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THE MAINTENANCE OF OBLIGATE SEX IN FINITE, STRUCTURED POPULATIONS SUBJECT TO RECURRENT BENEFICIAL AND DELETERIOUS MUTATION

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Although there is no known general explanation as to why sexual populations resist asexual invasion, previous work has shown that sexuals can outcompete asexuals in structured populations. However, it is currently unknown whether costly sex can be maintained with the weak structure that is commonly observed in nature. We investigate the conditions under which obligate sexuals resist asexual invasion in structured populations subject to recurrent mutation. We determine the level of population structure needed to disfavor asexuals, as calculated using the average F_{st} between all pairs of demes. We show that the critical F_{st} needed to maintain sex decreases as the population size increases, and approaches modest levels as observed in many natural populations. Sex is maintained with lower F_{st} if there are both advantageous and deleterious mutation, if mutation rates are sufficiently high, and if deleterious mutants have intermediate selective strengths, which maximizes the effect of Muller's ratchet. Additionally, the critical F_{st} needed to maintain sex is lower when there are a large number of subpopulations. Lower F_{st} values are needed to maintain sex when demes vary substantially in their pairwise distances (e.g., when arrayed along one dimension), although this effect is often modest, especially if some long-distance dispersal is present.

KEY WORDS: **Evolution of sex, Hill–Robertson effects, Muller's ratchet, multilocus simulations, population structure.**

Explaining the evolution and ubiquity of sex has been one of the most difficult problems in evolutionary biology. Sexuals suffer a variety of costs, including a twofold cost as a consequence of investing in male function, which can result in reduced fecundity in a sexual population (Maynard Smith 1978). Asexual females, on the other hand, invest only in daughters, so should quickly outcompete sexuals, all else being equal. Even in anisogamous populations, the time involved in switching from mitotic to meiotic division, as well as the risk of transmitting parasitic elements during syngamy, are potentially extremely costly (Lehtonen et al. 2012). Although the twofold cost can be partially compensated by paternal resource contributions (Agrawal 2001; Siller 2001), a convincing theory for the evolution of sex must demonstrate that costs of this magnitude can be overcome.

Of the many theories that have been proposed to explain the maintenance of costly sex, three have received the most attention on the grounds of their generality and potential explanatory power. First, costly sex can be maintained if the genomic

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rate of deleterious mutation (U) is high enough, and there exists synergistic epistasis between deleterious mutations (Kondrashov 1982). However, such epistatic interactions do not appear to be widespread in nature (Kouyos et al. 2007). Second, sex could have evolved as a defense against parasites (the "Red Queen" hypothesis), because sex creates new genotypes that can resist infection (Hamilton et al. 1990). It has been shown, however, that strong selection is necessary to maintain costly sex in models where rates of infection do not depend on population density (May and Anderson 1983; Otto and Nuismer 2004), so that parasites rapidly adapt to infect those with novel genotypes (Barton 1995). However, selection need not be strong in both hosts and parasites, and sex can be favored if selection against noninfecting parasites is strong (Salathé et al. 2008). Furthermore, if asexual populations have greater density than the sexual population, and if infection risk rises with density, then sex can be maintained despite its costs (Lively 2009, 2010). There also exists substantial empirical evidence demonstrating that sex is favored in the presence of parasitic infection (Jokela et al. 2009; King et al. 2009; Morran et al. 2009, 2011). Third, sex and recombination break down negative genetic associations between linked loci generated by selection and drift in a finite population ('Hill–Robertson effects) (Hill and Robertson 1966). By reducing these associations, modifier genes that increase recombination can increase the effectiveness of selection and spread throughout a population (Iles et al. 2003; Keightley and Otto 2006; Hartfield et al. 2010). Experimental evidence also suggests that breaking down negative associations between linked loci can overcome significant costs of sex (Colegrave 2002; Poon and Chao 2004; Goddard et al. 2005; Morran et al. 2009).

Although Hill–Robertson effects have gained substantial acceptance as an important driver of the evolution of recombination (Otto 2009; Barton 2010), the maintenance of costly sex in the face of invasion by rapidly reproducing asexual mutants remains unsolved. Geographically structured populations are better able to resist asexual invasion (Peck et al. 1999; Martin et al. 2006; Salathé et al. 2006), because structure increases the fixation time of asexual lineages, allowing more time for accumulation of deleterious mutations via Muller's ratchet (Muller 1964; Felsenstein 1974). This could therefore be a plausible general explanation for the maintenance of sex, because all populations are geographically structured to some extent.

However, previous work has not related the level of population structure needed to maintain sex to what is observed in natural populations, which is generally measured using Wright's F_{st} statistic (Wright 1951). Therefore, it remains to be investigated whether costly sex can be maintained with realistic levels of population structure, and how the spatial arrangement of the population affects the level of F_{st} needed to maintain sex.

Here, we extend previous simulations that investigated the evolution of a recombination modifier gene (Hartfield et al. 2010) to determine whether models involving realistic levels of population structure can maintain sex. Specifically, we model the invasion of an asexual mutant into a subdivided, obligately sexual population and determine the critical level of population structure needed to maintain sex, as measured using the average pairwise F_{st} value obtained between each pair of demes at neutral loci. We compare various types of structure, and examine the additional effect that advantageous mutations have on the maintenance of sex. Using our simulation results, we determine how overall population size, the number of subpopulations, and the overall migration rate between specific demes interact with each other to affect the maintenance of sex.

Materials and Methods

BASIC SIMULATION SETUP

The simulation was based on previous work to investigate the evolution of a recombination modifier in an asexual population (Hartfield et al. 2010). We only outline the basic simulation methods in this study, detailing the changes made to study the maintenance of sex in structured populations. Initially there were N mutant-free haploid chromosomes, each having 100 equally spaced loci (unless otherwise stated). New generations were formed by selection, recombination (if present), and mutation to create N offspring.

As in Hartfield et al. (2010), mutations were entirely deleterious (as in Keightley and Otto (2006)), entirely advantageous (similar to Iles et al. (2003)), or a mixture of both types. In the latter case, the ratio of advantageous to deleterious mutations was equal to $x = k/s_a$ (for $k = 0.00023$ and s_a the selection strength acting on the advantageous allele, as used in Hartfield et al. (2010)). The function k/s_a reflects the view that strongly advantageous mutants are less likely to appear in nature than weakly selected ones (Andolfatto 2007; Jensen et al. 2008). Thus, the overall proportion of advantageous mutation present was $(x/(1 + x))$. The number of mutants introduced into an individual offspring was drawn from a Poisson distribution with a mean set to U if there were only deleterious mutations, Ux if there were only advantageous mutations, and $U(1 + x)$ if there was a mixture of deleterious and advantageous mutations. Each site was equally likely to acquire a new mutation, and the fitness effects of new mutations were multiplicative, with no epistasis.

In most simulations, we assumed $U = 1.0$, which is on the order of estimates for several multicellular eukaryotes (Denver et al. 2004; Haag-Liautard et al. 2007; Eöry et al. 2010). Except where stated, selection coefficients for deleterious mutations were set to $s_d = 0.01$, while selection coefficients for advantageous mutations

(when present) were $s_a = 0.01$, with multiplicative fitness interactions across loci. This value of s_a leads to advantageous mutations comprising a small fraction of all mutations (around 2.2% in most simulations). We also examined the sensitivity of the asexual fixation rate to changes in the mutation rate and strength of selection on deleterious and advantageous mutations. Note also that under the default parameters of $U = 1.0$ and 100 loci, the per-locus mutation rate μ is 0.01, which is of the same order as the selection coefficients. That is, μ is not much less than s_d and s_a, as assumed in most analytical models. However, this is because each locus is representative of a nonrecombining area of the genome, as opposed to a single gene, and multiple mutations are allowed to accumulate in each region.

INVASION OF ASEXUALS INTO A STRUCTURED SEXUAL POPULATION

The population was subdivided into D demes, with $N_D = N/D$ individuals per deme, and an overall migration rate m between adjacent demes. The number of demes was equal to 25, except when we explored the effect of deme number. Demes were either arranged in a one-dimensional (1D) circular array or over a two-dimensional (2D) torus, unless otherwise stated.

Populations first underwent a cycle of selection, recombination, and mutation according to standard Wright–Fisher dynamics (Fisher 1930; Wright 1931), followed by migration, with each deme contributing the same proportion of individuals to the entire population (i.e., the population is subject to soft selection (Wallace 1975)). Specifically, new offspring were formed by picking one parent with probability proportional to its fitness. If this parent was an asexual then it was cloned, otherwise a second sexual parent was selected, then outcrossing occurred with the number of crossovers chosen from a Poisson distribution with mean $L = 1$, unless stated otherwise. Therefore, there is no gene flow between the sexual and asexual populations. To incorporate a cost of sex, the fitness of sexuals was reduced by a factor C relative to asexuals ($w_{sex} = w_{asex}/C$), for example, due to the allocation of resources to male function. Unless otherwise stated, $C = 2$, which represents a twofold cost of sex. Mutants were then added as described above. This was repeated N_D times to create a new population within each deme. After reproduction was completed for all demes, migration occurred. The number of migrants was chosen from a Poisson distribution with mean mN_D. By default, each migrant moved to a randomly chosen neighboring deme, and each neighboring deme was equally likely to be a migrant destination. If long-distance migration occurred, then a fraction, p, of migrants was moved to a randomly chosen other deme. The lifecycle was repeated for $10N$ generations to create a burn-in population. A relatively long burn-in time was used to ensure that the population's steady-state F_{st} value was reached (Whitlock and McCauley 1999) (see Fig. S1 for evidence that such a steady-state was approached).

The state of the population was then saved, then an individual in a single deme was changed into an asexual. This asexual was tracked until it was fixed or lost from the population. This process of asexual introduction was repeated N times for each burn-in population to establish a fixation probability u, which is reported relative to the fixation probability of a neutral mutant, $u^* = 1/N$. This process was repeated for 40 burn-in populations. Larger populations were run with more burn-ins (50) and fewer reintroductions per burn-in ($0.4N$), to reduce the standard errors (SEs) reported for the asexual fixation probability.

MEASURING F_{st} IN SIMULATIONS

Wright (1951) introduced F_{st} as a measure of the degree of mixing in a structured population (Hartl and Clark 2007). For example, $F_{st} = 1$ indicates that demes are isolated and $F_{st} = 0$ indicates that they are fully mixed. Appendix S1 reviews F_{st} values found in studies of natural populations. In groups of animal and fish with little physical distance between them, F_{st} values tend to be quite small (usually less than 0.01). For physically more distantly related animal populations, as well as plant populations that have limited gene flow between them, F_{st} values tend to be larger. In these cases F_{st} frequently lies between 0.1 and 0.5. In a general survey of F_{st} estimates observed in nature, Morjan and Rieseberg (2004) found that F_{st} values were commonly less than 0.15 in both animals and plants (see also Fig. 16.10 in Barton et al. (2007)). We use F_{st} as it is a standard metric for population structure, and it is frequently estimated in surveys of natural populations. It can therefore be used to relate the results from theoretical studies to empirical studies. In addition, with weak selection, Whitlock (2002, 2003) demonstrated that F_{st} accurately predicts how population structure affects the fixation probability and fixation time of a beneficial allele. Although selection favoring asexuals is not initially weak, F_{st} may nevertheless provide a rough indication of the time frame over which an invading asexual spreads within a structured population, during which asexuals may decline in fitness and eventually become disadvantageous. We also investigated other metrics that might better predict the asexual invasion probability (e.g., estimating F_{st} among the most distant demes).

To measure F_{st} within simulations, new neutral alleles were repeatedly introduced via mutation; the number added was drawn from a Poisson distribution with mean $2/N$, so that on average two new mutations were added per generation. This arbitrary value enabled an adequate number of neutral alleles to be sampled to obtain an accurate estimate of F_{st}. Each new mutant was assigned to its own unique biallelic locus, with a map distance drawn from uniformly from the integers $[1, m]$ (so that this locus also lay within one of the m loci at which selected mutations accumulated).

Neutral mutants that had either become fixed or lost from the population were cleared every 10 generations.

Every $N/4$ generations for the first $8N$ generations of the burn-in, and every $N/20$ generations for the remaining $2N$ generations, the pairwise F_{st} between each possible pairs of demes in the population was measured, using the $\hat{\theta}$ estimator (Weir and Cockerham 1984). Specifically, for each neutral locus k and for each pair of demes (i, j), we measured the mean allele frequency within the two demes, $\overline{p}_k$, and also the sample variance s_k^2 of neutral allele frequency between the pair of demes, where

$$s_k^2 = (p_{k,i} - \overline{p}_k)^2 + (p_{k,j} - \overline{p}_k)^2. \quad (1)$$

$\hat{\theta}$ was then calculated by summing the relevant numerators and denominators over all neutral loci, then taking the quotient as shown in equation 2:

$$\hat{\theta} = \frac{\sum_k s_k^2}{\sum_k \left[\overline{p}_k(1-\overline{p}_k) + s_k^2/2\right]}. \quad (2)$$

Note the presence of the $s_k^2/2$ term in the denominator, which was needed to correct for the fact that $\hat{\theta}$ was obtained from a sample of only two demes (if $\hat{\theta}$ were sampled over n demes, this term would equal s_k^2/n). Therefore, this term would tend to zero if $\hat{\theta}$ were sampled over a large number of demes, and the formula would approach the standard F_{st} calculation of $\sigma_p^2/(\overline{p}(1-\overline{p}))$, for σ_p^2 the population variance in allele frequency (Hartl and Clark 2007). Summing the numerators and denominators separately for each locus and then dividing by the sums corrects for cases where a neutral allele had fixed in both demes (Weir and Cockerham 1984).

To measure the average pairwise F_{st} for a particular migration rate, for each burn-in population the F_{st} values recorded for the final $2N$ generations were averaged to produce the F_{st} estimate for that run. These values were then averaged over all burn-in populations to obtain a final mean estimate.

FINDING THE CRITICAL F_{st} VALUES THAT MAKES SEX ADVANTAGEOUS

We measured the average pairwise F_{st} for each burn-in population. For each burn-in population, we plotted the asexual fixation probability u/u^* as a function of F_{st} (e.g., Fig. S2 for $N = 10,000$ across a 1D array of 25 demes). These curves had a characteristically exponential shape, so we performed a linear regression of $log(u/u^*)$ against F_{st} to estimate the critical average F_{st} value at which asexuals become selected against; that is, the F_{st} value where the fixation probability of an asexual mutant equalled that for a neutral allele ($u/u^* = 1$). We denote this value as $\bar{F}_{st}^c$. For example, in Figure S2 the $\bar{F}_{st}^c$ value is $\sim$0.59.

Each dataset was bootstrapped 1000 times to obtain estimates of the SE, and we report approximate 95% confidence intervals (CIs) for each $\bar{F}_{st}^c$ as $\pm 1.96\times$SE. Based on a simulation study (available from Dryad, doi: 10.5061/dryad.2qf2f), these CIs were generally appropriate (yielding $\sim$5% type I error rates), except that the CI were too narrow when the dataset contained migration rates where the asexual seldom fixed. This was due to a lack of variance in the data, reducing the power of the bootstrap. We thus interpret the CI as a rough indication of the uncertainty in $\bar{F}_{st}^c$ rather than as a strict CI.

Measuring maximum F_{st} in a population

For sexuals to persist, it must take asexuals long enough to reach the last remaining deme, so that Hill–Robertson effects cause the relative fitness of asexuals to drop below that of sexuals. Therefore, a more relevant measure of population structure might not be the average pairwise F_{st} but rather the degree of isolation of the most distant deme from the location where the asexual first arises. These distant demes might serve as "refuges" where sexuals persist, allowing them to take over again once asexual fitness has decayed. We thus estimated the F_{st} between the deme in which a mutation was introduced and the most physically distant deme, which we will refer to as "F_{st}(max dist)." This statistic is not simply the maximum of the pairwise F_{st} values, because of the stochasticity in F_{st} estimates, but rather the best estimate of the pairwise F_{st} to the most distant deme. We estimated F_{st}(max dist) using a regression, fit to a hyperbolic curve, which rises nearly linearly with distance for nearby demes but eventually asymptotes at a maximum of one. Figure S3 shows such a plot for $N = 10,000$, for demes spread out over 1D. We then performed a linear regression of $log(u/u^*)$ against F_{st}(max dist) to obtain the critical value of population structure, measured to the most distant deme, needed to give $u/u^* = 1$, which we denote as $\hat{F}_{max}^c$.

Results

EXPLORING THE CRITICAL AVERAGE F_{st} VALUES NEEDED TO MAINTAIN SEX

In the absence of population structure and with a twofold cost of sex, we found that asexuals generally rapidly invade fully sexual populations of up to 10,000 individuals. Specifically, the mean fixation probability u in a population of 10,000 individuals was 0.77 when mutations were deleterious only, and 0.71 when mutations were advantageous and deleterious. With sufficiently strong geographic structure, however, a sexual population could resist invasion. Furthermore, the critical average F_{st} value ($\bar{F}_{st}^c$) required to favor sex generally decreased as N increased (Fig. 1). In larger populations, asexuals took longer to fix and so had more time to accumulate deleterious mutations before sexuals were entirely lost. In addition, loci were more likely to be polymorphic in larger populations, increasing the benefits conferred by sex in creating fitter genotypes, due to Hill–Robertson effects.

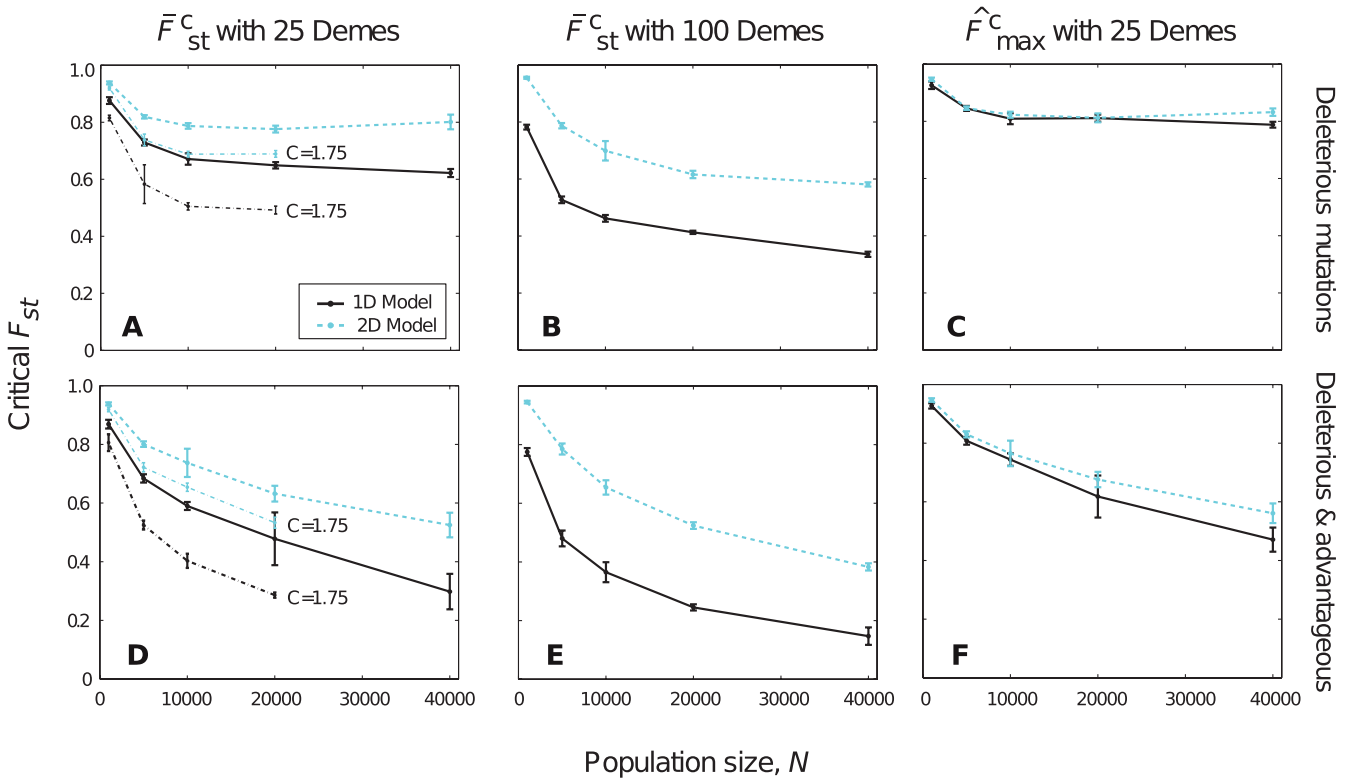

Figure 1. The critical level of population structure needed to protect a sexual population from asexual invasion, plotted against the overall population size, N. Panels report the critical average pairwise F_{st} ($\bar{F}^c_{st}$) at which asexuals invade with the same probability as a neutral allele, except the right-most panels (C, F), which report the critical F_{st} value for the most distant deme ($\hat{F}^c_{max}$). Top panels incorporate deleterious mutations only, while bottom panels incorporate both deleterious and advantageous mutations. By default, the cost of sex is twofold, although the effect of a reduced cost of sex is shown in the left panels ($C = 1.75$). Each population is uniformly spread out over 25 demes (A, C, D, F), or 100 demes (B, E), arranged in a one-dimensional structure (black) or over a two-dimensional torus (light blue). The mutational parameters are: $U = 1.0$, $s_a = s_d = 0.01$. Approximate 95% confidence limits give ±1.96 SE, based on 1000 bootstraps. If these are not visible then they lie within the plotted points.

We observed that lower $\bar{F}^c_{st}$ values were required to maintain sex with 1D spatial structure compared to the 2D model. This reflects the fact that asexuals took longer to establish when they were constrained to spread along only 1D. We observed the lowest $\bar{F}^c_{st}$ values needed to maintain sex if there were both advantageous and deleterious mutations (Fig. 1A, E), consistent with results showing that this scenario confers the greatest advantage to recombination (Hartfield et al. 2010). $\bar{F}^c_{st}$ values continue to decrease with increased population size if there is a mixture of advantageous and deleterious mutations for the population sizes investigated here. By separating advantageous alleles from poor genetic backgrounds, the fixation probability of advantageous alleles is increased, raising the fitness of associated sexuals (Fisher 1930; Peck 1994). Despite this additional advantage to sex, the $\bar{F}^c_{st}$ values required to maintain sex were high relative to empirical measurements when the population was subdivided into only 25 demes. The lowest $\bar{F}^c_{st}$ value that was found was 0.298, for demes spread out over a 1D structure with individuals subject to advantageous and deleterious mutation. Values of F_{st} this high are typically only seen for populations spread out over continents (see review of F_{st} estimates in Appendix S1).

It can be argued that asexuals have less than a twofold advantage because, for example, sexuals can offset some of their costs due to paternal investment (Lehtonen et al. 2012). We therefore investigated the $\bar{F}^c_{st}$ values needed to maintain sex if sexuals only suffered a 1.75 cost. As expected, populations need a greatly reduced level of population structure to maintain sex (Fig. 1A, D). For example, sex is maintained in a 1D population of $N = 20,000$ individuals subject to both advantageous and deleterious mutation if $\bar{F}^c_{st} \approx 0.3$ with a $C = 1.75$ cost, compared to a critical value of 0.48 with a twofold cost (Fig. 1D).

Next, we investigated how $\bar{F}^c_{st}$ changes with the number of demes. As the number of demes was increased, the $\bar{F}^c_{st}$ value needed to maintain sex decreased, implying that sex is more likely to be maintained in species clustered into many smaller demes (Figs. 1 and S4). With 100 demes, for example, Figure 1B and E show that the levels of populations structure needed to maintain sex are greatly reduced, compared to populations consisting of 25

Table 1. **Effect of increasing crossover rate. The critical level of population structure, measured using $\bar{F}_{st}^{c}$, needed to protect a sexual population from asexual invasion. Results are given to three significant figures, with figures in brackets representing 95% confidence intervals. The overall population size is $N = 10,000$ distributed across 100 demes for all results.**

		$L = 10$ (95% CI)	
Population type	$L = 1$ (95% CI)	100 loci	200 loci
1D model, deleterious only mutation	0.462 (0.0118)	0.374 (0.0113)	0.292 (0.0113)
1D model, advantageous and deleterious mutation	0.365 (0.0341)	0.257 (0.0170)	0.188 (0.0179)
2D model, deleterious only mutation	0.699 (0.0323)	0.682 (0.0163)	0.673 (0.0111)
2D model, advantageous and deleterious mutation	0.654 (0.0125)	0.594 (0.0105)	0.498 (0.0259)

demes (Fig. 1A and D). The lowest $\bar{F}_{st}^{c}$ value found was ~0.147, for individuals spread out over 1D that are subject to advantageous and deleterious mutation. These results likely reflect the interplay between two processes. First, because there are more demes, the invading asexual may take longer to reach the very last deme. Consequently, it is more likely to accumulate deleterious mutations and go extinct (Salathé et al. 2006), so lower levels of F_{st} are needed to maintain sex. The second mechanism is that with more demes for a fixed N, each deme consists of a smaller population, which can accelerate Muller's ratchet (Gessler 1995; Higgins and Lynch 2001; Gordo and Campos 2008), further reducing the fitness of asexuals.

The previous results were obtained assuming a mean crossover rate of $L = 1$ in sexuals. However, obligately sexual eukaryotes generally have higher crossover rates than this; for example, there is an average of 33 crossover events per generation in human meiosis (Broman et al. 1998; McVean et al. 2004). We therefore investigated how $\bar{F}_{st}^{c}$ changed when the crossover rate was increased from $L = 1$ to $L = 10$ and when the number of loci was changed from 100 to 200 (Table 1). In all cases, the critical level of population structure decreased when sexuals were better able to recombine their genomes. This result highlights how a higher per-genome recombination rate creates even fitter genotypes in sexuals, so less time is needed before an asexual population becomes excessively loaded with deleterious mutations, and goes extinct.

An ideal measure of population structure would predict the same critical value for sexuals to resist asexual invasion, regardless of how the population is arrayed over space. This is not true for $\bar{F}_{st}^{c}$, which differs for 1D and 2D arrangements of demes (Fig. 1). We thus also examined whether asexual invasion was better correlated with the average F_{st} value between the most distant demes in a population that maintained sex ($\hat{F}_{max}^{c}$). We predicted that the degree of genetic differentiation between a focal deme (in which the asexual first appears) and the most distant deme from it (as measured by $\hat{F}_{max}^{c}$) might be a better predictor of the critical degree of population structure needed to halt the spread of asexuals because it would better reflect how long it would take for the very last deme to be colonized by asexuals. Indeed, previous work had shown that an asexual's fixation probability is related to the total time needed to spread throughout the entire subdivided population (Salathé et al. 2006). We thus examined whether $\hat{F}_{max}^{c}$ was the same, regardless of the spatial arrangement of demes (e.g., in 1D or 2D). By plotting $\hat{F}_{max}^{c}$ alongside $\bar{F}_{st}^{c}$, we see that the $\hat{F}_{max}^{c}$ values for 1D and 2D populations appear to overlap if mutations are just deleterious (Fig. 1C). However, the $\hat{F}_{max}^{c}$ values continue to depend slightly on the arrangement of demes when mutations are advantageous and deleterious (Fig. 1F). Therefore, while $\hat{F}_{max}^{c}$ appears to be a better predictor of which population structures allow sexuals to withstand asexual invasion, it also appears not to capture fully the effects of spatial structure on the spread of asexuals.

So far, we have considered models in which individuals are only able to migrate to neighboring demes. In natural populations, however, it is expected that individuals migrate across a wide range of distances, and a small proportion of migrants may be able to travel over long distances (Wright 1931; Shigesada and Kawasaki 1997). To investigate the effects of long-distance migration, we estimated the $\bar{F}_{st}^{c}$ values if a proportion of migrants could travel to any deme, as opposed to just neighboring demes, for $N = 10,000$. We varied the probability of long-distance migration between 0%, so individuals could only migrate between adjacent demes, as used in previous simulations, and 10%. Figure 2 shows that, irrespective of the type of mutation present, the capacity for long-distance migration increases the $\bar{F}_{st}^{c}$ values needed to maintain sex and largely erases the differences observed between 1D and 2D populations. These effects are also seen at larger population sizes (Fig. S5). Interestingly, the results for 2D populations were hardly affected by long-distance migration. This is largely because of the small number of demes used (25), as well as the high level of connectedness among the demes in the 2D grid (migration allowed in four directions and the boundaries wrapped around). As a consequence, half of the other demes were reachable in only two migration steps, and the maximum distance between a pair of demes was only four migration steps. Thus, asexuals were likely able to explore the entire grid almost

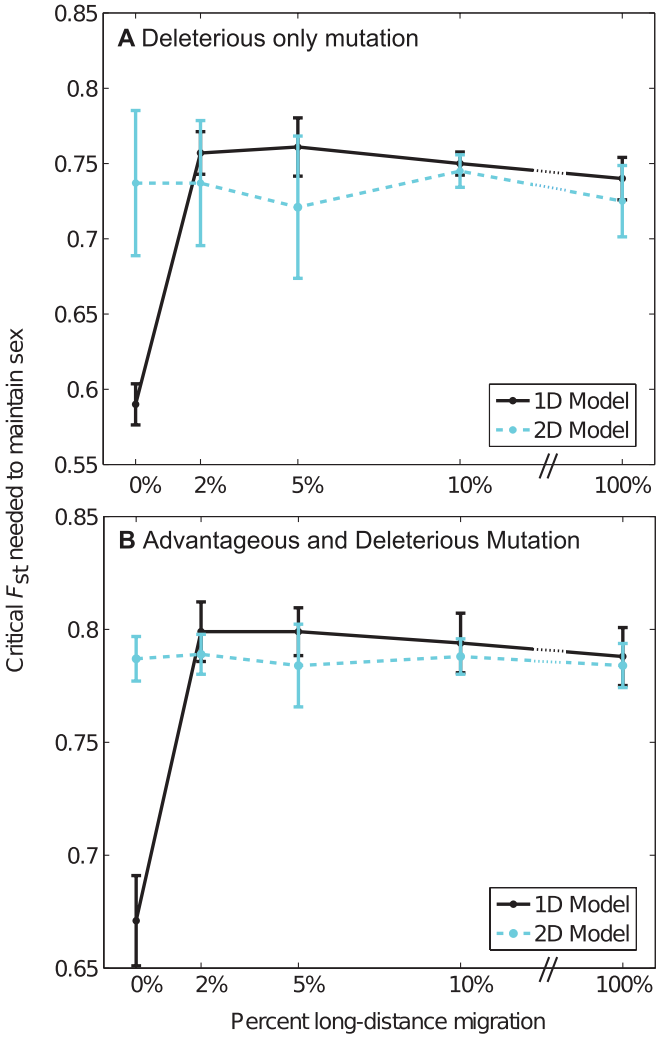

Figure 2. $\bar{F}_{st}^{c}$ **values plotted as a function of different proportions of long-distance migration. Mutations are solely deleterious (A), or advantageous and deleterious (B). Each population is equally spread out over 25 demes, either arranged in a one-dimensional structure (black), or over a two-dimensional torus (light blue).** $N = 10,000$ **and the mutational parameters are** $U = 1.0$, $s_a = s_d = 0.01$. **Confidence limits are based on 1000 bootstraps.**

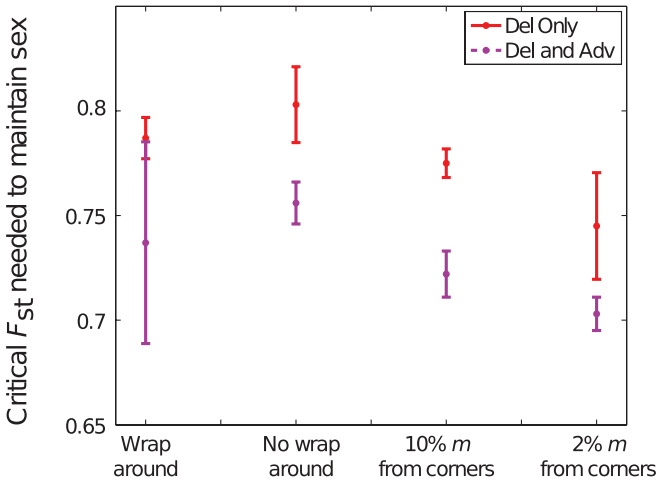

Figure 3. $\bar{F}_{st}^{c}$ **values in two-dimensional models with increasingly restricted migration. Mutations are solely deleterious (red), or advantageous and deleterious (purple). Each population is equally spread out over 25 demes, arranged over a two-dimensional torus (model type 0); a two-dimensional grid with no wrap-around (type 1); or a two-dimensional grid with no wrap-around and corner demes experiencing 1/10th (type 2) or 1/50th the migration rate of other demes (type 3).** $N = 10,000$ **and the mutational parameters are** $U = 1.0$, $s_a = s_d = 0.01$. **Confidence limits are based on 1000 bootstraps.**

as well by nearest-neighbor migration as by long-distance migration. Consistent with this explanation, the 2D results were similar to those observed in an island model, but both resisted asexual invasion better than a panmictic population because it still took time for the last deme to be reached.

Up to now, we have only examined the maintenance of sex in standard stepping-stone populations, where each deme is connected to the same number of neighbors, with a uniform migration rate between adjacent subpopulations. However we conjectured that sex could be maintained with lower $\bar{F}_{st}^{c}$ values in populations consisting of some demes that are more isolated from the rest of the population. This is because we expected that it would take longer, on average, for asexuals to spread to all demes (including the isolated ones), increasing their mutation load and making it more likely that a sexual population would recover. To test this hypothesis, we modified the population structure in the 2D model. First, we simulated asexual invasion into a 2D grid where migrants in edge demes would only travel to other demes within the array (as opposed to the torus model, in which the grid wraps around at the edges), and subsequently investigated asexual fixation probabilities if the overall rate of migration into and out of the corner demes is reduced by 1/10 and 1/50, respectively, compared to the migration rate between other adjacent demes.

Figure 3 plots the $\bar{F}_{st}^{c}$ for these populations, as well as that for the equivalent 2D torus model result. Contrary to our expectations, $\bar{F}_{st}^{c}$ values did not drastically fall as the corner demes became more isolated. In fact, $\bar{F}_{st}^{c}$ values rose when edge effects were introduced, compared to the torus model, before falling by a small amount as migration in and out of the corner demes was reduced. To determine why $\bar{F}_{st}^{c}$ was not strongly affected by the presence of isolated demes, we tracked the frequency of sexuals and asexuals in these populations, as well as mean sexual and asexual fitness in each deme. The supplementary *Mathematica* file shows the spread of an asexual invader in these population structures. We observe that in models with restricted migration at the corners, the mean fitness of the sexuals within those demes was greatly reduced compared to the rest of the population for the parameters investigated (particularly, with a deme size of only

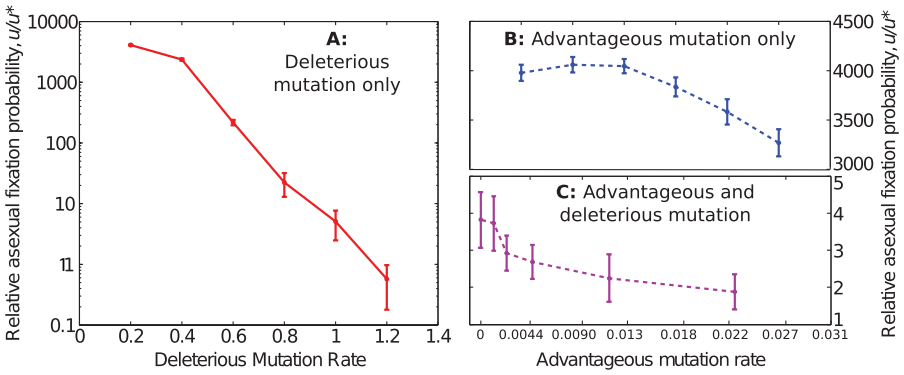

Figure 4. **Relative fixation probability u/u^* of an asexual invader, plotted as a function of the mutation rate U (see Methods section for how U is defined for different mutation schemes). Mutations are deleterious only (A), advantageous only (B), or advantageous and deleterious (C; U is fixed at 1 in this case). $N = 5000$, $s_d = s_a = 0.01$, $m = 0.003$ (yielding an average F_{st} value of 0.687 with only deleterious mutations for $U = 1$). A total of 25 demes are spread out over one dimension. Note that the y-axis of (A) is on a log scale, while those of (B) and (C) are on linear scales.**

400). Therefore, if an asexual invaded a corner deme then it was much more likely to establish in it. Second, we note that in most cases in which the sexual population eventually recovered, it was rare for an asexual to reach the majority of demes in the population so that the isolated nature of the corner demes rarely mattered. In other words, there was only a narrow range of migration rates where the asexuals would reach all demes except the corner demes before declining again in frequency, so that the $\bar{F}_{st}^{c}$ was only weakly affected. Overall, these two mechanisms help explain why isolated demes had little impact on the overall fixation probability of the asexual.

THE EFFECT OF VARYING THE MUTATION RATE ON ASEXUAL INVASION

Salathé et al. (2006) showed that sex is increasingly favored as the genomic deleterious mutation rate increases. Our results suggest that sex is most strongly selected in the presence of both advantageous and deleterious mutations. To determine to what extent the magnitude of the advantageous and deleterious mutation rate matters to the maintenance of sex, we evaluated the fixation probability of an asexual mutant in the presence of just advantageous mutations or just deleterious mutations, as we altered each mutation rate. Figure 4A shows that asexuals become less likely to establish in populations subject to increasing rates of deleterious mutation. If only deleterious mutations are present, the fixation probability of an asexual decreases in an approximately exponential fashion as the mutation rate increases, reflecting an increased likelihood of asexual mutational meltdown (Salathé et al. 2006).

The additional advantage to sex conferred by advantageous mutations depends on the advantageous mutation rate. This is still generally unknown for many higher eukaryotes. Shaw et al. (2002) estimated that 50% of mutations in *Arabidopsis thaliana* were beneficial (but see Keightley and Lynch (2003)). Joseph and Hall (2004) estimated that around 5.75% of mutations in diploid laboratory-adapted strains of *Saccharomyces cerevisiae* were beneficial. A follow-up study by Hall and Joseph (2010) further found that these proportions are higher for mutations that affect growth rate and sporulation efficiency (12.5% and 20%, respectively), but it was inferred that no beneficial mutations that affect spore viability were present, nor were any found in haploid strains. In *Drosophila melanogaster*, Schneider et al. (2011) estimated that the proportion of advantageous amino acid changing mutations lies between 0.5% and 3.5%. The value of 2.2% used in these simulations thus lies within this range of estimates.

Figure 4B shows the dependancy of the fixation probability of an asexual mutant on the advantageous mutation rate. If only advantageous mutations are present (occurring at rate 2.22% of U), asexuals always fixed at high rates. We conclude that advantageous mutations acting on their own, are ineffective at protecting structured sexual populations from asexual invasion, at least for the low frequencies at which they arise in these simulations. Nevertheless, combined with deleterious mutations, the presence of advantageous alleles greatly reduces the amount of population structure needed to resist asexual invasion (Fig. 4C), especially in larger populations (Fig. 1).

EFFECTS OF VARYING SELECTION STRENGTH

The previous simulations explored the invasion of asexual variants, assuming a single value for the fitness effects of mutations ($s_a = s_d = 0.01$). We next explored the effect of varying the selection coefficient on these results. Although the average selection coefficient against deleterious alleles is believed to be on this order, the distribution of fitness effects is very broad, with a leptokurtic distribution (Eyre-Walker and Keightley 2007). Advantageous mutations also have varying effects; Sattath et al. (2011), for example, estimated that in *D. simulans* one small class of

substitutions have mean $s_a \approx 0.005$, whereas the rest have a smaller effect (mean $s_a \approx 4 \times 10^{-5}$). It has been previously observed that the fixation probability of a recombination modifier depends on s_a (Hartfield et al. 2010), and s_d also affects the maintenance of sex in a structured population (Salathé et al. 2006). Therefore, we next examine how different strengths of mutation, both advantageous and deleterious, affect the maintenance of sex.

For cases of deleterious mutations only, and a mixture of advantageous and deleterious mutations, Figure 5 suggests that asexual invasion is least likely to occur for intermediate values of the selection coefficient against deleterious mutations. This is consistent with Muller's ratchet increasing the probability of extinction of asexual lineages when selection strengths are intermediate, because weakly deleterious alleles have little effect on asexual fitness while strongly deleterious alleles are unlikely to establish (Gabriel et al. 1993). Very similar results were found at smaller ($N = 1000$) and larger ($N = 10,000$) population sizes (Fig. S6), with the main qualitative difference being that sex was maintained for larger values of s_d when population size was reduced. If the population size is also altered, sex is maintained for larger values of s_d in populations of size $N = 1000$, compared to populations of size $N = 10,000$ (Fig. S6). This results presumably arises due to stronger effects of Muller's ratchet to click even with stronger deleterious alleles in smaller populations.

Finally, increasing the selective advantage of advantageous alleles increases the ability of sexual populations to be maintained, over the range considered, consistent with Hill–Robertson effects becoming stronger over this range (s_a varying from 0.001 to 0.05; Fig. S7).

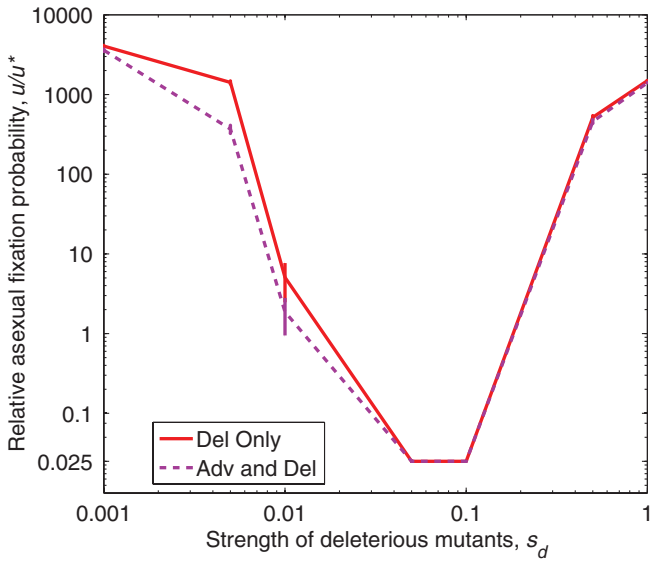

Figure 5. Relative fixation probability u/u^* of an asexual invader, plotted as a function of the strength of selection acting against a deleterious mutant s_d. Mutations are either deleterious only (red) or advantageous and deleterious (purple) with $s_a = 0.01$. Other parameters are $N = 5000$, $U = 1.0$, and $m = 0.003$ (yielding an average F_{st} value of 0.687 with only deleterious mutations, for $s_a = s_d = 0.01$). A total of 25 demes are spread out over one dimension. Fixation probabilities of zero were replaced with 0.025, representing a single fixation event over all replicates. See Figure S6 for equivalent results for $N = 1000$ and $N = 10,000$.

Discussion

In recent years, breaking apart Hill–Robertson interference between linked loci generated by selection in finite populations has become a strong candidate as the driving force favoring recombination (Barton 2010). However, less is known about whether this advantage of recombination can overcome strong costs of sex in structured populations, given the low F_{st} levels that one typically finds in nature. Our results are consistent with previous studies showing that obligate sexuals suffering a twofold cost are able to resist invasion by asexuals in structured populations (Peck et al. 1999; Salathé et al. 2006). Furthermore, the amount of structure needed to maintain sex, as measured using the critical average pairwise F_{st} value between demes ($\bar{F}_{st}^c$), decreases with population size to modest levels in populations consisting of 10,000 individuals or more, if the population is spread out over a large enough number of subpopulations (Fig. 1B and E). In the largest populations simulated ($N = 40,000$), for example, the lowest $\bar{F}_{st}^c$ observed needed to maintain sexuals suffering from a twofold cost was ~0.147, with 100 demes spread out over 1D and individuals subject both to advantageous and deleterious mutation (Fig. 1E). These results hold for a realistic eukaryotic genome-wide deleterious mutation rate, $U = 1.0$ (Denver et al. 2004; Haag-Liautard et al. 2007; Eöry et al. 2010). While sexuals are maintained predominantly because asexuals undergo deleterious mutational meltdown, which can lead to their extinction in a metapopulation (Higgins and Lynch 2001), we also observe that sex is most strongly favored in the presence of both advantageous and deleterious mutations. We also find that levels of $\bar{F}_{st}^c$ decreases if asexuals have a less than twofold advantage (Fig. 1A and C), or if the recombination rate is higher in sexuals, with recombination acting over more selected loci (Table 1). Taken together, these results suggest that sex can be maintained in subdivided populations with reasonably low $\bar{F}_{st}^c$ values. Most of our results (Fig. 1, but see Fig. S6) also suggest that if we were able to increase the population size further, as well as the recombination rate, the $\bar{F}_{st}^c$ value would continue to drop and be consistent with F_{st} values observed in many eukaryotic populations (Appendix S1). However, constraints on computing time limited the parameter space that we were able to explore.

However, if a small proportion of long-distance migration is introduced, then it appears that the $\bar{F}_{st}^c$ values increases in 1D populations, and is similar to the $\bar{F}_{st}^c$ needed in 2D populations

with no long-distance migration (Figs. 2, S5). This increase in $\bar{F}_{st}^{c}$ in 1D populations presumably reflects how a much lower overall rate of migration is needed to counteract the increased speed at which asexuals spread to distant demes with long-distance migration. This finding also highlights how $\bar{F}_{st}^{c}$ depends on the arrangement of demes when there is no long-distance migration, so it is not a sufficient statistic that can be used to determine whether an asexual will fix or not in a subdivided population. To this end, we introduced and tested the $\hat{F}_{max}^{c}$ statistic, which showed less sensitivity to the geometry of the underlying population structure (Fig. 1C and F).

Finally, contrary to expected results, we showed that isolating specific demes in a 2D model did not strongly expand the conditions favoring the maintenance of sex. This is because isolating specific demes also had an adverse effect on the fitness of the isolated sexual population, which was subject to mutational drift load, at least for the small deme sizes considered (400 individuals per deme). It was also found that restricting migration to a few demes made little difference when migration rates were very high (asexuals always won) or very low (asexuals never won), so that there was only a small window of migration rates within which having more isolated demes would matter. Therefore, the presence of isolated demes had little impact on the $\bar{F}_{st}^{c}$ value needed to prevent the spread of asexuals.

Possibilities for extending this study

Because these simulations are computationally intensive, we have been limited in exploring the parameter space of this complex multidimensional problem. In particular we have assumed that mutants have equivalent fitness effects, whereas in reality mutants have a distribution of selective effects (Eyre-Walker and Keightley 2007). However, by exploring the impact of different fitness effects (Figs. 5, S6, S7) we have obtained some information on the parameters that maximize the likelihood of the maintenance of sex. In particular, deleterious mutations of intermediate effect offer the greatest protection to sex, because these cause the fastest degradation in asexual fitness due to Muller's ratchet. Similarly, haploid populations were simulated, but it is known that selection on sex and recombination acts somewhat differently in diploid individuals. Specifically, if deleterious mutants are strongly recessive, then this can select against increased levels of sex and recombination in diploid populations subject to just deleterious mutation (Roze 2009; Roze and Michod 2010). Thoroughly investigating how diploidy affects the maintenance of sex in structured populations would be worthy of future study.

We also invoked specific assumptions about the ecology of the simulated populations, which only cover a small portion of biologically realistic scenarios. For example, demes could be subject to "hard selection" (Wallace 1975), where the contribution to other subpopulations of offspring from a deme depends on the mean fitness of the individuals within it. The presence of hard selection could have significant effects on the initial spread of asexuals. If demes with large numbers of asexuals are more fecund, then these demes might also produce more migrants, which would increase the speed at which asexuals travel throughout the population. This effect might be conteracted, however, when asexual demes start to accumulate a higher load of deleterious mutants, so that the sexual population might recover more quickly in a hard-selection regime. The net effect would be well worth exploring through simulations that relate deme size and/or migration rates to fitness.

Another scenario not considered is where there exists a continuous emergence of asexuals over time, as observed in the system of *Potamopyrgus antipodarume* snails (Dybdahl and Lively 1995; Jokela et al. 2003; Neiman et al. 2005; King et al. 2011), which can lead to parallel fixation of different asexual lineages in different parts of the range before any one asexual lineage has had time to decay substantially in fitness. This effect might become more apparent in large populations, where there exists a higher probability that independent lineages will arise (as found by Ralph and Coop (2010)). Investigating whether realistic levels of structure can maintain sex in the face of multiple asexuals emerging over time and space should be investigated in the future.

In this study, we focus on average pairwise F_{st} to measure the extent of population structure needed to maintain costly sex. However, while $\bar{F}_{st}^{c}$ can determine how population structure increases the fixation time of weakly beneficial alleles (Whitlock 2002, 2003), it might not be the most precise statistic to use in determining how population structure maintains sex in the face of strongly favored asexual lineages. Our $\hat{F}_{max}^{c}$ statistic more accurately predicts asexual fixation probability in a manner that is less sensitive to the geometrical arrangement of demes, but it is also sensitive to the arrangement of demes when mutations are advantageous and deleterious (Fig. 1F). Future theoretical and empirical work should therefore investigate whether alternative measures of population structure better predict the probability that sexual reproduction is lost through asexual invasion.

Summary

Our models have shown that in large populations spread out over a large enough number of demes, the level of structure needed to resist asexual invasion approaches realistic levels, compared to values observed in field studies (Appendix S1). Critical F_{st} values that maintain sex should, in most cases, be even lower in larger populations, especially those that are subdivided into multiple demes. It is therefore feasible that sex can be maintained in large, subdivided populations, due to the evolutionary advantage of reducing selective interference among a large number of selected loci.

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Supporting Information

The following supporting information is available for this article:

Appendix S1. Review of F_{st} values obtained in studies of natural populations.

Figure S1. Example of plots for average pairwise F_{st} in a population.

Figure S2. A typical plot used to find the critical average pairwise F_{st} where sex becomes advantageous, $\bar{F}^c_{st}$.

Figure S3. Estimating $\hat{F}^c_{max}$ in a population.

Figure S4. $\bar{F}^c_{st}$ values plotted against the number of demes simulated.

Figure S5. $\bar{F}^c_{st}$ values plotted against overall population size, N.

Figure S6. Relative fixation probability u/u^* of an asexual invader, plotted as a function of the strength of selection acting against a deleterious mutant s_d, for different population sizes.

Figure S7. Relative fixation probability u/u^* of an asexual invader, plotted as a function of the strength of selection acting on advantageous mutants, s_a, if there was a mixture of advantageous and deleterious mutations.

Supporting Information may be found in the online version of this article.

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