COMPLEX POLYMORPHISMS WHERE THE COUPLING AND REPULSION DOUBLE HETEROZYGOTE VIABILITIES DIFFER

P. A. PARSONS
Department of Zoology, University of Melbourne, Victoria

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1. INTRODUCTION

The general equations for polymorphisms maintained by linkage and epistasis between two loci (linkage balance equilibria) have been presented for a continuous time model by Kimura (1956) and a discrete time model by Lewontin and Kojima (1960) and Bodmer and Parsons (1962). If the two loci each with two alleles are A, a and B, b, 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 :

$$AB \times ab - Ab \times aB = \mathrm{D}.$$

The quantity D has been termed the linkage disequilibrium by Lewontin and Kojima (1960).

Bodmer and Parsons (1962) and Parsons (1963) found that viabilities of the ten possible genotypes at two loci each with 2 possible alleles, which corresponded roughly to those expected on Mather's (1943) concept of relational balance, lead to values of $|\mathrm{D}|$ considerably larger than on a model of cumulative heterozygote advantage. These models assumed that the viability of the coupling double heterozygote $\frac{AB}{ab}$ was equal to the viability of the repulsion double heterozygote $\frac{Ab}{aB}$. However, this need not necessarily be true in nature. For example, for a pair of chaeta determining loci studied by Gibson and Thoday (1959, 1962), the coupling double heterozygote was lethal and the repulsion double heterozygote viable. A theoretical analysis of this system is given by Parsons (1963).

2. FORMULATION

In this paper the genotypic viabilities below are assumed :

Homozygotes unbalanced		Single heterozygotes		Double heterozygotes	
$\frac{AB}{AB}$	$1-\gamma$	$\frac{AB}{Ab}$	$1-\beta$	$\frac{AB}{ab}$	$1+\alpha_1$
$\frac{ab}{ab}$	$1-\gamma$	$\frac{AB}{aB}$	$1-\beta$	$\frac{Ab}{aB}$	$1+\alpha_2$
balanced		$\frac{ab}{Ab}$	$1-\beta$		
$\frac{Ab}{Ab}$	1				
$\frac{aB}{aB}$	1	$\frac{ab}{aB}$	$1-\beta$		

The terms balanced and unbalanced refer to Mather's (1943) concept of balance. If genes A and B are + modifiers, and a and b are − modifiers for a character, gametes Ab $(+-)$ and aB $(-+)$ are balanced, while gametes AB $(++)$ and ab $(--)$ are unbalanced. Hence $\frac{AB}{AB}$ and $\frac{ab}{ab}$ are unbalanced homozygotes, and $\frac{Ab}{Ab}$ and $\frac{aB}{aB}$ are balanced homozygotes.

The derivation of the equilibrium equation will not be given. The

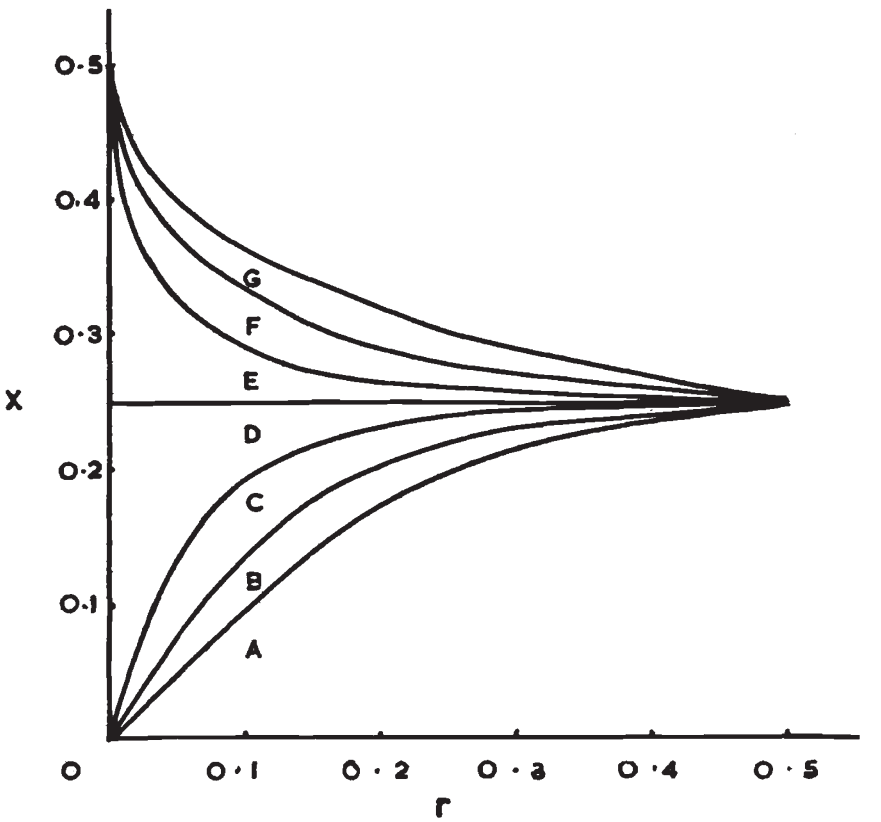

FIG. 1a.—Equilibrium values x for $\alpha_1 = \gamma = \beta = 0$ and variable values of α_2 plotted for values of r between 0 and 0·5. Graphs A, B, C, D, E, F and G correspond to $\alpha_2 = 1$, 0·5, 0·2, 0, −0·2, −0·5 and −1 respectively.

method for the discrete time model is given fully by Lewontin and Kojima (1960) and Bodmer and Parsons (1962). The equilibrium equation is

$$\begin{aligned} &8x^3[4\beta-\gamma+\alpha_1+\alpha_2] \\ &+4x^2[\gamma-6\beta-2\alpha_2-\alpha_1+r(\alpha_1-\alpha_2)] \\ &+2x\,[2\beta+\alpha_2+2r(1+\alpha_2)]-r(1+\alpha_2) = 0, \end{aligned}$$

where r is the recombination fraction between the two loci, and x is the frequency of the coupling gametes AB and ab, so that $\frac{1}{2}-x$ is the frequency of the repulsion gametes Ab and aB. On this model $D = x-\frac{1}{4}$, so that

there is a linkage disequilibrium when $x \neq \frac{1}{4}$. In figs. 1 and 2 stable values of x are plotted against r. The equilibrium is stable when

$$r(1+a_2) > -\beta - \frac{a_2}{2}$$
$$+2x[6\beta - \gamma + 2a_2 + a_1 + r(a_2 - a_1)]$$
$$+6x^2[\gamma - 4\beta - a_1 - a_2]$$

In fig. 1*a*, $\gamma = \beta = 0$ and $a_1 = 0$ with a_2 varying between 1 and -1, and in fig. 1*b* $\gamma = \beta = 0$ and $a_2 = 0$ with a_1 varying between 1 and -1.

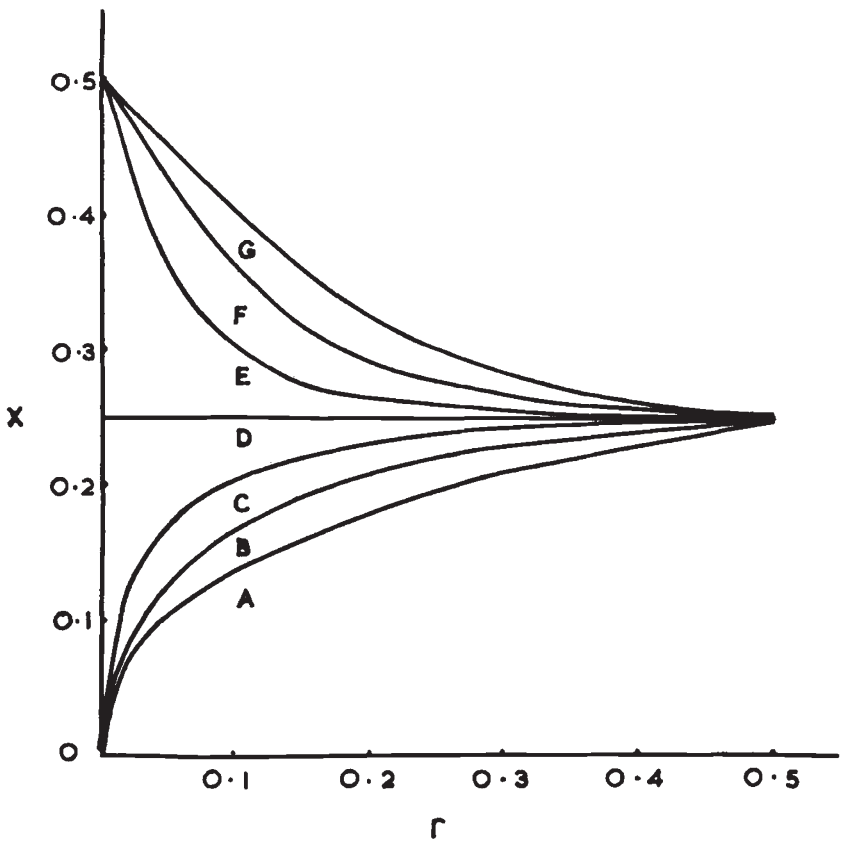

FIG. 1*b*.—Equilibrium values x for $a_2 = \gamma = \beta = 0$ and variable values of a_1 plotted for values of r between 0 and 0·5. Graphs A, B, C, D, E, F and G correspond to $a_1 = -1$, $-0{\cdot}5$, $-0{\cdot}2$, 0, 0·2, 0·5 and 1 respectively.

Thus all genotypes have a viability of 1 except the repulsion double heterozygote in fig. 1*a*, and the coupling double heterozygote in fig. 1*b*. In fig. 1*a* when $a_2 = 1$, *i.e.* the repulsion double heterozygote is very much fitter than the coupling double heterozygote, the linkage disequilibrium is large up to quite large values of r. The linkage disequilibrium, $|D|$, however, is smaller for given r when $a_2 = 0{\cdot}5$ and smaller still if $a_2 = 0{\cdot}2$. At $a_2 = 0$, when all genotypes are equally viable, $x = \frac{1}{4}$ so that all the gametic genotypes are equally frequent. This is merely the situation of random mating with no selection. Now when $a_2 < 0$ so that the repulsion double heterozygote is inferior in viability to all other genotypes, linkage balance

equilibria occur for $x>\frac{1}{4}$. This implies an excess of coupling gametes as might be expected since the repulsion double heterozygote is the only genotype with a viability <1. The greatest excess of coupling gametes occurs for $\alpha_2 = -1$.

In fig. 1*b*, the greatest deviations from $|D| = 0$ occur when $\alpha_1 = 1$ and -1. When $\alpha_1<0$ the equilibria are characterised by an excess of repulsion gametes ($x<\frac{1}{4}$) and when $\alpha_1>0$, there is an excess of coupling gametes ($x>\frac{1}{4}$) as might be expected.

In figs. 2*a* and 2*b*, $\gamma = 1$ and graphs for various values of α_1 and α_2 are plotted as before. This set of viabilities corresponds more to the concept

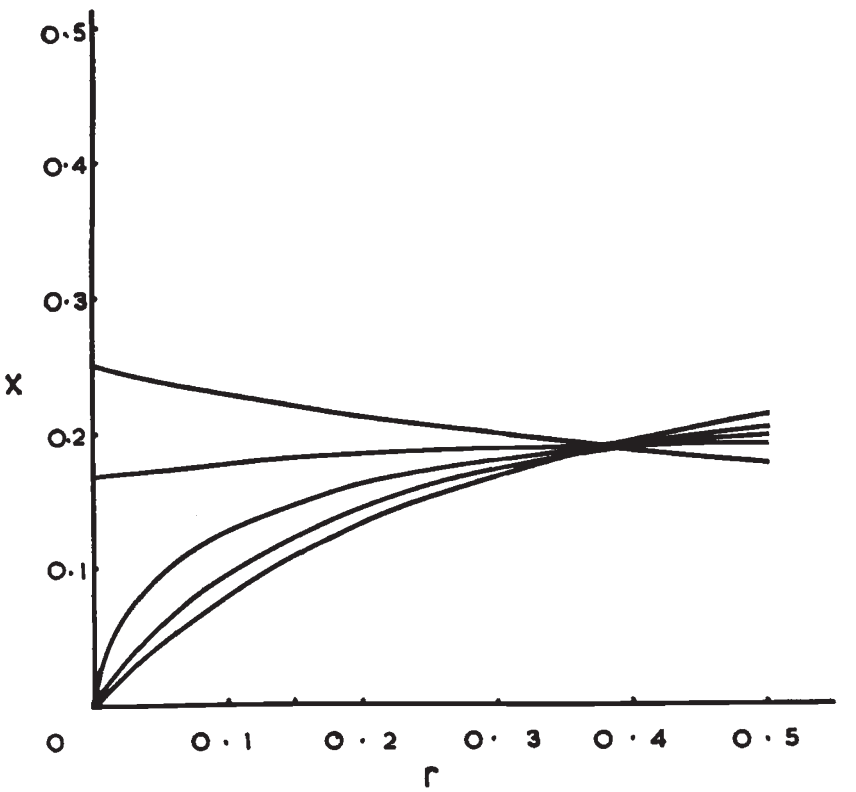

FIG. 2*a*.—Equilibrium values x for $\alpha_1 = \beta = 0$, $\gamma = 1$ and variable values of α_2 plotted for values of r between 0 and 0·5. From the bottom of the figure upwards for $r<0{\cdot}3$, the graphs correspond to $\alpha_2 = 1$, 0·5, 0, $-0{\cdot}5$ and -1 respectively.

of balance, since the homozygotes $\frac{AB}{AB}$ and $\frac{ab}{ab}$ are lethal, and the homozygotes $\frac{Ab}{Ab}$ and $\frac{aB}{aB}$, and the single heterozygotes have a viability of 1. The viability of the double heterozygotes is being varied by altering α_1 and α_2. In fig. 2*a*, $\alpha_1 = 0$ so that the coupling double heterozygote has a viability of 1. The greatest values of $|D|$ occur for the highest values of α_2 except when r is very large. As α_2 goes from 1 to -1 $|D|$ becomes smaller for given r. In general for $\alpha_2>0$ $|D|$ is greater than when $\gamma = 0$, which is reasonable since the lethality imposed by putting $\gamma = 1$ must lead to considerable

deviations from the value of $x = \frac{1}{4}$ when $|D| = 0$, since only the coupling gametes are affected by this lethality. In fig. 2*b*, $a_2 = 0$ so that the repulsion double heterozygote viability is 1. The greatest value of $|D|$ for given r occurs for $a_1 = -1$ and decreases as a_1 increases. Thus when the repulsion double heterozygote viability is greater than the coupling

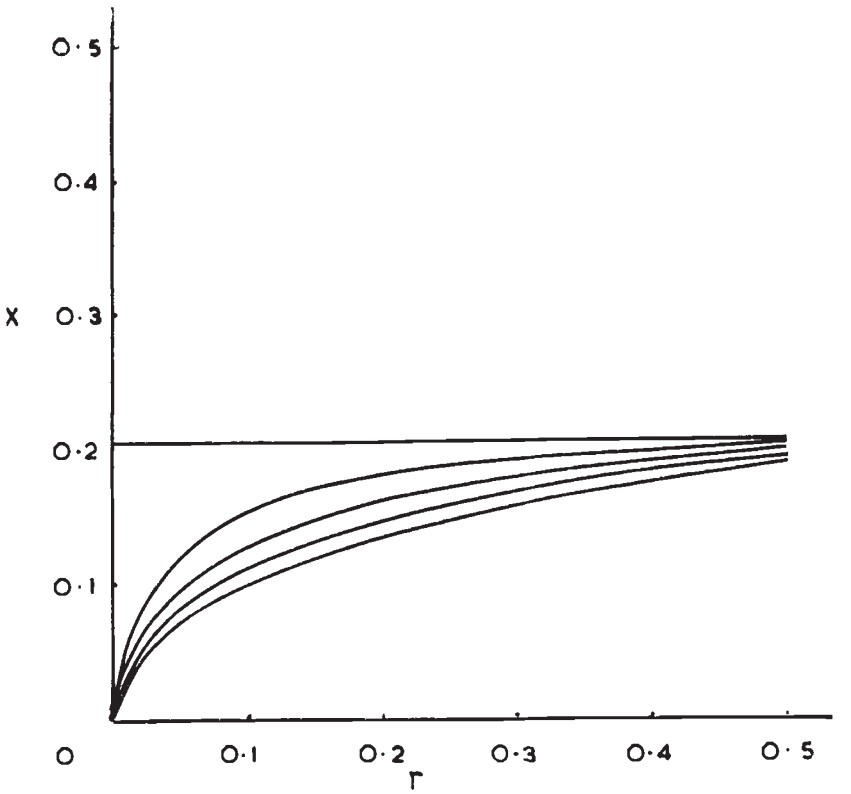

FIG. 2*b*.—Equilibrium values x for $a_2 = \beta = 0$, $\gamma = 1$ and variable values of a_2 plotted for values of r between 0 and 0·5. From the bottom of the figure upwards the graphs correspond to $a_1 = -1$, $-0{\cdot}5$, 0, 0·5 and 1 respectively.

double heterozygote viability (*i.e.* $a_2 > a_1$) deviations from $|D| = 0$ are usually greater than when $a_2 < a_1$. Graphs not given here for $\gamma = 0{\cdot}5$ gave results intermediate between $\gamma = 0$ and 1 as might be expected.

3. DISCUSSION

For a system of viabilities corresponding in essentials to Mather's concept of balance (figs. 2*a* and 2*b* where $\gamma = 1$), the greatest value of $|D|$, the linkage disequilibrium occurs for the greatest repulsion double heterozygote viability. These equilibria are characterised by an excess of repulsion gametes. This essentially is a model for selection for metrical characters under an outbreeding system where intermediate values are optimal (*stabilising selection*). Thus gametes *AbCdE*... and *aBcDe*... would be favoured by natural selection if we assume the alleles to be roughly of equal effect in the + or − directions as the case may be. It has been argued

by Mather (1943) and more recently by Bodmer and Parsons (1962) that stabilising selection will tend to preserve such repulsion linkages. It seems therefore likely that as in Gibson and Thoday's chaeta locus polymorphism the presence of repulsion combinations $+-$ and $-+$ in the base population is to be expected. Since r can be so much greater for the same degree of linkage disequilibrium when a_2 is large, compared with large a_1 for a system of viabilities corresponding to Mather's concept of balance, natural selection may favour the accumulation of repulsion linkages over long distances. For short distances, however, it is more possible that in some situations, coupling combinations may accumulate under stabilising selection. This may also occur when $\gamma \approx 0$ (figs. 1*a* and 1*b*) or the unbalanced homozygotes are not more inviable than the other genotypes, but under a highly outbred system this may be unlikely. It might be predicted that if repulsion combinations are in general favoured, then the repulsion double heterozygote viability will be higher than the coupling double heterozygote viability, since the repulsion double heterozygote will be exposed much more frequently to natural selection. The greatest present need is clearly for accurate data on balanced polygenic systems to see how realistic these models are.

4. SUMMARY

The effect of varying coupling and repulsion double heterozygote viabilities for polymorphisms for two linked loci is considered. It is shown for a system of viabilities corresponding to Mather's concept of balance that the greatest linkage disequilibria occur when the repulsion double heterozygote viability is high. It is argued that the analysis provides some theoretical justification for the likelihood of repulsion linkages in the balanced genotype subjected to stabilising selection. Under such circumstances, it is likely that natural selection will lead to the repulsion double heterozygote viability being gr ater than the coupling double heterozygote viability.

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