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NOTES AND COMMENTS

THE GOODNESS-OF-FIT TEST FOR DETECTING NATURAL SELECTION IN RANDOM MATING POPULATIONS

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The issue has recently been raised in the pages of this journal and elsewhere as to the possibility of judging the relative fitnesses of genotypes from the frequencies of these genotypes in populations. Wallace (1958) has provided several numerical examples where severe selection pressures do not result in appreciable deviations of the observed zygotic frequencies from expectation under Hardy-Weinberg equilibrium. Novitski and Dempster (1958) attempted by means of a digital computer to estimate the adaptive values of genotypes in *Drosophila melanogaster* using only the observed genotypic frequencies. They found that the computer produced an infinite variety of best fit values for the fitnesses. We are indebted to them for first calling our attention to this problem and to Dr. Bruce Wallace for urging us to publish our findings.

If the frequency of an allele B in a population is p and that of its alternate allele b is $q = 1 - p$, then following random mating but *before* any natural selection has occurred the zygotes will be in the relative frequencies

$$(1) \quad \begin{array}{ccc} BB & Bb & bb \\ p^2 & 2pq & q^2 \end{array}$$

Assume now that natural selection operates in such a way that the three genotypes have the fitnesses W_1 , W_2 , and W_3 . Then after selection the genotypes will be in the relative frequencies

$$(2) \quad \begin{array}{ccc} BB & Bb & bb \\ \frac{W_1 p^2}{\bar{W}} & \frac{2W_2 pq}{\bar{W}} & \frac{W_3 q^2}{\bar{W}} \end{array}$$

where $\bar{W} = W_1 p^2 + 2W_2 pq + W_3 q^2$. The frequency of B is no longer p but p' where

$$(3) \quad p' = \frac{W_1 p^2 + W_2 pq}{W_1 p^2 + 2W_2 pq + W_3 q^2}$$

Suppose, now, that a sample is taken from such a population and that the three genotypes are distinguishable. There will be three observed frequencies, n_1 , n_2 and n_3 , but only two *independent* observations since there is the linear restriction

$$n_1 + n_2 + n_3 = N_{\text{TOTAL}}$$

There are, however, four independent parameters, W_1 , W_2 , W_3 and p . Since the geneticist is usually not interested in the absolute values of

the W 's but only their relative magnitudes (partly because he does not know how to measure their absolute values), it is possible to reduce the number of independent parameters to be estimated to three, by making W_2 (or W_1 or W_3) equal to unity. However, there is still one more parameter to be estimated than there are available observations, clearly an impossibility.

If estimation of W_1 and W_3 is impossible, is it nevertheless possible to test some hypothesis about these two selection coefficients, or at least to make some judgment about their relative sizes from the observations? Specifically, the geneticist would like to test the hypothesis that $W_1 = W_3 = 1$, that is, that no natural selection is operating. Moreover, if such a hypothesis is rejected, he would, at least, like to know whether W_1 and W_3 are greater or less than unity so that some judgment about the order of fitness of the three genotypes can be made.

The standard procedure presently in use by geneticists is to estimate p by the usual method

$$\hat{p} = \frac{2n_1 + n_2}{2N}$$

and then to test the observed frequencies against the binomial proportions given by (1) with \hat{p} and \hat{q} in place of p and q . If the χ^2 with one degree of freedom is significant it is assumed that natural selection is operating (non-random mating having been ruled out by ancillary information). Moreover, the *directions* of the deviations from expectation are used as a basis for judging the type of selection operating. If, for example, there is an excess of the Bb class with a concomitant deficiency of BB and bb classes, it is assumed that heterozygotes have a greater fitness than homozygotes. A non-significant χ^2 is taken as evidence that $W_1 = W_2 = 1$, that is, that no natural selection is taking place.

What this procedure really amounts to is as follows. First, \hat{p} is an estimate of p' given by (3) and not of p before selection since no independent estimate of that quantity exists. Second, the expectations calculated are of the form

$$(4) \quad \begin{array}{ccc} BB & Bb & bb \\ p'^2 & 2p'q' & q'^2 \end{array}$$

Finally, the χ^2 calculated is a test of whether the sampled distribution (4) is the same as dis-

tribution (2). These distributions are the same if simultaneously

$$(5) \quad p'^2 = \frac{W_1 p^2}{\bar{W}}, \quad p'q' = \frac{W_2 pq}{\bar{W}},$$

and

$$q'^2 = \frac{W_3 q^2}{\bar{W}}.$$

The solution to these three equations is simply

$$(6) \quad W_2^2 = W_1 W_3.$$

Thus, what is really tested is that the product of the adaptive values of the homozygotes is equal to the square of the heterozygote fitness. This is a much less restrictive condition than the requirement that $W_1 = W_2 = W_3$. Adaptive values like

BB	Bb	bb
2	1	.50

give a theoretically perfect fit so that the χ^2 test will be significant only α of the time where α is the probability level chosen for the test. Of course if χ^2 is significant, there is evidence for natural selection, a point that should not be lost sight of.

The second question of importance is whether the direction of deviations in the goodness-of-fit test gives some hint as to the sort of selection operating. Specifically, does an excess of the heterozygous class mean that the heterozygote has a superior fitness?

The deviation of the heterozygotes from expected is an estimate of

$$(7) \quad \frac{2pqW_2}{\bar{W}} - 2p'q'$$

which may be greater than, equal to, or less than zero. These three conditions correspond respectively to an excess of heterozygotes, no deviation, and a deficiency of heterozygotes. Substitution of (3) into (7) yields the relationships:

- $W_1 W_3 < W_2^2$: excess of heterozygotes
- $W_1 W_3 = W_2^2$: expected heterozygotes
- $W_1 W_3 > W_2^2$: deficiency of heterozygotes

Thus, an excess of heterozygotes will appear whenever the geometric mean of the fitnesses of the homozygotes is less than the fitness of the heterozygote. This obviously includes the case of heterosis but is not restricted to it. For example, a recessive lethal will cause a considerable excess of heterozygotes since $W_1 W_3$ will be zero. Some numerical examples of this fact have been presented by Wallace (1958).

An extremely important qualification of these results is that they apply only to a population in which gene frequency is changing. If the gene frequencies are at equilibrium in the population, $p' = p$, and the deviations from the Hardy-Wein-

berg equilibrium are perfectly adequate for estimating W_1 and W_2 independently.

Our previous discussion may give the impression that any attempt to determine the sort of selection operating in nature by comparing observed with theoretical frequencies is hopeless. This is not entirely true. A consideration of the power of the χ^2 test show that it is relatively insensitive to some sorts of selection while being much more sensitive to others. Specifically, the test is much more powerful in detecting heterotic situations than cases of partial or complete dominance.

The power of a test is the probability that the null hypothesis will be rejected (that the test will be significant), when the true parameters of the population differ from the hypothesized parameters by a given amount. Clearly if the true parameters differ from the hypothesized ones by a very large amount, the test will have great power, while for small deviations the power will be small. In addition, for any given deviation, the power of the test will increase with increasing sample size. For a χ^2 test, the power is determined from the distribution of "non-central χ^2 " using a "non-centrality" parameter, λ . The larger λ is, the greater the power of the test. For the case in hand the parameter of non-centrality turns out to be:

$$\lambda = \left[\frac{p^2 q^2 (W_1 W_3 - 1)^2}{(pW_1 + 1)^2 (qW_3 + 1)} \right] N$$

where W_2 has been fixed at unity. As expected, λ will increase not only with increasing sample size, N , but also as the product $W_1 W_3$ deviates more and more from unity. Note that when $W_1 W_3$ equals unity, λ is zero and the power of the test is zero.

To illustrate the relationship between the kinds of selection and the power of the χ^2 test to detect them, table 1 has been calculated. It is assumed in this table that $p = q = \frac{1}{2}$ and $a=1$ though the numerical values change for other values of p , the qualitative results are the same. What the table shows is the size of sample necessary to be 90% or 50% sure of detecting different combinations of adaptive values of the two homozygotes ($W_2 = 1$).

It is assumed that the 5% level will be used as a significance criterion in the χ^2 test. Across the top of the table are possible values of W_1 , the fitness of BB, and along the left hand side are the values of W_3 , the fitness of bb. In the body of the table there are two numbers corresponding to each combination of W_1 and W_3 . The roman (lower) numbers are the minimum sample sizes necessary to be 90% sure of detecting selection when the true values of W_1 and W_3 are those given at the borders of the table. The italic (upper) numbers give the minimum sample size for 50% power and obviously will in every case be smaller than their corresponding 90% values.

TABLE 1. *Sample sizes necessary to be 50% sure (italic numbers) and 90% sure (roman numbers) of detecting selection when the true fitnesses are those given at the borders of the table*

		W ₁ = fitness of BB										
		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
W ₃ = fitness of bb	0.0	4										
		11										
	0.1	5	6									
		13	16									
	0.2	5	7	8								
		15	19	23								
	0.3	7	8	11	13							
		18	23	29	36							
	0.4	8	10	13	17	21						
		21	27	35	45	57						
	0.5	9	12	15	20	27	35					
		24	32	42	55	73	95					
	0.6	10	13	18	25	33	45	61				
		27	37	50	67	91	124	168				
	0.7	11	15	22	30	42	59	85	123			
		30	42	59	82	116	162	231	337			
	0.8	12	18	25	36	53	78	118	186	311		
		34	48	69	100	145	212	323	508	851		
	0.9	14	20	30	44	66	103	168	293	573	1387	
		38	56	81	120	182	282	459	801	1567	3794	
1.0	15	23	35	53	84	138	246	493	1244	5546	—	
	42	63	95	145	229	378	673	1349	3405	15,175	—	
1.2	18	29	46	77	134	262	607	2099	37,646	10,486	1859	
	50	80	126	210	368	716	1660	5742	102,999	28,691	5086	
1.4	22	36	61	111	224	553	2212	159,847	4978	1181	553	
	61	99	168	304	614	1513	6053	437,343	13,620	3233	151	
1.6	26	45	81	162	393	1460	41,544	5210	1072	484	2893	
	71	122	222	443	1074	3996	113,665	14,254	2934	1325	790	
1.8	30	54	106	240	753	6776	12,045	1288	504	283	188	
	82	149	290	658	2060	18,538	32,956	3523	1378	773	515	
2.0	35	65	138	365	1694	—	2212	625	311	195	138	
	95	179	378	999	4634	—	6053	1709	851	534	378	
2.2	39	78	181	575	5353	8850	983	443	221	148	109	
	108	214	494	1573	14,647	24,213	2690	1212	604	404	299	
2.4	44	93	236	957	54,910	2497	587	277	170	119	91	
	121	255	647	2619	150,234	6833	1606	759	465	326	248	
2.6	50	110	311	1738	60,980	1245	406	214	138	100	78	
	136	301	851	4756	166,841	3405	1112	585	378	274	213	
2.8	56	129	412	3662	7549	780	307	174	117	87	68	
	152	354	1129	10,018	20,655	2134	840	476	320	237	187	
3.0	61	152	553	10,386	3011	553	246	147	101	77	61	
	168	416	1513	28,416	8239	1513	673	401	277	210	168	
4.0	96	323	3457	4057	523	216	125	86	64	51	43	
	263	884	9458	11,100	2431	591	343	234	176	140	117	
10.0	465	—	669	196	101	65	48	37	31	26	23	
	1272	—	1831	537	276	179	130	102	84	71	63	

The table is divided into three sections by heavy lines. The diagonal stepped line running from the lower left hand corner to the right middle margin separates combinations of W_1 and W_3 which give *excesses* of heterozygotes (above the line) from those combinations giving *deficiencies* of heterozygotes (below the line). The upper area is then subdivided by a horizontal line into an upper region where heterosis obtains, and a lower one in which there is no heterosis. It is this second region which is so troublesome from the standpoint of interpretation of the observations. The worst situation occurs in the three cells containing dashes because here, despite intense selection, there is no observable deviation from expected proportions so that no sample size of whatever magnitude can detect the operation of selection. These are the cases where W_1 is the reciprocal of W_3 . The important point about the table is the way in which the sample sizes change with fitness. The upper left hand corner of the table, representing a balanced lethal situation, requires the smallest sample size for detection. Progressing downward and to the right in the table the necessary sample sizes increase until the diagonal is reached, whereupon

N begins to decrease. In the case of heterozygote excess it is easier to detect cases of heterosis (above the horizontal line) than those of partial dominance. The χ^2 test is more sensitive to heterotic selection than to other types and is completely incapable of detecting some extreme cases of partial or complete dominance.

It should not be supposed that if the χ^2 test is significant with a sample size of 10, say, that heterosis is demonstrated simply because $N = 10$ happens to fall above the horizontal line in the table. *Any* type of selection may give a significant χ^2 with *any* sample size. As a matter of fact even when no selection is operating χ^2 will be significant 5% of the time if this is the significance level chosen. All that the table shows is that for a given sample size heterotic situations will be more often detected than non-heterotic ones.

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NOTES ON RELATIVE FITNESS OF GENOTYPES THAT FORMS A GEOMETRIC PROGRESSION.

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Let the three positive numbers W_1 , W_2 , W_3 denote the relative selective value (or fitness) of the three genotypes BB, Bb, bb, respectively. In a random mating population the frequencies of the three genotypes are in simple binomial proportions (p^2 , $2pq$, q^2) at birth or, more generally, before selection takes place. In the preceding paper Lewontin and Cockerham (1959) have shown that if $W_2^2 = W_1W_3$, the genotypic frequencies *after* the operation of selection in the population will again be in simple binomial proportions (p'^2 , $2p'q'$, q'^2) where p' and q' are the new gene frequencies after selection. This fact yields the important conclusion that under such a selective scheme, the observed adult genotype and gene frequencies—presumably those after the operation of selection—will tell us nothing about the value of the W 's. The relation $W_2^2 = W_1W_3$ simply means that the three numbers W_1 , W_2 , W_3 constitute a geometric series. To the author's knowledge, Dempster (1955) is the first who considers such a set of fitness values,

taking the W 's to be 1, $(1-s)$, $(1-s)^2$ in studying the problem of balance between mutation and selection. The purposes of this note are to supply a model for the genesis of the geometric selective scheme; to point out some simple properties of such a type of selection; and to extend the results to more general cases.

1. First of all, let us review briefly the main result of Lewontin and Cockerham. For their purposes, they find it convenient to make $W_2 = 1$. For our present purpose, however, it is more convenient to take $W_1 = 1$, $W_2 = r$, $W_3 = r^2$, where r may be greater or smaller than unity. When $r = 1$, there is no selection operating. The procedure of analysis and the selection result may be summarized in a tabular form (see table 1). The columns of table 1 are numbered to correspond with the serial number of the expressions in the preceding paper. The only discrepancy is that the common denominator \bar{W} of their expression (2) has been put at the bottom of our column (2). The imposed condition (5) is to