The Strehler-Mildvan correlation is a degenerate manifold of Gompertz fit

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Abstract

Gompertz empirical law of mortality is often used in practical research to parametrize survival fraction as a function of age with the help of mere two quantities: the Initial Mortality Rate (IMR) and the Gompertz exponent, inversely proportional to the Mortality Rate Doubling Time (MRDT). The IMR is often found to be inversely related to the Gompertz exponent, which is the dependence, commonly referred to as the Strehler-Mildvan (SM) correlation. In this Letter, we address fundamental uncertainties of the Gompertz parameters inference from experimental Kaplan-Meier plots and show, that a least squares fit often leads to an ill-defined non-linear optimization problem, which is extremely sensitive to sampling errors and the smallest systematic demographic variations. Therefore, an analysis of consequent repeats of the same experiments in the same biological conditions yields the whole degenerate manifold of possible Gompertz parameters. We find, that whenever the average lifespan of species greatly exceeds MRDT, small random variations in the survival records produce large deviations in the identified Gompertz parameters along the line, corresponding to the set of all possible IMR and MRDT values, roughly compatible with the properly determined value of average lifespan in experiment. The best fit parameters in this case turn out to be related by a form of SM correlation. Therefore, we have to conclude, that only the combined property, such as the average lifespan in the group, rather than the IMR and MRDT values separately, may be reliably determined experiments, even in perfectly homogeneous animal cohort due to its finite size and/or low age-sampling frequency, typical for modern high-throughput settings. We support our findings by careful analysis of experimental survival records obtained in cohorts of *C. elegans* of different sizes, in control groups and under the influence of experimental ther-

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apies or environmental conditions. We argue, that since SM correlation may show up as a consequence of the fitting degeneracy, its appearance is not limited to homogeneous cohorts only. In fact, the problem persists even beyond the simple Gompertz mortality law. We show that the same degeneracy occurs exactly in the same way if a more advanced Gompertz-Makeham aging model is employed to improve the modeling. We explain how SM type of relation between the demographic parameters may still be observed even in extremely large cohorts with immense statistical power, such as in human census datasets, provided that the systematic historical changes are weak in nature and lead to a gradual change in the mean lifespan.

Keywords: aging parameters, Gompertz law, Gompertz-Makeham law, Strehler-Mildvan correlation, fitting parameters degeneracy, biostatistics

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1. Introduction

Aging in most animals, including humans, leads to exponential increase of mortality $M(t) = M_0 \exp(\alpha t)$ with age t, the dependence commonly referred to as the Gompertz law [4]. It has been long assumed, based on both empirical evidence and theoretical arguments, that the Initial Mortality Rate, M_0 or IMR, and the Gompertz exponent slope, α, are universally related by the Strehler-Mildvan (SM) correlation

$$\log M_0 - \ln K = -\alpha/B. \tag{1}$$

Here K and B are constants, introduced in [8], and α is inversely proportional to the Mortality Rate Doubling Time (MRDT). SM correlation is not a trivial fact and may not be universal. For instance, it is inconsistent with a recently observed scaling law in [9], which implies that the surviving fractions of *C. elegans* worms under different environmental conditions or mutants with different lifespans can be cast into a universal function of a properly rescaled dimensionless age. This is, indeed, remarkable, since the experiment establishes the proportionality between IMR and α, rather than that of $\log M_0$ and α, as would be predicted by Strehler and Mildvan. To make sense of the apparent contradiction, we re-analyzed the problem of the Gompertz parameters inference from experimental survival fraction curves (lifetables).

We start by addressing the performance of a least squares fit method and immediately find, that it may easily lead to an ill-defined non-linear optimization problem, which is extremely sensitive to sampling errors and the smallest systematic demographic variations. We find, that whenever the average lifespan of species greatly exceeds MRDT, small variations in survival records are amplified and produce large deviations in the identified Gompertz parameters along the line, corresponding to the set of all possible IMR and MRDT values, roughly compatible with the properly determined value of the average lifespan in the experiment. The best fit estimates in this case turn out to be related by a

form of SM correlation. Therefore, we have to conclude, that under most common circumstances the combined property, such as the average lifespan, rather than the IMR and MRDT values separately, can only be reliably determined in experiments with a homogeneous animal cohort due to its finite size and/or a low age-sampling frequency, typical for modern high-throughput settings.

We support our theoretical findings by careful analysis of experimental survival records obtained in a recent series of experiments with *C. elegans* under the influence of lifespan modifying treatments or environmental conditions [12, 9]. The data provides a unique opportunity since, in contrast to similar human mortality records, the laboratory experiments are well controlled for genetic and environmental variations. We start by sampling the worms life histories from the control groups into cohorts of various size and show that the immediately apparent SM correlation in such perfectly homogeneous cohorts is the direct consequence of the hyper-sensitivity of the least squares fit procedure exacerbated by a large sampling error due to insufficiently large number of the animals in the cohorts. In agreement with our theoretical considerations, we find that it is easy to produce a reliable estimate for the average lifespan of such small and homogeneous cohorts, yet it is considerably more difficult to yield reliable estimates of the Gompertz parameters unless a Kaplan-Meier plot is extremely smooth to infer a unique solution.

We conclude observing, that since SM correlation may show up as a consequence of the Gompertz fit degeneracy, which is closely related to the extreme exponential nature of mortality, its appearance may not be limited to homogeneous cohorts only. We show that the same degeneracy along with the extreme dependence of the parameter estimates remains to be an issue with more advanced, such as e.g. the Gompertz-Makeham, models. Finally, we explain how the SM type of relation between the demographic parameters may persist even in extremely large cohorts with immense statistical power, such as in human census datasets, provided that the systematic historical changes are weak in nature and lead to a gradual change in the mean lifespan.

2. The Strehler-Mildvan correlation is a degenerate manifold of the Gompertz fit

To investigate the influence of a factor, such as therapy or a mutation, on aging, one may want to estimate the effects of the experimental design conditions on aging model parameters, such as, for example, commonly used quantities M_0 and α of the Gompertz law. A natural way to achieve the goal is to analyze Kaplan-Meier plots and fit an experimentally observed fraction of the animals surviving by the age t, $N(t)$, onto the model prediction. A typical behavior of the survival fraction is qualitatively depicted in Fig. 1A. Often, the average lifespan, $\bar{t}$, exceeds the MRDT. The survival fraction as a function of age, in this case, drops from 1 to 0 in a short age interval, $\triangle t \sim \alpha^{-1} \ll \bar{t}$, around the mean lifespan $\bar{t}$, so that $N(\bar{t}) \sim 0.5$ and $\bar{t} = t_{1/2}\left[1 + O\left(\triangle t/\bar{t}\right)\right]$. According to the Gompertz law, the mortality at a given age, t, is the exponential function of age, $M(t) = M_0 \exp(\alpha t)$. Accordingly, the fraction of the animals alive by

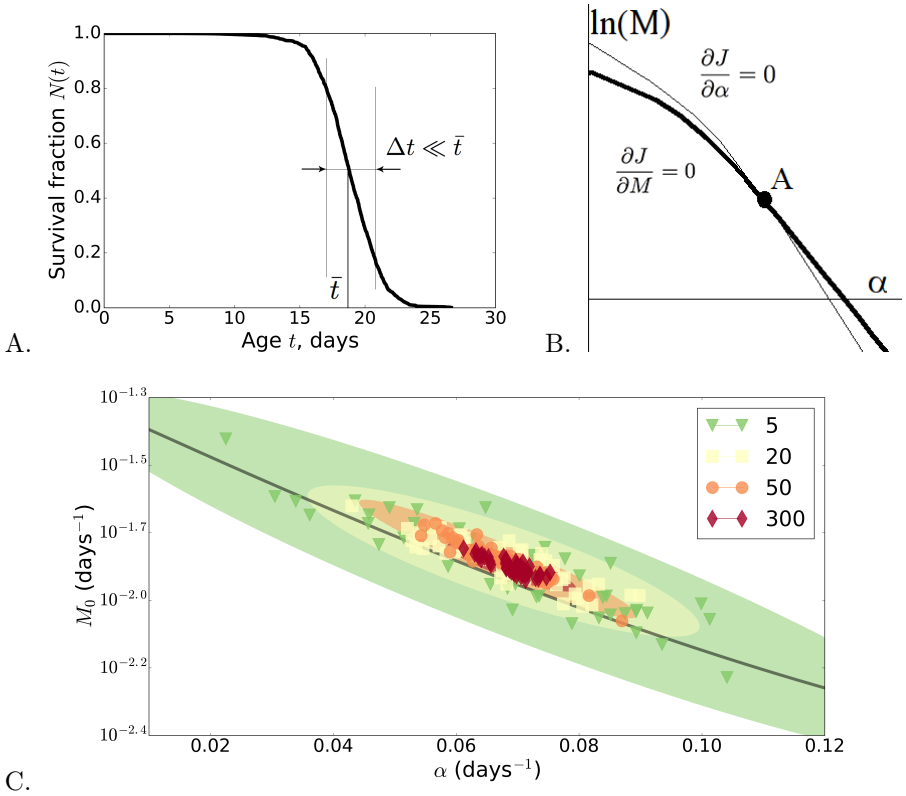


Figure 1: A. The Kaplan-Meier survival fraction for a wild-type control cohort from Stroustrup et al. [9]. The function drops from 1 to 0 in a short age-interval, Δt, usually considerably shorter than the average lifespan $\bar{t}$; B. A graphic solution of Eqs. (3) in $\ln M$ and α plain. The thick and the thin lines correspond to the vanishing derivatives of the objective function J with respect to the parameters M and α, see Eq. (3); C. The Gompertz parameters M_0 and α obtained from the least-squares fit (2) for the sub-groups of the wild-type control animals (the data from 768 control cohorts from [12]). Here the number of randomly chosen cohorts in sub-groups is $N_{coh} = 5, 20, 50$ and 300 (approximately 10 worms in each cohort). The colours differentiate the numbers of cohorts. For every randomly selected sub-group a Kaplan-Meier survival curve is obtained and a random realization of the Gompertz parameters is defined from it. Each dot represents a fitting result obtained using data from a particular randomly selected sub-group of the wild-type control animals. The black line represents the iso-average-lifespan curve for the average lifespan calculated for all wild-type control experiments. The variations in determination of M_0 and α for different random selections of sub-groups allow us to estimate their fitting uncertainty, which is represented graphically by the characteristic guide-to-eye ellipses in M_0 versus α plane.

the same age is given by the expression $N_G\left(t|\alpha, M_0\right) = \exp\left[\frac{M_0}{\alpha}\left(1-e^{\alpha t}\right)\right] = \exp\left[e^{-\Lambda}\left(1-e^{T}\right)\right]$, where $T = \alpha t$ is the dimensionless age and the Gompertz logarithm or curvature, $\Lambda = \log\left(\alpha/M_0\right) = \log\left(1/M\right)$ is expected to be large: for human subjects we have $\alpha\bar{t} \approx \Lambda \approx 10$. Hereinafter we refer to this parameter range as the extreme Gompertizian limit.

One way to fit an experimentally observed dependence $N(t)$ to its Gompertz law estimate is to minimize the mean squared error between expected and observed values of the surviving fraction. Normally, the values of $N(t)$ are known at a series of discrete age-points. To simplify the analysis we will assume, that the number of the observation and the experimental cohorts size are large enough, so that the discrete set of observations $N(t)$ can be viewed as consequent measurements of a smooth function of age. Under the circumstances, the objective function can be represented as the integral

$$J\left(\alpha, M\right) = \int_0^\infty dt\left[N_G\left(t|\alpha, M\right) - N\left(t\right)\right]^2, \tag{2}$$

instead of the sum over all observations, to be minimized with respect to the values of α and M. The procedure can be understood as a standard log-likelihood minimization. The full analysis of the optimization problem is presented in Appendix A. Let us summarize briefly in this section the results most important for the discussion below.

First of all, the best fit Gompertz parameters are solutions of the system of equations

$$\frac{\partial J}{\partial \alpha}(\alpha, M) = \frac{\partial J}{\partial M}(\alpha, M) = 0. \tag{3}$$

A graphical solution is represented in Fig. 1B. The slopes of the lines, representing the solutions of Eqs. (3) at the intersection point differ by a mere factor C_2/Λ^2, with $C_2 = O(1)$ is a constant. For sufficiently long lived species, $\Lambda \gg 1$, and hence the solutions are practically indistinguishable from each other near the intersection point, defining the extremum.

The near collinearity of the directions defined by Eqs. (3) is established in Appendix A, is a consequence of the step-wise nature of the Gompertz survival curve and thus is a signature of a degeneracy of the original inference problem. In Appendix B we show in sufficient details, that should the observed values of $N(t)$ change a little, $N(t) \to N(t) + \delta N(t)$, either due to sampling errors or to minor systematic biological effects, the estimated quantities will also change, but very strongly,

$$\delta\alpha \approx \frac{\Lambda^2}{\bar{t}}\delta N(\bar{t}),\ \delta\Lambda \approx \Lambda^2 \delta N(\bar{t}), \tag{4}$$

respectively. Remarkably, even though the demographic parameters are subject to a large uncertainty separately, the resulting estimates can only vary in a tightly correlated way

$$\delta\alpha \approx \frac{1}{\bar{t}}\delta\Lambda + O(\frac{1}{\Lambda^2}). \tag{5}$$

Eqs. (4) and (5) are the central result of the presented study and highlight extreme sensitivity of the Gompertz fit in Eq. (2) to the slightest variations of the survival fraction. Therefore, instead of a single and well-defined solution, under most common circumstances one rather gets the whole degenerate manifold of possible values, even in the most idealistic case, when the biological conditions are exactly the same for all experimental replicates and the animal groups under investigation are biologically homogeneous. Any minor survival curve variations lead to the estimates deviations, which are strongly amplified along the line in the (α, Λ) plane, defined by Eq. (5) close to the pair of the optimal values, while the fluctuations of the determined parameters greatly suppressed in the orthogonal direction. The appearance of the SM correlation and the instability of the Gompertz parameters estimates are demonstrated by the numerical analysis of simulated cohorts of different size, see Fig. A.4 in the Appendix.

The established degeneracy of the fit has a surprising and unintended consequence. Let us assume that the experiments are repeated in exactly the same conditions. Then, the sampling error is the only source of the uncertainty in the survival records, and, therefore, each of the possible fits corresponds to the correct value of the average lifespan of the demographically homogeneous cohort, $t_{exp} = \int dt N(t)$. Since, in this case, $\bar{t} \approx t_{exp}$ is the same in every calculation, Eq. (5) can be integrated to yield

$$t_G(\alpha, M) \approx t_{exp}, \tag{6}$$

where $t_G(\alpha, M)$ is the Gompertz law prediction for the mean lifespan. This means, that every pair of $M = M_0/\alpha$ and α values, satisfying Eq. (6) can, in principle, be obtained from the analysis of different realizations of the same experiment. To support our conclusion, we checked this sensitivity in a numerical simulation (Fig. A.4). Since $t_{exp} \approx \Lambda/\alpha$ in the Gompertz model in $\Lambda \gg 1$ limit, the degeneracy manifold is approximately defined by $\log M_0 - \log \alpha = -\alpha t_{exp}$, which is nothing else but a form of SM correlation, defined by Eq. (1)! We propose, that the "canonical" form of SM relation (1) can be viewed as an approximation to the "exact" form (6) in the strong Gompertzian limit, $\Lambda \gg 1$. The restriction on Λ is totally unnecessary, though leads to a more tractable form of Eq. (6). A more accurate, but somewhat cumbersome, approximation for the average lifespan $t_G(\alpha, M)$ from the Gompertz law for an arbitrary value of Λ and therefore a more precise form of the expected SM correlation in homogeneous cohorts is derived in the appendix, see Eq. (C.1).

3. Gompertz fit examples in homogeneous populations

To support our theoretical arguments and back up the conclusions below we turn to a set of relevant experimental data. We choose to investigate the Kaplan-Meier plots from two recent high-throughput experiments, addressing effects of a series of pro- [12] and anti- [9] longevity environments or interventions. All the data is obtained in the fully controllable settings in the studies with genetically homogeneous cohorts. The level of control is, of course, totally unmatched in any kind of studies of human mortality.

The first data set [12] describes life histories of 1416 experimental cohorts of the same animals, living under various laboratory conditions. Typically, each of the cohorts consists of about 10 worms. A few of the experiments were repeated to achieve higher significance. 768 or almost half of the cohorts are control. We used the data to estimate the uncertainty of the Gompertz fit parameters in the ideal case of a genetically homogeneous population under identical experimental conditions in a particular laboratory. The data lets us simulate results of a Gompertzian fit in a typical demographic study of an aging population. To do this we choose a subset of N_{coh} cohorts at random from all 768 available aging control cohorts. We used $N_{coh} = 5, 20, 50$ and 300 and calculated the Kaplan-Meier survival plots each time using the subset of the animals and fed it to the least squares fit. The procedure was repeated enough times to get a reliable estimate of the fitting parameters uncertainty for every chosen value of N_{coh}. The results of the computational experiment are presented in Fig. 1C. Every simulated cohort is represented by a dot in the $(\alpha, \log M_0)$ plain. The uncertainty of the estimates is larger for smaller cohorts. To support our conclusion, the obtained result was checked on a numerically simulated data set (Fig. A.4 in Appendix A). This is totally expected if the sampling error is due to the finite number of the animals in the group and is therefore smaller in the larger groups. Even though the Gompertz logarithm $\Lambda \approx 1.3$ is not particularly large, the uncertainty of the fit is amplified along SM correlation line, according to Eq. (5). Therefore, we are able to show that SM correlation may show up even under such an ideal study protocol, when there is no, by definition, any underlying biological difference between the subsequent repeats of the same experiment.

In addition to the life histories of the control cohorts, the data set provides information on life-prolonging effects of a large number of currently used and experimental drugs. We selected the cohorts under the treatments, with the largest number of experimental replicates and, hence, with the least expected degeneracy of the Gompertz parameters. We can assume that for each of the treatments the corresponding cohorts are homogeneous, since all other experimental and genetic conditions are controllable and are exactly the same in all the replicates. We estimated the effects of the fitting degeneracy by selecting 2/3 of the animals in each treatment group at random, and producing the Gompertz parameters from the corresponding simulated Kaplan-Mayer plots. The procedure lets us estimate the uncertainty of the fit and represent it graphically by the characteristic ellipses in M_0 versus α plane in Fig. 2. To compare, we also plotted a red black-edged ellipse corresponding to the same kind of estimate for the largest control group, corresponding to $N_{coh} = 300$ (~ 3000 animals). Remarkably, the degeneracy of the fit is still pretty profound, even for such a reasonably large group. We estimate the relative error in the determination of the Gompertz parameters in the control groups to be about 15%, and hence the Gompertz exponent estimate $\alpha_{wt} = 0.07 \pm 0.01$ days^{-1} for the wild type animals. The iso-average-lifespan curves (SM correlation curves) are plotted and coloured according to the average lifespan in the cohorts as shown in the inset. In agreement with Eq. (4), the calculations demonstrate, using the real world

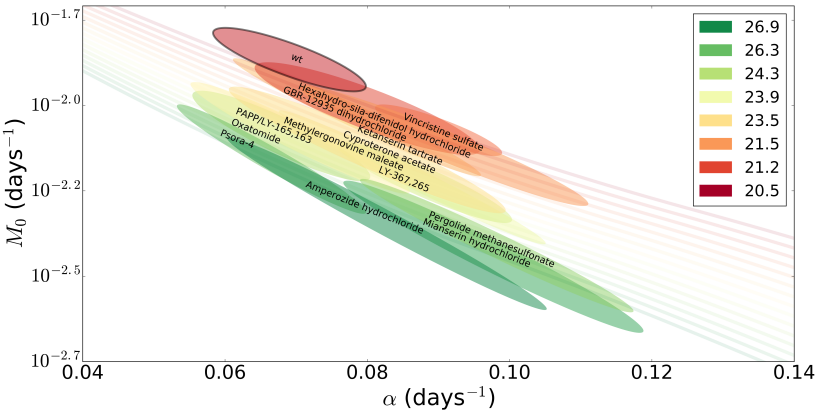


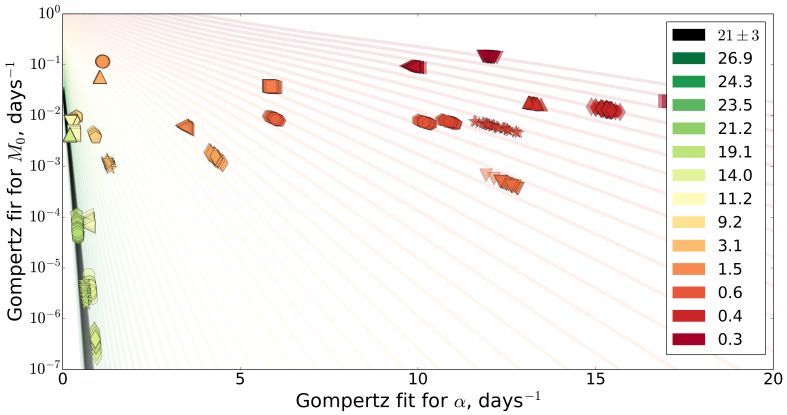
Figure 2: The IMR (M_0) versus the Gompertz exponent slope α estimates obtained with the least-squares fitting procedure using lifetables from the pro-longevity *C. elegans* experiment [12]. To obtain the uncertainty of the Gompertz parameters (depicted by the sizes of ellipses) for each of these drug-treatments the same random selection procedure as in Fig. 1C was employed, but for each drug-treatment 2/3 of all the available cohorts (roughly 20 cohorts, 10 worms in each) were randomly selected to calculate of a particular random realization Kaplan-Meier plot and the corresponding random realizations for the Gompertz parameters. The coloured solid lines correspond to the analytical, asymptotic expressions representing the iso-average-lifespan manifolds defined by Eq. (C.2), where the colours mark the corresponding average lifespans. The position and size of the red black-edged ellipse indicate the best estimates for the Gompertz fit parameters and their uncertainty for the control wild-type experiment with 300 cohorts ($\sim$ 10 worms in each), which corresponds to the red dots in Fig. 1C. The coloured ellipses (from green to red) represent the typical Gompertz parameters with their uncertainty for pro-longevity treatments [12], each of them corresponds to a particular drug-treatment experiment with roughly 30 cohorts ($\sim$ 10 worms in each) on average, which is 10 times smaller than for the wild-type control case with 300 cohorts of roughly 10 worms in each, thus it leads to a much larger uncertainty in the Gompertz parameters estimation (larger ellipses).

data, that small fluctuations of a survival curve even for homogeneous cohorts, due to a finite number of animals in them or a low age-sampling rate, lead to the strong fluctuations of the fitting parameters along SM curves, whereas fluctuations orthogonal to these SM curves are substantially suppressed.

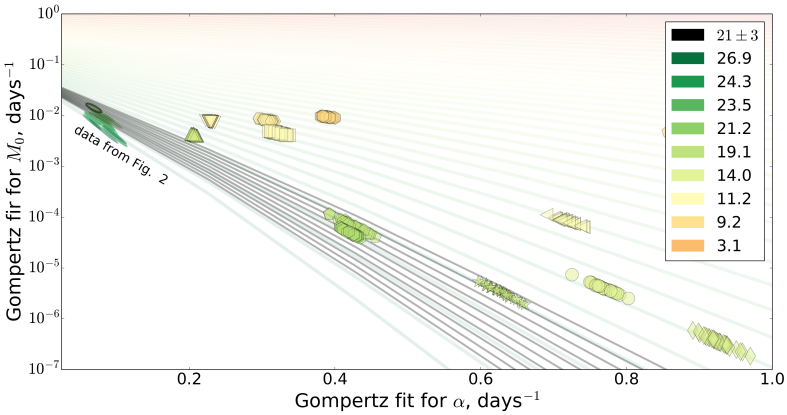
The life histories from the experiment, reported in [9], represent another interesting limit, since the death events are now sampled at a very high frequency (almost every second for several thousands of animals in a single cohort), and therefore the resulting Kaplan-Meier survival plots are extremely smooth and the Gompertz parameter estimates are perfectly reliable. Figs. 3A and B summarize the analysis of the two experiments, [12] and [9] all the data points are plotted on the same graphs and recoloured according to the new global age-pseudocolour scale. Once again, the figures demonstrate that the Gompertz parameters determination uncertainty in every homogeneous cohort manifests itself as fluctuations amplified along the iso-average-lifespan curves, although the error margins are now much smaller due to a dramatically higher precision of the Kaplan-Meier plots. The IMR and Gompertz slope values estimated from [9] appear to be very reliable representations of the underlying biology. Therefore the independence of IMR from α, is significant and hence is the experimental proof of a very non-SM-like relation between the parameters.

4. Conclusions and Discussion

Throughout the paper we employ the least squares fit of survival fraction in the form of Eq. (2) as a practical and mathematically tractable way of the Gompertz parameters inference. A commonly accepted alternative is to produce the fit using the log-transformed values of empirical mortality rate in a data set. The latter possibility looks immediately more attractive from a conceptual viewpoint, but its practical applications may be hindered by the following considerations. The mortality rate needs to be estimated by numerical differentiation of experimental survival lifetables, which are by no means continuous and differentiable, especially late in life. On top of that, the empirical mortality does not necessarily follow the Gompertz law. For example, the risk of death may grow exponentially first and then saturate at a constant level at extreme ages (the phenomenon known as the mortality deceleration, see e.g. [10]). Whenever this happens to be the case in the data, an extra assumption is required to specify the age range, where the Gompertz fit is to be performed. Normally, one restricts the analysis to a reasonable vicinity of the age, corresponding to the average lifespan of animals in the experiment. The procedure suggested here may not be necessarily better, but it is easier to understand using analytical tools, requires only raw experimental data points, a survival curve, and produces a unique answer without extra assumptions. We show, that the minimization of Eq. (2) yields the best Gompertz approximation of the data, using the data points mostly close to the average lifespan in the cohort, and therefore is consistent with the "standard" definition, whenever the Gompertz fit works well.



A.



B.

Figure 3: A. A combined IMR (M_0) versus the Gompertz exponent slope α plot, summarizing the estimates obtained by the least-squares procedure using the *C. elegans* lifetables from experiments [12, 9]. The colours denote the average lifespans in days. Each pair (colour, marker) corresponds to a single realisation of an experimental cohort, to estimate variation of the Gompertz parameters inside the homogeneous cohorts the replicates are obtained by the same reshuffling procedure as for Fig. 1 and 2. The coloured curves are the analytical asymptotic expressions corresponding to the iso-average-lifespan manifolds defined by Eq. (C.2). The black curves are the iso-average-lifespan curves within a narrow interval of lifespans 21 ± 3 days B. A zoom into $\alpha \in [0, 1]$ interval in Fig. 3A. The points from Fig. 2 are also shown, recoloured according to the new age-pseudocolour scale.

The immediate and somewhat surprising conclusion from the presented study is that the two-parametric Gompertz fit under the most common circumstances may easily turn out to be an ill-defined mathematical procedure. Therefore it should be used with a lot of care, since the results are extremely sensitive to minute sampling and experimental errors, even for homogenous cohorts. In fact, we show that the average lifespan in an experiment is often the only reliably obtainable quantity. In turn, the lifespan is a combination of the Gompertz parameters, which appear to end up correlated, whenever the lifespan variation is of the order of MRDT.

We demonstrated, that a form of SM correlation occurs every time when the survival fraction is changed, even by a small bit, either due to sampling errors or true biological reasons. The coordinated change of the IMR and α values, amplified along the line of SM correlation, corresponding to the expected value of the mean experimental lifespan, is a property of the Gompertz survival function in the limit, when the mean lifespan exceeds MRDT. This is especially true in human demographic data, where SM correlation was identified first and gets most of the attention in the literature ever since. A possibility of superficial nature of SM correlation has been already highlighted by L. and N. Gavrilovs in [2, 3], where a more sophisticated aging model, the Gompertz-Makeham version of the mortality law, was invoked to produce a more stable fit. In Appendix D we show, that the Gompertz-Makeham form of mortality law may help fit the experimental data in a different aging regime with a significant age-independent component in mortality rate, whenever it is required. However, the inclusion of the term does not help to improve considerably the stability of the fit in a situation, when an experimental Kaplan-Meier plot is insufficiently sampled due to a limited number of animals in a cohort or a low age-sampling rate, and it would anyway produce a degenerate set of solutions.

Ageing in humans is an extreme case, corresponding to $\Lambda \approx 10$. It should thus be not surprising, that after more than half a century after the publication of the original work [8], the idea of SM correlation and biological picture behind it are deeply rooted in ageing studies (see e.g. [13, 11, 1, 6, 7] as examples of recent works) but there is still no consensus explanation of its origin. Most notably, heterogeneity of ageing populations was recently investigated and proposed to explain SM correlation [11, 13, 5]. For example, [13] observed SM correlation in human mortality data from 1955 to 2003 and showed that its parameters evolve over time. This goes well along with our expectations, since we believe that human demography changes rather slowly over time and for every period of several years any human population can be considered nearly homogeneous with a constant lifespan. Therefore, there must exist an approximate form of SM correlation as was shown in the present study. Needless to say, the lifespan and the quality of environmental conditions, such as the available achievements of medicine, progress steadily in nearly all countries and their effect on the shape of the survival curve and hence on the Gompertz parameters can be observed on a larger timescale as a gradual change of SM correlation parameters. For example, [6] observes a breakdown of the long-term SM trend in the mid 1950s. In Appendix B we show, how a gradual demographic change

produces distortion to the SM correlation plot, which is usually a collection of familiar iso-average-lifespan manifolds, corresponding to the practically homogeneous sub-populations born in the interval of several adjacent years with neither appreciable lifespan nor the outer environment differences. The intra-group differences are greatly amplified along the tangent lines, described by Eq. (5), followed eventually by a fundamental trend in improving quality of life.

We believe, that the outlined fitting difficulty, limited statistical power due to the low age-sampling frequency (once a year) and hence not smooth enough Kaplan-Meier survival plots, together with the narrow distribution of lifespans for the chosen countries led to the error in the Gompertz parameter $\alpha = 0.08 \pm 0.04$ years^{-1} of the order of 50% in the original paper and the initial observation of the linear correlation between α and $\log M_0$ [8]. The dependence is then nothing but the narrow stripe enclosing the Gompertz parameters degenerate manifold corresponding to the average lifespans in the interval 59 ± 9 and 62 ± 9 years for males and females respectively. To grasp the relative narrowness of the human lifespan distributions compare in Fig. 3 the area covered with the black curves, depicting typical lifespans for human population in Strehler and Mildvan [8], re-scaled to the *C. elegans* timescale 21 ± 3 days, with the full range of *C. elegans* lifespans realizations from 0.4 to 27 days Ye et al. [12], Stroustrup et al. [9] presented with the coloured curves in Fig. 3A.

A number of theories, suggesting some physical or biological background behind SM correlation, have been proposed since its discovery. In our work, we come to the conclusion that any biological interpretations should be used cautiously, especially those based on experimental data sets with the poor quality of an experimental Kaplan-Meier survival plot, due to a limited number of animals in a cohort or a low age-sampling rate. Otherwise, one might misinterpret the spurious SM correlation between the Gompertz parameters in homogeneous cohorts (i.e. an iso-average-lifespan manifold in the Gompertz parameters plane) as the actual dependence of MRDT on IMR, whereas to obtain the real relation between these parameters one should rely only on sufficiently large data sets with high quality experimental survival plots measurements. Our analysis still leaves the door open for an existence of a correlation between the the demographic parameters. It still may be the case that the IMR and MRDT are indeed related in a more sophisticated way, which has nothing to do with a linear SM correlation, as it may be seen from the example in Fig. 3 (see the analysis in Stroustrup et al. [9]). We are leaving these considerations for a future research.

Acknowledgements

We thank Prof. Petrascheck, Prof. Fontana and Nicholas Stroustrup for providing the raw survival data, the experimental lifetables from [12, 9]. We thank Ivan Molodtsov, Natalia and Leonid Gavrilovs, Aubrey de Grey for helpful discussions, Boris Zhurov for help with visualization software, Evgeny Getmantsev for proofreading. This work was supported by Gero LLC.

Appendix A. SM correlation in homogeneous cohorts is a degenerate manifold

For homogeneous cohorts in the derivation below the average lifespan is supposed to be constant, which is usually the case in experiment, the case of systematic variations in the survival curve changing the average lifespan is considered in Appendix B.

Let us start with the solution for the regression problem in Eq. (2), which can be found from the minimum conditions, $\partial J/\partial\alpha = 0$ and $\partial J/\partial M = 0$, where $M = M_0/\alpha$, $\Lambda = \log(\alpha/M_0) = \log(1/M)$. Using the relations $N_G = \exp(M(1-e^{\alpha t}))$, $\partial N_G/\partial\alpha = (t/\alpha)\partial N_G/\partial t$, and $\partial N_G/\partial M \approx (\alpha M)^{-1}\partial N_G/\partial t$, we obtain:

$$\frac{\partial J}{\partial\alpha} = \int_0^\infty dt\,[N_G(t) - N(t)]\,\frac{t}{\alpha}\frac{\partial N_G}{\partial t}, \tag{A.1}$$

and

$$\frac{\partial J}{\partial M} = \frac{1}{\alpha M}\int_0^\infty dt\,[N_G(t) - N(t)]\,\frac{\partial N_G}{\partial t}. \tag{A.2}$$

Both $N(t)$ and $N_G(t)$ are step-like functions. In the extreme Gompertzian limit we approximate, $N(t) \approx \theta(\bar{t} - t)$ and $N_G(t) \approx \theta(t_G - t)$. It follows immediately from Eqs. (A.1) and (A.2) that up to terms with a relative error $\sim \triangle t/\bar{t}$, both conditions are equivalent and yield $t_G \approx \bar{t}$. This isa form of correlation between the Gompertz fit parameters:

$$\alpha\bar{t} \approx \Lambda.$$

The equation, of course, holds only if $\Lambda = \ln(\alpha/M_0) \gg 1$, for smaller Λ the precise and much more cumbersome Eq. (C.2) must be used. It can be generalized approximately to any values of the parameter Λ in a form

$$\alpha\bar{t} = \ln\left(1 + C_1 e^{\Lambda}\right), \tag{A.3}$$

where $C_1 \sim 1$.

Both expressions in the square brackets Eqs. (A.1), (A.2) and also the derivative $\partial N_G/\partial t$ behave as sharp peaks located at $t \approx \bar{t}$. Let us note that next to the intersection point A both curves, corresponding to the zero derivatives Eqs. (A.1), (A.2), $i = 1, 2$ behave as $\alpha - \alpha_A \approx k_i(M - M_A)$. The relative difference of slopes is invariant under transformations of variables, for example, for $t_G \approx \ln(1/M)/\alpha$, $\alpha - \alpha_A \approx K_i\left(t_G - t_G^A\right)$, where $K_i = k_i\left(dM/dt_G\right)_A$ we get

$$\xi = \frac{K_1 - K_2}{K_1} = \frac{k_1 - k_2}{k_1}. \tag{A.4}$$

To estimate this difference let us consider a steep survival function $N(t) = \theta(\bar{t} - t)$, then the first equation for the α derivative (A.1) can be rewritten as

$$J_1 + \bar{t}\int_0^\infty dt\,[N_G(t) - N(t)]\,\frac{\partial N_G}{\partial t} = 0,$$

where

$$J_1 = \int_0^\infty dt \left[N_G(t) - N(t)\right](t - \bar{t}) \frac{\partial N_G}{\partial t} =$$

$$= -\frac{1}{2} - \frac{1}{2}\int_0^\infty dt N_G + \int_0^{\bar{t}} dt N_G^2.$$

As a result, this equation with quadratic in $1/\Lambda^2$ precision reads

$$\alpha \approx \frac{1}{\bar{t}} \ln\left(1 + \frac{\ln 2}{M} + \frac{0.86}{M \ln M}\right) \approx$$

$$\approx \frac{1}{\bar{t}} \ln F \cdot \left(1 - \frac{1.2}{\Lambda^2}\right),$$

where the formula $\bar{t}_G = \frac{1}{\alpha}(\Lambda - \gamma)$ was used to get the relation $\ln F \approx \Lambda$.

The second equation for the M derivative (A.2) takes the form $N_G(\bar{t}) = 1/2$ that gives the relation similar to Eq. (A.3):

$$\alpha = \frac{1}{\bar{t}} \ln F, \; F = 1 + \frac{\ln 2}{M} \tag{A.5}$$

Therefore, the two solutions of the optimization problem in Eqs. (A.1), (A.2) are nearly equal $\frac{\partial J}{\partial \alpha} \propto \frac{\partial J}{\partial M}$ with the precision $\sim O\left(1/\Lambda^2\right)$ and the difference between the slopes of two solutions at the intersection point in Eq. (A.4) is

$$\xi \sim \frac{1}{\Lambda^2}.$$

It means that two curves $\log M(\alpha)$ given by Eqs. (3) goes very close to each other near an intersection point as qualitatively depicted in Fig. 1B. Due to this degeneracy of the solutions, any small perturbation to the survival function leads to large fluctuations in response along SM correlation direction (i.e. along iso-average-lifespan curves), which was simulated numerically in Fig. A.4.

Appendix B. Extreme sensitivity of the Gompertz fit estimates with respect to the survival plots variations

If a survival curve changes systematically in such a manner, that the average lifespan is not constant, for example the average human lifespan has been growing slowly over decades and centuries following a fundamental trend in improving quality of life and available medicine, one cannot consider such a population as homogeneous on a large timescale, but only on small time-intervals, for example, a decade for humans while demographic parameters are nearly constant. A more thorough examination of the Gompertz fitting procedure in this case should be considered.

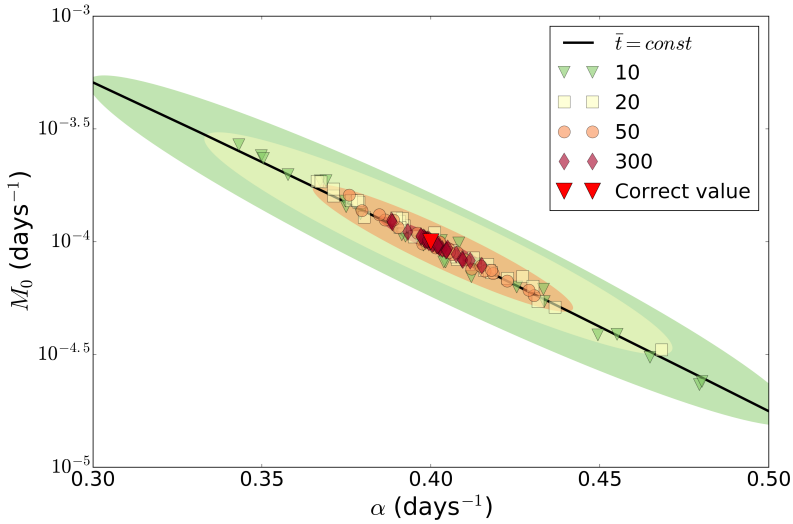


Figure A.4: The Gompertz parameters M_0 and α estimates obtained from the least-squares fit (2) for simulated cohorts with sizes $N = 10, 20, 50$ and 300. The colours differentiate the sizes of cohorts. For every simulated cohort a Kaplan-Meier survival curve is obtained and a random realization of the Gompertz parameters is defined from it. Each dot represents a particular realization. The black line represents the iso-average-lifespan curve for the average lifespan used in this numerical simulation. The variations in determination of M_0 and α for different random realizations of noise is represented graphically by the characteristic guide-to-eye ellipses in M_0 versus α plane.

From the M derivative in Eq. (A.2) after integration we get

$$-\frac{1}{2}-\int_0^\infty dtN\left(t\right)\frac{\partial N_G}{\partial t}=0. \tag{B.1}$$

For infinitesimally small, but systematic changes in the survival fraction $\triangle N\left(t\right)$:

$$N\left(t\right)=N_0\left(t\right)+\triangle N\left(t\right), \tag{B.2}$$

the average lifespan also changes slightly. For the sake of simplicity, we consider again the case of a steep survival fraction $N_0\left(t\right)=\theta\left(\bar{t}-t\right)$, then from Eq. (B.1):

$$N_G\left(\bar{t}\right)\approx\frac{1}{2}-\eta, \tag{B.3}$$

where $\eta=\int_0^\infty dt\triangle N\left(t\right)\frac{\partial N_G}{\partial t}$, $\quad|\eta|\ll 1$. Note that function $\frac{\partial N_G}{\partial t}$ is a narrow peak of the width Δt that resides next to the initial average lifespan $\bar{t}=t_0\approx\frac{\Lambda}{\alpha}$, where for human populations $\Lambda=\log\left(\alpha/M_0\right)=\log\left(1/M\right)\sim 8\div 10$. For $\triangle N\left(t\right)$ which is a slowly varying function on a time-interval Δt, it follows that $\eta\approx\triangle N\left(t_0\right)$.

From Eq. (B.3) we obtain the first curve equation:

$$\alpha=\frac{1}{\bar{t}}\ln\left(1+C_1e^{\Lambda}\right)\approx\frac{1}{\bar{t}}\ln\left(C_1e^{\Lambda}\right), \tag{B.4}$$

where $C_1=\ln\left(\frac{2}{1-2\eta}\right)\approx C_1^{(0)}+2\eta$ and $C_1^{(0)}=\ln 2$. Similarly, from the α derivative in Eq. (A.1) we get the second curve equation

$$\alpha\approx\frac{1+\beta}{\bar{t}}\ln\left(C_2e^{\Lambda}\right), \tag{B.5}$$

where $|\beta|\sim 1/\Lambda^2\ll 1$ and $C_2=C_2^{(0)}+A\eta$, $C_2^{(0)}\sim 1$, $|A|\sim 1$.

To find α and Λ after the perturbation $\Delta N(t)$ to the survival curve one should solve the system of two curve equations Eqs. (B.4) and (B.5), i.e. find the intersection point of these two curves. The solution is

$$\Lambda\approx\frac{1}{\beta}\ln\left(\frac{C_1}{C_2}\right)\approx\Lambda_0+\triangle\Lambda, \tag{B.6}$$

$$\alpha\approx\frac{1}{\bar{t}\beta}\ln\left(\frac{C_1}{C_2}\right)=\alpha_0+\triangle\alpha, \tag{B.7}$$

where $\Lambda_0=\frac{1}{\beta}\ln\left(\frac{C_1^{(0)}}{C_2^{(0)}}\right)$, $\alpha_0\approx\frac{1}{\bar{t}\beta}\ln\left(\frac{C_1^{(0)}}{C_2^{(0)}}\right)$, $\triangle\Lambda=\frac{B}{\beta}\eta$, $\triangle\alpha=\frac{B}{\bar{t}\beta}\eta$ and $|B|\sim 1$.

From the definition of the average lifespan from a survival curve $N(t)$

$$\bar{t}=\int_0^\infty dtN\left(t\right), \tag{B.8}$$

it follows that the average lifespan alters after the perturbations by a value

$$\triangle\bar{t} = \int_0^\infty dt \triangle N(t). \tag{B.9}$$

If we consider survival curves for homogeneous cohorts $N(t) = N_0(t) + \Delta N(t)$, it is natural to assume that $\triangle N(t)$ stands for a random measurement noise, which does not change the mean lifespan. In this case $\triangle\bar{t} = 0$ and SM relation between $\triangle\Lambda = \Delta \log(\alpha/M_0)$ and $\triangle\alpha$ follows from Eqs. (B.6) and (B.7)

$$\triangle\alpha = \frac{1}{\bar{t}}\triangle\Lambda \tag{B.10}$$

If there is a systematic change in a survival function, so that $\triangle\bar{t} \neq 0$ and the combined system of Eqs. (B.6), (B.7) and (B.9) should be considered. It follows from Eq. (B.10) that the slope $1/\bar{t}$ changes. It means that α and Λ go along another curve and therefore the Strehler-Mildvan relation fails.

Let us consider this property in more detail on the following peculiar example of the time dependence Eq. (B.2):

$$\triangle N(t) = \lambda \left[N_1(t) - N_0(t)\right],$$

where $0 < \lambda < 1$. So, $N(t) = N_0(t)$ at $\lambda = 0$, $N(t) = N_1(t)$ at $\lambda = 1$. Let us change λ by a small value $\triangle\lambda$. From Eqs. (B.6), (B.7) and (B.8) we get:

$$\bar{t}(\lambda) = \bar{t}_0 + \lambda\triangle\bar{t}, \quad \triangle\bar{t} = \bar{t}_1 - \bar{t}_0, \tag{B.11}$$

$$\eta \approx \triangle\lambda Q,$$

$$Q = N_G(\bar{t}_1) - N_G(\bar{t}_0) \approx \exp\left(-Me^{\alpha\bar{t}_1}\right) - \exp\left(-Me^{\alpha\bar{t}_0}\right),$$

$$\begin{cases} \frac{d\Lambda}{d\lambda} = D\Lambda^2 Q & , \\ \frac{d\alpha}{d\lambda} = \frac{D\Lambda^2}{\bar{t}(\lambda)} Q & , \end{cases} \tag{B.12}$$

where $|D| \sim 1$.

For $|\triangle\bar{t}| \ll \bar{t}_0$ from Eq. (B.12) it immediately follows that $\alpha = \Lambda/\bar{t}_0 = 1/\bar{t}_0 (\log\alpha - \log M_0)$, i.e. nothing but the Strehler-Mildvan correlation. It is important to realise that both $\bar{t}_0$, and $\bar{t}_1$ are specific to experimental conditions. It is impossible to calculate these values explicitly without a rigorous mathematical description of these conditions. It is clear that for large changes in lifespan $|\triangle\bar{t}| \gtrsim \bar{t}_0$ the Strehler-Mildvan correlation fails, that was shown in the present paper on the experimental data for *C. elegans* Stroustrup et al. [9], where the change in the average lifespans was large enough.

Appendix C. The Gompertz iso-average-lifespan curve

We have proven above, that the only parameter which is really robustly optimized by any gradient descent method in a homogeneous cohort is the average lifespan, which for the Gompertz law is written accurately as

$$\bar{t}_G = \int_0^\infty dt N_G = \frac{\exp e^{-\Lambda}}{\alpha} \Gamma\left(0, e^{-\Lambda}\right), \tag{C.1}$$

where $\Lambda = \ln(\alpha/M_0)$ and $\Gamma(0, e^{-\Lambda}) = E_1(e^{-\Lambda})$ is the upper incomplete gamma function (or a special function called the exponential integral) which has an expansion

$$E_1(e^{-\Lambda}) = \Gamma(0, e^{-\Lambda}) = -\gamma + \Lambda - \sum_{k=1}^{\infty} \frac{(-e^{-\Lambda})^k}{k(k!)},$$

where $\gamma \approx 0.577$ is the Euler-Mascheroni constant.

The experimental average lifespan should be equal to the Gompertz average lifespan:

$$\bar{t} = \bar{t}_G = \frac{\exp e^{-\Lambda}}{\alpha} \left(-\gamma + \Lambda - \sum_{k=1}^{\infty} \frac{(-e^{-\Lambda})^k}{k(k!)} \right). \tag{C.2}$$

For $\Lambda \gg 1$ the solution is rather simple

$$\bar{t}_G\left(\Lambda \gg 1\right) = \frac{1}{\alpha}\left(\Lambda - \gamma\right).$$

Although the convergence of the series on the right side is known to be slow for arguments of larger modulus ($\Lambda \lesssim 1$), but we still can obtain a divergent series approximation

$$\bar{t}_G\left(\Lambda \lesssim 1\right) = \frac{\exp e^{-\Lambda}}{\alpha} \left[1 - e^{\Lambda} + \sum_{n=2}^{N-1} \left(-e^{\Lambda}\right)^n n! \right] \tag{C.3}$$

For practical applications an accurate, simple and universal approximation to $\alpha\bar{t}$ for all possible values of Λ is

$$\alpha\bar{t} = \Lambda - \gamma + \exp\left(-\Lambda/e^{\gamma}\right) \left[\frac{e^{\gamma}}{3} + \gamma \right] \approx \Lambda - 0.58 + 1.18 \exp\left(-\Lambda/1.8\right). \tag{C.4}$$

For the approximate relation between Λ and $\bar{t}$ in two limits we obtain: $\Lambda = \alpha\bar{t} + \ln(\alpha\bar{t})$ for $\Lambda \lesssim 5$ and $\Lambda = \alpha\bar{t} + \gamma$ for $\Lambda \geq 5$. To compare these asymptotes with the Strehler-Mildvan correlation, for $\log M_0$ we now get the following expressions

$$\ln M_0\left(\alpha \to 0\right) = -\alpha\bar{t} + \ln\left(1/\bar{t}\right), \tag{C.5}$$

$$\ln M_0\left(\alpha \gg 0\right) = -\alpha\bar{t} + \ln\alpha - \gamma. \tag{C.6}$$

To plot these correlation curves in Fig. 2 we simply join these asymptotic expansions together with a spline at the intersection point $\alpha_{is} = e^{\gamma}/\bar{t}$, that is why the curves look smooth as the exact solution, which are pretty close to straight lines at first sight). The actual origin of the Strehler-Mildvan correlation is a visual misinterpretation of an intricate degenerate manifold of the Gompertz fit parameters. Commonly used gradient descent methods are unable to find a unique optimal solution, because any pair of parameters M_0 and α near the iso-average-lifespan curve makes corresponding derivatives in a gradient descent method be zero with a quadratic precision.

Appendix D. The Gompertz-Makeham iso-average-lifespan curve

Gavrilov [2, 3] proposes the Strehler-Mildvan correlation to be a spurious correlation due to the neglect of an age-independent background component of mortality in the original work of Strehler and Mildvan (use of the Gompertz law instead of the Gompertz-Makeham law) [8]. Let us investigate the Gompertz-Makeham law properties in the same manner as above.

$$S_{GM}(t|\alpha, M_0, A) = \exp\left(-At + \frac{M_0}{\alpha}\left(1 - e^{\alpha t}\right)\right).$$

The exact average lifespan for the Gompertz-Makeham law is

$$\bar{t}_G = \int\limits_0^\infty dt N_G = \frac{\exp\frac{M_0}{\alpha}}{\alpha}\left(\frac{M_0}{\alpha}\right)^{A/\alpha}\Gamma\left(-\frac{A}{\alpha}, \frac{M_0}{\alpha}\right),$$

which is indeed somewhat better then we had with the Gompertz law, because the Makeham parameter moves the centre of our expansion for the upper incomplete gamma function from the singular point near zero $\Gamma(0, \frac{M_0}{\alpha})$ to a better analytical point nearby non-zero point of $\Gamma\left(-\frac{A}{\alpha}, \frac{M_0}{\alpha}\right)$, therefore, one can expect the divergent series approximation as in Eq. (C.3) to disappear, whereas we now have the three-parametric fitting procedure, for which SM correlation will nevertheless exist. The degeneracy manifold in case of Gompertz's law arising from the vanishing slope between two optimization curves in case of the Gompertz-Makeham law emerges due to the shrinking slope between two optimization surfaces, therefore the Makeham parameter just determines the cross section of these surfaces, where the same degeneracy problem for the remaining two Gompertz parameters still persists. Even though the Makeham parameter A is well-defined as long as it is large enough, nevertheless for the common regime of human ageing it is not the case since a step-like behavior of survival curves is expected, hence the introduction of the Makeham parameter is of little consequence and the degeneracy is not eliminated.

References

[1] Finkelstein, M., 2012. Discussing the strehler-mildvan model of mortality. Demographic Research 26, 191–206.

[2] Gavrilov, L. A., Gavrilova, N. S., 1991. The biology of life span: a quantitative approach. New York New York/Chur Switzerland Harwood Academic 1991.

[3] Gavrilov, L. A., Gavrilova, N. S., 2001. The reliability theory of aging and longevity. Journal of theoretical Biology 213 (4), 527–545.

[4] Gompertz, B., 1825. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Philosophical transactions of the royal society of London 115, 513–583.

[5] Hawkes, K., Smith, K. R., Blevins, J. K., 2012. Human actuarial aging increases faster when background death rates are lower: a consequence of differential heterogeneity? Evolution 66 (1), 103–114.

[6] Li, T., Anderson, J. J., 2015. The strehler–mildvan correlation from the perspective of a two-process vitality model. Population studies 69 (1), 91–104.

[7] Shen, J., Landis, G. N., Tower, J., 2016. Multiple metazoan life-span interventions exhibit a sex-specific strehler–mildvan inverse relationship between initial mortality rate and age-dependent mortality rate acceleration. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, glw005.

[8] Strehler, B. L., Mildvan, A. S., 1960. General theory of mortality and aging. a stochastic model relates observations on aging, physiologic decline, mortality, and radiation. Science See Saiensu 132.

[9] Stroustrup, N., Anthony, W. E., Nash, Z. M., Gowda, V., Gomez, A., López-Moyado, I. F., Apfeld, J., Fontana, W., 2016. The temporal scaling of caenorhabditis elegans ageing. Nature.

[10] Vaupel, J. W., Carey, J. R., Christensen, K., Johnson, T. E., Yashin, A. I., Holm, N. V., Iachine, I. A., Kannisto, V., Khazaeli, A. A., Liedo, P., et al., 1998. Biodemographic trajectories of longevity. Science 280 (5365), 855–860.

[11] Wagner, P., et al., 2011. Vitality heterogeneity in the strehler-mildvan theory of mortality. Tech. rep., Max Planck Institute for Demographic Research, Rostock, Germany.

[12] Ye, X., Linton, J. M., Schork, N. J., Buck, L. B., Petrascheck, M., 2014. A pharmacological network for lifespan extension in caenorhabditis elegans. Aging cell 13 (2), 206–215.

[13] Zheng, H., Yang, Y., Land, K. C., 2011. Heterogeneity in the strehler-mildvan general theory of mortality and aging. Demography 48 (1), 267–290.