

EVOLUTIONARY GENETIC STABILITY OF MENDELIAN
SEGREGATION AND THE ROLE OF FREE RECOMBINATION
IN THE CHROMOSOMAL SYSTEM

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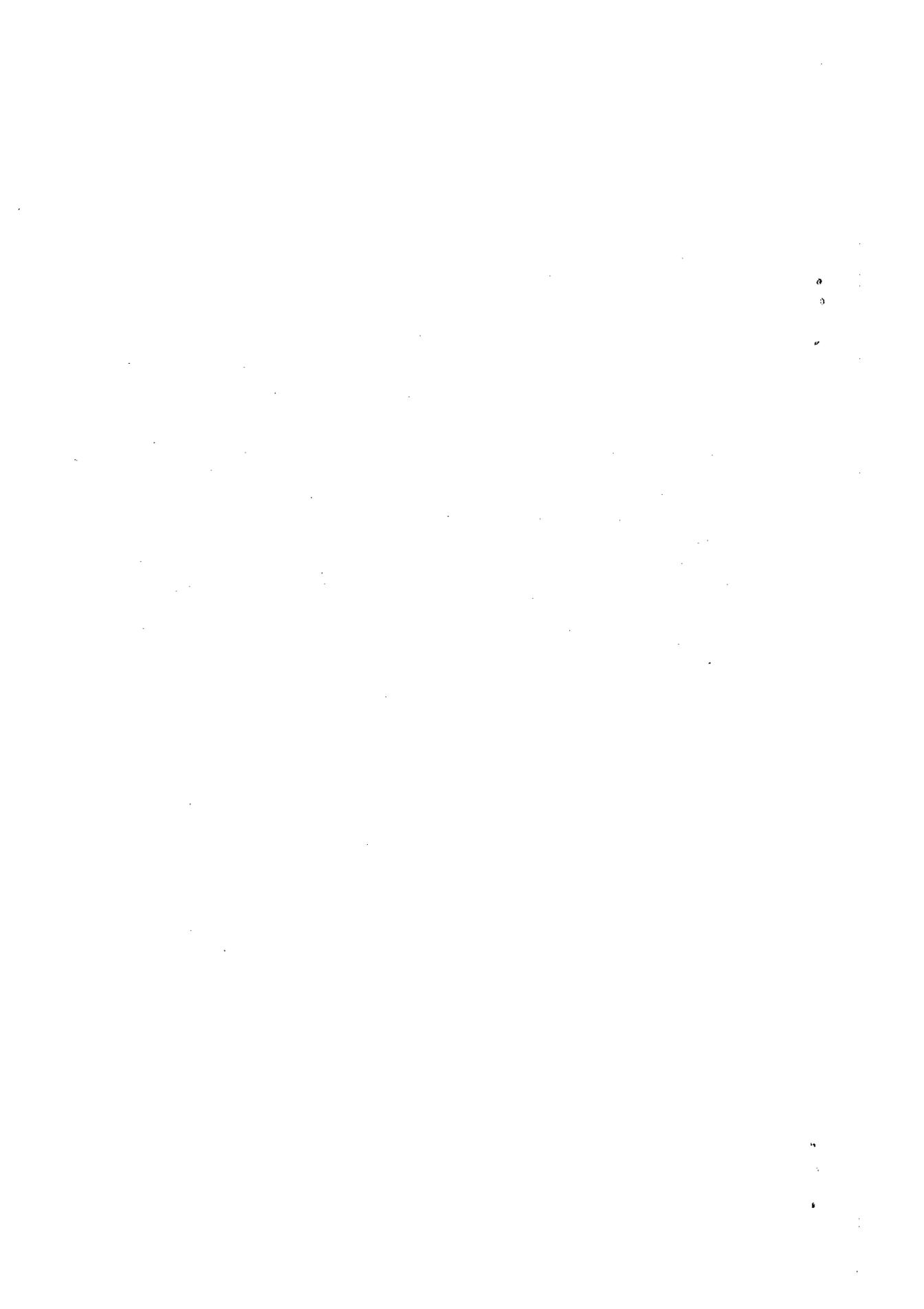
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While Mendel's laws of segregation are the rule in most observed populations, there are some documented counterexamples (e.g., Zimmering et al. 1970; Hartl and Hiraizumi 1976 and references therein). The possibility of segregation distortion raises questions about the nature of possible selective forces maintaining the Mendelian system throughout the course of evolution. Indeed any mutant allele with the ability of having more than its Mendelian share in the sexual cells of its carrier is likely to be selected for, and thus become established in the population. It is possible that such an allele, by replacing the wild type, will destroy any polymorphism at its locus. In this case, it can be argued (e.g., Charlesworth and Hartl 1978) that no segregation distortion will be observed. Yet segregation distortion can be balanced by selection. Moreover, for any Mendelian polymorphism maintained by heterozygote advantage, there is a range of moderate segregation distortion that will not destroy the polymorphism (Hiraizumi et al. 1960). Hence, one cannot explain the rarity of observed segregation distortion on the mere basis of distorter-fixation.

It is true, though, that in the face of heterozygote advantage, any deviation from Mendelian polymorphism created by segregation distortion has its cost in terms of mean fitness of the population. More important, reduction in fitness will always be higher, on the average, among carriers of the distorter. It is therefore expected that some mechanism controlling segregation distortion will be advantageous for the entire genome (e.g., Eshel 1983a).

With the discovery by Hartl (1973) that the *Sd* system of segregation distortion in *Drosophila melanogaster* consists of at least two genetic elements, the main element *Sd* and the modifier called *Rsp*, attention focused on two-locus systems with modifier alleles that affect segregation distortion at the main locus (Prout et al. 1973; Karlin and McGregor 1974; Hartl 1975; Liberman 1976; Thomson and Feldman 1976; Charlesworth and Hartl 1978). In a special model of segregation-selection balance with a lethal recessive allele at the main locus (Hartl 1975), it has been shown that, as expected, a modifier allele which reduces segregation distortion is favored by natural selection. Quite surprisingly, however, this is not always the case (e.g., Prout et al. 1973). Even more surprising, a local analysis of fixation



at the modifier locus has shown (Lieberman 1976) that for any rate of recombination $0 \leq r < 1/2$ between the main locus and the modifier, a polymorphism based on Mendelian segregation at the main locus is never stable against a modifier that introduces meiotic drive in favor of any of the segregating alleles.

An attempt to explain the apparent stability of the Mendelian system on the basis of its stability against symmetrically fluctuating segregation distortion (Lieberman and Feldman 1982) seems to lack generality and has been suggested only in order to provide at least one model in which Mendelian segregation is stable. Note, however, that contrary to many references, the analysis of Lieberman (and all other authors mentioned above), which is based on linear approximation, fails to yield a result in the special (but maybe important) case of $r = 1/2$. In fact, nonlinear analysis of this case appears to indicate a general stability of Mendelian segregation, once established in a population, against potential unlinked modifiers of the meiotic drive (I. Eshel and U. Lieberman, in prep.). This may account for the fact that no case of unlinked modifiers of the sort has ever been found. Yet, even if this is surprising because it is contrary to common knowledge, this finding alone cannot account for the persistence of Mendelian segregation in nature. With selective forces operating on linked loci in favor of distorting modifiers, the Mendelian system can be restored only if selective forces operate on other loci to actively reduce the meiotic drive.

In this paper I analyze the fate of new mutations at a modifier locus that governs the segregation distortion ratio at an unlinked locus. It is shown that for any configuration of alleles at the modifier locus, mutant alleles that initially reduce meiotic drive always increase in frequency, whereas mutant alleles that initially increase meiotic drive decrease in frequency.

Employing terminology originally developed for long-term evolution of the sex ratio (Eshel and Feldman 1982a), I speak of an Evolutionary Genetic Stability (EGS) of Mendelian segregation with respect to nonlinked modifiers (see sec. 1 and DISCUSSION): Long-term selection on the bulk of the genome is always operating to introduce new modifier alleles controlling deviations from the Mendelian system. I discuss a heuristic argument for the EGS property of Mendelian segregation, analogous to Fisher's argument for a 1:1 sex ratio. I show, however, why this argument (like Fisher's [1930] argument when applied to sex-linked modifiers) is false when applied to linked modifiers of the meiotic drive. Finally, the importance of free recombination as a means of preserving the Mendelian system is discussed.

I conjecture that preservation of the Mendelian system (when the alternative is a chaos of segregation distortion with drastic reduction of fitness) is a major advantage of free recombination and, as far as we know, the only advantage of that high rate of recombination (though not of some small but positive rates) in a constant environment (e.g., Maynard Smith 1978; Williams 1975).

THE GENERAL n -ALLELE MODEL FOR A MODIFIER OF THE MEIOTIC DRIVE

Following the notation of Prout et al. (1973) and Lieberman (1976) we assume two alleles, D and d , segregate with possible deviations from Mendel's law. This

deviation depends on the composition of alleles at another modifying (or responder) locus. Let m_1, \dots, m_n be the alternative alleles at the modifier locus and let k_{ij} ($0 \leq k_{ij} \leq 1$) be the frequency of the allele d in the gametes of a heterozygote Dd whose genotype at the modifying locus is $m_i m_j$. Following Prout et al. and Liberman, I assume no pleiotropic effect of the modifier. The main locus, however, is under viability selection with 1, w_1 , and w the relative fitnesses (viabilities) of DD , Dd , and dd , respectively.

We assume random mating, selection, recombination, and then segregation with meiotic drive.

Let x_{1i} and x_{2i} be the probabilities that a newborn offspring gets the gamete Dm_i or dm_i , respectively, from one parent. $x_1 = \sum x_{1i}$ is the proportion of the allele D among newborn offspring; $x_2 = 1 - x_1$ is the proportion of the allele d among newborn offspring; $x_1 = \sum x_{1i}$ is the proportion of the allele D among newborn offspring; $x_2 = 1 - x_1$. The proportion of the genotype Dm_i/Dm_j among newborn offspring is x_{1i}^2 for $i = j$ or $2x_{1i}x_{1j}$ when $i \neq j$. The proportion of Dm_i/dm_j is $2x_{1i}x_{2j}$ and that of dm_i/dm_j is x_{2i}^2 or $2x_{2i}x_{2j}$ if $i = j$ or $i \neq j$, respectively.

The proportion of the genotypes Dm_i/Dm_i , Dm_i/Dm_j , Dm_i/dm_i , Dm_i/dm_j , dm_i/dm_i , dm_i/dm_j after selection are, therefore,

$$\frac{1}{\bar{w}} x_{1i}^2, \frac{2}{\bar{w}} x_{1i}x_{1j}, \frac{2w_1}{\bar{w}} x_{1i}x_{2i}, \frac{2w_1}{\bar{w}} x_{1i}x_{2j}, \frac{w}{\bar{w}} x_{2i}^2, \frac{2w}{\bar{w}} x_{2i}x_{2j},$$

respectively, where

$$\bar{w} = x_1^2 + 2w_1x_1x_2 + wx_2^2. \quad (1)$$

After a proportion r of all $2w_1x_1x_2/\bar{w}$ gametes, carried by heterozygotes Dd , recombine ($0 \leq r \leq 1/2$, a fraction k_{ij} of the offspring of the genotype dm_i/Dm_j gets the gamete dm_i ($i, j = 1, 2, \dots, n$). Hence

$$x'_{1i} = \frac{1}{\bar{w}} [x_{1i}x_{1i} + 2w_1(1-r)x_{1i}\sum_j(1-k_{ij})x_{2j} + 2w_1rx_{2i}\sum_j(1-k_{ij})x_{1j}] \quad (2)$$

$$x'_{2i} = \frac{1}{\bar{w}} [wx_{2i}x_{2i} + 2w_1(1-r)x_{2i}\sum_j k_{ij}x_{1j} + 2w_1rx_{1i}\sum_j k_{ij}x_{2j}]. \quad (3)$$

When neither d nor D is fixed, one can define the average rate of segregation in the population

$$k = \frac{1}{x_1x_2} \sum_{ij} x_{1i}x_{2j}k_{ij}. \quad (4)$$

Definition: We speak of Evolutionary Genetic Stability (EGS) of the segregation rate k^* (with respect to a specific modifier locus) if the following condition is satisfied: If for some combination of alleles m_1, \dots, m_n at the modifier locus, the stable rate of segregation in the population is $k \neq k^*$, then a mutant m_{n+1} will be initially selected for if, and only if, its introduction into the population at a low frequency will render the population rate of segregation closer to k^* .

It immediately follows from a result of Liberman (1976) for $n = 1$ (fixation stability of 1 allele at the modifying locus) that, if $r < 1/2$, then any value $k \neq 1/2$ is unstable at least with respect to a "correcting" mutation, rendering the average segregation rate closer to one-half. However, segregation rates that are close to

or equal to one-half are unstable with respect to those modifying mutations which, as heterozygotes, determine segregation rates that are close to the extreme values, one or zero. Hence, for $r < 1/2$, neither the segregation rate $k = 1/2$ nor any other rate has EGS. The situation is different for $r = 1/2$. In this case I now show that for any combination of alleles at the modifying locus, a new allele will successfully enter the population if, and only if, it initially renders the average segregation rate in the population closer to one-half.

EVOLUTIONARY GENETIC STABILITY (EGS) OF THE MENDELIAN SEGREGATION WITH RESPECT TO UNLINKED MODIFIERS

When $r = 1/2$, equations (2) and (3) become

$$\bar{W}'_{x_{1i}} = x_1x_{1i} + w_1x_{1i} \sum_j (1 - k_{ij})x_{2j} + w_1x_{2i} \sum_j (2 - k_{ij})x_{1j} \tag{5}$$

and

$$\bar{W}'_{x_{2i}} = wx_2x_{2i} + w_1x_{2i} \sum_j k_{ij}x_{1j} + w_1x_{1i} \sum_j k_{ij}x_{2j}. \tag{6}$$

By a straightforward calculation we get

$$\bar{W}(x'_{1i} + x'_{2i} - x_{1i} - x_{2i}) = (x_1x_2 - x_2ix_1)[w_1 - w - (2w_1 - w - 1)x_1]. \tag{7}$$

Hence, all equilibrium points of the system satisfy at least one of the two conditions

$$x_1 = \frac{w_1 - w}{2w_1 - w - 1}; x_2 = \frac{w_1 - 1}{2w_1 - w - 1} \tag{8}$$

or

$$x_1x_{2i} = x_2x_{1i} \quad \text{for all } i = 1, 2, \dots, m. \tag{9}$$

Equilibrium points satisfying (9) will be called symmetric. Hence, all nonsymmetric equilibria satisfy (8).

At any equilibrium $x'_{2i} = x_{2i}$. Hence, by summing (6) over $i = 1, 2, \dots, n$, one obtains

$$\bar{W}x_2 = wx_2^2 + 2w_1 \sum_{ij} k_{ij}x_{1i}x_{2j} = wx_2^2 + 2kw_1x_1x_2$$

where k is defined in (4). By inserting the value of \bar{w} from (1) we therefore get

$$2kw_1x_1x_2 = x_1x_2(x_1 + 2w_1x_2 - wx_2). \tag{10}$$

For a nonsymmetric equilibrium, if it exists, we know $0 < x_1, x_2 < 1$ (any fixation point is, indeed, symmetric). Hence, by inserting (8) we then have

$$k = \frac{1}{2}. \tag{11}$$

Result 1.—For $r = 1/2$, all equilibrium points of the system (5), (6) are either symmetric or determine an average Mendelian segregation law in the population. (For a striking resemblance of this result with models of sex determination, the reader is referred to Eshel and Feldman [1982a], Eshel [1975], and Uyenoyama and Bengtsson [1979].)

We now concentrate on those equilibria, if they exist, at which the average rate of segregation k is different from one-half, i.e., on symmetric equilibria. Let m_{n+1} be a new mutant introduced into the modifier locus when the n -allele system is at a symmetric equilibrium.

Consider a heterozygote Dd which inherited the gamete dm_{n+1} from one parent. The probability of its inheriting the gamete Dm_i ($i = 1, 2, \dots, n$) from the other parent (conditioned on its being heterozygous at the main locus) is x_1/x_1 (provided the frequency of the mutant is negligible). Hence, the probability that it will pass the allele d to its offspring is $\sum_{i=1}^n (x_1/x_1) k_{n+1,i}$. In the same way, the probability that a heterozygote Dd that has inherited the gamete Dm_{n+1} from one parent will pass the allele d to its offspring is $\sum_{i=1}^n (x_2/x_2) k_{n+1,i}$. From (9) it follows that, at a symmetric equilibrium, these two values are equal, hence the value

$$k_{n+1} = \frac{1}{x_1} \sum_{i=1}^n x_1 k_{n+1,i} = \frac{1}{x_2} \sum_{i=1}^n x_2 k_{n+1,i} \quad (12)$$

is the average segregation rate of heterozygotes, carrying the modifier mutant m_{n+1} .

Let δ and ϵ be the probabilities that a newborn offspring in a given generation will get the gametes dm_{n+1} or Dm_{n+1} , respectively. Ignoring terms of the order $o(\epsilon, \delta)$, the corresponding values δ' and ϵ' after one generation are given by

$$\begin{pmatrix} \epsilon' \\ \delta' \end{pmatrix} = A \begin{pmatrix} \epsilon \\ \delta \end{pmatrix}$$

where

$$A = \begin{pmatrix} \frac{x_1 + (1 - k_{n+1})w_1x_2}{\bar{W}} & \frac{(1 - k_{n+1})w_1x_1}{\bar{W}} \\ \frac{k_{n+1}w_1x_2}{\bar{W}} & \frac{wx_2 + k_{n+1}w_1x_1}{\bar{W}} \end{pmatrix} \quad (13)$$

and \bar{W} is given by (1).

This is a positive matrix and its leading eigenvalue is, therefore, positive. A necessary and sufficient condition for this eigenvalue to be smaller than one is that the two following conditions will be simultaneously satisfied.

$$\rho(1) > 1 \quad (14)$$

where $\rho(\lambda) = \det(A - \lambda I)$, and

$$\rho'(1) > 0 \quad (15)$$

or equivalently,

$$\begin{aligned} & (2w_1 - w - 1)^2 x_1 x_2 + (2w_1 - w - 1) [x_1 + (w - w_1)x_2] \\ & + w - w_1 > [(2w_1 - w - 1)w_1(x_1 - x_2) + w_1(w - 1)]k_{n+1} \end{aligned} \quad (16)$$

and

$$\begin{aligned} & 2w_1x_1x_2 + wx_2^2 - x_1x_2 - (1 - k_{n+1})w_1x_2 + x_1^2 + 2w_1x_1x_2 \\ & - wx_1x_2 - k_{n+1}w_1x_1 > 0. \end{aligned} \quad (17)$$

From (10) we infer (for $x_1x_2 \neq 0$)

$$\begin{aligned}(2w_1 - w - 1)x_2 &= 2w_1k - 1 \\ (2w_1 - w - 1)x_1 &= 2w_1 - w - 2w_1k\end{aligned}$$

and (16) becomes

$$(k - k_{n+1})(1 - 2k) > 0. \quad (18)$$

From (10) it also follows that

$$\begin{aligned}x_1^2 + 2w_1x_1x_2 - wx_1x_2 &= 2w_1kx_1 \\ wx_2^2 + 2w_1x_1x_2 - x_1x_2 &= 2w_1(1 - k)x_2.\end{aligned}$$

Hence (17) becomes

$$w_1[x_1(2k - k_{n+1}) + x_2(1 - 2k + k_{n+1})] > 0. \quad (19)$$

This condition follows from (18) which remains as the only necessary and sufficient condition for the largest eigenvalue of (13) being less than one and, therefore, for natural selection operating against the mutant modifier. The meaning of (18) is that either $k_{n+1} < k < 1/2$ or $k_{n+1} > k > 1/2$, i.e., the average rate of segregation ratio, induced by a heterozygote mutant modifier is farther from one-half than the average rate of segregation at the old equilibrium.

In the same way, the largest eigenvalue of (12) is larger than one, so that selection initially favors the mutant modifier if either $k_{n+1} > k < 1/2$ or $k_{n+1} < k > 1/2$.

Result 2.—Any polymorphic equilibrium at the main locus with an average non-Mendelian segregation ratio is unstable with respect to unlinked modifier mutants which, when rare, render the average of segregation ratio closer to Mendel's rule. It is always stable against unlinked modifier mutants that further distort the segregation ratio.

With the general stability of the Mendelian system against nonlinked modifiers we conclude a third result.

Result 3.—Mendelian segregation at a given locus is an EGS strategy for unlinked modifiers of that locus. It is therefore suggested that meiotic drive, initiated by local segregation distorters and, possibly, amplified by modifiers on the same chromosome, is likely to be controlled by modifiers on other chromosomes.

Free recombination between chromosomes is, therefore, necessary for the preservation of the Mendelian system.

DISCUSSION

Evolutionary Genetic Stability (EGS) of Mendelian segregation with respect to nonlinked modifiers of meiotic drive has been demonstrated. More specifically, it has been shown that for any viability selection operating on the main locus and for any combination of alleles at the modifier locus, all two-locus equilibria are of two kinds: (1) so-called Mendelian equilibria, at which there is a probability of exactly one-half that a heterozygote Dd , chosen at random (if it exists), will pass the allele

d to its offspring; (2) so-called symmetric equilibria, at which no linkage disequilibrium exists between the main locus and any pair of modifying alleles.

Equilibria of the second kind may or may not be stable within the closed system (5)–(6) of given genotypes. But if corresponding to an average segregation rate different from the Mendelian rate of one-half, such equilibria are always unstable with respect to rare modifiers that initially reduce the segregation distortion. They are stable against mutant modifiers of opposite effect.

The analysis surprisingly resembles the one carried on for autosomal modifiers of the sex ratio (Eshel and Feldman 1982*a*). As in the case of the sex ratio, it is worth distinguishing between short-term selection, i.e., changes in relative frequencies within a given set of genotypes, and long-term selection, i.e., the fate of new mutant alleles. We distinguish between classic stability of genotype frequencies and long-term EGS of a population strategy with respect to mutants at a given locus (or loci). A population strategy x is said to have EGS with respect to a given genetic structure if any genetic equilibrium within this structure either determines the population strategy or is unstable with respect to those mutations that initially render the population strategy closer to x .

In a previous paper (Eshel and Feldman 1982*b*) it was shown that a sex ratio of 1:1 (determined by either father, mother, or self) has EGS for autosomal modifiers of the sex ratio but not for sex-linked ones. In this paper I have shown that Mendelian segregation has EGS for unlinked modifiers of meiotic drive but not for linked ones (see also Liberman 1976).

The EGS of the Mendelian segregation rate of one-half can be explained intuitively on the basis of the ESS theory (Maynard Smith and Price 1973), provided one chooses the expected number of grandoffspring as the evolutionarily appropriate payment function. If a meiotic drive in favor of one allele, say d , does not completely destroy polymorphism (in which case no meiotic drive can be observed), then it must be balanced by an average selective advantage of the allele D . Hence offspring carrying the allele D are more viable, on the average, than those of their siblings that carry the allele d . As a result, a heterozygote Dd which gives birth to more offspring with the allele D will have more grandoffspring on the average.

This argument is just the same as Fisher's argument for the evolution of a 1:1 sex ratio. The reason it does not hold for linked modifiers is the same as the reason for the failure of Fisher's argument for sex-linked modifiers of the sex ratio. Indeed, the expected number of grandoffspring is a crucial factor for natural selection only if the grandoffspring all carry the same number of one's genes. This is not the case, for example, for X -linked modifiers, affecting the father's sex ratio (they pass only to offspring of a daughter) (see Eshel 1984*a*). In a quantitatively less drastic manner, it is also not the case for linked modifiers of meiotic drive. It can readily be shown that, because of linkage disequilibrium, a grandoffspring carrying the allele d , favored by meiotic drive, is more likely to carry the modifier allele, responsible for the meiotic drive. As a result, it is possible that although individuals carrying the modifier allele will indeed have fewer grandoffspring, on the average, the modifier itself, by a sort of hitchhiking effect, will increase in frequency.

As in the case of modifiers of the sex ratio (Eshel 1984a), it appears that a linked modifier of the meiotic drive can be selected while decreasing the inclusive fitness of its carrier, thus creating an "intragametic conflict" (as defined for sex ratio distortion and inclusive fitness, Eshel 1983b). This is contrary to the usual Darwinian scheme according to which an allele can only promote itself by increasing the success of the entire genome (e.g., by increasing the carrier's fitness or, in the case of sex ratio distorters, its inclusive fitness).

Elsewhere (Eshel 1984b), I argued that important patterns in the evolution of the present structure of the genome can be understood only on the basis of the role of that structure in preventing or at least mitigating expected "intragametic conflicts," inevitably reducing the individual's success.

As shown in this paper, control of intragametic conflict resulting from meiotic drive becomes possible only when the chromosomal structure of the genome has free recombination between most loci. Without free recombination (i.e., if the entire genome consisted of 1 chromosome), there would be an initial advantage to any mutant modifier distorting the Mendelian system and producing harmful effects on the rest of the genome. With free recombination, however, it is shown that any meiotic drive, even if enhanced by linked modifiers, is bound to be alleviated by modifiers in the bulk of the genome.

Indeed, unless one resorts to group selection arguments, this finding alone cannot provide an explanation for the evolution of free recombination. In order to understand a selection mechanism that is possibly responsible for the weakening of the linkage between a segregation distorter and its modifiers (e.g., by translocation), one must resort to a three-locus model (a main locus, a modifier locus for the meiotic drive in the first one, and a modifier locus for recombination between both) such as the one developed by Thomson and Feldman (1974). The analysis of such a model is very complicated and has not yet been resolved.

SUMMARY

The Mendelian system of segregation is shown to be stably maintained in a diploid random-mating population only when the genome is divided into chromosomes, with free recombination among most loci. Meiotic drive at a given locus, enhanced by linked modifiers, is expected to be controlled by unlinked modifiers which are always selected to reduce the intensity of meiotic drive.

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