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Simulation of Quantitative Characters from Qualitatively Acting Genes

I. Nonallelic Gene Interactions Involving Two or Three Loci[1]

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Summary. The phenotypic values associated with the 3^n genotypes obtained from all combinations of genes at n segregating loci, each with two alleles, can be completely described in terms of 3^n parameters, $3^n - 1$ of which are attributed to the genetic effects of alleles at the n loci. The descriptions provide a system of linear equations, which can be solved for parameters specifying n additive, n dominance and $3^n - 2n - 1$ epistatic components of genetic effect. The solutions of the equations were obtained for two- and three-locus cases. The simple linear combination model was convenient for interpreting classical gene interactions in terms of biometrically definable parameters.

By the use of the unique solutions of the linear equations, the genetic parameters were directly estimated from the phenotypic values reported by three groups of workers for simplified genetic systems consisting of two or three loci. In most cases nonallelic gene interactions accounted for a major part of the total genetic effect. Conventional biometrical methods of partitioning genotypic sums of squares into various components were found to be inadequate for evaluating the role of epistasis in these simplified genetic systems.

In diploid organisms, if there are two alleles at each of n independent loci, then 3^n genotypes are possible by all combinations of genes. The phenotypes associated with these 3^n genotypes can be described in terms of $3^n - 1$ biometrical parameters ascribable to the genetic effects of these n loci. For two alleles at each of the ith and jth loci, the eight parameters are:

Parameter	Description
a_i	Additive effect of the ith locus
a_j	Additive effect of the jth locus
d_i	Dominance effect of the ith locus
d_j	Dominance effect of the jth locus
aa_{ij}	Interaction between a_i and a_j
ad_{ij}	Interaction between a_i and d_j
da_{ij}	Interaction between d_i and a_j
dd_{ij}	Interaction between d_i and d_j

To denote the above quantities in terms of the genetic effects of the $A-a$ and $B-b$ loci, Mather (1967 and earlier) used the notation d_a, d_b, h_a, h_b, i_{ab}, $j_{a/b}$, $j_{b/a}$ and l_{ab}, respectively, to denote deviations from the mid-parent value, considered for convenience as a natural zero point. Following Crow, Seyffert (1966) expressed the mid-parent value as a quantity Y, representing the residual phenotype when the ith and jth loci are not considered. Thus, Y can take any value including zero. Suppose that the phenotypes associated with the nine genotypes in a common genetic background are the following:

$$\begin{pmatrix} IIJJ & IIJj & IIjj \\ IiJJ & IiJj & Iijj \\ iiJJ & iiJj & iijj \end{pmatrix} = \begin{pmatrix} 22 & 21 & 20 \\ 12 & 11 & 10 \\ 02 & 01 & 00 \end{pmatrix}$$

Genotypes Phenotypes

then the complete description of phenotypes according to the model in Seyffert (1966) and Crow and Kimura (1970) is given by:

$$\begin{pmatrix} 22 & 21 & 20 \\ 12 & 11 & 10 \\ 02 & 01 & 00 \end{pmatrix} = \begin{pmatrix} Y + a_i + a_j + aa_{ij} & Y + a_i + d_j + ad_{ij} & Y + a_i - a_j - aa_{ij} \\ Y + d_i + a_j + da_{ij} & Y + d_i + d_j + dd_{ij} & Y + d_i - a_j - da_{ij} \\ Y - a_i + a_j - aa_{ij} & Y - a_i + d_j - ad_{ij} & Y - a_i - a_j + aa_{ij} \end{pmatrix}$$

Phenotypes Descriptions

If a metrical trait is controlled by the ith and jth loci, and if the nine genotypes are identified and their respective phenotypes measured, the elements in the phenotype matrix can be replaced by the observed phenotypic values and unique solution of the nine linear equations can be obtained. The solutions are:

$$\begin{pmatrix} Y \\ a_i \\ a_j \\ d_i \\ d_j \\ aa_{ij} \\ ad_{ij} \\ da_{ij} \\ dd_{ij} \end{pmatrix} = \frac{1}{4} \begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & -1 \\ 1 & 0 & -1 & 0 & 0 & 0 & 1 & 0 & -1 \\ -1 & 0 & -1 & 2 & 0 & 2 & -1 & 0 & -1 \\ -1 & 2 & -1 & 0 & 0 & 0 & -1 & 2 & -1 \\ 1 & 0 & -1 & 0 & 0 & 0 & -1 & 0 & 1 \\ -1 & 2 & -1 & 0 & 0 & 0 & 1 & -2 & 1 \\ -1 & 0 & 1 & 2 & 0 & -2 & -1 & 0 & 1 \\ 1 & -2 & 1 & -2 & 4 & -2 & 1 & -2 & 1 \end{pmatrix} \times \begin{pmatrix} 22 \\ 21 \\ 20 \\ 12 \\ 11 \\ 10 \\ 02 \\ 01 \\ 00 \end{pmatrix} \quad [A]$$

Parameters Coefficients Phenotypes (P)

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These are then direct estimates of the nine parameters, eight of which, a_i, a_j, d_i, d_j, aa_{ij}, ad_{ij}, da_{ij} and dd_{ij}, can be attributed to the genetic effects of the alleles at the ith and jth loci. When variances of the mean phenotypic values are known, the standard errors of the estimates of the parameters can be readily computed. For example, an estimate of the standard error of a_i is the square root of the quantity,

$$\frac{1}{16}(V_{00} + V_{02} + V_{20} + V_{22}),$$

where the terms within the parentheses are variances of the phenotypes 00, 02, 20 and 22, respectively, and the covariance terms are ignored. The complete variance matrix is,

$$\begin{pmatrix} V_y \\ Va_i \\ Va_j \\ Vd_i \\ Vd_j \\ Vaa_{ij} \\ Vad_{ij} \\ Vda_{ij} \\ Vdd_{ij} \end{pmatrix} = \frac{1}{16} \begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 1 & 4 & 0 & 4 & 1 & 0 & 1 \\ 1 & 4 & 1 & 0 & 0 & 0 & 1 & 4 & 1 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 4 & 1 & 0 & 0 & 0 & 1 & 4 & 1 \\ 1 & 0 & 1 & 4 & 0 & 4 & 1 & 0 & 1 \\ 1 & 4 & 1 & 4 & 16 & 4 & 1 & 4 & 1 \end{pmatrix} \times \begin{pmatrix} V_{22} \\ V_{21} \\ V_{20} \\ V_{12} \\ V_{11} \\ V_{10} \\ V_{02} \\ V_{01} \\ V_{00} \end{pmatrix} \quad [B]$$

Variances — Coefficients — Variances of phenotypes

It can be easily verified that a dihybrid segregation ratio, 9:3:3:1, in the F_2 generation is produced with complete dominance, i.e., $d_i = a_i$ and $d_j = a_j$, either in the presence or absence of interallelic interactions, but only when the relationship, $aa_{ij} = ad_{ij} = da_{ij} = dd_{ij}$ holds. The main effects a_i and d_i at the ith locus and a_j and d_j at the jth locus can be independently positive or negative, but never zero, whereas the interaction terms can be positive, negative or zero irrespective of the sign and magnitude of the main effects. When additive and dominance effects of both loci are equal, i.e., $a_i = a_j = d_i = d_j$, we obtain a 9:6:1 segregation ratio in F_2. Other digenic segregation ratios characteristics of various classical types of epistasis are produced by modifications of the above basic relationships (Table 1).

Tab. 1. *The relationships among the eight genetic parameters producing digenic segregation ratios in the F_2 generation characteristic of classical epistasis*

Nature of epistasis	Relationships among parameters	F_2 ratio
Complementary	$a_i = a_j = d_i = d_j = aa_{ij} = ad_{ij} = da_{ij} = dd_{ij}$	9:7
Recessive epistasis	$a_i \neq a_j$, $a_i = d_i$, $a_j = d_j = aa_{ij} = ad_{ij} = da_{ij} = dd_{ij}$	9:3:4
Duplicate	$a_i = a_j = d_i = d_j = -aa_{ij} = -ad_{ij} = -da_{ij} = -dd_{ij}$	15:1
Dominant epistasis	$a_i = d_i \neq a_j$, $a_j = d_j = -aa_{ij} = -ad_{ij} = -da_{ij} = -dd_{ij}$	12:3:1
Inhibitory	$a_i = d_i = -a_j = -d_j = aa_{ij} = ad_{ij} = da_{ij} = dd_{ij}$	13:3

The relationships among parameters clearly indicate that the necessary conditions for obtaining any of the eight digenic ratios considered above are that additive genetic effects must be present at both loci and dominance must be complete (i.e., $a_i = d_i$ and $a_j = d_j$). The F_2 segregation ratios characteristic of the six classical types of gene interactions presented in Table 1 are produced only when the four interaction terms are non-zero and have the same sign and magnitude. Whereas with complementary, duplicate or inhibitory interactions the magnitude of epistasis is always twice the additive or dominance effects of genes, their relative magnitudes are not constant with recessive or dominant epistasis, as $|a_i| \neq |a_j|$.

Genetic systems may, however, occur such that dominance and/or epistasis are present but there are no tangible additive effects of the genes. Consider, for example, two alleles at each of the ith and jth loci with phenotypically indistinguishable homozygous genotypes, $I_1I_1J_1J_1$, $I_2I_2J_2J_2$, $I_1I_1J_2J_2$ and $I_2I_2J_1J_1$. Let each of the genotypes produce 100 units of a measurable phenotype and let the hybrids between any two of these homozygous lines show transgressive segregation, so that in the F_2 of the cross $I_1I_1J_1J_1 \times I_2I_2J_{22}$ or $I_1I_1J_2J_2 \times I_2I_2J_1J_1$ the following phenotypes are obtained:

$$\begin{pmatrix} I_1I_1J_1J_1 & I_1I_1J_1J_2 & I_1I_1J_2J_2 \\ I_1I_2J_1J_1 & I_1I_2J_1J_2 & I_1I_2J_2J_2 \\ I_2I_2J_1J_1 & I_2I_2J_1J_2 & I_2I_2J_2J_2 \end{pmatrix} = \begin{pmatrix} 100 & 105 & 100 \\ 105 & 110 & 105 \\ 100 & 105 & 100 \end{pmatrix}$$

Genotypes (G) — Phenotypes

with a ratio of 1(100):2(105):1(110). The parameters are $Y = 100$, $a_i = a_j = aa_{ij} = ad_{ij} = da_{ij} = dd_{ij} = 0$ and $d_i = d_j = 5$. The genes show no effect when homozygous. The transgressive segregation is obviously due to dominance effects at both loci. *A positive dd_{ij}* interaction will cause more pronounced transgressive segregation of the double heterozygote.

When $a_i = a_j = aa_{ij} = ad_{ij} = da_{ij} = 0$, $d_i = 5$, $d_j = 7$ and $dd_{ij} = 1$, we obtain

$$(G) = \begin{pmatrix} 100 & 107 & 100 \\ 105 & 113 & 105 \\ 100 & 107 & 100 \end{pmatrix}$$

and an F_2 ratio of 1(100):1(105):1(107):1(113). If, however, $a_i = a_j = aa_{ij} = 0$, $d_i = -da_{ij} = 5$, $d_j = -ad_{ij} = 7$ and $dd_{ij} = -12$, there is a 6:1:1 ratio in the F_2. These are examples of two-locus genetic systems with appreciable dominance and nonallelic interactions in the complete absence of additive gene action.

An extreme situation is the absence of additive and dominance effects of genes where $a_i = a_j = a_i = d_j = 0$ but $aa_{ij} = ad_{ij} = da_{ij} = dd_{ij} = 5$. This results in

$$(G) = \begin{pmatrix} 105 & 105 & 95 \\ 105 & 105 & 95 \\ 95 & 95 & 105 \end{pmatrix}$$

with a 5:3 ratio in F_2.

The above three numerical examples are chosen to illustrate the fact that when dominance and/or epistasis is present in a genetic system, the presence of additive effect is not axiomatic. They also illustrate that dominance and/or epistasis may cause overdominance in the absence of additive effect. More commonly, however, overdominance is manifested if dominance and epistasis (ad_{ij}, da_{ij} and dd_{ij} types) are either singly or jointly greater than additive effects of the genes. It may be of interest to note that when either d_i and d_j or d_i, d_j and dd_{ij} are the only gene actions present in a system, an overdominance effect is produced yielding a 1:1:1:1 ratio in the F_2. With only additive and additive × additive interaction all the nine genotypes are recovered in F_2 with the 1:2:2:1:4:1:2:2:1 ratio.

Numerous other relationships among the eight parameters can be worked out, many of which would be of little significance in the present context. The important point to recognize is that definite relationships among the genetic parameters exist for any particular epistatic ratio in a segregating generation. Alterations of these relationships and/or changes in the magnitude of the parameters can blur the digenic ratios in such a way that continuous variation of non-discrete phenotypes characteristic of polygenic inheritance is produced. The parameters, aa_{ij}, ad_{ij}, da_{ij} and dd_{ij}, merely denote biometrical quantities specifying interactions between the ith and jth loci in four genetic phases, homozygous-homozygous, homozygous-heterozygous, heterozygous-homozygous and heterozygous-heterozygous. They do not reflect the subtle interactions among genes that might be taking place at molecular level for the development of a character. It is also important to recognize that the interaction terms are not multiplicative functions of a's and d's and that they may be in some cases independent of the magnitude and direction of additive and dominance effects of genes.

Three Loci

An extension of the digenic model to three or more loci is straightforward. For three loci with two alleles at each locus, 27 parameters (including Y) are required for a complete specification of 27 phenotypes (Table 2).

Gaussian elimination and simplification of the equations in Table 2 give unique solutions for the parameters (Table 3).

Table 2. *The descriptions of the 27 phenotypes corresponding to the 27 genotypes obtained from all combinations of genes at three loci, each with two alleles*

Phenotype matrix			Parameters describing phenotypes
222	221	220	$Y+a_i+a_j+a_k+aa_{ij}+aa_{ik}+aa_{jk}+aaa_{ijk}$
212	211	210	$Y+a_i+d_j+a_k+ad_{ij}+aa_{ik}+da_{jk}+ada_{ijk}$
202	201	200	$Y+a_i-a_j+a_k-aa_{ij}+aa_{ik}-aa_{jk}-aaa_{ijk}$
122	121	120	$Y+d_i+a_j+a_k+da_{ij}+da_{ik}+aa_{jk}+daa_{ijk}$
112	111	110	$Y+d_i+d_j+a_k+dd_{ij}+da_{ik}+da_{jk}+dda_{ijk}$
102	101	100	$Y+d_i-a_j+a_k-da_{ij}+da_{ik}-aa_{jk}+daa_{ijk}$
022	021	020	$Y-a_i+a_j+a_k-aa_{ij}+aa_{ik}+aa_{jk}-aaa_{ijk}$
012	011	010	$Y-a_i+d_j+a_k-ad_{ij}+aa_{ik}+da_{jk}-ada_{ijk}$
002	001	000	$Y-a_i-a_j+a_k+aa_{ij}-aa_{ik}-aa_{jk}+aaa_{ijk}$

=

$Y+a_i+a_j-a_k+aa_{ij}-aa_{ik}-aa_{jk}-aaa_{ijk}$
$Y+a_i+d_j-a_k+ad_{ij}-aa_{ik}-da_{jk}-ada_{ijk}$
$Y+a_i-a_j-a_k-aa_{ij}-aa_{ik}+aa_{jk}+aaa_{ijk}$
$Y+d_i+a_j-a_k+da_{ij}-da_{ik}-aa_{jk}-daa_{ijk}$
$Y+d_i+d_j-a_k+dd_{ij}-da_{ik}-da_{jk}-dda_{ijk}$
$Y+d_i-a_j-a_k-da_{ij}-da_{ik}+aa_{jk}+daa_{ijk}$
$Y-a_i+a_j-a_k-aa_{ij}+aa_{ik}-aa_{jk}+aaa_{ijk}$
$Y-a_i+d_j-a_k-ad_{ij}+aa_{ik}-da_{jk}+ada_{ijk}$
$Y-a_i-a_j-a_k+aa_{ij}+aa_{ik}+aa_{jk}-aaa_{ijk}$

Table 3. *The solutions for the parameters in a three-locus genetic system*

Parameters		Coefficient matrix																													Phenotype vector
Y		1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0	1			222
a_i		1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	−1	0	−1	0	0	0	−1	0	−1			221
a_j		1	0	1	0	0	0	−1	0	−1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	−1	0	−1			220
a_k		1	0	−1	0	0	0	1	0	−1	0	0	0	0	0	0	0	0	0	1	0	−1	0	0	0	1	0	−1			212
d_i		−1	0	−1	0	0	0	−1	0	−1	2	0	2	0	0	0	2	0	2	−1	0	−1	0	0	0	−1	0	−1			211
d_j		−1	0	−1	2	0	2	−1	0	−1	0	0	0	0	0	0	0	0	0	−1	0	−1	2	0	2	−1	0	−1			210
d_k		−1	2	−1	0	0	0	−1	2	−1	0	0	0	0	0	0	0	0	0	−1	2	−1	0	0	0	−1	2	−1			202
aa_{ij}		1	0	1	0	0	0	−1	0	−1	0	0	0	0	0	0	0	0	0	−1	0	−1	0	0	0	1	0	1			201
aa_{ik}		1	0	−1	0	0	0	1	0	−1	0	0	0	0	0	0	0	0	0	−1	0	1	0	0	0	−1	0	1			200
aa_{jk}		1	0	−1	0	0	0	−1	0	1	0	0	0	0	0	0	0	0	0	1	0	−1	0	0	0	−1	0	1			122
ad_{ij}		−1	0	−1	2	0	2	−1	0	−1	0	0	0	0	0	0	0	0	0	1	0	1	−2	0	−2	1	0	1			121
ad_{ik}		−1	2	−1	0	0	0	−1	2	−1	0	0	0	0	0	0	0	0	0	1	−2	1	0	0	0	1	−2	1			120
ad_{jk}		−1	2	−1	0	0	0	1	−2	1	0	0	0	0	0	0	0	0	0	−1	2	−1	0	0	0	1	−2	1			112
da_{ij}	= 1/8	−1	0	−1	0	0	0	1	0	1	2	0	2	0	0	0	−2	0	−2	−1	0	−1	0	0	0	1	0	1	×		111
da_{ik}		−1	0	1	0	0	0	−1	0	1	2	0	−2	0	0	0	2	0	−2	−1	0	1	0	0	0	−1	0	1			110
da_{jk}		−1	0	1	2	0	−2	−1	0	1	0	0	0	0	0	0	0	0	0	−1	0	1	2	0	−2	−1	0	1			102
dd_{ij}		1	0	1	−2	0	−2	1	0	1	−2	0	−2	4	0	4	−2	0	−2	1	0	1	−2	0	−2	1	0	1			101
dd_{ik}		1	−2	1	0	0	0	1	−2	1	−2	4	−2	0	0	0	−2	4	−2	1	−2	1	0	0	0	1	−2	1			100
dd_{jk}		1	−2	1	−2	4	−2	1	−2	1	0	0	0	0	0	0	0	0	0	1	−2	1	−2	4	−2	1	−2	1			022
aaa_{ijk}		1	0	−1	0	0	0	−1	0	1	0	0	0	0	0	0	0	0	0	−1	0	1	0	0	0	1	0	−1			021
aad_{ijk}		−1	2	−1	0	0	0	1	−2	1	0	0	0	0	0	0	0	0	0	1	−2	1	0	0	0	−1	2	−1			020
ada_{ijk}		−1	0	1	2	0	−2	−1	0	1	0	0	0	0	0	0	0	0	0	1	0	−1	−2	0	2	1	0	−1			012
add_{ijk}		1	−2	1	−2	4	−2	1	−2	1	0	0	0	0	0	0	0	0	0	−1	2	−1	2	−4	2	−1	2	−1			011
daa_{ijk}		−1	0	1	0	0	0	1	0	−1	2	0	−2	0	0	0	−2	0	2	−1	0	1	0	0	0	1	0	−1			010
dda_{ijk}		1	0	−1	−2	0	2	1	0	−1	−2	0	2	4	0	−4	−2	0	2	1	0	−1	−2	0	2	1	0	−1			002
dad_{ijk}		1	−2	1	0	0	0	−1	2	−1	−2	4	−2	0	0	0	2	−4	2	1	−2	1	0	0	0	−1	2	−1			001
ddd_{ijk}		−1	2	−1	2	−4	2	−1	2	−1	2	−4	2	−4	8	−4	2	−4	2	−1	2	−1	2	−4	2	−1	2	−1			000

The usual 27:9:9:9:3:3:3:1 trigenic ratio with complete dominance, is obtained when $a_i = d_i$, $a_j = d_j$, $a_k = d_k$, $aa_{ij} = aa_{ik} = aa_{jk} = ad_{ij} = ad_{ik} = ad_{jk} = da_{ij} = da_{ik} = da_{jk} = dd_{ij} = dd_{ik} = dd_{jk}$, and $aaa_{ijk} = aad_{ijk} = ada_{ijk} = add_{ijk} = daa_{ijk} = dda_{ijk} = dad_{ijk} = ddd_{ijk}$. If there is no difference in the dominance effects at the three loci, i.e., $d_i = d_j = d_k$ $(= a_i = a_j = a_k)$, the ratio reduces to 27:27:9:1. That the first and second order interactions (aa_{ij} etc. and aaa_{ijk} etc.) can be positive, negative or zero, irrespective of the sign and magnitude of the main effects (a_i, d_j etc.), imply that an F_2 population showing the above ratios may vary from considerable epistasis to no epistasis at all.

Some of the deviations which are extensions of the digenic epistasis presented in Table 1 are discussed next.

A complete complementation among the three loci involved in the production of a trait would yield an F_2 ratio of 27(*I-J-K-*):37 (phenotype of remaining combinations), when all of the 26 parameters have the same sign and magnitude, except zero. The relative role of epistasis in such populations is expected to be about seven times more than that of additive or dominance effects, whereas it is only twice the additive effects in a comparable two-gene system. Since with complete complementation the relationships among the components of genetic effect remain unchanged with an increase in the number of loci controlling a trait, the role of epistasis increases enormously when more than two or three loci are involved in the complementary type of gene interaction (see Table 4). It is very unlikely that a metrical trait will result from the joint effects of nine or ten genes acting in a completely complementary manner. The figures in Table 4 perhaps represent extreme conditions. Nevertheless, they do reveal the important role of epistasis in the inheritance of a quantitative trait even when nonallelic interactions occur among only a few genes.

In a three-locus system, the complementation may be such that a dominant allele at a particular locus, say the *i*th, and a dominant allele at any one of the remaining two loci are necessary for the production of a character. The parameters are related as follows:

(i) $a_i = d_i$,

(ii) $a_j = a_k = d_j = d_k = aa_{ij} = aa_{ik} = -aa_{jk} = ad_{ij} = ad_{ik} = -ad_{jk} = da_{ij} = da_{ik} = -da_{jk} = dd_{ij} = dd_{ik} = -dd_{jk} = -aaa_{ijk} = -aad_{ijk} = -ada_{ijk} = -add_{ijk} = -daa_{ijk} = -dda_{ijk} = -dad_{ijk} = -ddd_{ijk}$

producing a 45:19 ratio in the F_2. Here the relative importance of epistasis will vary according to the size of the additive effects at the *j*th and *k*th loci relative to that of the *i*th locus.

Yet another type of complementation among loci may be such that dominant alleles at any two of the three loci are sufficient for full development of the trait. In this case a 54:10 ratio is obtained in the F_2 when $a_i = a_j = a_k = d_i = d_j = d_k = -aaa_{ijk} = -aad_{ijk} = -ada_{ijk} = -add_{ijk} = -daa_{ijk} = -dda_{ijk} = -dad_{ijk} = -ddd_{ijk}$ and all first order interactions are zero. Clearly, under these conditions the epistatic

Table 4. *The relative magnitude of nonallelic interactions among n loci controlling a quantitiave character when the completely complementary type of epistasis is present. The role of epistasis relative to the additive effects of the loci is calculated as the ratio* $\frac{3^n-2^n-1}{n}$. *The epistatic component expressed as a percentage of the total genetic effect of the n loci under consideration is calculated as* $\frac{3^n-2^n-1}{3^n-1} \times 100$

Magnitude of epistasis	Number of loci (n)								
	2	3	4	5	6	7	8	9	10
Relative to additive effects	2.0	6.6	18.0	46.4	119.3	310.3	818.0	2184.9	5902.8
Expressed in percent of total genetic effect	50.00	76.92	90.00	95.87	98.35	99.63	99.76	99.91	99.97

effects are much smaller than for the preceding two cases of complementation.

With recessive epistasis, if the dominant allele at a locus, say the ith, alone produces a distinct phenotype, and if the phenotypes associated with the genotypes *I-J-kk* and *I-jjK-* are different, an F_2 ratio of 27 (*I-J-K-*):3(*I-jjkk*):9(*I-J-kk*):9(*I-jjK-*):16(*ii--*) will be obtained from the relationships,

(i) $a_i = d_i$,

(ii) $a_j = d_j = aa_{ij} = ad_{ij} = da_{ij} = dd_{ij}$,

(iii) $a_k = d_k = aa_{ik} = ad_{ik} = da_{ik} = dd_{ik}$,

(iv) $aa_{jk} = ad_{jk} = da_{jk} = dd_{jk} = aaa_{ijk} = aad_{ijk} = ada_{ijk} = add_{ijk} = daa_{ijk} = dda_{ijk} = dad_{ijk} = ddd_{ijk}$.

The parameters in group (iv) can be positive, negative or zero. In the latter case, the relative contribution of epistasis would be considerably reduced. It may be noted that the parameters in (ii) and (iii) can also be zero, even when the interaction terms in (iv) have non-zero values, and still yield the characteristic F_2 ratio. However, when $a_j = a_k$ ($d_j = d_k =$ etc.), the ratio will be reduced to 27:3:18:16.

The 63:1 triplicate gene ratio is obtained when:

$a_i = a_j = a_k = d_i = d_j = d_k = -aa_{ij} = -aa_{ik} = -aa_{jk} = -ad_{ij} = -ad_{ik} = -ad_{jk} = -da_{ij} = -da_{ik} = -da_{jk} = -dd_{ii} = -dd_{ik} = -dd_{jk} = aaa_{ijk} = aad_{ijk} = ada_{ijk} = add_{ijk} = daa_{ijk} = dda_{ijk} = dad_{ijk} = ddd_{ijk}$.

In this case, although the first order interactions are in the opposite direction to the case of complementary interaction, the relative contribution of epistasis to the total genetic effect is similar to that with completely complementary gene interaction. The percentage contribution of epistasis can be computed in the same way as in Table 4, by taking the absolute values. The relationship among main effects and first order interactions is identical to that with duplicate epistasis, but the second order interactions act in the same direction as the main effects.

With dominant epistasis, when $d_i \neq d_j \neq d_k$, an F_2 ratio of 48(*I-*):9(*iiJ-K-*):3(*iiJ-kk*):3(*iijjK-*):1(*iijjkk*) is obtained if the relationships are:

(i) $a_i = d_i$,

(ii) $a_j = d_j = -aa_{ij} = -ad_{ij} = -da_{ij} = -dd_{ij}$,

(iii) $a_k = d_k = -aa_{ik} = -ad_{ik} = -da_{ik} = -dd_{ik}$,

(iv) $aa_{jk} = ad_{jk} = da_{jk} = dd_{jk} = -aaa_{ijk} = -aad_{ijk} = -ada_{ijk} = -add_{ijk} = -daa_{ijk} = -dda_{ijk} = -dad_{ijk} = -ddd_{ijk}$.

If the dominance effects are $d_i \neq d_j = d_k$, groups (ii) and (iii) will merge giving a 48:9:6:1 ratio in the F_2.

A special case of the dominant epistasis is that the dominant allele at the ith locus has an inhibitory effect, so that a ratio of 49(*I---,iijjkk*):9(*iiJ-K-*):3(*iiJ-kk*):3(*iijjK-*) is obtained in the F_2 when the parameters are related as above. If the dominance effects of the jth and kth loci are equal, the F_2 ratio reduces to 49:9:6 as groups (ii) and (iii) merge.

It can be seen that in genetic systems with recessive or dominant epistasis the parameters in group (iv) are unrelated to the additive effects of the three loci. However, when there are complementary or triplicate gene types of epistasis, the magnitude of the parameters in group (iv) are dependent on the magnitude of the main effects and they cannot be zero if there is some additive effects of the genes. In the event of their being zero in any of the former cases, the overall contribution of epistasis to total genetic effect will be much smaller than that with complementary or triplicate gene interaction. The independence of these epistatic parameters from the main effects indicates that in some situations their relative importance can be very large even with recessive and dominant epistasis in three-gene systems.

The relationships among parameters also reveal that considerable epistasis may be present in a genetic system showing the usual digenic (9:3:3:1) or trigenic (27:9:9:9:3:3:3:1) F_2 ratio characteristic of complete dominance. The relative role of epistasis in the inheritance of a metrical trait is generally expected to increase with the increase in the number of loci controlling the trait. No segregation ratio resulting from classically interpretable interactions is possible when all parameters specifying nonallelic interactions are zero. On the other hand, substantial epistasis may be present in a genetic system in the

complete absence of additive and/or dominance effects.

Limitations of the Model

The genetic model describing phenotypic values of known genotypes as linear combinations of biometrical parameters appears to be quite useful in interpreting classical interactions in relation to additive and dominance effects of individually identifiable genes. This simple additive model not only provides direct estimates of the genetic effects ascribable to the loci under consideration, but also the direction of these effects. However, an assumption underlying the model is that the nonallelic interactions remain unchanged with the genotypic changes. For example, in a two-locus system the description of the phenotypes associated with the two double homozygotes are:

Genotype	Phenotype	Description
IIJJ	22	$Y + a_i + a_i + aa_{ij}$
iijj	00	$Y - a_i - a_j + aa_{ij}$

The parameter aa_{ij}, denoting interaction between the ith and jth loci when both are homozygous dominant, is assumed to be identical to their interaction when homozygous recessive. This is indeed an oversimplification for mathematical convenience with no biological basis for its support.

Another important assumption for mathematical convenience is that the phenotypes are linear combinations of genetic effects. The biochemical processes involved in the development of a character may be such that a multiplicative model of genetic effects is a better approximation of gene action than an additive model. The biological meaning of the components of genetic effect would then be quite different even after a logarithmic transformation to an additive scheme. Furthermore, the kinetic consequences of enzyme reaction may be such that the biochemical functions of genes in the production of the trait would be close to a combination of multiplicative and additive contributions of various genetic effects.

Most quantitative traits in higher organisms are unsuitable for genetic studies seeking biologically meaningful interpretation of the biometrical parameters specifying interlocus interactions. Quantitative genetic studies in microorganisms have been initiated by Simchen and Jinks (1964) with the hope that they will throw light on nonallelic interactions at the physiological and biochemical levels. An attempt to determine relationships among estimates of genetic parameters and gene actions at the molecular level meets with obvious difficulties. The parameters are biometrical descriptions of phenotypic differences among genotypes. In the absence of a relationship with the biological nature of gene action, they are merely mathematical indices. For an ideal character such as a biochemical substance produced in certain parts or tissues of an organism, the usual inheritance studies on the qualitatively identifiable phenotype provide adequate formal genetic information on the number of genes involved and their dominance and epistatic relationships. The biochemical processes preceding the development of the phenotype, the genes controlling various steps in the pathway and their effects on the molecule of the compound are well understood. Standard biometrical analysis of the continuous variation in the amount of the substance in tissues might then be useful in understanding the quantitative genetic system in the light of available biochemical information. A character like anthocyanins in plant tissue combines many of the desirable features for such studies. Jana and Seyffert submitted preliminary results from the investigations on two-gene systems controlling the production of anthocyanins in *Matthiola incana*. For two loci, each with two alleles, they produced nine genotypes by controlled crosses among four homozygous parents, all having an identical homozygous genetic background. By the use of the matrix solution method described in this article they estimated genetic parameters attributable to the effects of two loci. Their results suggest a considerable role for epistasis in genetic systems controlling pigment formation, where interactions among genes at molecular level are important features.

Application of the Model

That nonallelic gene interactions may constitute a major part of the total genetic variance in a simplified genetic system consisting of only two small chromosome segments was demonstrated by Fasoulas and Allard (1962). In backcross derived material of a cultivated barley variety they developed four homozygous lines which were isogenic except for genes at two loci, *O/o* and *R/r* (or short chromosome segments tightly linked to them):

Genotype of the line	Phenotype
OORR	White lemma, rough awn
OOrr	White lemma, smooth awn
ooRR	Orange lemma, rough awn
oorr	Orange lemma, smooth awn

By crossing the four homozygous lines in all combinations, nine genotypes were obtained. The marker genes or the tightly linked chromosome segment adjacent to them were found to be active for seven quantitative characters: heading time, plant height, number of spikes, yield of spikes, spike length, spike weight and spike density. By the use of the biometrical method described by Cockerham (1954) they estimated eight components of genetic variance. While additive genetic effects accounted for most of the genetic variance (65%), the contribution of epistasis was found to be considerable (32%). Dominance accounted for only 3% of the total genetic variance.

Table 5. *Estimates of the components of genetic effect attributed to the O/o and R/r loci in an isogenic background in barley. The direct estimates are deviations from Y, which is the residual phenotype when the effects of the two loci are not considered, obtained by solutions of nine simultaneous equations for seven characters separately. The subscripts i and j designate O/o and R/r loci, respectively*

Character Parameter	Heading time	Plant height	Number of spikes	Yield of spikes	Spike length	Spike weight	Spike density
a_i	−0.27**	4.21**	−1.29**	1.29	3.52**	0.13**	0.001
a_j	0.40**	−1.60**	0.94*	−0.61	−4.11**	−0.09**	0.008**
d_i	−0.31**	0.43	−0.43	2.14	2.86**	0.11**	0.002
d_j	−0.26**	0.45	0.58	3.65	0.73	0.08**	0.007**
aa_{ij}	−0.57**	1.89**	−0.99	−3.03**	−1.75	−0.02**	0.005**
ad_{ij}	−0.00	0.34	−1.24*	−3.13	0.79	0.00	−0.005
da_{ij}	−0.20	−0.59	−0.53	−0.79	−0.73	0.01	0.006*
dd_{ij}	0.13	1.20	−1.77**	−9.62**	−4.01**	−0.20**	−0.010*
Y	13.6	81.6	31.37	77.62	68.52	24.37	0.35

* Significant by Z-test at $P = .05$
** Significant by Z-test at $P = .01$
All Y's are significant at $P = .01$

Diallel analyses of two-gene systems were performed in two Upland cotton varieties by Lee, Cockerham and Smith (1968). Two independent loci, Gl_2/gl_2 and Gl_3/gl_3 can be qualitatively identified by the pattern of pigment glands produced on leaves, stems and carpel walls of the cotton plant. The normally glandular plant has the genotype, $G_2lGl_2Gl_3Gl_3$, while $gl_2gl_2gl_3gl_3$ is glandless. Gossypol is one of the polyphenolic substances produced by the pigment glands, and is stored in the cotton seed almost to the exclusion of any of the others. Thus the level of gossypol in the cotton seed can be considered as a quantitative estimate of a phenotypic value. The analyses of 4 × 4 diallel crosses showed that 94% of the total genetic variance was additive, 5% epistatic and dominance, although statistically significant, accounted for only 1%.

Recently, Russel and Eberhart (1970) extended Fasoulas and Allard's method of factorial analysis to a three-gene system in corn. Backcross derived sublines of an inbred line, differing at only three loci, were used in quantitative genetic analyses of nine plant and ear characteristics. The 27 genotypes obtained by all possible combinations of two alleles at each of these three loci, *Rp/rp*, *Rf/rf* and *Wx/wx*, were evaluated in a randomized complete block experiment with 20 replications. They observed considerable nonallelic interaction, ranging from 21 to 69 percent of the total genetic variance depending upon the trait. Averaged over all characters, the order of relative importance was 50.1% additive, 41.2% epistasis and 8.7% dominance variance.

A notable feature of all three investigations reviewed above is that, contrary to the usual practice of formulating a series of oversimplifying assumptions underlying the biometrical analyses, the experimenters developed simplified genetic systems of two or three loci in a common genetic background. The simple nature of these "model" experimental materials permitted reanalysis of the data by using the matrix solution method described in this article. The results of the alternative analyses are presented in the following section.

(1) Fasoulas and Allard (1962) presented the mean phenotypic values for seven characters of their nine barley genotypes. By substituting each set of these nine values in the phenotype vector P of [A] direct estimates of the parameters were obtained from the seven characters (Table 5). These estimates are positive or negative deviations from the residual phenotype, Y. In Table 6 the parameters are expressed as a percent of the total genetic effect, taking the absolute values of the parameters attributed to the genetic effects of *O/o* and *R/r* loci into account. A comparison with Fasoulas and Allard's results (reproduced in column *b* for each character) shows that dominance and interaction components are consistently underestimated by the factorial method, while additive genetic effects are generally overestimated. By the matrix method of analysis, on an overall basis, epistasis appeared to be most important (52.3%), followed by additive (34.0%) and dominance effects (13.7%).

(2) Lee, Cockerham and Smith (1968) analysed 4 × 4 diallel crosses among four homozygous parents, $Gl_2Gl_2Gl_3Gl_3$, $Gl_2Gl_2gl_3gl_3$, $gl_2gl_2Gl_3Gl_3$ and $gl_2gl_2gl_3gl_3$, in two isogenic backgrounds. They reported the gossypol level in percent of dried embryonic tissue summed over three plots. The sixteen crosses in each diallel can be regrouped on the basis of their genotypes to give the following phenotype vectors in 9-space.

Genotype	Phenotype	
	Coker 100-A	Empire 61 (WR)
$Gl_2Gl_2Gl_3Gl_3$	4.2120	3.7560
$Gl_2Gl_2Gl_3gl_3$	3.7475	3.5010
$Gl_2Gl_2gl_3gl_3$	2.8100	2.5450
$Gl_2gl_2Gl_3Gl_3$	3.0380	2.6485
$Gl_2gl_2Gl_3gl_3$	2.1055	1.8573
$Gl_2gl_2gl_3gl_3$	0.4120	0.2705
$gl_2gl_2Gl_3Gl_3$	1.2110	0.9950
$gl_2gl_2Gl_3gl_3$	0.1315	0.1430
$gl_2gl_2gl_3gl_3$	0.0640	0.0350

Substituting these values in vector P of [A] the nine parameters for gossypol level were directly estimated (Table 7, Column a). The relative magnitude of these parameters expressed as a percent of the total

Table 6. *Components of genetic effect (in absolute values) estimated by using the matrix method and expressed as the percentages of the total genetic effects of the O/o and R/r loci (column a). Column b for each character contains the components of genetic variance expressed in percent of the total genotypic variance, reproduced from Fasoulas and Allard's (1962) Table* 5. *The subscripts i and j designate the O/o* and *R/r loci, respectively*

Character Parameter	Heading time		Plant height		Number of spikes		Yield of spikes		Spike length		Spike weight		Spike density		Mean over loci and characters	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
a_i	12.8	17	39.6	77	16.6	61	5.3	0	19.0	38	20.5	64	2.8	0		
a_j	18.8	26	14.6	12	12.1	11	2.5	0	22.2	51	13.6	23	17.6	75	31.2	65
d_i	14.6	4	4.0	1	5.6	6	8.8	0	15.4	2	16.7	1	4.0	0		
d_j	12.1	1	4.2	1	7.4	0	15.1	0	3.9	0	12.0	0	16.5	3	20.0	3
aa_{ij}	26.4	52	17.7	9	12.8	13	12.5	42	9.5	6	3.5	0	10.8	10		
ad_{ij}	0.2	0	3.2	0	15.9	6	12.9	11	4.3	0	0.4	0	10.8	3		
da_{ij}	9.3	0	5.3	0	6.8	0	3.2	0	4.0	0	1.9	0	14.2	5		
dd_{ij}	5.8	0	11.1	0	22.8	3	39.7	47	21.7	3	31.4	12	23.3	4	48.8	32

Table 7. *Estimates of the components of genetic effect attributed to the Gl_2/gl_2 and Gl_3/gl_3 loci in two genetic backgrounds for gossypol level in Upland cotton seeds. Column a contains the values estimated by the matrix method. In column b the parameters are expressed in percent of the total genetic effect of these two loci computed from the absolute values of the estimates. Column c contains the corresponding percentages computed from Table 6 in Lee et al. (1968). The subscripts i and j designate Gl_2/gl_2 and Gl_3/gl_3 loci, respectively*

Background genotype Parameter	Coker 100-A			Empire 61 (WR)			Coker 100-A average over loci		Empire 61 (WR) average over loci	
	(a)	(b)	(c)	(a)	(b)	(c)	(b)	(c)	(b)	(c)
a_i	1.3177	35.4	70.9	1.4367	34.3	70.5	50.0	94.7	49.5	94.2
a_j	0.5427	14.6	23.8	0.6372	15.2	23.7				
d_i	−0.3732	10.0	0.2	−0.3493	8.4	0.4	10.3	0.6	11.6	1.0
d_j	−0.0175	0.3	0.4	−0.1347	3.2	0.6				
aa_{ij}	0.0628	1.7	0.0	0.0637	1.5	0.0	39.7	4.7	38.9	4.8
ad_{ij}	0.3613	9.7	1.4	0.3712	9.0	1.0				
da_{ij}	0.6463	17.3	2.8	0.6758	16.1	3.2				
dd_{ij}	0.4085	11.0	0.5	0.5152	12.3	0.6				
Y	1.8327			2.742						

genetic effect, computed from the absolute values of the estimates of parameters (column b) and the corresponding percentages of variance components estimated by Lee, Cockerham and Smith (1968) (column c) are presented in Table 7. The solutions of the linear equations in [A] reveal a larger contribution of dominance and epistasis than could be seen from the estimates of variance components from the diallel tables.

(3) Russel and Eberhart (1970) gave the mean phenotypic values for nine characters of the eight homozygous lines. Additional data were kindly supplied by Prof. W. A. Russel to complete the phenotype vectors in 27-space. The direct estimates of the parameters by using the solutions in Table 3 are presented in Table 8. The error mean squares from the experiments with 20 replications for each character were used to estimate standard errors of the mean phenotypic values. These standard errors were then used to obtain an estimate of the standard error of each parameter. For example, the standard error of the estimate of a_i was the square root of the following quantity, $V_{ai} = \frac{1}{64}(V_{222} + V_{220} + V_{202} + V_{200} + + V_{022} + V_{020} + V_{002} + V_{000})$.

A test of significance of a_i was then performed at the 0.05 and 0.01 levels of significance as $Z = a_i/$ S.E. of a_i. Table 9 presents the relative magnitudes of the various genetic effects calculated from the absolute values of the parameters in Table 8 and expressed in percent of the total genetic effect. Corresponding sums of squares in percent of the total sums of squares for genotypes are reproduced from Russel and Eberhart's Table 3. A comparison of the figures in columns a and b for each character indicates, as in the previous two cases, a much reduced role of additive genetic effects of the three loci compared with the results of factorial analyses. The relative importance of dominance and particularly epistasis appeared to be increased considerably.

Discussion

As a natural extension of Nilsson-Ehle's theory of polymery and East's multiple factor hypothesis, continuous variation in metrical characters is believed

Table 8. *Estimates of the components of genetic effect attributed to the Rp/rp, Rf/rf and Wx/wx loci in the common (B 14) genetic background in corn. The direct estimates are deviations from the residual phenotype Y, calculated for each character separately by the solutions of 27 simultaneous linear equations. The subscripts, i, j and k designate Rp/rp, Rf/rf and Wx/wx loci, respectively*

Character Parameter	Days to anthesis	Plant height cm	Ear height cm	No. of tussel branches	Ear row no.	Ear length cm	Ear diameter cm	Ear per plant	Yield per plant gms
a_i	− 0.29*	−1.62**	− 2.06**	0.06	− 0.11**	0.08	0.05	0.006	4.79**
a_j	0.04	−1.55**	− 2.49**	− 0.39**	− 0,01	− 1.20**	−0.25**	−0.086**	1.74
a_k	0.06	0.65*	− 1.11*	− 0.11	0.11**	− 0.38*	−0.03	0.009	−0.54
d_i	− 0.24	0.22	0.54	− 0.01	− 0.01	1.43**	0.27**	0.069**	13.11**
d_j	− 0.16	0.70	− 0.11	0.21*	0.06	0.97**	0.13	0.016	7.64**
d_k	− 0.29*	−0.58	− 0.16	0.09	0.06	1.08**	0.25**	0.054*	6.34**
aa_{ij}	0.44**	2.30**	0.04	0.11	0.19**	− 0.72**	−0.23**	−0.059**	−2.89**
aa_{ik}	0.06	−0.40	0.51	− 0.01	− 0.04	0.05	0.00	−0.009	−0.41
aa_{jk}	− 0.01	−0.38	0.34	− 0.01	0.06	0.08	−0.00	0.009	2.74**
ad_{ij}	0.19	−0.45	− 0.45	− 0.04	0.06	− 0.15	−0.05	−0.001	−1.94
ad_{ik}	− 0.09	0.47	0.16	− 0.01	− 0.04	0.45	0.13	0.031	1.91
ad_{jk}	0.14	0.45	0.59	− 0.16	− 0.04	− 0.52	−0.17	−0.031	−2.59
da_{ij}	0.39**	0.45	− 0.06	− 0.16	0.04	− 0.33	−0.05	−0.011	−2.26
da_{ik}	− 0.14	−0.55	0.26	0.01	− 0.14*	0.60	0.07	0.024	−0.44
da_{jk}	− 0.06	−0.23	1.46**	0.09	− 0.11	0.85**	0.28**	0.076**	0.14
dd_{ij}	0.34	1.70*	0.01	0.24	0.36**	− 2.05**	−0.43**	−0.099*	−9.86**
dd_{ik}	0.56**	1.73*	1.61*	− 0.04	0.01	− 1.30*	−0.35*	−0.056	−10.76**
dd_{jk}	0.04	−1.60*	− 0.29	− 0.11	− 0.01	− 1.70**	−0.25	−0.049	−8.44*
aaa_{ijk}	0.09	1.53**	0.31	0.24**	0.01	− 0.35	0.03	0.011	−1.64
aad_{ijk}	− 0.16	−1.60**	− 2.14**	− 0.11	− 0.04	− 0.80*	−0.10	−0.034	−1.11
ada_{ijk}	0.29*	0.67**	0.49	0.09	0.04	0.33	0.10	0.034	1.21
daa_{ijk}	0.09	−1.13*	− 0.84	0.06	− 0.04	0.05	0.05	0.009	−1.36
add_{ijk}	− 0.51*	1.65*	− 2.56**	0.29	− 0.01	− 0.48	−0.08	−0.036	−1.51
dad_{iik}	− 1.01**	−0.00	− 2.89**	0.56**	− 0.04	− 0.50	−0.03	−0.036	2.51
dda_{ijk}	0.19	2.82	− 0.91	0.26	0.14	− 1.67**	−0.32*	−0.084*	−3.56
ddd_{ijk}	0.04	0.35	− 0.56	0.21	− 0.26	1.43	0.35	0.036	9.56
Y	32.31	155.57	61.26	10.71	14.39	22.15	5.22	1.24	117.01

* Significant by Z-test at $P = .05$
** Significant by Z-test at $P = .01$

All Y's are significant at $P = .01$

Table 9. *Components of genetic effect attributed to the Rp/rp, Rf/rf and Wx/wx loci in maize in the B14 background, expressed as a percentage of the total genetic effect considering the absolute values of the estimates of parameters. Column (a) for each character contains the values obtained by the matrix method and column (b) reproduces the sums of squares in percentage of the total sums of squares for the genotypes presented in Table 3 of Russel and Eberhart (1970). The subscripts, i, j and k designate Rp/rp, Rf/rf and Wx/wx loci, respectively*

Character Parameter	Days to anthesis		Plant height		Ear height		No. of tassel branches		Ear row no.		Ear length		Ear diameter		Ear per plant		Yield per plant		Mean over loci and characters	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
a_i	4.9	26	6.3	26	8.9	35	1.7	2	5.5	20	0.4	0	1.3	2	0.7	1	4.7	30	11.8	50.1
a_j	0.6	3	6.0	14	10.9	40	10.5	63	0.6	1	6.1	58	6.2	52	8.8	57	1.7	0		
a_k	1.1	0	2.5	4	4.8	2	3.0	1	5.5	6	1.9	0	0.6	1	0.9	6	0.5	1		
d_i	4.0	1	0.9	6	2.3	2	0.3	1	0.6	4	7.3	2	6.8	1	7.0	1	12.9	25	12.3	8.7
d_j	2.8	0	2.7	2	0.5	0	5.8	9	3.1	13	5.0	0	3.1	1	1.7	1	7.5	3		
d_k	4.9	1	2.2	1	0.7	0	2.4	1	3.1	1	5.5	0	6.2	1	5.5	1	6.2	0		
additive × additive	8.7	31	12.0	21	3.9	4	3.6	1	14.0	34	4.3	16	5.6	21	7.8	17	6.9	16	7.4	17.9
additive × dominance	17.0	6	9.9	2	13.3	7	13.0	4	20.7	6	15.0	7	18.6	9	18.0	7	9.0	6	14.9	6.6
dominance × dominance	15.8	9	19.6	5	8.3	1	10.4	2	18.9	9	25.8	9	25.5	6	20.9	5	28.6	14	19.4	6.0
second order interaction	40.2	23	37.9	19	46.4	9	49.3	16	28.0	6	28.7	8	26.1	6	28.7	4	22.0	5	34.2	10.7

to be the result of cumulative effects of a large number of genes, each having relatively small effect and being interchangeable in function among themselves. Mather's theory of polygenes is a brilliant concept in a situation where neither the number, nor the effects of individual genes can be ascertained. East's (1916) classical work on the inheritance of corolla length in *Nicotiana*, and many later reports, notably Wehrhahn and Allard (1965), Spickett and Thoday (1966) and Law (1967) in recent years, have contributed to the increasing awareness of the fact that quantitative characters may often be controlled by fewer genes than ordinarily believed. Despite the fact that newer biometrical techniques have been developed for estimating the number of genes controlling a metrical trait (see Stewart 1969 for a review), their number in real populations is seldom known exactly. Consequently, standard biometrical analyses based on a series of oversimplifying assumptions become unavoidable. This problem can be at least partially removed in the quantitative genetic analysis of a "model" system like the one used by Fasoulas and Allard (1962). Their two-gene system in barley was genetically active for seven quantitative characters. For yield of spikes, no significant additive and dominance variance were observed. Nonallelic interactions were highly significant, and accounted for nearly 100% of the total genetic variance. Additive $\times$ additive epistasis was of considerable importance for heading time (52%). For plant height, the gene action was largely additive (89%), but there was a small amount of additive $\times$ additive interaction (9%) and negligible dominance (2%). Reanalysis of the data by the matrix method revealed a considerably larger role for epistasis in the inheritance of all characters except heading time, and on an average it was found to be the most important effect (48.8%).

Gossypol, a polyphenolic compound found in the cotton seed, is produced by the pigment glands in various plant parts. The formation of the pigment glands is controlled by genes at two independent loci. For gossypol level in cotton seed the quantitative differences associated with the nine genotypes presumably have less basis for interaction at the biochemical level than the relatively complex characters studied by Fasoulas and Allard. The components of genetic variance estimated from the analysis of variance tables of the diallel crosses indicated that although statistically significant, the relative contribution of epistasis to the total genetic variation was only 5%. The role of epistasis in both the Coker 100-*A* and Empire 61 (WR) genetic backgrounds in Upland cotton was found to be much larger (39%) by the matrix method of analysis. The overall relative importance of various genetic effects remained unchanged: additive $>$ epistasis $>$ dominance. The F_1 hybrid between a glandular ($Gl_2Gl_2Gl_3Gl_3$) and a glandless ($gl_2gl_2gl_3gl_3$) plant is intermediate in glandulosity, indicating little or no dominance. Thus it is not surprising that dominance accounted for only a small part (11%) of the total genetic effect.

The characters investigated by Russel and Eberhart (1970) in maize are likely to be the products of intricate interactions among gene products at the biochemical and physiological levels. Epistasis constituted the most important component of total genetic variance for days to anthesis, plant height, ear row number and yield per plant. On the average, epistasis accounted for 41.2% of the total genetic variance estimated by the factorial method. The order of importance was: additive $>$ epistasis $>$ dominance. This overall order changed drastically when direct estimates were obtained by the solutions of simultaneous equations: epistasis $>$ dominance $>$ additive, with epistasis accounting for 75% of the total genetic effect. Significant second order interactions were revealed by both methods of analysis. Epistasis seemed to play an increasing role with an increase in the number of loci controlling a trait. It is reasonable to conclude that substantial epistasis almost certainly underlies the inheritance of a quantitative character involving more than a few loci, particularly when the trait has complex biological causes of variation.

Large discrepancies were observed between the results of the variance component methods and the results of the matrix solutions. The latter method uncovered a much greater role of epistasis than could be detected by the former analyses. The reason for the discrepancies becomes evident from the statistical principles involved in estimating the genotypic sum of squares and partitioning it into sums of squares due to main effects and interactions representing various orthogonal components of the genetic effect. The variances are measured as deviations from the population mean, μ, which is clearly a function of Y. A complete description of μ in terms of Y and various genetic effects in a complete 4×4 diallel cross of a two-gene system where the two alleles at each locus have equal frequencies is given by:

$$\mu = Y + \tfrac{1}{2} d_i + \tfrac{1}{2} d_j + \tfrac{1}{4} dd_{ij} .$$

The variance for the complete diallel table, which is equivalent to the variance of the F_2 generation can be expressed as:

$$\begin{aligned} V = {} & \tfrac{1}{2}\left(a_i + \tfrac{1}{2} ad_{ij}\right)^2 + \tfrac{1}{2}\left(a_j + \tfrac{1}{2} da_{ij}\right)^2 \\ & + \tfrac{1}{4}\left(d_i + \tfrac{1}{2} dd_{ij}\right)^2 + \tfrac{1}{4}\left(d_j + \tfrac{1}{4} dd_{ij}\right)^2 \\ & + \tfrac{1}{4}\left(aa_{ij}^2 + \tfrac{1}{2} ad_{ij}^2 + \tfrac{1}{2} da_{ij}^2 + \tfrac{1}{4} dd_{ij}^2\right) \end{aligned}$$

The method of least squares employed in partitioning genotypic sum of squares into various components maximizes the magnitude of the additive effects of genes and minimizes the contribution of epistasis. Thus the variance component method of genetic ana-

lysis gives inflated estimates of the additive gene action. Consequently, the relative importance of dominance and particularly epistasis are consistently underestimated. A nonsignificant or relatively low estimate of the epistatic component of genetic variance cannot be regarded either as the absence of or as negligible nonallelic gene interactions in a genetic system. Standard biometrical techniques are far from adequate for evaluating the role of epistasis even in simplified genetic systems consisting of only two or three loci.

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Zusammenfassung

Die phänotypischen Werte der 3^n Genotypen, die aus allen Kombinationen der Gene an n spaltenden Loci mit je 2 Allelen resultieren, können mit Hilfe von 3^n Parametern vollständig beschrieben werden. Hiervon gehen 3^n-1 Parameter auf genetische Effekte der Allele an den n Loci zurück. Die Beschreibungen setzen ein System linearer Gleichungen voraus, die hinsichtlich der Parameter, die n additive, n Dominanz- und 3^n-2n-1 epistatische Komponenten genetischer Effekte spezifizieren, gelöst werden können. Die Lösungen werden für 2- und 3-Locus-Fälle gegeben. Das einfache Modell linearer Kombination eignet sich zur Interpretation klassischer Geninteraktionen mit Hilfe biometrisch definierbarer Parameter.

Die genetischen Parameter wurden anhand der einzigen Lösungen der linearen Gleichungen direkt aus den phänotypischen Werten geschätzt, die für vereinfachte genetische Systeme mit 2 oder 3 Loci von 3 Forschergruppen berichtet wurden. In den meisten Fällen waren nichtallele Geninteraktionen für den größten Teil des gesamten genetischen Effekts verantwortlich. Konventionelle biometrische Methoden zur Aufteilung der genotypischen Varianzen in verschiedene Komponenten erwiesen sich als unzureichend, das Ausmaß der Epistasie in diesen einfachen genetischen Systemen richtig zu bewerten.

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