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Adaptive evolution in a spatially structured asexual population

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Abstract

We study the process of adaptation in a spatially structured asexual haploid population. The model assumes a local competition for replication, where each organism interacts only with its nearest neighbors. We observe that the substitution rate of beneficial mutations is smaller for a spatially structured population than that seen for populations without structure. The difference between structured and unstructured populations increases as the adaptive mutation rate increases. Furthermore, the substitution rate decreases as the number of neighbors for local competition is reduced. We have also studied the impact of structure on the distribution of adaptive mutations that fix during adaptation.

1 Introduction

The population genetics of adaptation has been studied since long ago. Haldane (Haldane 1927) was the first to point out that a great number of newly arising beneficial mutations will be lost by chance even in a very large population. He showed that, for a large random mating sexual population, the probability of fixation of a newly arising beneficial mutation is only twice its selective advantage. This means that for mutations that increase fitness of only a few percent (as seems to be the case, (Imhof and Schlotterer 2001; Rozen, de Visser, and Gerrish 2002; Lenski, Rose, Simpson, and Tadler 1991; Sanjuan, Moya, and Elena 2004)) there is more than ninety percent chance that they get lost soon after their appearance. Due to the Hill-Robertson effect (Hill and Robertson 1966), asexual organisms or non-recombining regions of sexual organisms, such as mitochondria and the Y chromosome, suffer from an even smaller probability of fixing adaptive mutations. The Hill-Robertson effect says that selection at one locus reduces the efficacy of selection on another tightly linked locus. Indeed the rate of adaptation in asexuals was shown to be strongly affected both by the presence of deleterious mutations - namely background selection and Muller's ratchet - (Manning and Thompson 1984; Charlesworth, Morgan, and Charlesworth 1993; Orr 2000; Bachtrog and Gordo 2004; Wilke 2004) and by other competing beneficial mutations - namely clonal interference (Barton 1994; Barton 1995; Gerrish and Lenski 1998). For example, clonal interference puts a speed limit on the rate of adaptation of asexual organisms (Gerrish and Lenski 1998) and this limit depends upon the deleterious mutation rate (Campos and de Oliveira 2004; Orr 2000). It has also been shown that the distribution of mutations that get fixed during the adaptive process

is influenced both by the rate of deleterious mutations and by the rate of adaptive mutations (Campos and de Oliveira 2004). In asexual organisms with a high mutation rate, such as some viruses and mutator bacteria (Drake, Charlesworth, Charlesworth, and Crow 1998), the mean effect of adaptive mutations that are likely to get fixed can be higher than in organisms with lower mutation rate.
Most population genetic models for studying adaptation in asexuals have made the simplistic assumption that populations are homogeneous and that every individual competes with every other individual in the population. However the vast majority of species are to some extent structured into local populations where individuals compete with nearby individuals. It is therefore extremely important to know how population spatial structure influences evolutionary important quantities such as the rate of adaptation and the effects of fixed adaptive mutations.
The influence of population structure on the dynamics of mutations and the role of migration in patterns of neutral variability has been established for some models of population structure (Wright 1931; Maruyama 1970; Maruyama 1974; Slatkin 1981; Nagylaki 1980; Nagylaki 1982). For example, Maruyama (1970) has shown, that under certain types of population structure (such as the island model and other models that assume conservative migration), the probability of fixation of adaptive mutations is the same as in an undivided population. However the result that the fixation of adaptive mutations is independent of population structure is not valid for all types of structure. For example when extinction and recolonization are allowed to occur that result is no longer valid (see (Barton 1993; Whitlock 2002; Rose and Rousset 2003)). Here we analyze a model of spatial structure with local competition with the aim of studying the influence of structure on the rate of adaptive evolution in asexual organisms. We are particularly interested to know whether population structure affects the rate of adaptive evolution in asexual organisms subject to both beneficial and deleterious mutations.

2 The model

We consider a model for the evolution of spatially structured populations of asexual haploid organisms. Recently, several models of spatial structure have been introduced to investigate evolution in epidemiology and ecology (Campos et al. 2004; Keitt and Johnson 1995; Lipowski 1999; Keeling 1999; Ohsawa et al. 2002; Kisdi and Geritz 2003). In our model, the organisms are spatially arranged on a two-dimensional regular lattice of linear size L with periodic boundary conditions (i.e., we consider a torus-like lattice), and each of the $N = L \times L$ individuals in the

population occupies a cell of the lattice. Moreover, we consider different levels of structure by allowing individuals to compete with a different number of neighbors. We consider two levels of structure: the Moore neighborhood, in which each individual interacts with its eight nearest neighbors and the Von Neumann neighborhood, in which the interaction is reduced to four neighbors. The population evolves according to a modified version of the Wright-Fisher model which takes into account the spatial structure of the population. We assume non-overlapping generations, so that the individuals at time $t+1$ are descendants of individuals at time t. Furthermore, an individual at a given cell i can only be descendant of individuals which are located in cell i or in its neighborhood, i.e., the competition is local. In that context an individual i at generation $t+1$ is the offspring of an individual j at generation t with probability

$$p_{ij} = \frac{\pi_j}{\sum_l \pi_l} \tag{1}$$

where π_j denotes the fitness value of individual j and the sum is taken over cell i and its neighbor sites.

The mutational scheme is defined as follows. In our formulation we consider the infinite-sites model (Kimura and Crow 1964; Watterson 1975). Each newborn individual inherits all the mutations, beneficial and/or deleterious, from its parent genome and an additional amount of new deleterious mutations n taken from a Poisson distribution with parameter U, where U denotes the mean number of new mutations per individual per generation. For simplicity we have assumed that each deleterious mutation decreases the fitness of the sequence by a constant factor $(1-s_d)$. In addition, beneficial mutations take place at a constant rate U_b per individual, and they improve the fitness of the individual by a factor $(1+s_b)$. The probability distribution of selective effects of beneficial mutations is assumed to be exponential with parameter β (Gillespie 1991; Orr 2003; Rozen, de Visser, and Gerrish 2002):

$$g(s_b) = \beta \exp(-\beta s_b). \tag{2}$$

We have assumed a distribution of selection coefficients for beneficial mutations because we want to study how the distribution of fixed adaptive mutations is affected by structure.

The fitness of each individual depends on the quantities k and k_b, which correspond to the number of deleterious and beneficial mutations in its genome, respectively. The fitness is multiplicative across loci, and so its value π is given

by

$$\pi(k, k_b) = \left[\prod_{i=1}^{k_b}(1 + s_b(i))\right](1 - s_d)^k. \quad (3)$$

Before we present our results, we will discuss our simulation procedure for the spatially structured population. The initial population at time $t = 1$ consists of individuals that do not have any mutation. We then let the population evolve up to generation $t = 1000$ in order to reach an approximate equilibrium state, known as mutation selection balance (Haigh 1978). During this time, beneficial mutations do not take place. At $t = 1000$ we introduce one beneficial mutation in a randomly chosen individual. Subsequent advantageous mutations take place at a constant rate U_b per individual. We have ascertained that our results do not change whether we consider a sufficiently long period of equilibration.

We also have run Monte-Carlo simulations of unstructured populations in order to compare with the results of the structured ones. The initial configuration of the population is set up by a set of recursive equations (Haigh 1978), that determine the distribution of deleterious mutations in the population, and a period for equilibration is not required. In this case, the time $t = 1$ corresponds to the generation at which beneficial mutations start to be introduced in the population. The initial distribution of frequencies of the class of individuals with k deleterious mutations in the equilibrium regime, which we denote by $\bar{C}_k$, is calculated by the following set of equations

$$\bar{C}_k = \frac{1}{\pi_m - \pi_k}\sum_{j=m}^{k-1}\frac{U^{k-j}}{(k-j)!}\pi_j\bar{C}_j, \quad k > m \quad (4)$$

where $\pi_k = \pi(k, 0)$. By means of the above equation we recursively estimate the ratios $\bar{C}_k/\bar{C}_m$ and obtain $\bar{C}_m$ from the normalization condition $\sum_k \bar{C}_k = 1$ (de Oliveira and Campos 2004), where m is the index of the class of the fittest individuals existing in the population. In our study we assume $m = 0$.

As in the structured population model, the advantageous mutation at time $t = 1$ occurs in a randomly chosen individual, and subsequent mutations also take place at a constant rate U_b per individual. We let the population evolve for a sufficiently long period and then count the number of fixation events as well as other relevant quantities.

3 Results

We studied two different schemes of local competition. In the first scheme, we considered the Moore neighborhood where each individual interacts with its eight next-nearest neighbors. The second model regards the Von Neumann neighborhood, where each individual interacts with its four neighbors. These neighborhoods are commonly studied in cellular automaton models of pre-biotic evolution (Rosas, Ferreira, and Fontanari 2002; Boerlijst and Hogeweg 1991) and ecosystem dynamics (Wootton 2001).
We have studied the distribution of deleterious mutations in both models of structured populations, before introduction of beneficial mutations, and compared it to the one in a homogeneous population.

In an infinitely large homogeneous population at mutation-selection balance, the distribution of deleterious mutations is Poisson with mean U/s_d (Haigh 1978). The time taken to reach this distribution is close to $1/s_d$ in an effectively infinite homogeneous population (Johnson 1999). In a structured population with local competition we may expect a deviation from the Poisson distribution of mean U/s_d. Intuitively one can think that because in a structured population individuals compete locally, the effectiveness of selection will be reduced. In fact, it has been shown (Cherry and Wakeley 2003; Whitlock 2002) that a population conforming to Wright's island model can have a smaller selection coefficient than the actual selection coefficient. Although the island model that was studied is very different from the structured model studied here, we also expect a reduction in the efficacy of selection, due to local competition, which will result in a higher mean number of deleterious mutations. This deviation from the mean of U/s_d will depend both on the size of the neighborhood and on the value of the deleterious mutation rate. Since it is known that the time to achieve an equilibrium distribution of deleterious mutations is proportional to $1/s_d$, at least in an homogeneous population, we also expect that time to be increased in a structured population.

In Figure 1 we show the deviation from a Poisson distribution for the Moore and Von Neumann neighborhoods and for two different values of U.

In the case of the Moore neighborhood and for the higher value of the mutation rate, the distribution is very close to a Poisson distribution with a higher mean value than U/s_d (the mean value actually observed in the simulations is 1.43, whereas the value of U/s_d is 1, for the case where $U = 0.1$). This is consistent with the idea that in a structured population under local competition, the rate of loss of deleterious mutations is lower than in the homogeneous model, which means a reduced effective value of s_d. This implies that the smaller the neigh-

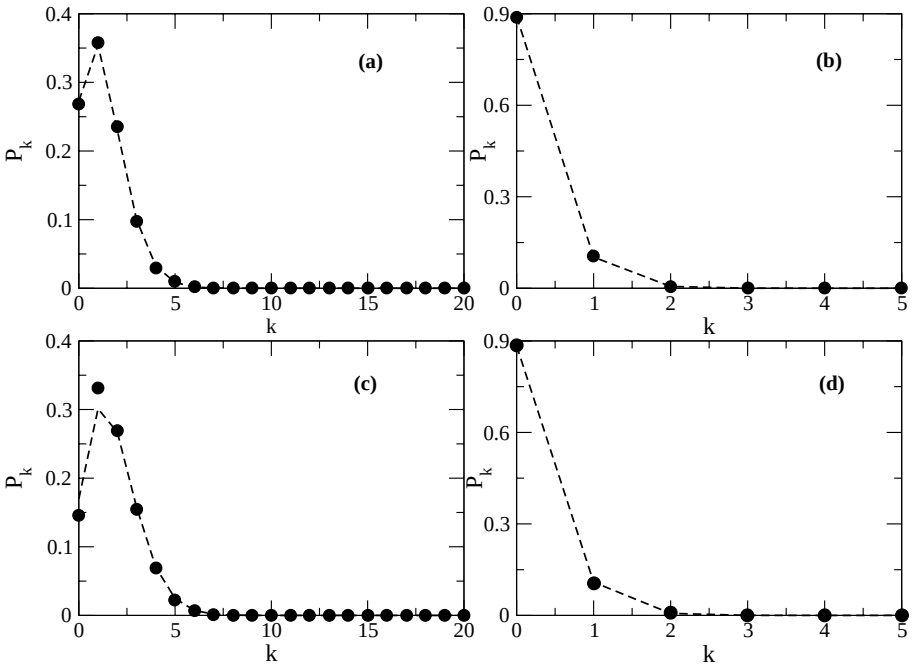

Figure 1: The distribution of deleterious mutations at mutation-selection balance in a structured population. The distribution is obtained before any introduction of beneficial alleles. In both cases, the population size is $N = L \times L = 2,500$ and $s_d = 0.1$. In figures a) and c) $U = 0.1$ and for b)and d) figures $U = 0.01$. Data points are the simulation results whereas dashed lines are the results of the Poisson distribution with fitted parameter. The Moore neighborhood is represented in figures a) and b) on the top panel. The Von Neumann neighborhood is represented in figures c) and d) on the low panel.

borhood size, the higher the effect of local competition and the more reduced is the efficacy of selection. This is compatible with the observed reduction in the frequency of individuals free of deleterious mutations, in the Von Neumann neighborhood when compared to the Moore neighborhood (see the left panels of Figure 1). Interestingly we observe that when the neighborhood size is very reduced, as in the case of the Von Neumann neighborhood, the distribution of deleterious mutations deviates from a Poisson (see Figure 1, left low panel, where the mean is 1.77 and the variance is 1.64).

In the case of low values of the mutation rate the distribution is very close to a Poisson distribution with a slightly higher mean than the value of U/s_d. This is

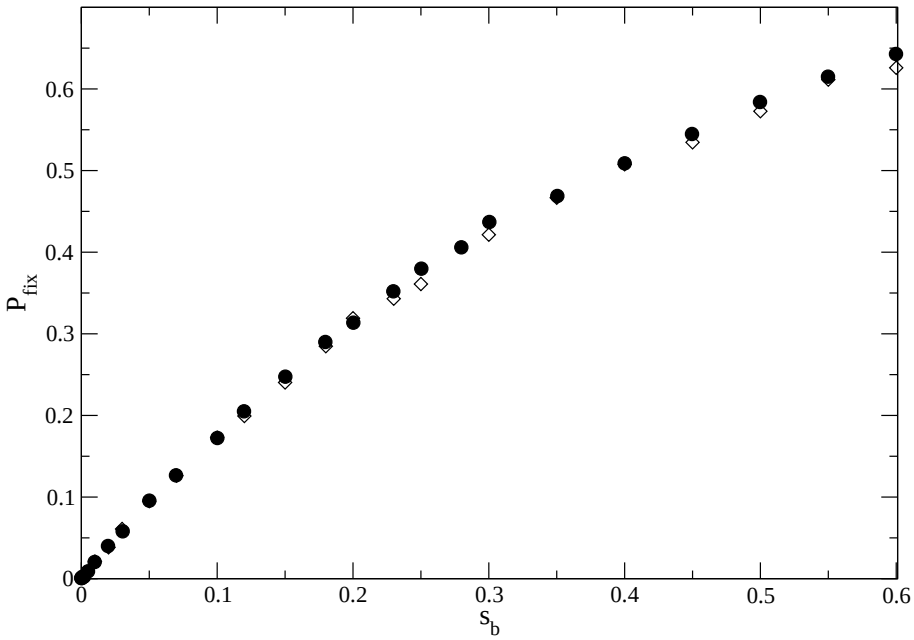

Figure 2: The probability of fixation P_{fix} as a function of the selection coefficient s_b. In the figure, we have considered that all beneficial mutations have the same effect instead of drawing from the exponential distribution (2). The full data points correspond to the simulation results for an unstructured population, and the open data points to the structured population with the Moore neighborhood. $N = L \times L = 2,500$ and $U = 0$.

observed for both types of structure.

When U is very large and/or U/s_d is large, the balance between mutation and selection may not emerge and the distribution can deviate considerably from a Poisson (Gessler 1995). In this case a rapid accumulation of deleterious mutations by Muller's ratchet occurs. We will study only cases where an equilibrium distribution can be attained and leave non-equilibrium situations for future work.

In every case that we have studied, the time to achieve and approximate equilibrium is always longer in the structured population with local competition. For example the time taken to reach equilibrium in the case of Figure 1 is 50 generations for the Moore neighborhood and 120 generations for the Von Neumann neighborhood.

Before studying the effect of population structure on the rate of adaptation under interference caused by both deleterious and beneficial mutations, we studied how the probability of fixation of a single beneficial mutation is affected by the type of population structure that we are modelling. Maruyama (Maruyama 1970) has shown that for some models of population structure such as Wright's island model, in which the pattern of migration does not change the frequency of a beneficial allele in the whole population, the probability of fixation of a beneficial mutation is the same as in a homogeneous population. Maruyama considered a simple model where 1 locus and two alleles were analyzed. In Figure 2 we show that the same result applies in our lattice model, for 1 locus two alleles, i.e. in the absence of deleterious mutations and clonal interference, the probability of fixation of a beneficial mutation is the same as in an unstructured population.

We now address the question of how the rate of adaptive evolution in structured populations is affected by both deleterious mutations and clonal interference. Figure 3 shows the rate of substitution of beneficial mutations k_b as a function of the rate of beneficial mutations U_b. We present the results for different values of the deleterious mutation rate U and compare homogeneous and structured populations where each individual competes with its 8 nearest neighbors. It is clear from the figure that for a given value of U_b and a given value of U, the substitution rate k_b is always higher for homogeneous populations than for spatially structured populations. However, in both situations, we observe that the substitution rate of advantageous mutations does not grow at a constant rate with U_b, instead its rate of growth declines as U_b increases, as a result of clonal interference. We notice that when U_b is very low and clonal interference amongst beneficial mutations is not a major force, the rate of adaptation is well approximated by the theoretical prediction of the branching process approximation (Johnson and Barton 2002; de Oliveira and Campos 2004) with $s_d = 0.071$ (i.e. the value of s_d compatible with the equilibrium distribution of deleterious mutations). For instance, when we consider $U_b = 10^{-6}$, our simulation results for the structured population with the Moore neighborhood provides $k_b = 7.1 \times 10^{-5}$, whereas in the theoretical approach $k_b = NU_bP_{fix}(U, s_d, \beta) = 7.9 \times 10^{-5}$, with $U = 0.1$, $s_d = 0.071$ and $\beta = 20$. In order to estimate the probability of fixation P_{fix} we have used the set of equations (12) and (13) in (Johnson and Barton 2002), and because the selective effects of favorable mutations are exponentially distributed, we have numerically integrated the solution provided in the previous step over all possible values of selective effects (see (de Oliveira and Campos 2004) for a detailed explanation).

Even though the branching process approximation assumes that each beneficial mutation is not influenced by other beneficial mutations (de Oliveira and Campos 2004) and no population structure, the simulation results are close to the prediction given by this approximation.
The substitution rate of adaptive mutations in the absence of deleterious mutations is higher than the rate of substitution when $U > 0$, since in that case there is no effect of background selection (Charlesworth, Morgan, and Charlesworth 1993). In Figure 3, we have calculated the expected rate of adaptive evolution in homogeneous populations using a slightly modified version of the approximations given by (Gerrish and Lenski 1998) and (Orr 2000). Orr's approximation takes into account both interference amongst beneficial mutations and background selection caused by deleterious mutations (Orr 2000). Although this approximation is only expected to work when the fitness effects of beneficial mutations are smaller than those of deleterious mutations, the assumed exponential distribution for beneficial mutations with $\beta s_d > 1$, implies that this is valid for most of the mutations. We have modified the approximation given by equation (8) in (Orr 2000):

$$k_b = 2NU_b \int_0^\infty \exp(-U/s_d) \exp(-I) s_b g(s_b) ds_b \tag{5}$$

where we have corrected the value of I, which is the expected number of interfering beneficial mutations that arise and can compete with the beneficial mutation that is on its way to fixation. Assuming a Poisson process, the term $exp(-I)$, is the probability that no events occur. The quantity I depends on the time to fixation of beneficial mutations (see (Gerrish and Lenski 1998) and (Orr 2000)). We have corrected the value of I given by equation (7) in Orr (Orr 2000), to take into account that the time to fixation of a beneficial mutation is smaller in the presence of deleterious mutations, as shown in simulations (see Table 1 in (Bachtrog and Gordo 2004)).

The corrected value has been approximated by:

$$I_c = 2U_b N Log(N \exp(-U/s_d)) \exp(-U/s_d) \beta \int_{s_b}^\infty v g(v) dv \tag{6}$$

This approximation is presented in Figure 3. As we can see for the range of parameters in the figure, the approximation reproduces reasonably well the simulation results.

Although this approximation is valid for a homogeneous population, we have tested it also for the case of a structured population. Here we have assumed a reduction in the value of s_d and also a reduction in the expected value of s_b. Figure

4 shows the results of the approximation with $s_d = 0.07$ and $\beta = 28.6$. We used a 0.7 reduction on the values of s_d because this is the reduction inferred from the distribution of deleterious mutations at approximate mutation selection balance prior to the introduction of beneficial mutations. We applied the same reduction for the selection coefficients for beneficial mutations. As we can see for the range of parameters in Figure 4 the approximation reproduces reasonably well the simulation results for small values of U, whereas it constitutes an underestimation for the large U and small values of U_b.

From Figure 3 we observe that the substitution rate k_b decreases with U both in homogeneous and in structured populations. This is expected since the effect of background selection occurs both in homogeneous and structured populations (Charlesworth, Nordborg, and Charlesworth 1997). However, the decrease in the adaptation rate when U increases is more pronounced in structured populations. For example when $U_b = 5 \times 10^{-6}$, the value of k_b drops approximately 2-fold when U increases from 0.01 to 0.1 in the homogeneous case, whereas it drops 3-fold in the spatially structured population (see Figure 3). This is compatible with the fact that, for a given value of U, the frequency of individuals free of deleterious mutations is smaller in the structured population, leading to larger effect of background selection in this model system.

In Figure 5 we plot the substitution rate of advantageous mutations k_b as a function of U_b for different values of U, but now we only consider spatially structured populations. In the Figure, we survey two different schemes of local competition with different neighborhood sizes: the Moore neighborhood and the Von Neumann neighborhood. The simulation results clearly indicate a smaller substitution rate of beneficial mutations when we consider the Von Neumann neighborhood. Except for that, we observe the same qualitative behavior. These results show a clear dependence of the rate of substitutions on the number of individuals that are competing at any one time.
The results also indicate that when U_b and U are very low, so that clonal interference and background selection are not very important, the substitution rate is poorly dependent on the neighborhood size. On the contrary, when U_b is large and there are many competing adaptive mutations, a structured population with a smaller neighborhood size has a much smaller rate of adaptation.

We have quantified the relative cost of structure as $\frac{K_b^{Homogeneous} - K_b^{structure}}{K_b^{Homogeneous}}$. Figure 6 shows that this cost is small when both U and U_b are small. But in the

absence of deleterious mutations when U_b increases, so does the effect of clonal interference, and the relative cost of structure increases, until it reaches a limit. This limit depends on the neighborhood size, with smaller neighborhoods leading to higher costs. On the other hand when both adaptive and deleterious mutations occur we observe that the relative cost of structure is practically independent of the U_b and is mostly due to the effect of background selection. This is higher for smaller neighborhoods leading to a larger cost in the Von Neumann type of structure.

We now ask: what are the average effects of mutations fixed in a structured population that is continuously adapting? It is known that in a homogeneous population, the average effect of fixed beneficial mutations is increased when the effects of clonal interference are augmented (de Oliveira and Campos 2004; Rozen, de Visser, and Gerrish 2002). Figure 7 shows the average selection coefficient of fixed mutations both in homogeneous and in structured populations with the same set of parameters. When U_b is small, both populations fix adaptive mutations with the same average effect. But when U_b becomes large, we can see that there is a difference between structured and homogeneous populations. Whereas in homogeneous populations the mean effect increases with U_b, in populations with spatial structure this value is much higher.

This pattern is observed for different values of β and different values of the population size.

For a given β, we have seen that when the population size increases, the difference between structured and unstructured populations in the mean value of fixed adaptive mutations increases.

We can better comprehend this distinct behavior between structured and unstructured populations by looking at the distribution of selective effects of favorable that have reached fixation. Figure 8 shows how the distribution of fixed mutations is affected by the adaptive mutation rate in the structured population (upper panel, figures a) and c)) and in the unstructured population (lower panel, figures b) and d)).

We also show, in the inset of Figure 8, the probability of fixation of beneficial mutations as a function of their selective effects s_b for both structured and homogeneous populations. The data points are averages over $1,000$ runs and are arranged in bins of size 0.01, which means that the first point comprises all those mutations with selective effect that ranges from 0.0 to 0.01. the second point takes into account mutations with selective effect that ranges from 0.01 to 0.02, and so on.

The shapes of the distributions of fixed adaptive mutations are very similar between structured and unstructured populations, although the mean is higher in the structured case. In both models high mutation rates lead to a shift in the distribution towards higher values of s_{fix}, but a smaller probability of fixation of mutations of any given effect. From the inset of Figure 8 we can see that mutations with larger fitness effects experience a smaller reduction in their probability of fixation than small effect mutations as U_b increases. These results point out that the clonal interference phenomenon is much more effective in structured populations.

4 Discussion

The rate at which adaptive mutations fix are amongst the important parameters in evolutionary biology since adaptation critically depends on how fast adaptive mutations are generated and how strong their effects are. There has been recent empirical evidence (Imhof and Schlotterer 2001; Rozen, de Visser, and Gerrish 2002; Lenski, Rose, Simpson, and Tadler 1991; Sanjuan, Moya, and Elena 2004; Nilsson, Kugelberg, Berg, and Anderson 2004; Joseph and Hall 2004) that rates of adaptive mutations are much higher than previously proposed (Kimura 1983). For example, very recently, evolution experiments of adaptation of the bacterium Salmonella typhimurium to mice have suggested that the adaptive mutation rate for that bacterium can be higher than 10^{-6}/cell/generation (Nilsson, Kugelberg, Berg, and Anderson 2004). Also a very high adaptive mutation rate has been found in yeast (Joseph and Hall 2004). These estimates for the mutation rate towards mutations that increase fitness in microorganisms suggest that clonal interference might be very important in driving their evolution. All natural populations, and in particular populations of microorganisms, are structured to some degree. Therefore the study of the process of adaptation in structured populations is of extreme importance.

We have considered a spatially structured population model of haploid asexual

individuals. The model adopts a local competition for replication, and only the neighbors of a given cell and the cell itself can generate an offspring to occupy the cell in the next generation. The model tries to capture the spatial structure observed in real biological populations. We have focused our study on the effects of the spatial structure in the dynamics of favorable mutations. Through extensive Monte Carlo simulations, we have investigated the dynamical properties of fixation of favorable mutations and compared the results with those obtained by considering homogeneous populations.

In order to better understand the structured model we have first examined the distribution of deleterious mutations as a function of the mutation rate U. In an unstructured population the distribution is Poisson with mean U/s_d (Haigh 1978). In our structured model we have established the occurrence of four distinct regimes for the long-term distribution. We have observed that the equilibrium distribution of deleterious mutations, P_k, is well described by a Poisson with mean U/s_d for very low mutation rate U. As we increase the rate of deleterious mutations U, the equilibrium distribution of deleterious mutations is still a Poisson distribution but with a larger mean value. A further increase of U generates a distribution which clearly deviates from a Poisson distribution. The mutation rate U at which this regime takes place depends on the neighborhood size. Specifically, a smaller neighborhood size means a smaller value of U at which this third regime becomes effective. From Figure 1 we see that a Poisson distribution with mean 1.43 describes precisely the distribution of deleterious mutations for a structured population with a Moore neighborhood and with $U = 0.1$ and $s_d = 0.1$. However, we have also checked that the result for a structured population with Von Neumann neighborhood deviates considerably from a Poisson. For very large values of mutation rate, the distribution P_k shifts towards higher values of U with time, which characterizes a non-equilibrium regime. Due to local competition in the structured model the efficiency of selection is reduced, the effect being larger the smaller the neighborhood size, and that reflects on a higher mean number of deleterious mutations in the structured population.

We have shown that the spatial structure can affect the fate of advantageous mutations. We have observed that the rate of fixation of advantageous mutations k_b for spatially structured populations is smaller than the rate for unstructured populations for the same set of parameters. Furthermore, as expected, the rate of fixation k_b depends on the number of competing individuals, as we can see in Figure 5. From the Figure, we ascertain that a smaller neighborhood size results in a smaller rate of adaptation. Our findings illustrate how the stochastic processes

governing the evolution of populations in the structured model are even more effective than in the unstructured case.

Not only have we observed that the rate of adaptation is smaller in a structured population than in a homogeneous population, we have also found that the difference between structured and homogeneous populations increases as the adaptive mutation rate increases, i.e. as the effect of clonal interference becomes more pronounced the cost associated with structure becomes more significant. However whereas for low deleterious mutations rates, the relative cost of structure achieves a limit at an intermediate value of the adaptive mutation rate, when deleterious mutations are produced at high rates the cost of structure is mainly determined by their effect.

When the adaptive mutation rate is high, clonal interference becomes important in both homogeneous and structured and that reflects both on the rate of fixation and on the distribution of fixed beneficial alleles. As in structured populations the time to fixation increases, the effect of clonal interference is more pronounced and the distribution of the fitness effects of fixed adaptive mutations has a larger mean than in the unstructured case.

One way to test experimentally the results of this model would be to perform several experimental evolution tests using a rapid growing asexual microorganism (Elena and Lenski 2003). The population could be propagated either in an homogeneous medium, as for example liquid media, and in a structured medium, such as a petri dish. The increase in mean fitness of the populations in both systems could then be compared to test if rates of adaptation are smaller in the structured populations.

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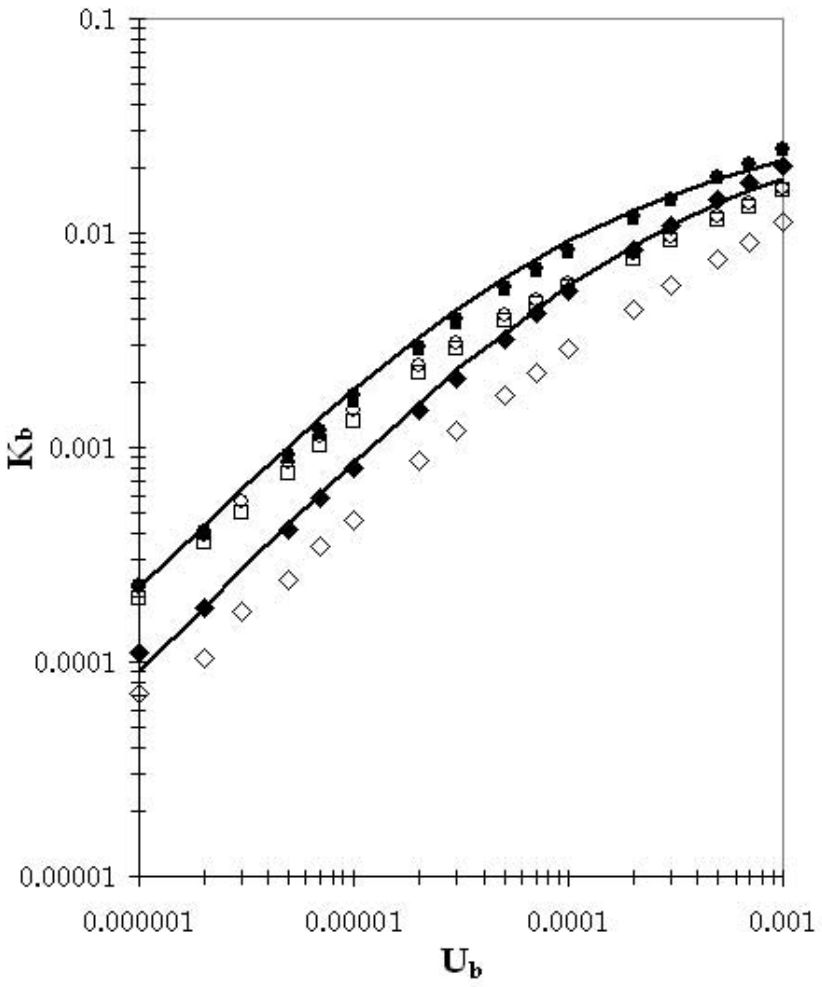

Figure 3: The rate of substitution k_b as a function of the rate of beneficial mutations U_b. The full data points correspond to the simulation results for a homogeneous population, and the full line to the analytical approximation. The open data points correspond to the simulation results of the spatially structured population of size $N = L \times L = 2,500$, where we have considered a Moore neighborhood. Circles correspond to $U = 0$, squares to $U = 0.01$ and diamonds to $U = 0.1$. The other parameters are $s_d = 0.1$ and $\beta = 20$.

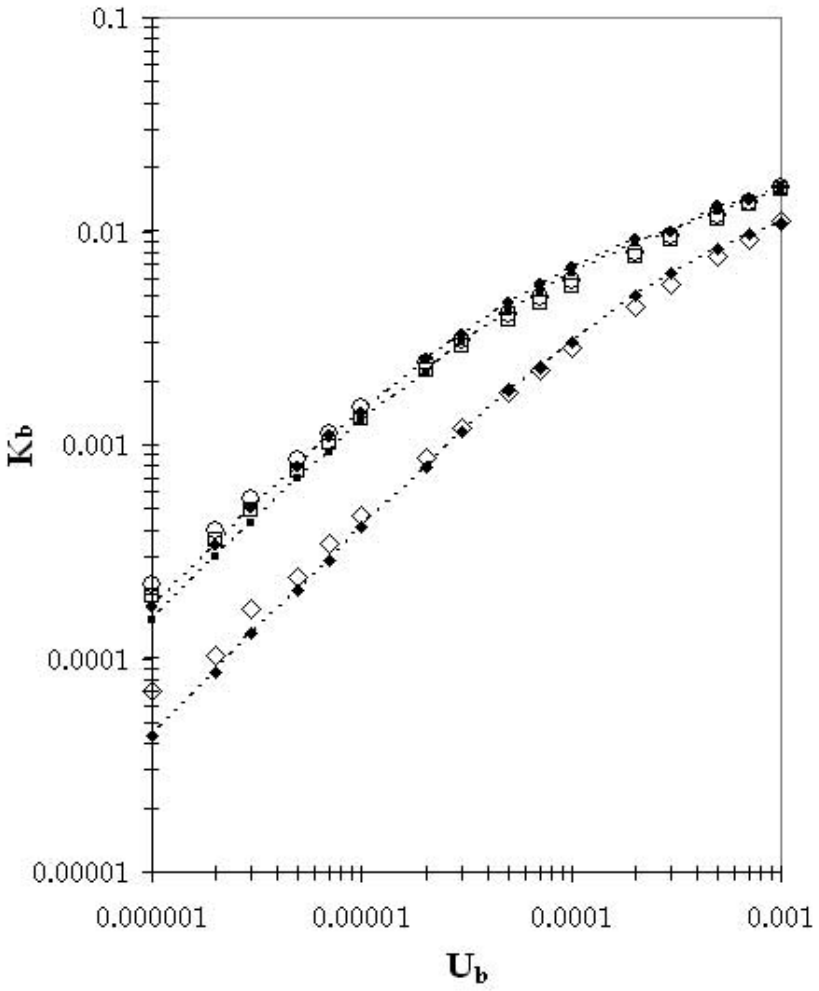

Figure 4: The rate of substitution k_b as a function of the rate of beneficial mutations U_b in a structured population. The dotted lines with the small points correspond to the analytical approximation for the structured population (see text for details). The open data points correspond to the simulation results of the spatially structured population with the Moore neighborhood. Circles correspond to $U = 0$, squares to $U = 0.01$ and diamonds to $U = 0.1$. The other parameters are as in Figure 3.

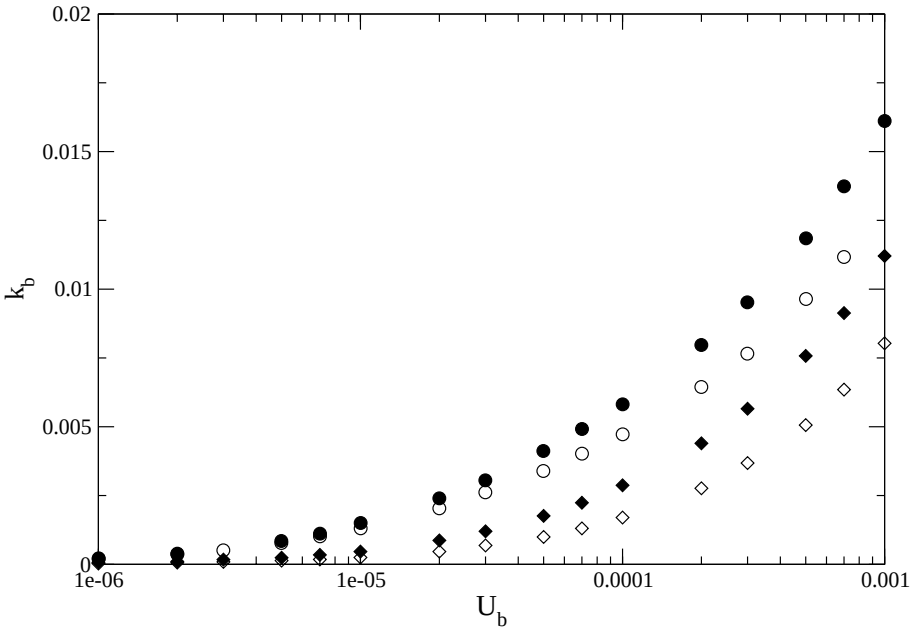

Figure 5: The rate of substitution k_b as a function of the rate of beneficial mutations U_b. The full data points correspond to the simulation results for the spatial model with the Moore neighborhood, whereas the open data points are the results for the model with Von Neumann neighborhood. Circles are for $U = 0$ and diamonds $U = 0.1$. In both cases, the population size is $N = L \times L = 2,500$ and other parameters are as in Figure 2.

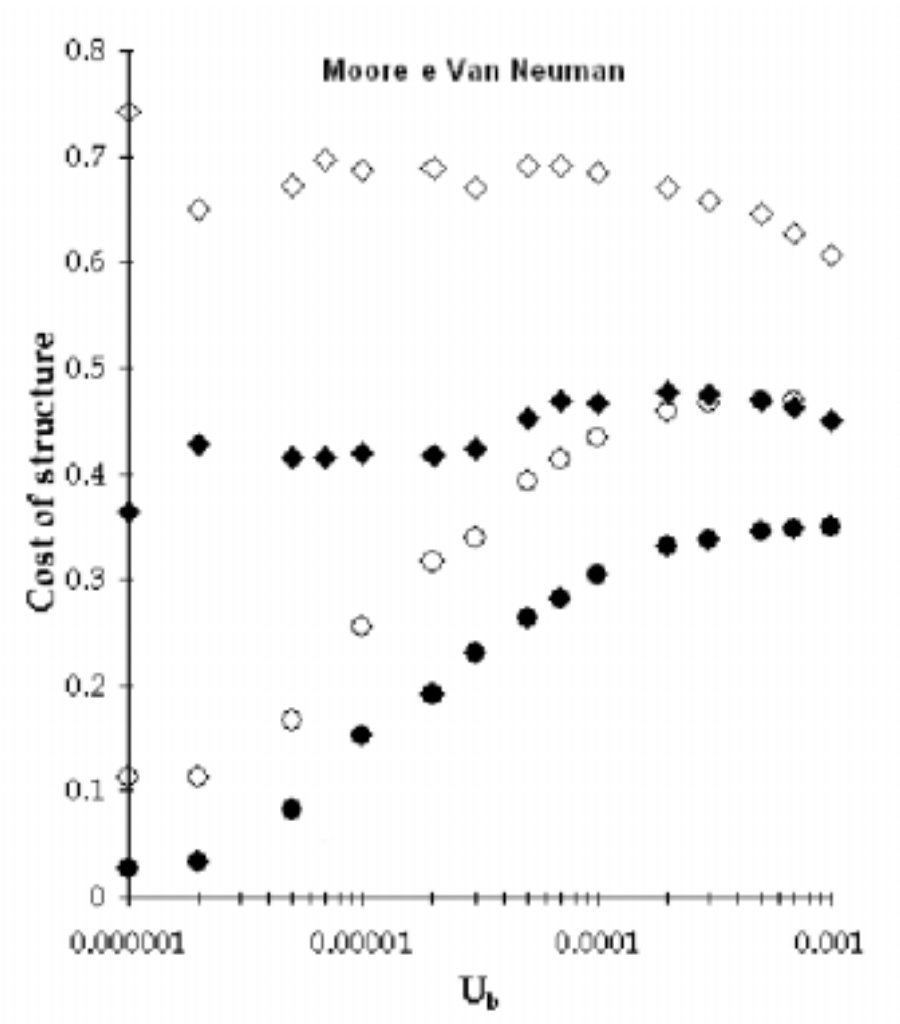

Figure 6: The cost of structure in the rate of adaptive evolution, measured by $\frac{K_b^{Homogeneous} - K_b^{structure}}{K_b^{Homogeneous}}$, as a function of the rate of beneficial mutations U_b. The filled data points correspond to the simulation results for the spatial model with the Moore neighborhood and the open data points to the Von Neumann neighborhood. Circles correspond to $U = 0$ and diamonds to $U = 0.1$ and other parameters are as in Figure 2.

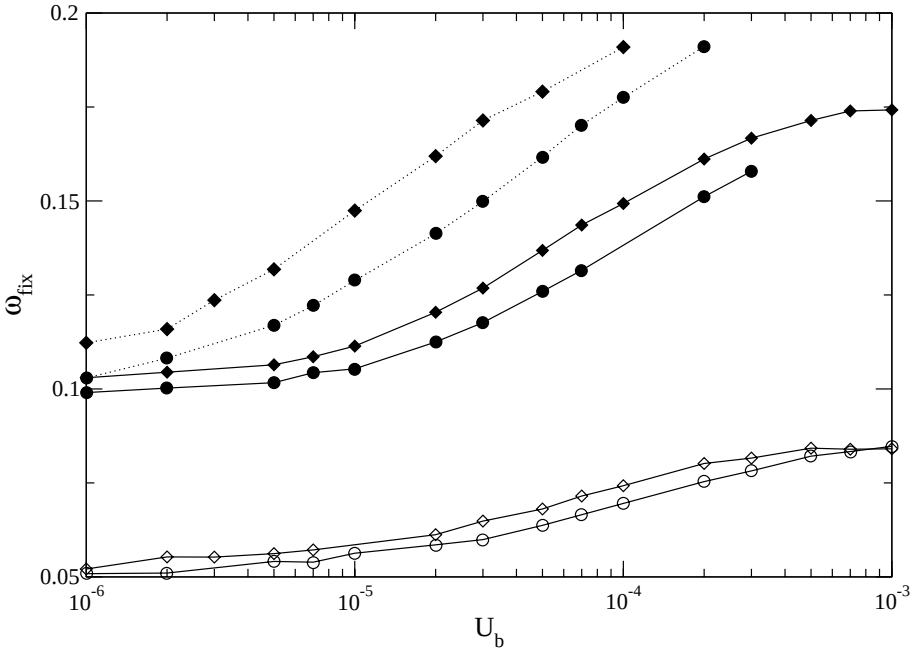

Figure 7: Expected value of selective effects of favorable mutations that have reached fixation ω_{fix} as a function of the rate of beneficial mutations U_b. Circles correspond to values for homogeneous populations and diamonds to structured populations with the Moore neighborhood. Population size is $N = 2500$ (with $L = 50$ in the structured case) and $U = 0$. Open data points are for $\beta = 40$ and full data points for $\beta = 20$. Data points joined by dashed lines correspond to population size of $N = 10000$ (with $L = 100$ in the structured case).

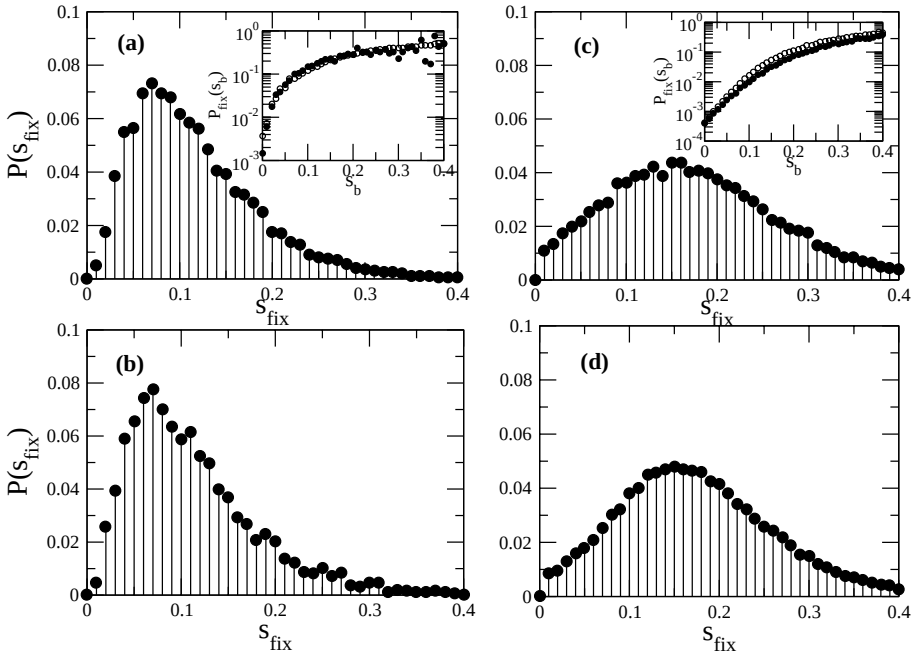

Figure 8: Distribution of the selective effects of favorable mutations that have reached fixation s_{fix} for different values of the rate of beneficial mutations U_b in the spatially structured model with the Moore neighborhood (top panel) and homogeneous model (low panel). In all figures $U = 0$ and $\beta = 20$. Figures a) and b) correspond to $U_b = 1 \times 10^{-5}$ and Figures c) and d) to $U_b = 1 \times 10^{-3}$. The inset of Figure c) shows the comparison of the probability of fixation of beneficial mutations of a given effect s_b in the structured (full data points) and unstructured (open data points) populations with $U_b = 1 \times 10^{-3}$.

* Response to reviewer's comments
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Dear Editor Dr. Tatiana Giraud,

We would like to thank you for considering our manuscript entitled "Adaptive evolution in a spatially structured asexual population" for publication in Genetica.
We also would like to thank the Reviewer 1 for pointing out that the results of Figure 8 in our paper should be clarified and discussed in more depth.

When trying to achieve a clarification following the Reviewer's suggestions we have realized that we had a bug in the program that simulates the structured populations. We have fixed the problem in the program and revised all the results in the paper. The results in Figures 1, 2, 3, 4 and 6 remain qualitatively the same as before and the main conclusions attached to these are the same. However, there are changes in the results of Figures 5, 7 and 8. These new Figures are clearly consistent with an enhanced increase of clonal interference in structured populations, which leads to an increase in the mean fitness effects of fixed advantageous mutations in structured populations with Ub (result in the new Figure 7). Actually, we observe that the mean fitness effect is always higher in structured populations than in populations without spatial structure. Consequently, the scenario in Figure 8 changes according to these new results.

This is exactly the key point that Reviewer 1 has pointed out in the previous version, and that we think will be now completely clear and consistent.

Thus we would to like to resubmit the manuscript including the aforementioned changes.

Yours sincerely,

The Authors.