

LETTER

Mutation accumulation in space and the maintenance of sexual reproduction

Marcel Salathé,¹Rahel Salathé,²Paul Schmid-Hempel² and Sebastian Bonhoeffer¹

¹Theoretical Biology, Institute of Integrative Biology, ETH Zürich, ETH-Zentrum CHN, 8092 Zürich, Switzerland

²Experimental Ecology, Institute of Integrative Biology, ETH Zürich, ETH-Zentrum CHN, 8092 Zürich, Switzerland

Correspondence: E-mail: marcel.salathe@env.ethz.ch

Abstract

The maintenance of sexual reproduction remains one of the major puzzles of evolutionary biology, since, all else being equal, an asexual mutant should have a twofold fitness advantage over the sexual wildtype. Most theories suggest that sex helps either to purge deleterious mutations, or to adapt to changing environments. Both mechanisms have their limitations if they act in isolation because they require either high genomic mutation rates or very virulent pathogens, and it is therefore often thought that they must act together to maintain sex. Typically, however, these theories have in common that they are not based on spatial processes. Here, we show that local dispersal and local competition can explain the maintenance of sexual reproduction as a means of purging deleterious mutations. Using a spatially explicit individual-based model, we find that even with reasonably low genomic mutation rates and large total population sizes, asexual clones cannot invade a sexual population. Our results demonstrate how spatial processes affect mutation accumulation such that it can fully erode the twofold benefit of asexuality faster than an asexual clone can take over a sexual population. Thus, the cost of sex is generally overestimated in models that ignore the effects of space on mutation accumulation.

Keywords

Cost of sex, limited dispersal, Muller's ratchet, mutation accumulation, spatial structure.

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The twofold cost of sex necessitates an adaptive explanation for the maintenance of sexual reproduction (Maynard Smith 1978; Bell 1982; Barton & Charlesworth 1998). Many theories have been proposed that provide such an explanation (Kondrashov 1993; Barton 1995; West *et al.* 1999), but they all require that very restrictive conditions be met in order to compensate fully for the twofold cost. The most widely accepted ecological explanation for the maintenance of sex, the Red Queen hypothesis (Jaenike 1978; Hamilton *et al.* 1990), requires very severe effects of the pathogen on host fitness (May & Anderson 1983; Howard & Lively 1994, 1998). Genetic explanations based on purging deleterious mutations, such as the mutational deterministic hypothesis (Kondrashov 1988, 1993) or the escape from Muller's ratchet (Muller 1964) require genomic mutation rates higher than commonly observed (Howard 1994; Keightley & Eyre-Walker 2000). Moreover, the mutational deterministic hypothesis requires negative epistasis, yet on balance the evidence is inconsistent with support for positive, negative or no epistasis (Elena & Lenski 1997; Rice 2002; Bonhoeffer *et al.* 2004). The lack of

a theory that can account for the twofold cost of sex in isolation has led to the proposition that the maintenance of sex can only be explained by a combination of factors (West *et al.* 1999).

We propose that local dispersal and local competition provide an explanation why an asexual clone may fail to invade and replace a sexual population, and we show that the maintenance of sex in a spatial model requires neither epistatic fitness interactions nor high mutation rates. Consider a single sexual population of size N in the absence of fitness-affecting mutations, where one individual mutates and becomes asexual. If the asexual mutant does not disappear due to random effects, it will expand in the population and replace the sexuals because it enjoys the twofold fitness benefit of asexuality (Maynard Smith 1978). The speed at which the replacement occurs is strongly depending on spatial processes. In a non-spatial model of competition between asexuals and sexuals, the asexual subpopulation grows at a constant rate per capita. Initially, the proportion of asexuals doubles in each generation, but the rate of increase of frequency declines towards the end of

the asexual takeover (Maynard Smith 1978). Thus, assuming an average constant per capita growth-rate a , the proportion of asexuals in the total population, p_{asex} , increases approximately exponentially with time, and the time to fixation of asexuality, t_{fix} , scales with $\log N$ (since $a^{t_{\text{fix}}} = N$). However, in a spatial model where dispersal and competition are local, most competition occurs between individuals of the same type (West *et al.* 2002) (i.e. sexuals compete against sexuals, and asexuals compete against asexuals). Competition between asexuals and sexuals occurs only at the edge of the expanding asexual subpopulation. Therefore, the asexual clones can only benefit locally from their competitive advantage, and hence, the radius r of an expanding cluster of asexuals increases linearly in time. As the number of individuals in the cluster scales with its area (i.e. $N \sim 2\pi r^2$), t_{fix} scales with \sqrt{N} . We verified these results with a spatially explicit individual-based model (see Appendix) (Fig. 1a–c).

In a finite asexual population, the genotype with the fewest mutations may continually be lost due to stochastic effects (Haigh 1978; Gessler 1995), leading to an ongoing

loss of fitness over time (Muller's ratchet). A fitness loss of 50% relative to sexuals fully erodes the twofold advantage of asexuality, and we denote the time for this to occur by t_{mut} . If the time for fixation of an asexual clone is so long that mutation accumulation reduces fitness by 50% before fixation, an expansion of asexuality can be stopped, and sexual reproduction can be maintained. Hence, the evolutionary maintenance of sex requires that the inequality $t_{\text{fix}} > t_{\text{mut}}$ is satisfied. In asexuals, mutation accumulation is irreversible (barring rare back mutations), and the rate at which it occurs depends strongly on the population size (Gessler 1995; Gordo & Charlesworth 2000). Mutation accumulation will therefore be accelerated when competition is local, because local populations can be small.

While in a non-spatial model, an asexual mutant will typically replace a sexual population so quickly that mutation accumulation cannot create enough mutational load to prevent the asexual expansion in time, the situation may be more favourable to sexual reproduction in a spatial model with local dispersal and local competition. To calculate the minimal population size for the maintenance of sex in a simple spatial model, we will now make the following approximations: deleterious mutations occur with rate U per genome and generation, and the selection coefficient against such a mutation is denoted by s . Assuming multiplicative fitness, the number of generations needed for mutation accumulation to reduce fitness by 50% is

$$t_{\text{mut}} = \frac{\log 0.5}{U \log(1-s)}. \quad (1)$$

This approximation assumes that Ut mutations accumulate in asexuals in t generations (i.e. that mutations accumulate at the neutral rate). This assumption is justified for two reasons. First, individuals that are in close proximity are likely to have a recent common ancestor, and thus have a similar number of mutations. Hence, local selection differentials are very small, and selection will be negligibly weak. Second, local populations are small and therefore drift effects may override selection. Furthermore, we assume that an asexual mutant clone is recently derived from the sexual lineage which is at mutation-selection equilibrium, and hence an absolute fitness decrease of 50% within the asexual population also corresponds to a 50% fitness decrease relative to the sexual population. As the time for complete fixation of an asexual mutant in a spatial model is approximately \sqrt{N} , the condition for the maintenance of sexual reproduction is

$$N > \left(\frac{\log 0.5}{U \log(1-s)} \right)^2. \quad (2)$$

Figure 2 shows that the minimal population size above which sex is maintained can be small, even for small values

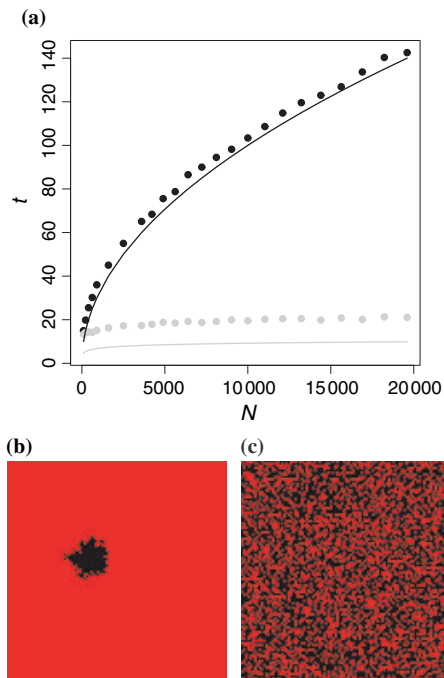


Figure 1 (a) Time in number of generations to full fixation of an asexual clone with the full twofold fitness advantage in a spatial model without mutations, with local (black) and global (grey) dispersal. The circles are average values of 10 simulation runs for a given population size N . The black line shows $t = \sqrt{N}$, the grey line shows $t = \log N$. (b) and (c), the spread of an asexual clone (black) in a world of sexuals (red) after $t = 15$ generations in a stochastic individual-based model with local (b) and global (c) dispersal (see main text and Appendix).

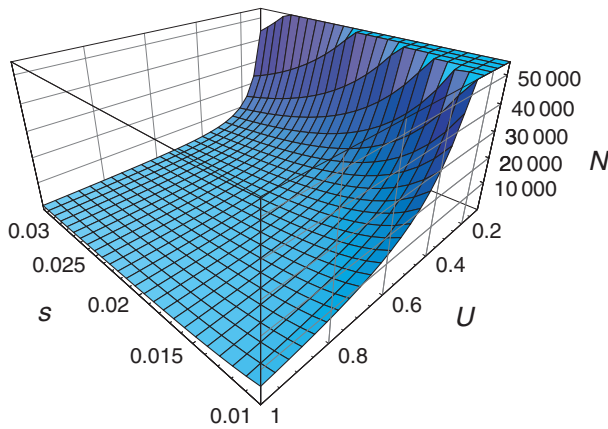


Figure 2 Influence of genomic mutation rate U and the selection coefficient against a deleterious mutation s on the minimal population size N . If a population size is larger than the minimal population size, sex can be maintained.

of U and s . We verified these approximations by using the spatially explicit individual-based model described in the Appendix. Simulations of various combinations of s , U and N , both with local and global dispersal, show that sex can win in the latter case only with high mutation rates ($U \sim 1$) and severe fitness effects of mutations ($s \sim 0.03$). In the local dispersal

model, however, sex can be maintained despite its twofold cost even with low mutation rates and moderate fitness effects when the entire population size is large enough. The results of the stochastic simulations are in excellent agreement with the approximate predictions of eqn 2 (Fig. 3).

Figure 4a shows that the spread of asexuality is halted around the time when the mutational load has eroded the full twofold fitness advantage of asexuals. An important requirement for the long-term maintenance of sex is that asexual clones are eliminated at least as fast as they are generated by mutation. We tested this by allowing for mutations that change an individual's reproduction mode, occurring with probability $P = 10^{-6}$ at birth. A mutant switching from sexuality to asexuality immediately gains the full twofold fitness advantage without suffering from the mutational load accumulated over time. This mutant may quickly increase in frequency, and such 'resettings' of average fitness differences generates oscillations in reproduction modes similar to those observed in host-parasite coevolution systems (Howard & Lively 1994) (Fig. 4b).

In many species, dispersal is neither fully global nor completely local, but intermediate. In our model, larger dispersal distances require larger population sizes in order to maintain sex. The reason for this is that any increase in dispersal distance reduces the time to fixation of an asexual

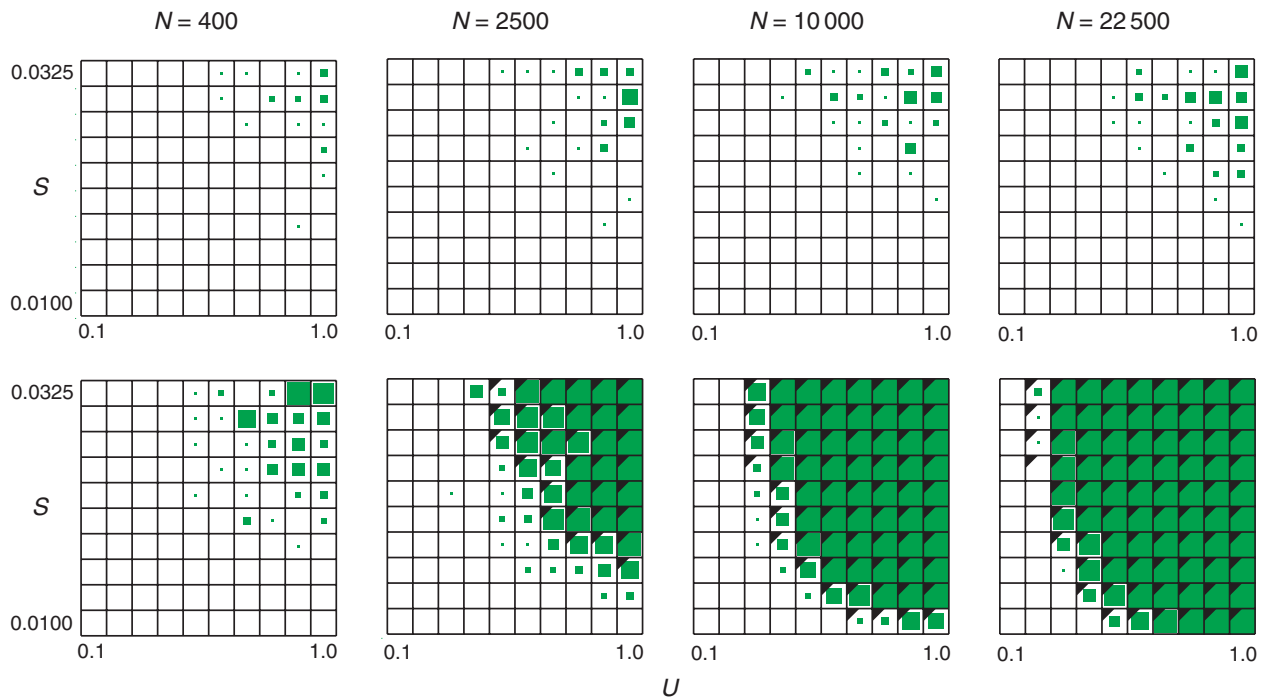


Figure 3 Results of individual-based computer simulations. The upper row shows results with global dispersal, approximating the non-spatial case, the lower row shows results with local dispersal. For each combination of s and U , 10 simulations were run, and the green area shows the proportion of the runs where sex was maintained. In the lower row, rectangles with a black triangle represent a parameter setting where sex should be maintained according to eqn 2 (see main text). All runs are with $P = 0$.

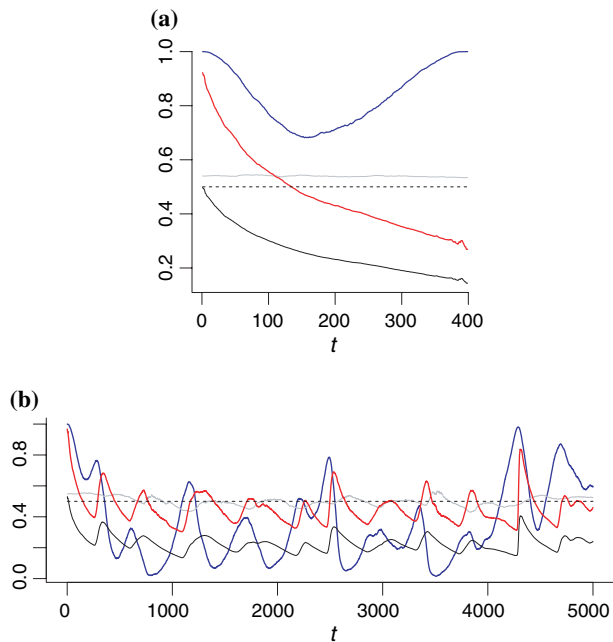


Figure 4 Dynamics of reproduction mode frequencies and average fitness values. The blue line shows the proportion of sexuals, the gray line shows the average fitness \bar{w}_{sex} of the sexual subpopulation, the black line shows the average fitness \bar{w}_{asex} of the asexual subpopulation, and the red line shows $\bar{w}_{\text{asex}}/\bar{w}_{\text{sex}}$. The asexual invasion is halted around the time when the red line crosses the dashed line showing $\bar{w}_{\text{asex}}/\bar{w}_{\text{sex}} = 0.5$. (a) $P = 0$, (b) $P = 10^{-6}$. The following parameters were used for both figures: $N = 22\,500$, $d = 1$, $U = 0.4$, $s = 0.02$. The simulation run used for (b) was stopped after 5000 generations. Note that the fitness decrease in sexuals is mainly due to inbreeding.

mutant, t_{fix} , by maximally the same factor as the dispersal distance increases. Just as an increase in dispersal distance favours parthenogenesis (because it reduces t_{fix}), an increase in the population size favours sex (because it increases t_{fix}). To illustrate this, we simulated the case of $N = 22\,500$ (i.e. grid length and width of 150) and $d = 3$. As can be seen in Fig. 5, the results look similar to those obtained for $N = 2500$ (i.e. grid length and width of 50) and $d = 1$. According to the reasoning above, this result matches the expectation: an increase in dispersal distance by a factor 3 reduces t_{fix} by a factor 3, and since t_{fix} scales with \sqrt{N} , the population size must be increased by a factor 3^2 in order to obtain equivalent results.

Compared with non-spatial models, a spatially explicit model allows for both dispersal and competition to be local processes, resulting in three important effects that help to maintain sexual reproduction. Firstly, local dispersal slows down the spread of an advantageous mutant, which leaves more time for mutation accumulation. This effect was first observed in a metapopulation model (Peck *et al.* 1999).

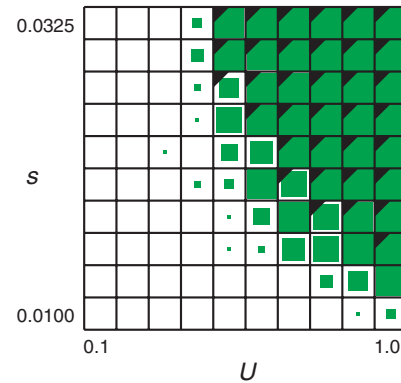


Figure 5 The effect of intermediate dispersal on the maintenance of sex. The representation of this figure is the same as in Fig. 3, with $N = 22\,500$ and $d = 3$. The black triangles indicate where sex should be maintained according to eqn 2, with $N = 2500$ and $d = 1$ (completely local dispersal, as assumed in the equation).

Secondly, local competition reduces the strength of selection and increases drift effects, since local populations can be small, and consequently, mutations can accumulate faster (Gessler 1995; Gordo & Charlesworth 2000). Finally, since dispersal is limited, populations have a low genetic diversity on a local scale. As a consequence, selection differentials are small, and mutation accumulation is therefore accelerated. Since all three effects lead to increased mutation accumulation, they increase the selective advantage of sexual reproduction. At the same time, however, the lower genetic diversity in the sexual population due to limited dispersal results in an effect that reduces the selective benefit of sexual reproduction because it creates inbreeding depression (in the sense that it is more difficult for sex to purge deleterious mutations if matings occur between genetically very similar genotypes).

We have shown here that, taken together, the effects of local processes can explain the maintenance of sex with reasonable mutation parameters. It should be noted that in all simulations with limited dispersal, there is even a higher than twofold cost of sex, since mating is local, and individuals do not get to mate when there is no other sexual individual nearby. The predictions of the model presented here are also in agreement with the well-known pattern of increased parthenogenesis in marginal habitats [known as geographic parthenogenesis (Bell 1982)], since marginal habitats and their populations tend to be small. Although marginal habitats are often fragmented and patchy, and dispersal distances are therefore reduced, small habitats favour parthenogenesis, independent of whether dispersal is global or very restricted (Fig. 3).

Generally, any process that would affect either t_{fix} or t_{mut} is expected to have an effect on the conditions required for the maintenance of sex. For example, large local population

sizes would slow down the fitness decrease by mutation accumulation in asexuals as the speed of Muller's ratchet depends on population size (Haigh 1978; Gessler 1995; Gordo & Charlesworth 2000), while spatial heterogeneity would increase the time for fixation of a locally dispersing asexual clone. Ecological factors, such as niche diversity (Bell 1982; Doncaster *et al.* 2000), parasites (Jaenike 1978; Hamilton *et al.* 1990; Howard & Lively 1994, 1998; Keeling & Rand 1995) and sexual selection (Agrawal 2001; Siller 2001) can further decrease the fitness penalty of sexual reproduction, and although local processes may theoretically explain the maintenance of sexual reproduction alone, multiple factors may still affect the evolutionary fate of sex simultaneously (West *et al.* 1999). Of note in this context, however, is the recent finding that spatial structure and dispersal might serve as a cheap alternative to sex in the fight against pathogens (Sasaki *et al.* 2002). Whether sex is more important in purging deleterious mutations or in fighting pathogens may eventually depend on spatial processes, but more research is necessary in order to transform such speculation into a testable hypothesis.

The fundamental change caused by the explicit treatment of space is that if competition occurs only at a local scale, any fitness advantage of sexuality vs. asexuality is irrelevant if the local area does not contain both types of reproduction modes, a reasoning that is true for any trait causing a change in fitness (West *et al.* 2002). Since ecosystems are always spatial, local processes are appealing as an explanation for the widespread abundance of sexual reproduction.

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APPENDIX. DETAILED DESCRIPTION OF THE INDIVIDUAL-BASED COMPUTER MODEL (JAVA CODE AVAILABLE FROM CORRESPONDING AUTHOR ON REQUEST)

The model incorporates space explicitly as a two-dimensional grid of length and width \sqrt{N} width N cells where maximally

one individual can inhabit each cell. The grid has no boundaries, i.e. individuals that cross the border on any side re-enter the grid on the opposite side. Individuals are haploid and possess 512 mutation loci where mutations can accumulate over time. Each mutation locus can have two possible alleles (0 and 1) where 1 denotes a deleterious mutation with fitness effect s . Additionally, one locus determines the reproduction mode (sexual or asexual). Initially, all cells are filled with a sexual individual without any mutations in the mutation loci. We then let the completely sexual population converge towards a mutation-selection equilibrium for 500 generations (although the equilibrium is usually reached much earlier). At this point, a single asexual individual is introduced into the population by choosing a random sexual individual and switching its reproduction mode to asexual.

Individuals reproduce asexually or sexually, depending on their allele at the reproduction mode locus. A sexual individual (the 'chooser') at location $[x,y]$ has to find a sexual mating partner (the 'chosen') in its local neighbourhood, which is any adjacent cell on the quadratic sub-grid spanned by the corners $[x \pm 1, y \pm 1]$. If no sexual host is available in the neighbourhood, no reproduction can occur. Otherwise, if multiple sexual hosts are available, one is picked at random. Mutational loci recombine in the following way: for each locus, one of the parent allele is chosen at random to create the genome of the offspring host, simulating a genome with all loci being completely unlinked.

Sexual individuals reproduce with a probability of 0.5 [which reflects the twofold cost of sex (Maynard Smith 1978)]. Each pair of reproducing individuals produces 10 offspring. An offspring individual survives with probability $(1-s)^n$, where n denotes the number of mutations in the mutation loci, simulating a multiplicative fitness function (i.e. no epistasis). The mutation loci of each offspring accumulate on average U new mutations per generation (the number of mutations per individual genome is drawn from a binomial distribution, and the loci where the mutations occur are then chosen randomly). Additionally, an offspring

individual changes its mode of reproduction with a probability P .

After reproduction, offspring individuals disperse on the grid according to the dispersal parameter d . An offspring individual will be placed on a random cell in the neighbourhood, i.e. the sub-grid that is spanned by the cells $[x \pm d, y \pm d]$ (for sexual individuals, x and y are taken from the choosing individual). To simulate local dispersal, we used $d = 1$, and to simulate global dispersal, we used $d = \sqrt{N/2} - 1$. The parent generation dies after reproduction (except in the rare case when a cell receives no offspring individual). In cells that contain more than one offspring individual, a random individual is chosen as the survivor of this cell, maintaining a maximal population size of N .

A simulation is run until a reproduction mode, sexual or asexual, has fixed in the population. If the population is fully sexual before 10 timesteps after the introduction of the asexual mutant (due to the random loss of the asexuals), the simulation is restarted and not included in the final census.

We have tested various modifications of the spatial dispersal process, such as giving each individual precise floating-number coordinates and letting offspring disperse unboundedly, e.g. using an exponential distribution of individual dispersal distances with an upper confidence interval of 95% of d . We have also tested how a distribution of selective coefficients with mean s (using a gamma distribution with an approximate range of 10^{-4} to 10^{-1} , where most mutations are only mildly deleterious), would influence the results. Furthermore, we have tested the robustness of the model to back mutations. All modifications have a minor quantitative effects, and the results are not affected qualitatively.

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