Recessive Mutations and the Maintenance of Sex in Structured Populations

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ABSTRACT

The evolutionary maintenance of sexual reproduction remains a controversial problem. It was recently shown that recessive deleterious mutations create differences in the mutation load of sexual *vs.* asexual populations. Here we show that low levels of population structure or inbreeding can greatly enhance the importance of recessive deleterious mutations in the context of sexual *vs.* asexual populations. With population structure, the cost of sex can be substantially reduced or even eliminated for realistic levels of dominance.

ALL else being equal, asexual populations have a twofold fitness advantage over their sexual counterparts (Maynard Smith 1971, 1978; Williams 1975; Bell 1982). Among a variety of possible explanations for the continued prevalence of sexual reproduction (Kondrashov 1993; Hurst and Peck 1996; Barton and Charlesworth 1998), the mutational deterministic hypothesis is one of the leading proposals. If the mutation rate is sufficiently high and deleterious mutations interact synergistically, then sexual populations can clear mutations more efficiently and thus enjoy a much higher mean fitness at mutation-selection balance than asexual populations (Kimura and Maruyama 1966; Kondrashov 1982, 1988; Charlesworth 1990).

Although there is some theoretical support for synergistic epistasis (Szathmary 1993; Peck and Waxman 2000), there is little experimental support for this type of gene interaction (Willis 1993; Elena and Lenski 1997). In contrast, there is wide support for the dominance of wild-type alleles over their deleterious counterparts (Lynch and Walsh 1998). Chasnov (2000) recently showed that differences in mutation load (Haldane 1937; Müller 1950; Crow 1970) due to recessive deleterious mutations alone (*i.e.*, no epistasis) can result in a substantial advantage to sexual reproduction over asexual reproduction under some conditions. This result is perhaps unsurprising as dominance creates mutational synergy within loci (whereas epistasis creates it among loci). The advantage to sex exists because heterozygous parents can produce homozygous offspring through sexual reproduction but not through asexual reproduction (except by mutation). Relative to asexual populations, a greater fraction of segregating mutations in sexual populations exist in the homozygous state where they can be more efficiently eliminated by selection. Population structure or inbreeding increases the proportion of homozygotes and thus allows selection to be even more efficient in sexual populations (Crow 1970). We show that biologically reasonable levels of population subdivision greatly expand the parameter space over which sexuals experience reduced mutation load relative to asexuals.

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Consider a single locus that mutates from the wild-type allele, A, to the deleterious allele, a, with probability u. The fitnesses of the three genotypes AA, Aa, and aa are 1, $1 - hs$, and $1 - s$, respectively. The degree of dominance of the a allele is described by h, where values of 0 and 1 represent completely recessive and dominant alleles, respectively. The frequencies of A and a alleles in the sexual population are given by p and q, respectively. Using Wright's inbreeding coefficient, f, as a measure of population subdivision, the genotype frequencies before and after selection are given in Table 1. The calculations implicitly assume hard selection such that a deme contributes to the metapopulation in proportion to its mean fitness.

Allowing for mutation to occur between generations, the frequency of the mutant allele in the next generation is

$$q' = \frac{u + [1 - u - sh(1 + u) - sf(1 - h(1 + u))]q - s(1 - f)(1 - h(1 + u))q^2}{w_{\text{sex}}}, \quad (1)$$

where the average fitness of individuals in the sexual population with respect to this locus is

$$w_{\text{sex}} = 1 - s[2h + f(1 - 2h)]q - s(1 - f)(1 - 2h)q^2. \quad (2)$$

The equilibrium frequency of the a allele at mutation-selection balance can be found by solving (1) for $q' = q$ (Crow 1970; Crow and Kimura 1970). One solution is $q = 1$, and the other two solutions are roots of the quadratic equation

TABLE 1

Single-locus genetic model

Genotype	AA	Aa	aa
Fitness	1	$1 - sh$	$1 - s$
Frequency in zygote	$p^2 + pqf$	$2pq(1 - f)$	$q^2 + pqf$
Frequency after selection	$\frac{p^2 + pqf}{w_{sex}}$	$\frac{2pq(1 - f)(1 - sh)}{w_{sex}}$	$\frac{(q^2 + pqf)(1 - s)}{w_{sex}}$

Note that $p + q = 1$ and $w_{sex} = 1 - s(2hpq + q^2) - s(1 - 2h)pqf$.

$$s(1 - f)(1 - 2h)q^2 + s(f + h(1 - f)(1 + u))q - u = 0 \quad (3)$$

(Crow 1970). An approximate solution to (3) for $u \ll 1$ and h, s, $f \gg u$ is determined by neglecting terms of order u^2 and assuming $q = O(u)$:

$$q \approx \frac{u}{s[f + h(1 - f)]}. \quad (4)$$

The mutation load per locus, $l_{sex} = 1 - w_{sex}$, corresponding to this solution is

$$l_{sex} \approx u\frac{f + 2h(1 - f)}{f + h(1 - f)}. \quad (5)$$

To determine when mutation load provides an advantage to sexual reproduction, we consider the ratio W_{sex}/W_{asex}, where W_{sex} and W_{asex} are the genome-wide mean zygote fitnesses (with respect to load) for sexual and asexuals, respectively. Any value of $W_{sex}/W_{asex} > 1$ indicates that sexual populations have an advantage over asexual populations with respect to mutation load. When $W_{sex}/W_{asex} > 2$, this advantage completely compensates for the twofold cost of sex.

Assuming loci are in linkage equilibrium and no epistasis, Chasnov (2000) has shown that

$$W_{sex}/W_{asex} \approx \exp[n(\langle l\rangle_{asex} - \langle l\rangle_{sex})], \quad (6)$$

where n is the number of diploid genes per genome and $\langle l\rangle$ is the average contribution to load from a single locus. For $s > u(2 - u)$ and $h > u/s$, the mutation load per locus for asexual reproduction is $2u$ (Kimura and Maruyama 1966; Chasnov 2000).

Taking the same value of u, s, and h at each locus and defining $U = nu$ as the haploid genome-wide mutation rate, the relative fitness of sexual individuals to asexual individuals is

$$W_{sex}/W_{asex} \approx \exp\left[\frac{fU}{f + h(1 - f)}\right]. \quad (7)$$

Comparison of this analytical approximation to exact numerical evaluations demonstrates reasonable agreement provided f, h, and s are not too small (Figures 1 and 2). How is (7) to be interpreted? First, (7) shows no advantage to sex when $f = 0$ (random mating) because of the inherent assumption $h \gg u/s$. The case $f = 0$ is solved in detail by Chasnov (2000). Second, to leading order in u, the advantage to sex is independent of the selection coefficient, s. Third, the advantage to sex ranges from a maximum when $h \ll f$ of approximately $\exp(U)$ to a minimum when $h \gg f$ of $\exp(fU/h)$.

The value of W_{sex}/W_{asex} depends strongly on the genome-wide mutation rate $U = nu$. If this value is on the

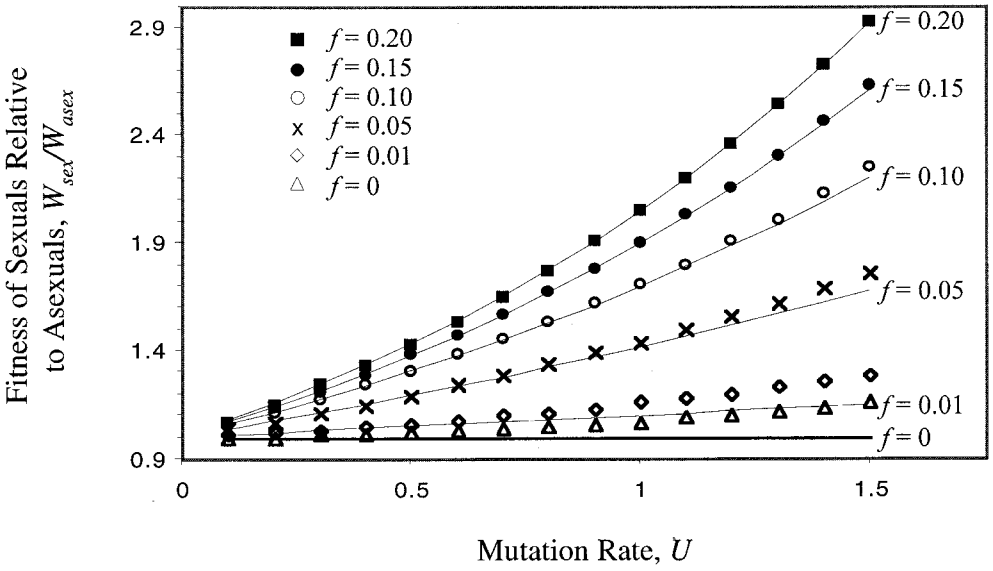

Figure 1.—Mutation rate and the advantage of sexual reproduction. The mean fitness of sexual relative to asexual individuals, W_{sex}/W_{asex}, is plotted as a function of the genome-wide mutation rate, $U = nu$. Six different levels of population structure, f, are plotted. $n = 10^5$, $s = 0.01$, and $h = 0.1$ while u was varied from 1×10^{-6} to 1.5×10^{-5}. Symbols show exact values of W_{sex}/W_{asex} found by numerical evaluation. The solid lines represent the analytical approximation given in (7). The analytical approximation underestimates the advantage to sex at very low levels of population structure $f = 0$, 0.01.

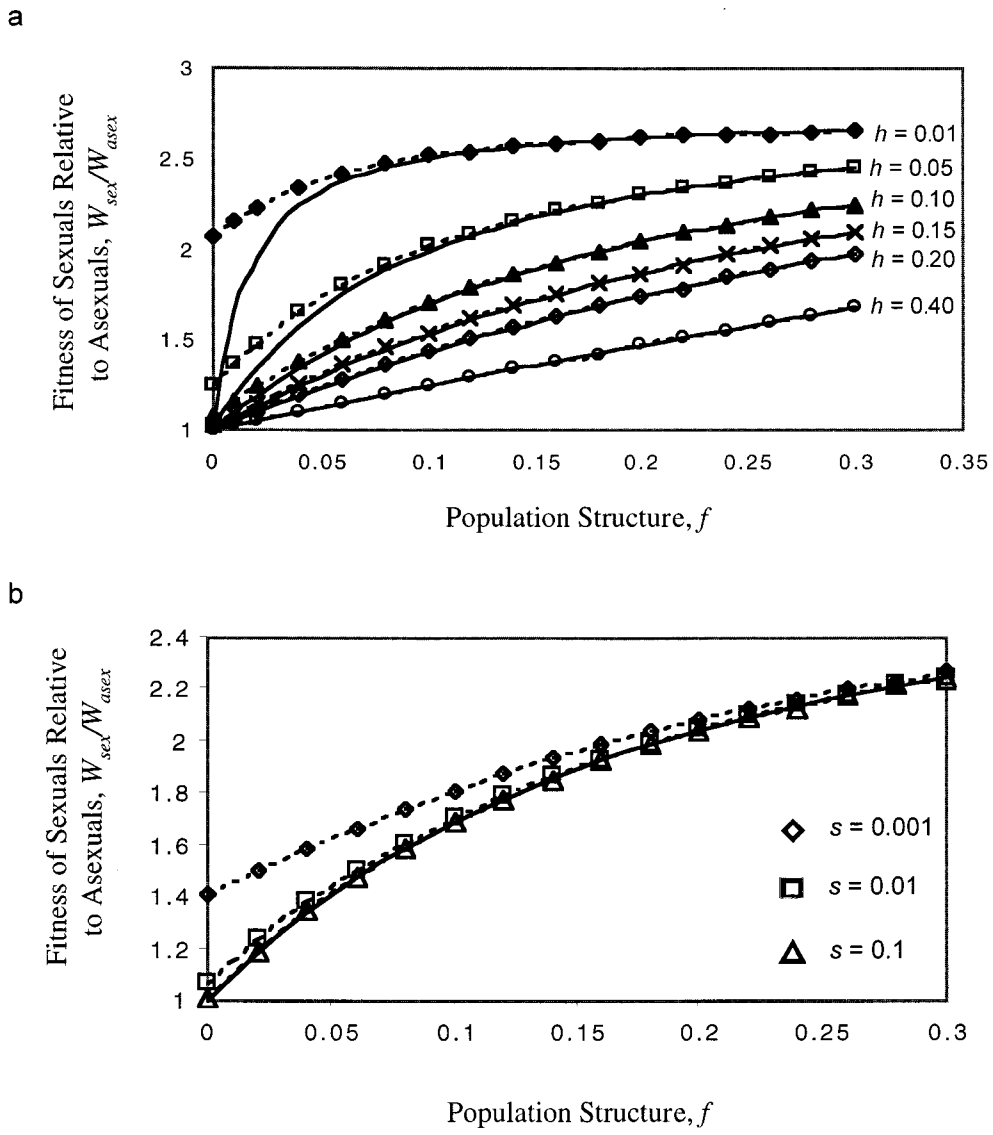

FIGURE 2.—Population structure and the advantage of sexual reproduction. The mean fitness of sexual females relative to asexual individuals, W_{sex}/W_{asex}, is plotted as a function of the extent of population subdivision or inbreeding, f. $n = 10^5$, $u = 10^{-5}$, and $U = nu = 1$. (a) $s = 0.01$ and six levels of the dominance coefficient, h, are shown. (b) $h = 0.1$ and three levels of the selection coefficient, s, are shown. Dashed lines connect exact values of W_{sex}/W_{asex} found by numerical evaluation. Solid lines represent the analytical approximation shown in (7).

order of 0.1 or smaller, then $W_{sex}/W_{asex} \approx 1$. As U increases, W_{sex}/W_{asex} increases exponentially when there is some degree of population structure (Figure 1). For values of U on the order of 1, W_{sex}/W_{asex} can take on values substantially greater than unity. As shown by CHASNOV (2000), when there is no population structure (*i.e.*, $f = 0$), W_{sex}/W_{asex} is highly sensitive to the degree of dominance, h (Figure 2). Without population structure, values of $W_{sex}/W_{asex} \gg 1$ occur only with extremely low dominance [*i.e.*, $h = O(\sqrt{u/s})$; see CHASNOV 2000].

Small increases in the amount of population structure, f, can cause substantial increases in W_{sex}/W_{asex}. Figure 2a shows that the addition of population structure reduces the sensitivity of W_{sex}/W_{asex} to h and allows W_{sex}/W_{asex} to be >1 with more realistic levels of dominance. For example, assuming $U = 1$, $s = 0.01$, and $h = 0.1$, there is little advantage to sex, and $W_{sex}/W_{asex} = 1.07$ without population structure ($f = 0$). With some population structure ($f = 0.1$), the sexual population experiences a much reduced mutation load, $W_{sex}/W_{asex} = 1.71$. In general, W_{sex}/W_{asex} is larger for smaller values of the selection coefficient, s, although this effect diminishes with increasing levels of population subdivision (Figure 2b).

What are the actual values of the relevant parameters? There is general agreement that the mutation rate for prokaryotes such as *Escherichia coli* is much less than unity whereas it is greater than unity for long-lived eukaryotes such as humans (KEIGHTLEY and EYRE-WALKER 1999; LYNCH *et al.* 1999). However, the genome-wide mutation rate for most eukaryotes is hotly contested. Some estimates suggest that it is on the order of one mutation

per genome per generation (Lynch *et al.* 1999) while other estimates suggest that it is at least an order of magnitude less (Keightley and Eyre-Walker 1999, 2000). The average value of s for spontaneous deleterious mutation is in the range 0.01–0.1 (Lynch *et al.* 1999). Although previous estimates have been higher, a recent analysis suggests that the average value of h is ~0.1 (García-Dorado and Caballero 2000). It is questionable whether any species are truly panmictic (Hastings and Harrison 1994), so f is probably always >0. For example, the average values of f for insects, including *Drosophila melanogaster*, are in the range 0.03–0.15 (Wade and Goodnight 1998). Reported f values are even higher in a variety of other organisms.

The work presented here focuses on the importance of population structure for creating low levels of inbreeding. Other consequences of spatial structure have been noted. In "tangled bank" models of sex (*e.g.*, Bell 1982), genetically variable offspring (produced through sexual reproduction) compete less with one another for local resources than do genetically identical offspring (produced through asexual reproduction). Peck and Waxman (2000) showed that physiologically independent mutations may have synergistic fitness effects when individuals compete for local resources. Lenormand and Otto (2000) found that spatial heterogeneity in strength of selection may be important for the evolution of recombination.

Our results should be interpreted with caution. The model applies only to a comparison between sexual diploids and asexual apomictic diploids. The model neglects haploid life stages where deleterious alleles may be exposed and readily removed by selection. As with most other mutation models (Kimura and Maruyama 1966; Kondrashov 1982, 1988; Charlesworth 1990), our model compares the equilibrium fitnesses of sexual and asexual populations. A new asexual clone could carry very few mutations and might be able to eliminate a sexual population before being burdened by its equilibrium load (Charlesworth 1990; Howard 1994; West *et al.* 1999). Although the model shows that inbreeding can generate an advantage to sex over asex, it leaves open the question of why sexuals do not always self (see Fisher 1941; Charlesworth 1980; Agrawal and Lively 2001).

Like synergistically interacting mutations, recessive deleterious mutations can lead to higher mutation loads for asexual populations relative to sexual ones (Chasnov 2000). As with the mutational deterministic hypothesis, a mutation rate on the order of unity is required (Kondrashov 1982, 1988; Charlesworth 1990). Unlike synergistic epistasis, there is much experimental evidence for recessive gene action. When population structure is incorporated into the model, recessive deleterious mutations alone (*i.e.*, no epistasis) can create an advantage to sexual reproduction through reduced mutation load that helps compensate for the twofold cost of sex over a range of conservative parameter estimates. When the effects of recessive deleterious mutations are combined with epistasis or other advantages of sexual reproduction (Howard and Lively 1994; West *et al.* 1999), the twofold cost of sex could be completely overcome.

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