

GAMETIC DISEQUILIBRIUM IN MULTIGENIC SYSTEMS UNDER NORMALIZING SELECTION¹

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THERE is a considerable literature on the occurrence of gametic disequilibrium in two locus systems. (See KIMURA 1956; LEWONTIN and KOJIMA 1960; KOJIMA and KELLEHER 1961; BODMER and PARSONS 1962; LEWONTIN 1964; KOJIMA 1965). A measure of gametic disequilibrium which has been frequently used is

$$D_{ij} = g_{00}g_{11} - g_{10}g_{01}$$

$D > 0$, coupling disequilibrium
 $D = 0$, gametic equilibrium
 $D < 0$, repulsion disequilibrium

where g 's stand for the four gametic frequencies possible from alleles at locus i and locus j and subscripts stand for the four gametes 11, 10, 01, and 00 when 1 and 0 are used to denote a pair of alternative alleles at each locus.

This measure is sensitive to gene frequencies, reducing to zero at fixation. LEWONTIN (1964) introduced a modification to reduce the gene frequency dependence. He used a measure, D' , which is the ratio of D to the maximum possible for given gene frequencies.

It is possible, under normalizing selection, for $D \neq 0$, even when the two loci are not linked and the older term "linkage disequilibrium" has, therefore, been dropped in favor of the less restrictive term, "gametic disequilibrium." It is of interest in the analysis of the effects of normalizing selection on multigenic systems to distinguish between the various causes of gametic disequilibrium. This paper suggests two approaches to the problem.

LEWONTIN (1964) considered the effect of symmetric double truncation selection on a five-locus model with additivity on the primary scale. He superimposed an advantage of heterozygosity in that increased heterozygosity was correlated with a decreased environmental variability. This model resulted in stable equilibria at equal allelic frequencies ($q_i = 0.5$) in marked gametic disequilibrium. He gives the arrays of gametic frequencies in Tables 10 and 11, with values of D'_{ij} for various of the possible pair wise combinations of the five loci. He states, "Starting in linkage equilibrium the populations at first all produce repulsion linkages, but as the gene frequencies reach equilibrium, some of these repulsion linkages disappear and are replaced by coupling linkages." The gametic disequilibrium in his Tables 10 and 11 are markedly of the 01010 and 10101 gametes, and he states, "The particular linkages shown in Table 10 are not the only

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possible equilibria. There are ten alternative configurations in which the majority of gametic types form a pair 11100/00011 or 10110/01001, or etc. All these equilibria have the same mean fitness." This latter statement is only valid for complete linkage, i.e. in the multiple allele system, and for free recombination. The partial suppression of recombination results in repulsion combinations having an advantage over coupling combinations. (See MATHER, 1941, 1942, 1943 and BODMER and PARSONS 1962.) The 01010/10101 conformation will be advantageous over the 11100/00011 type of conformation.

There are different effects of recombination that affect the values of gametic disequilibrium in a multigenic system and it is necessary to devise ways of discriminating between them. Consider a model of three loci in which $q_i = 0.5$. The vector of gametic frequencies can be stated as

$$\{g_{000}, g_{001}, g_{100}, g_{010}, g_{101}, g_{011}, g_{110}, g_{111}\}$$

Symmetric normalizing selection will result in a reduction of the g_{000} and g_{111} terms because these gametes have the lowest combining ability. They have the lowest probability of combining with other gametes to produce zygotes with a high average fitness. This reduction can be included in the vector of gametic frequencies. Only the first four terms are given, since the model is symmetric.

$$\{g_{000} - \alpha, g_{001} + \alpha/3, g_{100} + \alpha/3, g_{010} + \alpha/3, \dots\}$$

Such selection against gametes with extreme potency will not differentiate between the 001, 100, and 010 types of gametes, since these all have the same potency. Another effect of normalizing selection does result in such a differentiation. The 010 type of gamete will, if there is partial suppression of recombination, combine with other gametes to produce zygotes which have a lower recombination load. They have a lower rate of recombining to form the unbalanced gametes, 000 and 111. This advantage of the 010 type will result in its having an increased frequency which can be included in the vector of gametic frequencies.

$$\{g_{000} - \alpha - \beta/3, g_{001} + \alpha/3 - \beta/3, g_{100} + \alpha/3 - \beta/3, g_{010} + \alpha/3 + \beta, \dots\}$$

The three D terms are then given by,

$$\begin{aligned} D_{12} &= \{g_{000} + g_{001} - 2/3(\alpha + \beta)\} \{g_{111} + g_{110} - 2/3(\alpha + \beta)\} \\ &\quad - \{g_{010} + g_{011} + 2/3(\alpha + \beta)\} \{g_{100} + g_{101} + 2/3(\alpha + \beta)\}, \\ D_{23} &= \{g_{000} + g_{100} - 2/3(\alpha + \beta)\} \{g_{111} + g_{011} - 2/3(\alpha + \beta)\} \\ &\quad - \{g_{001} + g_{101} + 2/3(\alpha + \beta)\} \{g_{010} + g_{110} + 2/3(\alpha + \beta)\}, \\ D_{13} &= \{g_{000} + g_{010} - 2/3(\alpha + \beta)\} \{g_{111} + g_{101} - 2/3(\alpha - \beta)\} \\ &\quad - \{g_{001} + g_{011} + 2/3(\alpha - \beta)\} \{g_{100} + g_{110} + 2/3(\alpha - \beta)\}. \end{aligned}$$

The two modes of gametic disequilibrium expressed by the terms, α and β , have different effects on the values of the D terms. If α and β are positive then D_{12} and D_{23} will be negative. (These pairs of loci will be in repulsion disequilibrium). D_{13} will only be negative, however, if $\alpha > \beta$. If $\alpha < \beta$ then D_{13} will be positive. (There will be coupling disequilibrium for these two loci.) The difference between D_{13} and D_{12} , D_{23} is a measure of the gametic disequilibrium consequent from selection favoring zygotes with low recombination loads.

This approach can be extended to any number of loci. Consider the D_{ij} matrix for a five locus model.

D_{12}	D_{13}	D_{14}	D_{15}
	D_{23}	D_{24}	D_{25}
		D_{34}	D_{35}
			D_{45}

With free recombination, or complete suppression of recombination, the effect of normalizing selection will be to reduce all of the D terms by an equal amount. Commencing with gametic equilibrium ($D_{ij} = 0$) all of the D terms will become equally negative. With partial suppression of recombination the effects of normalizing selection are more complex. The shift into the negative of the $D_{i:i+1}$ and $D_{i:i+3}$ sets will be augmented, whereas that of $D_{i:i+2}$ and $D_{i:i+4}$ sets will be reduced. This can be seen in LEWONTIN's data. The values of D'_{12} , D'_{13} , D'_{23} , and D'_{24} from his Tables 10 and 11 are shown in Figure 1.

In both sets of data the D_{12} and D_{23} values become increasingly negative with reduction of the rate of recombination. The D_{13} and D_{24} values are less negative than the D_{12} , D_{23} values even at the loose linkage of 0.234 indicating that selection against recombination load is effective. The D_{13} , D_{24} values become increasingly less negative than the D_{12} , D_{23} values with reduction of recombination; they eventually become positive. An interesting feature is that the D_{12} values are more negative than the D_{23} values over a wide range of rates of recombination. Selection against recombination load is apparently more effective in generating repulsion disequilibrium for terminal loci than it is for interstitial loci.

A simple illustration will show how selection against recombination load will result in a greater repulsion disequilibrium for terminal than for interstitial loci. Consider a 4 locus model under normalizing selection, in which there is overdominance for reproductive fitness, as in LEWONTIN's model. Essentially, there

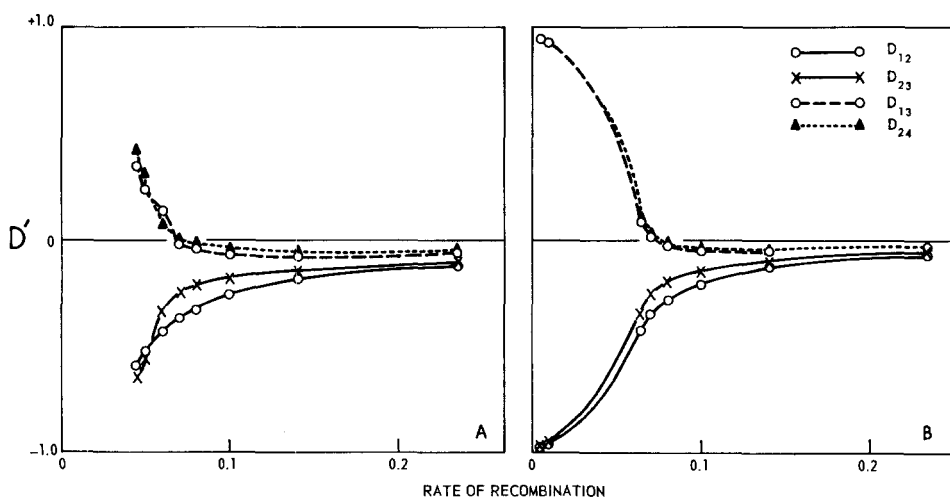


FIGURE 1.—Values of D'_{12} , D'_{13} , D'_{23} , D'_{24} from LEWONTIN's data of equilibrium states for normalizing selection acting on a five locus model with two levels of heterozygous advantage (model A and B) and several rates of recombination.

Genotype	Frequency	Single recombinants by potency				
		0	1	2	3	4
$\frac{0011}{1100}$	a	0000	0100,0010	1011,1101	1111
$\frac{0110}{1001}$	b	0001,1000	0101,1010	0111,1100
$\frac{0101}{1010}$	c	0010,0100	0110,1001	1101,1011

will be only three selected genotypes which are identical in selective value, but which differ markedly in their recombinational load.

Selection will act to reduce a on the basis of the greater recombination load of the 0011/1100 genotype relative to the other two genotypes. It will also act to reduce b relative to c , because the recombinants from the 0110/1001 type have a greater coupling than those from the 0101/1010 type. We can conclude that $a < b < c$.

If the rate of recombination is small, then the gametic frequencies for the terminal and interstitial pairs of loci are,

Terminal	$\frac{11}{a}$	$\frac{00}{a}$	$\frac{01}{b+c}$	$\frac{10}{b+c}$
Interstitial	b	b	$a+c$	$a+c$

The terminal loci will show a greater repulsion disequilibrium if $a < b$, as we have argued will occur from the effects of selection against recombinational load.

Clearly, the D matrix has many complex features deserving detailed study.

Two other measures have been used for the description of multigenic systems; the potency and the recombination index (FRASER, MILLER, and BURNELL 1965). The potency is the additive value of a gamete e.g. a 11100 gamete has a potency of 3. The recombination index is the number of changes of type of allele along a chromosome stated as a ratio of the maximum possible number of changes, e.g. a 10101 gamete has a recombination index of 1.0 whereas a 11001 gamete has a recombination index of 0.5.

A five locus model specifies 32 types of gametes. In LEWONTIN's model $q_i = 0.5$, and all 32 types occur equally frequently at gametic equilibrium. The grouping of gametes into potency classes will result in a frequency distribution of potency classes having the binomial proportions (1:5:10:10:5:1). The average recombination indices within potency classes are 0.0, 0.4, 0.6, 0.6, 0.4, 0.0 respectively, averaging to 0.5. One aspect of the gametic disequilibrium produced by normalizing selection is the positive kurtosis of the frequency distribution of potency classes. This is shown for LEWONTIN's data in Figure 2. This positive kurtosis can be considered as occurring without any change of the relative frequencies of gametic types within potency classes. Average recombination indices have been calculated using the frequencies of potency classes, on the relationship $\overline{ri}_p = 0.4f_1 + 0.6f_2 + 0.6f_3 + 0.4f_4$, where f_i = frequency of gametes with potency of i .

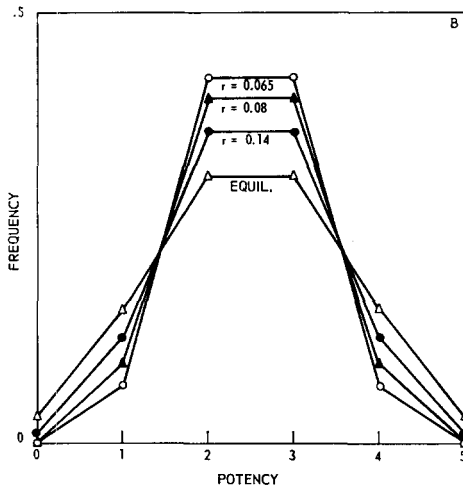


FIGURE 2.—Frequency distributions of potency classes for LEWONTIN'S model A showing the positive kurtosis that results from normalizing selection.

Average recombination indices have been calculated from the individual gametic frequencies $\bar{r}i_g = \sum r \cdot g_r$, where g_r = frequency of gametes with a recombination index of r .

The values of $\bar{r}i_p$ and $\bar{r}i_g$ from LEWONTIN'S data are shown plotted against the rate of recombination in Figure 3. The results plotted in Figure 3 show that as the rate of recombination decreased there was (a) an effectively linear increase of $\bar{r}i_p$, and (b) a markedly curvilinear increase of $\bar{r}i_g$ with an inflexion between the 0.05 and 0.10 rates of recombination. Selection against recombination load becomes increasingly effective as the rate of recombination is decreased below 0.10. This will tend to a limit with the population consisting entirely of 01010 and 10101 types, having a value of $\bar{r}i_g$ of 1.0. This limit has been effectively

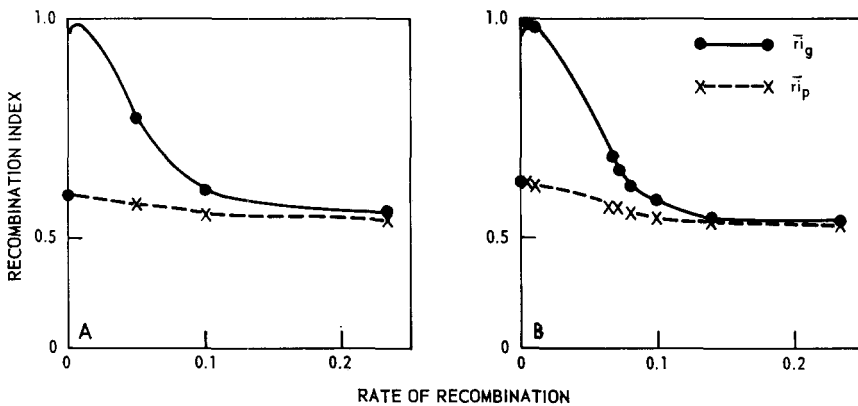


FIGURE 3.—Values of $\bar{r}i_p$ and $\bar{r}i_g$ plotted against rate of recombination, calculated from the data of LEWONTIN (1964). See Figure 1.

reached in model B at rates of recombination of 0.01 and 0.005. With complete suppression of recombination there will be no recombination load and at equilibrium the gametic distribution would consist only of gametes with potencies of two and three. The frequencies of types of gametes within these potency classes would be unchanged from those at gametic equilibrium and the average recombination index would be 0.6.

It appears reasonable to distinguish three aspects of the relationship of the rate of recombination to the gametic disequilibrium consequent from normalizing selection. These can be termed (a) "potency" disequilibrium (b) "relational balance" disequilibrium, and (c) "multiple allele" disequilibrium. In a freely recombining system, $D_{ij} \neq 0$, measures (a). In a system of no recombination $D_{ij} \neq 0$ measures (c), and with partial suppression of recombination, $D_{ij} \neq 0$, measures the joint effects of (a) and (b).

SUMMARY

Gametic disequilibrium in a multigenic system under normalizing selection, is considered in terms of the effects of restricted and unrestricted recombination.

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