COMPLEX POLYMORPHISMS WITH RECOMBINATION DIFFERING BETWEEN SEXES*

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Equilibria for polymorphisms maintained by linkage and epistasis between two loci (linkage balance equilibria) have been discussed by Lewontin and Kojima (1960) for a model implying cumulative heterozygote advantage. They concluded that such equilibria were only important for low recombination values (say $< 10\%$). Bodmer and Parsons (1962) considered viability systems with features similar to the balanced polygenic complex of Mather (1943). Parsons (1963) extended these results and found in general that stable linkage balance equilibria were possible for the balanced complex for values of the recombination fraction up to and including 50%.

Formulation for a model where the recombination fraction does not differ between sexes is given fully by Bodmer and Parsons (1962). It is proposed here to analyse briefly the general case of recombination differing between sexes.

There are four gametic genotypes which can be formed with two alleles at each of two loci (A, a) and (B, b), namely the coupling gametes AB and ab, and the repulsion gametes Ab and aB. Ten zygotic genotypes can be formed which fall into three categories:

(i) four genotypes homozygous at both loci;

(ii) four genotypes heterozygous at a single locus; and

(iii) two double heterozygotes.

The four gametes AB, ab, Ab, and aB, are given suffixes 1, 2, 3, and 4 respectively so that x_2, for example, is the frequency of gamete 2, i.e. ab, and a_{23} is the relative viability of the zygotic genotype carrying gametes 2 and 3, i.e. ab/Ab (Table 1).

In Table 1, the zygotic frequencies of the 10 genotypes with the gametes they give are presented. The recombination fraction in the female is denoted by r and in the male by r^1, and the proportion of non-recombinants is s and s^1 respectively such that $r+s = r^1+s^1 = 1$.

We now assume the symmetrical system discussed by Bodmer and Parsons (1962). This system is

$$a_{33} = a_{44} = 1,$$
$$a_{12} = a_{34} = (1+\alpha),$$
$$a_{24} = a_{23} = a_{14} = a_{13} = (1-\beta),$$

and

$$a_{11} = a_{22} = (1-\gamma).$$

If $\gamma > \beta > 0$ and $\alpha > 0$, the model corresponds to the concept of balance (Bodmer and Parsons 1962). If $\gamma = 0$ and $\beta < 0$, but $\alpha > |\beta|$, then the model corresponds to a system of cumulative heterozygote advantage.

At equilibrium it is easily shown that $x_1 = x_2$ and $x_3 = x_4$, so that $x_1 = \frac{1}{2}-x_3$. If we let $x = $ the frequency of the coupling gametes AB and ab, then the frequency of the repulsion gametes is $\frac{1}{2}-x$. The equilibrium frequencies of the coupling gametes is given by

$$16x^3[4\beta+2\alpha-\gamma]+8x^2[\gamma-6\beta-3\alpha]+4x[2\beta+\alpha+(r+r^1)(1+\alpha)]-(r+r^1)(1+\alpha) = 0 \quad (1)$$

The joint effects of linkage and epistasis can be measured by the difference between the product of the frequency of the coupling gametes and the product of the frequency of the repulsion gametes thus:

$$(AB \times ab)-(Ab \times aB) = D.$$

This expression equals $(x-\frac{1}{4})$ for the symmetrical model being analysed. When $x \neq \frac{1}{4}$ there is a linkage balance equilibrium determined by the joint effects of linkage and epistasis. Lewontin and Kojima (1960) refer to $|D|$ as the "linkage disequilibrium".

TABLE 1

RELATION BETWEEN GAMETIC AND GENOTYPIC FREQUENCIES FOR THE 10 POSSIBLE GENOTYPES INVOLVING TWO LINKED LOCI

Zygotes	Zygotic Frequency	Gametic Genotype Frequencies				Relative Viabilities
		AB	ab	Ab	aB	
AB/AB	x_1^2	1				a_{11}
ab/ab	x_2^2		1			a_{22}
Ab/Ab	x_3^2			1		a_{33}
aB/aB ·	x_4^2				1	a_{44}
AB/Ab	$2x_1x_3$	$\frac{1}{2}$		$\frac{1}{2}$		a_{13}
AB/aB	$2x_1x_4$	$\frac{1}{2}$			$\frac{1}{2}$	a_{14}
ab/Ab	$2x_2x_3$		$\frac{1}{2}$	$\frac{1}{2}$		a_{23}
ab/aB	$2x_2x_4$		$\frac{1}{2}$		$\frac{1}{2}$	a_{24}
AB/ab	$2x_1x_2$	$\frac{1}{4}(s+s^1)$	$\frac{1}{4}(s+s^1)$	$\frac{1}{4}(r+r^1)$	$\frac{1}{4}(r+r^1)$	a_{12}
Ab/aB	$2x_3x_4$	$\frac{1}{4}(r+r^1)$	$\frac{1}{4}(r+r^1)$	$\frac{1}{4}(s+s^1)$	$\frac{1}{4}(s+s^1)$	a_{34}

Firstly we can put $\alpha = 0 \cdot 10$ and $\beta = 0 \cdot 05$, and vary γ. Two cases are given (Fig. 1) where $\gamma = 1$ and $0 \cdot 05$, comparing the situation where $r = r^1$ (i.e. equal recombination in both sexes) with the situation where $r^1 = 0$ (i.e. recombination occurs only in one sex). In this and the figures that follow the solid lines represent the model where $r^1 = r$, and the dotted lines the model where $r^1 = 0$. Provided that $\gamma > 0 \cdot 05$, the relative viabilities correspond to the concept of balance. For both values of γ, $|D|$ is larger when $r^1 = 0$ as expected, since the restriction of recombination to one sex effectively increases the tightness of linkage between loci. Deviations from $|D| = 0$ are particularly large when $\gamma = 1$, which implies lethality of the unbalanced homozygotes. When $\gamma = 0 \cdot 05$ and when r is small three equilibria are obtained. The values of r for this to occur are greatest when $r^1 = 0$. In Figure 1 only the stable equilibria are plotted. The equilibrium for the high frequency of unbalanced gametes $(x > \frac{1}{4})$ is probably unimportant from the point of view of natural selection as, in general for this model, only where a stable value of x increases

with r will natural selection favour any gametes tending to reduce the value of r (Bodmer and Parsons 1962).
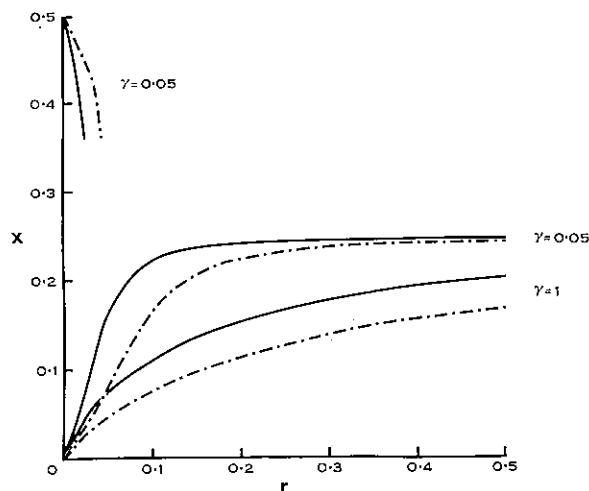

Fig. 1.—Stable equilibrium values x of the unbalanced gametes for $\alpha = 0 \cdot 10$ and $\beta = 0 \cdot 05$ with $\gamma = 1$ and $0 \cdot 05$ for $r = r^1$ (———) and $r^1 = 0$ (—·—·—).
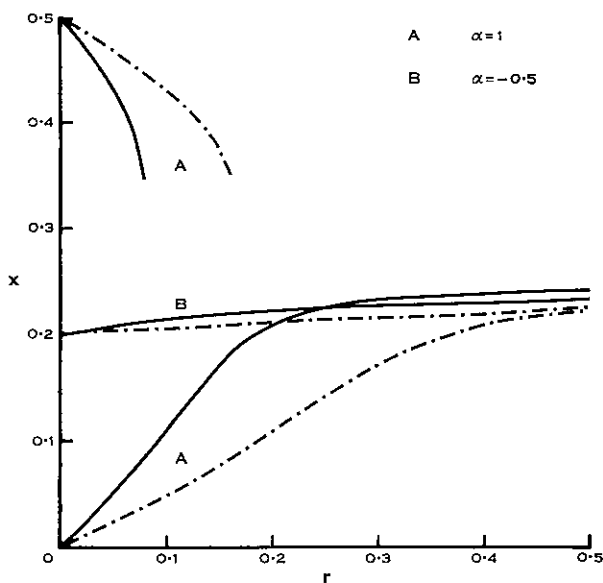

Fig. 2.—Stable equilibrium values x of the unbalanced gametes for $\beta = 0 \cdot 05$ and $\gamma = 0 \cdot 20$ with $\alpha = 1$ and $-0 \cdot 5$ for $r = r^1$ (———) and $r^1 = 0$ (—·—·—).

In Figure 2, $\beta = 0 \cdot 05$, $\gamma = 0 \cdot 20$, and two values of α are taken namely $\alpha = 1$ and $-0 \cdot 5$. For $\alpha = 1$, a situation implying extreme heterozygote advantage and

corresponding to the concept of balance, $|D|$ is large until r becomes large especially when $r^1 = 0$. Two stable equilibria occur for low values of r. When $\alpha = -0.5$, a situation not corresponding to the concept of balance, $|D|$ is smaller, but as expected when $r^1 = 0$, $|D|$ is very slightly greater than when $r = r^1$.

In Figure 3, $\alpha = 0.10$, $\gamma = 0.20$, and the effect of varying β is studied. When $\beta = 0.40$, $|D|$ is substantially increased when $r^1 = 0$, but the increase is smaller for $\beta = -0.05$ which is a situation implying cumulative heterozygote advantage. When $\beta = -0.40$, the graphs for $r = r^1$ and $r^1 = 0$ are almost identical so that only the graph for $r = r^1$ is plotted.
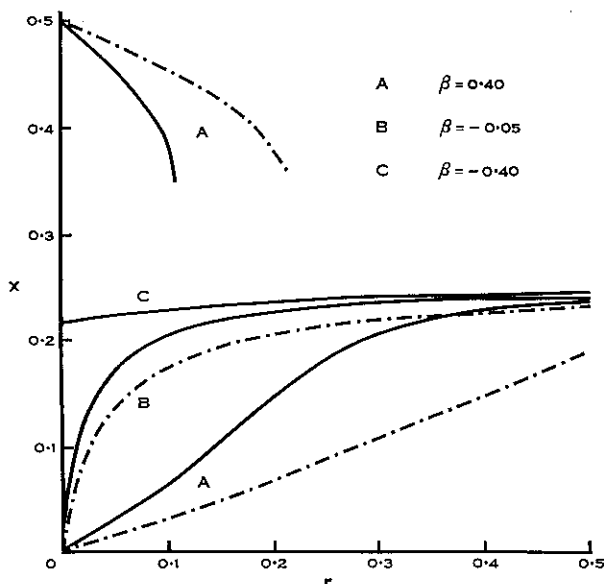

Fig. 3.—Stable equilibrium values x of the unbalanced gametes for $\alpha = 0.10$ and $\gamma = 0.20$ with $\beta = 0.40$, -0.05, and -0.40 for $r = r^1$ (———) and $r^1 = 0$(—·—·—).

Finally situations implying cumulative heterozygote advantage are examined in further detail by putting $\gamma = 0$ and $\beta = -0.5$ (Fig. 4). A root of $\frac{1}{4}$ is always obtained when $\gamma = 0$ and two roots from

$$8x^2(2\beta+\alpha)-4x(2\beta+\alpha)+(r+r^1)(1+\alpha) = 0, \qquad (2)$$

which are real when

$$r+r^1 < (2\beta+\alpha)/2(1+\alpha), \qquad (3a)$$

so that when $r^1 = 0$

$$r < (2\beta+\alpha)/2(1+\alpha). \qquad (3b)$$

Thus the maximum value of r is twice as big when $r^1 = 0$ compared with $r^1 = r$. The comparison is presented in Figure 4 for $\alpha = 1.5$ and 5.

The real roots satisfying (2) are both stable; the root of $\frac{1}{4}$ being unstable. However, when (3a) is not satisfied the root of $\frac{1}{4}$ is stable. For this model, therefore,

when r is large, $x = \frac{1}{4}$ and $D = 0$ so that there is no longer a linkage balance equilibrium. This is in direct contrast to the situations given in the earlier figures corresponding to the concept of balance. In general $|D|$ is larger for situations corresponding to the concept of balance than for situations not corresponding to the concept of balance, especially when $r^1 = 0$.
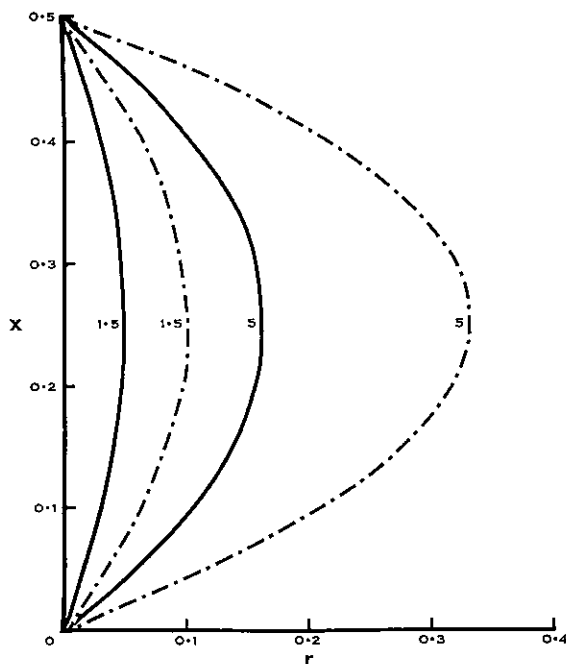

Fig. 4.—Stable equilibrium values x of the unbalanced gametes satisfying inequality (3a) for $\beta = -0 \cdot 5$ and $\gamma = 0$ with $\alpha = 1 \cdot 5$ and 5 for $r = r^1$ (———) and $r^1 = 0$ (—·—·).

Discussion

The restriction of recombination to one sex generally increases the deviation of D from 0, and in some cases the value of r for which linkage balance equilibria are possible. For some sets of viabilities, in particular those corresponding to the concept of balance, the effect of restricting recombination to one sex can be quite appreciable. It is clear that with the viability differences between genotypes which are being found today, stable interacting complexes can be envisaged as covering the whole of the chromosome, even apart from various mechanisms reducing crossing over. Only one such crossover-reducing mechanism is being considered here. In conjunction, for example, with inversion heterozygosity (which is found so frequently in *Drosophila*) or chiasma localization, linked complexes can be even more readily envisaged as covering whole chromosomes. The greatest present need is to discover interacting genes which are as amenable to analysis as the pair of interacting chaeta loci of Gibson and Thoday (1959, 1962) in *D. melanogaster* in an attempt to find out

whether our models are realistic. These chaeta loci are separated by a map distance of 20 cM and preliminary work demonstrates stable linkage balance equilibria for all recombination fractions up to and including 50%. Thus the observation of 20 cM seems not unreasonable. Fewer lethal gametes would be produced if the map distance were < 20 cM but in a species with a high reproductive potential, such as *D. melanogaster*, the intensity of natural selection to reduce this value may not be very great, especially when we remember that there is no crossing over in the male.

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