Genet. Res., Camb. (1961), **2**, *pp.* 96-105
Printed in Great Britain

Polygene analysis

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(*Received* 15 *August* 1960)

This paper considers why polygene practice is less successful than polygene theory. It introduces an alternative approach to the analysis of quantitative inheritance.

DISCUSSION

It is usual to argue from discrete Mendelian genes to discrete polygenes. This is not strictly valid since Mendelian genes form an extremely unrepresentative sample of the total genetic material. They are mutants of quite exceptional effect which do not happen to be lethal and which show good penetrance. In other words, we select them from the total of all mutants precisely because they have large, independent effects. We might nevertheless suppose that the chromosome is one long graded functional unit which cannot meaningfully be chopped into a series of discrete non-overlapping functional units. But microbial genetics provide evidence against this supposition. Pritchard (1955) finds a map-length between functional units (genes) of the same order as that between mutational sites within genes. Genes are therefore discrete. But the same evidence shows that recombination within the gene is at least as frequent as recombination between genes. This may not matter if the genes are Mendelian, for the products of recombination within a Mendelian locus can be expected to give roughly the same effects as one or other of the original alleles, rather than some intermediate effect. This is not true of genes controlling smaller differences; given two alleles determining two forms (of differing efficiencies) of the same enzyme, within-gene recombination can and does lead to the formation of enzymes of intermediate efficiencies. Thus, if polygenes are identified with functional units, within-gene recombination (which happens relatively often) can give quite different alleles from the original pair. If, on the other hand, polygenes are taken to be the mutational sites, they certainly do not act additively even at enzyme level, let alone at the level of the complete organism; their interactions (statistically speaking) are as large as their main effects.

This impasse can be avoided by forgetting about genes and starting at the other end of the scale. Statistical analysis of progeny means of crosses between various parents invariably shows that complete genomes have approximately additive effects; interactions, although they occur, are less important than main effects. The same is true of the effects of individual (marked) chromosomes. We may therefore hope that it will also be true of pieces of chromosomes. It must be expected that (since a genotype is a closely integrated structure) the smaller the pieces, the more important interactions will be. The trouble is, of course, that (unlike other

https://doi.org/10.1017/S0016672300000586 Published online by Cambridge University Press

applications of the statistical method of fitting constants) we do not know which individuals contain which pieces of chromosome.

Mangelsdorf (1952) expects that in any individual, development of a particular character will be limited by a small subset of all the genes concerned with that character, and that different individuals will be limited by different subsets. Mendelian genes are characterized by the peculiarity that the subset is the one gene for all individuals. Thus Harborne (1960) finds that a gene controlling a particular flower pigment does so by causing the hydroxylation of a flavonol. There must obviously be a lot of indispensable genes concerned with the production of the flavonol in the first place, yet we are pleased to call this hydroxylating gene 'the' gene for this particular flower colour! Mangelsdorf's quite reasonable idea emphasizes the necessity of the pragmatic approach by 'lengths of chromosome'. If polygene analysis on this basis were found to work, it would be just as rash to argue from it to conclusions about gene action as to argue from the successful use of main effects in fertilizer trials to conclusions about nitrogen metabolism inside the plant. Estimates of polygene 'linkage' or 'unfixable genetic variation' should, I submit, be taken with a plentiful dose of salt. Fortunately, except perhaps in the case of heterosis, the breeder is exclusively concerned with phenotypes. Polygene analysis, regarded in this way as an attempt to analyse chromosomal effects, still offers some hope as a method of prediction. The question of homozygosity may also be considered in this light. Although it is unlikely that the mathematical theory of inbreeding is exactly fulfilled in practice, the remarkable effects of inbreeding on normally outbreeding organisms leads us to expect that the difference between two homologous chromosomes of an inbred line will be much less than differences between two chromosomes taken from different strains, and this is all that is required to justify the working assumption that inbred parents are homozygous.

In the simplest case of hypothetical strains of *Drosophila* with exactly one crossover per chromosome in the female (and none in the male) we would be dealing in the F_2 and first backcross generations with chromosomes, each derived as one length from one parent joined to one length from the other parent. These lengths will of course differ in different individuals. Chromosomes composed of four shorter lengths (of the parental chromosomes) would appear in the F_3. It would be better to use means, rather than variances, when comparing different generations; for the chromosome pieces are of different lengths in different individuals and in different generations, and this will affect the variances but not, so much, the means. It may also be noted that the number of 'effective factors' will be at least twice or thrice the haploid chromosome number. As long as estimates of this number of effective factors take impossibly low values, little confidence can be placed in the other results of polygene analysis. The more complicated an analysis, the more desirable it is to be able to check on the plausibility of the model employed. The number of effective factors is the only criterion available here, so that it is very dangerous to gloss over the unfortunate estimates actually obtained.

In polygene algebra it is usual to assume that any gene substitution has a particular effect on the phenotype irrespective of the composition of the rest of the genotype.

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Any deviation from this is treated as gene interaction. However, it seems reasonable to suppose that the effect of a 'good' gene may be less in a 'good' genotype than in a 'bad' one; in other words, that a law of diminishing returns will operate. (The word 'gene' here means 'chromosome length' as above.) Rasmusson (1933) explores one aspect of this idea. Such curvature of the gene response-curve may certainly be described in terms of interaction between additive genes, but only as a combination of many small interactions of all orders, so that in practice the additive way of thinking is very poorly adapted to the situation. It appears that polygene analysis is peculiarly sensitive to this type of interaction. As an example, we may consider a case of eight fully dominant genes, each with effect $+1$, in an experiment involving F_2 and backcrosses. The genes all act in the same direction in each parent, so that if the value for the smaller parent is 100, that for the larger is 108. An 8% difference between parents seems reasonable in breeding material. The linear and non-linear gene response curves are taken to be:

	Number of genes								
	0	1	2	3	4	5	6	7	8
	Phenotype								
A	100	101	102	103	104	105	106	107	108
B	100	102·1	103·8	105·1	106·1	106·9	107·4	107·8	108
C	100	100·97	101·94	102·93	103·92	104·93	105·94	106·97	108

Here A is the additive case, B a case of 'diminishing returns', and C a purely multiplicative system where each successive gene multiplies the phenotypic value by 1·00967. Since we know that the genes all act in the same direction in each parent, we are entitled to estimate the number of effective factors. The means, variances, and estimates of D, H and k are:

	A		B		C	
	Mean	Variance	Mean	Variance	Mean	Variance
Parent 1	100	0	100	0	100	0
Parent 2	108	0	108	0	108	0
F_1	108	0	108	0	108	0
B_1	104	2	105·8	1·816	103·93	2·000
F_2	106	1.5	107·3	0·451	105·95	1·553
B_2	108	0	108	0	108	0
D	2		$-1·83$		2·21	
H	2		5·46		1·79	
k	8		$-8·7$		7·2	

Example A of course fulfils the assumptions of the analysis perfectly, and so the estimates are correct. Example B is quite severe, but not at all unreasonable. As may be expected, a local flattening or steepening of the gene response curve alters the variances considerably, but the means only slightly. The estimates of D

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and H, obtained as differences between multiples of the variances, are affected even worse. In example C there is a very slight deviation from the additive model in any individual phenotype, amounting to at most 0·08% (or 1% of the difference between the two parents). The means are affected to a similar extent, but one of the variances is increased by 3·5% and the estimates of D, H and k have consequently altered by 10%. This hardly bears out the opinion of Mather (1949) that 'a small departure from additiveness is not in any case likely to engender serious difficulties or errors'. Small but systematic departures can cause big trouble. A similar conclusion applies to other estimates of the number of effective factors, for such estimates are usually the square of a statistic of order n divided by another statistic of order $2n$.

Now, as Mather (1952) points out, scaling tests are an essential part of the analysis. The means in examples B and C fail two of the three possible scaling tests and consequently it is not permissible to make the estimates of D, H and k until the data have been transformed. Unfortunately, the above examples show that, since the means are so much more stable than the variances, scaling tests may be satisfied to within the limits of experimental error while the variances remain quite misleading. Examples in the next section, using real data, show that genuine (and recognizable) departures from additivity can occur which the scaling tests are too insensitive to pick up. In practice the means must be estimated more accurately than they are at present if scaling tests are to be of any use. A further objection is that a particular scale may appear to suit a given set of data, but might have failed to satisfy scaling tests on further crosses (involving the same material) which have not in fact been grown. This objection, trivial until the extreme importance of scaling tests is realized, appears to be insuperable. There is of course no guarantee that a scale that suits the genes *on average* will suit each individual gene. This objection is minimized if we consider only the means, not the variances.

It is obviously important, in any type of statistical analysis, to use a method that not merely gives the right answer if the assumptions involved are exactly fulfilled, but is not ruined by reasonable deviations from these assumptions. Such methods are called 'robust' by Box & Andersen (1955), who discuss the robustness of various commonly-used statistics. We see that polygene analysis, which uses the means to provide a check and the variances as sources of estimates, is not robust since the variances are considerably more sensitive than the means. It is in fact well known to professional statisticians that the variance-ratio and Bartlett's test, concerned with variances *per se*, are more sensitive to deviations from Normality than is the t-test. Once again, it would be better to estimate from the means and use the variances as a check. As in normal statistical practice, transformations would then be used only if demanded by the error structure (or as an aid in solving maximum likelihood equations). Since the situation is sensitive to curvature of the gene response curve, it seems reasonable to allow for such curvature in the analysis. Of course, it cannot be expected that such an analysis will more than approximate to the true situation, but it may be sufficiently robust to permit useful estimation of possible short-term selection results. On the other hand, it may not. The matter is

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explored further in the next section, but it is clear that little confidence can be placed in the detailed results of polygene analysis in its present form. 'If you get on the wrong track with the Mathematics for your guide, the only result is that you get to the Valley of Mare's Nests much quicker; get there so smoothly and easily that you do not realize where you are and it may be hard to unbeguile you' (Yule, 1920).

ALGEBRA

This section explores a way of increasing the robustness of polygene analysis. It appeared above that it would be preferable to use family means, rather than variances, for estimation. This is impossible as long as the additive hypothesis is adopted, since this hypothesis imposes certain constraints on the means. If the means actually observed do not satisfy these constraints ('scaling tests') the only thing to do is to transform the data as directed by these scaling tests. Unfortunately, these tests have to be very precisely satisfied before we can have much confidence in estimates derived from the variances. An alternative approach is to loosen the constrictions imposed by the additive hypothesis. I shall consider here the substitution of a gene response curve of the type $(a+x)\,\theta^x$ instead of the additive $(a+x)$. This new function, by combining additive and multiplicative gene action, can give a wide range of curves of different types, including (1) a 'diminishing returns' curve ($\theta < 1$) where the effect of any one gene decreases as the phenotype departs from the origin a, (2) the additive system ($\theta = 1$), and (3) a multiplicative type of action ($\theta > 1$, x/a small). It leads to tractable—even elegant—algebra and can, of course, be extended to include sines and cosines by taking imaginary values of θ. It may turn out that, by fitting such a flexible hypothesis to the observed means, a sufficiently good approximation to the true situation can be made. Extreme caution is necessary since, the more complicated a statistical analysis, the less trustworthy are its results (and conversely, the simpler an explanation of a biological phenomenon, the more superficial it is likely to be). All the same, it is worth while attempting direct estimation from the means. The advantages include the statistical robustness discussed in the previous section, the fact that we can average over the effects of chromosomes broken by different numbers of crossovers and at different places (whereas the variances must be inflated as a consequence of the variability of crossover positions) and the consideration (since we are interested in predicting genetic advance under selection) that prediction from means to means is likely to be safer than from variances to means when the assumptions on which the analysis is based go wrong.

I shall consider a simple experiment consisting of two (homozygous) parents, their F_1, F_2 and two backcrosses B_1 and B_2. Of the $(f+g)$ loci at which the parental genotypes differ, $f\,(>g)$ are homozygous for 'good' alleles in P_1. The phenotype of an individual homozygous for l 'good' alleles, n 'bad', and heterozygous at m loci is

$$(b+\overline{l-n}\,d+mh)\,\theta^{l-n}.$$

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Then the generation means are:

P_1 $[b+(f-g)d]\,\theta^{f-g}$

F_1 $b+(f+g)h$

B_1 $\left[b+\frac{f\theta-g}{1+\theta}d+\frac{f+g\theta}{1+\theta}h\right]\theta^{-g}\left(\frac{1+\theta}{2}\right)^{f+g}$

F_2 $\left[b+\frac{\theta-1}{1+\theta}(f+g)d+(f+g)\frac{2h\theta}{(1+\theta)^2}\right]\theta^{-f-g}\left(\frac{1+\theta}{2}\right)^{2f+2g}$

P_2 and B_2 are obtained by exchanging f and g in the expressions for P_1 and B_1.

At first sight, we may hope to omit the dominance term; apparent dominance might be explained by curvature of the gene response curve. But we shall see below that published data require the retention of a term for dominance. The means may then be written (approximately) as:

P_1 $(b+2d_2)x^2$

P_2 $(b-2d_2)x^{-2}$

F_1 $b+2h_1$

B_1 $(b+d_1+d_2+h_1+h_2)x$

B_2 $(b+d_1-d_2+h_1-h_2)x^{-1}$

F_2 $b+2d_1+h_1$

F_3 $b+3d_1+\frac{1}{2}h_1$

where $$2d_1 = \frac{\theta-1}{\theta+1}(f+g)d, \qquad 2d_2 = (f-g)d,$$

$$2h_1 = (f+g)h, \qquad 2h_2 = \frac{1-\theta}{1+\theta}(f-g)h,$$

$$x = \theta^{\frac{1}{2}(f-g)} \quad\text{and}\quad \left(\frac{1+\theta}{2}\right)^2 \text{ is approximated by } \theta.$$

These expressions are symmetric in the sense that P_1 and P_2 can be interchanged by reversing the signs d_2 and h_2 and reciprocating x. Evidently d_1, d_2, h_1, h_2 represent average genetic effects. At first sight it seems that if $\theta = 1$, $x = 1$ and $d_1 = h_2 = 0$. Further consideration of these formulae shows, however, that x represents a general curvature of the scale of measurement while d_1 is a kind of interaction between $(\theta-1)$ and d; it is in fact concerned with the possibility that the size of the contribution $\pm d$ may be different for 'positively' and 'negatively' homozygous loci. Incidentally, it should be noted that d_1 becomes more important in later generations with greater scatter of the genotypes. Thus x, d_1 and h_2 each measure their own characteristic kind of departure from additivity; it is quite possible to have $x = 1$ and yet find non-zero values for d_1, h_2. On the face of things we would expect h_2 (a second-order interaction) to be less important than x or d_1. If we regard x and d_1 as independent entities in their own right, we are freed of the assumption (made above implicitly) that all genes have the same numerical effect.

Now

$$F_2^2-B_1B_2 = (d_2+h_2)^2+d_1(2b+3d_1+2h_1),$$

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so that negative values of d_1 permit the F_2 mean to be significantly less than the geometric mean of the two backcrosses. It may be that these cases arise in practice only for artificial characters like average fruit weight where the natural direction of increase of the denominator (fruit number) is reversed. For clearly, if

$$F_2^2 > B_1 B_2, \quad \text{then} \quad \left(\frac{1}{F_2}\right)^2 < \frac{1}{B_1} \cdot \frac{1}{B_2}.$$

None the less, we still want to be able to analyse artificial characters as they stand, at any rate until it transpires that separate analyses of numerator and denominator are obligatory. Now, such cases are impossible in additive polygene analysis, for the scaling equalities

$$2B_1 = P_1 + F_1, \qquad 2B_2 = P_2 + F_1,$$
$$4F_2 = 2F_1 + P_1 + P_2$$

lead immediately to $16(F_2^2 - B_1 B_2) = 4(B_1 - B_2)^2 = (P_1 - P_2)^2$. There are four published cases (Mather, 1949; and Smith, 1952) which satisfy these scaling tests and also permit us to compare these three quantities.

	Mather, p. 44		Smith, p. 164	
	$D \times J$ 1938	$D \times J$ 1939	Plant height	Leaf length
$16(F_2^2 - B_1 B_2)$	26·90	52·47	−1022·4	−32·00
$4(B_1 - B_2)^2$	14·82	8·36	492·8	4·00
$(P_1 - P_2)^2$	13·32	8·09	364·8	1·21

It appears that these three estimates of the same genetic trait can be quite contradictory even when the scaling tests are satisfied to within sampling error. $(P_1 - P_2)^2$ is used in estimating the number of effective factors. Since from the genetical point of view we could equally well use either of the other expressions (or a combination of all three), it appears that the estimate is to a large extent at the choice of the experimenter. The trouble is, of course, that $F_2^2 - B_1 B_2$ is the relatively small difference between two large quantities, so that an insignificant change in F_2, B_1 or B_2 can convulse $F_2^2 - B_1 B_2$. As may be expected, $4(B_1 - B_2)^2$ comes out similar to $(P_1 - P_2)^2$, but sometimes so much bigger as to alter seriously the estimate of the number of effective factors.

The negative values of $F_2^2 - B_1 B_2$, although not significant, suggest that Smith's acceptance of an additive genetic system needs re-examination. Putting non-significant parameters zero, we find that for plant height $b = 37·5$, $h_1 = 3·1$, $x = 1·140$, and for leaf length $b = 11·15$, $x = 1·032$. These figures give expectations:

	Plant height		Leaf length	
	Observed	Expected	Observed	Expected
P_1	47·8	48·8	11·6	11·87
P_2	28·7	28·8	10·5	10·47
F_1	43·2	43·7	11·1	11·15
F_2	40·6	40·6	11·2	11·15
B_1	47·3	46·3	11·8	11·51
B_2	36·2	35·6	10·8	10·80

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In the case of plant height the additive dominance term could be replaced by a multiplicative type, so that it appears that a multiplicative genetic system would be more appropriate to these sets of means than an additive system. *The scaling tests are not good enough to guarantee additivity.* The $D \times J$ 1938 data used by Mather provide a further example. In the following analysis I have pooled the errors of the six means and have consequently used unweighted least squares. Fitting the additive model (i.e. setting $d_1 = h_2 = 0$, $x = 1$), the goodness-of-fit χ^2 is 5·207 (3 d.f.), which bears out the result of the individual scaling tests that no departure from additivity is apparent. However, closer investigation shows that a non-additive model fitting d_1 but keeping $h_2 = 0$ and $x = 1$ reduces this value of χ^2 to 0·760 (2 d.f.), i.e. the χ^2 due to fitting d_1 is 4·447 (1 d.f.). This procedure certainly involves an element of selection, but nevertheless it again appears that the new analysis is capable of picking up deviations from additivity that pass unnoticed by the scaling tests, i.e. is more sensitive than the additive analysis.

Now it can be seen that as long as we restrict ourselves to the first and second generations, it will be difficult to separate the effects d_1 and h_1 accurately. This means that any practicable polygene experiment restricted to F_2 and first back-cross will, however analysed, be rather insensitive to interactions of the type epitomized by d_1. Such interactions are precisely the sort best calculated to ruin predictions of genetic advance. To avoid this impasse, further generations must be included even though the parental chromosomes are further broken up by recombination and there is now the possibility of selection. Comparison of F_1, F_2 and F_3 means gives a direct test of the existence of d_1, independent of x.

It may be objected that, with the curved gene response, an arbitrary change of origin is no longer entirely absorbed by a corresponding change in b. This difficulty will not be very serious if $x \simeq 1$, and in any case there is usually a natural origin. Another point is that where F_2^2 significantly exceeds $B_1 B_2$, two solutions are possible. This difficulty, which again can be removed by including the F_3, is unimportant since the alternative solution is an improbable one wherein x is considerably different from 1.

CONCLUSION

There are two possible ways of meeting the difficulties. One is to retain the usual polygene analysis of second-degree statistics, but paying much more attention to the question of scale. The scale should be tailored to fit the observed means, rather than be taken ready-made from a book of mathematical tables. It is clear that once the curved model has been fitted to a set of means, a back transformation can be used to return to an additive model. If, from the infinity of possible transformations we choose the one that restores our curved model to linearity everywhere, the additive analysis of the transformed data will correspond exactly to the curved analysis of the original data. This reverse transformation cannot (in general) be expressed as an explicit algebraic function. Now it is generally understood that the method of unweighted least squares, formerly advocated for the estimation of polygene components of variance, is inefficient (and therefore misleading) and must

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be replaced by weighted least squares or maximum likelihood. I submit that the arbitrary selection of scale must also be replaced by more accurate methods.

But in my opinion it is asking for trouble to subject second-degree statistics to any more searching analysis than, say, division into genetic and environmental components (and even this gives unsatisfactory results only too often). I consider that the more complicated analysis into components for dominance, epistacy and the like leads in practice only to self-deception or frustration. This certainly seems to be true at the present time, and the considerations mentioned above suggest that it will go on being true. If, as seems advisable, we restrict ourselves to a more modest analysis of means (using variances only as indicators of accuracy), it will be simpler to work in terms of the curved model. It may also make better biological sense, for the curved gene response curve is a combination of additive and multiplicative effects, whereas the reverse transformation must usually appear somewhat arbitrary. The data of Giesbrecht (1959), published in sufficient detail for us to try the effect of transformations, illustrate this point.

The estimates are:

	Days to silking		Days to pollen shedding	
	1954	1955	1954	1955
x	0·93	1·065	0·88	1·05
b	93·0	77·8	93·7	74·2
d_1	−1·0	−0·3	−1·8	−0·5
d_2	13·6	1·8	17·8	2·3
h_1	−6·5	−2·8	−7·7	−2·1
h_2	0	0·6	−0·1	0·6

It again appears that the analysis is capable of quite credible results, in that d_1 and h_2 do not come to much. Indeed, we might profitably set h_2 permanently zero. On the other hand, quite similar sets of data give rise to dissimilar estimates. The present situation is perhaps as over-flexible as the additive analysis is inflexible, so that inclusion of the F_3 is essential to steady the estimation. Now, as Giesbrecht points out, it is difficult to find a satisfactory transformation to linearity. In the case of 1954 'days to silking', for example, only one of the scaling tests fails. All would be well if the lower parental mean were $1\frac{1}{2}$ days earlier. It appears, therefore, that the required scale will be roughly linear except for a sharp drop at the lower end. When constants are fitted to this lower end, however, we find from the distributions quoted by Giesbrecht (p. 333) that a suitable scale would replace 1, 2, 3, 4, 5, 6, etc., by 0, 17, −6, 7, 5, 6, etc. The simplest polynomial transformation is equally unsatisfactory, for it rises and then falls again with time instead of steadily increasing. I have no doubt that a more sensible scale could be found; but it will not be found easily. Similar difficulties arise with Giesbrecht's other data, and indeed are likely to be common once the necessity for precise scaling is accepted. This new type of analysis therefore seems to offer some advantage in flexibility—and credibility—over the usual linear model. It is clear that a large experiment is

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essential for the investigation of any polygenetic situation; no satisfactory approximation to reality can be obtained from half a dozen family means. This conclusion—scarcely surprising—suggests that such sophisticated analysis will always be too expensive for practical breeding work. The curvilinear analysis does, however, show some promise for strictly genetical purposes. Even if it turns out to be still insufficient to describe the complexities of real life, it can at least keep the mathematicians occupied.

SUMMARY

The usual conventions are relaxed to permit the introduction of a curved genetic model that shows some attractive features. Linear polygene analysis is examined in the light of this more flexible model. It is shown that great care is necessary in the choice of scale, since variances are more sensitive than means to small deviations from additivity. Inclusion of the F_3 is necessary for successful prediction by extrapolation. The genetical validity of any type of polygene analysis is discussed. The new model is quite promising for the analysis of means; but I think that the (more ambitious) analysis of variances is likely to remain intractable, for both genetical and statistical reasons.

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