Theory of Reliability and Biological Aging: From Analogy to Knowledge

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Abstract

Despite phenotypic variety of organisms, aging is governed by the common quantitative laws, such as the existence of species-specific maximal life-span potentials (T_l) and Gompertz law of mortality. Moreover, the T_l values are inversely related to the resting metabolic rates of the species ('Rubner scaling relation'). The universal laws of aging are naturally explained on the basis of the systems theory of reliability. Reliability ('robustness') is ability of a device to perform its function for a given time under given conditions. The regular conferences on the problems of reliability of biosystems which were organized in the former SU, starting from the first conference which was held in Kiev (Ukraine, former SU) in 1975, have given a strong impetus to research in this direction (Grodzinsky et al., 1987).

The systems approach, that was developed in our papers, is based on the following general principles:

(i) biomolecular constructions are designed in keeping with the genetic programs in order to perform the programmed functions ("original idiotype" of the molecular design);

(ii) all biomolecular constructions operate with limited reliability, namely, for each and every biological device or bionanoreactor, starting from the level of enzymes, normal operation alternates with accidental malfunctions (failures);

(iii) just as in engineering, preventive maintenance replacement of unreliable functional elements in cells and tissues, the so-called turnover, is the main line of assuring the high systems reliability in biology;

(iv) there is a finite number of critical, longevity-assurance, genetic structures of the highest hierarchic level (LAS) which perform the supervisory functions over the turnover;

(v) malfunctions of enzymes in the mitochondrial electron transport chains are of first importance since these malfunctions produce superoxide free radical (SR) and its chemically reactive products.

Inasmuch as all reliability facilities, among them - preventive maintenance, repair, and redundancy of functional elements, are genetically limited, stochastic damages in LAS accumulate up to the threshold dysfunction levels. Thus, aging is the stochastic consequence of the programmed deficiency in reliability of biomolecular constructions. The mortality rate functions, generated from this theory, supply the good quantitative fits to the experimental data, contrary to other models, which provide only qualitative descriptions. Using mortality curves from available literature, we estimated that the number of LAS is about 10 that corresponds, by the order of magnitude, to the numbers of the so-called longevity-assurance genes in nematodes, flies and mammals. Basing on this reliability-theory approach, we estimated that the longevity of human brain could reach 250 years, should the antioxidant defense against SR and its reactive products be perfect.

1 Introduction

Despite the phenotypic variety of organisms, aging is governed by common quantitative laws (see, for example, Sacher, 1977). First, there is a specific maximal life-span potential T_l for each species. Second, the growth of mortality rate with age obeys to the statistics of extremes, the so-called Gompertz law of mortality, $h(t) = h_0 \exp(\gamma t)$, where h_0 and γ are the time-independent parameters. This empiric law has been confirmed for people (of age approximately from 30 to 90 years), other mammals, flies, mollusks and even for prokaryotes. Furthermore, the values of T_l are inversely related to the resting metabolic rates of the species (the so-called Rubner scaling relation). The purpose of this essay is to show that these

universal laws of aging originate from the limited reliability of all biological nanoreactors and systems at all functional levels, starting from the level of enzymes.

2 Methods

The new field of systems biology, in dealing with the problem of reliability, incorporates theoretical and experimental studies on quantitative characteristics and mechanisms of failure and renewal processes in biological systems. It also includes the elaboration of methods for testing the reliability and predicting the failures in biological systems. Apart from the formal fitting to the mortality data, the theory of reliability can serve as an investigative approach for searching for realistic mechanisms of aging (Grodzinsky et al., 1987; Koltover, 1997; 2008).

3 Results and Discussion

3.1 Modeling longevity and aging on the basis of the theory of reliability

Modeling longevity and aging on the basis of the theory of reliability, we reason from some basic principles. First, following the template principle of organization of living systems, we assume the existence of a finite number (N) of information longevity-assurance structures (LAS) in an organism, each being characterized by initial flaws, m_j ($j = 1, 2, \ldots, N$). Second, we reason from the principle that each biological system of any organization level performs its function with the preset limited reliability, in accordance with the genetic programs. Hence, we suggest an upper limit value for m_j at which LAS fail ($0 < m < m_c$). Third, we believe that preventive maintenance replacement of functional elements, which follows a pattern preset in the genome, is of primary concern among the lines of creating reliable biological systems from unreliable components.

This reliability-theory approach successfully works even in the case of the very simple mathematical model, in the frame of which we obtained the following expression for the survival function (Koltover, 1981):

$$R(t) = \{1 - [\exp(\gamma t) - 1] \,/\, [\exp(\gamma T) - 1]\}^N$$

Here γ is a/b, where $a > 0$ is a distribution parameter for m_j, $b > 0$ is the reciprocal of the growth rate of the dysfunction parameter m with time, $T = bm_c$. As a result, the following mortality rate function is easily derived for not very high values of age:

$$h(t) = h_0 \exp(\gamma t), \text{ where } h_0 = \gamma N / [\exp(\gamma T) - 1].$$

Thus, the Gompertz law of mortality obtains its natural explanation on this reliability-theory basis even in the frames of the simplest mathematical model. Taking into consideration that the maximum life-span for human populations, on the average, is about 95 years, the magnitude of γ varies from 0.0612 to 0.119 years^{-1} and the magnitude of h_0 varies from $0.820 \cdot 10^{-3}$ to $0.022 \cdot 10^{-3}$ years^{-1} (Sacher, 1977), one can estimate from our reliability-theory model that the number of LAS for man is of the order of 10. Although an analytical transition from the abstract "longevity-assurance structures" to real bio-molecular structures seems to be no easier than similar transitions from the "generalized co-ordinates" in theoretical physics, it is yet noteworthy that this estimation corresponds, by the order of magnitude, to the number of the so-called "longevity-assurance genes". Such the genes have been recently discovered in various types of organisms, including mice, nematodes, yeasts and drosophilae (Vijg, Suh, 2005).

There are reports on a deceleration of the mortality-rate function in cohorts of flies at the advanced age (see, for example, Arking et al., 2002). The similar findings for humans were taken up in the literature, notwithstanding the facts that the statistical data on human mortality at geriatric ages are poor. A qualitative attempt to highlight this limitation of the classical Gompertzian approach was undertaken by assuming a simple mixture of few homogeneous populations (Koltover, 1984). Furthermore, the question of how population heterogeneity, i.e. - genetic or phenotypic variability of populations, may affect behavior of the reliability model was examined quantitatively (Yashin et al., 1985; Koltover, 1997). In our papers, the parameters T and γ of the homogeneous reliability model were averaged over the ensemble assuming the normal distribution for the parameters T and γ with the respective probability density functions. At the advanced time values, the mortality rate function generated from this model may accelerate its run,

slow it down, display a maximum or level off depending on the parameters of the statistical heterogeneity of LAS (Koltover, 1997). Basing on this reliability approach, one can formulate a more complex, non-linear reliability mathematical model, capable to explain even so sophisticated cases as the demographic profiles of *Drosophila melanogaster* strains which left unexplained by the simple mathematical models.

3.2 Free radical theory of aging from the reliability-theory point of view

The random malfunctions of respiratory enzymes in cell mitochondria are of the first importance since they produce toxic free radicals, such as the oxygen anion-radical (free superoxide radical, SR) and its chemically reactive products. There is a special antioxidant enzyme in mitochondria, the so-called superoxide dismutase (SOD), which catalyzes the reaction of dismutation of superoxide radicals into hydrogen peroxide (H_2O_2) and oxygen (O_2) thus protecting sub-cellular structures from SR. This enzyme works in cooperation with other antioxidant enzymes, catalase and glutathione peroxidase, which catalyze decomposition of (H_2O_2) into the harmless reaction products (H_2O_2) and (O_2).

From the reliability-theory point of view, the antioxidant enzymes provide the preventive maintenance (prophylaxis) against the active forms of oxygen. Yet, inasmuch as all defense systems (antioxidant enzymes, DNA-repair enzymes and so on) operate with the limited reliability, stochastic irreparable damages accumulate up to the threshold dysfunction level in the longevity assurance structures. In the case of genetic damages due to superoxide radicals, the following equation was derived for the maximum lifespan:

$$T = bm_c \approx m_c/[(qV/E)u + D]$$

In this equation q is the probability of a mitochondrial redox-enzyme malfunction leading to the superoxide occurrence, V is the respiration rate, E is the activity of SOD in LAS, u is the probability of realization of the free-radical hits in functional violations. Deleterious effects of free radicals, which slipped through the antioxidant defense, are of less concern if the preventive replacement of the damaged biomolecules is properly maintained in cells and tissues. D is the index to incorporate other damage factors that are not associated with oxygen free radicals (see Koltover, 1997, and the references therein). From this equation, the value of T is inversely related to the respiration rate. Thus, the correlation of longevity with the species-specific metabolism rate, 'Rubner relation', is naturally explained on this reliability-theory basis. Furthermore, from this equation, it was estimated that the longevity of human brain could reach 250 years, should the reliability of the cell defense against oxygen free radicals be absolutely perfect (Koltover, 1997).

Following this reliability-approach, we have first showed that the so-called 'antioxidants' make their beneficial effects against oxygen free radicals *in vivo* not directly, by the trapping of active radicals, but indirectly, through the preventive maintenance mechanisms (prophylaxis) via the hormonal regulation (Koltover, 1992).

The similar reliability-theory approach holds promise for applications in other fields of biology and medicine including the problems of radiation biology and radiation ecology (Grodzinsky et al., 1987; Kutlakhmedov, Korogodin, Koltover, 2003). The harmful effects of ionizing radiation mainly arise from direct hits, i.e. - ionizations and excitations of atoms inside LAS. If experimental animals are given single sub-lethal doses of ionizing radiation, then chromosomes of the dividing cells occur to be mostly injured entailing the critical shortage in redundancy of the functionally competent immune cells. On the Gompertz mortality functions, it shows up as the increase of h_0 while γ is unaltered. If irradiation occurs daily for the duration of life, the radiation-induced changes in LAS of the post-mitotic cells dominate, entailing the deterioration in performance of the defense systems. On the Gompertz functions, it shows up as the dose-dependent increase of γ while h_0 remains constant. The theory of reliability also provides an explanation for the hormetic effects of low doses of radiation.

4 Conclusions

The general approach to the problem of reliability of biological systems is founded on the basic theoretical principles that: (i) all bio-molecular constructions are designed in keeping with genetic programs in order to perform the preprogrammed functions and (ii) all bio-molecular constructions perform their functions with the limited reliability predetermined by the genetic program. Among several lines of creating

reliable biological systems from unreliable components, the preventive maintenance replacement seems to be of primary concern. Since all remedies for the improving of reliability, including renewal, repair, and redundancy are genetically preset and limited, stochastic damages in cells and tissues accumulate up to the threshold dysfunction level. As a result, each organism has a limit life-span potential. As a matter of fact, each of us is a victim of the preprogrammed deficiency in the reliability of our bio-constructions - from enzymes up to the organism as the whole. As far as the longevity is determined by the genetically preset deficiency in the reliability of biological constructions, aging is the programmed process. However, realization of the aging program is of stochastic nature since it is practiced through random malfunctions at all functional levels starting from the level of enzymes. Apart from the formal fitting to the mortality data, the theory of reliability can serve as an investigative theoretical approach to experimental searching for realistic mechanisms of aging and anti-aging medicine.

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