Simulations of a mortality plateau in the sexual Penna model for biological aging

V. Schwämmle[1,2] and S. Moss de Oliveira[1]
[1]*Instituto de Física, Universidade Federal Fluminense, Avenida Litorânea, s/n Boa Viagem, 24210-340, Niterói, Rio de Janeiro, Brazil*
[2]*Institute for Computer Physics, University of Stuttgart, Pfaffenwaldring 27, D-70569 Stuttgart, Germany*
(Received 23 February 2005; published 19 September 2005)

The Penna model is a strategy to simulate the genetic dynamics of age-structured populations, in which the individual genomes are represented by bit strings. It provides a simple metaphor for the evolutionary process in terms of the mutation accumulation theory. In its original version, an individual dies due to inherited diseases when its current number of accumulated mutations, n, reaches a threshold value T. Since the mean number of diseases increases with age, the probability to die is zero for very young ages ($n<T$) and equals 1 for the old ones ($n\geqslant T$). Here, instead of using a step function to determine the genetic death age, we test several other functions that may or may not slightly increase the death probability at young ages ($n<T$), but that decrease this probability at old ones. Our purpose is to study the oldest old effect, that is, a plateau in the mortality curves at advanced ages. By imposing certain conditions, it has been possible to obtain a clear plateau using the Penna model. However, a more realistic one appears when a modified version, that keeps the population size fixed without fluctuations, is used. We also find a relation between the birth rate, the age structure of the population, and the death probability.

DOI: 10.1103/PhysRevE.72.031911 PACS number(s): 87.23.−n, 87.10.+e

I. INTRODUCTION

The mechanism of aging is still an important task of recent research and the mutation accumulation hypothesis is one of the most acceptable theories. The mortality can be measured by the so called mortality function

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

where $S(x)$ is the probability to survive from birth to age x. In the 19th century Gompertz found that the mortality function increases exponentially with age. Less or more pronounced decreases of this exponential growth of mortality at old ages, also known as the oldest old effect, have been observed in humans and mainly in flies [1].

The Penna model [2,3] is one of the most popular models for biological aging, which has been successfully applied to reproduce the Gompertz law [2,4], to study the preference for sexual rather than asexual reproduction [5] and more recently, to study sympatric speciation [6–8]. Its asexual version was solved analytically by Coe *et al.* [9], who showed that the replacement of a sudden death rule after the accumulation of T deleterious mutations (step function) by a probability to survive given by a Fermi function leads to a plateau in the mortality curve. Numerically, only a very short plateau was observed before [10,11].

In our simulations of the original sexual Penna model, we obtain that when the genetic death probability at advanced ages is given by a smooth function instead of the usual step function, but is greater than zero at very young ages, the birth rate has to be greatly increased to avoid population meltdown. In this case it is very difficult to measure the oldest old effect, since very few individuals survive until old ages. A small plateau has been observed by imposing a death probability equal to zero for very young ages ($n<T$), as in the original Penna strategy.

By using a model where the population size is constant without fluctuations, we obtain a very clear plateau in the mortality curves, even considering nonzero values for the probability to die at young ages. We also obtain that the age distribution of the population changes dramatically according to the smoothness of the death probability functions at old ages.

In Sec. II the original Penna model is briefly explained, the genetic death probability functions that are used in order to study the oldest old plateau are introduced, and the corresponding results are presented. In Sec. III we describe the model in which the population size is kept constant and show the results obtained for the same death probability functions of the previous section. In Sec. IV we present the conclusions.

II. THE PENNA MODEL FOR SEXUAL POPULATIONS

In this section only a short description of the Penna model is given. A more detailed one can be found in [3]. In the original version of the model two strings of 32 bits that are read in parallel represent the diploid genome of an individual. A deleterious mutation is defined by two set bits at the same position of both strings or by a single set bit at a dominant position. At the beginning of the simulation a fixed number of dominant positions are picked and positioned without bias along the genome and remain fixed during the whole process. At every iteration or "year" one more bit position becomes active and the corresponding individual becomes one year older. It dies for genetic reasons if its current number of deleterious mutations reaches the threshold T, which corresponds to the following genetic death probability $f(n)$:

$$f(n) = \Theta(n - T), \tag{2}$$

where n is the current number of deleterious mutations and $\Theta(x)$ is the step or Heaviside function. In order to limit the

population size P, an additional death probability $V = P(t)/P_{\max}$, the so called Verhulst factor, is used to keep the population size below $P_{\max}$. It is applied to each individual independently of its age or genome.

At every iteration, any female with age equal to or above the minimum reproduction age R randomly chooses a male, also with age $\geqslant R$, to breed and generate b offspring. To construct one offspring genome first the two bit strings of the mother are cut in a random position (crossing), producing four bit-string pieces. Two complementary pieces are chosen to form the female gamete (recombination). Finally, one deleterious mutation is randomly introduced. The same process occurs with the male's genome, producing the male gamete. These two resulting bit strings form the offspring genome. The sex of the baby is randomly chosen, with a probability of 50% for each one. This whole strategy is repeated b times to produce the b offspring.

A. Approximations to the step function

We use the following approximations of the step function, in order to smooth the original genetic death rule, applied at every iteration, of killing the individual after the accumulation of exactly T deleterious mutations:

$$\text{Fermi-like function} \quad f_1(n) = \frac{1}{1 + e^{-2p(n-T)/32}}, \tag{3}$$

$$\text{Arctangent function} \quad f_2(n) = \frac{\arctan[2p(n-T)/32]}{\pi} + \frac{1}{2}, \tag{4}$$

$$\text{Error function} \quad f_3(n) = \frac{1}{2}\{\text{erf}[p(n-T)/32] + 1\}, \tag{5}$$

where n is the number of active deleterious mutations and p is a parameter that controls the smoothness of the approximations. When the value of p increases, the death probabilities given by Eqs. (3)–(5) converge to the one given by the step function [Eq. (2)]. Observe that what we call a Fermi like death function is in fact one minus a Fermi function.

Figure 1 compares the three approximations with $p=1$ and also the Fermi-like function with $p=10$, with the step function death probability.

B. Results

In simulations of N time steps, the mortality function $m(a)$ is measured over the last N_m time steps, in the following way:

$$m(a) = -\ln\left(1 - \frac{\sum_{t=N_m}^{N} D_{\text{gen}}(t, a+1)}{\sum_{t=N_m}^{N} P(t,a)}\right), \tag{6}$$

where $D_{\text{gen}}(t,a)$ is the number of genetic deaths (not produced by Verhulst) at age a and time step t, and $P(t,a)$ is the number of individuals with age a at time step t.

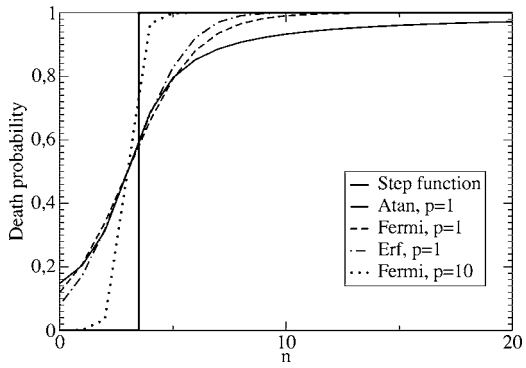

FIG. 1. Death probabilities according to the different approximations of the step function given by Eqs. (3)–(5), versus the number of accumulated diseases. The parameter p controls the smoothness of the functions. The step function case [Eq. (2)] is presented for comparison. Notice that for $p=1$ there is a finite probability for the very young (small n) to die, but the probability for the older to die is smaller than that given by the step function. For $p=10$, the behavior of the Fermi-like death probability becomes almost equivalent to the step function one.

In all simulations that follow, the values of the parameters are $T=3$, $R=10$, $b=1$, $P_{\max}=200\,000$, $N=100\,000$, $N_m=50\,000$, and the number of randomly chosen positions where the bits 1 are dominant is five.

The mortalities obtained using any of the death probabilities given by Eqs. (3)–(5) with $p \geqslant 10$ are equivalent to those obtained with the traditional step function, that is, no plateau appears. Smaller values of the smoothness p lead to population meltdown. This can be avoided by increasing the birth rate b to very high values ($b>100$ for $p<1$), which produces strong fluctuations in the population size, making it very difficult to observe a plateau. In fact, to observe a plateau in such conditions it was necessary to decrease the minimum reproduction age from $R=10$ to 8 and also to work with very large populations (about one million individuals) to avoid the fluctuations just mentioned and to have good statistics for the oldest old. We emphasize that in the original Penna model, considering only bad mutations, there is a minimum birth rate to avoid population meltdown, but no upper limit for it. However, a chaotic behavior as in the logistic map was found for high birth rates with a minimum reproduction age lower than the threshold T [12]. Nevertheless, the stronger selection is, the larger is the minimum birth rate. Another strategy to avoid population meltdown ($p<1$) is to set $R=1$, which was used in [9] to obtain the plateau.

In order to obtain the mortality plateau without restricting the minimum reproduction age R, we set all values of the death probability $f(n)$ to zero for $n<T$. In this way the birth rate $b=1$ does not need to be increased, and the mortality for different values of p is shown in Fig. 2, where the death probability is the one of Eq. (3). For young ages the mortality function follows the Gompertz law.

Now a nice plateau can be observed, similar to the results in [9]. Its length depends on the smoothness p. The different death probabilities of Eqs. (4) and (5), also setting to zero the genetic deaths for $n<T$, yield similar mortality functions, as shown in Fig. 3.

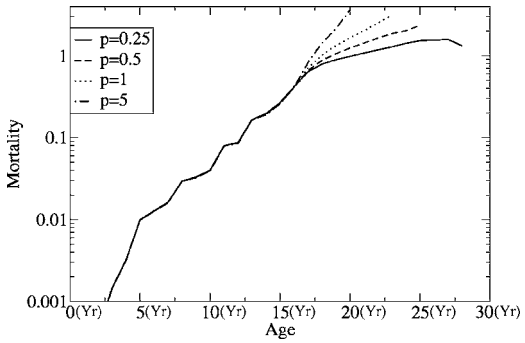

FIG. 2. Comparing the mortality functions for different values of p, using a Fermi-like death probability function. The results for small values of p are similar to those of the analytically solved asexual model.

III. MODEL WITH CONSTANT POPULATION

In order to study the population age structure using the death probabilities of Eqs. (3)–(5), but without neglecting deaths for $n<T$, we have implemented the sexual version of a model with constant population, introduced in [13]. This model has the advantages of avoiding the Verhulst factor already criticized by some biologists [14] and preventing chaotic fluctuations of the population size. The only difference between this model and the Penna one is that whenever an individual dies for genetic reasons, a male and a female are randomly chosen to mate and produce an offspring. So the population size does not fluctuate, since there is no Verhulst factor, and the measured data are much cleaner. Additionally, the birth rate is controlled automatically and population meltdown or unlimited growth is prevented. Nevertheless, the simulation can break down if there are no individuals older than the minimum reproduction age, which occurs for $p<1$ as well as for too small populations. The population size (200 000 individuals) and simulation time (1 000 000 time steps) have to be large, to produce a mortality function which ranges up to old ages. The genetic deaths and the age distribution are measured over the last 500 000 time steps.

Figure 4 shows that the mortality functions do not differ very much from the ones measured with the modified Penna model of Sec. II, Fig. 2, for old ages. But with decreasing values of p the mortality increases considerably at young ages. The exponential growth is replaced by an almost constant behavior until the minimum reproduction age. The mortality functions do not vary qualitatively for the different approximations of the step function (Fig. 5), as already observed in the simulations of the Penna model.

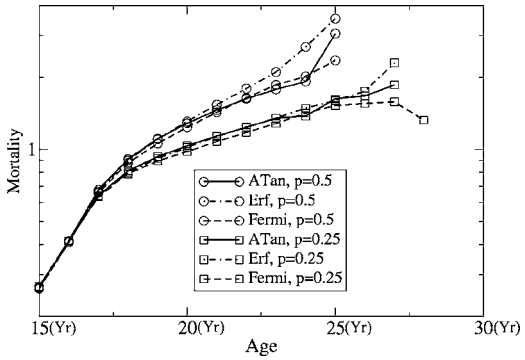

FIG. 3. Comparing the tails of the mortality for different death probability functions. They differ only slightly for different functions. Individuals with $n<T$ do not suffer genetic death.

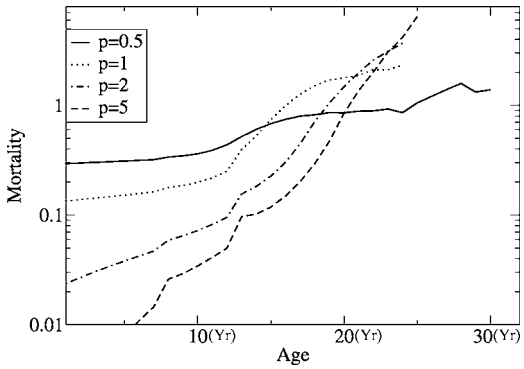

FIG. 4. Mortality functions using the constant population model with the Fermi-like death probability function, for different values of p. At young ages there is no Gompertz law for small p, due to the non-negligible genetic deaths for $n<T$.

Interestingly, we observe a change in the curvature of the population age distribution, depending on the value of p—Fig. 6. The smoother the death probability is, the smaller is the mean age of the population. Most of the individuals die at young ages before reaching the age of reproduction. The birth rate increases crucially in order to maintain the population constant. The very few individuals who reach advanced ages can live very long. The really small number of these individuals explains why the mortality plateau is not observed for small populations or short simulation times. Thus, the fluctuations of the values of the mortality function at very old ages, shown in Fig. 5, are due to poor statistics.

IV. CONCLUSION

With our sexual simulations we reproduce the asexual results of [9], by implementing a Fermi-like death probability

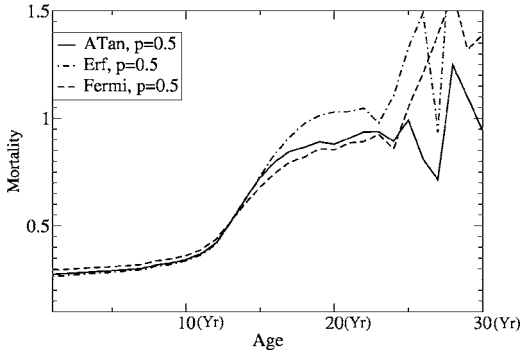

FIG. 5. Comparison between the mortality functions of different smooth death probabilities using the constant population model, in linear scale. The plateau appears for all of them. The fluctuations of the mortality functions for ages above 24 result from weak statistics.

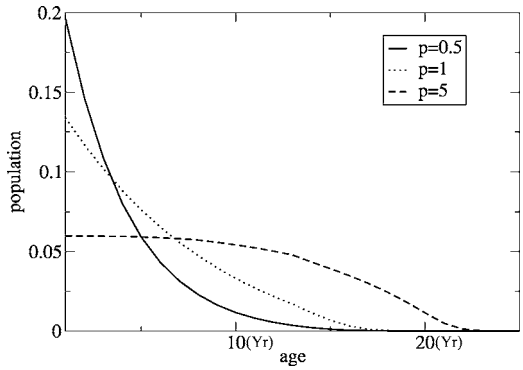

FIG. 6. The population density changes its curvature for small p. Only few individuals reach old ages.

function in the Penna model. The main differences between this model and the asexual model of [9] are that there, reproduction begins at birth, i.e., $R=1$, and its Fermi survival probability function depends on the age, while in our case $R=10$ and the death probability depends on the current number of deleterious mutations.

Our results reveal that the observation of a mortality plateau using the traditional Penna model with a Fermi-like or any other death probability function smoother than a step function is a rather complicated task. For a reproduction age $R>1$ most of the individuals die before reaching the minimum reproduction age R. The only way to avoid population meltdown is to increase the birth rate. Simulations with large population size and simulation time show a small plateau. Nevertheless, the high chaotic fluctuations of the population size due to the large birth rate make the simulations difficult. However, neglecting genetic deaths before the accumulation of T deleterious mutations, the model reproduces the Gompertz law up to old ages where the mortality function shows a plateau. Additionally, the birth rate does not need to be increased.

In order to avoid neglecting genetic deaths before the accumulation of T mutations, we have used a constant population model. Large populations and simulation times also lead to a clear plateau in the mortality function, which may not follow the Gompertz law, depending on the value of p. For small p, many individuals die before reaching the reproduction age, which may change completely the population age structure.

The different approximations of the step function that have been tested in both the modified Penna model and the constant population model have led to similar results for old ages. Thus, we conclude that the effect of the oldest old results from the smoothness of the genetic death probability at old ages, within the theory of mutation accumulation.

The existence of plateaus in the mortality curves of Drosophilae and other organisms is a matter of fact, as reported for instance in [1,15]. However, the number of Drosophilae surviving up to ages where the plateau appears is extremely small. This same effect has been observed with simulations using the constant population model, but not with the modified Penna model where a reasonable number of individuals survive until advanced ages. The reason is that to obtain the plateau with the Penna model, it is necessary to neglect deaths before the accumulation of T mutations, which allows many individuals to survive up to the minimum reproduction age. The very small number of individuals reaching an age to observe a plateau explains the difficulty to measure the oldest old effect in Nature. Only experiments with more than a million of Drosophilae yield clear mortality plateaus, and even so, their statistics still remain quite poor.

Comparing the very small mortality plateau of humans with the large ones of Drosophilae, medflies, wasps, and nematodes [1] we propose that there is a relation between the presence of a large mortality plateau and high birth rates, smooth death probabilities, and the curvature of the population age distribution. Organisms with a high death probability at young ages need a high birth rate in order to have sufficient individuals reaching the reproductive age. This leads to a mortality plateau and a population distribution with a positive curvature. We suppose that this relation is valuable for simple organisms. A similar relation between the mortality plateau and the population age distribution has already been observed in [16] for butterflies, as well as in [17] for zebrafish. Unfortunately, more data concerning more highly developed animals are still missing.

ACKNOWLEDGMENTS

V.S. is funded by the DAAD (Deutscher Akademischer Austauschdienst); S.M. d.O. is partially supported by the Brazilian Agencies CNPq and FAPERJ. We thank D. Stauffer for a critical reading of the manuscript.

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