The Evolution of Sex Dimorphism in Recombination

Thomas Lenormand[1]

CEFE-Centre National de la Recherche Scientifique, 34293 Montpellier, France

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ABSTRACT

Sex dimorphism in recombination is widespread on both sex chromosomes and autosomes. Various hypotheses have been proposed to explain these dimorphisms. Yet no theoretical model has been explored to determine how heterochiasmy—the autosomal dimorphism—could evolve. The model presented here shows three circumstances in which heterochiasmy is likely to evolve: (i) a male-female difference in haploid epistasis, (ii) a male-female difference in *cis*-epistasis minus *trans*-epistasis in diploids, or (iii) a difference in epistasis between combinations of genes inherited maternally or paternally. These results hold even if sources of linkage disequilibria besides epistasis, such as migration or Hill-Robertson interference, are considered and shed light on previous verbal models of sex dimorphism in recombination rates. Intriguingly, these results may also explain why imprinted regions on the autosomes of humans or sheep are particularly heterochiasmate.

MEIOSIS in males and females differs in several important respects. A female produces only one large gamete (ovule) from the four meiotic products whereas a male produces four small motile gametes (spermatozoa) from the four meiotic products. Often, the timing of male and female meiosis is different: in animals, for example, male meiosis tends to be continuous whereas female meiosis generally stops twice, just after meiosis begins and just before it ends. And at least sometimes, the amount of genetic recombination during meiosis differs between males and females because of differences in crossing over number and/or position. How did these meiotic differences evolve, and how are they maintained?

The first aspect—the evolution of anisogamy—has received considerable theoretical treatment (see, for example, Randerson and Hurst 2001); but aspects such as the evolution of dimorphism in recombination have received much less attention, especially with respect to formal models. The aim of this article is to determine the conditions under which a recombination dimorphism can evolve. I begin by reviewing the facts about recombination dimorphism and the different hypotheses that have been proposed to account for it. I then present a formal model for the evolution of recombination dimorphism on autosomes and on sex chromosomes.

A recombination dimorphism can occur on sex chromosomes (or close to a sex-determining locus) or on autosomes. In the autosomal case, recombination may be completely absent in one sex, a phenomenon known as achiasmy, or it may vary quantitatively between sexes, a phenomenon that I term "heterochiasmy."

Recombination dimorphism on sex chromosomes: In species with a large sex-chromosome heteromorphism (X *vs.* Y or Z *vs.* W), the sex chromosomes in the heterogametic sex do not exchange genetic material along much of their length. This is the most conspicuous and widespread recombination dimorphism between the sexes. Two related theories have been advanced to explain selection for reduced recombination around sex-determining loci: (i) recombination is disadvantageous for sex-linked alleles with opposite effects in the two sexes (Charlesworth and Charlesworth 1980), and (ii) recombinant genotypes have an "intersex" unfit genotype because of the accumulation of linked sex factors (Nei 1969).

Achiasmy: Although it has received less attention, recombination dimorphism on autosomes is also common. In the most conspicuous cases, achiasmy, one sex apparently lacks recombination completely. This is not related to the loss of meiosis that often occurs with parthenogenesis: achiasmy occurs in taxa where parthenogenesis is rare or unknown, *e.g.*, Lepidoptera, Trichoptera, Diptera, and isolated species of molluscs, water-mites, copepods, grasshoppers, and alder-flies (Bell 1982). When achiasmy occurs in dioecious species, it is almost always the heterogametic sex that is achiasmate, a phenomenon known as the "Haldane-Huxley rule" [Haldane 1922; Huxley 1928; for examples, see Bell 1982, Table 5.3; however, some species in Musca and Culex genera are possible exceptions (Bull 1983)]. The Haldane-Huxley rule has been explained either as a pleiotropic consequence of selection against recombination between X and Y (or Z and W)—the pleiotropy hypothesis—or as the consequence of the evolution of

[1]*Address for correspondence:* CEFE-CNRS, 1919 rte. de Mende, 34293 Montpellier, France. E-mail: lenormand@cefe.cnrs-mop.fr

the Y (or W) in the sex that initially had no recombination—the no-recombination hypothesis.

Both hypotheses are plausible in principle. However, both can be criticized in several ways. For example, the pleiotropy hypothesis provides no explanation for why the pleiotropic effect should be so extreme: after all, there is ample within-species genetic variation for recombination rates on autosomes. The hypothesis does not explain why achiasmate meiosis occurs in only one gender within hermaphrodites (*e.g.*, some Liliaceae in the genus Fritillaria; Noda 1975). It cannot explain why achiasmy has evolved in the heterogametic sex in species with a XX/XO sex-determination system (*e.g.*, according to White 1976 this has occurred eight separate times in Mantodea), unless one supposes that each XX/XO system has passed through an XX/XY system followed by the complete degeneration of the Y. Finally, the pleiotropy hypothesis does not explain why achiasmate meiosis in the heterogametic sex is maintained once sex-chromosome heteromorphism has evolved such that the sex chromosomes would no longer be homologous and able to recombine (*e.g.*, in the extreme case recombination on the sex chromosome cannot occur in XO individuals).

The no-recombination hypothesis provides no explanation for why sex differences in recombination should preexist the formation of Y or W. Furthermore, the assumption on which this hypothesis rests—that heterogamety will always gradually evolve in the sex with low recombination—will not always hold: if the sex-determining mechanism depends on a single locus (even if this is considered improbable; Charlesworth 2002), it does not depend on recombination and therefore the "heterozygote" sex, which is likely to become the heterogametic sex, should be equally likely to be the sex with or without recombination.

Heterochiasmy data: Measuring heterochiasmy is difficult. Most data that have been collected consist of chiasma counts. This method does not often take into account the position of crossing over along chromosomes, which in general varies between males and females, resulting in a strong bias (male chiasmata are often either proterminal or procentric; *e.g.*, Fletcher and Hewitt 1980). This difference of chiasma position between the sexes is also a problem in studies using map distance between few markers: depending on where the markers are along the chromosomes more recombination may appear to be in one sex or the other when in fact it is not. Molecular techniques have also revealed a large source of variation in recombination rates from chromosome to chromosome and from genotype to genotype (see Korol *et al.* 1994, p. 280, for examples). Analyzing heterochiasmy data can present further difficulties. For example, not knowing the rate of evolution of heterochiasmy can make it difficult to judge whether there is phylogenetic inertia and thus how many species or groups of species must be contrasted when attempting to test hypotheses.

Trivers (1988) and Burt *et al.* (1991) reviewed chiasma count data and found that differences between the sexes are often large. Recent map data tend to confirm their analyses, although these data have yet to be rigorously examined. Moreover, in ~75% of chiasmate species (whether dioecious or hermaphrodite), recombination rate, measured using either chiasma count (Burt *et al.* 1991) or map length (my personal observations), differs by >5% between male and female meiosis. In extreme cases, recombination in female meiosis can be as much as 3 times higher [for instance, in the zebrafish *Danio rerio,* which has no heteromorphic sex chromosome (Singer *et al.* 2002), and in the planarian *Schmidtea polychroa*, a hermaphrodite (Pongratz *et al.* 2001)] or ~1.5 times lower (*e.g.*, in the monecious species *Pinus taeda*; Sewell *et al.* 1999). Nonetheless, Trivers (1988) argued that in dioecious species the direction of heterochiasmy tends to be biased toward less recombination in male meiosis and is not affected much by heterogamety.

Heterochiasmy theories: Several ideas have been put forward to explain the occurrence of heterochiasmy. They fall into several groups that I briefly review before turning to the model.

Mechanistic explanations: A different internal environment between male and female tissue, due to physiological or molecular processes, is a potential cause of heterochiasmy. For instance, Bernstein *et al.* (1988) argued that higher recombination rates in females could be due to higher metabolic rates in females. This hypothesis is weak since, in hermaphrodites, both male and female meiosis occurs in the same individual. However, even in hermaphrodites, male and female meiosis may not occur at the same time—and therefore may occur under different conditions. For instance, in Pinus, male and female meiosis occurs in different seasons. Differences in temperature, which have been shown to influence recombination rates, could thus explain the observed heterochiasmy with more recombination in males in this genus (see Plomion and Omalley 1996). But without more data on the timing of meiosis in hermaphrodites, the extent to which timing may explain heterochiasmy cannot be evaluated. Another possibility is that heterochiasmy itself may be a way to control the timing of meiosis. Crossing over has been hypothesized to regulate segregation and DNA repair; chiasma number could also modulate the speed of meiosis. For example, as mentioned above, in gonochoric animals, male meiosis tends to be continuous whereas female meiosis generally stops twice; numerous chiasmata could stabilize the female meiosis when it stops (sometimes for long periods of time), whereas few chiasmata could allow males a fast gametogenesis. However, this hypothesis may not apply to most plants for which the timing of male and female meiosis does not seem to differ much.

Pleiotropic effect of sex-chromosome heteromorphism: The Haldane-Huxley rule could explain heterochiasmy as well as achiasmy (for instance Huxley 1928 invoked it

for marked heterochiasmy). However, at the very least, this is not a general explanation: counter examples are numerous, and a pleiotropic effect of the evolution of sex-chromosome heteromorphism cannot account for heterochiasmy in hermaphrodites (see Burt *et al.* 1991).

The neutral hypothesis: The evolution of the average recombination rate has been well studied theoretically (see, for review, Barton and Charlesworth 1998; Otto and Lenormand 2002) and some experiments have shown that it can evolve (*e.g.*, Korol and Iliadi 1994). On the other hand the evolution of the difference in recombination rates between males and females has neither theoretical nor empirical support. When Burt *et al.* (1991) failed to find support for a correlation between the magnitude of heterochiasmy and the opportunity for sex difference in selection (which, they argued, should be high in dioecious animals, intermediate in hermaphroditic plants, and low in hermaphroditic animals), they suggested that heterochiasmy might be neutral. A failure to find support for one hypothesis, however, does not mean that a trait is neutral—especially when, as in this case, the hypothesis under consideration had no clear theoretical foundation and no empirical justification.

Evolutionary explanations, sexual selection: Trivers (1988) proposed that heterochiasmy could be due to sexual selection. He supposed that because of the higher variance of reproductive success in males, "the genes and combinations of genes being passed in males would be superior on average, compared to genes passed in females" (p. 277). He concluded that "insofar as the actual combinations in which a male's gene appear are important to their success, then he will be selected to reduce rates of recombination (compared to females) in order to preserve these beneficial combinations." Trivers argued that this explains why males recombine less—and that exceptions can be accounted for by changes in the regime of sexual selection. However, this theory is largely inspired by models of evolution of sex chromosomes (Nei 1969) and has received as yet no theoretical foundation for autosomes. Worse, the opposite verbal model has been made: "As two potentially important sources of linkage disequilibrium are selection and drift, one might expect that the sex experiencing the more intense selection, or otherwise having the higher variance in reproductive system, should have more recombination" (Burt *et al.* 1991).

MODEL

Here, I present a three-locus model to determine the selection coefficient on a recombination modifier having different effects in males and females. Alleles at this modifier locus change the recombination rate between two loci subject to both haploid and diploid selection. A Mathematica notebook (Wolfram 1999) with the full recursions can be obtained at <http://www.cefe.cnrs-mop.fr/wwwgdyn>.

Genetic setting: Consider a sexual dioecious population with three autosomal loci $\{i, j, k\}$. Suppose that locus i is a sex-specific recombination modifier locus and that loci j and k are under viability selection. The aim is to compute the frequency change at the modifier locus over one generation to determine under which conditions a recombination dimorphism can evolve. I follow notation used in Barton and Turelli (1991) and Barton (1995) for variables (see Table 1). Each locus l has two alleles and is modeled using a random variable X_l, which takes the value of 0 or 1 for the first and second allele, respectively. Let $\mathbf{x_{(s)}} = \{X_{i(s)}, X_{j(s)}, X_{k(s)}\}$ and $\mathbf{x_{(s)}}^*$ represent a haploid set of alleles inherited from the father and the mother, respectively, in an individual of sex s ($s = m, f$ for male or female) and let the couple $(\mathbf{x_{(s)}}, \mathbf{x_{(s)}}^*)$ be a diploid genotype (which is either a male or a female). The subscript (s) denotes a sex-specific value throughout. The average frequency $\bar{p}_l$ ($\bar{p}_l = 1 - \bar{q}_l$) of the allele coded by 1 in the whole diploid population is the expectation of $X_{lm} + X_{lm}^* + X_{lf} + X_{lf}^*$. The linkage disequilibria between loci are measured by

$$C_{U,V} \equiv E\left[\prod_{l\in U}(X_l - \bar{p}_l)\prod_{l\in V}(X_l^* - \bar{p}_l)\right], \qquad (1)$$

where U, V represents the different possible sets of loci (*i.e.*, $U, V \in \{\varnothing, i, j, k, ij, ik, jk, ijk\}$) distributed on maternal and paternal chromosome and by convention $X_\varnothing = X_\varnothing^* = 1$ and $\bar{p}_\varnothing = 0$. In haploids, only the associations between loci on a single chromosome are needed (U or V is empty). I also assume for simplicity (and because I am not aware of any corresponding genetic mechanism) that sex-of-origin effects do not extend back more than one generation (*i.e.*, like with imprinting, meiosis resets eventual sex-of-origin marks of the previous generation). As a consequence, in haploids $C_{U,\varnothing(s)} = C_{\varnothing,U(s)}$ and we simply note the disequilibria $C_{U(s)}$.

Life cycle: The model describes a species undergoing the following events during its life cycle: diploid selection (D), meiosis (M), haploid selection (H), and syngamy (S). The superscripts D, M, H, and S denote these different events. By construction of the life cycle, male and female populations are strictly identical just after syngamy on autosomes because both male and female individuals are made from the fusion of a male and a female gamete and because I suppose for now that sex is determined at unlinked loci (I consider linkage to a sex-determining locus at the end of the model section). Therefore, I consider the start of a generation just after syngamy when male and female populations have exactly the same frequency and combinations of autosomal genes. The linkage disequilibria are measured within a generation relative to the gene frequency at this moment. Denote $C_{U,V}$ any value of linkage disequilibrium measured just after syngamy. Within one generation during the life cycle, the $C_{U,V}$ will vary around this value and these variations will be sex specific until the next syngamy event. I therefore denote $C_{U,V}$, $C^{\mathrm{D}}_{U,V(s)}$, $C^{\mathrm{DM}}_{U(s)}$, $C^{\mathrm{DMH}}_{U(s)}$, $C^{\mathrm{DMHS}}_{U,V}$ the linkage disequilibria values mea-

TABLE 1

Table of notations

Parameters	
a	Selection coefficient
α, β	Selection coefficient when partitioned in average effect ($\bar{\alpha}$), sex effect ($\hat{\alpha}$), sex-of-origin effect ($\tilde{\alpha}$), and sex-by-sex-of-origin interaction (β), [see (17)]
ε	Multiplicative epistasis [see (20–21)]
δ	Unspecified source of linkage disequilibrium between j and k loci
r	Recombination rate
ρ	Effect of allele 1 at the modifier locus on the recombination rate between loci j and k
Variables	
X	Haploid genotype at a locus taking value 0 or 1 for the first and second allele, respectively
$\mathbf{x}$ and $\mathbf{x}^*$	Set of loci inherited from the father and the mother, respectively
p and q	Allele 1 frequency and allele 0 frequency
C	Measure of association of alleles
Subscripts	
(s)	Refers to the value of a parameter or variable taken in an individual of sex s; s can be male/female (m or f) or homogametic/heterogametic (00/01)
U	Refers to a haploid set of loci
U, V	Refers to a diploid set of loci made up of two haploid sets: U inherited from the father and V inherited from the mother
l	Refers to a single locus
i, j, and k	Refer to the loci labeled i (the modifier locus), j (a selected locus or a sex-determining locus), k (a selected locus)
Superscripts	
D, M, H, S	Refer to the different events in the life cycle (diploid selection, meiosis, haploid selection, syngamy): when applied to a variable, it indicates its value after the last event listed [*e.g.*, V^{DM} is the value of the variable V after (1) diploid selection and (2) meiosis, in this order]; when applied to a parameter it indicates its value summed over the events listed (*e.g.*, P^{DH} is the sum of value of P in the haploid and diploid phases)
$\bar{V}$ or $\bar{P}$	A bar on a parameter or a variable indicates the average over male and female values
$\hat{V}$ or $\hat{P}$	A circumflex on a parameter or a variable indicate the difference between male and female values
$^\circ$	Refers to a QLE value for an association C
B	Refers to recombination rates in the absence of the modifier allele

sured along the life cycle (Figure 1), after syngamy, diploid selection, meiosis, haploid selection, and syngamy, respectively. Note that after meiosis, only the disequilibria defined on haploids are needed to describe the population. I follow these events in this order in the next sections.

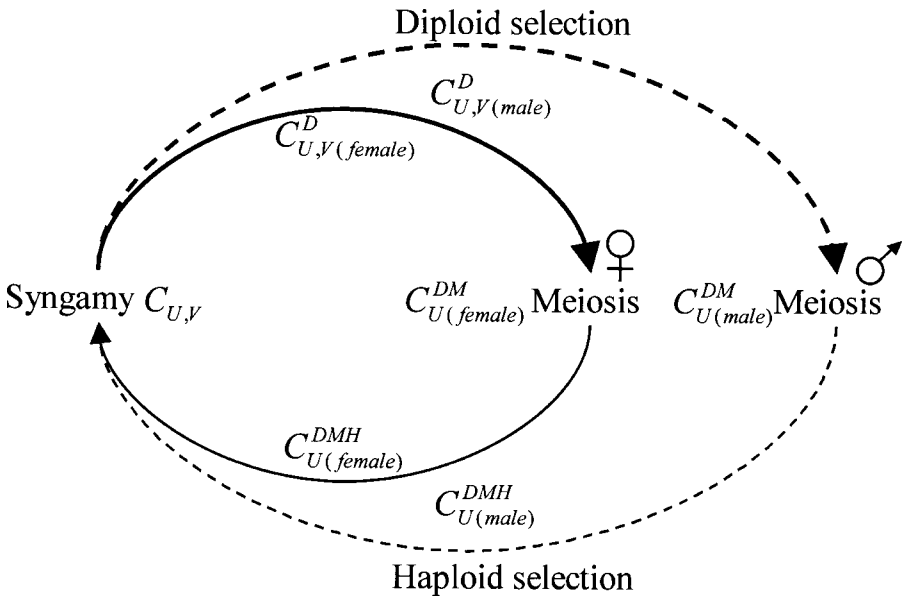

FIGURE 1.—Life cycle. Thick and thin lines represent diploid and haploid phases, respectively. Dashed and non-dashed lines represent male and female life cycles, respectively. The notation for the linkage disequilibria is described in the text.

Diploid selection: I use a sex-specific diploid fitness function that allows for dominance, *cis*-, and *trans*-epistasis terms (*i.e.*, a combination of genes may have different fitness effects if the genes are on the same or different chromosomes) and sex-of-origin effects (*i.e.*, a gene or combination of genes in a diploid individual is not considered to have the same fitness effect if it is contributed from the mother or the father). Selective interactions between more than two loci are ignored. Specifically, the fitness function is

$$W^{\mathrm{D}}(\mathbf{x}_{(s)}, \mathbf{x}^{*}_{(s)}) = \sum_{U,V} a^{\mathrm{D}}_{U,V(s)} \prod_{l\in U} X_{l(s)} \prod_{l\in V} X^{*}_{l(s)}, \qquad (2)$$

where U and V represent the set of selected alleles inherited from the father and the mother, respectively (*i.e.*, one of the following set of indices U, $V = \{\varnothing, j, k, jk\}$, with the convention that $a^{\mathrm{D}}_{\varnothing,\varnothing(s)} = 1$), (s) indicates the gender of the individual carrying the alleles (whether it is a male or a female), and the superscript D indicates that these parameters represent selection during the diploid phase. For instance $a^{\mathrm{D}}_{j,\varnothing(s)}$ is the additive effect of the selected allele at locus j during the diploid phase (D) in an individual of sex (s) when this allele is inherited from the father. Overall, for two loci, diploid selection is described using 30 independent parameters: there is no constraint on the fitness matrix (16 selected genotypes are in each sex and hence 15 relative fitness).

Assuming that the directional selection coefficients $a^{\mathrm{D}}_{j,\varnothing(s)}$, $a^{\mathrm{D}}_{k,\varnothing(s)}$, $a^{\mathrm{D}}_{\varnothing,j(s)}$, $a^{\mathrm{D}}_{\varnothing,k(s)}$ are small, of order ξ, a small parameter, and that all other selection coefficients—interactions between alleles—are smaller, of order ξ^2, the different disequilibria measured between loci i, j and k change after selection on diploids as

$$\begin{aligned}
C^{\mathrm{D}}_{jk,\varnothing(s)} &= C_{jk,\varnothing} + A \\
&\quad + (a^{\mathrm{D}}_{jk,\varnothing(s)} - a^{\mathrm{D}}_{j,\varnothing(s)} a^{\mathrm{D}}_{k,\varnothing(s)} + a^{\mathrm{D}}_{jk,j(s)} \overline{p}_j + a^{\mathrm{D}}_{jk,k(s)} \overline{p}_k + a^{\mathrm{D}}_{jk,jk(s)} \overline{p}_j \overline{p}_k + \delta^{\mathrm{D}}_{jk(s)}) \\
&\quad \times \overline{pq}_{jk} + o(\xi^2) \\
C^{\mathrm{D}}_{j,k(s)} &= C_{j,k} - A \\
&\quad + (a^{\mathrm{D}}_{j,k(s)} - a^{\mathrm{D}}_{j,\varnothing(s)} a^{\mathrm{D}}_{\varnothing,k(s)} + a^{\mathrm{D}}_{j,jk(s)} \overline{p}_j + a^{\mathrm{D}}_{jk,k(s)} \overline{p}_k + a^{\mathrm{D}}_{jk,jk(s)} \overline{p}_j \overline{p}_k + \delta^{\mathrm{D}}_{jk(s)}) \\
&\quad \times \overline{pq}_{jk} + o(\xi^2) \\
C^{\mathrm{D}}_{ij,\varnothing(s)} &= C_{ij,\varnothing} + a^{\mathrm{D}}_{k,\varnothing(s)} C_{ijk,\varnothing} + o(C_{ijk,\varnothing}\xi) \\
C^{\mathrm{D}}_{ijk,\varnothing} &= C_{ijk,\varnothing} + o(C_{ijk,\varnothing}), \qquad (3)
\end{aligned}$$

where

$$A = \overline{pq}_j \frac{a^{\mathrm{D}}_{j,\varnothing(s)} - a^{\mathrm{D}}_{\varnothing,j(s)}}{2} C_{k,\varnothing} + \overline{pq}_k \frac{a^{\mathrm{D}}_{k,\varnothing(s)} - a^{\mathrm{D}}_{\varnothing,k(s)}}{2} C_{j,\varnothing} + \overline{pq}_{jk} \frac{(a^{\mathrm{D}}_{j,\varnothing(s)} - a^{\mathrm{D}}_{\varnothing,j(s)})(a^{\mathrm{D}}_{k,\varnothing(s)} - a^{\mathrm{D}}_{\varnothing,k(s)})}{4} \qquad (4)$$

(with the value of $C_{j,\varnothing}$ and $C_{k,\varnothing}$ given in the syngamy section) and

$$\overline{pq}_U = \prod_{l\in U} \overline{p}_l (1 - \overline{p}_l). \qquad (5)$$

Symmetrical moments ($C^{\mathrm{D}}_{\varnothing,jk}$, $C^{\mathrm{D}}_{k,j}$, $C^{\mathrm{D}}_{\varnothing,ij}$, $C^{\mathrm{D}}_{\varnothing,ijk}$) can be obtained by permuting all U and V indices in (3) and (4). The recursions for $C^{\mathrm{D}}_{ik,\varnothing}$ and $C^{\mathrm{D}}_{\varnothing,ik}$ are equivalent to recursions for $C^{\mathrm{D}}_{ij,\varnothing}$ and $C^{\mathrm{D}}_{\varnothing,ij}$, respectively, with subscript j replaced by k throughout. Note that only the variations in the disequilibria that are useful below are given in (3) (for instance, diploid selection changes $C_{j,j}$, but this moment does not influence frequency change at the recombination modifier locus).

The assumption that selective interactions between alleles are smaller than directional selection allows the analysis of a case more general than the situation in which all selection coefficients have the same order (Barton 1995, see results section for details). For the sake of discussion, I also introduce in (3) an unspecified sex-specific source of linkage disequilibrium, $\delta^{\mathrm{D}}_{jk(s)}$, between the selected loci j and k during the diploid phase, which could be created by forces other than those considered in this model, such as migration (Lenormand and Otto 2000) or drift (Otto and Barton 1997).

Meiosis: Meiosis occurs after diploid selection in a sexual life cycle. Let $r^{\mathrm{B}}_{U(s)}$ equal the basal recombination rate between the set of loci U, *i.e.*, when the 0 allele at the modifier locus is fixed in the population. Each copy of the modifier allele at locus i modifies the recombination rate between the viability loci j and k by a small amount $\rho_{(s)} = O(\xi)$ in an individual of gender s. I simply denote $r_{U(s)}$ the average recombination between the set of loci U over the different genotypes at locus i in the population of gender s. Assuming that the loci are in the order *i-j-k*,

$$\begin{aligned}
r_{jk(s)} &= r^{\mathrm{B}}_{jk(s)} + \rho_{(s)} E[X_i + X^{*}_i] = r^{\mathrm{B}}_{jk(s)} + 2\rho_{(s)} \overline{p}_i \\
r_{ij(s)} &= r^{\mathrm{B}}_{ij(s)} \\
r_{ik(s)} &= r_{ijk(s)} - r^{\mathrm{B}}_{ij(s)} (r^{\mathrm{B}}_{jk(s)} + \rho_{(s)}) \\
r_{ijk(s)} &= r^{\mathrm{B}}_{ij(s)} + r^{\mathrm{B}}_{jk(s)} + \rho_{(s)} - r^{\mathrm{B}}_{ij(s)} (r^{\mathrm{B}}_{jk(s)} + \rho_{(s)}), \qquad (6)
\end{aligned}$$

where r_{ijk} is the chance that the trilocus genotype is broken apart by recombination. Note that when locus i is involved, the recombination rate does not depend on the frequency of the modifier allele because recombination matters only when locus i is heterozygous. After meiosis the different disequilibria measured between loci i, j, and k change as follows:

$$\begin{aligned}
2C^{\mathrm{DM}}_{jk(s)} &= (1 - r_{jk(s)})(C^{\mathrm{D}}_{jk,\varnothing(s)} + C^{\mathrm{D}}_{\varnothing,jk(s)}) + r_{jk(s)}(C^{\mathrm{D}}_{j,k(s)} + C^{\mathrm{D}}_{k,j(s)}) \\
2C^{\mathrm{DM}}_{ijk(s)} &= (1 - r_{ijk(s)})(C^{\mathrm{D}}_{ijk,\varnothing(s)} + C^{\mathrm{D}}_{\varnothing,ijk(s)}) \\
&\quad + \rho_{(s)} \overline{pq}_i (C^{\mathrm{D}}_{j,k(s)} + C^{\mathrm{D}}_{k,j(s)} - C^{\mathrm{D}}_{jk,\varnothing(s)} - C^{\mathrm{D}}_{\varnothing,jk(s)}) + o(C^{\mathrm{DM}}_{ijk(s)}). \qquad (7)
\end{aligned}$$

The recursion for $C^{\mathrm{DM}}_{ij(s)}$ (respectively $C^{\mathrm{DM}}_{ik(s)}$) is equivalent to recursion for $C^{\mathrm{DM}}_{jk(s)}$ with subscript k (respectively j) replaced by i.

Haploid selection: Haploid fitness is defined in the same way as diploid fitness except that there are no *trans*-effects and no sex-of-origin effects of alleles. A

superscript H indicates selection occurring during the haploid phase, with fitness equal to

$$W^{\mathrm{H}}(\mathbf{x}_{(s)}) = \sum_U a^{\mathrm{H}}_{U(s)} \prod_{l\in U} X_{l(s)}. \quad (8)$$

Overall, for two loci, haploid selection is described using six parameters (three relative fitnesses in each sex). Assuming, as for diploid selection, that $\alpha^{\mathrm{H}}_{j(s)}$, $\alpha^{\mathrm{H}}_{k(s)}$ are $O(\xi)$ and that $\alpha^{\mathrm{H}}_{jk(s)}$ is $O(\xi^2)$ the different linkage disequilibria change after selection on haploids as

$$\begin{aligned} C^{\mathrm{DMH}}_{jk(s)} &= C^{\mathrm{DM}}_{jk(s)} + (a^{\mathrm{H}}_{jk(s)} + \delta^{\mathrm{H}}_{jk(s)})\overline{pq}_{jk} + o(\xi^2) \\ C^{\mathrm{DMH}}_{ij(s)} &= a^{\mathrm{H}}_{k(s)} C^{\mathrm{DM}}_{ijk(s)} + o(C^{\mathrm{DM}}_{ijk(s)}\xi) \\ C^{\mathrm{DMH}}_{ijk(s)} &= C^{\mathrm{DM}}_{ijk(s)} + o(C^{\mathrm{DM}}_{ijk(s)}), \end{aligned} \quad (9)$$

where again, I introduce an unspecified, sex-specific source of linkage disequilibrium, $\delta^{\mathrm{H}}_{jk(s)}$, between the selected loci j and k during the haploid phase.

Syngamy: I assume that each new diploid individual results from the random fusion of a male and a female gamete and that its gender is independent of its autosomal genes. After syngamy the different disequilibria measured between loci i, j, and k change as

$$\begin{aligned} C^{\mathrm{DMHS}}_{U,V} = &\left(C^{\mathrm{DMH}}_{U(m)} + \sum_{S+T=U} C^{\mathrm{DMH}}_{S(m)} C^{\mathrm{DMH}}_{T(m)} + \sum_{S+T+W=U} C^{\mathrm{DMH}}_{S(m)} C^{\mathrm{DMH}}_{T(m)} C^{\mathrm{DMH}}_{W(m)}\right) \\ &\times \left(C^{\mathrm{DMH}}_{V(f)} + \sum_{S+T=V} C^{\mathrm{DMH}}_{S(f)} C^{\mathrm{DMH}}_{T(f)} + \sum_{S+T+W=V} C^{\mathrm{DMH}}_{S(f)} C^{\mathrm{DMH}}_{T(f)} C^{\mathrm{DMH}}_{W(f)}\right), \end{aligned} \quad (10)$$

where the sums are over disjoint partitions of U or V with the convention $S, T, W \neq \varnothing$ if these partitions exist [because U and V may contain less than three (two) loci, the triple (double) partition may not be possible] and

$$\begin{aligned} C_{l(m)} &= -C_{l(f)} = C_{l,\varnothing} = -C_{\varnothing,l} = (p^{\mathrm{DMH}}_{l(m)} - p^{\mathrm{DMH}}_{l(f)})/2 \\ &= \overline{pq}_l (a^{\mathrm{DH}}_{l,\varnothing(m)} + a^{\mathrm{DH}}_{\varnothing,l(m)} - a^{\mathrm{DH}}_{l,\varnothing(f)} - a^{\mathrm{DH}}_{\varnothing,l(f)})/4 \end{aligned} \quad (11)$$

in which the notation x^{DH} is shorthand for $x^{\mathrm{D}} + x^{\mathrm{H}}$.

Under random mating $C^{\mathrm{DMHS}}_{U,V} = C^{\mathrm{DMH}}_U C^{\mathrm{DMH}}_V$ (Barton and Turelli 1991). In this model, however, mating is not random (female gametes fuse with male gametes). Extra terms in $C^{\mathrm{DMHS}}_{U,V}$ arise because the frequencies of the selected alleles are different between male and female gametes before syngamy. These frequency differences are caused by differences in diploid and haploid selection between males and females. This extra source of linkage disequilibrium is analogous to the linkage disequilibria created by migration between populations with different gene frequencies (Lenormand and Otto 2000).

Frequency change at the modifier locus: The frequency change at the modifier locus over one generation is found by linearizing the exact recursions to order ξ^5,

$$\begin{aligned} \Delta\overline{p}_i &= \overline{p}^{\mathrm{DMHS}}_i - \overline{p}_i \\ &= \frac{1}{4} \sum_{s=m,f} \sum_{U=j,k,jk} (a^{\mathrm{D}}_{U,\varnothing(s)} C_{Ui,\varnothing} + a^{\mathrm{D}}_{\varnothing,U(s)} C_{\varnothing,Ui} \\ &\quad + a^{\mathrm{D}}_{jk,U(s)} \overline{p}_U C_{ijk,\varnothing} + a^{\mathrm{D}}_{U,jk(s)} \overline{p}_U C_{\varnothing,ijk} + 2a^{\mathrm{H}}_{U(s)} C^{\mathrm{DM}}_{Ui(s)}) + o(\xi^5), \end{aligned} \quad (12)$$

where $\overline{p}_{jk} = \overline{p}_j\overline{p}_k$. To simplify this expression, I use a quasi-linkage equilibrium (QLE) approximation (see Nagylaki 1976; Barton and Turelli 1991; Barton 1995) to determine the value of the different disequilibria after syngamy ($C_{U,V}$) or meiosis ($C^{\mathrm{DM}}_{U(s)}$).

QLE assumption: Assuming that recombination rates are of higher order than epistasis, the different disequilibria quickly reach "quasi-linkage" equilibrium, at which point their values, denoted with a circle superscript, can be obtained by solving to leading order in ξ the difference equation,

$$C^{\mathrm{DMHS}}_U - C_U = 0, \quad (13)$$

where C^{DMHS}_U is rewritten in terms of C_U using Equations 10, 9, 7, and 3. To simplify the result, it is much simpler to partition the selection coefficients into four terms: the average effect of a gene or gene combination over sex and sex-of-origin,

$$\overline{\alpha}^{\mathrm{D}}_{U,V} = (a^{\mathrm{D}}_{U,V(m)} + a^{\mathrm{D}}_{U,V(f)} + a^{\mathrm{D}}_{V,U(m)} + a^{\mathrm{D}}_{V,U(f)})/4, \quad (14)$$

the sex-effect averaged over sex-of-origin,

$$\hat{\alpha}^{\mathrm{D}}_{U,V} = (a^{\mathrm{D}}_{U,V(m)} + a^{\mathrm{D}}_{V,U(m)} - a^{\mathrm{D}}_{U,V(f)} - a^{\mathrm{D}}_{V,U(f)})/2, \quad (15)$$

the sex-of-origin effect averaged over sex,

$$\tilde{\alpha}^{\mathrm{D}}_{U,V} = (a^{\mathrm{D}}_{U,V(m)} + a^{\mathrm{D}}_{U,V(f)} - a^{\mathrm{D}}_{V,U(m)} - a^{\mathrm{D}}_{V,U(f)})/2, \quad (16)$$

and the interaction between the sex and the sex-of-origin effects,

$$\beta^{\mathrm{D}}_{U,V} = a^{\mathrm{D}}_{U,V(m)} + a^{\mathrm{D}}_{V,U(f)} - a^{\mathrm{D}}_{V,U(m)} - a^{\mathrm{D}}_{U,V(f)}, \quad (17)$$

which gives

$$\begin{aligned} a^{\mathrm{D}}_{U,V(m)} &= \overline{\alpha}^{\mathrm{D}}_{U,V} + \frac{\hat{\alpha}^{\mathrm{D}}_{U,V}}{2} + \frac{\tilde{\alpha}^{\mathrm{D}}_{U,V}}{2} + \frac{\beta^{\mathrm{D}}_{U,V}}{4} \\ a^{\mathrm{D}}_{U,V(f)} &= \overline{\alpha}^{\mathrm{D}}_{U,V} - \frac{\hat{\alpha}^{\mathrm{D}}_{U,V}}{2} + \frac{\tilde{\alpha}^{\mathrm{D}}_{U,V}}{2} - \frac{\beta^{\mathrm{D}}_{U,V}}{4} \\ a^{\mathrm{D}}_{V,U(m)} &= \overline{\alpha}^{\mathrm{D}}_{U,V} + \frac{\hat{\alpha}^{\mathrm{D}}_{U,V}}{2} - \frac{\tilde{\alpha}^{\mathrm{D}}_{U,V}}{2} - \frac{\beta^{\mathrm{D}}_{U,V}}{4} \\ a^{\mathrm{D}}_{V,U(f)} &= \overline{\alpha}^{\mathrm{D}}_{U,V} - \frac{\hat{\alpha}^{\mathrm{D}}_{U,V}}{2} - \frac{\tilde{\alpha}^{\mathrm{D}}_{U,V}}{2} + \frac{\beta^{\mathrm{D}}_{U,V}}{4}. \end{aligned} \quad (18)$$

The haploid selection coefficients $a^{\mathrm{H}}_{U(s)}$ and the modifier effects $\rho_{(s)}$ are rewritten in the same way (but without sex-of-origin and sex-by-sex-of-origin effect); *i.e.*, the overbar indicates an average value over males and females while a hat indicates a difference between male and female values.

The linkage disequilibrium between the selected loci C_{jk} does not enter directly in (12), but its average value produces C_{ijk} [see (7)], which in turn produces C_{ij} and C_{ik} [see (3) and (9)]. Its average QLE value measured after syngamy is

$$\frac{\mathring{C}_{jk,\varnothing} + \mathring{C}_{\varnothing,jk}}{2} = \overline{pq}_{jk}\left(\frac{(\overline{E} + \overline{D})}{\overline{r}_{jk}} - E^{\mathrm{D}}\right), \quad (19)$$

where

$$\overline{E} \equiv \overline{\varepsilon}_{jk}^{\mathrm{DH}} + (\hat{\alpha}_j^{\mathrm{H}}\hat{\alpha}_k^{\mathrm{D}} + \hat{\alpha}_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{H}} + \tilde{\alpha}_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{DH}} + \tilde{\alpha}_k^{\mathrm{D}}\hat{\alpha}_j^{\mathrm{DH}})/4$$

$$E^{\mathrm{D}} \equiv \overline{\alpha}_{jk}^{\mathrm{D}} - \overline{\alpha}_{j,k}^{\mathrm{D}} + (\tilde{\alpha}_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{DH}} + \tilde{\alpha}_k^{\mathrm{D}}\hat{\alpha}_j^{\mathrm{DH}})/2 + \hat{\alpha}_j^{\mathrm{DH}}\hat{\alpha}_k^{\mathrm{DH}}/4$$

$$\overline{D} = \overline{\delta}_{jk}^{\mathrm{D}} + \overline{\delta}_{jk}^{\mathrm{H}}. \tag{20}$$

Equation 20 summarizes the different forces producing the linkage disequilibrium between the selected loci: diploid multiplicative epistasis,

$$\overline{\varepsilon}_{jk}^{\mathrm{D}} \equiv \overline{\alpha}_{jk}^{\mathrm{D}} - \overline{\alpha}_j^{\mathrm{D}}\overline{\alpha}_k^{\mathrm{D}} + \overline{\alpha}_{jk,j}^{\mathrm{D}}\overline{p}_j + \overline{\alpha}_{jk,k}^{\mathrm{D}}\overline{p}_k + \overline{\alpha}_{jk,jk}^{\mathrm{D}}\overline{p}_j\overline{p}_k, \tag{21}$$

haploid multiplicative epistasis,

$$\overline{\varepsilon}_{jk}^{\mathrm{H}} \equiv \overline{\alpha}_{jk}^{\mathrm{H}} - \overline{\alpha}_j^{\mathrm{H}}\overline{\alpha}_k^{\mathrm{H}}, \tag{22}$$

mixing at syngamy of male and female gametes with different frequency (all terms including $\hat{\alpha}$); difference between average *cis*- and *trans*-epistasis ($\overline{\alpha}_{jk}^{\mathrm{D}} - \overline{\alpha}_{j,k}^{\mathrm{D}}$), and finally, the unspecified source of linkage disequilibrium that I introduced for generality ($\overline{\delta}_{jk}^{\mathrm{DH}}$). However, and more importantly, (19) shows that C_{jk} is made up of two terms: one depending on recombination (proportional to $\overline{E} + \overline{D}$) and another independent of recombination (proportional to E^{D}). As a consequence, the different forces summarized in E^{D} play no role for the evolution of recombination (for instance, average *trans*-epistasis $\overline{\alpha}_{j,k}^{\mathrm{D}}$ has no effect at all on the evolution of recombination rate, a result already mentioned by Pylkov *et al.* 1998 for the evolution of average recombination rates).

The QLE values of $C_{ij,\varnothing}$, $C_{\varnothing,ij}$, $C_{ik,\varnothing}$, $C_{\varnothing,ik}$, $C_{ijk,\varnothing}$, $C_{\varnothing,ijk}$ are more complicated but can be deduced from the values of

$$\begin{aligned} C^{\circ}_{ij,\varnothing} = -\frac{\overline{pq}_{ijk}}{2}\Bigg(& [4\overline{\alpha}_k^{\mathrm{H}}\bar{r}_{ij} + 2\hat{\alpha}_k^{\mathrm{H}} + (1-\bar{r}_{ij})(2\tilde{\alpha}_k^{\mathrm{D}} + \beta_k^{\mathrm{D}}\bar{r}_{ij})] \\ & \times \left[\frac{\overline{\rho}\hat{E}^{\mathrm{D}}}{4\bar{r}_{ij}} + \frac{\hat{\rho}(\overline{E}+\overline{D})}{4\bar{r}_{ij}\bar{r}_{jk}}\right] \\ & + [2\overline{\alpha}_k^{\mathrm{H}} + \hat{\alpha}_k^{\mathrm{H}}\bar{r}_{ij} + (1-\bar{r}_{ij})(2\overline{\alpha}_k^{\mathrm{D}} + \hat{\alpha}_k^{\mathrm{D}}\bar{r}_{ij})] \\ & \times \left[\frac{\overline{\rho}(\overline{E}+\overline{D})}{\bar{r}_{ij}\bar{r}_{jk}\bar{r}_{ijk}} + \frac{\hat{\rho}\hat{E}^{\mathrm{D}}}{4\bar{r}_{ij}\bar{r}_{ijk}}\right]\Bigg) + o(\xi^4) \end{aligned}$$

$$C^{\circ}_{ijk,\varnothing} = -\overline{pq}_{ijk}\left(\overline{\rho}\left(\frac{(\overline{E}+\overline{D})}{\bar{r}_{jk}\bar{r}_{ijk}} + \frac{\hat{E}^{\mathrm{D}}}{2}\right) + \hat{\rho}\left(\frac{\hat{E}^{\mathrm{D}}}{4\bar{r}_{ijk}} + \frac{(\overline{E}+\overline{D})}{2\bar{r}_{jk}}\right)\right) + o(\xi^3), \tag{23}$$

where

$$\hat{E}^{\mathrm{D}} \equiv \hat{\alpha}_{jk}^{\mathrm{D}} - \hat{\alpha}_{j,k}^{\mathrm{D}} + (\beta_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{DH}} + \beta_k^{\mathrm{D}}\hat{\alpha}_j^{\mathrm{DH}})/2. \tag{24}$$

$C^{\circ}_{ik,\varnothing}$ is obtained from $C^{\circ}_{ij,\varnothing}$ by switching j and k subscripts and the $C^{\circ}_{\varnothing,U}$ are obtained from the $C^{\circ}_{U,\varnothing}$ by switching the sign of all $\hat{\alpha}$, $\tilde{\alpha}$ and the sign of $\hat{\rho}$ (the male-female difference of the modifier effect). The three-way association C°_{ijk} is built at meiosis if *cis*- and *trans*-pairwise disequilibria between loci j and k do not equal one another ($C^{\mathrm{D}}_{jk(s)} - C^{\mathrm{D}}_{j,k(s)} \neq 0$) (note that C_{ijk} is only added to in Equation 7). This condition is easily met because C^{D}_{jk} accumulates through time whereas $C^{\mathrm{D}}_{j,k}$ is strongly reduced by segregation each generation [see (10)]. These QLE solutions are valid when there are differences between males and females in basal recombination rates (*i.e.*, when $r^{\mathrm{B}}_{U(\mathrm{male})} \neq r^{\mathrm{B}}_{U(\mathrm{female})}$) provided these differences are small (of order ξ). The more general result with a large difference in basal recombination rates between males and females is simple for the value of $(C^{\circ}_{jk,\varnothing} + C^{\circ}_{\varnothing,jk})/2$ [it adds a term equal to $-\overline{pq}_{jk}\hat{E}^{\mathrm{D}}\hat{r}_{jk}/4r_{jk}$ to its value in (19)] and for the values of $(C^{\circ}_{ijk,\varnothing} + C^{\circ}_{\varnothing,ijk})/2$ and $(C^{\circ}_{ijk,\varnothing} - C^{\circ}_{\varnothing,ijk})$ (it adds the same term times $-\overline{\rho}\,\overline{pq}_i/r_{ijk}$ and $-\hat{\rho}\,\overline{pq}_i$, respectively). However, with a large difference in basal recombination rates between males and females, the QLE values of C_{ij} and C_{ik} are complicated (see results below).

General result for autosomes: The frequency change at the modifier is obtained using Equation 12. The QLE values of the disequilibria measured after syngamy, C°_{U}, are given by Equation 23, and the QLE values of the disequilibria measured after meiosis, $C^{\mathrm{DM}\circ}_{U(s)}$, are gender specific and were computed using Equations 7 and 3 and the C°_{U} values. This gives

$$\begin{aligned} \Delta\overline{p}_i = -\overline{pq}_{ijk}\Bigg[& (\overline{E} + \Lambda)\left(\frac{\overline{\rho}(\overline{E}+\overline{D})}{\bar{r}_{ijk}\bar{r}_{jk}} + \frac{\hat{\rho}\hat{E}^{\mathrm{D}}}{4\bar{r}_{ijk}}\right) + (\hat{E}^{\mathrm{H}} + \tilde{E}^{\mathrm{D}}) \\ & \times \left(\frac{\overline{\rho}\hat{E}^{\mathrm{D}}}{4} + \frac{\hat{\rho}(\overline{E}+\overline{D})}{4\bar{r}_{jk}}\right)\Bigg] + o(\xi^5) \end{aligned} \tag{25}$$

with $\overline{E}$, $\hat{E}^{\mathrm{D}}$, $\hat{E}^{\mathrm{H}}$, Λ, $\overline{D}$:

$$\overline{E} \equiv \overline{\varepsilon}_{jk}^{\mathrm{DH}} + (\hat{\alpha}_j^{\mathrm{H}}\hat{\alpha}_k^{\mathrm{D}} + \hat{\alpha}_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{H}} + \tilde{\alpha}_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{DH}} + \tilde{\alpha}_k^{\mathrm{D}}\hat{\alpha}_j^{\mathrm{DH}})/4$$

$$\hat{E}^{\mathrm{D}} \equiv \hat{\alpha}_{jk}^{\mathrm{D}} - \hat{\alpha}_{j,k}^{\mathrm{D}} + (\beta_j^{\mathrm{D}}\hat{\alpha}_k^{\mathrm{DH}} + \beta_k^{\mathrm{D}}\hat{\alpha}_j^{\mathrm{DH}})/2$$

$$\tilde{E}^{\mathrm{D}} \equiv \tilde{\alpha}_{jk}^{\mathrm{D}} + \tilde{\alpha}_{jk,j}^{\mathrm{D}}\overline{p}_j + \tilde{\alpha}_{jk,k}^{\mathrm{D}}\overline{p}_k + \sum_{j\leftrightarrow k}\tilde{\alpha}_j^{\mathrm{D}}(\overline{\alpha}_k^{\mathrm{D}} + \overline{\alpha}_k^{\mathrm{DH}}/\bar{r}_{ik} + \beta_k^{\mathrm{D}}(1-\bar{r}_{ij})/4)$$

$$\hat{E}^{\mathrm{H}} \equiv \hat{\alpha}_{jk}^{\mathrm{H}} + \sum_{j\leftrightarrow k}\hat{\alpha}_j^{\mathrm{H}}(\overline{\alpha}_k^{\mathrm{H}} + \overline{\alpha}_k^{\mathrm{DH}}/\bar{r}_{ik} + \beta_k^{\mathrm{D}}(1-\bar{r}_{ij})/4)$$

$$\Lambda \equiv \overline{\alpha}_j^{\mathrm{DH}}\overline{\alpha}_k^{\mathrm{DH}}\left(\frac{1}{\bar{r}_{ij}} + \frac{1}{\bar{r}_{ik}} - 1\right) + \sum_{j\leftrightarrow k}\bar{r}_{ij}\hat{\alpha}_k^{\mathrm{D}}(\hat{\alpha}_j^{\mathrm{H}} + \tilde{\alpha}_j^{\mathrm{D}})/4$$

$$\overline{D} \equiv \overline{\delta}_{jk}^{\mathrm{D}} + \overline{\delta}_{jk}^{\mathrm{H}}. \tag{26}$$

$\overline{E}$, $\overline{D}$, and $\hat{E}^{\mathrm{D}}$ are already defined above but are repeated here for clarity. Sums over $j \leftrightarrow k$ indicate that a term with indices j and k switched must be added to the term in the sum. The same computations can be made by assuming that epistasis terms are of order ξ instead of ξ^2 (in which case recombination rates are assumed to be of order 1). In that case, the frequency change at the modifier locus is stronger (of order ξ^3) and is also given by (25) where only terms of order ξ are kept in $\overline{E}$, $\hat{E}^{\mathrm{D}}$, $\hat{E}^{\mathrm{H}}$, $\tilde{E}^{\mathrm{D}}$, Λ, that is, with

$$\begin{aligned} \overline{E} &= \overline{\varepsilon}_{jk}^{\mathrm{DH}} \\ \hat{E}^{\mathrm{D}} &= \hat{\alpha}_{jk}^{\mathrm{D}} - \hat{\alpha}_{j,k}^{\mathrm{D}} \\ \tilde{E}^{\mathrm{D}} &= \tilde{\alpha}_{jk}^{\mathrm{D}} + \tilde{\alpha}_{jk,j}^{\mathrm{D}}\overline{p}_j + \tilde{\alpha}_{jk,k}^{\mathrm{D}}\overline{p}_k \\ \hat{E}^{\mathrm{H}} &= \hat{\alpha}_{jk}^{\mathrm{H}} \\ \Lambda &= 0 \\ \overline{D} &= \overline{\delta}_{jk}^{\mathrm{D}} + \overline{\delta}_{jk}^{\mathrm{H}}. \end{aligned} \tag{27}$$

As a consequence, Equation 25 covers both cases and allows one to discuss situations where epistasis terms are

closer to zero (which is not possible with the strong epistasis approximation). A modifier allele will change in frequency because it causes the average recombination rate (when $\bar{\rho} \neq 0$) to evolve, because it causes a dimorphism in recombination rates between males and females to evolve (when $\hat{\rho} \neq 0$), or because of both. A modifier allele with an effect restricted to one sex will fall into this last category.

Evolution of the average recombination rate: The evolution of the average recombination rate has been determined several times in the literature. It has been found that increased recombination evolves when there is weak negative multiplicative epistasis (*i.e.*, when $-\Lambda < \bar{\alpha}_{jk} - \bar{\alpha}_j\,\bar{\alpha}_k < 0$, where Λ is a threshold value; Barton 1995, see below). This result has been shown to hold for both haploid and diploid selection (Barton 1995, Equation A1.5f). It can be obtained from Equation 25 assuming that there are no selective differences between males and females during both diploid and haploid phase, no selective differences associated with sex-of-origin of alleles, and no other source of linkage disequilibrium besides epistasis (*i.e.*, if

$$\hat{\alpha}_U = 0, \quad \tilde{\alpha}_U = 0, \quad \overline{D} = 0), \tag{28}$$

which leads to

$$\Delta\overline{p}_i = -\overline{pq}_{ijk}\left[\frac{\bar{\rho}\;\overline{E}(\overline{E} + \Lambda)}{\bar{r}_{ijk}\bar{r}_{jk}}\right] + o(\xi^5), \tag{29}$$

where the expressions for $\overline{E}$ and Λ simplify to

$$\overline{E} = \bar{\varepsilon}^{DH}_{jk}$$

$$\Lambda = \bar{\alpha}^{DH}_j\bar{\alpha}^{DH}_k\left(\frac{1}{\bar{r}_{ij}} + \frac{1}{\bar{r}_{ik}} - 1\right). \tag{30}$$

Thus, the weak negative epistasis result holds provided that assumptions (28) are fulfilled. However, Equation 25 shows that the average recombination rate may evolve by other means: it can evolve if

$$\Delta\overline{p}_i = -\overline{pq}_{ijk}\bar{\rho}\left(\frac{(\overline{E} + \overline{D})(\overline{E} + \Lambda)}{\bar{r}_{ijk}\bar{r}_{jk}} + \frac{\hat{E}^D(\hat{E}^H + \tilde{E}^D)}{4}\right) + o(\xi^5) \tag{31}$$

is nonzero, which suggests three other possibilities: it can evolve if $\hat{E}^D\,\hat{E}^H$ or $\hat{E}^D\,\tilde{E}^D$ is nonzero, which means that the difference between *cis*- and *trans*-epistasis is different in males and females during diploid selection or that there are sex-by-sex-of-origin selective interactions [*i.e.*, $\hat{E}^D \neq 0$; see definition of $\hat{E}^D$ in (26)] and haploid selection differences between males and females ($\hat{E}^H \neq 0$) or sex-of-origin effects during diploid selection ($\tilde{E}^D \neq 0$). The average rate of recombination can also evolve if there is another source of linkage disequilibrium ($\overline{D} \neq 0$), for instance, that produced by migration (Lenormand and Otto 2000) or drift (Otto and Barton 1997, 2001).

Evolution of a dimorphism in recombination rate: The frequency change of a modifier that affects only the difference in recombination rate between males and females (*i.e.*, with $\bar{\rho} = 0$, call it a "symmetric" modifier) captures the selection pressure acting on heterochiasmy, although a sexual dimorphism in recombination rate may evolve by selection on a modifier that also changes the average recombination rate. A symmetric modifier will change in frequency if

$$\Delta\overline{p}_i = -\overline{pq}_{ijk}\hat{\rho}\left(\frac{\hat{E}^D(\overline{E} + \Lambda)}{4\bar{r}_{ijk}} + \frac{(\hat{E}^H + \tilde{E}^D)(\overline{E} + \overline{D})}{4\bar{r}_{jk}}\right) + o(\xi^5) \tag{32}$$

is nonzero [where $\overline{E}$, $\hat{E}^D$, $\hat{E}^H$, Λ, $\overline{D}$ are given by (26)]. This result holds if the recombination rate does not differ much between male and female. When epistasis and directional selection are of the same order (ξ), only the QLE values of $C^{\circ}_{ijk,\varnothing}$ and $C^{\circ}_{\varnothing,ijk}$ are needed to compute the frequency change at the modifier locus to leading order. In that case, the more general result with a large male-female difference in basal recombination rates (noted $\hat{r}$) is not a lot more complicated than (32). The following term must be added to the expression in (32) in which the values of $\overline{E}$, $\hat{E}^D$, $\hat{E}^H$, $\overline{D}$ are given by (27):

$$\frac{\overline{pq}_{ijk}\hat{\rho}}{16}\left(\frac{\hat{E}^D\hat{E}^H\hat{r}_{ijk}}{\bar{r}_{ijk}} + \frac{\hat{E}^D(\hat{E}^H + \tilde{E}^D)\hat{r}_{jk}}{\bar{r}_{jk}}\right) + o(\xi^3). \tag{33}$$

A necessary condition for the evolution of dimorphism is therefore

$$\hat{E}^D \neq 0 \quad \text{or} \quad \hat{E}^H + \tilde{E}^D \neq 0, \tag{34}$$

in both cases [*i.e.*, in (32) and (33)] even if other unspecified forces generate nonrandom associations between the selected alleles (*i.e.*, even if $\overline{D} \neq 0$). Large differences in recombination rate between male and female matter in (33) if both conditions are met, which is very unlikely to be a common situation and is not discussed further here.

First, heterochiasmy can evolve if $\hat{E}^D \neq 0$, *i.e.*, if the difference between *cis*- and *trans*-epistasis is different in males and females during diploid selection ($\hat{\alpha}^D_{jk} - \hat{\alpha}^D_{j,k} \neq 0$) or if there are sex and sex-by-sex-of-origin effects on directional selection coefficients ($\beta^D_j\hat{\alpha}^{DH}_k + \beta^D_k\hat{\alpha}^{DH}_j \neq 0$). There is no simple reason why $\hat{\alpha}^D_{jk}$ and $\hat{\alpha}^D_{j,k}$ should differ. For instance, if epistasis is the consequence of the biochemical properties of two proteins coded by loci *j* and *k*, it should not matter whether these proteins are coded by alleles on the same or different chromosomes. As a consequence, a sex difference in diploid epistasis is not very likely to produce a selection pressure on heterochiasmy.

Second, sex dimorphism in recombination can also evolve if $\hat{E}^H \neq 0$ or $\tilde{E}^D \neq 0$. Sex effects during haploid phase ($\hat{\alpha}^H_U$) and sex-of-origin effects during the diploid phase $\tilde{\alpha}^D_U$ play a very similar role on the evolution of heterochiasmy [compare the expression of $\hat{E}^H$ and $\tilde{E}^D$ in (26)]. $\hat{E}^H \neq 0$ can be due to any selective difference between males and females during the haploid phase

($\hat{\alpha}^{H}_{jk} \neq 0$ or $\hat{\alpha}^{H}_{j} \neq 0$ or $\hat{\alpha}^{H}_{k} \neq 0$) and similarly, $\tilde{E}^{D} \neq 0$ can be due to any sex-of-origin effect during diploid selection. However, when epistasis and directional selection have the same order, $\hat{E}^{H}$ and $\tilde{E}^{D}$ are both dominated by epistasis terms [see (27)]. In this last situation, epistasis is also an important source of linkage disequilibrium (it is the main term in $\overline{E}$). As a consequence, having strong epistasis, $\overline{\alpha}^{DH}_{jk} = O(\xi)$, with a haploid sex effect or a diploid sex-of-origin effect, $\hat{\alpha}^{H}_{jk}$ or $\tilde{\alpha}^{D}_{jk} = O(\xi)$, is the simplest sufficient condition to have an important selection pressure for heterochiasmy. For instance, in the simple situation where selection occurs only during the haploid phase and where haploid epistasis is the main source of linkage disequilibrium, $\overline{D} = o(\xi)$, a lower recombination rate is expected to evolve in the sex with the strongest absolute value of epistasis.

Nevertheless, the condition (34) may be met even in the absence of epistasis, although this will tend to generate a weak selection pressure on heterochiasmy. In this situation, a mechanism other than epistasis generating the linkage disequilibrium C_{jk} is necessary in most cases for heterochiasmy to evolve. This mechanism may be a covariance in directional selection coefficients between sexes across loci across both haploid and diploid phases ($\hat{\alpha}^{H}_{j}\hat{\alpha}^{D}_{k} + \hat{\alpha}^{D}_{j}\hat{\alpha}^{H}_{k} \neq 0$) or the presence of both sex-of-origin effects and sex effects within or across phase ($\tilde{\alpha}^{D}_{j}\hat{\alpha}^{DH}_{k} + \tilde{\alpha}^{D}_{k}\hat{\alpha}^{DH}_{j} \neq 0$). This mechanism could also be unspecified in this model ($\overline{D} \neq 0$). In these last cases, the direction of evolution of heterochiasmy depends on the sign of these forces generating the linkage disequilibrium.

Evolution of recombination around a sex-determining locus: Consider the same model as above except that locus *j* is a sex-determining locus (*i.e.*, one sex is homozygous 00 and the other is heterozygous 01, and the genotype 11 does not exist). Locus *k* is a selected locus and locus *i* a recombination modifier locus, with alleles changing the recombination rate between *j* and *k*. As before, suppose that locus *k* is exposed to viability selection during both haploid and diploid phase. There is no epistasis term because there is only one selected locus. However, when selection at locus *k* differs between males and females, the situation is somewhat analogous to epistasis between the sex-determining locus and locus *k*. At QLE, the values for the different linkage disequilibria are

$$\begin{aligned} C^{\circ}_{jk(01)} &= -\frac{\hat{\alpha}^{DH}_{k} pq_k(1 - 2r_{jk})}{8r_{jk}} + o(\xi) \\ C^{\circ}_{jk(00)} &= -C^{\circ}_{ik(01)} = (1 - r_{ik})\, C^{\circ}_{ijk(01)} + o(\xi^2) \\ C^{\circ}_{ijk(01)} &= -\frac{\rho_{(01)}\hat{\alpha}^{DH}_{k} pq_{ik}}{2r_{jk}[r_{ik}(1 + r_{ij} + r_{jk}) - 2(r_{ij} + r_{jk})]} + o(\xi^2), \end{aligned} \tag{35}$$

where the subscripts 00 and 01 indicate genotypic values at locus *j* in the homogametic and heterogametic sex, respectively. Note that C_{jk} and C_{ijk} are zero in the homogametic sex because locus *j* cannot be heterozygous in this subpopulation. Frequency change at locus *i* is given by

$$\Delta\overline{p}_i = \frac{1}{2}\left(\overline{\alpha}^{D}_{k}\overline{C}^{\circ}_{ik} + \frac{1}{2}\hat{\alpha}^{D}_{k}\hat{C}^{\circ}_{ik} + (1 - \bar{r}_{ik})(\alpha^{H}_{k(00)}\, C^{\circ}_{ik(00)} + \alpha^{H}_{k(01)}\, C^{\circ}_{ik(01)})\right) + o(\xi^3), \tag{36}$$

which simplifies to

$$\Delta\overline{p}_i = -\frac{\rho_{(01)}\hat{\alpha}^{DH}_{k}[\hat{\alpha}^{D}_{k} + \hat{\alpha}^{H}_{k}(1 - \bar{r}_{ik})]\overline{pq}_{ik}}{4r_{jk}[r_{ik} + (2 - r_{ik})(r_{ij} + r_{jk})]} + o(\xi^3). \tag{37}$$

The effect of the modifier in the homogametic sex $\rho_{(00)}$ plays no role because recombination between loci *j* and *k* is irrelevant when the *j* locus is homozygous. This result indicates that a modifier allele that decreases the recombination rate between a sex-determining locus and a selected locus will always increase in frequency except if $\hat{\alpha}^{DH}_{k} = 0$ or if $\hat{\alpha}^{D}_{k}$ lies between $-\hat{\alpha}^{H}_{k}$ and $-\hat{\alpha}^{H}_{k}(1 - \bar{r}_{ik})$. The first condition indicates that there must be a sex difference in selection in either the haploid or the diploid phase for recombination to evolve on sex chromosomes. The second condition is unlikely as it requires that locus *k* be under both diploid and haploid selection, that within each phase selection differs between males and females, and that the male-female difference has opposite signs in the haploid and diploid phases and falls in a narrow interval. Note that the selection on the modifier is important even if the three loci recombine freely. These results are qualitatively consistent with results obtained by Nei (1969), who studied the case where allele 0 at locus *k* causes sterility in females (and is dominant in females) while allele 1 causes sterility in males (and is recessive in males).

DISCUSSION

The evolution of heterochiasmy: The model presented in this article indicates that heterochiasmy can evolve for three different reasons associated with sex differences in selection: (i) because of a difference in epistasis during the haploid phase between the gametes of males and females; (ii) because of a male-female difference in *cis*-epistasis minus *trans*-epistasis during the diploid phase; and (iii) because of a difference in directional selection during the haploid phase between the gametes of males and females if some linkage disequilibrium between the selected loci is produced by some mechanism. In parallel, heterochiasmy can evolve for three similar reasons associated with sex-of-origin differences in selection: (a) because of a difference in epistasis during the diploid phase between the chromosomes inherited from the father and the mother; (b) because of a sex effect and sex-by-sex-of-origin effects on diploid directional selection coefficients; and (c) because of a

difference in directional selection during the diploid phase between alleles inherited from mother and father if some linkage disequilibrium between the selected loci is produced by some mechanism.

It is difficult to judge the likelihood of these different conditions. Conditions i and a are the most straightforward as they require only that epistasis varies with the sex during haploid phase or with the sex-of-origin during the diploid phase (assuming that the average epistasis is not exactly zero, such that epistasis produces also the linkage disequilibrium); both mechanisms apply to hermaphroditic and gonochoric species. Condition i will arise, for instance, whenever genes are expressed and selected in combinations during the haploid phase in just one sex. It is probably the most general and likely condition. The general trend noted by Trivers (1988) toward more recombination in females could then be due to the fact that the haploid phase is often shorter in females, as there may be little opportunity for selection because female meiosis is often completed at fertilization (Cohen 1977). However, to work, this hypothesis also requires genes to be expressed during the haploid stage, a phenomenon that is common in plants (where a large fraction of genes are expressed in pollen and ovules), but may be less common in animals (where fewer genes are expressed at the haploid stage; McCormick 1991; Treier and Beck 1991; Kramer and Krawetz 1997; Taylor and Hepler 1997; Christians *et al.* 1999; Steger 1999; Xu *et al.* 1999). Condition a (like conditions b and c) requires a mechanism producing sex-of-origin effects in diploids such as imprinting. Even if this kind of mechanism has been described in plants and many groups of animals (see Lloyd *et al.* 1999), it may concern few genes in each case. For instance, Burns *et al.* (2001) estimated that imprinted genes may represent ~0.1% of genes in mammals. However, these conditions might explain an intriguing pattern that has been found recently in sheep and humans: imprinted regions of the genome (imprinted genes tend to be clustered and in most of these clusters, both maternally and paternally imprinted genes are found; Bartolomei and Tilghman 1997) seem to exhibit particularly high recombination dimorphism (Paldi *et al.* 1995; McLaren and Montgomery 1999). This pattern has been interpreted the other way around, with heterochiasmy the consequence rather than the cause of imprinting (Paldi *et al.* 1995), although this hypothesis may not work well because both maternal and paternal imprinted genes are often present in the same cluster.

Conditions ii and b are more difficult to meet as they require sex differences in *cis-* minus *trans*-epistasis in diploids or sex and sex-by-sex-of-origin effects in diploids, respectively, which may concern a very small fraction of genes within genomes. As with condition a, these conditions require a mechanism to produce *cis-trans* or sex-of-origin effects. Imprinting may cause both, but *cis-trans* effects may also be produced when genes undergo monoallelic expression with random parental allele expression (such autosomal genes, like genes coding for immunoglobulin, T-cell receptor, and olfactory receptor have been described; Burns *et al.* 2001). In addition, conditions ii and b require a sex difference in selection during the diploid phase and therefore do not apply to hermaphroditic species.

Conditions iii and c require sex effects on the directional selection coefficient during haploid phase or sex-of-origin effect on the directional selection coefficient during the diploid phase, respectively. Both conditions apply to gonochoric and hermaphroditic species. Condition iii, in particular, which requires haploid expression of genes but no epistasis, may be quite common. Condition c, like other conditions involving sex-of-origin effect, may not be very likely as it requires a mechanism like imprinting and may concern very few genes. However, both conditions require, in addition, a general mechanism generating the linkage disequilibrium between the selected loci ($\overline{E} + \overline{D} \neq 0$). Among the various possibilities, some are not very likely [when genes must be imprinted or selected in both haploid and diploid phases, see the expression of $\overline{E}$ in (26)] and others may be more common (haploid or diploid epistasis or some mechanism unspecified in the model such as migration or drift). In these last cases, conditions iii or c may occur but will tend to produce a weak selection pressure on a modifier of heterochiasmy.

Interference in the evolution of heterochiasmy: The different sets of conditions for the evolution of a dimorphism outlined above are valid for modifier alleles that have exactly opposite effects in males and females on autosomal recombination rates. However, any particular allele that modifies recombination can also change the average recombination rate over males and females and/or the recombination rate on sex chromosomes. Since the conditions for the evolution of recombination are different for each of these cases, the outcome may be quite complicated (see Equation 25). For instance, a modifier with a sex-limited effect (*i.e.*, acting only in one sex) on all chromosomes may be selected for because it changes the average recombination rate on autosomes, because it changes the difference in recombination rate between males and females on autosomes, and, if it acts in the heterogametic sex, because it changes the recombination rate between sex chromosomes. Genetic variation in recombination rates within species has been extensively demonstrated (Korol *et al.* 1994). However, whether there is ample and independent genetic variation for each of these "components" is less clear. The frequent association of sex-chromosome heteromorphism and achiasmy (perhaps also heterochiasmy) could suggest that there is not. On the other hand, the association within chromosomes of heterochiasmate and imprinted regions may indicate the opposite.

What to conclude about existing theories: The conditions for the evolution of (i) autosome average recombina-

tion rates, (ii) autosome heterochiasmy, and (iii) sex-chromosome heterochiasmy are very different. The autosome average recombination rate can be selected for or against at either the haploid or the diploid stage, depending on the relative values of the linkage disequibria and epistasis averaged over sexes. The autosome heterochiasmy can be selected in either direction but for different reasons in haploid and diploid phases (see above). Sex-chromosome heterochiasmy almost always evolves in the same direction, due to either haploid or diploid selection (*i.e.*, reduced recombination in the heterogametic sex), does not necessarily involve epistasis, and depends only on the effect of modifiers in the heterogametic sex. Furthermore, arguments based on models for the evolution of sex-chromosomes heterochiasmy do not extend to autosomes.

This model offers a set of predictions for when heterochiasmy will and will not evolve. For instance, heterochiasmy may be more pronounced in heterosporous ferns and other organisms with a lengthy haploid phase, especially if there is also a large male-female dimorphism for other traits. It may also be common within a genome, in regions where genes are under selection during haploid phase (*e.g.*, around meiotic drive genes) or under haploid-like selection (*e.g.*, around imprinted genes). In contrast, heterochiasmy cannot result from selection on diploids unless some very specific mechanisms are invoked (different *cis-trans* effects on epistasis or sex-of-origin effects), which is at odds with Trivers' sexual-selection hypothesis. More tentatively, the result of this model would suggest that gonochoric and hermaphroditic species should present similar levels of heterochiasmy because the most likely conditions for its evolution apply to both cases (although it is unclear how inbreeding should affect this prediction). In short, investigations of autosomal heterochiasmy must distinguish carefully between selection on haploid and diploid phases, a factor that previous studies do not seem to have considered. It would be valuable to repeat the analyses of Burt *et al.* (1991), altering their definition of "opportunity for selection" to account for haploid selection.

The two roles of epistasis in the evolution of recombination: To understand the evolution of the average recombination rate it is crucial to determine the main source of linkage disequilibrium (epistasis, migration, and/or drift); epistasis matters as a potential source of disequilibrium (role 1) and as a factor changing the mean fitness of recombined *vs.* nonrecombined offspring (role 2). However, to understand the evolution of heterochiasmy, the source of linkage disequilibrium does not matter much because the linkage disequilibrium is always almost identical in males and females; rather, the crucial parameter is the difference in epistasis between males and females or between genes inherited maternally or paternally.

It has proved difficult to move forward with empirical work on the evolution of the average recombination rate, because it is hard to quantify the different sources of linkage disequilibrium. The evolution of heterochiasmy is a simpler problem since variation in epistasis is its most likely selection-variation explanation. Studying heterochiasmy may thus provide a way to investigate the importance of epistasis. Empirical findings consistent with the predictions made here would shed light on the role of epistasis in molding recombination rates and would therefore strongly corroborate theories for the evolution of sex based on selection and variation, as opposed to mechanistic theories.

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