



A 2D analysis of correlations between the parameters of the Gompertz–Makeham model (or law?) of relationships between aging, mortality, and longevity

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Abstract When mortality (μ), aging rate (γ) and age (t) are treated according to the Gompertz model $\mu(t) = \mu_0 e^{\gamma t}$ (GM), any mean age corresponds to a manifold of paired reciprocally changing μ_0 and γ . Therefore, any noisiness of data used to derive GM parameters makes them negatively correlated. Besides this artifactual factor of the Strehler–Mildvan correlation (SMC), other factors emerge when the age-independent mortality C modifies survival according to the Gompertz–Makeham model $\mu(t) = C + \mu_0 e^{\gamma t}$ (GMM), or body resources are partitioned between survival and protection from aging [the compensation effect of mortality (CEM)]. Theoretical curves in (γ , $\log \mu_0$) coordinates show how μ_0 decreases when γ increases upon a constant mean age. Within a species-specific range of γ , such “isoage” curves look as nearly parallel straight lines. The slopes of lines constructed by applying GM to survival curves modeled according to GMM upon changes in C are greater than the isoage slopes. When CEM is modeled, the slopes are still greater. Based on these observations, CEM is shown to contribute to SMC associated with sex differences in lifespan, with the effects of several life-extending drugs, and with recent trends in

survival/mortality patterns in high-life-expectancy countries; whereas changes in C underlie differences between even high-life-expectancy countries, not only between high- and low-life-expectancy countries. Such interpretations make sense only if GM is not merely a statistical model, but rather reflects biological realities. Therefore, GM is discussed as derivable by applying certain constraints to a natural law termed the generalized Gompertz–Makeham law.

Keywords Aging · Lifespan · Mortality · Survival · Parametric analysis · Gompertz–Makeham law · Strehler–Mildvan correlation

“The more fundamental is a regularity, the simpler is its formulation”

Pyotr Kapitsa, Nobel Laureate in Physics

Background

The mean lifespan of living organisms is intimately associated with their mortality pattern. It is obvious that increasing the initial mortality, even without changes in the dependency of mortality on age, or accelerating the rate of the age-dependent increase in mortality, even without changing the initial conditions, will decrease the mean lifespan. Reciprocal changes in these two factors may nullify changes in the

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mean lifespan, in spite of, likely, significant shifts in the physiological characteristics beneath the initial susceptibility to the causes of death and the age-associated changes in this susceptibility.

Far less obvious is differentiating between these options upon experimental interventions or, concerning humans, upon studying lifespan as it depends on socioeconomic, cultural, environmental, or other conditions.

A conspicuously simple formula $\mu(t) = \mu_0 e^{\gamma t}$ widely used for analyzing the patterns of survival and mortality in experimental animals and in human populations [reviewed in Kirkwood (2015) and Stroustrup (2018)] is known as the Gompertz law (or model: see below). Here $\mu(t)$ is mortality rate, i.e. the proportion of those who have died during a certain period starting from age t among those who have been alive at age t , and γ is the rate of aging. The elaborations of the Gompertz model (GM) include the additional parameters thought to reflect the age-independent component of total mortality (the Gompertz–Makeham model, GMM: $\mu(t) = C + \mu_0 e^{\gamma t}$) or the heterogeneity of study cohorts or populations (the gamma-Gompertz model, GGM—see Table 1 below) [reviewed in Németh and Missov (2018)].

As far as μ_0 may be thought to capture, in an inverse manner, the initial resistance to causes of death (the initial vitality), and γ , to capture the rate of the age-dependent decline in vitality (the rate of aging), applying the Gompertz law/model to data on mortality or the respective survival patterns is believed to help in differentiating the contributions of the two determinants of longevity to its changes (de Magalhaes et al. 2005; Pletcher et al. 2000; Yen et al. 2008).

The Gompertz law was discovered almost 200 years ago upon analysis of mid-age mortality in human populations (Gompertz 1825). However, mortality patterns at early and late ages feature significant deviations from the law. The quest for more accurate analytical representations of human mortality, which are applicable to possibly longer age periods, resulted in the invention of a number of functions that perform better than the Gompertz law or any elaboration thereof with regard to fitting the empirical mortality data [see Basellini et al. (2018) and references therein]. The status of the Gompertz law was reduced to treating it as a model along with other models, each having its merits and drawbacks. The obvious merits of the GM are its simplicity and straightforward

interpretability in biologically meaningful terms. The obvious drawback is that only more or less significant parts of the whole time trajectories of mortality conform to the model.

A less obvious drawback of the GM is that, upon fitting of noisy data or accurate data that do not conform exactly to it, the estimates of its parameters applied to different datasets become cross-correlated. In fact, this is a general property of any nonlinear multiparametric models, as it has been highlighted in the paper (Johnson 2000) unrelated to gerontology and unnoticed in this research field. The paper, which addresses the kinetics of enzymatic reactions, was published long after and quite independently from the first observation (Strehler and Mildvan 1960) that GM parameters derived from human mortality data are negatively correlated. This correlation was suggested to reflect some fundamental biological regularity and, even more, to be deducible from the general theory of aging put forward by Strehler and Mildvan. Since that time, the Strehler–Mildvan correlation (SMC), which may be formalized as $\log \mu_0 = X - Y\gamma$, inspired much theorizing and numerous publications, e.g. Finkelstein (2012), Gavrilov and Gavrilova (1991, 2001), Golubev (2004, 2009, 2012), Li and Anderson (2015), Riggs and Hobbs (1998), Sasaki and Kondo (2016), Shen et al. (2017), Yashin et al. (2001) and Zheng et al. (2012). In particular, the SMC may be interpreted as reflecting the possibility that, in a given species, increasing the initial vitality or vigor is associated with increasing the rate of its age-dependent decline, i.e. the rate of aging.

Evidence that the SMC may include a significant artifact was provided in Gavrilov and Gavrilova (1991). GM parameters were shown to exhibit a SMC when the GM is applied to data conforming to the GMM and consistent with changes in the age-independent mortality. However, using the GMM to fit such data does not eliminate the SMC. The residual correlation between GM parameters, which was suggested to reflect a real tradeoff between vitality and the rate of its decline, was termed “the compensation effect of mortality” (CEM).

Recently, the SMC was challenged more severely (Burger and Missov 2016; Tarkhov et al. 2017). In particular, Tarkhov et al. (2017) have shown that SM parameters are correlated because GM-based age-at-death distributions may be treated as truncated forms of the extreme values distribution. SMC was

demonstrated to be present upon comparing the control datasets from studies of the standard model organism, the nematode *C. elegans*, even though there were no differences between the mean lifespans. The authors concluded that the SMC is “a degenerate manifold of Gompertz fit”. Examining *C. elegans* and human data showed that the SMC is not eliminated by modifying the GM with additional terms thought to capture the age independent mortality or the heterogeneity of study populations. Similar results were obtained with murine datasets (Golubev et al. 2018).

Taken together this might suggest that the SMC is nothing more than an artifact of curve fitting, and the GM as a model may be not just the least accurate, but actually the most misleading. With that, the existence of a correlation between the initial vigor and the rate of its decline in a given species follows, as discussed in Golubev (2009) and Golubev et al. (2017b, 2018), from recognized concepts of aging—the antagonistic pleiotropy, disposable soma and rate-of-living theories, each being supported with ample evidence (Austad and Hoffman 2019; Kowald and Kirkwood 2015; Lemaître et al. 2015; Redman et al. 2018). May it be that the GM does reflect some biological realities?

It will be argued here that the GM is a particular embodiment of what has been put forward as a generalized Gompertz–Makeham law (GGML) in Golubev (2009). The GGML could emerge upon the origin of life from the physicochemical world when the patterns of disintegration of prebiotic entities became transformed into the patterns of mortality of primordial biological objects. The derivation of the GM from the GGML is based on the assumptions that the age-independent component of mortality is negligible and the age-dependent decline in vitality is linear. Because both conditions are never observed exactly, the artifactual component of the SMC is inevitable even with the most accurate data. Therefore, the problem is to discern a possible real correlation attributable to the CEM from the inevitable artifactual one and the one attributable to the age-independent mortality. The latter is the main contributor to the correlation that was originally reported by Strehler and Mildvan (1960) and thus will be considered hereinafter as the SMC proper.

Of course, the above makes sense only if the GM is not regarded, based on purely statistical considerations, as just a more or less acceptable mathematical

tool for mortality data presentation and treatment, which is a dominant stance as of today [see in Golubev (2009) and Golubev et al. (2018) exemplary quotations expressing this attitude quite explicitly]. Because the present discussion is based on the belief that the GM is derivable from a real law of nature by applying arbitrarily assumed constraints to it, this belief should first be justified.

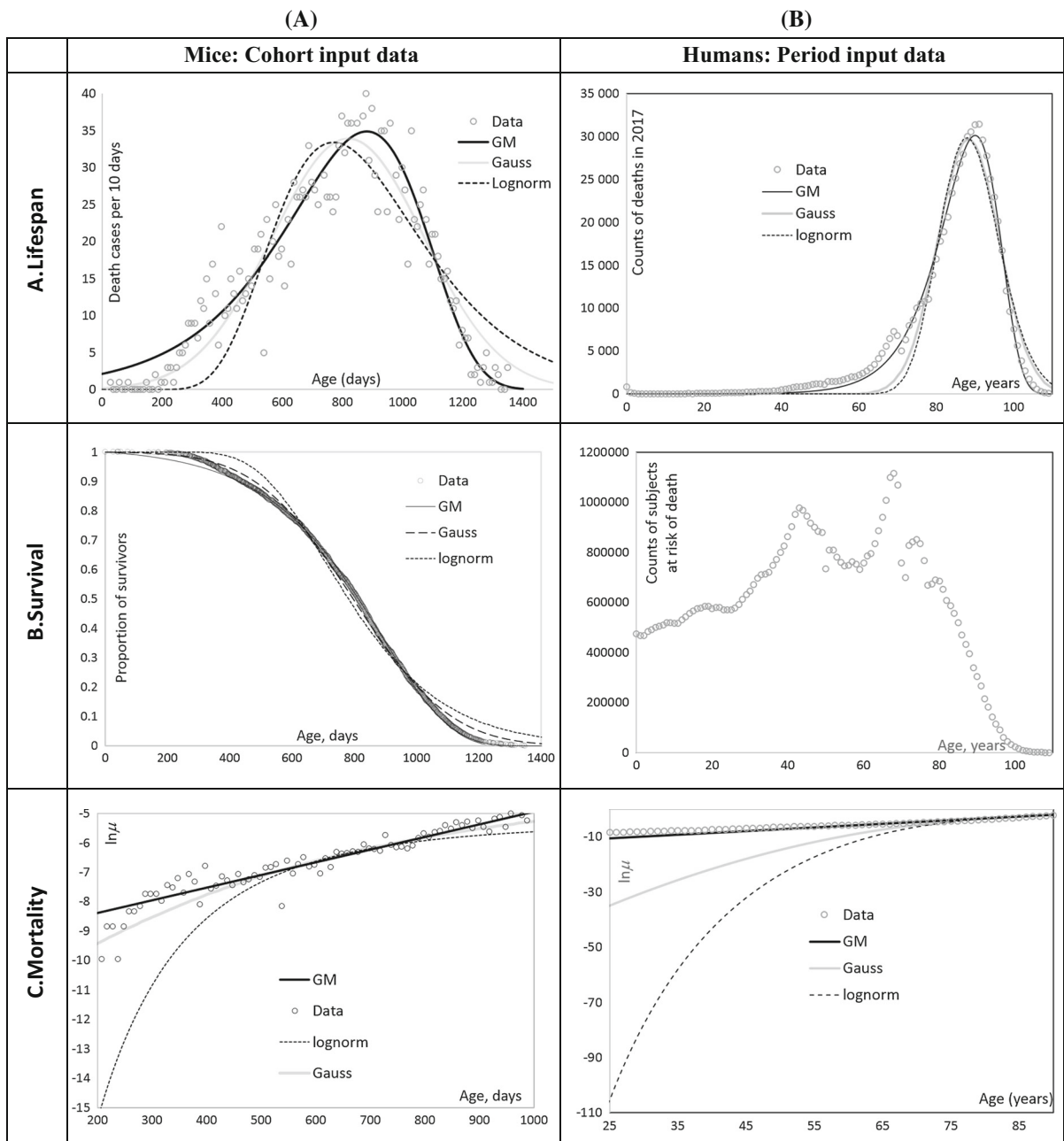
Gompertz–Makeham model versus (generalized) Gompertz–Makeham law for biology

The subsequent discussion is based on the analysis of (i) murine survival data downloaded from https://phenomedoc.jax.org/ITP1/Data_frozen_public/ (Interventions Testing Program: Effects of various treatments on lifespan and related phenotypes in genetically heterogeneous mice (UM-HET3)) and extracted from published survival curves as described in Golubev et al. (2018) and (ii) human age-at-death and survival data downloaded from <http://mortality.org> (Human Mortality Database, HMD). Numerical modeling was carried out with Mathcad ver. 13. Published and modeled data were approximated with parametric models using nonlinear maximum likelihood estimation procedures implemented in Table-Curve2D (TC2D) curve-fitting software (fully functional trial version is available at <http://www.sigmaplot.co.uk/downloads/download.php#tc2d>). Statistical procedures were carried out using the RealStat add-on (<http://www.real-statistics.com/free-download/real-statistics-resource-pack/>) to MS Excel 2013.

The primacy of mortality kinetics versus lifespan distributions and survival patterns

Two principal attitudes to defining relationships between lifespan, survival and mortality may be distinguished [discussed in Golubev et al. (2018) and Golubev (2019)]: one hinges upon data on survival, which may be traced longitudinally in the cohorts of experimental animals, and the other, upon age-at-death distributions derived from period (cross-sectional) studies, mainly of the human populations.

The Gompertz law is more consistent with the former attitude, which implies that the kinetics of mortality is the primary determinant of lifespan and its variability. The alternative attitude, which may be



traced back to A. Weisman [see Goldsmith (2004) and Walker (2017)], implies that lifespan itself is a primary evolved species-specific trait. Whatever the arguments in favor of the latter attitude, the trait must feature, similarly to all quantitative biological traits, some variability characterized by the respective mean and variance. The number of

deaths attributable to a defined age interval will increase with approaching the mean age, peak at this age (a sort of mean size in time), and decrease thereafter (see Fig. 1a). Accordingly, aging is treated as a process that leads to the attainment of a size in time within species-specific limits, the attainment being marked by the event known as death. The

◀ **Fig. 1** Age-at-death distributions and the respective plots of survival versus age and log-transformed mortality versus age in mice (a) and humans (b). Data on mice survival in cohorts relate to 2118 control UM-HET males used in the ITP1 project. Human period data relate to women in Japan as of 2017 (downloaded from HMD). Lifespan: *Mice* The RealStat add-on to MS Excel was used to distribute the primary age-at-death data in 10-days bins. The resulting number of bins is roughly equivalent to the number of age periods (years) for which annual counts of deaths and of subjects at risk of death may be determined in a human population. *Humans* Data are imported from HMD. Both the murine and the human datasets are approximated with either a GM, Gaussian, or lognormal distribution using TC2D curve-fitting tool. Survival: *Mice* Data points in the survival plot are so numerous that they merge. The dataset is approximated with a cumulative GM, cumulative Gaussian, or cumulative lognormal distribution. *Humans* Period data are imported from HMD. Mortality: *Mice* Data points are generated by dividing the size of each 10-days bin by the difference between 2118 and the sum of the sizes of all preceding bins. Only the survival data are primary in this case. *Humans* Data points are generated by dividing the primary age-at-death distribution data by the primary survival data. Mathcad Vol. 13 was used to construct numerically the modeled plots based on the estimates of their parameters derived from the approximations of the age-at-death distributions with GM, Gaussian, and lognormal models. The plots related to the Wald and lognormal distributions are virtually indistinguishable

commonly assumed distributions for the variabilities of the quantitative measures of such traits or for the times to their attainment are normal (Gaussian) for traits (the ages-at-death, in the present context) or inverse Gaussian, aka Wald, for times (times to death, in the present context). A reasonable alternative to the normal is the lognormal distribution (Limpert and Stahel 2017), which, so as the Wald distribution, is regarded as applicable to age-at-death distributions determined in populations or derived from survival/mortality patterns in cohorts (Stroustrup 2018).

If the age-at-death distribution is assumed as the primary property of a sample under study, integrating ages at death over age will yield the cumulative numbers of deaths at defined ages, and subtracting these numbers from the initial number of individuals will yield survival patterns. The calculation of mortality patterns is carried out, basically, by dividing the numbers of ages-at-death that fall into defined age intervals by the numbers of individuals that are still alive at respective ages. Noteworthy, in the period studies of human populations, the survival pattern, which is obtained by counting the numbers of individuals who have defined ages in a given year,

and the age-at-death distribution, which is obtained by counting individuals who have died at defined ages in the same year, are both used as primary sources for calculating the rates of mortality at defined ages; whereas in experimental cohort studies, only the survival data are primary, the age-at-death distributions being derived from them by attributing death cases to defined age intervals (binning). The generic shapes of the dependencies of these parameters on age are shown in Fig. 1.

The general analytical relationships of any age-at-death distribution with the respective patterns of survival and the rate of mortality (the hazard function in statistical terms), are shown in Table 1. Importantly, any of the formulas in Table 1 may be derived from any of its two neighbors. Therefore, any mortality model, such as the GM, may as well be regarded as a survival or a lifespan distribution model, and vice versa.

If one starts from an age-at-death distribution to estimate the parameters of survival and mortality, the accuracy of the estimates will increase with increasing the number of age intervals (bins) within the entire lifespan and the number of death cases in each interval. For this, human populations, which amount to millions, are the most adequate. In experiments with mice, the initial sizes of study cohorts (usually about 100, often about 50, and rarely more than 150) are too small for robust binning. Recently, the uniquely huge dataset composed of data on survival of thousands UM-HET mice used as controls in the ITP1 project became available at https://phenomedoc.jax.org/ITP1/Data_frozen_public/. This dataset is used here to derive an age-at-death-distribution from male mice survival data and to compare the compatibility of several parametric models with the mortality patterns derived from the primary data on the survival of mice and on the survival and lifespan distributions of humans (Fig. 1).

Based on fits to the survival datasets, the four models compared (the Wald and lognormal ones being virtually indistinguishable) are hardly discernible. Differences between the models are more apparent when they are applied to the age-at-death distributions. The distributions based on data are negatively skewed, in conformance with the GM and at difference from the Gaussian, Wald and lognormal models, which yield either symmetric or positively skewed age-at-death distributions. Even greater differences between

Table 1 Parameters used to describe relationships between lifespan, mortality, and aging

Basic Parameters	Lifespan: The mean age-at-death S and its variance σ		Mortality kinetics: The initial mortality μ_0 and the rate of its increase γ
Determinant function	Lifespan (age-at death) distribution $n(t)$ The fraction of the members of a population that die within age interval $(t, t+\Delta t)$	Survival distribution $N(t)$ The fraction of the members of a population that survive to age t .	The force of mortality at age t $\mu(t)$ The proportion of those that die within age interval $(t, t+\Delta t)$ among those that survive to age t
Relationships between determinant functions	$n(t) = \frac{-dN(t)}{dt} = \lim_{\Delta t \rightarrow 0} \frac{N(t+\Delta t) - N(t)}{\Delta t}$	$N(t) = 1 - \int_0^t n(t) dt$	$\mu(t) = -\frac{dN(t)}{dt} \times \frac{1}{N(t)}$
Lifespan distribution is assumed to be:	Normal (Gaussian) $= \frac{1}{\sqrt{2\pi\sigma^2}} \cdot e^{-\frac{(t-S)^2}{2\sigma^2}}$	$= 1 - \frac{1}{2} \cdot [1 + \operatorname{erf}(\frac{t-S}{\sigma\sqrt{2}})]^*$	No closed form formula
	Lognormal $= \frac{1}{\sqrt{2\pi\sigma^2}} \cdot e^{-\frac{[(\ln(t)-S)]^2}{2\sigma^2}}$	$= -\frac{1}{2} \cdot [1 + \operatorname{erf}(\frac{\ln(t)-S}{\sigma\sqrt{2}})]^*$	No closed form formula
Mortality kinetics is assumed to conform to:	GM $= \mu_0 \cdot e^{\gamma \cdot t - \frac{\mu_0 \cdot (e^{\gamma \cdot t} - 1)}{\gamma}}$	$= e^{-\frac{\mu_0}{\gamma} (e^{\gamma \cdot t} - 1)}$	$= \mu_0 \cdot e^{\gamma \cdot t} **$
	GMM ***	$= (C + \mu_0 e^{\gamma \cdot t}) \cdot \exp[-\frac{\mu_0}{\gamma} (e^{\gamma \cdot t} - 1) - C \cdot t]$	$= \mu_0 \cdot e^{\gamma \cdot t} + C **$
	LGM ***	***	$= \mu_0 \cdot e^{\gamma \cdot t} \frac{1}{1 + s \frac{\mu_0}{\gamma} (e^{\gamma \cdot t} - 1)} **$

**erf* error function which is not reducible to elementary functions

**The parameters λ , γ , and C are usually interpreted, respectively, as the initial mortality (the inverse of the initial vitality), the rate of aging, and the age-independent (background, external) mortality, and s , as quantifying the heterogeneity of a population (cohort)

***The cumbersome formulas are omitted

the models are apparent in the log-mortality versus age plots, which show that the patterns of data points directly derived from the age-at-death distributions are consistent with the GM, but not with the three other models.

The simplest formula making an age-at-death distribution skewed negatively relates to not the distribution itself but to the respective dependency of mortality μ on age t . The formula is $\mu(t) = \mu_0 e^{\gamma t}$, which is the Gompertz law. Noteworthy, the logarithmic transformation of $\mu(t) = \mu_0 e^{\gamma t}$ yields $\ln[\mu(t)] = \mu_0 + \gamma t$, i.e. a linear function, which is the simplest

and the most convenient for analysis. At the same time, the age trajectories of mortality consistent with the models that hinge upon age-at-death distributions are even not representable with closed form formulas.

The complexities of different functions used to describe mortality and survival patterns are commented here not so for practical considerations or mere curiosity but rather because of the belief that there is usually more natural reason at the base of a simple than of a complex apparent truth. This form of the principle of parsimony will be adhered to throughout the entire discussion that follows.

The origin of the exponential increase in mortality rate

Regardless of whether the relationships under discussion relate or not to a law of nature, they all relate to living beings. If life emerged out of the physicochemical world, evolution most likely passed through the stage of some loosely organized multimolecular complexes, from which protocells could have evolved [reviewed, e.g., in Kitadai and Maruyama (2018)]. The survival of the populations of such extremely unstable objects was possible only due to that their losses could be compensated for by the self-reproduction of those objects that remained intact more or less and able to multiply by division. The attempts to reproduce the composition of their primordial milieu suggest that it contained the numerous chemically interacting molecules that later were incorporated into the backbone of the metabolic system, including glycolysis, the pentose phosphate pathway, and the Krebs cycle (Keller et al. 2014; Ralser 2018; Muchowska et al. 2019). Among all possible chemical interactions between those molecules, only a part formed this backbone when there evolved the enzymes that catalyzed and controlled the chemical interactions that could increase object's abilities to resist or avoid disintegrating forces and/or facilitate the rate and/or fidelity of self-reproduction.

However, the rest of the reactivity of the chemical constituents of the prebiotic objects did not just disappear. It persisted as a sort of background or “other side” of metabolism (Golubev 1996) and constituted the “prototypical driving force of aging” (Golubev et al. 2017a), which could be supplemented with other forces but could not be nullified, so as metabolism could not be eliminated. This chemical background included hazardous products, which may be exemplified with methylglyoxal (Rabbani et al. 2016; Hipkiss 2017; Golubev 2019). This dicarbonyl compound is spontaneously formed from triose phosphates, which were initially present in the primordial soup and then became indispensable intermediates of glycolysis. The chemical properties of methylglyoxal make it highly toxic because of its ability to form covalent adducts to some amino acids, including those incorporated in enzymes and structural proteins, to nucleotides, including those incorporated in DNA, and to phospholipids, including those in membranes. The range of metabolites and the products of their

spontaneous transformations that possess potentially hazardous chemical potencies is far not limited to active carbonyl and oxygen species (de Crécy-Lagard et al. 2018; de Lorenzo et al. 2014; Hanson et al. 2016; Lerma-Ortiz et al. 2016; Linster et al. 2013). Thus, the primordial living objects were burdened from the very start with some inner chemistry that could compromise their vitality even under anaerobic conditions; however, the hazards generated by this chemistry were kept at tolerable stationary levels in the populations of such objects due to their turnover determined by balances between growth, self-reproduction by division, and disintegration.

Disintegration results from forces that exceed resistance to them. In chemistry, the relationship between the rate of disintegration of molecules and their resistance to disintegration is captured by the Arrhenius equation:

$$k = A \times e^{-\frac{E}{R \times T}}$$

where k is the rate constant of disintegration; A is reaction-specific constant; E , which may be thought of as a measure of resistance to disintegration, is activation energy, i.e. the minimum energy transferred to a molecule via random impacts of other molecules or radiation quanta that is sufficient to disintegrate the molecule; R is the universal gas constant; and T is absolute temperature (K°).

Importantly, Arrhenius equation is applicable as well to the temperature dependencies of the rates of inactivation of viruses and bacteria (De Paepe and Taddei 2006; Erkmén 2009).

Under conditions more relevant to biology, not only temperature but also the activation energy or barrier, i.e. the resistance to disintegration caused by coincidences of different impacts, may undergo changes. Thus, upon the origin of living objects from their inanimate ancestors, the chemical kinetics according to the Arrhenius equation could have been transformed (Golubev 2009), as shown in Fig. 2, to relationships termed the generalized Gompertz and Gompertz–Makeham laws. Importantly, the function for time course of changes in resistance to deadly stresses, which is linear in the canonical GM, is not specified in the generalized Gompertz law.

Unlike inanimate molecular complexes, living cells can proliferate and thus dilute any damage with newly formed undamaged material. To make comparing of

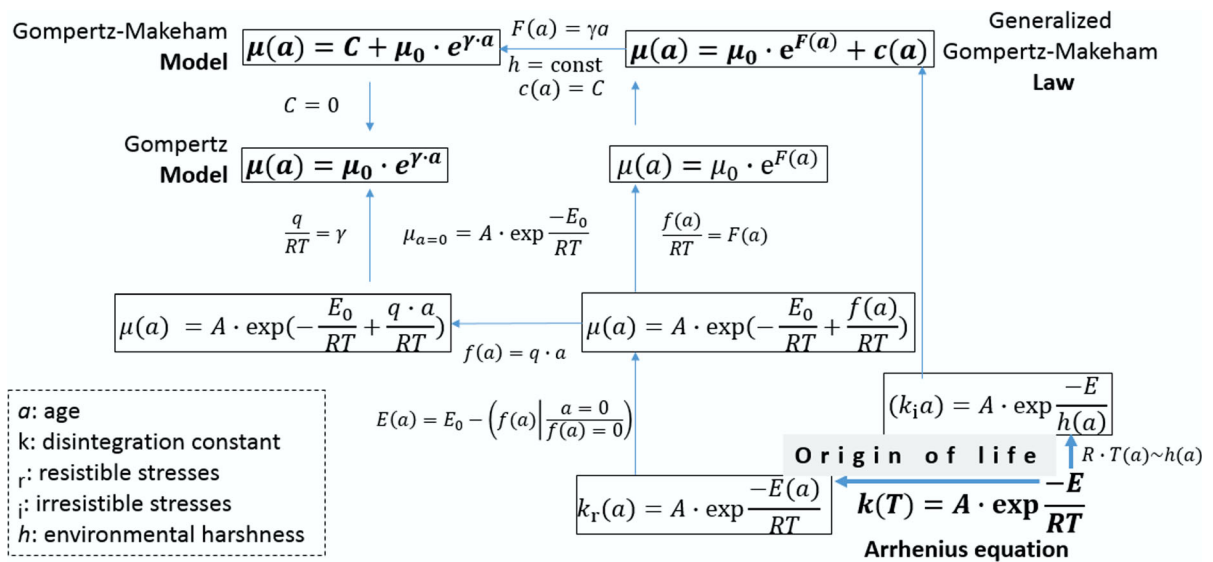


Fig. 2 Relationships between the chemical kinetics of disintegration of inanimate objects according to the Arrhenius equation and the kinetics of mortality of living objects according to the GGML and related models

inanimate and living objects sensible in the present context, the growth and proliferation of the latter must be halted. Under conditions making bacterial cells unable to proliferate, the amounts of macromolecules damaged by reactive byproducts of metabolism increase in bacteria with increasing age in initially an almost linear fashion (Dukan and Nyström 1999). The reactive byproducts include active carbonyl species, such as methylglyoxal (Kosmachevskaya et al. 2015). Because of damage accumulation, the resistance of bacterial cells to the causes of death must decline and mortality must increase correspondingly, i.e., by an exponent as follows from the above discussion of the Arrhenius equation. Indeed, under conditions making bacteria unable to proliferate, the rate of mortality of bacterial cells increases with time (Yang et al. 2018), and the increase is consistent with the GGM no less than the age-associated mortality increase in humans is (Fig. 3).

Taken together, the above makes it plausible that the populations of primordial living objects had inherited from the chemical world, from which they had emerged, not only the chemical reactivity of their constituents but also the kinetics of their mortality, albeit the role of the main variable had passed from the intensity of the external hazards (temperature in chemistry) to the ability to resist the effects thereof. This idea is derived essentially from the theory of

aging put forward by Strehler and Mildvan (1960), which is based on the Arrhenius equation in the final account (Strehler 2000). Answering the question of how could the primordial mortality pattern persist from bacteria via more to less primitive metazoans up to humans through all possible deviations, such as those described in Jones et al. (2014), relies more on philosophy than on reasoning (Golubev 2009) and will not be dwelt on here. The fact is that the pattern has been being quite pervasive (Fig. 3).

The origin of deviations from the exponential increase in mortality rate

Deviations from the exponential pattern of mortality are largely responsible for the apparent correlations between GM parameters (Golubev et al. 2018). With preference for the simplest explanations, two parsimonious models of the origins of such deviations (Golubev 2009) will be outlined.

First, the hazards able to kill living things are much more numerous in qualitative terms than the single cause of chemical disintegration, which is molecular collisions. Evolution was associated with increasing the number of abilities to resist specific causes of death and, correspondingly, with the transition of the irresistible causes of death to the category of the resistible ones. Those causes of death that still could

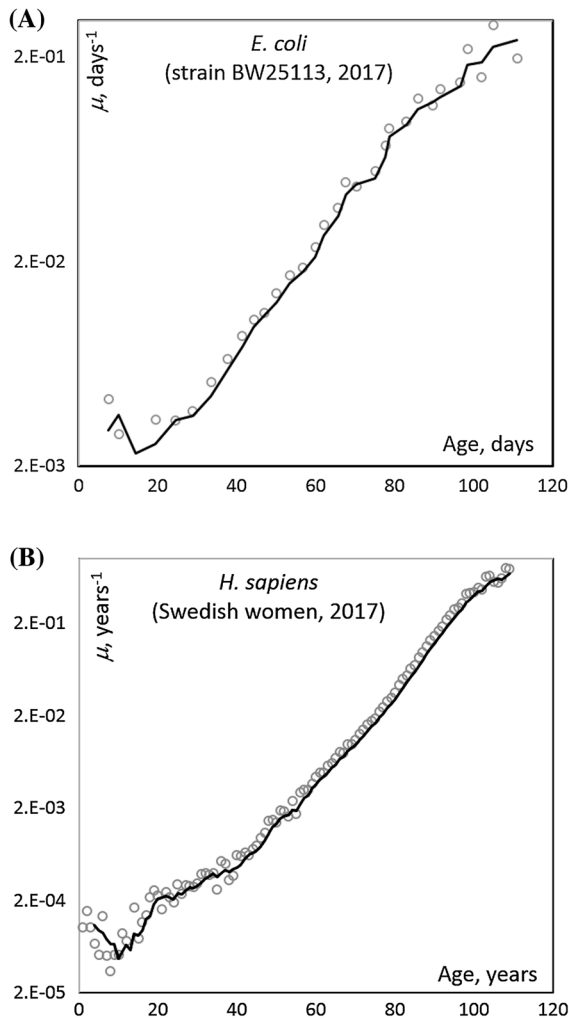


Fig. 3 Dependencies of the force of mortality upon age. **a** *E. coli* [data points are derived from a plot presented in Yang et al. (2018)]. **b** *H. sapiens* (<http://morality.org>). Trends represent two-point (**a**) or four-point (**b**) filtering

not be resisted continued being responsible for the components of mortality that are not included in the (generalized) Gompertz law. These components are not necessarily age-independent. For example, it may be that the adhesion of living objects to their substrate changes with increasing age; therefore, the exposure of such objects to the irresistible causes of death may change with age.

Thus, there emerges a relationship, which is captured by a generalized Gompertz–Makeham law (GGML) (Golubev 2009). The GGML includes an analog of the Makeham member of the GMM. The member was initially introduced as a constant

(Makeham 1860) to improve the fit of the GM to real human data. In the GGML, the essence of the analog of the Makeham member is not that it is a constant, but that it captures mortality attributed to the irresistible factors, whereas the Gompertz member captures mortality attributed to the resistible factors. Any change in the resistance to the latter is translated into the respective change in mortality by the exponential term of the GGML. This means that a function describing the time trajectory of organismal aging may be derived from the function best approximating the age-dependent component of demographic mortality, no matter how much it deviates from conformance to the canonical GM, in which the linearity of functional decline is implicit. However, infinite linearity is the least natural form of physiological changes, and any non-linear dependencies of functional decline on age will make age-associated mortality increases deviant from being strictly exponential.

The translation of the time trajectory of physiological changes into the time trajectory of changes in survival is mediated by changes in mortality, which are derived from physiological changes by exponentiation. Because the step from mortality rate to survival involves integration, any peculiarities in the time trajectory of physiological changes will be levelled out in the respective survival curve. This makes derivation of physiological changes from survival data a tricky matter. Still, reconstructing the time trajectories of mortality from the time trajectories of survival suggests almost invariably a deceleration of mortality at ages close to the maximum observed lifespan. According to the GGML, this could mean that the physiological decline slows down in the oldest old organisms. A more commonly accepted explanation of this effect is that, because of the heterogeneity of any cohort, the proportion of those of its members whose aging rate is slower increases with time [reviewed in Németh and Missov (2018)]. This explanation is captured by the gamma-Gompertz model. However, it does not rule out the possibility that the rate of aging decreases indeed at advanced ages.

The simple model of functional decline suggested in Golubev (2009) implies that decreasing are functional capacities involved in protection from both, the external hazards and the internal hazards that compromise the ability to withstand the external hazards. This will result in almost parallel and nearly linear

declines in all functional capacities ultimately down to zero. The resulting “no living, no aging” mode of existence is associated with a high susceptibility to death, which will not increase further with increasing age because there is little left to age further. Alternatively, but not exclusively, damage accumulation is limited by the amount of material that is still undamaged. Both factors will decelerate damage accumulation at later ages, and the resulting decrease in the rate of physiological aging will be translated by exponentiation, according to the GGML, into a deceleration of the rate of increase in demographic mortality.

As to the non-exponent member of the GGML, it is not merely an optional constant added in the GMM to improve GM fit to data; it is rather an essential component of any realistic model of mortality (Golubev 2004). The assumption that the component is constant will make a more or less useful model out of the GGML. The additional assumption that the ability to withstand the resistible causes of death declines in a linear fashion will transform the GGML into the GMM, which may be more useful while being less adequate. Still other assumption that the presumably age-independent component of the GMM is negligible will eventually transform the GGML into the GM, which is probably the most useful or, at least, the most widely used model, being at the same time the least adequate. “Essentially, all models are wrong, but some are useful” (Box and Draper 1987).

The usefulness of the GM may be improved if the artifacts, including correlations between its parameters upon its usage, are recognized and estimated theoretically, so that the results of application of the GM to data may be checked against such estimates.

The Gompertz model in two dimensions

Isoage lines

Plots showing how log-transformed μ_0 must depend on γ when the mean age, which is assumed to be defined according to the GM, is constant (isoage lines) were used in Tarkhov et al. (2017) to investigate relationships between GM parameters derived from datasets related to *C. elegans* and *H. sapiens* in support of the suggestion that GM parameters are negatively correlated because of the artifact called the

“degenerate manifold of Gompertz fit”. Below the same approach will be used to show, based on data related to mice and humans, that correlations between $\log\mu_0$ and γ are not always reducible to the artifact and may be consistent with either (i) changes in the Makeham term of GMM, which produce the Strehler–Mildvan correlation (SMC), or/and (ii) tradeoffs between vitality and the rate of its decline, i.e. with the compensation effect of mortality (CEM).

To construct the isoage lines shown in Fig. 4, μ_0 values were numerically adjusted to keep the mean age constant upon changes in γ . The linearity of the numerically modeled dependencies of $\log\mu_0$ on γ at defined ages is not strict. However, within the ranges typical for mice (ca. 0.003 to 0.013 days⁻¹), the dependencies may be approximated well with a linear equation: $\lg[\mu_0(\gamma)] = -0.0002A - 2.5732 + \gamma(-0.4347A + 46.61)$, where A is age (days). The equation was found by plotting the tangents of the linear trends of $\lg\mu_0$ versus γ plots at different ages (A) against those ages. The resulting points form a straight line, whose function is put in the round brackets of the above equation.

This approach allows constructing a sort of nomogram for checking empirical correlations between SM parameters against it (Fig. 5). Other theoretical reference regressions in Fig. 5 are obtained by applying GM to data generated according to GGML upon varying C . In this case, the slopes of the regressions of $\lg\mu_0$ on γ are greater than the slopes of the isoage lines (“degenerate manifolds of Gompertz fit”). Reference slopes may be still greater when data are generated by varying the values of γ and, simultaneously, of μ_0 according to a CEM.

Analysis of murine survival data

The numerically constructed relationships were compared with data, which are available at https://phenomedoc.jax.org/ITP1/Data_frozen_public/, on the survival of UM-HET mice used as controls at three research sites, Jackson Laboratories (JL), University of Michigan (UM) and University of Texas UT), in experiments performed during eight different periods. These comparisons might suggest that differences in C are at work in the male mice. At the same time, the female mice, as it may be inferred from the parallelism of the respective regression with the nearest isoage lines, are not subject to the effects of factors that

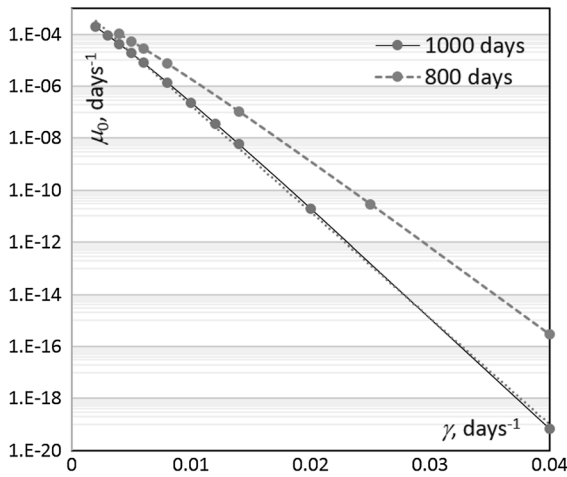


Fig. 4 Semilogarithmic plot of isoage lines showing relationships between GM parameters at two mean ages over a wider range of γ than it is typical for mice. Dots near the 1000-days plot show the linear trend

contribute to the age-independent mortality of male mice.

In reality, the most usual cases where C may be different relate to combinations of datasets where, even if the mean age could be the same at a constant C , GM parameters still vary in a negatively correlated manner because of the noisiness of data related to small samples drawn from a parent population. Modeling shows that relationships between $\log\mu_0$ and γ attributed to only noisiness must be linear within the range of γ typical for mice. Three situations that may erode this linearity are modeled in Fig. 6: increasing C are applied to increasing γ when μ_0 is decreasing simultaneously to make the mean age being 800 days, if not for changes in C ; increasing C are applied to decreasing γ and correspondingly increasing μ_0 within the same ranges; and increasing C values are randomly assigned to different γ and respective μ_0 within the same ranges as in the two above cases.

Only in the first case, the regression slope is definitely different from, i.e. is smaller than, the isoage slope. In the second and third cases, the respective slopes are closer to the isoage slope. The first and the second cases correspond to regular coincidences of higher C with either higher or lower γ . Both situations are unrealistic. The only realistic case is the third one, where there are no regularities in such coincidences. In this case, the slope of respective regression is the most

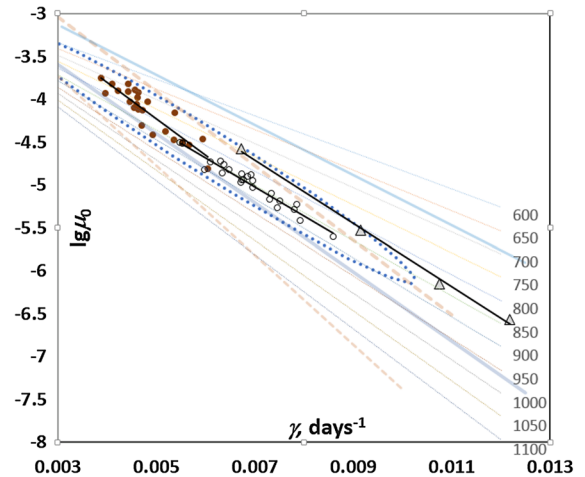


Fig. 5 An isoage nomogram for relationships between $\lg\mu_0$ and γ within ranges typical for murine samples. The thin straight lines correspond to the mean ages indicated at the right ends of the lines. The faint solid lines show regressions of $\lg\mu_0$ on γ obtained by applying GM to data generated by varying C in a GGM at two defined combinations of μ_0 and γ . Notably, the calculated points fit the straight lines exactly even upon negative C and thus are not shown. The faint dashed lines show regressions of $\lg\mu_0$ on γ obtained by assuming that $\lg\mu_0 = X - Y\gamma$ (SMC) at two combinations of the values of X and Y . The points that correspond to real survival data relate to 24 samples of control UM-HET male mice (dots), 24 samples of control UM-HET female mice (circles), and four control samples of C57/BL males (triangles) (Strong et al. 2013). The solid black lines shows the respective trends. The pointed ellipse outlines the 95% CI for all UM-HET mice

close to the isoage slope; however, the scatter of points around it is the highest. The GMM will eliminate such scatter only when applied to modeled data, but not to real data because of their noisiness. Thus, plots in Fig. 5 are consistent with that the age-independent component of mortality affects both males and females, males being more sensitive.

The longer axis of the 95% confidence ellipse for the totality of UM-HET data points in Fig. 5 is parallel to the respective isoage lines, and its length may thus be thought of as a manifestation of “degenerate manifold of Gompertz fit”. However, the totality of data points is not homogenous. UM-HET male and female data form two clearly discernible clusters, which are different from the cluster formed by data points related to C57BL male mice. The C57BL data are distinctive in their large scatter along the isoage direction. This may be a manifestation of relatively small sample sizes and, correspondingly, high noisiness of the primary survival data. The UM-HET data

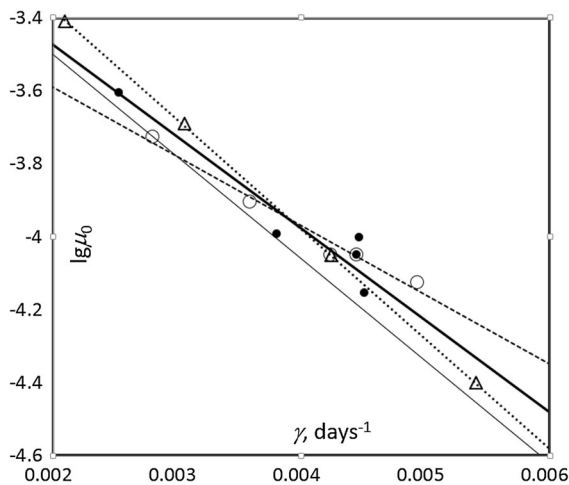


Fig. 6 The effects of changes in C on the positions of data points, which are obtained using the GM, relative to an isoage line. The 800-days isoage line is thin black. Open circles, dashed regression line: Increasing C are added to increasing γ . Triangles, dotted regression line: Increasing C are added to decreasing γ . Black dots, solid regression line: Different C are randomly added to different γ

taken together project onto a no less long segment of any of the nearest isoage lines. However, female data are grouped on the right from the male data. “Degenerate manifold” does not limit the spread of both, male and female, data along an isoage line. The existence of such limits must have some natural basis behind it. In GM terms, females, although their mean age is not much different from that of males (but see below), feature higher initial vitality (robustness, vigor...), which is associated with its faster age-dependent decline; and this is consistent with the CEM.

Other biologically relevant inferences may be drawn from UM-HET data stratified by time, site, and gender. In Fig. 7, each line is a linear trend based on three points related to either male or female UM-HET mice at three study sites in a defined year. The slopes of the trends related to the male mice are greater than even the CEM slopes, not to say about the SMC slopes, in six of eight cases. In two cases, one slope is smaller than and the other is parallel to the isoage slopes. On a whole, the conclusion that the slopes are consistent with the CEM is valid according to even the simplest nonparametric criterion of signs: six pluses, one zero, and one minus.

As to the female mice, their $\lg \mu_0$ versus γ trends are parallel to isoage lines; therefore, nothing more that

artificial is seen in relationships between GM parameters in this case.

In Fig. 8, males and females are compared at each of the study sites.

All vectors in Fig. 8 start from points related to male datasets and end at points, which are indicated with arrowheads, related to the corresponding female datasets (i.e. the same study year and site). Strikingly, all vectors are unidirectional. Almost every vector is directed from a shorter-lifespan isoage line to a longer-lifespan isoage line. Only at UM, two study periods are peculiar in that the median lifespan in females has been reported to be somewhat shorter than in males (Cheng et al. 2019). The only two respective vectors in Fig. 8 are directed from longer- to shorter-lifespan isoage lines, still following the general rightward downward trend. According to the “generate manifold” attitude to GM fits, a transition from one to another mean age may start at any point of the starting isoage line and end at any point of the other isoage line. Even if there are some species- and gender-specific constraints on the possible ranges of GM parameters (which is also beyond inferences from the degenerate manifold attitude), the overlap of the isoage ranges typical for males and females (see Fig. 5) makes it likely that some vectors from females to males may be directed upward to the left rather than downward to the right. Thus, in the present case, the lower μ_0 and correspondingly higher γ values in females compared with males are not artificial, and this suggests that females indeed are generally more robust than males initially, but age at a somewhat higher rate, in conformance with the CEM. Cheng et al. (2019) came to a similar conclusion based on other analytic techniques and expressed with other words.

Analysis of the effects of allegedly calorie restriction mimicking drugs

The control UM-HET datasets at the base of the above analysis accumulated during 10 years in the course of experiments where different substances were tested for their ability to extend lifespan. Among the substances, acarbose was found to be potent in males markedly and in females marginally (Harrison et al. 2019). Figure 9 shows how the results of experiments with acarbose look like in GM2D plots. The longest vector relates to JL females. The vector is, however,

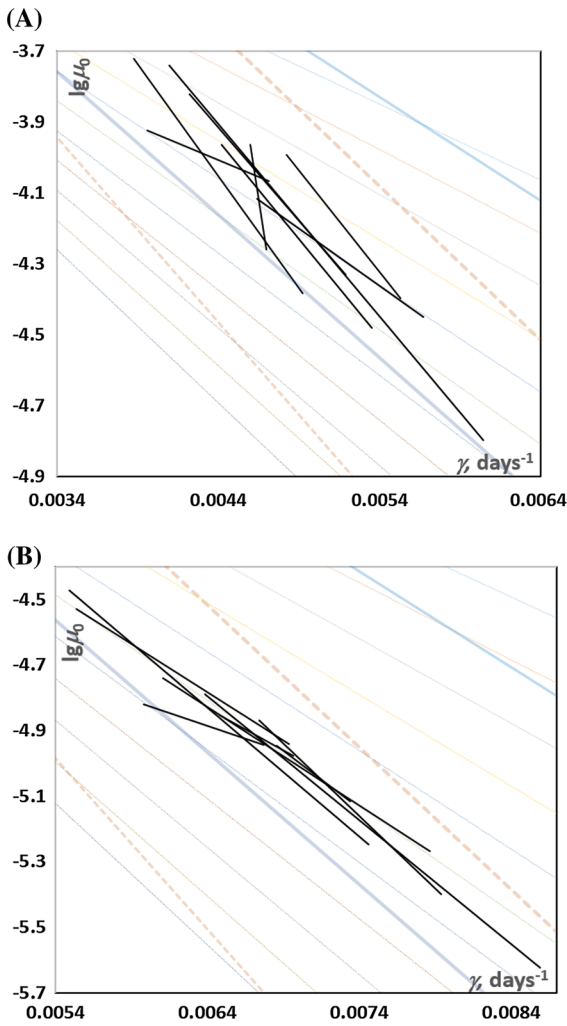


Fig. 7 Trends of differences in μ_0 and γ between study sites. **a** Male UM-HET mice. **b** Female UM-HET mice. Each line is the regression of $\lg \mu_0$ on γ based on three data points related to three different study sites, JL, UM and UT, in a particular study year. Faint and dashed lines are as in Fig. 5

parallel to the nearest isoage line, which means the lack of lifespan differences at vector ends. The two female-related vectors directed from shorter to longer lifespans transverse small age intervals. Only the UT female vector, which spans a greater space between isoage lines, is associated with a significant difference between the respective survival curves according to the log-rank test.

Among male-related vectors, the UM-related one spans a small space between isoage lines and thus is associated with an insignificant increase in the median lifespan. A conspicuous feature of the male-related vectors is that all three are unidirectional. As it was stressed above, nothing in the degenerate fit approach to the SMC suggests that unidirectional differences between mean ages must be associated with unidirectional orientations of the respective vectors in GM2D plots. For example, in the case of JL female mice, points related to two samples having the same mean age have quite different positions on the respective isoage line. Because of the noisiness of data derived from small samples of mice, it is reasonable to expect that a control and an experimental survival datasets must be mapped in a GM2D plot to not particular points, but rather to segments of the respective isoage lines. If the segments are as long as in the case of JL female mice, then the range of the orientations of a vector directed from the control to the experimental dataset may be very broad, the only constraint being that the head of a vector must be directed towards the longer lifespan.

The key issue at this point is the possible lengths of isoage segments related to all possible control and experimental samples of a particular size drawn from the ideal control and the ideal experimental population. A similar issue was encountered above upon

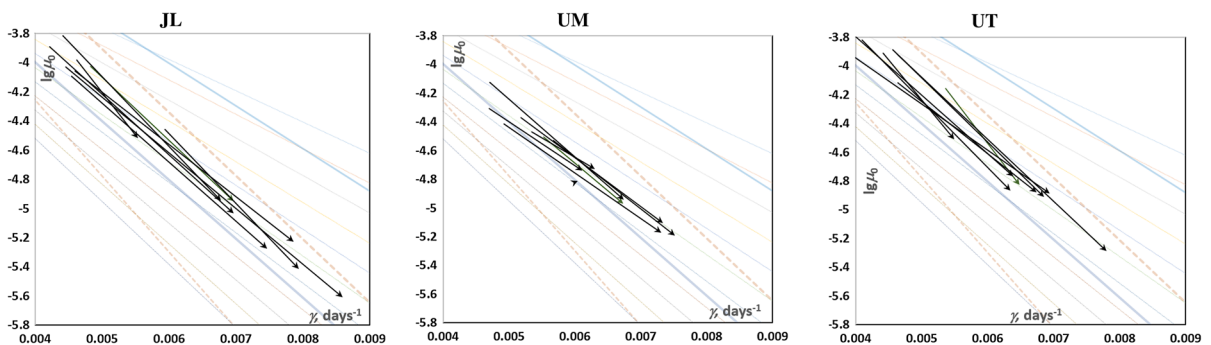


Fig. 8 GM parameters of male versus female mice at three study sites. Vectors are directed (arrows) from males to females

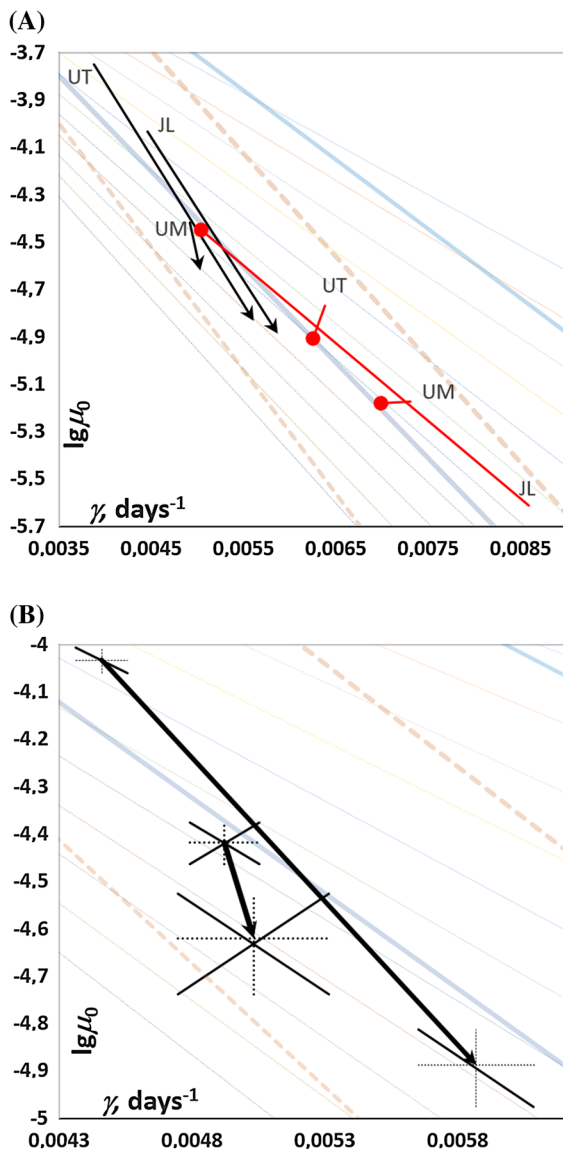


Fig. 9 The effects of acarbose on GM parameters in UM-HET mice. **a** The effects in male and female mice compared. Arrows (males) or dots (females) indicate datasets related to acarbose-treated mice. JL: Jackson Labs; UM: Univ. Michigan; UT: Univ. Texas. **b** A magnified area containing UM and JL males-related data. Dotted crosshairs: 95% CI for GM parameters. Solid crosshairs: 95% CI for position on an isoage (parallel to isoage lines) and for mean ages (almost normal to isoage lines)

comparing the totalities of control male and female UM-HET samples, which form two distinctive clusters, although their regressions of $\lg\mu_0$ on γ are almost identical (Fig. 5). An approach to tackling this issue may be based on the reason that the variances of the

estimates of GM parameters may indicate the length of the isoage segment related to a specific dataset. This is illustrated with crosshairs in the magnified fragment of the GM2D plot (Fig. 9b) where JL and UM control and experimental male data are compared. The dotted crosshairs show the 95% CI of $\lg\mu_0$ and γ estimates. The crosshairs are longer at the experimental points because more uncertainty is associated with the experimental samples, which are smaller than the control ones. The diagonals of the rectangles defined by the dotted crosshairs are presented as thin solid crosshairs. The solid crosshairs that are parallel to the isoage lines give an idea about the lengths of isoage segments where points related to a specific sample may be found. The crosshairs that are almost perpendicular to the isoage lines give an idea about the variances of the respective mean ages. Obviously, the least likely are the positions that are most distant from the points defined by the estimates of $\lg\mu_0$ and γ . Based on these considerations, it is clear that all possible slopes of the JL male vector will still be greater than the nearest isoage and SMC slopes. The age spans related to the control and experimental point do not overlap in this case, which is consistent with significant differences, according to the log-rank test, between the respective survival patterns. The same must be true for the UT male vector. As to the UM male vector, its possible slopes are less definite; nevertheless, their range is biased towards rightward downward directions.

Importantly, if survival is significantly better in experimental than in control animals, and if the slope of the respective vector in a GM2D plot is greater than the nearest isoage and SMC slopes, then CEM must be implicated in the effect; however, an additional SMC-related effect cannot be ruled out. In the cases where the slope of the vector is between the isoage and SMC slope, either CEM or/and SMC effects may be at work; however, none may be regarded for sure as the only possible factor.

In the earlier attempt (Golubev et al. 2018) to use a similar approach for analyzing the results of experimental interventions into survival of mice, regressions of $\ln\mu_0$ on γ based on controls from several experiments with mice of the same strain and gender were used to define reference slopes. It was reasoned that when decreases in μ_0 are associated with increases in γ that are smaller than the reference slopes would suggest, then the increases are within artifactual

ranges and thus are not indicative of a CEM. The present analysis, which is based on constructing of theoretical isoage lines, shows that this reasoning is a misinterpretation. The slopes of experimental regressions or vectors relative to the theoretical slopes is what really matters, and if they are greater than the isoage slopes and, even more, than the SMC slopes, they strongly suggest that there is a CEM behind such findings.

When the direction of a vector pointing to a greater mean age is close to being vertical downward, then only an increased initial survival without an associated CEM must be at work. A further leftward turn of the head of a vector means that decreases in both, the initial mortality and the rate of aging, are implicated in an increase in lifespan, and changes in aging rate become more important as vector orientation approaches to being parallel to the γ axis. This is what is regularly observed in data related to calorie restriction (Fig. 10). In fact, this is the only life-extending intervention whose effects are, especially in females, manifested consistently in this way, which means that decreased aging rate must be responsible, as a rule, for increased lifespan upon calorie restriction. This conclusion is in agreement with analyses using other GM-based techniques (Simons et al. 2013).

The effects of acarbose (Fig. 9) and metformin, rapamycin and aspirin (Fig. 11), which are often qualified, e.g. in Brewer et al. (2016) and Madeo et al. (2019), as drugs that mimic calorie restriction, are manifested in GM2D plots in other ways, which are mostly consistent with the CEM. In its turn, the CEM is consistent with that the drugs reallocate limited body resources from the current resistance to the causes of death towards protecting of functions behind the resistance from their age-associated decline. Anyway, the effects of calorie restriction and of allegedly calorie restriction mimicking drugs look so different in GM2D plots, that the difference warrants attention irrespective of its interpretations suggested herein or elsewhere.

The lack of an effect of a drug on lifespan is manifested in that the respective vector is parallel to the nearest isoage line, as in metformin-treated female mice, although the 129/Sv vector is quite long. However, once again, the effects of metformin are predominantly manifested as vectors directed rightward downward. The degenerate manifold of

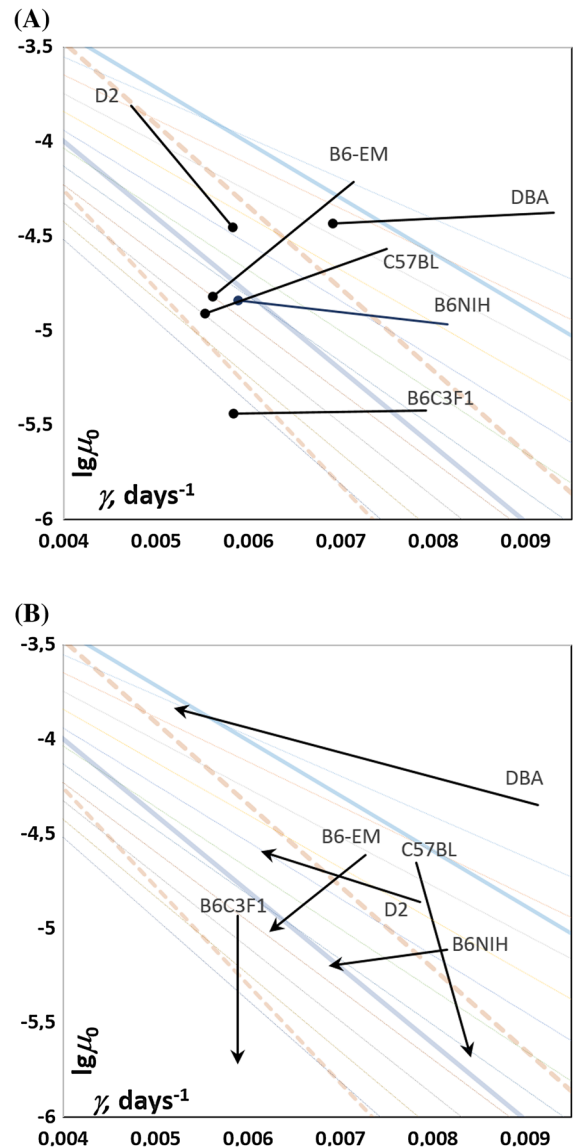
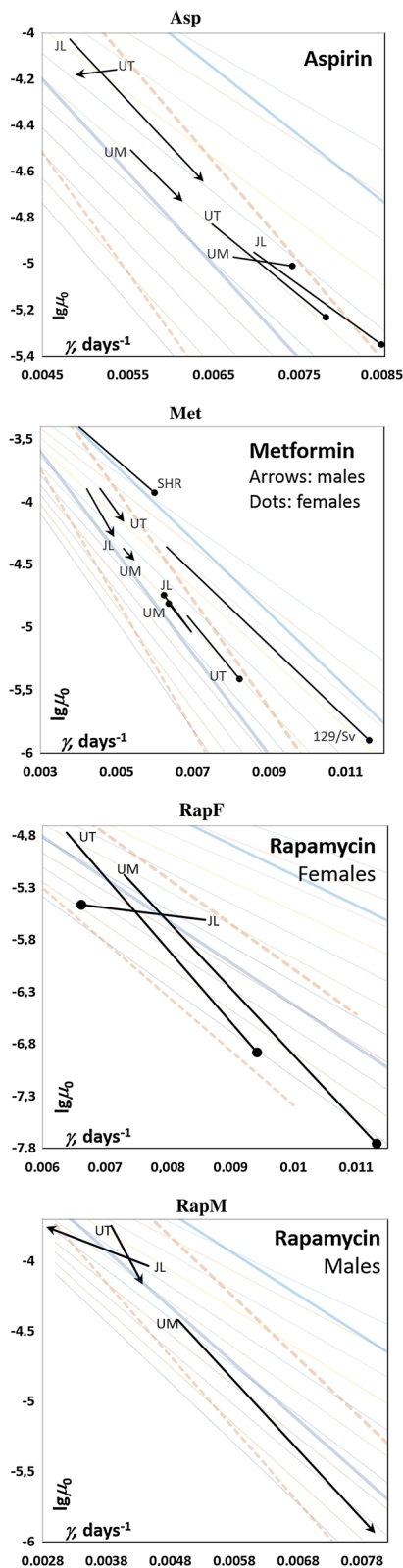


Fig. 10 Calorie restriction in GM2D plots. Dots in A (females) and arrows in B (males) are directed to calorie-restricted mice. DBA and C57BL data are derived from Mitchell et al. (2016). Other designations are adopted from Turturro et al. (1999), where the respective survival curves have been presented

Gompertz fit does not impose such limitations (see above). This may mean the metformin does modify body conditions by increasing the initial vitality at expense of its accelerated decline, which is consistent with the CEM.

When an age intervals spanned by a vector is less than 50 days, the respective effect is usually statistically insignificant, as in aspirin-treated females, in



◀ **Fig. 11** The effects of life-extending drug on GM parameters in GM2D plots. SHR and 129/Sv data are derived, respectively, from Anisimov et al. (2010, 2011)

which case small decreases in lifespan are actually seen in all cohorts. Increases in lifespan are most often associated, once again, with vectors directed rightward downward, whose slopes are greater than the isoage and SMC slopes. With rapamycin, exceptions represented by both male and female UM-HET mice conspicuously relate to the same site, i.e. to JL. The exceptions are still consistent with CEM: decreased aging rate comes at the cost of increased initials mortality.

Taken together, the above analysis of murine survival data suggests that the CEM may be at work upon pharmacological interventions in the lifespan of mice and is responsible for differences in survival patterns between males and females even if there are no differences in their mean lifespans. The effects of CEM being small, they may be easily obscured by artifactual correlations between GM parameters.

Analysis of human mortality data

The small magnitude of CEM effects may be nevertheless significant even in practical terms as concerns human populations. In particular, the causes and significance of the so-called “rectangularization” of human survival curves or of “compression of mortality” are debated (Börger et al. 2018; Cheung and Robine 2007; de Beer and Janssen 2016; Ebeling et al. 2018; Janssen and de Beer 2019; Wilmoth and Horiuchi 1999). Both terms relate to the apparent convergence of ages-at-death to increasingly narrow ranges around ca. 85 years. This effect is observed when human survival patterns in the past and at present in developed countries or in the present-day developed and developing countries are compared. One approach to the effect is based on the attitude to the age-at-death distributions as to manifestations of variances around some evolved species-specific lifespan. The approach implies that reducing the extrinsic age-independent causes of mortality must make an age-at-death distribution increasingly narrow by shrinking its left shoulder. The same may be suggested if preference is given to the alternative approach, which implies that age-at-death distributions are

generated by some patterns of the initial vitality and its age-associated decline. In this case, however, another possible factor is an increase in the initial vitality at the cost of its accelerated age-associated decline, which is nothing else than the CEM.

For tackling this issue in the same way as it was done above with murine survival patterns, a human isoage nomogram has been constructed. Simply extrapolating the murine nomogram to the human ranges of GM parameters is inappropriate because the isoage lines are not linear on large scales (Fig. 4). As illustrated in Fig. 12, points derived from real human datasets do not fall in the range of isoage lines built by the extrapolation of the murine pattern. Calculations carried out using the ranges of GM parameters (day^{-1}) typical for humans yield different estimates of isoage parameters for accommodating human γ and $\lg\mu_0$ (Fig. 12):

$$\mu_0 = -4.18697 + \gamma(-0.4279A + 1115.5),$$

where A is age (NB: days !!!).

Another point is that human, unlike murine, GM parameters are derived here from mortality rather than survival data, and mortality data are not calculated based on age-at-death distributions and the counts of subjects at risk of death (as in Fig. 1), but are downloaded directly from the HMD. With mortality data, the assumptions concerning the age range to be

used are always somewhat arbitrary. To minimize the contribution of the age-independent mortality for treating mortality data according to the GM, shorter intervals of higher ages, e.g. from 60 to 90, are preferable. To estimate better the contribution of the age-independent mortality, longer age intervals should be treated according to the GMM. In what follows, the age ranges chosen for analysis were such that they span the period from the age when mortality starts to increase monotonously (25 years) to the age immediately before the onset of the deceleration of the rate of increase in mortality (90 years). Clearly, age-independent mortality contributes to the overall mortality within this age range. Therefore, GM parameters were extracted from mortality data using both, the GM and the GGM. The results are compared in Fig. 13a.

When GM parameters are derived by applying the GGM to mortality data, μ_0 is somewhat underestimated and γ is overestimated compared with estimates derived by applying the GM. It is no wonder that the vectors from GGM-derived to GM-derived estimates are parallel to the SMC slope. Importantly, either of the two sets of estimates of GM parameters will yield similar conclusions when each of them is used consistently to compare different datasets. Using the GM for this purpose (just to keep continuity with the above analysis of murine data) shows that the slope of the regression of $\lg\mu_0$ on γ related to Swedish women in different years is greater than the SMC slope (Fig. 13b). Using the GGM suggests the same because data points are only shifted along the same regression line without showing deviations from it. Thus, changes in mortality patterns of Swedish women in 1954 through 2014 are consistent with increasing the initial vitality associated with accelerated aging. By contrast, differences between the patterns of GM estimates compared across developed countries, where life expectancies are among the highest in the world, are consistent with differences in the age-independent mortality, which cannot be zero in principle, but may be neglected, as it is done too often.

The slopes of vectors directed from males to females (Fig. 13c) related to the high-life-expectancy countries are greater than the SMC slope, whereas the slope of the vector related to Russia is smaller. This suggests that female versus male differences are consistent with the CEM when the contribution of the age-independent mortality is minimal, and are consistent with differences in the effects of the age-

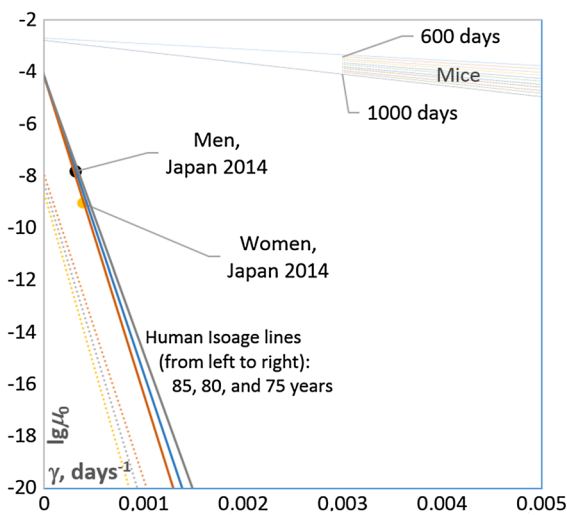


Fig. 12 Comparison of isoage lines in the ranges of GM parameters typical for mice and humans. The series of lines presented with dots is constructed by the direct extrapolation of murine isoage parameters to the human GM range

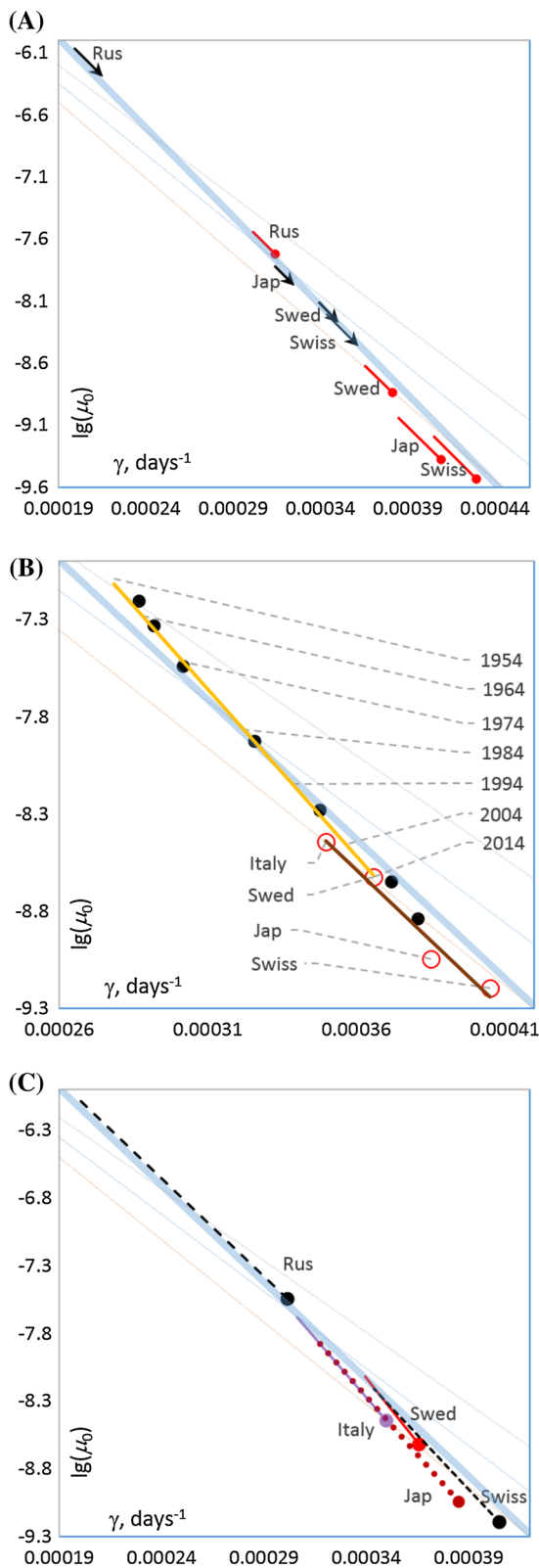


Fig. 13 GM2D plots for human data. Thin diagonals are isoage lines corresponding to the ages (left to right) 85, 80 and 75 years. The thick faint diagonal (SMC) is constructed by applying GM to fit data generated according to GGM by varying C . **a** Vector heads are directed from data points derived with GGM to those derived with GM. **b** The light straight line is the regression of $\lg\mu_0$ on γ related to different years, as indicated, in Swedish women. The dark line is the analogous regression for four different countries (open circles) in 2014. Both lines are constructed using GM to fit mortality data. Black dots show the results of applying GGM to the estimates of $\lg\mu_0$ and γ in Swedish women in different years. **c** Vector heads are directed from men to women

independent mortality on men and women when its contribution to total mortality is relatively high.

Discussion

Taken together the above analyses suggest that the causes of correlations between GM parameters are not limited to the omnipresent “degenerate manifold of Gompertz fit” suggested in Tarkhov et al. (2017). Obscured by this artifact, there may be the effects of the age-independent mortality, which are manifested as the original Strehler–Mildvan correlation (SMC), and of the compensation effect of mortality (CEM). These two types of effects are differentially manifested when survival/mortality data are treated according to the Gompertz or Gompertz–Makeham model (GM or GMM) in the way suggested herein. Being straightforwardly interpreted in terms of the generalized Gompertz–Makeham law (GGML), the parameters of both models have clear-cut biological meanings. It is not so easy to interpret the SMC and the CEM according to the increasingly dominant approach, which is neatly presented in Stroustrup (2018). The approach implies that the GM and the GMM are just handy statistical tools having no biological background. They may be more or less fit to a particular survival/mortality dataset and easily substituted with Wald, or Weibull, or lognormal, or whatever parametric model showing a better fit.

However, the lognormal model is as well applicable to time-to-death distributions in cases where there is no sense in talking about aging at all, such as the distributions of times from diagnosis to death of cancer patients (Chapman et al. 2013; Royston et al. 2008) or from birth to death in highly cancer prone

Her2/neu female mice, which die of mammary cancer long before the consequences of aging proper can make a significant contribution to mortality (Golubev et al. 2018). Thus, the alternative models are consistent with that the lifespan and its variance, rather than the initial vitality and its subsequent decrease, are the basic determinants of survival patterns. Ultimately, the alternative models imply that aging is a process that culminates in death at a specific age or leads to death at a specific rate (either the age or the rate featuring some variability), so as, e.g., the growth of a tumor leads to death. In the final account, a program whose implementation culminates in death emerges as the basic concept of aging. Although such models may be applicable to some specific ecological conditions, they are, generally speaking, incompatible with the basics of the evolutionary theory (Kowald and Kirkwood 2016). However, thinking of aging as the implementation of a program is attractive by suggesting that the program may be slowed down, switched-off or reversed.

The effects of both the SMC and the CEM upon decreasing C and μ_0 , respectively, are manifested in survival curves as initially less steep declines followed by increasingly steeper declines. In both cases, survival curves become looking increasingly rectangular, and the peaks of age-at-death distributions become sharper. Certain combinations of changes in GMM parameters can make a survival curve looking stretched or compressed along the timescale, and make an age-at-death distribution looking more narrow or broad or shifted along timescale.

The same changes may be described using the increasingly prevalent terms such as “survival curve scaling”, “temporal scaling of survival distributions”, “mortality compression”, “mortality delay”, “survival curve rectangularization” (Basellini et al. 2018; Börger et al. 2018; Cheung and Robine 2007; de Beer and Janssen 2016; Ediev et al. 2019; Wrycza et al. 2015). These terms are essentially descriptive at best and may be misleading at worst being compatible with the idea that aging is programmed and being indeed used to support this idea, as e.g. in Markov et al. (2016) and Shilovsky et al. (2016, 2017).

All of the effects described with the above terms may be interpreted in terms of the GGML, which is, basically, the law of translation of physiological changes that determine the ability to resist the causes of death into changes in mortality. The mode of the

translation is exponentiation. Because of that, any time trajectory of physiological decline will eventually make mortality so high that it will exhaust within a finite time any of finite cohorts, of which a population, even an infinite one, is comprised.

Qualifying the GGML as a law touches upon the debatable issue of whether there are laws at all in biology (Hamilton 2007; Weiss and Buchanan 2012). The GGML is suggested to be a one (Golubev 2009). Having emerged upon the origin of life from the physicochemical world, the law afterwards was an inevitable independent factor, with which the biological evolution had to cope with, rather than it was “molded by natural selection”, by the words once applied to senescence in Hamilton (1966). Molded indeed, with account for the factors envisioned in the antagonistic pleiotropy and disposable soma theories of aging, were the different embodiments of the GGML, including the one related to humans.

However, the GGML, so as any law of nature, may be observed exactly only by ideal entities, which in the present context are infinite cohorts of identical living objects existing under constant conditions. This is somewhat analogous to the laws of classical thermodynamics, which are observed exactly only by ideal gases experiencing infinitely slow changes. In any real situation, any basic law of nature must be modified by accounting for additional forces and by introducing of additional assumptions and respective parameters. Models result from such modifications in the final account. However, in physics, unlike biology, this does not mean that laws may be disregarded or must be refuted.

In a less esoteric context, the present analysis touches upon several still controversial issues.

Should the age-independent mortality be taken into account in analyzing the current changes in human lifespan? Comparing differences between men and women in Russia and in several countries featuring the highest life expectancies shows that, in Russia, men compared with women are more vulnerable to the age-independent mortality, whereas in high-life-expectancy countries, differences between men and women are attributable to the CEM (Fig. 13c). However, differences in the age-independent mortality are responsible for differences between survival patterns in the present-time high-life-expectancy countries (Fig. 13b), where “extrinsic” or “accidental” mortality is believed to be negligible.

Do females live longer because they age more slowly than males do? It follows from the present analysis that CEM is at work as concerns sex differences in mice. The causes of why women live longer than men are debated (Austad and Fischer 2016; Crimmins et al. 2019). Recent analysis of demographic data (Lenart et al. 2018) suggests that women are more robust initially at the cost of accelerated aging (CEM). The present analysis confirms this in the case of high-life-expectancy countries; however, the age-independent mortality is still a major determinant of gender differences in survival patterns in Russia.

Do lifespan-increasing pharmacological interventions slow down the rate of aging? No, they do not.

Is it true that decreases in the rate of aging were responsible for the general increases in human longevity? It was, upon the evolutionary emergence of humans from hominids. It was not afterwards. Earlier, longevity was increasing due to decreases in the age-independent mortality. Lately, the initial vitality was increasing, at the cost of accelerated aging according to the compensation effect of mortality interpreted in terms of the generalized Gompertz–Makeham law. The law inherited by life upon its origin from the physicochemical world has been being ever since a factor for evolution to cope with and continues to impose constraints on possible changes in the survival patterns of the species *Homo sapiens*.

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