

A joint explanation of infant and old age mortality

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Abstract

Infant deaths and old age deaths are very different. The former are mostly due to severe congenital malformations of one or a small number of specific organs. On the contrary, old age deaths are largely the outcome of a long process of deterioration which starts in the 20s and affects almost all organs. In terms of age-specific death rates, there is also a clear distinction: the infant death rate falls off with age, whereas the adult and old age death rate increases exponentially with age in conformity with Gompertz’s law. An additional difference is that whereas aging and old age death have been extensively studied, infant death received much less attention. To our knowledge the two effects have never been inter-connected.

Clearly, it would be satisfactory to explain the two phenomena as being two variants within the same explanatory framework. In other words, a mechanism providing a combined explanation for the two forms of mortality would be welcome. This is the purpose of the present paper.

We show here that the same biological effects can account for the two cases provided there is a difference in their severity: death triggered by isolated lethal anomalies in one case and widespread wear-out anomalies in the second. We show that quite generally this mechanism leads indeed, respectively, to a declining and an upgoing death rate. Moreover, this theoretical framework leads to the conjecture that the severity of the death effects, whether in infancy or old age, are higher for organisms which are comprised of a larger number of organs. Finally, let us observe that the main focus of the paper is the drastic difference of the age-specific death rates (i.e. decreasing versus increasing) because this difference is found in many species, whereas the question of the best fit (e.g. Gompertz versus Weibull) is rather specific to human mortality.

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1 Introduction: infant versus old age mortality

In this paper we consider the shape of the curves of death rates¹ as a function of age.

Deaths in infancy versus old age death can be characterized in two ways [1,2]: (i) their age-specific death rates (see Fig.1) (ii) the biological processes which are at work (wear-in versus wear-out as discussed below.)

1.1 Shape of the age-specific death rate

In infancy the death rate *decreases* with age whereas in old age it *increases* (Fig.1).

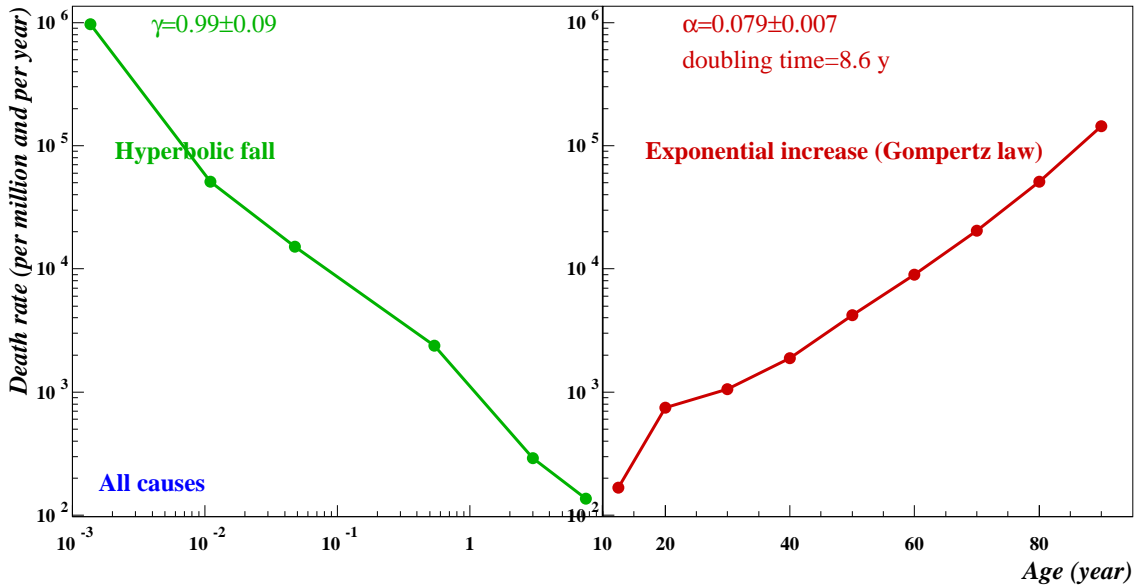


Fig.1: Infant versus old age human mortality. The data are for the US over the period 1999-2016. Between birth and the age of 10 (note the log-log scale) the infant mortality rate falls off as a power law: $\mu_b = A/x^\gamma$ where the exponent γ is usually of the order of 1. After the infant phase comes the aging phase (note the lin-log scale) during which the death rate increases exponentially $\mu(x) = \mu_0 \exp(\alpha x)$ in agreement with Gompertz's law. *Source: Wonder-CDC data base for detailed mortality.*

In medical terminology infancy refers to new born under one year of age. However, as the decrease of the death rate continues until the age of 10, it seems appropriate to extend the meaning of the term to the whole age interval over which the death rate is decreasing. This is what was done in the two papers cited above and we use the same terminology here.

For humans, the increase of the death rate is described by the well-known law of Gompertz [3]. This law can be summarized by saying that the death rate doubles approximately every 10 years of age.

1.2 Wear-in versus wear-out

In the terminology of reliability studies, infant mortality is described by a *wear-in* process, that is to say a phase during which the organs of the new-born start to work which results in the elimination of

¹We use the standard definitions of death rates, namely: $\mu(x) = \Delta y / (\Delta x \times y)$ where Δy is the number of deaths in a given age interval of size Δx and y is the size of the population at the beginning of the age interval under consideration. With this definition $\mu(x)$ is the probability (per unit of time) that a person who has reached age x , will die in the subsequent age interval, see appendix A.

the organisms which are beset with an organ which does not work appropriately.

On the contrary, old age death is described as a *wear-out* process in which all organs experience damages due to continuous use. The lungs catch less oxygen, the bones become more fragile, the arteries become less elastic, and so on. Death occurs eventually due to the failure of a crucial organ (usually the heart and lungs) but actually this failure is favored by the degradation of the whole organism. For instance, when the arteries become less elastic, when the lungs become less effective, it becomes more difficult for the heart to ensure blood circulation. This means that a heart failure does not come about in isolation but rather in relation with the wear of other organs.

The purpose of this article is to show how the feature (1) results from the feature (2). However, before coming to that we wish to explain how our study fits into the broad framework of aging and senescence studies.

Why do we think that infant mortality is an essential component in the understanding of aging? There are several reasons that are developed below.

2 The key-role of congenital malformations

2.1 The real challenges of aging models

Not surprisingly, the modeling of aging and senescence has received great attention. A comprehensive review can be found in two papers by Leonid Gavrilov and Natalia Gavrilova [4,5]. Readers will find in these papers a comprehensive and very readable account of the literature of aging models². In the following subsections we explain why infant mortality is a simpler and more fundamental effect than old age mortality.

2.2 Great diversity in the shape of the death rate in old age

Gompertz (1825) was the first to propose that the rapid rise in death rate of humans as they aged prior to death followed an exponential law. Other authors have since advocated a description based on Weibull functions. See for example [6,7,8]. An interesting review of the implications can be found in Roberto Ricklefs and Alex Scheuerlein [9]. Of especial note here is the proposal that the Weibull form holds for death by particular causes whereas the Gompertz form holds for death by all causes. We shall return to the point later. However neither form predicts the hyperbolic fall in deathrate which happens in early years. Neither the Weibull nor Gompertz forms yields insight into data for species which exhibit a levelling off of the death rate at very high ages.

Across species the hyperbolic decrease of the death rate in the infancy phase appears to be a phenomenon that is more widespread than its exponential (i.e. Gompertz-like) increase in adulthood. Indeed, there is much more diversity in old age death rates than in infancy death rates; see in Berrut et al. (2016) the graph based on zoo species.

In addition for some species documented in [5, p. 18 and 33] there is a marked effect of leveling-off in old age. For instance, house flies have a maximum life span of 40 days but around the age of 15 days the exponential growth of the death rate is replaced by a section where it is practically flat.

In humans the dominant diseases in old age are not the same nowadays as one century ago. Presently, there is a prevalence of heart, cancer and Alzheimer's disease whereas around 1900 infectious diseases

²Whereas these authors share our approach based on reliability science, and whereas infant mortality is a standard notion in reliability, they devote only one page (in a total of 58 for the two papers) to the question of infant mortality. This disproportion reflects the overwhelming predominance of aging and senescence studies.

were still common. Thus, with organisms being confronted to different challenges, one should not be surprised to see changes in the shape of the death rate in old age.

Finally, the individuals who reach old age were “filtered” and selected by the diseases to which they were confronted. If one could observe the signature of the immune system one would see that the immune system of persons of old age is not the same in 2020 than in 1900, and also not the same in developing countries than in developed countries.

2.3 Common characteristics of embryonic and infancy death rates

It has been shown recently [10] that for zebrafish³ the embryonic death rate is by far highest at the beginning of the embryogenesis, an observation which suggests that most of these deaths are due to mistakes in the manufacturing processes of the oocyte (femelle egg) and sperm cell. If instead the deaths would be due to mutations during the embryogenesis they would be uniformly distributed or even (through a cumulative effect) concentrated in the late phase of embryogenesis.

For humans embryonic deaths would in medical terminology be referred to as fetal deaths or still births. In statistical releases this pre-birth mortality is treated apart from infant mortality mostly because there is a great uncertainty about fetal death data. However, from a biological perspective, infant mortality is nothing but the continuation of fetal death, albeit in more severe form due to disconnection of the link with the organism of the mother.

Similarly, the infant death rate is by far highest immediately after birth. By the same argument, it appears that most of these deaths are due to faults in the manufacturing of the embryo. For instance, in mamals lung malformations are without consequence as long as the fetus receives its blood from the mother but they will lead to death as soon as this connection is interrupted. Embryonic and infant deaths along with the malformations which are not immediately lethal give us global information about the underlying manufacturing processes.

2.4 The effects of congenital defects and of aging occur jointly

At first sight it may seem that the infant death rate can be easily described and explained through the process of elimination of individuals with malformations. Clinical data show that in the first weeks after birth most of the deaths are due to congenital anomalies (percentage data are given in [1]. When the most serious malformations have been eliminated the rest of the cohort is less likely to die.

However, the previous explanation is not really satisfactory for the following reason. In fact, deaths due to congenital anomalies are not limited to young age but continue during the whole life. For instance, a congenital defect of heart valves may be of no consequence until the age of 60 or 70 when the defect becomes more serious because the valve’s leaflets become stiffer, see [11].

In other words, the wear-in and wear-out processes should not be seen as occurring successively but rather simultaneously; it is their strength, not their existence, which changes in the course of time. Immediately after birth, wear-in is completely dominant, whereas in old age it is wear-out which is predominant. I short, taken alone the elimination of congenital malformations cannot explain the decrease of the death rate. In order to make it work we need to define both wear-in and wear-out more precisely.

³For a study of embryonic death rates, zebrafish have two great advantages. (i) As for most species of fish, fertilization of the eggs occurs outside of the body of the female (ii) The shell of the eggs is transparent. Taken together, these two features imply that one can observe the embryos immediately after fertilization, something that is impossible either for humans, birds or rotifers.

In the next section we will use the feature already mentioned above, namely that the infant mortality is usually due to a congenital defect in one important organ (e.g. heart, lung, brain, liver, and so on) whereas the wear-out is due to parallel degradation of various important organs.

3 Modeling the wear-in and wear-out processes

3.1 Decomposition into vital organs

The first step is to decompose any organism into its vital organs. For instance, Fig.2 shows a decomposition into 4 organs, that could be heart, lung, brain and temperature regulation.

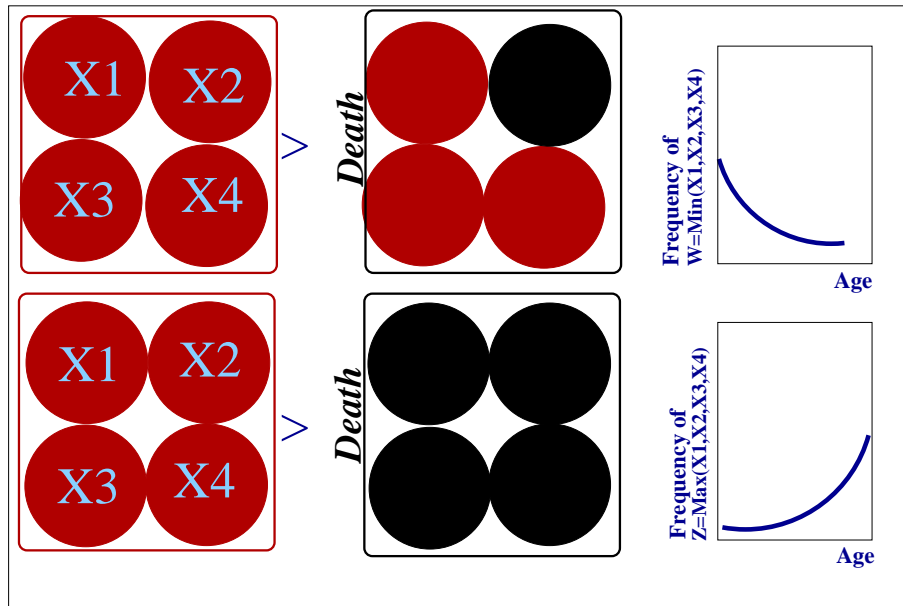


Fig.2 Decomposition of an organism into vital organs and difference between wear-in and wear-out mechanisms. The first line shows a wear-in death. It is the consequence of the failure of a single vital organ. The second line shows a wear-out death as the consequence of uniform deterioration of all vital organs. The graphs on the right-hand side show the implications of these mechanisms in terms of age-specific death rates: decreasing for wear-in as observed in infant death, increasing for wear-out as seen in old-age death.

3.2 Description of the organs' state by random variables

Secondly, we must find a way to describe mathematically whether each organ (as well as the whole organism) is alive. We do this by defining for each part a random variable X_i which is its age at failure. In the case of humans we could make this description fairly realistic by giving to the X_i values from interval $(0, 125)$ for it should be remembered that 125 years is an upper bound of human life⁴. However, as we do not wish to restrict ourselves to only the human species, we will normalize the interval of the X_i to $(0, 1)$ where 1 represents the maximum life span of the species.

Now comes the most important step which is to describe the wear-in and wear-out mechanisms. Let us begin with the simplest case which is the wear-out mechanism.

⁴This was shown to be a consequence of Gompertz's law in [12].

3.3 Wear-out

The fact that the death of an individual occurs when the last surviving organ fails is expressed by saying that if $X_1 = 0.5$, $X_2 = 0.3$, $X_3 = 0.7$, $X_4 = 0.1$ (the X_i denote the age at death of vital organs as shown in Fig.2), then the age of death represented by the random variable Z will be $Z = 0.7$, in other words:

$$Z = \text{Max}(X_1, X_2, X_3, X_4)$$

For the sake of simplicity we assume that the X_i are independent and identically distributed random variables. This assumption has the merit of making the analytical derivation possible. However, in specific applications one can take realistic distributions based on clinical data.

- If $f(x)$ and $F(x)$ respectively represent the density function and the cumulative distribution function of the X_i , what will be the density function, $f_Z(x)$, of Z ?

Let us first consider the case of only two organs.

$$F_Z(x) = P\{Z \leq x\} = P\{\text{Max}(X_1, X_2) \leq x\} = P\{X_1 \leq x \text{ and } X_2 \leq x\}$$

Now, the fact that X_1 and X_2 are independent means that:

$$P\{X_1 \in A \text{ and } X_2 \in B\} = P\{X_1 \in A\}P\{X_2 \in B\}$$

where A and B are two subsets of the set of real numbers. Therefore:

$$F_Z(x) = P\{X_1 \leq x\}P\{X_2 \leq x\} = [F(x)]^2$$

which, by differentiation leads to the density function of Z :

$$f_Z(x) = 2F'(x)F(x) = 2f(x)F(x)$$

For p parts instead of only two, one gets similarly:

$$F_Z(x) = [F(x)]^p \Rightarrow f_Z(x) = pf(x) [F(x)]^{p-1} \quad (1)$$

In order to see what is the shape of this function we consider the simple case of a random variable with a uniform density over the interval $(0, 1)$; in this case:

$$\text{for } x \in (0, 1) : f(x) = 1, F(x) = x$$

Thus,

$$\text{for } x \in (0, 1) : f_Z(x) = px^{p-1}$$

This function is shown in Fig.3b for $p = 2, 4, 8, 15$. We see that it is a fast *increasing* function of age. According to the analytical expression $f_Z(x)$ is a power law function. This is consistent with a Weibull distribution but when p becomes large it has the shape of an exponential (as shown in Fig.2b for $p = 15$), a result which is qualitatively consistent with Gompertz's law according to which the probability of death increases exponentially with age.

At this point it is interesting to recall earlier comments that the Weibull form appears consistent with deaths from particular causes. Here we find that the more elements are present the closer the death rate approaches a Gompertz exponential form. There are ways this prediction could be checked. One is to assess death rates from increasingly complex synthetic systems; another albeit more difficult could be to explore death rates of increasingly complex biological systems from single cell upwards. This may however be difficult since complexity in biology brings in multiple organisms but examining death rates from all causes should lead ultimately to the Gompertz form.

3.4 Wear-in

For the example considered above wear-in death would mean that the age of death is: $W = 0.1$, i.e.:

$$W = \text{Min}(X_1, X_2, X_3, X_4)$$

For the distribution function $F_W(x)$ we can write:

$$F_W(x) = P\{W \leq x\} = 1 - P\{W > x\} = 1 - P\{\text{Min}(X_1, X_2) > x\} = 1 - P\{X_1 > x \text{ and } X_2 > x\}$$

Again using the independence property, one gets:

$$F_W(x) = 1 - P\{X_1 > x\}P\{X_2 > x\} = 1 - [1 - F(x)]^2$$

Then, as above, this result generalizes to:

$$F_W(x) = 1 - [1 - F(x)]^p \Rightarrow f_W(x) = pf(x) [1 - F(x)]^{p-1} \quad (2)$$

For the case of uniform random variables, one gets:

$$\text{for } x \in (0, 1) : f_W(x) = p(1 - x)^{p-1}$$

which means that the probability of death is a *decreasing* function of age, consistent with what is expected for infant mortality. The decrease is illustrated in Fig.3a for $p = 2, 4, 8, 15$.

3.5 Special cases

One can gain an intuitive understanding of the theoretical framework by considering a number of special cases.

Firstly, we can consider the extreme case of an organism with a high number of components, say one million or if you prefer a number p which tends to infinity. Then, intuitively, the wear-in assumption gives a probability of death equal to 1 because for such a large number of components there will always be one which will fail almost immediately.

For the same reason the wear-out assumption gives a probability of death equal to zero for almost all ages because it will take a very long time to eliminate all and any components.

The other extreme case is an organism with only one vital component. Then, obviously, the two assumptions should give the same result. Indeed, the formulas (1) and (2) give: $f_W(x) = f_Z(x) = f(x)$. Here the shape of f_W and f_Z is completely determined by $f(x)$ which can have any shape, whether increasing or decreasing.

As the number p of components increases the factor $(1 - F)^p$, which is a decreasing function will become more and more predominant. Similarly, for old age, the factor F^p , which is an increasing function, will become predominant when p increases.

In summary, this discussion makes clear that equations (1) and (2) do not describe only one model but, by playing with p and $f(x)$, they can describe a whole spectrum of cases. It is in this sense that the model is really predictive.

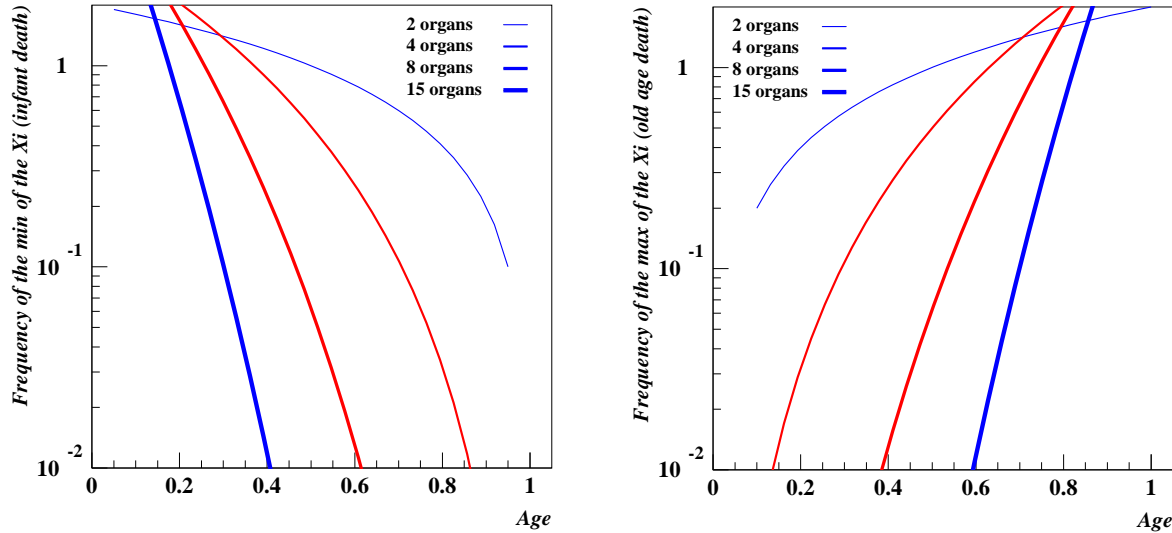


Fig.3a,b Graph of the density functions of the Min and Max of a set of random variables which represent the age-specific death rate in young and old age respectively. When the number of organs becomes large, the death rates become exponential.

3.6 Graphs of infancy and old age death rates

The density functions of the variables W and Z give the infant and old age death rates respectively (Fig.3a,b).

The graphs suggest the conjecture that the larger the number of components, the steeper the death rates with respect to age. When $p \rightarrow \infty$ it can be seen directly on the formulas that f_W falls vertically from $pf(0)$ to zero, whereas f_Z jumps vertically from zero to $pf(1)$.

As technical systems have often many well-defined, separate components it should be possible to test our conjecture. For instance microprocessors comprising a large number of chips should have steeper death rate curves than those with only a small number of chips. Unfortunately, for such technical systems there are almost no life-time data publicly available, probably for reasons of commercial confidentiality.

4 Conclusions

We have proposed two paradigms of death:

- (i) single-organ death which occurs through the failure (e.g. due to congenital malformation) of one crucial organ,
- (ii) multi-organ death which comes about through the deterioration of almost all organs.

At this point a distinction should be made between the underlying cause of death (e.g. cancer or an infectious disease) and the immediate cause of death. It is the former which is of interest and is reported in the death statistics by cause of death. On the contrary, the immediate cause of death is almost always the same, namely a heart failure.

For instance, a liver cancer will lead to blood poisoning which makes the heart unable to perform its function properly. It is because other organs (e.g. the kidneys) are also in poor shape that the partial defect of the liver eventually proves fatal. It is in this sense that death occurs as a kind of overall collapse.

The model predicts that the slope of the death rate is higher (whether for fall or increase) when the number of organs is larger. Can this conjecture be tested on biological systems? The answer is “yes” and “no”.

“Yes”, because a comparison of various species shows that there are indeed great differences in the number of organs. For instance, rotifers (a small swimming animal about 200 micrometers in length) have no heart, no blood, no lungs, no kidneys. In short, they have much less organs than fish.

“No” because there is a serious obstacle, namely the great difference in lifetimes. Whereas rotifers live about 5 days, zebrafish live about 5 years. Unless one knows how to normalize the respective times there can be no meaningful comparison for, needless to say, age normalization affects the measurement of the slope.

A Appendix A. Statistical versus probabilistic descriptions of the death process

In this appendix we discuss some particular aspects of the theoretical framework. The first subsection clarifies the connection between age and time in aging processes. The second subsection establishes the important connection between the density function of the ages of death and its frequency counterpart commonly referred to as the death rate.

A.1 Age versus time

Should we use age (noted x) or time (noted t)? At first sight, the question may seem irrelevant for if time is counted from the moment of birth the two variables are identical. It is not so simple however, as shown by the fact that in our min-max argument we had to introduce as many age of death variables X_1, X_2, \dots as there are vital organs. Moreover, for any organ, its real age is the time elapsed since it was created. For instance, in zebrafish the heart appears and starts to beat some 20 hours after fertilization. Most vital organs are created during embryogenesis which means that their age is not identical with time (measured after birth which for fish means hatching of the eggs). That is why X was a more appropriate variable than time.

However, in this appendix our perspective is different for we wish to consider the evolution of a whole population or more precisely of a cohort of individuals born at the same moment. Taking this moment as origin of the time axis makes the age of each individual numerically identical with the time given by an external clock.

Actually, to describe the evolution of a cohort, time seems a better variable than its age. Why? Although the population exists at any time, for external observers, it becomes real only when we can know its size and that occurs only when a census (or a survey) takes place. Censuses are conducted at specific time intervals (e.g. in the US every decade) and concern simultaneously all cohorts. That is why in this part calendar time seems to be the natural variable. Age will play a role only if we wish to consider different age groups.

A.2 Death rate versus probability density

As always, the tricky point is the relationship between the probabilistic notions and their statistical counterpart. The goal of this appendix is to recall the main notions and how they are related.

Let t denote the age of individuals in a cohort

Let $y(t)$ denote the size of the cohort at time t We wish to describe the decrease of the population in the course of time.

The probability that an individual would die in the time interval (t_1, t_2) (which is also an age interval) is:

$$(\text{Number of those who die})/(\text{number of those alive initially}) = [y(t_1) - y(t_2)]/y(t_1)$$

to get the probability of dying per unit of time we must divide by the length of the time interval $\Delta t = t_2 - t_1$.

$$\mu(t) = (1/\Delta t) [(y(t_1) - y(t_2)) / y(t)]$$

Note that $\mu(t)$ represents what is usually called the death rate, sometimes also called the hazard rate or the force of death. Note also that: $y(t_1) - y(t_2) = -\Delta y$.

Now, let us consider the case of a constant probability of dying. One is led to: $(1/y)(dy/dt) = -a$ which gives: $y(t) = y_0 \exp(-at)$. In other words, the survival function is a decreasing exponential.

Now let us consider a random variable T which represents the age of death of an individual. Its density function, defined by: $f(t)dt = P\{t < T < t + dt\}$, is the derivative of the distribution function: $F(t) = P\{T \leq t\}$. $f(t)dt$ is the probability that the death of the individual occurs in the age interval $(t, t + dt)$; $f(t)$ is the probability per unit of time.

Note that: $f(t) \sim \mu(t)$. In words, $\mu(t)$ is the statistical counterpart of the probability density function of T .

If we consider again the case of a constant probability of dying (for ages in a bounded interval and zero elsewhere), it means: $f(t) = \mu(t) = a$. Then, the distribution function is: $F(t) = at$, at least until at is equal to 1. The decreasing distribution function is:

$$G(t) = P\{T > t\} = 1 - F(t) = 1 - at$$

Note that $G(t)$ is different from the survival function.

Ethical statement

- 1 The authors did not receive any funding.
- 2 The authors do not have any conflict of interest.
- 3 The study is purely theoretical and does not involve any experiment with animals that would require ethical approval.
- 4 The study does not involve any participants that would have to give their informed consent.

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