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Sas, Arthur Alexander

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Gompertz' survivorship law as an intrinsic principle of aging

Arthur A. Sas [a,b], Harold Snieder [b], Jakob Korf [a,*]

[a] Department of Psychiatry, University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands
[b] Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

We defend the hypothesis that life-spanning population survivorship curves, as described by Gompertz' law and composed from cross-sectional data (here mortality), reflect an intrinsic aging principle active in each subject of that population. In other words Gompertz' law reflects aging of a prototypical subject, provided minimal (or no) external causes of death (i.e. fatal infections, starvation, accidents).

Our approach deviates from the traditional (exponential) Gompertz' hazard function. For instance, the here formulated Gompertz' law accurately describes old-age deceleration of both all-cause mortality and the incidence of some ageing-associated cancers, as illustrated for the Dutch population. We consider the possibility that the old-age expression and progression of cancer and other pathologies becomes suppressed, because of random (and exponential) accumulation of damage during life.

Gompertz' law may trigger new concepts and models describing life-spanning physiological and pathological processes of aging. We discuss (and reject) various aging models (e.g. a predominant role of individual variations at birth; reliability theory) and point to the explanatory potential of network models and systemic regulatory models.

Introduction

Population survivorship curves are used to assess quantitative parameters associated with aging or interventions affecting longevity [1–4]. These curves, showing all-cause mortality, cannot be accredited to a specific pathology and might be attributed to one or several underlying ageing processes. In a protective environment, i.e. with little external causes of death such as severe infections, starvation and accidents, a survivorship curve may be considered a population-specific characteristic. The survivorship patterns have been explained by assuming individual (often Gaussian) variability in – among other – frailty, genes or defective proteins [5–7]. Western human and many laboratory animal survival curves show relatively little mortality during the first period of live, thereafter the number of survivors shows an approximately exponential decline, whereas mortality decelerates at advanced age [1]. A characteristic of the human survivorship curve is its exceptionally long period of time (almost 60 years in the Netherlands) with low mortality. Old-age mortality deceleration has often remained unnoticed and has even been questioned [8].

From a biomedical point of view the question might be asked: given a population defined at birth, how can we understand the mortality pattern and is it possible to define what specific aging principle characterises the surviving individuals? In other words: can we describe life-spanning survivorship of a population as a biologically relevant and quantitative law? Here we consider life-spanning population survivorship and related time-to-event curves as cross-sectional data that reflect intrinsic time-related processes. We discuss this conceptualization with some alternative human survivorship models, thereby emphasizing that some models (e.g. [9–12]) do not necessarily apply to human survivorship data. In addition, implications of our hypothesis for biomedical research strategies, including the search for genes affecting longevity, are discussed.

Hypothesis

We defend the hypothesis that population survivorship datasets do not only describe life spanning survivorship pattern of a population, but disclose an intrinsic aging principle of each subject of that population as well. We focus on Gompertz' survivorship law [13,14], but do not exclude other time-to-event models. Gompertz' law is traditionally described as an exponentially increasing hazard function, that does not accurately describe the slowing of old-age mortality in a population. Instead we show that the present conceptualization of Gompertz' law describes accurately old-age deceleration of mortality. In Table 1 we present a SWOT (strengths, weaknesses, opportunities and threats) analysis of our conceptualization of Gompertz' survivorship law.

* Corresponding author. Address: University Medical Centre of Groningen, CG 64. University Centre of Psychiatry, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 361 2100.
E-mail addresses: j.korf@psy.umcg.nl, j-korf@home.nl (J. Korf).

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Table 1
Gompertz' survivorship law as an intrinsic principle of aging: strengths, weaknesses, opportunities and threats of the hypothesis.

Strengths
Gompertz' law relates population survivorship concepts to intrinsic individual aging processes
Our hypothesis explains old-age deceleration of mortality
Questions biomedical relevance of single exponential hazard functions to explain mortality
Gompertz' law distinguishes between age and non-age related pathology
Accuracy and simplicity: Gompertz' law requires estimation of only 2 free parameters
Model describes quantitatively life-spanning aging principle
Model is in line with a stochastic and system-biological conceptualizations of aging
Model provides quantitative parameters for normal and healthy aging and the development of pathology
Model predicts that pathology emerging at advanced age is not necessarily strongly associated with young-age characteristics
Weaknesses
Logistic, Weibull and some other models are sometimes equivalent or better to describe functional indices or the incidence of pathology during aging
Our hypothesis does not provide specific clues for underlying (i.e. molecular, genetic, cellular) aging processes
Our hypothesis is based in part on semi-quantitative assessments
Opportunities
Gompertz' survivorship law invites to develop alternative testable models (e.g. network models; systemic models)
To relate Gompertz model parameters to age-related physiological and pathological biological processes
To develop test-systems for modelling aging processes in vivo and in vitro
Threats
Development of alternatives that explain the time-course of aging and pathological processes more accurately

Gompertz law

The model

We preferred Gompertz' survivorship law, because it describes life-spanning population survivorship curves, rather than those of sub-populations during a relatively short life-time interval. The latter curves and analysis are relevant to estimate hazard rates in particular cohorts, but they do not per se disclose life-spanning mechanisms or processes underlying aging of an entire population.

The Gompertz' hazard function [13] is among the oldest models (1825) to explain population survivorship curves. It requires two free parameters, less than most other models. Conventionally the Gompertz' law (Eq. (1)) is presented as an exponential hazard function.

$$\mu_t = \alpha.e^{\beta t} \tag{1}$$

Here, μ_t is the proportional hazard rate at age t, often denoted as "force-of-mortality", and often expressed as the relative (e.g. per 100,000) number of deaths per unit of time (in the human population: per year) at age t; α and β are positive constants specific for the population in question. The so called Gompertz' slope β is usually derived from the logarithm of Eq. (1) [$(\ln{\cdot}\mu(t) = \beta{\cdot}t + \ln{\cdot}\alpha)$]. Although describing hazard rate accurately up to about 80% survivorship β ignores the deceleration of old-age mortality. We will show that Gompertz' law accurately accounts for late-age patterns of mortality.

The integrated Gompertz' equation (Eq. (2)) displays the real number or the proportion of survivors (S_t) of a defined population (S_0) at birth (or adulthood), instead.

$$S_t = S_0 e^{c(1-e^{kt})} \tag{2}$$

The parameters c and k are population specific; c is dimensionless. We preferred c, over the more conventional ratio α/β (Eq. (1)), because c is a dimensionless parameter, characteristic for the population, irrespective of the time units of k (per year, or month or day). Taking S_0 as 1 (unity), S_t is the fraction of the original population alive at age t. From Eq. (2) the mortality rate m_t is derived as the fraction of the original population (S_0) that dies per time unit:

$$m_t = S_t kce^{kt} \tag{3}$$

The mortality rate increases until a maximum and decreases thereafter [e.g. 14]. We estimated the age of inflection t_{ad} when accelerated mortality transits into decelerated mortality, from the derivative of Eq. (3) (=0 at t_{ad},).

$$t_{ad} = k^{-1}\ln c^{-1} \tag{4}$$

Often old-age deceleration of mortality has been attributed to the decreasing number of the population during aging. Consider for instance the possibility that the decrease of mortality was a single exponential decline function, then there would be no point at which mortality decelerates (inflection time/age, t_{ad}). This is in apparent contrast with the mortality patterns of human and most animal data sets. We illustrate the present approach with Dutch survival and pathology data (based on more than 10 million subjects) using quantitative and semi-quantitative fitting models. The data was quantitatively fitted using Graphpad Prism 5 (nonlinear regression option) using the relative number of the population or cohort (S_t/S_0); the free parameters c and k are given with confidence intervals. The semi-quantitative analyses were a computer overlay procedure guided by visual inspection, and illustrate similarities and deviance from Gompertz law in cohorts.

Dutch population

The data sets used for quantitative analysis were humans (total Dutch population (2003) and males and females separately (1994) [15]. The Dutch population is relatively healthy and homogeneous; it belongs to the longest living populations of the world and its epidemiology is well documented. Quantitative fits (whole population, female and male) are shown in Fig. 1; the legends of the figure summarizes the estimated free parameters. The best fitting curves connect nearly all data points. The estimates of t_{ad} are: 86.5 years

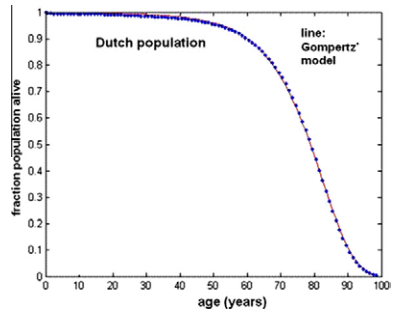

Fig. 1. Example of a quantitative Gompertz fit of survivorship data. Dutch (male + female) population (2003). Marks are observational data; thin line is the best fitting curve. The parameters and their confidence intervals of the best fitting Gompertz' model (Eq. (2)) are: c (95% confidence interval): 1.74×10^{-4} ($1.54–1.94 \times 10^{-4}$), k (years^{-1}): $0.102 \times (0.100–0.104)$; males (1994; number 7.585.000), parameters c 3.52×10^{-4} ($3.20–3.84 \times 10^{-4}$), k 9.83×10^{-2} ($9.72–9.95 \times 10^{-2}$); females (1994; 7.755.000), parameters c 1.12×10^{-4} ($9.41 \times 10^{-5} – 1.30 \times 10^{-4}$), k 0.105 (0.103–0.107). The life-time fitting shows deceleration of mortality at advanced age. Dutch population (2003: males + females, about 15.000.000 subjects), parameters: more details of the procedure and data are indicated in the text.

(whole Dutch population), 80.9 years (male) and 86.6 years (female).

Cross sectional data and ergodicity

Survivorship data and curves are based on cross-sectional measurements, because death is irreversible and can only be ascertained once per subject. Our hypothesis is that Gompertz' survivorship law describe an intrinsic principle of aging of all individuals, provided negligible external causes of death. Indeed, our basic assumption is the equivalence of longitudinal and cross-sectional observations of the current survivorship data. Let us explain this idea firstly in simple terms. Say that one wants to compose a growth curve (weight against age) of children. We consider two possible approaches. The longitudinal approach: compose a small and representative cohort of kids (theoretically one kid is sufficient) and weigh them every 3 months (or so). After 15 years a representative growth curve can be composed, being the average (or some other measure) of the various weights over time (age). The alternative, cross-sectional sampling, is based on the collection of data (here weight) of a large cohort of children of ages ranging from 0 to 15 years. Now every subject contributes only once to the data-set (like to a survivorship curve). If the subjects of both studies have the same growth properties either approach gives identical curves and enables to identify a prototypical (or representative) subject. In the present context, a life-spanning mathematical description of a survivorship curve of a population composed of (nearly) identical subjects applies to at least one individual of that population. Accordingly, the Gompertz' law should not only be considered as a biological characterisation of a population, but describes a typical (e.g. average or representative) life-spanning principle (or process) shared by all the individuals of that population. In other words: a population survivorship curve reflects some sort of a biological process in a prototypical subject. This converges to the idea what in physical sciences is known as the *ergodicity theorem* [17]. The *ergodicity theorem* asserts the equivalence of the longitudinal average over a single realization with the cross-sectional average of a fixed ensemble of static, stochastic processes. If this is so than the present Gompertz' model describes aging of any organism and possibly also of (some) organs and cells.

Some other approaches

In contrast to our hypothesis the shape of a survivorship curve has been attributed to characteristics of the population present early in life, such as variability of genes coding for longevity, birth complications or unfavourable environmental conditions (e.g. starvation during pregnancy or in the youth). For instance Rickels and Scheuerlein [11] compared Gompertz' exponential hazard function with a Weibull model. They assume that Gompertz' exponential hazard function applies exclusively to some (hidden) pathology already present early in life, and concluded that Gompertz's law does not include intrinsic aging processes. In our view this conclusion can be questioned. For instance a correction for extrinsic death can easily be incorporated in the Gompertz' expression of the population mortality rate (Eq. (3)); say for instance that the probability of extrinsic death is 1% (=0.01 S_t) per year. In this case the shape of the Gompertz' survivorship curve is still compatible with a major influence of intrinsic processes. Being an exponential function, Eq. (1) implies that during aging the hazard may increase independently of the previous condition; irrespective from already accumulated damage, or – as to be suggested later- functional state of the organism, cell or organ. It should be emphasized here also that a hazard function is a more or less theoretical construct, that has to be supported by observations, and that is mortality. As mentioned, many studies have shown that proportional mortality does not increase exponentially during life, with the largest deviation at advanced age. Hence the assumption of Rickels and Scheuerlein [11] that Gompertz 'curve exclude intrinsic aging processes seems premature. Another and related argument could be that the – presumably Gaussian – distribution of vitality of an organism, for whatever reason, determines the variation of mortality later in life [12]. We fitted our human data with cumulative distribution Gaussian function (overlay procedure) and noticed a superior accuracy of Gompertz' law (Eq. (2)). Human survivorship curves of many western societies show an exceptionally long period of life with little intrinsically caused mortality (particularly the Dutch; Fig. 1). Apparently, the longer this period is the less the initial variability of vitality determines the late-life patterns of mortality.

The present Gompertz' conceptualization may invite to consider other models for fitting. For instance we have tentatively fitted some network models (small-world models: [18,19]; synchronization models: [20]) with Gompertz' equation with the overlay procedure. Network models apply to any level of complexity: from molecule within cells, connections between cells or organs up to the entire organism. Aging might be understood as a gradual dissolution of well-ordered functional networks possibly as the result of accumulated molecular damage. Another approach worth considering is homeostatic regulation continuously being subjected to stochastic aging processes. Homeostasis at every level of an organisms might adequately be maintained during aging until collapse. Such concepts are in line with systems biology, assuming that an organism is a collection of single or multiple complex cooperating systems [21,22]. In contrast to single component effects (e.g. specific genes, proteins, telomeres, oxidative damage) systems biology underscores the multiple interactions of the various components (systems and subsystems) in an organism leading to a complex (and often unpredictable and stochastic) outcome. Although being promising, the suggested compatibility of Gompertz' law and various models needs further support with quantitative analysis.

Biomedical considerations

On aging hypotheses

Our interpretation of Gompertz' law might be seen as an extension of the *disposable soma theory* which focuses on the idea that cell maintenance (e.g. DNA repair, protein turnover) is costly and that the cell's capacity to maintain homeostasis is reduced during aging [6]. Consequently malfunctions and gene-mutations accumulate, as proposed in the *accumulation hypothesis,* stating that ageing is primarily caused the cumulative impact of cellular and molecular damage [6,22]. Several molecular mechanisms have been held responsible: accumulative damage of proteins, for instance progerin [23] and nucleic acids by radical oxygen species, methylation of DNA and spontaneous hydrolysis or rearrangements of genes [24,25]. Related to this conceptualization is the assumption of stochastic accumulation and telomere shortening as the result of oxidative damage of mitochondrial and nuclear DNA. [4,9]. Of possible interest are the interpretations of Hallén [26] and Shklovskii [27] who emphasize that the exponential part of Gompertz law might be interpreted as an increased content of cross-linked proteins or as a rare escape of abnormal cells escaping from immunological response, respectively. All these hypotheses might be compatible with a single exponential accumulation of damage in cells or organs and are in line with the assumption of an exponentially increasing hazard during life, but not necessarily with the mortality patterns as explained with the current conceptualization of Gompertz' law. Accordingly, a life-long accumulation of damage does not necessarily lead to an exponentially increasing death rate. Instead, it may

also challenge the organism by activating repair mechanisms, thereby preventing or attenuating future (possibly carcinogenic) gene mutations. Based on mathematical modelling, Finkelstein [10] came also to the conclusion that if aging were to be understood as some process of damage accumulation it does not necessarily lead to an increasing mortality rate [5]. In his modelling Finkelstein introduced the concept, that age related changes in an organism might adversely affect its vitality and functions. Gompertz' equation appears to be in line with these ideas: the "rate constant" (k) accounting (also) for old age decelerating mortality, might be explained by accumulating random perturbations (or damage) whereas the parameter c might reflect such hypothesised vitality of an organism. The parameter k remains often unaffected by external (including experimental) conditions. In line with the latter idea are human data indicating that k (equivalent with α, the Gompertz' slope) has not changed during several generations [16]. In short: we consider the parameters c and k as biological characteristics of the whole population or of a well defined cohort.

We suggest a biomedical explanation of the deceleration of old-age mortality. Old cells enter a state of senescence and may no longer divide, possibly because of telomere shortening in addition to some other mechanisms such as the stimulation of repair mechanisms. Related mechanisms have been explored in vitro with human tumour cells [28]. To develop a fatal pathology, several intact somatic functions are required. For instance, the transition of tumours from a dormant state to a malignant requires sufficient nutrients for growth; it 'parasitizes' its host's body by inducing – among other – angiogenesis. In line with these ideas is the notion that the progression of many (but not all) tumors slows down at advanced age [29–31]. Another example is auto-inflammatory disease; an age-related impaired defence against micro-organisms may protect against auto-inflammatory diseases and cardiovascular diseases (inflammation of the blood vessel wall). Hence, due to a random process (as for instance *genomic instability* [24,25]) pathology-supporting activity may become impaired as well. This leads to the idea that – paradoxically – stochastically accumulated damage might sometimes provide protection, in addition to fatal consequences.

Modelling incidence of pathology

Cancer is a major cause of mortality both in humans and in animals. In medical cancer research the incidence of a variety of cancers (new diagnosis per year per 100,000 persons) shows a nearly exponential increase during aging (e.g. [32–34]), although at higher ages the incidence rate is less than predicted by the exponential function (data in [31]). Exponential increases have been modelled to estimate the in vivo progression of tumours. The biology of aging may better be understood with our Gompertz' model, based on the real numbers of mortality or morbidity (number of new cases of the cohort per age). The latter idea was supported with semi-quantitative fits of age-related incidence patterns of prostate, colon and cervix cancer (source [15]). The incidence numbers firstly were transformed to real numbers of subjects diagnosed with the tumour (i.e. cohort specific data) per age interval (5 years), plotted and examined with Gompertz law functions (overlay procedure). It appeared that the prostate and colon cancer were nearly identical with whole population survivorship curves, including a tendency of the old-age deceleration. Other reported cancer data (e.g. in [35]) are in line with this conclusion. The incidence data on cervix carcinoma deviate clearly from Gompertz' law (Fig. 2, top panel). Indeed, this cancer is caused by an infection of the papilloma virus at young age. The latter example illustrates the potential of our approach to distinguish between predominantly intrinsically aging-associated *versus* extrinsically caused mortality.

In some reports (for instance on cardiovascular incidents [35] other models (e.g. Weibull) gave better fits than Gompertz law.

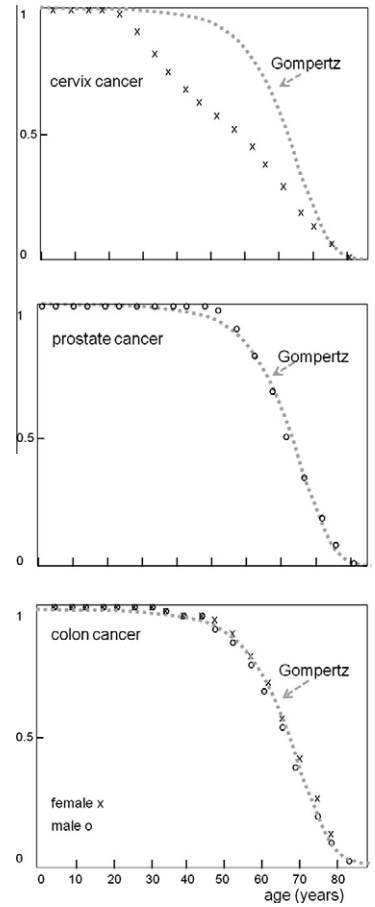

Fig. 2. Incidence curves of 3 carcinoma's, with overlays of Gompertz function. Plots are age *versus* proportion of the cohort diagnosed at indicated age-intervals of 5 years. Cervix carcinoma does not follow the Gompertz law, because of the most prevalent sexually transmitted virus (human papilloma virus) of the world is a major cause of sexually active (young) women. Male and female data of colon cancer were nearly identical. Prostate and colon cancer follow reasonably well Gompertz' law suggesting a close association with aging, unlike the cervix data. Curves are based on 2500–25,000 subjects. Data from ref. [38].

The latter study [35] did not analyze the data according to the procedure proposed here. Together with the current cervix data deviations from Gompertz' law may point to a rather loose or even lack of association with Gompertz aging model. Clearly, further testing is necessary for more pertinent conclusions.

The coincidence of the survivorship curves of all cause mortality and age-related incidence of various cancers and some other pathologies implies that progression of a specific pathology depends on intrinsic aging processes. This conclusion is in apparent

contradiction with reports suggesting that age-related incidence of cancer and related mortality depend primarily on the progression of the cancer, irrespective of aging-effects (e.g. [32–34]). We propose that intrinsic aging has to be taken into account to distinguish general aging processes from that governing the in vivo progress of a particular pathology. Human pathology such as cancer has been attributed to mutations, spontaneously arising in the human genome [24,35]. The involvement of DNA mutations in aging is also emphasized by syndromes of premature aging (progeria), due to failing DNA-repair [4,36,37]. The similarity of the age-patterns of incidence data of many cancers and all-cause mortality of the human population, suggests that genomic destabilization should be considered as a powerful mechanism driving aging, that is indeed in line with recent animal studies [24,25,37].

Concluding remarks

We showed that life-spanning survivorship data of humans can accurately be modelled with Gompertz' law, thereby also explaining old-age deceleration of mortality. We provide arguments for the hypothesis that Gompertz' law discloses basic aging principle that is already active early in life of each subject. Our and many other aging models assume (exponential) stochastic accumulation of dysfunctions. We want to emphasize that stochastic processes are indeterminate in an antegrade perspective, but not necessarily from a retrograde perspective. Indeed, even if the (near) future is unpredictable (with modelling), does not imply that the processes and course of aging or a disease (e.g. cancer) cannot well be understood. Hence the cause and progression of a (fatal) disease might well be described as a determinate pathway, that can be reconstructed fairly well afterwards. Such conclusion might have consequences in the search for specific genes modulating aging and age-related mortality. A stochastic model is consistent with a multifactorial cause of aging, pathology and death, implying the involvement of several genes. Hence the finding of specific sets of genes may fail, but this does – however – not exclude the possibility that in sub-cohorts specific genes might be identified. But even in such a case their explanatory and prognostic power might be modest.

The versatility, the simplicity and testability are among the strong aspects of the here defended hypothesis and we suggest some testable biomedical approaches (Table 1). We consider the present hypothesis as an opportunity for further research. Together, this report emphasizes that Gompertz' survivorship law should not only be considered a demographic model, but rather as a biomedical law describing intrinsic age-related processes in living organisms, including humans.

Conflict of interest statement

The authors declare that they have no personal or financial interests that have influenced the content of this article.

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