

Genetic Scrambling as a Defence Against Meiotic Drive

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Genetic recombination has important consequences, including the familiar rules of Mendelian genetics. Here we present a new argument for the evolutionary function of recombination based on the hypothesis that meiotic drive systems continually arise to threaten the fairness of meiosis. These drive systems act at the expense of the fitness of the organism as a whole for the benefit of the genes involved. We show that genes increasing crossing over are favoured, in the process of breaking up drive systems and reducing the fitness loss to organisms.

1. Introduction

The function of genetic recombination is a matter of controversy. Some argue that it is an unavoidable side effect of certain kinds of DNA repair. Others see recombination as the function of sex. We discuss these arguments in section 2. Here we present a new argument based on conflict between different elements of the genome, that we believe provides a persistent evolutionary advantage to recombination.

The possibility that genes can gain by breaking Mendel's rules is always present during meiosis, and we posit in section 2 that potential meiotic drive systems continually arise. The main point of this paper is to argue that owing to recombination, most such systems should fail to invade. Meiosis is a crucial time for genes because the resources of a diploid cell are to be divided among haploid products. Where this division is usually equal (e.g. spermatogenesis in animals, meiosis in many protists) a gene can gain by sequestering more resources for the haploid products that contain it, or by killing other haploid products and so reducing competition for fertilizations or food. Where the division is usually unequal (e.g. oogenesis in animals, megasporogenesis in monosporic angiosperms), a gene could gain by increasing its chance of inclusion in the surviving haploid genome.

A central assumption of the argument, developed in section 3, is that many potential meiotic drive systems consist of two main loci, which we shall call the *Killer* locus, with alleles *Killer* and *Non-killer*, and the *Target* locus, with alleles *Resistant* and *Non-resistant*. Other potential drive systems involve a *Killer* locus, but a non-heritable target such as a spindle pole.

The interaction of the loci creates coupling between the *Killer* and *Resistant* alleles, which if strong enough allows *Killer* to increase in frequency. This hitchhiking effect is what is meant by meiotic drive. Both Segregation Distorter in *Drosophila* and *t*-haplotypes in mice have two main loci of this type, as we discuss in section 3.

The success of a meiotic drive system depends on tight linkage between the *Killer* and *Target* loci. Genetic systems therefore differ in their proneness to meiotic drive

according to the likelihood that two loci are tightly linked. In a one chromosome system with no crossing over, *Killer* and *Target* loci anywhere in the genome will be tightly linked. With many chromosomes but without crossing over, the two loci must be on the same chromosome. With n equally sized chromosomes, this screens candidate drive systems so that only $1/n$ have any chance of working. Our proposal is that crossing over increases the efficiency of this screening by reducing linkage between loci on the same chromosome.

We hypothesize that recombination had to evolve to allow segregation, and that the present form of meiosis reflects the strategic consequences of conflict avoidance. In sections 4–6 therefore, we discuss a range of possible *Killer-Target* interactions under various genetic systems.

Recombination result in more efficient screening against agents of meiotic drive. Such screening is of advantage to individuals, because meiotic drive systems reduce the fitness of their host organism. But this does not settle the question whether natural selection would favour an allele at a third locus that increased recombination between *Killer* and *Target* loci? The question is whether the advantage such a gene would create for individuals in general would result in any advantage to the gene itself.

The main thrust of the paper is a positive answer to this question, given for non-heritable targets in section 7, and for heritable targets in Appendix C. This answer justifies our chief conclusion that recombination may function to quell incipient drive systems. It may seem eccentric to base an explanation of the widespread phenomenon of crossing over on the minor deviant habit of meiotic drive. Hartl (1977), however, argues that meiotic drive systems are likely to be widespread as they have been found in all genetically well-studied species, citing 20 examples, three in *Drosophila melanogaster* alone.

By introducing intragenomic conflict, our model reverses the general finding that fitness interactions among loci favour reduced recombination (Feldman, 1972; Feldman & Liberman, 1986). It is anchored in the genome, not in the highly variable realm of ecology, and can offer a simple and uniform explanation of crossing over. Thus, we have suggested an explanation for recombination given that sex exists. If the primary function of sex is not recombination, in line with DNA repair models (Bernstein *et al.*, 1985, 1988), our model can explain why recombination exists. If the long term advantage of sex is recombination, our model may provide important short-term advantages that overcome the short-term disadvantages of disrupting favourable gene combinations (Feldman & Liberman, 1986).

2. The Problem of Segregation without Recombination

The life cycle of sexual eukaryotes alternates between haploid and diploid stages. Two haploid nuclei unite to form a diploid nucleus. Then, at some later stage, haploidy is restored by the regular segregation of homologues. In this paper, *segregation* will refer to any reductional process in which the two copies of a locus present in a diploid each end up in a haploid product. Among eukaryotes, segregation

is variously achieved by a single reductional division (one-step meiosis) or by a sequence of two divisions (two-step meiosis) (Raikov, 1982). The haploid genomes that are generated by segregation usually contain genes from both parental haploids. We will refer to this mixing of genes from different sources as *recombination*, even if the parental haploids are genetically identical. We will refer to the combination of segregation and recombination as *segregational sex*, or *sex* for short.

Recombination can occur without segregation. In bacterial conjugation, one cell donates part of its genome to a recipient. The donor sequence is sometimes able to substitute itself for the homologous sequence of the recipient genome (Levin, 1988). Similarly, segregation can occur without recombination. Two haploid genomes could unite to form a temporary diploid partnership, and then dissolve the partnership to form new partnerships with different haploids, without there being any mixing of genes. Such a segregational cycle occurs in some basidiomycetes, in parallel with a more conventional cycle involving recombination (Martens & Vandendries, 1932; Nobles, 1935). Nevertheless, it is probably true to say that segregation is usually associated with recombination.

The association between segregation and recombination in eukaryotes would be explained if sex has evolved or is maintained for purposes of recombination (for a discussion of models see Felsenstein, 1988). On the other hand, Bernstein *et al.* (1985, 1988) have argued that the sexual cycle of fusion (karyogamy) and reduction (meiosis) has evolved to enable effective DNA repair. In the extreme version of this hypothesis, recombination is an incidental consequence of the repair mechanism. In this paper, we present a different perspective. We argue that segregation, for whatever purpose, would be evolutionarily unstable without recombination. Therefore, if alternation between haploid and diploid phases evolved for some function other than recombination, this function would automatically have created a selective requirement for recombination. We wish to emphasize that we are not passing judgement on whether recombination, repair, or something else is the principal adaptive function of sex.

Consider a hypothetical life cycle in which haploid cells conjugate for purposes of DNA repair and then separate without recombination. After repair, either genome could benefit from gaining sole control of the combined resources of the two cells. Such a system is clearly vulnerable to the evolution of sexual parasites that participate in mutual repair and then devour their partner. The partners in a transient diploid are confronted with a dilemma. Both would benefit from repair with fair segregation, but either could gain a greater benefit from parasitizing its partner's cell, provided (of course) that its partner was not also a parasite. If we assume that the partners do worse on average when both are parasites than when both are non-parasites, then we have a version of the familiar Prisoner's Dilemma (Axelrod, 1984). The only stable outcome is a population of parasites, even though the members of such a population are worse off than if all were non-parasites.

The above scenario presupposes that parasitic genomes are possible. A simple form of parasitism could occur if sexual repair proceeds normally, but one cell attacks its sister after segregation. More subtle forms of parasitism could involve one genome disabling its partner during the repair process to make the partner

vulnerable to attack after segregation. For example, a sexual parasite could incapacitate the opposite centrosome, damage one of its partner's chromosomes, deposit a lethal substance in the other half of the diploid's cytoplasm, or release a toxin for which it carries an antidote. If this superficial analysis is accepted, it is difficult to see how sexual repair could have evolved.

In this paper, we argue that most of the stratagems by which one genome could exploit its partner become self-defeating in the presence of recombination. Meiosis cannot be exploited by most kinds of sexual parasite, because recombination creates uncertainty about which genes will be associated together after segregation, and about which pole a gene will move towards at segregation. Thus, recombination avoids the Prisoner's Dilemma. Recombination not only changes the rules of the game, but also changes the definition of the players. In the absence of recombination, the relevant strategists are entire haploid genomes but, in its presence, the strategists are smaller genetic units.

3. Killers and Targets

First, consider a simple scenario of sexual parasitism, in which a *Killer* allele acts in the diploid phase to cause lethal damage to an intracellular target. After segregation, the damaged target causes the death of the cells with which it segregates. The dead cells are then cannibalized by the surviving cells. *Killer* can only exploit *Non-killer* when the two occur in a heterozygote. *Killer* wins if the damaged target segregates with *Non-killer*, but loses if the damaged target segregates with *Killer*.

We will assume that *Killer* alleles can arise at any position in the genome and damage a target that is one member of a pair of entities that segregate to different cells at a sexual division. Such pairs include the two copies of a locus, a pair of homologous centromeres, the two centrosomes, or the two halves of the zygote's cytoplasm. A target pair can be likened to a "locus" at which there are target and non-target alleles. The evolutionary problem for a *Killer* is whether there is any way to "choose" which member of a pair to damage.

A *Killer* can distinguish between targets and non-targets by a heritable or a non-heritable criterion. We will refer to the cellular location of a target pair as a *target locus* if the distinction between targets and non-targets is heritable, but as a *target site* if the distinction is non-heritable. An example of a heritable criterion would be if a *Killer* produces a lethal factor for which there are *Resistant* and *Non-resistant* alleles at the target locus. By this means, *Killer* would create a selective pressure favouring the *Resistant* allele at the other locus. *Killer* might be able to increase in frequency because it is preferentially associated with *Resistant*. Linkage disequilibrium arises because *Killer-Non-resistant* genomes are lethal.

The two best understood examples of meiotic drive exploit this hitchhiking effect. These are the Segregation Distorter system of *Drosophila* (Charlesworth & Hartl, 1978) and the *t*-haplotype system of mice (Silver, 1985). In both systems, the killer and target loci are closely linked: *Sd* (killer) and *Rsp* (target) on *Drosophila* chromosome 2, and *Tcd* (killer) and *Tcr* (target) on mouse chromosome 17. Linkage between killer and target loci is reinforced in both systems by inversions that function

as dominant suppressors of recombination. As Charlesworth & Hartl (1978) recognized, segregation distortion could not have become established in *Drosophila* without tight linkage between *Sd* and *Rsp*. Put another way, recombination is an obstacle to the invasion of *Killer* alleles. From this perspective, *Sd* and *Tcd* have been able to slip through the genome's defences because they are tightly linked to their targets, but recombination has probably prevented the accumulation of similar *Killers* with target loci at distant chromosomal locations. Furthermore, the association of killer and target loci within inversions has prevented natural selection from eliminating these meiotic drive systems by increasing recombination between the loci (see section 7 below).

Killers that employ a non-heritable criterion rely on positional information or some temporary "imprint" to distinguish between target and non-target "alleles". An example of positional information would be if a *Killer* damaged the copy of a locus on the opposite side of the metaphase plate, independently of its DNA sequence. In this case, the target site is also a genetic locus but this is not a necessary feature of target sites. An example of a temporary "imprint" is provided by the elimination of paternal chromosomes during male meiosis in mealy bugs. Paternal chromosomes are marked for elimination after syngamy in the egg cytoplasm (Chandra & Brown, 1975). The maternal chromosomes that are preferentially included in sperm in one generation may be eliminated as paternal chromosomes in the next generation. A *Killer* that employs a heritable criterion could sometimes find itself in a zygote without a target (a *Resistant* homozygote), whereas a *Killer* that employs a non-heritable criterion will generally have a target at each sexual division.

We present models below in which recombination provides a defence against some simple forms of exploitation that would be successful in the absence of recombination, but we do not attempt to describe all possible forms of sexual parasitism. Falsification of our argument requires a demonstration that the kinds of parasitism we describe would have been unfeasible in early eukaryotes, not a demonstration that some specific forms of sexual parasitism do not fit our models. We emphasize the relative fitness of *Killer* and *Non-killer* alleles in heterozygotes rather than their relative fitness in homozygotes because we are primarily interested in whether recombination alters the likelihood that a newly arisen *Killer* allele will be able to invade a population of *Non-killers*. Our emphasis in the main body of the text is on *Killer* alleles that employ non-heritable criteria to distinguish between targets and non-targets. Dynamic models of systems based on *Killer* alleles with heritable targets are analysed in Appendices A-C.

4. One-step Meiosis

Consider a hypothetical case of one-step meiosis, non-heritable targets and random conjugation, in which two haploid gametes conjugate to produce a diploid zygote. The zygote then divides to produce two haploid cells. Let the frequency of recombination between a *Killer* and its target be r . If two *Non-killers* conjugate, each receives a unit payoff. If a *Killer* and *Non-killer* conjugate, the survivor receives

a payoff a , where $1 < a < 2$, and the non-survivor receives zero. If two *Killers* conjugate, each receives a payoff b , where $b < 1$. The payoff matrix is given in Table 1. If $r = 0$, this matrix describes a Prisoner's Dilemma in which *Killer* does better than *Non-killer* at all gene frequencies. Recombination alters the payoffs from heterozygous matings because *Killer* sometimes segregates with the damaged target. As r increases, the payoff to *Killer* decreases as the payoff to *Non-killer* increases, until both receive $a/2$ when $r = 1/2$.

TABLE 1

The payoffs to different alleles at the Killer locus in the game theoretic model for fixed recombination given in the text

Payoff to	Paired with	
	<i>Non-killer</i>	<i>Killer</i>
<i>Non-killer</i>	1	ra
<i>Killer</i>	$(1-r)a$	b

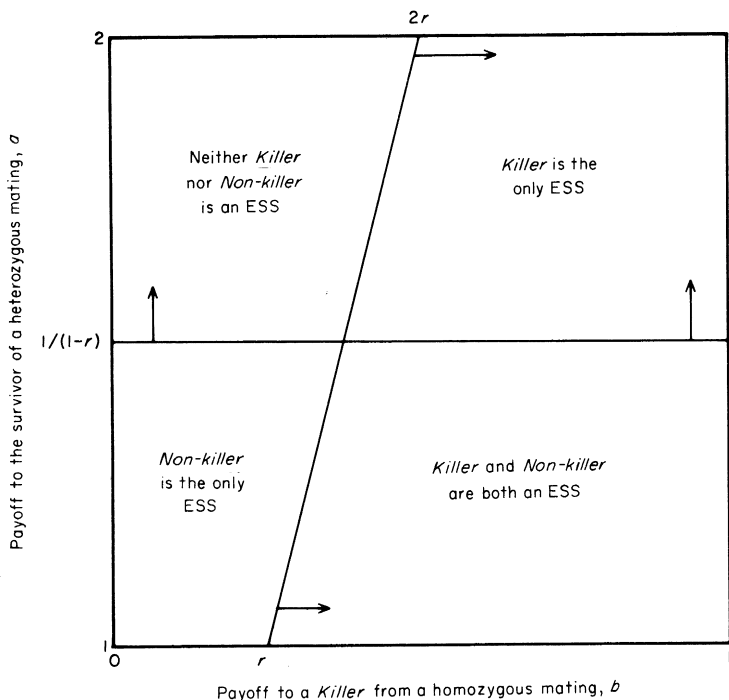


FIG. 1. Outcome of the *Killer* vs. *Non-killer* game for different values of a and b . *Killer* can invade a population of *Non-killers* for values to the right of the oblique line, $b = ra$. *Non-killer* can invade a population of *Killers* for values below the horizontal line, $a = 1/(1-r)$. The arrows indicate how the positions of these lines change as r increases.

A *Killer* can invade a population of *Non-killers* if $r < (a-1)/a$, whereas a *Non-killer* can invade a population of *Killers* if $r > b/a$. These conditions define the four possible outcomes of the evolutionary game (Fig. 1). *Killer* is the only evolutionarily stable strategy (ESS) when $r=0$, but *Killer* ceases to be an ESS for sufficiently high recombination ($r > b/a$). For values of r between b/a and $(a-1)/a$, a population of *Killers* and a population of *Non-killers* are both stable against invasion by the other allele provided that $b > a-1$, but neither is stable against invasion if $b < a-1$. In the latter case, an equilibrium population contains both alleles. When the *Killer* locus and target site assort independently ($r=1/2$), *Non-killer* and *Killer* are both ESSs if $b > a/2$, but *Non-killer* is the only ESS if $b < a/2$. We only consider stability conditions for $r \leq 1/2$, because segregation becomes vulnerable to *Killer* alleles with the opposite choice of target when $r > 1/2$.

This model has a simple interpretation. If linkage is complete, *Killer* has perfect information about its own segregation relative to the target site, but *Killer* has no information when it assorts independently of the target site. As r increases (up to $1/2$), *Killer* has less and less information with which to gain an advantage over *Non-killer*. For the cases of heritable targets analysed in the appendices, the information available to a *Killer* is measured by the linkage disequilibrium between the *Killer* and *Target* loci. Appendix A analyses a model with no recombination between *Killer* and *Target* loci. Appendix B analyses a model with fixed recombination. These appendices show that there is always some critical value of r (less than $1/2$) above which a *Killer* allele with a heritable target cannot invade a population of *Non-killers*.

5. Two-step Meiosis

Now, consider a simple scenario with two-step meiosis, random segregation and non-heritable targets. Two haploid gametes with replicated chromosomes conjugate to produce a diploid zygote. Then, this zygote divides twice to produce four haploid cells with unreplicated chromosomes. There are now two divisions at which a *Killer* and its target may segregate to different cells. Segregation at the *Killer* locus can be equational at the first division and reductional at the second division, or vice versa. The same applies to the target site. If the *Killer* locus and its target site are located on the same pair of chromosomes and there is no crossover between them, the two "loci" will segregate reductionally at the same division. Otherwise, they will segregate reductionally at different divisions.

Whether the first or second division is reductional for a locus depends on whether there is a crossover between the locus and the centromere, because centromeres always segregate reductionally at the first division. At loci distal to a single crossover, the first division is equational and the second division reductional. At loci proximal to crossovers, the first division is reductional and the second division equational. (A division is reductional if the two parental alleles at a locus segregate to different daughter cells. Otherwise the division is equational, and the daughter cells receive a copy of both alleles at the first division or a copy of the same allele at the second division. Proximal and distal refer to a locus's position relative to the centromere.)

We have assumed that the *Killer* locus and its target site are linked, because a *Killer* with an independently assorting target has no advantage over *Non-killer* in heterozygotes.

Three kinds of alleles at *Killer* loci are considered below: *TetradKillers*, *DyadKillers*, and *LateKillers*. *TetradKillers* damage their target before the first division, but have their lethal effect after the second division. In heterozygotes, a *TetradKiller* goes to two of the four haploid products, and two of the four products carry a damaged target. *TetradKiller* "wins" when present on a chromatid that does not recombine between the *Killer* locus and the target site, but "loses" when present on a chromatid that does recombine. The ESS analysis is essentially the same as for a *Killer* in one-step meiosis (see above).

DyadKillers cause damage at their target site before the first division, and this damage has its lethal effect before the second division. The opportunities for a successful *DyadKiller* are limited, because a *DyadKiller* cannot do better than its *Non-Killer* allele in heterozygotes if either the *Killer* locus or the target site segregates equationally at the first division. Equational segregation of the target site ensures that both products of the first division get a copy of the target, independently of whether the cells contain the *DyadKiller*, the *Non-killer*, or both. Similarly, equational segregation at the *Killer* locus ensures that both products of the first division contain the *DyadKiller* and its *Non-killer* allele. Only one crossover is necessary in the region that encompasses the *Killer* locus, target site and centromere to make a *DyadKiller* ineffective. Thus, two-step meiosis is only exploitable by *DyadKillers* that are tightly linked to their target site and the centromere.

LateKillers do not damage their target until after the first division. A *LateKiller* can only gain an advantage over *Non-killer* in those heterozygotes where the *Killer* locus segregates equationally at the first division. That is, there must be a crossover between the *Killer* locus and the centromere if the sister cells of the second division are to carry different alleles at the *Killer* locus.

Crossing over may be a particularly effective defence against *Killers* that attack one of the poles of a dividing cell as their target, because it creates uncertainty about which division will be reductional at the *Killer* locus and about which pole a *Killer* will move towards at anaphase. Among its other functions, the synaptonemal complex may conceal information about which genes are attached to which centromeres. As a consequence, orientation on the metaphase plate provides poor information about the likely pole of segregation for most loci. Genes closely linked to the centromere are an exception.

6. *SisterKillers* and an Advantage of Two-step Meiosis

From the previous discussion it is tempting to speculate that the greater complexity of two-step meiosis makes it less vulnerable than one-step meiosis to the evolution of *Killer* alleles. However, it could also be argued that the greater complexity provides more opportunities for parasitism. We believe that two-step meiosis is protected against a plausible class of *Killer* alleles that would be able to exploit one-step meiosis.

Consider a *SisterKiller* that causes its own cell to attack its sister cell after a sexual division. In the case of one-step meiosis, recombination provides no protection against *SisterKillers* because the two cells produced from a heterozygote will necessarily carry different alleles at the *Killer* locus. This corresponds to the payoff matrix in Fig. 1 when $r = 0$. In effect, the *Killer* locus is the target site. However, recombination does provide some protection against *SisterKillers* in two-step meiosis because either division can be reductional at the *Killer* locus depending on whether a crossover occurs between this locus and the centromere. A *SisterKiller* that acted after Meiosis 1 would be attacking a cell that contained a copy of itself whenever the first division was equational at the *Killer* locus, whereas a *SisterKiller* that acted after Meiosis 2 would be attacking a cell that contained a copy of itself whenever the first division was reductional.

7. Selection for Recombination

Our models so far have shown that a *Killer* allele is less likely to invade a population of *Non-killers* if there is recombination between the *Killer* locus and its target site. However, we have not yet shown that this advantage to *Non-killer* alleles favours genes at a third locus that increase r . Appendix C deals with the evolution of recombination rates in greater detail for heritable targets, and shows that selection does indeed favour higher recombination when targets are heritable. Here we briefly discuss the evolution of recombination between a *Killer* locus and its target site for the special case where the modifier of recombination assort independently of the *Killer* locus and the special case where the modifier of recombination is in complete linkage to the *Killer* locus. We assume that the *Killer* locus and target site are linked, because otherwise there can be no advantage to *Killer* alleles.

Our argument can be simply stated. From the point of view of the *Killer* or *Resistant* alleles, being in a *Killer-Resistant* genome may be no bad thing. They enjoy the fruits of drive, which decreases the overall productivity of the mating, but more than compensates the *Killer* and *Resistant* alleles by preferentially placing them in the surviving haploids. But for an allele at an unlinked locus, the reduced productivity associated with meiotic drive is simply disadvantageous, because the allele is equally distributed between the surviving and dying haploids. It follows that alleles at the third locus lose when in a *Killer-Resistant* genome, and so are selected to increase crossing over and increase their chance of joining a *Non-killer-Resistant* genome instead. This informal argument shows the effect to be a very general one. It results from the difference in transmission rules for the third locus and the driving loci, and is in the general direction that whatever increases organismic fitness will be selected at the third locus.

More formally, consider the effect of selection on alleles at a recombination locus, *Crossover*. Alleles at this locus influence r , the probability of recombination between a *Killer* and its target, but are otherwise selectively neutral. *Cross*⁺ alleles increase r and *Cross*⁻ alleles decrease r . Such alleles affect the outcome of meiosis only in heterozygotes at the *Killer* locus. If *Crossover* is in complete linkage with the *Killer* locus, *Cross*⁺ will be favoured if linked in coupling to a *Non-killer* allele, whereas

$Cross^-$ will be favoured in coupling to a *Killer* allele. This is because recombination causes *Killer* to segregate with the damaged target, and thus favours *Non-killer* (see Table 1).

If *Crossover* assorts independently of *Killer*, *Crossover* also assorts independently of the target. Therefore, a gene at the *Crossover* locus will be present in 50% of surviving products of a heterozygote for all values of r . However, the greater the value of r , the greater the proportion of survivors carrying the *Non-killer* rather than *Killer* allele, and an allele at the *Crossover* locus has different expected fitness at the next meiosis when present in *Non-killer* and *Killer* gametes (Table 2).

TABLE 2

The payoffs to alleles (possibly affecting recombination) at an unlinked locus in the game theoretic model of recombination given in the text

Payoff to a gene that assorts independently of the target site, in a gamete carrying	Paired with	
	<i>Non-killer</i>	<i>Killer</i>
<i>Non-killer</i>	1	$a/2$
<i>Killer</i>	$a/2$	b

A *Killer* entering a population of *Non-killers* always favours $Cross^+$ alleles at an unlinked modifier locus because $a/2 < 1$ (by assumption of the model). Selection for increased r will reduce the likelihood of successful invasion by the *Killer*. If $b < a/2$, a gene at an unlinked *Crossover* locus always has higher fitness in a *Non-killer* gamete, and selection will favour $Cross^+$ alleles at all non-zero frequencies of the *Non-killer*. In the absence of constraints on the free evolution of recombination, r should increase under selection until the *Killer* is eliminated from the population.

The model's predictions are less straightforward if $b > a/2$, because a gene at an unlinked locus has higher fitness in a *Non-killer* gamete when the gamete's partner is also a *Non-killer*, but has lower fitness when the partner is a *Killer*. Therefore, unlinked $Cross^+$ alleles will tend to increase in frequency when *Non-killer* is common, but decrease in frequency when *Killer* is common. A *Killer* entering a population of *Non-killers* will initially favour $Cross^+$ alleles, but, if the *Killer* can attain sufficiently high frequency, selection at the *Crossover* locus will be reversed. This is a two locus problem and is not analysed in this paper. Appendix C analyses the analogous problem for heritable targets (a three locus problem) and concludes that selection favours $Cross^+$ alleles.

Suppose that genes at most *Crossover* loci increase or decrease the probability of crossing-over for all chromosomal regions. This is more economical than having separate modifiers of recombination for smaller genomic segments. If the genome consists of several independently assorting chromosomes, most new *Killers* will be unlinked to any given *Crossover* locus. Therefore, it will usually be disadvantageous for an allele at the *Crossover* locus to occur in a gamete with a newly-arisen *Killer*. An allele that increases crossing-over throughout the genome will be favoured,

because it increases the probability that *Killers* will segregate with their damaged targets, and therefore increases its own chances of occurring in surviving gametes without *Killers*.

8. Examples of Segregation without Recombination

We have argued above that fair segregation is inherently unstable in the absence of recombination. Therefore, our model appears to be contradicted by situations in which pairs of homologues segregate without crossing over. In this section we discuss examples of achiasmatic segregation and show that, in some cases at least, alternative mechanisms exist that perform the protective functions we ascribe to recombination.

The non-pairing regions of sex chromosomes regularly segregate without recombination during meiosis in the heterogametic sex. Such a system should be particularly vulnerable to sex-linked *Killers*, because an X-linked *Killer* would never segregate to the same cell as a Y-linked target, nor would a Y-linked *Killer* segregate to the same cell as an X-linked target. This may explain why the sex chromosomes are often inactivated and heterochromatic during the critical stages of meiosis in the heterogametic sex. Thus, Lifschytz & Lindsley (1972) have noted that the X chromosome is usually heterochromatic during spermatogenesis in species with heterogametic males. The behaviour of X chromosomes in eutherian mammals is particularly instructive. In male eutherians, the X and Y chromosomes are sequestered in a transcriptionally inactive "sex vesicle" before synapsis of the autosomes. By contrast, female germ cells contain one active and one inactive X chromosome, but the inactive X is reactivated before oogenesis (Gartler & Riggs, 1983). In oogenesis, the two X chromosomes can crossover along their entire lengths and are thus protected against most potential *Killers*.

Some insects appear to have evolved additional mechanisms to prevent sex-linked drive in the absence of crossing over. Males of the crane fly *Tipula lateralis* are XY. During prometaphase, the sex univalents shuttle to and fro across the equator but only move to their definitive poles some minutes after the autosomes have segregated (Dietz, 1956). In the grasshopper *Melanoplus differentialis*, males are XO. The univalent X moves backwards and forwards between the poles an unpredictable number of times and spends an unpredictable length of time at each pole between trips. The autosomes only segregate after the X has completed a trip and the primary spermatocyte promptly divides (Nicklas, 1961). These behaviours could have simple mechanical explanations, but still function to create uncertainty until the last moment as to which pole a sex chromosome will segregate.

Several taxa have done without crossing over altogether in one sex. In all cases where meiosis is chiasmatic in one sex but achiasmatic in the other, it is the heterogametic sex that is achiasmatic (Bell, 1982). The problem of *Killers* with heritable targets is less acute for autosomes than for the sex chromosomes because crossing over in the homogametic sex reduces linkage disequilibrium between *Killer* alleles and resistance factors. However, recombination in the other sex does not protect against autosomal *Killers* which attack non-heritable targets.

The association of achiasmatic meiosis with the heterogametic sex could be

explained if one of the functions of crossing over is to protect against meiotic drive. As we have argued above, the heterogametic sex is expected to have evolved special mechanisms to ensure fair segregation of the sex chromosomes, and these mechanisms might also be adopted for segregation of the autosomes, making the protective function of crossing over redundant. Trivers (1988) has made the alternative suggestion that heterogamety will tend to evolve in that sex in which natural selection favours lower rates of recombination.

During prometaphase, bivalents of most species achieve bipolar orientation immediately on attachment to the spindle, because their chromosome structure is such that if one half-bivalent's kinetochores face one pole, those of its partner face the opposite pole (Nicklas, 1974). Perhaps significantly, the behaviour of kinetochores in the achiasmatic meiosis of *Drosophila* males differs from this usual pattern. During early prometaphase, each half-bivalent's kinetochores form a single hemispherical structure that allows simultaneous attachment to microtubules from both poles (Goldstein, 1981; Church & Lin, 1985). Moreover, bipolar orientation of a bivalent, once established, is frequently disrupted by simultaneous reorientation of homologous kinetochores to the opposite poles (Church & Lin, 1985). We do not know whether such behaviour is typical of species with achiasmatic meiosis, nor whether kinetochore behaviour in the chiasmatic meiosis of female *Drosophila* is similar to that in males. In the absence of crossing over, stable orientation on the metaphase plate would mean that any chromosome or other structure in the opposite half of the cell would be a stationary target for a *Killer* allele.

Among basidiomycete fungi, compatible homokaryons exchange haploid nuclei to form a stable dikaryon which often has a growth advantage over either homokaryon (Raper, 1966). Presumably, the two haploid genomes complement each other's biochemical weaknesses in a manner analogous to diploidy, though there is no nuclear fusion in the vegetative mycelium. The problem of fair segregation arises in the production of haploid dispersal structures. In general agreement with our model, dissolution of the dikaryon is usually achieved by the sexual production of basidiospores, which takes place in specialized basidia (the only diploid cells of the life cycle). The haploid partners fuse, immediately undergo meiosis with recombination, and then each of the four products of meiosis enters a basidiospore.

However, the dikaryons of some basidiomycetes form haploid oidia or conidia without karyogamy and recombination. We have found reports of fair as well as unfair segregation of nuclei into oidia. Both nuclear types are present in haploid oidia collected from dikaryons of *Collybia* but one nuclear type predominates and all oidia from individual compartments of the mycelium are of a single nuclear type (Aschan, 1952; Aschan-Åberg, 1960). Thus, this is a case of unfair segregation in the absence of recombination.

On the other hand, both nuclei from dikaryotic cells of *Peniophora* and *Corticium* enter an oidiophore and divide synchronously before forming oidia (Nobles, 1935, 1942). The segregation of a morphological mutant suggested a 1:1 ratio of the two nuclear types among oidia (Nobles, 1935). Similarly, in *Pholiota* dikaryons, a pair of nuclei enter a conidium, and a septum forms between them to produce two uninucleate cells. The cells are dispersed individually and germinate to produce a homokaryon, or are dispersed as pairs and germinate to re-establish the dikaryon

elsewhere (Martens & Vandendries, 1932). These cases of fair segregation without recombination are a challenge to our hypothesis and require further study. The natural history of these fungi would also provide a potentially useful test for theories of sex because the same dikaryon can produce haploid basidiospores by meiosis and haploid oidia without pairing for repair or recombination.

9. An Uneasy Partnership

Diploidy can be viewed as a temporary partnership between the two haploid genomes, or between the two copies of a locus, that join together at syngamy. Presumably, there are benefits to be gained from entering the partnership, but there are also dangers of being exploited when the partnership is dissolved. We have argued above that one effect of recombination and genetic scrambling is to reduce the information available to genes which they could use to exploit segregation. Specifically, we propose that most systems of meiotic drive involve an interaction between two kinds of loci which we have called killer and target loci. The success of a meiotic drive system depends on tight linkage between a particular *Killer* and its *Target* locus. With unlinked loci, *Killer* would kill itself as often as it killed *Non-killer*.

Put in other words, recombination prevents the evolution of most potential drive systems with heritable targets because crossing over breaks up coalitions of genes that could subvert the process of meiosis for their own ends. Natural selection favours alleles at unlinked loci that increase recombination between killer and target loci, because unlinked genes cannot benefit from segregation distortion at the target locus but do suffer from all the costs of meiotic drive. This contradicts the general conclusion that fitness interaction among loci favour reduced recombination (Feldman, 1972; Feldman & Liberman, 1986). However, such models have assumed that meiosis is fair and that interactions among loci have their effect on organismal fitness rather than on conflict within the genome. The tight linkage between killer and target loci in the few successful systems of meiotic drive has meant that segregation distortion has often been modelled as a single locus that combines killer and target functions. As a consequence, the protective function of crossing over has been neglected in models of the evolution of recombination.

These ideas have different implications for the two major groups of theories that attempt to explain the selective advantage of sex. If sex has evolved for purposes of recombination, protection against meiotic drive might be no more than a fortuitous side-effect of recombination though it could also provide a short-term advantage to counter short-term disadvantages caused by breaking up temporarily favourable gene combinations. It is an interesting question, though beyond the scope of the present paper, as to what balance will be struck between these opposing selection pressures on the recombination rate. On the other hand, if sex has evolved for purposes of genetic repair, we have identified a reason why sexual repair should be associated with recombination. Some such explanation is necessary, because gene conversion (repair without crossing over) and reciprocal exchange (repair with crossing over) are under partially independent genetic control (Carpenter, 1987; Engebrecht *et al.*, 1990).

The idea that the fairness of meiosis is somehow related to avoiding intragenomic conflict is not original with us. A number of authors (Leigh, 1987: 244; Crow, 1988: 71; Williams, 1988: 291) have recognized the advantages to be gained by the fairness of meiosis, but were uncertain as to how selection at the genetic level could bring it about.

Equally, recombination has been modelled before in the context of meiotic drive. Thompson & Feldman (1974) considered a drive locus (D), a neutral modifier of the intensity of drive (M) and a third locus (F) that controlled recombination between D and M . They found that crossing over is sometimes selected to increase, and sometimes to decrease. In terms of our model in Appendix 3, their D corresponds most closely to our *Target* locus and their M to our *Killer* locus, but the correspondence is by no means exact. One implication of their condition (6) is that selection at an unlinked F always favours increased recombination between D and M . We believe that our formulation has the conceptual advantage that a meiotic drive system is viewed as a coalition of genes at two loci rather than as a single drive locus with modifiers. First, the evidence is that meiotic drive systems do in fact consist chiefly of two loci like our *Killer* and *Target* loci, neither of which is neutral. Second, the idea that coalitions will arise in the absence of recombination provides a simple consistent advantage to crossing over. We have also argued that we should expect *Killer-Target* systems to be widespread, and that effects on meiotic drive systems may be the chief selective force at work increasing recombination rates.

Frank (1991) and Hurst & Pomiankowski (1991) have also made the link between meiotic drive and recombination. These authors develop an argument parallel to our own, namely that meiotic drive agents and their suppressors should be particularly prevalent where there is little recombination. Wu & Hammer (1991) have emphasized that meiotic drive mechanisms probably always involve interactions between two or more loci that must be tightly-linked.

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APPENDIX A

No Recombination

In this appendix we analyse a simple model with heritable targets. It serves to introduce important concepts for later appendices, in which recombination is introduced, as well as having some intrinsic interest. This first model is very similar to Charlesworth & Hartl's (1978) model, except that drive in their model is restricted to males. The models in all three appendices are of continuous reproduction, as this case is easier to analyse.

Our model of meiotic drive assumes that two loci are involved, which we shall call the *Killer* locus and the *Target* locus, whose wild-type alleles are *Non-killer* and *Non-resistant*, respectively. The idea is that an allele *Killer* can arise at the *Killer* locus that causes haploid products to die at the end of meiosis unless they carry an allele *Resistant* at the *Target* locus. The death of some haploid products benefits the survivors in some way: either by the acquisition of resources from the dead haploids, as might occur in protists, or by reduction of competition for fertilizations, as occurs in the Segregation Distorter system of *Drosophila* and the *t*-haplotype system in mice. The possession of *Resistant* is assumed to impose a viability cost, as compared with its allele *Non-resistant*. The presence of *Killer* in the population creates an advantage to *Resistant*, but no direct advantage to *Killer*. For *Killer* to gain, it must therefore be linked in coupling with *Resistant*. Coupling can come about only through a combination of linkage and selection.

We envisage that the *Killer* and *Target* loci are loci involved in meiosis with specific functions that are subverted when the *Killer* allele arises. Meiosis is a delicate

TABLE A1

This table gives the relative viabilities of gametes produced in matings in which the Killer and Target loci do not recombine. In matings apart from N/K matings where the two loci do recombine, the products of meiosis are the same, and in the same ratios, as the two contributing gametes. In N/K matings with recombination, half the products survive, and are R gametes with relative viability 1+j. In the model analysed in Appendix C there is a Crossover locus unlinked to the Killer and Target loci. The probability of recombination is r_0 in Cross⁻/Cross⁻ matings, r_1 in Cross⁻/Cross⁺ matings, and r_2 in Cross⁺/Cross⁺ matings

Viability of	When paired with		
	N	R	K
N	1	1-w	0
R	1-w	1-2w	1-v-2w
K	1+j	1-v-2w	k

time for genes, with much to gain and lose by foul play. There is scope for loci involved in meiosis to play the roles of *Killer* and *Target* loci in a meiotic drive system. The potential for drive was probably a serious handicap to the original evolution of meiosis, whatever its starting point, and it is our hypothesis that incipient drive systems continue to provide a strong selective advantage for recombination.

Our models are based on an imaginary protist life cycle, in which haploid organisms occasionally meet and meiate. There are three chromosome types in the population, if we consider only the *Killer* and *Target* loci: *Killer-Resistant*, *Non-killer-Non-resistant*, and *Non-killer-Resistant*, which for brevity we shall refer to as *K*, *N* and *R*, respectively, for *Killer*, *Non-resistant* and *Resistant*. The fourth type, *Killer-Non-resistant*, kills itself during the meiosis that might have created it.

The basic assumptions of all the appendices' models are shown in Table A1. It shows the relative viabilities of the products of each of three types of meiosis. The viability cost of resisting is w for each *Resistant* allele involved in the meiosis. The cost of an unsuccessful attempt to kill is v . The gain in relative viability obtained by a driving chromosome, compared to a gamete in an N/N mating, is j . When two *K*s meet, their relative viability is k . This is a reasonably general model. Its main restrictions are (i) the cost of resistance must be strictly additive (ii) when drive occurs (in N/K matings), it is 100% successful in that no gametes survive with *Non-resistant* alleles (iii) where drive does not occur (K/R and N/R matings), meiosis is completely fair—resistance is completely effective. Out of nine possible parameters in the 3×3 table, one is spent on standardizing N/N as being 1, two are spent in assuming symmetry in K/R and N/R matings, one is spent in assuming exact additivity of the costs of resistance, one is spent assuming the perfection of drive, and the four remaining parameters are v , w , j and k shown in the table.

In this appendix, we study the following simple model without recombination:

$$\begin{aligned}
 f_N &= p_N[p_N + (1-w)p_R] \\
 f_R &= p_R[(1-w)p_N + (1-2w)p_R + (1-v-2w)p_K] \\
 f_K &= p_K[(1+j)p_N + (1-v-2w)p_R + kp_K] \\
 \bar{w} &= f_N + f_R + f_K \quad \text{(System I)} \\
 \dot{p}_N &= f_N - p_N\bar{w} \\
 \dot{p}_R &= f_R - p_R\bar{w} \\
 \dot{p}_K &= f_K - p_K\bar{w}.
 \end{aligned}$$

The f_i are the chromosome frequencies among newly created gametes, and \bar{w} is chosen to ensure that the sum of rates of change of the p_i equals zero.

The system defines a flow over a triangle. The vertices are rest points, and the boundaries are invariant. The flow on the boundary is generally circular, from N to K to R to N . To investigate flow on the interior, we notice that this model is like an ESS model, in which N , R and K are strategies, and there is a constant

payoff matrix. This dynamic was first discussed by Taylor & Jonker (1978). A more recent and more formal discussion can be found in Hofbauer & Sigmund (1988). If the game matrix is represented by A , then the possible equilibrium is $A^{-1}1$, which leads to the vector

$$\begin{pmatrix} p_N \\ p_R \\ p_K \end{pmatrix} = \begin{pmatrix} (v+w)(1-v-2v)-kw \\ j(1-v-2w)+kw \\ w(j+v+w) \end{pmatrix} / [(1-v-w)(j+v+w)]. \quad (\text{A.1})$$

This is internal provided all elements are strictly between zero and one, which is true provided

$$k < \frac{(v+w)}{w} (1-v-2w).$$

We shall simply assume that this is so throughout all the appendices. Indeed we shall assume the stronger $k < 1-v-2w$, which is reasonable because it asserts that the products of a K/K mating are less viable than those of a K/R mating, presumably because the costs of attempting to kill depend on the dose of K . In the well-studied meiotic drive cases, k is very small indeed, even compared to $1-v-2w$, the viability in K/R matings, perhaps because *Non-killer* performs some essential function during meiosis. However, this may be a special feature of meiotic drive systems that survive as polymorphisms, rather than going either to fixation or extinction, in each case becoming undetectable. So we do not wish to assume that k is very small in general. (If there is no interior rest point, when k is large, then the K vertex is a global attractor.)

When the diagonal element is subtracted from each column, the game matrix becomes:

$$\begin{pmatrix} 0 & w & -k \\ -w & 0 & 1-k-v-2w \\ 1 & -v & 0 \end{pmatrix}$$

whose sign portrait is

$$\begin{pmatrix} 0 & + & - \\ - & 0 & + \\ + & - & 0 \end{pmatrix}.$$

According to theorem 6 of Zeeman (1980), such games have a single rest point in the interior, which is globally stable (unstable) according as the determinant of the adjusted game matrix is positive (negative). This condition for stability turns out to be that

$$k < \frac{j}{j+v} (1-v-2w). \quad (\text{A.2})$$

Summarizing the behaviour of System I, there is an interior rest point. If (A.2) then the interior rest point is stable, and is globally attracting. That is, there is a stable equilibrium at which N , K , and R chromosomes coexist in the population.

Otherwise, the interior rest point is unstable and heteroclinic cycling results. The boundary is then the attractor, with the cycles getting ever closer as the mathematical ideal of infinite populations becomes more and more implausible. The outcome in practice would be that one of the chromosome types would first go extinct, though which cannot be predicted. Then a second chromosome type would become extinct, leaving a monotypic population. Mutation could keep the population crawling round the boundary. Most of the time it would look like a monotypic population, as most time is spent very near the vertices. This has the implication that many drive systems, those with k high enough to falsify (A.2) may be very hard to detect. The well-known cases have low values of k and so do not show such heteroclinic cycling.

The mean fitness of the population at the internal rest point is

$$\frac{(j + v + w - jw)(1 - v - 2w) - kw^2}{(j + v + w)(1 - v - w)}$$

One notable feature is that the higher the value of k , which represents the viability of gametes in a K/K mating, the lower the population mean fitness at the rest point. Similarly, the higher the value of j , the relative viability of the surviving products in a K/N mating, the lower the population mean fitness. This illustrates starkly the conflict of interest between the drive system and the population.

APPENDIX B

Fixed Recombination

If the *Killer* and *Target* loci are not one and the same, or embedded in inversions, then there is likely to be some recombination. As a preliminary to studying the evolution of recombination, we now turn to the model with a fixed recombination rate r . When recombination occurs, K and N gametes fuse in meiosis, but the product is one R and one doomed *Killer/Non-resistant* product that dies immediately.

The model is again a flow on the triangle, and is as follows

$$\begin{aligned} f_N &= p_N [p_N + (1 - w)p_R] \\ f_R &= p_R [(1 - w)p_N + (1 - 2w)p_R + (1 - v - 2w)p_K] + r(1 + j)p_N p_K \\ f_K &= p_K [(1 - r)(1 + j)p_N + (1 - v - 2w)p_R + kp_K] \\ \bar{w} &= f_N + f_R + f_K \tag{System II} \\ \dot{p}_N &= f_N - p_N \bar{w} \\ \dot{p}_R &= f_R - p_R \bar{w} \\ \dot{p}_K &= f_K - p_K \bar{w}. \end{aligned}$$

The new feature, that a fraction r of the products of K/N matings are recombined to form R instead of K , destroys the parallel with the simple matrix game dynamics, though of course the case $r = 0$ reverts to it.

For very small r , the dynamics are only slightly perturbed from the game dynamic case. This may move the rest point, but should leave the qualitative picture only

slightly altered. If the attractor was the boundary for $r=0$, then the new attractor must be an internal limit cycle. The reason is that the $N-K$ boundary is not invariant, and pushes the flow up into the interior, preventing the boundary itself being an attractor. The instability of the internal rest point and the direction of flow round it remain unchanged, and so there must be an interior limit cycle attractor. Where the internal rest point is the attractor for $r=0$, then it continues to be for very small r .

Consider now the case of any $r>0$. Recall that we have assumed that

$$k < (1 - v - 2w),$$

and we shall first study case I, where also

$$k < \frac{v+w}{w}j.$$

Case II is slightly more complicated and will be dealt with later in the appendix. The key conclusions in Case I are

- (i) The K and R corners are always saddle nodes with non-zero eigenvalues. The $K-R$ and $R-N$ boundaries are invariant, with flow from K to R to N .
- (ii) The N corner is a saddle for $r < j/(1+j)$ and a sink for $r > j/(1+j)$.
- (iii) There is a unique interior rest point for $r < j/(1+j)$, whose position is a continuous function of r , which moves uniformly towards the N corner as r increases (i.e. p_N at the rest point is always increasing with r), meeting the N corner at $r = j/(1+j)$.
- (iv) For $r < j/(1+j)$, the boundary repels, and interior rest point or an orbit or orbits around it are the attractor(s) in the simplex.
- (v) For $r > j/(1+j)$, the N corner is the global attractor for the interior of the triangle.
- (vi) The interior rest point's stability at $r=0$ is determined by (A.2), as this is simply the no recombination case of section 2. As it approaches the N corner, the interior rest point is a sink.

To establish these conclusions, we first find a polynomial in p_N whose roots correspond to rest points of System II. Taking $p_K \dot{p}_N - p_N \dot{p}_K = 0$, using $\sum p_i = 1$ and solving for p_K in terms of p_N , we then substitute for p_K and $p_R = 1 - p_K - p_N$ in $\dot{p}_N = 0$. This yields a polynomial in p_N . It has two roots at $p_N = 0$, corresponding to the rest points at the K and R corners; one root at $p_N = 1$, corresponding to the rest point at the N corner; and a remaining factor, quadratic in p_N , as follows:

$$\begin{aligned} d(p_N) = & -2[j - r(1+j) + v + w][(j - r(1+j) - k)(1 - v - w) + r(1+j)(k + v + w)]p_N^2 \\ & + [(j - r(1+j))[(v + w)(1 - v - 2w) - k] + k[w(k + r(1+j) - w) \\ & - 2(v + w)(1 - v - 2w)] + r(1+j)(v + w)^2]p_N \\ & + 2k[(v + w)(1 - v - 2w) - kw]. \end{aligned}$$

Solutions to $d(p_N) = 0$ are internal rest points provided that the value of p_N together with the implied values of p_R and p_K satisfy $p_i > 0$, $\sum p_i = 1$. The implied value of p_K is greater than zero only when $p_N < (v + w)/(v + w + j - r - rj)$. Hence, any rest

point must correspond to a value of p_N between 0 and $(v+w)/(v+w+j-r-rj)$. Conversely, any such solution corresponds to a rest point, as the implied value of p_R is always positive. The value of the quadratic at the two ends of the possible interval are

$$d(0) = 2k[(v(1-v-2w) + w(1-k-v-2w))] > 0$$

$$\left[\text{by our assumption that } k < \frac{v+w}{w}(1-v-2w) \right]$$

$$d\left(\frac{v+w}{v+w+j-r-rj}\right) = -\frac{2(j-r-rj)w(k+v+w)^2}{(v+w+j-r-rj)},$$

$$\text{whose sign} = -\text{sign}\left(\frac{j-r-rj}{v+w+j-r-rj}\right).$$

Hence, if $r < j/(1+j)$ there is exactly one solution to $d(p_N) = 0$ in the required region, and so exactly one rest point. If $(v+w+j)/(1+j) > r > j/(1+j)$, there is exactly zero or two rest points. These facts will be essential for interpreting the graphs produced next.

Now we manipulate the equation $p_K \dot{p}_N - p_N \dot{p}_K = 0$, using $\sum p_i = 1$ and solving for p_N to define a function $g(p_K)$ which must equal p_N at a rest point:

$$g(p_K) = \frac{v+w-p_K(k+v+w)}{v+w+j-r-rj}.$$

Then we manipulate the equation $\dot{p}_N = 0$ in the same way to obtain another function $h(p_K)$ that must equal p_N at a rest point:

$$h(p_K) = \frac{w-p_K(1-w-2v) + p_K^2(1-k-2w-2v)}{w-p_K(1-j-2v-2w)}.$$

The notable features of these functions are that g is linear in p_K and that h is independent of r . This allows the graph shown in Fig. B1 to be constructed.

h passes through the shaded fan-shaped region, which consists of a family G of straight lines, corresponding to the values of r in order from 0 to $(v+w+j)/(1+j)$. Let G_0 be the subfamily that strike the vertical axis, G_1 be the member that strikes the point $(0, 1)$, and G_2 be the subfamily that strike the line $p_N + p_K = 1$. The line G_1 corresponds to $r = j/(1+j)$, while G_0 corresponds to lower r , and G_2 to higher r . Every point of h in the shaded region represents an internal rest point for the value of r corresponding to the member of G that passes through it. The behaviour of h in this region reveals much of the dynamics of System II.

In Case I, the slope of h at $p_K = 0$ $(-(j+w)/w)$ is steeper than the slope of $G_1[-(v+w+k)/(v+w)]$, and we recall our earlier result that for $r < j/(1+j)$ there is exactly one interior rest point. It follows that h passes downwards through G_0 , intersecting each member once, and exits G_0 at the solution for $r = 0$, which is given by (A.1). Notice that uniqueness of intersection within G_0 further implies that h then crosses the horizontal axis before $p_K = (v+w)/(v+w+k)$. We now show that after crossing the horizontal axis, h does not intersect the triangle again. The intersections of h and $p_N + p_K = 1$ occur at $p_K = 0$, and on the member of G

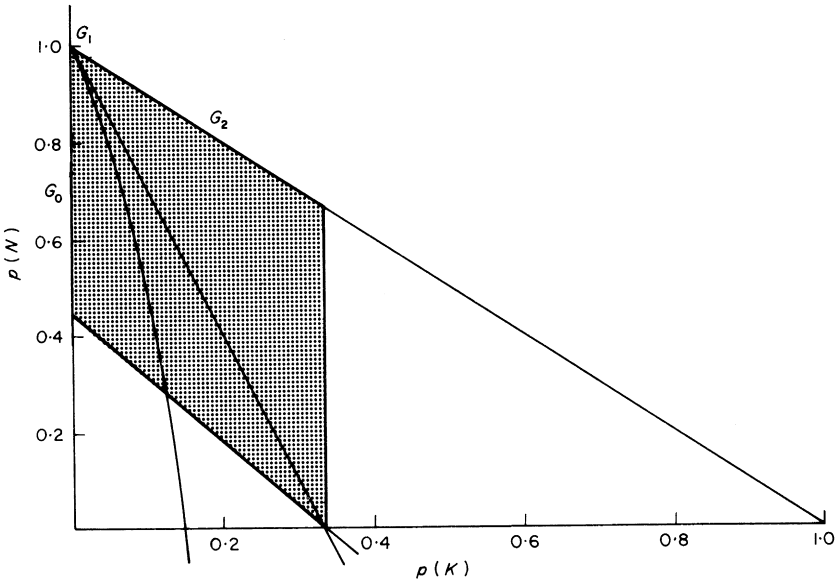


FIG. B1. This figure shows the solutions to System II, the fixed recombination model, in Case I. The parameter values in the example are $v = w = 0.1$, $j = 0.25$ and $k = 0.4$. The triangle with vertices at $(0, 0)$, $(1, 0)$, $(0, 1)$ represents the simplex. The curve passing through $(0, 1)$ is $h(p_K)$. The shaded region represents a family of straight lines $g(p_K)$ passing through the point $((v+w)/(v+w+k), 0)$ indexed by r . The subfamily that strikes the vertical axis is G_0 , the member that strikes the point $(0, 1)$ is G_1 , and the subfamily that strikes the line $p_N = 1 - p_K$ is G_2 . Each point of $h(p_K)$ inside the shaded region represents an interior rest point for the value of r corresponding to the member of G . h must pass downwards through G_0 , and can never enter G_2 .

corresponding to $r = 0$. Neither intersection can occur for $p_K \in (0, 1]$. Further, h has only two zeroes, and we have just seen that one must occur before $p_K = (v+w)/(k+v+w)$. It follows that h cannot enter the triangle when $p_K > (v+w)/(v+w+k)$, because it would not be able to get out again.

This picture establishes that as r increases towards $j/(1+j)$, p_N at the interior rest point increases, and approaches 1. For r above $j/(1+j)$, the only attractor in the simplex is the N vertex, and there are no rest points in the interior or on the boundary (apart from the other two vertices which are saddles). It follows that the N vertex is the global attractor for the interior of the simplex.

This completes the analysis of Case I, which provides a basis for the more complicated Case II to which we now turn. In Case II,

$$k > \frac{v+w}{w}j.$$

The essential difference is that here the slope of h at $p_K = 0$ is flatter than the slope of G_2 , and so the picture is now as shown in Fig. B2. When $r < j/(1+j)$ there is still a unique rest point in the interior, but for an interval of r above $j/(1+j)$ there are two. The slope of h at $p_K = 0$ (namely $-(j+w)/w$) is initially steeper than -1 , and the existence of exactly zero or two solutions means that we do not need to

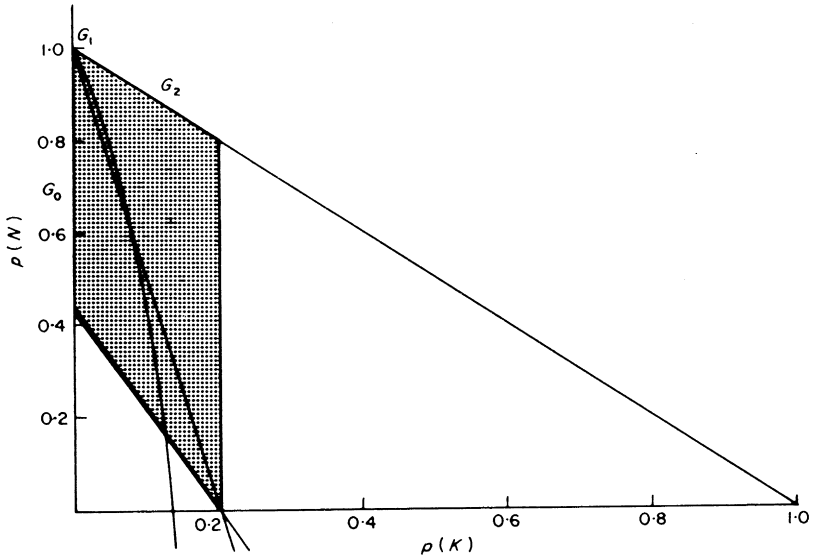


FIG. B2. This figure shows the solutions to System II, the fixed recombination model, in Case II, and is generally the same as in Fig. B1. The parameter values in the example are $v = w = 0.1$, $j = 0.25$ and $k = 0.8$. The difference is that the curve $h(p_K)$ has a shallower slope than G_1 at $p_K = 0$, and so passes through G_2 before passing through G_1 again and then down through G_0 . There are two solutions, and therefore two interior rest points, for the values of r corresponding to members of G_2 just above G_1

worry about h crossing the line $p_N + p_K = 1$. The argument of Case I still holds that there are no further intersections of h with the triangle. Now we turn to the behaviour of the dynamics of the flow in the interesting situation in which a second rest point appears in the interior of the simplex. The relevant pictures are shown in Fig. B3. The salient points are

- (i) for $r < j/(1+j)$, the N corner is a saddle, while for $r > j/(1+j)$, the N vertex is an attractor
- (ii) for r just greater than $j/(1+j)$, the basin of attraction of the N vertex consists of a strip next to the $N-R$ and $K-R$ vertices, with the remainder of the interior belonging to the basin of attraction of the original interior rest point
- (iii) as r increases, the strip expands, and the basin of attraction of the original rest point contracts to a line. The original rest point meets the new interior rest point on that line, and the two disappear.
- (iv) the new interior rest point is a saddle throughout.
- (v) for values of r higher than the value at which the two interior rest points meet and disappear, the N corner is the global attractor of the interior of the simplex.

This completes the analysis of Case II. We have not excluded the possibility that the basin of attraction of the original interior rest point breaks up into rings, with stable and unstable cycles around the rest point. But this has not appeared in simulations, and would not affect our biological conclusions.

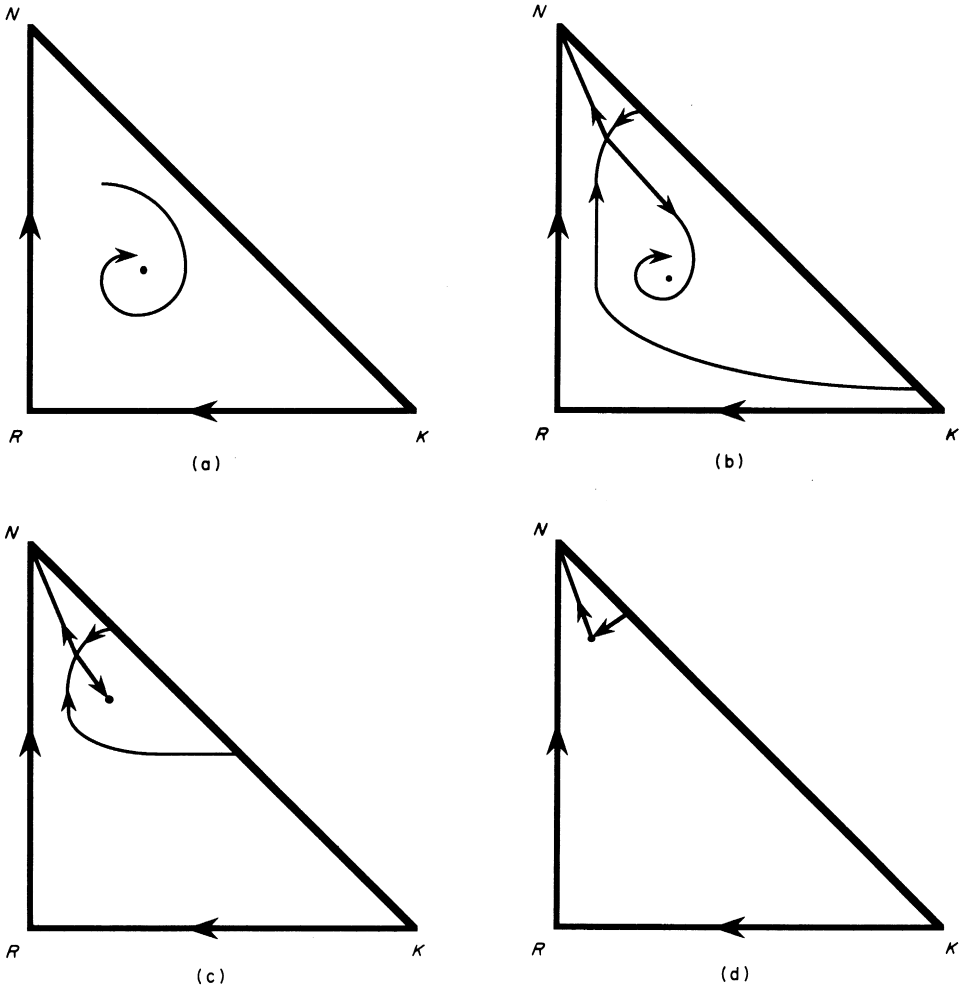


FIG. B3. This figure shows the flows of System II in Case II, as r moves from just below $j/(1+j)$ to just above it. (a) Shows the flow for $r < j/(1+j)$, which is circular and inwards towards the interior rest point. Just after $j/(1+j)$ there are two interior rest points, and the interior is divided into two basins of attraction. The basin for the N vertex extends round the $N-R$ and $R-K$ edges, while the remainder of the interior has the original rest point as its attractor. The new interior rest point is a saddle that lies on the separatrix. As r increases, the basin of attraction of the N vertex increases in size, while that of the original rest point diminishes (c). The basin finally vanishes as a line, at a value of r at which the two interior rest points meet (d) and disappear. For higher r , the global attractor is the N vertex. Hence, new drive systems can never invade once $r > j/(1+j)$, but to eliminate existing systems it may be necessary to increase r above $j/(1+j)$.

The conclusions from the study of System II are that (1) recombination protects against meiotic drive (2) there is a critical value of $r = j/(1+j)$ above which a *Killer* allele cannot invade a *Non-resistant* population (3) there is a slightly higher value of r (which varies according to parameter values, but is always less than $\frac{1}{2}$) above

which any existing meiotic drive system collapses, leading to an entirely *Non-resistant* population. In such a population there are no *Killer* or *Resistant* alleles, and so individuals pay no costs of killing or resistance.

APPENDIX C

Recombination Under Control of a Third Unlinked Locus

In the final model, the recombination rate depends on the contents of a third unlinked locus, say *Crossover*, with two alleles $Cross^+$ and $Cross^-$. The rate of recombination is r_0 , r_1 or r_2 according to the number of $Cross^+$ alleles in the zygote. We assume that $r_0 < r_1 < r_2$. There are six haploid genotypes to consider: N chromosomes together with $Cross^-$ (frequency p_N) or $Cross^+$ (p_{NX}); R chromosomes with $Cross^-$ (p_R) and $Cross^+$ (p_{RX}) and K chromosomes with $Cross^-$ (p_K) and $Cross^+$ (p_{KX}). The model is as follows:

$$\begin{aligned}
 f_N &= p_N[p_N + p_{NX} + (1-w)(p_R + p_{RX}/2)] + (1-w)p_{NX}p_R/2 \\
 f_{NX} &= p_{NX}[p_N + p_{NX} + (1-w)(p_R/2 + p_{RX})] + (1-w)p_Np_{RX}/2 \\
 f_R &= p_R[(1-w)(p_N + p_{NX}/2) + (1-2w)(p_R + p_{RX}) + (1-v-2w)(p_K + p_{KX}/2)] \\
 &\quad + (1-w)p_Np_{RX}/2 + (1-v-2w)p_{RX}p_K/2 + r_0(1+j)p_Np_K \\
 &\quad + r_1(1+j)(p_Np_{KX} + p_{NX}p_K)/2 \\
 f_{RX} &= p_{RX}[(1-w)(p_N/2 + p_{NX}) + (1-2w)(p_R + p_{RX}) + (1-v-2w)(p_K/2 + p_{KX})] \\
 &\quad + (1-w)p_{NX}p_R/2 + (1-v-2w)p_Rp_{KX}/2 + r_1(1+j)(p_Np_{KX} + p_{NX}p_K)/2 \\
 &\quad + r_2(1+j)p_{NX}p_{KX} \\
 f_K &= p_K[(1+j)((1-r_0)p_N + (1-r_1)p_{NX}/2) + (1-v-2w)(p_R + p_{RX}/2) \\
 &\quad + k(p_K + p_{KX})] + (1+j)(1-r_1)p_Np_{KX} + (1-v-2w)p_Rp_{KX}/2 \\
 f_{KX} &= p_{KX}[(1+j)((1-r_1)p_N/2 + (1-r_2)p_{NX} + (1-v-2w)(p_R/2 + p_{RX}) \\
 &\quad + k(p_K + p_{KX})] + (1+j)(1-r_1)p_{NX}p_K \\
 &\quad + (1-v-2w)p_{RX}p_K/2
 \end{aligned}
 \tag{System III}$$

$$\bar{w} = f_N + f_{NX} + f_R + f_{RX} + f_K + f_{KX}$$

$$\dot{p}_N = f_N - p_N\bar{w}$$

$$\dot{p}_{NX} = f_{NX} - p_{NX}\bar{w}$$

$$\dot{p}_R = f_R - p_R\bar{w}$$

$$\dot{p}_{RX} = f_{RX} - p_{RX}\bar{w}$$

$$\dot{p}_K = f_K - p_K\bar{w}$$

$$\dot{p}_{KX} = f_{KX} - p_{KX}\bar{w}$$

This system of equations defines a flow on the 6-simplex representing the possible values of $(p_N, p_{NX}, p_R, p_{RX}, p_K, p_{KX})$. It is convenient to present the system in a different form, with new variables defined by $s_i = p_i + p_{iX}$ and $\varepsilon_i = p_{iX}/s_i$. The s_i are simply the haploid genome types of N, K, R , ignoring the *Crossover* locus, while the ε_i are the fraction of each haplotype that have $Cross^+$ at the *Crossover* locus.

The equations for \dot{s}_i and $\dot{\varepsilon}_i$ are easily found in terms of s_i and ε_i . They represent a flow on the Cartesian product of a triangle (for the s_i) and a cube (for the ε_i). The equations for the ε part of the system are

$$\dot{\varepsilon}_N = -\mu(\varepsilon_N - \varepsilon_R)s_R \quad (\text{C.1})$$

$$\begin{aligned} \dot{\varepsilon}_R = & \rho(\varepsilon_K + \varepsilon_N - 2\varepsilon_R) \frac{s_N s_K}{2s_R} + \delta_0(1 - \varepsilon_K)(1 - \varepsilon_N)(\varepsilon_K + \varepsilon_N) \frac{s_N s_K}{2s_R} \\ & + \delta_2 \varepsilon_K \varepsilon_N (2 - \varepsilon_K - \varepsilon_N) \frac{s_N s_K}{2s_R} \\ & + (1 - 2\nu)(\varepsilon_R - \varepsilon_K)s_K + \mu(\varepsilon_K s_K - \varepsilon_R s_K + \varepsilon_N s_N - \varepsilon_R s_N) \end{aligned} \quad (\text{C.2})$$

$$\begin{aligned} \dot{\varepsilon}_K = & \rho(\varepsilon_K - \varepsilon_N) \frac{s_N}{2} - \delta_0(1 - \varepsilon_K)(1 - \varepsilon_N)(\varepsilon_K + \varepsilon_N) \frac{s_N}{2} - \delta_2 \varepsilon_K \varepsilon_N (2 - \varepsilon_K - \varepsilon_N) \frac{s_N}{2} \\ & - \nu(\varepsilon_K - \varepsilon_R)s_R - \mu(\varepsilon_K - \varepsilon_R)s_R - \frac{1}{2}((1+j)(\varepsilon_K - \varepsilon_N)s_N - (\varepsilon_K - \varepsilon_R)s_R) \end{aligned}$$

in which the following new symbols have been defined:

$$\mu = \frac{1}{2}(1 - w) \quad \text{note that } \mu > 0, 1 - 2\mu > 0$$

$$\nu = \frac{1}{2}(1 - v - w) \quad \text{note that } \nu > 0, 1 - 2\nu > 0$$

$$\delta_0 = (r_1 - r_0)(1 + j) \quad \text{note that } \delta_0 > 0$$

$$\delta_2 = (r_2 - r_1)(1 + j) \quad \text{note that } \delta_2 > 0$$

$$\rho = (1 + j)r_1 - \delta_0(1 - \varepsilon_K)(1 - \varepsilon_N) + \delta_2 \varepsilon_K \varepsilon_N.$$

The final symbol ρ represents the average value of recombination, times $(1 + j)$. It therefore lies between $r_0(1 + j)$ and $r_2(1 + j)$. The flow on the interior of the p_i, p_{iX} system is isomorphic to the flow on the interior of the ε_i, s_i system, but the boundaries are not isomorphic (and even have different numbers of vertices).

The aim of this appendix is to establish for System III the following results, on the assumption that $0 \leq r_0 < r_1 < r_2 \leq \frac{1}{2}$:

- (i) there is no rest point in the interior
- (ii) the $N-K-R$ face and the $NX-KX-RX$ face are invariant
- (iii) every interior rest point on the $N-K-R$ face repels flow from the interior
- (iv) every interior rest point on the $NX-KX-RX$ face attracts flow from the interior.

These points do not prove, but provide support for, the following

Conjecture. The attractors for the interior are in two categories (a) the attractors for the $NX-KX-RX$ face and (b) if the NX vertex is an attractor for the $NX-KX-RX$ face, then an interval of the $N-NX$ edge containing the NX vertex.

If this conjecture is true, then every system beginning with all three chromosome types and with both the recombination alleles will end up with *either* the higher recombination allele at fixation *or* the *Non-killer-Non-resistant* chromosome at fixation. The effect of selection is therefore to increase recombination and/or

eliminate the *Killer* and *Resistant* alleles. Numerical simulations support the conjecture, for a variety of parameter values and starting positions. We now turn to proving (i) to (iv). (ii) is trivial. Points (i), (iii) and (iv) are shown by considering the s_i, ϵ_i form of the system as shown above.

First we show (i), that there is no interior rest point. (C.1) implies that at any rest point $\epsilon_N = \epsilon_R$. $\dot{\epsilon}_R s_R + \dot{\epsilon}_K s_K$ must also be zero at an interior rest point, and when we make the substitution of ϵ_R for ϵ_N , we obtain

$$\dot{\epsilon}_R s_R + \dot{\epsilon}_K s_K = \frac{1}{2}(1+j-2\rho)(\epsilon_R - \epsilon_K) s_K s_N.$$

This implies that either ϵ_K too equals ϵ_R , which cannot be because then (C.2) shows that $\dot{\epsilon}_R$ consists of a sum of positive terms; or $\rho = \frac{1}{2}(1+j)$, which is again impossible because the average value of recombination cannot be greater than $\frac{1}{2}$ unless at least one of r_0, r_1 or r_2 is greater than $\frac{1}{2}$, which is contrary to assumption. There can therefore be no interior rest point.

Now we show (iii) and (iv). We do this by obtaining the Jacobian for the ϵ_i system at $\epsilon_i = 0$, and showing that it has all negative eigenvalues when $r_0 < r_1$ and one positive eigenvalue when $r_0 > r_1$. This establishes (iii) directly. (iv) is a symmetric case, simply swapping r_0 and r_2 . Let M^* be twice the Jacobian at $\epsilon_i = 0$. M^* is:

$-(1-w)s_R$	$(1-w)s_R$	0
$(1-w)s_N + \frac{(1+j)s_K s_N r_1}{s_R}$	$-(1-v-2w)s_K - (1-w)s_N$ $-2 \frac{(1+j)s_K s_N r_0}{s_R}$	$(1-v-2w)s_K + \frac{(1+j)s_K s_N r_1}{s_R}$
$(1+j)s_N - r_1(1+j)s_N$	$(1-v-2w)s_R$	$-(1+j)s_N - (1-v-2w)s_R$ $-(1+j)s_N r_1 + 2(1+j)s_N r_0$

which we can rewrite as M as follows

$-A$	A	0
$B + Q(r_0 + \Delta r)$	$-B - C - 2Qr_0$	$C + Q(r_0 + \Delta r)$
$D - D(r_0 + \Delta r)$	E	$-D - E - D(r_0 + \Delta r) + 2Dr_0$

where all the symbols are known to be positive, and in addition $CD = EQ$. Computation shows that

$$\begin{aligned} \text{tr}(M) &= -A - B - C - E - 2Qr_0 - D(1 - r_0 + \Delta r) < 0 \\ \det(M) &= -2A\Delta r(CD - D(1 - 2r_0)Q - EQ) = 2A\Delta rDQ(1 - 2r_0). \end{aligned}$$

Hence, $\det(M) > 0$ if $r_0 < \frac{1}{2}$ and $\Delta r > 0$, and if $r_0 > \frac{1}{2}$ and $\Delta r < 0$. $\det(M) < 0$ in the opposite cases. Hence, the sign of $\det(M)$ is positive if initial invasion of the mutant would move the population mean recombination rate towards $\frac{1}{2}$. It would make

TABLE C1

The eigenvalues for one point in each region of permissible values of (A, B, C, D, E, Q, r₀, Δr), assuming A = B = C = D = E = Q = 1. It shows that in the first and fourth regions there are no positive eigenvalues, while in the second and third regions there is exactly one positive eigenvalue

Region		Example	Eigenvalues
$r_0 > \frac{1}{2}$	$\Delta r > 0$	$r_0 = \frac{3}{4}, \Delta r = \frac{1}{10}$	-0.0109307, -4.54295, -1.25862
$r_0 > \frac{1}{2}$	$\Delta r < 0$	$r_0 = \frac{3}{4}, \Delta r = -\frac{1}{10}$	0.0112956, -4.45749, -1.24131
$r_0 < \frac{1}{2}$	$\Delta r > 0$	$r_0 = \frac{1}{4}, \Delta r = \frac{1}{10}$	0.00996526, -3.56144, -1.76103
$r_0 < \frac{1}{2}$	$\Delta r < 0$	$r_0 = \frac{1}{4}, \Delta r = -\frac{1}{10}$	-0.0104565, -3.43901, -1.73803

sense if the mutant invaded when its invasion would initially move the population mean recombination rate towards $\frac{1}{2}$, and this is what we now show. The rest point $\varepsilon_i = 0$ is stable if the real parts of the eigenvalues of M are all negative. We know that M has all real eigenvalues, under our assumptions that $A, B, C, D, E, Q, r, \Delta r > 0$, and $r_0 + \Delta r < \frac{1}{2}$ —because the positive orthant is forward invariant, while complex eigenvalues would imply flow out of the positive orthant. The number of positive eigenvalues can therefore change only at values of A, B etc at which the determinant is zero. The permissible values of $(A, B, C, D, E, Q, r_0, \Delta r)$ in \mathbf{R}^8 are divided into four simply connected regions, on whose boundaries alone $\det(M)$ is zero. The regions correspond to $(r_0 > \frac{1}{2}, \Delta r > 0)$, $(r_0 > \frac{1}{2}, \Delta r < 0)$, $(r_0 < \frac{1}{2}, \Delta r > 0)$ and $(r_0 < \frac{1}{2}, \Delta r < 0)$. We need therefore only count the positive eigenvalues for one example of each region. This exercise is carried out in Table C1.

Hence $(1 - 2r_0)\Delta r > 0$ implies exactly one positive eigenvalue, and instability of the $\varepsilon_i = 0$ equilibrium. This occurs when Δr is in the direction towards $\frac{1}{2}$ from r_0 . $(1 - 2r_0)\Delta r < 0$ implies three negative eigenvalues, and stability of the $\varepsilon_i = 0$ equilibrium. This occurs when Δr is in the direction away from $\frac{1}{2}$ from r_0 . This establishes (iii) and (iv). Notice that this result holds for any values of $s_i > 0$, and so applies to all interior rest points.

The major conclusion from the analysis of System III is that selection acts on unlinked loci to increase recombination between the *Killer* and *Target* loci. Thus, selection brought about by intragenomic conflict can provide straightforward selection in favour of recombination, which is noteworthy because selection acting on the organism as a whole tends to have the opposite effect.