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Evolution, Volume 46, Issue 3 (Jun., 1992), 775-782.

Stable URL:
http://links.jstor.org/sici?sici=0014-3820%28199206%2946%3A3%3C775%3AOGSATE%3E2.0.CO%3B2-A

Evolution, 46(3), 1992, pp. 775–782

ON GENETIC SEGREGATION AND THE EVOLUTION OF SEX

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Abstract.—It has recently been argued that because the genetic load borne by an asexual species resulting from segregation, relative to a comparable sexual population, is greater than two, sex can overcome its twofold disadvantage and succeed. We evaluate some of the assumptions underlying this argument and discuss alternative assumptions. Further, we simulate the dynamics of competition between sexual and asexual types. We find that for populations of size 100 and 500 the advantages of segregation do not outweigh the cost of producing males. We conclude that, at least for small populations, drift and the cost of sex govern the evolution of sexuality, not selection or segregation. We believe, however, that if sexual and asexual populations were isolated for a sufficiently long period, segregation might impart a fitness advantage upon sexuals that could compensate for the cost of sex and allow sexuals to outcompete asexuals upon their reunion.

Key words.—Cost of meiosis, evolution of sexual reproduction, genetic segregation.

Received March 4, 1991. Accepted October 20, 1991.

The past 25 years of research into the advantages of sexual reproduction over asexual has emphasized the evolutionary dynamics of recombination (see Michod and Levin, 1988, for reviews of this subject). Kirkpatrick and Jenkins (1989) (hereafter, KJ) recently drew attention to a different aspect of the evolution of sex, namely, the role of genetic segregation in diploids. Without segregation, loci may become homozygous for a new advantageous allele only after two independent mutations have occurred. With segregation, the process of assortment can create homozygous individuals after only one mutational event. If segregation produces the more fit homozygotes more often than mutation alone, then segregation might compensate for the classical twofold disadvantage of sexual reproduction.

In this note, we address three assumptions made by KJ (1989) and then examine the effects of two of these on the evolutionary advantage of segregation using a stochastic simulation. We find that, while there is generally some advantage gained through segregation, it is not sufficient to overcome the twofold cost of sex when sex is initially rare.

ASSUMPTIONS OF KIRKPATRICK AND JENKINS' FORMULATION

The problem is posed in terms of the genetic load that accrues to an asexual diploid population because of loci heterozygous for advantageous mutations that may occur at L loci, each of which is originally homozygous. At each locus, the fitnesses of the mutant heterozygote and homozygote are $1 + hs$ and $1 + s$, respectively, relative to 1 for that of the wild-type genotype ($s > 0$, $0 \leq h < 1$). It is assumed that only one of these L loci has a favorable mutation segregating at any time. This assumption is made so that there is no possible "advantage to sexual reproduction derived from recombination" (KJ).

Next it is assumed that the population is of size N and the mutation rate per allele to advantageous alleles is μ. KJ then calculate two "fixation rates": the first is that rate at which loci become "fixed" in the heterozygous state in asexuals, and the second is the rate at which loci fixed as heterozygotes are converted to advantageous homozygotes. The former is computed as $2NL\mu P_0$, where P_0 is the "probability that a single advantageous mutation at a homozygous type locus spreads" (to fixation in the heterozygous state). The second rate is μNnP_1, where P_1 is "the probability that a mutation converting a heterozygote to an advantageous homozygote spreads" (also to fixation), and n is the number of loci fixed in the heterozygous state. This leads to KJ's differential equation

$$\frac{dn}{dt} = 2N\mu LP_0 - \mu NnP_1, \qquad (1)$$

from which $n(t)$ converges to $2LP_0/P_1$ at the exponential rate μNP_1.

The values assumed for P_0 and P_1 come from the diffusion approximations to random genetic drift in haploids with selection. The diffusion analysis gives the probability of ultimate survival of a mutant with selective advantage σ over its wild-type allele as 2σ, provided that $N\sigma$ is not too small (see Ewens, 1979 p. 83). The favored heterozygote is assumed to arise via mutation and to begin at a frequency $1/N$ in a population of size N. KJ computed P_0 as the probability that "fixation" occurs on the heterozygous type with fitness $1 + hs$ relative to the wild-type genotype, namely, $P_0 = 2hs$. In the same way, P_1, the probability of fixation on the advantageous homozygote, has a fitness increment of $s(1 - h)/(1 + hs)$ over the heterozygote and is therefore $2s(1 - h)/(1 + hs)$. The segregational load borne by the asexuals at or near equilibrium is then said to be

$$W_s = \left(\frac{1 + s}{1 + hs}\right)^n, \qquad (2a)$$

where

$$n = 2LP_0/P_1 = 2Lh(1 + hs)/(1 - h). \qquad (2b)$$

When $W_s > 2$, the claim is that sex has overcome its twofold disadvantage and numerical examples with $L = 10, 50, 100, 500, 1{,}000$, and $s = 0.001, 0.005, 0.01, 0.05, 0.1$ are presented to show that W_s can be much larger than two.

We now proceed to an analysis of the following assumptions made by KJ: (1) only one mutant is segregating at a time, (2) there is a constant pool of wild-type loci, and (3) the sexuals and asexuals are independently evolving (i.e., their population sizes are independent of each other).

Number of Mutants Co-Segregating

To avoid the complicating effects of recombination, KJ restricted their parameter space such that only one mutation is segregating at any point in time. Specifically, they set $4NL\mu \ln(2Ns) \ll 1$. One heuristic way to derive a condition under which only one mutation at a time spreads through a sexual population is as follows. The probability that a new mutation with an initial frequency $1/2N$ and an advantage $s/2$ eventually fixes is approximately s. The rate of production of favorable mutations in the population is $2NL\mu$ per generation. Thus, the rate of production of favorable mutations that achieve fixation is $2NL\mu s$ per generation, yielding an average time between the occurrence of these mutations of $(2NL\mu s)^{-1}$. Denote the expected time to fixation (conditional on fixation) of a favorable mutant starting from a frequency p by $t_1(p)$. Ewens (pers. comm.) has pointed out that, with $h = 1/2$ as Ns becomes large (and N large as well) the value of $t_1(1/2N)$ is extremely well approximated by $4(\gamma + \ln 2Ns)/s$, where γ is Euler's constant, approximately 0.577. Thus, the condition that the time between appearances of favorable mutants destined for fixation exceeds their fixation time, $t_1(1/2N)$, is

$$(2NL\mu s)^{-1} \gg 4(\gamma + \ln 2Ns)/s, \qquad (3)$$

or $1 \gg 8NL\mu[\gamma + \ln(2Ns)]$. This inequality is consistent with KJ's condition that $1 \gg 4NL\mu \ln(2Ns)$.

In the numerical discussion by KJ, $\mu = 10^{-9}$ and $N = 10^5$. We have computed the values of $4NL\mu \ln(2Ns)$ for the parameters s and L of KJ's Table 1, and these are reported in our Table 1. For comparison, we have included in parentheses the corresponding values of $8NL\mu[\gamma + \ln(2Ns)]$. Clearly, for the majority of these parameter values, the conditions for a single segregating mutant are not met. In particular, when N is large, the conditions are unlikely to be met. As we discuss below, it is precisely these cases for which sexuals may be most favored. As pointed out by KJ, when more than one locus is segregating, the analysis becomes significantly more complicated by the effects of recombination. Recombination can either help or hurt sexuals in competition with asexuals, depending on the model and parameter values (see e.g., Eshel and Feldman, 1970).

Pool of Loci

The segregation load described by KJ entails some assumptions about the mechanisms by which evolution operates. First, there must be some mechanism by which a relatively constant pool (L) of wild-type loci are produced. This entails a certain degree of stasis over evolutionary time. Instead, it may be that evolution occurs in punctuated steps (Eldredge, 1971; Eldredge and Gould,

TABLE 1. Values of $4NL\mu \ln(2Ns)$ for several levels of selection, s, and numbers of loci, L.

s/L	10	50	100	500	1,000
0.001					2.12 (4.70)
0.005				1.38 (2.99)	2.76 (5.99)
0.01			0.30 (0.65)	1.52 (3.27)	3.04 (6.54)
0.05		0.18 (0.39)	0.37 (0.78)	1.84 (3.91)	3.68 (7.83)
0.1	0.04 (0.08)	0.20 (0.42)	0.40 (0.84)	1.98 (4.19)	3.96 (8.38)

Note: $N = 10^5$, $\mu = 10^{-9}$, and $h = 1/2$. Numbers in parentheses given $8NL\mu[\gamma + \ln(2Ns)]$. See text for the relationship of these values to the conditions for a single segregating mutant.

1972). In this case, occasional times when many loci (L) are capable of advantageous change are separated by long periods when few genetic changes are advantageous. During these extended periods of time, the asexuals would "catch up" to the sexuals and lose their segregation load; sexuals would then be unable to resist encroachment by an asexual population.

Second, under KJ's formulation, the population can accumulate and fix advantageous mutations indefinitely. We might assume, however, that loci from the mutant classes occassionally return to the wild-type class when these loci lose selective importance. The mechanism for this return could be a change in the environment that nullifies the advantage of previously favorable mutants. Clearly, by returning mutant loci periodically to the pool of wild-type loci, both the equilibrium number of heterozygous loci (n) and of homozygous mutant loci are reduced. It is straightforward to show that this effect uniformly reduces the load advantage to sexuals as given by (2a) and that the extent of this reduction can be drastic.

Thus, different conclusions can be reached depending on what is assumed about the fate of mutant loci over evolutionary time. Under the reasonable assumption that there exists some sort of turnover process for the mutant classes, a scenario can easily be envisaged in which the load of the asexuals is not that much greater than the load of the sexuals.

Population Regulation

The final assumption we address is that of local population regulation of the two groups. One of the criticisms often made of load arguments of the kind represented by Equation (2a) is that they do not actually address the process of competition that would occur between the types being compared, since they assume that each of the populations equilibrates in the absence of the other population (see e.g., Wallace, 1970). The same remark applies to the comment by Hedrick and Whittam (1989), who compared the frequency of the advantageous mutant in deterministic populations with different amounts of sexual reproduction. They do not ask whether sexual reproduction outcompetes asexual reproduction. Unless one is willing to assume that the sexual and asexual populations grow independently for a long time and then meet, an argument based on mean fitnesses of the two populations may not be useful.

In the second half of this paper, we explore via Monte Carlo simulation the effects of altering the assumptions about the number of loci subject to advantageous mutation and the level of population regulation. In our model, we fix the total number of loci subject to advantageous mutation. We also assume that the population size is fixed and that sexuals and asexuals compete for access to the next generation on the basis of their genotypes at these loci. We leave the question of recombination to be addressed elsewhere, although we allow more than one mutation to segregate simultaneously. Since the fitness scheme we describe is multiplicative, this should not have a qualitative effect on the results (see e.g., Maynard Smith, 1968).

A STOCHASTIC SIMULATION OF COMPETITION BETWEEN SEXUALS AND ASEXUALS

Model Description

All of the following results are for populations of 100 or 500 individuals in which *sexuals produce only sexuals* and *asexuals produce only asexuals.* This would be the case if the sexual-asexual dichotomy were controlled by one locus with the sexual phe-

notype recessive to the asexual. Each simulation was repeated 1,000 times. The model is a Monte Carlo simulation whereby individuals mate, reproduce, undergo selection and mutation, and then form the next generation of mature individuals. To begin, one individual is chosen at random. If it is sexual, another sexual is chosen at random as its mate, and an offspring is produced, receiving one chromosome from each parent. If it is asexual, it produces a clone, which carries both of its chromosomes. We examined two models of sexual reproduction, which we call "hermaphrodites" and "separate sexes." In the hermaphrodites model, sexuals can produce both male and female gametes, thus each individual can function as either mother or father, and the fecundity of sexuals is assumed to be the same as that of asexuals. This allows us to isolate the evolutionary effect of segregation from the cost of sex. In the two-sex model, sexuals are marked as male or female, asexuals as female. In the initial population, the sexuals are divided equally into males and females. The program searches for a female, and if she is sexual, it then searches for a male mate and reproduction occurs. (Both searches are with replacement.) Again, the offspring receives one chromosome from each parent. The sex of the offspring is determined at random with an equal probability of being male or female. If the mother is asexual, she produces a female clone of herself, and the offspring receives both of her chromosomes. In the two-sex model the "cost of sex" exists because at each mating, only half of the sexuals are "eligible" to be chosen as the primary parent (i.e., the females), whereas in the asexual population, and in the hermaphrodites model all individuals are eligible. Although males contribute to the next generation by mating, the effective size of the sexual population is the number of females. Since the sexual part of population is, on the average, half male, its effective size is half that of an asexual population of the same size every generation.

After an offspring is produced, it undergoes selection. The selection scheme is multiplicative in accordance with the model of Kirkpatrick and Jenkins described above. That is, at each locus, homozygous mutants have a fitness value of $1 + s$, heterozygotes have a fitness value of $1 + hs$, and homozygous wild-type individuals have a fitness value of 1. For example, with 10 loci an individual with two homozygous wild-type loci, one heterozygous locus, and seven mutant homozygous loci has a relative fitness value of $(1 + hs)(1 + s)^7/(1 + s)^{10}$. If an individual's relative fitness value is greater than a random number chosen uniformly in [0, 1], then it enters the next generation. If the individual is not saved, a new set of parents is chosen and a new offspring produced. Once an individual is saved, mutation to the advantageous alleles occurs at a rate μ, which we set at 0.001 for each locus. Mutation is recurrent and unidirectional, and more than one mutation may be segregating at any one time. Once the offspring has undergone mutation, a new parent is chosen, and the cycle continues until an entire new generation (100 or 500 individuals) is produced. Parameters in the model include s, h (which was set at 0.5 for comparison with KJ), the initial frequency of sexuals, and the mutation rate, μ. We considered either $L = 10$ or $L = 20$ loci under selection, all of which were absolutely linked.

Results

The results for the hermaphrodites model are reported in Table 2. For $s = 0.01$, the sexuals "win" (fix in the population) with about the frequency to be expected under a neutral model (approximately their initial frequency in the population). KJ predicted that sexuals will do better as s increases because the load advantage to sexuals will increase. In our simulation, this pattern does hold when the initial number of sexuals is low (4, 20, 50) but not when the number of sexuals is initially large (92, 96, 99). This is true for populations of both size 100 and size 500. Presumably, drift is the overriding force when initial conditions are extreme. When drift is not strong, the effect of increasing the strength of selection is striking. As s increases, the success of the sexuals improves dramatically (especially when their initial numbers are low, e.g., 4%; see Table 2, 10 loci column).

The simulations using two sexes are an attempt to address the case for which sexuals have a twofold cost with respect to fertility. The results are reported in the first

three columns of Table 3. In these simulations, the sexuals win only if they start at very high frequency. Based on our comparison of populations of 100 and 500 individuals, the initial frequencies of sexuals appear less crucial than the initial numbers in determining whether sexuals or asexuals will fix. For both $N = 100$ and $N = 500$, sexuals can win if there are fewer than four asexuals initially in the population. However, for an initial frequency of 99% sexuals, they can fix (about 20% of the time) in a population of 100 but can never fix in a population of 500. When the viability of the asexuals is halved in this model (in a population of 100 individuals), the last column of Table 3 shows that the sexuals do better but not as well as in the hermaphrodites model, implying that this two-sex model imposes a cost on sex that is greater than twofold.

In order to assess how long it takes for the build up of mutations to have some effect on the dynamics, we simulated populations that were either completely sexual or completely asexual and compared the mean fitness of the population at set time intervals. These results are seen in Figure 1. The sexual and asexual populations do diverge but not immediately. After 50 generations, the sexual and asexual populations had equal fitnesses (for all three values of s). For $s = 0.10$, the mean fitness of sexuals grew much faster than the asexuals soon after 50 generations. For $s = 0.01$, the mean fitnesses remained nearly constant and almost equal. If sexuals and asexuals were isolated from one another for sufficiently long, this mechanism could raise the fitness of sexuals enough so that they would be able to outcompete asexuals when they eventually came into contact with one another. However, this argument does not apply to populations that are in constant contact. For comparison, we kept track of the average number of generations until fixation in the two-sex simulations in which sexuals were eliminated ($N = 100$). For the starting condition with the lowest number of sexuals, it took two generations, on the average; in contrast, in runs with 99 sexuals initially present, the average time to elimination of sexuals was about 10 generations. Thus, segregation does, as claimed by KJ, give sexuals a fitness advantage over asexuals over time in our simulations. However, the exclusion of sexuals by asexuals appears to occur in much less time than the build up of advantageous mutations in a finite population. If we assume that sexual reproduction develops in isolation and remains isolated long enough, segregation may allow the sexuals to accrue an advantage sufficient to overcome its twofold disadvantage (subject to specific assumptions and conditions of the model). Another possibility that neither KJ nor our analysis takes into account is that a completely asexual population might accumulate mutations in the heterozygous state in the absence of sexuals. If sexuals then appear in low frequency within that population, it is unclear how they will fare.

Another possible scenario in which sexuals can accumulate advantageous mutants over a long period (allowing them to build up a fitness advantage) would be in a very large population. If the sexuals can be maintained at low frequency for a long time (which might be possible in a sufficiently large population), then they could build up advantageous mutations and eventually be able to outcompete the asexuals. As we saw, however, from the comparison of $N = 100$

TABLE 2. Number of wins by sexuals out of 1,000 (hermaphrodites model).

Initial % sexual	s	10 loci (100)	20 loci (100)	Sexuals' fertility halved (10 loci) (100)
4	0.01	37	39	0
	0.05	51	54	0
	0.10	79	58	0
20	0.01	224	*	0
	0.05	256	*	0
	0.10	269	*	0
50	0.01	498	*	0
	0.05	549	*	0
	0.10	586	*	0
92	0.01	928	943	0
	0.05	942	942	0
	0.10	934	959	0
96	0.01	965	962	1
	0.05	970	968	0
	0.10	966	977	1
99	0.01	992	988	194
	0.05	991	993	205
	0.10	989	993	218

Note: Population sizes in parentheses.
* Not done.

TABLE 3. Number of wins by sexuals out of 1,000 (separate-sexes model).

Initial % sexual	s	10 loci (100)	10 loci (500)	20 loci (100)	Even sex ratio (10 loci) (100)	Asexual viability halved (10 loci) (100)
4	0.01	0	0	0	0	13
	0.05	0	0	0	0	5
	0.10	0	0	0	0	20
20	0.01	0	0	0	0	88
	0.05	0	0	0	0	117
	0.10	0	0	0	0	150
50	0.01	0	*	*	0	317
	0.05	0	*	*	0	384
	0.10	0	*	*	0	431
88	0.01	0	*	*	0	*
	0.05	0	*	*	0	*
	0.10	0	*	*	0	*
92	0.01	0	0	0	0	*
	0.05	0	0	0	0	*
	0.10	0	0	0	0	*
96	0.01	2	*	1	1	*
	0.05	3	*	4	1	*
	0.10	1	*	4	0	*
99	0.01	201	0	194	216	*
	0.05	195	0	212	192	*
	0.10	188	0	194	179	*
99.6	0.01	*	46	*	*	*
	0.05	*	43	*	*	*
	0.10	*	36	*	*	*

* Not done.

and $N = 500$, the population would have to be orders of magnitude larger to have any effect.

Is the Cost of Sex Twofold?

Since the simulations of the two-sex model in which the viability of asexuals was halved suggested that the cost of sex is slightly greater than twofold in this model, we used simulations to investigate other factors that might have influenced the results. The effect of mutation was tested by comparing results with the two-sex model for $s = 0.0$ and $s > 0.0$ (0.01, 0.05, 0.10). We also tested the effect of doubling the mutation rate in the two-sex model. Neither of these alterations to the model significantly changed the results.

We also examined whether skew in the sex ratio could have raised the cost of sex to greater than twofold. This was tested by imposing a 50:50 sex ratio on the sexual subpopulation and by looking at the hermaphrodites model when the fitness of sexuals was halved relative to the asexuals. Neither of these changes improved the success of the sexuals to an appreciable degree. Thus, it appears that neither the mutation process itself nor sex-ratio selection in the sexuals accounts for the lower-than-expected success of sexuals in the two-sex model.

DISCUSSION

The overall conclusions that we draw from this study are that, like Muller's ratchet, segregation can under certain circumstances confer an advantage to sexual systems. However, this advantage is often negligible in finite populations and cannot pay the cost of sex for a newly arisen sexual population in the midst of asexual competitors. This should not be regarded as surprising since our simulations include the following two factors: (1) a fixed number of loci, resulting in a reduction in the number of wild-type loci with each fixation of a mutant; and (2) the apparent elimination of sexuals from the population before they have a chance to

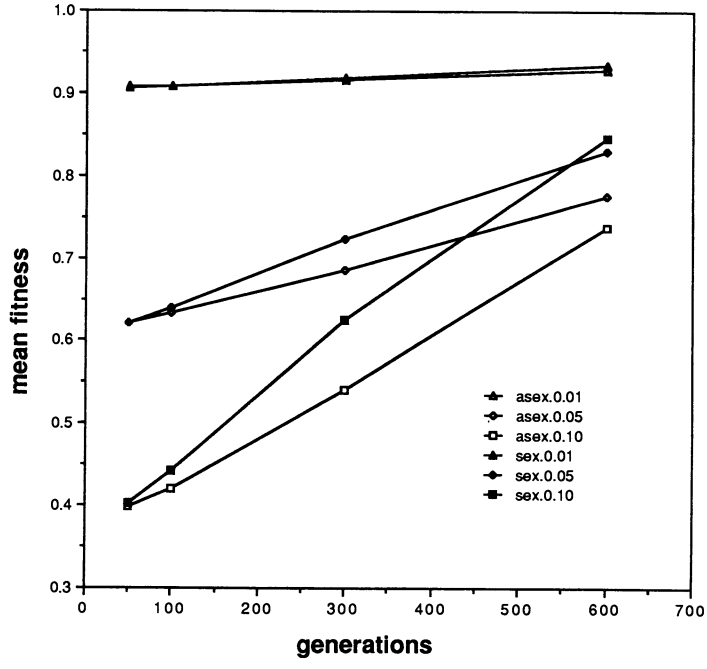

FIG. 1. Comparison of mean fitness over time between purely sexual and purely asexual populations with advantageous mutation. The selective advantage of mutant alleles, s, takes values 0.01, 0.05, and 0.10 and $h = 1/2$ at each of 10 loci in both cases. The population size is 100, and recurrent mutation occurs at rate 0.001 per locus per generation. In the sexual case, mating is by random union of gametes.

compete successfully against asexuals by acquiring advantageous mutations (in KJ's terms, before the asexuals build up a segregation load). Our model does involve a kind of group selection because there is no gene flow between the sexuals and asexuals. Kirkpatrick and Jenkins compared the two species only after attainment of the equilibrium defined by (1), whereas in our model there is *competition* to produce a fixed number in the population at every generation. The selection process at the viability loci is much slower than the competition process between the sexuals and asexuals. We conjecture that gene flow, or segregation among the sexuals and asexuals, would have even worse consequences for the sexuals if sexuals were able to produce asexual offspring but not vice versa. The cost of sex appears to be slightly higher than twofold, but we have been unable to describe it any more specifically in our relatively small populations. Note that KJ's condition for segregation to have an effect ($4N\mu \ln(2Ns) \ll 1$) is not met in most of the simulations. However, the sexuals do not fare better in our simulations when the condition is met than when it is not.

The mutation rate of 10^{-3} to advantageous alleles in our simulations almost certainly entails that more than one mutation is segregating at some time during the evolution of our population. Although the criterion (2a) does not involve μ, the rate at which the "equilibrium" that produces (2a) is approached is proportional to μ. If (2a) is the appropriate criterion, then a higher mutation rate to advantageous alleles will bring the population more quickly into equilibrium, at which point sexuals should enjoy their greatest advantage. In other words, it is unlikely that the inability of the sexuals to outcompete asexuals in our simulation is due to the mutation rate of 10^{-3}. In fact, with lower mutation rates, sexuals may do worse than in our simulations. Increased mutation rates, however, may also benefit the asexuals since they will remain "fixed" in the heterozygous state for shorter periods. It should be noted that high mutation rates

to *deleterious* alleles may produce an entirely different kind of theory because of the ability of sexuals to eliminate deleterious combinations. Models of this kind have been pursued by Kondrashov (1988) and Charlesworth (1990).

By assuming absolute linkage, we know that sexuals were not aided by recombination in our simulations even though more than one mutation could be segregating simultaneously. It is not at all clear, however, that the presence of recombination would benefit the sexuals. With multiplicative fitnesses (at least in large populations), recombination is expected to provide no advantage (Maynard Smith, 1968). With epistasis, it may be advantageous or disadvantageous (Eshel and Feldman, 1970), depending on the shape of the fitness surface. The effect of drift on the advantage of recombination is ambiguous, although the work of Karlin (1973) suggests that the expected time to fixation of the multiply favorable mutant chromosome may be increased by recombination. It therefore appears that a stochastic treatment of the process of accumulation of favored mutations does not support the idea that segregation either with or without recombination provides sufficient advantage to the sexuals when they are together in a population with asexual competitors.

Acknowledgments

The authors are grateful to W. Ewens, for numerous discussions and comments on the manuscript and for sharing his unpublished results, and to M. Uyenoyama, F. Christiansen, M. Nordborg, M. Kirkpatrick, and M. Turelli, who made a number of important suggestions. We also thank A. Bergman and M. Nordborg for helpful discussions about the Monte Carlo simulations. Finally, we are indebted to C. Nakashima for her excellence (and patience) in the preparation of this manuscript. Research supported in part by NIH grants GM 28016 and GM 10452 and by a grant from the US–Israel Binational Science Foundation.

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Corresponding Editor: J. Bull