ON THE OPPORTUNITY FOR POLYMORPHISM WITH SEX-LINKAGE OR HAPLODIPLOIDY[1]

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ABSTRACT

This paper addresses the assertion that X-linked and haplodiploid genetic systems are inherently limited with respect to the potential for selectively maintained genetic polymorphisms. Using a variation of HALDANE and JAYAKAR's (1964) parameterization of selection on an X-linked locus, analytical expressions are derived for the proportion of the total parameter space (P) in which stable diallelic polymorphism is attained. P is a function of the ratio of selection coefficients (r) associated with homozygous and hemizygous genotypes, and the intensity of selection (s). Analytical expressions for the opportunity for polymorphism at an autosomal locus (P_a) are also derived for comparison to the X-linked case. P and P_a are maximal and equal if the ratios of selection coefficients are —1 and selection is intense. Otherwise, P is slightly less than P_a, but the difference between autosomal and sex-linked loci is less than the range of values of P obtained over the range of r. Several arguments are presented suggesting that polymorphism arising from differential selection in the sexes ($r < 0$) is probabilistically and biologically feasible.

IT is well known that heterosis is not sufficient for stable diallelic polymorphism at an X-linked locus (BENNETT 1958; HALDANE and JAYAKAR 1964; CANNINGS 1967; CAVALLI-SFORZA and BODMER 1971). The conditions for existence of such a polymorphism depend on the relative fitnesses of five genotypes, in contrast with three genotypes in the autosomal case, and thus appear more stringent. These observations have been widely interpreted to mean that there is limited opportunity for selectively maintained genetic polymorphism in sex-linked and haplodiploid genetic systems (PRAKASH 1973; METCALF, MARLIN and WHITT 1975; PAMILO *et al* 1978; COOPER *et al* 1979; LESTER and SELANDER 1979). The probability that relative fitnesses satisfy the conditions for stable polymorphism has been derived for some special selection cases (COOPER 1976; PAMILO 1979; CROZIER and PAMILO 1979) and has been estimated in several Monte Carlo simulation studies (CROZIER 1970; LESTER and SELANDER 1979; CURTSINGER and FELDMAN 1980), but the general functional dependence of that probability on selective differences between the sexes and other factors is unknown.

A novel parameterization of the operation of natural selection on an X-linked

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locus is presented here. The parameterization is a variation on the model of HALDANE and JAYAKAR (1964), chosen for analysis because it facilitates quantification of the notion of "opportunity for polymorphism." Within that framework, analytical expressions are derived for the opportunity for polymorphism at X-linked and autosomal loci, and a model for re-analysis of published viability estimation data is considered.

THEORY

I. *X-linked polymorphism*

Consider a dioecious population in which two alleles are present at an X-linked locus. Following HALDANE and JAYAKAR (1964), let the genotypes have relative viabilities, all positive, as follows:

X_1X_1	X_1X_2	X_2X_2	X_1Y	X_2Y
$1+f$	$1+h$	$1-f$	$1+m$	$1-m$.

Define r such that $m = rf$, where $-1 \leq rf \leq +1$. The variable r will be referred to as the ratio of selection coefficients; it is positive if selection favors the same allele among hemizygotes and homozygotes.

The conditions for existence and stability of a polymorphic equilibrium are (I) $(1+f)\ (1+rf) < 1+h$, and (II) $(1-f)\ (1-rf) < 1+h$. The functions will be referred to as $A(f,r)$ and $B(f,r)$, respectively. The conditions are derived under the usual deterministic assumptions, are independent of the population sex ratio and follow directly from HALDANE and JAYAKAR (1964). Condition I is relevant if ($f > 0$ and $r > -1$) or ($f < 0$ and $r < -1$); otherwise, Condition II is relevant, i.e., Condition I is automatically satisfied if Condition II is satisfied.

The relevant conditions for existence and stability of a polymorphic equilibrium are shown in Figure 1, where $1+h$ is plotted against f for various values of r. For parameter sets to satisfy the conditions for polymorphism, the point $(f,1+h)$ must lie above the curve for the given value of r. For example, if $r = -0.5$, the point $(f,1+h)$ must lie above the arcs connecting the points $(-1,1)$, $(0,1)$ and $(0,1)$, $(1,1)$. Figure 1 clearly illustrates the fact that polymorphism can arise from heterosis or from selection favoring different alleles in the two sexes, the latter case occurring where r is negative.

In order to quantify the "opportunity for polymorphism," it is necessary to define three variables:

s: the maximal value of the selection coefficients f and h. $0 \leqslant s \leqslant 1$. The parameter s defines a square region on the plane of Figure 1. Fitnesses of genotypes of the homogametic sex lie in the interval $(1-s, 1+s)$. Throughout the following analyses, $|rs| \leqslant 1$ for positive fitness values.

P: the proportion of the area of the region defined by s in which conditions for existence and stability of a polymorphic equilibrium are satisfied.

x: the value of f at $A(f,r) = 1+s$ or $B(f,r) = 1+s$.

The functional dependence of P on r and s can be specified exactly if the values or r are divided into four ranges. In the following derivations, only the region of

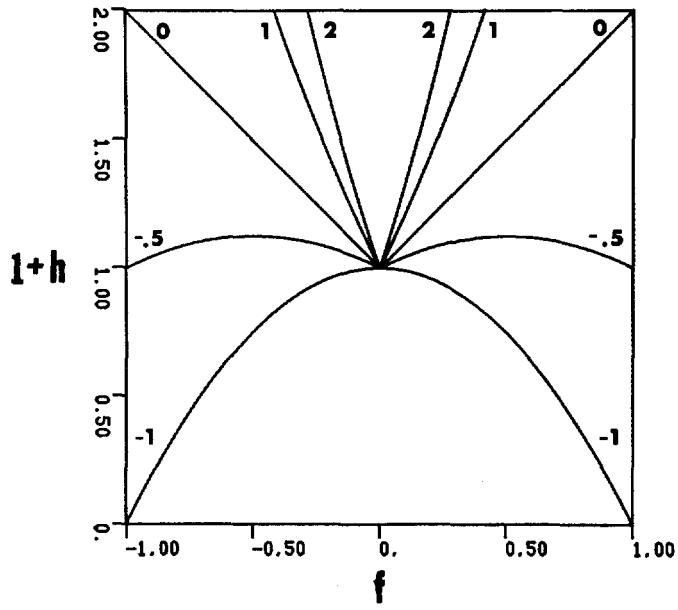

FIGURE 1.—Phase space illustrating the conditions for existence of a stable polymorphic equilibrium at an X-linked locus, where the genotypes X_1X_1, X_1X_2, X_2X_2, X_1Y and X_2Y have relative fitnesses $1+f$, $1+h$, $1-f$, $1+rf$ and $1-rf$, respectively. Curves are $A(f,r)$ or $B(f,r)$ and are labelled with the value of r, the ratio of selection coefficients. For stable polymorphic equilibrium with parameters f, h and r, the point $(f, 1+h)$ must lie above the appropriate r-curve.

Figure 1 in which $f \geqslant 0$ will be considered, as shown schematically in Figure 2; the relevant conditions are symmetric about the line $f = 0$, so that this has no effect on the value of P.

(1) $r > 0$. Condition I is the relevant condition for polymorphism. The value of x is given by solving for f in the equation $A(f,r) = 1 + s$:

$$x = \frac{-(1+r) + \sqrt{(1+r)^2 + 4rs}}{2r} . \tag{1}$$

It can be shown that $x < s$ if $r > 0$, as shown schematically in Figure 2a. The area of the region defined by s is $2s^2$. The area in which conditions for polymorphic equilibrium are satisfied is shown as the darkened region in Figure 2a.

Thus,

$$P = \frac{x(1+s) - {}_0\int^x A(f,r)\, df}{2s^2} . \tag{2}$$

Equation (2) simplifies to

$$P = \frac{x}{2s} - \frac{x^2(1+r)}{4s^2} - \frac{rx^3}{6s^2} . \tag{3}$$

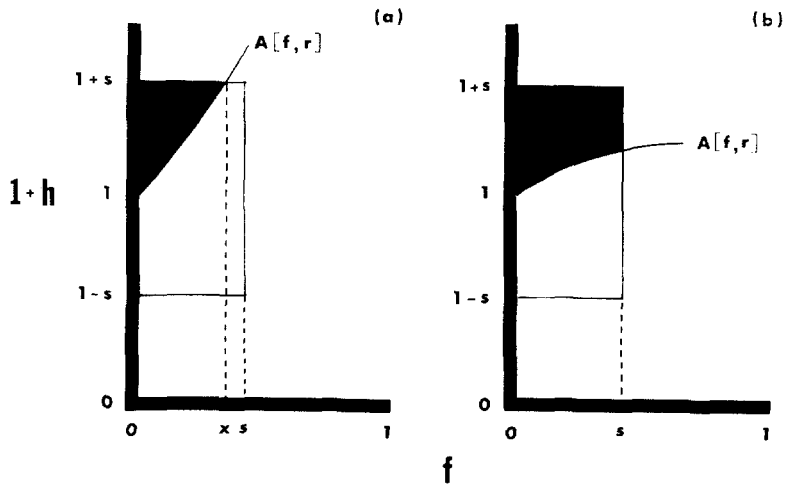

FIGURE 2.—Schematic representation of the conditions for existence of a stable polymorphic equilibrium when (a) $r > 0$, and (b) $-1 \leq r \leq 0$. This figure is a detail of the phase space shown in Figure 1 for $f > 0$. The parameter region defined by s, the intensity of selection, is shown in solid lines; the fitnesses of genotypes of the homogametic sex lie in the interval $(1 - s, 1 + s)$. Parameter sets satisfying the conditions for polymorphism are represented by points within the shaded areas.

(2) $-1 \leqslant r \leqslant 0$. Condition I is relevant. As shown schematically in Figure 2b, the appropriate integration limit is s, i.e., $A(f,r) < 1 + s$ at $f = s$. Then:

$$P = \frac{s(1+s) - {}_0\int^s A(f,r)\, df}{2s^2} . \tag{4}$$

Equation (4) simplies to:

$$P = \frac{(1-r)}{4} - \frac{rs}{6} . \tag{5}$$

(3) $\frac{2}{s-1} \leqslant r < -1$. Condition II is relevant. $B(f,r) < 1 + s$ at $f = s$; therefore s is the appropriate integration limit:

$$P = \frac{s(1+s) - {}_0\int^s B(f,r)\, df}{2s^2} . \tag{6}$$

Equation (6) simplifies to:

$$P = \frac{(3+r)}{4} - \frac{rs}{6} . \tag{7}$$

(4) $r \leqslant \frac{2}{s-1}$. Condition II is relevant. $B(f,r) > 1 + s$ at $f = s$. The appropriate integration limit is:

$$x = \frac{(1+r) + \sqrt{(1+r)^2 + 4rs}}{2r} . \tag{8}$$

Then,

$$P = \frac{x(1+s) - {}_0\int^x B(f,r)\,df}{2s^2} \quad . \tag{9}$$

Equation (9) simplifies to:

$$P = \frac{x}{2s} + \frac{x^2(r+1)}{4s^2} - \frac{rx^3}{6s^2} \quad . \tag{10}$$

Thus, equations (2), (4), (6) and (9) specify the functional dependence of P on the intensity of selection among genotypes of the homogametic sex and the ratio of selection coefficients. P is a maximum when $r = -1$ and $s = 1$, as shown in Figure 3.

The above results have been derived under the simplifying (and probably unrealistic) assumption that selection coefficients are uniformly distributed. In order to determine whether P is very sensitive to the selection coefficient probability density, Monte Carlo simulations have been performed by drawing selection coefficients from symmetrical triangular and V-shaped distributions on the interval $(-s, +s)$. Five thousand sets of parameter values for f and h were generated for each of thirty values of r and s, and the relevant condition for polymorphism was tested for each parameter set. P for a given value of r and s was estimated as the proportion of the 5,000 parameter sets for which the relevant condition for polymorphism was satisfied. For both the triangular and V-shaped distributions, the Monte Carlo estimation of P appeared to reasonably approximate that computed analytically under the assumption of a uniform distribution of selection coefficients. The maximum discrepancy was 0.07, suggesting that P is fairly robust with respect to symmetrical changes in the underlying selection coefficient probability density.

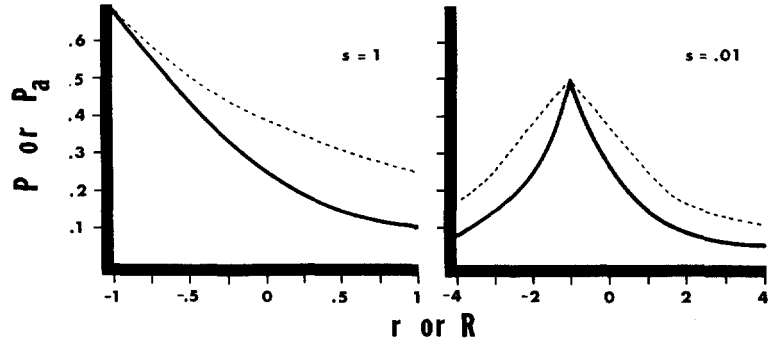

FIGURE 3.—Analytically computed values of the opportunity for polymorphism for X-linked (P) and autosomal (P_a) genes shown as a function of the ratio of selection coefficients. The X-linked case is shown in solid lines and the autosomal case in dashed lines. P and P_a for other values of s are similar to the values shown. Note that the range of P and P_a exceeds their difference.

II. *A model for re-analysis of experimental data*

While the most natural way to relate selective coefficients in the sexes involves comparison of homozygotes and corresponding hemizygotes, as described above, a different approach is needed for re-analysis of experimental data. In viability estimation experiments employing *Drosophila melanogaster* *X*-chromosome balancers, one homozygous genotype is absent from progeny of testcrosses. A parameterization of selection for that special case is developed in this section.

Let the balancer and tested wild-type chromosome be represented by X_B and X_+ respectively. The cross X_BX_+ by X_+Y results in the following progeny genotypes:

	X_+X_+	X_BX_+	X_+Y	X_BY
Number observed	N_1	N_2	N_3	N_4
Relative viability	$1+z$	$1-z$	$1+y$	$1-y$

$-1 \leq (z,y) \leq 1$. In the absence of viability differences between the genotypes, the four classes of progeny types are expected in equal frequencies. By parameterizing selection as above, it is possible to estimate z, y, and a modified ratio of selection coefficients, $\tilde{r}$, as follows:

$$\hat{z} = \frac{N_1 - N_2}{N_1 + N_2} \qquad \hat{y} = \frac{N_3 - N_4}{N_3 + N_4} \tag{11}$$

$$\hat{\tilde{r}} = \frac{\hat{y}}{\hat{z}} \, . \tag{12}$$

Assuming that the genotype X_BX_B is inviable, which is true for some *X*-chromosome balancers, there is one condition for the existence of a stable polymorphic equilibrium:

$$z[\tilde{r}(1+z) + 2] < 0 \, . \tag{13}$$

Nontrivial equilibria fall into two classes:

(1) $z < 0$ and $\tilde{r} > -2/(1+z)$. Polymorphism arises with heterosis among females, provided $\tilde{r}$ is greater than some negative value.

(2) $z > 0$ and $\tilde{r} < -2/(1+z)$. The wild-type homozygote is the most fit genotype among females, and the balancer-type is most fit among males. Polymorphism is maintained without heterosis, because selection favors different chromosomes in the two sexes.

If $z > 0$ and $\tilde{r} > 0$, then there is directional selection in favor of the wild-type chromosome, but ($z < 0$, $\tilde{r} > 0$) and ($z < 0$, $\tilde{r} < 0$) are admittedly difficult to interpret biologically, and do not clearly correspond to the correlation of homozygous and hemizygous effects described in Section I. However, $\tilde{r} < 0$ and $z > 0$ would constitute clear evidence for selection operating in different directions in the sexes.

There have been two studies employing *D. melanogaster* *X*-chromosome balancers that are suitable for re-analysis and estimation of a modified ratio of

selection coefficients, as defined in equations (11) and (12). KERR and KERR (1952) tested 59 wild-type X chromosomes for viability effects in males and females, and examined 48,128 progeny of testcrosses. WILTON (1979) tested 62 wild-type X chromosomes and examined 57,560 progeny. Even though the two studies employed different balancer chromosomes, they give quite similar estimates of the mean z, $\tilde{r}$ and γ:

	Mean z (S.E.)	Mean γ (S.E.)	Mean $\tilde{r}$ (S.E.)
KERR and KERR (1952)	0.054 (0.010)	0.159 (0.015)	1.87 (0.94)
WILTON (1979)	0.019 (0.007)	0.138 (0.009)	1.98 (1.42)

In computing the above means and standard errors, the two extreme outliers with respect to $\tilde{r}$ have been omitted from each study, for which $|\tilde{r}| > 90$. $\tilde{r}$ is generally positive in these data, suggesting that selection usually favors the same chromosome in males and females. However, the re-analysis has revealed one clear case of opposite selection in the sexes, for which $z = 0.0379$, $\gamma = -0.2326$, and $\tilde{r} = -6.1361$ (chromosome #55 of KERR and KERR 1952). The parameters satisfy the condition for stable polymorphism stated in equation (13): i.e., polymorphism arises because the wild-type homozygote is most fit among females, while the balancer-type is most fit among males.

It is difficult to generalize from this re-analysis because of several limitations of the available data. Viability is only part of total fitness, perhaps negligible compared to other fitness components. The data are probably biased towards positive values of $\tilde{r}$, since male and female larvae are likely to be more similar in their requirements for egg-to-adult survival than in other stages of the life cycle, such as sexual reproduction. Balancer males are almost always less fit than wild-type males. Chromosomes derived from iso-female lines might carry variants that are favorable in females, but not in males. Finally, the special parameterization required for the four-genotype case is not as biologically interpretable as the more general case with five genotypes. Balancer data for the autosomes would not suffer from that last problem, but I am unaware of appropriate published data.

III. *The autosomal case*

In this section the opportunity for polymorphism at an autosomal locus is calculated for comparison to the X-linked case.

Consider an autosomal locus with two possible alleles, A_1 and A_2, where the genotypes A_1A_1, A_1A_2, and A_2A_2 have relative viabilities $(1+F)$, $(1+H)$, $(1-F)$ among females and $(1+M)$, $(1+G)$, $(1-M)$ among males, respectively. By analogy with the sex-linked case, define R such that $M = RF$, where $-1 \leq RF \leq +1$. R is positive if selection favors the same allele among both male and female homozygotes.

For the following analyses, it will be assumed that $G = H$, allowing specification of the opportunity for polymorphism by the same techniques employed for the sex-linked case. With the usual deterministic assumptions, local analysis of the boundary equilibria corresponding to fixation of A_1 or A_2 shows that both fixation states are unstable if and only if:

$$1+H>\frac{2(1+F)\ (1+RF)}{2+F+RF}$$
$$\text{and} \tag{14}$$
$$1+H>\frac{2(1-F)\ (1-RF)}{2-F-RF}\ .$$

The functions will be referred to as $A(F,R)$ and $B(F,R)$, respectively. If these conditions are satisfied, then the population remains in some (unspecified) polymorphic state: i.e., polymorphism is "protected." Of course, there can exist multiple interior equilibria (OWEN 1952; KIDWELL *et al.* 1977).

Under the assumption of a uniform distribution of the selection coefficients F and H, the opportunity for polymorphism at an autosomal locus (P_a) is:

$$2S^2P_a=\begin{cases} X_1(1+S)-{}_0\!\int^{X_1}A(F,R)\,dF & \text{for } R>1\\ S\ (1+S)-{}_0\!\int^{S}A(F,R)\,dF & \text{for } -1<R\le 1\\ S\ (1+S)-{}_0\!\int^{S}1-F^2\,dF & \text{for } R=-1\\ S\ (1+S)-{}_0\!\int^{S}B(F,R)\,dF & \text{for } \dfrac{3-S}{3S-1}<R<-1, S<1/3\\ & \quad \text{or } R<-1, S\ge 1/3\\ X_2(1+S)-{}_0\!\int^{X_2}B(F,R)\,dF & \text{for } R\le\dfrac{3-S}{3S-1}, S<1/3 \end{cases} \tag{15}$$

where S is the intensity of selection, defined such that the fitnesses of all female genotypes lie in the interval $(1-S, 1+S)$, and

$$X_1=\frac{-(1+R)\ (1-S)+\sqrt{(1+R)^2\ (1-S)^2+16RS}}{4R}$$
$$X_2=\frac{-(1+R)\ (S-1)+\sqrt{(1+R)^2\ (S-1)^2+16RS}}{4R}\ .$$

Equations (15) simplify as follows:

$$P_a=\frac{1}{2}+\frac{S}{6} \tag{16}$$

$$\frac{X_1(1+S)}{2S^2}-\frac{RX_1^2}{2S^2(1+R)}-\frac{X_1(1+R^2)}{S^2(1+R)^2}-\frac{(1+R)^2-2(1+R^2)}{S^2(1+R)^3}\times$$
$$[\ln(X_1(1+R)+2)-\ln(2)]$$
$$\frac{1+S}{2S}-\frac{R}{2(1+R)}-\frac{1+R^2}{S(1+R)^2}-\frac{(1+R)^2-2(1+R^2)}{S^2(1+R)^3}\times$$
$$[\ln(S(1+R)+2)-\ln(2)]$$
$$\frac{1+S}{2S}-\frac{R}{2(-R-1)}-\frac{1+R^2}{S(-R-1)^2}-\frac{(-R-1)^2-2(1+R^2)}{S^2(-R-1)^3}\times$$
$$[\ln(S(-R-1)+2)-\ln(2)]$$
$$\frac{X_2(1+S)}{2S^2}-\frac{RX_2^2}{2S^2(-R-1)}-\frac{X_2(1+R^2)}{S^2(-R-1)^2}-\frac{(-R-1)^2-2(1+R^2)}{S^2(-R-1)^3}\times$$
$$[\ln(X_2(-R-1)+2)-\ln(2)]\ .$$

Some representative values are shown in Figure 3. Like P, P_a is a maximum where selection is intense and the ratio of selection coefficients equals -1. P_a is greater than or equal to P for all valid values of R and r. For the degenerate cases mimicking "one-sex" populations, $P(r=0)$ corresponds to $P_a(R=1)$.

DISCUSSION

The models analyzed here clarify the role of sex-specific fitness effects in generating stable polymorphic equilibria and suggest that polymorphism arising from differential selection in the sexes is feasible, in both the biological and probabilistic sense.

For the X-linked case, the genotypes X_1X_1, X_1X_2, X_2X_2, X_1Y, X_2Y have been assigned relative fitnesses $1+f$, $1+h$, $1-f$, $1+rf$, and $1-rf$, respectively. The ratio of selection coefficients is positive if selection favors the same allele among homozygotes and hemizygotes; otherwise r is negative, irrespective of the relative fitness of the heterozygous genotype. As shown in Figure 1, the region of the parameter space in which the conditions for existence of a stable polymorphic equilibrium are satisfied increases in area as r decreases from positive values to -1. That proportional area has been quantified with the variable P, which has the following interpretation: if genotypes of the homogametic sex were assigned fitnesses by randomly drawing f and h from a uniform distribution on the interval $(-s, +s)$ and genotypes of the heterogametic sex were assigned fitnesses by a given value of r, then a proportion P of the randomly generated sets of parameter values would be expected, on average, to satisfy the conditions for stable polymorphic equilibrium.

The exact functional dependence of P on r and s is given in equations (2), (4), (6) and (9) and shown graphically in Figure 3 for two values of the selection intensity. P is a maximum where selection is intense and of equal magnitude and opposite directions in the sexes ($r=-1$, $s=1$). As the absolute magnitude of r becomes very large, the intense directional selection in one sex causes P to decrease to zero.

For the autosomal case, the genotypes A_1A_1, A_1A_2, and A_2A_2 have been assigned relative fitnesses $1+F$, $1+H$, and $1-F$ among females, and $1+RF$, $1+H$, and $1-RF$ among males, respectively. The opportunity for polymorphism, P_a, is given in equations (16) and shown graphically in Figure 3. As in the sex-linked case, the opportunity for polymorphism is a maximum where the ratio of selection coefficients equals -1. The assumption of equal fitness of male and female heterozygotes has greatly facilitated analysis of the autosomal case, but might result in some loss of generality.

There are several limitations of the selective parameterizations put forward here. First, the techniques of analysis are limited to diallelic polymorphisms. The multi-allele case promises to be much more complex (see LEWONTIN, GINZBURG and TULJAPURKAR 1978 for some simulation results for the autosomal case). Second, the selective parameterizations do not allow description of the case in which male genotypes have unequal fitness and females have equal fitness. Third, it has been assumed that the selection coefficients are uniformly distributed. Fourth, for the autosomal case there can exist a locally stable poly-

morphic equilibrium, for certain special fitness values, when the conditions for protected polymorphism are not satisfied.

Within those limitations, preliminary answers to two questions of general interest can be offered:

(1) Are sex-linked and haplodiploid genetic systems inherently limited in the opportunity for selectively maintained genetic polymorphism? Since it is not generally known whether allele substitutions have similar selective effects in males and females, no biologically realistic answer can be given. The probabilistic answer is that sex-linked systems are not so limited; for some values of r and s, P is greater than 0.5, an arbitrary but undeniably high probability that a locus is polymorphic.

(2) How do autosomal and X-linked genes differ in the opportunity for polymorphism? If the ratios of selection coefficients are -1, then P equals P_a for all selection intensities, as shown in equations (5) and (16). Otherwise, P is less than P_a for comparable values of R and r. The difference between autosomal and X-linked genes in the opportunity for polymorphism is much less than the range of values of P or P_a obtained over the range of r and R, as shown in Figure 3.

The above conclusions apply only to selectively maintained genetic polymorphisms; the comparison of autosomal and sex-linked genes with respect to other sorts of genetic variability, such as that due to neutral alleles or recurrent mutation, has been discussed by CROZIER (1970). The paternal X-inactivation system found in certain marsupials has been analyzed by COOPER (1976) and CROZIER and PAMILO (1979). The only analytical results directly comparable to results presented here are due to PAMILO (1979), who considered three special cases of balancing selection at autosomal and X-linked loci with constant fitnesses and fixed correlations between the sexes. The more general models analyzed here support PAMILO's (1979) contention that the intensity of selection has little effect on the opportunity for polymorphism, but the equality of P and P_a at $(r,R) = -1$ has been overlooked in previous analyses.

It is clear from Figure 3 that polymorphism involving selection of different directions in the sexes is feasible, in the sense that a wide range of parameter choices can satisfy the conditions for polymorphism. It remains to be seen whether there are biological constraints on the ratio of selection coefficients, such as the suggestion of HARTL (1971) that dosage compensation might operate at the level of fitness. The re-analysis of viability data presented here gives only slight evidence of selection operating in different directions in the sexes, and is subject to several limitations (see Section II). Indirect evidence for a high frequency of genes with sex-limited effects has been offered by WILTON and SVED (1979), but they considered only recessive detrimental genes in their expanation of certain *D. melanogaster* population-cage data. There is now considerable evidence that detrimental genes are usually partially dominant (SIMMONS and CROW 1977), which would reduce the need to postulate sex-limited effects. MAYNARD SMITH (1959), KERR and KERR (1952) and DRESCHER (1964) have reported sex limitation in Drosophila, but such reports seem to be rare. Among the Lepidoptera, there is considerable sex-limited polymorphism, some of which

might be maintained by opposite selection in the sexes. The known sex-linked loci in the Lepidoptera are in fact lacking in dosage compensation (JOHNSON and TURNER 1979). In mammals, the mechanism of dosage compensation involves inactivation of one *X* chromosome in each somatic cell, a process known as "Lyonization," but the *X*-linked steroid sulfatase and Xg^a blood group loci in humans are apparently non-Lyonized (SHAPIRO *et al* 1979). As a final indication of possible exceptions to the equality of homozygous and hemizygous effects, it should be mentioned that dosage compensation is itself an evolving property—it is demonstrably incomplete at the level of transcription in *Drosophila miranda*, a species that possesses an evolutionarily recent *Y*-autosome chromosomal fusion (STROBEL, PELLING and ARNHEIM 1978). Further experimentation will be required to determine whether selection of different directions in the sexes is a common feature of naturally occurring genetic variability.

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