Lund University
School of Economics and Management
Department of Economic History

The Rate of Aging: concepts and directions for future research

Filipe Ribeiro

u évora
ESCOLA DE CIÊNCIAS SOCIAIS
DEPARTAMENTO DE SOCIOLOGIA

Sponsor: Max Planck Institute for Demographic Research
EDSD Advisor: James W. Vaupel (MPIDR)
EDSD Co-Advisor: Kirk Scott (Lund University)
Home Advisor: Maria Filomena Mendes (University of Évora)

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Abstract:

Successive improvements in human health resulted in a linear increase in the record life expectancy. This improvements, correlated with the discovery that after age 110 mortality levels off reaching a plateau, resulted in the assumption that the rate of aging can be a biological factor that is invariable for all individuals in all populations.
In this essay will be presented different concepts and theories trying to give a better understanding about the rate of aging, as well why the concept of a constant and shared rate of aging has emerged.
The demography and gerontology points of view will be presented, explaining how and where these two sciences disagree. Finishing, some conclusions based in the literature will be presented and some directions for future research as well.

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1. Introduction

"How long do we will live?" is one of, if not the most, important question to which every human would like to have an answer. However, the best answer that we have until now is that we are "broken limits" in what concerns to life expectancy (Oeppen & Vaupel, 2002).

In this direction, it is important to know and understand what is happening during our aging process, i.e., since we born until we die, and if in the future we will be able to understand the behaviour of the mortality curve, it will be possible to model it and have more and more accurate results.

Gerontology is one of the sciences that are studying this phenomenon and its main goal is "to preserve human health and well being, and extend healthy life" (de Magalhães, 2006). In this sense we can define aging as the age-related increase in vulnerability and decrease in viability (Comfort, 1964) over time, whether during development, young adult life, or senescence (Finch, 1990).

On the other hand, demographers are more interested in understanding the evolution and the impact of the rate of aging in mortality. And once that the mortality curve can be divided in three different levels, juvenile, middle, and senescent mortality, is at older ages that we can see the most important "gains", once that the ones that are able to reach older ages, have higher probabilities to live longer.

Although that the mortality observed in the first level is mainly due to the frailty of newborns, the causes of death registered on the second are typically due to reckless behaviour, and if we can suppress these "difficulties" and reach older ages we still have (generally) some (raising) years of life ahead.

Like Vaupel (2010) wrote in his *Nature* paper, *"mortality is by far the most important readily and reliably measured index of health"*, and if we are increasing our lifespan this can be an important indicator. However, this increase can be also explained based in the other different actions, like smoking, wrong diets, or reckless behaviour, once that "correct" changes in our behaviour during lifetime will result in an extension of our own years of life, even in a smaller scale (like diets or smoking) independently the age time that we change (Vaupel et al., 2003). In fact, some studies with *Drosophila* (a kind of medfly) showed that dietary restriction could extend lifespan (Mair et al., 2003).

One of the most important and old topics in demography is the description, with mathematical models, of the observed age patterns of adult mortality (Bongaarts, 2004). Benjamin Gompertz, in 1825, was one of the pioneers, creating the first "law of mortality" $[\mu_x = \alpha e^{\beta x}]$, where the force of mortality at age x – $[\mu_x]$, increases with age at a stable exponential rate. However, despite this model over age is able to explain the behaviour from a large part of the age range, young and very old ages are not included.

However, all populations are heterogeneous starting with our own composition, where all of us have different DNA and ones more than others are more susceptible to some diseases, or in social behaviours, that are different between cultures, sexes and ages.

Vaupel et al. (1979), claims that in a random population there are always frailer individuals than others, and the force of mortality for an individual should always take into account his frailty – $\mu(x, y, z)$.

Since that all populations are heterogeneous, this attrition will produce some instability in the life tables and it is possible that we are not measuring life expectancy in a reliable way.

The rate of aging is another important topic that should be taken into account, mainly because until now there isn't a consensus about its shape in heterogeneous populations. Research developments in this field can introduce great improvements in the study of mortality, and Vaupel in 2010 advanced with a very interesting and thoughtful point of view about the rate of aging, defending that it should be tested.

Nonetheless, in mortality forecasts, the topic of heterogeneity is not been taken into account, and if we want accurate results from these predictions we should include in the methodologies that the population is not homogeneous.

Furthermore than observing and understanding the population dynamics and influent factors, the performance of probabilistic population forecasts allows the interpretation of possible future growth and make an evaluation of the impact of these scenarios in society.

The main purpose in this essay, like the title suggest, is to introduce the concept of rate of aging and to achieve some conclusions that can lead to different directions to future research. To do this, I will start with a differentiation between *senescence* and *aging*; then some theories about aging will be presented; as well as how to measure the force of mortality and some chosen models to estimate mortality over age; after this is presented a chapter about the theory of heterogeneity; followed by another chapter focused in the rate of aging itself; and finishing with the Lee-Carter forecasting model example.

2. *Aging or Senescence?*

In view of the fact that dying will be the last step in life, we can say that death is part of life. In this direction, it is important that we understand what happens during the entire life course. An intrinsic characteristic of life course is aging, and usually senescence becomes "more likely" as life proceeds. The expression "more likely" was used between quotes because despite that senescence becomes more likely as life proceeds to some authors (Hamilton, 1966), to others it is not an inevitable condition (Baudisch, 2008).

Although the word aging be widely used, the meaning itself is not so easy to be described. Gerontology is one of the sciences that are studying this phenomenon and its main goal is "to preserve human health and well being, and extend healthy life" (de Magalhães, 2006). In this sense we can define aging as the age-related increase in vulnerability and decrease in viability (Comfort, 1964) over time, whether during development, young adult life, or senescence (Finch, 1990).

On the other hand, *aging* is very often used with the same meaning as *senescence*, however senescence is a more precise word that describes the decline in physiological functioning with age (Comfort, 1964; Finch, 1990).

To avoid some misunderstandings, Annette Baudisch used in her monograph (2008), the term *aging* to describe any good or bad variation in functioning with aging, and *senescence* to describe the deterioration in functioning.

Briefly, and once that senescence is something that humans experience until death, it can be said that is a complex process composed by several characteristics as an exponential increase in mortality with age; a functional decline due to physiological changes during the life course; and an increase in the propensity to certain diseases with age.

Henceforth, throughout this essay, the preference will be using aging has the biological process of growing older in a detrimental sense.

3. Theories of Aging

There were some authors that have been developing different approaches to explain whether the evolution of aging, whether why aging occurs.
Many efforts were done trying to give a classification of all the aging theories but it is not an easy task due to their number. Nevertheless, authors like Kirkwood in 1984 classified the theories of aging into *stochastic*, *programmed* and *evolutionary theories*, and Medvedev in 1990 gave a new arrangement, creating seven categories: *theories based on age changes*, *theories related to primary damage*, *genetic programme theories*, *evolutionary theories*, *tissue-specific theories*, *mathematical and physical-mathematical models*, and finally *united theories*.
However, many of these theories complement each other and we can do as many classifications as we want since that we do it in a coherent way. In this essay and since that the main goal is to understand the rate of aging and not to do a revision of the theories of aging, none special classification will be use, distinguishing only between why aging occurs and its evolution.
Starting by the *why*, we can find in the literature that some theories argue that senescence is the result of a continuous process of decline in physiological functioning that results in a decrease in survival and/or reproduction with age (Baudisch, 2008).
Despite many differentiations have been done during the years, to explain aging itself we can also differentiate between *damage-based* theories and *programmed* theories.
Secondly, the evolution of aging will be explaining, as the name itself suggests, into the light of the *evolutionary theories of aging*.
At the end, and as an attempt to explain aging as stochastic process, it will also be presented the *Strehler-Mildvan theory of aging* (1960).

3.1. Why do We Age?

As *damage-based* theories we can understand theories that assert aging as a result of a process, which is continuous, of damage accumulation by the organism during the entire lifespan. On the other hand, *programmed* theories state that aging is a genetically regulated process, i.e., predetermined, and occurs in a fixed timetable.
To have a better understanding about *damage-based* theories two examples will be presented. The first one is the *energy metabolism and aging* theory.
Rubner in 1908 discovered that animals with higher lifespan are on average bigger and they are able to spent less calories than the small ones (Medvedev, 1990), with short lifespan, i.e., animals born with a predetermined quantity of energy. Into the light of this theory, later was settled the rate-of-living theory (Pearl, 1928), proclaiming that the metabolic rate have a huge impact on aging, once that the faster the biochemical activity, the faster aging occurs.

As a second example, we can take the *DNA damage* theory, which postulates that DNA, due to its central role in life, should also play an important role in aging. Szilard, in 1959, hypothesized that damage accumulation in the DNA originates aging. However, since that time that some new discovers were done and in 1981, Gensler and Bernestein argued that is not only damage accumulation in DNA that causes aging, but also its own mutation.

On the other hand, as an example of *programmed* theories of aging, the *developmental theory of aging* can be presented, which postulates that aging is resultant of development, and these two (development and aging) are regulated by the same genetics mechanisms and process (Medvedev, 1990).

Another example is the explanation of aging into the light of the *existence of a biological clock for aging*, where the genetic basis is taken as the explanation for the observed differences in the lifespan potential between species or even sexes (Medvedev, 1990).

3.2. The Evolutionary Theories of Aging

As postulated by Darwin in 1859, and quoted in Baudisch (2008), life is shaped by a struggle for existence, where the stronger have higher chances to survive. Nevertheless this description seems to contradict what is being here described as the aging process, i.e., a constant increase in vulnerability that sooner or later will lead to dead, but in the end only the stronger ones will reach higher ages.

According to Medvedev (1990), the evolutionary theories of aging normally try to explain very extensive and interesting facts and observations of comparative gerontology. Nonetheless, despite that we can distinguish between two different approaches, first by assumption that aging is due to several deleterious mutations at later ages and second by taking aging as a by-product of an adaptive process controlled by trade-offs, both of them are founded on the assumption that the force of selection diminishes with age (Baudisch, 2008).

Some authors like Medawar (1952) and Hamilton (1966), share the opinion that a low number of survivors in higher ages correlated with the low significance that these ages have in the reproductive success, results in a decline in the force of selection with age.

This idea was theorized by Medawar in 1952, proposing the theory of mutation accumulation, where mutation is occurring persistently and this is seen as an evolutionary disadvantage just because the higher the age (small force of selection) the higher the mutations impact (more accumulation of mutations).

Hamilton in 1966, have even tried to prove this theory concluding that with the pressure of reproduction declining with age, the selection pressure is also declining, and this will shape the mortality age-pattern, where at maturity reproductive ages individuals experienced low mortality levels that will suffer an increase after this time.

Nonetheless in 2008, Baudisch demonstrated that, under some circumstances, the force of selection can increase with age. In her monograph, she proved, by doing some derivations based on Hamilton's framework, that alternative indicators can be achieved.

In this way, *"demographic schedules of mortality and fertility appear to be shaped largely by optimization of trade-offs rather by mutation accumulation"* and *"only at ages when remaining reproduction is low does the influence of mutation accumulation appear to become predominant"* (Baudisch, 2008).

As can be seen until now, one approach of the evolutionary theories of aging is trying to find a correlation, positive or negative, between maximal lifespan potentials and certain differences that can explain the differences in the maximal lifespan among different species (Medvedev, 1990). In this case many factors like the body size, the brain, the metabolism rate or even the existence of cellular turnover, are appropriate factors to explain, understand, and determinate the rate of aging.

As it was seen, Rubner proposed an inverse correlation between longevity and the *rate of living*, i.e., a negative correlation between longevity and the metabolic intensity (Medvedev, 1990). Nonetheless, this theory has been continuously criticized mostly because is not a transversal theory and there are even some data that can expose some contradictions (Finch, 1990). In any case, this theory is still the basis to the foundation of other ones like the rate of energy metabolism theory, which studies the correlation between life extension and caloric restriction diets. Sacher in 1966, related longevity and the brain size just because larger brains are associated to higher intelligence and this higher intelligence level leads to high capability of regulating the living environment and reducing the effect of damage factors (Medvedev, 1990).

Williams, in 1957, proposed the *antagonistic pleiotropy* theory of aging, where is postulated that genes play an important role in the aging process. The same genes that regulate individuals' organisms and help them to be vigorous in early stages are the same that leads to a detrimental process in later ages. In this sense, it is needed to preserve the genetic code and this lead us to the *soma theory* of aging (Kirkwood, 1977 & 1981), where is suggested that high levels of repair in the organisms leads to a higher lifespan.

3.3. The Strehler-Mildvan Theory of Aging

Strehler and Mildvan in 1960 elaborated a *general theory of mortality and aging* that is based on the *Gompertz's Law of Mortality* $\left[\mu_x = \alpha e^{\beta x}\right]$ and follows two different assumptions. The first one is that an organism is composed by other subsystems that have a maximum capability and ability to restore themselves after a challenge. In this situation, the death of an organism will occur when his capability to restore the original state is not enough to overcome the challenge effects. So, letting μ be the mortality rate, we have:

$$\mu - CX$$

where C is the total number of challenges per unit of time, and X is the fraction of challenges equal or greater than V.

In this case, *V* is the vitality, i.e., the capacity of an individual organism to stay alive and measured by an approximately weighted average of the maximum rate of work output less the basal power output of all the of the functional modalities contributing to survival in the normal environment (Strehler & Mildvan, 1960) :

$$V_t = V_0(1 - Bt)$$

The second assumption is concentrated in the magnitude of the challenges, claiming that these are distributed energetically like a Maxwell-Boltzmann distribution of energy among molecules:

$$\frac{n}{n_t} = k\left(E/RT\right)^{\frac{1}{2}} e^{-\frac{E}{RT}}$$, when $E > RT$

or,

$$\frac{n}{n_t} = \square K e^{-\frac{E}{RT}}$$, for $E >> RT$

where *E* is the energy of a state of a molecular system, *T* the absolute temperature, *R* the gas constant, *n* the number of molecules with energy equal or greater than *E*, and n_t the total number of molecules.
So, letting the energy *E* be designed by *V* and *RT* by the average demand for energy expenditure over and above the basal level – e^D – we have:

$$X = k'\left(V/e^D\right)^{\frac{1}{2}} e^{-\frac{V}{e^D}}$$

or,

$$X = \square K' e^{-\frac{V}{e^D}}$$

We can have the second assumption as:

$$\mu = \alpha e^{\beta x} = \mathbf{k}\left(V/e^D\right)^{\frac{1}{2}} e^{-\frac{V}{e^D}}$$

or, similarly:

$$\mu = \alpha e^{\beta x} = \square \mathbf{K}\, e^{-\frac{V}{e^D}}$$

Nonetheless, the authors stated an attrition coefficient that measures the fractional loss that the original vitality V_0 suffers, given by:

$$B = b + f(D)$$

where *b* is the attrition coefficient due to normal aging and $f(D)$ the attrition coefficient due to environmental factors.

In 2011, Zheng et al. tried to synthesize this theory and pointed out three important predictions and properties. The first one is the negative relation between the intercept $\ln \alpha$ and the slope β of the logarithm of the Gompertz mortality curve for all human populations, where:

$$\ln \alpha = -\frac{1}{B}\beta + \ln K$$

Secondly, the attrition coefficient that measures the fractional loss that the original vitality V_0. As it was explained before, this coefficient makes possible to combine in only one function the both impact of environment and normal aging.
As third and last point, it is also highlighted the fact that using the inverse of the fractional loss of vitality is a good estimate for the maximum lifespan attainable in a homogeneous population to which the population average parameters are applicable.
Nonetheless, and as will be seen further ahead in this essay, in this theory the rate of aging goes up over time, and that maybe it is not the correct approach.

4. Measuring and Estimating the Force of Mortality

The instantaneous death rate, the hazard rate, or as usually used, the force of mortality, is a mechanism applied to measure the number of deaths per head of population per unit of time. The creation of a model that be able to explain mortality over age will be a huge step in demography.
Since early years that many efforts were being done trying to create a correct law that result in accurate results and that can be used to do forecast human mortality. Nonetheless, until now it was not possible to reach an agreement.
In the next steps it will be seen either how it can be measured the force of mortality, either how it can be estimated, giving a glance by some of the developed models.

4.1. *Measuring* the Force of Mortality

Using the life table, it is possible to compute various probabilities involving mortality (Pollard, 1973). Based on this, and once that l_x is the life table survival function, the probability that an individual will survive from age x until age $x + t$, is given by l_{x+t}/l_x .
Letting μ_x be the force of mortality at age x, the probability of dying between age x and age $x + dx$ is given by $\mu_x . dx$, where μ_x is:

$$\mu_x = -\frac{1}{l_x}\frac{dl_x}{dx} = -\frac{d}{dx}\ln l_x$$

and lx the survival function of a given cohort, and the number of occurrences, i.e., the number of deaths, between age x and age $x + dx$ is $– dl_x$.
Nevertheless, the average force of mortality between ages x and $x + 1$ is very close to the force of mortality at age x + ½. So, still based in the life table functions, we have:

$$\mu_{x+\frac{1}{2}} \simeq \ln\left(\frac{l_x}{l_{x+1}}\right) \approx -\ln(1 - q_x)$$

where, q_x is the probability of dying within the next 12 months after achieve age x.
In 1973, Pollard demonstrated that the instantaneous death rate in the middle of the interval between age x and age $x + t$, is really close to the central death rate m_x:

$$m_x \approx \mu_{x+\frac{1}{2}}$$

Concluding, is very important to say that in any of these two cases, to the given approximations the associated errors are very small, don't exceeding 1% (Thatcher, 1999; Thatcher et al., 1998).
Nonetheless, the average mortality of the survivors in a population is given by:

$$\bar{\mu} = \int_0^\infty \frac{\mu_x \cdot l_x \, dx}{\int_0^\infty l_x \, dx} \Leftrightarrow \bar{\mu} = \frac{1}{\int_0^\infty l_x \, dx}$$

4.2. *Estimating* the Force of Mortality

Many efforts are taken trying to create an explanatory model that was able to estimate mortality over age, even though that until now we don't have a consensus about it.
One of the most important and old topics in demography is the description, with mathematical models, of the observed age patterns of adult mortality (Bongaarts, 2004). Benjamin Gompertz, in 1825, was one of the pioneers, creating the first "law of mortality":

$$\mu_x = \alpha e^{\beta x}$$

where the force of mortality at age x – $[\mu_x]$, increases with age at a stable exponential rate. α is the mortality level and β the rate of increase in mortality with age, being both parameters positive. Despite that this model is able to explain the behaviour from a large part of the age range, young and very old ages are not included though.
In this way, and with the intention of getting more accurate results, another "suggestions" were made, like Makeham (1860) that tried to improve the Gompertz's law, adding a constant term into the model:

$$\mu_x = \alpha e^{\beta x} + c$$

where c is the risk of death that does not depend of the aging process.
But still, besides the clear improvement brought by this constant into the model, at older ages the force of mortality was still overestimated.
Once that mortality behaviour is changing with the years, and this is a topic that is still receiving contributions from different authors, another model (among others) that can be enumerated is from Thatcher et al. (1998) and Thatcher (1999), which applied the logistic model:

$$\mu_x = \frac{\alpha e^{\beta x}}{1 + \alpha e^{\beta x}} + c$$

Nevertheless, even that the results from this model were very good, they are not perfect, and it should never be forgotten that in all populations are heterogeneous (Vaupel et al., 1979) and this must have to be taken into account.
Vaupel et al. (1979) tried to add some improvements to these mortality models by making a connection with frailty models (because in heterogeneous groups there are some individuals frailer than others), trying to explain mortality at older ages, and the result was the so-called Gamma-Gompertz model:

$$\mu_x = \frac{\alpha e^{\beta x}}{1 + \frac{\sigma_z^2 \alpha}{\beta \left(e^{\beta x} - 1 \right)}}$$

where σ_z^2 is the variance of frailty *z* among the individuals in the population.
Despite that there are some other models used to estimate the force of mortality in the literature, in this essay it was chosen to present only these four examples.

5. *Heterogeneity*

Like it was said before, one of the most important and old topics in demography is the description, with mathematical models, of the observed age patterns of adult mortality (Bongaarts, 2004). Although the model created by Benjamin Gompertz in 1825 to estimate mortality over age be able to explain the behaviour from a large part of the age range young and very old ages are not included.

Nonetheless, all populations are heterogeneous starting with individual genetic composition, where all organisms have different DNA and ones more than others have higher susceptibility to some diseases. Even disparities in social behaviours, that are different between cultures, sexes and ages.

Vaupel et al. (1979), claims that in a random population there are always frailer individuals than others, the force of mortality for an individual should always take into account his frailty – $\mu(x, y, z)$.

However, if the observed heterogeneity is able to create a variety of analytic opportunities for demographers, unobserved heterogeneity distorts the observed patters of change, creating several difficulties.

This problem is due to the population cohort members that gradually die off or drop out and to the structure, if a heterogeneous population cohort changes as the cohort die off. And in this situation, the frailer tend to die first, which results in a cohort compound by the stronger ones (Vaupel and Yashin, 2006).

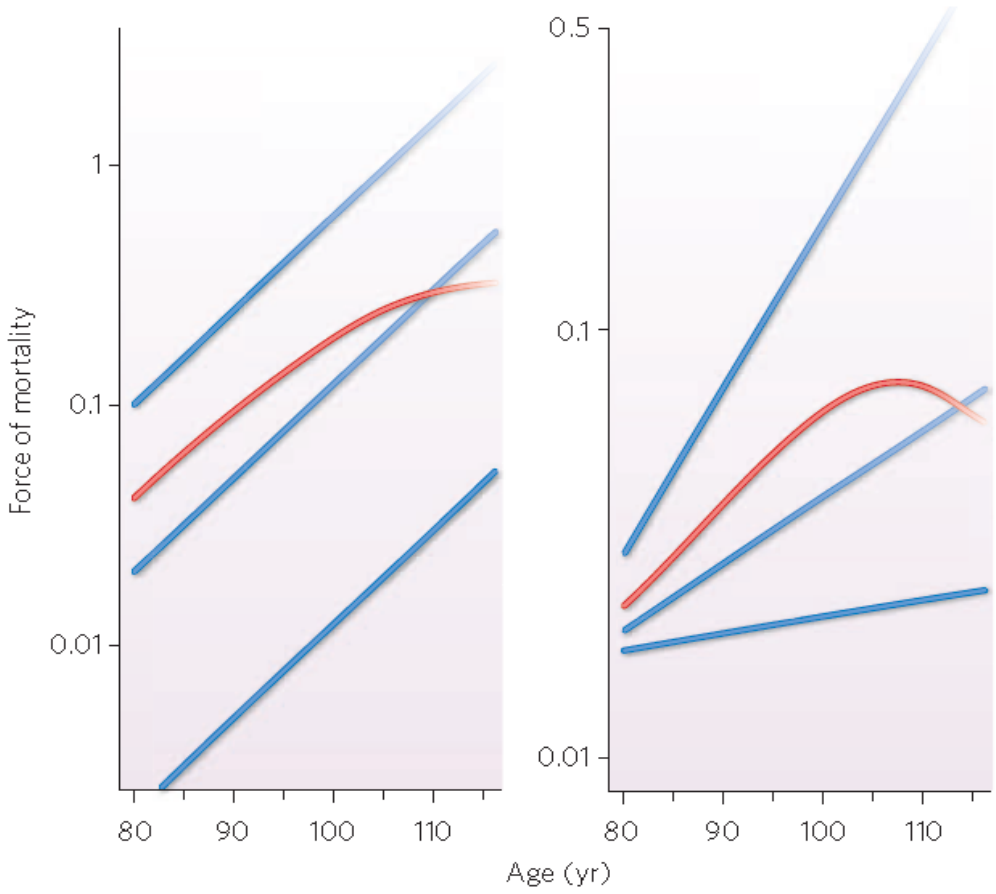
There are three levels of explanation for the observed patterns of change and to explain these levels, is commonly used the example that the increase in mortality with age slows at the older ages. While a *level 0* explanation to this report would be that the data are wrong, being distorted by some misreporting of deaths at older ages, a *level 1* explanation, would the explanation that at this ages, the probability of death increases relatively gradually with age. At last, the *level 2* explanation would be that with the drop off of frailer individuals from a cohort, the remaining members are the stronger ones.

Nevertheless, patterns of deceleration in different populations can be explained by a mixture of these three levels (Vaupel et al., 1979).

5.1. *Heterogeneous* populations

In all populations there is always a level of attrition due to heterogeneity that will influence the hazard's shape of a population, mainly because "*the members of many kinds of populations gradually die off or drop out*" (Vaupel and Yashin, 1985).
Taking the force of mortality as the measure for a cohort's death rate, it can be seen that all the individuals that born in a year *y* and aged *x*, deal with the same hazard rate, i.e., the same force of mortality. Conversely, this statement is only true for homogeneous populations. So, based on the assumption that all populations are heterogeneous, it can be said that heterogeneous populations are composed by different subgroups of homogeneous populations.
In this way, to calculate the mean force of mortality for an entire cohort $\bar{\mu}$, it is needed to take all these differences into account. In 1985, Vaupel and Yashin illustrated in different ways how the mortality pattern of a population.
Later in 2010, Vaupel in his paper *Biodemography of Human Aging*, published in *Nature*, gave another illustration about how this attrition can influence the age pattern of mortality for a heterogeneous population:

Figure 1: Mean force of mortality – $\bar{\mu}$ – for a heterogeneous population



Source: Vaupel, 2010

With these two graphs, Vaupel gave an excellent example about how the age pattern of mortality can differ from the subpopulations to the total population. These graphs are presented in a logarithmic scale, where the rate of aging for the subpopulations is drawn

using a blue colour and for the total population in red and the dropping off of the subpopulations is represented by a vanishing in the blue colour.
Starting with the graph on the left, it can be seen that despite the different levels of age-specific mortality, the pace of increase in mortality with age is constant in the three subpopulations. On the other hand, and observing the force of mortality for the population as a whole, i.e., the red line, it is obvious that while the individuals from the subpopulations with higher levels of age-specific mortality are dying out, the force of mortality suffers a decline to a constant value.
The graph on the right, presents a similar situation, but now showing different levels in the pace of increase in mortality with age. Is showed, again, that the true value of the force of mortality is somewhere between the different levels correspondent to the different subpopulations. Nevertheless, this example presents a decline in the force of mortality for the population as whole when the individuals with higher levels of mortality start dying out.
As it will be seen further in this essay, the graph from the right is not considered the correct interpretation for the force of mortality in a heterogeneous population.

5.2. *Definition* and *distribution* of frailty

Following Vaupel et al. (1979), we can see that, as pointed out before, in a random population there are always frailer individuals than others, the force of mortality for an individual should always take into account his frailty – $\mu(x, y, z)$. And if we want to calculate the real force of mortality in a cohort of individuals from a population, we should distribute the frailty by the entire cohort:

$$\bar{\mu}_i(x, y, z) = \mu_i(x, y, 1).\bar{z}_i(x, y)$$

In this situation, frail individuals will die first, resulting in a reduction in the average frailty of the cohort survivors that declines with age (Vaupel et al., 1979). However, this last equation implies that the force of mortality for individuals increases more rapidly than for the cohort the individuals belong to.
Nonetheless, to achieve this formula, is also needed to define frailty. So, assuming $\mu_i(x, y, z)$ as the force of mortality for an individual that lives in a population group called *i*, at exact age *x*, at some instant in time *y* and which frailty is *z*, we will be able to include individual differences in mortality rates:

$$\mu_i(x, y, z) = z \cdot \mu_i(x, y, 1)$$

where *z* can be considered the mortality risk of an individual as consequence of a combined age-adjustment of genetic and environmental characteristics (Horiuchi, 2003). In this formula is used *z* equals to 1, which means that the individual has a frailty of one, and an individual with a frailty of 1 might be called a “standard” individual.

Taking now this individual as the standard one, we can say that another individual with *z* equals to 2, is twice as possible to die than the standard one, or in the other way around, an individual with frailty of 0.5 is one-half likely to die, and so on. Nonetheless, is important to says that the definition of frailty assumes when an individual born, he born with a certain level of relative frailty that will go along with him until the end.

6. Understanding the Rate of Aging

Many factors are advanced as the reasons to population aging in industrialized countries. In 2000, Anderson and Hussey identified three main factors: the increasing in life expectancy; the decline in the fertility rates; and immigration, i.e., bad policies that don't allow the entrance of young people into the industrialized countries.
Nevertheless, this increase in life expectancy can be explained by different factors, and like it was pointed by Vaupel in 2010, *"mortality has been postponed considerably, as result not of revolutionary advances in slowing the process of aging but of ongoing progress in improving health"*.

6.1. Mortality Improvements

Against some expectations that theorized a limit to life expectancy, humans are breaking limits to life expectancy (Oeppen and Vaupel, 2002). Following the authors, if the most part of the gain in life expectancy was due to huge reductions in mortality at younger ages, after this period, in the second half of the century, were the improvements in survival after age 65 that contributed to an extension in the lifespan.
These contributions are result from an *"intricate interplay of advances in income, salubrity, nutrition, education, sanitation, and medicine"*, or to sum up, the result of large improvements in human health, *"with the mix varying over age, period, cohort, place, and disease"* (Riley – 2001, quoted in Oeppen and Vaupel, 2002).
Vaupel in 2010 wrote in his Nature paper that *"mortality is by far the most important readily and reliably measured index of health"*, and the truth is that the world's life expectancy rose more than the double in the last centuries due to low levels of mortality observed at all ages.
As it is known, there are many actions that can reduce an organism lifespan, like smoking (Vaupel et al., 2003), reckless behaviour, or even the choice of wrong diets (Mair et al., 2003). These are behaviours that lead to a cumulative imbalance between damage and repair resulting in senescence. Is because of this that progress in reducing damage and in increasing repair are two fundamental causes of health improvement (Vaupel, 2010).
Following this point of view, is very important to emphasize that senescence is being delayed not decelerated. Especially because, instead of a stretch in the period of senescence, senescence is being shifted to older ages.

There are two factors that are being pointed out as the main factors in the contribution to the postponement of senescence: prosperity and medicine (Vaupel, 2010). Prosperity is presented mainly because people with high resources have higher opportunities to live a healthier life due to their capability to satisfy the most basic needs (e.g., clothes, house with living conditions, healthy food, etc…).
Medicine was pointed mainly because all the improvements associated with health are of major importance to all persons in their senescent process.
Nevertheless, is the junction of these two factors that gives the major contribution to increase life expectancy, mostly because prosperity leads to higher education and consequent healthier and longer lives, and allows the population to have more opportunities to access better treatments.
Despite all the improvements that resulted in an increase in life expectancy, are people themselves that need to have proactive behaviours with the goal of achieve older ages in better shape: *"a person has little chance of surviving to very old age if he or she smokes cigarettes, gets little exercise and is grossly obese"*, however, *"even a person who strives to behave in a healthy manner has a probability of only a few percent of living to age 100 under current health conditions"* (Vaupel, 2010).
If all these improvements and resulting increase in life expectancy leaded to a decrease in the variance in age at death on one hand, on the other hand an increase in the average length of live is happening.
Studies made about centenarians are also very important to understand mortality behaviours. As it can be seen when the graphs presented to introduce the theory of heterogeneity, after age 110, mortality seems to level off. In 2010, Jutta Gampe discovered that after age 110 the force of mortality presents a constant value of 0.7, implying an annual probability of death constant at a level of 50% per year.

6.2. The Life-Table Aging Rate

The usual method to analyse and understand the mortality patterns is plotting the mortality rates in a logarithmic scale against age. In the most part of the cases this relation presents a linear pattern, and as consequence it is assumed that the associated slopes are constant. However, this slopes are not constant, and "*what appears to be an exponential increase in mortality with age may actually be an artefact resulting from forcing a straight line through data whose derivations are minimized due to a logarithmic transformation"* (Carey and Liedo, 1995).
As it was seen in the previous discussion about heterogeneity, understanding the rate of aging is one of the most important steps to estimate in an accurate way the force of mortality for a population.
In 1990, Horiuchi and Coale proposed a mortality measure with the intention to give a step ahead in the age pattern analysis of death rates and that is different from the conventional way to examine age variations in mortality (plotting the logarithm of the death rate against age). The measure itself can be called the *age-specific rate of mortality change with age*, or in an easiest way, the *life-table aging rate* (LAR) like it

was designated by Carey and Liedo in 1995, Horiuchi and Wilmoth in 1997 and 1998, and is denoted by $k(x)$:

$$k(x) = \frac{1}{\mu_x}\frac{d\mu_x}{dx} = \frac{d\ln(\mu_x)}{dx}$$

where $k(x)$, was it was explained, measures the rate of mortality change at age *x*.
According to the authors, this measure provides a better visual interpretation, when it is plotted, about the acceleration and deceleration in the mortality patterns and has at least four advantages. The first one is that this is a good tool to evaluate some of the mathematical mortality models, once that the age patterns of LAR implied by those models are significantly different. Secondly, it is also a plus in the understanding of heterogeneous populations, mainly because the age pattern of the obtained LAR should highlight the differences between subpopulations and their vulnerability to the risk of death. Thirdly, it is also useful in studying physiological aging due to the variations in the risk of death correlated with the pace of aging in LAR. Finally, the fourth advantage is the practical utility in detecting cohort mortality variations.
Horiuchi and Coale (1990), found that all the studied females populations presented a not constant value of $k(x)$, but instead, a *bell-shaped* pattern, where changes are systematic and that rises at younger old ages and after reaching a peak start to decline at older old ages. Males, on the other hand, did not present *bell-shaped* patterns in uniformly way, but fluctuating patterns instead. However, this deviance from the *bell-shaped* pattern is explained by the authors as a consequence of the First World War in some of the countries: *"it seems that those* $k(x)$ *curves that might be similar to the female curves have been confounded with cohort mortality variations that reflect long-term impacts of World War I upon the health of its survivors"*.
The obtained results, i.e., the *bell-shaped* patterns, and still following the authors can be explained due to a utilization of an estimation model that includes individual frailty, the Gamma-Gompertz-Makeham model. And as it was pointed out before in this essay through the *heterogeneity* theory, this means that mortality at younger ages is shaped by the chance factor and by selective survival at older ages.

6.3. The Rate of Aging

If the *age-specific rate of mortality change with age* shows a bell-shaped pattern and allows a better understanding about the age pattern of mortality in a population, the rate of aging is the *pace of increase in mortality with age*, like it was seen before when the theory of heterogeneity was introduced.
In the most part of the studies about aging, mortality is assumed to follow an exponential increase with age for most species after maturation (Carey and Liedo, 1995). As it was seen before, this exponential increase in mortality rates follows the law of mortality developed by Gompertz in 1825, and for authors like Finch (1990) these exponential rates can be the major determinant of average lifespan and maximal age.

However, and despite this "agreement" about the use of the Gompertz law, the opinions about the rate of aging are not the same.

Starting with the general theory of aging proposes by Strehler and Mildvan in 1960, it can be seen that the authors proposed that the rate of aging goes up with age. On the other hand, gerontologists employ mainly the general Gompertz model, obtaining a constant value of 0.087 for humans (Finch, 1990; Finch and Pike, 1996).

However they forgot, like the theory of heterogeneity postulates, that all populations are heterogeneous and in heterogeneous populations there are frailer individuals than others. This is the key that leads to a change in the force of mortality at older ages.

Taking again into account the example given by Vaupel in 2010 (*figure 1*), it can be seen that the different subpopulations can present different behaviours, but with the observed improvements in mortality and the mortality plateau discovered by Gampe (2010) after age 110 makes the graph from the left the most plausible (Vaupel, 2010). Consequently, it is highly probable that the rate of increase in mortality with age is constant for all the members in a population, or otherwise the force of mortality after age 110 will show a different behaviour.

So, in this case the Gamma-Gompertz model advanced by Vaupel et al. in 1979 is the most credible model to estimate mortality over age, resulting in a change in the rate of aging level.

In 2010, Vaupel and Zhang proved that the *"change with age* [in the hazard] *for the cohort equals the average of change in the hazard for the individuals in the cohorts minus the variance in the hazard across the individuals"*. Thus, based in the assumption that the mean force of mortality for a cohort is given by:

$$\bar{\mu}_x = \frac{ae^{\beta x}}{1 + \frac{a\gamma}{b}\left(e^{\beta x} - 1\right)} + c$$

the authors were able to elaborate an equation to estimate the LAR in heterogeneous cohorts (where *b* used instead of β , but with the same meaning):

$$\bar{b}(x) = b\left(1 - \frac{c}{\bar{\mu}_x}\right)\left(\frac{\bar{\mu}_* - \bar{\mu}_x}{\bar{\mu}_* - c}\right)$$

And at the same time showing that how and why the LAR, here given by $\bar{b}(x)$, differs from *b*, i.e., from the rate of increase in mortality with age, which is, as it was seen before, constant for all the members in a population. Where the force of mortality after age 110 is given by:

$$\bar{\mu}_* = {}^{b}\!/_{\gamma} + c$$

Later, already in 2011, Missov and Lenart expressed *"a relationship between period and cohort life expectancy as well as between their (constant) rates of change"*. And for this, they based their work in the Gompertz proportional hazards, which is given by:

$$\mu(x, y) = e^{-\rho y}\ a_0 e^{\beta x}$$

The obtained results showed a real good precision that resulted in very small errors. In this paper, the authors used a constant rate of aging of 0.14, which is higher than the value advanced by the gerontologists, but possibly more accurate.

7. Forecasting mortality over age and over time: the Lee-Carter method example

The higher the accuracy in the measurement of the force of mortality, the better and reliable will be the mortality forecasts.

However, in mortality forecasts, the topic of heterogeneity is not been taken into account, and if we want accurate results from these predictions we should include in the methodologies that the population is not homogeneous.

So, subsequent to the first examples about some models to explain mortality over age, and some modifications or add-ons that tried to improve their results, we should take a look into mortality models over age and over time. In this essay pt will be only presented the Lee-Carter model and some of its variants.

One of the most used methods for forecast mortality is the Lee-Carter method (Lee and Carter, 1992), which the authors applied to the total American population between 1900 and 1989:

$$\ln[m(x,t)] = a_x + b_x k_t + \varepsilon_{x,t}$$

where a_x, b_x and k_t are the parameters to be estimated, and $\varepsilon_{x,t}$ is the representation of the errors terms, or better, the set of disturbances that measure the divergence between the model and the observed log-death rates. Another important thing that should be said is that the variance – $[\sigma_\varepsilon^2]$ – is assumed to be constant for all *x* and *t*.

Once that in this model is used a set of factors for each considered age and time (Torri, 2009), and the described parameters will have the same length as the number of ages (*x*) and the defined time (*t*) periods, it is needed to add some constrains to the parameters to be successfully estimated (Camarda, 2008):

- ✓ b_x as the pattern of deviations from the previous ages as the parameter k_t changes, and: $\sum_x b_x = 1$;
- ✓ k_t as the time varying mortality level index, and: $\sum_t k_t = 0$.

With these constraints, a_x (the average deaths rates over time for each group *x*) becomes the average over time: $a_x = \frac{1}{n}\sum_{t=1}^{n}[\ln(m]_{x,t})$.

To forecast mortality over age and time with this method, it is needed to do it in two different stages, where in the first one the parameters are estimated using the actual mortality surfaces. In the second one is made a re-estimative of k_t, finding an appropriate ARIMA times series model for the mortality index k_t (Lee and Carter, 1992).

Nevertheless, there are some modifications that were made trying to improve the obtained results. In 2001, Lee and Miller suggested another approach to re-estimate the k_t parameter. In this approach the new level of mortality is found by the subsequent formula:

$$k'_t = \min_{k_t}\{s_0(t) - s'_0(t)\}$$

where the $s_0(t)$ is the observed life expectancy, and $s'_0(t)$ is the fitted life expectancy.

Another example is the alternative using a likelihood-based approach, in this case the Poisson log-linear regression approach (Brouhns et al., 2002), where is assumed that the number of deaths, as a random variable, follows a Poisson distribution:

$$D(x,t) \sim Poisson\,(N(x,t)\,m(x,t))$$

where $m(x,t) = e^{a_x + b_x k_t}$, and the constraints on the parameters from the original method are still valid.

8. Some conclusions and directions for future research

Throughout the reading of this essay it can be seen that there were some concerning about the correct explanation about some important concepts that are needed to understand the aging process.

Right at the beginning it was done a distinction between the concepts of aging and senescence, once that the first one can be seen as a good occurrence in life, just because in some cases becoming older is connected with wisdom. On the other hand, and as it was seen, senescence have no positive implication, being a decline in physiological functioning with age that leads to death (Comfort, 1964; Finch, 1990).

Many theories were developed with the intention to explain this inevitable deterioration that leads to a decline in physiological functioning. Nevertheless, and contradicting the evolutionary theories of aging, Baudisch in 2008 proved that senescence is not inevitable, and under some circumstances the force of selection can even increase with age, and instead of a stretch in the period of senescence, senescence is being delayed.

In the study of aging, many different models were developed with the intention of create a universal law of mortality that could estimate the force of mortality over age. Regardless of an agreement about a universal law, the assumption that the mortality rates for the most part of the species can be explained by an exponential increase is a consensus (Carey and Liedo, 1995). Finch in 1990 even stated that the Gompertz equation has been the major mortality rate model in gerontology for more than 60 years.

Nonetheless, the theory of heterogeneity postulates that all populations are heterogeneous, were frailer individuals tending to die first, and the simple use of the Gompertz distribution should be applied. Instead, and like it was advanced by Vaupel et al. in 1979, it should be used a model that "allows" the inclusion of frailty in the estimation, the so called Gamma-Gompertz model.

In this way, *"if the deceleration in the age-related mortality increase at older ages is due to heterogeneity and selection there are three main hypotheses that can be advanced"* (Horiuchi and Wilmoth, 1998): deceleration should be seen in the analysis of the different major causes of death; selectivity should start earlier in causes of death

originated by worst diseases; and deceleration should shift to older ages as the level in all the adult mortality in all population declines.

Following this description it can be said that whiles (some) demographers are studying aging into the light of the theory of heterogeneity hypotheses, gerontology elects the study of the individual-risk hypotheses (Horiuchi and Wilmoth, 1998).

In 1990, Horiuchi and Coale proposed LAR as a new mortality measure trying to improve the age pattern analysis of mortality, but despite that this measure have been presented as the *age-specific rate of increase in mortality with age*, it should not be taken as the rate of aging. While the rate of aging is the pace of increase in mortality with age, and like it was presented should be constant for all human populations (Vaupel, 2010), the LAR shows a bell-shaped pattern that varies with age. This difference was even demonstrated by Vaupel and Zhang in 2010, when they proved that the change in the hazard average equals the average change minus the variance.

Nevertheless, if the pace of aging captures the age-scale on which mortality progresses, the shape of aging does not depend on age, that captures how sharply mortality increases (or decreases) with age (Baudisch, 2011).

Mortality improvements, the discover that mortality after age 110 reaches a plateau by Gampe in 2010, and the assumption that all populations are heterogeneous, are the starting point for the difference in the rate of aging value between gerontologists and demographers.

However, even between the contributions for the aging study given by gerontology, there is no general consensus. Finch in 1990 and Finch and Pike in 1996 advanced with a stable rate of aging of 0.087 for humans (based in the "simple" Gompertz model, neither including frailty or the risk of death that does not depend of the aging process added to the model by Makeham – *c*), the Strehler and Mildvan's general theory of aging assumes a variable value, which is calculated based in the organism's linear decline in vitality with age.

On the other hand, for demographers, and into the light of the theory of heterogeneity, it is supposed that the value is a little bit higher (0.14), being really closer to the one proposed by Missov and Lenart (2011) when they proved the existence of a relationship between period and cohort life expectancy, as well between their constant rates of change.

To sum up, based on the mortality improvements that resulted in a linear increase in record period life expectancy discovered by Oeppen and Vaupel in 2002, correlated with findings like senescence is being delayed and not stretched (Vaupel, 2010) and mortality for humans, independently of sexes, is levelling off after age 110 (Gampe, 2010), culminates in the hypothesis *"that except for individuals with accelerated aging disorders, all other humans have a similar, and perhaps, essentially the same, rate of increase in mortality with age"*, i.e., the same rate of aging advanced by Vaupel in 2010. So, the rate of aging may be a biological constant invariant across individual and over time (Vaupel, 2010).

With all this findings, the rate of aging hypothesis advanced by Vaupel in 2010, should be tested and to do it there are many different ways. To finalize this essay, I will

advance with some directions that I believe that should be interesting to follow in future researches.

Similarly with Horiuchi and Wilmoth that in 1998 observed the behaviour of LAR by different causes of death, I think that it could be done the same to test the rate of aging hypothesis. Here the idea is to estimate the different the associated rate of aging for different subpopulations.

However, these behaviours should not only be analysed for recent years, but also for previous years, depending how far the data allow us to go.

Again, and if heterogeneity postulates that all populations are constituted by different subpopulations, the differences between sexes should also be taken into observation.

Nevertheless, and if we are speaking about an invariant rate of aging for all the individuals, the hypothesis should not be only tested over time, but also for different stages in the individuals life, i.e., differentiating populations by different age groups.

Following this directions, it would be also very interesting to estimate the variance in the rate of aging among individuals, just because if the observed variance subsists in very low levels can support the idea that it can be negligible, or vice versa.

If it is true that the rate of aging is a biological constant that is invariant across individuals over time, the obtained results should confirm this.

In the same way that gerontologists go across different species to have a better understanding about aging, I think that this hypothesis should also be tested for non-human populations, once that it would be very interesting to see if different species share the same invariability in the rate of increase in the chance of death due to senescence, independently of the different levels of this rate that could be observed from specie to specie.

Mair et al. in 2003 observed that the rate of aging for *Drosophila* can suffer some variations depending on temperature, but it is only higher temperatures that raise the rate of aging in insects?

If this invariability in the rate of aging be proved, this discovery will have a high impact in the models to estimate mortality over time and over age.

Estimating the force of mortality over age based in a constant rate of aging for the total population and for different years will allow to understand its evolution over years, and the simple employment of an adequate ARIMA times series model based on the μ_x, for example, can produce some accurate results.

This is similar to what is done with the Lee-Carter method. However, despite all the variations and add-ons that this model had suffered since the publication of the paper of Lee and Carter in 1992 and as it can be seen in the given two examples, there was no inclusion of the individual frailty that exists in population neither the use of a constant rate of aging to produce the forecasts.

In my way to finish, it should be said that the directions that were leaved here are only thoughts and very different ways to test the rate of aging hypothesis can be taken. The idea about the Lee-Carter method should be explored very carefully, possibly analyzing some other given contributions.

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