ISSN 2079-0570, Advances in Gerontology, 2023, Vol. 13, No. 3, pp. 164–177. © Pleiades Publishing, Ltd., 2023.

OPINION ARTICLES

Demographic Indicators of Probability Models

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Received December 3, 2023; revised December 15, 2023; accepted December 26, 2023

Abstract—Describing mortality dynamics using average indicators without considering variability can yield average results, impeding the analysis of survival-curve patterns during periods of significant mortality spikes, especially at the oldest or youngest ages. Therefore, instead of the generally accepted Gompertz method, other methods are increasingly used, which rely on comparisons of various demographic indicators. In humans, chronic phenoptosis, in contrast to age-independent acute phenoptosis, manifests as a rectangularization of the survival curve with a simultaneous increase in the life expectancy at birth due to the advancement of social, scientific, and technological progress. Rectangularization is difficult to notice solely by examining the optimal coefficients in the Gompertz—Makeham equation, primarily because of the inevitable calculation errors. This can be avoided by calculating demographic indicators based on the spread of the life expectancy: Keyfitz entropy, Gini coefficient, and coefficient of variation of lifespan. We examine several sub-Gompertzian models of mortality growth with age, which describe the aging of nematodes and insects. Within the sub-Gompertzian model of aging, the increase in mortality with age in invertebrates is quantified as a rectangularization of the survival function estimated by these demographic indicators. On the other hand, the increasing rectangularization of the survival function with the development of scientific and technological progress, demonstrated by a decrease in the Keyfitz entropy, along with a simultaneous increase in the life expectancy in humans, also aligns well with the hypothesis of an age-dependent increase in mortality in mammals overall. Calculations on aging models demonstrate the effectiveness of using Keyfitz entropy and the Gini coefficient as important demographic indicators. The use of these indicators seems preferable, especially for nematodes, where the sub-Gompertzian model of aging is applicable, and for vertebrates, primarily mammals, with certain restrictions, the Gompertz–Makeham law is applicable. Approaches that consider dynamic age-related shifts in improved survival, such as studying imbalances in lifespan, enhance our understanding of the mechanisms of aging. This, in turn, will contribute to the development of more accurate methods for assessing the effects of biologically active substances used in gerontology, such as anti-aging drugs and geroprotectors.

Keywords: aging, demography, Keyfitz entropy, Gini coefficient, coefficient of variation, life expectancy, Gompertz law, survival curves, phenoptosis

DOI: 10.1134/S2079057024600307

INTRODUCTION

Problems with assessing the aging process as an increase in the probability of death (the number of deaths in one age interval) have existed for a long time [1–3]. If the probability of death of an organism depended entirely on the degree of its wear and tear, which increases with age, then the mortality rate of multicellular organisms should increase with age, regardless of the position of the species on the evolutionary tree. However, large differences in mortality patterns across species have been found (increasing, constant, decreasing, convex, and concave mortality trajectories in both long- and short-lived species) [4–9]. Possible mechanisms for the emergence of such diversity in evolution are actively discussed [10–12]. There are known critical assessments of quantitative theories of aging and mortality, the main empirical basis of which was the Gompertz law [12].

MATERIALS AND METHODS

In this work, different approaches were assessed by comparing the statistical parameters of the distribution of lifespan according to the Max Planck Institute for Demographic Research (Germany), given in the work of Jones et al. [7]. The data obtained characterize the quantitative distribution of individuals according to lifespan, i.e., the percentage or proportion of individuals that died in each age interval (with 1 year usually considered as the base interval for vertebrates and 1 day for invertebrates). The level of variability in the

lifespan distribution (lifespan variation coefficient and Keyfitz entropy) was determined in 23 animal species, including primates, including the species *Homo sapiens* represented by Japanese people and Native Americans (Mongoloid race), as well as Swedish people (Caucasian race). To compare the main patterns the aging process in organisms representing different branches of the evolutionary tree, we sorted the data from the work of Jones et al. [7] into groups based on the ratio of mortality in terminal to middle age. All species considered were numbered in the same way as in the original work (decreasing the above indicator) and divided into four large groups, where group I includes species with the smallest change in mortality with age, and IV includes species with the largest, with their subsequent consideration (depending on the rate of aging) in one or another sub-Gompertzian model. The calculation of the average life expectancy, Keyfitz entropy, Gini coefficient, and coefficient of variation of the life expectancy for the considered aging models was carried out in the Maple program (https://maplesoft.com/), which is convenient for performing symbolic calculations. This program was previously used, for example, in [13].

RESULTS AND DISCUSSION

Demographics

The Gompertz law is a probabilistic mortality model that describes well the mortality of people aged 20 to 65 or up to 80 years. This law was proposed in the pioneering work of B. Gompertz and was initially used to assess risks in life insurance [1]. Despite the discussion of amendments to the Gompertz law [3, 14–19], its basic idea has remained unchanged for almost two hundred years: the law determines the dependence of the conditional probability density of death on age.

The probabilistic model assumes the possibility of living unexpectedly long compared to the average lifespan, although the probability of such an event may be low. On the contrary, deterministic (essentially non-Gompertzian) models, even with seemingly low mortality, lead to inevitable death. Deterministic models are fundamentally inapplicable to the study of long-lived individuals; such an attempt leads to the emergence of a singularity. The Gompertz law is an example of a completely different approach to modeling, which allows for much more complete use of the capabilities of mathematical analysis.

Let us consider an example of an essentially non-Gompertzian model. A cohort of N flies is given. Every day one individual dies. Let us try to simulate this deterministic model by means of a probabilistic model. At the beginning, the conditional probability density of dying for one surviving fly seems very small. But every day it grows as $1/(N - a)$, where through a the age of the fly is indicated. When there is only one fly left, the conditional probability density $1/(N - a)$ begins to grow rapidly. The next day a *pole* is found in this function, that is, direct calculation consists of dividing by zero. Trying to calculate a demographic indicator: be it the Keyfitz entropy or the Gini coefficient, using the usual formula containing an improper integral leads to computational difficulty; therefore, the numerical value of the demographic indicator cannot be calculated without applying some changes to the original formula. The trivial approach is to limit the range of integration when only a finite period of time is considered. But in fact, in the corresponding probabilistic model, the last fly is not obliged to die on a predetermined day. It can live another day. Therefore, this trivial approach can easily lead to systematic error. However, the error can be large for indicators sensitive to maximum lifespan. These include, for example, Keyfitz entropy. There is another probability model in which for early ages the conditional probability density of death is $1/(N - a)$, and for later ages is small enough to make the Keyfitz entropy rather large. Moreover, for early ages the expected behavior of the model is close to that for a deterministic model.

Deterministic models are fundamentally inconvenient for studying long-lived individuals, since their death is predetermined in the model and lifespan cannot exceed a set threshold. The Gompertz law is an example of a completely different approach to modeling, which allows you to more fully use the capabilities of mathematical analysis. But this is not the only probabilistic model. Some alternative models are considered in this work. On the one hand, in some species the observed mortality rate deviates from the Gompertz law. On the other hand, deviations from the Gompertz law are possible at older ages, which is especially interesting when taking into account those that live a long time and in works to determine the lifespan limit. The probability of mortality and life expectancy are the main functions of the life cycle. Although these parameters are useful for determining exactly how to characterize the value of mortality, they cannot be used to estimate the variability of mortality over a lifetime [20]. Approaches that take into account dynamic shifts by age in improving survival appear to be better than others. Studying the "imbalance" of lifespan inequality can also help improve our understanding of the dynamics of mortality, and, accordingly, the mechanisms of aging, which, in turn, will contribute to the development of more accurate methods for assessing the effect of anti-aging drugs and geroprotectors.

In theoretical calculations, it is a generally accepted technique to transition to a continuous change in age, as if one year in a person's life were only one moment. In practice, for humans, the unit of time is usually one year, less often, it is five years, and for species with a short lifespan (nematodes, fruit flies), it is one day. Moving from annual to five-year intervals can significantly distort the distribution. Therefore, annual intervals are preferable to five-year intervals, and for

species with short life spans, the intervals should be even shorter. Empirically, we came to the assumption that in any case, in order to avoid roughening the results and erroneous conclusions, the size of the interval should not exceed a tenth of the expected average lifespan. Frolkis [21] suggests that a person always has a constant number of intervals (ten), corresponding to certain phases of aging, but in practice this is very difficult to implement.

Let us denote by $m(a)$ the conditional probability density of death at age a, also called the force of mortality. Let us denote by $L(a)$ the monotonically nonincreasing survival function, equal to the probability of surviving to the age a. The survival function is uniquely determined by the function $m(a)$ and the initial condition $L(0) = 1$ (that is, at time zero, everyone is alive). This initial condition is due to the fact that only births are taken into account. The survival function $L(a)$ is equal to the exponent of the integral taken with the opposite sign with a variable upper limit from zero to age a on the conditional probability density of death $m(a)$. Let us denote by $e_{\exp}$ the life expectancy at birth, which is *equal to the improper integral from zero to infinity of the survival function*.

Next we will look at demographic indicators (Keyfitz entropy H, Gini coefficient G, and the coefficient of variation of lifespan CV_{LS}), each of which maps a real number to the survival function. These indicators do not depend on the time scale and vanish on the rectangularized survival function, equal to one up to a certain age and equal to zero at all higher ages. Informally, the graph of the rectangularized function is a step leading down. The value of the indicator can be considered as the numerical difference between the survival function and the rectangularized one. Similar indicators are considered in [22], but there the value of the indicator on the rectangularized function is equal to one. Rectangularization of the survival function is observed in people as a result of the development of society and scientific and technological progress. The survival functions of chimpanzees, Paraguayan Aché hunter gatherers and Swedes (in 1751, 1850, 1900, 1950, and 2010) indeed approach rectangularization as civilization develops [23, 24]. At the same time, the life expectancy still continues to increase over time [17]. This is in good agreement with the phenoptosis hypothesis [25–27]. Function $m(a)$ can grow without the influence of phenoptosis. However, the very presence of age-dependent phenoptosis as a phenomenon presupposes obligatory and pronounced growth $m(a)$, starting at a certain age.

Let's consider an example illustrating the importance of approximating the survival function to the rectangularized one. If representatives of a certain species die at 50% of the cohort per year, this species appears to be ageless, although the life expectancy is short. On the contrary, if in the first year 10% die, in the second 20% of those who survived (alive at the beginning of the interval), and so on, then the species demonstrates rapid aging with increasing age. In the second species, the survival function is closer to rectangularized. Testing possible geroprotectors in the first type is ineffective, since an increase in life expectancy can occur even with a deterioration in the quality of life of long-lived individuals (for example, when resources are redistributed in the population to reduce mortality in early and middle age). On the contrary, testing of the second type makes it possible to evaluate the effect of geroprotectors specifically on long-lived individuals.

The Keyfitz entropy H was introduced by demographer N. Keyfitz [28] and considered, for example, in [29–31]. It is equal to the relative life disparity. Namely, $H = e^{\dagger}/e_{\exp}$, where through $e^{\dagger}$ the disproportionality of life is indicated, equal to the improper integral from zero to infinity taken with the opposite sign of the product of the survival function by the natural logarithm of it. For the rectangularized survival function, the integrand in $e^{\dagger}$ is identically equal to zero, therefore, $e^{\dagger} = 0$ and $H = 0$.

$$e^{\dagger} = -\int_0^{\infty} \ell(t)\ln(\ell(t))dt.$$

The Gini coefficient G was proposed in 1912 by demographer C. Gini, see review [32]. The Gini coefficient was also used in demography in [33, 34]. Let us denote by e_n the improper integral of the square of the survival function. The Gini coefficient is $G = (e_{\exp} - e_n)/e_{\exp}$. The rectangularized survival function satisfies the equality $e_{\exp} = e_n$, hence, $G = 0$.

$$e_n = \int_0^{\infty} \ell^2(t)dt.$$

The coefficient of variation of life expectancy CV_{LS} was discussed in detail in the relevant works [22, 27, 35–37]. The difference between the coefficient of variation (CV) and the Keyfitz entropy and the Gini coefficient is that the formula for calculating it explicitly includes the first derivative of the survival function, equal to the product of the survival function and the conditional probability density of death $m(a)$. This derivative is usually called the distribution of deaths. The associated difficulties in calculating the coefficient of variation are described below.

The difference between the Keyfitz entropy and the Gini coefficient is determined by the behavior of the survival function near $e_{\exp}$ and at late ages. However, the difference in these demographic indicators depends little on the properties of the survival function at early ages. In particular, if we do not take into account infant-mortality data, the resulting change in the Keyfitz entropy and the Gini coefficient will be approximately the same. Although in theoretical models the initial concept is the conditional probability density of death $m(a)$, calculating the Keyfitz entropy

H and Gini coefficient G uses only the survival function. Therefore, knowing the survival function $L(a)$, these demographic indicators can be calculated directly.

In other cases, the function $m(a)$ itself is used. The value $m(a)$ is equal to the ratio of the first derivative of the survival function to the value of the survival function taken with the opposite sign $-L'(a)/L(a)$. Calculating the first derivative from the graph of a function known in practice for its approximate values at individual points usually leads to additional errors [38]. Therefore, the Keyfitz entropy and the Gini coefficient are more convenient for practical use.

However, some demographics based on function $m(a)$ are interesting because their meanings can be easily interpreted. The first and very rough demographic indicator considered in [22] is the ratio $m(0)/m(e_{exp})$. An obvious difficulty for its application in demography is the high infant-mortality rate. In addition, it is sensitive to errors at two ages that are not compensated for by data at other ages. In addition, this indicator does not allow one to distinguish the rectangularized survival function from others, which fundamentally distinguishes it from the Keyfitz entropy, the Gini coefficient, and the coefficient of variation of life expectancy. The second indicator is the weighted average of the first derivative of the function $m(a)$. This indicator also does not allow us to distinguish the rectangularized survival function from others.

Demographic Indicators Calculated by Summation

In practice, integrals are replaced by finite sums (since real lifespan is limited from above, and age is measured discretely). With a sufficiently large sample, the Gini coefficient is resistant to small errors: in particular, those associated with the inevitable difficulties in determining age.

Refining the step w of a change in age leads to sharp changes in the first derivative of the survival function, which is included in the formula for calculating the coefficient of variation of life expectancy CV_{LS}. However, the Keyfitz entropy H and Gini coefficient G depend only on the survival function itself. Therefore, refining the step does not deteriorate, but only improves the calculation of H and G. We will look at calculating the Keyfitz entropy H and Gini coefficient G for the conditional probability density of death $m(a) = \exp(a)$, which corresponds to the Gompertz law, for different step values w. For small step values, the result differs little from the result based on integration. The exact values are $H = 0.68$ and $G = 0.39$. Summation was carried out up to age 100 at the average life expectancy indicator $e_{exp} = 0.60$. For an age change step of 0.1, the values obtained are $H = 0.62$ and $G = 0.36$, which are close to correct. However, for step 1 the values obtained are $H = 0.27$ and $G = 0.13$, which are already very far from correct. As the step increases, the values of demographic indicators calculated by summation decrease. Such a decrease can be confused with the survival function approaching a rectangularized one, but this is only the result of a calculation error.

Although calculation of the Keyfitz entropy is resistant to age step lengths, the Keyfitz entropy is sensitive to small perturbations, particularly those associated with small sample sizes. This is the life disparity $e^{\dagger}$, which is in the numerator of the fraction equal to the Keyfitz entropy. The reason is that the graph of the function $x\ln(x)$ has a vertical tangent at $x = 0$. The first derivative of this function $(x\ln(x))' = \ln(x) + 1)$ tends to negative infinity in the limit $x \to +0$.

The reason for the difficulties encountered is demonstrated more strictly in the work of Wrycza et al. [22]. There are such sequences of monotonically nonincreasing functions L_k that the sequence L_k converges to the limit function L, but the sequence of values of the Keyfitz entropy $H(L_k)$ does not at all converge to the value $H(L)$. Following [22], by the convergence of a sequence of functions to the limit we mean pointwise convergence when the function value L at a point is equal to the limit of the function values L_k at this point. This is not the only way to determine convergence; however, pointwise convergence allows us to characterize an important difference between the Keyfitz entropy and the Gini coefficient: the Keyfitz entropy is more sensitive to the appearance of long-lived individuals.

Informally, such survival functions L_k correspond to a situation where almost everyone dies early at the same age, but it is very small and tends to zero with growth of the index k the proportion of long-lived individuals live for a very, very long time (unlimited, for example, for fish with unlimited growth or corals). By choosing the ratio between the proportion of long-lived individuals and the maximum lifespan, it is possible to achieve an unlimited increase in the Keyfitz entropy. Moreover, although the integration domain is infinite, it is sufficient to consider such survival functions L_k, each of which is different from zero only for a finite interval, i.e., its own for each index k.

Let's look at a specific example. Let for sufficiently large indices $k > \ln(e_{exp})$ the survival function value L_k equal one for ages up to $e_{exp} - 1$, which is equal to the number $\exp(-k)$ for ages from $e_{exp} - 1$ up to $M = e_{exp} - 1 + \exp(k)$, and vanish at ages higher than M. Then for large indices k the life expectancy is equal to the (previously chosen) number e_{exp}. The numerator of the fraction equal to the Keyfitz entropy is equal to k up to a sign change to the opposite one. Therefore, the Keyfitz entropy $H(L_k)$ is equal to the ratio k/e_{exp} and tends to infinity as $k \to$ *infinity*.

However, in the limit at $k \to$ *infinity* the survival-function graph L_k approaches a rectangular step of unit height at the point $e_{exp} - 1$, that is, rectangulariza-

tion of the survival curve. The limit survival function L is equal to one for ages up to $e_{exp} - 1$ and zero for greater ages. Obviously, at every point except the point $e_{exp} - 1$ function $L \ln(L)$ tends to zero. Therefore, the integral of it also vanishes (the value of the integral does not change when changing the value of the integrand at one point in the domain of definition). Therefore, the Keyfitz entropy $H(L)$ tends to zero.

In the example considered, when passing to the limit, the average life expectancy changes in a jump of one. However, by increasing the absolute value of the average life expectancy, its relative change can be made as small as desired.

In practice, this sensitivity of the Keyfitz entropy to small changes in the survival function (also called perturbations) that only slightly affect the life expectancy can lead to paradoxical results associated with taking into account long-lived individuals. Moreover, the considered example shows the unsatisfactory behavior of the Keyfitz entropy for a survival function close to the rectangularized function. On the other hand, the Keyfitz entropy could serve as an indicator of the very existence of long-lived individuals (for example, in problems of verifying demographic data on superlong-lived individuals or selection for longevity in *Drosophila*).

For the same reason, another indicator, called lifespan equality, turns out to be sensitive to small disturbances, which according to the formula $\ln(1/H) = -\ln(H)$ is expressed through the Keyfitz entropy. As the Keyfitz entropy decreases, this indicator grows rapidly and becomes infinitely large for the rectangularized survival function.

Makeham Term

Taking into account random death, the conditional probability density of which does not depend on age, leads to an additional term (the Makeham term). The new conditional probability density of death is equal to $m_u(a) = \exp(-s)u + \exp(ra - s)$. Such an amendment to the Gompertz law was proposed by W.M. Makeham [14]. Usually the value u is non-negative, but negative values can also be considered $u > -1$, corresponding to random death escape. This term corresponds to multiplication of the original survival function $L(a)$ by the factor $\exp(-\exp(-s)ua)$.

For example, for the lion *Panthera leo*, European roe deer *Capreolus capreolus*, red deer *Cervus elaphus*, chamois *Rupicapra rupicapra*, sheep *Ovis aries*, yellow-bellied marmot *Marmota flaviventris*, Bali myna *Leucopsar rothschildi*, and sparrowhawk *Accipiter nisus*, the conditional probability density of death has a nonzero minimum [7], which allows us to assume that the term is non-zero u. We can conclude that such mortality dynamics are typical for large mammals and some birds, which either have virtually no predators in nature (like the hawk) or are kept in zoos (like the Bali myna). Paradoxically for hydra *Hydra magnipapillata* such a term is redundant, since the Gompertz law is satisfied $m = \exp(-s)$ with zero coefficient value $r = 0$.

Since the demographic indicators, the Keyfitz entropy and Gini coefficient, do not depend on time scale [22], if the coefficient r in the Gompertz law is different from zero, then when calculating indicators in the model we can put $r = 1$. Further, for the convenience of calculations, we put $s = 0$. This is how we arrive at the function $m(a) = u + \exp(a)$, depending on only one parameter u. The survival function is $L_u(a) = \exp(1 - ua - \exp(a))$.

When increasing the parameter u the life expectancy at birth e_{exp} decreases because at each age the conditional probability density of death increases. Calculations show that with increasing parameter u the life expectancy e_{exp} decreases, and the Keyfitz entropy H, Gini coefficient G and coefficient of variation CV_{LS} increase, which corresponds to an increase in the difference between the survival function and the rectangularized one.

The value $u = 0$ corresponds to the Gompertz law $m(a) = \exp(a)$. For large values of parameter u the Keyfitz entropy, Gini coefficient, and coefficient of variation tend to values corresponding to the age-independent conditional death probability density when $H = 1$, $G = 0.5$, and $CV_{LS} = 1$ (Fig. 1).

Figure 1 shows that the rate of change for each indicator (H, G, and CV_{LS}) decreases quickly and monotonically with increasing parameter u (Makeham terms) and tends to zero.

Demographic indicators depend on the initial value $m(0) = \exp(-s)u$. And, lowering the initial value $m(0)$, that is, increasing s, these indicators can be made as small as desired. It will be shown below that reducing the initial value in the Gompertz formula leads to almost the same effect as delaying aging.

Deviations from the Gompertz–Makeham Law

According to [7], for some animal species, deviations from the Gompertz–Makeham law are observed [1, 14], when the sub-Gompertzian model obviously better describes the data. The most characteristic differences are for the nematode *Caenorhabditis elegans*, head louse *Pediculus humanus*, Mediterranean fruit fly *Ceratitis capitata*, and fruit fly *D. melanogaster*.

Also, deviations from the Gompertz–Makeham law are typical for plants, in particular for marbled agave *Agave marmorata*, grey mangrove *Avicennia marina*, cryptanth *Cryptantha flava*, geonoma *Geonoma orbignyana*, pine *Pinus sylvestris*, oak *Quercus rugosa*, rhododendron *Rhododendron maximum*, and viburnum *Viburnum furcatum*. However, further we will discuss only animals.

The Gompertz–Makeham law suggests that, starting at a certain age close to the age of maturation, the conditional probability density of death $m(a)$ either

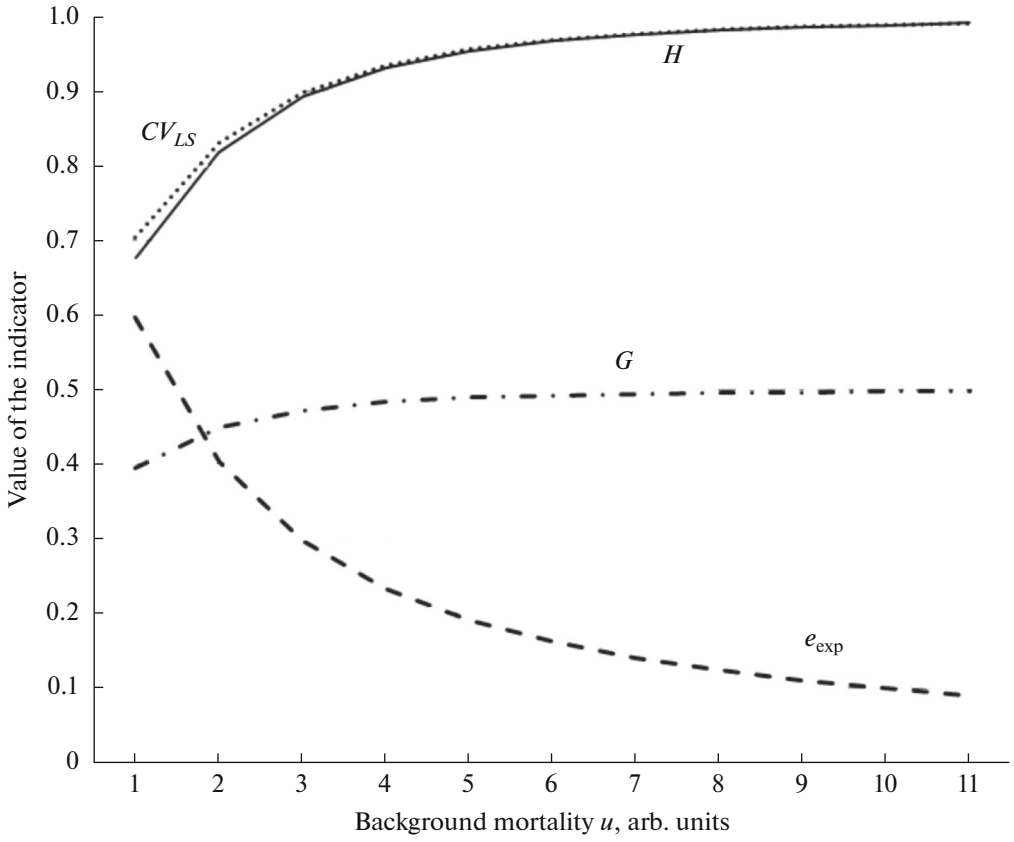

Fig. 1. Dependence of the life expectancy at birth e_{exp}, the Keyfitz entropy H, the Gini coefficient G, and the coefficient of variation of lifespan CV_{LS} from parameter u, which is associated with the Makeham term (i.e., the level of background mortality).

weakly depends on age (that is, determined by the Makeham term), or increases monotonically with increasing speed (the second derivative is positive). Moreover, the second derivative of the function $m(a)$ is almost always positive at early ages, that is, this sign does not depend on the difficulties of taking into account infant mortality, which makes it more reasonable.

No dependence of $m(a)$ on age is observed, in particular, in hydra *Hydra magnipapillata* and red abalone *Haliotis rufescens,* as well as hermit crab *Pagurus longicarpus* (raw data taken from Jones et al. [7]). We do not classify these cases as deviations from the Gompertz–Makeham law, although they correspond to a degenerate version of this law. For some species, including the tundra vole *Microtus oeconomus* and great tit *Parus major*, for whom a short lifespan is combined with a high risk to life, the function $m(a)$ is determined by the Makeham term.

For the desert tortoise *Gopherus agassizii*, the second derivative of the function $m(a)$ is positive, which is consistent with the Gompertz law, although the value of the function decreases monotonically with age. This may be due to the lack of data for older ages, when one can expect an increase in values $m(a)$. In some species with slow growth $m(a)$ the second derivative is also positive, which suggests qualitative agreement with the Gompertz law: specifically, the yellow baboon *Papio cynocephalus* and chimpanzee *Pan troglodytes*.

Good agreement with the Gompertz law is observed in many species, including daphnia *Daphnia longispina*, guppy *Poecilia reticulata*, lion *Panthera leo*, roe deer *Capreolus capreolus*, red deer *Cervus elaphus*, and humans *Homo sapiens*, for which the function $m(a)$ grows rapidly with age and its second derivative is positive.

Let's move on to discussing the most interesting cases of deviation from the Gompertz–Makeham law.

For the nematode *C. elegans* we used data on a cohort of 1000 individuals from [39], as well as data from some other works. The dependence of the conditional probability density of death on age is almost linear. Even if we limit ourselves to the data from [39], this is a large sample. The dependence of the function $m(a)$ on age is very close to linear; the second derivative is close to zero (contrary to the Gompertz law), but the first derivative is positive, which cannot be explained by the influence of the Makeham term. On the other hand, the presence of phenoptosis in the

nematode [26, 27] makes it possible to qualitatively explain the increase in the function $m(a)$ with age.

For head lice *Pediculus humanus* only 400 individuals were considered [40]. The small sample size may have skewed the function $m(a)$. The increase in value $m(a)$ with increasing age is close to linear, but experiences fluctuations in which the second derivative of the function $m(a)$ changes sign. Here, refinement of the data may lead to greater agreement with the Gompertz law. However, it is interesting to compare the louse with other insects discussed below.

For the Mediterranean fly *Ceratitis capitata* a cohort of 970 females were examined up to their death. In this case, with the exception of a small proportion at early ages, the second derivative of the function $m(a)$ is negative, which clearly contradicts the Gompertz–Makeham law. Here the function $m(a)$ is approximated by a logarithmic function of the form $s = \ln(ar + 1)$.

An even greater sampling for the fruit fly *D. melanogaster*. In this case, as for the louse, the second derivative of the function $m(a)$ changes sign. This also contradicts the Gompertz–Makeham law.

Sub-Gompertzian Models

According to the Gompertz law, starting from a certain age the function $m(a) = \exp(ra - s)$, where the coefficients r and s no longer depend on age [1]. However, below we will consider models of asymptotically *slower aging than provided by the Gompertz law*. We called such aging models *sub-Gompertzian*.

For each model, data on the survival of various animal species from the work by Jones [7] are presented, the aging of which can be approximately described by the corresponding model. Of course, such correspondence is very rough and does not at all mean that a similar function can be obtained by appropriately changing the coefficients in the Gompertz law. For some species the dependence is significantly different from others. For example, for the fruit fly *D. melanogaster* the above pattern corresponds to a sharp slowdown in aging, starting from a certain age. Just like the Gompertz law, the models considered do not take into account high early mortality. Therefore, one of the reasons for the discrepancy between the model and the data from the work [7] may be the lack of consideration in the model for the decrease in mortality soon after birth.

The simplest model corresponds to an age-independent positive constant $m(a) = m$. This model of aging is implemented, for example, in hydra *Hydra magnipapillata*, red abalone *Haliotis rufescens*, and hermit crab *Pagurus longicarpus* [7]. In this case $L(a) = \exp(-ma)$. The life expectancy at birth $e_{\exp} = 1/m$. The Keyfitz entropy is equal to $H = 1$; Gini coefficient is $G = 0.5$; coefficient of variation of lifespan is $CV_{LS} = 1$. These demographic indicators do not change with time scales. Therefore, they do not depend on the value of the constant m. In what follows, we will not explicitly indicate the coefficient (assuming it equal to one), which does not affect the values of the indicators.

Another model of very slow aging is $m(a) = \ln(1 + a)$. This model is approximately realized in the Mediterranean fruit fly *Ceratitis capitata* [7]. The survival function in this case is expressed by the formula $L(a) = \exp(-\ln(1 + a) - \ln(1 + a)a + a)$. The Keyfitz entropy is $H = 0.59$; the Gini coefficient is $G = 0.33$; the coefficient of variation is $CV_{LS} = 0.60$. Compared to *Hydra*, all three indicators decreased, which corresponds to rectangularization of the survival function.

Linear aging model $m(a) = a$. It is approximately implemented for the nematode *C. elegans*, and head louse *Pediculus humanus* [7]. The survival function $L(a) = \exp(-a^2/2)$. The Keyfitz entropy is $H = 0.5$; the Gini coefficient is $G = 0.29$; the coefficient of variation is $CV_{LS} = 0.53$. Compared to the previous model, both indicators decreased, which corresponds to further rectangularization of the survival function.

Models of accelerated aging are considered below. In general, for $m(a) = a^d$ the survival function is $L(a) = \exp(-a^d/d)$. The Keyfitz entropy is $H = 1/(d + 1)$. It tends to zero as the degree d of function $m(a)$ increases. The value of the Gini coefficient at $d = 2$ equals $G = 0.21$; at $d = 3$, it equals $G = 0.16$; at $d = 4$, it equals $G = 0.13$. The value of the coefficient of variation at $d = 2$ equals $CV_{LS} = 0.36$; at $d = 3$, it equals $CV_{LS} = 0.28$; at $d = 4$, it equals $CV_{LS} = 0.23$. For polynomial aging models with $m(a) = a^d$ the acceleration of aging with time leads to a decrease in the Keyfitz entropy, the Gini coefficient, and the coefficient of variation, which corresponds to rectangularization of the survival function. However, only the asymptotic behavior of the function $m(a)$ does not allow us to judge the approach to rectangularization.

Delayed mortality models. Next, we consider models with the function $m(a)$ equal to zero at an age up to some value b, starting from which this function grows. This model with delayed aging, called Teyssier's formula [41], is implemented, for example, in guppies *Poecilia reticulata* [7]. On the other hand, such a model $b = \exp(-s)$ and $m(a) = \exp(ra)$ can serve as a rough approximation to the Gompertz law; therefore, it allows one to make estimates of demographic indicators for a typical case using simplified calculation methods. An example of such a function is shown in Fig. 2, which shows the dependence of the values of the studied indicators (H, G, CV_{LS}) on the value M of mortality up to an age equal to the life expectancy (plotted on the X axis) and after reaching it (plotted in parentheses on the X axis). The calculations are based on an artificial sample and are not based on demographic data. The mortality values were selected so that the life expectancy always remained constant.

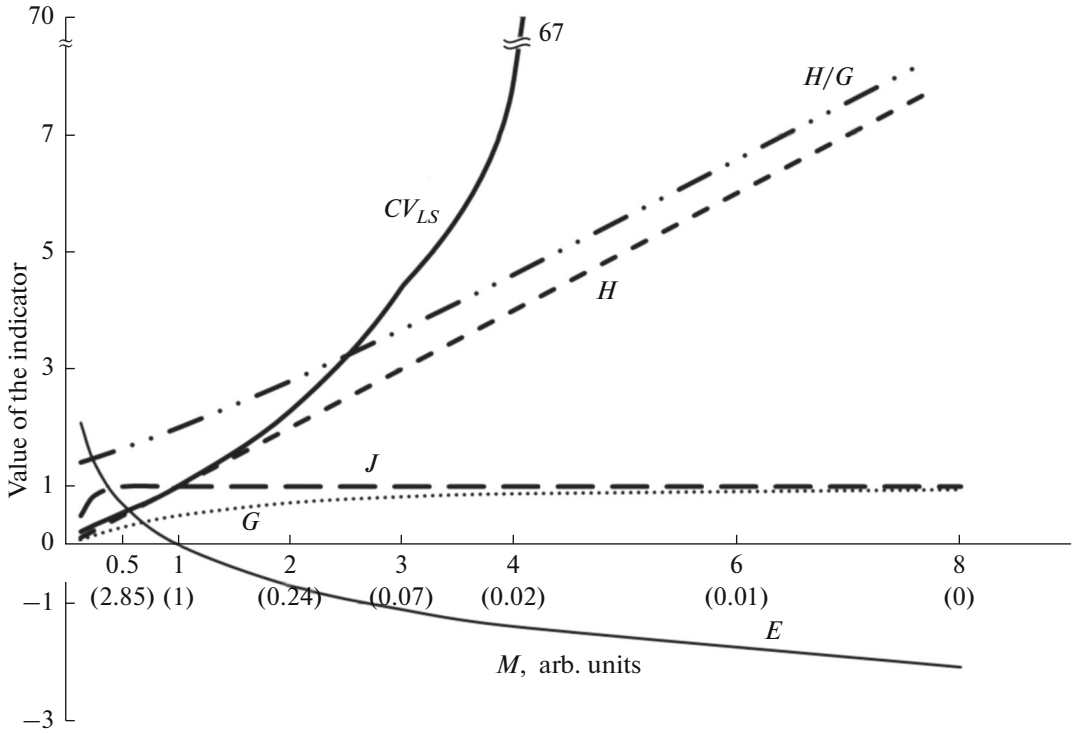

Fig. 2. Influence of fluctuations in mortality and life expectancy on the studied "entropy-based" indicators. e_{exp} indicates the life expectancy at birth, J is the metric used in the work of Jones et al. [7], H is the Keyfitz entropy, G is the Gini coefficient, CV_{LS} is the coefficient of variation of lifespan, and E is the lifespan equality. We show the dependence of the values of the studied indicators (H, G, CV_{LS}) on the mortality rate M before an age equal to the life expectancy (shown on the X axis), and after reaching it (shown on the X axis in parentheses). Calculations are based on an artificial sample and are not based on demographic data. The mortality values were selected so that the life expectancy at birth (e_{exp}) always remained constant.

These values were found by bisection (or dividing a segment in half), which usually requires a small number of iterations. This example allows you to demonstrate the dependence of indicators on one parameter M, and not from a combination of several parameters, as when working with real data. For the same reason, the values M are measured in conventional units, and changing the numerical value of the unit of measurement would only lead to stretching or compression of the picture as a whole.

A curve containing a discontinuity reflects the hypersensitivity of the coefficient of variation of lifespan (CV_{LS}) to inequality in life expectancy. Equality of mortality rates both before and after the point corresponding to e_{exp} (unit on the X axis), corresponds to $CV_{LS} = 1$ (i.e., 100%). Sharp inequality in life expectancy (for example, a mortality rate of 4 conventional units up to the point corresponding to e_{exp}, and a death rate close to zero after this point leads to ultra-rapid growth CV_{LS} up to 7000% (Fig. 2).

The survival function $L(a)$ generates a family of functions $L_b(a)$, equal to one at $a < b$ and equals $L(a - b)$ at $a > b$. Let us denote by e_{exp}, H, and G the life expectancy at birth, the Keyfitz entropy, and the Gini coefficient for survival function L. Depending on the amount of the shift b, the life expectancy increases as $e_{exp}(b) = b + e_{exp}$. The Keyfitz entropy decreases and is equal to $H(b) = He_{exp}/(b + e_{exp})$. Likewise, the Gini coefficient decreases by the same factor $G(b) = Ge_{exp}/(b + e_{exp})$. Moreover, the values of the indicators depend not only on b, but also on e_{exp}.

Burger [24] notes that the observed plasticity of age-related risk of death contradicts generally accepted theories of aging, but this can be explained by the "the theory of aging as part of the general program of ontogenesis," proposed by V.P. Skulachev [27].

So, based on the theory of phenoptosis, the authors can suggest the following scheme, which we called the "demographic snail" (Fig. 3), which allows us to explain the relationship between the theory of aging as a consequence of the interaction of a certain, but clearly more than one, number of aging and anti-aging programs (as a set of ontogenetic programs) [42–44]. Examples of such systems include DNA repair systems [21], systems for inducing the antioxidant activity of Nrf2 (Nuclear factor erythroid 2-related factor 2) or suppressing the activity of Nrf2 [42, 43], etc. Thus, the transcription factor Nrf2 appears to be a component of the antiaging program [42]. Nrf2 is considered the guardian of the healthspan and longevity [42].

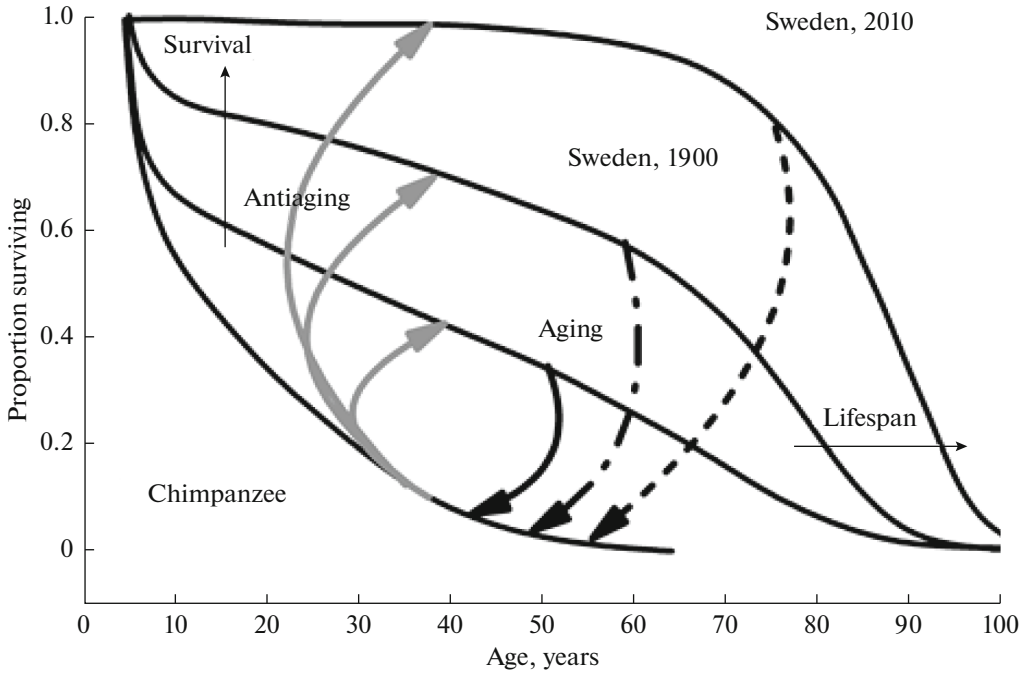

Fig. 3. Demographic meaning of phenoptosis ("demographic snail"). Light lines with an arrow indicate the effect of anti-aging programs that increase life expectancy and survival, and dark lines indicate aging programs. The possible disabling (in whole or in part) of some aging programs is indicated by a dotted line. An increase in the survival rate contributes to growth of the "snail" upward, while an increase in the average and maximum species-specific lifespan contributes to movement to the right. Survival data for Swedish people (1900 and 2010), Aché Native Americans, and chimpanzees are based on Burger et al. ([24], with modifications).

Nrf2 induces the expression of genes encoding ~200 antioxidant and detoxifying enzymes, including the most powerful natural antioxidants [43]. The signaling activity of Nrf2 is positively correlated with the species-specific lifespan [42]. The Nrf2 levels decrease in aged mice [44–46]. The protein antagonists of Nrf2 (β-TrCP, KEAP1, Bach1, and c-Myc) [42, 47, 48] and the generation of reactive oxygen species by mitochondria may be components of aging programs. The first three proteins are inhibited by reactive oxygen species, making the situation even more complex than simple competition between the anti-aging and aging programs. As indirect confirmation of the assumption that in long-lived species, in contrast to closely related short-lived ones, some aging programs can be turned off (Fig. 3) is the fact that in the naked mole-rat, compared to other species, the activity of systems that suppress Nrf2 activity is sharply reduced: β-TrCP, KEAP1 [43], along with clearly slowed (compared to other mammals) demographic aging [7, 44]. It should be noted that, in general, the number of substances and effects that slow down aging and increase life expectancy is much greater, for example, for a nematode than for humans [36]. Studying proteins located at the crossroads of signaling and regulatory pathways and comparing them using biochemical and bioinformatics methods in short- and long-lived species makes it possible to identify the molecular mechanisms underlying the processes and phenomena that determine longevity (including acute and chronic phenoptosis, neoteny, etc.) [27, 49–51].

When extinction proceeds exponentially, the probability of death does not increase with age, and we conditionally say that there is no aging (or rather, there is wear and tear, determined at least by the laws of thermodynamics), but there are other age-independent processes that have a greater influence on mortality (e.g., due to the pressure of predators) (Fig. 3). Likewise, L. Gavrilov and N. Gavrilova [16], analyzing historical trends in maximum lifespan in birth cohorts and the shape of age-related mortality trajectories after 110 years, found that the trend towards an increase in the number of lifespan records in subsequent birth cohorts is accompanied by a slight increase in the maximum recorded age of death for later cohorts, born after 1879. Although these data suggest possible temporal limits to human lifespan, the authors believe that there is still no convincing evidence of an inevitable, fixed biological limit to human lifespan. We partly agree with the conclusions presented in the mentioned work by L. Gavrilov and N. Gavrilova [16], assuming this barrier to be pushed back by a demographic snail, the movement of which will be determined by the ratio of the speeds of not one, but two processes: "growth" of the snail, determined by the ability of a particular species to ensure a

decrease in background mortality, leading to a "phenoptotically limited" rectangularization of the curve, and movement along the abscissa axis, increasing the average and maximum lifespan and leading to the appearance of long-lived individuals (Fig. 3).

An interesting observation is the relationship between the life expectancy and the Keyfitz entropy. An important result from the work of Colchero et al. [52] can be briefly formulated as follows: for people, the rate of change in the value $\ln(1/H)$, called lifespan equality, is constant, whereas for all primates the rate of change is not constant.

An increase in the standard of living of the population leads to a simultaneous decrease $e^{\dagger}$ and increase e_{exp}, which leads to a decrease in the Keyfitz entropy. At the same time, the increase e_{exp} looks quite natural, while the reduction $e^{\dagger}$ is a priori less obvious, but consistent with the phenoptosis hypothesis [27, 53]. If the increase in the life expectancy is caused by an increasing delay in the onset of aging during evolution or as a result of changes in living conditions, a decrease in the Keyfitz entropy will be simultaneously observed, and, consequently, there will be an increase in the equality of life expectancy $\ln(1/H) = -\ln(H) = \ln(e_{exp}) - \ln(e^{\dagger})$. Moreover, if the values b and e_{exp} are approximately equal to each other, then the growth $\ln(1/H)$ will depend almost linearly on b. So that the dependence $\ln(1/H)$ on the average life expectancy was linear over a large range of values corresponding to different populations, as observed in humans [27, 52], it is necessary to assume a simultaneous increase over time in both life expectancy and age b, starting from which the conditional probability density of death begins to increase rapidly. Obviously, a complete explanation must take into account other changes, in particular a decrease in the Makeham term associated with random death.

In humans, chronic phenoptosis [26, 27, 36], in contrast to age-independent acute phenoptosis, manifests itself as rectangularization of the survival function with a simultaneous increase in the life expectancy at birth as a result of the development of society and scientific and technological progress [27, 52, 54, 55, 57]. Despite the simple geometric interpretation of the rectangularization phenomenon, it is difficult to notice, tracing only changes in the optimal coefficients in the Gompertz–Makeham law [1, 14]. Moreover, the difficulties are not associated with deviations from this law, which are most noticeable for some invertebrates [7], but with high computational complexity, leading to an increase in calculation error. Therefore, it is necessary to calculate demographic indicators, of which the Keyfitz entropy H and the Gini coefficient G turned out to be convenient [22, 54]. Calculation of the coefficient of variation of lifespan is also used to assess rectangularization [37], but less accurately, which is confirmed both theoretically, due to the difficulty of calculating the derivative of the survival function [38], and using real demographic data [54].

However, approximation of the survival function to the rectangularized one is not the only thing that can be learned by comparing demographic indicators. The theoretical example we considered and the calculations of Németh [54] show that the Keyfitz entropy is more sensitive to the presence (or appearance) of long-lived individuals. Therefore, at small values H and G a much more pronounced scatter of values than with larger values of the same demographic indicators is demonstrated. Consequently, if for two populations (or two different animal species) with the same value of the Gini coefficient, the values of the Keyfitz entropy turned out to be different, then a larger value of the Keyfitz entropy indicates a larger proportion of long-lived individuals, considered relative to the average life expectancy. On the contrary, if for the same value of the Keyfitz entropy the Gini coefficients differ, then a higher value of the Gini coefficient corresponds to a relatively higher mortality rate at a young age. This may serve as a reason to cut off data concerning young ages.

It is easy to see that, for a fixed increase (that is, for a fixed difference $b-a$) in the age limit for some people from the value a to value $b > a$, the value of the Gini coefficient will undergo a greater change, the lower the age value a. On the contrary, with the same change in the survival curve, the Keyfitz entropy will undergo a greater change, the higher the age value a. In other words, the Keyfitz entropy is more sensitive than the Gini coefficient to an increase in the proportion of those who survive to a rather old age. By comparing both measures (the Gini coefficient and the Keyfitz entropy) as well as similarly calculated intermediate measures, it is possible to distinguish a survival curve that is close to one step or rectangular from a survival curve that is close to a step curve with two steps. Such an analysis is important to distinguish the effect of a certain geroprotector, which slows down the aging process, from the influence of other factors that increase life expectancy by reducing mortality at young ages. In the case where the survival curve is approximated by a step curve with two steps, a sharp change in the survival curve (the first step) at early ages is probably not associated with aging. Thus, a slight increase in the Keyfitz entropy with a large change in the Gini coefficient indicates changes that are in no way related to aging. On the contrary, a noticeable increase in the Keyfitz entropy with a relatively small change in the Gini coefficient indicates an increase in the proportion of those who lived for a very long time, say, in the range from 90 to 95% of the maximum lifespan.

The reason for such a different influence of perturbations of the survival function at different ages on the Keyfitz entropy and the Gini coefficient is that the integrands in the formulas for calculating $e^{\dagger}$ and e_n

change at different rates at different ages. At small ages, when the value of the survival function is close to unity, the integrand function in $e^{\dagger}$ is close to zero, and in e_n it is close to unity. On the contrary, at late ages, when the survival function is close to zero, both integrands in $e^{\dagger}$ and in e_n are close to zero, but decrease at different rates.

Actually in the work of Colchero et al. [52] it is not the Keyfitz entropy H itself that is used, but the value called the lifespan equality $\ln(1/H) = -\ln(H)$, which increases indefinitely with rectangularization of the survival function. The use of such values, that is, the transition to a logarithmic scale, allows us to show in detail the change in the survival function near the rectangularized one. At the same time, the life expectancy is growing slowly [16], and the Keyfitz entropy approaches zero much faster.

One of the reasons for the decrease in the Keyfitz entropy may be a decrease in background mortality, numerically expressed by the Makeham term. Another reason may be a decrease in mortality at young ages, which corresponds to a decrease in another coefficient in Gompertz law. It is probable that the observed change in the Keyfitz entropy is explained by the joint influence of both at the same time.

It was previously shown that the distribution of the deviation of the actual lifespans from the life expectancy at birth e_{exp} is not normal [37]. However, when averaging over a large sample set, the distribution of the deviation of the averaging result from the true value e_{exp} will be close to normal. However, no single sample size can be established. It significantly depends on the dispersion of the source data and on the average lifespan, since with a short lifespan the same absolute error will lead to a larger relative error and, therefore, will have a greater impact on the calculation of demographic indicators.

In the case where one sample set contains hundreds and another contains hundreds of thousands, there may be unexpected difficulties when the theoretical limit for the mean as the sample size increases indefinitely is infinite. However, when calculating the average lifespan, the expected value is finite and, therefore, increasing the sample should increase the reliability of the results.

CONCLUSIONS

We have no reason to reject the application of the Gompertz–Makeham law in vertebrate animals across a wide range of ages, except during periods of high infant mortality and at the oldest ages. Although for some invertebrates and plants, the applicability of this model does not seem justified (see also [18, 27, 37]). We conclude that, despite the fundamental applicability of the Gompertz–Makeham law under the specified restrictions, the use of the demographic indicators discussed in the article makes it possible to observe new patterns and also provides extensive opportunities for their visualization.

We examined several sub-Gompertzian models describing aging in nematodes and insects. Within the framework of the sub-Gompertzian model of aging, age-dependent phenoptosis in the nematode *C. elegans* [26] is quantified as rectangularization of the survival function compared to this function in hydra *Hydra magnipapillata*, red abalone *Haliotis rufescens*, and hermit crab *Pagurus longicarpus*. Rectangularization is evaluated based on demographic indicators (H, G, CV_{LS}), each of which is significantly lower for the nematode compared to the hydra, abalone, and hermit crab. On the other hand, rectangularization of the survival function, which increases with the advancement of scientific and technological progress, is evidenced by a decrease in the Keyfitz entropy [52]. This is accompanied by a simultaneous increase in the life expectancy in humans [55–57], which aligns well with the hypothesis of age-dependent chronic phenoptosis in mammals.

In general, calculations on aging models demonstrate the effectiveness of using Keyfitz entropy and the Gini coefficient as important demographic indicators. The use of these indicators appears preferable, especially for nematodes, where the sub-Gompertzian model of aging is applicable, and for vertebrates, primarily mammals, with certain restrictions where the Gompertz–Makeham law is applicable.

FUNDING

This work was supported by ongoing institutional funding. No additional grants to carry out or direct this particular research were obtained.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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