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The Reliability Theory of Aging and Longevity

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Reliability theory is a general theory about systems failure. It allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components. Reliability theory predicts that even those systems that are entirely composed of non-aging elements (with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are *redundant* in irreplaceable elements. Aging, therefore, is a direct consequence of systems redundancy. Reliability theory also predicts the late-life mortality deceleration with subsequent leveling-off, as well as the late-life mortality plateaus, as an inevitable consequence of *redundancy exhaustion* at extreme old ages. The theory explains why mortality rates increase exponentially with age (the Gompertz law) in many species, by taking into account the *initial flaws* (*defects*) in newly formed systems. It also explains why organisms "prefer" to die according to the Gompertz law, while technical devices usually fail according to the Weibull (power) law. Theoretical conditions are specified when organisms die according to the Weibull law: organisms should be relatively free of initial flaws and defects. The theory makes it possible to find a general failure law applicable to all adult and extreme old ages, where the Gompertz and the Weibull laws are just special cases of this more general failure law. The theory explains why relative differences in mortality rates of compared populations (within a given species) vanish with age, and mortality convergence is observed due to the exhaustion of initial differences in redundancy levels. Overall, reliability theory has an amazing predictive and explanatory power with a few, very general and realistic assumptions. Therefore, reliability theory seems to be a promising approach for developing a comprehensive theory of aging and longevity integrating mathematical methods with specific biological knowledge.

1. Introduction

Extensive empirical studies on species aging and longevity have proved successful in establishing many important facts and details about the aging process (Finch, 1990; Jazwinski, 1996, 1998) that have yet to be explained and understood. Empirical observations on this issue have become so numerous and abundant that a special encyclopedia, *The Macmillan Encyclopedia of Aging*, is now required for even partial coverage of the accumulated facts (Ekerdt, 2002). To transform these numerous observations into a comprehensive body of knowledge, a general theory of species aging and longevity is required.

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 (Strehler, 1978; Finch, 1990; Gavrilov

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& Gavrilova, 1991; Olshansky & Carnes, 1997). Specifically, he found that the force of mortality (known in modern science as mortality rate, hazard rate, or failure rate) 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). Moreover, he found that at advanced ages mortality rates increase less rapidly than an exponential function, thus forestalling two centuries ago the recent fuss over "late-life mortality deceleration" (Fukui *et al*., 1993, 1996; Khazaeli *et al*., 1996; Vaupel *et al*., 1998; Partridge & Mangel, 1999), "mortality leveling off" (Carey & Liedo, 1995; Clark & Guadalupe, 1995; Vaupel *et al*., 1998), and "late-life mortality plateaus" (Mueller & Rose, 1996; Tower, 1996; Pletcher & Curtsinger, 1998; Wachter, 1999). For a more in-depth analysis of the previous extensive studies on mortality leveling-off (Makeham, 1867; Brownlee, 1919; Perks, 1932; Greenwood & Irwin, 1939; Mildvan & Strehler, 1960; Strehler, 1960; Economos, 1979, 1980, 1983, 1985; Gavrilov & Gavrilova, 1991), see the recent thoughtful review by Olshansky (1998).

The Gompertz law of exponential increase in mortality rates with age is observed in many biological species (Strehler, 1978; Finch, 1990), including humans, rats, mice, fruit flies, flour beetles, and human lice (Gavrilov & Gavrilova, 1991), and, therefore, some general theoretical explanation for this phenomenon is required. Many attempts to provide such theoretical underpinnings for the Gompertz law have been made (see reviews in Strehler, 1978; Gavrilov & Gavrilova, 1991), and the problem now is to find out which of these models is correct.

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 age dependence for mortality increase (Haranghy & Balázs, 1980; Finch, 1990; 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, occasionally demonstrate leveling-off (late-life mortality plateau), or even a paradoxical decrease at extreme ages?

(4) How do we explain the so-called compensation law of mortality (Gavrilov & Gavrilova, 1991)? This paradoxical phenomenon refers to the observation 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. This is true for male–female comparisons, for international comparisons of different countries within the same sex, as well as for within-species comparisons of animal stocks (Gavrilov & Gavrilova, 1991). The theory of aging and longevity has to explain this paradox of mortality convergence.

Following a long-standing tradition of biological thought, the search for a general biological theory to explain aging and longevity has been made mainly in terms of evolutionary biology (Medawar, 1946, 1952; Williams, 1957, 1966; Hamilton, 1966; Rose, 1991; Carnes & Olshansky, 1993; Charlesworth, 1994) and genetics (Finch, 1990; Jazwinski, 1996, 1998; Finch & Tanzi, 1997; Carnes *et al*., 1999). However, the attempts to explain "late-life mortality plateaus" using evolutionary theory (Mueller & Rose, 1996) have failed so far because they required highly specialized and unrealistic assumptions (see critical reviews by Charlesworth & Partridge, 1997; Pletcher & Curtsinger, 1998; Wachter, 1999). It looks like the evolutionary theory is more appropriate to explain early successes of biological species (e.g. reproductive success), rather than their later failures (aging and death). There seems to be a missing piece in the theoretical arsenal of evolutionary biologists trying to explain aging,

and this missing piece is about the general theory of system failures. This theory, known as the theory of reliability (Lloyd & Lipow, 1962; Barlow *et al*., 1965; Barlow & Proschan, 1975; Kaufmann *et al*., 1977; Crowder *et al*., 1991; Aven & Jensen, 1999; Rigdon & Basu, 2000), allows researchers to understand many puzzling features of mortality and lifespan (Gavrilov, 1978, 1987; Gavrilov *et al*., 1978; Abernethy, 1979; Ďoubal, 1982; Gavrilov & Gavrilova, 1991, 1993; Bains, 2000) not readily explainable otherwise (i.e. the Gompertz law, mortality plateaus, and the compensation law of mortality).

The purpose of this article is to introduce the ideas and methods of reliability theory to a wider audience interested in understanding the mechanisms of aging, mortality, survival, and longevity. It is also important to review and summarize the recent scientific literature on reliability approach to the problem of biological aging (Miller, 1989; Gavrilov & Gavrilova, 1991; Abernethy, 1998; Bains, 2000). The main emphasis here is made on the accomplishments of the reliability approach rather than previous occasional mistakes, because some questionable models (Murphy, 1978; Skurnick & Kemeny, 1978; Koltover, 1983, 1997; Witten, 1985) were already reviewed elsewhere (Gavrilov, 1984, 1987; Gavrilov & Gavrilova, 1991). This theoretical review article also elaborates further some results and ideas published in the book on a related topic (Gavrilov & Gavrilova, 1991).

2. Reliability Theory: General Overview

Reliability theory is a body of ideas, mathematical models, and methods directed to predict, estimate, understand, and optimize the lifespan distribution of systems and their components (adapted from Barlow *et al*., 1965). *Reliability* of the system (or component) refers to its ability to operate properly according to a specified standard (Crowder *et al*., 1991). Reliability is described by the *reliability function* $S(x)$, which is the probability that a system (or component) will carry out its mission through time x (Rigdon & 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:

$$S(x) = P(X > x) = 1 - P(X \leqslant x) = 1 - F(x), \tag{1}$$

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* $\lambda(x)$, also called the *hazard rate* $h(x)$, is defined as the relative rate for reliability function decline:

$$\lambda(x) = -\frac{\mathrm{d}S(x)}{S(x)\,\mathrm{d}x} = -\frac{\mathrm{d}[\log_e S(x)]}{\mathrm{d}x}. \tag{2}$$

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

$$\lambda(x) = \lambda = \text{const}, \tag{3a}$$

$$S(x) = S_0 \exp(-\lambda x). \tag{3b}$$

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

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

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

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

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:

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

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

There are some exceptions both from the Gompertz law of mortality and the compensation law of mortality that have to be understood and explained. In some cases, the organisms die according to the *Weibull* (*power*) *law* (Hirsch & Peretz, 1984; Janse *et al*., 1988; Hirsch *et al*., 1994; Eakin *et al*., 1995; Vanfleteren *et al*., 1998):

$$\mu(x) = \lambda x^{\alpha} \quad \text{for } x \geqslant 0, \text{ where } \lambda,\ \alpha > 0. \qquad (6)$$

The Weibull law is more commonly applicable for technical devices (Barlow & Proschan, 1975; Rigdon & Basu, 2000) while the Gompertz law is more common for biological systems (Strehler, 1978; Finch, 1990; Gavrilov & Gavrilova, 1991). 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 in the next section of the article.

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 in the next two sections of this article. In short, 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 their deaths. Therefore, defects in such organisms do not accumulate, and the organisms themselves do not age—they just die when damaged. In more complex organisms with many vital structures and significant redundancy, every occurrence of damage does not lead to death because of this redundancy. Defects do accumulate, therefore, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence (trade-off) of systems redundancy that ensures increased reliability and lifespan of organisms. As defects accumulate, the redundancy in the number of elements finally disappears. As a result of this redundancy exhaustion, the organism degenerates into a system with no redundancy, that is, a system with elements connected in series, with the result being that any new defect leads to death. In such a state, no further accumulation of damage can be achieved, and the mortality rate levels off. The next two sections provide mathematical proof for these ideas.

3. Reliability Theory of Aging for Highly Redundant Systems Replete with Defects

In this section, we will show that the exponential growth in mortality rate, as well as other aging phenomena (late-life mortality deceleration and compensation law of mortality), follows naturally from a simple reliability model and two general features of biosystems.

The first fundamental feature of biosystems is that, in contrast to technical (artificial) devices which are constructed out of previously manufactured and tested components, organisms form themselves in ontogenesis through a process of self-assembly out of *de novo* forming and externally untested elements (cells). The second property of organisms is the extraordinary degree of miniaturization of their components (the microscopic dimensions of cells, as well as the molecular dimensions of information carriers like DNA and RNA), permitting the creation of a huge redundancy in the number of elements. Thus, we expect that for living organisms, in distinction to many technical (manufactured) devices, the reliability of the system is achieved not by the high initial quality of all the elements but by their huge numbers (redundancy). As will be shown later, this feature of organisms provides an explanation why the failure rate grows as an exponential rather than a power function of age, and it also enables researchers to understand the other mortality phenomena (e.g. compensation law of mortality).

Figure 1 presents a scheme explaining the causes of cardinal differences in reliability structure between technical devices and biological systems.

The fundamental difference in the manner in which the system is formed (external assembly in the case of technical devices and self-assembly in the case of biosystems) has two important consequences. First, it leads to the macroscopicity of technical devices in comparison with biosystems, since technical devices are assembled "top-down" with the participation of a macroscopic system (man) and must be suitable for this macroscopic system to use (i.e. commensurate with man). Organisms, on the other hand, are assembled "bottom-up" from molecules and cells, resulting in an exceptionally high degree of miniaturization of the component parts. Second, since technical devices are assembled under the control of man, the opportunities to pretest components (external quality control) are incomparably greater than in the self-assembly of biosystems. The latter inevitably leads to organisms being "littered" with a great number of defective elements. As a result, the reliability of technical devices is assured by the high quality of elements, with a strict limit on their numbers because of size and cost limitations [Fig. 2(a)], while the reliability of biosystems is assured by an exceptionally high degree of redundancy to overcome the poor quality of some elements [Fig. 2(b)].

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

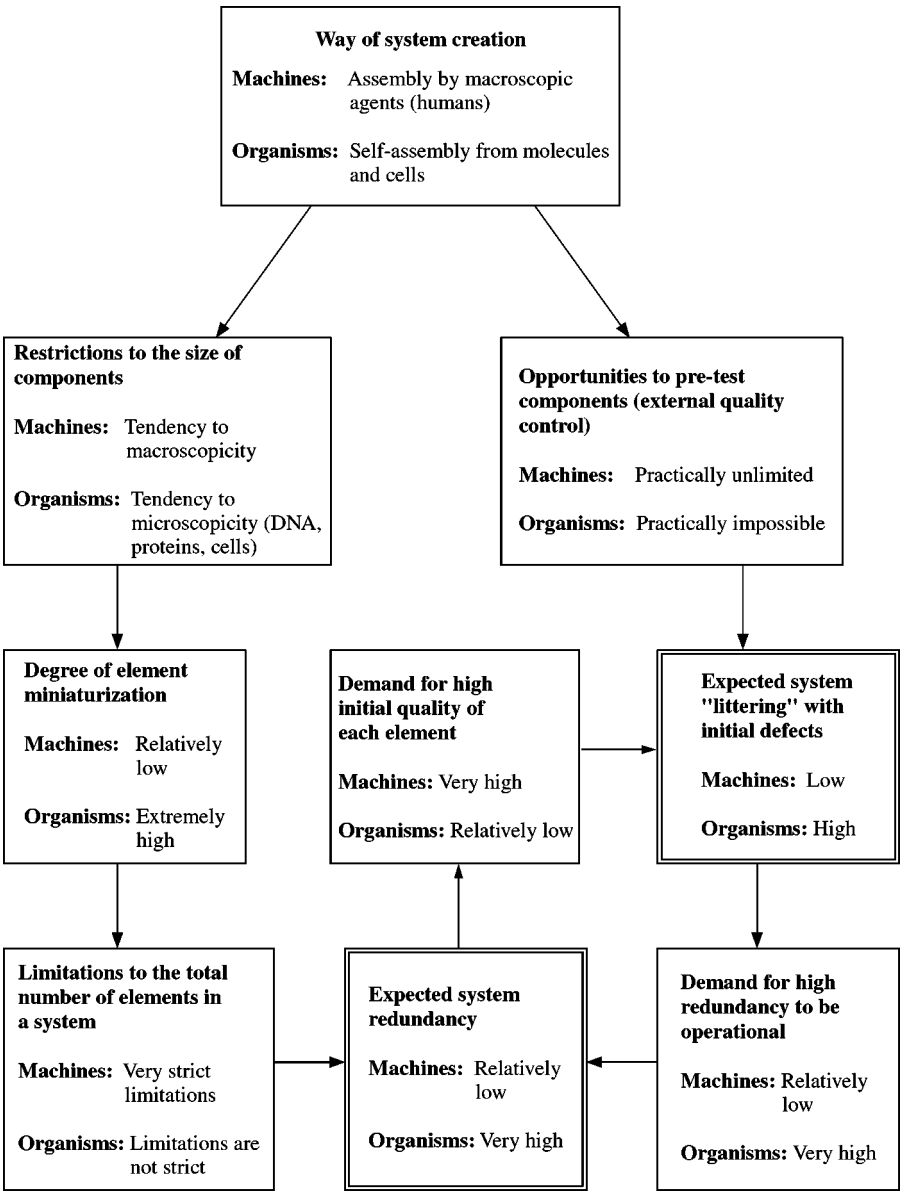

FIG. 1. Schema explaining why biological systems and technical devices may have different solutions to the problem of achieving consistent reliability. Owing to the different ways in which systems are created (self-assembly of organisms vs. external assembly of machines) two opposite strategies are used to achieve high reliability—either huge redundancy in numbers of loose components (biosystems) or high standards for each unique component (technical devices).

in constructing a mathematical model of aging and longevity for biological systems.

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

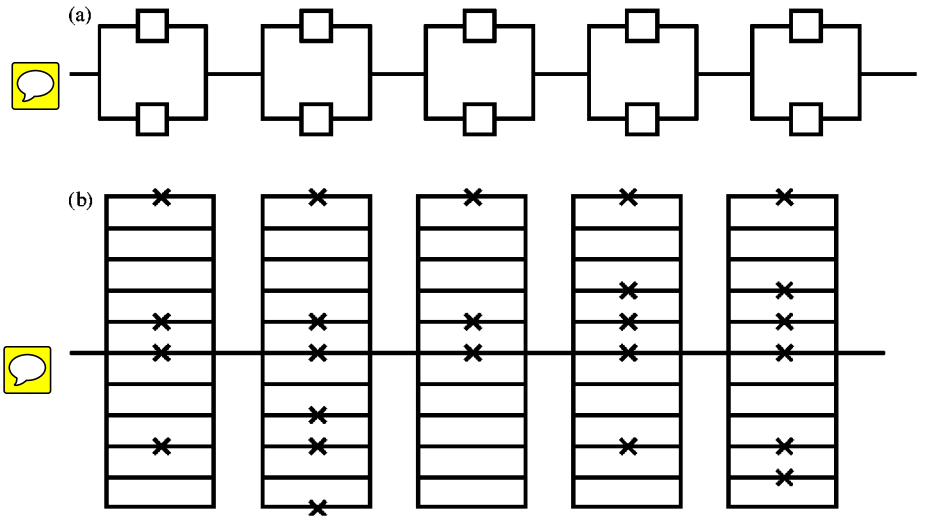

FIG. 2. Diagrams illustrating the differences in reliability structure between (a) technical devices and (b) biological systems. Each block diagram represents a system with m serially connected blocks (each being critical for system survival, five blocks in these particular illustrative examples) built of n elements connected in parallel (each being sufficient for the block being operational). Initially defective non-functional elements are indicated by crossing (x). The reliability structure of technical devices (a) is characterized by relatively low redundancy in elements (because of cost and space limitations), each being initially operational because of strict quality control. Biological species, on the other hand, have a reliability structure (b) with huge redundancy in small, often non-functional elements (cells). The theoretical consequences of these differences are discussed in the text.

the pre-implantation embryo, where some embryonic cells are genetically abnormal (McLaren, 1998), and this may have devastating consequences in later life. Another potential source of extensive initial damage is the birth process itself. During birth, the child is first deprived of oxygen by compression of the umbilical cord (Moffett *et al*., 1993) and suffers severe hypoxia (often with ischemia and asphyxia). Then, just after birth, the newborn child is exposed to oxidative stress because of acute reoxygenation when breathing begins. It is known that acute reoxygenation after hypoxia may produce an extensive oxidative damage through the same mechanisms that also produce ischemia-reperfusion injury (IRI) and asphyxia-reventilation injury (Martin *et al*., 2000). Thus, returning to Hamlet's metaphor, we may add that humans "*suffer the slings and arrows of outrageous fortune*" and have "*a sea of troubles*" from the very beginning of their lives.

Also, the system may behave as if it has a large number of initial defects when some of its components are apparently non-functional for whatever reason (because of impaired regulation, disrupted communication between components, or "self-ish" behavior of DNA, cells, and tissues, etc.). An apparent lack of any function is typical for many structures of living organisms, starting from the molecular level (e.g. non-functional, selfish DNA and inactive pseudogenes, see Griffiths *et al*., 1996), up to the level of the human brain (see Finger *et al*., 1988).

We begin to consider our model by first analysing the simplest case when all the elements of the system are initially functional (which is typical for technical devices) and have a constant failure rate k. If these non-aging elements are organized into blocks of n mutually substitutable elements so that the failure of a block occurs only when all the elements of the block fail (parallel construction in the reliability theory context), the failure rate of a block $\mu_b(n,k,x)$ can be written as follows (see Appendix A):

$$\mu_b(n,k,x) = -\frac{\mathrm{d}S_b(n,k,x)}{S_b(n,k,x)\,\mathrm{d}x} = \frac{nk\mathrm{e}^{-kx}(1-\mathrm{e}^{-kx})^{n-1}}{1-(1-\mathrm{e}^{-kx})^n} \tag{7}$$

$$\approx nk^n x^{n-1} \quad \text{when} \quad x \ll 1/k \quad \text{(early-life period approximation, when } 1-\mathrm{e}^{-kx} \approx kx\text{)}$$

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

Thus, the failure rate of a block initially grows as a power function of age (the Weibull law). Then the tempo at which the failure rate grows declines, and the failure rate asymptotically approaches an upper limit equal to k. Here, we should pay attention to three significant points. First, a block constructed out of non-aging elements is now behaving like an aging object: i.e. aging is a direct consequence of the redundancy of the system (redundancy in the number of elements). Second, at very high ages, the phenomenon of aging apparently disappears (failure rate levels-off), as redundancy in the number of elements vanishes. The failure rate approaches an upper limit which is totally independent of the initial number of elements, but coincides with the rate of their loss (parameter k). Third, the blocks with different initial levels of redundancy (parameter n) will have very different failure rates in early life, but these differences will eventually vanish as failure rates approach the upper limit determined by the rate of elements' loss (parameter k). Thus, the compensation law of mortality (in its weak form) is an expected outcome of this model.

If in its turn, a system is constructed out of m irreplaceable blocks in such a way that the failure of any of the blocks leads to the failure of the whole system (series construction in the reliability theory context), the failure rate of the system is equal to the sum of the failure rates of all the blocks:

$$\mu_s(x) = \sum_{j=1}^{m} \mu_b(j) = m\mu_b = \frac{mkne^{-kx}(1-e^{-kx})^{n-1}}{1-(1-e^{-kx})^n} \tag{8}$$

$\approx mnk^n x^{n-1}$ when $x \ll 1/k$ (early-life period approximation, when $1 - e^{-kx} \approx kx$)

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

In this model, the failure rate grows as a power function rather than as an exponential function of age. Therefore, this kind of a model seemed incapable of describing the exponential growth of the failure rate in biological systems for a long time, and attention was drawn to the search for more complex failure scenarios such as the avalanche-like failure models (Le Bras, 1976; Gavrilov & Gavrilova, 1991).

In this section, we demonstrate that the reliability model presented above has been undeservedly rejected merely because it started by analysing initially ideal structures in which all the elements are functional from the outset. This standard assumption may be justified for technical devices manufactured from pre-tested components, but it is not justified for living organisms, presumably replete with defects, for the reasons described earlier [see previous discussion of relevant publications (Dobzhansky, 1962; Finger *et al.*, 1988; Moffett *et al.*, 1993; Griffiths *et al.*, 1996; Handyside & Delhanty, 1997; McLaren, 1998; Martin *et al.*, 2000) and Figs 1 and 2]. It is therefore worthwhile to examine another particular case of the model in which initially functional elements occur very rarely with a low probability q. (This interpretation of the assumption could be relaxed. See the end of this section.)

In this case, the distribution of the blocks in the organism according to the number i of initially functional elements they contain is described by the Poisson law with parameter $\lambda = nq$, corresponding to the mean number of initially functional elements in a block. As shown in Appendix B, the failure rate in this case is given by

$$\mu_s = k\lambda mce^{-\lambda}e^{-kx}\sum_{i=1}^{n}\frac{\lambda^{i-1}(1-e^{-kx})^{i-1}}{(i-1)!(1-(1-e^{-kx})^i)}. \tag{9}$$

Thus, in the early life period (when $x \ll 1/k$ and, therefore, $1 - e^{-kx} \approx kx$), the mortality kinetics follows the exponential Gompertzian law:

$$\mu_s(x) \approx k\lambda mce^{-\lambda}\sum_{i=1}^{n}\frac{(\lambda kx)^{i-1}}{(i-1)!}$$

$$= R(e^{\alpha x} - \varepsilon(x)) \approx R\exp(\alpha x), \tag{10}$$

where $R = cm\lambda ke^{-\lambda}$, $\alpha = \lambda k$, $\varepsilon(x) = \sum_{i=n+1}^{\infty}(\lambda kx)^{i-1}/(i-1)!$. $\varepsilon(x)$ is close to zero for large n and small x (in early life period).

In the late-life period (when $x \gg 1/k$ and, therefore, $1 - e^{-kx} \approx 1$), the failure rate levels-off and the mortality plateau is observed

$$\mu_s(x) \approx mk. \tag{11}$$

Thus, the failure rate of an organism initially (for $x \ll 1/k$) grows exponentially with age following the Gompertz law. If the background, age-independent component of mortality (A) also exists in addition to Gompertz function, we obtain the well-known Gompertz–Makeham law described earlier. At advanced ages, the rate of mortality decelerates and asymptotically approaches an upper limit equal to mk.

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.

Indeed, according to the previous notations:

$$\ln(R) = \ln(k\lambda cm) - \lambda, \tag{12a}$$

$$\alpha = \lambda k, \tag{12b}$$

i.e. the quantities $\ln(R)$ and α are parametrically linked via the common parameter λ, which allows us to present $\ln(R)$ as a function of α in explicit form:

$$\ln(R) = \ln(cm\alpha) - \frac{\alpha}{k} = \ln(M) - B\alpha, \tag{13}$$

where $M = cm\alpha$, $B = 1/k$.

Thus, the compensation law of mortality is observed: lower mortality rate due to decreased parameter R is compensated by higher mortality acceleration due to increased parameter α. 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, k) 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 ($1/k$).

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. This optimistic prediction is supported by experimental evidence of increased offspring lifespan in response to protection of parental germ cells against oxidative damage just by feeding the future parents with antioxidants (Harman & Eddy, 1979). Increased lifespan is also observed among the progeny of parents with a low respiration rate (proxy for the rate of oxidative damage to DNA of germ cells, see Gavrilov & Gavrilova, 1991). The model also predicts that early life events may affect survival in later adult life through the level of initial damage. This prediction proved to be correct for such early life indicators as parental age at a person's conception (Gavrilov & Gavrilova, 1997a, b; 2000) and the month of person's birth (Doblhammer, 1999; Gavrilov & Gavrilova, 1999). The idea of fetal origins of adult degenerative diseases and early life programming of late-life health and survival is being actively discussed in the scientific literature (Lucas, 1991; Barker, 1992, 1998; Kuh & Ben-Shlomo, 1997; Leon *et al*., 1998; Lucas *et al*., 1999; Blackwell *et al*., 2001).

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, those readers who resist the idea that they are built-up of unreliable trash (or feel uncomfortable with the biological justification for this idea provided earlier), can choose a more comfortable interpretation for the same model and formulae,

namely 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). We believe that, with these reservations mentioned above, the earlier criticism of the suggested model as based on "biologically indefensible assumptions" that are "highly unlikely" (see Pletcher & Neuhauser, 2000, p. 530) could be also relaxed.

The conclusions of the model are valid for any value of the parameter λ (mean number of initially functional elements), no matter how large. This is important, because it is known that as parameter λ increases, the Poisson distribution approximates to the normal distribution (Feller, 1968). Thus, the proposed model in fact encompasses a wide spectrum of distributions of blocks according to their degree of redundancy, starting with a marked positive (right-sided) skewness (for small values of λ) and ending with distributions which are close to the symmetrical normal distribution (for large values of λ). In other words, the proposed model might also be called the model of series-connected blocks with varying degrees of redundancy. This rather general model is generalized even further in the next section.

4. Reliability Theory of Aging for Partially Damaged Redundant Systems

In the preceding section, we examined a reliability model for a system consisting of m series-connected blocks, each of which contains n parallel-connected elements. It was shown that the behavior of such a system depends decisively on the initial conditions. If the system is initially ideal, i.e. if the probability q that the elements are initially functional is unity, the model leads to a power function for failure rate increase with age (the Weibull law). On the other hand, if the system is from the very beginning replete with defects and the probability for a given element being initially functional is close to zero, the model leads to an exponential function for failure rate increase with age (the Gompertz law). In both cases, however, there exists an upper limit to the failure rate which is determined by the product of the number of blocks (m) and the failure rate of the elements (k).

In this section, we shall examine the more general case in which the probability of an element being initially functional can assume any possible value: $0 < q \leqslant 1$.

In the general case, the distribution of blocks in the organism according to the number of initially functional elements is described by the binomial distribution rather than the Poisson law. In this case (see Appendix C), the failure rate is given by

$$\mu_s \approx cmknq \sum_{i=1}^{n} \binom{n-1}{i-1} (qkx)^{i-1} (1-q)^{(n-1)-(i-1)}. \tag{14}$$

The sum represented in this expression is the binomial formula for the expression $[(1-q) + qkx]^{n-1}$. It is therefore possible to write

$$\mu_s \approx cmn(qk)^n \left(\frac{1-q}{qk} + x\right)^{n-1}$$

$$= cmn(qk)^n (x_0 + x)^{n-1}, \tag{15}$$

where $x_0 = (1-q)/qk$ and x_0 is a parameter named the *initial virtual age of the system, IVAS* (Gavrilov & Gavrilova, 1991). 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 previous section. However, when the system is not initially ideal ($q < 1$), we obtain the so-called *binomial law of mortality* (Gavrilov & Gavrilova, 1991):

$$\mu(x) = A + (b + cx)^n. \tag{16}$$

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

$$\mu_s \approx cmn(qk)^n x_0^{n-1} \left(1 + \frac{x}{x_0}\right)^{n-1}$$

$$\approx cmn(qk)^n x_0^{n-1} \exp\left[\left(\frac{n-1}{x_0}\right)x\right]. \tag{17}$$

Hence, for any value of $q < 1$, there is always 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

$$\mu_s = R\exp(\alpha x), \tag{18a}$$

where

$$R = cmn(qk)^n x_0^{n-1} = cmnqk(1-q)^{n-1} \tag{18b}$$

$$\alpha = \frac{n-1}{x_0} = \frac{kq(n-1)}{1-q}. \tag{18c}$$

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 Fig. 3 shows that the binomial law can reproduce the important features of observed mortality curves: exponential increase in mortality rates at younger ages (20–60 yr), and "mortality deceleration" in later life, when mortality rates increase with age at a slower pace compared to the Gompertz law. The mathematical proof of this statement (asymptotic analyses) is provided later [Formulae (21)–(23)].

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. Indeed, according to the above formulae:

$$\ln(R) = \ln(cmnqk) - (n-1)\ln\left(\frac{1}{1-q}\right), \tag{19a}$$

$$\alpha = \frac{kq}{1-q}(n-1), \tag{19b}$$

i.e. the quantities $\ln(R)$ and α are parametrically linked via the quantity $(n-1)$, allowing $\ln(R)$ to be represented as a function of α:

$$\ln(R) = \ln(cm\alpha(1-q) + cmkq] - \frac{\alpha(1-q)}{kq}\ln\left(\frac{1}{1-q}\right)$$

$$= \ln(M) - B\alpha, \tag{20a}$$

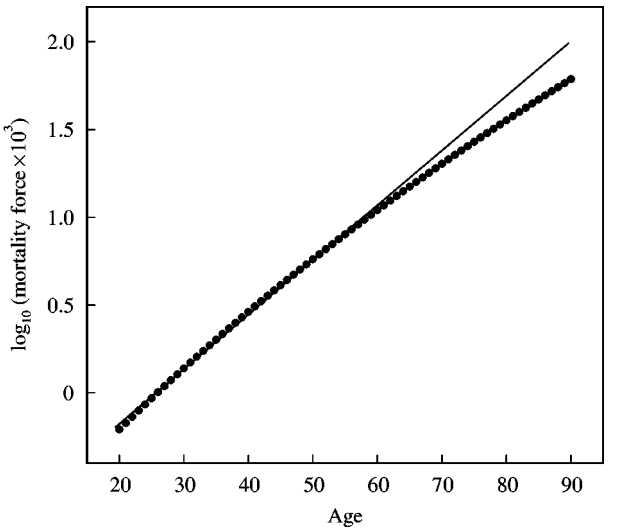

FIG. 3. The dependence of the logarithm of mortality force (failure rate) on age (computer simulation test). Note that at early ages (20–60 yr), the data simulated with the binomial law of mortality ($\mu = b(x_0 + x)^n$) are very close to the linear relationship corresponding to the Gompertz law: $\mu = Re^{ax}$. At older ages, however, mortality deceleration is observed, i.e. the mortality rates are increasing with age at a slower pace compared to the Gompertz law (straight line on a semi-log scale). The parameters of the binomial law of mortality in this illustrative example are: $x_0 = 100$ yr; $n = 10$; $b = 10^{-24}$ yr^{-11}. Although the choice of parameters is arbitrary in this computer simulation, the obtained mortality trajectory proved to be very close to the actual trajectory observed for human populations (see Gavrilov & Gavrilova, 1991, p. 150).

where

$$M = cm\alpha(1-q) + cmkq \tag{20b}$$

$$B = \frac{(1-q)}{kq}\ln\left(\frac{1}{1-q}\right). \tag{20c}$$

Thus, 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 k) 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 (maintaining the same temperature), but not for experiments conducted at different temperatures, presumably because temperature may influence the rate of element loss.

The length of the period when the failure rate grows exponentially depends on the value of q. In general, the q-dependent behavior of the system in the age interval $0 < x \ll 1/k$ can be reduced to the following three scenarios:

(1) $0 < q \leqslant 1/2$. This case corresponds to the situation when less than half the total number of elements is initially functional. In this case,

$$\frac{1-q}{q} \geqslant 1 \quad \text{and, therefore, } x_0 \geqslant 1/k. \quad (21)$$

Therefore, over the entire interval when $x \ll 1/k$, the condition $x \ll x_0$ is also valid. In this case, the failure rate grows exponentially with age throughout the interval under consideration.

(2) $1/2 < q < 1$. This case corresponds to the situation when more than half of all elements are initially functional. In this case,

$$\frac{1-q}{q} < 1 \quad \text{and, therefore, } x_0 < 1/k. \quad (22)$$

In these circumstances, the age-dependence of mortality in the age interval under consideration ($0 < x \ll 1/k$) consists of two stages:

(a) the first stage of the initial period, when $x \ll x_0$ and consequently the binomial law of mortality reduces to the Gompertz law.
(b) the second stage of the initial period, when $x \approx x_0$ and only the binomial law of mortality in its full form is valid, without any approximations.

(3) $1/2 \ll q < 1$. This case corresponds to the situation when only a small proportion of elements is initially defective. In this case,

$$\frac{1-q}{q} \ll 1 \quad \text{and, therefore, } x_0 \ll 1/k. \quad (23)$$

The age-dependence of mortality then consists of three stages:

(a) the first stage of the initial period, when $x \ll x_0$ and the binomial law of mortality reduces to the Gompertz law.
(b) the second stage of the initial period, when $x \approx x_0$ and only the binomial law of mortality is applicable.
(c) the third stage of the initial period, when $x_0 \ll x \ll 1/k$ and the binomial law of mortality reduces to the power law for failure rate increase with age (the Weibull law).

As q tends to unity, the length of the first stage of the initial period, with exponential growth in the failure rate, is sharply reduced, and the length of the third stage is sharply increased. In the extreme case of an initially ideal system ($q = 1$), we come to the Weibull law, valid over the entire age interval $0 < x \ll 1/k$. This case has been described in detail in the previous section.

The failure rate of the blocks asymptotically approaches an upper limit which is independent of the number of initially functional elements and is equal to k. Therefore, the failure rate of a system consisting of m blocks in series tends asymptotically with increased age to an upper limit mk, independent 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. In addition, the model clarifies the conditions under which we observe not the exponential law, but the power law for failure rate increase with age (the Weibull law). Finally, the model allows researchers to treat two at first sight mutually exclusive laws, the Gompertz law and the Weibull law, as special cases of a more general binomial law of mortality which follows from this model.

According to the proposed model, the fate of non-functional elements and their death has no effect whatsoever on the model's conclusions. Therefore, the model will be valid even when all the non-functional elements have already died by the time the adult organism has been formed, and

the adult organism consists only of functional elements (cells). What is important is that a *trace* nevertheless remains in the form of the binomial distribution of blocks according to the number of functional elements within the organism. In fact, this is the essence of the model, and considerations of initially defective elements are only one of the possible explanations for the existence of variability in the initial degree of redundancy. For this reason, the proposed model might also be called the model of series-connected blocks with varying degrees of redundancy.

Taking into account these notes, 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*. This statement is valid regardless of the shape of the binomial distribution of blocks in the organism according to their degree of redundancy: whether there is negative (left-sided) skewness, zero skewness (a normal distribution), or positive (right-sided) skewness. The only effect of the shape of the distribution is that in the case of a negative (left-sided) skewness of the distribution, the exponential growth in the failure rate may last only a short time, while in the case of a zero or positive skewness the period of exponential growth in the failure rate is significantly longer.

The model may also help in resolving an apparent contradiction between exponential increase in total mortality with age, as opposed to non-exponential (e.g. power) increase in mortality from particular causes of death. Indeed, the classification of diseases and causes of death is largely based on the anatomical principle and registration of the damage to particular organs and tissues of the organism. One of the interesting features of the model is that each component (block) may fail according to the Weibull (power) law, but this in turn may lead to exponential increase of failure rate for the whole organism. Indeed, it turned out that the Gompertz function is a better descriptor for "all-causes" of death and combined disease categories, while the Weibull function is a better descriptor of purer, single causes-of-death (Juckett & Rosenberg, 1993).

5. Concluding Remarks

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. As shown in this article, the theory provides explanations of the fundamental problems regarding species aging and longevity that were posed in the introduction of this paper:

(1) Reliability theory explains why 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 age dependence for mortality increase. The theory predicts that even those systems that are entirely composed of non-aging elements (with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are *redundant* in irreplaceable elements. Aging, therefore, is a direct consequence of systems redundancy. The "apparent aging rate" (the relative rate of age-related mortality acceleration corresponding to parameter α in the Gompertz law) increases, according to reliability theory, with higher redundancy levels. Therefore, a negligible "apparent aging rate" in primitive organisms (Haranghy & Balázs, 1980; Finch, 1990; Martinez, 1998) with little redundancy is a predicted observation for reliability theory.

At this point, however, evolutionary biologists have good reasons to argue with our suggested explanation for negligible senescence. This is because evolutionary theory also predicts negligible senescence among some primitive organisms, but for a completely different reason (lack of parent–offspring asymmetry, see Charlesworth, 1994, pp. 246–247). Evolutionary biologists believe that effective repair mechanisms are responsible for the negligible aging rate in some species and give the following arguments: "… unicellular organisms, such as bacteria, which propagate simply by binary fission, and the germ lines of multicellular organisms, have been able to propagate themselves without senescence over billions of years, showing that biological systems are capable of ongoing repair and maintenance and so can avoid senescence at the cellular level. Senescence cannot, therefore, just be an unavoidable

cumulative result of damage." (Charlesworth, 2000, p. 927). It is important, however, not to overlook two key related questions posed by reliability theory:

What are the actual death rates observed in populations of species with negligible senescence, as well as among germ cells?

Are these death rates really negligible (indicating perfect repair) or, on the contrary, quite high (indicating low redundancy of these cells and organisms)?

Debates on these issues may be expected in the future, but there are promising opportunities for merging the reliability and the evolutionary theories (Miller, 1989).

(2) The reliability theory explains why mortality rates increase *exponentially* with age in many adult species (Gompertz law) by taking into account the *initial flaws* (*defects*) in newly formed systems. It also explains why organisms "prefer" to die according to the Gompertz law, while technical devices usually fail according to the Weibull (power) law. Moreover, the theory provides a sound strategy for handling those cases when the Gompertzian mortality law is not applicable. In this case, the second best choice would be the Weibull law, which is also fundamentally grounded in reliability theory. Theoretical conditions are specified when organisms die according to the Weibull law: organisms should be relatively free of initial flaws and defects.

In those cases when none of these two mortality laws is appropriate, reliability theory offers more general failure law applicable to adult and extreme old ages. The Gompertz and the Weibull laws are just special cases of this unifying more general law (see earlier Sections 3 and 4).

(3) Reliability theory also explains why the age-related increase in mortality rates vanishes at older ages. It predicts the late-life mortality deceleration with subsequent leveling-off, as well as the late-life mortality plateaus, as an inevitable consequence of *redundancy exhaustion* at extreme old ages. This is a very general prediction of reliability theory: it holds true for systems built of elements connected in parallel, for hierarchical systems of serial blocks with parallel elements (see earlier Sections 3 and 4), for highly interconnected networks of elements (Bains, 2000), and for systems with avalanche-like random failures (Gavrilov & Gavrilova, 1991).

The reliability theory also predicts that the late-life mortality plateaus will be observed at any level of initial damage: for initially ideal systems, for highly redundant systems replete with defects, and for partially damaged redundant systems with an arbitrary number of initial defects (see earlier).

Furthermore, reliability theory predicts *paradoxical mortality decline in late life* (before eventual leveling-off to mortality plateau) if the system is redundant for *non-identical components* with different failure rates (Barlow *et al*., 1965; Barlow & Proschan, 1975). Thus, in those cases when "apparent rejuvenation" is observed (mortality decline among the oldest-old) there is no need to blame data quality or to postulate initial population heterogeneity and "second breath" in centenarians. The late-life mortality decline is an inevitable consequence of *age-induced population heterogeneity* expected even among initially identical individuals, redundant in non-identical system components (Gavrilov & Gavrilova, unpublished). Recently, this general explanation was also supported using computer simulations (Bains, 2000). Late-life mortality decline was observed in many studies (Barrett, 1985; Carey *et al*., 1992; Khazaeli *et al*., 1995; Klemera & Doubal, 1997) and stimulated interesting debates (Klemera & Ďoubal, 1997; Olshansky, 1998) because of the lack of reasonable explanation. Reliability theory predicts that the late-life mortality decline is an expected scenario of systems failure.

(4) The theory explains the compensation law of mortality, when the relative differences in mortality rates of compared populations (within a given species) decrease with age, and mortality convergence is observed due to the exhaustion of initial differences in redundancy levels. Reliability theory also predicts that those experimental interventions that change "true aging rate" (rate of elements' loss) will also suppress mortality convergence, providing a useful approach on how to search for factors affecting aging rate.

Overall, reliability theory has an amazing predictive and explanatory power and requires only a few general and realistic assumptions. It offers a promising approach for developing

a comprehensive theory of aging and longevity that integrates mathematical methods with biological knowledge including cell biology (Abernethy, 1998), evolutionary theory (Miller, 1989; Charlesworth, 1994) and systems repair principles (Rigdon & Basu, 2000).

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REFERENCES

ABERNETHY, J. D. (1979). The exponential increase in mortality rate with age attributed to wearing-out of biological components. *J. theor. Biol.* **80,** 333–354.

ABERNETHY, J. (1998). Gompertzian mortality originates in the winding-down of the mitotic clock. *J. theor. Biol.* **192,** 419–435, jt980657.

AVEN, T. & JENSEN, U. (1999). *Stochastic Models in Reliability*. New York: Springer-Verlag.

BAINS, W. (2000). Statistical mechanic prediction of non-Gompertzian ageing in extremely aged populations. *Mech. Ageing Dev.* **112,** 89–97.

BARKER, D. J. P. (1992). *Fetal and Infant Origins of Adult Disease*. London: BMJ Publishing Group.

BARKER, D. J. P. (1998). *Mothers, Babies, and Disease in Later Life*, 2nd Edn. London: Churchill Livingstone.

BARLOW, R. E. & PROSCHAN, F. (1975). *Statistical Theory of Reliability and Life Testing. Probability Models*. New York: Holt, Rinehart and Winston.

BARLOW, R. E., PROSCHAN, F. & HUNTER, L. C. (1965). *Mathematical Theory of Reliability*. New York: John Wiley & Sons, Inc.

BARRETT, J. C. (1985). The mortality of centenarians in England and Wales. *Arch. Gerontol. Geriatr.* **4,** 211–218.

BLACKWELL, D. L., HAYWARD, M. D. & CRIMMINS, E. M. (2001). Does childhood health affect chronic morbidity in later life? *Social Science & Medicine* **52**, 1269–1284.

BROWNLEE, J. (1919). Notes on the biology of a life-table. *J. Roy. Stat. Soc.* **82,** 34–77.

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.

CARNES, B. A. & OLSHANSKY, S. J. (1993). Evolutionary perspectives on human senescence. *Popul. Dev. Rev.* **19,** 793–806.

CARNES, B. A., OLSHANSKY, S. J., GAVRILOV, L. A., GAVRILOVA, N. S. & GRAHN, D. (1999). Human longevity: nature vs. nurture—fact or fiction. *Persp. Biol. Med.* **42,** 422–441.

CHARLESWORTH, B. (1994). *Evolution in Age-structured Populations*, 2nd Edn. Cambridge: Cambridge University Press.

CHARLESWORTH, B. (2000). Fisher, Medawar, Hamilton and the evolution of aging. *Genetics* **156,** 927–931.

CHARLESWORTH, B. & PARTRIDGE, L. (1997). Ageing: levelling of the grim reaper. *Curr. Biol.* **7,** R440–R442.

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

CROWDER, M. J., KIMBER, A. C., SMITH, R. L. & SWEETING, T. J. (1991). *Statistical Analysis of Reliability Data*. London: Chapman and Hall.

DOBLHAMMER, G. (1999). Longevity and month of birth: evidence from Austria and Denmark. *Demogr. Res.* [Online] **1,** 1–22. Available: http://www.demographic-research.org/Volumes/Vol1/3/default.htm.

DOBZHANSKY, T. (1962). *Mankind Evolving. The Evolution of Human Species*. New Haven and London: Yale University Press.

ĎOUBAL, S. (1982). Theory of reliability, biological systems and aging. *Mech. Ageing Dev.* **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. Soc. Biol. Struct.* **3,** 317–329.

ECONOMOS, A. C. (1983). Rate of aging, rate of dying and the mechanism of mortality. *Arch. Gerontol. Geriatr.* **1,** 3–27.

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

EKERDT, D. J. (ed.) (2002). *The Macmillan Encyclopedia of Aging*. New York: Macmillan Reference USA (in press).

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.

FINCH, C. E. & TANZI, R. E. (1997). Genetics of aging. *Science* **278,** 407–411.

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. *Proc. Natl Acad. Sci. USSR* (*Doklady Akademii Nauk SSSR, Moscow*) **238,** 490–492 (in Russian).

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

GAVRILOV, L. A. (1987). Critical analysis of mathematical models of aging, mortality, and life span. In: *Population Gerontology* [*Populyatsionnaya Gerontologia*] (Burlakova, E. B. & Gavrilov, L. A., eds), Vol. 6, pp. 155–189. Moscow: VINITI (in Russian).

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. (1993) Fruit fly aging and Mortalilty. *Science* **260,** 1565.

GAVRILOV, L. A. & GAVRILOVA, N. S. (1997a). Parental age at conception and offspring longevity. *Rev. Clin. Gerontol.* **7,** 5–12.

GAVRILOV, L. A. & GAVRILOVA, N. S. (1997b). When fatherhood should stop? *Science* **277,** 17–18.

GAVRILOV, L. A. & GAVRILOVA, N. S. (1999). Season of birth and human longevity. *J. Anti-Aging Med.* **2,** 365–366.

GAVRILOV, L. A. & GAVRILOVA, N. S. (2000). Human longevity and parental age at conception. In: *Sex and Longevity*: *Sexuality*, *Gender*, *Reproduction*, *Parenthood* (T.B.L. Kirkwood & M. Allard, J.-M. Robine eds), pp. 7–31. Berlin, Heidelberg: Springer-Verlag.

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. Gen. Biol.* (*Zh. Obshchej Biol. Moscow*) **39,** 734–742 (in Russian).

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. Lond.* A **115,** 513–585.

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 Edn. New York: W. H. Freeman and Company.

GUMBEL, E. J. (1958). *Statistics of Extremes.* New York: Columbia University Press.

HAMILTON, W. D. (1966). The molding of senescence by natural selection. *J. theor. Biol.* **12,** 12–45.

HANDYSIDE, A. H. & DELHANTY, J. D. A. (1997). Preimplantation genetic diagnosis: strategies and surprises. *Trends Genet.* **13,** 270–275.

HARANGHY, L. & BALÁZS, A. (1980). Regeneration and rejuvenation of invertebrates. In: *Perspectives in Experimental Gerontology* (Shock, N. W., ed.), pp. 224–233. New York: Arno Press.

HARMAN, D. & EDDY, D. E. (1979). Free radical theory of aging: beneficial effects of adding antioxidants to the maternal mouse diet on life span of offspring: possible explanation of the sex difference in longevity. *AGE* **2,** 109–122.

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.

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.

JAZWINSKI, S. M. (1996). Longevity, genes, and aging. *Science* **273,** 54–59.

JAZWINSKI, S. M. (1998). Genetics of longevity. *Exp. Gerontol.* **33,** 773–783.

JUCKETT, D. A. & ROSENBERG, B. (1993). Comparison of the Gompertz and Weibull functions as descriptors for human mortality distributions and their intersections. *Mech. Ageing Dev.* **69,** 1–31.

KAUFMANN, A., GROUCHKO, D. & CRUON, R. (1977). *Mathematical Models for the Study of the Reliability of Systems.* New York: Academic Press.

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.

KLEMERA, P. & DOUBAL, S. (1997). Human mortality at very advanced age might be constant. *Mech. Ageing Dev.* **98,** 167–176.

KOLTOVER, V. K. (1983). Theory of reliability, superoxide radicals, and aging. *Adv. Mod. Biol.* (*Uspekhi Sovremennoj Biol. Moscow*) **96,** 85–100 (in Russian).

KOLTOVER, V. K. (1997). Reliability concept as a trend in biophysics of aging. *J. theor. Biol.* **184,** 157–163.

KUH, D. & BEN-SHLOMO, B. (1997). *A Life Course Approach to Chronic Disease Epidemiology*. Oxford: Oxford University Press.

LE BRAS, H. (1976). Lois de mortalité et age limité. *Population* **31,** 655–692.

LEON, D. A., LITHELL, H. O., VÅGERÖ, D., KOUPILOVÁ, I., MOHSEN, R., BERGLUND, L., LITHELL, U.-B. & MCKEIGUE, P. M. (1998). Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15000 Swedish men and women born 1915–29. *Br. Med. J.* **317,** 241–245.

LLOYD, D. K. & LIPOW, M. (1962). *Reliability*: *Management*, *Methods*, *and Mathematics.* Englewood Cliffs, NJ: Prentice-Hall, Inc.

LUCAS, A. (1991). Programming by early nutrition in man. In: *The Childhood Environment and Adult Disease* (Bock, G. R. & Whelan, J., eds), pp. 38–55. Chichester: Wiley.

LUCAS, A., FEWTRELL, M. S. & COLE, T. J. (1999). Fetal origins of adult disease—the hypothesis revisited. *Br. Med. J.* **319,** 245–249.

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.

MARTIN, L. J., BRAMBRINK, A. M., PRICE, A. C., KAISER, A., AGNEW, D. M., ICHORD, R. N. & TRAYSTMAN, R. J. (2000). Neuronal death in newborn striatum after hypoxia-ischemia is necrosis and evolves with oxidative stress. *Neurobiol. Dis.* **7,** 169–191.

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

MCLAREN, A. (1998). Genetics and human reproduction. *Trends Genet.* **14,** 427–431.

MEDAWAR, P. B. (1946). Old age and natural death. *Mod. Q.* **2,** 30–49. [Reprinted in *The Uniqueness of the Individual* (Medawar, P. B., ed.), pp. 17–43. New York: Basic Books, 1958.

MEDAWAR, P. B. (1952). *An Unsolved Problem in Biology.* London: H. K. Lewis. [Reprinted in *The Uniqueness of the Individual* (Medawar, P. B., ed.), pp. 44–70. New York: Basic Books, 1958.

MILDVAN, A. & STREHLER, B. L. (1960). A critique of theories of mortality. In: *The Biology of Aging* (Strehler, B. L., Ebert, J. D., Glass, H. B. & Shock, N. W., eds), 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.

MOFFETT, D. F., MOFFETT, S. B. & SCHAUF, C. L. (1993). *Human Physiology*: *Foundations and Frontiers*, 2nd Edn. Dubuque, etc.: Wm. C. Brown Publishers.

MUELLER, L. & ROSE, M. R. (1996). Evolutionary theory predicts late-life mortality plateaus. *Proc. Natl Acad. Sci. U.S.A.* **93,** 15 249–15 253.
MURPHY, E. A. (1978). Genetics of longevity in man. In: *The Genetics of Aging* (Schneider, E. L., ed.), pp. 261–301. New York: Plenum Press.
OLSHANSKY, S. J. (1998). On the biodemography of aging: a review essay. *Popul. Dev. Rev.* **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 Ecol. Evol.* **14,** 438–442.
PERKS, W. (1932). On some experiments in the graduation of mortality statistics. *J. Inst. 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. & NEUHAUSER, C. (2000). Biological aging—criteria for modeling and a new mechanistic model. *Int. J. Mod. Phys. C* **11,** 525–546.
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.
RIGDON, S. E. & BASU, A. P. (2000). *Statistical Methods for the Reliability of Repairable Systems.* New York: John Wiley & Sons, Inc.
ROSE, M. R. (1991). *The Evolutionary Biology of Aging.* Oxford: Oxford University Press.
SKURNICK, I. D. & KEMENY, G. (1978). Stochastic studies of aging and mortality in multicellular organisms. I. The asymptotic theory. *Mech. Ageing Dev.* **7,** 65–80.
STREHLER, B. L. (1960). Fluctuating energy demands as determinants of the death process (A parsimonious theory of the Gompertz function). In: *The Biology of Aging* (Strehler, B. L., Ebert, J. D., Glass, H. B. & Shock, N. W., eds), pp. 309–314. Washington, D.C.: American Institute of Biological Sciences.
STREHLER, B. L. (1978). *Time, Cells, and Aging*, 2nd Edn. New York and London: Academic Press.
STREHLER, B. L. & MILDVAN, A. S. (1960). General theory of mortality and aging. *Science* **132,** 14–21.
TOWER, J. (1996). Aging mechanisms in fruit flies. *BioEssays* **18,** 799–807.
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.
WACHTER, K. W. (1999). Evolutionary demographic models for mortality plateaus. *Proc. Natl Acad. Sci. U.S.A.* **96,** 10 544–10 547.
WILLIAMS, G. C. (1957). Pleiotropy, natural selection and the evolution of senescence. *Evolution* **11,** 398–411.
WILLIAMS, G. C. (1966). Natural selection, the costs of reproduction, and a refinement of Lack's principle. *Am. Nat.* **100,** 687–690.
WITTEN, M. (1985). A return to time, cells, systems, and aging: III. Gompertzian models of biological aging and some possible roles for critical elements. *Mech. Ageing Dev.* **32,** 141–177.

APPENDIX A

Consider the simplest case of the model when all the elements of the system are initially functional (which is typical for technical devices) and have a constant failure rate k. If these non-aging elements are organized into blocks of n mutually substitutable elements so that the failure of a block occurs only when all the elements of the block fail (parallel construction in the reliability theory context), the cumulative distribution function for block failure, $F_b(n, k, x)$, depends on age x in the following way:

$$F_b(n, k, x) = P(X \leqslant x) = (1 - \mathrm{e}^{-kx})^n. \quad \text{(A.1)}$$

Therefore, the reliability function of a block, $S_b(n, k, x)$ can be represented as

$$S_b(n, k, x) = 1 - F_b(n, k, x) = 1 - (1 - \mathrm{e}^{-kx})^n. \quad \text{(A.2)}$$

The probability density function, $f_b(n,\ k,\ x)$ is defined as

$$f_b(n, k, x) = \frac{\mathrm{d}F_b(n, k, x)}{\mathrm{d}x} = -\frac{\mathrm{d}S_b(n, k, x)}{\mathrm{d}x}$$

$$= nk\mathrm{e}^{-kx}(1 - \mathrm{e}^{-kx})^{n-1}. \quad \text{(A.3)}$$

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

$$\mu_b(n, k, x) = -\frac{\mathrm{d}S_b(n, k, x)}{S_b(n, k, x)\,\mathrm{d}x} = \frac{f_b(n, k, x)}{S_b(n, k, x)}$$

$$= \frac{nk\mathrm{e}^{-kx}(1 - \mathrm{e}^{-kx})^{n-1}}{1 - (1 - \mathrm{e}^{-kx})^n}. \quad \text{(A.4)}$$

APPENDIX B

Consider the case when the distribution of the blocks in the organism according to the number i of initially functional elements they contain is described by the Poisson law with parameter $\lambda = nq$, corresponding to the mean number of initially functional elements in a block. Strictly

speaking, this distribution ought to be truncated on the right, since the number of functional elements (i), cannot exceed the total number (n) of elements in a block. In addition, for initially living organisms the distribution ought also to be truncated on the left, since according to the model, an organism which contains a block without any functional elements ($i = 0$) cannot be alive. Therefore, the distribution of blocks according to the number i of initially functional elements within initially living organisms is determined by the following probabilities P_i:

$$P_i = 0 \quad \text{for } i = 0,\ n+1,\ n+2,\ n+3,\ldots,$$

$$\text{instead of } P_i = \mathrm{e}^{-\lambda}\frac{(\lambda)^i}{i!}, \tag{B.1}$$

$$P_i = c\,\mathrm{e}^{-\lambda}\frac{(\lambda)^i}{i!} \quad \text{for } i = 1,2,3,\ldots,n; \tag{B.2}$$

$$\text{where } c = \frac{1}{1-\mathrm{e}^{-\lambda}-\mathrm{e}^{-\lambda}\sum_{i=n+1}^{\infty}(\lambda)^i/i!}. \tag{B.3}$$

Parameter c is a normalizing factor that ensures the sum of the probabilities of all possible outcomes is equal to unity:

$$\sum_{i=1}^{n} P_i = 1. \tag{B.4}$$

For sufficiently high values of n and λ, the normalizing factor turns out to be hardly greater than unity.

As has already been noted [see eqn (8)], 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 $\mu_b(i)$:

$$\mu_s = \sum_{j=1}^{m}\mu_b(i,j) = \sum_{i=1}^{n} mP_i\mu_b(i)$$

$$= mc\mathrm{e}^{-\lambda}\sum_{i=1}^{n}\frac{(\lambda)^i\mu_b(i)}{i!}. \tag{B.5}$$

In its turn, the failure rate of blocks with i initially functional elements is given by

$$\mu_b(i) = \frac{ik\mathrm{e}^{-kx}(1-\mathrm{e}^{-kx})^{i-1}}{1-(1-\mathrm{e}^{-kx})^i} \tag{B.6}$$

$\approx ik(kx)^{i-1}$ when $x \ll 1/k$ (early life period approximation, when $1-\mathrm{e}^{-kx} \approx kx$)

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

By putting together these two formulae, we obtain

$$\mu_s = k\lambda mc\mathrm{e}^{-\lambda}\mathrm{e}^{-kx}\sum_{i=1}^{n}\frac{\lambda^{i-1}(1-\mathrm{e}^{-kx})^{i-1}}{(i-1)!(1-(1-\mathrm{e}^{-kx})^i)}. \tag{B.7}$$

APPENDIX C

Consider the case when the distribution of blocks in the organism according to the number of initially functional elements is described by the binomial distribution. For an initially living organism, this distribution has to be truncated on the left, since according to the model, an organism which contains a block without any functional elements ($i = 0$) cannot be alive.

Therefore, the distribution of blocks according to the number i of initially functional elements within initially living organisms is given by the following probabilities:

$$P_i = 0 \quad \text{for } i = 0, \text{ instead of } P_0 = (1-q)^n, \tag{C.1}$$

$$P_i = c\binom{n}{i}q^i(1-q)^{n-i} \quad \text{for } i = 1,2,3,\ldots,n, \tag{C.2}$$

where

$$\binom{n}{i} = \frac{n!}{i!(n-i)!} = \frac{n}{i}\binom{n-1}{i-1}$$

$$\text{for } i = 1,2,3,\ldots,n, \tag{C.3}$$

$$c = \frac{1}{1-(1-q)^n} \geqslant 1, \tag{C.4}$$

Parameter c is a normalizing factor that ensures that the sum of the probabilities of all

outcomes is unity

$$\sum_{i=1}^{n} P_i = 1. \tag{C.5}$$

The failure rate of a system constructed of m series-connected blocks is equal to the sum of the failure rates of the blocks:

$$\mu_s = \sum_{j=1}^{m} \mu_b(i,j) = \sum_{i=1}^{n} mP_i\mu_b(i)$$

$$= cm \sum_{i=1}^{n} \binom{n}{i} q^i(1-q)^{n-i}\mu_b(i). \tag{C.6}$$

As has been already noted [see eqn (B.6)], at the initial moment in time, when $x \ll 1/k$, the failure rate of a block with i initially functional elements is given by

$$\mu_b(i) \approx ik(kx)^{i-1}. \tag{C.7}$$

Putting together these two formulae, we obtain

$$\mu_s \approx cm \sum_{i=1}^{n} \binom{n}{i} q^i(1-q)^{n-i} ik(kx)^{i-1}. \tag{C.8}$$

Since $i\binom{n}{i} = n\binom{n-1}{i-1}$ for $i = 1, 2, 3, \ldots, n$, we obtain

$$\mu_s \approx cmknq \sum_{i=1}^{n} \binom{n-1}{i-1} (qkx)^{i-1}(1-q)^{(n-1)-(i-1)}. \tag{C.9}$$