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Mutation load and the extinction of large populations

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Abstract

In the time evolution of finite populations, the accumulation of harmful mutations in further generations might lead to a temporal decay in the mean fitness of the whole population that, after sufficient time, would reduce population size and so lead to extinction. This joint action of mutation load and population reduction is called Mutational Meltdown and is usually considered only to occur in small asexual or very small sexual populations. However, the problem of extinction cannot be discussed in a proper way if one previously assumes the existence of an equilibrium state, as initially discussed in this paper. By performing simulations in a genetically inspired model for time-changing populations, we show that mutational meltdown also occurs in large asexual populations and that the mean time to extinction is a nonmonotonic function of the selection coefficient. The stochasticity of the extinction process is also discussed. The extinction of small sexual $N \sim 700$ populations is shown and our results confirm the assumption that the existence of recombination might be a powerful mechanism to avoid extinction.

1. Introduction

In the evolutionary process, deleterious mutations may arise when the genome of one individual is formed. In an asexual population, assuming that there is no reverse mutations, these deleterious mutations will be transmitted to the descendants. For a sexual population the recombination process either can remove harmful mutations from the offspring's genome or can accumulate them in a higher rate. Moreover, new deleterious mutations may occur (independent of the reproductive regime). One important question that arises in this context is: if we take into account the accumulation of

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deleterious mutations from one generation to the following, is it possible that the progressive reduction of the fitness over several generations will cause the extinction of the species?

The discussion of different evolutionary scenarios produced by mutation (beneficial or detrimental), started in the 30s and one can observe a common feature through these decades: the assumption of an equilibrium state reached by the populations and their genome; or in the Haldane's [1] words: "*abnormal genes are wiped out by natural selection at exactly the same rate as they are produced by mutation*". This equilibrium state is reached asymptotically, as cited by Wright [2] when discussing the variation of gene frequency due to different causes. Based on the equilibrium assumption, Crow [3] discussed the genetic load of a population. Some analytical results have been obtained assuming very large or infinite population, an assumption that works together with that of the equilibrium state. One important traditional result is that the fitness of an infinite population is reduced by e^{-U} , where U is the genome mutation rate. Discussing the mutation load in size varying (or small) populations, Kimura et al. [4] assumed Wright's distribution of gene frequency and observed that only for small populations $N_{eff} < 50$ and higher selection was the mutation load higher than 1% (mutation load is the reduction of the population mean fitness due to the accumulation of harmful mutations). Reverse mutations have been considered, with a rate one order of magnitude below the forward rate. Comparing the incorporation of beneficial mutations between sexual and asexual populations, Crow and Kimura [5] showed that for small populations there is no important difference in the reproductive regime. Moreover, the advantage of recombination may be lost when an equilibrium state is reached. It is interesting to cite here the comparison between natural selection and classical mechanics done by Crow and Kimura [6]: natural selection has both the static and dynamical aspects. However, these dynamical aspects refer basically to the times before equilibration. Our question now is: what could be done if the attractor of a specific dynamics were the extinction of the population?

Obviously, if the equilibrium state is assumed, there is no way to answer properly the question of the extinction of a species addressed in the first paragraph. However, discussing the relation between recombination and mutation load, Muller [7] stated that for an asexual population a progressive genetic deterioration should be observed, with a progressive random loss of better fitted individuals, a process called by Felsenstein [8] "Muller's ratchet". Felsenstein noticed the discrepancy between results about the role of recombination, when infinite or finite population sizes had been assumed. The "Muller's ratchet" in selfing populations has been studied by Heller and Maynard Smith [9], who observed that for a large class of mildly deleterious mutations the ratchet mechanism is likely to be important.

In spite of the ubiquity of the equilibrium state assumption (i.e. the use of a fixed population size and a time-independent distribution of mutations), signs denoting that this may not be a generally correct assumption can be observed in earlier works. Kondrashov [10] compared the evolution of the fitness under different reproductive regimes and observed that for different sets of the selection parameters, fitness always decreases.

Discrepancies between analytical and computer-simulated results can be observed in the work of Pamilo et al. [11], who pointed out that “*discrepancy arises because the computer simulation allows a continuous accumulation of harmful mutations, whereas the approximation used to derive Eq. (8) lead to a prediction of a steady state*”. Lynch and Gabriel [12] pointed out that the accumulation of deleterious mutations is expected to cause a gradual reduction in the population size down to zero, calling the synergistic interaction between fixation of harmful mutations and population reduction by “Mutational melt-down”. The problems of Muller’s ratchet operation and mutational meltdown are object of an increasing interest in the recent years [13–20]. One of the usual conclusions, confirming earlier assumptions, is that the extinction due to the fixation of detrimental mutations or loss of the better fitted individuals might be observed in “*small asexual populations or very small sexual populations with highly restricted recombination or outcrossing*” [15].

One important aspect of this mutational process is the evolution of senescence: natural selection will favour those genomes which accumulate mutations leading to detrimental effects at old ages [21]. In contrast with the results obtained with the steady-state assumption, Monte Carlo simulations on age-structured populations showed that mutational meltdown occurs even in large populations [22] (for a review of Monte Carlo simulations on biological ageing see [23]).

The aim of this paper is to study the time evolution of the populations away from equilibrium. In order to study this problem, we worked with computer simulation on a model introduced by Charlesworth [14]. Firstly, we are going to show that this model presents a scaling behaviour and that the basic assumption of fixed population cannot be considered as a general assumption. After that, as in previous work, we introduce a fixed population birth rate parameter allowing the time-changing of the population. Now we extend this previous study to a large range of selection values, discussing the role of slightly deleterious mutations. Environmental effects are also discussed. Moreover, we show that sexual reproduction can avoid the accumulation of harmful mutations.

2. Model

In this genetically inspired model a population of N hermaphrodite individuals is represented by two sets of computer words (meaning the two homologous chromosomes in a diploid organism) and each bit represents a locus (typically we used chromosomes with 1024 loci, i.e., 2×32 words of 32 bits). Thus, each gene may be expressed in two allelic forms (having two possible states, a bit=0 represents a normal allele whereas the bit=1 represents a harmful mutation). The type of reproduction in this model is defined by *Self*, a self-reproduction parameter in the interval 0–1. The *Self*=1 value means entirely self-reproduction, while for *Self*=0 one has only outcrossing (or sexual reproduction).

The evolutionary process is as follows: first we define an initial population and then mutation events take place. Thereafter one has the mating process and selection. After generating a population of N descendents the mutation process is resumed. In this part the population size is fixed and it will be changed below. Each combination of mutation, reproduction and selection represents one time step or one generation t . The mutations occur in loci selected at random in the entire genome and one assumes a Poisson distribution of mutation events with average rate $mutr$ (typically we have used $mutr = 0.1$, that means a mutation rate per locus $\sim 10^{-4}$). Back mutations are not accepted and if a selected locus has already a harmful mutation (bit=1), another one is chosen (this means that one has always $0 \rightarrow 1$ mutations).

In order to generate a zygote (an offspring), first one of the two chromosomes is drawn at random from a randomly selected individual and the number of crossovers N_r is calculated, assuming a binomial distribution of recombination events with recombination rate per locus $rechr$ (typically $rechr = 0.0$ – meaning no recombination; or $rechr = 0.001$ – on average $N_r = 1$). By choosing at random these N_r crossovers locations, we recombine the two individual chromosomes (taking and linking parts of each one) and one has the first gamete (for more details see Ref. [24]). After that, the second gamete is generated: if $Self = 1$ this gamete will be drawn from the same parent and in the other extreme, for $Self = 0$, the second gamete is drawn from another parent chosen at random. For $0 < Self < 1$ a random number between 0 and 1 is chosen and if this random number is larger than $Self$ an outcrossing reproduction is assumed; otherwise, a selfing reproduction occurs. The second gamete is obtained by using the same recombination procedure described above. The “fusion” of these two gametes results in a zygote; in our picture two new sets of computer words.

The fitness of this new zygote is computed as follows. When one gene occurs in dissimilar allelic forms at a specific locus it is called heterozygous; otherwise it is called homozygous. One assumes that the fitness f of the unmutated genotype is $f = 1$ and, by introducing one harmful mutation in the genotype, its fitness will decrease by a factor of $(1 - s)$ in the case of homozygous mutations or $(1 - hs)$ for heterozygous, s being the *coefficient of selection* and h the *dominance coefficient*. In the example shown below, an individual has 2 heterozygous alleles (loci 2 and 8) and 2 homozygous harmful alleles (loci 5 and 12) in the first 16 loci of its genome:

bit (locus)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
chrom. 1		0	1	0	0	1	0	0	0	0	0	1	0	0	0	0
chrom. 1'		0	0	0	0	1	0	0	1	0	0	0	1	0	0	0

In this paper we will take into account only positive values of s , though negatives values might be considered [11, 25]. In the results shown here we have assumed that the effect of these mutations are multiplicative (other definitions may be assumed [24, 26]). Thus, the fitness of a new zygote with μ homozygous and θ heterozygous mutations is

given by

$$f = (1 - s)^{\mu}(1 - hs)^{\theta}. \quad (1)$$

If the fitness is less than a random number (0,1), the zygote is rejected; otherwise it is accepted and the entire process is resumed until one has a number of surviving zygotes equal to N . Thus, the total population remains constant during the simulation. After reproduction-selection is finished, the zygote population substitutes the old individuals and therefore there is no overlap between the populations. New mutations occur and this process continues through the generations.

As one can see below, for several sets of parameters the mean fitness of the N individuals decays so that in later generation one needs to produce more zygotes than in the earlier. Since one needs to create more and more descendants generation after generation, this model has an increasing time-dependent birth rate. In later papers, Charlesworth et al. [15,16] observed that the fitness depends on the initial size of the population: the larger N is the slower the fitness decreases. Thus, they state that the problem of extinction arises only in small asexual population (or in very small outcrossing populations), when the fitness decreases fast. Similar statements can be observed in other papers.

3. Results and discussions for fixed populations

In an earlier paper [24] we have observed that this model shows an exponential scaling. Thus, one can assume that increasing the population, the time to observe a relevant decay on the fitness would be too long to be biologically relevant. However, those results have been obtained for a high value of the selection coefficient s . This means that the fixation of harmful mutations (the permanence of a given harmful allele in the population through the generations) is very unlikely (roughly speaking, when a new mutation appears, this new zygote is removed from the population, because this new mutation produces a strong decay in its fitness). A qualitatively similar result has been discussed by Gabriel et al. [27]. Now, we have performed simulations for a large range of the selection coefficient, in order to understand better the behaviour of this model. Fig. 1 shows our results for fitness versus generation t in asexual ($Self = 1$) populations without recombination with different sizes. We have assumed here the selection coefficient $s = 0.001$, dominance coefficient $h = 0.2$ and mutation rate $mutr = 0.1$. These results have been averaged over 20 samples and we have started the simulations with no mutations (all the loci have been set to zero). For small populations the fitness decays faster than for large populations but now, even for the largest population, the fitness shows clearly a permanent decay, instead of what we have observed for higher s . A different scaling behaviour was obtained in this case, shown in Fig. 2. There, a power-law scaling to $N_0 = 50$ has been computed: for a given population size N_i we divided the time t_i by the factor $(N_i/N_0)^\alpha$ and used $t'_i = t_i/(N_i/N_0)^\alpha$ as a new time variable. For the set of parameters cited above, $\alpha \simeq 0.12$ has been obtained. By changing s , keeping the other parameters as the same values as described above, we have obtained different values

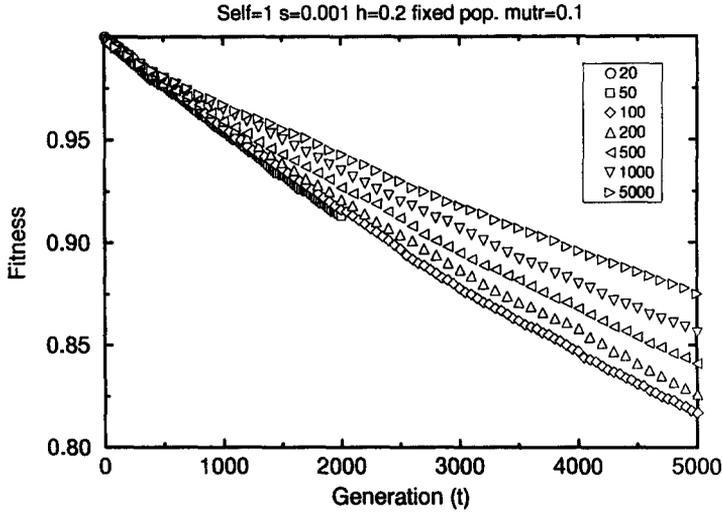


Fig. 1. Population mean fitness versus generation in selfing populations $Self=1$ obtained for different population sizes (provided in the figure legend) under multiplicative selection. The results were averaged over 20 samples. The simulations started with mutation-free genome. The selection coefficient is $s = 0.001$, dominance coefficient $h = 0.2$, recombination rate $regr = 0.0$ and mutation rate $mutr = 0.1$.

of α :

s	α
0.001	0.12
0.005	0.23
0.01	0.38
0.02	0.72

It means that for some value of the selection coefficient the scaling will be linear, before changing to an exponential scaling. Hence, we observe that the behaviour of the fitness as a function of the selection coefficient can be defined in two different regions.

In order to understand these different behaviours, we have performed simulations for a fixed population of $N = 50$ individuals varying the selection coefficient s and the results are shown in Fig. 3. For the lowest value $s = 0.001$, we observe a slow constant decay in the fitness (open circles). The fitness decays faster for increasing s , but, for $s = 0.05$, the decay of the fitness is similar to that observed for $s = 0.02$. Now, if we increase the s value the fitness decays slower. This nonmonotonic behaviour can be better observed in Fig. 4, which shows two sections for different times ($t = 1000$ and $t = 2000$) made in Fig. 3. For very low values of s , as well for high values, the fitness decays slower, showing a dip in the region $s \sim 0.03$. In this region we expect to observe the change in the scaling behaviour, from power law (low s) to exponential (high s). This nonmonotonic behaviour can be observed also in the results shown in Charlesworth et al. [16] (see, for example, their Table 2, p. 45). Thus, these results

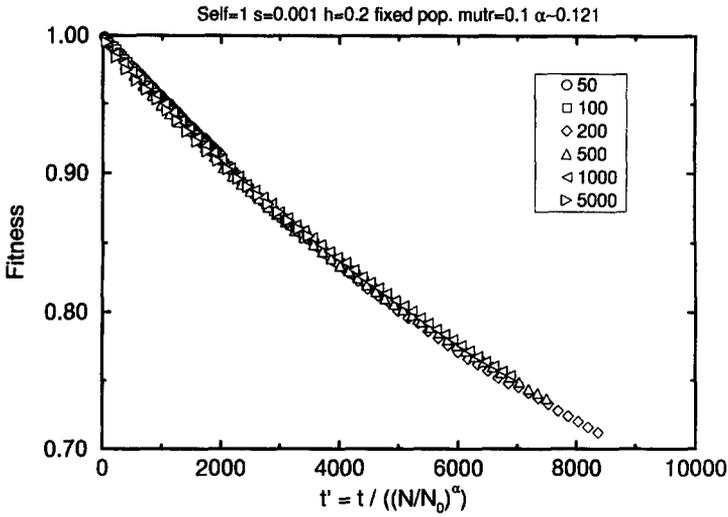


Fig. 2. Time scaling of the population mean fitness presented in Fig. 1. Here the time for each generation was divided by the factor $(N_i/N_0)^\alpha$ where $N_0 = 50$, with the values of N_i being shown in the legend. Note that all the curves overlap with that for $N_0 = 50$.

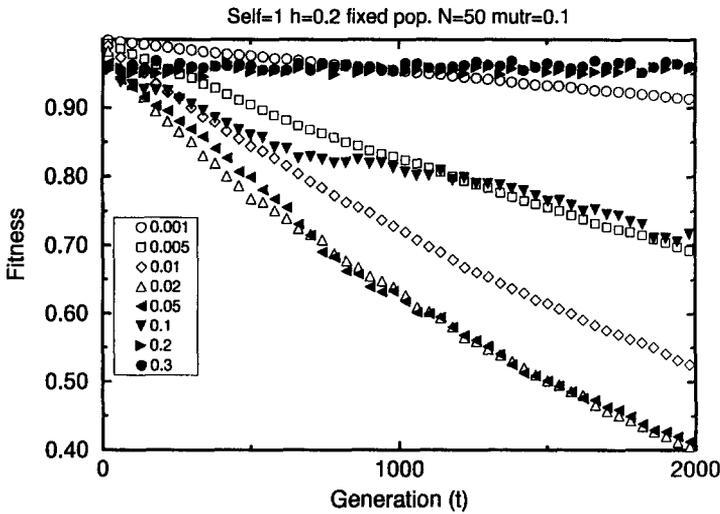


Fig. 3. Population mean fitness versus generation in selfing populations $Self=1$ obtained for different selection coefficient s (shown in the figure legend). Multiplicative selection has been assumed and the simulations have been performed for a fixed population of $N = 50$ individuals. The results were averaged over 20 samples ($s \leq 0.02$) and 30 samples ($s \geq 0.05$). The other parameters are the same as described in Fig. 1.

confirm our earlier statement that for any value of the selection coefficient s the fitness is a constantly decaying function of time and if the population increases the fitness decays slower, but it always decreases, and therefore this system will never reach an equilibrium state. Thus, even presuming that there exist one range of s where the decay of the fitness could be biologically irrelevant (though the equilibrium is never

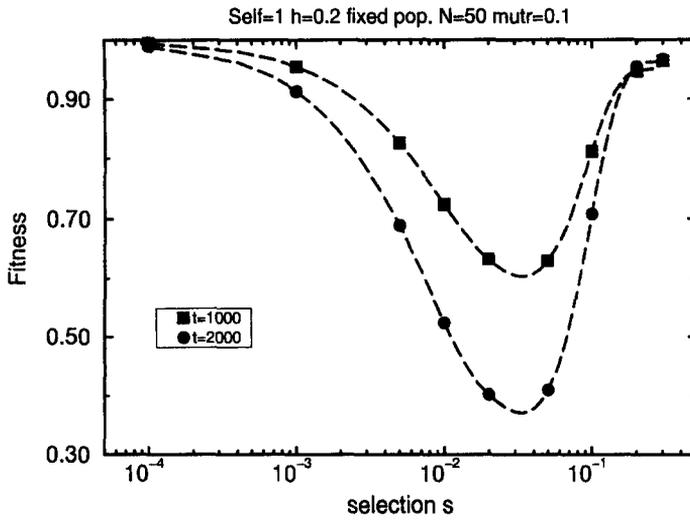


Fig. 4. Fitness values at different times: $t = 1000$ and 2000 (provided in the legend) obtained from the curves shown in Fig. 3. Here the nonmonotonic dependence of the fitness on the selection coefficient is clearly observed: for higher or lower values of s the fitness increases. The dashed curves are provided as a guide.

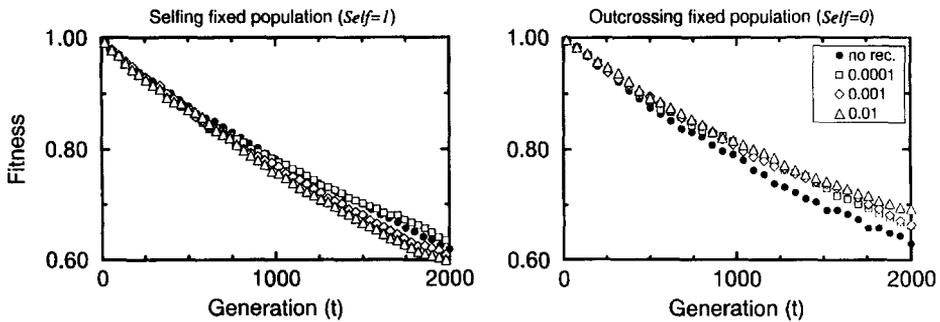


Fig. 5. Population mean fitness versus generation in asexual (left) and sexual (right) populations obtained for different recombinations (provided in the legend). A fixed population of $N = 100$ individuals has been used. All the simulations started with no mutation. The selection coefficient is $s = 0.01$, dominance coefficient $h = 0.2$ and mutation rate $mutr = 0.1$. The results were averaged over 10 samples.

reached), the equilibrium assumption cannot be assumed a priori, due to the fact that, by changing some parameters, the behaviour of the system might be unknown.

Another important question is the role of recombination. Under stronger s it has been shown that introducing recombination the fitness increases [15]. However, it was shown [24] that this improvement was more pronounced for selfing populations. In Fig. 5 we compare the behaviour of the fitness in selfing (plot at left) and outcrossing (at right) populations, now adopting a lower value for the selection coefficient: $s = 0.01$ (in the left region of Fig. 4, where a power-law scaling was observed). The

cases without recombination are shown with filled circles whilst the open symbols are related with different recombination rates (provided in the legend). Here we have used a fixed population of $N = 100$ individuals and the other parameters are the same as cited above. For outcrossing populations it is clearly seen that the introduction of the recombination compared to the case without recombination increases the population mean fitness. Moreover, the higher $rechr$ is, the slower the fitness decays. Once again, fitness always shows a constant decay with time, even for the highest value of the recombination rate ($rechr = 0.01$). For selfing populations, a slight increase in the fitness is observed when a low recombination rate is assumed ($rechr = 0.0001$). However, the fitness decreases for higher values of $rechr$. Our suspicion is that in this case the recombination process might be increasing the accumulation of deleterious mutations. If one compares the fitness for selfing and outcrossing populations, in contrast with the results obtained for higher s , now the better fitness has been obtained for outcrossing populations, though they are not too different.

At this point, we summarize the results obtained taking into account the fixed population assumption. This model shows two different scaling behaviours: a power-law scaling for weak selection and an exponential scaling for strong selection. It means that this system never reaches the equilibrium state and the equilibrium assumption cannot be assumed a priori. Under strong selection it has been shown that the recombination produces better results for selfing populations and now we showed that for weak selection the contrary occurs, though the increase for outcrossing populations does not allow one to assume that it might avoid a constant deterioration of the species. Moreover, for selfing populations under weak selection it is not clear the role of the recombination process. In the next section we shall describe the results obtained using a time-changing population.

4. Time-changing populations: evolution out of the equilibrium

To simulate a changing population, two new parameters have been introduced in the model. The first parameter represents the reproductive rate *Birth*, i.e., the total population can grow by the expression: $N(t + 1) = Birth \times N(t)$. To prevent the population $N(t)$ from growing to infinity, we introduced an environmental constraint factor which represents food and space restrictions. This Verhulst factor gives to each individual a probability $P_l(t) = 1 - N(t)/N_{max}$ of staying alive, N_{max} being the environmental carrying capacity. More terms can be introduced in P_l , simulating the presence of predators or catastrophic events [28]. Starting with a population of $N(0)$ free-mutation individuals, firstly the mutational process takes place, in the same way as described above. The reproduction again is defined by the *Self* parameter and – for a given time t – we attempt to produce $Birth \times N(t)$ offspring. For each one of these offspring, we compare $P_l(t)$ with a random number in the interval (0,1) and it survives if $P_l(t)$ is greater than this random number. After that we compute its fitness. If the fitness of this new zygote is less than another random number (again between 0 and 1) it does

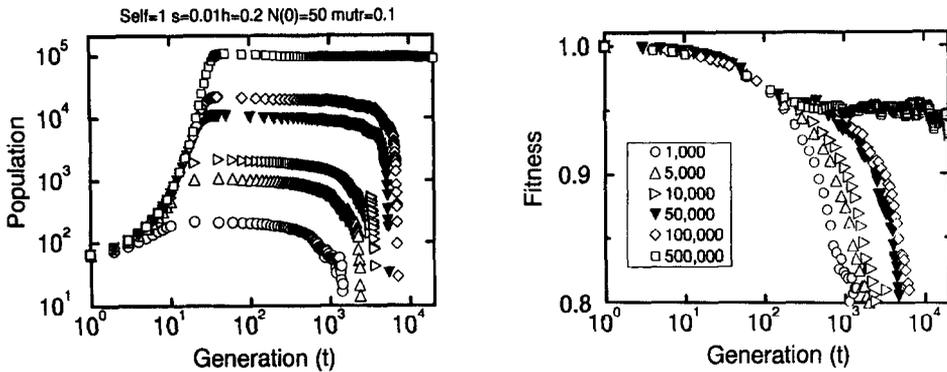


Fig. 6. Time evolution of the population (left) and population mean fitness (right) for selfing $Self=1$ populations under multiplicative selection obtained for initial population $N(0) = 50$ and different environmental carrying capacities N_{max} (provided in the figure). No recombination has been assumed. The general parameters are: $s = 0.01$, $h = 0.2$ and $mutr = 0.1$. For $N_{max} \leq 10\,000$ the results were averaged over 20 samples while for $N_{max} \geq 50\,000$ the result obtained for just one sample is shown.

not survive. However, it is not substituted by another trial (as one has been done to the fixed population case). The population at generation $(t + 1)$ is formed by those zygotes which survive at time t .

In the following, we are going to show the results obtained taking into account different situations. All the results were averaged over several samples, though very large simulations represent just one sample (cited in the figure captions). When an extinction was observed (in the case of parallel run), the quantities of interest were averaged only over the remaining samples.

4.1. The effect of environmental carrying capacity

In Fig. 6 we show the results obtained for a selfing population without recombination. The initial population is $N(0) = 50$ individuals, with $Birth = 1.3$ and different environmental carrying capacities N_{max} were used (the values are provided in the legend). In these results we have assumed: selection coefficient $s = 0.01$, dominance coefficient $h = 0.2$, mutation rate $mutr = 0.1$. The evolution of the total population (at left) and the population mean fitness (at right) are shown. Initially, the population grows, attaining a maximum value imposed by the environmental carrying capacity. A further slow decline in the population size can be observed, due to the fact that more and more zygotes do not survive. This corresponds to the decay in the population mean fitness, as one can observe in the right plot. Finally (except for the largest N_{max}), the population extincts. Thus, the reduction of the population mean fitness leads to a reduction in the population size. Even for $N_{max} = 500\,000$ a slight decline in the population mean fitness is observed in the last 10 000 generations.

It is interesting to observe the evolution of the population growth rate which is defined by the product of the population mean fitness by the reproductive rate. When

the population growth rate is greater than 1, the population tends to grow (here this growth is limited by the environmental carrying capacity). However, for a decaying fitness this growth rate sinks to 1 and when this growth rate is less than 1 ($fitness < Birth^{-1}$), the population shrinks fast. Increasing the environmental carrying capacity (for different simulations, since N_{max} is kept constant in each simulation), one observes that the time to extinction also increases. Here, larger populations lead to a slower decay in the population mean fitness. However, for $N_{max} = 100\,000$ this decay is observed in an effective population of about 19 000 individuals (which fluctuates around this value through almost 800 generations). It is important to compare this results with that expected to be obtained with the traditional formulations. If one computes the supposed fitness for a population of 19 000 individuals, taking into account the traditional analytical formulations and using the parameters here defined, it would not be possible to predict the extinction of this population, because that formulation leads to a higher value (~ 0.9) than this obtained here.

For selfing populations, the size of the initial population does not seem to change appreciably the extinction time, if one takes into account the same value for N_{max} . Fig. 7 shows the finite size effects observed for a selfing population without recombination (using the same values for s , h and $mutr$ as defined for Fig. 6). For $N(0) = 50$ and $N_{max} = 10\,000$ the curve is the same as that in Fig. 6 (open circles). Increasing both $N(0)$ and N_{max} by a factor of 10 ($N(0) = 500$ and $N_{max} = 100\,000$ (filled circles)), we observe that the curves are nearly parallel, leading to an increase in the extinction time (note that here the results for $N_{max} = 10\,000$ were averaged over 20 samples whilst that for $N_{max} = 100\,000$ represents just one sample). However, the maximum size attained by the populations for $N_{max} = 100\,000$ are about the same for the three different initial populations: 50, 500 and 5000. The extinction time is slightly enlarged for larger populations, due to the fact that the population attains the maximum size faster. Thus, the maximum population size (defined by the environmental carrying capacity) will be the main determinant of the extinction time (if the other parameters are kept fixed). It is remarkable that in these results might change for higher mutation rate.

4.2. The effect of the selection pressure in selfing population

Our interest now is focused on the role of the selection coefficient. For a fixed population simulation, we have shown that the fitness has a nonmonotonic behaviour. Fig. 8 shows the evolution of the population (left) and the population mean fitness (right) for a selfing population without recombination for different selection coefficients. The dominance coefficient has been assumed as $h = 0.2$ and mutation rate $mutr = 0.1$. In order to save computer time, we have assumed in this set of simulations $N_{max} = 5000$. Initially, for all the different values of s , the population grows, attaining a maximum value imposed by the environmental carrying capacity. For $s = 0.0001$ the population fluctuates around 1100 individuals up to 2000 generations, but then a further decay is observed. This decay seems to stop around 24 000 generations (not shown in

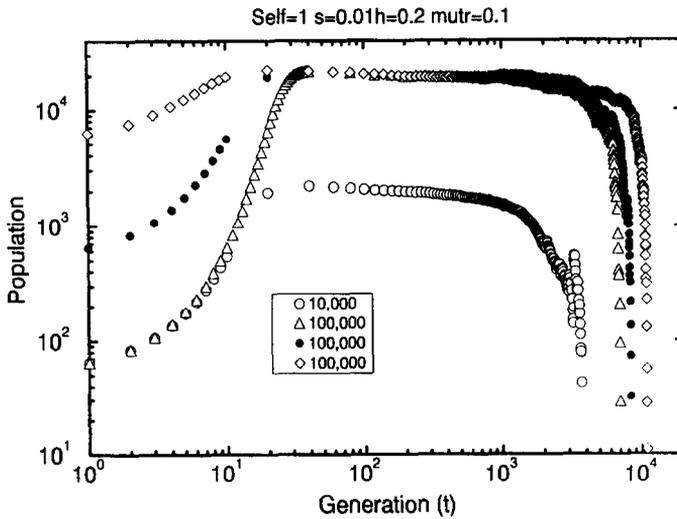


Fig. 7. Finite size effect. Evolution of the population for selfing $Self=1$ populations without recombination obtained for different initial populations and different environmental carrying capacities N_{max} (provided in the figure). The general parameters are the same as in Fig. 6. For $N_{max} = 10\,000$ the results were averaged over 20 samples while for $N_{max} = 100\,000$ the result obtained for just one sample is shown.

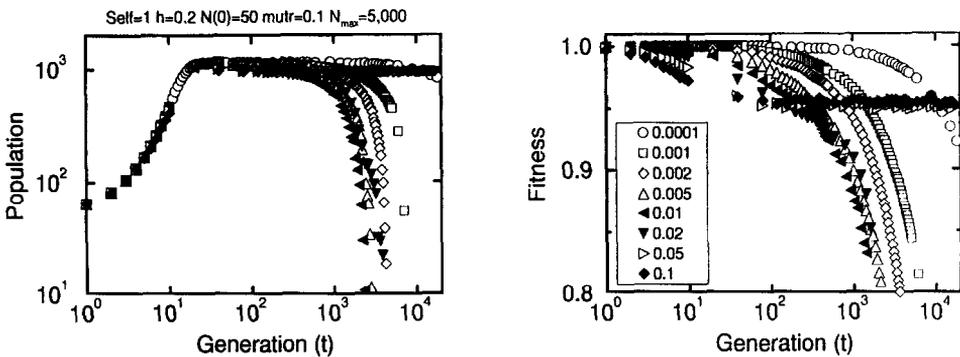


Fig. 8. Selection and extinction. Time evolution of the population (left) and population mean fitness (right) for asexual populations ($Self=1$ and $recr = 0.0$) obtained for initial population $N(0) = 50$ and different selection coefficients s (provided in the figure), assuming $N_{max} = 5000$. The general parameters are: $h = 0.2$ and $mutr = 0.1$. All the results were averaged over 10 samples.

the figure), keeping the fitness in the value of 0.903 up to 30 000 generations (when the simulations were interrupted). Increasing the selection coefficient to $s = 0.001$ the 10 different populations vanished within 7200 generations. As one can observe in the figure, the higher s is the faster is the extinction. However, this tendency is interrupted at $s \sim 0.02$, when the time for extinction becomes longer. Finally, for $s = 0.05$ as well for $s = 0.1$ the population seems to equilibrate, but one has to take this apparent equilibration with caution, because in this region the probability for fixation of a mutant allele is very low (in this region the model showed a exponential scaling when a fixed

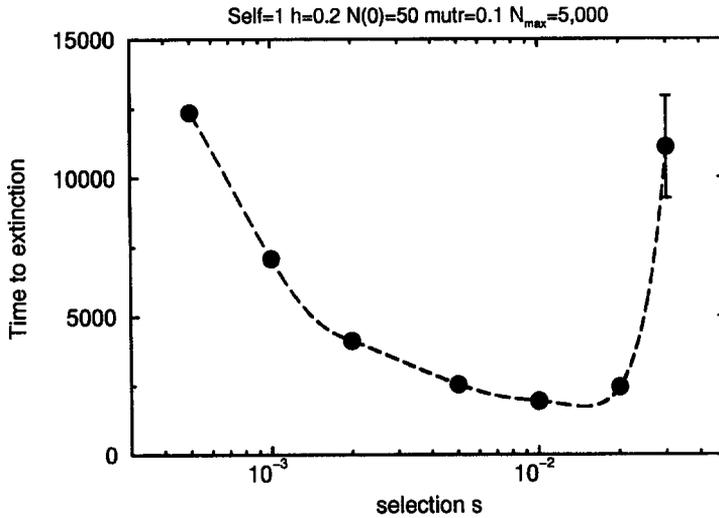


Fig. 9. Mean time to extinction as a function of the selection coefficient s for asexual populations. All the simulations started with an initial population of $N(0) = 50$ individuals and the environmental carrying capacity was assumed as $N_{max} = 5000$. Dominance coefficient and mutation rate are $h = 0.2$ and $mutr = 0.1$. These results were averaged over 10 samples and for most of the points the error bars are less than or equal to the size of the symbols used in this plot.

population has been simulated). Note that when the population seems to stabilize, the value of the fitness is near that predicted by the traditional theory.

We thus found a nonmonotonic curve for the mean time to extinction as a function of the selection coefficient, shown in Fig. 9. For strong and very weak selections s the time to extinction grows fast. However, the behaviour of the system is not the same at these extremes. This can be observed in the larger error bars obtained for $s = 0.03$ (for the other values of s the error bars are about the size of the symbol used in the plot). For lower s , the fixation of deleterious alleles seems to be a progressive process (a continuously accumulation of deleterious mutations) and all the statistically independent populations extinct at times not too different. However, for higher s this process might be understood as a step random process. After some mutations were fixed an individual is immediately removed of the population when a new harmful mutation arises. Note in Fig. 8 that the fitness for higher s initially decays faster, but also “stabilizes” faster). Due to the extreme randomness of this process, the accumulation of deleterious mutation occurs differently in the independent populations, which explains the strong fluctuations observed in the average time to extinction for high s . It is important to note that the same type of nonmonotonic behaviour has been obtained by Gabriel et al. [27] in a different model. Moreover, in their results, the value of s which produces maximum vulnerability (called by them as s^*), i.e., that causes the minimum time to extinction, progressively shifts to lower values as increasing the carrying capacity. Extrapolating their results, in order to compare with ours, the value of their s^* is about the same as we have obtained here: $s^* \sim 0.02$.

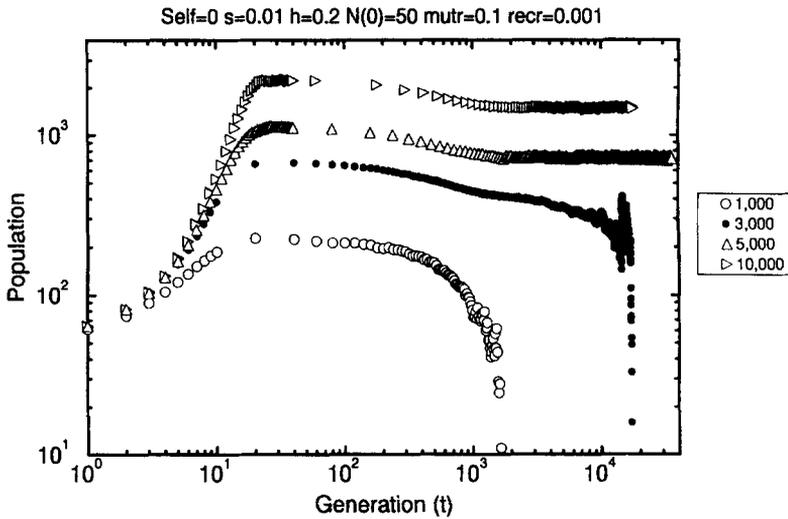


Fig. 10. Time evolution of the population for sexual ($Self=0$ and $recr = 0.001$) populations ($N(0) = 50$), obtained for different environmental carrying capacities N_{max} (provided in the legend). Selection coefficient is $s = 0.01$, dominance coefficient $h = 0.2$ and mutation rate $mutr = 0.1$. All the results were averaged over 20 samples, except that for $N_{max} = 3000$ which was averaged over 110 samples.

4.3. Sexual reproduction

Fig. 10 shows the results obtained for outcrossing populations $Self=0$ with recombination rate $recr = 0.001$ for a initial population of $N(0) = 50$ individuals and different environmental carrying capacities. In contrast with the results shown in Fig. 6, here the action of recombination represents a strong mechanism to avoid extinction. For $N_{max} = 1000$ and 3000 we observe the same path to extinction as described to the selfing population. For $N_{max} = 5000$ the population seems to stabilize around 700 individuals after 35 000 generations, though an extremely slow decay can be observed in the population mean fitness (discussed below). Finally, for $N_{max} = 10\,000$ the population seems to stabilize around 1500 individuals. In comparison with the results obtained for asexual populations, here the extinction was avoided for a much smaller population. For asexual populations the stabilization was observed only for a population of about 100 000 individuals (Fig. 6) whilst here this is observed for 700 individuals. However, even this small sexual population which survived is an order of magnitude greater than that supposed, for instance, by Charlesworth et al. [16].

Fig. 11 shows the evolution of the population mean fitness for the cases described above. For $N_{max} = 1000$ and 3000 the fitness remains constant while the population grows, decaying after the population has reached the maximum value. The strong fluctuations observed for $N_{max} = 3000$ are caused by the different moments of extinction observed in the simulations. The cases $N_{max} = 5000$ and $10\,000$ are shown in detail in the small upper right plot (5000) and in the small lower right plot (10 000) of the figure. For $N_{max} = 5000$ it is possible to note an extremely slow decaying trajectory

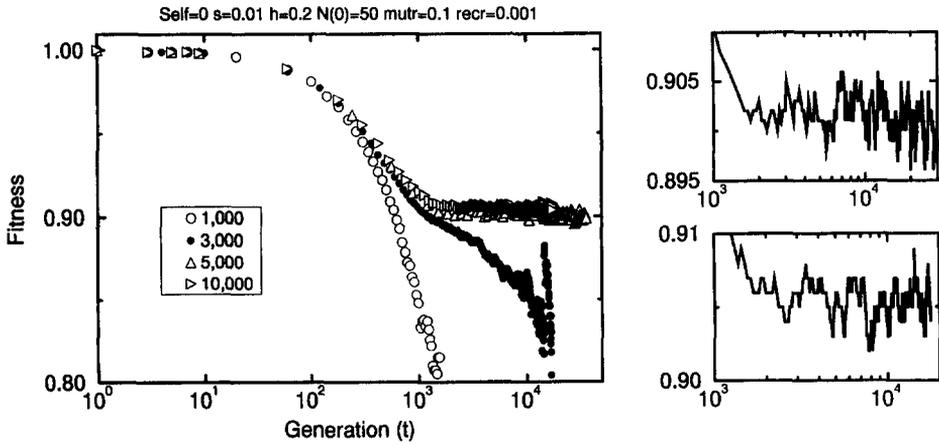


Fig. 11. Time evolution of the population mean fitness for the simulations shown in Fig. 10. The upper right plot shows a detail of the fitness obtained for $N_{max} = 5000$, where a slow decreasing trend seems to appear in the last 20 000 generations. The lower right plot shows a detail for $N_{max} = 10000$, where an opposite trend seems to appear in the last 10 000 generations.

in the fitness, though there are fluctuations which do not allow a conclusive statement. However, for $N_{max} = 10000$ an opposite trend might be assumed. There, a very slight increase in the fitness seems to appear after 10 000 generations, though a simulation for just one sample for longer periods (40 000 generations) does not show a conclusive result. It is important to emphasize that in this model only forward mutations are accepted and the recombination process seems to produce better genotypes. This fact might confirm that traditional Muller's picture (cited in Ref. [5]) on the higher probability of getting better genomes in sexually reproductive populations than in asexually ones.

Recently, Bürger and Lynch [19] have observed that, even with the knowledge of the mean time to extinction for a given set of parameters describing the evolution of a species (or a population), it is not possible to draw conclusions about the evolution of a single population. The stochasticity of the extinction process can be observed in Fig. 12. There, a histogram of frequency of extinctions versus time to extinction is shown. It represents the results obtained for the case $N_{max} = 3000$ discussed in Fig. 10. The mean time to extinction is $\bar{t}_e = 8185$ generations (averaged over 110 samples), whereas the maximum and minimum observed times are $t_e^{max} = 17120$ and $t_e^{min} = 2500$ generations. It is remarkable that the same kind of stochastic process can be observed also in the Penna model for biological ageing, when the mutations events are Poisson distributed [23].

5. Conclusions

Many works have been developed in the past in order to understand the impact of different factors (mutation, segregation, migrations, etc.) in the gene distribution or

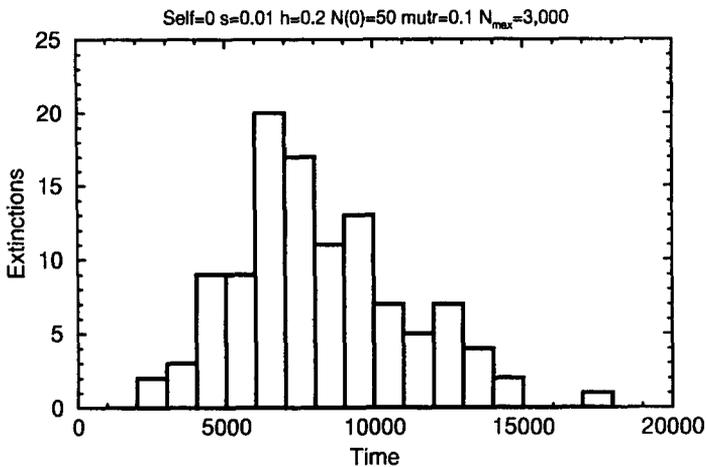


Fig. 12. Frequency of extinctions versus time to extinction obtained for the simulations showed in Fig. 10 for $N_{max} = 3000$. This result was obtained for 110 statistically independent runs.

in the population mean fitness in evolutionary populations. Traditionally, the dynamical aspect of evolution was ignored by assuming that the population should attain an equilibrium state. However, it seems that nature prefers to work out of equilibrium in several contexts and it might be assumed the same for the evolution of the populations, since life is clearly a nonequilibrium phenomenon. Different types of attractors can be found when modeling evolutionary systems: oscillatory patterns (like in the Lotka–Volterra equations), self-organized criticality in extinction events, a fixed point (extinctions being the example we have discussed here), etc. [29]. Hence, the fixed population equilibrium must be understood as a very artificial state or a metastable state where a population stays for a given period (how long it is not possible to state in advance) [12, 19].

Firstly, we have discussed the equilibrium assumption and showed that signs of a nonequilibrium dynamics can be observed in earlier computer simulations. The problems in nonequilibrium dynamics are very hard to treat analytically and there has been an increased use of computer simulations. Working in a model introduced by Charlesworth et al. we observed three different aspects when performing the simulations by using the fixed population prescription:

- the population mean fitness shows a scaling behaviour which is different under weak or strong selection, but for a fixed population the fitness always decays with time;
- under strong selection, the existence of recombination produces a higher fitness, but better results appeared for selfing populations. Under weak selection, the existence of recombination had little effect for selfing populations, though for outcrossing populations a slight increase in the fitness was obtained with recombination;
- a nonmonotonic behaviour is observed in the fitness by changing the selection coefficient. We have not tested what kind of behaviour could be obtained by changing the dominance coefficient.

These different aspects show how the use of the fixed population prescription obscures the evolution of the populations and we have adopted a time-changing population, by introducing a fixed reproductive rate and an environmental carrying capacity. In order to describe the path to extinction in this new scenario, we have just taken into account variations in the selection coefficient s and in the environmental carrying capacity N_{max} for different reproductive regimes: selfing populations without recombination (asexual) and outcrossing with recombinations (sexual).

Our results confirm the assumption that under strong selection harmful mutations are unlikely to be fixed in the population. However, as discussed by Kondrashov [20], the existence of very slightly deleterious mutation might lead to a high mutation load if a long period is taken into account. Thus, we focused our attention here in the region of weak selection.

For asexual population, we observed the extinction of populations which reached a maximum size of about 20 000 individuals. The value of the fitness in this case is very different from that which would be calculated by using the traditional expressions. The variation of the fitness with the selection coefficient is again nonmonotonic. It is important to say that our results are in good agreement with that obtained by Gabriel et al. [27] in a different model.

Moreover, the stochasticity of extinction events was observed. It shows that is very difficult to state in advance the temporal behaviour of a single population, as recently pointed out by Bürger and Lynch [19].

However, the most important aspect observed is the difference in the evolution when populations without and with recombination are compared (see Figs. 6 and 10). The powerful mechanism of recombination can be observed when simulating a sexual population. Populations of about 1000 individuals escaped from extinction and for larger populations, a slight trend to increase the mean fitness was noticed, though our results are not yet conclusive. Our results confirm the basic assumptions of the evolution of sex [30] and also confirm those obtained through Monte Carlo simulations in the Penna model [23]. They disagree with those obtained by Redfield [31], who obtained better results for asexual reproduction. Thus, our results might suggest an answer to the question addressed by Kondrashov [20]: *Why have we not died 100 times over?* Even considering the supposed costs of recombination [30] or still the assumption of a higher male mutation rate [32], it is well known that all the living beings either can produce genetically diverse offspring (by recombination) or, at least, are capable to mimic the recombination process. Our results showed that recombination strongly reduces the probability of extinction.

Several questions remain open and are object for further investigations. An important matter of attention are the mutation rates (forward and reverse). Even taking into account that most of the authors consider that the forward rate must be higher than the reverse rate, reverse mutations can be easily introduced in this model, providing a way to study several assumptions. Other question is the existence of interaction between different loci, that could be also introduced in the model. Finally, the complete Fortran code is available upon request.

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