death is the same for all organisms and grows exponentially with age, in the second model there initially exist n subpopulations of living organisms with different risks of death which grow as a power function rather than exponential function of age. However, these different models seem to lead to virtually coincident interpretations of certain mortality phenomena. For example, the compensation effect of mortality is only possible, according to any of the models, when the rate of irreversible age changes is approximately constant within a given species. This interpretation of the compensation effect of mortality is not only a feature of the three models examined in this paper, but also of other models (Gavrilov, 1978; Gavrilov et al., 1978; Strehler and Mildvan, 1960).

Thus, the heterogeneous population model provides an explanation for all the basic mortality phenomena (the exponential growth of the force of mortality in the initial period, with the subsequent mortality deceleration, as well as the compensation effect of mortality) even in the simplest case when the organism consists of a single vital block with n parallel elements. Generalizing the model to the case of *m* blocks connected in series in each organism does not present any problems if the blocks are independent of each other with respect to their reliability (Gavrilov & Gavrilova, 1991).

D. Models of avalanche-like destruction

"For want of a nail
the shoe was lost,
For want of a shoe
the horse was lost,
For want of a horse
the rider was lost,
For want of a rider
the battle was lost,
For want of a battle
the kingdom was lost,
And all for the want
of a horseshoe nail".

(English nursery rhyme)

The models described in previous sections (A-C) assumed that the failures of elements in the organism occur independently of each other. This assumption may be acceptable as the first approximation. In real biological systems many aging phenomena may be represented as a "cascade of dependent failures" which occurs when one of the organism's systems randomly fails (Gavrilov, 1978; Gavrilov et al., 1978). The idea that an avalanche-like mechanism is involved in the destruction of an organism during natural aging is worth further consideration. In fact, it is well-known that defects in an organism have a tendency to multiply following an avalanche-like mechanism: for example, if there are n cancer cells in the organism, each of which is capable of division, the rate at which the organism is transformed into a state with n + 1 cancer cells increases with the growth of the number of cancer cells (n) already accumulated. Infections of the organism follow similar regularities. The positive feedback between the degree and the rate of an organism's destruction also follows from the fact that when parts of the structure fail, the load on the remaining structures increases, accelerating the wearing-out. It seems that aging may be caused by similar cascades of dependent failures developing over long periods in a hidden, preclinical form. Therefore mathematical models of the avalanche-like destruction of the organism are of particular interest.

Consider the simplest model of the avalanche-like destruction of the organism (Gavrilov & Gavrilova, 1991). Let S_0, S_1, …, S_n denote the states of an organism with 0, 1, 2, ..., n ... defects. Let λ_0 be the background rate at which defects accumulate being independent on the stage of destruction, which the organism has reached. Correspondingly, let μ_0 be the age-independent mortality (the Makeham term). In the simplest case, both these quantities arise from random harmful effects of the external environment. In tandem, there is also an induced rate of deterioration (parameter λ) and an induced failure rate (parameter μ) which grow as the number of defects increases. At a first approximation, it can be assumed that both the induced rate of deterioration and the induced failure rate are proportional to the number of defects, so that for an organism with n defects the induced rate of deterioration is equal to $n\lambda$, and the induced failure rate is $n\mu$.

With these assumptions, we can present the avalanche-like destruction of the organism by the schema presented in Figure 14.

This schema corresponds to the following system of differential equations:

$$dS_0/dx = -(\lambda_0 + \mu_0) S_0$$
$$dS_1/dx = \lambda_0 S_0 - (\lambda_0 + \mu_0 + \lambda + \mu) S_1$$
$$\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots$$
$$dS_n/dx = [\lambda_0 + (n-1)\lambda] S_{n-1} - [\lambda_0 + \mu_0 + n(\lambda + \mu)] S_n$$

A similar system of equations (not taking into account the age-independent mortality) was obtained and solved in a mathematical model linking the survival of organisms with chromosome damage (Le Bras, 1976). However, this 'chromosomal' interpretation of the avalanche model could be applicable to

unicellular organisms only, while for multicellular organisms including humans, where chromosomes are compartmentalized in separate cells, this model needs to be revised, or provided with a different 'non-chromosomal' interpretation (as it is suggested in this section).

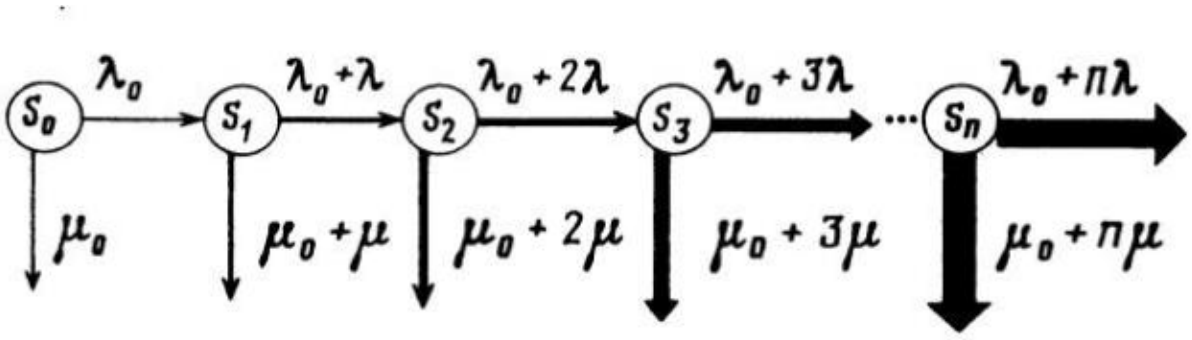

Figure 14. Avalanche-like mechanism of organism's destruction with age.
In the initial state (S_0) organism has no defects. Then, as a result of random damage, it enters states S_1, S_2, … S_n, where n corresponds to the number of defects. Rate of new defects emergence has avalanche-like growth with the number of already accumulated defects (horizontal arrows). Hazard rate (vertical arrows directed down) also has an avalanche-like growth with the number of defects.

In the particular case when the rate at which defects multiply, parameter λ, is significantly greater than the induced failure rate, parameter μ, ($\lambda >> \mu$), the hazard rate of an organism in the initial stage (with low values of x) grows according to the Gompertz-Makeham law:

$$\mu(x) \approx \mu_0 + \frac{\mu\lambda_0(1 - e^{(\lambda+\mu)x})}{\lambda e^{(\lambda+\mu)x}} \approx A + Re^{\alpha x}$$

where $A = \mu_0 - \frac{\mu\lambda_0}{\lambda}$; $R = \frac{\mu\lambda_0}{\lambda}$; $\alpha = \lambda + \mu$

This model of the avalanche-like destruction of the organism not only provides a theoretical justification for the well-known Gompertz-Makeham law, but also explains why the values of the Makeham parameter A sometimes turn out to be negative (when age-independent mortality, μ_0, is small as for populations in the developed countries and the background rate of destruction, λ_0, is large).

Another advantage of the avalanche-like destruction model is that it correctly predicts mortality deceleration (deviations from the Gompertz-Makeham law) at very old ages. In this extreme age-range, the failure rate grows with age according to the formula:

$$\mu(x) \approx \mu_0 + \lambda_0(1 - e^{-(\lambda+\mu)x})$$

Thus the model predicts an asymptotic growth of failure rate with age with an upper limit of $\mu_0 + \lambda_0$.

Alongside the strengths already listed, the avalanche-like destruction model has one significant limitation: it does not conform to the compensation law of mortality in its strong form (Gavrilov & Gavrilova, 1991). Nevertheless, the idea that organisms undergo cascade destruction is one of the promising ideas in further mathematical modeling of aging.

E. Accumulation of defects with constant rate of damage flow.

A wide variety of concepts about the destruction of the organism can lead to the model where the rate of damage flow, numerically equal to the mean number of "hits" per unit of time, is practically

independent of the state of the organism and is on average constant in time. In the simplest case, the model corresponds to a situation in which the organism is affected by a random flow of traumatic loads with an on average constant rate independent of the state of the organism (exogenous environmental damage like cosmic radiation, viruses, etc.)

However, there is also the possibility of other mechanisms of destruction leading to this particular model of the accumulation of defects. In particular, this model can be obtained after a critical reinterpretation of the assumptions underlying the previously described models (sections A-C). In fact, these models contain an assumption that the death of the organism occurs only when all the elements in a block fail. It is possible that this hypothesis may be justified for some of the organism's systems (stem cell populations, for example). However, in the majority of cases this hypothesis seems controversial. For example, it is hard to imagine that a single surviving liver cell (hepatocyte) can assume the functions of an entire destroyed liver. Significantly more realistic is the hypothesis that the system initially contains an enormous number of elements which greatly exceeds the critical number of defects leading to the death of the organism. In this case we arrive at a schema for the accumulation of damage in which the rate of damage flow (equal to the product of the number of elements and their failure rate) turns out to be practically constant in view of the incommensurability of the high initial numbers of elements, and the much smaller permitted number of defects (Gavrilov & Gavrilova, 1991).

Another advantage of this model is that it allows to take into account the influence of living conditions on the value for the critical number of defects incompatible with the survival of the organism. The key to the solution of this problem is the replacement of the parallel connection hypothesis (assumed in models A-C) with the more realistic assumption that there exists a critical number of defects incompatible with the survival of the organism. In this case, it is natural to expect that under harsher conditions the critical number of defects leading to death might be less than under more comfortable living conditions. In particular, in the wild, when an animal is deprived of care and forced to acquire its own food, as well as to defend itself against predators, the first serious damage to the organism can lead to death. It is therefore not surprising that the mortality of many animals (in particular, birds) is practically independent of age in the wild. This follows directly from the single-stage destruction of the organism model. On the other hand, the greater the number of defects the organism can accumulate while remaining alive, the greater its life span will be.

If the rate of the damage flow equals *k*, and an organism dies after the accumulation of n defects, the density of the survival distribution is identical to the density of the gamma function (see Barlow and Proschan, 1965; 1975). At the initial moment in time, this distribution corresponds to a power (Weibull) law of mortality with an exponent equal to (n - 1).

A fundamentally different result is obtained when the initial damage of organisms is taken into account (Gavrilov & Gavrilova, 1991). If at the initial moment in time the average number of random defects in the population equals λ, the probability of encountering a living organism, P_i, with *i* defects may be approximated by the Poisson law (see Gavrilov & Gavrilova, 1991, pp. 272-276, for more detail).

Since the death of an organism with *i* defects occurs after *n - i* additional hits, the density of the life span distribution for such organisms is given by:

$$f_i(x) = \frac{k(kx)^{n-i-1}e^{-kx}}{(n\text{-}i\text{-}1)!}$$, where $i < n$

The density of the survival distribution for the whole population, which is a mixture of organisms with *i = 0,1,2 ... n-1* initial defects, equals:

$$f(x) = \sum_{i=0}^{n-1} P_i f_i(x) = Cke^{-(\lambda + kx)} \sum_{i=0}^{n-1} \frac{\lambda^i (kx)^{n-i-1}}{i!(n\text{-}1\text{-}i)!} = \frac{Ck(\lambda + kx)^{n-1}e^{-(\lambda + kx)}}{(n\text{-}1)!}$$

It is not difficult to see that at the initial moment in time this model leads to the binomial law of mortality, with an initial virtual age of the population equal to λ/k. A more detailed analysis of the model is formally similar to the analysis of the other models described in sections (A-C). We merely note that

during the initial time period when x << λ/k, the model leads to an exponential growth of failure rate with age (the Gompertz law) with an exponent, α, of *k(n-1)/λ* and a pre-exponential factor, *R*, of $\frac{Ck\lambda^{n-1}}{(n\text{-}1)!}$. It is easy to see that an inverse relationship between these Gompertz parameters (the compensation effect of mortality) can arise both as a result of variation in parameter λ (the degree to which the organisms are initially damaged), and of variation in parameter *n* (the critical number of defects, dependent on the harshness of living conditions).

Thus the basic mortality phenomena can equally be explained within the framework of the model of accumulation of defects with the constant rate of damage flow, as long as the organisms initially contain a significant number of defects.

Summarizing this brief review of reliability models, note the striking similarity between the formulas and conclusions of the considered models. It must however be noted that we are only dealing with a superficial similarity in behavior between fundamentally different and competing models. The existence of a multitude of competing models is therefore compatible with the reliable and meaningful interpretation of a number of mortality phenomena, since pluralism of models does not preclude their agreement on a number of issues. All these models predict a mortality deceleration, no matter what assumptions are made regarding initial population heterogeneity, or its complete initial homogeneity. Moreover, these reliability models of aging produce mortality plateaus as inevitable outcome for any values of considered parameters (Gavrilov & Gavrilova, 1991). The only constraint is that the elementary steps of the multi-stage destruction process of a system should occur by chance only, independent of age. The models also predict that an initially homogeneous population will become highly heterogeneous for risk of death over time (acquired heterogeneity).

VI. Conclusions

Theoretical reliability models of system failure in aging considered in this paper lead to the following conclusions:

(1) *System 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 over time (fail more often with age), 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 death rates are also demonstrated to be negligible.

Reliability theory also persuades a re-evaluation of the old belief that aging is somehow related to limited economic or evolutionary investments in systems longevity. The theory provides a completely opposite perspective on this issue – aging is a direct consequence of investments into systems reliability and durability through enhanced redundancy. This is a significant statement, because it helps to understand why the expression of aging (differences in failure rates between the younger and the older age groups) may be actually more profound in more complicated redundant systems, designed for higher durability.

(3) During the life course the organisms are running out of their cells (Gosden, 1985; Herndon et al., 2002) losing reserve capacity (Bortz, 2002; Sehl & Yates, 2001), 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. The observation that mammalian species do not demonstrate mortality deceleration at advanced ages agrees well with the prediction of reliability theory of aging according to which more complex living systems/organisms with

many vital subsystems (like mammals) may experience very short or no period of mortality plateau at advance ages in contrast to more simple living organisms.

(4) Living organisms seem to be formed with a high *load of initial damage,* and therefore their lifespan 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 the "true biological aging". On the contrary, the attempts to build an intellectual firewall between biogerontological research 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 and frail (Bortz, 2002).

Reliability theory suggests general answers to both the ‘why’ and the ‘how’ questions about aging. It explains ‘why’ aging occurs by identifying the key determinant of aging behavior -- system redundancy in numbers of irreplaceable elements. Reliability theory also explains ‘how’ aging occurs, by focusing on the process of redundancy loss over time as the major mechanism of aging.

Ageing is a complex phenomenon (Sehl & Yates, 2001), and a holistic approach using reliability theory may help to analyze, understand and perhaps to control it. We suggest, therefore, adding theoretical reliability models of system failure in aging to the arsenal of methodological approaches for the studying of human aging.

Glossary

Aging -- in models of systems failure, aging is defined as a phenomenon of increasing risk of failure with age of a system.

Compensation law of mortality -- the observation that higher death rates at young ages in disadvantaged populations are compensated by lower pace of mortality acceleration with age, so that the relative differences in mortality between populations tend to decrease with age (also known as mortality convergence in later life).

Failure -- the event when a required function is terminated. Failures are often classified into two groups: (1) degradation failures, where the system or component no longer functions properly, and (2) catastrophic or fatal failures - the end of system's or component's life.

Failure rate (also known as hazard rate) -- risk or frequency of a system's failure. Mathematically it is defined as the relative rate of reliability (survival) function decline.

Gompertz law of mortality -- the law of exponential increase in death (failure) rates with age. It was first suggested by the British actuary Benjamin Gompertz in 1825 for use in the life insurance business. This law was found to be applicable not only to humans but also to fruit flies, nematodes, the human lice, flour beetles, mice, rats, dogs, horses, mountain sheep, baboons and many other biological species. According to the Gompertz law, the logarithm of death rates is increasing linearly with age.

Gompertz-Makeham law -- an extension of the Gompertz law of mortality when the additional, age-independent component of mortality (failure) is taken into account. This law was suggested by the British actuary William Makeham in 1867.

IVAS ("Initial Virtual Age of a System") -- a parameter in theoretical models of systems failure describing the load of initial damage. This parameter has the dimension of time, and corresponds to the age by which an initially ideal system would have accumulated as many defects as a real system already has at the starting age (at $x = 0$).

Late-life mortality deceleration law -- the observation that the pace of mortality growth with age decelerates from an expected exponential curve at extreme old ages, so that mortality rates level-off and, therefore, aging apparently fades away.

Redundancy -- the use of more components than are needed to perform a function; this can enable a system to operate properly despite failed components.

Redundancy exhaustion -- the process when an initially redundant system degenerates into a system with no redundancy because of damage accumulation.

Reliability -- the ability of a system (or its component) to operate properly according to a specified standard.

Reliability function, $S(x)$ -- the probability that a system (or component) will carry out its mission through time x. The reliability function (also called the survival function) evaluated at time x is just the probability P, that the failure time X, is beyond time x.

Reliability structure -- the arrangement of components that are important for system reliability. Reliability structure is graphically represented by a schema of logical connectivity (e.g. components connected in series, or in parallel).

Reliability theory -- a general theory of system failure. Reliability theory is a body of ideas, mathematical models, and methods directed to predict, estimate, understand, and optimize the lifespan and failure distributions of systems and their components.

System reliability theory -- a branch of reliability theory, which studies reliability of an entire system given reliability of its components and components' arrangement (reliability structure).

Weibull law -- the model predicting that failure rates are increasing as a power function of age. It was initially suggested by the Swedish engineer and mathematician Waloddi Weibull in 1939 to describe the strength of materials. According to the Weibull law, the logarithm of failure rates is increasing linearly with the logarithm of age.

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References

Andersen B. B., Gundersen H. J., Pakkenberg B. (2003). Aging of the human cerebellum: a stereological study. J Comp Neurol., 466, 356-65.

Andreadis, S. & Palsson, B. O. (1997). Coupled effects of polybrene and calf serum on the efficiency of retroviral transduction and the stability of retroviral vectors. Hum. Gene Ther., 8, 285-291.

Austad, S. N. (2001). Concepts and theories of aging. In E. J. Masoro and S. N. Austad. Handbook of the biology of aging. San Diego, CA: Academic Press, 3-22.

Aven, T. & Jensen, U. (1999). Stochastic models in reliability. New York: Springer-Verlag.

Ayyub, B.M. & McCuen, R.H. (2003). Probability, statistics, reliability for engineers and scientists. Boca Raton, FL: Chapman & Hall/CRC.

Baizabal, J.M., Furlan-Magaril, M., Santa-Olalla, J., & Covarrubias, L. (2003). Neural stem cells in development and regenerative medicine. Arch Med Res., 34, 572-88.

Barlow, R.E., Proschan, F. & Hunter, L.C. (1965). Mathematical theory of reliability. New York, etc.: John Wiley & Sons, Inc.

Barlow, R.E. & Proschan, F. (1975). Statistical theory of reliability and life testing. Probability models. New York, etc.: Holt, Rinehart and Winston.

Beard, R. E. (1959). Note on some mathematical mortality models. In: G. E. W. Wolstenholme and M.O'Connor (Eds.). The lifespan of animals (pp. 302-311). Boston: Little, Brown.

Beard, R. E. (1971). Some aspects of theories of mortality, cause of death analysis, forecasting and stochastic processes. In. W. Brass (Ed.), Biological aspects of demography (pp. 57-68), London: Taylor & Francis.

Bebbington M, Lai CD, Zitikis R. (2011). Modelling Deceleration in Senescent Mortality. Math.Pop.Studies, 18: 18-37.

Bongaarts, J. 2005. "Long-range trends in adult mortality: Models and projection methods." *Demography* 42(1):23-49.

Bongaarts, J. 2009. "Trends in senescent life expectancy." *Population Studies-a Journal of Demography* 63(3):203-213.

Bortz, W. M. (2002). A conceptual framework of frailty: a review. J. Gerontol. Ser. A, 57, M283-288.

Brock, T. D., Madigan, M. T., Martinko, J. M., & Parker, J. (1994). Biology of microorganisms (7^{th} ed.), Englewood Cliffs, NJ: Prentice-Hall.

Bronikowski, A.M., Alberts, S.C. , Altmann, J., Packer, C., Carey, K. D., & Tatar, M. (2002). The aging baboon: comparative demography in a non-human primate. Proc. Natl. Acad. Sci. U.S.A., 99, 9591-9595.

Bronikowski, A.M., J. Altmann, D.K. Brockman, M. Cords, L.M. Fedigan, A. Pusey, T. Stoinski, W.F. Morris, K.B. Strier, and S.C. Alberts. 2011. "Aging in the Natural World: Comparative Data Reveal Similar Mortality Patterns Across Primates." *Science* 331(6022):1325-1328.

Brooks, A., Lithgow, G. J., & Johnson, T. E. (1994). Mortality rates in a genetically heterogeneous population of Caenorhabditis elegans. Science, 263, 668-671.

Burns, J. Clarke, G., & Lumsden, C. J. (2002). Photoreceptor death: Spatiotemporal patterns arising from one-hit death kinetics and a diffusible cell death factor. Bull. Math. Biol., 64, 1117-1145.

Calne, D.B. (1994). Is idiopathic parkinsonism the consequence of an event or a process? Neurology, 44, 5-10 (1994).

Capogrossi, M. C. (2004). Cardiac stem cells fail with aging: a new mechanism for the age-dependent decline in cardiac function. Circ Res., 94, 411-3.

Carey, J.R. & Liedo, P. (1995). Sex-specific life table aging rates in large medfly cohorts. Exp. Gerontol., 30, 315-325.

Carey, J.R., Liedo, P., Orozco, D. & Vaupel, J.W. (1992) Slowing of mortality rates at older ages in large Medfly cohorts. Science, 258, 457-461.

Cargill, Sh. L., Carey, J. R., Muller, H.-G. & Anderson, G. (2003). Age of ovary determines remaining life expectancy in old ovariectomized mice. Aging Cell, 2, 185-190.

Carnes, B.A., Olshansky, S.J., & Grahn, D. (1998). An interspecies prediction of the risk of radiation-induced mortality. Radiat. Res., 149, 487-492.

Caselli, G., L. Pozzi, J.W. Vaupel, L. Deiana, G. Pes, C. Carru, C. Franceschi, and G. Baggio. 2006. "Family clustering in Sardinian longevity: A genealogical approach." *Experimental Gerontology* 41(8):727-736.

Choi, J. H., Kim, K. L., Huh, W., Kim, B., Byun, J., Suh, W., Sung, J., Jeon, E. S., Oh, H. Y., & Kim, D. K. (2004). Decreased number and impaired angiogenic function of endothelial progenitor cells in patients with chronic renal failure. Arterioscler Thromb Vasc Biol., 24, 1246-52.

Clark, A.G. & Guadalupe, R.N. (1995). Probing the evolution of senescence in Drosophila melanogaster with P-element tagging. Genetica, 96, 225-234.

Clark, V. A. (1975). Survival distribution. Annual Review of Biophysics and Bioengineering, 4, 431-448.

Clarke, G., Collins, R. A., Leavitt, B. R., Andrews, D. F., Hayden, M. R., Lumsden, C. J., & McInnes, R. R. (2000). A one-hit model of cell death in inherited neuronal degenerations. Nature, 406, 195-199.

Clarke, G., Lumsden, C. J., & McInnes, R. R. (2001). Inherited neurodegenerative diseases: The one-hit model of neurodegeneration. Hum. Mol. Genet., 10, 2269-2275.

Clarke, G., Collins, R. A., Leavitt, B. R., Andrews, D. F., Hayden, M. R., Lumsden, C. J., & McInnes, R. R. (2001). Addendum: a one-hit model of cell death in inherited neuronal degenerations. Nature, 409, 542.

Cohen, H. Y., Miller, C., Bitterman, K. J., Wall, N. R., Hekking, B., Kessler, B., Howitz, K. T., Gorospe, M., de Cabo, R., & Sinclair, D. A. (2004). Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science, 305, 390-2.

Commo S., Gaillard O., & Bernard B. A. (2004). Human hair greying is linked to a specific depletion of hair follicle melanocytes affecting both the bulb and the outer root sheath. Br J Dermatol., 150, 435-43.

Crowder, M .J., Kimber, A. C., Smith, R. L. & Sweeting, T. J. (1991). Statistical analysis of reliability data. London: Chapman & Hall.

Curtsinger, J.W., Fukui, H., Townsend, D., & Vaupel, J. W. (1992). Demography of genotypes: Failure of the limited life-span paradigm in *Drosophila melanogaster*. Science, 258, 461-463.

Curtsinger, J.W., N.S. Gavrilova, and L.A. Gavrilov. 2006. "Biodemography of Aging and Age-Specific Mortality in Drosophila melanogaster." Pp. 261-288 in *Handbook of the Biology of Aging*, edited by E.J. Masoro and S.N. Austad. San Diego: Academic Press.

Davis, B. D., Dulbeco, R., Eisen, H. N., & Ginsberg, H. S. (1990). Microbiology (4th Ed.), Philadelphia, PA: Lippincott.

Doubal, S. (1982). Theory of reliability, biological systems and aging. Mech. Ageing and Devel., 18: 339-353.

Eakin, T., Shouman, R., Qi, Y.L., Liu, G.X. & Witten, M. (1995). Estimating parametric survival model parameters in gerontological aging studies. Methodological problems and insights. J. Gerontol. Ser. A. 50, B166-B176.

Economos, A.C. (1979). A non-gompertzian paradigm for mortality kinetics of metazoan animals and failure kinetics of manufactured products. AGE, 2, 74-76.

Economos, A.C. (1980). Kinetics of metazoan mortality. J. Social Biol. Struct., 3, 317-329.

Economos, A.C. (1983). Rate of aging, rate of dying and the mechanism of mortality. Arch. Gerontol. and Geriatrics, 1, 3-27.

Economos, A. (1985). Rate of aging, rate of dying and non-Gompertzian mortality - encore… Gerontology, 31, 106-111.

Edelberg, J. M., Tang, L., Hattori, K., Lyden, D., & Rafii, S. (2002). Young adult bone marrow-derived endothelial precursor cells restore aging-impaired cardiac angiogenic function. Circ Res., 90, E89–93.

Feller, W. (1968). An introduction to probability theory and its applications. Vol.1, New York: Wiley and Sons.

Finch, C. E., (1990). Longevity, senescence and the genome. Chicago: University of Chicago Press.

Finch, C. E., & Kirkwood, T. B. L. (2000). Chance, development, and aging. New York, Oxford: Oxford University Press.

Finger, S., Le Vere, T.E., Almli, C.R. & Stein, D.G. (Eds.) (1988). Brain injury and recovery: Theoretical and controversial issues. New York: Plenum Press.

Fukui, H. H., Xiu, L. & Curtsinger, J. W. (1993). Slowing of age-specific mortality rates in Drosophila melanogaster. Exp. Gerontol., 28, 585-599.

Fukui, H. H., Ackert, L. & Curtsinger, J. W. (1996). Deceleration of age-specific mortality rates in chromosomal homozygotes and heterozygotes of Drosophila melanogaster. Exp. Gerontol., 31, 517-531.

Galambos, J. (1978). The asymptotic theory of extreme order statistics. New York: Wiley.

Gavrilov, L.A. (1978). Mathematical model of aging in animals. Doklady Akademii Nauk SSSR Biological Sciences, 238, 53-55 (English translation).

Gavrilov, L.A. (1980). Study of life span genetics using the kinetic analysis. Thesis, Moscow, Russia: Moscow State University.

Gavrilov, L. A. (1984). Does a limit of the life span really exist? Biofizika, 29, 908-911.

Gavrilov, L. A., & Gavrilova, N. S. (1979). Determination of species length of life. Doklady Akademii Nauk SSSR Biological Sciences, 246, 905-908 (English translation).

Gavrilov, L. A., & Gavrilova, N. S. (1991). The biology of life span: A quantitative approach, New York: Harwood Academic Publisher.

Gavrilov, L. A., & Gavrilova, N. S. (2001). Biodemographic study of familial determinants of human longevity. Population: English Selection, 13, 197-222.

Gavrilov L. A., & Gavrilova N. S. (2003a). The quest for a general theory of aging and longevity. Science's SAGE KE (Science of Aging Knowledge Environment) for 16 July 2003; Vol. 2003, No. 28, 1-10. Available: http://sageke.sciencemag.org

Gavrilov, L. A., & Gavrilova, N. S. (2003b). Early-life factors modulating lifespan. In: Rattan, S.I.S. (Ed.). Modulating aging and longevity (pp. 27-50), Dordrecht, The Netherlands: Kluwer Academic Publishers.

Gavrilov, L. A., & Gavrilova, N. S. (2004a). The reliability-engineering approach to the problem of biological aging. Ann. N.Y. Acad. Sci., 1019, 509-512.

Gavrilov, L. A., & Gavrilova, N. S. (2004b). Early-life programming of aging and longevity: The idea of high initial damage load (the HIDL hypothesis). Ann. N.Y. Acad. Sci., 1019, 496-501.

Gavrilov, L.A., & Gavrilova, N. S. (2004c). Why we fall apart. Engineering's reliability theory explains human aging. IEEE Spectrum, 9, 2-7.

Gavrilov, L.A., & Gavrilova, N. S. (2006). Reliability theory of aging and longevity. In E. J. Masoro and S. N. Austad. Handbook of the biology of aging. San Diego, CA: Academic Press, pp.3-42.

Gavrilova, N.S.and L.A. Gavrilov. 2007. "Search for Predictors of Exceptional Human Longevity: Using Computerized Genealogies and Internet Resources for Human Longevity Studies." *North American Actuarial Journal* 11(1):49-67.

Gavrilov, L.A., Gavrilova, N.S. & Iaguzhinskii, L.S. (1978). Basic patterns of aging and death in animals from the standpoint of reliability theory. J. General Biology (Zhurnal Obshchej Biologii, Moscow), 39, 734-742 (In Russian).

Gilchrest, B. A., Blog, F. B., & Szabo, G. (1979). Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol., 73, 141-3.

Goldschmidt-Clermont, P. J. (2003). Loss of bone marrow-derived vascular progenitor cells leads to inflammation and atherosclerosis. Am Heart J., 146(4 Suppl), S5-12.

Golubev, A. (2004) Does Makeham make sense? Biogerontology, 5, 159-167.

Gompertz, B. (1825). On the nature of the function expressive of the law of human mortality and on a new mode of determining life contingencies. Philos. Trans. Roy. Soc. London A, 115, 513-585.

Gosden, R. G. (1985). The biology of menopause: The cause and consequence of ovarian aging, San Diego, CA: Academic Press.

Gouda, M. D., Singh, S. A., Rao, A. G., Thakur, M. S., & Karanth, N. G. (2003). Thermal inactivation of glucose oxidase: Mechanism and stabilization using additives. J. Biol. Chem., 278, 24324-24333.

Greenwood, M. & Irwin, J. O. (1939). The biostatistics of senility. Hum. Biol., 11, 1-23.

Griffiths, A. J. F., Miller, J. H., Suzuki, D. T., Lewontin, R. C., & Gelbart, W. M. (1996). An introduction to genetic analysis (6th ed.). New York: W. H. Freeman and Company.

Gumbel, E.J. (1958). Statistics of extremes. New York: Columbia University Press.

Hall, J.C. (1969). Age-dependent enzyme changes in Drosophila melanogaster. Exp. Gerontol., 4, 207-222.

Hallen, A. (2009). Makeham's addition to the Gompertz law re-evaluated. *Biogerontology*, 10: 517-522.

Haranghy, L., & Balázs, A. (1980). Regeneration and rejuvenation of invertebrates. In: N. W. Shock (Ed.), Perspectives in experimental gerontology (pp. 224-233). New York: Arno Press.

Heintz, N. (2000). One-hit neuronal death. Nature, 406, 137-138.

Herndon, L. A., Schmeissner, P. J., Dudaronek, J. M., Brown, P. A., Listner, K. M., Sakano, Y., Paupard, M. C., Hall, D. H., & Driscoll, M. (2002). Stochastic and genetic factors influence tissue-specific decline in ageing C. elegans. Nature, 419, 808-814.

Hirsch, H.R., & Peretz, B. (1984). Survival and aging of a small laboratory population of a marine mollusc, Aplysia californica. Mech. Ageing Dev., 27, 43-62.

Hirsch, A.G., Williams, R.J., & Mehl, P. (1994). Kinetics of medfly mortality. Exp. Gerontol., 29, 197-204.

Horiuchi, S.and J.R. Wilmoth. 1998. "Deceleration in the age pattern of mortality at older ages." *Demography* 35:391-412.

Janse, C., Slob, W., Popelier, C.M. & Vogelaar, J.W. (1988) Survival characteristics of the mollusc Lymnaea stagnalis under constant culture conditions: effects of aging and disease. Mech. Ageing Dev., 42, 263-174.

Jay, J. M. (1996). Modern food microbiology. New York: Chapman and Hall.

Johnson, T. E. (1987). Aging can be genetically dissected into component processes using long-lived lines of Caenorhabditis elegans. Proc. Natl. Acad. Sci. U.S.A., 84, 3777-3781.

Johnson, T. E. (1990). Increased life span of age-1 mutants in Caenorhabditis elegans and lower Gompertz rate of aging. Science, 249, 908-912.

Kannisto, V. 1988. "On the survival of centenarians and the span of life." *Population Studies-a Journal of Demography* 42:389-406.

Kannisto, V. 1994. *Development of Oldest-Old Mortality, 1950-1990: Evidence from 28 Developed Countries*. Odense: Odense University Press.

Kaufmann, A., Grouchko, D. & Cruon, R. (1977). Mathematical models for the study of the reliability of systems. New York: Academic Press.

Keller, G., Zimmer, G., Mall, G., Ritz, E., & Amann, K. (2003). Nephron number in patients with primary hypertension. N Engl J Med., 348, 101-8.

Khazaeli, A.A., Xiu, L. & Curtsinger, J.W. (1995). Stress experiments as a means of investigating age-specific mortality in *Drosophila melanogaster*. Exp. Gerontol., 30, 177-184.

Khazaeli, A.A., Xiu, L. & Curtsinger, J.W. (1996) Effect of density on age-specific mortality in Drosophila: a density supplementation experiment. Genetica, 98, 21-31.

Klein, J. P., & Moeschberger, M. L. (1997). Survival analysis. techniques for censored and truncated data. New York: Springer-Verlag.

Koltover, V.K. (1983). Theory of reliability, superoxide radicals and aging [*Advan*. *Mod*. *Biol*. (*Uspekhi Sovremennoj Biologii*, *Moscow) 96: 85-100* (in Russian).

Kundi, M. (1999). One-hit models for virus inactivation studies. Antivir. Res., 41, 145-152.

Kunstyr, I., & Leuenberger, H.-G. W. (1975). Gerontological data of C57BL/6J mice. I. Sex differences in survival curves. J. Gerontol., 30, 157-162.

Kurganov, B. I. (2002). Kinetics of protein aggregation. Quantitative estimation of the chaperone-like activity in test-systems based on suppression of protein aggregation. Biochemistry (Moscow), 67, 409-422.

Le Bras, H. (1976). Lois de mortalité et age limité. Population, 31, 655-692.

Leeuwenburgh, C. (2003). Role of apoptosis in sarcopenia. J. Gerontol. A, 58, 999-1001.

Libby, P. (2003). Bone marrow: a fountain of vascular youth? Circulation, 108, 378-9.

Lindop, P.J. (1961). Growth rate, lifespan and causes of death in SAS/4 mice. Gerontologia, 5: 193-208.

Lloyd, D.K. & Lipow, M. (1962). Reliability: Management, methods, and mathematics. Englewood Cliffs, New Jersey: Prentice-Hall, Inc.

Makeham, W. M. (1860). On the law of mortality and the construction of annuity tables. J. Inst. Actuaries, 8, 301-310.

Makeham, W. M. (1867). On the law of mortality. J. Inst. Actuaries, 13, 325-358.

Martinez, D.E. (1998). Mortality patterns suggest lack of senescence in hydra. Exp. Gerontol., 33, 217-225.

Masoro, E. J. (2003). Subfield history: caloric restriction, slowing aging, and extending life. Sci Aging Knowledge Environ., 2003(8), RE2.

Massof, R. W., Dagnelie, G., Benzschawel, T., Palmer, R. W. & Finkelstein, D. (1990). First order dynamics of visual field loss in retinitis pigmentosa. Clin. Vision Sci., 5, 1-26.

McKiernan, S. H., Bua, E., McGorray, J., & Aiken, J. (2004). Early-onset calorie restriction conserves fiber number in aging rat skeletal muscle. FASEB J., 18, 580-1.

Mildvan, A. & Strehler, B. L. (1960). A critique of theories of mortality. In: B. L. Strehler, J. D. Ebert, H. B. Glass & N. W. Shock (Eds.). The biology of aging (pp.216-235), Washington, D.C.: American Institute of Biological Sciences.

Miller, A. R. (1989). The distribution of wearout over evolved reliability structures. J. theor. Biol., 136, 27-46.

Mueller, L. & Rose, M.R. (1996). Evolutionary theory predicts late-life mortality plateaus. Proc. Natl. Acad. Sci. USA, 93, 15249-15253.

Nyengaard, J. R., & Bendtsen T. F. (1992). Glomerular number and size in relation to age, kidney weight, and body surface in normal man. Anat Rec., 232, 194-201.

Olshansky, S. J. (1998). On the biodemography of aging: a review essay. Population and Development Review, 24, 381-393.

Olshansky, S. J., & Carnes, B. A. (1997). Ever since Gompertz. Demography, 34, 1-15.

Partridge, L. & Mangel, M. (1999). Messages from mortality: the evolution of death rates in the old. Trends in Ecology and Evolution, 14, 438-442.

Pearl, R., & Miner, J. R. (1935). Experimental studies on the duration of life.XIY.The comparative mortality of certain lower organisms. Quart.Rev.Biol., 10, 60-79.

Peleg, M., Normand, M. D., & Campanella, O. H. (2003). Estimating microbial inactivation parameters from survival curves obtained under varying conditions--the linear case. Bull. Math. Biol., 65, 219-234.

Perks, W. (1932). On some experiments in the graduation of mortality statistics. Journal of the Institute of Actuaries, 63, 12-57.

Pletcher, S.D. & Curtsinger, J.W. (1998) Mortality plateaus and the evolution of senescence: why are old-age mortality rates so low? Evolution, 52, 454-464.

Pletcher, S. D., Khazaeli, A. A. & Curtsinger, J. W. (2000). Why do life spans differ? partitioning mean longevity differences in terms of age-specific mortality parameters. J. Gerontol., 55A, B381-B389.

Prescott, L. M., Harley, J. P., & Klein, D. A. (1996). Microbiology (3rd ed.), Dubuque, IA: WCB.

Rausand, M. & Hoyland, A. (2003). System reliability theory: Models, statistical methods, and applications (2nd ed.), Hoboken, NJ: Wiley-Interscience.

Rauscher, F. M., Goldschmidt-Clermont, P. J., Davis, B. H., Wang, T., Gregg, D., Ramaswami, P., Pippen, A. M., Annex, B. H., Dong, C., & Taylor, D. A. (2003). Aging, progenitor cell exhaustion, and atherosclerosis. Circulation, 108, 457-63.

Ricklefs, R. E., & Scheuerlein, A. (2002). Biological implications of the Weibull and Gompertz models of aging. J. Gerontol. Ser. A, 57, B69-76.

Rigdon, S.E. & Basu, A.P. (2000). Statistical methods for the reliability of repairable systems. New York: John Wiley & Sons, Inc.

Rockstein, M. & Lieberman, H.M. (1959). A life table for the common house fly, *Musca domestica*. Gerontologia, 3: 23-36.

Rose, M.R. (1991). The evolutionary biology of aging. Oxford: Oxford University Press.

Rosenwaike, I.and L.F. Stone. 2003. "Verification of the ages of supercentenarians in the United States: Results of a matching study." *Demography* 40(4):727-739.

Sacher, G.A. 1956. "On the statistical nature of mortality, with especial reference to chronic radiation mortality " *Radiology* 67:250-257.

Sacher, G.A.. 1966. "The Gompertz transformation in the study of the injury-mortality relationship: Application to late radiation effects and ageing." Pp. 411-441 in *Radiation and Aging*, edited by P.J. Lindop and G.A. Sacher. London: Taylor and Francis.

Sacher, G.A. (1966). The Gompertz transformation in the study of the injury-mortality relationship: Application to late radiation effects and ageing. In P. J. Lindop and G. A. Sacher (eds.) Radiation and ageing (pp. 411-441). Taylor and Francis, London.

Sacher, G.A. (1977). Life table modification and life prolongation. In C. E. Finch and L. Hayflick. Handbook of the biology of aging (pp. 582-638), New York: Van Nostrand Reinhold.

Schulzer, M., Lee, C. S., Mak, E. K., Vingerhoets, F. J. G., & Calne, D. B. (1994). A mathematical model of pathogenesis in idiopathic parkinsonism. Brain, 117, 509-516.

Sehl, M. E. & Yates, F. E. (2001). Kinetics of human aging: I. Rates of senescence between ages 30 and 70 years in healthy people. J. Gerontol. Ser. A, 56, B198-208.

Sesso, H.D., R.S. Paffenbarger, and I.M. Lee. 2000. "Comparison of National Death Index and World Wide Web death searches." *American Journal of Epidemiology* 152(2):107-111.

Strasser, H., Tiefenthaler, M., Steinlechner, M., Eder, I., Bartsch, G., & Konwalinka, G. (2000). Age dependent apoptosis and loss of rhabdosphincter cells. J Urol., 164, 1781-1785

Strehler, B. L. (1960). Fluctuating energy demands as determinants of the death process (A parsimonious theory of the Gompertz function). In: B. L. Strehler, J. D. Ebert, H. B. Glass & N. W. Shock (Eds.). The biology of aging (pp.309-314), Washington, D.C.: American Institute of Biological Sciences.

Strehler, B.L. (1978). Time, cells, and aging (2nd ed.), New York and London: Academic Press.

Strehler, B. L. & Mildvan, A. S. (1960). General theory of mortality and aging. Science, 132, 14-21.

Strohman, R. (2003). Thermodynamics-old laws in medicine and complex disease. Nature, Biotechnol., 21, 477-479.

Strohman, R. (2002). Maneuvering in the complex path from genotype to phenotype. Science, 296, 701-703.

StataCorp. (2009). *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.

Tatar, M., Carey, J. R., & Vaupel, J. W. (1993). Long-term cost of reproduction with and without accelerated senescence in *Callosobruchus maculatus*: Analysis of age-specific mortality. Evolution, 47, 1302-1312.

Thatcher, A.R., V. Kannisto, and J.W. Vaupel. (1998). *The Force of Mortality at Ages 80 to 120*. Odense: Odense University Press.

Vanfleteren, J.R., De Vreese, A. & Braeckman, B.P. (1998). Two-parameter logistic and Weibull equations provide better fits to survival data from isogenic populations of Caenorhabditis elegans in axenic culture than does the Gompertz model. J. Gerontol. Ser. A, 53, B393-403.

Vaupel, J.W., Carey, J.R., Christensen, K., Johnson, T., Yashin, A.I., Holm, N.V., Iachine, I.A., Kannisto, V., Khazaeli, A.A., Liedo, P., Longo, V.D., Zeng, Y., Manton, K. & Curtsinger, J.W. (1998). Biodemographic trajectories of longevity. Science, 280, 855-860.

Wallace, W. H. & Kelsey, T. W. (2004). Ovarian reserve and reproductive age may be determined from measurement of ovarian volume by transvaginal sonography. Human Reproduction, 19, 1612-1617.

Weibull, W. A. (1939). A statistical theory of the strength of materials. Ingeniorsvetenskapsakademiens Handlingar, Nr 151, 5-45.

Weibull, W. A. (1951). A statistical distribution function of wide applicability. J. Appl. Mech., 18, 293-297.

Willcox, D.C., B.J. Willcox, Q. He, N.C. Wang, and M. Suzuki. 2008. "They really are that old: A validation study of centenarian prevalence in Okinawa." *Journals of Gerontology Series a-Biological Sciences and Medical Sciences* 63(4):338-349.

Wilmoth, J. R. (1997). In search of limits. In Wachter, K. W. & Finch C. E. (Eds.), Between Zeus and the salmon. The biodemography of longevity (pp. 38-64). Washington, DC: National Academy Press.

Wilmoth, J.R., K.F. Andreev, D. Jdanov, and D.A. Glei. 2007. "Methods protocol for the Human Mortality Database. Version 5. Available at http://www.mortality.org/Public/Docs/MethodsProtocol.pdf."

Yashin AI, Begun AS, Boiko SI, Ukraintseva SV, Oeppen J. (2002). New age patterns of survival improvement in Sweden: do they characterize changes in individual aging? Mech.Ageing Devel., 123: 637-647.

Young, R.D., Desjardins, B., McLaughlin, K., Poulain, M., Perls, T.T. (2010). Typologies of extreme longevity myths. *Current Gerontology and Geriatrics Research*, 1-12, doi:10.1155/2010/423087.

Zheng, H; Yang, Y; Land, KC. (2011). Heterogeneity in the Strehler-Mildvan General Theory of Mortality and Aging. Demography, 48: 267-290.