Chapter 12: Parallel lines: nothing has changed?

Maarten P. Rozing[1], Rudi G.J. Westendorp[1]

From the [1]Department of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands.

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Abstract

The exponential increase in mortality rate with age is a universal feature of aging and is described mathematically by the Gompertz equation. When this equation is transformed semi-logarithmically, it conforms to a straight line, the slope of which is generally used to reflect the rate of senescence. Historical and contemporary data of human and non-human populations show that adverse environmental conditions do not always change the slope of the log mortality rate over age. From these latter observations it is sometimes mistakenly inferred that the rate of senescence is unaffected by environmental conditions. Current biological inference emphasizes that gene action is dependent on the environment in which it is expressed. Here, we propose using the tangent line of the Gompertz equation to assess whether the rate of senescence has altered. Such an approach unmasks different rates of senescence when parameter G has remained constant, an observation that is in line with the notion that a plastic life history trait such as the rate of senescence results from the interplay of both genes and environment.

Senescence is quintessentially defined as an increased probability of dying with age[1]. This probability is estimated when following populations with similar genetic background for mortality over time and is expressed as mortality rate per year. Already 180 years ago it was noted by Benjamin Gompertz that mortality rates of human populations increase exponentially for most age ranges [2]. This exponential increase in mortality rate (m(t)) over age (t) is mathematically expressed by the equation:

$$m(t) = A_0 e^{G t} \quad \text{(Eq. 1)}$$

When the Gompertz equation is transformed semi-logarithmically, it conforms to a straight line described as:

$$\ln m(t) = \ln A_0 + Gt \quad \text{(Eq. 2)}$$

The slope of this straight line is determined by the Gompertz coefficient (G) and equals the derivative of equation 2.

The Gompertz coefficient (G) is commonly used as an estimate of the rate of senescence [3]. It is generally interpreted as a measure of intrinsic susceptibility of a biological system to withstand stressors. This intrinsic susceptibility leads to an accumulation of permanent damage to cells and tissues, loss of function and ultimately death, the rate of which is specific for the various species. Current reasoning prevails that decreasing the Gompertz coefficient provides decisive evidence that the rate of senescence is positively influenced.

The parameter A_0 is generally referred to as the "initial mortality rate", and is alternatively designated as "intrinsic vulnerability" [4] or "frailty" [5]. The parameter A_0 is commonly estimated at the age of puberty when development is completed and mortality from senescence is at its minimum. When A_0 is estimated that way, it also includes mortality from extrinsic hazards, i.e. environmental mortality that is age independent [6]. To account for this source of mortality separately, Makeham proposed a modification of the Gompertz' law of mortality [7].

$$m(t) = C_0 + A_0 e^{G t} \quad \text{(Eq. 3)}$$

In which C_0 represents the age independent causes of extrinsic mortality, for example accidents and homicide.

As the rate of senescence is expressed as the acceleration of mortality rate over time, it can take all values. This acceleration can approach negligible values if population mortality rates remain equal over time, and it is inferred that such a population, e.g. hydra, does not undergo senescence [8]. The acceleration of mortality rates over time can also level off at advanced ages [9] or mortality rates can decelerate as seen during development. It must be emphasized, however, that even in the absence of senescence mortality rates are unlikely to be zero as there are remaining deaths from environmental causes. Immortality is difficult to achieve.

The logic that mortality from intrinsic causes and environmental causes are two independent mechanisms leading to death follows from classic observations of which an example is illustrated in **figure 1a**. The figure shows on a semi-log scale age specific mortality rates of prisoners of war in a Japanese concentration camp. When it is compared to the mortality rates of the Australian civilian population over a similar calendar period, the two lines are parallel [10, 11]. This parallelism of the mortality curves over age shows that the adverse environment has left the slope (G) unchanged. The general inference of these data is that the rate of senescence is unaffected by an increasingly adverse environment [3]. If anything, the process of senescence occurs at an earlier age when exposed to adverse conditions.

When the same data on age specific mortality data from the Australian populations are plotted on a linear scale, such a presentation sheds a different light on the interpretation of the parallel curves in the semi-log plot. From **figure 1b** it follows that, when plotted on a linear scale, the difference in age-specific mortality between the prisoners of war and the civilian population is manifold larger in old age when compared to young age. At age 21-25 the mortality rate is 2.3 deaths / 1000/ year among the internees whereas it is 0.7 deaths / 1000/ year in the civilian population (estimated from Jones[11]). The difference in mortality rate between these populations is 1.6 deaths / 1000/ year. As the two populations are assumed to have a similar genetic background, the extra number of 1.6 deaths/ 1000/ year must be attributable to the incremental environmental hazards to which the internees were exposed. Due to senescence, mortality rate in the civilian population at age 80 has increased to 145.0 deaths/ 1000/ year. When the intrinsic susceptibility and the environment do not interact, we would have expected mortality rate among the internees to be 146.6 deaths/ 1000/ year (145.0 plus 1.6 deaths/ 1000/ year). However, mortality rate among the prisoners of war at age 81-85 is 750.0 deaths/ 1000/ year. The excess number of deaths among 1000 elders who were interned for one year can thus be calculated as 750.0 deaths minus 145.0 deaths as expected from senescence, minus an extra 1.6 death due to the increased environmental hazards in the camp. In the prevailing logic this excess number of 603.4 deaths among the older

internees cannot be accounted for by environmental hazards and is unexplained when the rate of senescence is assumed to be constant.

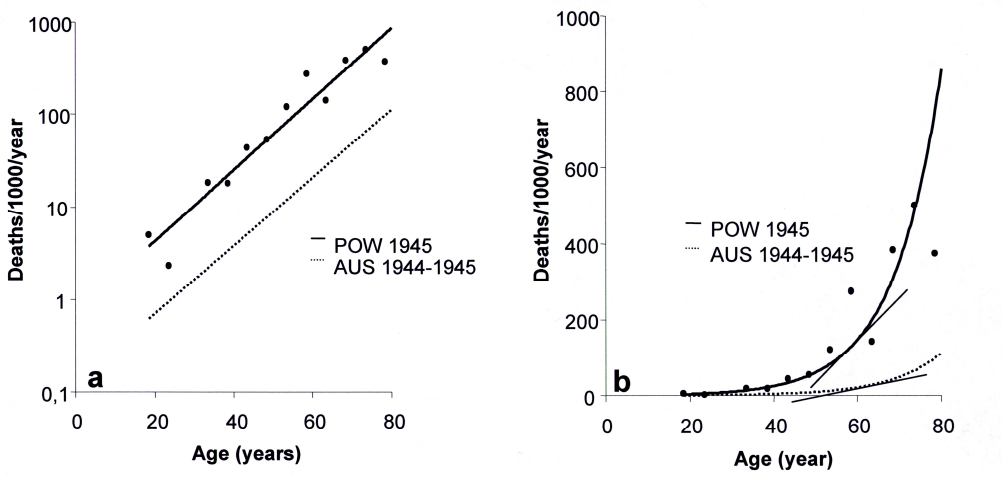

Figure 1. Mortality rates as a function of age for a human population under adverse and affluent conditions. *POW: prisoners of war held in concentration camps by the Japanese army during 1945; Aus: Civilians in Australia, 1944-1945. 1a; Plot of the mortality rates as function of age for POW versus Australian civilians on a semi-logarithmic scale 1b; Plot of the mortality rates as a function of age for POW versus Australian civilians on a linear scale. The tangent lines at age of 60 for prisoners of war and civilians are highlighted in blue. Redrawn from Finch* [3].

When to mathematically describe a biological interaction of risk factors the use of additive models is recommended rather than using multiplicative models [12]. It is generally ignored that using linear regression on log transformed data, it effectively has become a multiplicative model. When fitting the regression line, the coefficient presents the *added* value of log mortality when age increases with one unit (equation 2). However, when the equation is exponentiated, to arrive at describing actual mortality rates, it has become the factor with which the mortality rate should be *multiplied* when age increases with one unit. This phenomenon is illustrated when comparing figure 1a and 1b. When the mortality trajectories are plotted on a semi-log scale, visual inspection shows that the lines have shifted upwards but remain parallel. On a linear scale, however, the acceleration of mortality over age under adverse conditions is unmasked. This higher rate of senescence under adverse conditions explains the excess number of 603.4 deaths/ 1000 among the 60 year old prisoners of war that is not accounted for when the rate of senescence is assumed constant, an incorrect conclusion when modeling log transformed data.

It is a striking oddity that when parameter G is used to estimate the rate of senescence, the rate of senescence is not only invariant under different environmental conditions, but is even unaffected by the elapse of time. This would imply that the rate of senescence in a 20 year old civilian is equal to the rate of senescence in an 80 year old internee. This conclusion calls into question the validity of parameter G as an estimate for the rate of senescence.

The enigma of biology is to explain phenotypic characteristics as the result of genes that are expressed in a specific environment. Phenotypic characteristics can be markedly dissimilar in different environments despite the genetic background of the organism being identical [13-15]. Gene-by-environmental interactions account for a large component of the variance in gene expression and there is no reason to assume that senescence should be exempt. It follows that the rate of senescence results from an interaction between intrinsic susceptibility and specific environmental conditions. Despite the constancy of parameter G in the Gompertz equation, the rate of senescence can vary widely under different conditions and in different age categories.

Following the notion that genes interact with environmental cues and that the rate of senescence can best be studied using absolute figures, the slope of the Gompertz curve would be the most appropriate estimate of the rate of senescence. When mortality rates are expressed on an absolute scale (figure 1b) the slope of the tangent line at the age 60 years is much steeper among the prisoners of war when compared to the civilian population, indicating that the rate of senescence is far higher under adverse conditions. The slope of the Gompertz curve, i.e. the first derivative, can be expressed for every given age (t) as:

$$m'(t) = A_0 \; G \; e^{G\,t} \quad \text{(Eq. 4)}$$

with the expression unit being (deaths/ 1000 persons/ year) per year, which is the derivative of equation 1. Whatever may be the biological substrate for the parameters A_0 and G, it is apparent that the rate of senescence m'(t) results from a multiplication of both parameters and varies with age (t).

When using equation 4, describing the slope of the tangent line to estimate the rate of senescence as the combined effect of genetic background and environmental cues, it becomes clear that the Gompertz equation may reasonably well describe the patterns of mortality over age, but does not line up with current biological knowledge. The Gompertz law of mortality was formulated long before molecular insights in the biology of aging were accrued.

Alternative to the Gompertz model, power functions like the Weibull model are also used to express the mortality rate in a population [16]:

$$W(t) = C_0 + \alpha t^{\beta} \text{ (Eq. 5)}$$

In equation 5 the age-dependent component αt^{β} is added to the initial mortality rate C_0. The slope of the Weibull model, an estimate for the rate of senescence, is expressed by the first derivative of equation (5):

$$W'(t) = \alpha\beta t^{(\beta-1)} \text{ (Eq. 6)}$$

The rate of senescence described by equation (6), results from the interaction of two parameters, α and β. Similar to the derivative of the Gompertz model 4, the rate of senescence W'(t) is dependent on age (t). Over the adult range, curve fitting leads to no clear preference of one model over the other [17]. Although, the derivatives of the Weibull and Gompertz models both adequately describe the rate of senescence in mathematical terms, the isolated parameters cannot be interpreted in biological terms.

Classic inference from the Gompertz law may have lead to incorrect conclusions. In industrialized human societies worldwide, mortality rates have been declining steadily for over a century. These declines have been associated solely with a reduction in initial mortality rates, with no reduction in the slope of the mortality trajectory [18]. This lowering of the mortality trajectory has been taken to indicate that overall health at all ages has improved, but that the underlying process of accumulation of permanent damage has not been ameliorated.[19] Here, we argue that this conclusion may be mistaken.

In model organisms, there are various examples of interventions which that have been shown to extend the average and maximum lifespan, and, some are reflected in a lower slope of the mortality trajectory [20, 21]. Many of these experiments involve the restriction of calorie intake [4, 22]. In contrast, various data on genetic manipulation of experimental models also show an increase of average and maximal lifespan, but when expressed on a semi-log scale the age specific mortality trajectories have shifted parallel when compared to the control strains[23-26]. For these latter examples, the nowadays interpretation is one of disappointment, as if the process of senescence had not be influenced positively. The correct interpretation of these data, however, is that the tangent line, i.e. the acceleration of mortality, is markedly different. Despite the fact that the tangent line better reflects the decreased rate of senescence, the mathematical formula however,

does not allow for testing biological plausible hypotheses. There is an urgent need for new mathematical models that adequately fit the increase of mortality rate over age and at the same time enable studying the biology of senescence that lines up with current scientific insights.

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