POPULATION GENETIC PERSPECTIVES ON THE EVOLUTION OF RECOMBINATION

Marcus W. Feldman

Department of Biological Sciences, Stanford University, Stanford, California 94305

Sarah P. Otto

Department of Zoology, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada

Freddy B. Christiansen

Department of Ecology and Genetics, University of Aarhus, Ny Munkegade, DK-8000 Aarhus C, Denmark

> It is not generally realized that genetics has finally solved the age-old problem of the reason for the existence (i.e. the function) of sexuality and sex, and that only geneticists can properly answer the question, "Is sex necessary?"
>
> HJ Muller (100, p. 118)

ABSTRACT

Optimality arguments and modifier theory are reviewed as paradigms for the study of the evolution of recombination. Optimality criteria (such as maximization of mean fitness) may agree with results from models developed in terms of the evolution of recombination at modifier loci. Modifier models demonstrate, however, that equilibrium mean fitness can decrease during the evolution of recombination rates and is not always maximized. Therefore, optimality arguments do not successfully predict the conditions under which increased or decreased recombination will evolve. The results from modifier models indicate that decreased recombination rates are usually favored when the population is initially near a polymorphic equilibrium with linkage disequilibrium. When the population is subject to directional selection or to deleterious mutations, increased recombination may be favored under certain conditions, provided that there is negative epistasis among alleles.

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INTRODUCTION

The importance of recombination is usually discussed in the context of its significance for the success of sexual systems over asexual ones. Most arguments hold that independent segregation of chromosomes and recombination within chromosomes (*a*) allow greater mixing of the genome (78, 95; reviews in 97); such genetic mixis permits the maintenance and production of genetic diversity and, in particular, allelic combinations that might be useful in novel environments (e.g. 7, 54, 100); (*b*) increase the chance that favorable mutations at different loci could be collected into the same genome (29, 30, 48, 100, 101), or (*c*) facilitate the removal of deleterious mutations in finite populations (45, 81, 82, 101).

These verbal arguments have been difficult to convert into coherent, general evolutionary conclusions. This is partly because of the large number of ways in which the evolutionary advantage of recombination may be quantified. Many of these were surveyed in early reviews (45, 47). Since then, there has been considerable progress on the mathematical front, and computer simulation has become a much more powerful tool for the analysis of selection and recombination. Indeed, we refer later in this article to aspects of computer science that have incorporated ideas from evolutionary theory.

Felsenstein (45) concentrated on what he called "intrinsic" theories for the evolution of recombination. Such theories do not posit a mechanism for the change in recombination that might be subject to individual selection. They are actually couched (usually tacitly) in terms of group selection. The first part of the present review returns to this class of theories, which we call here "optimality" arguments. Some property of the evolutionary process is believed to be of central importance in nature, and critical values of this property are sought. This can be viewed as a group selection argument because the success of recombination is inferred by a comparison of values of the property each of which can be construed as characteristic of a group. It is then assumed (often implicitly) that groups with a more optimal value of the property will outcompete and replace other groups, leading eventually to the survival only of groups near the optimum. The second part of our discussion addresses what Felsenstein (45) called "extrinsic" analysis, referring to theories for the evolution of genes that control rates of recombination. We review recent mathematical and numerical evolutionary theory for genes that control the rate of recombination. We refer to this as *modifier theory* rather than extrinsic analysis because it involves models of individual selection in which rates of recombination change as a consequence of evolution at recombination-modifying loci. Felsenstein & Yokoyama (47) presented numerical simulations of this second kind of model.

We review first several of the group selection arguments that have been proposed to account for the evolution of recombination. In each case, arguments using the optimality approach generally do not predict the results that emerge from population genetic models structured in terms of modifiers of recombination.

OPTIMALITY ARGUMENTS FOR RECOMBINATION

Optimality reasoning in evolutionary genetics proceeds as follows (108). A criterion is chosen to evaluate the success of different values of a parameter of interest (e.g. recombination rate). The criterion may or may not represent a function (like the mean fitness) that appears naturally in an evolutionary genetic model. The properties of this criterion as a function of the parameter under investigation are then evaluated. Frequently, in the case of recombination, this is mathematically intractable, and recourse is usually made to a comparison between the states of the criterion under complete linkage and under free recombination. It is then assumed that evolution proceeds in the direction that optimizes the chosen criterion with respect to the parameter under study.

The best known example of such a paradigm is the mean fitness in Fisher's (48) Fundamental Theorem of Natural Selection where, if natural selection acts as viability differences among genotypes at one locus, the average fitness in a large randomly mating population increases throughout the evolutionary trajectory (33, 76). In this case, the mean fitness would constitute such a criterion and, in comparing two totally separate populations, that with the higher average fitness might be said to have the evolutionary advantage. Note that no model of competition between populations has been introduced here.

We now turn to the ways in which this optimality reasoning or group selection argument has been applied to the evolution of recombination.

Equilibrium Mean Fitness

Kimura (73) studied the equilibrium properties of a two-locus two-allele viability model of the generalized symmetric type (16, 68). He demonstrated that at equilibrium the mean fitness, $\bar{w}$, was a decreasing function of the recombination. The title of the paper "A genetic model which leads to closer linkage by selection" summarizes his conclusion from this property of his criterion ($\bar{w}$) with respect to the rate of recombination R: $\partial\bar{w}/\partial R < 0$. Note that no mechanism for the evolution of recombination was included. The same reasoning was used by Lewontin (86) who showed that for any equilibrium of a two-locus viability system, $\partial\bar{w}/\partial R$ evaluated at $R = 0$, was negative. For larger values of R, equilibrium values of $\bar{w}$ may decrease with R or be nonmonotonic in R. However, at loci that control recombination, alleles that decrease it are favored.

There is, therefore, no correspondence between the properties of $\bar{w}$ and the evolution of genes that control recombination. Thus, $\bar{w}$ is not a satisfactory optimality criterion for the evolution of recombination within a population.

Times and Rates

Fisher (48) and Muller (100, 101) argued that in the presence of recombination, advantageous mutations at different loci will be incorporated into the same individual more often than in its absence. Without recombination at least two mutations must occur in the same lineage to produce the multiple mutant, and if the favorable mutations do not fix more rapidly than they arise, this process is accelerated by recombination. Fisher explicitly recognized that this was a group selection argument in that it compared species with and without recombination. In translating the original suggestion into formal models, however, a number of possible criteria emerge. Muller (101) compared the time "to get one new advantageous mutant" in populations with and without recombination, and found that in the time that it took an asexual (i.e. recombination absent) population to get one new advantageous mutant, the sexual (i.e. recombination present) population incorporated Nf such mutants, where N is the population size and f the frequency of advantageous mutations per individual. He concluded that as long as more than one advantageous mutant arose in the population per generation, the rate of evolution with recombination would exceed the rate without it.

Crow & Kimura (29) presented a more rigorous evaluation of this comparison of rates of evolution with and without recombination. They found that the advantage to recombination using this criterion was greater with larger N and larger μ/s, the ratio of the rate of mutation to advantageous alleles to their fitness advantage. The arguments of Muller and Crow & Kimura are deterministic in setting but use finite population size; problems of sampling are ignored. Their conclusions are frequently referred to in terms characteristic of stochastic population genetic models, e.g. through rates of substitution, because the occurrence of mutations is viewed as a stochastic process.

The formulation of Muller's rate criterion has stimulated a fascinating line of research with more formally specified models and more and better defined optimality criteria for recombination. Bodmer (15), for example, considered two loci in a haploid population with an initial majority of ab chromosomes. Mutants Ab and aB initially each have the low frequency x_0 and fitness $1 + s$ relative to ab. Using a deterministic argument, Bodmer compares the average time until the double mutant AB is produced by recombination with that produced by mutation alone. He finds that recombination is more than twice as fast if $x_0 > 4\mu/R$, approximately, where μ is the mutation rate from a to A and b to B and R is the recombination rate. With $x_0 = 1/N$ and free recombination,

$R = 1/2$, this requires

$$8N\mu < 1, \qquad\qquad\qquad\qquad\qquad 1.$$

a condition that is easier to meet in a small population than a large population. This differs from the conclusion of Crow & Kimura (29), but the models and the optimality criterion are different in the two investigations. Bodmer evaluates the waiting time until production of the double mutant, whereas Crow & Kimura compare rates of incorporation under the assumption that all favorable mutations will be incorporated in the presence of recombination. This assumption explains why the recombination rate does not enter into the optimality criterion of Crow & Kimura.

Felsenstein (45) compared the rate of increase of advantageous mutant alleles per genome in a finite population with free recombination and with absolute linkage over a 100-generation period of computer simulation. He viewed this criterion as a surrogate for the rate of fixation of these alleles and found that the 100-generation rate of increase was higher with recombination than without, concluding that the rate of substitution of favorable alleles was increased by recombination.

We continue our assessment of group-selection criteria that involve rates of substitution and times after a digression into other responses to the work of Crow & Kimura (29).

Frequency as an Optimality Criterion

Bodmer's result is derived from an interpretation of the initial increase in the frequency of gamete AB in a deterministic model. The difference between his conclusions and those of Crow & Kimura may be illuminated by considering a large haploid population with resident alleles a and b at two loci subject to mutation from a to A and b to B at rate μ per generation. The fitnesses of ab, Ab, aB, and AB are $1 : \sigma_2 : \sigma_2 : \sigma_4$. After selection, the frequencies x_1, x_2, x_3, and x_4 of these chromosomes become

$$Wx_1' = (1 - \mu)^2 x_1 - RD(1 - \mu)^2 \qquad\qquad 2a.$$

$$Wx_2' = \sigma_2\big[(1 - \mu)x_2 + \mu(1 - \mu)x_1 + RD(1 - \mu)^2\big] \qquad 2b.$$

$$Wx_3' = \sigma_2\big[(1 - \mu)x_3 + \mu(1 - \mu)x_1 + RD(1 - \mu)^2\big] \qquad 2c.$$

$$Wx_4' = \sigma_4\big[x_4 + \mu(x_2 + x_3) + \mu^2 x_1 - RD(1 - \mu)^2\big] \qquad 2d.$$

where $D = x_1 x_4 - x_2 x_3$ is the linkage disequilibrium and W is the sum of the right-hand sides. Mutation rates to single mutants and their fitnesses have

been assumed equal, an assumption that detracts little from the generality of the qualitative conclusions.

Maynard Smith (94) pointed out that if the viabilities are multiplicative, i.e. $\sigma_4 = \sigma_2^2$ and if D is initially zero, then D remains zero throughout the subsequent evolution. In this case, even if $\sigma_2 > 1$ so that single mutations are favorable, recombination has no effect on the time-dependent behavior of the frequency of the double mutant. In other words, if the effect of recombination is measured by the frequency of AB, it cannot be said to be advantageous. Although this example was originally proposed as a counter example to the theory of Crow & Kimura, it cannot really be regarded as such (30) because use of the model specified by Equation 2 in a deterministic context entails the immediate existence of the double mutant at low frequency, and with certain fixation, which violates the assumptions of Crow & Kimura.

Eshel & Feldman (31) developed Maynard Smith's model further and showed that the effect of R on the frequency of AB depends on the initial sign of D. If initially only ab is present, then when $\sigma_4 > \sigma_2^2 > 1$, D becomes positive immediately and thereafter the frequency of AB is actually less with recombination than without. This we call the *supermultiplicative* case. In the *submultiplicative* case $1 < \sigma_2 < \sigma_4 < \sigma_2^2$, on the other hand, D becomes negative immediately and recombination results in a higher fraction of AB. The role of the sign of D in the initial stages of evolution seems to play an important role in other arguments about the evolution of recombination, as we see later.

The fraction of double mutants in the population therefore depends on recombination when viabilities are not multiplicative. Used as an evolutionary criterion, it turns out to interact delicately with the arrangement of viabilities and therefore the sign of the linkage disequilibrium. This criterion cannot be used to construct a true counter example to the argument of Crow & Kimura since it ignores the stochastic loss of favorable genotypes. It highlights, however, the need for precision in both the posing of the model and the definition of the criterion. As we now see, this is particularly the case in discussions of rates and times.

Times and Rates Again

Karlin (66) presented the first mathematical treatment of a time-related criterion that included random genetic drift. He took the model specified by Equations 2 but without selection, so that all chromosomes were equally fit ($\sigma_4 = \sigma_2 = 1$). Random genetic drift was incorporated using Wright-Fisher multinomial sampling superimposed on this deterministic model (33). Two evolutionary criteria were examined as functions of the recombination rate: the expected time until the first occurrence of the double mutant AB and the expected time until fixation in AB. Karlin's investigation was carried out analytically for a population of

size 2 and numerically for larger populations. For a population that is initially 100% *ab*, the major analytical conclusions were: (*a*) The expected time until formation of the first double mutant *AB* is indeed decreasing as a function of *R*. (*b*) The expected time until the population is fixed on the double mutant increases slightly as a function of *R*. A further numerical result was obtained for the case in which the linkage disequilibrium is originally negative, i.e. there is an initial bias towards the single mutants *Ab* and *aB*: in this case, the expected time until fixation of *AB* decreases with increasing recombination. Karlin also presents an order of magnitude for the time until first appearance and fixation of the double mutant when recombination is absent. The expected time until first appearance, *T*, is approximately

$$T = k(\mu^2 N)^{-1/2}, \qquad\qquad 3.$$

where *k* is determined by the initial frequencies of the single mutant gametes.

We have recently returned to the issue of waiting times with some numerical (107) and mathematical (27) analysis. The numerical treatment (107) simulated Karlin's (66) model with only *ab* initially present. In the absence of selection, the average time until the first appearance of *AB* definitely decreases as *R* increases. The average time until fixation showed no consistent dependence on the amount of recombination, *R*, even with 10,000 replicates and a population size of 1000. Karlin's earlier analysis for $N = 2$ suggests that this should be a very weak trend indeed.

We asked the same questions under various selection regimes; multiplicative, submultiplicative, supermultiplicative, and extremely supermultiplicative. In all cases, the average time to first appearance decreases with increasing recombination, but the average time to fixation is more complicated. With submultiplicative and multiplicative selection, the average time to fixation decreased with increasing recombination for all combinations of population size and mutation rate tested. The same was true even with weak supermultiplicative selection, but the average fixation time increased with *R* when the multiplicative epistasis was sufficiently strong. We conjecture that the threshold value of the epistasis at which this qualitative change occurs shifts towards zero as *N* increases.

Christiansen et al (27) have focused on an analytical approximation of the expected time to first appearance of *AB* in the selectively neutral case in the presence of recombination. We have obtained a very simple proof that the average time to production of *AB* when $R = 0$ is approximately $(\mu^2 N)^{-1/2}$ (see Equation 3 above) and that when *R* is large, *N* is large, and μ is small, the average waiting time decreases to T_R, where

$$T_R \approx (R\mu^2 N)^{-1/3}. \qquad\qquad 4.$$

We also found a useful approximation to T_R using a diffusion approach with a killing term (71, 72).

Genetic Algorithms and Optimization

Genetic algorithms (GAs) are computational tools used in engineering and other applications to find optima of complicated functions by means of computer programs that simulate Darwinian natural selection (6, 51, 57, 58). Potential solutions are treated as strings of symbols that are subject to mutation and that may be recombined to form new strings. The new strings are subject to selection on the basis of their performance at the task set by the user. Our recent work (27, 107) on the formation of new allelic combinations, described in the previous section, was stimulated by discussions at the Santa Fe Institute with computer scientists who use genetic algorithms. Their primary goal is to circumscribe the class of fitness regimes for which GAs can find the optimum faster than other more standard techniques (49). The correspondence with problems in multilocus evolution is clear (55, 112), and the central questions of GAs may be addressed by studying under what fitness conditions recombination accelerates improvement of fitness and attainment of a global optimum. Experiments suggest that the topology of the fitness surface is important for the performance of GAs; e.g. the more jagged is the fitness surface, i.e. the more local optima, the harder it is for these programs to find the global optimum (50).

An example of this effect was provided by Otto et al (107). We simulated a finite haploid population with 20 genes each having alleles 1 or 0. Fitness depended on a genotypic value equal to the sum of the allelic values, i.e. to the number of 1s in a genotype. Fitness had a local maximum for a genotypic value of zero, with a decrease towards a minimum at 5 and an increase towards a global maximum at 20. The population was started with an average genotypic value close to zero, and the objective was to produce the fittest chromosome, namely that carrying all 1s. The criteria used to describe the effect of recombination were the average time until this chromosome first appeared and the average time until it fixed. As measured by either criterion, the efficacy of recombination depended on the initial constitution of the population, even when, on average, all genes are initially in linkage equilibrium. For more on the general class of optimization problems touched on here see Holland (58, 59) and Forrest (49).

To summarize, for two genes, the time to first appearance of a double mutant in a finite population must decrease with increasing recombination, whether such mutations are advantageous or not. With multiple loci and nonmonotonic fitness landscapes the first appearance of a "desirable" chromosome behaves in a complicated manner as a function of recombination, the initial conditions, and the shape of the fitness surface. Fixation of such a chromosome as a function

of recombination is also extremely complicated, and we might expect that the waiting time until a specific chromosome reaches a preset fraction of the population would be no less complicated.

Loads

The above arguments have focused on the role of recombination in generating advantageous gene combinations. A major alternative argument for the advantage of recombination is that it aids in the elimination of deleterious mutations. With synergistic epistasis such that multiple deleterious mutations reduce fitness more than expected under multiplicative interaction, selection acts strongly against genomes with multiple mutations. Any process (such as recombination) that can recreate the genomes with a large number of mutations without changing the number of mutations in the population will tend to suffer a lower genetic load (defined here as the reduction in mean fitness due to mutation) because mutations will tend to be eliminated with the death of fewer, but more highly mutant, individuals (82). Kimura & Maruyama (74) showed that populations with free recombination (sexual) had lower loads than populations with no recombination (asexual) and that the advantage to recombination was approximately twofold with quadratic epistasis and even more extreme with threshold selection. This hypothesis was studied further by Kondrashov (80) who confirmed that recombining populations can have a substantially lower load than nonrecombining populations when there is synergistic epistasis.

Ratchets

In a finite population subject to recurrent deleterious mutations, the most fit genotype may fail to leave offspring in any particular generation and may be lost from the population. As long as the component alleles still exist within the population, this genotype may be regenerated by recombination in a sexual species. In an asexual species however, only back mutations (assumed to be rare or nonexistent) can recreate the lost genotype. This process causes the fitness of an asexual lineage to progressively decrease in a ratchet-like fashion every time the most fit genotype is lost from the population (101).

Early numerical simulations (45) to test the effect of recombination on Muller's ratchet evaluated the rate of increase in the number of deterious mutants per generation over 100 generations, and although the results were not uniform, for $N\mu$ large and Ns intermediate, with s the fitness disadvantage of each mutation, recombination tended to prevent the accumulation of deleterious mutations, thereby decreasing the mutational load and increasing fitness.

Lynch & Gabriel (92) focused less on the genetic load and more on the time to extinction of a finite population in a study of the relationship between Muller's ratchet and recombination. They modeled a population subject

to density-dependent growth, where the survival (but not fecundity) of an individual depended on the number of deleterious mutations borne. The population would go extinct if all members of the population failed to survive in a particular generation. They confirmed that the ratchet occurred in asexual populations and that even very large populations would go extinct within a fairly short evolutionary time. Recombination, however, essentially halted the ratchet; only extremely small recombining populations went extinct within a reasonable time.

Thus, both genetic load and the time to extinction have been used to assess the effect of recombination on Muller's ratchet. Although these models do not directly address the evolution of recombination within a particular population, they may explain the relatively depauperate distribution of asexual lineages, especially ancient asexual lineages.

Remarks

Optimality arguments can be very useful when they inform the analysis of the underlying evolutionary dynamics. It is important, however, to test whether population genetic models support arguments made in terms of optimality. For the criteria described above, whether they actually work in the sense of predicting the dynamics of recombination depends on three classes of factors: (*a*) the size of the population, (*b*) the shape of the fitness surface, and (*c*) initial conditions for the underlying dynamic system. Whether a criterion works in the sense of providing information about the evolutionary trajectory of recombination in a population requires detailed investigation of the underlying dynamical system, and this is frequently difficult. In the next part of this review we discuss a population genetic theory for the evolution of recombination that, in a strong sense, provides a system of checks (if not balances) on the optimality approach.

MODIFIER THEORY

The Model

Nei (103, 104) devised a genetic model for the study of the evolution of recombination. He divided a multilocus genetic system into two parts, one containing two or more genes under selection, and the other consisting of genes that controlled the amount of recombination among the genes in the first part. Nei analyzed a model with two *major* genes under selection and one *modifier* gene whose different genotypes determined different recombination rates between the major genes. Each of the major and modifier genes was diallelic. Thus the first major gene is supposed to have alleles A_1 and A_2, and the second has alleles B_1 and B_2. The modifier locus has alleles M_1 and M_2, and individuals of genotypes M_1M_1, M_1M_2, and M_2M_2 produce gametes through meiosis with

recombination rates R_{11}, R_{12}, and R_{22}, respectively, between the loci of A and B. Selection is due to viability differences among the genotypes with respect to the major genes, and the population is large enough to neglect the effects of random genetic drift. Mating is assumed to be random, and there is no mutation.

The modifier locus in this model is selectively neutral in terms of its direct effects on the fitnesses of various genotypes. It must be distinguished, therefore, from such modifier genes as have been used in models for the evolution of dominance (39) where each modifier genotype has a different viability. Modifiers of recombination, as proposed by Nei, evolve only as a result of selection induced upon them by associations with the major genes.

Using a series of approximations concerning the dynamics of the genotype frequencies at the major loci, Nei proposed that the frequency of an allele at the modifier locus that reduced the recombination frequency in its carriers would increase in frequency. Nei's assumptions allowed analysis in terms of the allele frequencies at the modifier locus. He demonstrated critical dependence on the linkage disequilibrium between the major genes.

Initial Increase: Random Mating and Two Major Loci

Feldman (34) studied the conditions for the incorporation into the population of new variants at the modifier locus in Nei's model. Initially, only M_1 is present in the population so that the recombination rate between A and B is R_{11}. Now assume that the frequencies x_{11}, x_{12}, x_{21}, and x_{22} of the chromosomes $A_1 B_1$, $A_1 B_2$, $A_2 B_1$, and $A_2 B_2$ achieve an equilibrium under the effects of viability selection interacting with R_{11}. The viability selection may be represented by the 4×4 viability matrix $\mathbf{W} = \|W_{ij,k\ell}\|$, with $W_{ij,k\ell}$ the viability of genotype $A_i B_j / A_k B_\ell$ with $i, j, k, \ell = 1, 2$. Write the equilibrium as the vector $\mathbf{x}^* = (x_{11}^*, x_{12}^*, x_{21}^*, x_{22}^*)$. The evolution of recombination is then posed in terms of the initial increase of the allele M_2 introduced in the neighborhood of this equilibrium. The issue boils down to the local stability of $\mathbf{x}^*$ for $A_1 B_1 M_1$, $A_1 B_2 M_1$, $A_2 B_1 M_1$, $A_2 B_2 M_1$ in the eight-dimensional space of chromosomes $A_1 B_1 M_1$, $A_1 B_2 M_1$, $A_2 B_1 M_1$, $A_2 B_2 M_1$, $A_1 B_1 M_2$, $A_1 B_2 M_2$, $A_2 B_1 M_2$, and $A_2 B_2 M_2$. The linear order of the genes is unimportant; to be specific, assume the order ABM and that R is the recombination rate between B and M.

Feldman's (34) first answer to this question was partial in that results were obtained for those viability matrices $\mathbf{W}$ for which the equilibrium vector $\mathbf{x}^*$ had been obtained explicitly, namely additive, multiplicative, and symmetric viabilities. It was also assumed that there was no interference in recombination among the three loci. Of course, posing the question in this way assumes that $\mathbf{x}^*$ is stable as a two-locus polymorphism in the absence of M_2. Under these conditions, the local stability of $\mathbf{x}^*$ to invasion by M_2 is governed by two

properties, the linkage disequilibrium D^* at $\mathbf{x}^*$, and the relationship between R_{11} and R_{12}. If $D^* \neq 0$ then M_2 increases when rare (near $\mathbf{x}^*$) if $R_{12} < R_{11}$ and decreases in frequency if $R_{12} > R_{11}$. If $D^* = 0$, as occurs in the additive viability model and may occur for loose linkage in the others, or if $R_{11} = R_{12}$, this local analysis is uninformative because the leading eigenvalue is unity.

Karlin & McGregor (70) suggested that underlying this result, that recombination should be reduced, was a mean fitness principle: If we write $\bar{w}^*$ for the mean fitness at $\mathbf{x}^*$, $\bar{w}^* = \sum_{ij} \sum_{k\ell} x_{ij}^* x_{k\ell}^* W_{ij,k\ell}$, then $\partial \bar{w}^* / \partial R < 0$. Counterexamples to this principle were produced later (67, 113), although for the symmetric viability model, the principle is true.

The examples for which M_2 succeeded when it reduced recombination suggested that the result might be more general. Feldman et al (38) showed that for *any* viability matrix $\mathbf{W}$ that supports a stable polymorphism $\mathbf{x}^*$, the same result holds: If M_2 is introduced near $\mathbf{x}^*$, and if $D^* \neq 0$, M_2 increases when rare if $R_{12} < R_{11}$. These reduction results are independent of the order of the genes and the value R of the recombination between the major loci and the modifier locus. Again, if $D^* = 0$ or $R_{11} = R_{12}$, local analysis is uninformative.

Modifier Polymorphisms

The reduction results refer to evolution in the neighborhood of polymorphisms where a single modifier allele is fixed. Thus, if for example $R_{11} > R_{12} > R_{22}$ and $\mathbf{x}_{M_1}^*$ and $\mathbf{x}_{M_2}^*$ refer to stable, four-chromosome polymorphisms with M_1 and M_2, respectively, fixed in the population, then M_2 increases when rare and M_1 decreases when rare. This suggests, but does not prove, that M_2 will increase all the way to fixation. Such global results remain to be proved. If $R_{11} < R_{12}$ and $R_{12} > R_{22}$, then both $\mathbf{x}_{M_1}^*$ and $\mathbf{x}_{M_2}^*$ are stable to the introduction of the alternative allele. Finally, if $R_{11} > R_{12}$ and $R_{22} > R_{12}$, then both M_1 and M_2 increase when rare so that the modifier locus is in a state of protected polymorphism (109) and variation at the modifier locus is maintained in the population.

The first such polymorphism was found when the viabilities at the major loci were symmetric (36). In general, if either

$$R_{11} > R_{12} < R_{22} \qquad\qquad 5a.$$

or

$$R_{11} < R_{12} > R_{22} \qquad\qquad 5b.$$

a polymorphism exists and takes the form

$$p_{M_1} = (R_{12} - R_{22})/(2R_{12} - R_{11} - R_{22}), \qquad\qquad 6.$$

where p_{M_1} is the population frequency of allele M_1 (40). This gene frequency equilibrium has exactly the form of the classical polymorphism under heterozygote advantage or disadvantage in viability selection but with the recombination

rates replacing the viabilities. Such equilibria were called *viability-analogous* in the context of kin-selection theory (117).

One class of viability analogous equilibria has turned out to be informative for the more general study of modifier evolution. Suppose that at the modifier locus there may be *multiple* alleles $M_1, M_2, \ldots, M_n$ such that $M_i M_j$ produces the recombination fraction R_{ij} between loci A and B, each of which are diallelic, as before. Recombination between the A and B genes may then be represented by the matrix $\mathbf{R} = \|R_{ij}\|$. Let the vector $\mathbf{y}^*$ solve the equation

$$\mathbf{y} \circ \mathbf{Ry} = (\mathbf{y}, \mathbf{Ry})\mathbf{y}, \qquad\qquad 7.$$

where $\circ$ designates the Schur product and $(\cdot, \cdot)$ is the usual scalar product of vectors. Equation 7 is the standard one-locus multiple-allele viability equilibrium relation, with the recombination matrix replacing the viability matrix [see (33)]. Now suppose that $\tilde{\mathbf{x}}^*$ is an equilibrium of the two-locus system with viabilities $W_{ij,k\ell}$, as before, but with recombination given by the population average value among the R_{ij}'s at the equilibrium $\mathbf{y}^*$, namely $R^* = (\mathbf{y}^*, \mathbf{Ry}^*)$. Then there is a polymorphic equilibrium of the full three-locus system given by

$$\mathbf{z}^* = \tilde{\mathbf{x}}^* \otimes \mathbf{y}^*, \qquad\qquad 8.$$

where $\otimes$ designates the Kronecker product vector.

The equilibrium (Equation 8) is the generalization to n modifier alleles of the two-allele point in Equation 6. Feldman & Liberman (42) termed this equilibrium *viability-analogous Hardy-Weinberg* (VAHW) because it is viability analogous (40, 117), and it represents a state of linkage equilibrium between the n alleles at the M locus and the major loci. Such VAHW equilibria characterize mutation and migration modification in addition to the case of recombination discussed here (87–89) as well as other models of neutral modifiers (1).

The evolutionary significance of the equilibrium in Equation 8 is determined by its stability properties. Complete analysis of this stability has been elusive, but some results have been obtained (87). First, a necessary condition for stability is that the eigenvalues of $(\mathbf{y}^* \circ \mathbf{R})$ all be positive. This may be viewed as a kind of "reverse" condition to the famous Kingman condition (77) for the stability of a viability-related one-locus polymorphism (see e.g. inequalities 5a). Intuition as to the "reverse" nature is extracted from the results of the previous section where the modifier allele that reduced recombination succeeded, whereas in the case of viabilities, it is the allele with the higher fitness that succeeds. Given this condition, inference about stability of Equation 8 may be derived from classical results on selection and recombination with two loci. Thus, since $\mathbf{z}^*$ involves linkage equilibrium between modifier and major genes, it would be expected that small values of R (i.e. tight linkage of the modifier

to the major genes) would entail instability of $\mathbf{z}^*$, while R close to 0.5 (loose linkage between major and modifier genes) would enable $\mathbf{z}^*$ to be stable. Beyond these results, little is known about the general stability of $\mathbf{z}^*$, although equilibria that are *not* VAHW and that could apparently be internally stable have been exhibited (36).

The reduction principle (37) for the initial increase of a modifier variant at a monomorphic modifier locus may now be extended to cover the initial increase of a new variant at a VAHW polymorphism (an equilibrium with one allele is trivially a VAHW equilibrium). A new modifier allele M_{n+1} is introduced into a population polymorphic for n modifier alleles and two diallelic major loci. The population is supposed to be at the VAHW equilibrium $\mathbf{z}^*$ given by Equation 8, and prior to the arrival of the new modifier allele, the average rate of recombination between A and B is R^*. Individuals carrying the new allele appear to have the average recombination rate $\tilde{R} = \sum_{i=1}^{n} R_{i,n+1} y_i^*$, where $R_{i,n+1}$ is the recombination rate between A and B with $M_i M_{n+1}$ at the modifier locus. Then M_{n+1} increases in frequency if $\tilde{R} < R^*$ and is expelled if $\tilde{R} > R^*$, and so the average recombination is reduced near a VAHW equilibrium (87). This indicates that from the point of view of long-term evolution, zero recombination has the property of evolutionary genetic stability (EGS) (32), as do zero mutation and zero migration in corresponding models for modification of mutation and migration (42, 87–88). The result, however, remains to be generalized to attainable equilibria that are not of the form given by Equation 8.

Initial Increase: Random Mating and Multiple Major Loci

Three studies have examined aspects of the reduction principle when selection acts on more than two major loci and where the modifier locus is initially fixed on allele M_1. Altenberg & Feldman (2) developed a classification of evolutionary dynamical systems that include (but are not restricted to) recombination, mutation, and migration. With standard Mendelian segregation, random mating and viability selection, most deterministic genetic models belong to a class these authors called linear. Within this linear class, if the modifier rarely recombines with the major genes, M_2 will increase if it reduces the parameter it modifies, for example, the rate of recombination. Only one of recombination, mutation, or migration may be included in the system for this result to hold. Reduction in this context entails bringing the recursion system closer to one that is independent of the allelic configuration at the modifier locus, and that may include an arbitrary number of selected loci.

Altenberg & Feldman's results were obtained under the condition that the modifier gene is absolutely linked to the major genes. The results will also hold for sufficiently small values of the recombination between these. Under loose

linkage between major and modifier genes, Zhivotovsky et al (119) examined weak epistatic selection on the major genes so that only pairwise linkage disequilibria were important. The number of loci under selection (L) was not limited. The modifier gene was initially fixed on the allele M_1, and a new modifier allele M_2, introduced near a polymorphic equilibrium, increases in frequency provided the quantity

$$\tilde{\rho} = \sum_{\substack{s=1 \\ s \neq t}}^{L} \sum_{s=1}^{L} A_{st} \rho_{st} / R_{st} \qquad 9.$$

is negative, where A_{st} is positive when loci s and t are in linkage disequilibrium, R_{st} is the recombination rate between loci s and t with $M_1 M_1$, and $R_{st} + \rho_{st}$ is the recombination rate with $M_1 M_2$ at the modifier locus. Thus, if M_2 reduces all pairwise rates of recombination, it succeeds; if it increases them, it is eliminated. However, it may increase some and decrease others and still succeed, provided that the weighted average, in the sense of Equation 9, amounts to a decrease. A modifier that eliminates all recombination among arbitrary numbers of selected genes will always succeed (2).

With multiple linked loci, the phenomenon of interference in recombination must be taken into account. Most interaction between crossover events is inhibitory, with a crossover event in one chromosome segment reducing the chance of another nearby. There has been little evolutionary analysis either of this kind of interference, positive, or of the rarer negative interference. Goldstein et al (52) examined this question in the simplest possible framework, with three genes under symmetric multiplicative selection and a modifier M, which controlled only the interference between crossover rates in the A–B and B–C intervals. Using a combination of analytical and numerical approaches, they showed that allele M_2 invades a population at equilibrium fixed on M_1 provided its effect on interference is to reduce the overall recombination rate between A and C.

Random Mating and Viability Selection

The strength of selection on the modifier allele as it initially enters the population and reduces the population average recombination is very weak. Although the exact value of the leading eigenvalue that governs this increase is usually not available, a rough estimate is $1 + K$ where K is of the order of the product of two terms; the difference between the average resident recombination rate and the new marginal average recombination rate, and the square of the linkage disequilibrium among the major genes prior to the appearance of the new modifier allele. Thus, although K is positive, it is very small and vanishes when there is initial linkage equilibrium between the major genes.

The success of the multidimensional local analysis is due to the Perron-Frobenius theory for positive matrices; this theory guarantees a unique largest eigenvalue associated with a strictly positive eigenvector for the local stability matrices that arise in these problems. At a VAHW equilibrium with two major loci, it is usually possible to demonstrate that this largest eigenvalue of the $4n \times 4n$ local stability matrix is actually also the largest eigenvalue of a 4×4 matrix that can be manipulated directly to produce the reduction principle.

The successful analysis of stability with respect to the introduction of an allele that is not initially present in the population contrasts with the difficulty of obtaining general results for the stability of even the two-locus polymorphism with a fixed recombination rate, not to mention the stability of the VAHW equilibria. This internal stability analysis, however, is never governed by a positive matrix, and few general mathematical results are available. The Perron-Frobenius theory for positive matrices is generally applicable in the analysis of external stability of an equilibrium, where by external stability we mean the introduction of a variant that is not initially present in the population.

This analysis works extremely well under the assumptions described above:

1. the populations are large enough to ignore drift;

2. the selection on the major loci acts at the level of genotypic viabilities;

3. the viabilities are constant over time and the population is at equilibrium;

4. mating is random;

5. mutation is absent;

6. no sex differences exist.

With these assumptions and initial linkage disequilibrium, recombination (and indeed mutation and migration) decreases. Perhaps it is the violation of these assumptions in nature that permits the genotype not to "congeal" (115). We now proceed to review studies in which one or more of these assumptions are violated. It is worth noting that each of these violations of the reduction principle involves a departure from what we have called linear variation in the transmission system across generations (2). All systems that are linear in this sense satisfy the reduction principle. It should also be noted that the inclusion of simple forms of density dependence in the selection regime does not result in the failure of the reduction principle (118).

Failure of the Reduction Principle in Large Populations

SEX DIFFERENCES   The population genetic theory of viability selection with differences between the sexes, whether for autosomal or sex-linked genes, is

usually significantly more complicated than the classical model for which viabilities are the same in both sexes. It might therefore be expected that the evolution of modifiers of recombination, mutation, or migration should be qualitatively different if selection were more general in this sense. In fact, with fitness differences between the sexes, the reduction principle for mutation may fail, and the direction of evolution may depend on the recombination R between the modifier and major genes (116). In a numerical study, we found, however, that if the viability in one sex is one minus that in the other (sex-ratio evolution), only reduction of recombination appeared possible. In two interesting cases, however, the reduction principle remains valid in its original form (38, 87). The first (90) assumes that the major loci reside on the X chromosome, so that male and female genotypes have viabilities that are not really comparable, and recombination between the selected loci occurs only in females. The second (91) assumes that the two major loci are autosomal, but recombination occurs only in one sex, and fitnesses differ among sexes. In each of these cases, a rare allele introduced near a VAHW equilibrium increases in frequency if it reduces the recombination rate below the average in the resident population.

OTHER MODES OF SELECTION   Most analytical, numerical, and verbal discussions of the evolution of recombination are couched in a framework of viability selection on the zygote-to-adult phase of the life cycle [e.g. see (85)]. The main reason for this is the extremely complicated dynamics of genotype frequencies under selection at the level of fertility (41, 53). Under fertility selection (and also in the case of mixed random mating and outcrossing discussed below), chromosome frequencies are insufficient to describe the evolution; multilocus genotype frequencies must be used, and the dimensionality of the problem is massively increased.

The effect of fertility selection on the reduction principle has been investigated for modifiers of the mutation rate. In these studies, fertility selection on the mating types is determined by a single diallelic locus with mutation (possibly in both directions) of the alleles at this locus. A modifier that increases the mutation rate may invade such a population when the fertility of matings between individuals of different genotypes exceeds that of at least some matings between like genotypes (62). This result violates the reduction principle. In addition, the evolution at the modifier locus may depend on the linkage between the neutral modifier and the selected locus: Loose linkage of these genes is most conducive to increase of the mutation rate. Multiplicative fertilities are dynamically equivalent to selection at the viability level, which differs between the sexes (14, 38), and, indeed, similar results have been found for this case (116). From these results it is reasonable to infer that under fertility selection, or sex-dependent viability selection, recombination-increasing alleles might

be favored under some linkage restrictions between the selected and modifier loci.

MEIOTIC DRIVE   The evolution of recombination may be severely complicated by the presence of meiotic drive. The most detailed analyses have been made when one locus is under viability selection and a second locus controls the amount of segregation distortion that may occur in the gametic output of heterozygotes at the first locus. The linkage between these genes profoundly influences their joint evolution (21, 110, 114). The fate of a modifier of recombination introduced near equilibrium in this system depends on the ordering of the three loci, and a recombination-increasing allele is very likely to succeed (113). In some cases, however, any alteration (up or down) of recombination is favored so that the population is expected to move towards a polymorphic state at the modifier locus (24). Similar results were found (43) for another "segregation-distortion" model of sex-determination in which distortion at one locus altered the offspring sex ratio, as in the mosquito *Aedes aegypti* (93). A common feature of these models is that the linkage disequilibrium between the two selected genes is largest for intermediate values of recombination, unlike what we know and like about standard viability selection, where linkage disequilibrium is strongest with tight linkage and decreases more or less monotonically with increasing recombination (44, 114).

NONRANDOM MATING   Most studies of the effect of departures from random mating on the evolution of recombination have been restricted to the classical model with two diallelic linked loci under selection, and a diallelic recombination modifier. Two kinds of departures from random mating have been studied: population subdivision and self-fertilization. The effect of population subdivision was studied in a population split into two semi-isolated demes where the major loci were subject to the same symmetric viability selection. A stable equilibrium exists that has linkage disequilibria of opposite signs in the two populations, and at this equilibrium the reduction principle holds for recombination and migration modification (25).

Under pure selfing, very strong overdominance in fitness is required to maintain a polymorphism [see e.g. (65)], and near such a polymorphism alleles that increase recombination will be selected against (35) [alleles that increase mutation may succeed, however (60)].

With mixed selfing and random mating, all dynamics should be written in terms of genotype frequencies, so that even with three diallelic loci, the dimensionality is great. Under simple symmetric-viability selection on two genes, however, Holden (56) exhibited properties of some of the polymorphic equilibria. In models with mixed selfing and random mating, however, the simple

symmetric viability system has some unfortunate properties. Most important is the fact that the stable polymorphic equilibria have gene frequencies equal to a half, and these equilibria exist for any strength of selection, in contrast to equilibria that are asymmetric in the gene frequencies (75). Indeed, important dynamical aspects of two-locus viability selection are neglected in the symmetric-viability model (26).

Besides Holden's analysis, most studies of the evolution of recombination in mixed mating systems have been numerical. The results are surprisingly complicated, and although they leave no doubt that the inclusion of partial selfing can cause the reduction principle to fail, for any specific set of parameters, the fate of a recombination modifier is difficult to predict.

For the range of recombination parameters examined by Charlesworth et al (22), increased selfing led to stronger selection for recombination-reducing alleles. However, this result may have been partly due to the values of the recombination parameters chosen (59). Charlesworth et al (23) showed that for some range of selfing, and selection of the symmetric type (56), recombination-increasing alleles may succeed.

The following points are consequences of the inclusion of nonrandom mating (59, 61). (*a*) For some fitness regimes, high and low levels of selfing may result in selection for lower recombination with increased recombination favored under intermediate levels of selfing. (*b*) With partial selfing, more than one kind of stable two-locus polymorphism may occur, and the direction in which recombination evolves may depend on which equilibrium is the starting point for modification; i.e. historical considerations may be important. (*c*) The extent of recombination in the population when a recombination-modifying allele is introduced may determine its fate. (*d*) A classification of selection regimes that permit selection for increased recombination in at least some range of selfing rates has not been possible but remains a worthwhile goal in light of the fact that self-pollinating plants often have more frequent chiasmata than close relatives that outcross (111, but see also 105).

DIRECTIONAL SELECTION

The reduction principle reflects the intuitive expectation that parents that survive selection in a constant environment and faithfully reproduce their genotypes will be fitter than those that generate new genotypic combinations in their offspring. This interpretation does not necessarily apply, however, if the population is subject to directional selection (as may be caused by a shifting optimum) or if there is mutation (which displaces the population mean from an optimum). Under these circumstances, offspring survival may be improved by creating new genotypic combinations by recombination. Most optimality arguments in

favor of recombination involve either adapting populations (29, 48, 100, 101) or populations subject to mutation (80–82, 85, 92, 100).

Barton (4) recently provided a fairly general treatment of the dynamics of a modifier locus changing recombination among a set of loci subject to directional selection. He assumed that the modifiers alleles have only a small effect on recombination rates, and that the change in the frequency (p_i) of modifier allele M_i is given by

$$\Delta p_i = \sum_{\Lambda} \tilde{a}_{\Lambda,\phi} C_{i\Lambda}, \qquad\qquad 10.$$

where the summation is over all possible subsets Λ of the set of loci $\{1, 2, \ldots, L\}$, $\tilde{a}_{\Lambda,\phi}$ represents the residual selection acting on the loci in Λ above and beyond the selection acting on the loci in subsets of Λ, and $C_{i\Lambda}$ measures the association between M_i and Λ (a kind of linkage disequilibrium). If selection is weak compared to the effect of recombination, then the population approaches a "quasi-linkage equilibrium" (5, 102), where the selection coefficient on allele M_i may be written

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx - \sum_{\text{All sets}} \delta R_{\Lambda} (|\Lambda|! \tilde{a}_{\Lambda,\phi})^2 \frac{p_{\Lambda} q_{\Lambda}}{R_{\Lambda} R_{i\Lambda}}. \qquad\qquad 11.$$

Here δR_{Λ} is the effect of the modifier on the probability (R_{Λ}) that recombination will break up the set Λ, and $p_{\Lambda} = 1 - q_{\Lambda}$ is the frequency of that set; $R_{i\Lambda}$ measures the probability of a breakup of the set $\Lambda \cup \{\text{modifier}\}$ and $|\Lambda|$ is the number of major loci. The sign of s_i is the opposite of the "prevailing" sign of δR_{Λ}, and so only modifiers that tend to reduce recombination will increase in frequency. Thus, in the limit as directional selection becomes weak, the reduction principle applies.

If directional selection is relatively strong, however, the selection coefficient on allele M_i contains an additional term:

$$s_i \approx - \sum_{\Lambda} \delta R_{\Lambda} (|\Lambda|! \tilde{a}_{\Lambda,\phi})^2 \frac{p_{\Lambda} q_{\Lambda}}{R_{\Lambda} R_{i\Lambda}}$$
$$- \sum_{j<k} \delta R_{jk} \frac{p_j q_j p_k q_k}{R_{jk} R_{ijk}} \left[\tilde{a}_{j,\phi} \tilde{a}_{k,\phi} \left(\frac{1}{R_{ij}} + \frac{1}{R_{ik}} - 1 \right) \right] \epsilon_{jk}, \qquad 12.$$

where δR_{jk} is the effect of the modifier on the recombination rate (R_{jk}) between loci j and k and ϵ_{jk} is the multiplicative epistasis between loci j and k. The new term in Equation 12 can favor increased recombination, but only if the epistasis tends to be negative ($\epsilon_{jk} < 0$). Strong negative epistasis, however, may cause the first term of Equation 12 to overwhelm this effect, and overall,

recombination may be favored under directional selection, but only if epistasis is negative and satisfies

$$\tilde{a}_{j,\phi}\tilde{a}_{k,\phi}\left(\frac{1}{R_{ij}} + \frac{1}{R_{ik}} - 1\right) + \epsilon_{jk} > 0. \qquad 13.$$

Bergman et al (12) simulated a three-locus version of this model and found that the above results hold qualitatively even when many of the assumptions of Barton's analysis are relaxed (e.g. modifiers may have quite strong effects).

Charlesworth (19) examined the evolution of a modifier of recombination among a set of major loci, assuming Gaussian optimizing selection, i.e. the fitness of an individual depends on the difference between its phenotype z and the optimum phenotype θ:

$$w_z = e^{-(z-\theta)/(2\omega^2)}, \qquad 14.$$

where ω measures the strength of selection. Gaussian selection exhibits weak negative epistasis, and so from Barton's analysis (4) we expect that modifiers that increase recombination should be favored as long as directional selection is strong enough. For biologically reasonable values of the parameters, Charlesworth found that a genome with free recombination would be stable to invasion by a modifier allele if the optimum were changing faster than approximately 0.13 times the additive genetic standard deviation. Similarly, recombination modifiers could invade a population with no recombination if the environment were changing faster than about 0.04 additive genetic standard deviations. Interestingly, these two conditions indicate that an intermediate recombination rate may be favored under certain circumstances.

It is unlikely that directional selection continues indefinitely. Rather, fluctuations in the direction of selection may occur (see next section) or a population may evolve under directional selection up to a point and then experience stabilizing selection. Maynard Smith's (95) studied L major, diallelic loci each with allelic values 0 and 1. The phenotype z of a diploid individual is the sum of the values of the alleles in the genotype ($0 \leq z \leq 2L$), and fitness is given by Equation 14. If the mean phenotype is initially at θ, then the population experiences stabilizing selection, whereas if it starts far from θ, then a period of directional selection will ensue. Simulations showed that a modifier that increases recombination rates could be favored during the directional phase of selection. If, however, the mean and the optimum are initially close to one another, the directional phase may be too short to favor recombination, and Bergman & Feldman (10) produced examples where recombination increases during the initial phases of selection, but then decreases, ending up below its initial value. These studies are consistent with (19) and (4): directional

selection with negative epistasis is a necessary but not sufficient condition for the evolution of increased recombination.

FLUCTUATING SELECTION   Fluctuating selection can assume several different forms (79). Most commonly, fluctuating selection is modeled either with (*a*) cyclical variation following a given deterministic formula or (*b*) stochastic variation following a Markov model. Cyclical models of selection have been especially important because they mimic expected patterns of frequency-dependent selection in predator-prey and host-parasite models. Jaenike (64) suggested that (haploid) genotypes AB, Ab, aB, and ab might be subject to frequency-dependent selection such that common genotypes are at a selective disadvantage with respect, say, to predation. Predator-prey cycles would result that may allow recombination to produce more advantageous types for future selection. Hamilton (54) placed Jaenike's speculation on a more formal level with a two-locus haploid model subject to frequency-dependent selection by a parasite. He showed that the presence of recombination increased the geometric mean fitness in the population and later wrote that "sex has the useful function of continually recombining a set of preserved defensive elements" (55). One flaw in this argument is that frequency-dependent selection due to the interaction between genotypes in a host and a disease agent may not be able to maintain genetic variation in the host (3).

Modifier models with cyclic selection have been studied both numerically and analytically. In a numerical study, Charlesworth (17) subjected two major loci to symmetric viability selection (16, 68) that cycled in such a way that under one regime the linkage disequilibrium would become positive and in the other it would become negative. If the period of this cycle is greater than one generation, a recombination-increasing allele may succeed, although with very long periods, reduced recombination would again be favored. The degree of linkage between the major gene and the modifier played a role, with tighter linkage resulting in higher recombination. Charlesworth (19) analyzed cyclic selection by assuming that the optimal phenotype in Equation 14 changed sinusoidally over time. Here he found that the amplitude of the cycles is critical, with larger fluctuations being more likely to select for recombination. With such dramatic fluctuations in fitness, however, the geometric mean fitness of the population would be very low. Furthermore, selection for recombination was always fairly weak. The conclusion is that the cyclic optimum model is an "implausible" explanation for the evolution of recombination (4, 19). Whether cycles in general are a major force in nature contributing to the maintenance of recombination remains controversial (95).

Other models of fluctuating selection allow fitness to vary randomly over time. For example, Charlesworth (19) allowed the fitness optimum in

Equation 14 to change over time according to a linear stationary Markov process with a given autocorrelation between generations. This model allowed the evolution of recombination over a broader range of parameters than under cyclic selection, especially if the autocorrelation between generations was high. Again, however, the selection for recombination was generally weak. Thus, fluctuating selection appears not to be as effective as pure directional selection in favoring the evolution of recombination [see also (79)].

DELETERIOUS MUTATION

New mutations continually arise that decrease the fitness of an organism. Data on the rate of mutations across a genome are limited, but the average number of new deleterious mutations per diploid genome per generation, U, is at least $1/2$ and perhaps substantially higher (20, 63, 84, 99). Mukai (98) observed a significant nonlinear relationship among mutations, such that the deleterious effects of mutations were even greater in combination than expected ("synergistic" or negative epistasis). Crow (28) fitted a quadratic fitness function to these data, finding that the fitness of an individual bearing n homozygous mutations was approximately

$$W(n) = 1 - 0.014n - 0.011n^2. \qquad \qquad 15.$$

The efficiency of the process of purifying selection depends upon several factors, including the epistatic interactions among mutations, the recombination rate between them.

If the fitness of an organism, W, were simply the product of the fitness consequence, $(1 - s_i)$, of each mutation carried within the genome, i.e. if $W = \prod_{i=1}^{n}(1 - s_i)$, then genetic associations would not develop between loci. Between two loci, for example, linkage disequilibrium is absent at an equilibrium between mutation and multiplicative selection (38), as expected based on analogy with directional selection (31, 94). In the absence of genetic associations, the level of recombination becomes immaterial since haplotypes cannot be further randomized. With epistasis, however, disequilibria develop and recombination can play an important role in determining the distribution of mutations in a population.

Feldman et al (37) investigated the evolution of recombination in both haploid and diploid models with two major loci and one modifier locus. We focus on the results for the haploid model (see Equation 2a–d), since they are qualitatively the same as for the diploid model. At the major loci, the normal alleles A and B are subject to recurrent deleterious mutations (to a and b) at a rate μ. Selection acts against these mutations, such that the viabilities of AB, Ab, aB, and ab are 1, $1 - s$, $1 - s$, and $(1 - s)^2 + \epsilon$, respectively, where ϵ measures the

multiplicative epistasis. When ϵ is negative, mutations have a more deleterious effect on fitness in combination than expected if fitnesses were multiplicative ("synergistic" epistasis), whereas if ϵ is positive, mutations have a weaker effect on fitness when combined ("diminishing-returns" epistasis).

With only one modifier allele present, M_1 say, the system equilibrates at a two-locus mutation-selection balance where the linkage disequilibrium, $\hat{D}$, between the two viability loci has the same sign as ϵ. A new modifier allele invades the population if

$$(r_2 - r_1)\hat{D}\, g(R) > 0, \tag{16.}$$

where $g(R)$ is a quadratic function of the recombination rate (R) between the modifier and the first selected locus (37). When $R = 0$, $g(R)$ is negative. Thus with tight linkage between the modifier and the major loci, the evolution of increased recombination is favored by negative (synergistic) epistasis (ϵ, $\hat{D} < 0$), while decreased recombination is favored by positive (diminishing-returns) epistasis. If epistasis is weak or if it is positive, the result at $R = 0$ continues to apply for all biologically reasonable values of R (106). If, however, epistasis is strong and negative (synergistic), a critical value of R ($R^\star$, say) exists above which *decreased* recombination is favored.

As an example, the data from (99) suggest that for n small in Equation 15, $s \approx 0.025$ and $\epsilon \approx -0.023$, assuming that the fitness effects of homozygous mutants and haploid mutants are approximately equal. For this case, $R^\star$ is shown in Table 1 where we see that the value of $R^\star$ is fairly insensitive to both the mutation rate and the other recombination rates. In all cases, $R^\star$ is fairly low, indicating that, for these parameters, only the most tightly linked modifier loci would permit increased recombination between the viability loci (106).

If epistasis is very weak or if the modifier is tightly linked to the viability loci, synergistic epistasis favors the evolution of increased recombination while diminishing-returns epistasis favors decreased recombination. With diminishing-returns epistasis, decreased recombination continues to be favored regardless of the linkage relationships or the strength of the epistasis. With moderately strong synergistic epistasis, however, the stability condition switches as R increases so that decreased recombination is favored by loosely linked modifier loci. These results are strongly analogous to those obtained under purely directional selection. Modifier alleles that increase recombination will have a higher fitness by eliminating the disequilibrium present in the equilibrium population only if the additive epistasis is positive, i.e. $-s^2 < \epsilon < 0$. Therefore, under both directional selection and purifying selection, if epistasis is strongly negative ($-s^2 > \epsilon$) the immediate decrease in fitness of a modifier that increases recombination can overwhelm its positive association with the fittest genotype [see also (4)].

Table 1 The value for R above which the stability condition reverses, determined by a numerical analysis of the stability matrix. See text for parameter values.

Selection	Epistasis	Mutation	Recombination	R^*
$s = 0.025$	$\epsilon = -0.023$	$\mu = 0.01$	$r_1 = 0.20, r_2 = 0.25$	$R^* = 0.043$
$s = 0.025$	$\epsilon = -0.023$	$\mu = 10^{-5}$	$r_1 = 0.20, r_2 = 0.25$	$R^* = 0.035$
$s = 0.025$	$\epsilon = -0.023$	$\mu = 10^{-6}$	$r_1 = 0.20, r_2 = 0.25$	$R^* = 0.035$
$s = 0.025$	$\epsilon = -0.023$	$\mu = 0.01$	$r_1 = 0.05, r_2 = 0.10$	$R^* = 0.056$
$s = 0.025$	$\epsilon = -0.023$	$\mu = 10^{-5}$	$r_1 = 0.05, r_2 = 0.10$	$R^* = 0.047$
$s = 0.025$	$\epsilon = -0.023$	$\mu = 10^{-6}$	$r_1 = 0.05, r_2 = 0.10$	$R^* = 0.047$
$s = 0.025$	$\epsilon = -0.001$	All	All	No $R^* (\uparrow$ recombination$)$
$s = 0.025$	$\epsilon = -0.0001$	All	All	No $R^* (\uparrow$ recombination$)$
$s = 0.025$	$\epsilon = +0.023$	All	All	No $R^* (\downarrow$ recombination$)$
$s = 0.025$	$\epsilon = +0.001$	All	All	No $R^* (\downarrow$ recombination$)$
$s = 0.025$	$\epsilon = +0.0001$	All	All	No $R^* (\downarrow$ recombination$)$

Thus, increase in the recombination frequency occurs under restricted conditions. The selection on the modifier is very weak because the selective forces on the major loci are of the order of magnitude of the mutation rate when mutation-selection balance is achieved. However, the evolution of recombination in response to the interaction of deleterious mutants is still interesting because of their ubiquity, and there may be a sizeable cumulative effect on the recombination apparatus if a general pattern of interactions exists among mutants.

The features observed in the three-locus model extend to models with multiple loci. These models tend to focus on the effects of recombination on the distribution of the number ℓ of mutations carried by an individual. Recombination generally increases the variance of this distribution (18, 80–82), but does not always increase the equilibrium mean fitness of the population (18). Even when recombination does increase the equilibrium mean fitness, modifier alleles that increase recombination rates are not always favored (18, 113).

Kondrashov (81) was the first to study alleles that modify recombination rates among a large number of loci. He examined three types of synergistic epistasis as a function of ℓ: truncation selection where all individuals with more than k mutations die, intermediate selection ($W_n = 1 - (\frac{\ell}{k})^2$, as found by Mukai 98); and linear selection ($W_n = 1 - (\frac{\ell}{k})$). He focused on the case of an unlinked modifier locus whose different alleles M_l lead to exactly l crossover events in the zygote.

Kondrashov found by simulation that a modifier allele that leads to free recombination between all loci would fix in the population if approximately $\frac{U}{\sqrt{k}} > 0.35$ under truncation selection, $\frac{U}{\sqrt{k}} > 0.1$ under intermediate selection

and for all values under linear selection. When these conditions were not met, an intermediate value of recombination was favored as long as $U > 0.69$. Kondrashov notes that $\frac{U}{\sqrt{k}} \approx \sqrt{Us}$ since the selection coefficient against each mutant at equilibrium is $s \approx \frac{U}{k}$. With an average selection coefficient against deleterious mutations of 0.02 (99), U would thus have to be greater than 6 for free recombination to be favored under truncation selection and greater than 0.5 under intermediate selection. Since most estimates of the mutation rate tend to be underestimates (84), Kondrashov (80) concludes that increased recombination is likely to be favored under synergistic epistasis. The strength of this selection for recombination depends, however, on the number of chromosomes carrying the mutant loci, approximately halving with each doubling of the number of chromosomes. In large genomes, then, the amount of indirect selection acting upon modifier alleles might be extremely weak.

Charlesworth (18) further analyzed this problem by noting that if the distribution of ℓ is normal, it will remain normal after selection if

$$W(\ell) = e^{-(\alpha\ell + \frac{1}{2}\beta\ell^2)}, \qquad\qquad 17.$$

which is very similar to the quadratic fitness function (Equation 15) if selection against a mutation is weak, and is similar to Kondrashov's intermediate selection scheme if α is small and β is positive. The data of Mukai et al (99) are consistent with the values of $\alpha \approx 2 \times 10^{-3}$ and $\beta \approx 8 \times 10^{-4}$ in Equation 17.

Into an equilibrium population satisfying these conditions, Charlesworth (18) introduced a modifier allele that has a small effect on recombination. When recombination rates are low between all loci (including the modifier), the fitness effects of the new allele can be predicted by the dependence of the equilibrium mean fitness on recombination. Thus, for biologically reasonable values of the parameters, alleles that increase recombination are favored under synergistic epistasis ($\beta > 0$), and alleles that decrease recombination rates are favored otherwise ($\beta < 0$), a result consistent with the effects of recombination on mean fitness in this model (18). These results continue to hold for arbitrary recombination rates between loci when there is diminishing-returns epistasis, but the condition for recombination to be favored under synergistic epistasis becomes more stringent. With synergistic epistasis, modifier alleles that increase recombination rates could invade the population only if mutation rates were sufficiently high. For the selection coefficients suggested by the data of Mukai et al (98, 99), increased recombination was favored for values of U greater than about 0.29. When $U < 0.29$ the *equilibrium* mean fitness would rise if recombination rates increased, but modifier alleles that increase the recombination rate cannot invade the population because they lead to an immediate, but transient,

decrease in fitness (4, 18). Thus, with synergistic epistasis, an intermediate level of recombination is favored if genome-wide mutation rates are low, and if mutation rates per genome per generation are 0.5 or greater (82, 83), free recombination would be favored under synergistic epistasis.

Barton (4) also studied modification of recombination in the presence of deleterious mutations, again assuming that the effects of the modifier on recombination are small. The selection coefficient acting upon a new modifier allele was approximately

$$s_i \approx -\frac{1}{2} \sum_{\Lambda} \delta R_{\Lambda} \ V_{|\Lambda|} \ E\left[\frac{1}{r_{i\Lambda} r_{\Lambda}}\right]$$

$$-\frac{1}{2} \ E[\delta R_{jk} \ \epsilon_{jk} \ \mu_j \ \mu_k] \ E\left[\frac{1}{R_{ijk} R_{jk}}\left(\frac{1}{R_{ik}} + \frac{1}{R_{ij}} - 1\right)\right]. \qquad 18.$$

This equation shares many terms with Equation 12. In addition μ_j is the mutation rate at locus j, E is the expectation over all loci of the quantities in parentheses, and $V_{|\Lambda|}$ is the variance in log fitness due to epistatic interactions among sets of the size of Λ. This formula is accurate as long as the expected recombination rate between loci is not very small, although Barton discusses reasonable approximations for closer linkage.

Equation 18 is entirely analogous to that derived under directional selection (Equation 12), thus formalizing the similarity between directional and purifying selection. The first term in both of the equations for s_i measures the fitness effects of changing genetic associations between all sets of loci, while the second term measures the effects on the additive genetic variance of changing the linkage disequilibria between pairs of loci. Thus, selection on modifier alleles comes from two sources: immediate changes to fitness (by changing the linkage disequilibrium) and genetic associations with the fittest genotypes (by changing the additive genetic variance). The second term in Equations 12 and 18 indicates that increased recombination rates are favored if epistasis is synergistic, while decreased recombination rates are favored if there is diminishing-returns epistasis. The first term in the equations, however, always selects for modifiers that reduce the recombination rate, regardless of the epistatic regime. Whether increased or decreased recombination will be favored under synergistic epistasis depends, therefore, on the relative magnitudes of the two terms in Equation 18. If the modifier locus is tightly linked to the viability loci, the second term in Equation 18 becomes large (because the second expectation within it becomes large) and the sign of the epistasis always determines the evolution of recombination, exactly as found in the three-locus and multilocus models. If the modifier is loosely linked, however, the first term may dominate so that reduced recombination can be favored even under synergistic epistasis. Barton

(4) finds by numerical analysis that this is likely to happen when the genome-wide mutation rate is low ($\approx$ 0.1) [see also (18, 80)]. An analytical proof that high mutation rates favor recombination under synergistic epistasis in this general multilocus model would be valuable.

The general conclusion from these models is that synergistic epistasis always favors recombination if all loci are tightly linked. When the modifier is loosely linked, however, recombination will only be favored with synergistic epistasis if the epistasis is sufficiently weak or the mutation rate is sufficiently high.

Gene Conversion

Close to a crossover point on a chromosome, abnormal segregation of alleles may occur in the products of meiotic division. In Ascomycetes, for instance, a low frequency of 3:1 segregations is observed among the usual 1:1 segregations in asci, and a high proportion of these abnormal asci show recombination in the neighborhood of the locus with the abnormal segregation. This phenomenon of gene conversion is understood in terms of the molecular processes that occur at the Holliday junction of chromosomal chiasmata. Gene conversion may happen both in connection with a genetic crossover and with alternative resolutions of the Holliday junction, leading effectively to a double crossover with extremely close breakpoints, i.e. a small piece of one chromosome is inserted into the other. Usually gene conversion does not lead to deviations from the Mendelian segregation ratio when viewed over a large number of meioses, but instances of a strong bias in gene conversion for or against certain mutations are known (8).

Bengtsson (8) suggested that biased gene conversion may be important in the evolution of recombination. Bengtsson & Uyenoyama (9) investigated the evolution of genetic modifiers of the rate of gene conversion, which should be closely related to the rate of recombination in a chromosome segment. Biased gene conversion is a kind of meiotic drive, but the relevant modification questions are qualitatively different; gene conversion is a very local phenomenon, and a modifier of gene conversion is unlikely to hitchhike with the drive. As a result, this analysis shows that modification of gene conversion is similar to modification of recombination or mutation. That is, lower rates evolve in a population at equilibrium with respect to viability selection. Higher rates may evolve with purifying selection at the major locus, if on average biased gene conversion repairs mutational damage.

Directional Selection, Finite Populations, and the Reduction Principle

Here we review some recent finite-population simulations (11, 13) that compare recessive and dominant recombination modifiers and haploid and diploid

selection of the form proposed by Maynard Smith (96), namely Gaussian selection skewed so that there is directional selection over a large range of the phenotype.

The two cases considered are a diploid population of 100 individuals and a haploid population of 200 individuals. There are 20 loci under selection in the former and 40 in the latter. Each locus may have allele 1 or 0 and the phenotype is the sum of the 1s and therefore, in each case, varies between 0 and 40. Gaussian selection with mean 30 is imposed on the phenotype, and we tune the variance, ω^2, to determine the strength of selection. The modifier alleles M_H and M_L originally have equal allele frequencies, and M resides outside the genes under selection. In the recessive case, genotypes $M_H M_H$, $M_H M_L$, and $M_L M_L$ allow a recombination event to occur with probabilities 0.5, 0.01, 0.01, respectively, while in the dominant case, $M_H M_L$ has a recombination chance of 0.5. These numbers are the probabilities that a recombination event occurs at one location across the 20 (or 40, in the haploid case) intervals, and when such an event occurs, it is equally likely to occur between any pair of these genes. One thousand simulations to fixation of either M_H or M_L were carried out and, under neutral expectations, 50% of the runs should fix on each. Two experiments with mutation were carried out: one with mutation from allele 1 to allele 0 at rate 0.005 per locus per generation, and another with mutation at this rate from allele 0 to allele 1.

Bergman et al (13) found that when M_H is recessive to M_L, haploid selection is more likely to favor high recombination than low, and the same is also true of most dominant cases. We might speculate that there is some tendency to maintain a level of polymorphism in the diploids that, as described above, favors M_L. The recessive action of M_H produces higher average recombination than does dominant, a fact also observed by Felsenstein & Yokoyama (47) for a completely different selection scheme. Again, this may be due to the tendency of high average recombination to produce faster fixation, i.e. eliminate polymorphism, in finite populations [e.g. (69)]. These results (13) are sensitive to the strength of selection as determined by the standard deviation ω. With $\omega = 1$ (strong selection), there is a strong tendency to maintain both polymorphism and linkage disequilibrium, favoring M_L, as in the deterministic setting. As ω increases (selection weakens), the tendency to favor M_H becomes strong with haploids, but remains relatively weak for diploids. The final observation (13) concerns mutation. With mutation in the direction $1 \rightarrow 0$, throughout much of the phenotypic range, the process is analogous to the mutation-selection balance of Felsenstein & Yokoyama (47). Especially in haploids, this has a tendency to favor M_H, but when M_H is recessive, it also supports an increase in average recombination. The effect is absent when selection and mutation act in the same direction.

To summarize, it is difficult to state unequivocally that the finiteness of the population is itself a trigger for selection in favor of high recombination. Under directional selection, at least, the strength of selection, direction of mutation, and dominance of the modifier all play important roles. Further, in haploids, which have no opportunity for selectively maintained polymorphism, selection for higher recombination is easier than in diploids.

The Shape of the Fitness Surface and the Reduction Principle

In our discussion of the reduction principle, the nature of the selection regime on the major loci was general except insofar as it supported a stable polymorphism at which there was linkage disequilibrium. Most discussions of nonequilibrium situations, however, have focused on specific forms of directional selection (47, 96), and even with these models, the specific parameters may be important for the fate of recombination-controlling genes. Bergman & Feldman (11) took this analysis a stage further by examining the fate of recombination-controlling alleles when the major genes are under different classes of selection regimes that belong to a one parameter family (11). Again, the model setting is 20 loci with alleles 0 and 1 in a population of 100 diploids with a twenty-first locus that has recombination alleles M_H and M_L. The phenotypic value, z, is additive, ranging from 0 to 40, and a fitness model is constructed as

$$\psi(z) = \sum_{k=1}^{n} R(k) \sin \frac{\pi z}{40\sqrt{k}}, \qquad \qquad 19.$$

where $R(k)$, $k = 1, 2, \ldots, n$ are random numbers chosen uniformly on $[0, 1]$. Then the fitness of phenotype z is defined as

$$F(z) = \frac{\psi(z) - \min[\psi(z)]}{\max[\psi(z)] - \min[\psi(z)]}. \qquad \qquad 20.$$

This defines a family of fitness regimes whose jaggedness is controlled by varying n. For a fixed value of $n \in \{2, 3, 30, 40\}$, 50 sets of the random numbers $R(k)$ are chosen $\{R(k); k = 1, 2, \ldots, n\}$. For each set of $R(k)$, 500 simulations of the evolution of the population, starting with the selected loci on average in linkage equilibrium and with M_H at 5% were carried out. If recombination were neutral, 25 of the 500 runs in each case would be expected to fix on M_H. Dominant and recessive action of M_H were treated in the same sense as the previous section. With the jagged fitness surfaces, i.e. $n = 20$, $n = 40$, high recombination is at a severe disadvantage. It does much better with $n = 2$ or 3, but the effect is not nearly as striking as for the high values of n.

From these few simulation experiments we may speculate that with a very bumpy fitness surface, directional selection cannot persist for any length of

time, and stabilizing selection persists, at least for some genes. This gives M_L its advantage. Investigations of the surfaces with $k = 2$ or 3 that favored high recombination revealed that they were strongly disruptive, so that the initial populations may well have been subject to directional selection. Here, the consequences of linkage disequilibrium due to selection are difficult to disentangle from those due to drift (46). More detailed investigations of these and other families of fitness surfaces might help tie this theory of recombination modification to the optimization analysis in the genetic algorithm literature (50), where the inclusion of recombination does not lead to easier determination of global optima when fitness surfaces are very jagged.

SUMMARY

Modifier models have produced exact conditions under which alleles that increase or decrease recombination rates invade a population. This body of research has found that evolution tends to lower recombination rates when the population is near an equilibrium configuration with nonzero linkage disequilibrium (a result known as the reduction principle). While factors such as selfing or meoitic drive can lead equilibrium populations to violate this principle, important exceptions to the reduction principle come from populations that are not at a selective equilibrium. With directional selection such that a population is initially far from an equilibrium, increased recombination can be favored, provided that there is negative epistasis and that this epistasis is not too strong. With mutations creating a displacement from a selective equilibrium, increased recombination can also be favored under negative (synergistic) epistasis. Again, synergism is not a sufficient condition for recombination to be favored; decreased recombination can instead be favored under strong synergism with low mutation rates and loosely linked modifiers. This last example illustrates the point that optimality arguments are not always able to predict the outcome of evolution via successive modification of a trait. Optimization arguments predict that increased recombination should always be favored with synergistic epistasis, whereas this is now known to be a necessary, but not sufficient, condition for the evolution of increased recombination.

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