Mutational Meltdown in Large Sexual Populations

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J. Phys. I France **5** (1995) 1501–1515 NOVEMBER **1995**, PAGE 1501

Classification
Physics Abstracts
05.40+j — 87.10+e

Mutational Meltdown in Large Sexual Populations

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(Received 12 July 1995, accepted 31 July 1995)

Abstract. — When a new individual is formed (independently of the reproduction process) it inherits harmful mutations. Moreover, new mutations are acquired even in the genetic code formation, most of them deleterious ones. This might lead to a time decay in the mean fitness of the whole population that, for long enough time, would produce the extinction of the species. This process is called Mutational Meltdown and such question used to be considered in the biological literature as a problem that only occurs in small populations. In contrast with earlier biological assumptions, here we present results obtained in different models showing that the mutational meltdown can occur in large populations, even in sexual reproductive ones. We used a bit-string model introduced to study the time evolution of age-structured populations and a genetically inspired model that allows to observe the time evolution of the population mean fitness.

1. Introduction

'Why people get old?' It is a question that we ask ourselves at least once a year. However, this question should be more properly formulated in the terms: 'Why do we become at each year weaker and slower? Why in the later years increases the probability to suffer new and worse disease?' One of the most important assumptions trying to answer these questions is that we inherit deleterious mutations from our parents. Moreover, when our genetic code is formed by the junction of our parent's gametes, new mutations can occur, most of them are deleterious mutations. If one of these deleterious mutations leads a serious disease that will be developed in childhood, before one attains the reproductive age, it has a low probability to spread in the whole population. A harmful mutation that attacks the individual before the breeding age will reduce the population growth, being therefore more dangerous for the whole species. Otherwise, if a mutation leads to diseases in adulthood or old age it will be given before to the offspring and therefore will spread in the population reducing the survival rate in further generations, i e., reducing the fitness of the next generation. The accumulation of deleterious mutations is the strongest theory trying to explain the ageing problem [1, 2]. One

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important question that arises in this context is: if we take into account the accumulation of deleterious mutations from one generation to the following, is it possible that the reduction of the fitness for several generations will cause the extinction of the species? This question was introduced some years ago and is known as Mutational Meltdown. In the past few years it has been an important theme for debate [3-9] although often ignored in the aging literature. In asexual populations this process was described as a progressive loss of the most genetic capable individual: first the extinction of individuals free of harmful mutations, afterwards of that of individuals carrying one harmful mutation in a progressive process of accumulation of deleterious mutations in the whole population (Muller's ratchet) [10], which leads to a decaying with time of the fitness of all individuals. It is important to note that the frequency of backward mutations (reverse mutation deleting harmful ones) is about 1/100 the frequency of forward mutations [6]. Diploid reproduction or sexual reproduction with recombination might be ways to avoid this transmission of deleterious mutations to further generation, by the creation of new gene combination [11, 12].

Charlesworth *et al.* suggested that the mutational meltdown only occurs among "small asexual populations or very small sexual populations with highly restricted recombination or outcrossing" [4], which agrees with results obtained by different authors [6-8]. In contrast with these results, Monte Carlo simulations on asexual age-structured populations showed that mutational meltdown occurs even in big populations, though is possible to avoid it by changing some parameters (mutation rate, birth rate etc) [13-16,19]. One important question that arises from reading these different papers is that some authors fixed the total of individuals during the simulation, calculating the important variables assuming that the population behaves in a quasi-stable equilibrium [4, 5, 7, 8]. Of course this kind of fixed population prescription should be applied only if one is sure that the system is in a stable configuration, otherwise it can obscure the results. Moreover, the theories of ageing working with constant population growth rate do not allow the study of mutational meltdown [1, 19].

In this spirit, we present here some results obtained by using two different models. The first model was introduced by Charlesworth *et al.* [5] to calculate the time evolution of the population mean fitness by changing several parameters: mutation rate, recombination rate, type of reproduction etc. The second model was introduced by Penna and Stauffer to describe the temporal behaviour of age-structured asexual populations. Extensions of this model showed its robustness [19]. Now we apply this model to sexual reproduction, introducing some simple aspects. It is important to note that we consider only inherited mutations or those occurring in reproduction process, that means, we do not consider somatic mutations, which could be acquired during life (skin cancer as a example) but are not transmitted to its offspring, though other simulations took into acount this feature [16].

2. The Charlesworth Model

First of all, some relevant concepts for people — like the editor — that never have listened about flowers and bees. Our genetic constitution — *genotype* — is coded within all our cell nuclei in strings called chromosomes, that carries some specific chemical compounds, which will define the entire inherited characteristics of the living being. These are the genes. The chromosomes occur in pairs (*homologous*) in the cell nucleus and each gene — occurring also twice — occupies a defined place, called *locus*. Each gene can occur in various form — *alleles* — (corresponding, for example, to blue, black, green or brown eyes etc). When one gene occurs in dissimilar allelic forms at a specific locus it is called *heterozygous*, and the phenotype (observed) characteristic will be given by the *dominant* form. The *recessive* allele determine the phenotype only when present in both alleles. When the same allele occurs at a specific

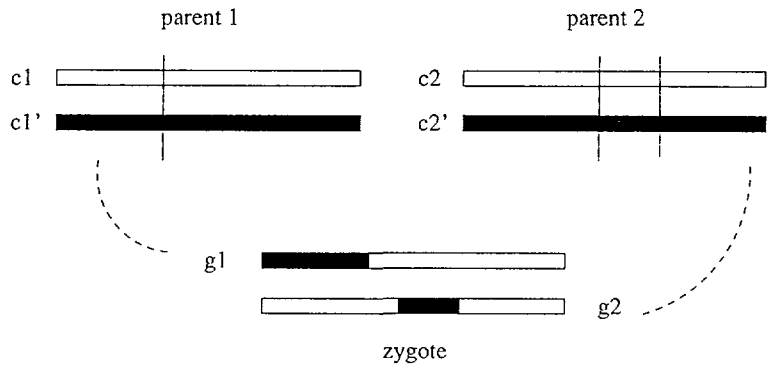

Fig. 1. — Schematic representation of the mating process. **Parent** is a diploid cell with two paired (homologous) chromosomes. A recombination event generates the gamete g1. Similarly, the gamete g2 is generated from the **parent 2**. The fusion of these two gametes results in the **zygote**. For details and description see text.

locus (dominant or recessive, does not matter) it is called *homozygous*. The usual cell division is known as *mitosis* and the resulting two daughter cells are copies of the mother cell (not considering eventual random mutations). If all nuclei divided by mitosis, a sex cell or *gamete* would contain the same number of chromosomes as every other cell of a multicellular organism, all of then derived from the same *zygote*. Consequently, the number of chromosomes per *zygote* would increase in successive generations, since the *zygote* is a combination of two *gametes*. The chromosome number does not increase from one generation to the next, however. This stability is possible because *gametes* contain only one member of each pair of chromosomes.

Most of the species (plants and animals) show a complex way for reproduction. Before sexual maturity, certain special cells in the sex glands divide by the same mitotic process. However, when the individual becomes sexually mature these cells will divide by a different process: *meiosis*. The two members of each pair of chromosomes present in the cell nucleus come together in close union and the strings duplicates, twist and cross over, breaking at identical positions. The broken ends exchange, *recombining* the genes. Now, each chromosome has a full set of genes, but not identical with which it started. The two doubled chromosomes then pull away from each other to the poles of cell *segregating* at random. The mother cell divides and divides again, resulting in four daughter cells — *gametes* — each with half of the number of chromosomes (one of each pair). When a male gamete unites with a female gamete a fertilized egg cell results: *zygote*. A gamete is a *haploid* germ cell having a single set of unpaired chromosomes and a zygote is a *diploid* cell having paired *homologous* chromosomes. Obviously it is a simplified description of the reproduction process, but we believe it clears the terms used below. Figure 1 shows a picture of the mating process: c and c' represent the homologous chromosomes in a diploid cell. In **parent 1** one has one crossover whereas in **parent 2** one has two crossovers (occurring at random). The first part of c1' recombine with the second part of c1 giving the gamete g1, a haploid cell. Similar process gives the second gamete g2. The fusion of these two gametes gives a zygote, restoring a diploid cell.

In this genetically inspired model a population of N hermaphrodite individuals is defined, each of them represented by its diploid, i.e., by two paired chromosomes, which are here defined as a sequence of computer words and each bit in this sequence represent a locus (typically we used chromosomes with 1024 loci) and therefore each gene might be expressed in two

allelic forms. The type of reproduction in this model is defined by S, a self reproduction parameter in the interval 0 up to 1. The $S = 1$ value means entirely self reproduction (the gametes that produce a descendent come from one parent), uniparental or diploid-asexual reproduction, while for $S = 0$ one has outcrossing reproduction, that one can consider as a sexual biparental 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. Each combination of mutation, reproduction and selection represents one time step or one generation. 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 $mutr = 0.1$ or 0.5). Nevertheless back mutations are not accepted.

After mutation have been performed in all diploids, the reproductive process takes place. In order to generate one zygote, first one chromosome is drawn at random from a individual and the number of crossovers N_r is calculated, assuming a binomial distribution of recombination events with recombination rate *recr* (typically $recr = 0.00001$ up to 0.001). By choosing at random these N_r crossovers locations we recombine the two individual chromosomes (taking and linking parts of each one, according the locations calculated before) and we have the first gamete. Now, the second gamete is made: if $S = 1$ the gamete comes from the same parent and in the other extreme, for $S = 0$, the second gamete is drawn from another parent chosen at random. The second gamete is obtained by using the same recombination procedure described above. The "fusion" of these two gametes results in the zygote, in our picture two new sets of computer words. The number of heterozygous and homozygous alleles are computed and the fitness is calculated (explained below). Following Charlesworth et al prescription, the fitness is compared with a random number between 0 up to 1. If the fitness is less than this random number, 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, i.e., the total population remains constant during the simulation. After reproduction-selection is finished new mutations occur in the population (described above) and this process continues through the generations.

For several sets of parameters the mean fitness of the N individuals decays with generation (how fast or slow will depend on these parameters), that means, in later generation one needs to produce more babies than in the earlier. Since one needs to create more and more descendents generation after generation, this models has an increasing time dependent birth rate. This procedure obscures the time evolution of the population, as one can see below. Moreover, in later papers Charlesworth et al observed that the fitness depends on the initial size of the population: for increasing N the fitness decreases slower. From this fact, Charlesworth et al state that the problem of mutational meltdown arises only in small population, when the fitness decreases fast.

As is well known the survival propabilities of individuals are not changed for some inherited characters (such as blood groups, for instance). However, as discussed above, it is clearly not true for many others characters, where changes can produce individuals better fitted to survive with better reproductive performance and hence contributing with more surviving offsprings to the next generation. Therefore any realistic model must make some allowance for *selection*. We assume that the fitness f of the favoured genotype in any selection is $f = 1$. 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, being s the *coefficient of selection* and h the *dominance coefficient*. In this paper we will take into account only positive values of s, though negatives values might be considered [6, 20]. When $h = 0$ the fitness of the new zygote is the same as that of the favoured genotype, i e., the initial allele is dominant, whereas for $h = 1$ the new fitness decreases by a factor of $(1 - s)$ and the harmful allele is dominant.

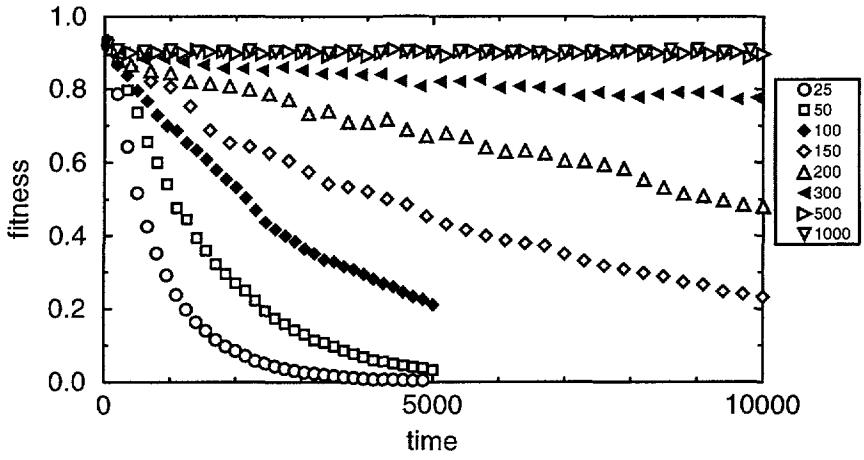

Fig. 2. — Population mean fitness versus generation in outcrossing populations $S = 0$ obtained for different population sizes: $N = 50$, 100, 200, 500, 1,000 and 10,000 using multiplicative selection. The meaning of the symbols are presented in the legend. For populations size 50 up to 1,000 the results were averaged over 20 samples while for $N = 10,000$ the result obtained for one sample is shown. In text are mentioned the value of distinct parameters.

We have found in literature controversial experimental values for the selection coeffient: from $s \sim 0.0025$ [21] up to $s \sim 0.2$ [17] . From this definition, the *multiplicative* [18] fitness of a new zygote with μ homozygous and θ heterozygous mutations is given by

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

Some authors compared results obtained using different selection regimes [5, 7], for example, to simulate the cases when two pairs of genes affecting the same trait interact phenotypically by superposition, antagonism or cooperation (*epistasis*). From this assumption of synergistic selection the fitness is calculated from the "effective number of mutations" [5] $n = h\theta + \mu$ by

$$f = \exp\left[-\alpha n - \frac{\beta n^2}{2}\right], \tag{2}$$

where α and β are defined coefficients.

Firstly we present our study in fitness behaviour. We show results for simulations on outcrossing populations ($S = 0$) using multiplicative fitness, although the behaviour we are going to describe is qualitatively the same for synergistic fitness. Since our interest is to study the behaviour of fitness with population size, we used a typical set of parameters used in Charlesworth et al paper, namely the selection coefficient against homozygotes for the mutant alleles $s = 0.1$, dominance coefficient of these alleles $h = 0.2$, recombination rate $recr = 0.00001$. Mutation rate was assumed as $mutr = 0.1$. We start the simulations clearing all the bits in the diploids of the whole population, i e., starting with a mutation-free genotype. Starting with a distribution of mutations as done by Charlesworth gave similar results. Figure 2 shows our results for fitness versus generation in outcrossing populations with different sizes, namely $N = 25$, 50, 100, 150, 200, 300, 500 and 1,000, which represent average over 20 samples. The behaviour of the fitness is about the same as observed by Charlesworth et al. For small populations the

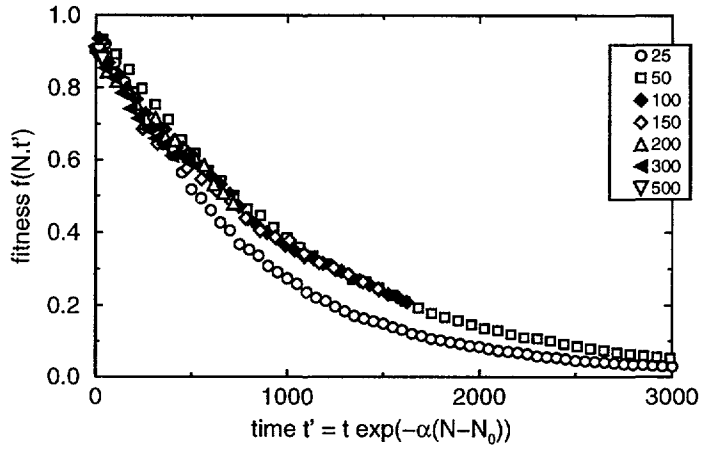

Fig. 3. — Time scaling of the population mean fitness presented in Figure 2. Here the time step for each generation was multiplied by the factor $\exp(-\alpha(N_i - N_0))$, where $N_0 = 25$ and N_i vary from 50 up to 1,000.

fitness decays faster than for large populations. In the case with population $N = 500$ and $N = 1,000$ the fitness seems to stabilize around 0.9.

To understand this behaviour we scaled all the fitness curves for a population size of $N_0 = 25$, finding a typical exponential scaling, that means, for a given population size N_i we multiplied the time t_i by the factor $\exp(-\alpha(N_i - N_0))$ and used $t'_i = t_i \exp(-\alpha(N_i - N_0))$ as a new time variable. We have obtained $\alpha \sim 0.015$. Figure 3 shows this scale applied to the results shown in Figure 2. For population size $N_0 = 25$ the curve is the same as in Figure 2. The fitness for $N = 50$ decays similar to the one for $N_0 = 25$ whereas the curves for the other populations overlap with that for $N = 50$ and therefore the fitness has a decreasing behaviour. Hence, if the population increases the fitness decays slower, but it always decreases, and therefore this system will never reach an equilibrium state. Due this exponential scaling, for large populations the decay of the fitness is extremely slow and, to study the time evolution of this model, we have to allow a free evolutionary population. For population size $N = 500$ we did simulations up to 50,000 generations (not shown in figure) confirming this trend. Thus, to test if the system can reach an equilibrium state, we have to allow a changing population, by fixing the birth rate and allowing the free evolution of the system, which is, from our guess, the correct procedure from the point of view of the time evolution of a complex system.

In the results we are going to show, we introduced two parameters: now we fixed the birth rate *Birth*, i.e., each individual produces *Birth* offsprings on average, or the total population can grow by the following expression: $N(t+1) = Birth \times N(t)$. To avoid the population growth to infinity we multiplied the birth rate by an environmental constraint factor, the Verhulst factor, given by $(1 - N(t)/N_{\max})$. For each generation the sequences are the same as that described above: mutation, reproduction, selection. However, in the reproduction part we fix the number of trials by the expression above and perform the reproduction constrained by the Verhulst factor. In selection we compare the fitness of a newborn with a random number. If the fitness is less than the random number the newborn baby does not survive, but now it is not substituted by another trial (as in the original fixed population version). Figure 4 show our results for selfing populations ($S = 1$) or uniparental reproduction. Here we used $mutr = 0.1$ and $recr = 0.00001$ for a initial population of $N(0) = 10,000$ individuals and Verhulst factor

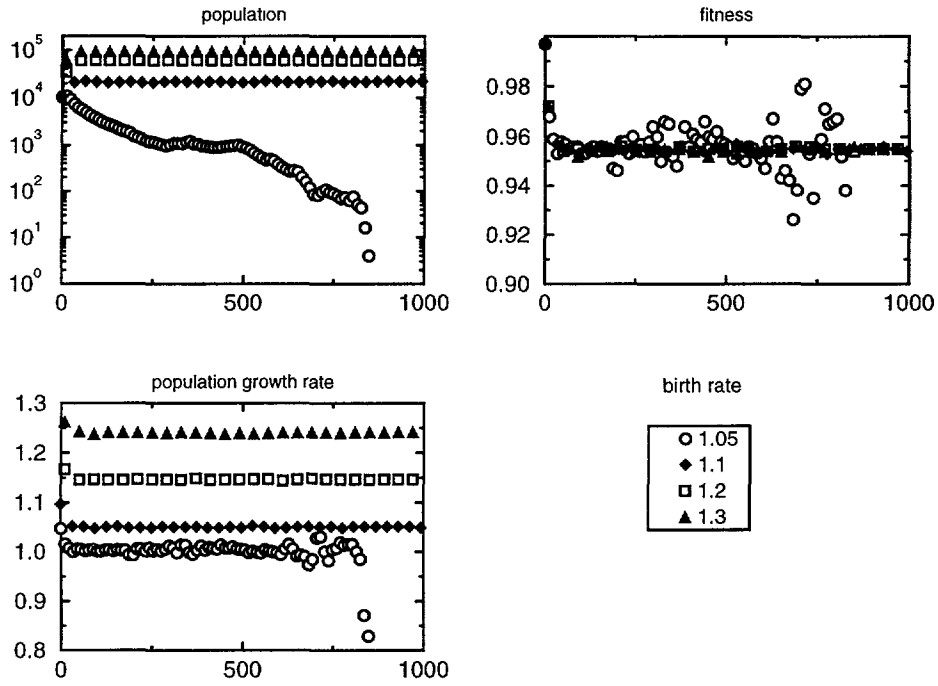

Fig. 4. — Time evolution of the population (on top-left), population mean fitness (on top-right) and fitness times birth rate (the population growth rate r) for selfing $S = 1$ populations under multiplicative selection obtained for different birth rates (presented in the legend). For birth rate $Birth = 1.1$, 1.2 and 1.3 the population stabilizes around different values, as well as the population growth rate and instead of it the fitness stabilizes around the same value. For $Birth = 1.05$ we observe the mutational meltdown of these species. For all simulation we start with $N(0) = 10,000$. In text are mentioned the value of the distinct parameters.

$N_{\max} = 500,000$. Different birth rates were tested. For $Birth = 1.05$ the population decreases exponentially and vanishes, in contrast to that observed in the other cases ($Birth = 1.1$, 1.2 and 1.3), when the population reaches equilibrium (just the results of 1,000 generations are shown, although we performed the calculations for 3,000 generations). It is interesting to note that the value of fitness is almost the same for the later three values of birth rate, independently of the size of the stable population, which is in agreement with that observed above: for large population the decay of the fitness is too slow. For $Birth = 1.1$ the population stabilizes around 22,000 individuals, while for $Birth = 1.2$ around 61,000 and for $Birth = 1.3$ around 95,000. For these stable values the fitness fluctuates around 0.95. One interesting feature to observe in this figure is the behaviour of the fitness times the birth rate. This product give us the population growth rate. When the population stabilizes one has this product greater than one. Note that the stabilization of the population size comes from the fact that we have introduced an environmental constraint factor. However, for $Birth = 1.05$ the population growth rate tends to 1 and fluctuates around this value, that means the population does not grow. In recent Monte Carlo simulations of temporal evolution of asexual populations we have shown that for the population growth rate tending to one we can observe the shrinking of the populations, leading to its extinction [19]. However, the species extinction here has been obtained basically due the small birth rate.

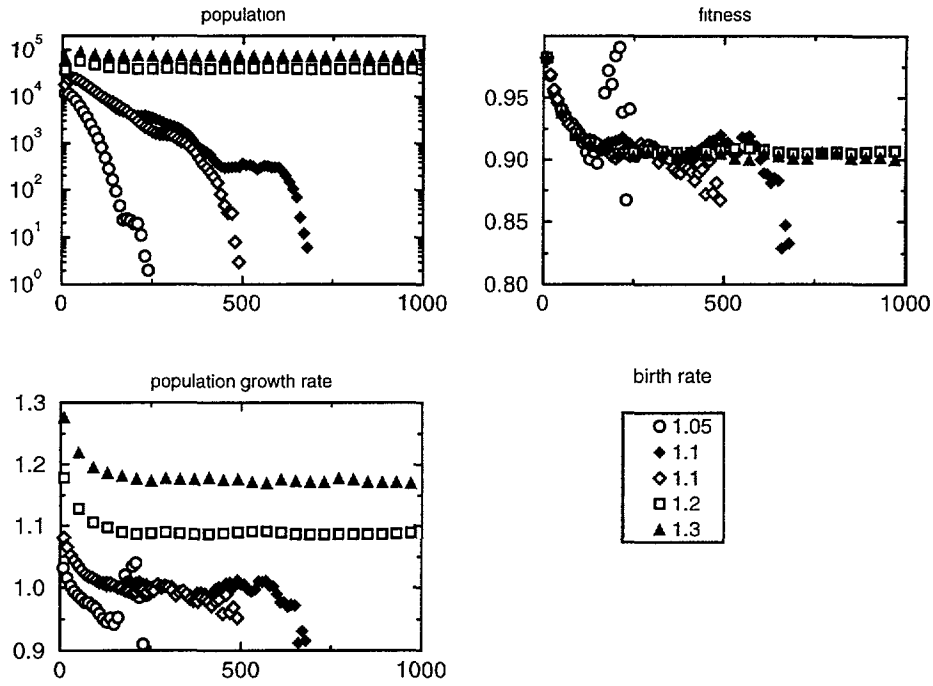

Fig. 5. — Time evolution of the population (on top-left), population mean fitness (on top-right) and population growth rate r for outcrossing $S = 0$ populations under multiplicative selection obtained for different birth rates (presented in the legend). For birth rate $Birth = 1.2$ and 1.3 the population stabilizes around different values, as well as the population growth rate and instead of it the fitness stabilizes around the same value. For $Birth = 1.05$ and 1.1 we observe the mutational meltdown of these species. For all simulation we start with $N(0) = 10,000$. For $Birth = 1.1$ we performed two different simulations using different seeds for the random number generator, in order to avoid mistakes due statistical fluctuations. One can observe the fluctuation of the fitness around the characteristic value of this set of parameters for $Birth = 1.1$ before extinction (black diamonds). In text are mentioned the value of the distinct parameters.

In order to compare results obtained with different mating types, we performed simulations using the same set of parameters as in the example described above, but now for outcrossing or biparental-reproductive populations ($S = 0$) and we show in Figure 5 these results. One important feature of this model appears when we compare the results shown in Figures 4 and 5: for a biparental species to survive it needs a birth rate somewhat greater than that in the uniparental ($S = 1$) reproduction. For $Birth = 1.05$ and $Birth = 1.1$ the population decrease which leads its extinction. In the case $Birth = 1.1$ we performed simulations with two different seeds of the random number generator and qualitatively observed the same behaviour: initial exponential decaying of the population, fluctuations and extinction. The case signalized with black diamonds shows the fluctuations around a fitness value of 0.9 (basically the same for all the different values of birth rate) while the product fitness times birth rate fluctuates around 1 for a long time before the extinction of the species. We mentioned above that in this model the biparental reproduction is worse than a uniparental reproduction, in the aim of surviving. The same feature could be observed in Charlesworth paper, although it is not pointed out. This fact has to be understood from the definition of the model. In fact, in the uniparental ($S = 1$)

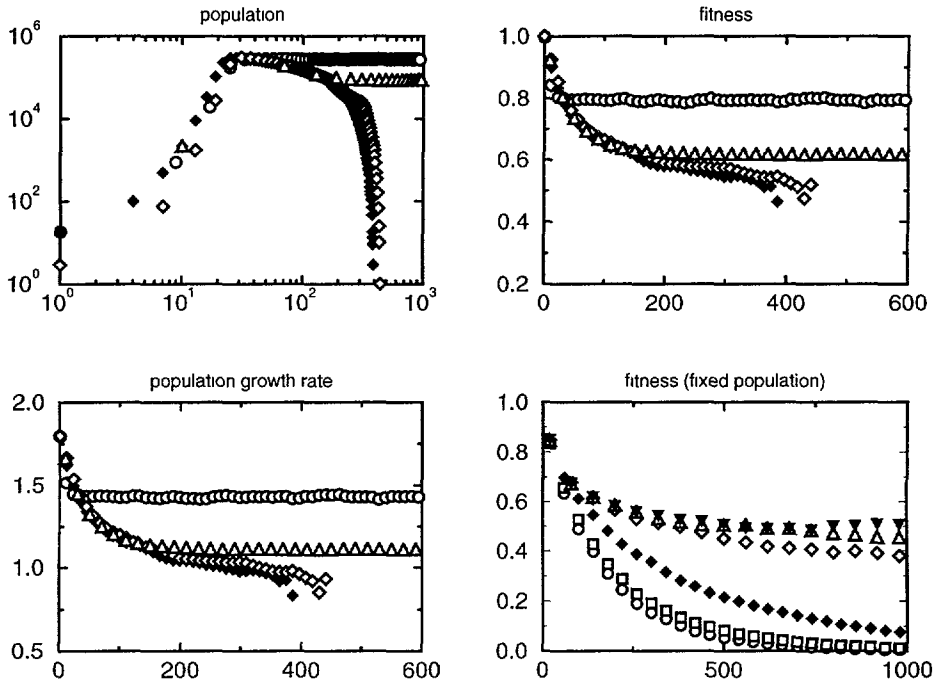

Fig. 6. — Time evolution of the population (on top-left), population mean fitness (on top-right) and the population growth rate (bottom/left) for selfing $S = 1$ or outcrossing $S = 0$ populations under multiplicative selection obtained for initial population $N(0) = 10$ and $N(0) = 2$ (white diamonds) and different recombination rate *recr* (described in text). We used here $mutr = 0.5$, $Birth = 1.8$ and the Verhulst parameter $N_{\max} = 1,000,000$, the selection coefficient and the dominance coefficient have the same value cited above. The bottom/right plot shows the time evolution of the fitness for fixed population (from bottom to top in the figure the symbols represent population sizes $N = 50$, 100, 500, 5,000, 10,000 and 20,000, averaged over 20 samples).

reproduction the two gametes come from the same diploid and for half of the choices on the reproduction events different gametes were chosen. Due the definition of mutation, it is very unlikely that two mutations were produced in the same locus in the different gametes (without recombination and considering each chromosome with 2^{10} loci, a homozygous mutation has probability equal to 2^{-20}) However, for the biparental reproduction, when one chooses the gametes from different individuals it is more likely to obtain mutations at the same loci (in the same example, this probability is now $\sim 2^{-10}$)

To better compare the different behaviour of the system, we show in Figure 6 the results obtained for $mutr = 0.5$, $Birth = 1.8$, $recr = 0.00001$ and Verhulst factor $N_{\max} = 1,000,000$. The top/left plot shows the time evolution of population, the top/right plot shows the time evolution of the population mean fitness and in the bottom/left plot the time evolution of the population growth rate is shown. We performed simulations for this set of parameters using the fixed population prescription and this result is shown in the bottom/right corner of this figure. For the free evolutionary population case, due to computational limitations we used small initial populations, since for this birth rate the population increases almost twice for each time step. For $S = 1$ and initial population $N(0) = 10$ (white circles) the population grows exponentially reaching the equilibrium around 280,000 individuals. The effect of the strong

mutation rate can be observed in the plot of the fitness versus generations. Due the high birth rate, in spite of the smaller value of fitness, the population growth rate stabilizes around 1.47. The behaviour of the system for $S = 0$, biparental reproduction, is shown with black diamonds ($N(0) = 10$) and white diamonds ($N(0) = 2$, the famous Adam and Even assumption). In contrast with the previous result ($S = 1$), now — for $S = 0$ — we observed the extinction of the species in the same bad conditions where a uniparental population has survived. For both samples, the population grows, attaining a maximum around 310,000 individuals in few generations, but thereafter falls down. In this case, the population growth rate decays reaching the value 1, which represents the beginning of this species extinction. The similar behaviour obtained with different initial populations comes from the environmental restriction factor used here, which does not allow the free growth of those populations.

To explore the role of the recombination rate we performed simulation for biparental reproduction case ($S = 0$, represented by white triangles), but now with $recr = 0.001$ instead $recr = 0.00001$. The population size increases in the beginning, attains a maximum around 313,000 individuals, decreases slowly and finally reaches the equilibrium state, close to 90,000 individuals (although it is not shown in the plot, this value was obtained after 2,000 generations). Initially, the fitness decays together that value for $recr = 0.00001$. However, this new value of $recr$ allows the fitness to stabilize, avoiding the extinction. The time evolution plot of the fitness for fixed population shows the same aspect as observed in Figure 2: fast decay for small population and slow decay for large ones (from bottom to top in the figure the symbols represent population sizes $N = 50$, 100, 500, 5,000, 10,000 and 20,000), though faster than in Figure 2 due the stronger mutation rate. The fact that the fitness seems to stabilize does not guarantee the equilibrium of the system, as we have pointed out above. The whole population still dies out if the fitness is too low. In this case we have also observed the same exponential scaling behaviour with $\alpha \sim 0.0002$.

The mutational meltdown is better shown in Figure 7, where we performed different simulations changing the environmental restriction factor. These results were obtained for $mutr = 0.2$, $recr = 0.$, $Birth = 1.3$, $S = 0$ and $N(0) = 10$. We used here again multiplicative fitness with the same selection and dominance cofficients cited above. The simulations in outcrossing populations without recombination are justified because we are interested here in describing the dynamics of mutation accumulation. For $N_{\max} = 1,000$ (white circles - averaged over 100 samples) we observe the fast extinction of the species. The fast decay of the fitness comes from the accumulation of harmful mutations. For $N_{\max} = 10,000$ (averaged over 50 samples) and 100,000 (averaged over 20 samples) the picture is qualitatively the same. However, for $N_{\max} = 100,000$ the population attained a maximum of 12,000 individuals before its decay, which must to be considered a large population. For $N_{\max} = 1,000,000$ (one sample) the multiplication of the individuals and its diversification avoid the mutational meltdown. In this case the population stabilizes around 67,000 individuals.

3. The Penna Model

In the previous calculation the individual was defined by its diploid and the fitness can be calculated, allowing the operation of selection mechanism. In that case, we do not take into account the individual age. In contrast with that definition, in the Penna model each individual can live at most 32 time intervals, which for simplicity we denote here as 32 years. The genetic code relevant for one year is called a codon and is just one bit in a bit-string model. For each year, a serious disease may or may not be inherited, corresponding to bit = 1 or bit = 0 in the single 32-bit computer word representing the genome of the individual. During life, all sicknesses are active which correspond to the given or an earlier age of this individual and when

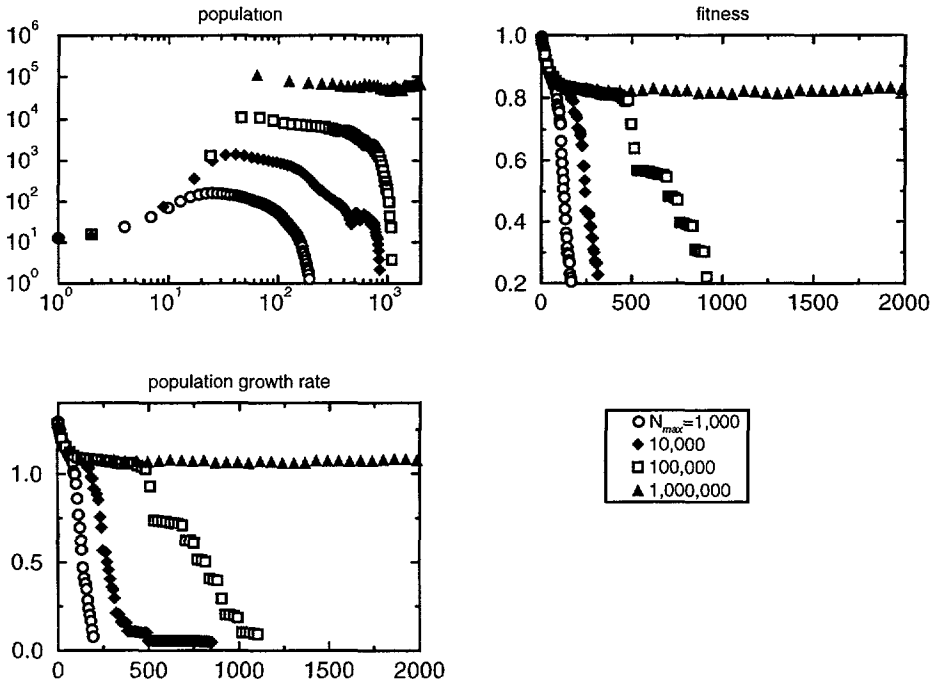

Fig. 7. — Time evolution of the population (on top-left), population mean fitness (on top-right) and the population growth rate (bottom/left) for outcrossing $S = 0$ populations under multiplicative selection obtained for initial population $N(0) = 10$ with different $N_{\max}$ (shown in the legend). The collapse of the species can be avoided by a enough growth, that means, diversification.

the total of these diseases attain a defined threshold *limit* the individual dies. Beyond an age of *min_age* years an individual can reproduce with a probability *birthr*. After reproduction, the genetic code of the descendent receives new deleterious mutations in at least one of his codon with a mutation rate m. In most of the simulations reverse mutations were avoided. In the original model and extensions, sexual reproduction is ignored, but the mutation of one bit compared with the parental bit string can be regarded as approximating the variations arising from sex. No other hereditary or somatic mutations occur.

As in the same way described above, to prevent the population N from growing to infinity, the survival probability is reduced by a Verhulst factor $1 - N/N_{\max}$. In the sexual reproduction version of this model, we create two arrays of individuals, namely males and females with the same features described above. First one has the selection process, in which individuals can die if the number of deleterious mutations is greater than *limit*, if it is 32 years old or due environmental restrictions. After selection, the mating process takes place. Now one female older than *min_age* chooses at random a male older than *min_age* also and produce a offspring with probability *birthr*. The genetic code of the offspring is obtained by combining the codons of the parents by an AND instruction, i e., in this case we consider all mutation as recessives. New mutations are acquired with a frequency m, all of them harmful. Finally the offspring gender is chosen at random: 50% male, 50% female. This process is repeated for all females older than *min_age* and when it is finished, the selection is resumed. If the population stabilizes we can calculate the age-distribution of the population, the survival rate, that means, the probability that an individual living at an age of t years will survive to the next year with

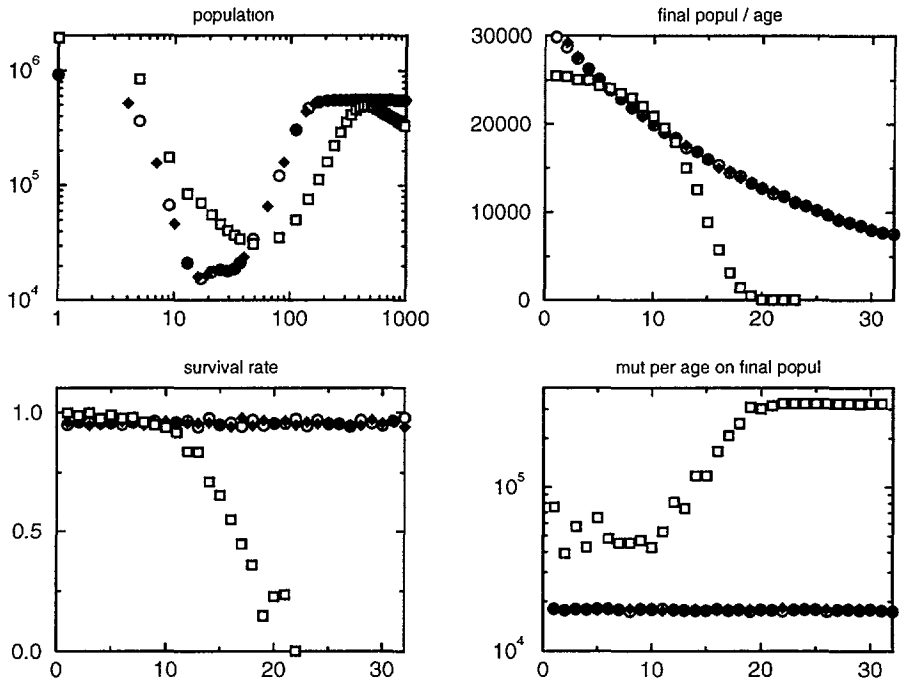

Fig. 8. — Penna model: temporal evolution of the population (on top-left), age-distribution of population (top-right), survival rate (bottom-right) and distribution of deleterious mutations in final populations for $m = 1$, $limit = 3$, $birthr = 0.2$, $min\_age = 8$ and initial populations 2×10^6. The final populations stabilizes (not showed for asexual reproduction). Black diamonds and white circles represent sexual individuals (males and females, respectively). White squares represent asexual population. Note that the survival rate for sexual populations remains constant (for discussion see text).

age $t + 1$ and the number of deleterious mutations present in total population distributed by different years.

Figure 8 shows the result obtained with the parameters: $birthr = 0.2$, $m = 1$, $limit = 3$ and $min\_age = 8$. The initial populations are 2×10^6 individuals each of them with half of genetic code with diseases randomly chosen (for sexual populations one has 10^6 males and 10^6 females). Initially we observe the decay of total population followed by a rapid growing (figure at top/left). The sexual population stabilizes, but the asexual population attains a maximum and decays once again (due to the accumulation of bad mutations). Progressively the rate of decay diminishes until the total population attain a stable value (not shown in the figure). The assumption of all recessive diseases for the sexual population seems to be here very unrealistic, since the survival rate (bottom/left) as well as the distribution of mutation versus age (bottom/right) in the final population remains constant, in spite of the experimental observation [1, 2], which was qualitatively reproduced by simulation of asexual populations. However, the assumption of recessive diseases has to be combined with strong mutation rate (again we have found controversial experimental data for mutation rates, but it seems a good estimate that the human being genetic code suffer around 1 new mutation per genome/generation [11, 21, 22]).

Figure 9 shows the results obtained with $m = 8$, initial population 2×10^6, $min\_age = 8$ and different $birthr$. Now one can see the effect of the strong mutation rate. For sexual populations

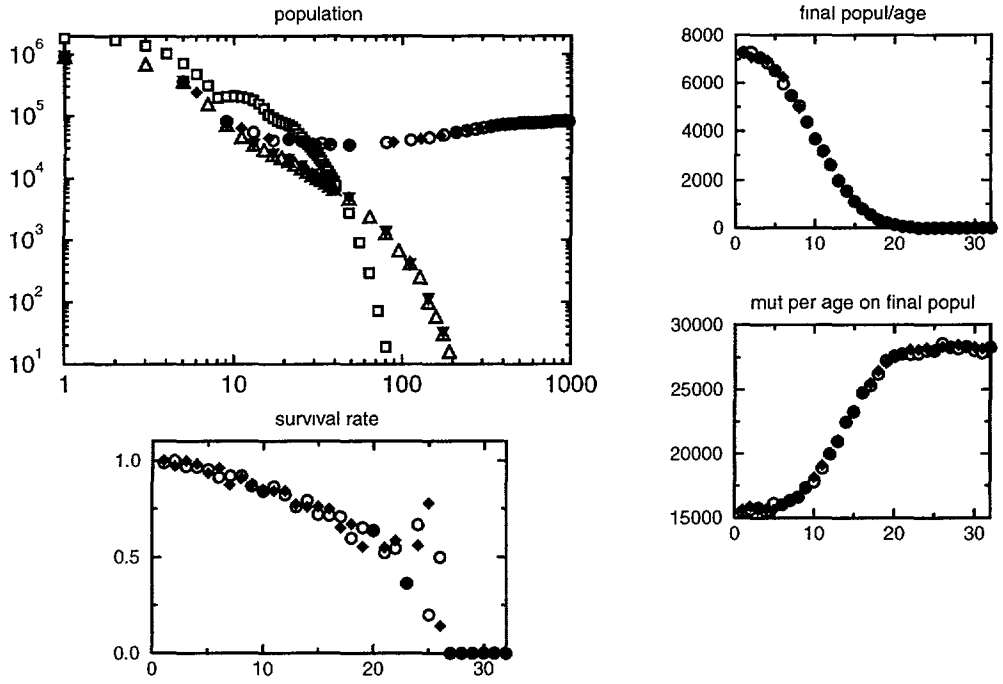

Fig. 9. — Penna model: temporal evolution of the population (on top-left), age-distribution of population (top-right), survival rate (bottom-right) and distribution of deleterious mutations in final populations with $m = 8$, $limit = 3$, $min\_age = 8$ and initial populations 2×10^6 for different birth rate. Black and white triangles (males and females, respectively) represent sexual population with $birthr = 0.4$. Due to the accumulation of harmful mutations the population becomes extinct. By changing the birth rate to 0.7 (black diamonds and white circles) we can avoid the extinction of the species and the populations stabilizes. Now the survival rate decays with age and we can observe an accumulation of harmful mutations in old ages. The asexual population does not survive with the same parameters (white squares).

with a small birth rate 0.4 (black triangles for males and white triangles for females) the population shrinks to zero. However, by increasing the birth rate to 0.7 we can avoid the extinction of the species (white circles for males and black diamonds for females). The effect of this strong mutation rate can be observed in the distribution of final population per age (top/right): most of the individuals are less than 10 years old. Now the combination between the recessive assumption with the strong mutation rate produces a reasonable survival rate plot. By changing from sexual reproduction to asexual reproduction we observe that the species goes extinct (white squares). This results agrees with the general assumptions of the advantage of sexual reproduction.

4. Conclusions

We have tested the assumption of the mutational meltdown in large populations with different sexual reproduction by using different models. Initially we test the model proposed by Charlesworth to study the evolution of populations. First we showed that the fitness has a time/size scaling behaviour and that the fixed population assumption is unrealistic to study the

population equilibrium state. Furthermore we showed that the mutational meltdown occurs due to the accumulation of harmful mutations, not restricted to small asexual or very small sexual populations. However, confirming earlier assumptions, the mutational meltdown might be avoided with a little increase in the recombination rate (due computational limitations we have not tested the behaviour of the population mean fitness for long times in the case of free evolutionary population). One important parameter observed here is the fitness times the birth rate. For products greater than one the population can increase (we used the food/space constraints to stabilize this growth). Population size stabilizes when the population growth rate tends to one, in a dangerous equilibrium, due to the fact that after some time all the individuals accumulate more and more deleterious mutation and finally the population falls down when this factor is less than one. Another question to be pointed out is that this model shows better performance in uniparental reproduction instead biparental ones, in contrast to most accepted theories on the arising of sexual reproduction.

Secondly we changed the Penna model in order to simulate sexual reproduction, by introducing two arrays of individuals and producing offspring by the crossing of males and females with further charge of deleterious mutations. For weak mutation rate we observe that the all-recessive assumption is unrealistic (the individual never gets old, that could be the paradise... — except for young scientists needing a job). However we known from biology that sexual reproduction occurs within complex species with strong mutation rates. Increasing the mutation rate we have observed the extinction of sexual populations, that can be avoided by changing the birth rate. In the same bad conditions an asexual population does not survive.

It is not our aim in this work to compare the different types of reproduction, though that our results showed the best surviving possibilities for sexual reproduction (in the sexual version of the Penna model or by increasing the recombination rate in the Charlesworth model). The role of recombination is shown in the Charlesworth model and it has to be used as a important argument on the study of the worth of the different mating types. Even considering the costs of sex [12] or still the assumption of the highest mutation male rate [23], sex is the widespread way Nature chose for the reproduction of her sons and daughters. Further investigations in this subject are in progress, trying to compare different types of reproductions and different assumptions on the role of recessiveness and dominance.

Acknowledgments

We would like to thank D. Stauffer for introducing me to this problem and T. Penna for questions and fruitful discussions. This work is partially supported by the Brazilian Agency Conselho Nacional para o Desenvolvimento Científico e Tecnológico - CNPq.

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