THE COMPLEXITY OF BIOLOGICAL AGEING

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The present review deals with the computer simulation of biological ageing as well as its demographic consequences for industrialized societies.

1 Introduction

Life usually ends with death, and ageing is defined here by the increase of the mortality rate with increasing age. Merryl Streep and Goldie Hawn showed in the movie "Death becomes her" the consequences of an elixir giving us eternal life. The present review instead deals with the consequences present foreseeable trends have on the demography of developed countries, and with the biological reasons of ageing.

2 Demography

The mortality rate q is the fraction of people of age x who die within the next time unit, i.e. before they reach age x + 1: q(x) = [S(x+1) - S(x)]/S(x). Here, S(x)is the probability to survive from birth to age x. This quantity q can by definition not increase beyond q = 1. It depends on the time unit which is typically a year for humans and a day for flies and worms. A better quantity, which can increase beyond unity, is the derivative μ for infinitely small time steps instead of discrete time steps,

$$\mu(x) = -d\ln S(x)/dx \quad , \tag{1}$$

called here the mortality function (also denoted as hazard rate or force of mortality ¹). If life tables with yearly units are published, then μ can be approximated through

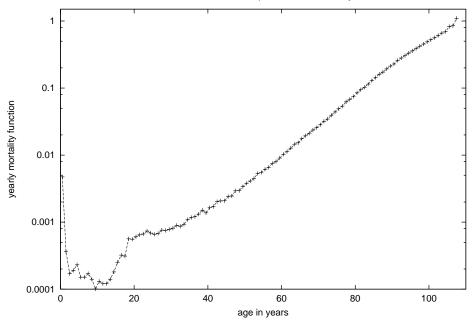
$$\mu(x+1/2) \simeq \ln S(x) - \ln S(x+1))$$
(2)

which also can increase beyond unity. The astronomer Halley tried about three centuries ago to find some laws governing human mortality, but only in the 19th century Gompertz found the law which is valid when childhood diseases are overcome, Fig. 1:

$$\mu \propto \exp(bx) \tag{3}$$

with an empirical parameter b increasing for humans over the centuries. It holds also approximately for many animals in protected environments like zoos and laboratories ², while in the wild many animals are eaten by predators before they reach their genetically possible age. Below the age of 25 years for humans, deviations are seen: The mortality (rate or function) is high at birth (most human embryos die before birth), then sinks to a broad minimum between 5 and 12 years, and only then increases monotonically up to old age.

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From recent life tables of Swedish men, with Gompertz law for 30 to 90 years, and childhood diseases

Figure 1. Gompertz law ad middle age, childhood deviations, and possible downward deviation from Gompertz law for centenarians among Swedish men. From life tables 1993-1997 of the central statistical bureau in Sweden: Ewa.Eriksson@scb.se (1999).

For humans, the last two centuries have seen a doubling of the life expectancy at birth, $\int S(x)dx = \int x\mu(x)S(x)dx$, from 40 to 80 years. Figure 2 shows, for Swedish women since 1750, both the prolongation of life and the increasing reliability. (We did not all die at age 40 in earlier centuries. If half of the babies die in their first year, and the other half lives until 80, then the life expectancy is 40 years.) We see clearly that the life expectancy no longer increases as fast as in the first half of the 20th century, but the present lower rate of increase showed no sign of further reduction during the last decades. Figure 3 shows that this increase of life expectancy comes not only from the reduction of child mortality but also from an increase of the remaining life expectancy at age 65.

Much more recent is the reduction of the birth rate (number of children born per women during her lifetime) below the replacement level of about 2.1. The two German states started this around 1970, due to "the pill", and in West Germany the birth rate scattered about 1.4 in the last three decades. In France it is higher, in Spain and Italy lower. World War II was started by Nazi Germany with the excuse of "Volk ohne Raum", than the Germans needed more living space; so a reduction of the native population (enlarged by immigration) did not seem bad around 1970. In the meantime, however, the reduction in the number of young people coupled with the increase in the number of old people is seen as a threat to the usual way in which you should finance my retirement. If the strongest age cohort in the year

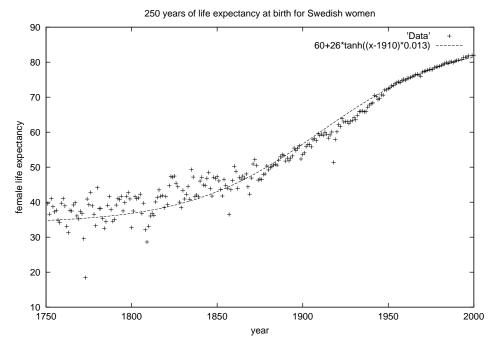


Figure 2. Life expectancy for Swedish women for 250 calendar years. From Wilmoth's Berkeley Mortality Data Base.

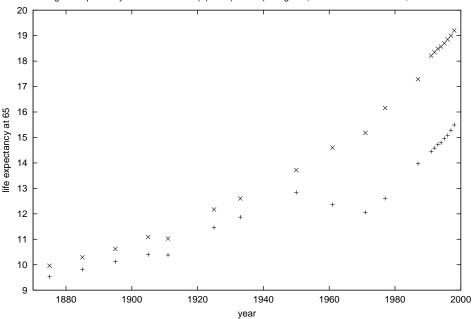
2030 will be people at age 70, we can hardly afford an average retirement (healthy Germans) at 62.

Thus we 6 (and others) predicted the future ratio of pensioners to working-age people, assuming that after the year 2011 the retirement age is increased from 62 years by 0.6 years for every year by which the life expectancy at birth increases, and that starting in 2005 an immigration of 0.38 percent per year (of the population) of people aged 6 to 40 years keeps the total population stable. We see that the dangerous peak around the year 2030 is followed by a plateau in this ratio. (Working was assumed to start at age 20.)

In a comparison of life tables for different countries and different countries, a certain degree of universality was found for the human Gompertz law $\mu \propto \exp(bx)$: The mortality for centenarians was about the same 3,4,5 . Thus

$$\mu \simeq 7b \cdot \exp[b(x - X)] \tag{4}$$

with a characteristic age of $X \simeq 103$ years for the whole human species, while $b \sim 0.1$ increases with time. (For x < X the differences between q and μ are quite small.) Moreover, Azbel ⁷ found (with some deviations) a universality even for the younger ages where Gompertz is invalid, Figure 1. He found the mortality $q_x(c,t)$ at age x (for country c and calendar year t) to be a universal function f_x of infant mortality $q_0 = q_{x=0}(c,t)$ and age x: $q_x(c,t) = f_x(q_0)$. The function f_x no longer



Remaining life expectancy for German men (+) and (women) of age 65, Statistisches Jahrbuch, www.destatis.de

Figure 3. Remaining life expectancy at the German legal retirement age of 65.

depends explicitly on c and t, in contrast to q_x . Thus if country A has at present a known mortality function of age, then another country B roughly has the same mortality function if we change the calendar year t such that the infant mortality in B at time t agrees with the present infant mortality in A. If the Gompertz law would be valid for all ages, Azbel's universality ⁷ would already follow from Eq.(4) since it contains only one free parameter b for all human societies. These universality laws suggest that extrapolations like Fig. 4 may, with some shift in time t, be valid also for developing countries, if they do not take early action to keep the birth rate near the replacement level of 2.1 or whatever else is needed to offset deaths and net emigration.

A decade ago, mortality maxima were observed 8,9 for flies. Have they found the fountain of youth such that we get healthier again with increasing age ? Humans at least, Fig. 1, do not show such maxima in reliable statistics, though USA data published in the 1990 showed them. (Reliability seems to increase from USA to Western Europe and from there to Sweden.) Perhaps above 110 years human mortality reaches a plateau 1,10 . But a comparison of Figures 3 and 4 in 10 shows that for the more reliable half of the European data, the highest claimed ages were appreciably below those of all the data: The more reliable the data are the smaller are the deviations from the Gompertz law. Perhaps for the oldest old the mortality still increases with age, but only linearly 13 and not exponentially: Neither acceleration nor deceleration of mortality. More arguments against mortality deceleration

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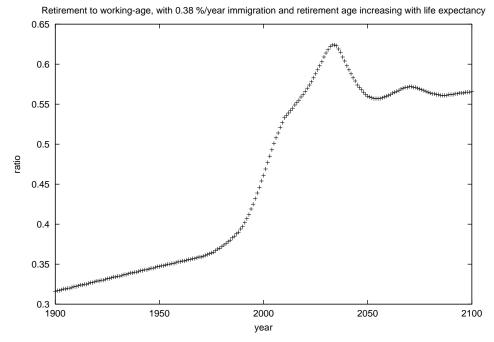


Figure 4. Ratio of people above retirement age, to working-age people older than 20 years, as predicted in Ref. 6 using extrapolated Gompertz laws.

for humans are given elsewhere 11,12.

While at present we thus should be cautious about buying fountains of youth for humans, future decades might produce genetically modified humans with longer life expectancies. The little worm *Caenorhabditis elegans* survives bad times (no food, ...) by reducing all life functions during a "dauer" state, in agreement with computer simulations 14 . Even flies and some mammals live longer if put on a starvation diet 15 . But do we want to live longer if the gained life span is spent in a coma, or in hunger? More attractive is a very old elixir of youth, red wine. According to 16 , the polyphenol resveratrol in red wine activates the Sir2 gene and lets yeast cells life 70 % longer. Indeed, Jeanne Calment is widely (though not universally) believed to be the oldest human being and died in 1997 at age 122 in Southern France, having drunk red wine moderately. Let me see if drinking it beyond moderation lets me beat her world record.

3 Why do we age?

It may be an exaggeration that there as many theories of ageing as there are ageing theorists, but nevertheless we have lots of theories. They even might all be correct, since ageing may have many causes. Also, some theories do not exclude each other, describing only different aspects of the same phenomenon.

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120 years ago, Weismann suggested that we die to make place for our children 17. This is very altruistic but also very unrealistic, since of two different races of the same species the one which produces more children will win the Darwinian struggle of survival of the fittest. Those who live longer at otherwise unchanged parameters produce more children and thus win in the short term even if on long time scales they drain the environmental resources stronger and might finally destroy the ecosystem, including themselves. (If, however, longer lifetime is coupled to lower birth rates, the Weismann idea becomes viable as explained later.)

Medawar ¹⁸ suggested more than half a century ago the still relevant mutation accumulation theory: Bad mutations killing us in young age before we get children will die out since they are not given on to the offspring; bad mutations killing us after we produced many children are given on to future generations. Thus after some time the population should contain few hereditary diseases affecting us in young age, but many affecting us in old age. Thus the probability to die from them increases with increasing age.

A now widespread idea are oxygen radicals created by metabolism and destroying the DNA, carrier of heredity, during our life. This theory is not necessarily in contradiction with the mutation accumulation; instead it is a biochemical explanation for these mutations.

Telomeres are sections at the end of the DNA which are lost at every duplication of the cell. If the number of telomeres in this way has become too small, the cell stops dividing: Hayflick limit. A recent ageing theory ¹⁹ is based on these telomeres, and perhaps at the time of the conference I can present more simulations.

Longevity genes would prolong life, have been found to work for many animals, and are perhaps connected with the red wine effect mentioned at the end of section 2. Again, their existence does not contradict the other theories: A longevity gene may produce more telomerase, an enzyme which restores lost telomeres. Or it may enhance scavenging of dangerous oxygen radicals and thus reduce the mutation rate relevant for mutation accumulation.

Reliability theory ⁴ may work also for the ageing of automobiles and was connected to the Penna model (see below) in ²⁰, see also ²¹. It assumes the organism or car to consist of m irreplaceable blocks; failure of one of these blocks causes the whole system to fail. Each block consists of many equivalent elements; the initial numbers of properly working elements within a block follow a Poisson distribution. A block fails if all its elements fail; each element ages with a constant failure rate 1/X. Then Gavrilov and Gavrilova ⁴ recovered analytically the Gompertz law, Eqs.(3,4), for age $x \ll X$ and a mortality plateau $\mu = m/X$ for very high age $x \gg X$. The characteristic age X in Eq.(4), valid for all humans, then is the average lifetime of the single elements.

The following sections will report computer simulations of the mutation accumulation idea.

4 Simulations of mutation accumulation

This section restricts itself to those individual-based ageing models which were investigated in papers of different groups. Historically the first are those of Partridge-

Barton type 22 , followed by the most widely used Penna model 23 , while the Stauffer model 12 is more of conceptual than of practical value but therefore forms our starting point.

In contrast to Weismann, we do not die to make place for our children. But if we fix the number of children, then the idea 12 works: The birth rate (per iteration) is assumed to be inversely proportional to the time between the minimum age of reproduction, x_m , and the genetic death age, x_d . Hereditary mutations accumulate over the generations, and each may independently change both characteristic ages x_m and x_d by one time unit. Individuals may die before Thai genetic death age from hunger etc, which is taken into account by a Verhulst death probability proportional to the population size, as in a logistic equation. Then automatically a reasonable distribution of death ages emerges and death is explained as coming from random mutations plus a trade-off between longevity and high birth rate. The catastrophic senescence of Pacific salmon, the death of Northern cod though over-fishing, the minimum population size for social animals, and the emergence of female menopause were simulated successfully 24,25,26. However, in general 27 the mortality increases linearly with age, instead of the desired exponential Eq.(3). Also, the minimum age of reproduction is distributed among unrealistic short ages, even in a much more complicated model of a whole ecosystem 28 .

This trade-off between longevity and high birth rate is mentioned a lot in the biological literature. The most direct but not the only way to realize it genetically are mutations with antagonistic pleiotropy 22,29: these genes have positive effects in youth and negative ones at old age.

Computer simulations of ageing started by putting fluctuations into the phenomenological model of Partridge and Barton 22,30,31,32,14,33,34. Originally it assumed only three ages zero, one and two, with a juvenile survival rate J from zero to one, and an adult survival rate A from one to two. It was first thought to give unrealistic mortality functions and difficulties if generalized to many age levels, but 33 repaired this by slight modifications, and 34 included sexual reproduction in it. But the lack of an explicit genome makes it less attractive than the Penna model described now.

The Penna model is by far the most widespread method to simulate biological ageing. Most of the literature up to 1998 is cited in 35 , and later work up to 2000 in 12 for asexual and 36 for sexual reproduction. The genome is represented by a bit-string $(10^1 \dots 10^3)$ bits were simulated) giving bad mutations. A bit set to zero is healthy, a bit set to one means that a hereditary disease starts to reduce the health at the age to which the bit position corresponds. The first bits describe diseases starting in youth, which are rare, and the latest bits correspond to the much more frequent diseases at old age. Three active diseases kill, and so does a Verhulst death probability proportional to the total population size. Each time interval, every individual above the minimum age of reproduction produces offspring which differs from the parent by a random mutation of the bit-string genome. In the sexual version with recombination of the two bit-strings of the genome, dominant

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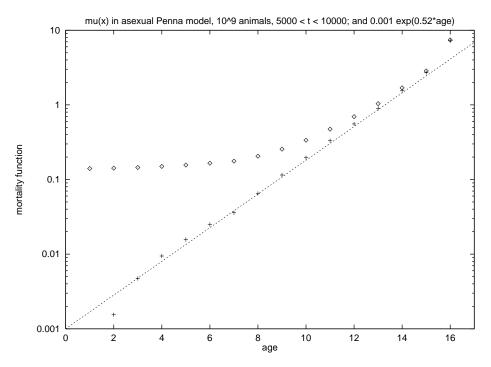
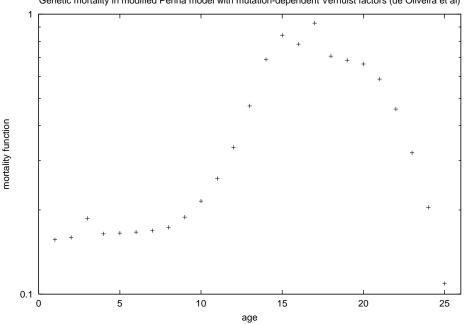


Figure 5. Mortality function μ for the standard as exual Penna model, with (upper data) and without (lower data) the deaths from the Verhulst factor.

mutations affect the health already if only one bit-string is mutated, while recessive mutations become dangerous only if both bit-strings are mutated. Bigamy with three bit-strings was discussed in 37 .

Figure 5 from 35 shows the resulting mortalities, with and without the deaths from starvation or lack of space. The purely genetic deaths follow nicely the exponential Gompertz law, except for the youngest and oldest ages. The limit of exactly three mutations killing can be softened 38 to give slight downward deviations from the Gompertz law as in Swedish mortalities, Fig. 1, or a mortality plateau as claimed in 10 . It can also be abolished in favour of Verhulst factors depending on the number of active mutations; then a mortality maximum even more pronounced than for flies 8,9 is obtained in Fig. 6 from 39 . Simulations of biologists, in contrast, could not yet get such mortality maximum 40 . Pacific salmon, Northern cod, and Alaskan wolves were simulated successfully long ago 35 , and Lyapunov exponents 45 , Brazilian lobsters 42 , child mortality 46,47 , prey-predator relations on lattice 43 , and speciation more recently 41,44 . Particularly relevant for our section 2 are the Penna model simulations of the demographic changes in the 20th century 48 . The mortalities do not change much 49 if the genome may contain the same gene in several copies called "paralogs" 21 .

This section ends with a technical warning: If the population is kept constant



Genetic mortality in modified Penna model with mutation-dependent Verhulst factors (de Oliveira et al)

Figure 6. Semilogarithmic plot of mortality function in a modified Penna model

artificially, as is tradition in theoretical biology, instead of being allowed to fluctuate as in nature, then the results are only qualitatively, not quantitatively, the same 50.

5 Sex

Sexual reproduction was introduced into the Penna model long ago 35 , for the Partridge-Barton type 34 and the Stauffer model 26 only recently. Even bacteria exchange genome via "parasex" 51 , and computer simulations with the Penna model showed this parasex to give fitter individuals than pure asexual cloning 52 . These simulations included ageing of bacteria, as found later experimentally 53 . Less clear is the need for males in species with two sets of chromosomes, from father and mother 36 . Only with some effort 55 could feeding the males be justified in the Penna model; and no simulation yet showed hermaphroditism to be by far the fittest way of reproduction. On the other hand, sexual reproduction is clearly preferable as a protection against parasites or environmental catastrophes 36 . So, the sex wars can continue 54 .

Menopause or it's analog is the cessation of female reproductive power at middle age. In spite of widespread prejudice, it is not restricted to humans (and pilot whales) but even occurs in some flies 56. Computer simulations showed, without

any specific human assumptions like tradition of knowledge, that menopause can emerge automatically 57,26 , provided the risk for the mother of giving birth increases with increasing age and/or the child depends on the mother for its initial survival. Are men needed for survival of the children? Only indirectly 35 : without them women would follow Pacific salmon and die rapidly after giving birth; the lack of a male analog for a sharp menopause makes males useful for producing children even at older age, thus prevented evolution to kill females after their cessation of reproduction.

6 Conclusion

Computer simulation of mutation accumulation models has advanced a lot in one decade and has applications like retirement rules. Particularly important seem the menopause explanations 57,26 showing that such effects are not restricted to humans. Simulations of alternative theories of biological ageing 19 are mostly lacking.

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