The Mechanics of Aging and Death: A Primer for Economists

Part II: Measuring Aging

Holger Strulik[*]

This Version: April 2010

Abstract. This paper is written for (health-) economists with an interest in the conceptualization and modeling of aging in demography, biology, and bio-gerontology. It reviews two alternative methods to measure aging and a theory that explains the outcome of both these measurements. It explains how aging, conceptualized as increasing probability to die, can be accurately and conveniently measured by the Gompertz-Makeham law. It discusses the historical stability of the estimated parameters of the law, inferences about human life-span, and the similarities and differences of aging across sexes, countries, and species. Alternatively, aging can be measured as accumulation of bodily deficits. The paper reviews the frailty index, designed to measure biological aging, and demonstrates important similarities and differences between the force of mortality and frailty accumulation. The paper provides also an introduction to reliability theory and shows how increasing mortality and frailty can be explained as a stochastic process of loss of built-in redundancy of organisms. The analysis provides some tentative conclusions about the future of human aging and some suggestions for the modeling of health and mortality in economics.

Keywords: Aging, Mortality, Life-span, Frailty, Reliability Theory.

JEL: D91, J17, J26, I12.

It's better to burn out 'cause rust never sleeps.
(Neil Young)

1. The Force of Mortality

Aging is defined as the intrinsic, cumulative, progressive, and deleterious loss of function that eventually culminates in death (Arking, 2006, Masoro, 2006). Here we focus on aging of organisms (mostly humans) but everybody who is driving a car will recognize that the definition of aging applies to non-living matter as well. Actually, living and inanimate systems are aging in a similar way, a phenomenon to which we return later. Sometimes aging and senescence are used synonymously (Masoro, 2006), sometimes senescence is reserved for the period of obvious functional decline in the later years of an animal's life-span (Arking, 2006).

Aging can be measured by directly accounting for the accumulated deficits, a concept to which we return later, or by its consequences for mortality, which we discuss next. Demographers employ several indices of mortality. For example, the probability to survive to age x, the life-expectancy at age x, or the probability of dying in the age interval $x + \Delta x$. Of these, the probability to die is the most suitable measure of aging because it provides the *age-specific* impact on mortality independently from age-specific events at other age groups. To see this note that, for example, the probability of dying in the age interval (0,1) clearly affects the survival probability to any age $x > 1$ as well as life expectancy at age 0, but not the other way around.

Biologists and gerontologists are also emphasizing that individual aging must be understood as an event-dependent not as a time-dependent process (Arking, 2006). Hence, according to this view there is no such thing as a "biological clock"; the probability of dying is just a measure of how members of a population (a species, a population of country) age *on average*. Another implication of this view is that is that the probability to die is not useful to assess or even to explain *individual* survival prospects.

Given a sample of a population and the observation (from a life table) that a number S_x thereof survives to age x and a number $d_x = S_x - S_{x+\Delta x}$ dies between age x and $x + \Delta x$, the probability to die in age interval $x + \Delta$ is given by $q_x = d_x/S_x$. The discrete-time measure has the inconvenient side-effect that the probability to die depends on the length of the age-interval

x. In order to get rid of this problem we take the continuous limit

$$\mu(x) = \lim_{\Delta x \to 0} = \frac{S(x) - S(x + \Delta x)}{\Delta x S(x)} = -\frac{\dot{S}(x)}{S(x)}$$

which provides the *force of mortality*: the conditional probability to die at age x given survival up to age x. Note that age x is conceptualized as continuous and that $\mu(x)$ is not bounded from above by one.

From the empirical data the force of mortality can be approximated using, for example, the trapezoidal rule on $\mu(x) = -\mathrm{d}(\log S(x))/\mathrm{d}x$:

$$\mu(x) = \frac{1}{2\Delta x} \left[\log S(x - \Delta x) - \log S(x + \Delta x) \right].$$

The notion of the force of mortality should be familiar not only to engineers (as the failure rate) but also to economists as the hazard rate; the hazard here is to expire at age x. The "perpetual youth" models built on Blanchard (1985) and Yaari (1968) investigate the special case $\mu(x) = \lambda$ for all x. The assumption that the probability to die at age x is independent from x, constitutes, in fact, the definition of a non-aging organism in biology (Arking, 2006). Thus, the most popular economic models that are taking the finiteness of human life into account are inherently unsuitable to display and discuss aspects of human aging.[1]

2. The Gompertz-Makeham Formula

The force of mortality for humans (and other organisms) increases with age in a particular way. This is shown exemplarily for US Americans in Figure 1, in which dots represent the actual age-specific force of mortality. Human life can be roughly subdivided into two periods: an initial *phase of development* ranging from birth to puberty during which the probability to die decreases (from A to B in Figure 1), immediately followed by the *phase of aging* during which the probability to die increases. Remarkably, almost nowhere along the human life cycle is the probability to die constant.[2]

---

[1]This is of course acknowledged by the developers of the model by coining the "perpetual youth" expression.

[2]This rough division of human life is possibly good enough an approximation for economists interested in aging. Yet at a closer look the picture gets more complicated and puzzling for evolutionary biologists and gerontologists. The trough of the mortality rate is actually not constant. It was falling over the last century and is now reached in fully developed countries around age 10, i.e. several years before sexual maturity (Milne, 2006). Moreover, aging understood as the increasing loss of bodily function starts at least at birth if not earlier since infants are already subject to somatic mutations and telomere shortening (Frenck et al. 1998). See also PART 3 of this review.

Figure 1: Age-specific Mortality Rate: United States 1959-1961
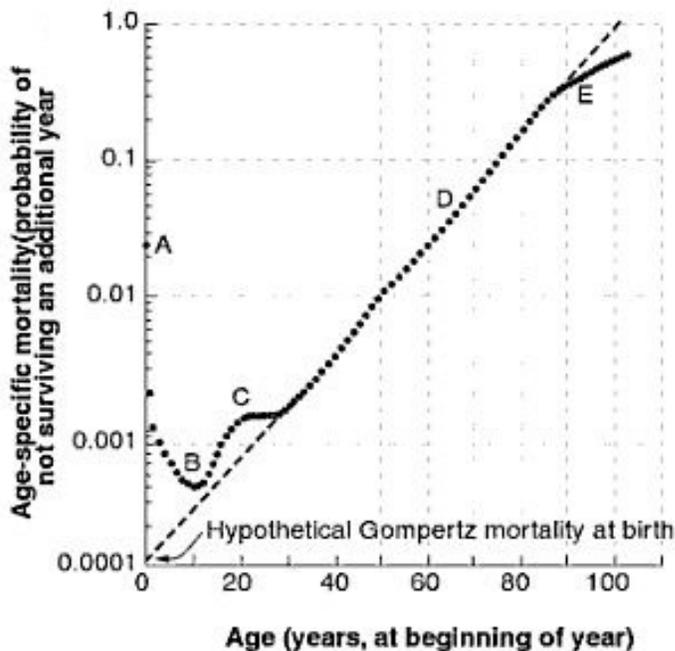
Dots indicate data points, the straight line shows the Gompertz esti-
mate. Figure taken from Arking (2006).

The most striking feature of Figure 1 is the long period of life, ranging from about 30 to 90 years of age, for which age and the force of mortality are log-linearly related. This relationship is known as Gompertz law after actuary Benjamin Gompertz (1825) who first observed and stated it formally: $\log \mu(x) = a + \alpha x$, or equivalently,

$$\mu(x) = R \exp(\alpha x). \tag{1}$$

For humans the estimate of α is around 0.1 implying that the probability to die doubles approximately every 10 years. The Gompertz formula was further improved by William Makeham (1860) who noticed that not all causes of death are age related. Consequently, a constant, reflecting an age-unrelated force of mortality, is added to yield the famous Gompertz-Makeham formula.

$$\mu(x) = A + R \exp(\alpha x). \tag{2}$$

Subsequently, many researchers from various disciplines have tried to further improve the formula to little avail (see Gavrilov and Gavrilova, 1991, Ch. 2 for a detailed discussion). Taking

3

both simplicity and precision into account, the Gompertz-Makeham formula is to the present day the most appropriate, concise, and widely used formal description of aging (Olshansky and Carnes, 1997). Not only for humans are its parameters estimated with great precision with coefficient of determination, also species as different as yeast, fruitflies, rats, and horses, have been shown to age according to the Gompertz-Makeham formula. The estimated coefficients, of course differ greatly, reflecting the large variation in life-span across species (Arking, 2006, Gavrilov and Gavrilova, 1991).

The fact that the Gompertz-Makeham law so precisely describes aging from young adulthood onwards makes it a convenient tool to describe mortality of a representative individual in dynamic overlapping generations models, i.e. within a modeling framework which usually neglects decision making during childhood and assumes that a household's choices are made by persons at the onset of young adulthood. For these kinds of analyses the Gompertz-Makeham law (2) clearly shows that there exists no upper limit to human life-span. Formally, $\mu(x)$ is finite for finite x; there exists no age x at which $\mu(x)$ converges towards a pole. Or more vividly put "no matter how old one is, the probability to die on the next day is never unity". This statement may sound like platitude but, in fact, until recently many biologists were convinced that there exists a maximum human life-span (e.g. Fries, 1980). With respect to economic overlapping-generations modeling the Gompertz.Makeham law implies that there is no capital T marking "the end of the second period", i..e. the end of life.

Figure 2: Aging according to Gompertz-Makeham vs. Probabilistic Death
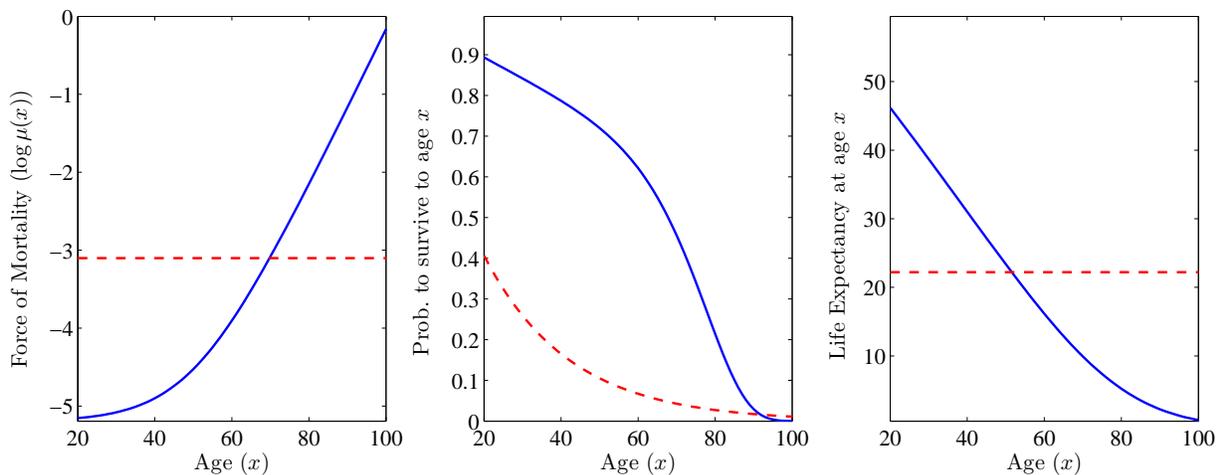
Solid lines: Estimates from Swedish life tables: $A = 0.00552$, $R = 0.000033$, $\alpha = 0.1013$ (Gavrilov and Gavriolova, 1991), own calculations. Dashed lines: hypothetical perpetual youth scenario: $\lambda = 0.025$.

4

Figure 2 compares mortality according to Gompertz-Makeham estimated for Swedish men alive 1901-1910 with mortality of an individual of perpetual-youth. The panel on the left-hand side shows the log of the force of mortality. It can be seen that the Gompertz part becomes dominating at ages around 50, from which on the force of mortality appears to be log-linearly increasing in age. The perpetual youth model clearly overestimates mortality of young adults and underestimates it for the old. Notice, by comparing Figure 1 and 2, how the Makeham-amendment leads to a much better approximation of μ for young adults. While the Gompertz formula approximates human mortality reasonably good for ages between 40 and 80 years, the Makeham amendment yields a good approximation for ages between 15 and 90 years (Carnes et al., 2006).

The middle panel of Figure 2 shows the probability to survive to age x (or the fraction of the original cohort size still alive at age x). It is obtained as the solution of $\dot{S}(x) - \mu(x)S(x) = 0$ given that $S(0) = 1$, implying for Gompertz-Makeham

$$S(x) = \exp\left(-Ax - \frac{R}{\alpha}\left(\exp(\alpha x) - 1\right)\right) \tag{3}$$

and, trivially, for the perpetually youth agent $S(x) = \exp(-\lambda x)$. According to Gompertz-Makeham, $S(x)$ is concave: the probability to survive decreases relatively little with age at young ages and strongly at old ages. The perpetual youth model predicts just the opposite, i.e. steeply falling survival prospects at young ages.

The panel on the right hand side of Figure 2 shows life-expectancy (expected remaining years to live) at age x

$$e(x) = \frac{\int_x^\infty S(a)\mathrm{d}a}{S(a)}.$$

For the perpetual-youth agent life-expectancy is independent of age (and equals $1/\lambda$) while, actually, according to Gompertz-Makeham life-expectancy is almost linearly falling with age in the range of 20 to 70 years, after which it levels off.

At the upper age range, for the *oldest old*, the Gompertz-Makeham formula loses precision. In contrast to what one might have expected, at ages of above 90 the force of mortality increases *less* than log-linearly with age . Again, this phenomenon is not unique to humans but visible in other species as well. Various amendments to the original formula have been suggested to take the oldest old into account (e.g. Perks, 1932). If this leveling off become so strong that the force of mortality stops to increase, the oldest old become indeed non-aging. The possibility that –

once a certain age has been reached – we turn out to be not exactly immortal but non-aging has, of course, inspired research and debate in biology, demography, and gerontology (Wachter and Finch, 1997, Oeppen and Vaubel, 2002, Carnes and Olshansky, 2007).

For a correct assessment note, however, that at best the force of mortality reaches a high plateau. It does not relapse to the level of background mortality A. Speaking of *negligible senescence* (Finch and Austad, 2001) with respect to the oldest old is literally correct but may nevertheless be misleading. Nowhere is the probability to die as high as for the oldest old. Intellectually, the biological foundation of a constant mortality rate is relatively easy to grasp (we return to that in section 5). Intellectually more fascinating is the Gompertz-Makeham law on which we focus now.

3. Stability of the Gompertz-Makeham Law: History and Science Fiction

Over the last century human life expectancy at birth has increased by more than 20 years in most of the fully developed countries (Riley, 2001). It is interesting to investigate how these huge improvements of human longevity have affected the Gompertz-Makeham law. For this purpose the notion is helpful that the Makeham-parameter A is not an inherently stochastic influence on human survival (as suggested by the perpetual youth model) but rather reflects the age-unrelated forces of mortality, i.e. the background mortality or extrinsic mortality (Carnes and Oshansky, 2007). In particular we expect prevention, eradication, or cure of age-unrelated diseases to be reflected in A. We expect progress with respect to the aging process itself to be reflected in a change of Gompertz-parameters R and/or α.

By estimating the Gompertz-Makeham law using life tables for a sample of countries over a very long horizon, Gavrilov and Gavrilova (1991) were able to show that the age-dependent parameters R and α vary across countries and across sexes but are strikingly stable over time. With contrast, the background risk parameter A has been found to be sex independent and (for most countries) continuously falling over time. For Sweden, for example, the parameter A fell over the last century by about one order of magnitude from 0.55 percent to 0.048 percent. From this they conclude that so far in human history advances in longevity manifested themselves almost exclusively in reduced background risk. Human ingenuity has not yet been able to manipulate much the biological mechanism behind the aging process, captured by the age related parameters R and α.

Figure 3: Aging In Sweden 1901-1910 and 1983
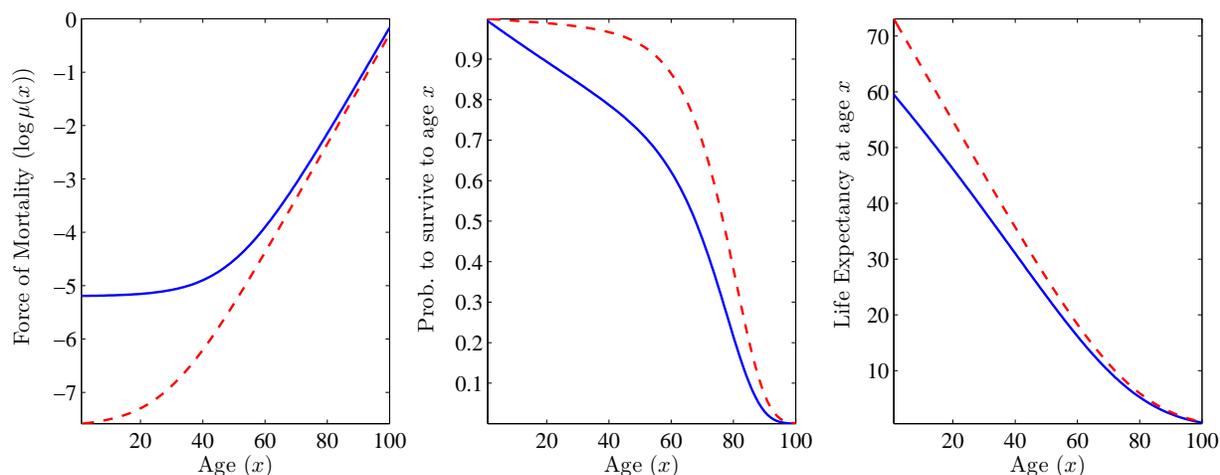
Parameters estimated from Swedish life tables for men in 1901-1910 (solid lines) and in 1983 (dashed lines) Estimates from Gavrilov and Gavriolova (1991) and own calculations.

Carnes et al., 1996, follow a different approach by trying to partition for a population sample extrinsic causes (i.e. through exposure to risk) and intrinsic causes of death and by estimating R and α for the subsample of intrinsic deaths. This way they document a downward trend for R over the last 40 years for 5 fully developed countries. From this they conclude that the "mortality signature" for humans has already been modified. Unfortunately they did not let the data decide whether the extrinsic Makeham parameter is still significantly present so that the two studies are not comparable. Actually, as the authors admit, it is often difficult to partition deaths in extrinsic and intrinsic categories. Getting killed by a road accident, for example, is at least partly intrinsic since, c.p. older victims are more likely to succumb to their injuries. The age distribution of pedestrians killed by road accidents parallels the distribution of deaths from all causes (Comfort, 1979).

Moreover, there appears to be evidence for an impact of nutrition and health in infancy and early childhood on the Gompertz parameter R. Note that an increase in R would be visible diagrammatically by a downshift of the $\log(\mu)$–curve at all ages whereas an increase in A shifts the curve predominantly at young ages such that curves for different A converge at high ages as shown in Figure 2. Finch and Crimmins (2004) observe – by eyeballing – such a parallel downshift of the mortality curve for Sweden over the last century and argue in favor of a causal effect of inflammatory exposure and nutrition during early childhood on this shift.

Some of the implications of the stability of the Gompertz-parameters can be discussed with help of Figure 3, which shows for Swedish men the estimated Gompertz curve for 1901-1910 (solid lines, replicating Figure 2) and for 1987 (dashed lines), together with its implication for the probability to survive to age x and life-expectancy at age x. The Figure impressively shows that so far technological, economic, and cultural progress has predominantly improved the survival probabilities for young people. Life-expectancy at age 80 in 1983 differs little from what it has been at the beginning of the 20th century.

The structural stability of the Gompertz-parameters is also helpful to explain the popular ideas of "rectangularization" and "compression of morbidity" (Fries, 1980). The middle panel of Figure 3 conveys the information that compared to the begin of the century a higher share of Swedish men reaches an old age of, say 70 years, and expires then more quickly during their last years before death. Visually, the survival curve becomes closer to rectangular over time. On average, an *individual* spends more of his or her life in a relatively healthy condition, an observation that has inspired the notion of a "compression of morbidity". Across individuals, however, there is no compression of morbidity. In fact, the panel on the left showing the force of mortality supports the opposite prediction: over time less young and intrinsically healthy people are killed from exogenous forces implying a rising share of the population displaying age-related frailties and chronical illness.

Figure 3 is also useful to shed light on the often controversially led discussion about the *human life* span. It has already been shown that strictly speaking such a thing as *maximum* human life-span does not exist. Even under time-invariance of the Gompertz-Makeham parameters, the simple fact that the "sample size" of people who ever lived on earth is continuously rising lets us expect that the maximum ever-observed life-length will rise as time proceeds.

Finch and Pike (1996) suggest to define T as the estimated age at death of the last survivor of a population of given finite size. This definition allows to calculate explicitly how life-span depends on sample size N. Plugging $S(x) = 1/N$, i.e. the probability to be the last man standing out of N, into (3) and ignoring background risk ($A = 0$) provides

$$\frac{1}{N} = \exp\left(-\frac{R}{\alpha}\exp(\alpha T) + 1\right) \quad \Rightarrow \quad T = \frac{1}{\alpha}\log\left(\frac{\alpha}{R}\log N + 1\right).$$

Given their estimates of the Gompertz parameters Finch and Pike obtain life-span as 105 years for $N = 10^3$ and 114 for $N = 10^7$. It turns out, that – without taking an oldest-old

amendment into account – the Gompertz law predicts actually life-span of local human and animal populations quite well. For example, it predicts for the sample size of US females in 1980 $T = 115$ years while it was actually 112 years. Note also the strong inverse relationship between T and α suggesting large potential improvements of T for small improvements of the pace of mortality α.

For constant α, however, life-span does not improve much through changes of N or R. Sensitivity of life-span with respect to background risk A can be read off from Figure 3. Inspection of the right and middle panel clarifies that the statement that "life-expectancy at birth (or at age 20) went up tremendously during the last century" is supported by the same data that lead to the conclusion that life-expectancy at age 100 or life-span (x for $S(x) = 1/N$) has not improved much.

The observation that increasing life-expectancy was overwhelmingly brought forth by declining background mortality inspired the following experiment. Suppose the Gompertz-Makeham law holds and the Gompertz parameters are indeed stable over time. To fit the curve to life-expectancy at birth in medieval England (1330-1479) which was about 22 years (Clark, 2007). A is set to 0.043. The implied predictions of the Gompertz-Makeham model are shown by dotted lines in Figure 4, which for better comparison also re-iterates from Figure 2 mortality for Sweden in the 20th century (solid lines) and the perpetual youth scenario (dashed lines).

The middle panel of Figure 4 clearly shows that survival according to Gompertz-Makeham under the high medieval background mortality is visibly not very different from the prediction of the "perpetual youth" model (dotted lines). The force of mortality, shown in the left panel, follows almost a straight line until about age 50, i.e. until an age to which less then 10 percent of population survive. In other words, although intrinsically present and not different from today, the mechanics of aging are not visible. The large majority of individuals dies from extrinsic causes. The notion that survival probabilities were about the same in human paleontology as in medieval England (Clark, 2007, Gurven and Kaplan, 2007) inspires a first attempt towards an *explanation* of human aging: we age because under high extrinsic mortality there was little evolutionary pressure for non-aging humans.[3]

The time-(in)-variance of the Gompertz-Makeham parameters can also be used to assess predictions about *future* gains in human life-expectancy. If future life-expectancy could be

---

[3]Evolutionary theories of aging are discussed in PART 4 of this review.

Figure 4: Aging in the 20th-century and in Pre-Modern times vs. Probabilistic Death
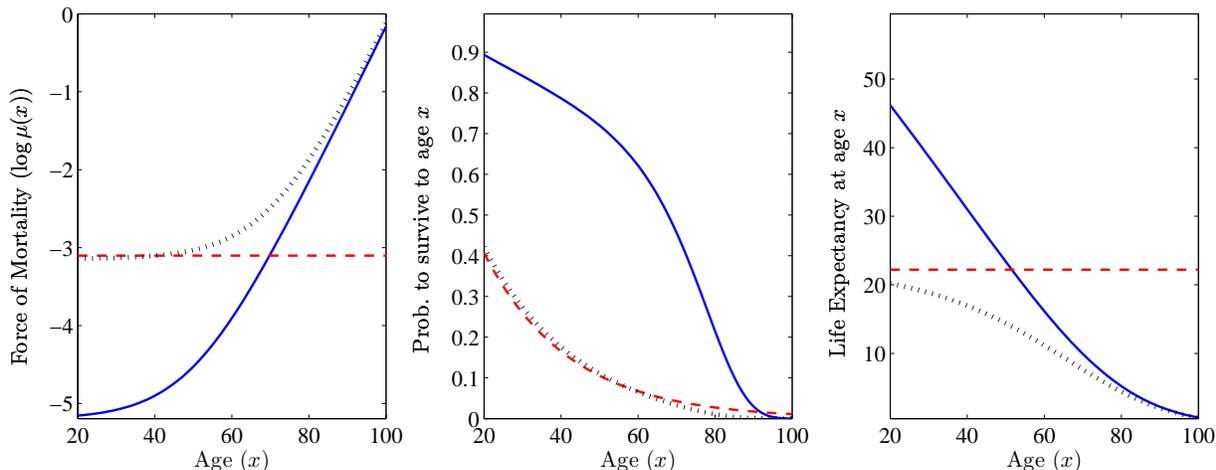
Solid lines: Estimates from Swedish life tables as in Figure 2. Dashed lines: hypothetical perpetual youth scenario: $\lambda = 0.025$ as in Figure 2. Dotted lines: Gompertz-Makeham with elevated background risk $A = 0.43$.

derived from interpolating historic trends, one can indeed arrive at the conclusion that life-expectancy at birth will improve by about 3 month per year of birth (Oeppen and Vaupel, 2002). The Gompertz-estimates, however, lead to a completely different conclusion. Because A is already close to zero for most developed countries, there will be little more future gains in life-expectancy as long as technological progress improves almost exclusively background mortality and future life-expectancy at birth will unlikely exceed 85 years (Fries, 1980, Carnes and Olshansky, 2007).

One problem with the stability hypothesis for the Gompertz parameters is that if improvements in mortality were exclusively through declining A and A is by now close to zero in fully developed countries, we should observe convergence behavior. Age-specific mortality across fully developed countries should converge over time and the age-distribution of deaths within countries should converge towards a limiting distribution. Yet, Wilmoth (1997) cannot find such convergence behavior in the data.

In any case, future technological progress may make it possible (e.g. through gene therapy) to reduce the Gompertz parameter α and it is illuminating to discuss briefly how this would be reflected by the mortality statistics. Technological progress operating through α would be very different from anything observed so far: it would effectively slow down the aging process. Note that curtailing or even abolishing major causes of death (like, for example, cancer or diabetes) would *not* be expressed as reduction of α. Without a reduction of α any successful fight against

one bodily impairment entails inescapably the occurrence of another impairment in the near future.[4]

Figure 5: Aging Before and After the Wonka-Vite
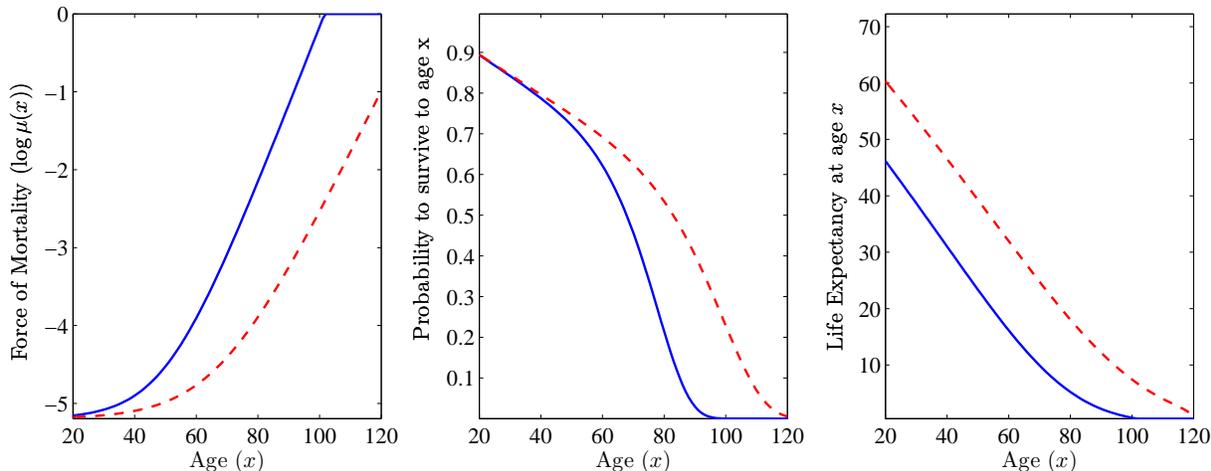
Solid lines: historical data as in Figure 2. Dotted lines: hypothetical reduction of α from 0.101 to 0.08.

Figure 5 shows the consequences of the introduction of a "Wonka-Vite" (Dahl, 1987, Kirkwood, 1999) i.e. a hypothetical pill that reduces α from 0.101 to 0.008. The difference to the observed historical evolution of aging shown in Figure 3 is striking. The Wonka-Vite effectively increases life-expectancy at *every* age by about 15 years and thus does indeed raise human life-span. While it does not produce a rectangularization of the survival curve or a compression of morbidity it effectively increases the health status at every age thus implying the prediction of less age-related deaths at every age and a lower share of unhealthy (morbid) individuals in the population.

4. SPECIES-SPECIFIC INVARIANTS: THE STREHLER–MILDVAN CORRELATION

While the Gompertz-parameters α and R seem to be invariant over time they differ indeed across sexes and across countries. On average, people age in different ways depending on their sex and provenience. On average, across countries, women face a lower R and a higher α (Garilov and Gavrilova, 1991), indicating that women have an initial advantage of lower aging, which is with rising age eventually caught up by men. In fact, there is a strong inverse (log-linear) association between R and α known as the Strehler-Mildvan correlation or the compensation effect of mortality (Strehler and Mildvan, 1960, Gavrilov and Gavrilova, 1991). Figure 6 shows the association between these parameters for 30 countries.

---

[4]A health-economic model in this spirit has been developed by Becker and Phillipson (1998).

Figure 6: The Strehler-Mildvan Correlation
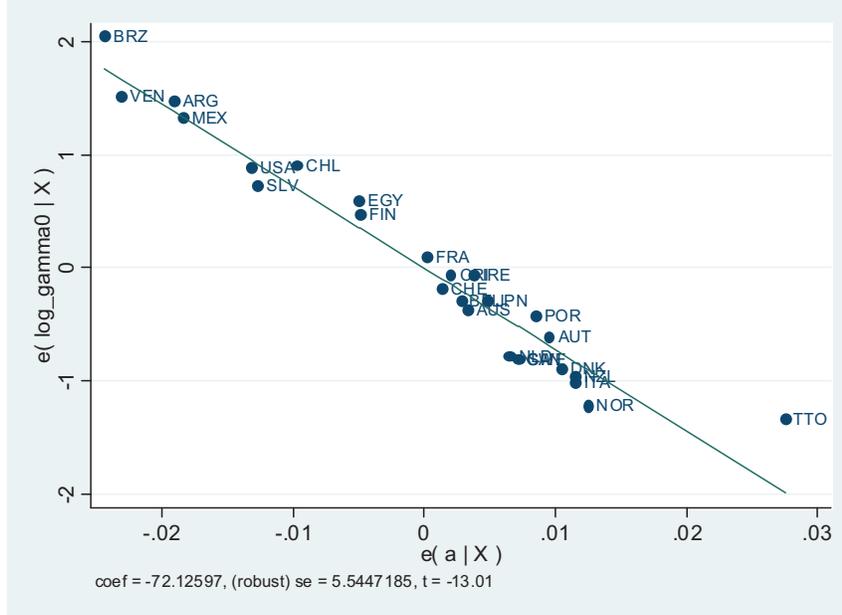
Data for 31 countries from Strehler and Mildvan (1950), Parameter a (measured along the abscissa coincides with α in the text. Parameter $\gamma0$ (measured in logs along the ordinate) coincides with R in the text.

The presence of the Strehler-Mildvan correlation has inspired the search for a species-invariant component of aging and a new definition of human life-span (Gavrilov and Gavrilova, 1991). To see this, suppose the estimated Strehler-Mildvan correlation is given by

$$\log R_i = \log M - \cdot \alpha_i T \tag{4}$$

where for $i = 1, \ldots, n$ the R_i and α_i are the country- and sex-specific realizations of the Gompertz parameters and M and T are the invariant coefficients of the Strehler-Mildvan correlation. Thus $\mu_i = A_i + R_i \exp(\alpha_i x)$ is the country and sex-specific force of mortality. Inserting into this the Strehler-Mildvan correlation provides:

$$\mu_i - A_i = M \exp\left[\alpha_i(x - T)\right]. \tag{5}$$

Observe that the modified Gompertz-Makeham law implies a fixed point. It predicts that – controlling for country-specific background risk – men and women across countries share a common force of mortality M at age T. This implication is visualized for a sample of three lifetime tables in Figure 7. Since the focal point (T, M) is assumed approximately by all observations

it can be interpreted as a *species-specific* constant. For humans the point estimate is $T = 95$ years. Gavrilov and Gavrilova (1991) have shown that such a species-invariant focal point is also observable within animal societies for different populations of drosophila and of labor rats. The time invariance of the Gompertz law and the Strehler-Mildvan correlation suggests that – controlling for country-specific background risk (degree of economic development) humans share a common mechanism of aging, a common stochastic process according to which individual bodies lose function over time and bodily failures and impairments are accumulated.

Figure 7: The Strehler-Mildvan Correlation
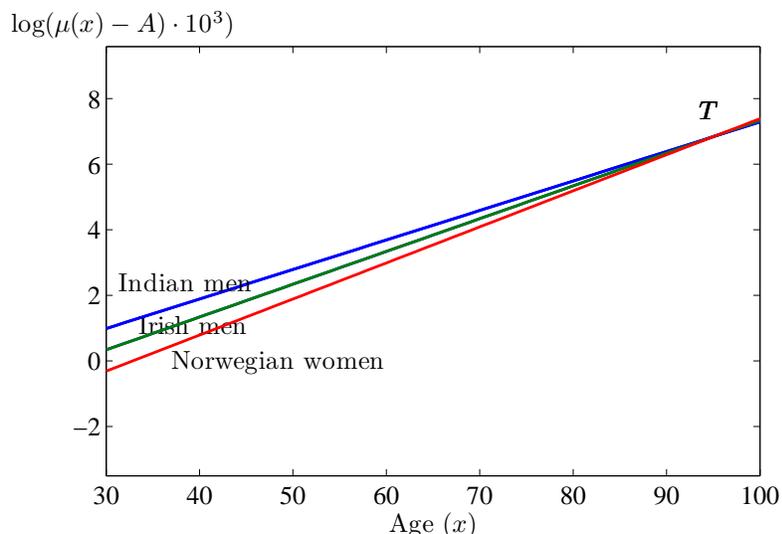
Data from Gavrilov and Gavrilova (1991) and own calculations.

A general pattern emerging from the Strehler-Mildvan correlation is that economically more advanced countries are characterized by a lower R and higher α, i.e. by a lower initial mortality rate and faster speed of aging. This implies that although lifespan T seems to be unaffected by economic advances, the mortality rate is everywhere, i.e. for all ages below T, lower in the economically advanced country. An important conclusion from this is that aging quickly (having a high α) is actually not a burden but an indication of superior fitness. This notion will be further substantiated in the next section on reliability. Finally note that if R falls continuously and α rises such that lifespan T remains constant, we would nevertheless expect that life-expectancy is continuously improving and that the record of the highest so far observed age at death (the conventional measure of lifespan) is rising as well.

5. Reliability Theory

The fact that all humans appear to age according to a common formula, which we moreover share with fruitflies, rats, and other animals, motivates the search for a common process that drives aging. The quest for such a process is challenging because, as emphasized already, there exists no biological clock. Trying to explain aging following a line of reasoning by stating that humans age because their organs (e.g. the cardiovascular system) age, and that organs age because the tissue they are made of ages etc. will turn out to be utterly futile. At some point a micro-level will be reached that consists of non-aging entities, for example atoms. Eventually, we want to explain why a system ages that consists of non-aging elements.[5]

In explaining aging systems biologists do not have to start from scratch. They can built upon a subdiscipline in engineering, reliability theory, which is concerned just with this particular problem, i.e. the problem how complicated mechanical systems consisting of non-aging elements (like cars) are increasingly losing function over time so that the failure rate, i.e. the probability of the expiry of the system increases with age (Barlow and Proschan, 1975). The task for biologists is to modify and extend the available theory such that it is capable of motivating the Gompertz-Makeham law (and possibly other important phenomena of human aging, like the Strehler-Mildvan correlation or non-aging of the oldest-old). There are several, sometimes complementing, reliability theories available (Gavrilov and Gavrilova, 1991, Novoltsev, 2006, Finkelstein, 2008). Here we try to explain the idea by describing two particularly straightforward models in detail after which we briefly mention existing extensions. The presentation follows Gavrilov and Gavrilova (1991) who were the first to integrate reliability research into the realm of biology.

Consider an organism constructed of n non-aging blocks. Non-aging means that the failure rate λ is constant over time. Given age x the probability of a block to fail is $1 - \exp(-\lambda x)$. Blocks are connected in parallel and the organism lives as long as at least one block is in order. The probability that the organism expires before age x is given by $F(x) = [1 - \exp(-\lambda x)]^n$ and the probability to survive to age x is $S(x) = 1 - F(x)$. The unconditional probability to die at age x is thus given by $\mathrm{d}F/\mathrm{d}x = -\lambda n \exp(-\lambda x)[1 - \exp(-\lambda x)]^{n-1}$ and the force of mortality is

$$\mu(x) = \frac{\lambda n \exp(-\lambda x)[1 - \exp(-\lambda x)]^{n-1}}{1 - [1 - exp(-\lambda x)]^n}.$$

---

[5]Of course, the claim that atoms do not age is justified only within a reasonable time-frame. If the time frame gets long enough, even the universe ages.

Taking a Taylor-approximation around zero, implying $1 - \exp(-\lambda x) \approx \lambda x$, the expression simplifies to $\mu(x) \approx n\lambda^n x^{n-1}$ and using L'Hospital's rule we obtain $\lim_{x \to \infty} \mu(x) = \lambda$.

The simple model is thus capable of explaining aging: the force of mortality $\mu(x)$ is increasing with age x. Aging is explained as a *loss of redundancy* over time. This notion of aging as accelerated loss of organ reserve is in line with the mainstream view in the medical science. For example, initially, as a young adult, the functional capacity of human organs is estimated to be tenfold higher than needed for survival. (Fries, 1980).

The model is also useful to explain mortality of the oldest-old. With increasing age the organism loses redundancy until survival depends, in the limit, just on the survival of the last functioning non-aging block. Thus the organism converges towards the constant mortality rate λ of its non-aging elements. This is a general result from reliability theory: the rate of aging, i.e. the age-dependent component of the mortality rate (the failure rate), is increasing in the complexity (redundancy) of the system. We can expect that, for example, light bulbs and bacteria, age at a much lower rate than cars or humans. Seen this way, aging appears as a positive trait. It occurs because complex systems start out at a high level of redundancy and are thus less likely to expire at young age.

The problem with the simple model is that the derived $\mu(x)$ at young ages does not follow the Gompertz-Makeham law. It follows – similar to the failure rate of mechanical systems – a Weibull distribution. In order to describe the aging process of humans, the model has to be made "more human". Next we consider one of several possible extensions.

Suppose an organism consists of m *irreplaceable* blocks, i.e. blocks connected in series such that the organism dies if one block fails. Each block consists of n elements, connected in parallel with age-independent failure rate λ. Following the computations from above we know that the failure rate of a block is $n\lambda^n x^{n-1}$ for small x and approaches the constant λ for large x. Because blocks are connected in series (each of them being essential), the failure rate of the organism equals the sum of failure rates of blocks i.e. $m \cdot n\lambda^n x^{n-1}$ for small x and $m\lambda$ for large x.

Next suppose that many elements are initially defect. The probability of an initially functioning element is given by q. The failure rate of a block with i initially functioning elements is thus $\mu_b(i) = i\lambda^i x^{i-1}$ for small x and $\mu_b(i) = \lambda$ for large x. Blocks, ordered according to their number of initially functioning elements, are binomially distributed. We approximate the Binomial with

a Poisson distribution

$$P(i) = c \cdot \exp(-k) \frac{k^i}{i!}$$

where $k \equiv nq$ is the mean number of initially functioning elements and c is a normalizing constant ensuring that the sum of probabilities equals one. The failure rate of the system, computed as the sum of the failure rate of blocks, is then obtained as

$$\mu(x) = \sum_{i=1}^{n} m P(i) \mu_B(i) = mc \exp(-k) P(i) = mc \cdot \exp(-k) \sum_{i=1}^{n} \frac{k^i}{i!} \mu_B(i).$$

Inserting $\mu_B(i)$ we obtain that for young age (small x) the failure is approximately

$$\mu(x) \approx R \sum_{i=1}^{n} \frac{(k\lambda x)^{i-1} \cdot i}{i!} = R \cdot \left[\sum_{i=1}^{\infty} \frac{(k\lambda x)^{i-1}}{(i-1)!} - \sum_{i=n+1}^{\infty} \frac{(k\lambda x)^{i-1}}{(i-1)!} \right].$$

with $R \equiv mc\lambda k \exp(-k)$. Now consider a complex, redundant organism with a large number of elements. In the limit, for $n \to \infty$, the last term in brackets converges to zero. The first term in brackets simplifies to $\exp(k\lambda)$.

Inserting into $\mu(x)$ the $\mu_B(i)$'s for large x we get the failure at high age approximately as

$$\mu(x) \approx mc \exp(-k) \sum_{i=1}^{n} n \frac{ki}{i!} \lambda = mc\lambda \exp(-k) \left[\sum_{i=1}^{\infty} \frac{k^i}{i!} - \sum_{n+1}^{\infty} \frac{k^i}{i!} \right].$$

Again the last term in brackets is approximately zero for large n. The first term equals $\exp(k)$ such that the expression simplifies to $\mu(x) = cm\lambda$. Collecting results we have

$$\mu(x) \approx \begin{cases} R \mathrm{e}^{\alpha \cdot x} & \text{for small } x \\ c \cdot m \cdot \lambda & \text{for large } x. \end{cases} \tag{6}$$

with $\alpha = k\lambda$. The organism ages according to Gompertz law. For large ages (the oldest old) the force of mortality converges to a high plateau.

Taking log's of R we get $\log R = \log(cmk\lambda) - k$ and inserting $\alpha = k\lambda$ we arrive at

$$\log R = \log M - \alpha T \tag{7}$$

with $M = \alpha mc$ and $T = 1/\lambda$, which is the Strehler-Mildvan correlation. The reliability model is capable to generate the most important regularities of human (and other animals) aging.

For an interpretation of parameters, first note that T is uniquely pinned down by λ, the age-independent failure rate of an element. If λ is a species-specific constant, then the model

predicts a unique focal point (life-span) T for the species. Across species, T depends inversely on the robustness of its non-aging elements. Let's reasonably assume that m, the number of irreplaceable blocks, is also a species dependent constant. Then all variation within a species results from variation of a k, the mean number of initially functioning elements.

The parameter k is a compound parameter $k = nq$. Consider first variation in n, the number of elements per block. For humans these differences could exist across countries, because their citizens are on average of different size. This could in principle come through country-specific diet and/or Darwinian selection because optimal body-size depends on ambient temperature and the disease environment. The model then predicts that $\alpha = k\lambda = nq\lambda$ is small in countries were people are on average relatively short (say, India) and R is small in countries were people are on average tall (say, the Netherlands). While the model predicts the same life-span for Dutchmen and Indians, it also predicts that the Dutch start out at lower mortality rates at younger years and are aging faster. In fact, the Dutch's headstart is caught up by the Indians just at T implying that everywhere below T survival prospects are better and life-expectancy is higher in the Netherlands. Generally, the model predicts in line with the evidence a positive association between body size and life-expectancy. The explanation is redundancy. Larger humans have a larger organ reserve to life off.[6]

Next, hold n constant and consider variation of q, the probability for an element to be initially functioning. Here it is probably more reasonable to consider within country variation over time (say Indians now and 50 years ago, or Dutchmen now and 300 years ago). The idea here is that available nutrition (for mother and child) and disease exposure early in life have shaped q. Taking the historic improvement in nutrition and health into account, the model then predicts that both Indians and Dutchmen are aging faster now but starting out much better at younger age. Consequently, survival prospects and life-expectancy have improved at any age. Actually, both Indians and Dutchmen are also predicted to be taller because of the generally improved conditions (Fogel, 1994) so that mortality would have improved because of the simultaneous and amplifying effect of q and n on $k = nq$. But even holding body size (n) constant, the model predicts through better initial functionality "fetal origins" (Barker, 1995, Black et al., 2007), i.e. lasting consequences of early events in life on later mortality and morbidity.

_____

[6]PART 3 of this review discusses the interaction of body size and mortality in detail.

While the model does a fairly good job in explaining basic mechanisms of human aging,a better approximation of the actual aging process can be achieved by adding more details, i.e. more complexity, Important extensions of the basic model include cascading effects, i.e. the phenomenon that failure of one element of the system entails failure of other elements (Gavrilov and Gavrilova, 1991) and mechanisms of imperfect (cell-) maintenance and repair (Finkelstein, 2008). The most recent model of Milne (2009) includes also a mechanism for redundancy expansion in early life and is complex enough to redraw with great precision actually observed mortality data.

A common characteristic of all reliability-based models is that organisms are conceptualized as complex systems consisting of essential parts (e.g. organs, tissue) connected in series, which are in turn built of smaller entities connected in parallel. Parallel connectivity means that every reliability theory is built upon the idea of redundancy. Another common theme is a stochastic failure rate for the basic entities. The notion of aging as driven by a "natural" stochastic process helps to explain the "unfair" nature of human fate, i.e. why we actually observe large difference of aging on the individual level. Reliability theory can explain why individuals raised under equal conditions and/or built from the same genes (monozygotic twins) can age and eventually die in a very different ways. At the same time the models provides a toehold to explain how population- (e.g. country-) specific characteristics and the environment early in life have a bearing on aggregate aging behavior of entire populations and/or sub-populations. In short, it integrates "good luck" as a major third important driver of longevity besides "good genes" and "good behavior". By now the new view that aging and death are probably best conceptualized as accidental stochastic shocks on the molecular level is firmly established in the natural sciences and has entered the biology textbooks (Arking, 2006).

6. Aging, Frailty, and Morbidity

Although age is such a powerful predictor of mortality on the aggregate level, it is a relatively poor predictor on the individual level and biologists are tirelessly emphasizing that aging should not be conceptualized as time-dependent but as an event-dependent process. We thus turn next to the measurement of how aging is *expressed* in individuals and the question how – on the aggregate level – the expression of aging is related to age. These questions are frequently addressed under the heading of *biomarkers.* A biomarker in general is an indicator of the

biological state of an organism. In bio-gerontology a set of biomarkers is an indicator of the *biololigcal age* of an individual. On the individual level biomarkers allow us to disentangle chronological age and individual age, i.e. to understand why a 40 year old person feels like being 60 and vice versa. On the aggregate level it is interesting to investigate how biomarkers develop with age and how chronological age and biological age are related.

There exists no unified theory how biomarkers for aging should look like and consequently the literature has followed different approaches (e.g. Comfort, 1979, Borkan and Norris, 1980, Shock, 1981, Weale, 1997, Jackson et al., 2003). A common theme is the development of an index, i.e. a whole set of biomarkers measuring physiological (and sometimes also the cognitive) variables followed by an investigation of how the developed index correlates with age and how well it predicts mortality. Typical age- and mortality-related biomarkers are systolic blood pressure, grip strength, forced expiratory volume, white blood cell count, hearing loss, and reaction time.

Next we survey one indicator, the so called frailty index, in more detail because for this indicator the literature went farthest to explore its relation to mortality. The frailty index has been established and investigated by Mitniski and Rockwood and several coauthors in series of articles (e.g. Mitniski et al, 2002a, 2000b, 2005, 2010). The following exposition is mainly based on Mitnitski et al., 2002a).

The frailty index counts for a large sample of individuals the bodily impairments which are actually present out of a list of potential impairments, ranging from mild deficits (reduced vision, incontinence) to near lethal ones (stroke, cancer). Mitnitski and Rockwood consider a sample of 15 to 79 years old Canadians and 38 impairments. They then show that the relative number of deficits, i.e. the frailty index D, of an individual correlates with age in the exponential Gompertz-Makeham fashion. Specifically, deficit accumulation evolves with age x according to

$$D_i(x) = B + Q_i \exp(\beta_i x) \tag{8}$$

where $i = \{m, w\}$ is an index taking sex-specific differences into account.

Given the large sample size, the result can be interpreted as the probability of having D percent of all possible frailties at the age of x. The parameters of the frailty accumulation law are estimated with great precision. The point estimate and the 95 percent confidence interval for Canadian men are $B = 0.02 \pm 0.001$, $\log Q_m = -5.77 \pm 0.06$, and $\beta_m = 0.043 \pm 0.001$ with an R^2 of 0.97. Women are estimated to face the same initial frailty B and a lower β ($\beta_w = 0.031 \pm 0.001$)

and a higher Q ($\log Q_w = -4.62 \pm 0.06$). This means that men are estimated to start out better and then to accumulate frailties at higher speed i.e. to age faster than women.

The fact that men are initially less impaired and accumulate deficits faster implies that the sex-specific frailty curves are meeting each other at some age T_D. Following the Streher-Mildvan approach we get

$$D_i = B + D_T \cdot \exp\left[\beta_i(x - T_D)\right]. \tag{9}$$

Implying that men and women share the same frailty $B + D_T$ at age T_D. While the fact that such an intersection exists is not surprising, the striking result here is that the estimate of $T_D = 94 \pm 2$ years coincides with the focal point of mortality (life-span) estimated by Gavrilov and Gavrilova (1991). The result suggests – at least for Canadians – that the mechanisms behind frailty accumulation and mortality are probably very similar. It supports, indirectly the reliability theory of aging and mortality.

Using $T = T_D$, the strong association between mortality and frailty, both apparently governed by a Gompertz-Makeham law, can be made even more visible by solving (9) for T_D and substituting the result for T in (2) using the definition $M \equiv R \exp(\alpha T)$. This provides the positive functional association between mortality and frailty as

$$\mu_i(D_i) = A + M \cdot \left(\frac{D_i - B}{D_T}\right)^{v_i}, \tag{10}$$

where $v_i \equiv \alpha_i/\beta_i$.

Apparently the association between frailty and mortality is non-linear. Recalling that α is about 0.1 the exponent v_i is larger than unity, suggesting a convex shape. In words, another bodily impairment affects mortality relatively little when frailty is low compared to another impairment when frailty is already high. An intuitive explanation could be that less severe frailties, like impaired vision or backpain, are on average taken up earlier in life compared to (near) lethal ones like cardiac infarction or stroke.

The striking result here is that the exponent is lower for men than for women reflecting the fact that the force of mortality increases faster for women (α is larger for women) than for men while frailties are accumulated faster by men (β is larger for men). It implies that for ages below $T_D = T$, women display more frailties than men but men are more likely to die.

The fact that (Canandian) men have a comparative advantage in frailty accumulation can be straightforwardly explained by reliability theory. Men are on average larger and have thus a

larger organ reserve, a larger redundancy n (more bone mass, more muscle muss) to wear off during aging. Male Organs are thus more reliable than female and are predicted to fail later in life.

The puzzling effect here is that women are nevertheless predicted to have a comparative advantage in mortality. One possible explanation for this could be found by taken into account the size and singularity of organs. Eyes, for example, usually come in pairs of about the same size for men and women. This opens the door for q, the probability of an initial functioning element, to have an impact. Suppose q is larger for women. Recalling that the mean probability of a block (say an organ) to fail is given by the compound qn, it is imaginable that women have a comparative advantage when size n of the organ does not matter much for function (e.g. the cardiovascular system) whereas men have a comparative advantage when size is important (e.g. muscle strength and bone mass). Consistently with the mortality-frailty data, the model would then predict that men are on average more likely to develop, for example, a blocked neck artery (a stroke) but are less likely to suffer from back pain and osteoporosis.

The discussion leads us, finally, to a distinction between loss of function (measured by the frailty index) and morbidity and their specific interaction with age and mortality. While the frailty index is just a counter of personal health experiences, the term morbidity is commonly used with an emphasis on the *quality* of being unhealthy, in particular with relation to disability. Although the evidence is sometimes conflicting, there exist several studies documenting for the U.S. and other developed countries a decline of disability among the old.[7]

The fact that the old, given age, experience less disability today than past generations entails no contraction to the adamant loss of bodily function with age predicted by reliability theory, Both phenomena are compatible once technological progress is taken into account. For example, before the invention of glasses or hip replacement, cataract or arthritis may have caused disability while today these age-dependent impairments are at best mild nuisances. Seen this way, disability prevalence among the old is not a good indicator of aging but a good indicator of medical technological progress (and, possibly, of efficiency and equality of health care provision).

Technological progress, however, has also driven a wedge between mortality and frailty by postponing death from age-related causes. Contemplating the fact that the Mitnitskiy and

---

[7]Note that declining disability among the old does not imply a compression of morbidity at the population level (Section 2.3). The rising population share of old and potentially disabled persons works in the opposite direction. See Freedman et al. (2002) Crimmins (2004), and Parker and Thorslund (2007) for surveys on trends of disability and morbidity among the old.

Rockwood's frailty-counter advances by one if for, example, a person has *survived* a heart attack or a stroke, may lead to the conclusion that the frailty index is actually a better measure of aging than the force of mortality. In any case it highlights the double role of medical technological progress. To summarize, extrapolating past technological trends we expect more people to survive towards a state of less functionality in less redundant bodies. But we also expect less disability, since loss of bodily function will be increasingly repaired by technology. With contrast, a yet to come bio-medical progress affecting the accumulation rates α and β (as, hopefully, epi-genetic advancements) would have a very different quality. It promises improvement of *both* measures of aging, i.e. lower mortality and higher body functionality at any given age.

The Gompertzian accumulation of frailties suggests for (health-) economists a straightforward improvement of modeling of health deterioration with age. Normally, health is introduced as a state variable similar to human capital evolving like $\dot{H} = I - \delta H$, where a dot signifies a derivative with respect to age and I is health investment, see e.g. Ehrlich and Chuma (1990) and PART 1 of this survey. Keeping δ constant the model predicts, counterfactually, that health loss is largest when the state of health is best (δH is largest when H is highest). Of course, health researchers are aware of this contradiction of the facts, and try to repair the health equation by introducing an age-dependent depreciation rate $\delta(x)$. But how exactly should the deprecation function look like so that the model provides an acceptable approximation of real health deterioration? An intuitive and readily implemented approach is available by Gompertzian frailty accumulation.

Suppose actual health is defined as best attainable health minus accumulated frailties, $H = \bar{H} - D$ where $\bar{H}$ could be the state of health of a healthy 10 year old. This implies $\dot{H} = -\dot{D}$. Taking the derivative in (9) with respect to age and ignoring sex-specific indices we get

$$\dot{D} = \beta Q \exp(\beta x) = \beta(D - B). \tag{11}$$

Inserting this into $\dot{H}$ and re-substituting D provides

$$\dot{H} = \beta \left(\bar{H} - H - B \right). \tag{12}$$

Equation (12 constitutes)a simple linear differential equation for health, which – in line with the facts – predicts that health loss is small at a good state of health and increasing losses are predicted when the health stock deteriorates. In fact, the model is, at least for Canadians, readily calibrated with the available data. After all that has been discussed so far it is also clear

where successful health investments would enter the equation. After the Wonka-Vite, they will reduce the β. Today, they will reduce the B because no health investment has yet the power to slow down the pace of aging,

7. Conclusion

This paper has shown a strong log-linear association between age and the force of mortality, known as the Gompertz-Makeham law, and its implications for survival and life-expectancy. It has used the formula to discuss the history and science fiction of human aging. It has then shown another strong association holding between the parameters of the law, known as the Strehler-Mildvan correlation, and developed its implication for human life-span and the idiosyncracies of the aging process across countries and sexes.

These observations have set the stage for an explanation of aging using reliability theory from engineering, a theory that explains aging of organism and other systems constructed of non-aging elements by the intricate interplay of stochastic processes operating in series and in parallel, i.e., in short, by the depletion of initial functional redundancy within the system. The theory was then confronted with an empirical measure of functional loss, the frailty index. Again a strong association between the log-linear accumulation of frailties with age and the Gompertz-Makeham law emerged. The overall conclusion is thus the notion of aging as the increasing loss of bodily function with age. Although this loss of function can be best conceptualized as being purely stochastic at the cell level it manifests itself as a "law of aging" at the aggregate level. This has lead to some first suggestions for the modeling of health deterioration and maintenance, which hopefully turn out to be useful to answer future (health-) economic questions and, in particular, for the assessment of the long-run economic perspectives of aging societies.

Some important aspects aging have not been addressed at all in this paper, for example how evolution has shaped human aging, how aging relates to physiological processes, in particular to metabolic activity, and how different elements of bodily function age differently, i.e. how different aspects of human capital (e.g. muscle strength, different functions of the brain) deteriorate with age. These questions are in detail addressed in Part 1,3, and 4 of this review.

REFERENCES

Arking, R., 2006, *The Biology of Aging: Observations and Principles*, Oxford University Press, Oxford.

Barker, DJP, 1996, Fetal origins of coronary heart disease, *British Medical Journal* 311, 171-174.

Barlow, R.E. and Proschan, F., 1975, *Statistical theory of reliability and life testing: Probability models*, Holt, Rinehart and Winston, New York.

Blanchard, O.J., 1985, Debt, deficits, and finite horizons, *Journal of Political Economy* 93, 223-247.

Borkan, G.A and Norris, A.H, 1980, Assessment of biological age using a profile of physical parameters, *Journal of Gerontology* 35, 177-184.

Carnes, B.A. and Holden, L.R. and Olshansky, S.J. and Witten, M.T. and Siegel, J.S., 2006, Mortality partitions and their relevance to research on senescence, *Biogerontology* 7, 183–198.

Carnes, B.A. and Olshansky, S.J., 2007, A realist view of aging, mortality, and future longevity, *Population and Development Review* 33, 367- 381.

Comfort, 1979, *The Biology of Senescence*, 3rd edition, Elsevier, New York.

Crimmins, E.M., 2004, Trends in the health of the elderly, *Annual Review of Public Health* 25, 79–98.

Dahl, R, and Foreman, M., 1987, *The Complete Adventures of Charlie and Mr Willy Wonka*, Puffin Books.

Ehrlich, I. Chuma, H., 1990. A Model of the Demand for Longevity and the Value of Life Extension, *Journal of Political Economy* 98, 761-782.

Finkelstein, M.S., 2008, *Failure Rate Modeling for Risk and Reliability*, Springer, London.

Finch, C.E. and Pike, M.C., 1996, Maximum life span predictions from the Gompertz mortality model, *Journal of Gerontology* 51, 183–194.

Finch, C.E and Austad, S.N, 2001, History and prospects: symposium on organisms with slow aging, *Experimental Gerontology* 36, 593–597.

Finch, C.E. and Crimmins, E.M, 2004, Inflammatory exposure and historical changes in human life-spans, *Science* 305, 1736-1739,

Fogel, R.W., 1994, Economic growth, population theory, and physiology: The bearing of long-term processes on the making of economic policy, *The American Economic Review* 84, 369–395.

Freedman, V.A. and Martin, L.G. and Schoeni, R.F., 2002, Recent trends in disability and functioning among older adults in the United States: a systematic review, *JAMA* 288, 3137-3146.

Frenck, R.W. and Blackburn, E.H. and Shannon, K.M., The rate of telomere sequence loss in human leukocytes varies with age, *Proceedings of the National Academy of Sciences of the United States of America* 95, 5607-5610.

Fries, J.F., 1980, Aging, natural death, and the compression of morbidity, *New England Journal of Medicine* 303, 130-135.

Gavrilov, L.A. and Gavrilova, N.S., 1991, *The Biology of Human Life Span: A Quantitative Approach*, Harwood Academic Publishers, London.

Gavrilov, L.A. and Gavrilova, N.S., 2001, The reliability theory of aging and longevity, *Journal of theoretical Biology* 213, 527–545.

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.

Grossman, M., 1972, On the Concept of Health Capital and the Demand for Health, *Journal of Political Economy* 80, 223-255.

Gurven, M. and Kaplan, H., 2007, Longevity among hunger-gatherers: a cross-cultural examination, *Population and Development Review* 33, 321-365.

Jackson, S.H.D. and Weale, M.R. and Weale, R.A., 2003, Biological agewhat is it and can it be measured?, *Archives of Gerontology and Geriatrics* 36, 103–115

Kirkwood, T.B.L., 1990, The Disposable Soma Theory of Aging, in: *Genetic Effects on Aging II*, D.E. Harrison, (Ed.), Caldwell, N.J.: Telford Press, 9-19.

Kirkwood, T.B.L.,, 1999, *Time of Our Lives: The Science of Human Aging*, Oxford University Press, Oxford,

Makeham, W.M., 1860, On the law of mortality and the construction of annuity tables, *Journal of the Institute of Actuaries* 8, 301–310.

Masoro, E.J., 2006, Are age-associated diseases and integral part of aging?, in: Masoro, E.J. and Austad, S.N., (eds.), *Handbook of the Biology of Aging*, Academic Press.

Medawar, P.B., 1952, *An unsolved problem of biology*, Lewis, London.

Milne, E.M.G., 2006, When does aging begin, *Mechanisms of Aging and Development* 127, 290-297.

Milne, E.M.G., 2008, The natural distribution of survival, *Journal of Theoretical Biology* 255, 223-236.

Mitnitski, A.B. and Mogilner, A.J. and MacKnight, C. and Rockwood, K., 2002a, The accumulation of deficits with age and possible invariants of aging, *Scientific World* 2 2, 1816–1822.

Mitnitski, A.B. and Mogilner, A.J. and MacKnight, C. and Rockwood, K., 2002b, The mortality rate as a function of accumulated deficits in a frailty index, *Mechanisms of ageing and development* 123, 1457–1460.

Novoseltsev, V.N, 2006, Mathematical modeling in biology: Systems capable to live and die, *Automation and Remote Control* 67, 835–855.

Perks, W., 1932, On some experiments in the graduation of mortality, *Journal of the Institute of Actuaries* 63, 12-57.

Philipson, T.J. and Becker, G.S., 1998, Old-age longevity and mortality-contingent claims, *Journal of Political Economy*106, 551–573.

Oeppen, J. and Vaupel, J.W., 2002, Broken limits to life expectancy, *Science* 296, 1029–1031.

Olshansky, S.J. and Carnes, B.A., 1997, Ever since Gompertz, *Demography* 34, 1-15.

Parker, M.G. and Thorslund, M., 2007, Health trends in the elderly population: getting better and getting worse, *Gerontologist* 47, 150–158.

Riley, J.C., 2001, *Rising life expectancy: a global history*, Cambridge University Press, Cambridge.

Rockwood, K. and Song, X. and MacKnight, C. and Bergman, H. and Hogan, D.B. and McDowell, I. and Mitnitski, A., 2005, A global clinical measure of fitness and frailty in elderly people, *Canadian Medical Association Journal* 173, 489-495.

Rockwood, K. and Rockwood, M.R.H. and Mitnitski, A., 2010, Physiological redundancy in older adults in relation to the change with age in the slope of a frailty Index,, *Journal of the American Geriatrics Society* 58, 318–323.

Shock, N.W., 1981, Indices of functional age, in: *Aging: A Challenge to Science and Society*, D. Danon et al. (eds), Oxford University Press, Oxford.

Strehler, B.L. and Mildvan, A.S., 1960, General theory of mortality and aging, *Science* 132, 14-21.

Wachter, KW and Finch, CE., 1997, *Between Zeus and the Salmon: The Biodemography of Aging*, Washington, DC: National Academy of Sciences.

Weale, R.A., 1997, Human biological decline and mortality rates, *Mechanisms of Aging and Development* 97, 55-72.

Williams, G.C., 1957, Pleiotropy, Natural Selection, and the Evolution of Senescence, *Evolution* 11, 398–411.

Wilmoth, J.R., 1997, In search of limits, in: Wachter, KW and Finch, CE. (eds) *Between Zeus and the Salmon: The Biodemography of Aging, Washington, DC: National Academy of Sciences*, 38-63.

Yaari, M.E., 1965, Uncertain lifetime, life insurance and the theory of the consumer, Review of Economic Studies 32, 137-1350.