Coefficient of Variation of Lifespan Across the Tree of Life: Is It a Signature of Programmed Aging?

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Abstract—Measurements of variation are of great importance for studying the stability of pathological phenomena and processes. For the biology of aging, it is very important not only to determine average mortality, but also to study its stability in time and the size of fluctuations that are indicated by the variation coefficient of lifespan (CV_{LS}). It is believed that a relatively small (~20%) value of CV_{LS} in humans, comparable to the coefficients of variation of other events programmed in ontogenesis (for example, menarche and menopause), indicates a relatively rigid determinism (N. S. Gavrilova et al. (2012) *Biochemistry (Moscow)*, **77**, 754-760). To assess the prevalence of this phenomenon, we studied the magnitude of CV_{LS}, as well as the coefficients of skewness and kurtosis in diverse representatives of the animal kingdom using data provided by the Institute for Demographic Research (O. R. Jones et al. (2014) *Nature*, **505**, 169-173). We found that, unlike humans and laboratory animals, in most examined species the values of CV_{LS} are rather high, indicating heterogeneity of the lifespan in the cohorts studied. This is probably due to the large influence of background mortality, as well as the non-monotonicity of total mortality in the wild, especially at the earliest ages. One way to account for this influence is to "truncate" the data (removing the earliest and latest ages from consideration). To reveal the effect of this procedure, we proposed a new indicator, the stability coefficient of mortality dynamics, which indicates how quickly CV_{LS} is reduced to values that characterize a relatively homogeneous population (33%) when the data are "truncated". Such indicators facilitate the use of the parameters of survival curves for analysis of the effects of geroprotectors, lifestyle, and other factors on lifespan, and for the quantification of relative contributions of genetic and environmental factors to the dynamics of aging in human and animal populations, including those living in the wild.

Organism aging is manifested biologically in the appearance of age-related diseases, decrepitude, organism deterioration, and mathematically in age-related increase in death probability [1]. If this parameter (probability of an organism's death) depended entirely on the degree of its "wear" growing with age, then the mortality rate of multicellular organisms should have been increasing with age regardless of the position of the species on the evolutionary tree. However, great differences in the dynamics of mortality in different species (increasing, constant, decreasing, convex and concave mortality trajectories, both in long- and short-lived species) have been found [2-4]. V. P. Skulachev pointed to this contradiction and proposed the concept of programmed death [5]. According to this concept, there is a fast programmed death of the organism (acute phenoptosis) or death caused by triggering the genetic self-elimination program of the individual (chronic phenoptosis). Thus, according to this concept, aging can be considered as a slow (chronic) phenoptosis. "Programmed aging" is understood as a set of step-by-step instructions (cascades) recorded in the genome. These cascades could develop due to selection supporting genetic variants that provided optimal rates of age-related decrease in viability. Computer models have been developed demonstrating evolutionary benefit of phenoptosis in certain situations [6]. It is important to note that recently the process of phenoptosis contributing to the survival of a population under unfavorable conditions has been described in the ascidium *Botrylloides*

Abbreviations: CV, coefficient of variation; LS, lifespan.
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leachii (subtype tunicates, type chordates) [7]. The so-called temporal scaling phenomenon also speaks in favor of the existence of individual cascades that control mortality (see below).

Historically, the fact that properties developing after the end of the reproduction period are not subject to natural selection was seen as the main objection to the concept of aging resulting from adaptive evolution [8-10]. In fact, in many animals (and especially in social ones), skills useful to the population and acquired in the post-reproductive period, are transferred to reproductive individuals during training, increasing their fitness, and, in general, increase the resistance of the population to environmental impact [11]. In social species with developed cultural (social) inheritance, selection should support "genes of longevity". The longer the older generation lives, the more it educates young individuals, including their own descendants [12]. The group of social animals with intersecting young and old generations includes not only mammals, but also many social insects, birds, and some other organisms.

Another mechanism of the possible inheritance of post-reproduction properties is associated with the correlation of the organisms' properties and gene pleiotropy. "Genes of longevity", being correlated with some adaptive feature, can therefore be fixed in the population. Pleiotropy can be used to postulate the presence of genes that enhance reproductive success at a young age despite their delayed negative effects in old age [13-15]. This hypothesis is confirmed, for example, by the phenomenon of aging of dividing cells (irreversible cessation of division of damaged cells), which stimulates viability at an early age by decreasing the incidence of cancer and at the same time limits lifespan due to the accumulation of senescent cells [16-18].

If we consider aging as slow (chronic) phenoptosis, then the increasing or weakening of mechanisms contributing (or hindering) this process in consecutive generations can be seen as the evolution of aging. If longevity is supported by selection, organisms can develop special protective and repair systems that slow chronic phenoptosis. Since lifespan is the same stable species characteristic as body size or fecundity, lifespan (i.e., the moment of death), as well as its mechanisms, should be at least partially programmed in the genome [19, 20].

Weismann [21] considered limitation of the number of divisions of somatic cells (unlike unrestrictedly proliferating germ cells) to be the biological mechanism of such a program. He explained the interspecific differences in animal lifespan by a different number of cellular generations. Presence of programmed aging is confirmed by the appearance of the so-called "longevity programs" based on genes that support an organism's survival by repair of somatic cells [15]. Knockout of repair genes results in decreased lifespan and accelerated aging. This program can act alongside the known mechanisms of aging, which

can even be a part of it. Septic shock is an example of pathology showing signs of phenoptosis. Apparently, rapid fatal outcome (due to mass ejection of apoptosis-inducing cytokines by macrophages) is specially organized by the infected organism to prevent the development of an epidemic [5]. Programmed aging is also confirmed by the discovery of dozens of mutations that increase lifespan and affect the organism's resistance to stress [22-25].

Many experimental data suggest that aging is accompanied and probably determined by epigenetic changes (epigenetic program and transcription "signatures" of aging) [26, 27]. A longevity program could have developed in evolution to adapt to short-term extreme external influences (fluctuations in temperature/humidity, amount of food resources) that prevented reproduction [15, 22]. We know an example when in a population of opossums that accidentally populated a separate islet, the average lifespan increased and physiological aging (determined by collagen structure of the tail tendons) slowed compared to "mainland" animals [28].

Thus, the concept suggested by V. P. Skulachev combines Weismann's hypothesis of aging as an adaptive mechanism of programmed death with an alternative view of aging being the result of accumulation of lesions and errors [5, 29].

The assertion that time variation of aging-related events is much greater than that of ontogeny-programmed events is one of the arguments of the opponents of the programmed aging theory. Thus, the main task of N. S. Gavrilova, L. A. Gavrilov, F. F. Severin, and V. P. Skulachev [1] was to test the validity of this argument. They used the spread of lifespan values to assess the degree of its programming by comparing the CV_{LS} with the CV of events associated with reproduction (ages of onset of menarche and menopause). The results of that work indicate that the values of CV_{LS} as a measure of the extent to which the aging process and lifespan are "genetically programmed" are very promising. Since the article of N. S. Gavrilova et al. was dedicated to the parameters of lifespan distribution only in humans, it seems interesting to check the situation in other representatives of the animal kingdom, which is the subject of the present work.

Statistical study of the mathematical parameters of aging and choosing the most appropriate ways of describing them are important both for fundamental biology and for geriatrics [2, 4, 30-39]. Determination of the effectiveness of geroprotectors requires knowledge of the behavior of mortality curves at older ages. The choice of mathematical criteria for lifespan analysis should be approached with deep understanding of their biological meaning. For example, the well-known Gompertz equation does not always adequately describe the behavior of survival curves in the initial and final sections [3, 40]. Another of its drawbacks is that mortality is considered only at the population level. For all people in the same age

range, death probability is the same. In addition, although, for example, measuring methylation of certain DNA loci makes it possible to determine biological, and not the passport age [26], successful attempts to overcome this discrepancy using such methods are still few.

For example, Mitnitski proposed to determine a parameter he called the frailty index (FI) instead of measuring death probability [39, 41]. Gavrilov [34] was the first to note that there is a certain transition of the organism from the "survivalist" to the "non-survivalist" state. Mitnitski has shown that this index varies with age similarly to death probability, but its growth is two times slower. It is based on approximately 30 indicators of health, measured in each person, thus being integrative. This indicator makes it possible to compare separate individuals with the group. It is interesting to note that, unlike death probability, FI does not grow to 100%, but only up to about 70%.

Jones et al. [2] analyzed mortality of animals and plants from the onset of puberty to the age corresponding to 95% extinction of the initial sexually mature cohort. The criterion chosen by them (ratio of mortality at the age corresponding to 95% cohort extinction to the average for the entire period studied) led to several clearly extravagant conclusions. For example, the great tit was attributed to non-aging species and placed next to hydra, although the tit simply does not have time to grow old due to high background mortality. Because of the impact of high background mortality, LS_{95} for pine was determined as 30 years, a tortoise was declared the most non-aging animal, while the crocodile was in the middle of the list, and the long-lived (Japanese) and animals capable of maintaining mortality at practically zero level for a very long time (southern fulmar) were attributed to the most aging species.

Jones' method allows us to characterize mortality throughout the entire biologically significant part of the life cycle only for some species. As for long-lived species with a less pronounced increase (or even a decrease) in age-related mortality (for example, for Johnstone's crocodile, hermit crab, or Scots pine), as well as animals with average lifespan that reach a 5% survival margin prior to physiological aging, Jones' method allows characterization of only a small part of their life cycle and does not provide an opportunity to analyze manifestations of aging in its late stages. We concluded [42] that the classification proposed by Jones et al. [2], allows approximate divisions of animals and plants only based on the increase in age-related death probability, whereas it is necessary to develop more complex models for the assessment of susceptibility to physiological aging.

This article is devoted to analysis of both already known statistical parameters of animal lifespan distribution and parameters introduced by our group. We compare the two approaches to assessing the "stability of dynamics" of mortality (its background and age-dependent components), which we call the spread and monotonicity of mortality change in age intervals.

Akif'ev and Potapenko noted that although in nature probabilities of many events have a normal distribution, the dynamics of mortality significantly differs from Gauss distribution (curves of lifespan distribution have a non-zero excess (a peakedness) and asymmetry) [43]. They conclude that death results not only from random processes (for example, accumulation of damage), but also from the operation of a certain mechanism, and thus the coincidence of survival curves suggests that the mechanisms of aging and death of various species have some common basis [43]. At the same time, the normality of lifespan distribution in case of mortality being the consequence of only random processes, in our opinion, is not unambiguous.

To characterize lifespan distribution, we used the coefficient of variation of lifespan (CV_{LS}), since this parameter was shown to have an important biological meaning [1].

Gavrilova et al. [1] verified the well-known assertion that the spread of individual lifespan and the timing of the onset of aging-related events significantly exceeds the spread of the onset of events associated with the development program. To do that, the authors compared the variability (CV) of parameters determined by the development program of the organism (age at puberty onset) and parameters related to aging (age at the onset of menopause and death) using data from the National Survey of Midlife Development in United States (MIDUS). It was found that for age of puberty onset CV = 8-13%, for age of menopause onset CV = 7-11%, and for age of death CV = 16-21%. Thus, Gavrilova et al. showed that relative variability of age of death is similar in magnitude to the relative variability of the age of puberty and the onset of menopause [1]. Thus, the "programming" of lifespan (as the age of death) was also shown by statistical methods.

Now most authors to some extent recognize the role of genetic programs in the determination of longevity and aging [44-50].

In addition, Stroustrup et al. suggested [37] that we can observe in compared cohorts the phenomenon of temporal scaling, when a certain impact only slows or accelerates the process of changing mortality with age, without changing the shape of the survival curve.

When studying lifespan as one of the organism's characteristics, it is suggested that if the degree of its genetic regulation is low (lifespan is poorly determined), then one should expect a high spread in lifespan in the studied population [1]. On the other hand, if lifespan regulation by the genome is high, then lifespan variability in the population should be lower.

Another difficulty in interpreting the degree of lifespan programming based on CV_{LS} is because the ratio of the contribution of genes and non-genetic component

(environment + stochastics) to variability of a given trait in each individual is not a constant, but depends on the circumstances. It is obvious that the same allele can reduce animal lifespan under adverse conditions, but have no effect on the lifespan in ideal conditions. Genes that affect lifespan of Indians might have no effect on the lifespan of Japanese. For example, in a society with no hard physical labor, the gene affecting the wear rate of joints or any other organs important in heavy physical work does not affect aging, but in primitive society, it surely does. Thus, habitat conditions can radically change the system of lifespan genetic determination in the same species.

It should also be taken into account that phenotypic manifestation of a gene (or a group of genes responsible for the trait) can vary in the degree of manifestation of this trait (the gene can manifest itself in varying degrees). This phenomenon is called gene expressivity. The action of a gene can be rather constant, persistent in its manifestation, or unstable, variable. We quite often encounter variability of gene expressivity in different organisms. In *Drosophila*, mutation of the *eyeless* gene results in the appearance of a mutant form with a strongly reduced number of facets. However, when looking at the offspring of one parental couple, when all the flies bear this mutation, one can see that in some flies the eyes are almost completely devoid of facets, while in others the number of eye facets reaches half the normal number. The same phenomenon is observed in relation to many properties in other animals and plants [51].

One and the same trait can be manifested in some, but not in other individuals (penetrance). With full penetrance (100%), the mutant gene manifests itself in every individual; with incomplete penetrance (less than 100%), the gene manifests its phenotypic effect in a certain percentage of individuals. Expressivity and penetrance are caused by gene interaction in the genotype and various reactions of the latter to the environmental factors affecting the course of ontogenesis [51].

MATERIALS AND METHODS

In this work, we have evaluated various approaches by comparing statistical parameters of lifespan distribution based on data from the Max Planck Institute for Demographic Research (Germany), which were provided in Jones et al. [2].

These data characterize the quantitative distribution of individuals by lifespan value, i.e., percentage or fraction of individuals that died in each age interval (with the base interval for vertebrates usually being 1 year, for invertebrates 1 day). The level of variability of lifespan distribution CV_{LS} was analyzed for Japanese females, Swedish females, and Aché Indians, as well as for 23 animal species — 18 vertebrates and 5 invertebrates (see the table). Species from different systematic groups were con-

sidered: invertebrates — 5 species (3 types), bony fish — 1 species, reptiles — 3 species from all 3 orders, birds — 7 species from 5 orders, mammals — 8 species from 3 orders (4 species of rodents, 1 species of cetaceans, and 3 species of primates). Among the primates, the species *Homo sapiens* is represented by Japanese females and Indians (Mongoloid race) and Swedish females (Caucasoid race). All the examined species differed in the size of the sample (the cohort used to determine the parameters of mortality and lifespan distribution), living conditions (in the wild, captivity), and geographical distribution (i.e., environmental conditions).

The following parameters were considered: CV_{LS}, coefficients of skewness (A_s) and kurtosis (E_s). The data were rounded up to the second decimal place. Data were processed using Statistica 11. The results are shown in the table (A-D). Additional CV studies were performed using Excel 2007 software.

To compare the main regularities of the aging process in animals located on different branches of the evolutionary tree, we sorted the survival data of 46 species published by the Institute for Demographic Research (Germany) [2]. We numbered all the examined species in the same way as they are mentioned in the text of the original article [2] (from 1 to 48 based on the decrease in the ratio of mortality at the age of 5% survival to the average mortality) and subdivided them into four large groups, where group I includes species with the lowest age-related change in mortality, and IV embraces species with the highest change ([42] and the table).

For vertebrates, we calculated the ratio of the value of LS_{95} to the maximal LS (see table) so that to determine to what extent the lifespan corresponding to the time when only 5% of the cohort remains alive (LS_{95}) characterizes the life cycle of a particular species. Data on other species are unfortunately incomplete and contradictory, and quite often the value of the maximal lifespan from the databases was lower than LS_{95} provided by Jones (see, for example, [52]). The values of the maximum LS (unless otherwise indicated) were taken from the database of the Institute for Demographic Research (Rostock, Germany/ Odense, Denmark) [2, 53].

The table also indicates whether the animals were observed in the wild or in captivity. To avoid the widespread objection that there is no aging in the wild and this phenomenon is manifested only in laboratory conditions, Jones [2] presents data on animals that live in the wild (mainly in national parks), except for laboratory animals (fruit flies, nematode), as well as such animals as rotifers, voles — in this case registration of the demographic structure in the wild is not possible.

Statistical parameters and their properties. Left-sided skewness may indicate the existence of a variety of genetic and environmental factors that allow an individual to die at an earlier age, while delaying death is much more difficult [1]. In the case of right-sided skewness,

Parameters of animal lifespan distribution

Species (Latin name)	Order (Latin name)	Group No.	Wild (W)/ Captivity (C)	LS_{95}	LS_{95}/LS_{max}	Jones No.	Number of truncated years (from birth)	CV_{LS}, %	A_s	E_s
1	2	3	4	5	6	7	8	9	10	11
A. Mammals										
Japanese females (*Homo sapiens*) in 2009	Primates	IV	C	102	0.84	1	**0** 10	**15.53** 16.15	**−2.23** −1.73	**8.28** 4.63
Orca (*Orcinus orca*)	Cetacea	III	W	59	0.66	7	**0** 10	**53.36** 34.16	**−0.64** −0.43	**−0.79** −0.05
Swedish females (*Homo sapiens*) born in 1881	Primates	IV	C	89	0.73	2	**0** 1 10	**57.92** 46.63 37.11	**−0.6** −0.85 −0.91	**−1.12** −0.51 −0.08
Tundra vole (*Microtus oeconomus*)	Rodentia	II	C	0.92	0.51	23	**0**	**62.41**	**0.77**	**0.18**
Baboon (*Papio cynocephalus*)	Primates	III	W	24	0.6	10	**0** 1 4	**77.18** 61.59 53.86	**0.34** 0.09 0.1	**−1.18** −1.08 −0.95
Yellow-bellied marmot (*Marmota flaviventris*)	Rodentia	II	W	11	0.52	27	**0** 2	**87.03** 75.76	**2.47** 1.05	**6.41** 0.11
Chimpanzee (*Pan troglodytes*)	Primates	II	W	49	0.82	16	**0** 1 2 7	**97.62** 84.65 76.65 59.22	**0.78** 0.54 0.4 0.15	**−0.72** −1 −1.09 −0.99
Indians (*Homo sapiens*)	Primates	IV	W	81	0.66	5	**0** 2 10	**101.22** 60.46 54.54	**0.54** −0.1 −0.17	**−1.25** −1.29 −1.2
Fish										
Guppy (*Poecilia reticulata*)*	Cyprino-dontiformes	IV	C	3.17	0.53	4	**0**	**26.46**	**−0.29**	**−1.01**
B. Birds										
Southern fulmar (*Fulmarus glacialoides*)	Procellarii-formes	IV	W	33	0.73	6	**0**	**29.60**	**0.3**	**−0.88**
Collared flycatcher (*Ficedula albicollis*)	Passeri-formes	I	W	5	0.51	35	**0**	**40.07**	**1.4**	**1.79**
Alpine swift (*Apus melba*)	Apodiformes	II	W	16	0.62	21	**0**	**53.16**	**1.12**	**0.59**
Great tit (*Parus major*)	Passeri-formes	I	W	4	0.26	37	**0**	**54.36**	**1.36**	**2.16**
Rothschild's mynah (*Leucopsar rothschildi*)	Passeri-formes	IV	W	18	0.72	3	**0**	**66.05**	**0.2**	**−1.18**

Table (Contd.)

1	2	3	4	5	6	7	8	9	10	11
Eurasian sparrowhawk (*Accipiter nisus*)	Accipitri-formes	II	W	8	0.4	28	**0**	**69.88**	**1.11**	**0.1**
Mute swan (*Cygnus olor*)	Anseriformes	II	W	16	0.23	22	**0** 3	**76.52** 47.49	**1.36** 1.03	**1.23** 0.28

C. Reptiles

1	2	3	4	5	6	7	8	9	10	11
Viviparous lizard (*Lacerta vivipara*)	Squamata	I	W	6	0.55	32	**0** 1	**69.28** 55.92	**2.41** 0.84	**5.3** −0.29
Agassiz's desert tortoise (*Gopherus agassizii*)	Testudines	I	W	64	0.8	47	**0** 1 11	**160.00** 135.31 117.16	**5.59** 4.42 1.89	**44.9** 26.51 3.3
Johnstone's crocodile (*Crocodylus johnsoni*)	Crocodilia	II	W	40	0.8	26	**0** 1 2 11	**194.52** 91.50 60.38 34.19	**3.46** 1.08 0.79 0.86	**12.44** 0.38 −0.01 0.38

D. Invertebrates

Species (Latin name)	Phylum	Class/Order	Group	Wild (W)/ Capti-vity (C)	Jones No.	Number of truncated years (from birth)	CV_{LS}, %	A_s	E_s
Nematode (*Caenorhabditis elegans*)	Nematoda	Chromadorea/ Rhabditida	III	C	14	**0**	**34.13**	**0.27**	**−0.30**
Mediterranean fruit fly (*Ceratitis capitata*)	Arthropoda	Insecta/ Diptera	II	C	20	**0**	**37.07**	**0.49**	**0.38**
Bdelloid rotifers (*Macrotrachela quadricornifera*)	Rotifera	Bdelloidea/ Bdelloida	III	C	11	**0**	**39.40**	**0.93**	**0.39**
Fruit fly (*Drosophila melanogaster*)	Arthropoda	Insecta/ Diptera	III	C	17	**0**	**45.28**	**0.25**	**0.09**
Daphnia (*Daphnia longispina*)	Arthropoda	Branchiopoda/ Cladocera	III	C	8	**0**	**46.25**	**−0.20**	**−1.09**

Note: Coefficients of variation (CV_{LS}), skewness (A_s), and kurtosis (E_s) of lifespan (LS) in vertebrates (A-C) and invertebrates (D). LS_{95} corresponds to the age when only 5% of the cohort remain alive; LS_{max} — maximum LS; C — animals were observed in captivity, W — in the wild; CV_{LS} — coefficient of variation of lifespan; A_s — coefficient of skewness; E_s — coefficient of kurtosis. Values for the complete cohort are shown in bold. Vertebrate species within each class (1A-C) and invertebrates (1D) are grouped according to increase in CV in the *complete* cohort and within the species (if conducted) − by the truncation size (increase in number of years (from birth) excluded from consideration).
 * Fish.

higher values of the trait prevail, and this may indicate the existence of many genetic and environmental factors that increase the survival of individuals at a young age, which in turn can lead to the selection of "worthy" representatives of the species that leave more descendants. All substandard and unadapted, as well as the "unlucky" individuals, die at an earlier age. Those who have reached older age (in some species also bigger size) can apparent-

ly relieve the pressure of factors that do not depend on the individual itself; we can assume that their subsequent survival depends on their own genetic component (at least in case of pronounced right-sided asymmetry).

A large (in modulus) kurtosis indicates a significant difference in distribution compared to normal. Positive kurtosis suggests that the distribution has a steeper peak. In this case, the values of the characteristics that are close to the mean value prevail. We can say that the higher the value of kurtosis, the narrower the interval of intensive extinction of a population.

A negative kurtosis indicates that the values of the characteristic are not concentrated in the middle range but are distributed more evenly, or there are several peaks in the distribution. The smaller the kurtosis value, the more evenly mortality is distributed over the ages, or there are several age intervals with increased mortality.

High CV_{LS} means the presence of strong lifespan heterogeneity (genetically determined and environmental). Low CV_{LS} indicates low cohort heterogeneity in relation to lifespan (this may be facilitated, for example, by a low level of background mortality).

In addition, for species with high CV_{LS} values (>33%, indicating sample heterogeneity in relation to lifespan, apparently associated with a greater effect of background mortality, and also with nonmonotonicity of total mortality in the wild, especially at the earliest ages), we proposed a new indicator in order to reveal the effect of one of the most well-known ways to take into account this impact ("data truncation", that is, removal of the earliest and latest ages from consideration): coefficient of mortality dynamics stability, which demonstrates how quickly after truncation CV_{LS} is reduced to values characteristic of a relatively homogeneous population (33%). The effect of truncation of age intervals on CV_{LS} change was checked. To do this, age intervals were consecutively deleted, and CV_{LS} values in the remaining samples were determined. Removal of age intervals resulted in CV_{LS} decrease. They were removed until CV_{LS} became equal to 33%. T_1 is the age at which CV_{LS} drops to 33% after consecutive truncation of initial intervals. T_2 is the age at which CV_{LS} drops to 33% after consecutive truncation of final intervals. The coefficient was determined as the ratio of the described ages (T_2 and T_1).

RESULTS AND DISCUSSION

Data on lifespan distribution is presented in the table (A-D). They are grouped according to increase in CV_{LS}. For comparison, the table shows classification based on increase in the number according to Jones et al. [2] (by the ratio of mortality rate at the age of 5% survival to the mean for the entire studied period, i.e., from puberty to the age corresponding to 5% survival, within each class).

We revealed that, in contrast to humans and laboratory animals, high CV_{LS} values are characteristic for most of the examined species, indicating the heterogeneity of samples in relation to lifespan. Apparently, this is due to the greater effect of background mortality, as well as to the nonmonotonicity of overall mortality in the wild, especially at the earliest ages.

Gavrilova et al. [1] rightly argue that data on total mortality include also the so-called unnatural mortality from external causes (accidents, suicide, etc.). To exclude child mortality, they suggest "truncating", that is, studying the cohort not at its entirety, but only starting from the age of ten, since this is the age when mortality starts increasing, that is, it can be considered the age of the onset of aging. Jones et al. [2] also truncated data, starting to calculate mortality at puberty (respectively, 12, 13, and 15 years for Indians, Swedish females, and Japanese females, respectively). Nevertheless, it can be noted that this truncation did not always lead to decrease in CV_{LS} level to values indicating sample homogeneity in relation to a studied characteristic (see table).

The lowest CV_{LS} value was observed in Japanese females: for a full cohort, $CV_{LS} = 15.53\%$, i.e., the population is extremely homogeneous (table, part A). These data coincide with the data of Gavrilova et al. [1]. Infant mortality is not expressed. A significant increase in mortality is observed only at an older age, over 50 years: $A_s = -2.23$, $E_s = 8.28$ − anomalously high value of the indicator, pronounced concentration of values near the median, significant left-sided skewness. In the cohort without individuals that died in the first 10 years of their life, CV_{LS} and A_s hardly changed, and the peakedness declined.

A study [1] showed left-sided skewness also for American females: $A_s = -1.81$ for the entire population (−1.26 for mortality at age of over 10 years). In case of left-sided skewness, the tail of the left side of the distribution is longer than the tail of the right side, and the bulk of the data (including the peak of the most probable age of death) is to the right of the mean value, i.e., many genetic and environmental factors accelerate the onset of aging, while delaying this process is much more difficult [1].

In Swedish females, $CV_{LS} = 57.92\%$ for the full cohort, i.e., the population is heterogeneous, and there is high mortality rate in the first years: $E_s = -1.12$, and two peaks are observed. When we truncate the first year of life, in the remaining cohort $CV_{LS} = 46.63\%$, i.e., the population is not homogeneous: $A_s = -0.85$, significant left-sided skewness; $E_s = -0.51$, two peaks are observed. Truncation of individuals who died in the first 10 years of life leads to $CV_{LS} = 37.11\%$ − the population is close to homogeneous, left-sided skewness did not change significantly ($A_s = -0.91$), whereas kurtosis decreased ($E_s = -0.08$). Significant increase in mortality is observed only at an older age.

Aché Indians: after truncation of the first two years of life, CV_{LS} in the cohort constitutes 60.46%, i.e., the

sample is not homogeneous, mortality in the first years is high: $A_s = -0.10$, slight left-sided skewness; $E_s = -1.29$, there are no peaks. After the truncation of the first ten years of life, $CV_{LS} = 54.54\%$, i.e., the cohort is still heterogeneous. We concluded that data truncation "according to Gavrilov" is effective for the study of human populations, although it does not always lead to CV decrease to 33% (as in other representatives of the order Primates).

For laboratory mice (*Mus musculus*) and rats (*Rattus norvegicus*), CV_{LS} values in various lines (differing by LS_{95}!) practically never exceeded 33%, which indicates homogeneity of their populations, probably due to a decrease in the level of background mortality and genetic diversity. The same applies to laboratory invertebrates (table, part D) and fish (guppies) (table, part A).

Summarizing the data on lifespan distribution in birds (table, part B), we note that in small (weight <1 kg) birds in the wild A_s varies from 0.29 to 1.4, and E_s from −0.88 to 2.16 (see table and text), i.e., deviations from normality are not pronounced. CV_{LS} ranges from 29.6 to 69.9%, indicating a significant contribution of background mortality to overall mortality.

This suggests that most representatives of this group are characterized by high heterogeneity in mortality as well as moderate and significant right-sided skewness. They are also heterogeneous in relation to kurtosis value − from an approximately uniform distribution to concentration of values near the mean. The lowest values for all three indicators are characteristic of the southern fulmar, which is knocked out of this row by all parameters, probably due to a long period of practically zero mortality (see also [54]). In case of large birds (swan) with lifespan up to 29 years in the wild and 70 in captivity [55], as well as birds with few enemies (sparrowhawk and southern fulmar), the CV_{LS} ranges from 29.5 to 73.8%, skewness from 0.29 to 1.11, and kurtosis from −0.88 to 1.11, which hardly differs from the parameters of the group of small birds considered above. If we compare these data with the data for Rothschild's mynah kept in captivity (in zoos), which is threatened with extinction and therefore special efforts were made to eliminate its background mortality, this bird basically fits the general series ($CV_{LS} = 66\%$, $A_s = 0.19$, $E_s = -1.17$). In relation to the last two parameters, it is closer to the fulmar, while by weight and lifespan to swift. Captivity had little effect on its CV_{LS}. In general, summarizing data on birds, we can say that birds are very heterogeneous in relation to all the discussed parameters.

The most inhomogeneous sample is characteristic of reptiles (table, part C) and of the *Gopherus agassizii* gopher: for the total cohort $CV_{LS} = 160.00\%$, $A_s = 5.59$, $E_s = 44.90$ − an extremely high value (at such E_s values, it can be assumed that neither CV_{LS} nor the mean characterize the studied population, apparently despite the long lifespan and resistance to aging, the effect of child mortality is too great).

In the cohort resulting from the truncation of individuals who died in the first year of life, $CV_{LS} = 98.31$ − high infant mortality was eliminated, $A_s = 4.42$, $E_s = 26.51$. Truncation of the first 11 years of life resulted in $CV_{LS} = 56.42\%$. Although, after subtracting the first eleven years, CV_{LS} dropped (due to elimination of child mortality and reduction of the general size), in the end it remained very high: $A_s = 1.89$, $E_s = 3.30$ − these parameters decreased due to removal of the first years of life with high mortality values.

In all three cases, $A_s > 0$, i.e., there is a significant right-sided skewness. High mortality is observed only at early ages; later it becomes low and does not grow with age. Kurtosis is positive in all three cases, and peaked character is observed with respect to the normal distribution and concentration of values near the average. In further calculations, we found that to achieve homogeneity of the cohort in relation to lifespan (33%), no less than the first 25 years of life need to be truncated in case of tortoise. At earlier ages, tortoise lifespan depends more on background mortality. Perhaps this is the reason for the recent heated discussion on whether the tortoises and turtles are aging (or whether the probability of their death increases with age). Note: in 2011, the species *Gopherus agassizii* was divided into two [56].

It should be noted that although tortoises as well as reptiles in general were considered an "icon" of longevity not prone to aging [57, 58], recent studies have advocated the opposite point of view [38], although so far, this discussion has involved not the large tortoises with unlimited growth, but several small turtles considered to be non-aging despite the limited growth (marsh turtle, carolina box turtle, Blanding's turtle, and painted turtle). In this regard, measuring the sustainability of mortality and the characteristics of lifespan distribution becomes even more important.

Johnstone's crocodile (*Crocodylus johnstoni*): for the complete cohort, $CV_{LS} = 194.52\%$, i.e., the sample is extremely heterogeneous: $A_s = 3.94$, $E_s = 12.44$. In a cohort without the first year of life, $CV_{LS} = 91.50\%$, $A_s = 1.08$, $E_s = 0.38$, and heterogeneity is reduced by eliminating infant mortality. In a cohort without the first two years of life, CV_{LS} is reduced to 60.38%, and without the first eleven years of life ("Jones truncation" till the age of puberty) $CV_{LS} = 34.18\%$. Skewness and kurtosis do not undergo any significant change.

Thus, truncating two years is enough to eliminate the effect of extremely high infant mortality, while truncating the years till the age of puberty makes the cohort virtually homogeneous. In all cases, there is a significant right-sided skewness, showing a high mortality rate at early age, which decreases in later years. The value of kurtosis for a full cohort is unacceptably high, and in other cases kurtosis is close to zero.

With the *Lacerta vivipara* lizard, for the full cohort $CV_{LS} = 69.28\%$, $E_s = 5.30$ − high kurtosis coefficient due

to high mortality in the first year. Truncation of the first year of life results in $CV_{LS} = 55.92\%$, $E_s = -0.29$ – kurtosis is insignificant, but CV_{LS} indicates preservation of population heterogeneity.

Coefficient of variation of lifespan (CV_{LS}). Earlier [59], we concluded that identification of temporal scaling based on CV_{LS} equality in compared cohorts allows us to distinguish first the quantitative differences in the dynamics of aging from qualitative ones.

Statistical description of the phenomenon will be incomplete if we confine ourselves to the parameters of the central tendency, i.e., mean values, mode, and median. In some cases, the values of the parameter are concentrated closely to the center, while in others there is considerable dispersion, although the average value may be the same.

Here is an example of this phenomenon: individual lifespan deviations (caused not by general conditions and causes, but by personal circumstances of peoples' lives) of people that are in the same age range, and therefore probability of their death is by definition the same. Therefore, studying deviations of individual parameters from the average values and patterns of their distribution is of great interest for the biology of aging. This is important, first, for assessing the homogeneity of the population, which is characterized by a given average value, since the more homogeneous the population, the smaller its variation. Consequently, the smaller CV_{LS}, the more qualitatively homogeneous is the population, and the more typical and objective is the average value characterizing it.

Calculated CV_{LS} values indicate a greater lifespan variation in Swedes (37.11%) and Indians (54.54%) compared to Japanese females (16.15%), despite the longer lifespan in the latter. Thus, CV_{LS} is an objective characteristic of the population as a whole, showing that the population of Japanese females as a whole is more homogeneous (for comparison, in Gavrilova et al., $CV_{LS} = 20.5\%$ for American females aged over 10 years [1]). It is generally accepted that at CV_{LS} exceeding 33%, the population is not homogeneous (in our case this means a significant contribution of background mortality).

At CV_{LS} values exceeding 67%, it is generally assumed that the average does not characterize the population, i.e., the calculated average lifespan (and, consequently, the relative spread around it, i.e., CV_{LS}) does not characterize the true state of the population. For example, if, when calculating mortality data for Indians, we consider all age intervals (i.e., also infant mortality), the average lifespan will be 27-30 years, which is clearly an irrelevant characteristic of human lifespan. Moreover, it is not recommended to apply CV_{LS} (as well as the mean) also at excessively high kurtosis, as the probability of artifacts becomes high; it is necessary to ensure that after truncation the kurtosis coefficient would be reduced to acceptable values (no more than 3) (see above, values for total reptile cohorts).

It has already been noted that "truncated" data sets are used to overcome this problem, i.e., lifespan distribution parameters are calculated in the cohort, starting at the age of 10 (which is considered to be the age when age-related mortality starts to increase [1]), or at 12-15 years – the age of puberty [2]. In addition to that, Jones also uses truncation of late age intervals to 95% mortality. It should be noted that in case of this truncation, CV_{LS} declines well below the threshold value of 33%, reaching 15-20%. CV_{LS} characteristic of twins (i.e., with near-zero difference in the genetic component effect) has a similar value [60].

In addition, the method of data truncation (removing a certain number of years from consideration), being convenient for human populations, is difficult to apply to other representatives of the animal world, since many of them, even the long-lived swans and southern fulmars, have no pronounced postnatal peak in the first year of life, or the age of puberty is reached in the first year of life, not allowing, according to Jones's method, to cut off the first few intervals. Checking the prevalence of this phenomenon, we studied the CV_{LS} values as well as the coefficients of skewness and kurtosis in various representatives of the animal kingdom using the data provided by the Institute for Demographic Research [2]. We found that, unlike humans and laboratory animals, most of the examined species are characterized by heterogeneous parameters due to the significant effect of background mortality, as well as the nonmonotonicity of total mortality in the wild, especially at the earliest ages. One way to account for this effect is to "truncate" data (removing a certain number of years from consideration).

To reveal the effect of this procedure, we proposed a new indicator, the stability coefficient of mortality dynamics (hereinafter – stability coefficient), indicating how quickly during "truncation" CV_{LS} will drop to values characteristic of a relatively homogeneous population (33%).

Therefore, we decided to determine how quickly the truncation of the initial age intervals will make lifespan distribution homogeneous, i.e., will reduce CV_{LS} to 33%. At the initial stages, contribution of the age component to total mortality is low; since there are no individuals that have aged (even progerias do not appear instantaneously). CV_{LS} reduction to 33% (T_1) excludes a strong effect of background mortality on the lifespan distribution curve.

However, it is also possible to solve the opposite task – to test the stability margin of mortality dynamics, by truncating intervals from the opposite side, i.e., removing intervals with the most aged individuals. This identifies the "power" of the age component. In this case, after CV_{LS} drops to 33% (T_2), the age component has practically no effect on the parameters of lifespan distribution. Thus, by deleting several final intervals, Jones greatly reduces the contribution of the age-dependent mortality component.

Thus, T_1 is the age when CV_{LS} drops to 33% after the sequential truncation of initial intervals. T_2 is the age when CV_{LS} drops to 33% after sequential truncation of the final intervals. We assume that the ratio of the described ages (T_2 and T_1), $CV_{LS33\%}$, will be higher in species that are "resistant" to aging (long-lived or slowly aging species), and will be lower in rapidly aging and/or short-lived species. Thus, for crocodile this parameter was 17.5, for orca — 11, swan — 5, marmot — 4, vole — 3.75, great tit — 3, lizard — 2.75, sparrowhawk — 2.5, guppy — 2.25, swift — 1.75, and collared flycatcher — 1.5. It reaches its greatest value in humans (102 in Japanese females), as well as in southern fulmar (35), chimpanzee — 44, tortoise — 26, and baboon — 22.

These results support Cohen's view that aging is very different in long-lived and short-lived species, and that in some cases long-lived animals (including birds and bats) might be better models for studying human aging than laboratory animals with short lifespan, despite a closer phylogenetic relationship between humans and, e.g., laboratory mice and rats [61].

Finally, when speaking about non-aging animals, it is impossible to not omit mention of the naked mole rat, *Heterocephalus glaber*. Mortality of naked mole rats is very low and depends little on age; as a result, their lifespan is over 30 years, which makes them very different from other rodents [50]. V. P. Skulachev suggested that the longevity of highly social mammals, such as naked mole rats and humans, is primarily due to neoteny (prolongation of youth) [50]. In both of these species, aging cannot function as a mechanism stimulating natural selection, since the pressure of selection is greatly reduced: in naked mole rats due to the social structure where only one female is involved in reproduction, and in humans due to technological progress that has replaced slow biological evolution.

Data on the survival of the naked mole rats were not used by Jones et al. because of inadequate, in their opinion, data on mortality in the first year. Nevertheless, based on the shape of the survival curve, naked mole rats should be attributed to the group of non-aging animals (group I) [42]. In our research, we calculated the stability coefficient for the naked mole rat, based on the data provided by Buffenstein [62, 63]. This coefficient was ~12, which is less than in primates, and is comparable to that of crocodile and orca. It should be noted that this value may be somewhat underestimated because the available survival data for the naked mole rat embrace only the period to 24 years, whereas its lifespan can be at least 1.5 times longer.

The longer is lifespan and the slower is aging, the higher is the proposed parameter, the coefficient of stability. In particular, it avoids such mistakes as the attribution of two exceptionally slowly aging species (tortoise and southern fulmar) with radically different dynamics of aging, respectively, to the non-aging (tortoise) and strongly aging species (southern fulmar) [2]. In essence, the ratio of the coefficient of stability to the maximum lifespan is the indicator of "instant stability of life": the smaller it is, the higher the probability of death of an individual of the given species at any moment in the life cycle.

We assume that the coefficient of stability reflects the "stability of the dynamics" of aging (i.e., it plays the same role as the "compensation effect" [34, 64] and the Strehler–Mildvan correlation in its various modifications [35, 65]), connecting the initial level (preexponential factor) and the growth rate (exponent index) of mortality in the Gompertz equation.

The approach of the Gavrilovs has a different theoretical basis that does not intersect with the question of the shape of the survival curves and their change. They put forward the idea of the presence of a characteristic level of variability inherent in ontogenetic event onset time [1]. For example, $CV_{LS} = 20\%$ on the average LS of 80 years, obtained for Caucasian women in the developed countries (one of the most prosperous human populations), suggests that about two-thirds of them will die in the 64-96 age range.

The fact that we do not know the degree of genetic heterogeneity of the samples presents another difficulty in implementing the proposed approach. If the sample is characterized by a large variability in lifespan-affecting genes, then CV_{LS} can be high even if lifespan is very rigidly regulated by the genes of each individual. Hence, it seems interesting to study, using the approach proposed in this article (with truncation of young ages, until the CV_{LS} decreases to 33%), long-lived laboratory animals whose background mortality is close to zero.

In addition, it is important to understand what lifespan distribution we expect to see under any given assumptions. For example, let us consider the situation when aging is completely absent, and probability of the organism's death is independent of its age. In other words, death is a random event caused by some external factors and is independent of the state of the organism. In this case, the survival curve will have exponential form, and lifespan distribution will not be normal (for example, in the first year, 20% of the cohort died, in the second year, 20% of the remainder, etc. — this will be a sharply asymmetric distribution with right skewness, where the mode will be much to the left of the mean). Thus, right skewness may indicate stochastic mortality and a low contribution of genes to determination of lifespan.

Symmetrical lifespan distribution is expected when lifespan is strictly controlled genetically, and some random scatter is observed around the "ideal", genetically programmed, lifespan. The survival curve will then look like that of Japanese and Swedish females: very low mortality for a long time, and then all relatively quickly die. Thus, we assume that the degree of right-sided skewness in lifespan distribution is positively correlated with the degree of stochasticity in lifespan determination and neg-

atively with gene contribution to this determination. Left-sided skewness probably means that the death of young individuals can sometimes be caused by tragic accidents (or, perhaps, a particularly unfortunate genotype), but in mature individuals the role of chance is minimized, and genetic lifespan determination comes to the fore. In other words, the larger part of the population (except for those who died in youth for one reason or another) is limited by genetically determined maximum lifespan (maximum for concrete living conditions, of course). This can be true for both orcas and modern people from developed countries.

It should always be taken into account that variability of any character, including lifespan, consists of two components: hereditary (genetic) and non-hereditary, which can be divided into environmental or modificational (according to Darwin, it is determinate variation) and stochastic. Most importantly, the ratio of the contribution of genes and (environmental + stochastics) to variability of any given trait is not a constant, but depends on the circumstances. For example, in case of lifespan this ratio depends on lifestyle, sociality, security, etc.

If a population is placed in some constant favorable conditions and these conditions are leveled for all individuals, then environmental variability will be reduced to a minimum, and almost the entire remaining variability in the population will be due to the genetic component. Apparently, this is observed in Japanese and Swedish females. They live in protected standard conditions created by civilization. Accidental mortality is almost excluded under these conditions, especially after the individuals with defective genotypes had already been eliminated. Therefore, all individuals live as long as it is "recorded" in their genes, with a margin of small remaining non-hereditary variability.

The main problems we face when studying survival curves are the presence of too many unknowns: for example, we do not know the level of genetic variability (heterogeneity) in the samples and the mechanisms of gene−environment interactions. It is obvious that the same allele can reduce lifespan when conditions are unfavorable, but it does not affect lifespan in ideal conditions. Genes that affect the lifespan of Indians may have no effect of lifespan of Japanese. For example, one can imagine a gene that helps to endure starvation or survive after a bite of a poisonous snake. Alternatively, a gene that affects the rate of deterioration of joints (or heart, or other important organs) involved in heavy physical work. In a society with no hard physical labor, this gene does not affect aging, but in a primitive society its impact is very strong. Thus, habitat conditions can radically change the system of lifespan genetic determination in the same species.

Earlier, V. P. Skulachev suggested that not all age-related changes in an organism, as well as changes in environmental conditions, will immediately affect age-related increase in death probability (oral communication). Thus, they can affect the shape of the survival curve in different ways (A. V. Khalyavkin refers to this as the modal environmental pressure [35]), leading to an increase in mortality not in the original, but in subsequent age intervals, depending on the overall "stability" of the organism (the conditions of its existence, etc.). The coefficient of stability of mortality dynamics depends on this type of mortality. Thus, we assume that the greater the value of the T_2/T_1 ratio, the more time will pass from the appearance of any damages to organisms to their manifestation on the Gompertz curve (age-related increase in death probability) and the more it will be "guaranteed" that the negative effect will be manifested not via accidental mortality (its background component), but through the age-dependent component. Otherwise, it will be difficult to distinguish between the slow growth of mortality with age (slow aging) and the absence of such growth due to other reasons (constant predator pressure). We have already discussed the result of such a misinterpretation − attribution of rapidly dying animals (e.g. great tits) to non-aging species (see also [42]), when analyzing classification of animals based on the pace and shape of aging (see, for example, [2, 66, 67]). Direct comparison of the death rate in the final interval with the average parameter for the entire studied period in different populations sometimes leads to a different conclusion than comparison of the relative variation parameters.

Earlier, we discussed the conclusions drawn in previous studies, that CV_{LS} reflects also the degree of the programmed character of aging [1], as well as its rate and mechanism [5, 37, 68]. We assume that CV_{LS} "dynamics" (degree of change) after the removal of initial and final age intervals can serve as an indicator of the "stability" of population mortality and, consequently, the organism's ability to resist it. Depending on the homogeneity of the population, variability of characteristics may be large or small [69-73]. Therefore, there is a need to measure lifespan variations with respect to the mean value (CV_{LS}), both for studying the dynamics of mortality in the wild and in the laboratory, and for studying the efficacy of various drugs and geroprotectors that increase not only the mean and median lifespan, but also the duration of a healthy life (healthspan).

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