SELECTION ON RECOMBINATION IN A MULTI-LOCUS SYSTEM

D. CHARLESWORTH* AND B. CHARLESWORTH*

Laboratory of Environmental Mutagenesis,
National Institute of Environmental Health Sciences,
P. O. Box 12233
Research Triangle Park, North Carolina 27709

Manuscript received June 23, 1978
Revised copy received September 29, 1978

ABSTRACT

The model of WILLS and MILLER (1976) for selection on recombination rates in finite populations was studied by means of a computer model involving 80 selected loci and a linked or unlinked modifier gene affecting the map length occupied by the selected loci. The selected loci were subject to heterozygote advantage, and multiplicative fitness interactions between loci were assumed. In all cases studied, selection for reduction in recombination outweighed any selection for increased recombination that may have been present.

WILLS and MILLER (1976) proposed "a model for outbreeding populations in which there can be selection for relatively free recombination," which they claim "does not rely on group selection to explain the advantage of recombination." These authors did not give any definite proof that natural selection in this model will increase recombination, in the sense of producing an increase in the frequency of an allele at a locus that modified recombination rates. Rather they studied a model that gave results suggesting that recombination would be favored. The present paper describes an attempt to find out whether that is really the case; we first reproduce the results of WILLS and MILLER and then study the fate of alleles affecting recombination rates, segregating in populations under the conditions which, it is suggested, would promote recombination. We shall show that there is no evidence for selection in favor of an allele increasing recombination Before giving these results, we shall describe the model system of WILLS and MILLER, and their reasons for suggesting that it will generate selection for increased recombination.

THE MODEL

WILLS and MILLER (1976) pointed out that a locus at equilibrium under selection can be perturbed away from equilibrium by changes in the allele frequencies at a linked locus, when there is linkage disequilibrium between them. This force is central to another model of selection on recombination rates (STROBECK, MAYNARD SMITH and CHARLESWORTH 1976); the first locus in that model was

* Present address: School of Biological Sciences, University of Sussex, Brighton, Sussex BN1 9QG, England.

maintained at equilibrium by some form of balancing selection, and the second was a new, advantageous mutation. This model was shown to generate selection for increased recombination.

In WILLS and MILLER's model, they envisage a finite population, so that loci will be perturbed from their equilibria by sampling effects, and their return to equilibrium will be hindered by linkage disequilibrium with other loci. WILLS and MILLER consider that, if there is variation in recombination rates between individuals, this effect will mean that the progeny of those with high recombination will tend to be more heterozygous than the average for the population. If fitness increases with the number of loci for which an individual is heterozygous, this would promote an increase in the frequency of high recombination alleles. Their paper is therefore devoted to demonstrating that populations with high recombination are more heterozygous than ones with less recombination.

A large number (100 or 400) of loci were assumed, each segregating for two alleles, and subject to selection, which could be of various types, with heterozygotes having higher fitness than homozygotes. Populations with N (presumably diploid individuals) equal to 100, were simulated, assuming either free recombination between the loci, or with some linkage. There was random mating. Two forms of selection were investigated. The first was truncation selection based on the number of heterozygous loci; some fraction of the population having the lowest number of heterozygous loci was discarded each generation, and replaced with duplicates of individuals having higher scores. This selection scheme gives expected equilibrium frequencies of 0.5 at all loci. In the second scheme, each locus was pre-assigned an equilibrium value, and the previous method was modified to take into account the selection coefficients at the particular loci for which the individual was homozygous [see WILLS and MILLER (1976) for details of the method]. Truncation selection on these scores was performed as before. Populations were started either with all loci having an expected allele frequency of 0.5, or with a uniform distribution of allele frequencies between zero and one, the actual frequency for each locus being determined randomly. The two methods of setting up the population gave similar results (WILLS and MILLER 1976).

We have run very similar simulations, using a population of 100 diploid individuals, and with 80 loci. Since their theoretical discussion gives no special reason for the particular modes of selection chosen by WILLS and MILLER (which in any case yield similar results), we preferred to use the multiplicative selection scheme of FRANKLIN and LEWONTIN (1970). The multiplicative scheme gives the same range of qualitative phenomena as truncation selection based on the number of heterozygous loci (FRANKLIN and LEWONTIN 1970, p. 726), so that we expected our results to be comparable with those of WILLS and MILLER's first selection scheme. We used selection values $W_1 = W_3 = 0.9$, $W_2 = 1.0$ for all loci. Four map lengths were used: 0, 10, 25, and 200; a map length of 100 units is equivalent to a mean of one crossover per chromosome. As in WILLS and MILLER's simulations, the number of recombination events per chromosome was assumed to follow a Poisson distribution. We did not study the case of completely unlinked loci.

The simulations showed the same effect as that described by WILLS and MILLER (1976), *i.e.*, the cases with tight linkage initially lost polymorphisms faster than those with loose linkage (Figure 1). With a map length of 200, all 80 loci remained segregating after 200 generations, in three replicate runs; by that time the runs with tighter linkage had lost variability at a number of loci, and then stopped changing because only two chromosome types remained in the population, with all individuals heterozygous at all the remaining segregating loci. This reduction in the level of heterozygosity with tighter linkage is expected, since when selection acts on a set of linked genes, the effective population size is reduced (due to hitch-hiking effects), thus leading to a lower level of heterozygosity (HILL and ROBERTSON 1966; FELSENSTEIN 1974). Our results are similar to those of WILLS and MILLER (1976), except that the effects are more marked than in most of their cases. We compared a small amount of recombination with the case of very tight linkage, whereas they contrasted a small amount of recombination with completely free recombination. This difference probably accounts for the difference in the magnitude of the effects observed.

FATE OF A MODIFIER OF RECOMBINATION

The next step was to do runs like those just described, but with the addition of genetic variation at a locus affecting the recombination rate between the selected loci. We first studied the case of a recessive gene for increased recombination (individuals carrying the dominant allele had no recombination). The modifier was assumed to segregate independently of the selected loci. Figure 2 shows the results of sets of ten runs of this case, with various map lengths in homozygotes for the modifier. The initial frequency of the modifier was 0.5, and each gamete was assigned one or other allele at random when the starting population was set up. Figure 2 shows that the modifier tended to decline in frequency in all cases, though it did not always reach zero in the hundred generations that were run.

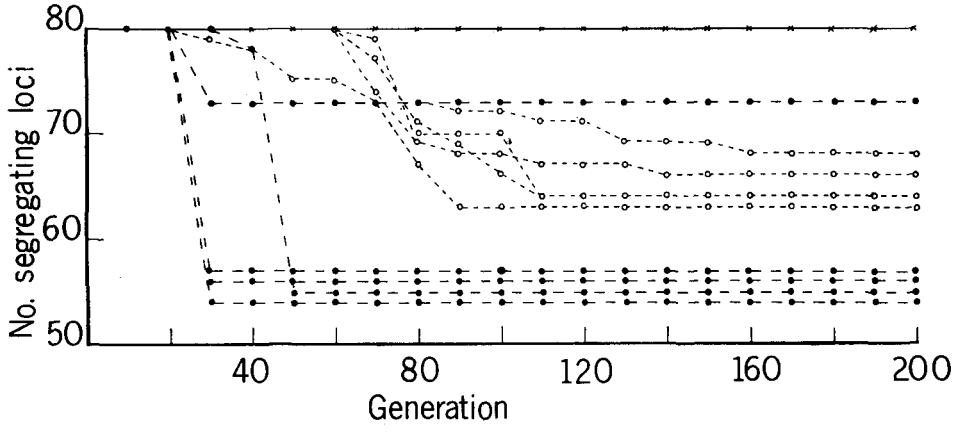

FIGURE 1.—Number of loci that are still segregating at different times, with no modifier present. ×———× : map length 200. ○ - - - - ○ : map length 50. ●— — ● : map length 0.

A further set of five runs with a map length of 25 was run for 200 generations. Although at generation 100 the modifier was lost in only one run, it was lost in four of the five cases by 200 generations. There is therefore no sign of stabilization at some recombination fraction above zero.

A modifier with intermediate dominance behaved in much the same way, and was eliminated in seven of ten runs of 100 generations; a map length of 200 was assumed in this case for the modifier homozygotes, and 100 for the heterozygotes. The detailed course of the changes in the modifier frequency resembled the runs

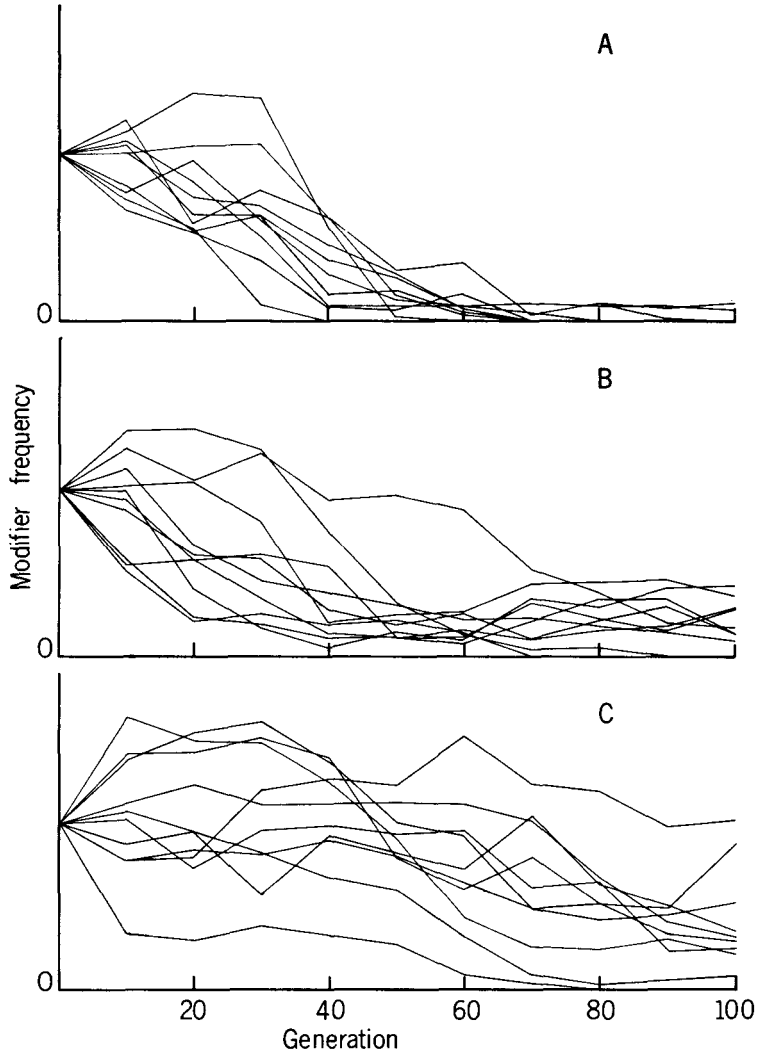

FIGURE 2.—Frequency of a recessive modifier increasing the recombination rate. The modifier was always started at an average frequency of 0.5 and was unlinked to the selected loci. (A) modifier homozygotes have a map length of 200. (B) modifier homozygotes have a map length of 25. (C) modifier homozygotes have a map length of 10. Other genotypes at the modifier locus have no recombination between the selected loci.

with small map lengths shown in Figure 2, except that loss of the modifier was more common, as mentioned above.

The second case that we have studied again assumed that the allele for increased recombination was completely recessive, but now it was assumed to be linked to the selected loci. Since heterozygotes, as well as homozygotes, for the alternative allele had no recombination, the gamete carrying the modifier allele was simply assumed to be transmitted intact to the progeny. In homozygotes for the modifier, all progeny gametes would of course receive the modifier allele. In these runs, a frequent outcome was elimination of all but two chromosomes, as in the runs with no modifier gene. When this occurred, the modifier could be present in both, one or neither of the two. Out of a total of 60 runs, the modifier was present in both chromosomes at the end of the run in only five cases (all five were cases with a map length of 10 in the modifier homozygotes). The modifier was present in just one of the remaining chromosomes, resulting in a modifier frequency of exactly one-half, in 23 cases; these runs therefore had a recombination fraction of zero, since the modifier is assumed to be recessive. In the other runs, the modifier frequency at generation 100 was below 0.5, and was often zero (see Figure 3).

When the modifier was started at an initial frequency of 0.25, instead of 0.5, the frequency of elimination was greater. With a map length of 10 in the modifier homozygotes, loss occurred in 12 of 20 cases run for 100 generations, and there were no fixations; in 20 runs with an initial modifier frequency of 0.5, only four lost the modifier in this length of time. Assuming no selection on the modifier, we expect that once the population has lost all but two chromosomes, the probability that neither chromosome contains one particular allele at the modifier locus is given by the square of the initial frequency of the other allele. With the modifier started at a frequency of 0.5, we therefore expect it to be lost in a quarter of the runs, and with a starting frequency of 0.25, we would expect loss in about 56% of the runs. In the case of a modifier giving a map length of 10, the frequency of loss is so close to these predicted values that we can conclude that the process is dominated by chance events. The cases with larger map lengths therefore clearly demonstrate the action of selection for reduced recombination.

In conclusion, these runs give no evidence of a net selection pressure for increased recombination. It appears that the strong selection for reduced recombination that must be operating, due to the gene interactions that exist in this type of system (NEI 1967; FELDMAN 1972; CHARLESWORTH and CHARLESWORTH 1973), outweigh any selection for increased recombination that may exist.

LITERATURE CITED

CHARLESWORTH, B. and D. CHARLESWORTH, 1973 Selection of new inversions in multi-locus genetic systems. Genet. Res. **21**: 176–183.

FELDMAN, M. W., 1972 Selection for linkage modification: I. Random mating populations. Theoret. Pop. Biol. **1**: 88–100.

FELSENSTEIN, J., 1974 The evolutionary advantage of recombination. Genetics **78**: 737–756.

FRANKLIN, I. and R. C. LEWONTIN, 1970 Is the gene the unit of selection? Genetics **65**: 707–734.

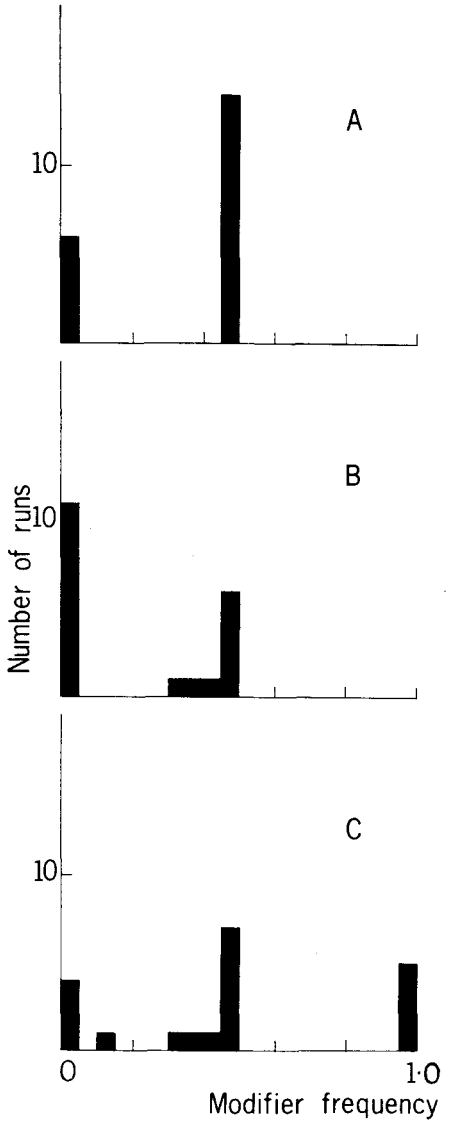

FIGURE 3.—Frequency of a linked, recessive modifier gene after 100 generations. A, B, and C denote the same modifier effects as in Figure 2.

HILL, W. G. and A. ROBERTSON, 1966 The effect of linkage on limits to artificial selection. Genet. Res. **8**: 269–294.

NEI, M., 1967 Modification of linkage intensity by natural selection. Genetics **57**: 625–641.

STROBECK, C., J. MAYNARD SMITH and B. CHARLESWORTH, 1976 The effects of hitch-hiking on a gene for recombination. Genetics **82**: 547–558.

WILLS, C. and C. MILLER, 1976 A computer model allowing maintenance of large amounts of genetic variability in Mendelian populations. II. The balance of forces between linkage and random assortment. Genetics **82**: 377–399.

Corresponding editor: M. NEI