

Population Genetic Perspectives on the Evolution of Recombination

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“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?’.”

H.J. 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.

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 mixing permits the maintenance and production of genetic diversity and, in particular, allelic combinations that might be useful in novel environments [e.g. 54, 7, 100]; (b) increases the chance that favorable mutations at different loci could be collected into the same genome (48, 100, 101, 29, 30) or (c) facilitates the removal of deleterious mutations in finite populations (101, 45, 82, 83).

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 shall refer later in this article to aspects of computer science which 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 will return 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. These arguments could as well be entitled “group selection” arguments 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. The second part of our discussion addresses what Felsen-

stein (45) called “extrinsic” analysis, referring to theories for the evolution of genes that control rates of recombination. We shall 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 and 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 (76, 33). 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 : $\partial\bar{w}/\partial R < 0$. It should be noted 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 which 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 that without it.

Crow and 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 and 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

$$8N\mu < 1, \tag{1}$$

a condition that is easier to meet in a small population than one which is large. This differs from the conclusion of Crow and 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, while Crow and Kimura compare rates of incorporation under the assumption that all favorable mutations will be incorporated in the presence of recombination. This explains why the recombination rate does not enter into the optimality criterion of Crow and 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 shall 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 and 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 and 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

$$Wx'_1 = \{(1 - \mu)^2 x_1 - RD(1 - \mu)^2\} \quad 2a.$$

$$Wx'_2 = \sigma_2 \{(1 - \mu)x_2 + \mu(1 - \mu)x_1 + RD(1 - \mu)^2\} \quad 2b.$$

$$Wx'_3 = \sigma_2 \{(1 - \mu)x_3 + \mu(1 - \mu)x_1 + RD(1 - \mu)^2\} \quad 2c.$$

$$Wx'_4 = \sigma_4 \{x_4 + \mu(x_2 + x_3) + \mu^2 x_1 - RD(1 - \mu)^2\}, \quad 2d.$$

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 and 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 and Kimura.

Eshel and 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 shall 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 and 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 shall 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

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

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 (105) and mathematical (27) analysis. The numerical treatment (106) 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 small the average waiting time decreases to

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

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 (57, 58, 51, 6). Potential solutions are treated as strings of symbols that are subject to mutation and 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 (106, 27) on the formation of new allelic combinations, described in the previous section, was stimulated by discussions 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 (106). We simulated a finite haploid population with twenty 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 1's in a genotype. Fitness had a local maximum for a genotypic value of zero, with a decrease towards a minimum at five and an increase towards a global maximum at twenty. 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 1's. 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 non-monotonic 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 (83). Kimura and Maruyama (75) showed that populations with free recombination (sexual) had lower loads than populations with no recombination (asexual) and that the advantage to recombination was approximately two-fold with quadratic epistasis and even more

extreme with threshold selection. This hypothesis was studied further by Kondrashov (81) who confirmed that recombining populations can have a substantially lower load than non-recombining 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 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 non-existent) 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 deleterious 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 and 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 or not they actually work in the sense of predicting the dynamics of recombination depends on three classes of factors: 1) the size of the population, 2) the shape of the fitness surface, and 3) 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 which controlled the amount

of recombination among the genes in the first part. Nei analysed 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_1B_1 , A_1B_2 , A_2B_1