POPULATION DYNAMICS OF THE SEGREGATION DISTORTER POLYMORPHISM OF *DROSOPHILA MELANOGASTER*

BRIAN CHARLESWORTH

National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, North Carolina 27709

AND

DANIEL L. HARTL*

Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907

Manuscript received September 16, 1977
Revised copy received January 12, 1978

ABSTRACT

Two two-locus models of the population dynamics of the segregation distortion (SD) polymorphism of *Drosophila melanogaster* are described. One model is appropriate for understanding the population genetics of SD in nature, whereas the other is a special case appropriate for understanding an artificial population that has been extensively analysed. The models incorporate the general features of the *Sd* and *Rsp* loci which form the core of the SD system. It is shown that the SD polymorphism can be established only when there is sufficiently tight linkage between *Sd* and *Rsp*. An approximate treatment, valid for tight linkage, is given of all the equilibria of the system and their stabilities. It is shown that the observed composition of natural and artificial populations with respect to the *Sd* and *Rsp* loci is predicted well by the model, provided that restrictions are imposed on the fertilities of certain genotypes. Highly oscillatory paths towards equilibrium are usually to be expected on the basis of this model. The selection pressures on inversions introduced into this system are also investigated.

SEGREGATION distorter (SD) chromosomes were first discovered in 1956 in a natural population of *Drosophila melanogaster* in Madison, Wisconsin (see HIRAIZUMI and CROW 1960). Since then, they have been found to be at a frequency of 1–3% in most natural populations throughout the world (reviewed in HARTL 1975a).

SD chromosomes are of interest because, in males, they violate the Mendelian rule of segregation; males that are heterozygous for naturally occurring SD chromosomes produce progeny among which 95% or more carry SD. The mechanism of distortion is the dysfunction of a large fraction of sperm that carry the genetically normal homologue of SD (reviewed in HARTL and HIRAIZUMI 1976). Recent evidence suggests that the sperm dysfunction involves a defect

* Work supported by Public Health Service grant GM21732 and Research Career Award GM0002301, and by National Science Foundation grant BMS74-19708.

during spermiogenesis in the normal transition from relatively lysine-rich somatic histones to relatively arginine-rich sperm histones (KETTANEH and HARTL 1976, TOKUYASU, PEACOCK and HARDY 1977).

Genetically, SD chromosomes carry two mutations flanking the centromere of chromosome *2*. The mutation on the left arm is called *Sd* (for segregation distorter), that on the right arm is called *Rsp* (for responder). Wild-type alleles are denoted Sd^+ and Rsp^+. The loci interact in such a way that segregation distortion in favor of *Rsp* occurs in Rsp/Rsp^+ heterozygous males unless the males are also homozygous for Sd^+. Thus, Sd^+ behaves formally as a recessive suppressor of the non-Mendelian segregation involving *Rsp* (HARTL 1974). Males homozygous for *Sd Rsp* have extensive sperm dysfunction, leading to severely reduced fertility (HARTL 1973).

From the standpoint of population genetics, segregation distortion is of interest because it is associated in nature with a coadapted system of inversions and modifiers of distortion held in strong linkage disequilibrium (SANDLER and HIRAIZUMI 1960; KATAOKA 1967; WATANABE 1967; HARTL 1970a, 1975a, 1977a). Modifiers of distortion enhance or suppress the segregational effects of segregation distortion, and they are found on the *X* chromosome and on both major autosomes (KATAOKA 1967; HARTL 1970a; TRIPPA and LOVERRE 1975). Despite these complexities, it seems likely that the core of the system is the pair of loci, *Sd* and *Rsp*; other features of the system seem to be secondary responses to natural selection at these two loci. Indeed, HARTL and HARTUNG (1975) have shown that naturally occurring second chromosomes that are insensitive to distortion by *Sd Rsp* are largely Sd^+ *Rsp* in genotype. Since Sd^+ *Rsp* chromosomes attain high frequencies both in nature and in laboratory populations (HARTL 1977b), the bulk of second-chromosome suppressors also have at their core the interactions between *Sd* and *Rsp*.

Segregation distortion therefore comprises a two-locus system of meiotic drive. Two-locus models of meiotic drive in which one of the loci is assumed to be an otherwise selectively neutral modifier of the segregation ratio have been extensively analyzed recently and have generated extremely interesting theoretical results (PROUT, BUNDGAARD and BRYANT 1973, HARTL 1975b, FELDMAN and KRAKAUER 1976; THOMSON and FELDMAN 1976) Unfortunately, the *Sd* locus is not a selectively neutral modifier; it modifies the segregation ratio, to be sure, but it also interacts with *Rsp* to impose fitness effects of its own.

Our purpose, in this paper, is to develop models of the population dynamics of *Sd* and *Rsp* that incorporate features of the whole system as they are currently understood. Because segregation distortion occurs only in males and recombination occurs only in females, gametic frequencies in the two sexes are not necessarily the same and have to be treated separately. For a reasonably realistic model, moreover, a number of fertility parameters and parameters measuring departures from Mendelian segregation must be used. We show here that, with biologically realistic parameter sets, the system can be fairly well understood, and that predictions of the model can be related to known features of the pattern of variation at the *Sd* and *Rsp* loci in natural and artificial populations.

BASIC MODELS AND ASSUMPTIONS

Hereafter we denote *Sd* by S and *Rsp* by R and assume that there are two alleles at each of the loci—$S/+$ and $R/+$—giving four gametic types: $++$, $+R$, $S+$, and SR. These will be denoted by the indices 1, 2, 3, and 4, respectively. Let the frequency of gamete type i among the functional sperm in a given generation be x_i $(i = 1, \ldots, 4)$ and let the corresponding frequency in eggs be y_i. The means of these frequencies are written as $z_i = \frac{1}{2}(x_i + y_i)$ for $i = 1, \ldots, 4$. The S and R loci are assumed to affect only male fertility and segregation ratios, and male fertility is assumed to be affected in such a way that the fertility of each genotype can be measured by a fixed relative fertility parameter. This is reasonably realistic since the segregation distorter system controls the amount of functional sperm produced and there is no scope here for mating interactions between male and female genotypes. There is normally no crossing over in males of *D. melanogaster*; the frequency of recombination between the S and R loci in females is denoted by c.

For compactness of notation, let k_{ij} $(i \neq j)$ be the proportion of functional sperm bearing gamete type i among all functional sperm produced by a male of genotype ij. For convenience put $k_{ii} = \frac{1}{2}$. Let u_{ij} be the relative fertility of a male of genotype ij. Letting $w_{ij} = 2k_{ij}u_{ij}$ $(i, j = 1, \ldots, 4)$ provides a set of "fitness" parameters that measure the relative contributions of males to the pool of functional sperm. For $i \neq j$, $\frac{1}{2} w_{ij}$ represents the relative frequency with which an ij male contributes i gametes to the functional sperm pool; $\frac{1}{2} w_{ji}$ represents his relative contribution of j gametes. These two quantities summarize the effects of segregation distortion and fertility reduction for the genotype in question. For homozygous males of genotype ii, w_{ii} simply measures the relative fertility of the genotype.

Assuming random mating and infinite population size, it is straightforward to derive recurrence relations for x'_i and y'_i, the values of x_i and y_i in the next generation. It is, however, convenient for our purposes to deal in terms of average gametic frequencies in the sexes and deviations from the averages. Accordingly, let $x_i = z_i + \delta_i$, $y_i = z_i - \delta_i$. Define $w_i = \sum_j z_j w_{ij}$; $\bar{w} = \frac{1}{2} \sum_i \sum_j (x_i y_j + x_j y_i) w_{ij}$; $D = z_1 z_4 - z_2 z_3$; $\Delta^* = \delta_1 \delta_4 - \delta_2 \delta_3$. Noting that $\frac{1}{2}(x_i y_j + x_j y_i) = z_i z_j - \delta_i \delta_j$, we obtain

$$\bar{w}(z'_i + \delta'_i) = z_i w_i - \delta_i \sum_j \delta_j w_{ij} \tag{1a}$$

$$z'_i - \delta'_i = z_i \pm c D \mp c \Delta^* \tag{1b}$$

where the sign of cD is negative for $i = 1, 4$ and positive for $i = 2, 3$.

In order to obtain meaningful detailed results with this system of equations, it is necessary to specify the w_{ij}'s further. Actually, we must consider two models. The parameters of the first one, called model 1, are shown in Table 1. This model is appropriate for a long-term artificial population containing S and R, which was established by Y. HIRAIZUMI and extensively analyzed by HARTL

TABLE 1

Parameterization of male fertilities and segregation ratios in model 1

	+ +	+ R	S +	S R
	Fertility Segn. ratio	Fertility Segn. ratio	Fertility Segn. ratio	Fertility Segn. ratio
+ +	1 -	$1-s_1$ 1/2	1 1/2	$1-s_2$ k
	$w_{11}=1$	$w_{12}=1-s_1$	$w_{13}=1$	$w_{14}=2(1-k)(1-s_2)$ $=1-K_1$
+ R	$1-s_1$ 1/2	$1-s_3$ -	$1-s_2$ k	$1-s_4$ 1/2
	$w_{21}=1-s_1$	$w_{22}=1-s_3$	$w_{23}=2k(1-s_2)$ $=1+K_2$	$w_{24}=1-s_4$
S +	1 1/2	$1-s_2$ k	1 -	$1-s_2$ k
	$w_{31}=1$	$w_{32}=2(1-k)(1-s_2)$ $=1-K_1$	$w_{33}=1$	$w_{34}=2(1-k)(1-s_2)$ $=1-K_1$
S R	$1-s_2$ k	$1-s_4$ 1/2	$1-s_2$ k	$1-s_5$ -
	$w_{41}=2k(1-s_2)$ $=1+K_2$	$w_{42}=1-s_4$	$w_{43}=2k(1-s_2)$ $=1+K_2$	$w_{44}=1-s_5$

This model is appropriate for certain artificial populations segregating for S and R. The parameter k is the fraction of functional R-bearing sperm produced by $R/R+$ males in which segregation distortion occurs. For each genotype ij $(i \neq j)$, w_{ij} is equal to twice the product of the fertility and the fraction of functional i-bearing sperm produced by the genotype.

(1977b). As far as possible, the parameters in Table 1 are based on known features of the S and R alleles segregating in this population. $S\,R/+\,+$ males produce about 85% $S\,R$-bearing functional sperm and have a reduction in fertility. The parameter k $(k > \frac{1}{2})$ measures the fraction of $S\,R$-bearing sperm among functional sperm produced by $S\,R/+\,+$ males, and s_2 measures the reduction in fertility of this genotype; these features define w_{14} and w_{41}. Homozygous $S\,R$ males have drastically reduced fertility (HARTL 1969). s_5, which measures this effect, is such that $s_5 >> 0$; s_5 specifies w_{44}. With respect to segregation distortion and male fertility, $S+$ and$+\,+$ seem to behave equivalently in combination with $S\,R$ (HARTL 1974; HAUSCHTECK-JUNGEN and HARTL 1978); these equivalences define w_{34} and w_{43}. Genotype $S+/+\,R$ produces a fraction k of $+\,R$-bearing functional sperm and appears to have a corresponding reduction in fertility (HARTL 1974; HAUSCHTECK-JUNGEN and HARTL 1978); thus w_{23} and w_{32} are defined. $S\,R/+\,R$ males have Mendelian segregation but reduced fertility (HARTL 1969; HIHARA 1974); s_4 measures this fertility reduction in the definition of w_{24} and w_{42}. Cytological studies of spermatogenesis by HAUSCHTECK-JUNGEN and HARTL (1978) have shown abnormalities, principally in spermatid nuclear elongation, in $+\,R/+\,+$ genotypes and even more in $+\,R/+\,R$ genotypes, though $S+/S+$ and $S+/+\,+$ are normal; thus, we set $w_{11} = w_{13} = w_{31} = w_{33} = 1$, $w_{12} = w_{21} = 1 - s_1$, and $w_{22} = 1 - s_3$, where s_1 and s_3 measure the fertility reductions realized in $+\,R/+\,+$ and $+\,R/+\,R$ males, respectively.

Model 2, defined by the parameters in Table 2, is similar to model 1, but generalized somewhat to account for the segregation distorter system as it exists in natural populations. Naturally occurring *S R* chromosomes usually carry a strong enhancer of distortion near the tip of the right arm of the chromosome (SANDLER and HIRAIZUMI 1960) and polygenic enhancers distributed along the whole right arm (MIKLOS and SMITH-WHITE 1971). The segregation ratio of *S R*/+ + males is 95% or more, a ratio denoted in Table 2 by k_1. Naturally occurring + *R* chromosomes are not completely insensitive to such strongly distorting *S R* chromosomes; thus, *S R*/+ *R* males produce about 80% *S R*-bearing offspring (HARTL 1977a). This segregation ratio is denoted k_3. For chromosomes from natural populations, the segregation ratio of + *R*/*S* + males is not known, but it is probably about 60% in favor of + *R* (HARTL, unpublished). In Table 2, this segregation ratio is denoted k_2, and the relative fertility of + *R*/*S* + males is denoted $1 - s_6$. Other than these modifications in w_{23}, w_{32}, w_{24}, and w_{42}, models 2 and 1 are identical.

When $k_2 = k_1$, $s_6 = s_2$, and $k_3 = \frac{1}{2}$, then model 2 reduces to model 1. These conditions amount to setting $K_3 = K_2$, $K_4 = K_1$, and $K_5 = -K_6 = s_4$. Although the focus of our analysis is on model 2, we prefer to treat the models as distinct because they apply to very different situations. Moreover, certain aspects of the analysis can be pushed farther for model 1 than for model 2.

TABLE 2

Parameterization of male fertilities and segregation ratios in model 2

	+ +		+ *R*		*S* +		*S R*	
	Fertility	Segn. ratio	Fertility	Segn. ratio	Fertility	Segn. ratio	Fertility	Segn. ratio
+ +	1	-	$1-s_1$	1/2	1	1/2	$1-s_2$	k_1
	$w_{11}=1$		$w_{12}=1-s_1$		$w_{13}=1$		$w_{14}=2(1-k_1)(1-s_2)$ $=1-K_1$	
+ *R*	$1-s_1$	1/2	$1-s_3$	-	$1-s_6$	k_2	$1-s_4$	k_3
	$w_{21}=1-s_1$		$w_{22}=1-s_3$		$w_{23}=2k_2(1-s_2)$ $=1+K_3$		$w_{24}=2(1-k_3)(1-s_4)$ $=1-K_5$	
S +	1	1/2	$1-s_6$	k_2	1	-	$1-s_2$	k_1
	$w_{31}=1$		$w_{32}=2(1-k_2)(1-s_6)$ $=1-K_4$		$w_{33}=1$		$w_{34}=2(1-k_1)(1-s_2)$ $=1-K_1$	
S R	$1-s_2$	k_1	$1-s_4$	k_3	$1-s_2$	k_1	$1-s_5$	-
	$w_{41}=2k_1(1-s_2)$ $=1+K_2$		$w_{42}=2k_3(1-s_4)$ $=1+K_6$		$w_{43}=2k_1(1-s_2)$ $=1+K_2$		$w_{44}=1-s_5$	

This model is appropriate for natural populations containing *S* and *R*. We define k_1 as the fraction of functional *S R*-bearing sperm produced by *S R*/+ + or *S R*/*S* + males, k_2 as the fraction of functional + *R*-bearing sperm from + *R*/*S* + males, and k_3 as the fraction of functional *S R*-bearing sperm from *S* +/+ *R* males. The w_{ij}'s are as defined in the legend of Table 1.

ESTABLISHMENT OF THE SEGREGATION DISTORTER POLYMORPHISM

Ancestral populations of *D. melanogaster* were presumably homozygous + +, and contemporary populations are known that are apparently free of all the components of the segregation distorter system (HIRAIZUMI, SANDLER and CROW 1960; HARTL 1977a). It is therefore of interest to consider the conditions under which a wild-type population can be invaded by the components of segregation distortion as a result of the occurrence of mutations to the S and R alleles in the same population. Let ε_2, ε_3, and ε_4 be the frequencies of + +/+ R, + +/S +, and + +/S R zygotes, respectively. It is assumed that these are initially very rare. Equations (1) and the parameters of model 2 then yield the following difference equations:

$$\varepsilon_2' - \varepsilon_2 = -\frac{\varepsilon_2 s_1}{2} + \frac{c\,\varepsilon_4}{2} \tag{2a}$$

$$\varepsilon_3' - \varepsilon_3 = \frac{c\,\varepsilon_4}{2} \tag{2b}$$

$$\varepsilon_4' - \varepsilon_4 = \frac{\varepsilon_4}{2}(K_2 - c)\ . \tag{2c}$$

These equations are derived by adding (1a) and 1b), and neglecting second-order terms in the ε_i and δ_i. The S R gamete type can therefore increase in frequency asymptotically if and only if $K_2 > c$, *i.e.*, if

$$k_1(1 - s_2) > \frac{1 + c}{2}\ . \tag{3}$$

Since + +/S R males have substantially reduced fertilities, it seems likely that the segregation distorter system could not have evolved by this sort of dynamics unless the recombination fraction between S and R were less than some critical value given by equation (3). Because of our ignorance of the segregation ratio and fertility reduction of the hypothetical original S R/+ + genotype, no precise value can be set for this critical value of c. From considerations set out in the discussion, it seems likely that it is of the order of 10–15 map units at most. In fact, the S–R distance is about 1 map unit (HIRAIZUMI and NAKAZIMA 1967).

It is of interest in this context to note that, because of the absence of crossing over in male *D. melanogaster*, it is theoretically possible from expression (3) for a segregation distorter polymorphism to arise with $c = 0.5$, given a sufficiently low value of s_2. With free recombination in both sexes this would not be possible. The establishment of a polymorphic system with the S and R loci on separate chromosomes would be impossible even in *D. melanogaster*. If the recombination fraction between S and R in males is denoted r, then equation (2c) becomes

$$\varepsilon_4' - \varepsilon_4 = \varepsilon_4\left[\frac{(1 + K_2)(1 - r)}{2} + \frac{(1 - c)}{2} - 1\right]$$

When $r = c = 0.5$ this reduces to $\varepsilon_4' - \varepsilon_4 = (\varepsilon_4/4)(K_2 - 2)$, which is always negative.

EQUILIBRIA WITH SMALL c VALUES

Understanding of systems with small c values can, by continuity, be obtained by studying the $c = 0$ case (*cf.*, KARLIN and MCGREGOR 1972). For sufficiently small c, the dynamics will closely resemble those of the corresponding $c = 0$ case. Since the c value between the S and R loci is known to be small, results based on the $c = 0$ case will provide a good approximation to reality. The rest of this section will be based largely on this fact.

The system can be simplified further by noting that the $S+$ gamete type will, with most realistic parameter sets, be at a severe selective disadvantage because it is distorted in combination with both $+\ R$ and $S\ R$. Hence with $c = 0$, only the three-gamete systems composed of the other gamete types need be considered in detail, and with small c values the frequency of $S+$ can usually be neglected. In APPENDIX 1, we show that, when $c = 0$, there can be no stable polymorphism with all four gametes present except with special parameter sets, and that all equilibria with $S+$ are unstable. Numerical calculations of exact population trajectories when $c = 0.01$, close to its real value, show that $S+$ is always rare (< 0.005). Three-gamete systems can conveniently be represented by a triangular barycentric coordinate system in which each gametic frequency corresponds to the length of the perpendicular erected from the appropriate margin of an equilateral triangle (*e.g.*, LI 1955, p. 47).

In the remainder of this section, we consider the existence and stability properties of the various possible equilibria with $c = 0$ and then compare the analytic results with some exact computations of population trajectories with arbitrary c values. Some general properties of $c = 0$ equilibria will first be mentioned.

General properties of $c = 0$ *equilibria*: From equation (1b) we see that at equilibrium $\hat{\delta}_i = 0$ for each i. At equilibrium, therefore, gametic frequencies are equal in eggs and functional sperm. This generalizes the result of DUNN and LEVENE (1961). Adding equations (1a) and (1b) gives the equilibrium equation

$$\hat{\bar{w}} = \sum_j z_j \hat{w}_j = \hat{w}_i \tag{4}$$

where the subscript i runs over the indices of the gametes present in the equilibrium population.

Equations (4) have obvious analogies with the standard equations for equilibria at multi-allelic loci (CROW and KIMURA 1970), but are not identical because, here, $w_{ij} \neq w_{ji}$.

The fact that $\hat{\delta}_i = 0$ means that, in the neighborhood of equilibrium, a linearized stability analysis can be carried out by ignoring terms in δ_i^2. We obtain

$$2\,\bar{w}^*\,z_i' = z_i\,(w_i + \bar{w}^*) \tag{5a}$$

$$2\,\bar{w}^*\,\delta_i' = z_i\,(w_i - \bar{w}^*) \tag{5b}$$

where $\bar{w}^* = \sum_i z_i w_i$.

It follows from this that the local stability analysis can be conducted solely in terms of the z_i; the stability of system (5a) is sufficient for that of (5b).

These general results can now be applied to the various equilibria possible under equations (4). Except where otherwised stated, the results will be given for the more general Model 2. The results for Model 1 can be obtained by setting $k_1 = k_2 = k$, $k_3 = \frac{1}{2}$, $K_3 = K_2$, $K_4 = K_1$ and $K_5 = -K_6 = s_4$.

The + +/S R marginal equilibrium: This equilibrium corresponds to the one usually considered in standard one-locus, two-allele models of meiotic drive (*e.g.*, HIRAIZUMI, SANDLER and CROW 1960). We have $z_2 = z_3 = 0$ and, from equations (4),

$$\frac{z_1}{z_4} = \frac{s_5 - K_1}{K_2} .$$

This equilibrium exists and is stable to perturbations on the $+ +/S\ R$ margin if and only if (iff) $K_2 > 0$ and $s_5 > K_1$. An equilibrium that is stable on the margin is unstable to the introduction of $+ R$ iff

$$\beta = K_2 (K_1 - K_5) + s_1 (K_1 - s_5) > 0 . \tag{6}$$

This inequality is satisfied for most realistic parameter values.

The marginal equilibrium obviously cannot exist if $c \neq 0$, but there will be a nearby internal equilibrium if the $c = 0$ equilibrium is stable to the introduction of $+ R$.

The + +/+ R marginal equilibrium: This equilibrium will not ordinarily exist. It exists and is stable to perturbations on the margin iff $s_1 < 0$ and $s_1 < s_3$. It is unstable to the introduction of $S\ R$ iff

$$\gamma = K_2 (s_3 - s_1) - s_1 (s_1 + K_6) > 0 . \tag{7}$$

The S R/+ R marginal equilibrium: Here, equations (4) yield

$$\frac{z_4}{z_2} = \frac{s_3 + K_6}{s_5 - K_5} .$$

The equilibrium exists and is stable on the margin iff $s_3 > -K_6$ and $s_5 > K_5$. A stable marginal equilibrium is unstable to the introduction of $+ +$ iff

$$\alpha = -K_6 (K_1 - K_5) - s_3 (K_1 - s_5) - s_1 (s_5 - K_5) > 0 . \tag{8}$$

The corner equilibria: The $+ +$ corner is unstable to $S\ R$ iff $K_2 > 0$, but is stable to $+ R$ when $s_1 > 0$ or $s_1 = 0$ and $s_3 > 0$. The $S\ R$ corner is unstable to $+ +$ iff $s_5 > K_1$, and it is unstable to $+ R$ if $s_5 > -K_5$. The $+ R$ corner is unstable to $+ +$ iff $s_3 > s_1$, and it is unstable to $S\ R$ iff $s_3 > -K_6$.

The interior equilibrium: Solving the equations $w_1 = w_2 = w_4$, we obtain

$$z_1 = \alpha/B,\ z_2 = \beta/B,\ z_4 = \gamma/B , \tag{9}$$

where $B = \alpha + \beta + \gamma$, and α, β and γ are as defined above.

An interior equilibrium exists if either

$$\alpha,\ \beta,\ \gamma > 0 \tag{10a}$$

or

$$\alpha,\ \beta,\ \gamma < 0\ . \tag{10b}$$

Considering the biologically relevant range of parameter values, it is reasonable to assume that $s_3 \geq s_1$ and $s_1 + K_6 < 0$. Thus $\gamma > 0$, and the relevant interior equilibrium is that existing under conditions (10a). Conditions (10a) correspond to conditions (6), (7) and (8), which guarantee the instability of all three marginal equilibria to the missing gamete type.

The effects of varying the selection parameters on the composition of the population at the interior equilibrium are shown in Table 3. All the equilibria displayed are locally stable, using the criteria of APPENDIX 2, and the range of variation in the parameters is close to that suggested earlier as being realistic. Data from natural populations indicate that, if present at all, $S\,R$ gametes generally have a frequency of 0.01–0.03 (HARTL 1975a); in the only natural population so far studied extensively for the frequency of $+\,R$, the value was about 0.5 (HARTL and HARTUNG 1975). It should be mentioned here that the presence of inversions on naturally occurring $S\,R$ chromosomes reduces the recombination fraction between S and R to about 0.001 and thus makes our $c = 0$ approximation a very good one. Naturally occurring $S\,R$ chromosomes usually carry recessive lethals, too, but this has virtually no effect on the equilibrium frequency of $S\,R$ owing to its low frequency in the first place. Inspection of Table 3 shows that equilibrium frequencies of the order found in natural populations are produced only when s_1 and s_3 are quite small, certainly much less than 0.1.

Equations (10) are considerably simplified when Model 1 is appropriate. In full they become

$$z_1 = [s_4\,(K_1 - s_4) - s_3\,(K_1 - s_5) - s_1\,(s_5 - s_4)]/B = \alpha/B \tag{11a}$$

$$z_2 = [K_2\,(K_1 - s_4) + s_1\,(K_1 - s_5)]/B = \beta/B \tag{11b}$$

$$z_4 = [K_2\,(s_3 - s_1) - s_1\,(s_1 - s_4)]/B = \gamma/B\ , \tag{11c}$$

where $B = (s_3 s_5 - s_4^2) + K_1 K_2 + 2\,s_2\,(s_4 - s_3) - s_1\,[s_1 + 2\,(s_5 - s_4 - s_2)] = \alpha + \beta + \gamma$.

We can be fairly sure that $s_3 \geq s_1$ and $s_4 > s_1$, so that γ, and hence α and β, must be positive. As before, this guarantees that all three marginal equilibria are unstable to the introduction of the relevant missing gamete type.

Representative values of the equilibrium gamete frequencies are shown in Table 4. Analysis of Hiraizumi's artificial population, for which this model seems appropriate, has yielded equilibrium frequencies of 0.12 for $S\,R$ and 0.79 for $+\,R$ (HARTL 1977b). In order to approximate these values, we must again have rather small values of s_1 and s_3, though not nearly as small as those required

TABLE 3

Composition of the equilibrium population for realistic parameter values in model 2 when c = 0

(a) $s_1 = 0$					(b) $s_1 = \frac{1}{2}s_3$				
	$k_1 = 0.95$, $k_3 = 0.80$		$k_1 = 0.95$, $k_3 = 0.70$			$k_1 = 0.95$, $k_3 = 0.80$		$k_1 = 0.95$, $k_3 = 0.70$	
s_3	z_2	z_4	z_2	z_4	s_3	z_2	z_4	z_2	z_4
				$s_2 = 0.35$, $s_4 = 0.40$					
0.005	0.837	0.024	0.590	0.010	0.005	0.852	0.014	0.594	0.008
0.01	0.820	0.047	0.585	0.020	0.01	0.850	0.028	0.594	0.017
0.02	0.789	0.090	0.575	0.039	0.02	0.846	0.054	0.593	0.033
				$s_2 = 0.35$, $s_4 = 0.50$					
0.005	0.531	0.020	0.436	0.009	0.005	0.535	0.018	0.437	0.011
0.01	0.522	0.039	0.432	0.018	0.01	0.530	0.036	0.436	0.021
0.02	0.506	0.075	0.426	0.036	0.02	0.520	0.069	0.432	0.041
				$s_2 = 0.40$, $s_4 = 0.40$					
0.005	0.766	0.021	0.464	0.008	0.005	0.781	0.014	0.468	0.008
0.01	0.754	0.042	0.462	0.015	0.01	0.784	0.027	0.469	0.016
0.02	0.733	0.081	0.457	0.030	0.02	0.793	0.053	0.472	0.032
				$s_2 = 0.40$, $s_4 = 0.50$					
0.005	0.407	0.015	0.317	0.007	0.005	0.410	0.018	0.318	0.010
0.01	0.403	0.029	0.315	0.013	0.01	0.408	0.034	0.317	0.020
0.02	0.395	0.056	0.312	0.026	0.02	0.404	0.067	0.316	0.040

Natural populations seem to have z_2 in the range 0.4–0.5 and z_4 in the range 0.01–0.03. To achieve comparable values in the model, very small values of s_1 and s_3 must be stipulated. All cases in the table have $s_5 = 0.90$.

TABLE 4

Composition of the equilibrium population for realistic parameter values in model 1 when $c = 0$

	(a) $s_1 = 0$			(b) $s_1 = \frac{1}{2} s_3$	
s_3	z_2	z_4		z_2	z_4
			$s_2 = 0.10,\ s_4 = 0.10$		
0.05	0.782	0.062		0.838	0.038
0.10	0.730	0.116		0.838	0.073
0.20	0.646	0.205		0.845	0.137
			$s_2 = 0.10,\ s_4 = 0.20$		
0.05	0.674	0.065		0.713	0.045
0.10	0.629	0.119		0.703	0.086
0.20	0.554	0.209		0.690	0.159
			$s_2 = 0.20,\ s_4 = 0.10$		
0.05	0.743	0.056		0.794	0.037
0.10	0.692	0.105		0.809	0.070
0.20	0.619	0.188		0.854	0.132
			$s_2 = 0.20,\ s_4 = 0.20$		
0.05	0.604	0.054		0.641	0.043
0.10	0.570	0.102		0.642	0.082
0.20	0.512	0.183		0.651	0.152

HIRAIZUMI's artificial population has $z_2 \approx 0.8$ and $z_4 \approx 0.12$. To achieve comparable values in the model, small values of s_1 and s_3 are required, although these values must be considerably larger than those necessary to account for the gametic frequencies in natural populations (*cf.*, the values of s_1 and s_3 in Table 3). All cases in the table have $k_1 = 0.85$ and $s_5 = 0.80$.

to account for gamete frequencies in natural populations. Why s_1 and s_3 must be small can be seen from equations (11) in the case $s_1 = 0$. Then

$$\frac{z_2}{z_4} = \frac{K_1 - s_4}{s_3} < \frac{1}{s_3} ,$$

and, if s_3 is not too large,

$$z_4 \approx s_3/K_1 \geq s_3 ,$$

neglecting second-order terms in the fertility effects.

Local stability of the internal equilibrium: The equations describing the stability properties of the internal equilibrium point are given in APPENDIX 2. The conditions for stability in general are too complex to be analyzed fully, but one general point is worth noting. Equation (A.2.4a) implies that *det* is positive if $B > 0$. This condition corresponds to instability of all the marginal equilibria with respect to the introduction of missing gamete types (see above). Hence, from condition (A.2.1a) we can conclude that such instability of the marginal equilibria, if they exist, is necessary for the stability of the interior equilibrium.

In order to obtain fuller insight into the stability of the internal equilibrium, we have carried out a complete analysis of Model 1 with the special condition $s_1 = 0$. The details are given in APPENDIX 2: the results, taken together with the conditions for the existence and stability of the marginal and corner equilibria, are presented in the next two sections. Although these conclusions have been derived for the $c = 0$ case, they are valid for small c, and the numerical illustrations have been calculated with $c = 0.01$, which is close to the true value in an $S\,R$ chromosome lacking inversions. The general properties of this specialized case undoubtedly extend to more complex situations.

Margins and corners all unstable (Model 1 with $s_1 = 0$). From the analysis given in the APPENDIX, it follows that the condition $s_5 > K_1$, which guarantees the existence of the $++/S\,R$ marginal equilibrium, and condition (6), for the instability of this equilibrium to the introduction of $+\,R$, are sufficient for the existence and stability of the internal equilibrium. Condition (6) here reduces to the simple form $s_4 < K_1$. Moreover, if the $+\,R/S\,R$ equilibrium exists and is stable on the margin, its instability to the introduction of $++$ is guaranteed by condition (6) when $s_5 > K_1$. The $+\,+/+\,R$ equilibrium is nonexistent when $s_1 = 0$. The existence and instability towards $+\,R$ of the $+\,+/S\,R$ marginal equilibrium in this case, and it implies the instability of the other marginal and corner equilibrium when they exist.

These conditions might well have held in the original segregation distorter polymorphism before the evolution of the system of modifiers on chromosome 2 that enhance the distorting effect of $S\,R$ (SANDLER and HIRAIZUMI 1960; MIKLOS 1972). As shown in APPENDIX 2, there may easily be complex eigenvalues associated with the stability matrix, which cause damped oscillations in the neighborhood of a stable interior equilibrium. Numerical solutions of the stability conditions suggest that this is usually true under more general conditions than those analyzed in detail here.

Figure 1 shows the kind of population trajectory that is generated with an $S\,R$ chromosome having a high k value. As can be seen, there are violent oscillations that result in the almost complete loss of $S\,R$ chromosomes for a substantial time. With lower k values, such as would probably have characterized a population evolving the SD polymorphism *de novo*, before the establishment of enhancing modifiers of segregation distortion, the oscillations tend to be less marked, although the general pattern is similar.

The oscillations are basically due to selection for the $S\,R$ chromosome generating an advantage for the insensitive $+\,R$ chromosome. When $+\,R$ reaches a high frequency, $S\,R$ becomes deleterious and declines in frequency, resulting in a net disadvantage to the $+\,R$ chromosomes, which then declines in frequency, allowing an increase in the frequency of $S\,R$ to occur again.

The S R *corner is stable to* $+\,+$ *(Model 1 with* $s_1 = 0$). This situation is probably less realistic than the others and is of interest in the present context only if the other marginal and corner equilibria, where existent, are unstable. This is the case if $K_1 > s_5$, but the other instability criteria are satisfied (*i.e.*, if $s_3, s_5 > s_4$ and condition (8) hold, or if $0 < s_3 < s_4 < s_5$). The results below are based on

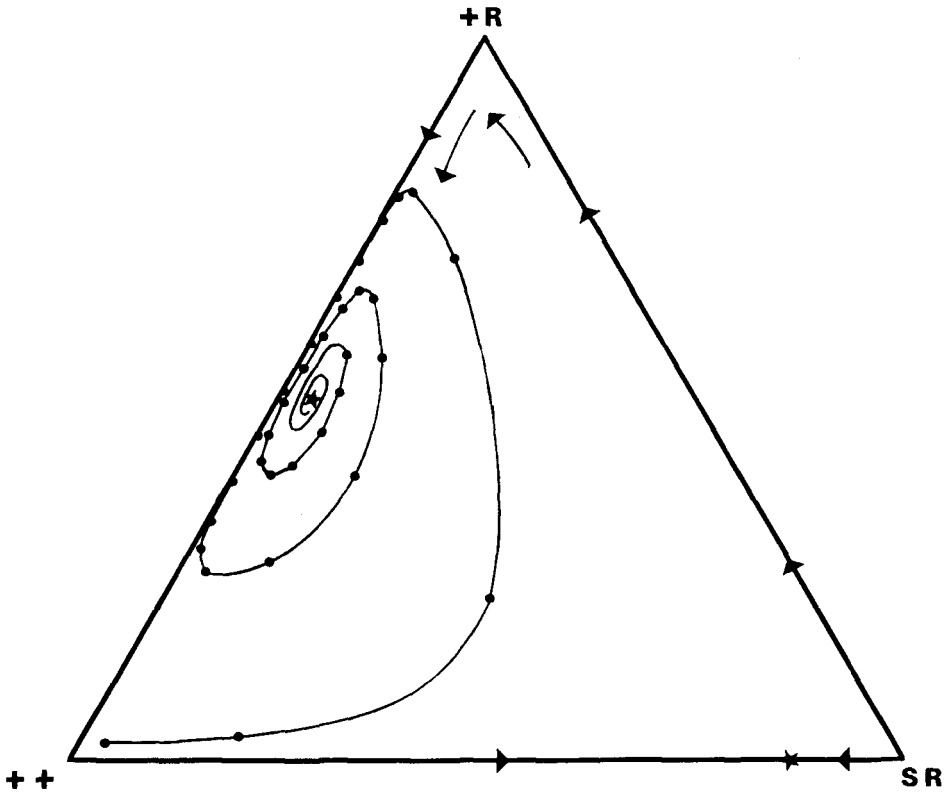

FIGURE 1.—Population trajectory in model 1 showing violent oscillations in gametic frequencies in the early generations. Here we assume $c = 0.01$ and $s_1 = 0.025$, $s_2 = 0.3$, $s_3 = 0.05$, $s_4 = 0.25$, $s_5 = 0.9$, and $k = 0.9$. Smaller k values reduce the amplitude of the oscillations, but the qualitative pattern remains the same. Analysis of the eigenvalues in model 1 are presented in APPENDIX 2. The stars represent the positions of the two nontrivial equilibria; the arrows indicate the general direction of changes in gamete frequencies. The population started close to fixation for $+ +$.

the analysis of the $s_1 = 0$ case. but qualitatively similar results are obtained with $0 < s_1 < s_3$.

(a) $s_3 < s_4$. There is always an interior equilibrium. If s_4 is sufficiently close to s_5, analysis of equation (A.2.1) shows that the interior equilibrium is unstable. Since inequality (A.2.2) implies the existence of complex eigenvalues in this situation, and since none of the corner or marginal equilibria are stable to all perturbations, it seems likely that a stable limit cycle or some other form of indefinitely oscillating behavior will result when the interior equilibrium is unstable (*c.f.*, OSTER 1976). Numerical evaluation of the eigenvalues of the stability matrix indicates that they are generally close to the unit circle centered at -1, so that the amplitude of oscillations in the final state might normally be very small. Computations of population trajectories indicate that this is the case, so that the interior equilibrium is effectively stable, although the system may

oscillate rather violently for a long time. Furthermore, the amplitude of the oscillations on the approach to the final state is sensitive to the value of c. For c close to zero, the amplitude is very large.

(b) $s_3 > s_4$. Here the stability behavior is more regular. Again when $s_1 = 0$, a stable interior equilibrium exists if the $S\,R/+\,R$ marginal equilibrium is unstable to $+\,+$. This suggests that if the $S\,R/+\,R$ marginal equilibrium is stable, the population will eventually come to equilibrium there; if unstable, the population will converge to the interior equilibrium. This proposition has been confirmed by numerical examples.

SELECTION FOR INVERSIONS

The existence of strong linkage disequilibrium in populations at interior equilibria, implied by the rarity of $S+$ gametes, suggests that there may be selection for reducing c (*cf.*, THOMSON and FELDMAN 1974; FELDMAN and KRAKAUER 1976). Probably the simplest way to study this process is to consider that fate of an inversion introduced into one of the gametic types, which has the effect of completely suppressing crossing over between the S and R loci when heterozygous, but which has no effect on fitness of its own (NEI 1967; DEAKIN 1972; CHARLESWORTH and CHARLESWORTH 1973). The mathematics of this process in the present case closely resembles that for more conventional two-locus systems.

Consider an inversion introduced into an $S\,R$ gamete. Let the frequency of inversion-bearing gametes be z_5, averaged over both sexes. The system including the inversion is described by equations (1) and (12) below, where the summations run up to i and j equal to 5. (Note that $w_{5i} = w_{4i}$ and $w_{i5} = w_{i4}$.)

$$\bar{w}\,(z'_5 + \delta'_5) = z_5 w_4 - \delta_5 \sum_j \delta_j w_{4j} \tag{12a}$$

$$z'_5 - \delta'_5 = z_5\ . \tag{12b}$$

These equations can be used to investigate the conditions for a new inversion to spread and the type of equilibrium finally attained by the population. Small c values are again assumed.

Spread of a new inversion: The inversion is assumed to be introduced into a population at a stable interior equilibrium. Neglecting terms in δ_i^2 and z_5^2 we obtain

$$\Delta z_5 = z_5\,(\hat{w}_4 - \hat{\bar{w}})/2\,\hat{\bar{w}}\ .$$

Now; the equilibrium form of equations (1), neglecting terms in δ_i^2 gives

$$(\hat{w}_4 - \hat{\bar{w}})/2\,\hat{\bar{w}} = c\,\hat{D}/2\,\hat{z}_4$$

For small c we can approximate D by $z_1 z_4$, where z_1 and z_4 can in turn be approximated by equations (9). Hence, finally, we have for small c,

$$\Delta z_5 \approx s z_5 \tag{13a}$$

where

$$s = \frac{1}{2} c\hat{z}_1 \ . \tag{13b}$$

For an inversion introduced into a + + gamete we have a similar result, but with

$$s = \frac{1}{2} c\hat{z}_4 \ . \tag{13c}$$

Inversions introduced into S + or + R chromosomes are selected against.

Since the chance of establishment in a large population of a gene with selection coefficient s is approximately $2s$ (HALDANE 1927), and since the chance that an inversion occurs in a given gametic type is proportional to the frequency of that gamete, the overall chance of establishment of an inversion in the segregation distorer system is, by equations (13), the same for inversions introduced into + + and $S\,R$ gametes, and it is equal to $c\hat{z}_1\hat{z}_4$.

Computations of population trajectories confirm that equations (13) provide a sufficiently accurate description of the progress of a rare inversion.

Equilibria with an inversion present: Without loss of generality, we can confine ourselves to the case of an inversion in gametic type 4 ($S\,R$). It is shown in APPENDIX 3 that the only possible equilibria with the inversion present are those in which, to order c^2 at most, the frequencies of z_1, z_2, z_3, and $z_4 + z_5$ are equal to the corresponding values for the original two-locus equilibrium with $c = 0$; $z_1z_4 - z_2z_3$ equals zero in the inversion-containing equilibrium, however. In the cases discussed earlier in which $z_3 = 0$ in the $c = 0$ equilibria, this implies that $z_4 = 0$, *i.e.*, the inversion will have completely replaced the noninverted $S\,R$ gamete. (A corresponding and analogous result holds when the inversion occurs in the + + gametes.)

The local stability of the inversion-containing equilibrium can be examined using the method of CHARLESWORTH (1974). (Note the correction made by FELDMAN and KRAKAUER 1976). The details are omitted here. The conclusion is that the inversion-containing equilibrium is, for sufficiently small c, stable under the same conditions as the correspond equilibrium population into which the inversion was originally introduced. Taken together with the other results, this strongly suggests that an inversion introduced into $S\,R$ or + + gametes in a population at a stable interior equilibrium will spread to an equilibrium that is identical to the former equilibrium with the same parameters and $c = 0$, except that the inversion completely replaces the corresponding noninverted gametic type. Computations of population trajectories confirm that this is the case.

DISCUSSION

The analysis of the conditions for the establishment of the SD polymorphism suggests that it can occur only if the amount of recombination between the *Sd* and *Rsp* loci is less than some critical value. The close linkage observed between

the two loci is therefore probably no accident; variation at the *Sd* and *Rsp* loci would not have been detected in the absence of the polymorphism, and the polymorphism would not have arisen if the genes were not closely linked. It seems that constraints on the tightness of linkage may be involved in the evolution of other examples of closely linked polymorphic loci. SHEPPARD (1959) and CHARLESWORTH and CHARLESWORTH (1975) have suggested this sort of explanation for the mimicry supergenes of Papilio species, and it may also be valid for the sex chromosomes of higher plants (CHARLESWORTH and CHARLESWORTH 1978). BODMER and PARSONS (1962) gave the first mathematical analysis of this process.

It is difficult at present to be very sure about the value of the critical recombination fraction in the SD polymorphism, since the fertilities under natural conditions are not known. The laboratory data of HARTL, HIRAIZUMI and CROW (1967) is probably the best information available. Averaging over all the heterozygous SD lines listed in their Table 4, one obtains an estimate of K_2 of 0.14; from inequality (3), this is equal to the critical recombination fraction. However, the measured value of K_2 was obtained under conditions in which, as far as possible, the number of offspring produced by a mating was limited by the number of functional sperm transferred by the male during copulation. (Had theoretically ideal conditions been achieved, K_2 would have been zero.) In nature, it seems unlikely that the number of functional sperm transferred will be as strongly limiting a factor on the effective fertility of SD males, since a female may well die before exhausting her supply of sperm. On the other hand, multiple matings and sperm displacement in nature may tend to reduce K_2. In *D. pseudoobscura*, the *X*-chromosome meiotic drive factor "sex ratio" induces dysfunction of *Y*-bearing sperm in males that carry it in a way similar to the dysfunction of wild-type sperm in SD males. POLICANSKY (1974) has shown that the effective fertility of sex-ratio males in nature is close to one-half normal, which is similar to that obtained by laboratory brooding experiments of the type used in the SD system. While it is obviously dangerous to draw conclusions across species and genetic systems, this suggests that there is a real possibility that SD males may have substantially reduced fertilities. Unfortunately, the SD system is less amenable to the experimental methods used by POLICANSKY, but it might be worthwhile to attempt to obtain similar data. Finally, we may note that whatever the value of the critical recombination fraction, equation (2c) implies that a closely linked pair of genes will have a higher initial rate of increase in frequency than a loosely linked pair, and so in all probability a higher chance of establishment, thus creating a sieve for closely linked mutations.

Further implications of this work arise from the equilibrium gamete frequencies given by equations (9) and (11). In the first place, these show that the insensitive Sd^+ *Rsp* chromosomes can rise to quite high frequencies even if the *Sd Rsp* chromosome itself is rare. HARTL and HARTUNG (1975) report a high frequency of Sd^+ *Rsp* (45% of non-*Sd Rsp* chromosomes) in a population from North Carolina. Furthermore, HIRAIZUMI, SANDLER and CROW (1960) initiated

a population cage with 50% *Sd Rsp* and 50% Sd^+ Rsp^+; within about 20 generations they found a significant frequency of insensitive chromosomes. HARTL (1977b), in examining a similar population cage, has shown these insensitive chromosomes to be Sd^+ *Rsp* in genotype. The trajectory plotted in Figure 1 shows how these results can be understood in terms of the present model; Sd^+ *Rsp* chromosomes are generated by recombination and quickly increase in frequency under selection.

It should also be noted that our model predicts the sort of equilibrium frequencies found in natural and artificial populations only when s_1 and s_3 are nonzero and both small (see Tables 3 and 4). Although, as discussed above, there are great difficulties in obtaining satisfactory estimates of the fertility parameters, this is a prediction that needs direct testing. Abnormalities in spermiogenesis found in $+R/++$ males by HAUSCHTECK-JUNGEN and HARTL (1978) suggest that the prediction may hold.

Another point of interest is the strongly oscillatory nature of the paths to equilibrium, which is suggested by our analysis of the dynamics of the system (*e.g.*, Figure 1). Such behavior should be relatively easy to detect in experimental populations.

The results noted above indicate that there is weak selection for an inversion suppressing crossing over between *Sd* and *Rsp*, and that an inversion is equally likely to establish itself in an Sd^+ Rsp^+ or *Sd Rsp* gamete, but cannot be selected in association with Sd^+ *Rsp*. It is known that virtually all *Sd Rsp* chromosomes are associated with a pericentric inversion that severely reduces recombination between *Sd* and *Rsp* (*cf.*, HARTL 1975a). On the other hand, two *Sd Rsp* chromosomes lacking a pericentric inversion have been recovered from natural populations [SD (ROMA) and SD-5]. This is at first sight in conflict with the results that predict that the inversion-bearing chromosome should replace the corresponding noninverted gametic type. There are some additional factors to be considered, however. In the first place there may be other loci in the region subjected to interactive selection, and this might interfere with the progress of the inversion. Secondly, the *Sd* alleles found in natural populations appear to form a multiple allelic series that exhibits intracistronic complementation with respect to effects on male fertility (HARTL 1973). This will tend to generate a situation in which the heterozygotes for different *Sd* alleles will have higher male fertilities than homozygotes, and this will tend to maintain a variety of *Sd* alleles in the population. (It is important to note in this context that, because Sd^+ *Rsp* chromosomes are maintained at high frequencies once the initial polymorphism has been established, new *Sd Rsp* chromosomes may arise by mutation in Sd^+ *Rsp* chromosomes, as well as from pre-existing *Sd Rsp* chromosomes.) A small inversion arising in a given type of *Sd Rsp* chromosome will be permanently associated with one *Sd* allele, and will probably be unable to replace all the noninverted *Sd Rsp* gametes.

It may be useful to point out the differences between the present models and those of PROUT, BUNDGAARD and BRYANT (1973), THOMSON and FELDMAN

(1974, 1976), and HARTL (1975b), which involve a system of two loci, one of which is subject to meiotic drive and natural selection and the other of which is an otherwise neutral modifier of the segregation ratio at the first locus. With close linkage between the loci, equilibria with two predominant gametic types are created, in contrast to the present models where three gametic types occur at equilibrium. All models share the feature of selection in favor of closer linkage, though THOMSON and FELDMAN (1974) have shown that some cases of their model can generate selection for looser linkage.

Finally, a word about the theoretical population genetics of non-Mendelian segregation is in order. Virtually all "general" principles of population dynamics are violated when segregation is non-Mendelian: average fitness is not maximized at equilibrium in random-mating populations, even for a single locus (HIRAIZUMI, SANDLER and CROW 1960); the fundamental theorem of natural selection does not hold (HARTL 1970b); standard modifier theory (KARLIN and MCGREGOR 1974) is violated because linked neutral enhancers of distortion can increase in frequency and thereby reduce average fitness (HARTL 1975b); standard two-locus theory is violated because reduction of the recombination fraction between a distorter and a neutral modifier does not always lead to a greater average fitness at equilibrium and does not always reduce the equilibrium linkage disequilibrium (THOMSON and FELDMAN 1976). It makes one wonder whether there are *any* general principles of population genetics whose validity does not depend decisively on the supposition of Mendelian segregation.

LITERATURE CITED

BODMER, W. F. and P. A. PARSONS, 1962 Linkage and recombination in evolution. Advan. Genet. **11**: 1–100.

CHARLESWORTH, B., 1974 Inversion polymorphism in a two-locus genetic system. Genet. Res. **23**: 259–280.

CHARLESWORTH, B. and D. CHARLESWORTH, 1973 Selection of new inversions in multi-locus genetic systems. Genet. Res. **21**: 167–183. ——, 1978 A model for the evolution of dioecy and gynodioecy. Am. Naturalist (in press).

CHARLESWORTH, D. and B. CHARLESWORTH, 1975 Theoretical genetics of Batesian mimicry II. Evolution of supergenes. J. Theoret. Biol. **55**: 305–324.

CROW, J. F. and M. KIMURA, 1970 *An Introduction to Population Genetics Theory*. Harper and Row, New York.

DEAKIN, M. A. B., 1972 A model for inversion polymorphism. J. Theoret. Biol. **35**: 191–212.

DUNN, L. C. and H. LEVENE, 1961 Population dynamics of a varient *t*-allele in a confined population of wild house mice. Evolution **15**: 385–393.

FELDMAN, M. W. and J. KRAKAUER, 1976 Genetic modification and modifier polymorphisms. pp. 547–583. In: *Population Genetics and Ecology*. Edited by S. KARLIN and E. NEVO, Academic Press, New York.

GOLDBERG, S., 1961 *Introduction to Difference Equations*. John Wiley, New York.

HALDANE, J. B. S., 1927 A mathematical theory of natural and artificial selection. Part V: Selection and mutation. Proc. Cambridge Philosophical Soc. **28**: 838–844.

HARTL, D. L., 1969 Dysfunctional sperm production in *Drosophila melanogaster* males homozygous for the segregation distorter elements. Proc. Natl. Acad. Sci. U.S. **63**: 782–789. ——, 1970a Meiotic drive in natural populations of *Drosophila melanogaster*. IX. Suppressors of segregation distorter in wild populations. Can. J. Genet. and Cytol. **12**: 594–600. ——, 1970b Population consequences of non-mendelian segregation among multiple alleles. Evolution **24**: 538–545. ——, 1973 Complementation analysis of male fertility among the segregation distorter chromosomes of *Drosophila melanogaster*. Genetics **73**: 613–629. ——, 1974 Genetic dissection of segregation distortion, I. Suicide combinations of *SD* genes. Genetics **76**: 477–486. ——, 1975a Segregation distortion in natural and artificial populations of *Drosophila melanogaster*. pp. 83–91. In: *Gamete Competition in Plants and Animals*. Edited by D. L. MULCAHY, North-Holland, Amsterdam. ——, 1975b Modifier theory and meiotic drive. Theoret. Population Biol. **7**: 168–174. ——, 1977a How does the genome congeal? pp. 65–82. In: *Lecture Notes in Biomathematics 19: Measuring Selection in Natural Populations*. Edited by F. B. CHRISTIANSEN and T. M. FENCHEL, Springer-Verlag, Berlin. ——, 1977b Mechanism of a case of genetic coadaptation in populations of *Drosophila melanogaster*. Proc. Natl. Acad. Sci., U.S., **74**: 324–328.

HARTL, D. L. and N. HARTUNG, 1975 High frequency of one element of *Segregation Distorter* in natural populations of *Drosophila melanogaster*. Evolution **29**: 512–518.

HARTL, D. L. and Y. HIRAIZUMI, 1976 Segregation distortion. pp. 615–666. In: *Genetics and Biology of Drosophila*, Vol. 1b. Edited by M. ASHBURNER and E. NOVITSKI, Academic Press, New York.

HARTL, D. L., Y. HIRAIZUMI and J. F. CROW, 1967 Evidence for sperm dysfunction as the mechanism of segregation distortion in *Drosophila melanogaster*. Proc. Natl. Acad. Sci., U.S. **58**: 2240–2245.

HAUSCHTECK-JUNGEN, E. and D. L. HARTL, 1978 DNA distribution in spermatid nuclei of normal and segregation distorter males of *Drosophila melanogaster*. Genetics **89**: 15–35.

HIHARA, Y. K., 1974 Genetic analysis of modifying systems of segregation distortion in *Drosophila melanogaster*. II. Two modifiers for SD system on the second chromosome of *D. melanogaster*. Japan J. Genet. **49**: 209–222.

HIRAIZUMI, Y. and J. F. CROW, 1960 Heterozygous effects on viability, fertility, rate of development and longevity of Drosophila chromosomes that are lethal when homozygous. Genetics **45**: 1071–1084.

HIRAIZUMI, Y. and K. NAKAZIMA, K., 1967 Deviant sex ratio associated with segregation distortion in *Drosophila melanogaster*. Genetics **55**: 681–697.

HIRAIZUMI, Y., L. SANDLER and J. F. CROW, 1960 Meiotic drive in natural populations of *Drosophila melanogaster*. III. Populational implications of the segregation-distorter locus. Evolution **14**: 433–444.

KARLIN, S. and J. MCGREGOR, 1972 Polymorphisms for genetic and ecological models with weak coupling. Theoret. Population Biol. **3**: 210–238. ——, 1974 Towards a theory of the evolution of modifier genes. Theoret. Population Biol. **5**: 59–103.

KATAOKA, Y., 1967 A genetic system modifying segregation-distortion in a natural population of *Drosophila melanogaster* in Japan. Jap. J. Genet. **42**: 327–337.

KETTANEH, N. P. and D. L. HARTL, 1976 Histone transition during spermatogenesis is absent in segregation distorter males of *Drosophila melanogaster*. Science **193**: 1020–1021.

LI, C. C., 1955 *Population Genetics*, University of Chicago Press, Chicago.

MIKLOS, G. L. G., 1972 An investigation of the components of Segregation-Distorter systems in *Drosophila melanogaster*. Genetics **70**: 405–418.

MIKLOS, G. L. G. and S. SMITH-WHITE, 1971 An analysis of the instability of segregation-distorter in *Drosophila melanogaster*. Genetics **67**: 305–317.

NEI, M., 1967 Modification of linkage intensity by natural selection. Genetics **57:** 625–641.

OSTER, G., 1976 Internal variables in population dynamics. pp. 37–68. In: *Some Mathematical Questions in Biology VII.* Edited by S. LEVIN, American Mathematical Society, Providence, R.I.

POLICANSKY, D., 1974 "Sex ratio," meiotic drive and group selection in *Drosophila pseudoobscura.* Am. Naturalist **108:** 75–90.

PROUT, T., J. BUNDGAARD and S. BRYANT, 1973 Population genetics of modifiers of meiotic drive I. The solution of a special case and some general implications. Theoret. Population Biol. **4:** 446–465.

SANDLER, L. and Y. HIRAIZUMI, 1960 Meiotic drive in natural populations of *Drosophila melanogaster.* IV. Instability at the Segregation-Distorter locus. Genetics **45:** 1269–1287.

SHEPPARD, P. M., 1959 The evolution of mimicry; a problem in ecology and genetics. Cold Spring Harbor Symp. Quant. Biol. **24:** 131–140.

THOMSON, G. and M. W. FELDMAN, 1974 Population genetics of modifiers of meiotic drive. II. Linkage modification in the segregation distortion system. Theoret. Population Biol. **5:** 155–162.

THOMSON, G. and M. W. FELDMAN, 1976 Population genetics of modifiers of meiotic drive. III. Equilibrium analysis of a general model for the genetic control of segregation distortion. Theoret. Population Biol. **10:** 10–25.

TOKUYASU, K. T., W. J. PEACOCK and R. W. HARDY, 1977 Dynamics of spermiogenesis in Drosophila. VI. J. Ultrastructure Res. **58:** 96–107.

TRIPPA, G. and A. LOVERRE, 1975 A factor on a wild third chromosome (III^{Ra}) that modifies the Segregation Distortion phenomenon in *Drosophila melanogaster.* Genet. Res. **26:** 113–125.

WATANABE, T. K., 1967 Persistence of lethal genes associated with SD in natural populations of *Drosophila melanogaster.* Japanese J. Genet. **42:** 375–386.

Corresponding editor: W. W. ANDERSON

APPENDIX I

Exclusion of S + *from* c = 0 *equilibria*

Several types of equilibria containing $S+$ are possible. Here we show that, with biologically relevant parameters, these equilibria either cannot exist or, if they exist, are unstable to the introduction of new gametic types.

(1) The $S+$ corner (of the $++/+\ R/S\ +/S\ R$ tetrahedral simplex) is unstable to $S\,R$ if $K_2 > 0$ and unstable to $+\,R$ if $K_3 > 0$.

(2) An $S+/S\,R$ marginal equilibrium is unstable to the introduction of $+\,R$ if $K_2(K_1 - K_5) + K_3(s_5 - K_1) > 0$. In model 1, a necessary and sufficient condition for this inequality to hold is $s_5 > s_4$.

(3) An $S+/+\,R$ equilibrium is unstable to the introduction of $+\,+$ if $K_4 > s_1$. A sufficient condition for this is $s_6 > s_1$. For model 1 the condition reduces to $K_1 > s_1$, for which $s_2 > s_1$ is sufficient.

(4) An $S+/+\,+$ equilibrium is unstable to $S\,R$ if $K_2 > 0$.

(5) An equilibrium on the $S+/S\,R/+\,R$ face is unstable to the introduction of $+\,+$ if $K_4 > s_1$, as in case (3) above.

(6) An equilibrium on the $S+/+\,R/+\,+$ face cannot exist; its existence would require that $\hat{w}_1 = 1 - s_1 z_2 = \hat{w}_3 = 1 - K_4 z_2$, which cannot be unless $K_4 = s_1$. For model 1 the condition for nonexistence of this equilibrium is simply $K_1 \neq s_1$.

(7) An equilibrium on the $S+/S\,R/+\,+$ face can be shown to exist and be locally stable on that plane iff $s_5 > K_1$ and $K_2 > 0$. It is unstable to the introduction of $+\,R$ if

(a) when $K_3 > -s_1, K_2(K_1 - K_5) + s_1(K_1 - s_5) > 0$,

or (b) when $K_3 < -s_1, K_2(K_1 - K_5) - K_3(K_1 - s_5) > 0$. (A.1.1)

Since there are no strong coupling-repulsion effects of the S and R loci (HARTL 1974), we expect K_3 to be fairly close to K_2 and certainly positive. Case (a) then obtains, and note that the condition is simply $\beta > 0$, which from (10) and (A.2.4a) is necessary for the existence of a stable $++/+R/S\,R$ equilibrium. Such an equilibrium cannot, therefore, coexist with a $++/S+/S\,R$ equilibrium that is stable to the introduction of $+R$. On the other hand, with rather extreme parameter values, a $++/S+/S\,R$ equilibrium can exist and be stable to $+R$; if this occurs, then, with a small amount of recombination, the equilibrium population would be expected to contain rather few $+R$ chromosomes generated by recurrent recombination between $++$ and $S\,R$.

(8) No equilibrium can exist within the $++/+R/S+/S\,R$ tetrahedron. The existence of such an equilibrium would imply that $\hat{w}_3 = 1 - z_2K_4 - z_4K_1 = \hat{w}_1 = 1 - z_2s_1 - z_4K_1$, which is impossible unless $K_4 = s_1$, as in case (6) above.

(9) Finally, we note that a stable $++/+R/S\,R$ equilibrium *is* stable to the introduction of $S+$. Around the equilibrium, $\hat{w}_3 - \bar{w} = z_2(s_1 - K_4)$, so that $S+$ cannot invade if $K_4 > s_1$. This condition is the same as that in case (3) above.

APPENDIX II

The stability of the interior equilibrium with $c = 0$.

General considerations: It is convenient to introduce the variables $X_1 = z_2$ and $X_2 = z_4$. The stability of the system is determined by the 2×2 matrix $A = \{a_{ij}\} = \{\partial(\Delta X_i)/\partial X_j\}$ where ΔX_i is the change per generation in X_i. The derivatives are evaluated at the equilibrium point. The standard necessary and sufficient conditions for stability (GOLDBERG 1961) are equivalent to the following expressions, where *tr* and *det* are the trace and determinant of A, respectively.

$$det > 0 \tag{A.2.1a}$$

$$-(tr + det) > 0 \tag{A.2.1b}$$

$$4 + 2\,tr + det > 0. \tag{A.2.1c}$$

The necessary and sufficient condition for real eigenvalues is

$$tr^2 > 4\,det\,. \tag{A.2.2}$$

In the present case we have

$$\begin{aligned} a_{11} &= z_2[(K_1 + K_2)z_4 - (s_3 - s_1) - (K_5 + K_6)z_4]/2\bar{w} \\ a_{12} &= z_2[(K_1 + K_2)(1 - z_2) - (K_5 - s_1) + (K_5 + K_6 z_2]/2\bar{w} \\ a_{21} &= z_4[(K_1 + K_2)z_4 - (-K_6 + K_2) - (K_5 + K_6)z_4]/2\bar{w} \\ a_{22} &= z_4[(K_1 + K_2)(1 - z_2) - (K_2 + s_5) + (K_5 + K_6)z_2]/2\bar{w}\,. \end{aligned} \tag{A.2.3}$$

Considerable algebra yields a remarkably simple result:

$$det = B\,z_1\,z_2\,z_4/4\bar{w}^2 \tag{A.2.4a}$$

$$tr = -[(s_5 - K_5)z_4 - s_1\,z_1]/2\bar{w}\,. \tag{A.2.4b}$$

Since the equilibrium gamete frequencies are known explicitly in terms of the selection and segregation distortion parameters, these expressions enable ready evaluation of conditions (A.2.1) for a given numerical case. It is not easy to express them in a simpler form, except in the special case of Model 1 with $s_1 = 0$, considered below.

Model 1 with $s_1 = 0$. Stability condition (A.2.1a) reduces, using (A.2.4a) and equations (9) to conditions (6) and (8), since $\gamma > 0$ by virtue of the assumption that $s_1 = 0$. If $s_5 > K_1$, it can easily be seen that condition (8) is satisfied whenever condition (6) holds. If condition (A.2.1a) is satisfied, a necessary condition for (A.2.1b) to hold is $tr < 0$. In the present case, we have

$$tr = -z_4(s_5 - s_4)/2w \tag{A.2.5}$$

so that $s_5 > s_4$ is necessary for stability. Condition (A.2.1b) in full reduces to

$$2(s_5 - s_4)(B - s_3K_1K_2) - K_2(K_1 - s_4)\cdot det > 0\,. \tag{A.2.6}$$

If $s_5 \geq K_1$, a sufficient condition for (A.2.6) to hold is

$$2(B - s_3K_1K_2) > B + K_2s_4 - K_1K_2 - s_3K_2\,.$$

Given condition (8), this is satisfied if $B > s_3K_1K_2$, which holds under conditions (6) and (8).

If $s_5 < K_1$ and $s_4 < s_5$, it can be seen by inspection that condition (A.2.6) may be violated if s_5 is sufficiently close to s_4. Under these circumstances, therefore, the equilibrium exists but is unstable. If $s_5 < K_1$ and $s_3 > s_4$, however, it can be shown as follows that condition (A.2.6) holds given conditions (6) and (8). We have in this case $K_1 (s_4 - s_3) < s_5 (s_4 - s_3)$, so that

$$det < (s_3s_5 - s_4^2) + s_5 (s_4 - s_3) = s_4 (s_5 - s_4) .$$

A sufficient condition for (A.2.6) is thus

$$2B - 2 s_3K_1K_2 - s_4K_2 (K_1 - s_4) > 0 ,$$

which can be shown to hold given conditions (6) and (8).

It remains to consider condition (A.2.1c). If the necessary conditions $det > 0$, $tr < 0$ are satisfied, this holds if $|tr| < 2$. This can be shown to be satisfied in all cases of interest, but the details will be omitted here.

In conclusion, we note that condition (A.2.2) for real eigenvalues reduces to

$$s_3 (s_5 - s_4) [(s_5 - s_4) - 4 (K_1 - s_4)] - 4 (K_1 - s_4)^2 (s_4 - s_3) > 0 . \qquad \text{(A.2.7)}$$

When $s_3 < s_4$ and $K_1 > s_5$, this condition can never be satisfied. If $s_3 < s_4$ and K_1 is close to s_5, as will normally be the case for high k values, the same is true. With $s_3 > s_4$, the second term of (A.2.7) is positive, so that there will be situations when it is satisfied. Even when condition (A.2.6) is violated, the moduli of the imaginary parts of the eigenvalues will be less than in the corresponding situations with $s_3 < s_4$, implying oscillations of smaller magnitude.

APPENDIX III

Equilibria with an inversion present

The equilibrium version of equation (12b) gives $\delta_5 = 0$. Equation (1b) implies

$$\delta_1 = \delta_4 = c (D - \Delta^*) \qquad \text{(A.3.1a)}$$

$$\delta_2 = \delta_3 = -\delta_1 \qquad \text{(A.3.1b)}$$

so that $\Delta^* = 0$. This implies that either

$$\delta_4 = 0, D = 0$$

or

$$\delta_4 = c D \neq 0 .$$

Equations (12a) and the fact that $\delta_5 = 0$ imply

$$\bar{w} = w_4 . \qquad \text{(A.3.2)}$$

Similarly,

$$\bar{w} (z_4 + \delta_4) = z_4w_4 - \delta_4 \sum_{j=1}^{4} \delta_j w_{4j} .$$

From (A.3.2), this implies that either

$$\delta_4 = 0$$

or

$$w_4 = -\sum_{j=1}^{4} \delta_j w_{4j} = -cD (w_{41} + w_{44} - w_{42} - w_{43}) . \qquad \text{(A.3.3)}$$

In the first case, equations (A.3.1) imply that all the δ_i are zero. In the second case, the parameterization of the w_{ij} in Tables 1 or 2 gives

$$|w_{41} + w_{44} - w_{42} - w_{43}| < 2 .$$

Equation (A.3.3) therefore implies $|cD| > w_4/2$, or

$$c > 2 w_4 . \qquad \text{(A.3.4)}$$

Unless w_4 is of order c, this inequality cannot be satisfied, in which case the equilibrium must have all $\delta_i = 0$ and $D = 0$. Since populations with small c are of primary interest here, the possibility that (A.3.4) holds can safely be discounted, since it implies high sterility of the equilibrium population. Even if it is satisfied, analysis of the conditions for equilibrium for the other gametic types in the equilibrium population shows that

$$w_i - \bar{w} = O (c^2), i = 1, \ldots, 4.$$

Thus, to terms of order c^2, the population is at an equilibrium with $\delta_i = 0; z_1$, z_2, and $z_4 + z_5$ are given by the same equations as the equations for z_1, z_2, and z_4 with no inversion and $c = 0$. If inequality (A.3.4) is violated, on the other hand, then the result is exact.