Reprinted from THEORETICAL POPULATION BIOLOGY
Vol.1, No. 1 May 1970
Printed in Belgium


# On the Evolutionary Effect of Recombination*

ILAN ESHEL

*Department of Mathematics, Tel Aviv University*

AND

MARCUS W. FELDMAN

*Department of Biology, Stanford University, Stanford, California 94305*

Received October 20, 1969

## 1. INTRODUCTION

Crow and Kimura (1965) constructed a model to quantify the arguments originally due to Fisher (1930) and Muller (1932) that recombination accelerates evolution because it enables mutations originally occurring in distinct individuals to be combined in a single descendent. The model contained the assumption that even though the population be large, the mutation rate should be so small that the double mutant may not exist in the same individual (see, also, Crow and Kimura (1969)). In particular, Crow and Kimura concluded that the advantage conferred by recombination is greatest when the population is large.

Maynard Smith (1968) contested these findings by producing a "counter-example." This consisted of a deterministic two locus model with multiplicative viabilities in which, at any time, the frequency of the double mutant is the same with recombination as without it. In this article, we also treat the completely deterministic model, that is, an effectively infinite population so that chromosome *frequencies* suffice to describe the population. However, we do not assume that the relative fitness of the double mutant is exactly equal to the product of the relative fitnesses of the single mutants. We consider the case of two loci so that initially the population can be thought of as being all AB. Mutation occurs from A to a and from B to b. Fitnesses of the mutant genotypes are normalized to the original type.

We first show that if the mutations are favorable and the double mutant is fitter than expected under simple multiplicity, then the frequency of the double

* Research supported in part under Grant NIH 10452 and in part by Contract N0014-67A-0112-0115 at Stanford University.





mutant in the asexual case (i.e., without recombination) will always be larger than that when recombination occurs. Our second result concerns the case in which the single mutations are deleterious, but not worse than semilethal while the double mutant is advantageous but not too advantageous. If this is so and mutation is sufficiently rare, we prove that when recombination occurs, the frequency of the double mutant cannot increase to fixation. In fact, the frequency of this double mutant cannot progress beyond a number which is of the order of the mutation rate. On the other hand, it is obvious that without recombination under the above conditions, the double mutant becomes fixed.

These results are quite surprising since it is the prevalent belief that the advantage of recombination is principally to hasten the appearance and increase the frequency of double mutants which are favorable and cooperative in the above sense. However, it should be stressed that our results pertain to the case of an infinitely large random mating population which while being a frequently observed mathematical phenomenon is perhaps rather rare in nature. In the discussion, we take up the meaning of these restrictions in light of the ubiquity and, hence, presumably, the advantage of recombination. It is our feeling that previous explanations are inadequate, and deeper thinking is necessary to explain this advantage.

## 2. THE MODEL

Consider a population of AB individuals such that A can mutate to a with chance $\mu$ per generation and B can mutate to b with chance $\mu$ per generation so that AB mutates to ab with chance $\mu^2$ per generation. The relative fitnesses of the types AB, Ab, aB, and ab are assumed to be 1, $\sigma_2$, $\sigma_2$, and $\sigma_1$, respectively. Initially, there are only AB individuals in the population. Following the first occurrence of mutation, we consider the evolution of the population in two ways. In the first, the population reproduces asexually so that the double mutant can only be formed by mutation. Here we let $x_1$, $x_2$, $x_3$, $x_4$ be the frequencies of ab, aB, Ab, and AB, respectively. In the second reproduction is "sexual" in the sense that recombination occurs. (This is the only sense in which the word sexual will be used.) The frequencies of ab, aB, Ab, AB, in this case, are $y_1$, $y_2$, $y_3$, and $y_4$, respectively. We are interested in the relation between $x_1$ and $y_1$ as time passes for various values of the selection parameters $\sigma_1$ and $\sigma_2$.

## 3. RESULTS

*Case* (a). $1 < \sigma_2^2 < \sigma_1$.

This might be the case when ab is a favorable combination of favorable mutants. We call this the *super-multiplicative case*. When this holds, after the

first generation the frequency $x_1$ of the double mutant in the asexual population is always greater than $y_1$, that in the sexual population. The order of the mutation, selection and recombination events is immaterial. The proof is given in Section 4.

*Case* (b). $1 < \sigma_2 < \sigma_1 < \sigma_2^2$.

Here, after the first generation, the sexual population contains more double mutants than the asexual population. See Remark 2 to Section 4.

*Case* (c). (i) $\sigma_1 > 1 > \sigma_2 > \sigma_2^2 > (1-r)\sigma_1$.

(ii) $\sigma_2 > \frac{1}{2}$.

Assume that selection occurs after recombination which follows mutation. Then there exists $\mu_0$ and a region $G$ specified by

$$G = \begin{cases} 1 - y_4 \leqslant \delta(\mu_0) \\ y_1 \leqslant K y_2^2 \end{cases}$$

with $\delta > 0$ and $0 < K < \infty$, such that if $\mu < \mu_0$, then after the first generation the population never escapes from $G$. $\delta$ may be chosen as small as we please provided $\mu_0$ is sufficiently small. The proof of this result is given in Section 5.

## 4. Analysis of Case (a) $1 < \sigma_2^2 < \sigma_1$

Since the fitnesses of Ab and aB are equal, and the population is initially all AB, we may write, at any time, $x_2 = x_3$ and $y_2 = y_3$. If the superscript $t$ denotes the generation number, then we prove $x_1^{(t)} > y_1^{(t)}$ for $t > 1$. Here, a generation refers to the occurrence of the three events: mutation, selection, and recombination in any order. This strengthens the findings of Maynard Smith, that if $\sigma_1 = \sigma_2^2$, then $x_1^{(t)} = y_1^{(t)}$. Where there is no ambiguity, the generation number will be suppressed. Let $r$ be the recombination fraction in the sexual case, and in the usual notation let $D_y = y_1 y_4 - y_2^2$ be the linkage disequilibrium function for the sexual case. Define $u_x = x_1/x_2$, $u_y = y_1/y_2$ and write $p_x = x_1 + x_2$, $p_y = y_1 + y_2$ for the gene frequencies of the mutants in the asexual and sexual cases, respectively. Obviously,

$$x_1 = p_x u_x/(1 + u_x), \qquad x_2 = p_x/(1 + u_x), \qquad x_4 = 1 - x_1 - 2x_2. \tag{1}$$

After the first occurrence of mutation,

$$x_1 = \mu^2 = y_1, \qquad x_2 = x_3 = y_2 = y_3 = \mu(1-\mu), \qquad x_4 = (1-\mu)^2, \tag{2}$$

so that at this stage

$$\begin{aligned} u_x &= \mu/(1-\mu) = u_y \\ p_x &= \mu = p_y \\ D_y &= 0. \end{aligned} \tag{3}$$



Now, if recombination occurs in the sexual case, since $D_y = 0$, there will be no change in the relations (3). If selection then occurs

$$p_x = \frac{\sigma_1\mu^2 + \sigma_2\mu(1-\mu)}{\sigma_1\mu^2 + 2\sigma_2\mu(1-\mu) + (1-\mu)^2} = p_y,$$

but

$$D_y = \frac{(\sigma_1 - \sigma_2^2)\,\mu^2(1-\mu)^2}{\{\sigma_1\mu^2 + 2\sigma_2\mu(1-\mu) + (1-\mu)^2\}^2} > 0 \quad \text{since} \quad \sigma_1 > \sigma_2^2. \tag{4}$$

On the other hand, if selection occurred first, then recombination, we would have, since $D > 0$ after selection,

$$u_x = \sigma_1\mu/\sigma_2(1-\mu) > u_y$$

and

$$p_x = p_y$$

while recombination simply reduces $D$ in (4) by the factor $(1 - r)$.

Thus, after the first cycle commencing with mutation and followed by recombination and selection, we conclude that

$$u_x^{(1)} \geqslant u_y^{(1)}, \qquad p_x^{(1)} = p_y^{(1)} \qquad \text{and} \qquad D_y > 0. \tag{4}$$

Let us assume that at a given phase of evolution the relations

$$p_x^{(t)} \geqslant p_y^{(t)}, \qquad u_x^{(t)} \geqslant u_y^{(t)}; \qquad D_y^{(t)} > 0 \tag{5}$$

are true. We now prove that after mutation, recombination, and selection occur (in any order), the relations

$$p_x^{(t+1)} > p_y^{(t+1)}, \qquad u_x^{(t+1)} > u_y^{(t+1)}; \qquad D_y^{(t+1)} > 0 \tag{6}$$

hold. To this end, denote by a superscript, $m$, a variable following mutation, by a superscript, $r$, a variable following recombination, and a superscript, $s$, a variable following selection.

(i) Assuming (5) to hold, we show that it remains true after the occurrence of mutation. After mutation, we have

$$\begin{aligned} y_1^{(m)} &= y_1 + 2\mu y_2 + \mu^2 y_4 = (1-\mu^2)\,y_1 + 2\mu(1-\mu)\,y_2 + \mu^2 \\ y_2^{(m)} &= y_3^{(m)} = (1-\mu)\,y_2 + \mu(1-\mu)\,y_4 = (1-\mu)[\mu - \mu y_1 + (1-2\mu)\,y_2] \\ y_4^{(m)} &= (1-\mu)^2\,y_4 = (1-\mu)^2\,(1 - 2y_2 - y_1). \end{aligned} \tag{7}$$

Similar relations hold with $x_i^{(m)}$ and $x_i$ substituted for $y_i^{(m)}$ and $y_i$ throughout (7) ($i = 1, 2, 3, 4$). Then, an easy calculation shows

$$D_y^{(m)} = (1-\mu)^2 D_y > 0. \tag{8}$$

Further,

$$p_x^{(m)} = \mu + (1-\mu)p_x \geqslant \mu + (1-\mu)p_y = p_y^{(m)}.$$

Using (1) in (7) we obtain

$$\begin{aligned} u_x^{(m)} &= \frac{(1-\mu^2)p_x u_x + 2\mu(1-\mu)p_x + \mu^2(1+\mu)}{(1-\mu)[\mu(1+\mu) - \mu p_x u_x + (1-2\mu)p_x]} \\ &= \frac{1}{1-\mu}\left\{\frac{[\mu^2 + (1-\mu^2)p_x]u_x + 2\mu(1-\mu)p_x + \mu^2}{\mu(1-p_x)u_x + (1-2\mu)p_x + \mu}\right\} \\ &= f_m(p_x, u_x), \quad \text{say.} \end{aligned}$$

The function $f_m(p_x, u_x)$ is a linear fractional function in each argument and since

$$\begin{aligned} &[\mu^2 + (1-\mu^2)p_x][\mu + (1-2\mu)p_x] - [\mu^2 + 2\mu(1-\mu)p_x]\mu(1-p_x) \\ &\quad = (1-\mu)^2 p_x^2 + \mu(1-\mu)p_x > 0, \end{aligned}$$

we have $\partial f_m/\partial u_x > 0$.

Again, we may write

$$f_m(p_x, u_x) = \frac{1}{1-\mu}\left\{\frac{[(1-\mu^2)u_x + 2\mu(1-\mu)]p_x + \mu^2(1+u_x)}{[1-2\mu-\mu u_x]p_x + \mu(1+u_x)}\right\}$$

as a linear fractional function of $p_x$. Since

$$\begin{aligned} &[(1-\mu^2)u_x + 2\mu(1-\mu)]\mu(1+u_x) - [1-2\mu-\mu u_x]\mu^2(1+u_x) \\ &\quad = \mu(1+u_x)(\mu+u_x) > 0, \end{aligned}$$

we have $\partial f_m/\partial p_x > 0$. Since $p_x^{(t)} \geqslant p_y^{(t)}$, $u_x^{(t)} \geqslant u_y^{(t)}$, it is now clear that

$$u_x^{(m)} = f_m(p_x, u_x) \geqslant f_m(p_y, u_y) = u_y^{(m)}. \tag{9}$$

(ii) Recombination acts on the sexual population only. Denoting by the superscript $r$ the value of a variable after recombination, we see that

$$\begin{aligned} D_y^{(r)} &= (1-r)D_y > 0, \\ p_y^{(r)} &= p_y \leqslant p_x. \end{aligned} \tag{10}$$



Further, since $D > 0$,

$$u_y^{(r)} = (y_1 - rD)/(y_2 + rD) < y_1/y_2 = u_y \leqslant u_x.$$

Thus, recombination does not affect the truth of (5) but, indeed, changes $u_y \leqslant u_x$ to a strict inequality.

(iii) Now assume $p_x \geqslant p_y$, $u_x > u_y$, and $D_y$ is positive. We show that following selection (6) is true. Variables following selection are denoted by the superscript so that

$$D_y^{(s)} = \sigma_1 y_1 y_4 - \sigma_2^2 y_2^2 = \sigma_2^2 D_y + (\sigma_1 - \sigma_2^2)y_1 y_4 > D_y > 0.$$

Also,

$$u_x^{(s)} = \frac{\sigma_1 x_1}{\sigma_2 x_2} = \frac{\sigma_1}{\sigma_2}u_x > \frac{\sigma_1}{\sigma_2}u_y = u_y^{(s)}.$$

Now we have, using (1),

$$\begin{aligned} p_x^{(s)} &= \frac{\sigma_1 x_1 + \sigma_2 x_2}{\sigma_1 x_1 + 2\sigma_2 x_2 + 1 - 2x_2 - x_1} \\ &= \frac{\sigma_1 p_x u_x + \sigma_2 p_x}{[(\sigma_1 - 1)p_x + 1]u_x + 2(\sigma_2 - 1)p_x + 1} = f_s(p_x, u_x), \quad \text{say.} \end{aligned} \tag{11}$$

Under the hypothesis of the model, as a function of $p_x$, $f_s$ is of the form $Ap_x/(Bp_x + C)$ with $A$, $B$, $C > 0$. Therefore, $f_s$ increases with $p_x$. It also increases in $u_x$ provided

$$\sigma_1 p_x[2(\sigma_2 - 1)p_x + 1] - \sigma_2 p_x[(\sigma_1 - 1)p_x + 1] > 0,$$

or more neatly,

$$(\sigma_1\sigma_2 - 2\sigma_1 + \sigma_2)p_x + (\sigma_1 - \sigma_2) > 0. \tag{12}$$

The left side of (12) is a linear quantity in $p_x$ and since $\sigma_1 - \sigma_2 > 0$, the inequality holds at $p_x = 0$ while, since $\sigma_1(\sigma_2 - 1) > 0$, it holds at $p_x = 1$. It is, therefore, true for $0 \leqslant p_x \leqslant 1$.

We have, therefore, proved that if $u_x > u_y$, $p_x \geqslant p_y$, before selection, then after selection $u_x > u_y$ and $p_x > p_y$. Thus, after the general generation of mutation selection and recombination, (6) remains true in all subsequent generations. But in this case,

$$\frac{p_x}{x_1} = 1 + \frac{1}{u_x} < 1 + \frac{1}{u_y} = \frac{p_y}{y_1}$$

and $p_x > p_y$ so that $x_1 > y_1$ which is the conclusion we sought.

*Remark* 1. If $\sigma_1 = \sigma_2^2$ (as is the case in Maynard Smith's model), it is easy to see that starting with all AB individuals, so that $D^{(0)} = 0$, we must have $D^{(t)} = 0$ for every subsequent $t$. Thus, in this case, $p_x^{(t)} = p_y^{(t)}$ and $u_x^{(t)} = u_y^{(t)}$ and the frequencies of the respective types are the same in the asexual and sexual cases. This holds true even if the fitnesses of Ab and aB are $\sigma_2$, $\sigma_3$, respectively ($\sigma_2 \neq \sigma_3$) with $\sigma_1 = \sigma_2\sigma_3$. In this more general multiplicative setting, the equality of the sexual and asexual systems was concluded by Maynard Smith as an approximation. In fact, it is precisely true.

*Remark* 2. Using the same sort of arguments as above, it can be shown that if $1 < \sigma_2 < \sigma_1 < \sigma_2^2$ (a submultiplicative case), the sexual system will always be advantageous. Indeed, if we begin as before, it is clear that after the first selection $D_y$ will be negative. Recombination and a subsequent mutation do not alter this, nor do succeeding selection events. However, since $D_y < 0$, recombination causes $u_y$ to become larger than $u_x$ without changing $p_y$. As before, after mutation $p_x^{(m)}$ and $u_x^{(m)}$ are increasing functions of $p_x$ and $u_x$. Since $1 < \sigma_2 < \sigma_1$, the same is true of $p_x^{(s)}$ and $u_x^{(s)}$. The inequalities $u_x < u_y$ and $p_x < p_y$, which hold after the second generation, will persist and the sexual population contains more double mutants.

*Remark* 3. The construction of the above proof makes it clear that permuting the order of the mutation, selection and recombination events will not alter the conclusion. Obviously, if, after the first mutation, selection occurs, then recombination at the end of the first generation $u_x > u_y$ while if recombination occurs before selection at the end of the first generation, $u_x = u_y$. However, as we have proved, (6) is true after the second generation.

## 5. Analysis of Case (c)

Assume, as in Case (a), that the population is initially all AB. Assume further that recombination follows any occurrence of mutation and then selection occurs. As in Case (a), $y_2^{(t)} = y_3^{(t)}$ for every $t$. We first prove

Lemma 1. *Starting with $y_4 = 1$ (so that $y_2^{(t)} = y_3^{(t)}$ for $t \geqslant 1$), then after any recombination*

$$y_1/y_2^2 < A = 4\sigma_2^2/[\sigma_2^2 - \sigma_1(1 - r)] \tag{13}$$

*holds true as long as $1 - y_4 < h$, provided that $h$ and $\mu$ are small enough.*

*Proof.* After the first recombination,

$$y_1/y_2^2 = 1/(1 - \mu)^2 < 4 < A.$$



We proceed by induction. Assume that (13) holds after a given recombination event. Then with the prime denoting values after selection,

$$\frac{y_1'}{(y_2')^2} = \frac{\sigma_1 y_1}{\sigma_2^2 y_2^2} T < \frac{4\sigma_1}{\sigma_2^2 - \sigma_1(1 - r)} T,$$

where $T = \sigma_1 y_1 + 2\sigma_2 y_2 + y_4 = 1 - 2(1 - \sigma_2) y_2 + (\sigma_1 - 1) y_1$. In view of the induction hypothesis $y_1 = O(y_2^2)$ with $y_2 < h$, so that for $h$ small enough, we have $T < 1$. Then, we have

$$\frac{y_1'}{(y_2')^2} < \frac{4\sigma_1}{\sigma_2^2 - \sigma_1(1 - r)} = \frac{\sigma_1}{\sigma_2^2} A. \tag{14}$$

Suppose now that $(1 - y_4) < h$ and consider $y_2$ following mutation and recombination:

$$\begin{aligned} y_2' &= (1 - \mu)(y_2 + \mu y_4) + r(1 - \mu)^2(y_1 y_4 - y_2^2) \\ &> (1 - \mu) y_2 + \mu(1 - \mu) y_4 - y_2^2 \\ &= \mu(1 - \mu) y_4 + y_2(1 - \mu - y_2) \\ &> \mu(1 - \mu) y_4 > (1 - \mu)(1 - h)\mu, \end{aligned}$$

if $h$ is small enough. According to the induction hypothesis, $y_1 = O(y_2^2)$ and $y_2 < h$ so that the mean fitness of the population after selection is less than one. Thus, after selection,

$$y_2 > \sigma_2(1 - \mu)(1 - h)\mu = [(1 + 2\alpha)/2]\, \mu(1 - \mu)(1 - h), \tag{15}$$

where $\alpha = \sigma_2 - \frac{1}{2} > 0$ by hypothesis; $\alpha$ is, also, independent of $\mu$ and $h$. We make use of (15) to show that a mutation event cannot increase $y_1/y_2^2$ by more than 4. To do this, we must show

$$\frac{y_1 + 2\mu y_2 + \mu^2 y_4}{(1 - \mu)^2 (y_2 + \mu y_4)} < \frac{y_1}{y_2^2} + 4. \tag{16}$$

Since the left side of (16) decreases in $y_4$, we need only show

$$(y_1 + 2\mu y_2)/(1 - \mu)^2 y_2^2 < (y_1 + 4y_2^2)/y_2^2$$

or, equivalently,

$$\mu(2 - \mu) y_1 < 2y_2[2y_2(1 - \mu)^2 - \mu]. \tag{17}$$

Suppose that $\mu$ and $h$ are so small that $(1 - \mu)^3(1 - h) > (1 + \alpha)/(1 + 2\alpha)$, say $\mu, h < \alpha/4(1 + 2\alpha)$. Then from (15), we have

$$2y_2(1 - \mu)^2 > (1 + 2\alpha)(1 - \mu)^3(1 - h)\mu > (1 + \alpha)\mu,$$

so that

$$2y_2[2y_2(1-\mu)^2-\mu] > 2y_2[(1+\alpha)\mu-\mu] = 2\mu\alpha y_2 .$$

But for $h$ small enough, since $y_2 < h$, $y_1 = O(y_2^2)$, it is clear that $y_1 < \alpha y_2$ so that

$$2\mu\alpha y_2 > 2\mu y_1 > (2-\mu)\mu y_1$$

which completes the proof of the validity of (16).

Combining (14) and (16), we have shown that after selection and mutation,

$$y_1/y_2^2 < \sigma_1/\sigma_2^2 A + 4. \tag{18}$$

From (18), we need, for the proof of the lemma, that after a subsequent recombination

$$y_1'/(y_2')^2 < A.$$

But after recombination,

$$\begin{aligned}
\frac{y_1'}{(y_2')^2} &= \frac{(1-r)y_1 + r(y_1+y_2)^2}{\{y_2 + ry_1 - r(y_1+y_2)^2\}^2} \\
&= \frac{(1-r)y_1 + ry_2^2}{y_2^2} + O(y_2^2). \\
&< (1-r)\frac{\sigma_1}{\sigma_2^2}A + 4(1-r) + r + O(y_2^2) \qquad \text{[by (18)]} \\
&< A - \left[1-(1-r)\frac{\sigma_1}{\sigma_2^2}\right]A + 4 - 3r + O(y_2^2) \\
&< A - \frac{1}{\sigma_2^2}[\sigma_2^2 - (1-r)\sigma_1]\frac{4\sigma_2^2}{\sigma_2^2-(1-r)\sigma_1} + 4 \quad \text{(by definition of } A) \\
&= A.
\end{aligned}$$

This completes the proof of Lemma 1.

*Remark.* From the proof of Lemma 1 we can see that if $h$ is small enough and $1 - x_4 < h$, then after mutation $y_1 \leqslant [(\sigma_1/\sigma_2^2)A + 4]y_2^2$ so that $y_1 = O(y_2^2)$.

LEMMA 2. *There is a $\delta$ with $0 < \delta < h$ such that if, after mutation $1 - y_4 < \delta$ with $y_1 \leqslant [(\sigma_1/\sigma_2^2)A + 4]y_2^2$, then $1 - y_4^{(t)} < \delta$, subsequently, as long as $y_1^{(t-1)} \leqslant [(\sigma_1/\sigma_2^2)A + 4](y_2^{(t-1)})^2$ and $\mu$ is small enough.*

*Proof.* Again, the proof is by induction; after recombination and selection,

$$\begin{aligned}
1 - y_4' &= 2y_2' + y_1' = 2y_1' + O(y_2^2) \\
&= \frac{2\sigma_2[y_2 + ry_1 - r(y_1+y_2)^2]}{T} + O(y_2^2),
\end{aligned} \tag{19}$$



where $T$ is the mean fitness after recombination and selection. Clearly, since $\sigma_2 < 1$, for $\delta$ small enough,

$$1 \geqslant T = y_4 + 2\sigma_2 y_2 + \sigma_1 y_1 + O(y_2^2) > y_4 > 1 - \delta$$

so that $1/T < 1 + 2\delta$. Then $1 - y_4' < 2\sigma_2 y_2 + O(\delta^2) < 1 - y_4$. This means that for $\delta$ small enough $1 - y_4 \leqslant \delta$ after mutation, and (18) ensures that following recombination and selection $y_4' > y_4$.

Now, for any $\epsilon$ such that $0 < \epsilon < \delta$, the set

$$S = \{(y_1, y_2, y_3, y_4) \mid \epsilon \leqslant 1 - y_4 \leqslant \delta; y_1 \leqslant Ky_2^2, K \text{ const}\}$$

is a compact set over which $y_4' - y_4$ (here, $y_4'$ is $y_4$ after recombination and selection) is a continuous positive function. Thus, there is a $\theta = \theta(\epsilon, \delta) > 0$ such that on $S$, $y_4' - y_4 \geqslant \theta$.

After a subsequent mutation,

$$y_4' - y_4 = (-2\mu + \mu^2)y_4 > -2\mu,$$

so that if $\mu < \frac{1}{2}\min(\theta, \delta - \epsilon)$, we have on $S$ after recombination selection *and* mutation

$$y_4' - y_4 > \theta - 2\mu > 0,$$

in other words, $1 - y_4' \leqslant \delta$. On the other hand, if $1 - y_4 < \epsilon$, then after recombination selection and mutation $y_4' - y_4 > -2\mu$ so that $1 - y_4' < \epsilon + 2\mu < \delta$. In any event, $1 - y_4 \leqslant \delta$ and $y_1 < Ay_2^2$ imply $1 - y_4' < \delta$.

Now, after the first recombination event (13) holds, and for sufficiently small $\mu$, we have $1 - y_4 < \delta$. This means that (13) remains true by Lemma 1 as long as $1 - y_4 < \delta$, and $1 - y_4 < \delta$ remains true by Lemma 2 as long as $y_1 < Ay_2^2$. Hence, both inequalities subsequently hold. This completes the proof of Case (c).

*Remark* 1. Since the point (0, 0, 0, 1) is inherently unstable in the presence of mutation, the result of Case (c) would imply, if convergence of the recursion system is assumed, that a stable equilibrium exists close to the $y_4 = 1$ corner, i.e., in $S$. $S$ is a region of stability in the sense that once the population enters the interior of $G$ it cannot escape.

*Remark* 2. The sexual population remains trapped in $S$ under the conditions of the model, while it is obvious that in the absence of recombination the population would fix on the advantageous double mutant. Thus, in an evolutionary sense, the effect of recombination is not favorable.

*Remark* 3. In Case (e), the assumption $\sigma_2^2 > (1-r)\sigma_1$ is precisely that needed to ensure limiting quasilinkage equilibrium in a deterministic model

without mutation [Feldman and Crow (1970)]. However, recent calculations made by Professor S. Karlin indicate that this condition is not the best possible.

## 6. Discussion

Our primary aim in this work has been to check rigorously whether the commonly held view that the main advantage of recombination is to enable favorable cooperative double mutants to appear faster and in higher frequency is a valid one. Our results demonstrate that for a deterministic random mating population with constant fitnesses, exactly the opposite is true. (a) If the population is initially all AB and the fitness of the double mutant ab is greater than the product of the fitnesses of the favorable single mutants, then an asexual population will always contain more double mutants than the corresponding population with recombination. (b) The same result is true if there is another type of gene interaction; namely, if the single mutants are deleterious (but not extremely so) and the double mutant is favorable (but not extremely so).

If two mutations are considered to be cooperative when the double mutant is fitter than the product of the fitnesses of the two single mutants, then these two cases cover almost all possibilities.

One can see the first result intuitively from the fact that in the case with recombination, starting with all AB, after selection the linkage disequilibrium becomes positive. From this point on, the loss of double mutants by recombination with the original type is the key factor in the difference between this and the asexual population in which no such loss occurs.

The result (b) is perhaps more interesting. The limitations we have imposed on $\sigma_1$ and $\sigma_2$, the fitnesses of the double and single mutants, respectively, are not at all stringent: $\sigma_2 > \frac{1}{2}$ and $\sigma_1(1-r) < \sigma_2^2 < 1$. The latter of these two conditions is precisely the condition under which, as fixation in AB occurs in the absence of mutation, limiting quasilinkage equilibrium is approached (Feldman and Crow (1970)). As pointed out by Crow and Kimura, this also entails, when mutation is absent, the existence of an unstable equilibrium between the two stable fixations in AB and ab. It is a priori by no means clear what the effect of a steady flux of mutation will be in this case. We have shown that the way in which recombination stops the progress of the double mutant in this case is not through the original unstable *adaptive valley*, but a new mutation selection balance with the double mutant in low frequency. (Presumably, there exists another unstable equilibrium with higher frequencies of the mutants.)

Heuristically, the validity of result (b) can be seen through the following three stages of reasoning.



(1) As long as the frequencies of the new genes are low, which they will be initially, the frequency of the double mutant is of the order of the square of the single mutant frequencies provided these single mutants are not too deleterious.

(2) As long as most of the new genes are in the form of disadvantageous single mutants, selection favors the original genotype.

(3) As long as mutation is rare, the mutation pressure is insufficient to push the frequencies outside the small region in which our arguments are valid.

The first part of our proof shows, in particular, that our argument is valid when we make the assumption made by Bodmer (1970) and others that the double mutant frequency may be negledted in the beginning. In fact, the initial frequency vector $(0, \epsilon, \epsilon, 1-2\epsilon)$ will be in the *trap region* for $\epsilon$ small enough, so that with a steady flux of mutation the frequencies of the new mutants will remain very low.

The requirement that the single mutants be not too deleterious may seem strange at first glance. However, it seems plausible that if these single mutants were, say, nearly lethal, then with or without recombination the frequency vector would be pushed toward the AB — ab edge of the frequency tetrahedron. From here, selection in favor of ab may pull the population into the state of fixation in ab. Even in this case, though, since $D$ becomes positive, the rate of evolution with recombination will be slower in the same way as in Case (a).

In spite of our results, recombination is ubiquitous in nature and it would be difficult to believe that it does not possess some crucial evolutionary advantage. In fact, our results are true under very restrictive biological conditions. We have considered a very large random mating population in an unchanging environment. So far we do not have a clear picture of what happens in small populations, although the studies by Crow and Kimura (1965), Bodmer (1970) and Karlin and McGregor (unpublished) indicate that in this case recombination will hasten the appearance of the first double mutant. But the subsequent evolution of the population under the influence of drift, selection and recombination is quite unknown, so that the significance of the first double mutant is questionable. Indeed, if there is no selection and the population is small, Karlin and McGregor (unpublished) have shown that the expected time until the whole population consists of double mutants is an *increasing* function of the recombination fraction.

We do know, however, that modification of the mating system, in particular through the evolution of incompatibility systems, can be advantageous. These could have been the precursors of sexual systems with the advantage conferred not necessarily by recombination, but possibly by genetic incompatibility itself.

The asexual population, as we have shown, fixes on the double mutant faster. Eventually, however, the disadvantage of recombination in slowing the progress of the double mutant may become an advantage in the case of a changing environment. Rather than hastening the fixation in the double mutant, the advantage of recombination may be in prolonging the polymorphic state.

These speculations are a few of many that can be made to account for our results. We feel that our results need explanation and that some of the more interesting questions remain to be answered. For example, it is not clear from our work or the work of others whether recombination will increase the speed with which a sizable fraction, say 50 %, of a small population becomes double mutants. New and deeper thinking is needed on such problems as this and the general question of the advantage of recombination and sex.

## Acknowledgments

The authors are grateful to Professor Samuel Karlin for a number of stimulating discussions and for allowing us to see his unpublished results with Professor James McGregor.

## References

Bodmer, W. F. 1970. The Evolutionary Significance of Recombination in Prokaryotes. (To Appear).

Crow, J. F., and Kimura, M. 1965. Evolution in sexual and asexual populations, *Amer. Nat.* **99**, 439.

Crow, J. F., and Kimura, M. 1969. Evolution in sexual and asexual populations, A Reply, *Amer. Nat.* **103**, 89.

Feldman, M. W., and Crow, J. 1970. "Quasilinkage equilibrium and the fundamental theorem of natural selection, *Theor. Pop. Biol.* **1**, in press.

Fisher, R. A. 1930. "The Genetical Theory of Natural Selection," Oxford Univ. Press (also reprinted, 1958, by Dover Publication), London/New York.

Muller, H. J. 1932. Some genetic aspects of sex, *Amer. Nat.* **8**, 118.

Smith, M. J. 1968. Evolution in sexual and asexual populations, *Amer. Nat.* **102**, 469.

PRINTED IN BELGIUM BY THE ST. CATHERINE PRESS, TEMPELHOF, 37, BRUGES, LTD.