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Reliability Concept as a Trend in Biophysics of Aging

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The vitality of a living system is determined by the reliability characteristics of its functional elements at different organizational levels—from enzymes up to the organism as a whole. The new field of biophysics, 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.

Introduction

Studies of the structural and functional mechanisms of biosystems at different levels of complexity have become the traditional problems of biophysics. Biosystems perform their functions in the presence of a great number of random factors that disturb all functional strata, beginning at the enzyme level. Therefore, random failures may be induced at all levels of any biosystem. The new field of biophysics, in dealing with the problem of reliability, incorporates studies on systematization and classification of failures in biosystems; the investigations of quantitative characteristics and the mechanisms of failures and renewal processes; and the elucidation of possible ways of evaluating molecular failures in functional breaks. It also includes the elaboration of methods for testing the reliability in biological systems and predicting the failures. In engineering, reliability is defined as the ability of a device to perform its function for a given time under given conditions (see, for example, Lloyd & Lipov, 1977). The same intuitive definition and idea of the theory of reliability has been used in attempted explanations of the problems of creating reliable biological systems from unreliable components (Von Neumann & Burks, 1966), phenomena of behavioural resistance to massive brain damage (Glassman & Smith, 1988), social networks of ants (Herbers, 1981), and the neural basis of the improvement of psychophysical reliability for the identification of a visual target by animals (Zohary *et al*., 1990). The regular conferences to deal with the problem of reliability of biosystems have given a strong impetus to research in this direction in the former U.S.S.R. (Grodzinsky *et al*., 1987). The intention of this mini review is to present some examples of the reliability analysis of biosystems at different functional levels and to show that the reliability-theory approach to the problem of aging is heuristic.

Reliability of Enzymes

The self-obvious analogy between the inactivation of enzymes and failures of technical devices was pointed out by Berezin & Varfolomeev (1979). As a rule, inactivation of enzymes at work (i.e. their operational stability) obeys the rules of exponential kinetics (Berezin & Varfolomeev, 1979; Grodzinsky *et al*., 1987).

The violation of selectivity, when an enzyme catalyzes a reaction with an analogue of the enzyme substrate instead of the reaction with the "substrate-

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in-law'', is another kind of enzyme failure. Normally, enzyme selectivity should decrease with temperature due to the thermal conformational fluctuations of the protein macromolecules (Koltover, 1983, 1985). However, one can expect that a definite conformation along with an optimal conformation lability correspond to the given catalytic conditions, to ensure not only high efficiency but also high reliability of the enzymes in the cell. Conversely, any factors capable of tuning the enzyme conformation away from its physiological optimum, should set a limit to the reliability of that enzyme.

This ''theorem'' may serve as a guideline for designing special experiments on the problems of reliability. A case in point is our work with ATPase (CF_1-factor isolated from pea chloroplasts) in which we have shown that the increase in temperature up to its physiological value leads to the conformational change of the enzyme, resulting in an essential increase in the enzyme's selectivity (Koltover, 1985; Koltover *et al*., 1985).

Among the enzyme systems that are known to play key roles in controlling the long-term stability of cells, failures of the translation apparatus should be considered. For example, malfunction in selectivity of aminoacyl-tRNA synthetases may produce errors in translation of genetic information from DNA into proteins (Kowald & Kirkwood, 1994).

The enzymes of mitochondrial electron transport chains (ETC) manifest another type of very important failures. The energetic demands of every operation in a living system are met by molecules of ATP, synthesized during oxidative metabolism in the cellular mitochondria. Normal elementary acts of electron transfers on the ETC alternate with the formation of free superoxide anion-radicals (Chance *et al*., 1979). For the theory of reliability, the ''free-radical failures'' are the random malfunctions (recurrent failures) of the mitochondrial redox-enzymes (Koltover & Kutlakhmedov, 1980; Koltover, 1981). An essential increase in the free-radical failure rate should be expected when the catalytic conditions for the ETC's enzymes move away from the physiological optimum. Indeed, an inadequate supply of oxygen under short-term anoxia/ischemia conditions causes an increase in reactivity of the mitochondrial ubisemiquinones to oxygen, along with the relevant increase in superoxide production (Nohl *et al*., 1993; Koltover, 1996). As reviewed recently by Ames *et al*. (1995), the active oxygen radicals initiate cellular injuries to DNA and other cellular structures and may play the crucial role in aging and age-associated clinical disorders.

Reliability and Mortality of an Organism as the Whole

An analogy between the failure of a technical device and the death of a living system is appealing. For example, the reliability function:

$$R(t) = \mathrm{Prob}(\tau > t),$$

for the probability of failure-free operation during a given time, t, that is taken to be a measure of reliability in engineering, is quite analogous to the survival function (the probability of being alive at a given moment, t). In addition, the so-called hazard or failure-rate function:

$$h(t) = -\mathrm{d}(\ln R)/\mathrm{d}t,$$

that has the meaning of the conditional probability of failure per unit time provided the object operated failure-free up to the given moment, is analogous to the mortality rate function (e.g. Lloyd & Lipov, 1977; Sacher, 1977). Therefore, the same mathematical theory of reliability is essentially applicable to the mathematics of mortality.

In engineering, the failure rate of a device begins to grow with time when wear-out of functional elements comes into play and, similarly, aging of people and of animals results in growth of the mortality rate. There are many simple models in the mathematical reliability theory that result in monotonic increase of the failure rate with time (Lloyd & Lipov, 1977). Thereupon, a number of formal reliability-theory models of human mortality, based on abstract serial, parallel or serial–parallel element systems have been published (e.g. Abernethy, 1979; Koltover, 1981; Doubal, 1982; Witten, 1985; Miller, 1989).

Apart from the formal fitting to the mortality data, the theory of reliability can also be used as a guide-line for searching for realistic mechanisms of aging. It is possible for a complex system to exhibit global programmable modes of failures that are not associated with local subsystem failures. According to Rosen (1978), that may be the case when a system is replete with a ''wired-in'' model. The life-span is programmed into the system, since it ultimately reflects the properties of this wired-in model as compared to the global behaviour of the system in which it is embedded (Rosen, 1978). If that is the case, the aging process is determined by the rate at which reliability of the wired-in model is lost. However, there are more reasons for supposing that aging is influenced by numerous gene loci, including mitochondrial DNA, and proceeds through stochastic failures in local subsystems (Schaechter *et al*., 1993).

Following a general idea about structural and functional heterogeneity and the resulting hierarchy

of living systems, Koltover (1981) and Witten (1983) suggested the reliability models of aging based on the assumption that there are critical structures that perform supervisory functions over the organism's repair and renewal processes. With time, these "longevity-assurance" structures (LAS) accumulate stochastic flaws resulting in disarray of their functions.

In the Koltover model, the set of initial values of the flaws in the LAS: m_j (where $j = 1, 2, \ldots, Q$), was assumed to represent a random sample of the exponential, though truncated, distribution with the density function:

$$f(m) = \alpha \cdot \exp(-\alpha m)/[1 - \exp(-\alpha m_c)],$$

where $\alpha > 0$ is a parameter of this distribution, and $0 < m < m_c$ (Koltover, 1981, 1982). To underlay this hypothetical density function, some simple arguments were brought into account. As the flaws to LAS occur as rare events, the probability of getting an extensive flaw should obviously be less than the probability of getting a smaller one. The exponent was used as the simplest asymmetric distribution known from mathematical statistics. Account was also taken of another widespread peculiarity of living systems, i.e. the existence of threshold values for the most important functional parameters. According to this general idea, there is to be an upper limit value, m_c, at which LAS fail. The organism has been assumed to perish the moment that any of the LAS develops the threshold dysfunction, i.e. the expected life-span $\tau = \min\ \tau_j$, where $\tau_j = b(m_c - m_j)$ and $b > 0$ is the reciprocal of the dysfunction growth rate in LAS with time (Koltover, 1982). Then, the survival function is given by the smallest value of the random sample of size Q:

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

where Q is a number of LAS, $T = bm_c$ and $\gamma = \alpha/b$ (Koltover, 1982). For not very high values of time, the following approximation can easily be derived:

$$R(t) \approx \exp\{(h_0/\gamma)[1 - \exp(\gamma t)]\},$$

with the relevant expression for mortality rate being:

$$h(t) = h_0 \exp(\gamma t),$$

where $h_0 = \gamma Q/[\exp(\gamma T) - 1]$, (Koltover, 1981, 1982).

Hence, this reliability model gives rise to the exponential growth of the mortality rate with time. The life-span limit (T) has appeared as the direct result of the existence of the limit dysfunction, m_c, for the LAS. It is the lifespan of an "ideal" organism having no flaws at $t = 0$. Indeed, it is common knowledge that there are neither mice nor rats exceeding 3–4 years of age, and that a human lifespan does not exceed 120 years provided we take reliable data into account, not sensational press reports or legends (Economos, 1985; Robine & Allard, 1995). The limited lifetime of diploid cell strains *in vitro* is also a well-known phenomenon (e.g. for a review, see Vojta & Barrett, 1995).

The exponential relationship between overall mortality rate and age for people, was noted about 150 years ago by Gompertz in 1825, and that observation has been confirmed since then for age groups from approximately 35 to 90 years. There are many examples in the gerontological literature in which other species of mammals, *Drosophila* imagos, molluscs and even *Acholeplasma laidlawii* (in the stationary phase of cell culture) exhibit the Gompertzian mortality curves (Sacher, 1977; Comfort, 1979; Grodzinsky *et al*., 1987).

M. Witten made use of the very similar reliability theory ideas to derive the Gompertzian mortality function (Witten, 1985). In his model a critical time (t^*) was postulated as the time at which the critical deviation for a critical element is reached. However, he set the exponential density distribution not for random initial defects, as had been done by Koltover (1982), but for the time-to-failure operation of critical elements. Therefore, the reliability function of the element in his model is:

$$R(t) = 1 - [1 - \exp(-\alpha t)]/[1 - \exp(-\alpha t^*)],$$

where α is a failure-rate parameter of the distribution. As a result, Witten obtained the following approximate expression for the "system reliability":

$$R_{\text{sys}}(t) \approx \exp\{(-mk)[1 - \exp(-\alpha t)]\},$$

where m is a number of the critical elements, and $k = 1/[1 - \exp(-\alpha t^*)]$. According to Witten (1985), this is the Gompertzian with the mortality function $h(t) = h_0 \exp(\gamma t)$, where $h_0/\gamma = -mk$ and $\gamma = -\alpha$. However, considering that γ in the Gompertzian mortality law is always positive (e.g. see Sacher, 1977) it means that α must be negative. This may scarcely have a physical sense, because α has been stated as the failure-rate parameter, i.e. it is the conditional probability of failure in Witten (1985). Hence, within the framework of this model, the Gompertzian mortality law does not stem from the theory of reliability but is a result of a formal fit.

Reliability and Mortality of Real Populations

It is common knowledge that aging results from complex and diverse interactions, with different acceleration rates and many regulatory mechanisms.

Therefore, the real question arises: why may the kinetics of aging be so frequently approximated with the Gompertzian mortality law? The mathematical theory of reliability provides the means for tackling this question. Indeed, the Gompertzian mortality function corresponds to the Type 1 asymptotic distribution for the minimum value, known from the so-called statistics of extremes (Gumbel, 1962). Thus, the hazard function for a complex physical system consisting of a large number of components increases exponentially whenever the components are connected in series and are all subjected to a "wearing-out" process, in which the risk of failure increases progressively (Gumbel, 1962; Abernethy, 1979). This limit theorem of the statistics of extremes makes the Gompertzian mortality law appear as if it is almost universally valid, much like the central-limit theorem makes the normal distribution appear as the very appropriate model in the theory of errors.

There are instances in which the Gompertz approximation works poorly (Comfort, 1979). The other limit probability models from the theory of reliability may be useful in these cases. For example, there is the Type III asymptotic distribution for the smallest value that is equivalent to the Weibull distribution with the hazard function $h(t) = \alpha\lambda t^{\lambda-1}$, where $\alpha, \lambda > 0$ (Gumbel, 1962; Lloyd & Lipov, 1977). This "power law" of mortality is the limiting model for the distribution of the smallest independent random value ($n \to \infty$) at various initial distributions bounded at the left (Gumbel, 1962). There have been attempts to use the Weibull distribution for modelling mortality data for humans (Hirsch & Peretz, 1984; Eakin *et al*., 1995) but not yet for investigating the mechanisms of aging. Moreover, the Gompertzian and power functions were reported to fit the mortality-rate data of some animals with equally good results (Hirsch & Peretz, 1984). However, the numbers of animals involved in laboratory mortality studies are apt to be small for practical reasons. Therefore, statistical fluctuations present serious difficulties in fitting the empirical mortality rate functions.

Another "in-limit" time-to-failure model of great importance is the exponential distribution, $R = \exp(-\lambda t)$ with the failure-rate parameter $\lambda > 0$ independent of time. This works for complex systems with a large number of components, none of which individually contributes very heavily to the total failure probability even if the distributions for the individual components are not exponential. Among other processes, it applies to the distribution of the time between failures for a complex system if the failed component is replaced immediately by another component of the same type (Lloyd & Lipov, 1977). This is why the exponential distribution plays a central role in engineering. It is true for non-aging technical devices in which rare chance failures during the "normal operation period" occur unexpectedly, due to accidental overloading (Lloyd & Lipov, 1977). It is also true for people killed in accidents. A well-known extension of the Gompertzian mortality "law" below the age of ≈ 35 is the Makeham function, which includes a constant term, in addition to the exponential one:

$$h(t) = \lambda + h_0 \exp(\gamma t).$$

The constant λ is independent of time and reflects environmental influences on mortality as distinct from the senescent changes reflected by the exponential term (Sacher, 1977). Survival curves of wild animals also fall exponentially with constant mortality-rate parameters. It means that the wild animals die mostly not because of senescence but because of random accidents (Sacher, 1977; Comfort, 1979).

It is pertinent to note here that the survivorship curves for a genera of extinct clams, rudists (a group of specialized Mesozoic clams), also follow the exponential kinetics rule (Van Valen, 1973). From the reliability-theory point of view it means that the species succumbed because of "chance failures". This finding corresponds to the well-known idea of A. Weissmann, who, in 1882, stated that the germ cells of species can be considered as potentially immortal compared to an aging soma. A comprehensive review of Weismann's ideas can be found in Kirkwood & Cremer (1982).

Khazaeli *et al*. (1995) reported recently a deceleration of the mortality-rate function in cohorts of *Drosophila* imagos at the advanced age. Similar findings for humans were taken up in the literature, notwithstanding the facts that the statistical data on mortality at geriatric ages are poor (Economos, 1985). A qualitative attempt to highlight this limitation of the classical Gompertzian approach was undertaken by assuming a simple mixture of a few homogeneous populations (Koltover, 1983, 1985). Thereafter, the question of how an inhomogeneity of populations may affect the behaviour of the reliability model was examined quantitatively by Koltover *et al*. (1993).

In that paper, the parameters T and γ of the homogeneous reliability model were averaged over the ensemble assuming a normal distribution with the respective probability density functions of: $g(T,T_0,\sigma_T)$ and $\varphi(\gamma,\gamma_0,\sigma_\gamma)$. In essence, the survival functions for

the inhomogeneous systems were calculated as follows:

$$R(t) = \iint\{1 - [\exp(\gamma t) - 1]/ [\exp(\gamma T) - 1]\}^{Q} g(T)\varphi(\gamma)\mathrm{d}T\mathrm{d}\gamma.$$

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 upon the extent of inhomogeneity of the ensemble, thereby, behaving in a similar manner to the mortality rate curves of the real populations (Koltover *et al*., 1993). Indeed, the deceleration of mortality rates at the most advanced age was observed in cohorts of *Drosophila* flies (Khazaeli *et al*., 1995) whereas the maxima in the geriatric areas of the mortality curves was reported for men (Doubal, 1982; Barret, 1985).

Furthermore, it was shown that this reliability model allowed realistic mortality data for humans to be fitted with a rather high accuracy. In part, the life-tables of the 1969–1973 calendar period for men in Sweden in the age range 35–105 years have been computed (Koltover *et al*., 1993). It is to be pointed out that the set of fitting parameters $Q = 46$, $T_0 \pm \sigma_T = 120.0(\pm 0.3)$ years and $\gamma_0 \pm \sigma_\gamma = 0.095(\pm 0.001)$ year^{-1} gave an agreement between the reliability model and the overall mortality data with an accuracy of not less than 13% (Koltover *et al*., 1993). This confirms the basic realism of the postulates underlying this model.

Although the longevity-assurance structures enable one to represent the dynamics of aging in a rather simple way, an analytical transition from these abstract entities to real biomolecular structures seems to be no easier than similar transitions from the "generalized" co-ordinates in theoretical physics. However, the above-listed estimations may hardly be considered to be random figures. Indeed, the human lifespan has been reported to reach 120 years. As to the value of Q estimated from the overall mortality data, it coincides with the number of chromosomes in human diploid cells. Furthermore, the lifespan limits for mouse, rat, domestic sheep and African buffalo were estimated within the framework of the reliability model (Koltover *et al*., 1993). The numbers obtained (about 3, 4, 20 and 30 years, respectively) are in good agreement with the values known from the gerontological literature (Comfort, 1979; Miller, 1989). When estimated from the overall mortality data, the LAS may be thought of as multigenetic complexes associated with nuclear chromosomes.

These structures are differently fallible since they are initially flawed to statistically varying degrees. However, they were postulated to have the same values for the reliability characteristics m_c, α and b. This was certainly assumed for the sake of mathematical simplicity. However, an evolutionary mechanism can be proposed to support this assumption. The arrangement of the appropriate level of reliability for the LAS falls into the basic cell maintenance processes of defence, restore and renewal because each of them is vitally important. All processes of this kind are found to be metabolically expensive (Kirkwood & Rose, 1991). Meanwhile, the energy budget of a cell is limited. If the organism perishes the moment that any one of the LAS fails there is no use in natural selection making some of them more reliable than others. The acquisition of the greater maintenance for any one than is necessary for others should require an excess cost.

Thus, from the reliability-theory point of view, the limited reliability of "molecular machines" is the reason for aging. Among the others, the enzymes of anti-radical defense and renewal seem to be of great importance (Koltover, 1992; Kowald & Kirkwood, 1994; Ames *et al*., 1995). In the case of genetic damage due to superoxide radicals, the following equation was derived for the maximum lifespan value (Koltover, 1982):

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

where 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 superoxide dismutase (the anti-oxidant defence enzyme), u is the probability of realization of the free-radical hits in functional violations, and D is the index to incorporate other damage factors that are not associated with oxygen free radicals. Using this equation, the experimental data of R. Cutler's group on the superoxide dismutase in brain, liver and heart tissues of men and animals were used to plot the reciprocal of maximum lifespan ($1/T$) as a function of the ratio V/E (Koltover, 1982). Straight lines with the correlation coefficients close to unity were obtained, in agreement with the prediction of the model. By using the free coefficient D, it was estimated that the longevity of human brain could reach 250 years, should the reliability of the anti-oxidant enzymes be absolutely perfect (Koltover, 1982, 1992).

A similar reliability-theory approach might also be applied for analyzing the part in aging played by malfunctions of the enzymes that translate genetic information from DNA into proteins.

The reliability-theory approach seems to be heuristic enough so that a more complex reliability-theory model taking into account the interaction

between LAS, their inhomogeneity and structural pattern, environmental hazards, and other nonlinear effects will not leave unexplained the cases in which the simple models of aging do not work properly.

In conclusion, it is worth noting that the extrapolation of experience with failures in engineering may also be of use in reliability testing in biology. Considerable recent attention has been focused on fluctuations and variability in physical and biological systems (e.g. Bak *et al*., 1987; Lloyd & Lloyd, 1995). There are many examples in engineering when a growth of noise predicts the wear-out failure of an electronic device. One can expect that failures in living systems are also preceded by increasing noise of the relevant physiological parameters (Grodzinsky *et al*., 1987). In general, noise is characterized by its correlation functions and power spectra (Cramer & Leadbetter, 1967). However, values of variance and of the undimensional variation coefficient may serve as simple indexes of the reliability for steady-state stochastic processes (Koltover, 1983; Stolyarov & Chernavsky, 1992). Inasmuch as the phenomenon of growth in variability for transient processes is common for biological systems, a simple method of testing the reliability at all functional levels can be set on this basis.

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