THE EVOLUTIONARY ADVANTAGE OF RECOMBINATION[1]

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ABSTRACT

The controversy over the evolutionary advantage of recombination initially discovered by FISHER and by MULLER is reviewed. Those authors whose models had finite-population effects found an advantage of recombination, and those whose models had infinite populations found none. The advantage of recombination is that it breaks down random linkage disequilibrium generated by genetic drift. HILL and ROBERTSON found that the average effect of this randomly-generated linkage disequilibrium was to cause linked loci to interfere with each other's response to selection, even where there was no gene interaction between the loci. This effect is shown to be identical to the original argument of FISHER and MULLER. It also predicts the "ratchet mechanism" discovered by MULLER, who pointed out that deleterious mutants would more readily increase in a population without recombination. Computer simulations of substitution of favorable mutants and of the long-term increase of deleterious mutants verified the essential correctness of the original FISHER-MULLER argument and the reality of the MULLER ratchet mechanism. It is argued that these constitute an intrinsic advantage of recombination capable of accounting for its persistence in the face of selection for tighter linkage between interacting polymorphisms, and possibly capable of accounting for its origin.

A number of authors have recently investigated the effect of natural selection on modifiers of recombination fractions between polymorphisms (NEI 1967, 1969; LEWONTIN 1971; FELDMAN 1972). Their conclusion, as unanimous as it is convincing, is that natural selection will favor modifiers which reduce the recombination between interacting linked polymorphisms. This would seem to provide the basis for the conclusion that natural selection should be operating to eliminate sexual recombination. Its continued presence could only be explained if it were the byproduct of some other cellular process such as chromosome pairing or DNA repair. The question therefore arises as to whether recombination exists because it is itself beneficial, or as the result of some "extrinsic" process. To maintain an "intrinsic" theory of the evolution of recombination, we need to find an evolutionary advantage resulting from the presence of recombination. Such an advantage is provided in the classical theory of FISHER (1930) and MULLER (1932), which has more recently been a source of controversy (CROW and KIMURA 1965, 1969; MAYNARD SMITH 1968, 1971a; ESHEL and FELDMAN

[1] This paper is dedicated to the memory of KEN-ICHI KOJIMA. He had a continuing interest in the evolutionary effects of recombination, and made major contributions toward clarifying our understanding of the interaction between recombination and natural selection.

1970; BODMER 1970; KIMURA and OHTA 1971; KARLIN 1973). It is neither my purpose in this paper to discuss "extrinsic" theories of recombination, nor to speculate about the molecular events involved in the evolution of recombination. Instead, the question addressed here will be whether we have a theory of the intrinsic advantage of recombination sufficient to explain its presence. Even if there is such a theory, until we know more about genetic systems at a molecular level we cannot say whether the events in the theory bear any relation to the process involved in the initial evolution of recombination. But we must not only be able to explain how recombination evolved initially, but also why it has not subsequently been eliminated by natural selection. It will therefore be relevant to discuss "intrinsic" theories, whether or not they accurately describe the initial steps in the evolution of recombination. The term "recombination" in this paper will always refer to sexual recombination. Neither the evolution of recombination in asexual organisms nor the evolution of dioecy will be discussed here.

The purpose of this paper is primarily synthetic: to point out the close connection between recent work by HILL and ROBERTSON (1966) and the classical FISHER-MULLER theory of the evolution of recombination, and to point out the relatedness, relevance, and importance of the "ratchet mechanism" of MULLER (1964). Computer simulations will be presented which verify the arguments of the FISHER-MULLER theory, and which verify the "ratchet mechanism". A crude approximation to the effect of recombination when favorable mutants occur continually is also presented.

THE CONTROVERSY

Any review of the course of the controversy over the FISHER-MULLER theory of the evolution of recombination must necessarily be vague and impressionistic. For more precise discussions, the original papers should be consulted, as there is no room to repeat their equations here. The purpose of this review is to point out that those authors who have allowed finite-population effects into their models have been the ones who found an advantage to having recombination, while those whose models were completely deterministic found no consistent advantage.

FISHER (1930) and MULLER (1932) stated essentially identical theories of the evolutionary advantage to a population of having recombination. They imagined a population in which new, favorable mutants are occurring at many different loci. If the population has recombination, the fixation of mutants at different loci will be more or less independent. Favorable mutants which arise in different individuals can ultimately be combined into the same genome by recombination. But if there is no recombination in the population, two mutants can both succeed in fixing only if the second occurs in one of the offspring of the first. Otherwise their offspring can at best compete with one another, and only one of the two muants can ultimately succeed in fixing. Thus, many of the newly-occurring mutants must be lost, more than would be the case in the presence of recombination. A population with recombination can therefore evolve faster than one without it. Since the argument has always been stated in terms of advantage to

the population as a whole, it seems to rely on group selection to establish and maintain recombination. MULLER does not seem to have discussed this point, but FISHER (1930) wrote that he discounted the importance of "interspecific" selection "with the possible exception . . . of sexuality itself, which could be interpreted as evolved for the specific rather than for the individual advantage." All of the arguments in this paper will implicitly be couched in terms of group selection, but in a subsequent paper I hope to show that the FISHER-MULLER argument can also be stated in terms of individual selection.

Following these papers, tthere was little or no controversy for over thirty years, although MULLER (1958, 1964) did publish papers repeating his views. In the latter paper, MULLER pointed out a "rachet" effect which would cause *disadvantageous* mutants to accumulate in populations lacking recombination. This effect turns out to be conceptually equivalent to the original FISHER-MULLER argument which was stated for advantageous mutants. This will be discussed more fully below.

In 1965, CROW and KIMURA published a calculation of the relative increase in the rate of substitution of favorable mutants in a population which had recombination. Their model assumes a haploid organism with a great many loci. Genetic drift is absent. New favorable mutants arise at the rate of U per genome, each at a different locus. If recombination is present, all of the favorable mutants will ultimately be fixed. But if there is no recombination, a mutant can be successful only if it occurs among the descendants of the most recent successful mutant. CROW and KIMURA calculate the time until the next favorable mutant occurs among these descendants, assuming that the previous successful mutant started at a gene frequency of $1/N$ and increased deterministically with selective advantage s. They obtained a formula for the increase in the rate of evolution which results from having recombination. They concluded from this formula that the advantage of having recombination is greater the larger are N and U/s.

MAYNARD SMITH (1968) questioned these conclusions. He presented a counterexample in which recombination has no effect on the rate of evolution. In his model, each mutant is originally at a low equilibrium frequency in the population, maintained by a balance between recurrent mutation and natural selection against the mutant. The population is infinite, so that there is no genetic drift. He also assumes, as did CROW and KIMURA, that the fitness of a genotype is the product of the fitnesses at the different loci, so that there is no interaction between loci. Under these conditions, there will be no initial linkage disequilibrium between any pair of loci, whether there is recombination or not. MAYNARD SMITH points out that natural selection with multiplicative fitnesses will not create linkage disequilibrium where none exists initially. Since recombination can have an effect on the population only by breaking down linkage disequilibrium, in this case its presence or absence will make no difference to the genotypic composition of the population. Evolution will proceed at the same rate whether or not there is recombination, the frequency of a haploid genome being at all times the product of the frequencies of the alleles which make it up. MAYNARD SMITH also points out the possible importance of CROW and KIMURA's assumption that each favor-

able mutant is a unique event. If, instead, each possible mutant recurs many times in each generation, a population having recombination cannot incorporate all of the favorable mutants which occur, since some are simply recurrences of the same mutant. Furthermore, a population lacking recombination can then incorporate two favorable mutants at different loci even if the mutant at the second locus originally occurs only in individuals not having the mutant at the first locus. The mutant at one locus will sooner or later recur in descendants of individuals mutant at the other locus. Thus at best CROW and KIMURA's argument will overstate the rate of evolution in a population having recombination, and will understate it in a population having no recombination. When the favorable mutations recur instead of being unique events, CROW and KIMURA's calculation must exaggerate the advantage to a population of having recombination.

CROW and KIMURA (1969) replied to MAYNARD SMITH's first criticism by pointing out that if the favorable mutants were initially rare, there would almost never be any individuals carrying two or more of them. Rare alleles in a finite population would not be in a state of linkage equilibrium, since that would require double mutant as well as single mutant genomes to be present. It was, therefore, relevant to make an argument of the FISHER-MULLER sort, involving the ability of recombination to combine favorable mutants which originally arose in different individuals. BODMER (1970) argued along similar lines. He considers a population containing mutants at two loci, each mutant initially at a frequency x_0. He calculates the length of time necessary for a double mutant genome to arise in a population which has recurrent mutation but no recombination, compared to the time necessary in a population with recombination but no recurrent mutation. He assumes that each single mutant increases deterministically from frequency x_0 as a result of its selective advantage. BODMER concludes that recombination will do the job more than twice as quickly as recurrent mutation if, approximately,

$$x_0 > 4\mu/r ,$$

where μ is the mutation rate to the favored alles and r is the recombination fraction. If each allele is present only once, $x_0 = 1/N$, so that if $r = 1/2$, the condition becomes

$$8N\mu < 1 .$$

From this, BODMER concludes that recombination will have a greater advantage in a small population than in a large one, and therefore a greater advantage on the average in eukaryotes than in prokaryotes.

BODMER does not calculate the time to production of a double mutant when *both* recombination and recurrent mutation are present. Since it seems unlikely that the presence of recombination would be accompanied by reduced mutation rates, BODMER's argument must be taken as defining conditions under which recombination is of importance, rather than conditions under which it is advantageous. He also assumes that both mutants are present in the initial generation, each at frequency x_0. This is less general than CROW and KIMURA's (1965) treatment in which the second mutant need not initially occur in the same generation

as the first. BODMER's argument concerns only two given mutants, and does not take into account the larger number of favorable mutants which can occur in a large population. This will increase the advantage of recombination in a large population, and may reverse BODMER's conclusion about the effect of population size. However, BODMER's approach does allow for recurrent mutation, while CROW and KIMURA's does not.

KARLIN (1973) examined a finite population with mutation and recombination, but without selection. For the case of unidirectional recurrent mutation, he found by exact matrix methods for small N and by simulation for larger N that, starting from a population free of both mutants, the time until production of the first double mutant haploid genome was decreased by recombination, but the time until fixation of that genome was *increased*. This latter effect was pronounced only with small population size. Since there was no selection, it is impossible for recombination to affect the time course of gene substitution by genetic drift at either locus. Its only effect is to reduce the correlation between the gene frequencies at the two loci. The correlation affects the time of the appearance of the first double mutant genome, as well as the time of its final fixation. KARLIN's result can be extended (KARLIN, personal communication) to cases in which selection coefficients are small. Since this is done by invoking the method of small parameters (for which see KARLIN and MCGREGOR 1972), the phenomenon is not the result of the natural selection.

BODMER's and KARLIN's approaches raise the question of whether first appearance and final fixation times of multiple mutant genomes are relevant to the evolutionary advantage of recombination. If favorable mutants are recurring by mutation, the most relevant variable would seem to be the average long-term rate of increase of the number of favorable mutants per genome. If only a finite number of substitutions are possible, evolution ceasing when they are completed, the substitutional load created by the existence of the unfavorable alleles would seem most relevant. Both of these quantities are the sum of expectations for individual loci. In KARLIN's cases, the mean dynamics at individual loci cannot be affected by recombination, since there is no selection. It is therefore doubtful that the phenomena he found are relevant to the questions under discussion here. Another aspect of KARLIN's paper will be discussed below.

At this point, it will be useful to discuss the contrast between those models which have the favorable mutants initially present in many copies, and those in which they occur as new mutants. We can distinguish between two sorts of gene substitution. There are those mutants which are initially present in the population at a low frequency, being maintained by a balance between recurrent mutation and their selective disadvantage. A change in the environment or in the genetic background occurs and makes them selectively advantageous, and they increase in frequency. The second sort of substitution begins as a result of the occurrence of a previously absent mutant which has selective advantage. This sort of substitution is not necessarily closely associated with a change in the environment or in the genetic background. Of course, to the extent that the adaptation of the species is increasing in the long run, the number of such substi-

tutions possible will gradually decline. When a change in the environment (or the background) does occur, many alleles previously deleterious may start to substitute. As a result of random genetic drift, some of these rare alleles will be lost even though selectively advantageous. This will increase the number of loci at which the second sort of substitution is possible. The number of loci in this category will therefore be determined by an equilibrium between the entry of loci into the category, due to loss of favorable alleles by drift, and the exit of loci from the category, which will be a function of population size, rates of mutation, and the probabilities of fixation of the new mutants. Suppose that it can be shown that populations without recombination are more likely to lose favorable alleles during the first sort of substitution, *and* are less likely to incorporate new mutants during the second sort of substitution. This would imply that in a steady state in which environmental changes occur at a relatively fixed rate, populations having recombination will be better adapted than those lacking it (all other things being equal). For obvious reasons no one has attempted a general model incorporating both of these types of substitution events. It should be kept in mind that the models discussed here must be regarded as approximations to different parts of this complex process.

ESHEL and FELDMAN (1970) generalized MAYNARD SMITH's model. They considered an infinite population which is initially fixed at each of two loci. At each locus a favorable mutant allele recurs at a certain rate of mutation. Thus, unlike MAYNARD SMITH, they consider the second of the two types of substitution defined above. In one of the cases they consider, fitnesses are multiplicative, so that the fitness of a genotype is the product of fitnesses at the different loci. This same assumption is made by CROW and KIMURA (1965), MAYNARD SMITH (1968), and BODMER (1970), and is implicit in the work of FISHER (1930) and MULLER (1932). For this case, ESHEL and FELDMAN obtain results compatible with those of MAYNARD SMITH. Recombination has no effect on the rate of gene frequency change, as no linkage disequilibrium ever occurs. There is a difference between their assumptions and those of MAYNARD SMITH (1968), in that he assumed that both mutants were initially present at frequencies determined by mutation-selection balance. Their model is also more symmetric than MAYNARD SMITH's, with equal mutation rates and equal selection at the two loci. But the qualitative conclusions about the effect of recombination are the same.

ESHEL and FELDMAN extend the analysis to cases where there are interactions between the two loci. If the double mutant is more fit than we would predict from the product of single mutant relative fitnesses, recombination actually retards progress under natural selection. ESHEL and FELDMAN pay considerable attention to this case. They appear to believe (wrongly, I think) that this is the case being considered by FISHER and MULLER. They also state results for the opposite case, where the double mutant is less fit than we would predict by taking the product of the single mutant genotype fitnesses. In this case, recombination speeds the increase of the mutants. So the effect of recombination depends on the type of gene interactions, there being no effect when fitnesses are multiplicative.

KARLIN (1973) has stated results which further extend ESHEL and FELDMAN's

findings. He has relaxed their restrictions requiring symmetry between the two loci, coming to the same conclusions. He allows arbitrary initial gamete frequencies. This enables him to study the effect of initial linkage disequilibrium. Coupling linkage disequililibrium speeds substitution at both loci, and repulsion retards it. In some cases, these effects of initial linkage disequilibrium are more important than the effects of the linkage disequilibrium which is created by gene interaction. Thus if initial linkage disequilibrium is sufficiently large and negative (repulsion), populations having recombination will substitute the favorable alleles at the two loci faster, since recombination breaks down the disequilibrium. An analogous principle favors a lack of recombination when there is initially strong coupling of favorable alleles.

In a re-examination of the evolution of recombination, MAYNARD SMITH (1971a) considered a model somewhat similar to that of CROW and KIMURA, coming to the conclusion that recombination *would* accelerate the rate of evolution, and thereby refuting his own earlier paper. He argued that this effect would be greater in a large population than in a small one. MAYNARD SMITH's proof is remarkable in that it takes genetic drift into account by using rough but reasonable approximations to correct for the loss of favorable mutations by genetic drift during the first few generations after they occur. MAYNARD SMITH presents the first computer simulation evidence which has been brought to bear on this problem. It supports his conclusions. However, his simulations are largely deterministic, except that there is a risk of immediate loss of each new favorable mutant. Genetic drift was not fully simulated. KIMURA and OHTA (1971) have independently presented a similar modification of the calculations of CROW and KIMURA. They made some of the same approximations as MAYNARD SMITH. However, their treatment allows only for the loss of new mutants, and not for the increase in the frequency of the remaining mutants, which must also result from genetic drift. They concluded that there would be an advantage associated with recombination, increasing with Nu and independent of s.

Two other papers must be mentioned as relevant, although they will not enter into this discussion. MAYNARD SMITH (1971b) pointed out a disadvantage associated with the production of haploid gametes by a diploid organism. If the number of eggs which the organism can produce is the same whether the eggs are haploid or diploid, there will be a 50% disadvantage associated with producing haploid eggs. Each gamete contains only half as much genetic material if it is haploid. A simple model of fitness optimization shows that an hermaphroditic organism should partition its limiting resources equally between male and female gametes. Only if at least twice as many haploid gametes as diploid gametes can be produced will there be no disadvantage to meiotic reproduction. WILLIAMS and MITTON (1973) have presented a model of the evolution of recombination which differs from all those discussed so far. Meiosis occurs when the resulting offspring are to invade a new habital, and this invasion is followed by asexual reproduction within the new habitat. Each habitat is supposed to be colonized by more than one propagule, all tending to come from the same parent habitat. Within each habitat the environment is different. Clonal reproduction results in intense

competition within the habitat, and it is assumed that only one genotype survives. If a habitat is invaded by both meiotically- and asexually-produced propagules, the latter will all be of the same genotypes if they come from the same parent clone. But the sexual propagules will be of different genotypes even if they result from mating between only two parent clones. Thus the winning genotype in the new habitat is many times more likely to be found among the sexually-produced offspring, giving a powerful advantage to sexual reproduction.

The arguments presented in the above papers are stated in very diverse terms, and may superficially appear to be unrelated. But a pattern emerges when we compare those papers which found an advantage to recombination between non-interacting loci with those which did not. It turns out that those authors who assumed a finite population (FISHER 1930; MULLER 1932, 1958, 1964; CROW and KIMURA 1965, 1969; BODMER 1970; MAYNARD SMITH 1971a; KIMURA and OHTA 1971; WILLIAMS and MITTON 1973) found an advantage associated with recombination. Those who assumed an infinite population (MAYNARD SMITH 1968; ESHEL and FELDMAN 1970) found no such advantage if there was no epistasis and no initial linkage disequilibrium. KARLIN's (1973) deterministic model fits this pattern. In his stochastic model, there are contrasting effects of recombination on the first appearance and final fixation times of multiple-mutant genomes.

The introduction of genetic drift into the argument is crucial. The original argument of FISHER and MULLER centered around the likelihood that the second mutant occurs in an individual which is not the descendant of the preceding successful mutant. Whether or not it occurs in a nonmutant genotype, there will be initial linkage disequilibrium between the two loci. This disequilibrium results from random sampling effects in a finite population. Of course, the disequilibrium will not always be negative (repulsion) disequilibrium. A small fraction of the time, the second mutant will occur in a descendant of the first, and in that case, the linkage disequilibrium will be strong positive (coupling) disequilibrium. Recombination will tend to break down this initial linkage disequilibrium as well as any disequilibrium which is subsequently produced by genetic drift. There will be an average advantage to recombination if, in its absence, the negative linkage disequilibrium is more important as a force retarding incorporation of both mutants than the positive linkage disequilibrium is as a force promoting incorporation. Although the average initial linkage disequilibrium is zero, its effect would have to be on the average to retard evolution.

THE HILL-ROBERTSON EFFECT

This interaction of genetic drift, linkage, and selection is precisely the phenomenon described by HILL and ROBERTSON (1966). They found that even when there is no initial linkage disequilibrium and no interaction between two linked genes, they will on the average interfere with each other's fixation if the population is finite. They presented theoretical reasoning explaining this effect and simulations verifying it. The following is equivalent to theirs, but is stated in somewhat different terms. ROBERTSON (1961) pointed out that selection at a locus

will, in effect, increase the amount of genetic drift at a second, unlinked, locus. This is because the number of descendants of a given allele in the next generation will vary not only as a result of the usual random variation in offspring number, but also as a result of the fitness effects of the unlinked "background" locus which is under selection. Genes which happen to occur against a good background will tend to be represented in the next generation many times, and those occurring against a poor background will tend to be copied only a few times. Thus, selection in the genetic background will increase the variance of offspring number, and thereby increase the amount of genetic drift which accompanies selection. We may regard this as equivalent to a reduction of the effective population number. Since the effectiveness of selection at a locus depends largely on the quantity $N_e s$, the product of effective population number and selection coefficient, different genes under selection will on the average interfere with one another's fixation.

The HILL-ROBERTSON effect is simply the extension of this argument to the case of linkage. In the case of free recombination, a gene occurring against a favorable background will tend to be copied many times. But in the next generation, each of these copies will occur against a different genetic background. In the case of tight linkage, however, the random associations of genes will persist for many generations, and their effects will therefore be greatly magnified. If a gene occurs against a highly fit background, its frequency will be increased, not just for one or two generations, but for as long as the association between the genes persists. The correlations between background fitness in different generations will reduce the tendency of different backgrounds to cancel out each other's effects. The less the recombination between genes, the longer chance associations will persist. Of course, the frequency of an allele will be affected not only by the background genotype, but also by its own fitness. So there will still be selection acting to increase the frequency of the favorable genes. But linked genes will on the average interfere with each other's fixation by increasing the variance of offspring number and thereby decreasing the effectiveness of selection. If there is free recombination, the organism will largely avoid this effect.

It should be evident that this is the same phenomenon invoked by FISHER and MULLER in their arguments as to the advantage of recombination, particularly if one considers their statements that in the absence of recombination a favorable mutant can fix only if it occurs in one of the progeny of the previous successful mutant. Considering the evolutionary advantage of recombination to be a consequence of the HILL-ROBERTSON effect helps clarify things. It allows us to deal with the situation evisaged by MAYNARD SMITH (1968). In his model, each allele which is to be substituted is initially present in many copies, having previously been maintained by a balance between mutation and selection against the allele. The allele has become favorable as the result of an environmental change. Recurrent mutation makes it certain that the favorable allele will recur in any population which loses it. Even under these circumstances there should still be an advantage to recombination. The HILL-ROBERTSON effect will occur whatever the initial frequency of the favorable mutants. Of course, its quantitative strength will depend on the initial frequency as well as other factors. But even when there

are initially many copies of each favorable mutant, a finite population should build up linkage disequilibrium by random genetic drift, and the average effect of such disequilibrium should be that different loci interfere with one another's fixation. So the chance that favorable mutants fix must be less in a population without recombination than in one having recombination. After some favorable mutants are lost, they must recur by mutation and ultimately become fixed. During this second phase of the process random linkage disequilibrium will occur whenever more than one locus is segregating in the population. The net effect of the disequilibrium will be to reduce the chance of fixation of each recurring favorable mutant. If the long-term overall fitness of the population results from a balance between the loss of fitness through environmental change and its recovery by fixation of these previously deleterious mutants, the HILL-ROBERTSON effect makes it clear that a population having recombination will reach a higher average equilibrium fitness than one lacking it.

It should be re-emphasized that the HILL-ROBERTSON effect occurs even in the absence of any interaction between loci. Fitnesses have here been assumed to be multiplicative over different loci. Interaction effects such as those found by ESHEL and FELDMAN (1970) will presumably be superimposed on the interference between linked loci predicted by HILL and ROBERTSON. No quantitative study has yet been made of the way in which these evolutionary forces affect one another.

MULLER'S RATCHET

In a little-noticed passage in his 1964 paper, H. J. MULLER introduced what may be the most quantitatively important evolutionary effect of recombination. He considered the case, not of advantageous alleles in the process of substitution, but of disadvantageous alleles recurring by mutation and being eliminated by natural selection. MULLER pointed out that "an asexual population incorporates a kind of ratchet mechanism, such as it can never get to contain, in any of its lines, a load of mutation smaller than that already existing in its at present least-loaded lines." If, as a result of genetic drift, there were a generation in which each genome contained at least one unfavorable mutant, natural selection in the absence of recombination could never reduce the minimum number of unfavorable mutants below this number. If there were recombination, genomes each of which contained different unfavorable mutants could produce mutant-free offspring. A population without recombination could not achieve this except by back mutation, which would be a very slow process. One would therefore predict that the mutational load would be higher in a population lacking recombination.

It is not difficult to see that MULLER's ratchet mechanism is not conceptually different from his original argument of the evolutionary advantage associated with recombination. Immediately after each unfavorable mutant occurs, we may regard the wild-type allele as undergoing a substitution by natural selection, starting at a gene frequency of perhaps 0.99999 and ending up at a gene frequency of one. Although the initial gene frequency is totally different from the frequency of a favorable mutant originating by mutation, the HILL-ROBERTSON argument still tells us that the different loci undergoing this sort of "substitution"

should on the average interfere with one another's fixation. When we have a generation in which each genome contains at least one unfavorable mutant, as MULLER envisages, this is a state of linkage disequilibrium. If linkage equilibrium existed, there would have to be some genomes which had no unfavorable mutants. The favorable alleles are in repulsion linkage disequilibrium with each other, and are competing with each other just as they do in the original FISHER-MULLER argument. The HILL-ROBERTSON argument predicts an increase in the rate of fixation of unfavorable alleles in the absence of recombination. The MULLER ratchet mechanism predicts, for exactly the same reason, an increase in the average number of unfavorable mutants present per genome. If there is a very large number of loci at which unfavorable mutants occur, we would expect that in the long run the rate of fixation should be the same as the rate of increase of the number of unfavorable mutants per genome. Thus both the mutational load and the rate of complete fixation of deleterious mutants should be increased for the same reason in the absence of recombination.

Of course, the quantitative effects of the interference between selection at different loci will not be the same in the case of the ratchet as in the case of favorable mutants. Whatever the strength of this interference between loci, one simple fact makes the ratchet mechanism of great possible importance: there must be far more unfavorable mutants occurring than favorable ones. Favorable mutants can interfere with one another only when two or more such loci are segregating in the same generation. This might be a relatively infrequent event. But unfavorable mutants are occurring continually in large numbers, so that it is at least possible that the ratchet mechanism is the major reason why natural selection should favor the existence of recombination.

I will not attempt here to predict from theory the quantitative effect of the ratchet mechanism. Involving natural selection, mutation, and genetic drift at many linked loci, the problem poses enormous difficulties for the application of population genetics theory. But the possible significance of the phenomenon makes it important that some theoretical treatment should be attempted. The ratchet mechanism has been unjustly ignored by theoretical population genetics.

COMPUTER SIMULATIONS

MAYNARD SMITH (1971a) seems to have been the first to carry out computer simulation studies of the effect of recombination on the rate of evolution. However, his simulations did not fully take account of stochastic changes in gene frequencies due to finite population size. In fact, he was essentially simulating a deterministic situation, the only genetic drift allowed in his simulations being a random decision whether a new mutant would die out instantly or would increase instantly to a frequency of $1/2Ns$. Since the population sizes in his simulations were very large, he was probably not seriously misled by ignoring most genetic drift. However, for a more careful test of the predictions of the rather crude theory which is all one can use in such cases, it would be desirable to do computer simulations which allow fully for the effects of random genetic drift.

Of the mathematical theory developed so far, none takes the interaction of

genetic drift and natural selection fully into account. Some papers (MAYNARD SMITH 1968; ESHEL and FELDMAN 1970) are wholly deterministic. Others (CROW and KIMURA 1965, 1969; BODMER 1970) allow finite population size to have an effect only in that initial gene frequencies are $1/N$ (in haploids). The papers of MAYNARD SMITH (1971) and of KIMURA and OHTA (1971), as well as part of the argument given below, allow genetic drift only during the first few generations after occurrence of a favorable mutation. KARLIN (1973) does take genetic drift fully into account, but his models involve no natural selection, and therefore cannot be expected to show the HILL-ROBERTSON effect. With the exception of KARLIN, no one has been able to incorporate the full process of genetic drift into the equations—all models are at least partly deterministic.

I have carried out computer simulations of both the case of new favorable mutants and the "ratchet mechanism". The following model was used:

1. The population consists of a fixed number, N, of haploid genomes.
2. Each genome contains an infinite number of exactly equivalent loci. In the absence of recombination, genotypes are specified by the number of these loci which contain mutant alleles.
3. The fitnesses at the different loci are multiplicative, so that the relative fitness of an individual with k mutant alleles is $(1+s)^k$.
4. The number of new mutants occurring in each offspring each generation is drawn independently from a Poisson distribution with the mean number of new mutants per genome being u.
5. Starting from the adults of a given generation, each individual produces an infinite number of offspring, adding to the number of mutant alleles in each offspring a random number drawn from the above Poisson distribution. The adults of the next generation are then produced by sampling the N adults from these offspring at random, the probability of choosing each particular offspring being proportional to its fitness as determined by the new number of mutant alleles after the mutation process.

This statement of the model assumes that there is no recombination. For the case of free recombination, the model would be the same, except that each offspring would be produced by recombination among two parents chosen at random, sampling with replacement from the N adults. Simulating such a case would be difficult, since each mutant would have to have its map position specified. In the absence of recombination the simulations are easier, since each genome can be represented in the computer by a single integer specifying the number of mutant alleles present. No simulations of the case of free recombination were done. Instead, the values for this case were approximated by calculating the expected number of substitutions per generation from

$$N_R = N\,u\,U(s), \tag{1}$$

where the fixation probability, $U(s)$, was calculated from KIMURA's (1962) formula

$$U(s) = \frac{1 - e^{-2s}}{1 - e^{-2Ns}}. \tag{2}$$

The use of these formulas involves two approximations: the diffusion approxi-

mation in equation (2) and the assumption that unlinked loci will show no mutual interference with each other's fixation. ROBERTSON (1961) found such interference, which will be greater the larger the coefficient of variation of fitness. This interference will cause us to overestimate the effects of recombination by using equations (1) and (2). However, HILL and ROBERTSON (1966) found the interference with free recombination negligible compared to the interference with tight linkage.

Simulations were run on the CDC 6400 computer at the University of Washington. Aside from the trivial limitations of machine word length, the model was violated in two additional ways:

1) The "random" sampling was performed using pseudo-random integers generated by the multiplicative congruential method with multiplier 5^{19} and congruence modulo 2^{48}.

2) The Poisson distribution was truncated above 9. This is unlikely to be a problem, since the highest value of u used was 1, and $e^{-1}/10!$ is about 10^{-7}.

Each run started with a population free of any mutant alleles. An initial period of simulation was performed to allow some mutant alleles to arise and accumulate, and following this the mean number of mutant alleles per genome was recorded at the beginning and end of a 100-generation period of further simulation. The rate of increase of the number of mutant alleles per genome should be the same as the rate of fixation of these alleles in the long run. The initial period of simulation was intended to remove effects of the initial population configuration, to make the results more typical of the long-term rates of substitution. With deleterious mutants whose selection coefficients are $s = -0.001$, each new mutant is expected to remain in the population for an average of only 6.2 generations (KIMURA and OHTA 1969), and alleles which are more deleterious remain a shorter length of time. So the initial period of 100 generations allowed in the case of deleterious mutants was probably sufficient to allow the population to "turn over" many times and reach a configuration typical of the long-run situation. For neutral mutants, about 200 generations will be required to drift to fixation. Advantageous mutants will fix more quickly. Thus the period of 300 generations allowed in such cases was probably sufficient. Considerations of cost prevented longer initial periods from being used.

SIMULATION OF THE FISHER-MULLER CASE

Table 1 shows the results of simulations with the following set of parameters:

$$N = 100,$$
$$u = 0.001,\ 0.01,\ 0.1,\ \text{and}\ 1,$$
$$\text{and}\quad s = 0.001,\ 0.01,\ 0.1,\ \text{and}\ 1.$$

Note that u is the rate of occurrence of (favorable) mutations *per genome* per generation. Each combination of the above parameters was simulated in ten replicates. The table shows the means and estimated standard errors of the rates of increase of the number of favorable mutant alleles per genome per generation in the absence of recombination. Underneath each of these is the expected rate of

TABLE 1

Simulation results for Fisher-Muller case

Each entry in the table shows the increase per generation in the average number of favorable mutants present in the population in the absence of recombination, followed by its estimated standard error based on ten replicates. The number in parentheses below these values is the average number of substitutions predicted for the case of free recombination by applying equations (1) and (2). Below that is R, the observed ratio of rates of increase of mutants with and without recombination.

u	Nu	s / Ns 0.001 / 0.1	0.01 / 1	0.1 / 10	1 / 100
0.001	0.1	0.0016±0.0008	0.0027±0.0017	0.0165±0.0037	0.0883±0.0051
		(0.0011)	(0.0023)	(0.0181)	(0.0865)
		0.68	0.85	1.10	0.98
0.01	1.0	0.0109±0.0038	0.0166±0.0020	0.0833±0.004	0.3116±0.005
		(0.0110)	(0.0229)	(0.1812)	(0.8647)
		1.01	1.38	2.17	2.78
0.1	10	0.1189±0.011	0.1691±0.007	0.3534±0.009	1.163±0.011
		(0.1102)	(0.2290)	(1.812)	(8.647)
		0.93	1.35	5.13	7.44
1	100	1.033±0.025	1.346±0.021	2.044±0.086	5.278±0.026
		(1.102)	(2.290)	(18.127)	(86.466)
		1.07	1.70	8.87	16.38

increase in the presence of free recombination, as approximated by applying equations (1) and (2). As previously noted, the rate of increase of the number of mutant alleles per genome should be the same as their rate of fixation over a sufficiently long period of time.

The results of simulations agree qualitatively with the original arguments of FISHER and MULLER. Given the absence of simulations at a different value of N, we cannot tell whether the effects of N, u, and s are mediated through Nu and Ns. On the rather vague grounds that this is always true in diffusion approximations, and that these approximations are usually quite accurate, it will be assumed that Nu and Ns are the relevant variables. There is an increased rate of substitution of favorable alleles in populations having recombination. This advantage is small or nonexistent when Nu or Ns are small, but is quite substantial when Nu and Ns both exceed 1. The relative advantage of recombination is an increasing function of u and s.

An approximation to these results can be developed by modifying the formula of CROW and KIMURA (1965). They assumed that there were Nu favorable mutants expected to occur every generation, all of those which occur in descendants of the previous successful mutants being destined to be fixed. Each mutant was assumed to change its frequency deterministically, starting from an initial frequency of $1/N$. MAYNARD SMITH (1971a) and KIMURA and OHTA (1971) pointed out that even if a favorable mutant occurs in a descendant of the previous favorable mutant, its chance of surviving the first few generations of genetic drift is only about $U(s)$, this quantity being given in equation (2). MAYNARD SMITH (1971a) further pointed out that after these initial generations of genetic

TABLE 2

Relative rate of incorporation of new favorable mutants in a population having recombination compared to one lacking it

Entries are values of R calculated from equations (2) and (3).

u	Nu	s / Ns	0.1 / 0.1	0.01 / 1	0.1 / 10	1 / 100
0.001	0.1		1.0652	1.0973	1.1017	1.1022
0.01	1		1.1881	1.8611	2.2287	2.2836
0.1	10		1.5245	4.8278	12.8175	17.3224
1	100		1.3856	4.5342	21.194	60.185

drift, a mutant allele would have drifted upward to a frequency of approximately $1/(N\,U(s))$ if it survived the risk of loss during the first few generations. We can roughly approximate genetic drift when Ns is large by assuming that there are $N\,u\,U(s)$ mutants per generation which survive the risk of loss during the first few generation, that each of these mutants has an initial frequency of $1/NU(s)$, and that all further changes are deterministic. Following CROW and KIMURA's original argument with these altered values, we readily obtain

$$R = \frac{N u U(s)}{s} \log_e[N\,U(s)\; e^{\frac{s}{N u U(s)}} - N\,U(s) + 1] \qquad (3)$$

as the relative advantage of recombination. Values of R are given in Table 2 for the same parameters used in the simulations. Comparing these to Table 1, it is clear that while the theoretical and simulated values show the same trends (increasing with increases of Nu and Ns), equation (3) overestimates the advantage of recombination. Table 1 can also be compared to the predictions of some previous authors. CROW and KIMURA (1965) predict a smaller advantage of recombination with increasing s. KIMURA and OHTA (1971) predict no effect of s on the relative advantage of recombination. Both of these predictions are contradicted by the simulation results. The results of BODMER (1970) and MAYNARD SMITH cannot be compared directly with the simulation results in Table 1. BODMER seems to be discussing a model in which pre-existing mutants substitute in response to an environmental change. The calculations of MAYNARD SMITH refer to the time until a certain number of substitutions is completed, where only a fixed number of substitutions is possible.

Despite the qualitative success of equation (3) in predicting the trends in the simulations, it fails to predict the advantage of recombination quantitatively. In the lower right-hand corner of Table 1, the advantage of recombination is consistently less than predicted by the values in Table 2. This is not surprising, since the arguments involve a large number of crude approximations. There are at least three sources of this bias in the approximations used in developing equation (3). All would lead us to underestimate the rate of substitution in a population having no recombination.

First, the expression $U(s)$ underestimates the probability of initial success of

new mutants. These mutants may have a selective advantage s relative to the genomes in which they occur, but their selective advantage relative to the population as a whole is what matters. This will exceed s, since not every individual in the population will carry all previously successful mutants. Second, the time lag to occurrence of an initially successful favorable mutant is overestimated, since for the reasons just given the previous successful mutant has probably increased at a rate faster than its selection coefficient s would indicate. Third, the next successful mutant actually need not occur in the progeny of the previous successful mutant. It is possible for two or more mutants to occur in an inferior genome, thereby jumping it ahead of the best pre-existing genome. All of these objections have the greatest force when u is large, so that many mutants are in the process of substitution at the same time. We would expect equation (3) to be more accurate when $2Nu$ is small while $2Ns$ is large, a condition not unlikely to be met in nature. The right-hand part of the second row of Table 1 is roughly consistent with this expectation. It should be noted that when $2Ns$ is large, but s is small (compared to 1), $U(s) \simeq 2s$ and we can approximate equation (3) by

$$R = 2Nu \log_e[2Ns\, e^{\frac{1}{2Nu}} - 2Ns + 1]. \tag{4}$$

SIMULATION OF MULLER'S RATCHET MECHANISM

Table 3 shows the results of simulations in which the mutants were assumed to be deleterious. The parameter values used were:

for $N = 100$,
$u = 0.001,\ 0.003,\ 0.01,\ 0.03,\ 0.1,\ 0.3,\ 1.0,$
and $s = -0.001,\ -0.003,\ -0.01,\ -0.03,\ -0.01,\ -0.3,\ -0.9.$
For $N = 50$, the values
$u = 0.001,\ 0.01,\ 0.1,\ 1.0,$
and $s = -0.001,\ -0.01,\ -0.1,\ -0.9$
were simulated.

Although there is no reason to believe that the mean number of mutants incorporated in a period of 100 generations should be normally distributed, we can invoke the robustness of the t-distribution, and use it to test for the presence of the ratchet effect. Entries where there is an effect of recombination significant at the 0.05 level are marked by an asterisk. It should be borne in mind that the theoretical values for free recombination are bound to exaggerate the effect of recombination. For $N = 100$, except for one value with $u = 0.003$, all significant values are in the rows for $u = 0.1$, 0.3, or 1.0. For very small s, recombination does not affect the fixation of unfavorable mutants, which is mostly the result of drift unaffected by the very weak selection. As Ns reaches 1, the ratchet effect becomes visible. When s is large, the chance of fixation of an unfavorable mutant is small whether or not there is recombination. Even though the rate of fixation in the absence of recombination may be many times higher than in its presence, both rates are so small that they can hardly be of much evolutionary importance. So the conditions for importance of the ratchet effect seem to be that Nu be large

and Ns intermediate. When $N = 50$, the same general conclusions seem to be valid. Comparing the values for $N = 50$ and $N = 100$, with Nu and Ns held constant, there is a suggestion that the ratchet effect is more visible in the smaller population. The following argument would lead us to expect this: Assume that for a given N, u, and s, the population behaves very much like its approximation by a (multidimensional) diffusion process. In that approximation, the dynamics of the population are functions only of Nu and Ns, provided that time is measured in units of N generations. So two populations with equal values of Nu and of Ns will incorporate unfavorable mutants at the same rate on this time scale. A population of size $N = 50$ will on the average incorporate as many unfavorable mutants in 50 generations as a population of size 100 will in 100 generations. The ratio of rates with and without recombination should be the same in the two cases. Note that equations (1) and (2) also show the property that if Nu and Ns are held constant (for small s), N_R is inversely proportional to N. So the ratchet should have as much relative effect at one population size as at another, but the rate of its operation should be inversely proportional to N.

Of course a more relevant comparison might be to hold u and s constant and increase N. In this case it is not obvious what should happen in cases with different N, since the rate of substitution should decrease with $|Ns|$ larger, but should increase as Nu is increased. It should be borne in mind that in examining the long-term rate of increase of unfavorable mutants, we ignore the standing mutational load due to loci still segregating. This load will also affect the total mutational load in a real population which is in equilibrium between forward and back mutation. It would have to be taken into account in any quantitative theory of the ratchet mechanism.

The potential evolutionary importance of MULLER's ratchet mechanism would make it desirable to carry out careful quantitative studies on its operation.

OVERVIEW

The picture of evolution of populations with and without recombination which emerges from the foregoing is as follows: Every so often there is an environmental change. Some previously unfavorable mutants, maintained by a balance between selection and mutation, become favorable and begin substituting. As a result of random genetic drift, some of these now-favorable alleles are lost. Recurrent mutation at those loci ultimately will cause the substitutions to occur, but the loss of new mutants by drift will delay these substitutions. At the same time, unfavorable mutants continue to occur at all loci, and are maintained by mutation-selection balance. When an unfavorable mutant accidently drifts to fixation, back mutation will ultimately unfix it.

Recombination affects these processes at several points:

(1) It makes loss of favorable mutants after the environmental change less likely,

(2) It makes more likely the fixation of the favorable mutants which recur after loss of the original favorable allele,

(3) It decreases the average burden of unfavorable mutants by retarding random fixation of the unfavorable mutants which continually recur at all loci, but

(4) It may reduce the average number of unfavorable mutants segregating in the population and thereby reduce somewhat the ability to respond to a new environmental change.

Points (2) and (3) have been demonstrated by the simulations in this paper, and also follow directly from HILL and ROBERTSON's (1966) result, as does point (1). Point (4) seems unlikely to offset the advantages associated with recombination. It may tentatively be concluded that in the FISHER-MULLER argument and the associated MULLER ratchet mechanism we have an "intrinsic" theory capable of accounting for the persistence of recombination, and possibly for its origin as well.

Until multiple-locus models involving genetic drift, selection, and recombination can be treated exactly or by diffusion approximation, quantitative conclusions on the effect of recombination may be difficult to draw. Given the difficulty of the problem, one could hardly have expected even FISHER or MULLER to have

TABLE 3

Simulation results for the Muller "ratchet mechanism"

		N = 50			
	s	-0.001	-0.01	-0.1	-0.9
	Ns	-0.05	-0.5	-5	-45
u	Nu				
0.001	0.05	$1.5\times10^{-3}\pm9.2\times10^{-4}$	$5.6\times10^{-4}\pm8.6\times10^{-4}$	$2.0\times10^{-5}\pm1.9\times10^{-5}$	$0\pm?$
		(9.5×10^{-4})	(5.9×10^{-4})	(5.0×10^{-7})	(2.1×10^{-40})
0.01	0.5	0.0070 ± 0.0016	0.0074 ± 0.0031	$2.0\times10^{-4}\pm4.5\times10^{-4}$	$2.0\times10^{-5}\pm1.9\times10^{-5}$
		(0.0095)	(0.0059)	(5.0×10^{-6})	(2.1×10^{-39})
0.1	5	0.0867 ± 0.0115	0.0696 ± 0.0060	0.0064 ± 0.0029	$-1.0\times10^{-4}\pm5.8\times10^{-5}$
		(0.0952)	(0.0588)	(5.0×10^{-5})	(2.1×10^{-38})
1	50	0.9965 ± 0.0179	0.7485 ± 0.0134	0.3208 ± 0.0086	$-1.8\times10^{-4}\pm2.0\times10^{-4}$
		(0.9517)	(0.5878)	(5.0×10^{-4})	(2.1×10^{-37})
		*	*	*	

Each entry in the table shows the observed average rate of increase per generation of the number of deleterious mutants present per individual, followed by the standard error of that quantity based on ten replicates (this has been omitted where no variation between replicates occurred). The numbers in parentheses below these values are the average rates of increase predicted in the case of free recombination by applying equations (1) and (2). The asterisks indicate significant differences ($P < 0.05$) between the rates with and without recombination.

TABLE 3—Continued

N = 100

		s -0.001	-0.003	-0.01	-0.03	-0.1	-0.3	-0.9
		Ns -0.1	-0.3	-1	-3	-10	-30	-90
u	Nu							
0.001	0.1	$-3.4\times10^{-4}\pm5.6\times10^{-4}$ (9.0×10^{-4})	$1.5\times10^{-3}\pm8.4\times10^{-4}$ (7.3×10^{-4})	$1.6\times10^{-3}\pm8.5\times10^{-4}$ (3.2×10^{-4})	$9.0\times10^{-5}\pm1.9\times10^{-4}$ (1.5×10^{-5})	$-1.0\times10^{-5}\pm1.1\times10^{-4}$ (4.6×10^{-11})	$-2.0\times10^{-5}\pm2.4\times10^{-5}$ (7.2×10^{-28})	$1.0\times10^{-5}\pm9.5\times10^{-6}$ (3.4×10^{-79})
0.003	0.3	0.0020 ± 0.0009 (0.0027)	0.0010 ± 0.0006 (0.0022)	$4.2\times10^{-4}\pm1.2\times10^{-3}$ (9.5×10^{-4})	$7.1\times10^{-4}\pm2.4\times10^{-4}$ (4.6×10^{-5}) *	$6.0\times10^{-5}\pm8.6\times10^{-5}$ (1.4×10^{-10})	$-7.0\times10^{-5}\pm6.9\times10^{-5}$ (2.2×10^{-27})	$0\pm?$ (1.0×10^{-78})
0.01	1	0.0141 ± 0.0038 (0.0090)	0.0067 ± 0.0023 (0.0073)	0.0045 ± 0.0024 (0.0032)	$9.0\times10^{-5}\pm1.1\times10^{-3}$ (1.5×10^{-4})	$-1.7\times10^{-4}\pm3.7\times10^{-4}$ (4.6×10^{-10})	$1.2\times10^{-4}\pm5.6\times10^{-5}$ (7.2×10^{-27})	$0\pm?$ (3.4×10^{-78})
0.03	3	0.0293 ± 0.0029 (0.0271)	0.0215 ± 0.0032 (0.0220)	0.0161 ± 0.0054 (0.0095)	$8.9\times10^{-4}\pm1.9\times10^{-3}$ (4.6×10^{-4})	$3.0\times10^{-5}\pm7.8\times10^{-4}$ (1.4×10^{-9})	$1.8\times10^{-4}\pm1.3\times10^{-4}$ (2.2×10^{-26})	$4.0\times10^{-5}\pm1.5\times10^{-5}$ (1.0×10^{-77}) *
0.1	10	0.0992 ± 0.0775 (0.0904)	0.0686 ± 0.0055 (0.0732)	0.0622 ± 0.0047 (0.0316) *	0.0200 ± 0.0051 (1.5×10^{-3}) *	$5.7\times10^{-4}\pm1.0\times10^{-3}$ (4.6×10^{-9})	$3.5\times10^{-4}\pm2.5\times10^{-4}$ (7.2×10^{-26})	$-4.0\times10^{-5}\pm2.1\times10^{-5}$ (3.4×10^{-77})
0.3	30	0.2586 ± 0.0180 (0.2713)	0.2396 ± 0.0114 (0.2196)	0.1915 ± 0.0114 (0.0949) *	0.1228 ± 0.0054 (0.0046) *	0.0282 ± 0.0052 (1.4×10^{-8}) *	$8.1\times10^{-4}\pm6.7\times10^{-4}$ (2.2×10^{-25})	$1.7\times10^{-4}\pm8.1\times10^{-5}$ (1.0×10^{-76})
1	100	0.9284 ± 0.0213 (0.9042)	0.8168 ± 0.0169 (0.7320) *	0.6950 ± 0.0161 (0.3162) *	0.5028 ± 0.0216 (0.0154) *	0.2720 ± 0.0084 (4.6×10^{-8}) *	0.0082 ± 0.0029 (7.2×10^{-25}) *	$2.0\times10^{-4}\pm1.8\times10^{-4}$ 3.4×10^{-76})

provided us with a quantitative theory of recombination. In retrospect, it is remarkable that they should have seen so much, so clearly, and so early.

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