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THE OLDEST OLD AND THE POPULATION HETEROGENEITY

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We have simulated the effect of the diversity of the late expressed genes in the genetic pool of population on the phenotypes of individuals in the late ages. Using Penna model based on the Monte Carlo method we have obtained for the oldest fractions of populations lower mortality rates than predicted by the exponential Gompertz function. Such deviations from the expected exponential increase of mortality are the characteristic for populations which are not in equilibrium with the environment, or if a relatively high probability of reversions was assumed, or if the population is heterogeneous. In such populations, the genes expressed in the late ages, are under the very weak selection pressure and thus, highly-polymorphic. As an effect, the probability of the genetically-determined death of the oldest organisms does not grow as fast as predicted by the Gompertz exponential curve describing mortality during earlier periods of life.

Keywords: Biological aging; Monte Carlo simulation; Gompertz law; human mortality.

1. Introduction

Mortality of the human population measured as a logarithm of fraction of population not surviving the next year of life and plotted against the age shows a characteristic linear behavior for periods after the minimum reproduction age. This exponential increase of mortality with age was described in 1825 by Gompertz and is known as the Gompertz law. Nevertheless, this law is not applicable for the period of life before the minimum reproduction age. Furthermore, a deviation from the exponential increase of mortality is often stated for the late periods of the human life — for the "oldest old". In this period the increase of mortality is slower than expected from the Gompertz curve. This specific behavior of the mortality function is universal and for many studied species it follows the specific shape, often called plateau.[1]

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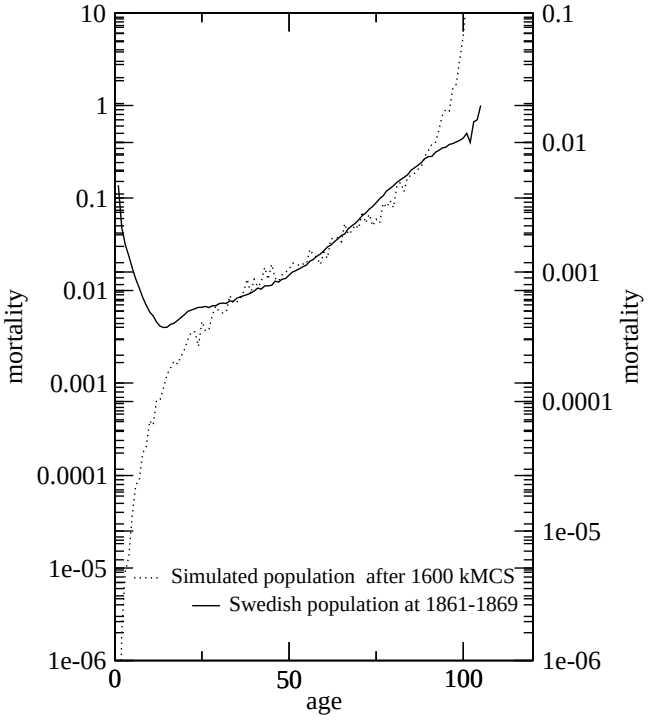

Fig. 1. Gompertz curves for the Swedish populations males and females together at 1861–1869 (left scale, —) and for the simulated populations; genomes 640 bits long after 1 600 000 MC steps (right scale, $\cdots$). Age scale (X-axis) for the simulated population was rescaled to fit the real human population, as described in Ref. 15.

One of the most interesting hypotheses which try to explain the mortality function and the senescence itself is a mutation accumulation theory[2,3] which assumes that there is a gradient of selection pressure on genes in the genetic pool of population. Genes expressed before the minimum reproduction age are under strong selection while genes expressed after the minimum reproduction age are under weaker selection pressure. There is a simple model,[4] based on a Monte Carlo simulation, exploring the hypothesis of mutation accumulation. Rough comparisons of mortality of simulated populations and real human populations or populations of other organisms have shown that Penna model can reproduce the Gompertz exponential mortality law.[5] However, precise comparisons of the trajectories describing the mortality of both natural and simulated populations revealed differences significant for the periods of life before the reproduction age and for the very late periods of life (see Fig. 1).

Nevertheless, the mortality of the "oldest old" remains the most controversial part of the trajectory. Experimental demonstrations with laboratory animals: *Drosophila melanogaster*, *Ceratitis capitata*, *Anastrepha ludens* and *Caenorhabditis*

elegans have established a basic finding that mortality decelerates at older ages, or at least does not grow exponentially as in the earlier periods of life.[6–8] Some estimates done for human populations up to the age of about 110 or even 120, indicated that human mortality also decelerates.[1]

Mueller and Rose[9] developed extensions to the evolutionary theory of aging, which indicate that "such late-life mortality plateaus are to be expected when enough late life data are collected". According to Azbel phenomenological theory,[10] the deviation from the Gompertz law for the oldest fraction of population could be expected if the population was heterogeneous. However, in the recent paper Mueller *et al.*[11] concluded that the life-long heterogeneity model could not give a reasonable biological explanation of the plateau. Below we argue that the mutation accumulation theory as described by the Penna model can give the mortality rates for the oldest fractions of populations lower than predicted by the Gompertz law.

The usually-used version of the Penna model gives "S-shaped" curve indicating an acceleration of the mortality rate at the old ages. Recently Coe *et al.*[12] shown that it is possible to get the mortality plateau for the oldest fraction of populations in the Penna model if Fermi survival function is applied. This solution could be particularly interesting for analyzing the mortality of the inbred strains, i.e., genetically homogeneous populations. However, there are some modifications to the Penna model which produce the mortality plateau. One of this modifications assumes that organisms can "forget" the deleterious effects of defective genes expressed in younger ages, like one can forget about acne.[13]

Another interesting way of producing the plateau is antagonistic pleiotropy, proposed by Sousa and Moss de Olivera.[14] They assumed that some genetic configurations increase the risk of the disorder in younger ages while the same configurations can be profitable in older ages. Such an effect could be justified also by the memory of the immune system. For further discussion of the problem of plateau, see Ref. 1.

Since it is a high frequency of defects in the late expressed genes that is responsible for the accelerated mortality of the oldest fraction of population in the Penna model, there should be some biologically justified premises which could produce the plateau.

2. Model

Detailed description of the model can be found in Ref. 5. In our version with the sexual reproduction, individuals are represented by two haplotypes (bitstrings 128 or 640 bits long). At each time step (year) two alleles at the consecutive locus are switched on. If at least one of them is correct — the function can be performed, otherwise the defect is counted. If at the given step the threshold $T = 3$ of expressed defects is reached — the individual dies. When the individual reaches the age $R = 20$ — it can reproduce.

To reproduce, the female produces a gamete by crossing over between two parental haplotypes at a randomly-chosen locus and then one locus is

randomly-chosen for mutation. If the chosen allele is set for 0 it is replaced by 1, if it is set for 1 it stays 1 unless reversion is allowed with a given probability. Each of these gametes is joined with another one, produced in the same way by randomly-chosen male at the reproduction age. The newborn can survive with a probability: $V = 1 - N_t/N_{\max}$ where $N_{\max}$ — the maximum population size and N_t — the current population size. The sex of the newborn is randomly-chosen with an equal probability male/female. After a given number of Monte Carlo steps the age distribution and the distribution of defective genes of the simulated populations are analyzed. Some modifications of this model used in the simulations are detailed in the Results and Discussion section.

3. Results and Discussion

In Fig. 1 the Gompertz curves for a real human population (Swedish population of males and females together at the end of the 19th century[16]) and the simulated population are shown. In this modification, the genomes of individuals were represented by bit strings 640 bits long and the minimum reproduction age was set for 200 bits. Even after rescaling the data for the simulated populations, the shapes of curves are different, particularly for the periods before the minimum reproduction age and for the oldest fraction of the populations. The methods of the prediction of the higher mortality of younger individuals in the model have been discussed earlier by Łaszkiewicz *et al.*[15]

The simplest method for fitting the oldest part of the simulated population to the real one is to stop the simulation before the population reaches the equilibrium. If we assume that natural populations never reach the equilibrium, only pursue the changing environment instead, the distribution of defective genes expressed in the late ages is different for steady state, as shown in Fig. 2. In this figure we have shown the series of plots representing the distribution of defective genes in the populations simulated for different number of Monte Carlo steps. The corresponding age distributions of these populations are shown in Fig. 3. One of these populations (after 80 000 MC steps) fits the Gompertz curve for the real human population (Fig. 4) as it was shown elsewhere.[17]

The main difference between the population after 80 000 MC steps and the population after 1 600 000 MC steps is a higher diversity of the fraction of the late expressed genes after 80 000 MC steps of evolution. In the population after 1 600 000 MC steps, all alleles at the loci 400 and switched on later are defective while in the populations after fewer MC steps of evolution the fraction of defective alleles at this part of the genomes is significantly lower. There are some other methods which could produce an effect of deviation from the Gompertz law for the oldest fraction of population. In our standard version of the model, there are no reversions which means that if at a locus randomly-chosen for mutation a defective gene is found, it stays defective. After introducing some frequency of reversions to the model (in our modification if the defective gene is

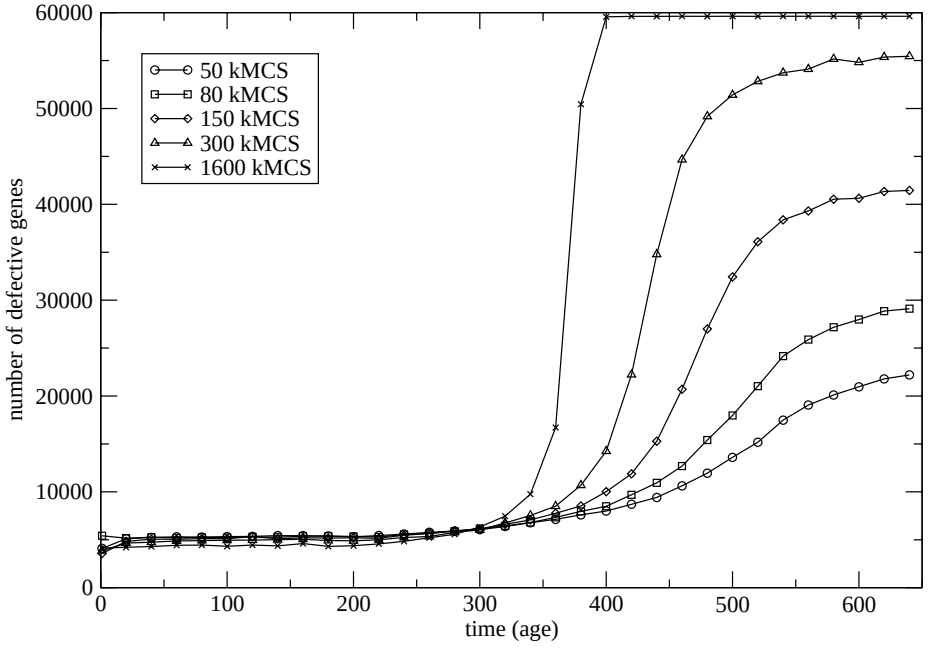

Fig. 2. The distribution of the defective alleles in the genomes in populations simulated for different number of Monte Carlo steps. The length of the bit strings — 640 bits, minimum reproduction age — 200.

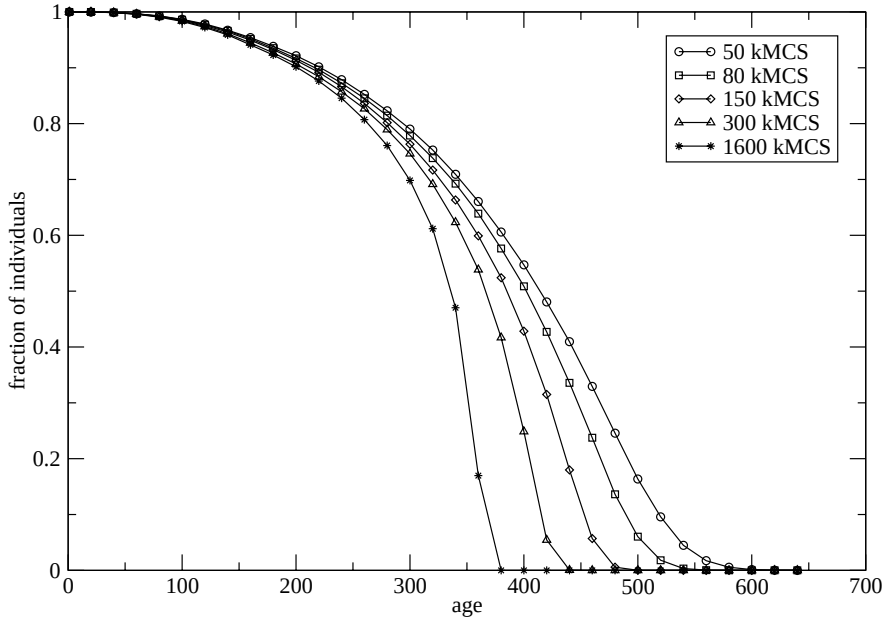

Fig. 3. The age distribution of the simulated populations after different number of Monte Carlo steps of simulation, parameters as in Fig. 2.

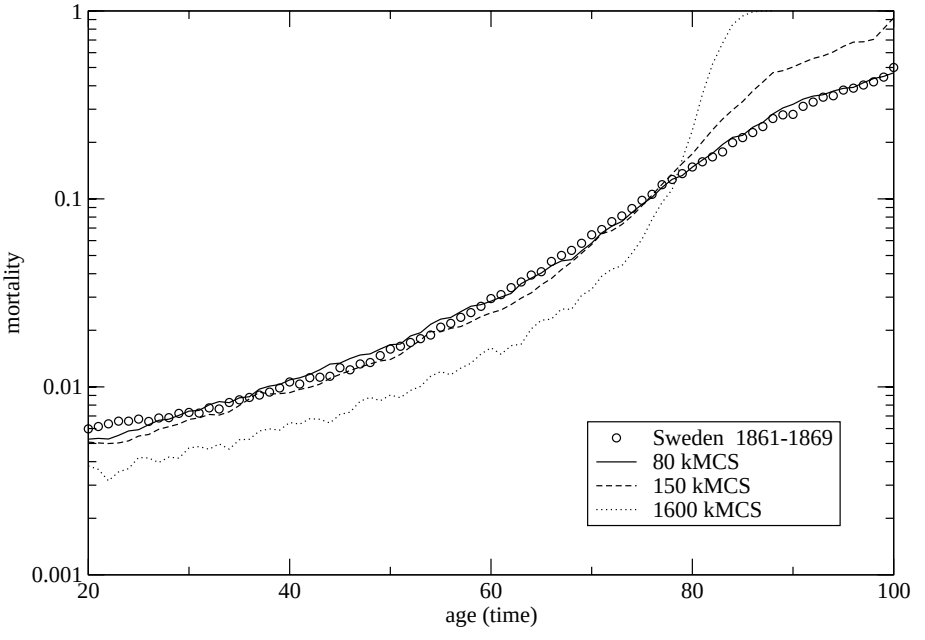

Fig. 4. Gompertz curves for the real Swedish population shown in Fig. 1 and for three populations shown in Fig. 3. Age scale (X-axis) for simulated populations was rescaled.

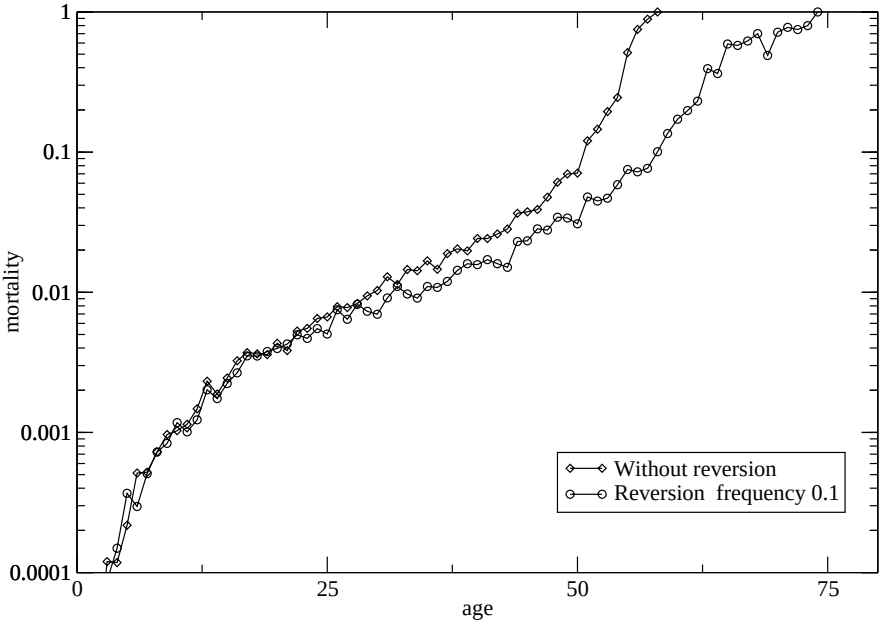

Fig. 5. Gompertz curves for the simulated populations without reversion and with the probability of reversion 0.1. The genomes 128 bits long, minimum reproduction age 20.

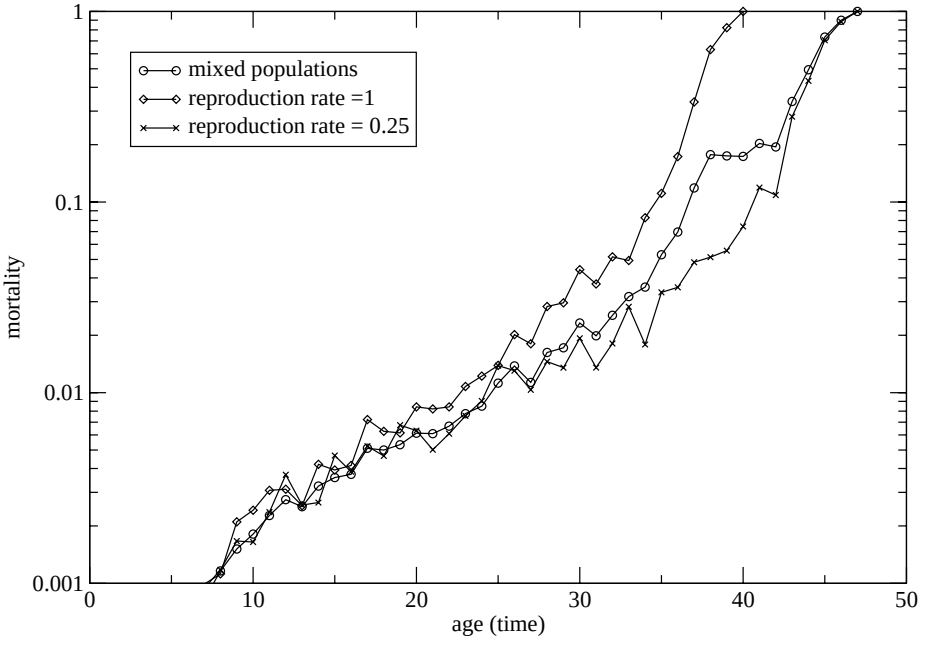

Fig. 6. Gompertz curves for the two populations which evolved under different reproduction rates and then mixed with the allowed crossbreeding.

selected for mutation it will be "repaired" with probability 0.1) the results of simulations are different than in the standard model (Fig. 5) and show significantly decreased rate of mortality at the older ages.

One can argue that the reversion frequency introduced into this modification of the model is too high, probably in the Nature it is much lower. However, in the Nature, this effect of reversions could be replaced by other phenomena introducing heterogeneity into the genetic pool of population. One of such mechanisms could be outbreeding — mixing two populations which were separated before. We have performed such simulations with two populations which evolved with different reproduction strategies. Both populations evolved in the environment where Verhulst factor operated on the whole population but the birth rates were different. The genetic pools of such populations differ significantly, especially in the section of genes expressed during the late ages. Thus, two populations were generated — one with a longer reproduction period and another one with a shorter reproduction period. When these two populations were allowed to crossbreed — the deviation from the Gompertz exponential law was observed (Fig. 6). It is expected that this effect would be "smoother" if more different populations were allowed to crossbreed. The deviation from the Gompertz law was also observed when the recombination rate was reduced in comparison with the standard model parameters.[15] Reduced recombination rate leads to the formation of genetic linkages, which induce different

strategies of reproduction, i.e., sacrificing the youngest individuals in the restricted environment size and higher diversity at the late expressed loci.

In conclusion, the deviation from the Gompertz exponential law of mortality of the oldest part of the population can be obtained in the Penna model if the genetic pool of the simulated population is not homogeneous in respect to the late expressed genes. This effect can be obtained either in populations which are not in equilibrium with the environment or in mixed populations which evolved under different reproduction regimes. Simple decrease in the recombination rate during the gamete production produces the plateau. It seems that such assumptions are justified from the biological point of view.

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