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Mutation-Selection Balance, Dominance and the Maintenance of Sex

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ABSTRACT

A leading hypothesis for the evolutionary function of sex postulates that sex is an adaptation that purges deleterious mutations from the genome, thereby increasing the equilibrium mean fitness of a sexual population relative to its asexual competitor. This hypothesis requires two necessary conditions: first, the mutation rate per genome must be of order one, and, second, multiple mutations within a genome must act with positive epistasis, that is, two or more mutations of different genes must be more harmful together than if they acted independently. Here, by reconsidering the theory of mutation-selection balance at a single diploid gene locus, we demonstrate a significant advantage of sex due to nearly recessive mutations provided the mutation rate per genome is of order one. The assumption of positive epistasis is unnecessary, and multiple mutations may be assumed to act independently.

SEXUAL reproduction predominates among eukaryotes, and in general though with some important exceptions (Judson and Normark 1996) asexual clones tend to be short-lived offshoots from sexual species. However, there are several well-known inefficiencies to sexual reproduction—including the twofold cost of males in a species with separate sexes (Maynard Smith 1978)—and for species to maintain themselves against reproductively isolated but ecologically sharing asexual relatives, selective advantages must outweigh disadvantages. Various hypotheses, not necessarily mutually exclusive, have been proposed that purport to give sex the necessary advantage (for reviews, see Bell 1982; Kondrashov 1993; Crow 1994; Hurst and Peck 1996; Barton and Charlesworth 1998). One of the most appealing of such hypotheses due to its wide applicability to populations of all sizes in all ecologies is that sex is maintained as a way of efficiently purging deleterious mutations from the genome (Kondrashov 1982). The simplest analytic form of this model assumes truncation selection for which all individuals with more than a threshold number of mutations are selectively eliminated, while those with a fewer number survive and reproduce. Compared to an asexual population, a smaller proportion of the sexual population is eliminated each generation but with a larger number of mutations per individual. With mutation rates of order one per genome per generation, a population of sexually reproducing organisms can have a much higher mean fitness than a population of asexual relatives. Although truncation selection is an idealization, the basic idea also applies to more general types of synergistic epistasis among deleterious mutations. However, if mutations at different loci act independently, resulting in a multiplicative reduction in fitness with increasing number of mutations, Kondrashov's model yields no advantage for sex. Experimental support of this model has been sought: the deleterious mutation rate per genome has been difficult to measure experimentally (Peck and Eyre-Walker 1997), though rates of order unity are plausible. Some evidence against positive epistasis for deleterious mutations in bacteria, however, has been reported (Elena and Lenski 1997).

Here, we show that as much as a twofold advantage to sexual reproduction can be realized for mutation rates per genome of order unity even for the simpler and more general situation in which deleterious mutations at different loci act independently provided that the mutations are nearly recessive. To develop our argument, we first reconsider the mathematical theory of mutation-selection balance at a single diploid gene locus. It is perhaps surprising that anything new can be discovered in this regard since such calculations have a long history (Haldane 1937; Muller 1950). In fact, it is often stated that the mutational load contribution from a single locus is either one or two times the mutation rate for recessive or partially dominant mutations, respectively, and is independent of both the selection coefficient and the mating system. However, the precise dependence of the load on the dominance differs significantly for sexual and asexual reproduction and this seems to have been overlooked previously.

Now recessivity of deleterious mutations can be viewed as intralocus synergistic epistasis in contrast to the interlocus epistasis assumed in the Kondrashov model. However, a completely recessive lethal mutation is like truncation selection acting at a single locus, and here the mutational loads for sexual and asexual reproduction are identical as a consequence of diploid genetics.

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Nevertheless, intralocus epistasis due to small dominance values does yield an advantage to sex, and this is quantified in this article.

Since our entire thesis hinges on the equilibrium solutions of mutation-selection balance, we first redevelop this mathematical theory in perhaps greater detail than done previously. Multiple equilibrium solutions for both sexual and asexual mating systems are determined and their stability investigated. Armed with these exact analytical results, the corresponding mutational loads are compared and a range of dominance values are determined for which sexual reproduction has a large advantage. Our article concludes with a discussion as to whether this advantage may actually be realized in nature.

THE MODEL

The standard model for mutation-selection balance is summarized in Table 1. We assume an infinite population with separated generations and a deleterious mutation rate u, which randomly converts an effective (wild-type) gene A to a nonfunctional (mutant) gene a; back mutations are neglected. The selective advantage of A is parameterized by s and its dominance by h, where $0 \leq s, h \leq 1$; selection is assumed to act on the diploid. We unify the treatment of both sexual and asexual reproduction by assuming a population in which each individual on average produces a proportion α of progeny asexually and $1 - \alpha$ sexually. Asexual reproduction ($\alpha = 1$) produces offspring that, in the absence of mutation, are genetically identical to the parent; sexual reproduction ($\alpha = 0$) is assumed to be with random mating.

Let p and q denote the frequencies of the wild-type gene A and the mutant gene a, and P, Q, and R the frequencies of the genotypes AA, Aa, and aa, respectively. We take P and p as our independent frequencies; the other three frequencies are determined from

$$q = 1 - p, \quad Q = 2(p - P), \quad R = 1 - 2p + P. \tag{1}$$

If primes denote the frequencies in the next generation, standard analysis using Table 1 and assuming random mating during sexual reproduction results in

TABLE 1

Standard diploid model for mutation-selection balance

Genotype	AA	Aa	aa
Fitness	1	$1 - sh$	$1 - s$
Frequency in zygote	P	Q	R
Frequency in adult	P/w	$(1 - sh)Q/w$	$(1 - s)R/w$

Genotype frequencies add to unity: $P + Q + R = 1$. The mean zygote fitness is $w = 1 - shQ - sR$.

$$p' = \frac{(1 - u)[(1 - sh)p + shP]}{w}, \tag{2}$$

$$P' = \frac{\alpha(1 - u)^2 P}{w} + (1 - \alpha)p'^2, \tag{3}$$

with the mean zygote fitness of the present generation given in terms of p and P by

$$w = 1 - s + 2s(1 - h)p - s(1 - 2h)P. \tag{4}$$

The evolution equation (2) for the gene frequency p does not contain α explicitly: direct changes in gene frequencies depend only on selection and mutation and are independent of the mating system. However, the influence of the mating system is evident in the evolution equation (3) for the genotype P, and gene frequencies subsequently change because of selection and mutation acting on the genotypes.

RESULTS

Sexual reproduction: Here $\alpha = 0$, and (3) reduces to

$$P' = p'^2, \tag{5}$$

which is the celebrated Hardy-Weinberg law, attained after a single generation of random mating.

Equilibrium solutions to (2) and (5) are determined by setting primed and unprimed frequencies equal. The equations simplify slightly if written for the mutant gene frequency q. Assuming at least one generation of random mating, the evolution equation for q' in terms of q is given by the single equation

$$q' = \frac{u + [1 - u - sh(1 + u)]q - s[1 - h(1 + u)]q^2}{1 - 2shq - s(1 - 2h)q^2}, \tag{6}$$

and with $q' = q$, a cubic equation is obtained with three possible solutions, denoted here as q_1, q_2, and q_3. The first solution is $q_1 = 1$, obtained due to the neglect of back mutation in the model. The other solutions q_2 and q_3 are the two roots of the quadratic equation

$$s(1 - 2h)q^2 + sh(1 + u)q - u = 0 \tag{7}$$

(Crow 1970), given explicitly by

$$q_2 = \frac{h(1 + u)}{2(2h - 1)}\left[1 + \sqrt{1 - \frac{4(2h - 1)u}{sh^2(1 + u)^2}}\right], \tag{8}$$

$$q_3 = \frac{h(1 + u)}{2(2h - 1)}\left[1 - \sqrt{1 - \frac{4(2h - 1)u}{sh^2(1 + u)^2}}\right]. \tag{9}$$

The special case $h = \frac{1}{2}$ for which the quadratic equation becomes linear can be determined directly from (7). The mean zygote fitness w (4) corresponding to the equilibrium solutions q_1, q_2, and q_3 is given by

$$w_1 = 1 - s, \quad w_{2,3} = (1 - u)(1 - shq_{2,3}). \tag{10}$$

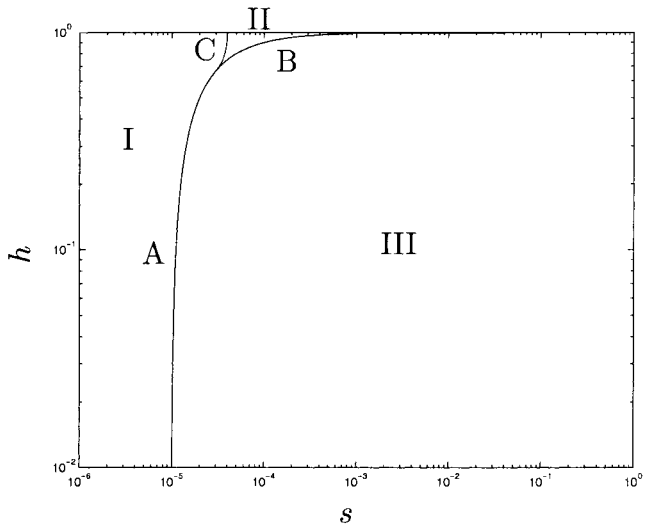

FIGURE 1.—Regions in the *s-h* parameter space with different sexual solutions of the mutation-selection balance equations. The mutation rate is taken as $u = 10^{-5}$.

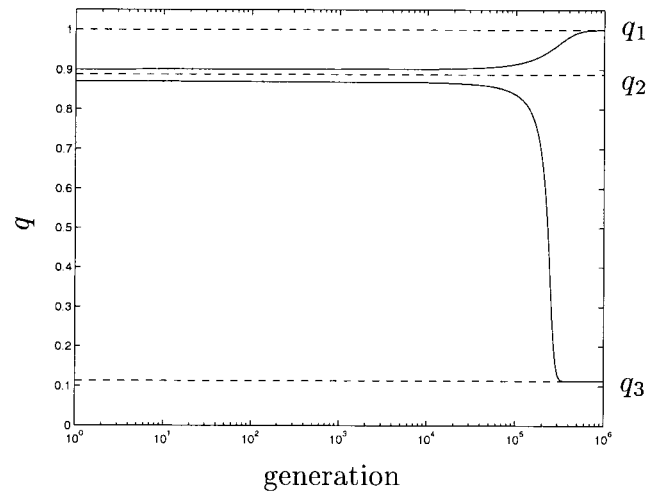

FIGURE 2.—Evolution of q in region II of Figure 1 with initial conditions above and below q_2. Dashed lines are the analytical equilibrium solutions and solid lines are the numerical results. Here, $u = 10^{-5}$, $h = 1.0$, and $s = 10^{-4}$.

The solution q_1 exits for all s and h; the solutions q_2 and q_3 exist only if the square root is real and the solutions lie between zero and unity. In Figure 1, the solution domain is represented by the *s-h* plane, and three distinct regions denoted by I, II, and III are shown. The boundary curves labeled A, B, and C are determined from solutions of the equations $q_1 = q_3$, $q_1 = q_2$, and $q_2 = q_3$, respectively, and are given by

$$\text{A, B: } h = \frac{s - u}{s(1 - u)}; \quad \text{C: } s = \frac{4(2h - 1)u}{h^2(1 + u)^2}. \quad (11)$$

The intersection of these three curves occurs at $(s, h) = (u(3 - u)/(1 + u), 2/(3 - u)) \approx (3u, 2/3)$ and is the point at which A splits into B and C. Solution q_2 exists only in region II; solution q_3 exists in regions II and III.

The stability of the three solutions may be determined analytically from (6) or by numerical experiment. One finds q_1 is stable in regions I and II and q_3 is stable in regions II and III. The solution q_2 is nowhere stable.

These results may be interpreted as follows. Moving from region I directly to region III across the boundary curve A, the solutions q_1 and q_3 exchange stability. In region II both solutions q_1 and q_3 are stable to small perturbation while solution q_2 is unstable. Furthermore, initial conditions for which $q < q_2$ converge to the solution q_1 while for $q > q_2$ the solution converges to q_3. The simultaneous existence of two equilibrium solutions is demonstrated by numerical solution of (6) within region II, shown in Figure 2 for two different initial values of q. The equilibrium solutions q_1, q_2, and q_3 are shown by dashed lines, and the numerical evolution of q is shown by solid lines. We have assumed the values $u = 10^{-5}$, $h = 1.0$, and $s = 10^{-4}$, and initial conditions corresponding to $q = 0.87$ and 0.90. For these values, $q_1 = 1$, $q_2 = 0.8873$, and $q_3 = 0.1127$.

The bifurcation diagram obtained by moving across regions I, II, and III horizontally along the line $h = 0.9$ is shown in Figure 3. The solid (dotted) lines represent stable (unstable) solutions. The initial appearance of q_2 and q_3 when they become real at $s = 4(2h - 1)u/h^2(1 + u)^2 \approx 4 \times 10^{-5}$ is called a saddle-node bifurcation. The collision of q_2 with q_1 at $s = u/[1 - h(1 - u)] \approx 10^{-4}$ is called a transcritical bifurcation.

Asexual reproduction: Here $\alpha = 1$, and (3) reduces to

$$P' = \frac{(1 - u)^2 P}{w}. \quad (12)$$

There are now two coupled evolution equations given by (2) and (12), although again there are three equilibrium solutions. Solving for the genotype frequencies P_i,

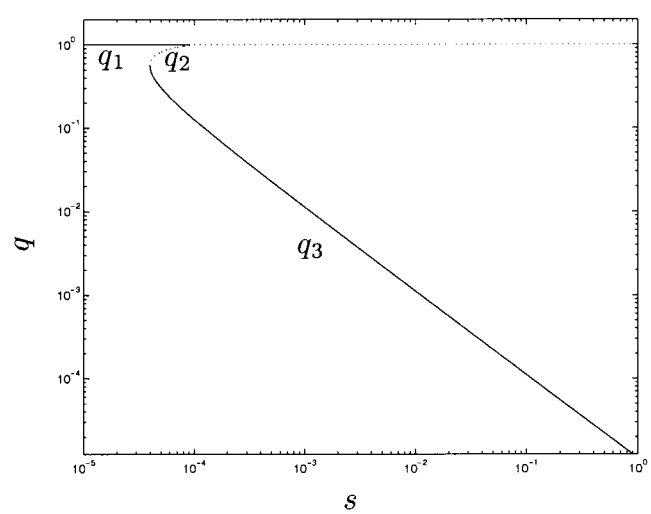

FIGURE 3.—Bifurcation diagram varying s for fixed $h = 0.9$, $u = 10^{-5}$.

Q_i, R_i, with $i = 1, 2, 3$, the equilibrium solutions are

$$P_1 = 0, \quad Q_1 = 0, \qquad R_1 = 1; \tag{13}$$

$$P_2 = 0, \quad Q_2 = 1 - \frac{u(1 - sh)}{s(1 - h)}, \quad R_2 = \frac{u(1 - sh)}{s(1 - h)}; \tag{14}$$

$$P_3 = \frac{(sh - u)[s - u(2 - u)]}{s[sh + u(1 - 2h)]},$$

$$Q_3 = \frac{2u[s - u(2 - u)]}{s[sh + u(1 - 2h)]},$$

$$R_3 = \frac{u^2(2 - sh - u)}{s[sh + u(1 - 2h)]}. \tag{15}$$

The first solution is identical to that obtained from sexual reproduction and exists for all values of s and h. The second solution exists provided $Q_2 \geq 0$ and is unique to asexual reproduction: sexual reproduction necessarily produces wild-type homozygotes AA from the matings $Aa \times Aa$. The third solution exists provided P_3, $Q_3 \geq 0$. The mean zygote fitnesses corresponding to the equilibrium solutions are given by

$$w_1 = 1 - s, \quad w_2 = (1 - u)(1 - sh), \quad w_3 = (1 - u)^2, \tag{16}$$

and w_3 is observed to be independent of both s and h. The solution for w_3 is obvious from (12) with $P' = P$ provided $P \neq 0$. Note also that when $h = 0$, (2) with $p' = p$ has solutions $p = 0$ or $w = 1 - u$. The first solution corresponds to $R = 1$ and the second to $R = u/s$, and both solutions are independent of the mating system. However, if $R = u/s$ the corresponding solutions for P and Q must be determined using (3) and therefore depend on the mating system.

The stability of the equilibrium solutions for asexual reproduction may be guessed intuitively and confirmed numerically: in the region of the parameter space in which more than two equilibrium solutions exist, the stable solution is the one with the greatest mean zygote fitness. From (16), the first solution is stable only when it is the unique solution, the second solution is stable only when it and the first solution are the only solutions, and the third solution is stable wherever it exists. These results are shown graphically in Figure 4. Three distinct regions denoted I, II, and III are evident, corresponding to the regions in which the first, second, and third equilibrium solutions are stable, respectively. The boundary curves labeled A, B, and C are given by

$$\text{A: } h = \frac{s - u}{s(1 - u)}; \quad \text{B: } s = u(2 - u); \quad \text{C: } h = u/s; \tag{17}$$

and all three curves intersect at the point $(s, h) = (u(2 - u), 1/(2 - u)) \approx (2u, 1/2)$. The solutions exchange stability as the boundary curves are passed within the s, h parameter space.

Finally, if a back mutation rate v (from a to A) is included in the genetic model the mathematical structures of the sexual and asexual solutions are modified. In particular, unstable solutions no longer exist. However, for $0 < v \ll u$, the stable solutions determined above are well approximated with the main difference being that the genotype frequencies are never identically zero. For instance, in region I of Figures 1 and 4, $P = O(v^2)$ and $Q = O(v)$; and in region II of Figure 4, $P = O(v)$.

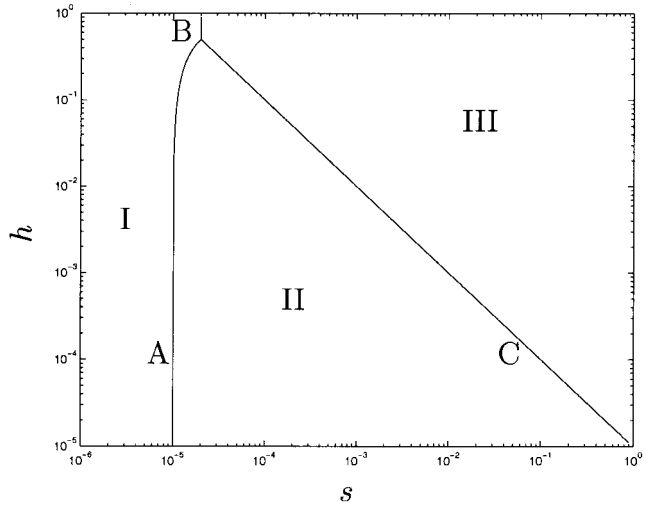

FIGURE 4.—Regions in the s-h parameter space for which three different asexual solutions of the mutation-selection balance equations are stable. The mutation rate is taken as $u = 10^{-5}$.

Comparison of reproductive systems: We consider n diploid genes per genome ($n \gg 1$) and $U = nu$, where U, of order unity, is the (haploid) genome mutation rate. Assuming fitnesses to be multiplicative and genes to be in linkage equilibrium and defining here w_i to be the mean zygote fitness contributed from locus i and $l_i = 1 - w_i$ to be the corresponding genetic load, the mean fitness of a population is given by

$$W = \prod_{i=1}^{n} w_i = \prod_{i=1}^{n} (1 - l_i) \approx \exp(-n\langle l \rangle), \tag{18}$$

where $\langle l \rangle$ is the average contribution to the genetic load from a single locus. Thus the relative advantage to sexual reproduction is given by

$$W_{\text{sex}}/W_{\text{asex}} = \exp[n(\langle l \rangle_{\text{asex}} - \langle l \rangle_{\text{sex}})], \tag{19}$$

and it is evident from (19) that for there to be a significant advantage to sexual reproduction, $\langle l \rangle_{\text{asex}} - \langle l \rangle_{\text{sex}} = O(u)$.

We look for differences in the mean genetic loads between asexual and sexual reproduction by fixing the selection coefficient s and varying the dominance h. The mutant gene is completely recessive when $h = 0$ and completely dominant when $h = 1$; we define the value of h for semidominance to be when the fitness of the heterozygote is the geometric mean of the fitnesses of the homozygotes, *i.e.*, $1 - sh = \sqrt{1 - s}$, or

TABLE 2

Genotype frequencies for asexual and sexual reproductive systems when $h = 0$

Genotype	AA	Aa	aa
Frequencies	P	Q	R
(asexual)	0	$1 - u/s$	u/s
(sexual)	$(1 - \sqrt{u/s})^2$	$2\sqrt{u/s}(1 - \sqrt{u/s})$	u/s

$$h_{\mathrm{sd}} = \frac{1}{1 + \sqrt{1 - s}}, \quad \text{semidominance.} \tag{20}$$

Furthermore, we call the mutant gene partially recessive when $0 < h < h_{\mathrm{sd}}$ and partially dominant when $h_{\mathrm{sd}} < h < 1$ (though the more common usage for partial dominance is simply $h > 0$). Note that h_{sd} takes the minimum value of ½ when $s = 0$ (neutral mutation) and increases to unity when $s = 1$ (lethal mutation).

The equilibrium genotype frequencies obtained for sexual and asexual reproduction are identical for semidominance. In fact, under the assumption that $P = p^2$ initially, (3) can be shown assuming semidominance to reduce to $P' = p'^2$, independent of α. For $h = h_{\mathrm{sd}}$, the diploid gene under asexual reproduction is equivalent to two haploid genes with multiplicative fitnesses, and these genes then satisfy the Hardy-Weinberg law in equilibrium even without Mendelian segregation.

When the mutant gene is partially recessive, zygotes produced by sexual reproduction have higher equilibrium mean fitness than those produced asexually, with the reverse being true when the mutant gene is partially dominant. Although in principle semidominance is an important dividing line between the two reproductive systems, when s, $h \gg u$ an expansion of the genotype frequencies in powers of the mutation rate $u \ll 1$ shows that for both sexual and asexual reproduction $P = 1 + O(u)$, $Q = 2u/sh + O(u^2)$, and $R = O(u^2)$. The mutational load $l = s(hQ + R)$ thus has contribution of $O(u)$ only from the heterozygote and is well approximated by $2u$, a long-established result (Haldane 1937). The genetic load contribution from mutant homozygotes differs in the two reproductive systems but is $O(u^2)$ and thus negligible in (19).

It is only for $h = O(u)$ that a genetic load difference of order u can be found between sexual and asexual reproduction. For completely recessive mutations, the genotype frequencies of the asexual and sexual reproductive systems are given in Table 2; as noted previously the values of R are identical and a genetic load of u is contributed by the mutant homozygotes in both populations. However, the values of P and Q differ widely between the two reproductive systems. Under asexual reproduction, P is necessarily zero since there is no selection in heterozygotes to balance the mutation of AA to Aa; with sexual reproduction AA is produced each generation by the matings $Aa \times Aa$. Also, eliminated mutant homozygotes are replenished each generation in the asexual population by direct mutation of heterozygotes and in the sexual population primarily by the mating of two heterozygotes. For nearly recessive mutations with $h = u/s$ an additional genetic load of u is contributed by the heterozygotes in the asexual population, whereas the contribution from the heterozygotes in the sexual population is smaller by a factor proportional to $\sqrt{u/s}$. The depression of heterozygosity in the sexual population when the mutant gene is nearly recessive thus reduces its genetic load.

It is therefore of interest to compute the genetic load for $h = \xi u/s$, with $u/s \ll 1$. For the asexual mating system we obtain an exact result from (16),

$$l_{\mathrm{asex}} = \begin{cases} u + \xi u(1 - u), & \text{if } \xi < 1; \\ u(2 - u), & \text{if } \xi \geq 1; \end{cases} \tag{21}$$

and for the sexual mating system from (10) to leading-order in u/s with $h \ll \sqrt{u/s}$,

$$l_{\mathrm{sex}} \approx u(1 + \xi\sqrt{u/s}). \tag{22}$$

Substituting in the genetic loads for the sexual and asexual populations into (19), and for convenience assuming that the probability distributions of u, s, and ξ are sharp, we obtain our main result, valid to leading-order in u/s:

$$W_{\mathrm{sex}}/W_{\mathrm{asex}} = \begin{cases} \exp(\xi U(1 - \sqrt{u/s})), & \text{if } 0 \leq \xi \leq 1; \\ \exp(U(1 - \xi\sqrt{u/s})), & \text{if } 1 \leq \xi \ll \sqrt{s/u}. \end{cases} \tag{23}$$

The maximum advantage of sex occurs at $\xi = 1$, corresponding to a nearly recessive mutation with $h = u/s$. Here, the advantage of sex is approximately $\exp(U)$, independent of s. The advantage decreases sharply for $\xi < 1$ as the mutant gene becomes completely recessive, but decreases gradually for $\xi > 1$. When $h = \sqrt{u/s}$, another calculation shows that the advantage of sex is approximately $\exp(\alpha U)$, with $\alpha = (3 - \sqrt{5})/2 \approx 0.38$. For $h \gg \sqrt{u/s}$, the mean fitnesses of the sexual and asexual populations are approximately the same. Thus an appreciable advantage for sex when U is of order unity is found within the range of dominance values given by $u/s \leq h < \sqrt{u/s}$. In Figure 5, the precise numerical result for $W_{\mathrm{sex}}/W_{\mathrm{asex}}$ is plotted *vs.* h for $u = 10^{-5}$, $n = 10^5$ (so that $U = 1.0$), and for $s = 1.0$, 0.1, 0.01; and the numerical results agree with our approximate analysis.

If the probability distributions of u, ξ, and s are not sharp—for instance the distribution of s is likely to be bimodal with one group of mutations being lethal and another group having intermediate effects—the above analysis requires modification in the computation of the average mutational load per locus. Nevertheless, the

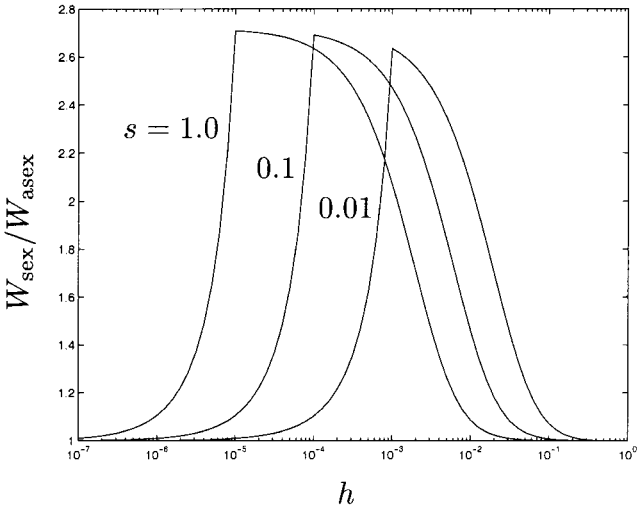

FIGURE 5.—Ratio of the mean fitness of the sexual population to that of the asexual population *vs.* the dominance h for three representative values of s. We have assumed $u = 10^{-5}$ and $n = 10^5$ so that $U = 1.0$.

simplified calculation presented here serves as a useful approximation and clearly demonstrates what was a previously unrecognized advantage to sexual reproduction if a sufficient number of mutations are nearly recessive.

DISCUSSION

The important question remains as to whether a sufficient number of genes have dominance values lying within the range $u/s < h < \sqrt{u/s}$ for which sexual reproduction has a substantial selective advantage. It is long known (MULLER 1950) that the great majority of mutant genes are partially recessive, and Drosophila data suggest that h is negatively correlated with s (CHARLESWORTH 1979). Drosophila studies (CROW and SIMMONS 1983) also give the estimate $u = 2 \times 10^{-6}$ for the lethal ($s = 1$) mutation rate affecting ~5000 loci. For lethal mutations to contribute to the advantage of sex in our model requires $h < \sqrt{u}$, corresponding to a smaller than two-tenths of 1% viability decrement for the heterozygote; however, the data suggest viability decrements of ~2%, which seems an order of magnitude too large for our results to be applicable. Nevertheless, the genome mutation rate from lethal mutations is only ~0.01 so that if our model is biologically relevant most of the advantage for sex is likely to come from mildly deleterious mutations for which the Drosophila estimates are much less reliable, though here, too, evidence points to appreciable heterozygous effects on fitness.

Another relevant question concerns the evolution of dominance, which is an important fundamental problem with a long history of debate beginning with FISHER (1928). Expanding on earlier work of WRIGHT (1934), a proximate argument for the nearly recessive nature of most mutant genes has been given in terms of biochemistry (KACSER and BURNS 1981); however, a generally applicable adaptive argument is still lacking (CHARLESWORTH 1979; BOURGUET 1999), and our work offers the intriguing suggestion that the evolution of dominance and the maintenance of sexual reproduction may be related. For instance, one could envision a genetic model in which dominance values evolve in a sexually reproducing species in response to competition with reproductively isolated asexual competitors.

We have compared the mutational loads for asexual and sexual reproduction. Our model equations (2) and (3) also apply to organisms that reproduce asexually with frequency α. Numerical solution of our model for a range of values of α shows that a little sex is almost as advantageous as a lot, in agreement with other model results (GREEN and NOAKES 1995).

Finally, the advantage to sex demonstrated here arises from deleterious mutations segregating on single loci. Another but different advantage to sex also due to Mendelian segregation (KIRKPATRICK and JENKINS 1989) arises from beneficial mutations. In this earlier work, it is assumed that the mutant homozygote is of highest fitness, the heterozygote of intermediate fitness, and the wild-type homozygote of lowest fitness. Rare mutations are expected to occur first as heterozygotes. In the sexual population, homozygous mutants result from the mating of two heterozygotes for which the mutant gene may be identical by descent; in the asexual population, mutant homozygotes arise only if the beneficial mutation occurs in descendants of the original mutated ancestor. The latter process has much smaller probability than the former, and it is likely that the beneficial mutation will become fixed in homozygous form earlier in the sexual than in the asexual population. The sexual population will thus have a higher mean fitness. Both this advantage to sex from beneficial mutations and the advantage demonstrated in our work from deleterious mutations require selection to be acting on diploids and cannot contribute to the maintenance of sex in species that are haploid for most of their life cycle (MABLE and OTTO 1998).

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