

# On the Evolutionary Advantage of Fitness-Associated Recombination

Lilach Hadany<sup>\*,†,1</sup> and Tuvik Beker<sup>‡</sup>

<sup>\*</sup>*School of Mathematical Sciences, Tel Aviv University, Tel Aviv 69978, Israel,* <sup>†</sup>*Department of Biological Sciences, Stanford University, Stanford, California 94305 and* <sup>‡</sup>*Interdisciplinary Center for Neural Computation, Hebrew University, Jerusalem 91904, Israel*

Manuscript received December 31, 2002

Accepted for publication June 20, 2003

## ABSTRACT

The adaptive value of recombination remains something of a puzzle. One of the basic problems is that recombination not only creates new and advantageous genetic combinations, but also breaks down existing good ones. A negative correlation between the fitness of an individual and its recombination rate would result in prolonged integrity of fitter genetic combinations while enabling less fit ones to produce new combinations. Such a correlation could be mediated by various factors, including stress responses, age, or direct DNA damage. For haploid population models, we show that an allele for such fitness-associated recombination (FAR) can spread both in asexual populations and in populations reproducing sexually at any uniform recombination rate. FAR also carries an advantage for the population as a whole, resulting in a higher average fitness at mutation-selection balance. These results are demonstrated in populations adapting to new environments as well as in well-adapted populations coping with deleterious mutations. Current experimental results providing evidence for the existence of FAR in nature are discussed.

THE evolutionary function of recombination has not yet been fully understood, despite more than seven decades of theoretical research in the field (MAYNARD SMITH 1978; BELL 1982). The models put forward to explain its possible adaptive benefits can be divided into two classes. One class of models dealt with the long-term effects of recombination at the population level. Under a constant environment and no mutations, mean fitness tends to decrease with recombination (KIMURA 1956; LEWONTIN 1971). MULLER (1964) suggested deleterious mutation and finite population effects to explain the advantage of recombination. His “ratchet” argument is based on the fact that in a small population subject to deleterious mutations the superior type present in the population at any given time is bound to eventually be lost to drift. KONDRASHOV (1988) suggested a similar argument that is not restricted to small populations. Under an assumption of synergistic epistasis between deleterious mutations, recombination can increase average fitness even in an infinite population. Recombination has an identical effect in both situations, breaking the linkage disequilibrium and recreating individuals with a low number of deleterious mutations.

FISHER (1930) suggested that recombination might accelerate adaptation to a changing environment, since it allows different beneficial mutations to appear together in the same individual more frequently. While this is true in some cases (CROW and KIMURA 1965;

HAMILTON 1980), there are also counter-examples where this effect is disadvantageous. Under certain fitness landscapes and initial conditions, recombination tends to break fitter combinations more than it acts to create new ones (ESHEL and FELDMAN 1970). It thus seems that an ideal form of recombination (in terms of the whole population) is one that breaks down unfit combinations with a higher probability than it breaks fitter ones. In other words, recombination that is negatively correlated with fitness (ZHUCHENKO and KOROL 1983; REDFIELD 1988) gains the benefit of bringing together beneficial alleles without breaking apart good combinations. Hereafter we term such a form of recombination “fitness-associated recombination” (FAR) to distinguish it from the classical model of recombination at a uniform rate (UR).

Another approach to the dynamic effects of recombination, initiated by NEI (1967), studies selectively neutral modifier genes that control the rate of recombination. This approach is oriented at the level of the individual, studying the evolution of recombination as the change in the frequencies of modifier genes. In the absence of deleterious mutations or environmental changes, a recombination modifier would tend to increase from rarity only if it reduces the recombination rate between selected loci (LIBERMAN and FELDMAN 1986). If deleterious mutations are assumed, it was shown by FELDMAN *et al.* (1980) that in a two-locus model uniform recombination might evolve only if there is negative epistasis between the selected loci. Negative epistasis is also necessary for recombination to be favored in a model assuming directional selection (BARTON 1995). Similar to the population level, a different

<sup>1</sup>*Corresponding author:* Department of Biological Sciences, 371 Serra Mall, Stanford University, Stanford, CA 94305 5020.  
E-mail: lilach@charles.stanford.edu

result can be obtained by relaxing the assumption of uniform recombination. If recombination is negatively associated with fitness, the gene controlling recombination would tend to appear more frequently together with advantageous genomic backgrounds (GESSLER and XU 2000). As a result, FAR could spread in the population.

In this article we study the evolvability of FAR using a series of haploid models, showing that an allele for FAR will tend to increase from rarity to fixation in any population with a uniform recombination rate. This includes both sexual populations with a uniform recombination rate and asexual populations, regarded as having a recombination rate zero. Furthermore, FAR is stable against back mutations to UR. In addition, we study the effect of FAR on the average population fitness. We show that populations with fitness-associated recombination tend to have a higher average fitness than populations with a uniform recombination rate. These results do not require negative epistasis between the selected loci or a small population size—fitness-associated recombination can evolve even from an initial linkage equilibrium in an infinite population.

#### THE ASSOCIATION BETWEEN FITNESS AND RECOMBINATION

For an association between fitness and recombination to occur, it is sufficient that some correlating factor  $s$  exist, which is associated with fitness  $f$  and affects the recombination rate  $r$ . The association between  $s$  and  $r$  could be a consequence of the properties of  $s$  itself. For example, high temperatures may lead to increased recombination by directly affecting enzymes involved in the meiotic process. However, it is also possible that  $r$  has evolved to be correlated with  $s$  partly due to the correlation between  $s$  and  $f$ . For instance, recombination may have evolved to increase with indications of starvation, as this would lead to less fit individuals performing more recombination than fitter ones. In this section we review the evidence for existence of negative correlations between recombination rates and fitness in biological systems, suggesting various possible factors for the role of  $s$ .

Results that show a negative correlation between recombination rates and fitness can be divided into four categories: evidence for recombination induced by DNA damage, evidence for recombination induced by various types of stress, correlations between age and recombination, and direct estimates of the correlation between recombination and fitness within and between populations. Of particular interest are results that suggest a regulation mechanism behind this correlation. As previously mentioned, such regulation can have a selective advantage regardless of other functions it may serve.

Damage-induced recombination has been found in both prokaryotes and eukaryotes (BERNSTEIN 1987; BERN-

STEIN and JOHNS 1989; WOJCIECHOWSKI *et al.* 1989; KUPIEC 2000). When the source of the recombining DNA is two different individuals (*i.e.*, transformation in bacteria or meiotic recombination in eukaryotes) these data are supportive of FAR: massive DNA damage of the kind usually studied in these works is well correlated with reduced fitness. Moreover, DNA damage can induce recombination not only close to the damaged site, but also up to 30 kbp away from it (GOLUB and LOW 1983; SMITH 2001; YOUNG *et al.* 2002). In a classical experiment, FABRE and ROMAN (1977) showed elevated levels of recombination in diploid yeast that was crossed with an irradiated chromosome. The effect was present even when fusion between the two nuclei was inhibited, suggesting that it was mediated by cytoplasmic proteins.

Elevated recombination levels in response to various types of stress have been observed in many organisms, from simple prokaryotes to mammals (see BELL 1982 and PARSONS 1988 for extensive reviews and HOFFMAN and HERCUS 2000 for a more recent treatment of the subject). In the bacteria *Haemophilus influenza* and *Bacillus subtilis*, starvation has been shown to increase competence for DNA uptake (DUBNAU 1991; REDFIELD 1993; JARMER *et al.* 2002). Induction of a sexual cycle due to nitrogen starvation has been observed also in the haploid unicellular chlorophyte *Chlamydomonas reinhardtii* (HARRIS 1989).

In yeast, regulation of recombination can be achieved at two levels. The first level is regulation of the switch from mitotic growth to meiosis and gametogenesis. Starvation, heat stress, and DNA damage all increase the tendency for that switch (KASSIR *et al.* 1988; BERNSTEIN and JOHNS 1989; MAI and BREEDEN 2000). The actual mechanism by which stress and starvation regulate the entry to meiosis is beginning to be revealed: in *Schizosaccharomyces pombe*, the stress-induced Wis1-Spc1 protein kinase cascade phosphorylates the transcription factor Atf-Pcr1, which is necessary for meiosis (DAVIS and SMITH 2001). In *Saccharomyces cerevisiae*, transcription factor IME1 is required for the initiation of meiosis and is activated by starvation (KASSIR *et al.* 1988; DAVIS and SMITH 2001). At a second level, nutritional stress has been shown to increase meiotic recombination frequencies (ABDULLAH and BORTS 2001). Various transcription factors are known to activate recombination hotspots (WHITE *et al.* 1993; KON *et al.* 1997; NICOLAS 1998), and at least two of these factors are also related to stress responses. Production of transcription factor Gcn4p is induced by glucose, purine, or amino acid starvation. This factor induces increased recombination at the HIS4 hotspot (ABDULLAH and BORTS 2001). Similarly, transcription factor Mts1/Mts2, which activates the recombination hotspot M26 (KON *et al.* 1997), is involved in a variety of stress responses (TAKEDA *et al.* 1995; WATANABE and YAMAMOTO 1996).

An increase in recombination rate due to heat stress has been observed in plants and nematodes (see GRELL

1978; ZHUCHENKO *et al.* 1986; HOFFMAN and PARSONS 1991, and references therein). *Drosophila melanogaster* also shows an increase in recombination rate following stress induced by either extreme temperatures (PLOUGH 1917; CHANDLEY 1968; GRELL 1978; TRACEY and DEMPSEY 1981) or starvation (BERGNER 1928; NEEL 1941; PARSONS 1988). Finally, behavioral stress has been shown to increase recombination rates in the house mouse, *Mus musculus* (BELYAEV and BORODIN 1982).

Age is another factor correlated with recombination rates. Negative correlations between recombination rates and age (at least at the early stages of life) fit well within the framework of FAR, since age is obviously correlated with survivorship. On the other hand, the correlation between age and fitness can be weakened by trade-offs between life span and fertility and/or young-age viability (KOKKO 1998). Moreover, accumulation of germ-line mutations means that old individuals are likely to pass lower-quality genes to their offspring (CROW 1993). Combining these considerations with the idea of FAR, one would expect recombination rates to decrease with time at early stages of life, but possibly start increasing again at older age. A significant decrease in recombination rates associated with age has indeed been demonstrated in plants (GRIFFING and LANGRIDGE 1963) as well as in *Drosophila* (NEEL 1941; HAYMAN and PARSONS 1960). In mammals, a fall in recombination with maternal age has been found in *M. musculus*, although correlation with paternal age has been inconsistent (WALLACE 1957; BODMER 1961; REID and PARSONS 1963). An increase in recombination rates at older age has been consistently reported in *Drosophila* (REDFIELD 1966; ASHBURNER 1989).

Direct examination of intrapopulation variation in fitness and its correlation with recombination rates could provide more evidence supporting the existence of FAR in nature. Few works have studied this correlation directly. Those who did study it indeed found a negative correlation between the two variables (see MARINKOVIĆ *et al.* 1980; TUCIĆ *et al.* 1981; CVETKOVIĆ and TUCIĆ 1986; several references within KOROL *et al.* 1994; and to some extent NEVO 1997).

#### DETERMINISTIC MODELS

**Modeling the correlation between fitness and recombination:** A given factor  $s$  can affect the recombination rate  $r$  through a change in the number of chiasmata occurring during meiosis. In facultative sexual haploids, the transition between sexual and clonal modes of reproduction can also be regarded as a regulation of recombination rate, switching it between a positive rate and rate zero. This form of regulation is of particular interest in modeling the appearance and spread of recombination in an asexual population.

In this article we study a series of FAR models sharing a basic modeling assumption, corresponding to the simplest form of FAR. In all of them, there are two possible

recombination rates—either zero or a fixed positive rate. When FAR occurs, the actual recombination rate used is negatively correlated with the organism’s fitness. This assumption is a natural one for modeling of FAR in facultative sexual haploids and a simplification in the case of obligatory sexual haploids.

**FAR spreads in a UR population:** To study the evolvability of FAR, let us first consider the simplest possible model. In this model there are only two loci. The first locus, with alleles  $A$  and  $a$ , determines fitness ( $f_{A^*} = 1$ ,  $f_{a^*} = 1 - s$ ). The second locus determines the recombination strategy. Allele  $C$  determines recombination at a fixed rate  $r_c$  (UR strategy) between the two loci, regardless of the allele at the other locus. Allele  $V$  determines fitness-associated recombination (FAR strategy): the superior haplotype  $AV$  has probability  $\gamma > 0.5$  to reproduce asexually and probability  $1 - \gamma$  to make the wrong choice and reproduce sexually, with a positive recombination rate  $r_v \geq r_c$ . The inferior haplotype  $aV$  has probability  $\gamma$  to reproduce sexually with recombination rate  $r_v$  and probability  $1 - \gamma$  to reproduce asexually. A negative correlation between fitness and recombination exists for any  $\gamma > 0.5$ , and the correlation coefficient approaches  $-1$  as  $\gamma$  approaches 1. To make the model more tractable, we assume that if two individuals with different recombination rates meet, the rate of recombination between them would be the average of their recombination rates (additive modifier). The latter assumption can be relaxed, and simulations have proven that the model is robust to other types of interactions between the recombination rates of the two partners. Note that in this model there is only one selected locus, and therefore recombination cannot have any effect on average population fitness. The situation is different in other models discussed below.

For the simplicity of the analytical treatment let us first assume unidirectional mutation at rate  $m$  from  $A$  to  $a$ . After mutation, the frequencies  $P^*$  become

$$P_{Ai}^* = (1 - m)P_{Ai} \tag{1}$$

$$P_{ai}^* = P_{ai} + mP_{Ai} \quad (i \in \{C, V\}). \tag{2}$$

The next generation frequencies are then given by

$$\omega \cdot P'_j = f_j(P_j^* - \Delta) \quad (j \in \{AV, aC\}) \tag{3}$$

$$\omega \cdot P'_k = f_k(P_k^* + \Delta) \quad (k \in \{aV, AC\}), \tag{4}$$

where  $f_i$  are the fitnesses of the corresponding genotypes,  $\omega$  is the average fitness in that generation (equal to the sum of the right-hand sides in Equations 3 and 4), and

$$\Delta = \frac{r_c + (1 - \gamma)r_v}{2} P_{AV}^* P_{aC}^* - \frac{r_c + \gamma \cdot r_v}{2} P_{aV}^* P_{AC}^*. \tag{5}$$

We limit the discussion to two cases. In both cases the allele  $V$  acts as described above, coding for  $AV$  to reproduce asexually and for  $aV$  to recombine at the rate

$r_v$  (with error probability  $1 - \gamma$ ). In the first case allele  $C$  codes for asexual reproduction; *i.e.*,  $r_c = 0$ . In the second case, allele  $C$  codes for sexual reproduction with uniform recombination rate  $r_c = r_v$ . In the two cases, the dynamical system resulting from mutation and recombination according to Equations 1–4 has the same equilibrium points. One group of equilibria entails extinction of the superior allele, *i.e.*,  $P_{AV} = P_{AC} = 0$ , and is unstable as long as  $m < s$ , which we assume. The two other equilibrium points describe a mutation-selection balance between  $a$  and  $A$  with either allele  $C$  or  $V$  and extinction of the allele for the alternative reproduction strategy. Analyzing the equilibria of the system leads to the following result:

**Result 1:** For any  $\gamma > 0.5$  (*i.e.*, for any negative correlation between fitness and recombination), the equilibrium  $\{P_{AC} = 1 - m/s, P_{aC} = m/s\}$  is unstable. The only stable equilibrium of the system for  $0 < m < s$  is  $\{P_{AV} = 1 - m/s, P_{aV} = m/s\}$ , meaning that the FAR allele is bound to eventually fix in the population (note that because there are no internal equilibria, cycling can be ruled out). The opposite is true when  $\gamma < 0.5$ , *i.e.*, when the correlation between recombination and fitness is positive.

A model with bidirectional mutation between alleles  $A$  and  $a$  (*i.e.*, probability  $m$  for a mutation in either direction) would result in two equilibria only:  $\{P_{AC} = 1 - \delta, P_{aC} = \delta\}$  and  $\{P_{AV} = 1 - \delta, P_{aV} = \delta\}$ , wherein

$$\delta = \frac{s - 3sm - 2m - \sqrt{4m^2 - 4m^2s + m^2s^2 - 2ms^2 + s^2}}{2s(1 - 2m)}$$

for any  $m \neq 0.5$ , and  $\delta = (1 - s)/(2 - s)$  in the singular case  $m = 0.5$ .

In accordance with the result for unidirectional mutation, the second equilibrium is stable while the first is not for any  $\gamma > 0.5$  and for any value of  $m$  and  $s$ .

In the above model, the initial increase of the  $V$  allele is driven only by its ability to hitchhike on the superior allele  $A$  and break off from the inferior allele  $a$  (MAYNARD SMITH and HAIGH 1974). There is no possible effect of alleles  $V$  or  $C$  on the fitness in this model.

#### **FAR populations tend to have a higher average fitness:**

The effect of FAR on the average population fitness in the presence of mutations can be studied using an infinite-population two-locus model with alleles  $A/a$  and  $B/b$ .

We consider all unimodal fitness landscapes with  $AB$  as the superior type and equal fitness for the two single mutants. The relative fitnesses are thus given by  $f_{AB} = 1$ ,  $f_{Ab} = f_{aB} = 1 - s_1$ ,  $f_{ab} = 1 - s_2$ , where  $0 < s_1 < s_2 < 1$ . Bidirectional mutation occurs at rate  $m$  at the two fitness-determining loci. We compare populations that are homogeneous with respect to the recombination mode—FAR or UR.

Denoting the alternative allele (at the same locus) for allele  $i$  by  $\bar{i}$ , so that  $\bar{A} = a$ , etc., the effect of bidirec-

tional mutation (no matter what the recombination strategy is) is given by

$$P_{hk}^* = (1 - m)^2 P_{hk} + m(1 - m)(P_{\bar{h}k} + P_{h\bar{k}}) + m^2 P_{\bar{h}\bar{k}} \quad (h \in \{A, a\}, k \in \{B, b\}). \quad (6)$$

In the case of the UR population, the frequencies after recombination follow the equations

$$\omega P_i' = f_i(P_i^* - r_c D) \quad (i \in \{AB, ab\}) \quad (7)$$

$$\omega P_i' = f_i(P_i^* + r_c D) \quad (i \in \{Ab, aB\}) \quad (8)$$

wherein  $\omega$  is again the average fitness, and

$$D = P_{AB}^* P_{ab}^* - P_{Ab}^* P_{aB}^*. \quad (9)$$

In the case of the FAR population the frequencies after recombination are given by the same equations, replacing  $r_c D$  by  $r_v \Delta$ , where

$$\Delta = \frac{1}{2} P_{AB}^* P_{ab}^* - \gamma P_{Ab}^* P_{aB}^*. \quad (10)$$

Note that (10) is *not* an expression for the linkage disequilibrium in this system. Linkage disequilibrium is expressed by  $D$  (Equation 9) in both cases.

Numerically solving Equations 6–10, we examined the average population fitness  $\omega = \sum_{i \in \{AB, Ab, aB, ab\}} f_i P_i$  at mutation-selection-recombination balance, starting from various starting points and for different values of the parameters  $m$ ,  $r_c$ ,  $r_v$ ,  $s_1$ , and  $s_2$ . Compared to a UR population with either  $r_c = 0$  or  $r_c = r_v$ , the FAR population had a higher average fitness for the entire parameter range where selection is stronger than mutation (*i.e.*,  $m < s_1$ ). Figure 1 plots the differences between the average population fitness of a FAR population (with  $\gamma = 1$ ) and that of the two UR populations. In the entire parameter range, the average fitness of the FAR population is higher than that of either sexual or asexual UR. The greatest differences are obtained for relatively low selection values— $s_1$  of the order of  $10^{-3}$ – $10^{-4}$ , namely in the range of slightly deleterious mutations.

Comparing a FAR population to a sexual UR population with  $r_c = r_v$ , the latter performs more recombination on average per generation. Some of the difference in average fitness could have been attributed to this effect. As a control eliminating it, we ran a simulation in which each generation the average recombination rate of the FAR population was calculated, and the recombination rate of the UR population was set to the same value. The resulting difference in fitness between the two populations remained positive throughout the parameter range and very close to the values of Figure 1A.

Of special interest is the case of multiplicative fitness landscape. In an infinite population under multiplicative fitness, uniform recombination has no fitness effect ( $D = 0$  at mutation-selection balance). This is not the case for FAR: due to its inherent asymmetry, FAR creates a positive linkage disequilibrium between fitness-deter-

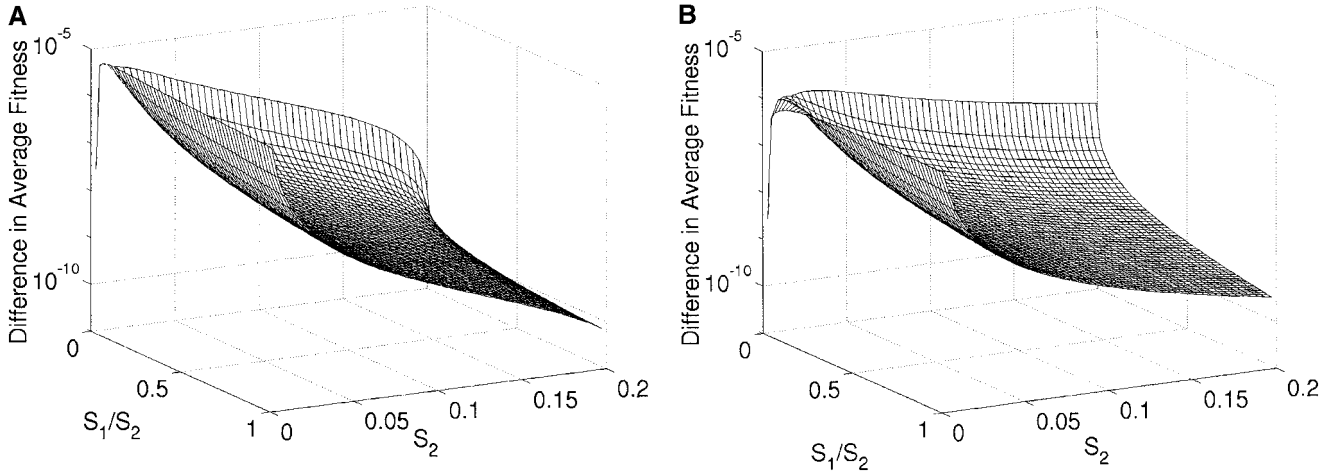


FIGURE 1.—FAR performs better in terms of average population fitness. (A) The difference between the average fitness of a population employing FAR with  $r_v = 0.5$  and one employing UR with  $r_c = 0.5$ . (B) The difference between the average fitness of a population employing FAR with  $r_v = 0.5$  and one employing UR with  $r_c = 0$ . The correlation between recombination and fitness is perfect ( $\gamma = 1$ ). The mutation rate is  $m = 10^{-5}$ . The difference between equilibrium values is plotted for the range  $m < s_1 \leq s_2 < 0.2$ . The equilibrium values do not depend on the initial conditions. In the range  $s_1, s_2 > 0.2$  the difference is lower but still positive.

mining loci. Figure 2A plots the linkage disequilibrium  $D$  as a function of time for the multiplicative selection case. Starting from linkage equilibrium, both the sexual and the asexual UR populations stay in linkage equilibrium. In the FAR population, on the other hand, positive linkage disequilibrium between the fitness-determining loci is gradually created. The latter is true also for the additive case (Figure 2B), where negative linkage

disequilibrium appears in the two UR populations due to the effect of mutation. In both cases, positive linkage disequilibrium appears in the FAR population for any  $\gamma > 0.5$ . Figure 2B demonstrates the case  $\gamma = 1$ .

The creation of positive linkage disequilibrium in the FAR population results in a higher average fitness compared with the UR populations, for any  $\gamma > 0.5$ . This is demonstrated in Figure 3, which presents the difference

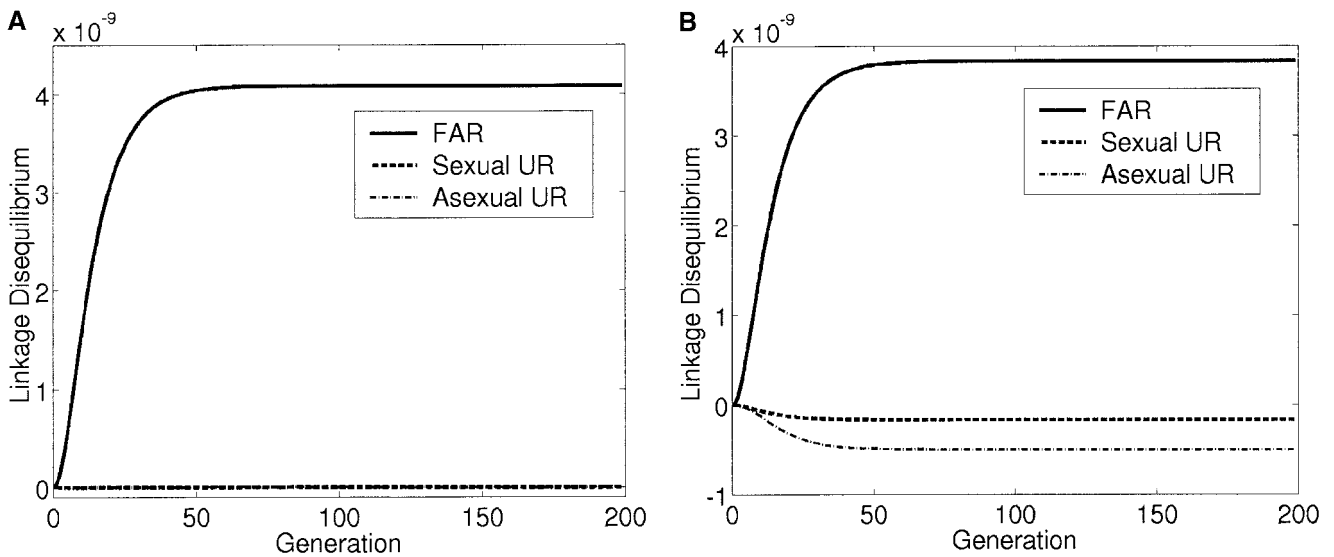


FIGURE 2.—The effect of FAR on linkage disequilibrium. (A) Multiplicative fitness,  $f_i = f_2^2$ . (B) Additive fitness,  $f_2 = f_3 = 1 - s_1$ ,  $f_4 = 1 - 2s_1$ . Linkage disequilibrium is plotted as a function of time, starting from fixation of  $AB$ , for  $s_1 = 0.1$ ,  $\gamma = 1$ . Under multiplicative fitness (A), linkage disequilibrium remains zero for both sexual and asexual UR. In the FAR population, on the other hand, positive disequilibrium is gradually produced. Under additive fitness (B) the difference is even more noticeable: negative disequilibrium appears in the two UR populations, whereas a positive disequilibrium is created in the FAR population, leading to an increased fitness. The result is robust to changes in  $s_1$  and  $\gamma$ .

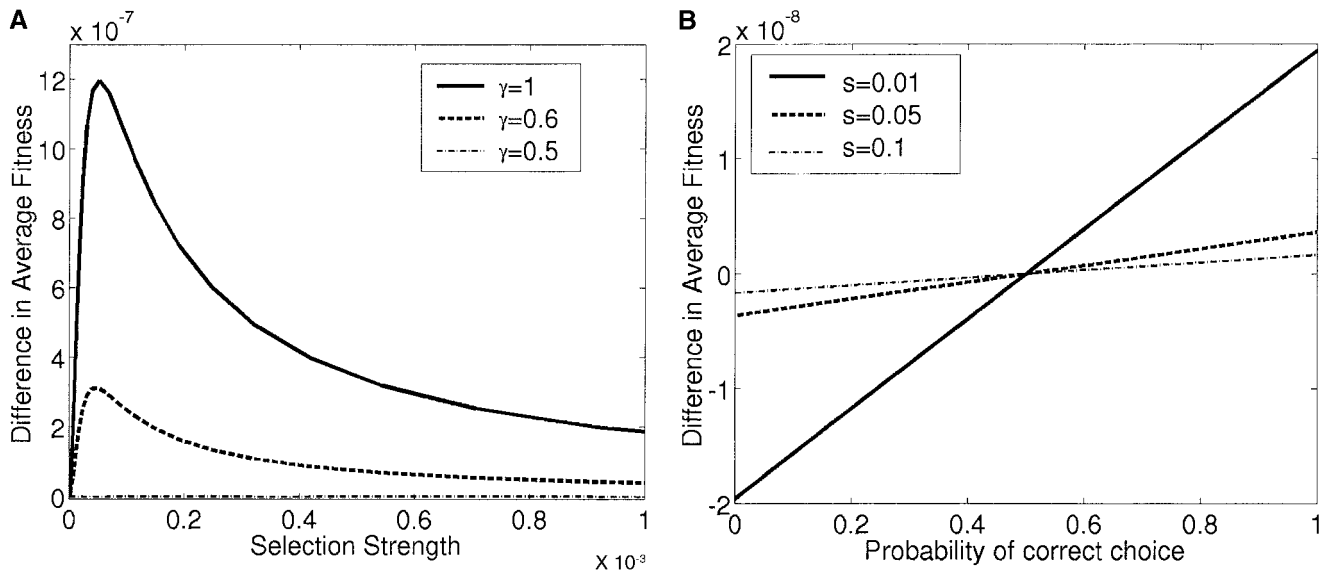


FIGURE 3.—Population-level advantage as a function of selection intensity and error probability. The difference between the average fitness of a population employing FAR and that of a population employing UR in a multiplicative fitness landscape is shown. The advantage in an additive fitness landscape, relative to either asexual or sexual UR (see text for details), is also reliably illustrated. (A) The fitness difference is plotted as a function of the selection parameter  $s_1$ , for three levels of correlation strength:  $\gamma = 1$  (perfect correlation),  $\gamma = 0.6$  (weak correlation), and  $\gamma = 0.5$  (zero correlation, random choice). As expected, for  $\gamma = 0.5$  no difference in fitness appears between the FAR and the UR populations. For the higher values of  $\gamma$  the difference is positive and is highest for low values of  $s_1$ , of the order of  $10^{-4}$ . (B) The fitness difference is plotted as a function of  $\gamma$  for three values of  $s_1$ . FAR is advantageous whenever  $\gamma > 0.5$  (*i.e.*, whenever there is a negative correlation between recombination and fitness), and the difference is an increasing function of  $\gamma$ . Note that a larger difference is attained for the lower selection values.

between the average fitness of a FAR population and that of a sexual UR population, in a multiplicative fitness landscape:  $f_1 = 1$ ,  $f_3 = f_2 = 1 - s_1$ , and  $f_4 = (1 - s_1)^2$ . As demonstrated in Figure 3A, the effect is strongest for relatively low selection parameters, of the order of  $10^{-4}$  (in accordance with Figure 1). Figure 3B shows how the difference in fitness depends on the error probability  $1 - \gamma$ . As can be seen, FAR maintains an advantage for any  $\gamma > 0.5$ . Naturally, the advantage increases with  $\gamma$ . We also studied a corresponding additive fitness model, with  $f_1 = 1$ ,  $f_3 = f_2 = 1 - s_1$ , and  $f_4 = 1 - 2s_1$ . The differences between the multiplicative case and the additive one, and between the sexual and asexual UR populations in the additive fitness landscape, are all too small to show on the scale of the figure, being of the order of  $10^{-10}$ . In the multiplicative case, the average fitness of the asexual UR populations is identical to that of the sexual UR one. Thus, Figure 3 reliably depicts the situation in these scenarios as well.

To complement the analytical treatment, we examine a three-locus model where recombination is associated with the relative rather than with the absolute fitness. In this model, a proportion  $\alpha$  of the FAR population, composed of the best individuals, would have the lower recombination rate, and the rest would have the higher rate. The equations for this model are detailed in the APPENDIX. In this model, the average frequency of recombination events in the FAR population does not

change between generations. To make the comparison between the FAR and sexual UR populations more accurate, we used  $r_c = (1 - \alpha)r_v$ , so that the average recombination rates in the two populations were exactly the same.

Figure 4 shows the advantage of FAR (in this relative fitness implementation) relative to a sexual UR population with the same average recombination rate, for three values of the mutation rate. Similar to the result shown in Figure 3 for the absolute fitness implementation, the relative fitness model of FAR also maintains a population-level advantage relative to UR.

## SIMULATION MODELS

The deterministic models presented above provide the basic intuition as to the dynamics behind the advantage of FAR. To establish this potential advantage in a wider context, we use several different multilocus simulations, comparing recombination strategies in two different evolutionary scenarios and at two different levels. The two scenarios examined are coping with deleterious mutations and adaptation to environmental changes. For each of these scenarios, separate simulations were performed to study the dynamics of rare FAR mutants within a UR population and vice versa and to compare the dynamics of homogeneous FAR populations to those of homogeneous UR populations.

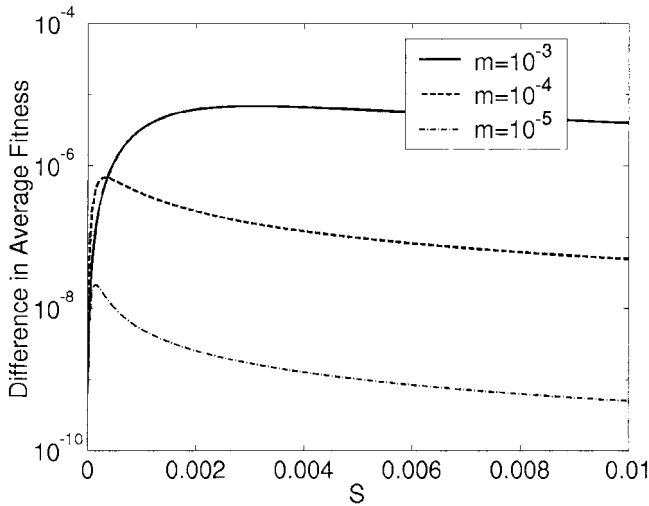


FIGURE 4.—Advantage of FAR in a relative fitness implementation. The difference in average fitness between a FAR population and a sexual UR population is plotted as a function of the selection parameter  $s$ , for three different mutation rates. The fitness landscape is the same multiplicative landscape of Figure 3, but the implementation of FAR here is based on correlation with the relative rather than with the absolute fitness. See the APPENDIX for the detailed description of this model.

All the simulation models share a common framework, by which FAR-type individuals or populations are compared to individuals or populations performing recombination at a uniform rate (UR type). This uniform rate could be zero, corresponding to asexual reproduction, or positive, corresponding to sexual reproduction with a fixed recombination probability. The fitness landscape examined is again a multiplicative one: the fitness of an individual decreases multiplicatively with the number of loci differing from a “target genome” determined by the environment.

The basic idea behind FAR is that less fit individuals would tend to perform recombination more than fitter ones. As in the deterministic models, we use the simplest realization of this idea, with only two possible recombination rates—a fixed high rate for the less fit and rate zero for the fitter individuals. In the simulations presented here, we assumed again that the recombination rate is negatively correlated with the relative fitness of the individual. FAR individuals in the top 5% of the population (with respect to fitness) had probability  $\gamma > 0.5$  to have recombination rate zero and probability  $1 - \gamma$  to have the higher recombination rate  $r_v$ . The opposite was true for all other FAR individuals. Here again, we fixed  $r_c = (1 - \alpha)r_v$ , to obtain the same average recombination rate in the UR population as in the FAR one.

The following numbers are taken from simulations using  $\gamma = 1$ . Simulations using lower values of  $\gamma$  ( $\gamma = 0.6, 0.8$ ) gave qualitatively similar results, but the difference between FAR and UR was smaller (results not shown). Each simulated population consists of 1000 individuals

with biallelic haploid genomes. Each simulation trial lasts 10,000 generations, if not terminated earlier by one of the termination conditions detailed below. Each generation, pairs of parents are randomly chosen and mated, producing 1 offspring, until 1000 viable offspring are produced. Offspring survive with probability equal to their genotypic fitness. The gene controlling the recombination strategy is assumed to be unlinked to the fitness-determining loci.

Recombination takes place after selection. Similar to the deterministic models of the previous section, a pair of parents recombines in these simulations with probability equal to their average recombination rate. If they do not recombine, each reproduces asexually, producing a copy of itself. When recombination does take place, a pair of complementary offspring genomes is produced, with a single crossover point occurring at a random location within the fitness-determining loci. In addition, a recombination event between the locus for recombination strategy and the rest of the genome occurs with probability 0.5. The offspring then undergo point mutations at a given rate. We examined a wide range of bidirectional mutation rates, from  $m_g = 0.003$  mutations per genome per generation to  $m_g = 1$ . The qualitative results were robust to these changes, and the results presented here are from simulations with  $m_g = 0.05$ .

**Coping with deleterious mutations:** Adjusting to the accumulation of deleterious mutations has long been recognized as one of the major advantages of recombination (MULLER 1964; KONDRASHOV 1988). We tested the performance of FAR compared to UR in a deleterious mutation model with 10,000 loci, where each mutation (compared to the perfect sequence) induces a multiplicative decrease of 2% in fitness. The effect of the different recombination strategies was examined both at the level of the individual and at the population level.

*The individual level:* To assess the relative advantage of FAR compared to uniform-rate recombination, we checked the initial increase of rare FAR mutants in a homogeneous UR population and the initial increase of rare UR mutants in a FAR population. We start from a homogeneous population with 1000 individuals of one of these two types. The population is first initialized near mutation-selection balance, by letting each individual have a number of mutations drawn from a Poisson distribution with mean  $m_g/s$ , where  $m_g$  is the genome mutation rate and  $s$  is the fitness decrease due to a single mutation. The population is then allowed to stabilize for 50 generations, after which 5% of the population are chosen at random and mutated to employ the other recombination strategy.

The simulation ends when the mutant type either goes extinct or takes over at least 99% of the population. Repeating this experiment 5000–10,000 times, we calculated the takeover frequencies of FAR mutants in both sexual and asexual UR populations and the takeover

frequencies of sexual and asexual UR mutants in FAR populations. As controls, we checked the takeover frequency of asexual UR individuals within a sexual UR population, the takeover frequency in the opposite direction, and the takeover frequency of neutral mutants. The rate  $r_v$  was fixed at 1. As before, the recombination rate for the sexual UR population was  $r_c = (1 - \alpha)r_v$ , to ensure that the FAR population and the sexual UR population have the same average recombination rate. Note that  $r_c$  and  $r_v$  are recombination rates per genome; *i.e.*,  $r = 1$  means one recombination point along the genome.

*The population level:* A strategy that has a local benefit at the individual level can still perish in the long run if its overall effect is negative once established in a subpopulation. To test the population-level effects of FAR, we compared a sexual UR population, an asexual UR population, and a FAR population. In these simulations the population was initialized free of deleterious mutations and monitored for a period of 10,000 generations.

**Adaptation to environmental changes:** An environmental change may dramatically alter the fitness landscape, emphasizing few beneficial mutations rather than the many weakly deleterious ones. For modeling adaptation to a changing environment, we assumed 16 fitness-determining loci. One can think of these loci as distributed uniformly along the 10,000 loci of the previous model. This time we neglect slightly deleterious mutations in the majority of loci and concentrate on the 16 loci where mutations can have a relatively large impact on fitness. An environment is characterized by a target sequence. Each mismatch between an allele in 1 of these 16 loci and the target sequence results in a multiplicative 5% decrease in fitness. The population is initialized near mutation-selection balance in each of the fitness loci relative to a given environment and is allowed to stabilize in that environment. The environment is then changed, by changing all 16 alleles in the target sequence so that the complementary sequence becomes the target. From that point on, the population adapts to the new environment.

*The individual level:* Each individual in a homogeneous FAR or UR population is initialized with a random number of deleterious mutations, drawn from a binomial distribution with a mean corresponding to the theoretical mutation-selection balance. After a stabilization period of 50 generations the environment is changed. At the same time 5% of the population are chosen at random and mutated to employ the other recombination strategy. The takeover frequency is registered and compared to the same controls as in the deleterious mutation model.

*The population level:* Homogeneous FAR and UR populations are initialized at the target sequence. The environment is then changed to the complementary sequence, to reflect a radical environmental change. The population is given 10,000 generations to readapt to

the new environment, during which its average fitness is monitored.

## SIMULATION RESULTS

**The individual level:** Figure 5 summarizes the results of simulations at the individual level. For each of the two basic scenarios (deleterious mutations and environmental changes), takeover rates are plotted for six cases: FAR mutants in sexual and asexual UR populations; asexual and sexual UR mutants in a FAR population; and as controls also asexual UR mutants in sexual UR populations, and vice versa. In all the simulations we used  $r_v = 1$ , and in the sexual UR populations we took  $r_c = (1 - \alpha)r_v$ , to ensure the same average recombination rate as the FAR population ( $\alpha = 0.05$  throughout the simulations, meaning that the best 5% of the population do not initiate recombination if they carry the FAR allele). For reference, a horizontal line indicates the expected takeover rate of an individual with a neutral mutation (0.05 in this case, since the rare mutants start with that proportion in the population). Performing the same simulations with true neutral mutations indeed gave takeover rates very close to that value. A takeover rate  $>0.05$  indicates a positive initial increase and a rate  $<0.05$  means that the overall effect of the mutation in question is negative.

Figure 5 clearly demonstrates that the success of FAR mutants in both sexual and asexual UR populations is very high (bars A and D), whereas the success of UR mutants in FAR populations is negative (*i.e.*, significantly lower than that of a neutral mutant; bars B and E). Moreover, the initial increase of FAR within UR populations of both types is much higher than the increase of sexual UR mutants within an asexual UR population or vice versa (bars C and F). The same experiments were also carried out with other  $r_c$  values, with qualitatively similar results. Simulations incorporating a single mutant rather than 5% of the population also gave similar, albeit noisier, results.

**The population level:** To study population-level effects of the reproduction strategy, we compare three populations, employing sexual UR, asexual UR, and FAR. The parameters  $r_c$ ,  $r_v$ , and  $\alpha$  were the same as in the individual-level simulations. Figure 6A compares the average population fitness of the three populations, for the deleterious mutation model. While the asexual population quickly deteriorates (reaching a steady state with fitness close to zero), both the sexual UR population and the FAR population stabilize on a relatively high average fitness. The stable state of the FAR population is significantly higher than that of the sexual UR population (comparing the average fitnesses over independent trials for a given generation yielded  $P < 0.001$  for each of the last 100 generations).

Figure 6B presents the average population fitnesses for the case of adaptation to a new environment. The

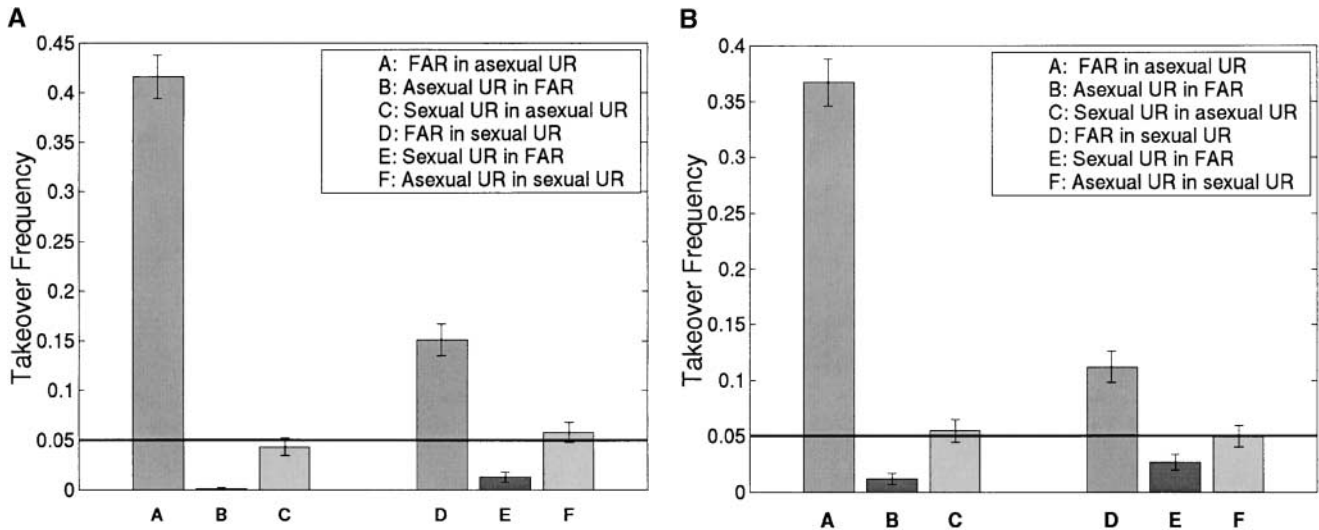


FIGURE 5.—Individual-level simulations. (A) Deleterious mutations. (B) Adaptation to environmental change. In each case, the takeover rate by rare mutants in 1000 trials is plotted for six different scenarios: FAR mutants in an asexual population (bar A), asexual mutants in a FAR population (B), sexual mutants in an asexual population (C), FAR mutants in a UR sexual population (D), UR sexual mutants in a FAR population (E), and asexual mutants in a UR sexual population (F). The horizontal line indicates the expected takeover rate of a neutral mutant.

asexual population does more poorly than the other two, which behave more or less the same, with a slight advantage to FAR. Given enough time, all three populations reach a balance around the target genotype. Note that this model incorporates relatively strong selection and low mutation rates—conditions where we would expect FAR to have a particularly small advantage, on the basis of the results of the analytical models (see Figures 3 and 4).

DISCUSSION

We examined the possible evolutionary advantages of FAR, using deterministic two-locus infinite-population

haploid models and stochastic multilocus finite-population simulations. We showed that fitness-associated recombination is far more successful than UR: FAR mutants tend to spread in UR populations, whereas FAR populations are stable against UR mutants. Specifically, FAR mutants spread from rarity in asexual UR populations and are stable against back mutations (*Result 1*, Figure 5). This holds true even in infinite-population models with no epistasis, where sexual UR mutants do not increase in frequency within an asexual population (FELDMAN *et al.* 1996). In addition, FAR populations tend to have a higher average fitness than UR populations, either sexual or asexual (Figures 1, 3, 4, and 6). The advantages of FAR were analyzed in general fitness

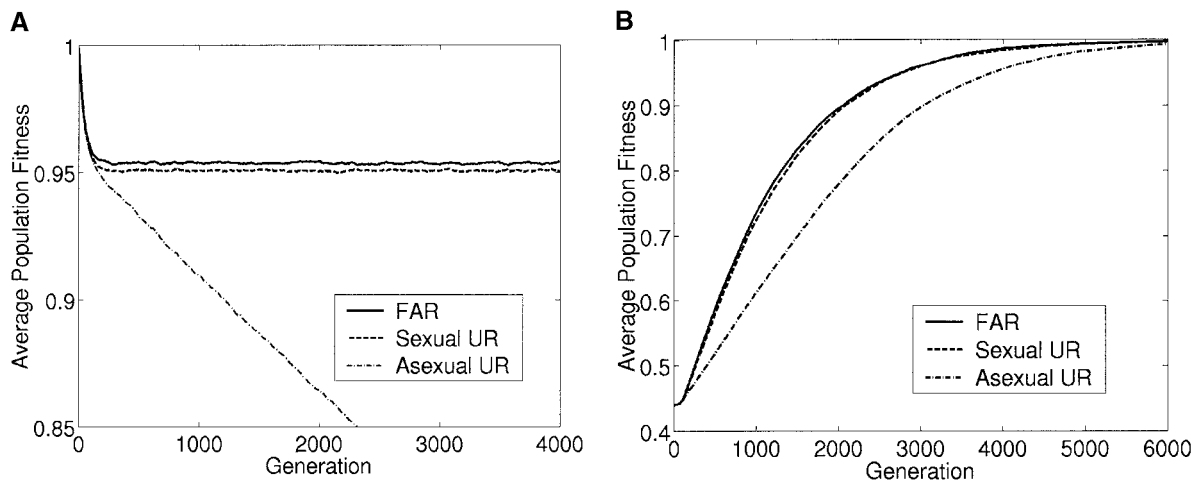


FIGURE 6.—Population-level simulations. (A) Deleterious mutations. (B) Adaptation. Average population fitness is plotted as a function of time, for three populations: asexual UR, sexual UR, and FAR. The average recombination rate in the sexual UR population is the same as in the FAR population (see text for details).

landscapes with two and three loci. They were verified using multilocus simulations in multiplicative fitness landscapes.

These results have a few implications. First, sexual reproduction is more likely to arise if recombination is fitness associated. Second, sexual recombination is more likely to be maintained (both within a population and between populations) if recombination is fitness associated. Third, even if there were no *a priori* physiological reason for recombination to be negatively correlated with fitness, a regulator of recombination that induces such correlation (by suppressing recombination in the more fit, increasing recombination in the less fit, or both) is likely to spread and be maintained due to its association with the more fit genotypes in the population (*Result 1*, Figure 5).

It should be noted that the effects of FAR are not limited to multiplicative landscapes. In a general unimodal fitness landscape with two loci, FAR leads to a higher average fitness than does either sexual or asexual UR (see Figure 1). In another work (HADANY and BEKER 2003) we extended our examination of these effects to the problem of adaptation on rugged adaptive landscapes. In that scenario FAR turns out to have a much more dramatic effect on the average population fitness and on the speed of adaptation.

Most explanations for the advantage of recombination have to do either with reconstruction of good combinations from bad ones created by mutation (MULLER 1964; KONDRASHOV 1988) or with adapting to a changing environment (FISHER 1930; CHARLESWORTH 1976; BARTON 1995). In both cases, an essential prerequisite is the existence of some source of linkage disequilibrium to begin with. In the words of John Maynard Smith (referring to a simplified deterministic model): “The only effect which sexual reproduction and free recombination can have on genotype frequencies is to bring them closer to linkage equilibrium” (MAYNARD SMITH 1978, p. 14). Thus a necessary (though insufficient) condition for uniform recombination to have any positive effect is the existence of some other force that drives the population to linkage disequilibrium.

In the case of fitness-associated recombination the situation is different. FAR can in itself produce linkage disequilibrium. This can be intuitively understood, as FAR is an inherently asymmetrical process. It creates good combinations at a rate higher than the rate at which it breaks them down. The production of linkage disequilibrium by an asymmetrical recombination process has been previously noted by CLARK and FELDMAN (1981), who assumed different recombination rates between *cis* and *trans* inversion heterozygotes. In a population subject to FAR, the steady state would be similarly biased toward linkage disequilibrium. FAR results in positive linkage disequilibrium between fitness-determining loci (Figure 2)—the extreme genotypes are over-represented, and the variance in fitness within the popu-

lation increases. Natural selection thus becomes more effective and the average fitness increases (Figures 1, 3, 4, and 6). Our results are consistent with those of REDFIELD (1988), who studied the evolution of bacterial transformation under deleterious mutations. In a set of simulations assuming high mutation rates ( $m_g = 0.5, 1$ ), Redfield showed that transforming populations sometimes had a higher average fitness than asexual populations, even when the source of DNA uptake was dead cells. When the fittest individuals completely avoided transformation, the average fitness of the transforming population was higher than that of the nontransforming population. Our results show that even if both partners determine the effective rate of recombination, so that the superior type cannot altogether avoid it, even if the negative correlation between recombination and fitness is imperfect, and even if recombination is correlated with relative fitness rather than with absolute fitness, FAR would still carry a population-level advantage.

ZHUCHENKO and KOROL (1985) studied the evolution of an allele for environmentally induced recombination in a changing environment. They studied a model with a periodic two-state environment and a corresponding two-rate recombination strategy of the entire population. Under specific epistatic interactions, there are two-rate recombination strategies that yield a higher average fitness than the optimal uniform-rate strategy yields under the same fluctuating environment. Moreover, an allele for such environmentally induced recombination can increase in frequency within the population, probably due to the increased average fitness of the subpopulation carrying it. While this model ignores intrapopulation variance in recombination rates, it resembles FAR for periods immediately following extreme changes, when the whole population is likely to experience a considerable decrease in fitness. However, as soon as adapted combinations appear in the population, the two models differ. FAR would result in some protection for these combinations from being broken down by recombination, whereas an adjustment of the recombination rate in the population as a whole would not.

The ability of FAR mutants to spread from rarity in asexual UR populations is an important difference between FAR and UR. Whereas a modifier for a higher uniform rate of recombination would not increase under multiplicative fitness in a large UR population starting from linkage equilibrium (FELDMAN *et al.* 1996), an allele for FAR would, by linking to the superior types and breaking from the inferior ones (see Figure 5). This “generalized hitchhiking” ability allows FAR to spread and be maintained in any UR population, even without its long-term effect on the average fitness. Even when the rest of the genome is limited to a single gene and no linkage disequilibrium can appear between fitness-determining loci, FAR can still spread due to its association with the superior genotype (*Result 1*).

Spreading of an allele for recombination was demon-

strated before in several works suggesting a physiological explanation for the advantages of recombination (BERNSTEIN *et al.* 1985; MICHOD 1998). These works assume that recombination is capable of DNA repair. As shown by MICHOD (1998), an allele that carries repair properties and dictates selfish sex (*i.e.*, recombine only when damaged) is a much more robust repair strategy than cooperative sex, especially when both are compared with asexual diploidy. Unlike this model, and similar to the model presented by GESSLER and XU (2000), our treatment assumes neither direct repair nor true “selfishness,” in the sense that superior haplotypes are not immune to recombination with inferior ones.

GESSLER and XU (2000) were the first to propose that an allele coding for a negative correlation between recombination and fitness can spread in an asexual population. They used simulations to study the evolution of recombination in a deleterious mutation model with a low mutation rate. Their model assumed that an individual is more likely to instigate recombination if it has acquired a mutation in the current generation. Under these assumptions, they showed that an allele for such mutation-induced recombination could spread in an asexual population even if it does not actually carry any repair property. They further demonstrated that fitness-induced recombination could do so as well. In contrast with our results, GESSLER and XU (2000) did not find any increase in average population fitness or disequilibrium between fitness-determining loci under any of their recombination strategies. This difference might result from the details of the model they studied. For a deleterious mutation scenario with low mutation rates, almost all individuals would have either 0 or 1 deleterious mutation. The difference between the UR and FAR populations in terms of linkage disequilibrium and average fitness would be very small. These small differences were probably concealed by the high stochastic noise of the simulations. As our results suggest, FAR can in fact be advantageous in a much wider context than that of low-rate deleterious mutations. Our model was robust to variations in the genome mutation rate, covering the whole range suggested in the literature, from  $m_g = 0.003$  mutations per genome per generation to  $m_g = 1$  (DRAKE *et al.* 1998). It was also robust to variation in the strength of the negative correlation between recombination and fitness. Furthermore, it proved effective not only in coping with deleterious mutations, but also in the case of adaptation to environmental changes.

Current experimental evidence suggests that a negative correlation between fitness and recombination exists in nature. Whether evolved or coincidental, we showed that such fitness-associated recombination is advantageous compared to uniform-rate recombination, both in terms of the average population fitness and in terms of its ability to spread and be maintained against asexual reproduction. Furthermore, our results suggest that a regulatory mechanism modifying the rate of recombina-

tion on the basis of factors associated with the fitness is likely to spread within a population undergoing uniform recombination. Finally, these results are relevant to the way we understand the basic effects of recombination. If recombination in nature is indeed fitness associated to a significant extent, we should perhaps part with the long-standing dogma that the only effect of recombination is breaking linkage disequilibrium. While this is true for models that assume a uniform recombination rate for the whole population, more explicit modeling of the regulation of recombination yields a different result.

We are greatly indebted to Ilan Eshel for numerous comments and suggestions. Many thanks are due to Marcus Feldman for his careful reading, comments, and references. Sally Otto, Uzi Motro, Henri Atlan, Eytan Ruppin, and Ranit Aharonov read an earlier version of the manuscript and provided many valuable comments. We thank an anonymous referee for many helpful remarks. Research was supported in part by National Institutes of Health grant GM28016.

#### LITERATURE CITED

- ABDULLAH, M. F. F., and R. H. BORTS, 2001 Meiotic recombination frequencies are affected by nutritional states in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **98**: 14524–14529.
- ASHBURNER, M., 1989 *Drosophila: A Laboratory Handbook*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- BARTON, N. H., 1995 A general model for the evolution of recombination. *Genet. Res.* **65**: 123–144.
- BELL, G., 1982 *The Masterpiece of Nature*. University of California Press, Berkeley, CA.
- BELYAEV, D. K., and P. M. BORODIN, 1982 The influence of stress on variation and its role in evolution. *Biol. Zentbl.* **100**: 705–714.
- BERGNER, D. A., 1928 The relation between larval nutrition and the frequency of crossing over in the third chromosome of *Drosophila melanogaster*. *J. Exp. Zool.* **50**: 107–163.
- BERNSTEIN, C., 1987 Damage in DNA of an infecting phage T4 shifts reproduction from asexual to sexual allowing rescue of its genes. *Genet. Res.* **49**: 183–189.
- BERNSTEIN, C., and V. JOHNS, 1989 Sexual reproduction as a response to H<sub>2</sub>O<sub>2</sub> damage in *Schizosaccharomyces pombe*. *J. Bacteriol.* **171**: 1893–1897.
- BERNSTEIN, H., H. C. BYERLY, F. A. HOPF and R. E. MICHOD, 1985 Genetic damage, mutation and the evolution of sex. *Science* **229**: 77–81.
- BODMER, W. F., 1961 Viability effects and recombination differences in a linkage test with pallid and fidget in the house mouse. *Heredity* **16**: 485–495.
- CHANDLEY, A. C., 1968 The effect of X-rays on female germ cells of *Drosophila melanogaster*. III. A comparison with heat-treatment on crossing-over in the X-chromosome. *Mutat. Res.* **5**: 93–107.
- CHARLESWORTH, B., 1976 Recombination modification in a fluctuating environment. *Genetics* **83**: 181–195.
- CLARK, A. G., and M. W. FELDMAN, 1981 Disequilibrium between linked inversions: an alternative hypothesis. *Heredity* **46**: 379–390.
- CROW, J. F., 1993 How much do we know about spontaneous human mutation rates? *Environ. Mol. Mutagen.* **21**: 122–129.
- CROW, J. F., and M. KIMURA, 1965 Evolution in sexual and asexual populations. *Am. Nat.* **99**: 439–450.
- CVETKOVIĆ, D., and N. TUCIĆ, 1986 Female recombination rates and fitness in *Drosophila melanogaster*. *Z. Zool. Syst. Evolutionsforsch.* **24**: 198–207.
- DAVIS, L., and S. R. SMITH, 2001 Meiotic recombination and chromosome segregation in *Schizosaccharomyces pombe*. *Proc. Natl. Acad. Sci. USA* **98**: 8395–8402.
- DRAKE, J. W., B. CHARLESWORTH, D. CHARLESWORTH and J. F. CROW, 1998 Rates of spontaneous mutation. *Genetics* **148**: 1667–1686.

- DUBNAU, D., 1991 Genetic competence in *Bacillus subtilis*. *Microbiol. Rev.* **55**: 395–424.
- ESHEL, I., and M. W. FELDMAN, 1970 On the evolutionary effect of recombination. *Theor. Popul. Biol.* **1**: 88–100.
- FABRE, F., and H. ROMAN, 1977 Genetic evidence for inducibility of recombination competence in yeast. *Proc. Natl. Acad. Sci. USA* **74**: 1667–1671.
- FELDMAN, M. W., F. B. CHRISTIANSEN and L. D. BROOKS, 1980 Evolution of recombination in a constant environment. *Proc. Natl. Acad. Sci. USA* **77**: 4838–4841.
- FELDMAN, M. W., S. P. OTTO and F. B. CHRISTIANSEN, 1996 Population genetic perspectives on the evolution of recombination. *Annu. Rev. Genet.* **30**: 261–295.
- FISHER, R. A., 1930 *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford.
- GESSLER, D. D. G., and S. XU, 2000 Meiosis and the evolution of recombination at low mutation rates. *Genetics* **156**: 449–456.
- GOLUB, E. I., and K. B. LOW, 1983 Indirect stimulation of genetic recombination. *Proc. Natl. Acad. Sci. USA* **80**: 1401–1405.
- GRELL, R. F., 1978 A comparison of heat and interchromosomal effects on recombination and interference in *Drosophila melanogaster*. *Genetics* **89**: 65–77.
- GRIFFING, B., and J. LANGRIDGE, 1963 Factors affecting crossing over in the tomato. *Aust. J. Biol. Sci.* **16**: 826–837.
- HADANY, L., and T. BEKER, 2003 Fitness associated recombination on rugged adaptive landscapes. *J. Evol. Biol.* **16**: 862–870.
- HARRIS, E. H., 1989 *The Chlamydomonas Sourcebook*. Academic Press, New York.
- HAMILTON, W. D., 1980 Sex versus non-sex versus parasite. *OIKOS* **35**: 282–290.
- HAYMAN, D. L., and P. A. PARSONS, 1960 The effect cold temperature, age and an inversion on recombination values and interference in the X-chromosome of *Drosophila melanogaster*. *Genetica* **32**: 74–88.
- HOFFMAN, A. A., and M. J. HERCUS, 2000 Environmental stress as an evolutionary force. *BioScience* **50**: 217–226.
- HOFFMAN, A. A., and P. A. PARSONS, 1991 *Evolutionary Genetics and Environmental Stress*. Oxford University Press, New York.
- JARMER, H., R. BERKA, S. KNUDSEN and H. H. SAXILD, 2002 Transcriptome analysis documents induced competence of *Bacillus subtilis* during nitrogen limiting conditions. *FEMS Microbiol. Lett.* **206**: 197–200.
- KASSIR, Y., D. GRANOT and G. SIMCHEN, 1988 IME1, a positive regulatory gene of meiosis in *S. cerevisiae*. *Cell* **52**: 853–862.
- KIMURA, M., 1956 A model of a genetic system which leads to closer linkage by natural selection. *Evolution* **10**: 278–287.
- KOKKO, H., 1998 Good genes, old age and life-history trade-offs. *Evol. Ecol.* **12**: 739–750.
- KON, N., M. D. KRAWCHUK, B. G. WARREN, G. R. SMITH and W. P. WAHLS, 1997 Transcription factors Mts1/Mts2 (Atf1/Pcr1, Gad7/Pcr1) activate the M26 meiotic recombination hotspot in *Schizosaccharomyces pombe*. *Proc. Natl. Acad. Sci. USA* **94**: 13765–13770.
- KONDRASHOV, A. D., 1988 Deleterious mutations and the evolution of sexual reproduction. *Nature* **336**: 435–440.
- KOROL, A. B., L. A. PREYGEL and S. I. PREYGEL, 1994 *Recombination Variability and Evolution*, Chaps. 6 and 9. Chapman & Hall, London.
- KUPIEC, M., 2000 Damage induced recombination in the yeast *Saccharomyces cerevisiae*. *Mutat. Res.* **451**: 91–105.
- LIBERMAN, U., and M. W. FELDMAN, 1986 A general reduction principle for genetic modifiers of recombination. *Theor. Popul. Biol.* **30**: 125–142.
- LEWONTIN, R. C., 1971 The effect of genetic linkage on the mean fitness of a population. *Proc. Natl. Acad. Sci. USA* **68**: 984–986.
- MAI, B., and L. BREEDEN, 2000 CLN1 and its repression by Xbp1 are important for efficient sporulation in budding yeast. *Mol. Cell. Biol.* **20**: 478–487.
- MARINKOVIĆ, D., N. TUCIĆ and D. CVETKOVIĆ, 1980 Genetic variation and ecological adaptations. *Genetica* **53** (53): 249–262.
- MAYNARD SMITH, J., 1978 *The Evolution of Sex*. Cambridge University Press, Cambridge, UK.
- MAYNARD SMITH, J., and J. HAIGH, 1974 Hitch-hiking effect of a favorable gene. *Genet. Res.* **23**: 23–35.
- MICHOD, R. E., 1998 Origin of sex for error repair. III. Selfish sex. *Theor. Popul. Biol.* **53**: 60–74.
- MULLER, H. J., 1964 The relation of recombination to mutational advance. *Mutat. Res.* **1**: 2–9.
- NEEL, J. V., 1941 A relation between larval nutrition and the frequency of crossing over in the third chromosome of *Drosophila melanogaster*. *Genetics* **26**: 506–516.
- NEI, M., 1967 Modification of linkage intensity by natural selection. *Genetics* **57**: 625–642.
- NEVO, E., 1997 Evolution in action across phylogeny caused by microclimatic stresses at “Evolution Canyon.” *Theor. Popul. Biol.* **52**: 231–243.
- NICOLAS, A., 1998 Relationship between transcription and initiation of meiotic recombination: toward chromatin accessibility. *Proc. Natl. Acad. Sci. USA* **95**: 87–89.
- PARSONS, P. A., 1988 Evolutionary rates: effects of stress upon recombination. *Biol. J. Linn. Soc.* **35**: 49–68.
- PLOUGH, H. H., 1917 The effect of temperature on crossing over in *Drosophila*. *J. Exp. Zool.* **24**: 148–209.
- REDFIELD, H., 1966 Delayed mating and the relationship of recombination to maternal age in *Drosophila melanogaster*. *Genetics* **53**: 593–607.
- REDFIELD, R. J., 1988 Evolution of bacterial transformation: Is sex with dead cells ever better than no sex at all? *Genetics* **119**: 213–221.
- REDFIELD, R. J., 1993 Genes for breakfast: the have-your-cake-and-eat-it-too of bacterial transformation. *J. Hered.* **84**: 400–404.
- REID, D. H., and P. A. PARSONS, 1963 Sex of parent and variation of recombination with age in the mouse. *Heredity* **18**: 107–108.
- SMITH, G. R., 2001 Homologous recombination near and far from dna breaks: alternative roles and contrasting views. *Annu. Rev. Genet.* **35**: 243–274.
- TAKEDA, T., T. TODA, K. I. KOMINAMI, A. KOHNOSU, M. YANAGIDA *et al.*, 1995 *Schizosaccharomyces pombe* Atf1 (+) encodes a transcription factor required for sexual development and entry into stationary phase. *EMBO J.* **14**: 6193–6208.
- TRACEY, M. L., and B. DEMPSEY, 1981 Recombination rate variability in *Drosophila Melanogaster* females subjected to temperature stress. *J. Hered.* **72**: 427–428.
- TUCIĆ, N., F. J. AYALA and D. MARINKOVIĆ, 1981 Correlation between recombination frequency and fitness in *Drosophila melanogaster*. *Genetica* **56**: 61–69.
- WALLACE, M., 1957 A balanced three-point experiment for linkage group V of the house mouse. *Heredity* **11**: 223–258.
- WATANABE, Y., and M. YAMAMOTO, 1996 *Schizosaccharomyces pombe* Pcr1 (+) encodes a CREB/ATF protein involved in regulation of gene expression for sexual development. *Mol. Cell. Biol.* **16**: 704–711.
- WHITE, M. A., M. DOMINSKA and T. D. PETES, 1993 Transcription factors are required for the meiotic recombination hotspot at the HIS4 locus in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA* **90**: 6621–6625.
- WOJCIECHOWSKI, M. F., M. A. HOELZER and R. E. MICHOD, 1989 DNA repair and the evolution of transformation in *bacillus subtilis*. II. Role of inducible repair. *Genetics* **121**: 411–422.
- YOUNG, J. A., R. W. SCHRECKHISE, W. W. STEINER and G. R. SMITH, 2002 Meiotic recombination remote from prominent DNA break sites in *Schizosaccharomyces pombe*. *Mol. Cell* **9**: 253–263.
- ZHUCHENKO, A. A., and A. B. KOROL, 1983 Ecological aspects of the recombination problem. *Theor. Appl. Genet.* **64**: 177–185.
- ZHUCHENKO, A. A., and A. B. KOROL, 1985 The evolutionary role of the dependence of recombination on environment. *Theor. Appl. Genet.* **69**: 617–624.
- ZHUCHENKO, A. A., A. B. KOROL, T. A. GAVRILENKO and T. Y. KIBENKO, 1986 The correlation between the stability of the genotype and the change in its recombination characteristics under temperature influences. *Genetika* **22**: 966–974.

Communicating editor: M. W. FELDMAN

#### APPENDIX: A RELATIVE FITNESS MODEL OF FAR IN THREE LOCI

Here we assume that recombination is associated with the relative fitness rather than with the absolute one. We implement this form of FAR similarly to the way we

did in HADANY and BEKER (2003): a fixed proportion  $\alpha$  consisting of the fittest individuals has recombination rate 0 (if  $P_{AB} > \alpha$  the group would include only the AB type; if  $P_{AB} < \alpha$ , other types would be included as well), while the rest of the population has recombination rate  $r > 0$ . After mutation, we subdivide the four major types to two subtypes, so that for type  $i$  ( $i \in \{AB, Ab, aB, ab\}$ ),  $P_i^0$  is the proportion of individuals of type  $i$  with recombination rate zero, and  $P_i^1$  is the proportion of individuals of the same type with recombination rate  $r$ . Thus  $P_i^0 +$

$P_i^1 = P_i$  and  $\sum_i P_i^0 = \alpha$ . The system follows the dynamics determined by Equations 6–9, with  $\Delta$  replaced by  $\Delta_{\text{relative}}$ :

$$\begin{aligned} \Delta_{\text{relative}} &= P_{AB}^1 P_{ab}^1 - P_{Ab}^1 P_{aB}^1 \\ &+ \frac{1}{2}(P_{AB}^1 P_{ab}^0 + P_{AB}^0 P_{ab}^1 - P_{Ab}^1 P_{aB}^0 - P_{Ab}^0 P_{aB}^1). \end{aligned}$$

We iterated these equations to equilibrium, and the results are plotted in Figure 4.

