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The effect of spatial structure in adaptive evolution

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Abstract. We study the dynamics of adaptation in a spatially structured population. The model assumes local competition for replication, where each organism interacts only with its nearest neighbors and is inspired by experimental methods that can be used to study the process of adaptive evolution in microbes. In such experiments microbial populations are grown on petri dishes and allowed to adapt by serial passage. We compare the rate of adaptation in a structured population where the structure is maintained intact to those where movement of individuals can occur. We observe that the rate of adaptive evolution is higher and the mean effect of fixed beneficial mutations is lower in intact structures than in structures with mixing.

PACS. 87.23.-n Ecology and evolution – 87.23.Cc Population dynamics and ecological pattern formation – 87.23.-Kg Dynamics of evolution

Introduction

Adaptation by Natural Selection is a very important aspect of the evolution of natural populations but it is still far from being completely understood. Early theoretical works tried to predict the fate of beneficial mutations in simple populations, particularly those with no structure. One of the most striking results of this is that in finite populations, not all beneficial mutations that arise will be fixed. More specifically, Haldane showed that when populations are large and the fitness advantage conferred by a new mutation is small, the probability that a beneficial mutation will be fixed is only twice its selective value [1]. His model was a very simple one where one locus with two alleles was the sole responsible for the fitness of an individual and it holds true for populations with sexual reproduction where each locus can be thought of as segregating independently of the rest due to frequent recombination.

As more loci are considered and if recombination is infrequent, the mutations can not be thought of as evolving independently. In fact, asexual populations are affected by the Hill Robertson effect, which states that selection at one locus reduces the efficacy of selection at a linked locus [2]. As a consequence of this effect, adaptation in asexual organisms has been shown to be strongly affected by the presence of deleterious mutations [3–6] and of other competing beneficial mutations segregating in the population [7–9]. This last type of interference was named clonal interference and has been shown theoretically and experimentally to limit the rate of adaptation of asexual populations [2,9–11]. The increase of the rate of fixation of beneficial mutations slows down as the mutational input on the population becomes very large. It has also been shown that clonal interference affects the distribution of mutations that get fixed: the bigger the mutational input, the more competition there is, so higher effect mutations get fixed [12]. Furthermore, the importance of this interference depends on the deleterious mutation rate [4,12].

The dynamics of adaptation has also been studied in some models of structured populations where competition is local as opposed to the unstructured model which assumes that every individual competes with all others. Indeed in natural populations competition is probably more commonly local. The dynamics of adaptation in such a population has been well established [13–18]. In particular, Maryuama, demonstrated that for some types of structure (such as the island model and other models that assume conservative migration) the same predictions hold as in the unstructured population. But this is not valid when extinction and recolonization are allowed [19–21]. More recently, Gordo and Campos [22] have shown that when more than one locus is considered, clonal interference causes the structure to have a cost on adaptation, i.e., the probability that a beneficial mutation is fixed decreases if there is structure and this decrease is bigger the higher the mutational input.

A great number of bacteria species live as populations structured in space. In particular, many species can form complex structures called biofilms, in which individuals may stay imprisoned in the biofilm matrix or have some degree of freedom to move [23] (and for a review

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see [24]). This movement depends on the species and on environmental conditions. So we can consider two simple extremes: no movement of individuals in space and a large degree of mixing in the structured population. Bacteria adaptation in biofilms should lie at an intermediate between these extremes. Here we extend on the model used in [22], relaxing the assumption that the structure remains intact. Competition remains local but now the neighbors are randomized after a given number of generations. Since we assume bacteria biofilms to be an intermediate between an intact structure and one with mixing, we want to test how mixing affects the adaptation of a population. Furthermore, the results obtained here can be readily tested in experimental evolution with bacteria cultures growing on a static environment [25] or be completely randomized [26,27].

The model

We consider a population of asexual haploid organisms. The individuals are arranged in a two-dimensional regular lattice of linear size L with periodic boundary conditions and where each organism occupies a cell in the lattice. The population size is $N = L \times L$.

The evolution of the population follows a modified Wright-Fisher model to account for the chosen spatial structure. In each generation the individuals are all descendant from the previous one (non-overlapping generations) and competition is local. We consider the Moore neighborhood, where each individual competes with its eight nearest neighbors, so that an organism occupying cell i can only be the descendant of individuals that occupied neighboring cells in the previous generation. The probability that an individual occupying cell i at generation $t+1$ is the offspring of the individual occupying cell j at t generation is given by:

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

where π_j denotes the fitness value of individual j and the sum is taken over cell i and its eight neighbor sites. To model mutation events, we consider the infinite sites model. Each individual inherits all the mutations from its parent plus an additional number of deleterious mutations given by a Poisson with parameter U. Every deleterious mutation is assumed to decrease fitness by a constant factor $(1 - s_d)$. Beneficial mutations occur at a constant rate U_b per individual and they increase fitness by $(1+s_b)$. The s_b for each beneficial mutation is taken from an exponential distribution with parameter β [28–31].

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

Although a more realistic model would be to consider a distribution of effects for deleterious mutations, up to the present what has been determined for microorganisms is only the mean deleterious effect [32]. So, lacking experimental support for assuming a given distribution, we make the simplest assumption of a constant s_d. On the other hand, for beneficial mutations, there are both theoretical reasons [28,29,31] and experimental evidence [33] for assuming an exponential distribution. The fitness of each individual depends on the number of deleterious (k) and beneficial (k_b) mutations its genome has, such that its fitness is given by:

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

At time $t = 1$ all individuals are free of mutations. Then there is an additional equilibration period (of 100 generations) with no beneficial mutations being introduced. After this period 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 longer period of equilibration.

We assume that the individuals are mixed randomly in the population periodically. Every T generations we randomly place the individuals in the lattice such that in the next generation they will have new competitors. By doing this we try to mimic the evolution experiment that can easily be done with bacteria in the laboratory, allowing in this way to directly test our results. When $T \to \infty$ then the structure of the population is intact and our results will be the same as those previously studied [22]. This way T will modulate the randomness of the competition.

Results

1. Probability of fixation of a beneficial mutation

The rate of adaptation (K_b) is defined as the rate at which beneficial mutations fix in a population. This is affected by both the rate of appearance of new beneficial mutations (U_b) as well as their probability of fixation (P_{fix}). To understand how mixing of a spatially structured population affects its adaptation, we first ask whether the probability of fixation of a given beneficial mutation is affected by the periodicity of this mixing. In order to do this, we introduce a beneficial mutation with a given selective value s_b at time $T = 0$. After T generations, the population is randomized so that each individual now competes with a different (and random) set of neighbors in the population. We let the simulation run until the beneficial mutation is either fixed or lost. Several simulations allow us to estimate the frequency of fixations. It was previously shown [22] that the probability of fixation of a beneficial mutation in this type of intact structure is the same as in an unstructured population for this simple one locus model.

Intuitively one could expect that, the more frequent mixing is, the more global competition will be and so the result would approach the unstructured model. However, this is not the case. Figure 1 shows how mixing of the environment affects the probability of fixation of a beneficial mutation.

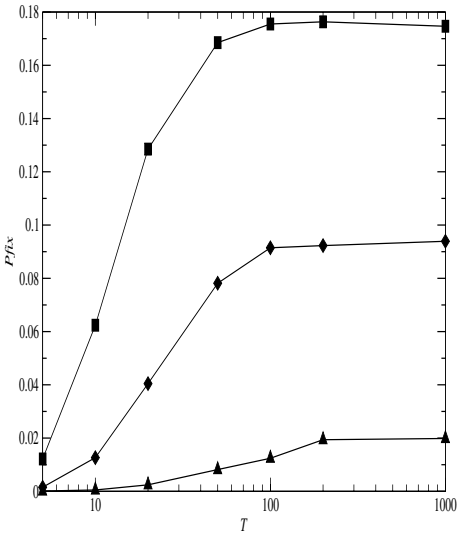

Fig. 1. Probability of fixation (P_{fix}) of a beneficial mutation as a function of the periodicity of mixing T. The squares correspond to $s_b = 0.1$, diamonds to $s_b = 0.05$ and triangles to $s_b = 0.01$. In all simulations the population size is 2500 individuals.

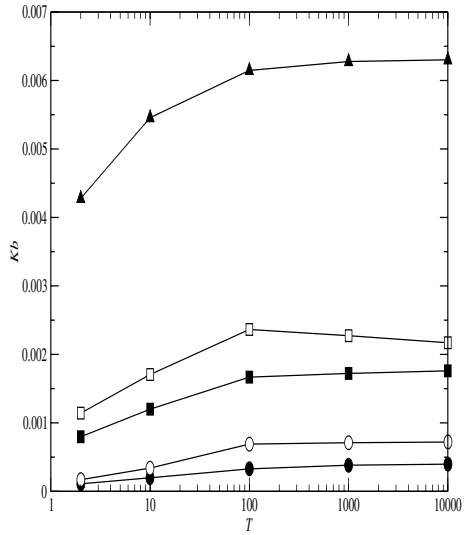

Fig. 2. The rate of fixation of adaptive mutations (K_b) as a function of the periodicity of mixing (T). The data are averages over 100 independent simulations. The lattice size is $L = 50$ (full symbols) and $L = 100$ (open symbols). We have considered $\beta = 100$ in all cases, triangles correspond to $U_b = 0.001$, squares to $U_b = 0.0001$, and circles $U_b = 0.00001$. No deleterious mutations were introduced.

As expected [22], we see in Figure 1 that when $T \to \infty$ the probability of fixation is approximately twice the selective value of the mutation. However, when mixing is frequent (for example when $T = 10$ generations), the probability of fixation of a beneficial mutation becomes much smaller. Furthermore, the value of T above which we recover the result for an unstructured population depends on s_b. From Figure 1, when $s_b = 0.1$, values of T bigger than 50 lead to a P_{fix} of approximately $2s_b$ but for $s_b = 0.01$ this occurs for $T > 200$. This suggests that the frequency at which a mutation is, at the time of mixing, will influence its probability of fixation (see also [22]).

The probability that a beneficial mutation is lost due to drift depends on its frequency [34,35]. In our model, when mixing occurs early after the appearance of the mutation, the mutant individuals will be scattered throughout the lattice. So locally, their frequency will become low and their probability of loss increases. This accounts for the fact that a low T decreases greatly the probability of fixation. If enough generations pass before a shuffling occurs, the mutation will have the chance to grow in frequency (provided it escaped the initial stochastic loss) before it is scattered. This will increase the chance that individuals with beneficial mutations are grouped together and thus increases the probability of their fixation. The number of generations needed to reach this critical frequency will depend on the selective value of the mutation.

2. Adaptation and mixing

It is known from studies in both unstructured populations [9] and for intact structures [22] that when multiple loci are considered, the rate of increase of the adaptation rate (K_b) with the mutation rate to beneficial mutations (U_b) diminishes as larger mutation rates are considered. This is due to the fact that if many beneficial mutations are segregating in the population, they compete with each other and their probability of fixation diminishes. This effect has an impact not only on K_b but also on the mean effect of mutations that eventually reach fixation (s_{bfix}), which increases with U_b [9,22].

We have studied how K_b and s_{bfix} depend on the frequency of mixing for different mutation rates (U_b). Figures 2 and 3 summarize the results.

As expected from the results in Figure 1, the adaptation rate increases with T. When mixing is frequent, most mutations are lost and those that get fixed have a high selective coefficient (Fig. 3). Again this suggests that the frequency that mutations reach at the time of mixing is critical to their fate. As a consequence, for large values of T, there are more fixations and the mean selective value of the mutations that become fixed is lower. In a sense, it becomes easier to fix a mutation if there is no mixing, even if it has a low effect. Furthermore, above a certain value of T, K_b and s_{bfix} become constant. This critical value depends on the mean selective value of the newly arising mutations which suggests that when the mutations reach a certain frequency, mixing becomes irrelevant.

In microorganisms, the population sizes are much higher than the ones we have considered. However, our qualitative results are independent on the population size. For example, in Figure 2 we see the same kind of dependence of K_b on T, for a much larger N. However, for the same value of T, K_b and s_{bfix} are bigger in a larger population because the mutational input (NU_b) is higher. Nevertheless, mixing has the same qualitative effect on the adaptation dynamics.

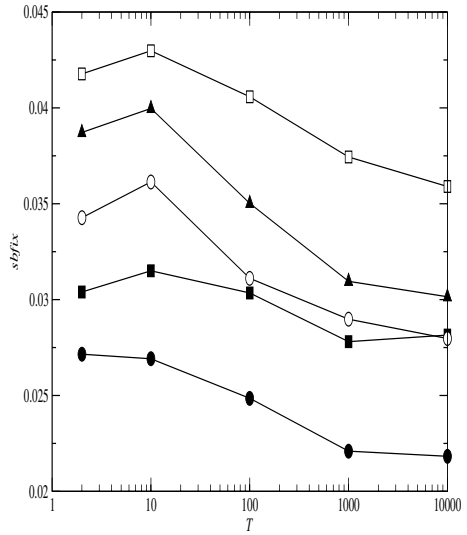

Fig. 3. Mean selective value of the fixed mutations as a function of the periodicity of mixing (T). The data are averages over 100 independent simulations. The lattice size is $L = 50$ (full symbols) and $L = 100$ (open symbols). The other parameters are $\beta = 100$, $U_b = 0.001$ (triangles), $U_b = 0.0001$ (squares), and $U_b = 0.00001$ (circles). No deleterious mutations were introduced.

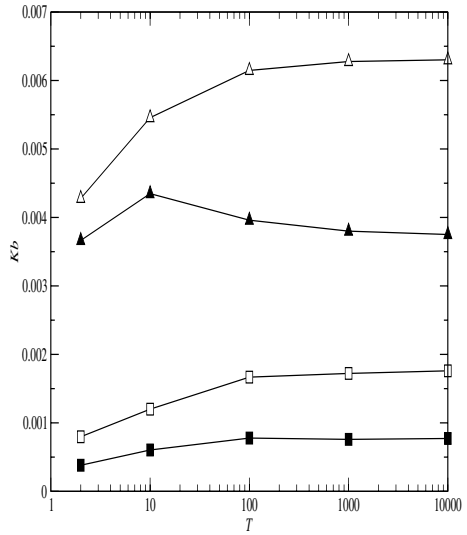

Fig. 4. Mean selective value of the fixed mutations as a function of T. The data are averages over 100 independent simulations. The parameter values are $L = 50$, $\beta = 100$, and the beneficial mutation rate is $U_b = 0.0001$ (squares) and $U_b = 0.001$ (triangles). Open symbols correspond to $U = 0$ and full symbols correspond to $U = 0.1$ and $s_d = 0.1$.

Given the effect of mixing on the probability of fixation of a beneficial mutation with a given s_b (Fig. 1), we expect the same qualitative results if a different distribution of selection coefficients is considered.

3. Adaptation in the presence of deleterious mutations

Since most newly arising mutations are deleterious, we next examined how they affect the dynamics of adaptation in our model. As previously shown for the intact structure [22], if the deleterious mutation rate (U) is low, which implies that the mean number of deleterious mutations is small, they have very little effect on K_b and on s_{bfix}. If, however, their rate of appearance is high, they decrease the adaptation rate in intact structure populations [22].

In Figures 4 and 5 we show how deleterious mutations affect both K_b and s_{bfix} as we introduce mixing in our structure. We have studied two different values of U_b: a low value and a high value where clonal interference is most pronounced.

From Figure 4 we observe that K_b becomes less dependent on T, when deleterious mutations are present. The overall reduction in K_b reflects the reduction in the proportion of mutation-free genotypes when $U \neq 0$. This can be interpreted as a lowering of the effective population size, so fewer adaptive mutations are fixed [3]. The reduction is higher for intact structures and high values of U_b.

Figure 5 also shows that if mixing is frequent, the mean selective value of fixed beneficial mutations is almost unchanged by the presence of deleterious mutations. This is expected as long as the effect of deleterious mutations is solely to cause a decrease in the effective population size. However, as mixing becomes less frequent, the mean effect of mutations that get fixed is reduced (Fig. 5). It is in this regime that clonal interference plays a more important role because more mutations are segregating in the population. Deleterious mutations can reduce clonal interference [5,12] and that can account for the reduction of the mean fitness effect of fixed beneficial mutations as T increases.

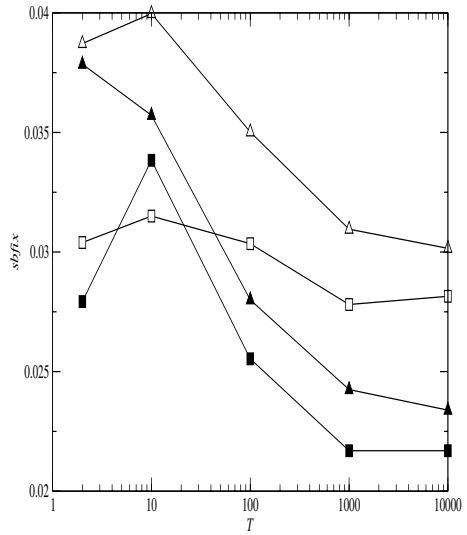

Fig. 5. The rate of fixation of adaptive mutations as a function of T. The data are averages over 100 independent simulations. The parameters are $L = 50$, $\beta = 100$ and $U_b = 0.0001$ (squares) and $U_b = 0.001$ (triangles). Open symbols correspond to $U = 0$ and full symbols correspond to $U = 0.1$ and $s_d = 0.1$.

Discussion

We have studied a population with a simple spatial structure where the individuals are arranged in a regular lattice and competition is local. Gordo and Campos [22] demonstrated that in such a structure, the adaptation rate is lower than without structure due to an increase of the clonal interference phenomenon. Since in natural populations a completely intact structure is probably not realistic, we have studied the impact of mixing on the process of adaptation. In the model, we periodically randomize the neighbors so that each individual can now compete with a different set of competitors than his ancestors did. It is certain that during the long evolutionary process of microorganisms, they will find different competitors as they move from host to host.

Unlike what one could expect, this did not approximate the results for an unstructured population where each individual competes with all others in the population. In fact, the more we randomize individuals, the lower the adaptation rate is. This result is explained by an increment of the effect of genetic drift. The difference is that in both unstructured and intact structured populations, drift is less important as the frequency of the mutant with the beneficial mutation increases; by scattering a beneficial mutation, our model returns it to a state of low frequency locally where it may be lost due to drift.

In the natural world most bacteria aggregate as biofilms. In fact biofilms are now one of the hottest topics in microbiology, as they are a common cause of persistent bacterial infections [24] (and for a review see [23]). In these biofilms there is spatial structure and some movement of individuals. So, their adaptation dynamics does not correspond either to the unstructured model, or to an intact structure. It corresponds to a structure where individuals compete locally but may also move to other places in the biofilm or even colonize a different space altogether (which may or may not already have other bacteria). As such, the adaptation dynamics of biofilms should be an intermediate between our regime of frequent mixing and that of no mixing. This implies that their adaptation is slower than in an intact structure but quicker than in one with complete mixing as is illustrated by Figure 6.

In laboratory conditions, bacteria can grow on fixed media, thus competing only locally. Furthermore these cultures may be propagated by maintaining the structural integrity or by randomizing them periodically. Some experiments have been done using this kind of experimental procedure [25,26]. However, these authors were studying very particular aspects of adaptation. Namely, in one case [25] the population was structured in space but it also varied such that there were three distinct environmental conditions to which bacteria could adapt. The authors focused on an analysis of the interactions between organisms adapted to different niches. It would be interesting to investigate adaptation within each niche and compare it to our results. In the second case [26], no comparisons with the intact structure were made. However, the same experimental setup may be used to test our results experimentally.

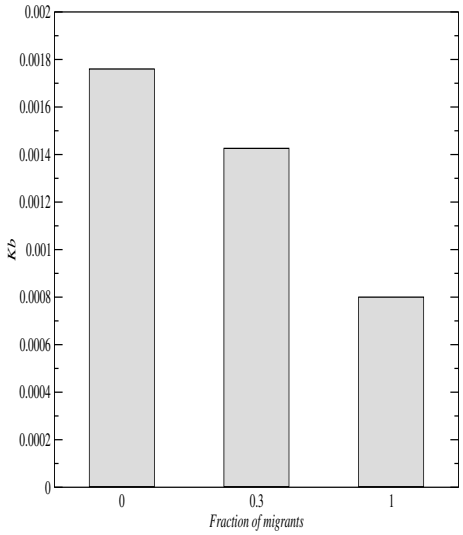

Fig. 6. Adaptation rate as a function of the fraction of organisms that are mixed. Simulations were done as described previously except in the middle column where only a random 30% of individuals were taken from their positions and randomly redistributed in the lattice every T generations. The Parameters are $L = 50$, $\beta = 100$ and $U_b = 0.001$ for all simulations, and $T = 2$ for the simulations with mixing. Data correspond to the mean values of 100 independent simulations.

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