Contribution of Quantitative Methods of Estimating Mortality Dynamics to Explaining Mechanisms of Aging

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Abstract—Accumulation of various types of unrepaired damage of the genome because of increasing production of reactive oxygen species and decreasing efficiency of the antioxidant defense system and repair systems can cause age-related diseases and emergence of phenotypic signs of senescence. This should lead to increasing vulnerability and to mortality monotonously increasing with age independently of the position of the species on the evolutionary tree. In this light, the survival, mortality, and fertility curves for 45 animal and plant species and one alga published by the Max Planck Institute for Demographic Research (Germany/Denmark) are of special interest (Jones, O. R., et al. (2014) *Nature*, **505**, 169-173). We divided all species treated in that study into four groups according to the ratio of mortality at the terminal age (which corresponds to 5% survival) and average mortality during the entire studied period. For animals of group IV (long-lived and senescent), including humans, the Jones method makes it possible to trace mortality during the entire life cycle. The same applies to short-lived animals (e.g. nematodes or the tundra vole), whether they display the Gompertz type of senescence or not. However, in long-lived species with a less pronounced increase in mortality with age (e.g. the freshwater crocodile, hermit crab, or Scots pine), as well as in animals of average lifespan that reach the terminal age earlier than they could have enough time to become senescent, the Jones method is capable of characterizing only a small part of the life cycle and does not allow judging how senescence manifests itself at late stages of the life cycle. Thus, it is known that old trees display signs of biological senescence rather clearly; although Jones et al. consider them non-senescent organisms because less than 5% of sexually mature individuals survive to display the first manifestations of these characters. We have concluded that the classification proposed by Jones et al. makes it possible to approximately divide animals and plants only by their levels of the Gompertz type of senescence (i.e. actuarial senescence), whereas susceptibility to biological senescence can be estimated only when principally different models are applied.

The purpose of this study was to review and critically assess studies that investigate the process of senescence and its evolution and to compare the main patterns of aging in representatives of different lineages.

There are two main historically developed approaches to the study of aging. The first approach is focused on the search for mechanisms and molecular "substrates" of senescence. It deals above all with the accumulation of DNA damage caused by exogenous and endogenously generated radicals [1-5]. The accumulation of DNA damage and decreasing ability of cells to repair this dam-

age and respond to it as the organism ages should lead to poorer functioning of particular cells, tissues, organs, and the entire organism (eventually leading to higher chances of its death). A living cell produces reactive oxygen species (ROS), which damage various macromolecules, including DNA, affecting cellular functions and, possibly, the development of age-related changes [2, 6-11]. The ability of the organism to neutralize the ROS produced can be an important factor in determining individual and species-specific lifespan (LS) [12]. Therefore, animals that have greater LS should, ceteris paribus, have a better ability to respond to ROS and to DNA damage caused by ROS. This conclusion is confirmed, among other things, by the positive correlation between the activity of systems

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Abbreviations: LS, lifespan; ROS, reactive oxygen species.
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involved in DNA repair and maximum LS in mammals [13-16].

The second main approach, which started in the 19th century from the work of Gompertz, a mathematician specialized in life insurance, has also become quite widespread [15, 17-24].

Gompertz showed that humans display senescence, which he defined as increasing probability of death with age. It turned out that if human life is divided into a number of equal intervals, the probability of death (the ratio of the number of those who die during each interval and those who survived to its beginning) inevitably grows with age ("the law of mortality") [22].

Survival tables and curves were later made and analyzed for many other animals (Tables 1-3). It turned out that absence of senescence (the Gompertz type of senescence) does not necessarily lead to long LS (see below), i.e. a cohort that successfully stands against the tendency of increasing probability of death with age does not necessarily function longer than other cohorts do. It was found that those species in which the probability of death does not increase with age could nevertheless display signs of biological senescence, i.e. decline of physiological functions and accumulation of some degenerative changes (which are not lethal *per se*). Finch proposed two criteria of negligibly slow aging: absence of increase in mortality and negligibly small functional degradations with age [25].

Many theories have been proposed to explain the emergence of the phenomenon of senescence and its changes in the course of evolution [2, 23, 26-31].

Weismann was the first to suggest that since non-senescent individuals are bad for the population, because they occupy the place of younger ones, evolution should produce a senescence program aimed at purging the population from aged individuals [26]. He believed that the biological mechanism of senescence was based on the limited number of divisions of somatic cells (in contrast to the unlimited proliferation of sex cells) and explained interspecies differences in LS in animals by the numbers of cell generations.

However, the existing theoretical approaches provide no complete explanation of the fact that senescence has evolved in some species, but not in others [32], and that even relatively closely related species sometimes display quite considerable differences in LS: (i) **vertebrates**: *mammals*: naked mole rat (*Heterocephalus glaber*), 32 years, and house mouse (*Mus musculus*), 3 years; *birds*: eagle owl (*Bubo bubo*), 68 years, and elf owl (*Micrathene whitneyi*), 6 years; raven (*Corvus corax*), 69 years, and hooded crow (*Corvus cornix*), 17 years; *reptiles*: giant tortoise (*Testudo gigantea*), 180 years, and panther chameleon (*Chamaeleo pardalis*), 2 years; *amphibians*: Japanese giant salamander (*Megalobatrachus japonicus*), 65 years, olm (*Proteus anguinus*), 68 years, and blue-legged mantella (*Mantella expectata*), 3 years; (ii) **inver-tebrates**: *mollusks*: freshwater pearl mussel (*Margaritana margaritifera*), 100 years, and bay scallop (*Argopecten irradians*), 2 years; (iii) *echinoderms*: red sea urchin (*Strongylocentrotus franciscanus*), 60 years, West Indian sea egg (*Tripneustes ventricosus*), 3 years, mosaic sea star (*Plectaster decanus*), 60 years, and sea cucumber (*Isostichopus badionotus*), 5 years; (iv) *nematodes*: a parasitic nematode (*Loa loa*), 15 years, and a free-living nematode (*Caenorhabditis elegans*), 0.017 year [23, 33-37].

Since LS as a species-specific character is as stable as body size or fecundity, it can be assumed that LS (i.e. the moment of death) and its mechanisms should be at least partly programmed in the genome. The suggestion about programmed death of the organism, put forward by Weismann more than a century ago, can be fairly appreciated only now, when the phenomena of self-liquidation have been described for cells and separately for mitochondria, making it possible to propose the new theory of programmed death [38, 39]. According to modern notions, programmed death of an organism, i.e. death caused by triggering the start of the genetic program of self-liquidation of the individual, is a real phenomenon. Such regulation of LS should be distinguished from purely chemical aging, not programmed in the genome. One example of chemical aging is the L→D-isomerization of amino acids in crystallins, proteins of the eye lens, in whales. Because of this spontaneous process, in 200-year-old whales about 40% of L-aspartate in crystallins turns into the D-isomer, presumably having a negative effect on the properties of this protein, which, once formed in the lens, is retained there for the entire life. Other examples of non-programmed, chemical aging include the processes of carbonylation and deamidation of proteins [11, 40].

Thus, Weismann's theory of senescence as an adaptive mechanism of programmed death can be combined with the alternative view that senescence is a result of accumulation of damage and mistakes. Accumulation of damage could be traced by special systems that send a lethal signal to activate the phenoptosis program (programmed death of the organism) when the damage reaches some critical level. This program is adjusted to eliminate the damaged object before it makes the existence of the organism (or another living system) impossible. Such a mechanism is aimed at preventing the emergence of asocial monsters that can destroy the community and the entire population. This is how the "Samurai" law of biology manifests itself: "It is better to die than to make a mistake". This system is responsible for the following functions: (i) prevention of oxidation-related or any other damage to the genome, (ii) repair of damaged genome, and (iii) purging living systems of potential monsters with damaged genomes. One example of pathology that displays features of phenoptosis is septic shock. Many of its features indicate that its rapid lethal effect is specially

organized by the organism itself after it becomes subject to a large-scale bacterial invasion. It prevents the development of an epidemic. Sepsis is accompanied by large-scale release of cytokines by macrophages, which induces apoptosis [11, 41].

As a rule, phenoptosis is encoded in the genome and consists of a chain of biochemical events that ultimately result in self-destruction of the organism. Less often, such death results from a behavioral reaction encoded in the genome of the organism's sexual partner [40, 42-46].

Worsening environmental conditions, like any other deviation of the system from the optimum, should weaken the defenses of the organism and thus increase the probability of mutations and accumulation of damage, which, in turn, stimulates phenoptosis. This probability increases also as fecundity increases and alteration of generations accelerates, i.e. as LS decreases. For instance, in some killifish species of the genus *Nothobranchius*, LS varies by a factor of up to five, depending on the natural habitat occupied by the species [47]. Austad provides an example of average LS increasing and senescence (determined from the structure of collagen in tendons of the tail) decreasing in a population of opossums that accidentally colonized a small isolated island and ended up under conditions of weakened selection pressure compared to continental populations for lack of predators [15, 48].

Rapid phenoptosis is often associated with reproduction. In such cases, mating includes a behavioral or biochemical suicidal program. In squids, the male tears the skin of the female, injects a spermatophore, and immediately dies after mating; the female dies after laying a clutch of eggs [49]. Salmonid fish of the genus *Oncorhynchus* become senescent and die one or two months after spawning, not because of exhaustion of the organism, but because of triggering a special program in which the key role is played by steroid hormones of the adrenal glands. Lampreys and eels, like salmonids, die soon after breeding [41]. In lampreys, life can be prolonged by removal of gonads or the pituitary gland; in eels, it can be prolonged by prevention of mating. Such death is also known among mammals, e.g. Australian marsupials of the genus *Antechinus*, in which males commit biochemical suicide immediately after the breeding season [50]. In some animals, the very structure of the body is incompatible with life of any considerable length, e.g. adult mayflies are unable to eat for lack of mouthparts and die of hunger soon after mating [11].

Bamboo lives for 10 to 15 years with vegetative reproduction and then blossoms and dies after ripening of the seeds. Arabidopsis with two genes knocked out grows almost normally, blossoms, and bears fruit more poorly, but it has LS longer by at least an order of magnitude; it has thicker stem and leaves and additional rosettes of leaves [51, 52]. In the Mexican agave, which usually lives for ten years, annual removal of the flower-ing shoot increases LS by a factor of ten. Rapid senescence and death of soy can be prevented by removal of fruits or seeds ripening inside them [53, 54]. It can be suggested that phenoptosis exists in any species that breed only once.
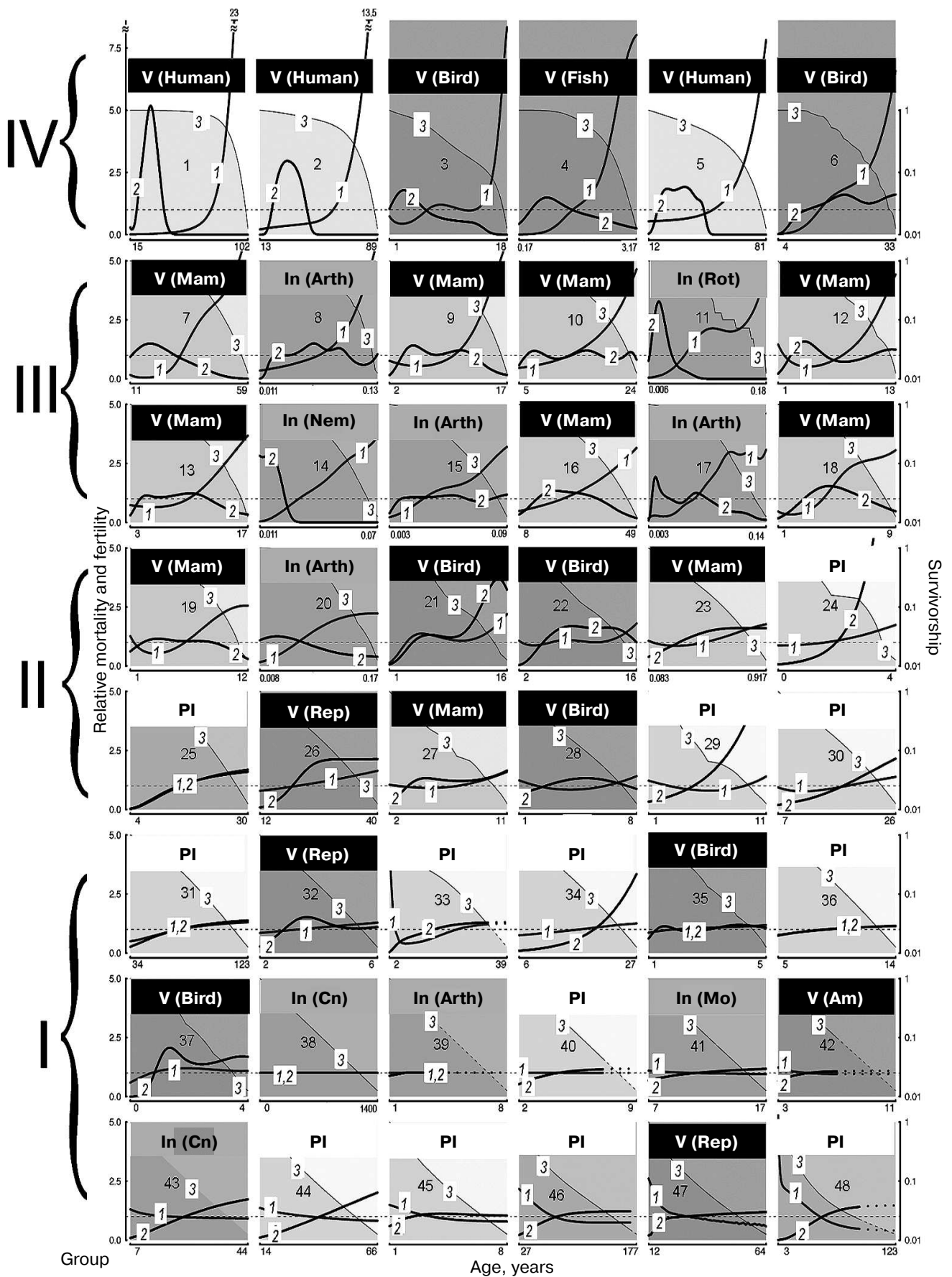
Senile phenoptosis could appear as sudden death, which happens when the individual reaches some critical age. Bowles mentions one species of marine birds that suddenly die when they are about 50 years old, showing no signs of senescence [55].

Usually, however, death from old age is the result of a very prolonged process (slow phenoptosis). However, in case of individuals with multiple reproduction it can prove more beneficial for the species than rapid apoptosis: the presence of a beneficial character in an individual can for some time compensate adverse effects of senescence, thus giving the individual advantages in breeding. Phenoptosis in natural environments is beneficial above all for survival and evolution of communities under aggressive conditions. A considerable role in this process is played by epigenetic modifications of chromatin [56, 57]. In contrast to situations treated by mutation accumulation and disposable soma theories, which assume constant pressure of adverse environmental conditions (predators or diseases), such a program could have evolved for adaptation to short-term extreme external influences (fluctuations of temperature or humidity of the environment or of levels of food resources) [58, 59].

Analysis of mortality curves. Scientists of the Max Planck Research Group on Modeling the Evolution of Aging (Rostock, Germany, and Odense, Denmark), headed by A. Baudisch, studied mortality and fecundity curves [1].

Analysis of functional changes (in fecundity, mobility, and memory) that happen during senescence shows that different organs and tissues undergo age-related disturbances at different rates. In addition, LS varies from individual to individual. Even genetically similar or identical individuals (e.g. workers and queens of social insects) can have fundamentally different LS trajectories. Contrary to the opinion that evolution should inevitably lead to mortality increasing and fertility decreasing with age after maturation, considerable differences between species have been shown in the dynamics of these parameters (increasing, stable, decreasing, convex, or concave mortality curves) in both long-lived and short-lived species (figure) [1].

Vaupel has shown that in some species (those with the so-called negative senescence, group I) (figure, lower row, and Tables 2 and 3), such as the desert tortoise (*Gopherus agassizii*), fertility continues to increase and probability of death decreases with age after maturation [1, 60]. In other cases, initial decrease is followed by a long period of constant mortality level (e.g. in Mexican oak, *Quercus rugosa*), while in most species mortality increases. This variability of curves is not predicted by

Group

Age, years

Relative mortality and fertility

Survivorship

standard evolutionary theories of aging, which assume that mortality only increases and fertility only decreases with age [27, 28, 61-63], but do not explain differences in the scale of these changes.

Survival curves. Survival curves (concave, linear, and convex) are known among biologists [64, 65], but they were usually drawn for LS beginning with birth rather than beginning with sexual maturity as in the study discussed here [1]. Similar survival curves can be found in species that strongly differ in LS. Thus, lions and chimpanzees are close to animals with rapid life cycles, such as louse (*Pediculus humanus*), daphnia (*Daphnia longispina*), or fruit fly (*Drosophila melanogaster*) [1].

After the terminal age, sample size is usually rather small, and identification of age is often problematic.

Baudisch supposes that the shape of the curve is a more informative parameter for the study of aging than the rate of mortality increase [32, 66].

METHODS OF INVESTIGATION

To compare the principal patterns of the senescence process in organisms that represent different evolutionary lineages, we sorted the data of Jones et al. [1] into groups according to the mortality at the terminal age and average mortality. We numbered all species treated as they were numbered in that study (from 1 to 48, in decreasing order of the above-mentioned parameter) and divided them into four large groups, group I comprising species with the smallest changes in mortality with age, and group IV comprising species with the greatest changes in mortality with age. Jones et al. [1] provided normalized mortality and fertility curves for a broad range of taxa (11 mammals, 12 other vertebrates, 10 invertebrates including five arthropods, two cnidarians, one mollusk, one nematode, and one rotifer, 12 vascular plants, and one brown alga).

For arthropods, we calculated the ratio of the LS until the moment by which only 5% of the cohort survives (LS_{95}) and the maximum LS to reveal how well LS_{95} characterizes the life cycle of each species (the data are given in Table 2). The data on other species are unfortunately incomplete and contradictory, and the table value of the maximum LS was often lower than LS_{95} given by Jones (see, e.g. [23]). The values of maximum LS (unless specified otherwise) are taken from the database of the Max Planck Research Group on Modeling the Evolution of Aging (Rostock, Germany, and Odense, Denmark) [35]. We also indicated in the Table 2 whether the animals were observed in natural environments or in captivity. To avoid the widespread objection that senescence is not found in nature and manifests itself only under laboratory conditions, Jones et al. [1] presented data on animals that live in the wild (mainly in nature reserves and game parks), except for domestic animals (sheep), laboratory animals (fruit flies and the nematode), and animals whose demographic structure cannot be recorded under natural conditions (rotifers, louse, and crab).

RESULTS AND DISCUSSION

The results are shown in three tables for different taxa (Table 1 for vascular plants and the brown alga; Table 2 for chordates (in this case vertebrates); Table 3 for the other animal phyla), which contain the English and Latin names of the species and specify to which taxa of higher rank they belong.

LS and mortality. Although the demographic trajectories shown in the figure vary over a broad range, careful analysis of the graphs has revealed that they can be divided into four large groups according to the degree of "accumulated mortality" (defined as the ratio of mortality at the terminal age and average mortality): strongly

Demographic trajectories according to Jones et al. [1] (modified, reproduced by the courtesy of the NPG group). The relative mortality (curve *1*) and fertility (curve *2*) are shown as functions of age, from the moment of maturity to the age at which only 5% of adults survive; mortality and fertility are normalized relative to average values (calculated for all living adults from maturity to terminal age) (curve *1*, axis Y to the left). The dashed lines are trajectories obtained by mathematical calculations. Mortality and fertility averaged for all ages are shown with horizontal dashed gray lines. Survivorship (ratio of the size of the cohort still alive at this age and the number of surviving individuals by the moment of sexual maturity) (curve *3*, axis Y to the right) is represented in logarithmic scale. The graphs are numbered from 1 to 48 in decreasing order of relative mortality by the terminal age from the highest level of relative mortality at the terminal age (top left) to the lowest level (bottom right), and they are arranged sequentially, row by row and left to right. The dimension of axis X (age) is given in years. 1) Humans, female Japanese born in 2009 (*Homo sapiens*); 2) humans, female Swedes born in 1881 (*Homo sapiens*); 3) Bali mynah (*Leucopsar rothschildi*); 4) guppy (*Poecilia reticulata*); 5) humans, hunter-gatherers (*Homo sapiens*); 6) southern fulmar (*Fulmarus glacialoides*); 7) killer whale (*Orcinus orca*); 8) water flea (*Daphnia longispina*); 9) lion (*Panthera leo*); 10) yellow baboon (*Papio cynocephalus*); 11) bdelloid rotifers (*Macrotrachela* sp.); 12) roe deer (*Capreolus capreolus*); 13) red deer (*Cervus elaphus*); 14) nematode worm (*Caenorhabditis elegans*); 15) human louse (*Pediculus humanus*); 16) chimpanzee (*Pan troglodytes*); 17) fruit fly (*Drosophila melanogaster*); 18) chamois (*Rupicapra rupicapra*); 19) Soay sheep (*Ovis aries*); 20) Mediterranean fruit fly (*Ceratitis capitata*); 21) alpine swift (*Apus melba*); 22) mute swan (*Cygnus olor*); 23) tundra vole (*Microtus oeconomus*); 24) St. John's wort (*Hypericum cumulicola*); 25) Scots pine (*Pinus sylvestris*); 26) freshwater crocodile (*Crocodylus johnsoni*); 27) yellow-bellied marmot (*Marmota flaviventris*); 28) sparrow hawk (*Accipiter nisus*); 29) yellow cryptantha (*Cryptantha flava*); 30) agave (*Agave marmorata*); 31) geonoma palm (*Geonoma orbigny*ana); 32) common lizard (*Lacerta vivipara*); 33) dwarf gorse (*Ulex minor*); 34) borderea (*Borderea pyrenaica*); 35) collared flycatcher (*Ficedula albicollis*); 36) great rhododendron (*Rhododendron maximum*); 37) great tit (*Parus major*); 38) hydra (*Hydra magnipapillata*); 39) hermit crab (*Pagurus longicarpus*); 40) armed saltbush (*Atriplex acanthocarpa*); 41) red abalone (*Haliotis rufescens*); 42) red-legged frog (*Rana aurora*); 43) red gorgonian (*Paramuricea clavata*); 44) viburnum (*Viburnum furcatum*); 45) oarweed (*Laminaria digitata*); 46) netleaf oak (*Quercus rugosa*); 47) desert tortoise (*Gopherus agassizii*); 48) white mangrove (*Avicennia marina*). Designations: Am, amphibians; Arth, arthropods; Cn, cnidarians; In, invertebrates; Mam, mammals; Mo, molluscs; Nem, nematodes; Pl, plants; Rep, reptiles; Rot, rotifers; V, vertebrates

Table 1. Age-related dynamics of fertility and mortality in plants and algae

Species, name		Class	Division	LS_{95}, years	No. [1]	ΔF	ΔM	ΔM_{95}	Group
Latin	English								
Avicennia marina	white mangrove	Dicotyledonea	Angiospermae	123	48	↑	↓	0.5	I
Quercus rugosa	netleaf oak	Dicotyledonea	Angiospermae	177	46	↑	↓	0.7	I
Laminaria digitata	oarweed	Phaeophyceae	Ochrophyta	8	45	↑	↓	0.8	I
Viburnum furcatum	viburnum	Dicotyledonea	Angiospermae	66	44	↑	↓	0.8	I
Atriplex acantho-carpa	armed saltbush	Dicotyledonea	Angiospermae	9	40	↑	≈	1	I
Rhododendron maximum	great rhododendron	Dicotyledonea	Angiospermae	14	36	≈	≈	1.1	I
Borderea pyrenaica	borderea	Monocotyledonea	Angiospermae	27	34	↑	≈	1.1	I
Ulex minor	dwarf gorse	Dicotyledonea	Angiospermae	39	33	≈	↓≈	1.1	I
Geonoma orbigny-ana	geonoma palm	Monocotyledonea	Angiospermae	123	31	↑	↑	1.2	II
Agava marmorata	agave	Monocotyledonea	Angiospermae	26	30	↑	≈	1.2	II
Cryptantha flava	yellow cryptantha	Dicotyledonea	Angiospermae	11	29	↑	≈	1.2	II
Pinus sylvestris	Scots pine	Pinopsida	Coniferae	30	25	↑	↑	1.5	II
Hypericum cumu-licola	St. John's wort	Dicotyledonea	Angiospermae	4	24	↑	≈↑	1.8	II

Note: ↑, increasing; ↓, decreasing; ≈, constant; ΔF, change of fertility with age; ΔM, change of mortality with age; LS_{95}, cohort age of 5% survival; ΔM_{95}, ratio of mortality at the terminal age (LS_{95}) and average mortality. The data are grouped in decreasing order of mortality (decreasing number according to Jones et al. [1]).

increasing with age (IV), markedly increasing (III), weakly increasing (II), and decreasing or constant (I).

Thus, for humans, which belong to group IV (Nos. 1-6 in figure and Table 2), this ratio was the highest: 23 for female Japanese (No. 1 in figure and Table 2), 13.5 (No. 2) for female Swedes and 7.5 for Ache Native Americans (No. 3). Such a pronounced growth of relative mortality with age that can be found in humans (and which emerged largely over the last century because of increasing LS_{95}) was explained by the effects of behavioral and ecological changes (including advances of healthcare) rather than genetic changes [66-68].

This ratio is also high (8 and 7.5, respectively) in fish kept in captivity (No. 4, guppy) and birds (No. 3, the Bali mynah, which was on the verge of extinction, and its population size was supported by all possible means) [69].

The next group, group III, in which senescence is less pronounced, comprises more species (Nos. 7-18); it is more heterogeneous and includes the killer whale, lion, ungulates, and primates (baboon and chimpanzee), as well as the fruit fly, nematode worm, and rotifers. This group is characterized by considerable although less pronounced growth of mortality: from 5.5 in the killer whale (No. 7) to 3.5 in the chamois (No. 18).

Group II is characterized by rather low values of the ratio of mortality at the terminal age and average mortality: from 2.5 in the sheep (No. 19) to 1.2 in the agave (No. 30). Finally, group I, which comprises the greatest number of species (Nos. 31-48), is not characterized by any considerable changes in mortality with age (from 1.1 in the geonoma palm (No. 31) to 0.5 in the white mangrove (No. 48)); essentially, these species are non-senescent. Since the species were selected for analysis by Jones et al. [1] not for being preferably non-senescent but for providing the most comprehensive available data on survival, such a great number of species that successfully withstand aging is remarkable. It can be suggested that in many species LS_{95} is too different from the maximum LS, and 95% individuals in the population die before they can show any pronounced signs of senescence (as shown, e.g. in Table 2).

Fertility. Jones et al. [1] used fertility as the parameter of vitality. Using this parameter (in spite of its evolu-

Table 2. Age-related dynamics of fertility and mortality in vertebrates

Species, name		Class	C/W	LS_{95}	LS_{95}/LS_{max}	No. [1]	ΔF	ΔM	ΔM_{95}	Group
Latin	English									
Gopherus agassizii	desert tortoise	Rep	W	64	0.80	47	↑	↓	0.6	I
Lacerta vivipara	common lizard	Rep	W	6	0.55	32	≈	≈	1.1	I
Crocodylus johnsoni	freshwater crocodile	Rep	W	40	0.80	26	↑	≈	1.5	II
Rana aurora	red-legged frog	Am	W	11	0.73	42	≈	≈	0.9	I
Parus major	great tit	Bird	W	4	0.26	37	↑	≈	1.0	I
Ficedula albicollis	collared flycatcher	Bird	W	5	0.51	35	≈	≈	1.1	I
Accipiter nisus	sparrow hawk	Bird	W	8	0.40	28	≈	≈	1.3	II
Cygnus olor	mute swan	Bird	W	16	0.23	22	≈	≈↑	2.2	II
Apus melba	alpine swift	Bird	W	16	0.62	21	↑	↑	2.4	II
Fulmarus glacialoides	southern fulmar	Bird	W	33	0.73	6	↑	↑	7	IV
Leucopsar rothschildi	Bali mynah	Bird	C	18	0.72	3	↓	↑	7.5	IV
Marmota flaviventris	yellow-bellied marmot	Mam	W	11	0.52	27	↑	≈	1.4	II
Microtus oeconomus	tundra vole	Mam	C	0.92	0.51	23	≈	≈↑	2.0	II
Ovis aries	Soay sheep	Mam	C	12	0.53	19	↓	↑	2.5	II
Rupicapra rupicapra	chamois	Mam	W	9	0.51	18	↓	↑	3.5	III
Pan troglodytes	chimpanzee	Mam	W	49	0.82	16	↓	↑	3.5	III
Cervus elaphus	red deer	Mam	W	17	0.63	13	≈↓	↑	4	III
Capreolus capreolus	roe deer	Mam	W	13	0.74	12	↑	↑	4.6	III
Papio cynocephalus	yellow baboon	Mam	W	24	0.60	10	≈	↑	4.8	III
Panthera leo	lion	Mam	W	17	0.63	9	≈↓	↑	5.5	III
Orcinus orca	killer whale	Mam	W	59	0.66	7	↓	↑	5.5	III
Homo sapiens	humans, hunter-gatherers	Mam	W	81	0.66	5	↓	↑	7.5	IV
Homo sapiens	humans, female Swedes born in 1881	Mam	C	89	0.73	2	↓	↑	13.5	IV
Homo sapiens	humans, female Japanese born in 2009	Mam	C	89	0.73	1	↓	↑	23	IV
Poecilia reticulata	guppy	Fish	C	3.17	0.63	4	↓	↑	8	IV

Note: Mam, mammals; Rep, reptiles; Am, amphibians; ↑, increasing; ↓, decreasing; ≈, constant; C, observed in captivity; W, observed in wild; LS_{max}, maximum LS; ΔF, change of fertility with age; ΔM, change of mortality with age; LS_{95}, cohort age of 5% survival; ΔM_{95}, ratio of mortality at the terminal age (LS_{95}) and average mortality. The data within each class are grouped in decreasing order of mortality (decreasing number according to Jones et al. [1]).

Table 3. Age-related dynamics of fertility and mortality in invertebrates

Species, name		Class	Type	C/W	LS_{95}	No. [1]	ΔF	ΔM	ΔM_{95}	Group
Latin	English									
Paramuricea clavata	red gorgonian	Anthozoa	Cnidaria	W	44	43	↑	↓	0.9	I
Hydra magnipapillata	hydra	Hydrozoa	Cnidaria	C	1400	38	≈	≈	1.0	I
Haliotis rufescens	red abalone	Gastropoda	Mollusca	W	17	41	≈	≈	0.9	II
Pagurus longicarpus	hermit crab	Malacostraca	Arthropoda	C	8	39	≈	≈	1.0	I
Ceratitis capitata	Mediterranean fruit fly	Insecta	Arthropoda	C	0.17	20	↓	↑	2.4	II
Drosophila melanogaster	fruit fly	Insecta	Arthropoda	C	0.14	17	↓	↑	3.5	III
Pediculus humanus	human louse	Insecta	Arthropoda	C	0.09	15	≈	↑	3.5	III
Daphnia longispina	water flea	Branchiopoda	Arthropoda	C	0.13	8	≈	↑	5.5	III
Caenorhabditis elegans	nematode worm	Chromadorea	Nematoda	C	0.07	14	↓	↑	3.8	III
Macrotrachela sp.	bdelloid rotifers	Bdelloidea	Rotifera	C	0.18	11	↓	↑	4.7	III

Note: ↑, increasing; ↓, decreasing; ≈, constant; C, observed in captivity; W, observed in wild; LS_{95}, cohort age of 5% survival; ΔF, change of fertility with age; ΔM, change of mortality with age; ΔM_{95}, ratio of mortality at the terminal age (LS_{95}) and average mortality. The data within each phylum are grouped in decreasing order of mortality (decreasing number according to Jones et al. [1]).

tionary importance), they could not reveal considerable variation in the studied series of organisms. Thus, considerable decrease in fertility with age can be observed only in the groups of species with strongly pronounced increase in mortality (groups III and IV; figure and Tables 2 and 3). In the other groups, independently of the taxon, fertility either remains constant or even increases. Even the decrease in fertility found at later ages (closer to LS_{95}) is rather small, and there is almost no species in which the curve falls below the average level for the entire study period from the moment of maturity. If we disregard the most short-lived species (rotifers, nematode worm, and fruit flies), then a strong decrease in fertility is found only in some ungulates (red deer (No. 13) and chamois (No. 18)) and in two animals kept in captivity: guppy (No. 4) and Bali mynah (No. 3); only humans (Nos. 1, 3, 5) and killer whales (No. 7) (and partly chimpanzees, No. 16) additionally have bell-shaped fertility curves, with the peak reached already at a young age, i.e. these species have acquired a capability to live rather long during the post-reproductive period (figure). This suggests that such a phenomenon is widespread under the conditions of decreasing selection pressure [27, 28, 62, 63, 70]. It should be noted that all the above-mentioned species (humans, killer whales, and chimpanzees) are highly social and highly capable of learning. Therefore, their

long post-reproductive periods could be an adaptation determined by the value of old, experienced individuals for the survival of groups and for raising the young (the so-called "grandmother hypothesis"; see e.g. [15]). For instance, it has been shown that old non-fertile killer whales more often become leaders of the school than fertile females or males, especially in years with deficient food resources [71].

Therefore, in spite of its evolutionary importance, fertility proved insufficient as a parameter for comparative analysis of the dynamics of senescence, although it confirmed the conclusions drawn from division of animals and plants into groups according to mortality curves (Tables 1-3).

In addition, the mortality and fertility trajectories of any species depend on the environment in which they are measured. Ecological and genotypic variations have been recorded in laboratory studies of nematodes, the Mediterranean fruit fly, *Drosophila* fruit fly, and other model species [5, 72]. In laboratory rats (*Rattus norvegicus*) and mice (*Mus musculus*), the shapes of mortality curves, although they clearly indicate that in these animals mortality considerably increases with age (see group III), show considerable variance of data (especially in mice), which probably reflects genetic changes that have accumulated under laboratory conditions [1].

Discussing non-senescent animals, we must separately mention the hydra and the naked mole rat (*Heterocephalus glaber*) [36, 73].

In the hydra (*Hydra magnipapillata*, No. 38) living in the laboratory, mortality risk, and stable for all adult ages, is so small that 5% of adults should remain alive after 1400 years [1]. Khokhlov suggested that destructive changes leading to biological senescence are triggered by cell proliferation limitation, which does not allow, "diluting" damaged cells in time with "fresh" undamaged cells [4, 74, 75]. This theory explains the existence of some non-senescent species, which display no degenerative changes over their entire life cycles, such as the hydra [75]. Nevertheless, data on other non-senescent species (tortoises, which grow much more slowly than the hydra and thus cannot have equally rapid renewal of cells) show that there are some non-senescent species with unlimited growth over their entire life (e.g. the giant tortoise *Testudo gigantea* or desert tortoise *Gopherus agassizii*), but there are also rather small tortoises that stop growing by an age of 30-40 years (e.g. the three-toed box turtle *Terrapene carolina*) [23, 76, 77].

Data on the mortality and fertility of the naked mole rat were provided by Buffenstein [36]. They were not used by Jones et al. because of the values of initial mortality, inadequate in their opinion. However, Jones et al. [1] used such a format of data representation in which mortality at the moment of sexual maturity rather than at birth was viewed as initial mortality. In this case the naked mole rat would belong to non-senescent animals (group I), occupying in the figure an honorable place next to the "immortal" hydra.

Views vary on the susceptibility of angiosperms to aging [78-80]. In our opinion, the available data reveal no clear signs of the Gompertz type of senescence in plants or algae (Table 1).

It was repeatedly stated [66, 81] that in plants, in contrast to animals, aged cells die rather than accumulate, and they do so in a programmed way rather than randomly. In addition, dead plant cells are not discarded, but included in supporting or vascular structures. Thus, plants may have evolved a mechanism that allows them to fight aging by means of programmed cell death.

Phylogenetic models of senescence. It has been suggested that asexual reproduction [82], modularity [83], absence of division into the germ line and soma [84, 85], absence of predator pressure and presence of protected shelters [86], capability of regeneration, and small number of cell types [87] in some cases can facilitate escape from senescence [1]. Many species of group I (reptiles, the coral, vascular plants, and the alga) continue growing to become much larger after reaching reproductive maturity. In these species with unlimited growth, mortality does not increase with age, whereas fertility somewhat increases; i.e. their aging patterns are principally different from those found in species with limited growth [25, 32,

60]. In addition, methods of computer modeling have shown that under some conditions sedentary, attached forms (known among both animals and plants) can evolve phenoptosis (programmed senescence and death) as a result of kin selection, and the evolutionary benefits of such acquisition have been proved [88].

As noted in the disposable soma theory [28], differences between species in LS and in the optimal distribution of resources between vital processes can help explain empirical data on differences in mortality and fertility trajectories [32, 89, 90]. Senescence rate decreases in evolutionary lineages with increasing body weight, duration of pregnancy, age of sexual maturity, and flight capacity [91].

It should also be noted that survival curves display the mortality of a general, genetically heterogeneous cohort. As the age of the cohort increases, the proportion of individuals that have genotypes conducive to longevity inevitably grows. If some individuals in the population acquire alleles that facilitate decelerated increase in the probability of death, the survival and mortality curve for the entire population will change [14, 25]. It is difficult to distinguish from survival curves a situation in which the probability of death of each individual decreases with age from a situation in which the probability of death of each individual remains constant, but initially the cohort was strongly polymorphic in alleles that affect longevity and therefore the proportion of individuals with inherited tendency to live long increases with time. This is partly confirmed by the opinion about decelerated mortality at later ages [15]. Gavrilov and Gavrilova [92] warned about the existing methodological difficulties, since according to their calculations the Gompertz law continues to work even in long-living individuals, until the age of 106 years in humans. In addition, those authors together with L. S. Yaguzhinsky showed as early as 1978 the existence of the so-called compensation effect: attempts to decrease the level of the age-related component of mortality in the Gompertz−Makeham equation (e.g. by improving environmental conditions) increase the relative rate of growth with age for this component [17, 19]. A number of genes have already been revealed that mutate to produce beneficial effects on LS through preventing age-related diseases (e.g. there are such data on the gene *APOE*) [15, 21]. An additional difficulty is the fact that LS in humans is rather poorly inherited and strongly depends on environmental conditions [21, 93]. One promising approach could be to study the so-called "blue zones" of the planet, in which the proportion of long-lived persons is dramatically higher than average; one of them is Okinawa, Japan [15]. In this case, the presence of a great number of centenarians would be conductive to growth of LS_{95} (figure and comments to it), and therefore, according to Jones, to prolongation of reliable survival curves to later ages and thus an opportunity to reveal genes responsible for longevity and decelerated growth of mortality.

It can be noted that for animals of groups III and IV (including humans; see figure and Table 2) (long-lived and senescent), the method of Jones et al. [1] characterizes mortality during almost the entire life cycle. The same is true of short-lived animals, e.g. the tundra vole or rotifers, whether they display the Gompertz type of senescence or not. As for long-lived species with a less pronounced increase (or even decrease) in mortality (e.g. the freshwater crocodile, desert tortoise, or Scots pine) and short-lived non-senescent animals, in them the Jones method can characterize only a small part of the life cycle and does not make it possible to judge how senescence manifests itself at later stages of the cycle. For instance, it is known that in old trees signs of senescence are rather clear [94, 95], but less than 5% of individuals that reach maturity survive to become senescent. As a result, senescence in trees cannot be analyzed by that method.

It seems clear from analysis of the graphs provided by Jones et al. [1] that many animals fall among the eliminated 95% long before they reach their maximum LS. This fact does not make the analysis less reliable if mortality already considerably increased before LS_{95} (e.g. as in groups III and IV) (Nos. 1-18 [1]) (figure and Tables 2 and 3). It should be notes that these groups include no plants or algae.

As for cases of intense mortality in nature caused mainly by environmental factors, it turns out that those authors fall into "the trap of Medawar", who insisted that senescence does not exist in natural environments [62]. In fact, the size of the cohort in such cases, e.g. in the mute swan (No. 22), collared flycatcher (No. 35), or great tit (No. 37), falls very rapidly (figure); as a result, the cohort of animals that includes 5% surviving individuals long before they become old, is considered non-senescent. We tested this conclusion by comparison with data on the maximum LS of species from groups I and II (Table 2). Even though Jones et al. [1] repeatedly criticized maximum LS, this parameter is given in most databases and reference books on gerontology (e.g. [23, 33-35]).

For instance, Jones et al. [1] note that it was extremely difficult to find signs of either the Gompertz type of senescence or biological senescence in the mute swan [96]. LS_{95} of the swan (No. 22, group II; figure and Table 2) is 16 years, but it can live at least 29 years in nature and up to 70 years in captivity [97].

Role of phylogenetic relatedness. All mammals are concentrated in the upper part of figure (Table 2). It can be suggested that senescence is especially strong, apart from mammals, in species with the greatest number of postmitotic cells, i.e. insects (Table 3).

Considerable variation in senescence of the Gompertz type can be seen among birds, from the Bali mynah (No. 3, group IV) to the great tit (No. 37, group I) (Table 2). In spite of the conclusions of Jones et al. [1], large birds (fulmar, No. 6; swan, No. 22; sparrow hawk,

No. 28) are also senescent, but their biological senescence can begin to manifest itself at a rather late age, which may be reached by less than 5% of the initial cohort. As for senescence of small birds, which are short-lived and have many enemies, it really cannot be revealed in nature, as predicted by Medawar [62].

Amphibians and reptiles fall into group I (only one species, the crocodile, No. 26, is in group II) and have flat mortality curves (figure and Table 2). Reptiles can live and remain capable of reproduction extremely long, but the proportion of long-lived individuals is probably also no greater than 5% of the initial cohort, and the dynamics of their senescence is also difficult to analyze by the Jones method (because it also requires that mortality until the terminal age LS_{95}, which is nothing outstanding for these species, does not increase with age). Amphibians are represented in that study by only one species (the red-legged frog, No. 42), but most of the mortality curve was unfortunately obtained mathematically (figure). On the whole, frogs are not distinguished by great LS or resistance to senescence [23], in contrast to some caudate amphibians, such as the Japanese giant salamander (*Megalobatrachus japonicus*), olm (*Proteus anguinus*) (see above), or the spotted salamander (*Ambystoma maculatum*) [23, 37, 98].

Different invertebrate phyla are scattered among all groups, beginning with bdelloid rotifers and water fleas (group III; figure and Table 3), which have mortality curves similar to those of mammals.

Mollusks, represented in the study by the red abalone (No. 41), are known for their longevity and resistance to biological senescence [23, 99], but the champions in longevity and resistance to senescence among the animals considered are cnidarians – the hydra (No. 38) and the red gorgonian (No. 43). Furthermore, while the hydra is capable of displaying its exceptional abilities only in the laboratory [87], the red gorgonian, which grows in nature by 1-2 cm in height and 0.36 mm in diameter per year, can follow this pattern for several centuries and possibly even millennia [100, 101].

As noted above, we could not reveal from the provided data any signs of the Gompertz type of senescence in plants or algae (Table 1). In our opinion, data on changes in fertility have only confirmed the conclusion about lack of changes in their mortality with age. We suggested above that plants have evolved a mechanism of fighting aging by programmed cell death. Thus, we can rather tentatively state that the very definition of the term "senescence" as "increasing probability of death with age" requires some specification, because, as noted above, there is some discord between the Gompertz type of senescence and biological senescence. As for the often-used definition of biological aging as "processes that lead to increased probability of death with age", it appears somewhat vague.

We have concluded that the classification proposed by Jones et al. [1] makes it possible to approximately

divide animals and plants only by their levels of the Gompertz type of senescence, whereas susceptibility to biological senescence can be estimated only when principally different models are applied (see, e.g. [19, 21]).

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