

Selfish Genes, Pleiotropy and the Origin of Recombination

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ABSTRACT

If multiple linked polymorphisms are under natural selection, then conflicts arise and the efficiency of natural selection is hindered relative to the case of no linkage. This simple interaction between linkage and natural selection creates an opportunity for mutations that raise the level of recombination to increase in frequency and have an enhanced chance of fixation. This important finding by S. Otto and N. Barton means that mutations that raise the recombination rate, but are otherwise neutral, will be selectively favored under fairly general circumstances of multilocus selection and linkage. The effect described by Otto and Barton, which was limited to neutral modifiers, can also be extended to include all modifiers of recombination, both beneficial and deleterious. Computer simulations show that beneficial mutations that also increase recombination have an increased chance of fixation. Similarly, deleterious mutations that also decrease recombination have an increased chance of fixation. The results suggest that a simple model of recombination modifiers, including both neutral and pleiotropic modifiers, is a necessary explanation for the evolutionary origin of recombination.

CONSIDER the recombinational behavior of DNA molecules that are the genomes of organisms, most of which are capable, via their phenotypes, of breaking and joining with other DNA molecules. This molecular behavior is often highly choreographed and occurs regularly at specific stages of a life cycle. For many eukaryote genomes it occurs at the life cycle stage of transition from diploid to haploid cells (*i.e.*, meiosis) between two similar genome copies that came together at the time of transition from haploid to diploid cells (*i.e.*, syngamy). For prokaryote genomes there is no meiosis and syngamy, yet the breaking and joining of DNAs may still occur with high frequency (Lenski 1993). This article addresses the question of why the breaking and joining behavior has evolved. The basic approach is to consider a world of molecular replicators, DNA molecules that generate copies of themselves (Dawkins 1976), and ask why natural selection might have favored those that are capable of breaking and joining with other DNAs. This highly reduced replicator perspective is not the only way to inquire of the evolutionary origins of sex, but it is simple. Furthermore, if findings generated with this approach are not in error, then they are at least necessary components of fuller answers that emerge from less reduced and more complex perspectives.

We can begin a search for an evolutionary explanation for recombination by considering the possible fates of a stretch of linked nucleotides that is in turn linked,

perhaps on either end, to other chains of nucleotides. For convenience, this stretch of DNA is referred to as a gene, though this is done without implying any particular functional capacity or boundaries. We can belabor a view of natural selection at the level of the gene by pointing out that any particular gene (again, meaning just a stretch of linked nucleotides) may either leave descendants (*i.e.*, copies of itself) or it may not, and by pointing out that all presently existing genes (indeed all nonsynthetic DNA molecules) are the descendants of ancestral copies that were successful in this regard. Then our question on the origin of recombination becomes: why is it so, that genes capable of breaking with linked genes and then joining up with others, have left more descendants than those that have not?

The answer, or at least part of it, lies in the fact that the persistence of a gene depends very strongly on the capacity of the DNA to which it is linked, to leave descendants. If a gene is linked to other genes that collectively act as a good replicator, then there is a good chance that together they will leave descendants. Conversely, if the gene is linked to others that collectively act as a poor replicator, then they will all perish together. Thus a gene that is capable of recombination might persist because the recombination causes the gene to pass from a state of linkage to genes that collectively have low fitness to ones that have high fitness. However, the reverse is also true—recombination will also sometimes move the gene into a worse situation—and it may seem that this exercise leads to a conclusion that recombination has no net effect. But it is not a zero-sum game for an initially rare mutation that is subject to essentially random processes of reproduction and occasional recombination that create large amounts of random link-

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age disequilibrium between the mutation and other segregating alleles (Felsenstein 1974). A gene with a capacity for recombination leads to variation in linkage relationships among copies of the gene. Some copies may be linked to good genes, and some to bad, but as long as some are linked to good genes, then the gene has a better chance of leaving descendants. In short, a gene that can leave descendants that vary randomly in their fitnesses, because of variation in their linkage relationships to other genes, will have a larger chance of persistence, on average, than one with a fate determined by just one linkage relationship.

This narrative model is simple, and accessible for its simplicity, but it could be in error for a variety of reasons common to nonquantitative models. Fortunately this narrative version follows a more rigorous quantitative model (Otto and Barton 1997). Otto and Barton inquired of the evolutionary fate of a mutation that is a neutral modifier of recombination and that occurs in a finite population of chromosomes that are segregating multiple beneficial mutations. They began with a well known result, that in the absence of recombination, natural selection cannot simultaneously cause the fixation of multiple beneficial mutations that do not occur on the same chromosome. The difficulty is that some beneficial mutations may arise on chromosomes of relatively low fitness, and remain linked to genes that are not beneficial. The solution, recombination, permits a beneficial mutation to move onto another chromosome that has other beneficial mutations. This theory, stated by Fisher (1930) and Muller (1932), predicts that populations capable of recombination will have higher rates of adaptation. The model can also be interpreted in terms of selection conflicts, that in the absence of recombination the probability that a beneficial mutation becomes fixed in a population is reduced because of linkage relationships and selection on mutations at other loci. Hill and Robertson (1966) studied this process in a two-locus model with selection favoring one allele at each locus, and with linkage between the loci. They found that selection on one locus hindered the probability of fixation of the beneficial allele at the other locus. Furthermore, the effect on the probability of fixation was much as if the effective population size had been reduced and the rate of random genetic drift increased. In essence, selection at one locus acts as an effectively random source of variation in reproductive success for a second locus, and vice versa. Felsenstein (1974) provided a memorable discussion of the Hill-Robertson effect, specifically in the context of the origin of recombination, and he explained why the Hill-Robertson effect is a very general expectation that will occur to some degree whether the selection coefficients on individual mutations are large or small, negative or positive. What Otto and Barton showed is that when the Hill-Robertson effect is occurring, meaning multiple loci under directional selection and linkage, then a neu-

tral mutation that increased recombination will have an increased chance of fixation relative to a neutral mutation that does not alter recombination. The reason is that by increasing recombination, both for itself and for all loci, the modifier has a larger chance of leaving descendants that are linked to beneficial mutations on chromosomes of high fitness. Then as these mutations increase in frequency, the modifier mutation hitchhikes along and also increases in frequency. The recombination modifier has no direct effect on the phenotype, yet it has an increased probability of fixation just as if it was a favorable mutation (Otto and Barton 1997). Indeed, from the perspective of the neutral modifier, the recombination effect conveys a positive selection coefficient, with an effect on fixation that is indistinguishable from that for a gene with a mutation that is beneficial in some more direct way.

For practical reasons, it will be useful to have a name for this theory, and at least for the remainder of this article it will be called the "escape model" of the origin of recombination. This name reflects a wish for brevity and a handy mnemonic, and it conveys the idea that a gene can escape the constraints of the Hill-Robertson effect, and have a greater chance of leaving descendants, if it experiences a mutation that increases the recombination rate.

It is worth emphasizing that the escape model does not require any kind of epistasis, relying only on a Hill-Robertson effect, which will arise regardless of epistatic interactions among loci. The results also fly in the face of a large portion of recombination modifier theories, which generally show that modifiers are not favored except under some patterns of epistasis or environmental change (Kondrashov 1993; Feldman *et al.* 1997). The failing of these theories is that they assume a very large population size and ignore the stochastic effects that largely determine the fate of new mutations, and that are exacerbated by the Hill-Robertson effect (Otto and Barton 1997).

In some respects, the value of the escape model is not easily overestimated. The model has very few assumptions (natural selection, linkage, and the appearance of neutral mutations that increase recombination) and if these occur, then recombination is expected to evolve. Two of these assumptions, natural selection on DNA sequence variation and linkage, are ubiquitous aspects of the genomes of living things. Thus for its simplicity and realistic assumptions, the escape model seems to be a necessary component of any complete explanation of the evolutionary origin of recombination. However, the model may not ultimately resolve very many of the questions regarding the origins of recombination. It is almost certainly not a sufficient explanation (at least in the limited form presented here) of all aspects of recombination that presently exist, and it is possible that it will explain only a minor piece of the larger puzzle. For example, the frequency of mutation to neu-

tral recombination modifiers may be very low. Similarly, the magnitude of the effect quantified by Otto and Barton can be very slight if the modifier is slight in its effect or if recombination is already loose, and depending on the amount of selection that is occurring at other loci. On balance, the escape model describes a mechanism that apparently must occur to some degree and that may be envisioned as a kind of evolutionary pressure or tendency, but that is expected to be weak for any one modifier, and may not even be strong over evolutionary time.

The remainder of this article concerns a simple addition to the escape model that supposes that the recombination modifier is not neutral, but exerts some other effect on the phenotype besides recombination. This modification is motivated by an appreciation that neutral modifiers of recombination are probably rare. Suppose that a mutation arises that does modify the recombination rate; then how likely is it that it is strictly neutral and does not affect other aspects of the phenotype? Consider that the phenotype arises from many intertwined processes coded in the genotype; and that a change in the genotype that alters one or a few biochemical processes can be expected to alter multiple features of the phenotype. Indeed, pleiotropy is probably a universal property of nonneutral mutations, though it can be easily overlooked in population genetic models (Wright 1929; Rice and Hostert 1993). Probably most, if not all, mutations that have some effect on gene exchange also have other effects. These other effects must also partly determine fitness, though they may be strong or so slight as to be effectively neutral. More specifically it is not difficult to envision that genes that code for proteins that bind or interact with DNA may sometimes incur mutations with effects on gene exchange *and* on other aspects of the phenotype that bear on fitness. Similarly, some mutations that alter the likelihood that different genomes will come in contact will probably affect the likelihood of gene exchange, in addition to other effects that partly determine fitness.

BENEFICIAL MUTATIONS

Consider a mutation that increases the likelihood that the gene in which it lies leaves descendants. From the perspective of a gene, such a mutation is beneficial by definition, though it may not be beneficial for the rest of the genome or the organism in which it resides. Indeed, we have seen that a mutation that increases recombination, with no other effects, will be beneficial under this view. Suppose for the moment that there is free recombination and that the mutation is beneficial to the gene by some other means than recombination, such as by increasing the organism's opportunity to leave offspring. From a population perspective, and in the complete absence of linkage, we know that the probability that a new beneficial mutation goes to fixation in

a constant population of N gene copies is approximately equal to

$$\frac{1 - e^{-2s}}{1 - e^{-2Ns}}, \quad (1)$$

where s is the selection coefficient (Kimura 1962). When N is very large and s is positive, this is approximately equal to $2s$. Now consider a model, call it *model I* or *MI*, in which the mutation is beneficial to a gene by some positive effect on the larger phenotype, but the gene is linked to other genes carrying alleles that are also under selection. Under this view, Equation 1 is not accurate, and the probability of fixation is expected to be reduced because of the Hill-Robertson effect, which is tantamount to an accelerated rate of genetic drift and smaller effective population size (Hill and Robertson 1966). We can also compare this model to another, call it *MII*, that differs from *MI* only in having a higher rate of gene exchange, and thus a smaller Hill-Robertson effect. In this case the probability of fixation is expected to be higher and closer to $2s$. Thus we are considering two situations (*MI* and *MII*) with assumptions that differ only in the magnitude of the recombination rates, and the comparison reveals that beneficial mutations are more likely to fix when there is a higher recombination rate. Barton (1995) has extensively modeled the probability of fixation of a beneficial mutation, as a function of the exchange rate. These models incorporated selection at other linked loci (*i.e.*, a Hill-Robertson effect) and they reveal, for a variety of kinds of natural selection, the reduction in the probability of fixation relative to $2s$.

Again consider the models *MI* and *MII* that differ only in recombination rates, but let us alter model *MII*, call the new model *MIII*, and suppose that the higher rate of recombination in that model is not a property of the population or of all the genomes in the population, but rather is the result of a pleiotropic effect of the beneficial mutation. Both models *MII* and *MIII* consider the fate of a beneficial mutation when recombination is higher than in model *MI*, but in model *MIII* just those genomes that carry the beneficial mutation will experience the higher rate of exchange. Despite the fact that higher recombination is limited to those carrying the beneficial mutation, the effect on the probability of fixation may be the same in model *MIII* as for model *MII*, in which the entire population had a higher recombination rate. This is because the exchange events that matter most in the history of a particular mutation are those associated with genomes that carry that mutation. As with the case of the neutral modifier (Otto and Barton 1997), a new beneficial mutation that recombines early in its history will have more opportunities to become associated with genomes of higher fitness, than a mutation that must reside in the background in which it occurred. However, in the case of

the beneficial mutation, recombination leads not only to an opportunity to hitchhike with other beneficial mutations. It also causes the beneficial mutation to be present in a variety of backgrounds, which effectively permits natural selection to perceive the mutation and to be more effective.

SIMULATIONS

A computer simulation approach was taken to examine the probability of fixation of selected mutations with pleiotropic effects on recombination. Simulations assumed a small, constant size, population of haploid genomes. Each genome consisted of a large number of segments, each of which could segregate at most one mutation at a time. Unless the mutation rate was very high, this model approximated the infinite sites model (Kimura 1969). Background mutations were added randomly to the genomes each generation, and these could have either beneficial or deleterious effects. Either way, their contribution to the process was to generate a Hill-Robertson effect. Single beneficial mutations that modify the basal recombination rate were added at intervals and monitored for fixation or loss. In some respects the distinction between background and monitored mutations was arbitrary because both contribute to a Hill-Robertson effect, and both are subject to fixation and loss. However, only the monitored mutations had a modifying effect on recombination. Gene exchange was modeled by randomly forming pairs of genomes, and then for each pair generating two new genomes via reciprocal gene exchange. The number of exchanges for each pair was Poisson distributed with a mean of the basal recombination rate. If one or both of the genomes carried a modifier of exchange then the mean number of exchanges was m times the basal recombination rate. After gene exchange, the genomes were grouped by fitness, and the numbers in each class in the next generation were generated by randomly sampling from a multinomial distribution having parameters that were the expected number of individuals in each fitness class following selection. The next generation was formed by randomly drawing (with replacement) for each class the number of individuals that were specified by the multinomial random number for that class.

Figure 1 shows the results of some simulations in which a population experiences numerous selected background mutations (results for both beneficial and deleterious mutations are shown) and occasional beneficial mutations that also modify the rate of gene exchange. The probability of fixation of these beneficial mutations, relative to the case of no pleiotropic effect on exchange rate, is shown as a function of that pleiotropic effect. Mutations that increase exchange have an increased probability of fixation and those that reduce it have a decreased probability of fixation. This is true regardless of the sign of the selection coefficient on

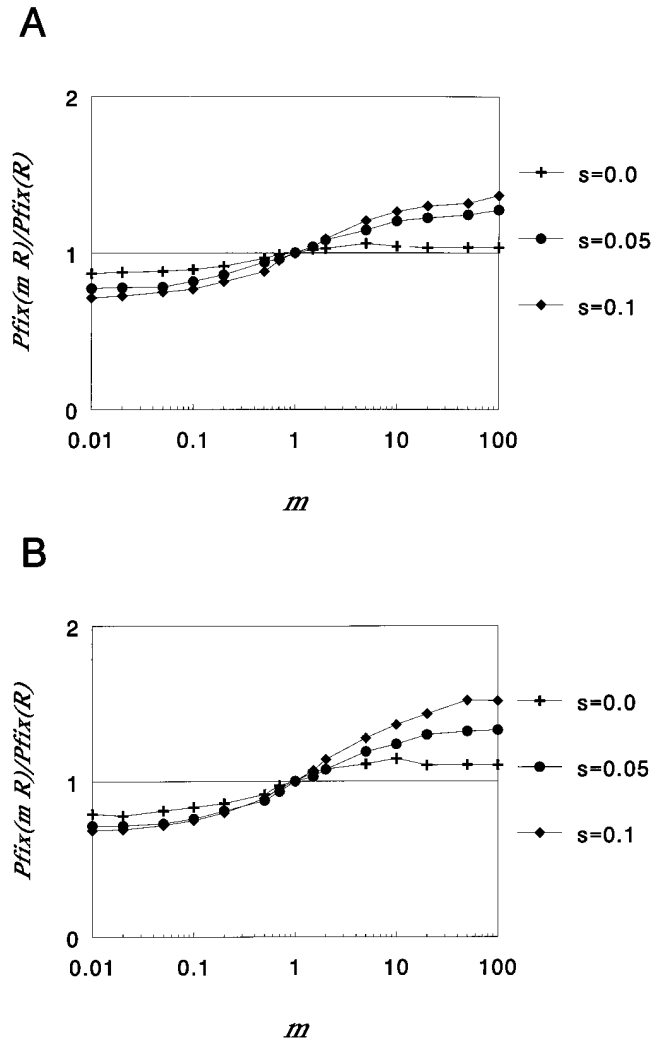


Figure 1.—The effect of recombination modification on the probability of fixation. The effect is shown by dividing the probability of fixation of a beneficial mutation that modifies the rate of gene exchange, $Pfix(mR)$, by the probability of a similar mutation with no effect on gene exchange, $Pfix(R)$. (A) The selection coefficient of background mutations (S) is -0.1 . (B) The selection coefficient of background mutations is $+0.1$. m is the amount of gene exchange modification. A value of $m = 1$ means no modification, so that all curves pass through a ratio of 1 at that point. s is the fitness of exchange modifier mutations. For all simulations, the population size was 20, the genome length was 320 units, the background mutation rate U was 0.5 per individual per generation, and the basal exchange rate, R , was 0.5 per individual per generation. Each point was estimated based on 50,000 independent exchange modifier mutations. The actual probabilities of fixation under these parameters with no exchange modification [$Pfix(0.5)$] are: 0.050 for $S = -0.1$, $s = 0.0$; 0.082 for $S = -0.1$, $s = +0.05$; 0.123 for $S = -0.1$, $s = +0.1$; 0.050 for $S = +0.1$, $s = 0.0$; 0.077 for $S = +0.1$, $s = +0.05$; and 0.105 for $S = +0.1$, $s = +0.1$. See text for additional explanation.

the background mutations, as the effect of pleiotropic modifiers is similar in deleterious (Figure 1A) and beneficial background mutation models (Figure 1B).

Figure 1 also reveals, as expected (Otto and Barton

1997), that even neutral modifiers ($s = 0.0$) of the level of gene exchange will experience a change in fixation probability. The effect of a neutral modifier is similar in kind, though less in magnitude, to that of pleiotropic modifiers with beneficial effects. Again, in a background with multiple selected mutations, a neutral mutation that increases the exchange rate is more likely to hitchhike in frequency with a beneficial mutation or haplotype than a neutral mutation that does not alter the exchange rate.

It is important to point out that the consequence of a pleiotropic effect on recombination is greater for more strongly favored mutations—the higher s is, the more a given effect on recombination will affect the probability of fixation. It should also be noted that a reduction in recombination rate reduces the probability of fixation, and that this effect is also greater for higher values of s .

Some aspects of the pleiotropic model can be compared directly with analytical results of multilocus selection models. Consider a population subject to a steady rate U of deleterious background mutations each having selection coefficient $-S$. Then there will be a balance between mutation and selection leading to an equilibrium frequency of mutations of approximately U/S (assuming a multiplicative fitness model). Barton (1995) has modeled the probability of fixation of a beneficial mutation, as a function of the basal genomic recombination rate, in this type of Hill-Robertson background. Since the recombination events that most affect the probability of fixation of the beneficial mutations are those that involve chromosomes carrying the beneficial mutation, Barton's analytical results for this model should also apply to a model in which the beneficial mutation changes the recombination rate only for chromosomes that carry it. Barton's expression (22) describes the probability of fixation under linkage effects, relative to the probability with no linkage effects. It follows that the ratio of two such expressions can be used to assess the probability of fixation with an exchange rate modifier (and linkage effects) relative to the probability without the modifier (but still with a basal rate of gene exchange and associated linkage effects). Let $\Pi(R, U)$ be Barton's expression, which is a function of the basal genome map length, R , and the deleterious mutation rate, U . Then, with Barton's expression (22a), the effect of a modifier, m , can be described with $\Pi(mR, U)$, and the effect of the modifier relative to the case without the modifier can be described by

$$\frac{\Pi(mR, U)}{\Pi(R, U)} = \frac{e^{(-2U/mR\theta)(1-1/3\theta)} / (1 + 4US)}{e^{(-2U/R\theta)(1-1/3\theta)} / (1 + 4US)} \quad (2)$$

Assume, for example and simplicity, that the magnitude of the selection against individual deleterious mutations (S) is the same as for the beneficial mutation (s), al-

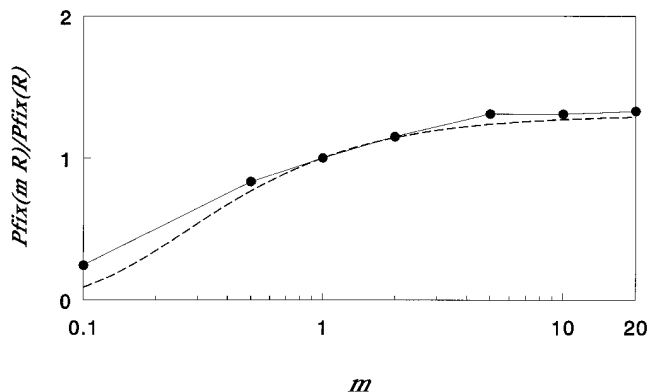


Figure 2.—Simulated and expected values for the ratio of fixation probabilities as a function of gene exchange modification. The simulated values were generated in the same manner as for Figure 1, except for the following parameter changes: population size = 100, genome length = 32,000, $R = 10$; $U = 2$; $S = -0.1$; and $s = +0.1$. The dotted line is the curve $e^{-8(1-m)/(30m)}$, which is Equation 3 with the appropriate parameter value substitutions. Each point was estimated based on 5000 independent exchange modifier mutations.

though of opposite sign. In Barton's notation this assumption is expressed by stating that $s = S$, and that θ (defined as s/S) is equal to 1. Then by substitution and simplification, (2) is equal to

$$e^{-4U(1-m)/3mR} \quad (3)$$

Figure 2 shows a good fit between results of simulations and values calculated using (3). Barton's approximation assumes a very large population size, and a value of R that is considerably greater than one. Nevertheless, we see that at least for some ranges of parameters, it applies to the pleiotropic model for very modest population sizes.

DELETERIOUS MUTATIONS

Not all mutations that leave descendants have beneficial effects, and because of stochastic effects some deleterious mutations will occasionally leave many descendants and become fixed in populations. The probability of fixation of a deleterious mutation (given by Equation 1 but with negative s) will be extremely small unless Ns is small. However, the overall rate of deleterious mutation may be high, so that there may be an appreciable fixation rate, especially for weakly deleterious mutations. If we are to allow that some beneficial mutations also modify recombination rates, then we must also consider the probability of fixation of deleterious mutations with pleiotropic effects on recombination. The expectation is that deleterious mutations associated with high recombination rates are more likely to be exposed to natural selection just as are beneficial mutations. However in this case, exposure to natural selection leads to loss of the mutation from the population. Thus we ex-

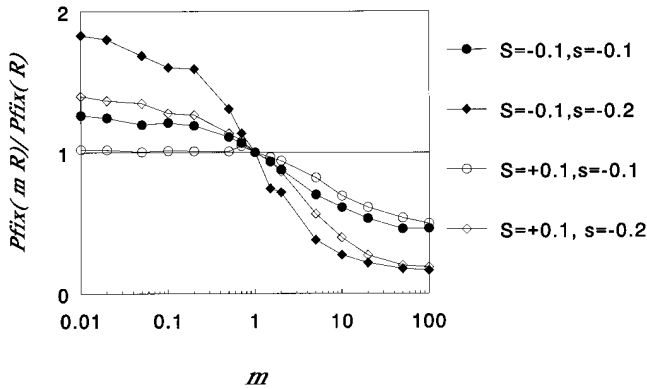


Figure 3.—The probability of fixation of a deleterious mutation that modifies gene exchange, relative to the probability of a similar mutation with no effect on gene exchange. This figure was generated in a manner identical to that for Figure 1, except the sign and magnitudes of s , the selection coefficient of the pleiotropic mutation, are different. The actual probabilities of fixation under these parameters with no exchange modification are: 0.0156 for $S = -0.1$, $s = -0.1$; 0.0039 for $S = -0.1$, $s = -0.2$; 0.020 for $S = +0.1$, $s = -0.1$; and 0.0074 for $S = +0.1$, $s = -0.2$. Each point was estimated based on 200,000 independent exchange modifier mutations.

pect that deleterious mutations that also reduce recombination will have a higher probability of fixation than those that cause an increase. Among genes with mutations that reduce the chance of leaving descendants, those with mutations that also reduce recombination are more likely to leave descendants.

The results of simulations demonstrating this effect are shown in Figure 3. Regardless of whether the background mutations are favorable or not, deleterious mutations that increase the rate of recombination have a reduced chance of fixing in the population, relative to those that have no effect. It is also important to note that deleterious mutations that reduce recombination experience an increased probability of fixation. The effect is essentially reversed from that for beneficial mutations that modify the recombination rate. The exception to this symmetry is that neutral modifiers of recombination behave like beneficial modifiers rather than having no effect (*i.e.*, both beneficial and neutral modifiers that raise recombination are more likely to be fixed; see Figure 1; Otto and Barton 1997). Also, as is the case for beneficial mutations, the stronger the selection coefficient, the greater the relative effect of recombination modification (Figure 3).

The shorthand term “escape model” can still be used to include genes with deleterious mutations that benefit from reducing recombination. In contrast to a beneficial mutation that can escape the frequently negative fitness effects of its original linkage configuration, a deleterious mutation may sometimes escape the action of natural selection on its deleterious effect by remaining in its original linkage configuration.

LEVELS OF SELECTION

Necessarily, the genes that presently exist had ancestors that were successful at leaving descendants. One approach to understanding the evolution of the ways that genes work is to consider how the successful ancestors may have differed from their unsuccessful contemporaries. We have seen that genes that carry a mutation that increases the recombination rate may experience an increased chance of leaving descendants and of becoming fixed in populations. However, this is only true if the mutation is also beneficial in other ways, or if it is otherwise neutral in its effects. If the mutation causes the gene to have a reduced chance of leaving descendants, then an additional effect of increasing recombination will further reduce the chance of leaving descendants.

At the level of the population, a general process of adaptation, whereby beneficial mutations repeatedly proceed to fixation, is expected to lead to higher rates of gene exchange. This is because those beneficial mutations that fix are expected to be enriched for a subset that also elevates rates of gene exchange. Neutral mutations that increase recombination will also be fixing at high rates when beneficial mutations are becoming fixed (Otto and Barton 1997). However, this parallel increase in population fitness and gene exchange may be offset by the fixation of deleterious alleles. Those deleterious mutations that fix are also expected to be enriched for a subset that decreases gene exchange. Whether pleiotropic effects lead to an overall increase or decrease in gene exchange rates will depend on the relative rates of fixation of beneficial and deleterious mutations, and the frequencies and magnitudes of pleiotropic effects in each group.

To help understand how population fitness and the rate of recombination may covary over the course of evolution, the major patterns evident in Figures 1 and 2 are summarized in Table 1. Mutations that fall in the lower left and upper right cells of the 2 by 2 table are more likely to become fixed, relative to the likely fate of identical mutations without the recombination modifier effect, than are the mutations that fall in the other cells of Table 1. The effect on population fitness can be seen by considering that when a mutation, having a selection coefficient s , increases in frequency and becomes fixed in the population, the mean fitness of the population necessarily changes by the same amount (*i.e.*, s). Thus we can see that with repeated mutations and fixations, a population is more likely to evolve toward high recombination and high fitness, or low recombination and low fitness, than to either high recombination and low fitness or low recombination and high fitness. If we were to plot recombination rate versus population fitness, either for multiple independent populations or for one population over time, the simple pattern in Table 1 leads to the expectation of a positive correlation be-

TABLE 1
The effect of a recombination modifier on the probability of fixation

Recombination modifier effect, m^b	Selection coefficient, s^a	
	Negative ($s < 0$)	Positive ($s > 0$)
Increase recombination, ($m > 1$)	Decrease P_{fix}^c	Increase P_{fix}
Decrease recombination ($m < 1$)	Increase P_{fix}	Decrease P_{fix}

^a s is the pleiotropic effect, the selection coefficient of the recombination modifier.

^b m is the amount of recombination modification (see Figure 1).

^c P_{fix} is the probability of fixation. The table shows the effect of a recombination modifier on P_{fix} , relative to the case without the modifier. In general, the actual value of P_{fix} will be much lower for a mutation with $s < 0$ than for one with $s > 0$.

tween recombination rate and population mean fitness. In fact it is not difficult to construct a simple mathematical model that generates predictions of the correlation coefficient (results available upon request).

DISCUSSION

Kondrashov wrote that “*randomization of population genetic structure* (meaning the effect of recombination on a population) *will be advantageous only when it increases the frequency of genotypes with many useful alleles*” (Kondrashov 1988), and it is this basic idea that has inspired many models that jointly consider the production of variation and the role of natural selection [called Variation and Selection models by Kondrashov (1993)]. Some older models were posed in terms of selection on groups of individuals. For example, Felsenstein considered several models, including the basic Fisher-Muller model, under which recombination is expected to be advantageous for the population (Felsenstein 1974). However, in some contexts these same models can be cast in terms of individual selection (Felsenstein and Yokoyama 1976). Other Variation and Selection models focus explicitly on the fate of mutations that modify recombination (Feldman *et al.* 1997). The escape theory discussed in this article, while strongly relying on the Hill-Robertson effect, is clearly a modifier theory. However, unlike many modifier theories that assume effectively infinite population sizes, the escape theory clearly falls in the class of stochastic linkage disequilibrium theories identified by Felsenstein (1974, 1988) in discussion of the Hill-Robertson effect.

The escape model of the origin of recombination, including both neutral and pleiotropic modifiers of recombination, benefits from simplicity and realism. The major assumptions are natural selection and linkage. All genomes must have some linkage—simply because DNA is a linear polymer and the genetic information lies in the sequence of nucleotides—though linkage may persist only for short times under high recombination rates. Natural selection also must be pervasive, insofar as resources are limiting and genes vary in their rate

of leaving descendants. The escape theory also seems even more plausible when pleiotropy is included, as most modifiers of recombination probably also have other effects. However, the escape theory is not without some shortcomings.

Assumptions about the directionality of modifiers: Any complete model that assumes the occurrence of mutations that modify recombination must allow that some will increase recombination and some will reduce it. Thus for example, the effect that Otto and Barton described for neutral mutations that increase recombination could be overwhelmed if for some reason neutral mutations that reduce recombination are much more common than those that increase it (Otto and Barton 1997). For the escape model with pleiotropy, the relative rates of these two kinds of mutations can have large effects on the outcomes. Although the likelihood of a beneficial mutation becoming fixed in a population is far greater than for any one deleterious mutation, it is possible that the overall rate of fixation of deleterious mutations will be higher than for beneficial mutations. If this occurs, then those deleterious mutations should also be enriched for a subset that reduces recombination. In short, the escape model that is cast in terms of the persistence of genes with recombination modifier mutations does not necessarily predict an increase in recombination rates. However, if population selection is also invoked, then the model does predict that populations that do persist will be those with higher recombination rates.

Assumptions about the covariance of modifiers and their fitness effects: The escape model also carries a partially hidden, but important assumption, that is revealed by considering the relationship between the sign of the selection coefficient and the direction of recombination modification (Table 1). In a simple analysis of this pattern, specifically one that assumes that the two properties of mutations (selection coefficient and recombination modification) are independent, a positive correlation is expected to arise between population mean fitness and recombination rate. In other words, there is an assumption that the sign of the selection

coefficient does not affect the likelihood of a particular effect on recombination. A failure of this assumption—if on average there is a negative interaction between the selection coefficient of a mutation and its effect on recombination—could undermine the model. One example would be, if engaging in recombination tends to have a direct negative effect on the likelihood that a gene will leave descendants, perhaps because it is risky or energetically expensive, then a large proportion of mutations that increase recombination may be otherwise deleterious. If this overabundance was sufficiently large, then the escape model would predict that recombination would not evolve (and thus the model would fail, at least for the majority of genomes capable of recombination).

Another example of the kind of interaction that could undermine the model is if there is a tendency for beneficial mutations that modify recombination to preferentially be reducers, and not increasers, of recombination. This situation may exist for genes in many anisogamous organisms. Consider a gene in a female of an anisogamous species and suppose a mutation occurs that halts the reduction of chromosomes in meiosis, and leads instead to eggs with a full diploid complement of chromosomes. Such a mutation will cause the gene to leave lots of descendants (*i.e.*, it is beneficial for the gene) and it will effectively stop recombination. Indeed, the frequency of anisogamy, and the possibility of mutations of this kind that could undermine it, have been much discussed as the cost of anisogamy (Maynard Smith 1971, 1978; Dawkins 1978). Such mutations do occur, giving rise to parthenogenetic lineages in the process. However, most eukaryotes are not parthenogenetic and most do engage in recombination, and to explain the persistence of both parthenogenetic populations and anisogamous recombining ones, we must invoke something beyond the escape model. One possibility is that the covariation of mutational effects, between sign of selection and the direction of effect on recombination, varies among genomes and that for most genes in most organisms, but not all, that mutational spectrum leads to the evolution and maintenance of recombination, consistent with the escape model. Another possibility that is often discussed is to invoke something outside of the escape model, and that is that the parthenogenetic populations have low long-term fitness compared to populations with recombination (see, *e.g.*, Bell 1982).

These considerations certainly bear on the usefulness of the escape model in understanding the maintenance of recombination among the very large number of anisogamous organisms. However, they do not bear directly on the evolutionary origin of recombination. The evolution of anisogamy almost certainly followed the evolution of amphimixis (the meiosis/syngamy cycle) and the escape theory is not intended to be a theory of the origin of anisogamy.

It is also important to note that there are specific

contexts in which it seems likely that mutations that elevate sex, or that contribute to circumstances that make it more likely, would be expected to have a beneficial pleiotropic effect. In particular, there are at least two models for prokaryotes in which the acquisition of foreign DNA has a direct benefit for the organism, one that includes the foreign DNA as an important component of DNA repair (Bernstein *et al.* 1988), and a second in which foreign DNA is beneficial for its nutritional value (Redfield 1993).

The sufficiency of the escape model: A final complaint that may be directed at the escape model is that the mechanism that has been described—the selective advantage to beneficial or neutral genes that engage in recombination, and the advantage to deleterious genes that avoid it—may not be sufficient to explain the origin of recombination. The process that has been identified may occur but actual mutation rates to modifiers of the appropriate kinds may be too low, or the advantage to mutations accrued by also modifying recombination may be so subtle that in the long run it cannot explain much of the recombination that occurs. Indeed, the effect described by Otto and Barton (1997) is weak for individual mutations, over much of the parameter space; and this is also true, though considerably less so, for pleiotropic mutations (Figure 1). It is also possible that other phenomena that have been mostly overlooked in this article play a larger role in the evolution of recombination than do the processes considered under the escape model. For example, the escape model does not require epistasis among selected loci, but epistasis like pleiotropy is probably a fairly ubiquitous property of nonneutral alleles. Furthermore, if epistasis and limited recombination lead to stable multilocus polymorphisms, then a mutation that increases recombination will tend to be removed by natural selection (Nei 1967; Feldman *et al.* 1980, 1997). An interesting puzzle can be foreseen in a conflict that will arise between the general phenomenon, whereby selection on multiple loci generates a Hill-Robertson effect (and favors increased recombination), and a specific form of multilocus selection that leads to stable multilocus polymorphisms (and favors decreased recombination).

Another shortcoming of the escape model is that it is difficult to test, both because it concerns quantities that are hard to measure and because it ultimately concerns a molecular behavior that evolved long ago. In particular, one of the difficulties with gauging the relative frequency and relevance of different types of pleiotropic effects is the context in which the origin of recombination probably occurred—that is, the very early stages in the origin of life (Margulis and Sagan 1986). Given the prevalence of systems of gene exchange among prokaryotes and the fact that some basic molecular components are shared by prokaryotes and eukaryotes (Shinohara *et al.* 1993; Sung 1994; Gupta *et al.* 1997), recombination was probably an adaptation that

arose (at least once, but maybe many times) early in the evolution of life.

Nevertheless, a reliance on mutations of certain kinds, and difficulties in testing, are in no way peculiar to the escape model of the origin of recombination. These are difficulties faced by every evolutionary model that has been proposed. On balance, the escape model is one that was overlooked before the work of Otto and Barton (1997), and yet it is one of the simplest of models. Given the simplicity and realistic major assumptions, the escape model seems to be a necessary component of any full theory that tries to explain the origin of recombination, and there is the chance that it is a largely sufficient theory.

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