NOTES AND COMMENTS

THE INITIAL PROGRESS OF NEW GENES WITH VIABILITY DIFFERENCES BETWEEN SEXES AND WITH SEX LINKAGE

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1. INTRODUCTION

Bodmer and Parsons (1960) considered the initial progress of new genes with three genetic systems; namely the introduction of a third allele into a two-allele balanced polymorphism, a random mating tetrasomic population with and without double reduction, and a diploid population in which there is mixed selfing and random mating. They concluded that in an outbreeding population some heterozygote advantage is essential for a new gene to become established in a population, but with some inbreeding this is no longer a pre-requisite. In general, if F is Wright's inbreeding coefficient and p, q the gene frequencies of A, a respectively such that $p+q = 1$, and the relative viabilities of the three genotypes AA, Aa and aa are a, h, and b respectively, then the frequency of the 3 genotypes after selection will be

$$
\begin{aligned}
AA &\quad a(p^2+pq\mathrm{F})/\mathrm{T} \\
Aa &\quad 2hpq(1-\mathrm{F})/\mathrm{T} \\
aa &\quad b(q^2+pq\mathrm{F})/\mathrm{T}
\end{aligned}
$$

where T is a total such that the genotypic frequencies after selection add to unity. If, initially, the population is all aa, and the gene A is introduced, assuming p to be very small, and neglecting terms in p^2, the gene frequency p' in the next generation is

$$
p' = \frac{p[a\mathrm{F}+h(1-\mathrm{F})]}{b}.
$$

Thus for gene A to increase in frequency

$$
a\mathrm{F}+h(1-\mathrm{F})>b \quad \text{(Parsons and Bodmer, 1961)}.
$$

For F = 0, or random mating, $h>b$ as shown by Bodmer and Parsons (1960), implying that the heterozygote Aa must be fitter than the old homozygote aa. At F = 1, or complete inbreeding, $a>b$, *i.e.* the viability of genotype $AA>aa$ showing that the selective value of the heterozygote Aa is not relevant. As F goes from 0 to 1, the importance of h in determining what happens to gene A decreases. It clearly follows, as emphasised by Bodmer and Parsons (1960), that heterozygote advantage will be produced by outbreeding systems.

In this paper we will examine two situations previously examined from the point of view of conditions for equilibria. One is where viabilities of genotypes differ between sexes (Owen, 1953), and the other is for sex-linked genes (Bennett, 1957, 1958, and Mandel, 1959).

2. VIABILITY DIFFERENCES BETWEEN SEXES

Let the relative viabilities of genotypes AA, Aa and aa be respectively a_1, h_1 and b_1 in the females and a_2, h_2 and b_2 in the males. Let the gene frequency of A be p_1 in females and p_2 in males, and let the gene frequency of a be q_1 in females and q_2 in males. Then the genotypic proportions amongst mature individuals are:

Genotype	AA	Aa	aa
Females	$a_1 p_1 p_2$	$h_1(p_1 q_2 + p_2 q_1)$	$b_1 q_1 q_2$
Males	$a_2 p_1 p_2$	$h_2(p_1 q_2 + p_2 q_1)$	$b_2 q_1 q_2$

The gene frequency of A in the next generation in females is given by:

$$p_1' = \frac{a_1 p_1 p_2 + \tfrac{1}{2} h_1(p_1 q_2 + p_2 q_1)}{a_1 p_1 p_2 + h_1(p_1 q_2 + p_2 q_1) + b_1 q_1 q_2}. \qquad . \qquad . \qquad . \qquad (2.1)$$

If initially a population only has gene a, and gene A has been introduced by mutation, we can for the initial changes assume p to be small. Neglecting terms in p^2, equation (2.1) becomes

$$p_1' = \frac{h_1}{2b_1} p_1 + \frac{h_1}{2b_1} p_2 \qquad . \qquad . \qquad . \qquad . \qquad (2.2)$$

and, similarly, in the males

$$p_2' = \frac{h_2}{2b_2} p_1 + \frac{h_2}{2b_2} p_2. \qquad . \qquad . \qquad . \qquad . \qquad (2.3)$$

To find the conditions for which gene A increases, the 2 equations in p_1 and p_2 may be represented as a 2×2 matrix and the latent roots λ found. The magnitude of the dominant (largest) latent root λ_1 will determine whether or not the gene will increase in frequency. For an increase in frequency $\lambda_1 > 1$. The two latent roots are $\lambda = 0$ and

$$\lambda_1 = \tfrac{1}{2} \left(\frac{h_1}{b_1} + \frac{h_2}{b_2} \right) \qquad . \qquad . \qquad . \qquad . \qquad (2.4)$$

the dominant latent root. Thus when $\lambda_1 > 1$

$$h_1 b_2 + h_2 b_1 > 2 b_1 b_2 \qquad . \qquad . \qquad . \qquad . \qquad (2.5)$$

which implies that at least a " cumulative " heterozygote advantage is necessary for gene A to be established. If we put $h_1 = h_2 = 1$, $b_1 = 1 - \beta_1$, $b_2 = 1 - \beta_2$, then equation (2.5) becomes

$$\beta_1 + \beta_2 > 2 \beta_1 \beta_2$$

or, for small β_1 and β_2,

$$\beta_1 + \beta_2 > 0 \qquad . \qquad . \qquad . \qquad . \qquad (2.6)$$

again implying a " cumulative " heterozygote advantage of both sexes. It is also obvious from this equation that β_1 or β_2 could be negative, provided that the above equation still held. The heterozygote advantage in one sex must therefore exceed any possible heterozygote disadvantage in the

other sex. Such a case would be represented by $\beta_1 = 0.05$ ($b_1 = 0.95$), and $\beta_2 = -0.02$ ($b_2 = 1.02$), giving $\beta_1 + \beta_2 = 0.03$.

3. SEX LINKED LOCUS

Assuming that the males are heterogametic, let the relative viabilities of genotypes AA, Aa and aa be respectively a_1, h_1, b_1 in the females and in the males let a_2 and b_2 represent the two genotypes A and a. The gene frequencies are defined as in the previous section.

The gene frequency of A in the next generation of females is given by

$$p_1' = \frac{a_1 p_1 p_2 + \frac{1}{2} h_1 (p_1 q_2 + p_2 q_1)}{a_1 p_1 p_2 + h_1 (p_1 q_2 + p_2 q_1) + b_1 q_1 q_2}. \qquad . \qquad . \qquad . \qquad (3.1)$$

If, as before, the population was initially a, and A is introduced, then we get on neglecting terms in p^2

$$p_1' = \frac{h_1}{2b_1} p_1 + \frac{h_1}{2b_1} p_2. \qquad . \qquad . \qquad . \qquad . \qquad (3.2)$$

In the males, however, the gene frequency of A is given by

$$p_2' = \frac{p_1 a_2}{p_1 a_2 + q_1 b_2} \qquad . \qquad . \qquad . \qquad . \qquad (3.3)$$

and, on neglecting terms in p^2 we obtain

$$p_2' = \frac{a_2}{b_2} p_1. \qquad . \qquad . \qquad . \qquad . \qquad (3.4)$$

The characteristic equation from the 2×2 matrix made up by equations (3.2) and (3.4) is

$$\lambda^2 - \frac{h_1}{2b_1} \lambda - \frac{h_1 a_2}{2b_1 b_2} = 0 . \qquad . \qquad . \qquad . \qquad (3.5)$$

which has roots

$$\frac{1}{2} \left[\frac{h_1}{2b_1} \pm \sqrt{\frac{h_1^2}{4b_1^2} + \frac{2h_1 a_2}{b_1 b_2}} \right].$$

Putting $h_1 = 1$, $b_1 = 1 - \beta_1$, $b_2 = 1 - \beta_2$, $a_2 = 1 - \alpha_2$ and neglecting terms of order $\alpha\beta$ gives the two roots

$$\lambda_1 = \tfrac{1}{3}[3 + 2\beta_1 + \beta_2 - \alpha_2]$$

$$\lambda_2 = \tfrac{1}{3}[-3 - \beta_1 - 2\beta_2 + 2\alpha_2].$$

We have

$$\lambda_1 - \lambda_2 = \tfrac{1}{3}[9 + 5\beta_1 + 4\beta_2 - 4\alpha_2]$$

which is positive if

$$9 + 5\beta_1 + 4\beta_2 - 4\alpha_2 > 0$$

which is so since α, β are defined as small. Hence λ_1 is the dominant latent root and is > 1 if

$$2\beta_1 + \beta_2 - \alpha_2 > 0. \qquad . \qquad . \qquad . \qquad (3.6)$$

If $\alpha_2 = \beta_2$, then $\beta_1 > 0$ for the gene to increase, or $h_1 > b_1$ which implies that $Aa > aa$ in the females. If, however, $\beta_1 = 0$ then for the gene to increase $\beta_2 > \alpha_2$ or $A > a$ in the males. Of course, if $\beta_2 < \alpha_2$, then the heterozygote advantage required in the females will be larger than when $\beta_2 \geq \alpha_2$ for gene A to increase in frequency. Similarly, if $\beta_1 < 0$, implying heterozygote disadvantage in the females, β_2 must be considerably greater than α_2 for gene A to increase.

4. DISCUSSION

Bodmer and Parsons (1960) found that in a predominantly outbreeding population, some heterozygote advantage over the prevailing homozygote is essential for a new gene to become established, whereas with some inbreeding this is no longer a pre-requisite. In the situation in which there are differences in relative viabilities in the two sexes with random mating, heterozygote advantage in one sex must exceed any possible heterozygote disadvantage in the other sex for a gene to increase. Thus we see that overall heterozygote advantage is necessary, but that heterozygote advantage is not necessary within any particular sex. Since the conditions for equilibria have not been fully solved in this problem (Owen, 1953), it is not possible to relate these conditions for the initial increase of a gene to the conditions for an equilibrium.

The sex-linked case is of special interest, since heterozygotes can only occur in females. Thus, in some circumstances a simple advantage of the new allele over the old in the male will lead to the establishment of the new gene irrespective of the situation in the homogametic female. Conversely, if the new allele is at a disadvantage in the male, heterozygote advantage in the female is essential for the new gene to become established. The relative importance of heterozygote advantage therefore depends on a balance between the genotypic viabilities in the two sexes.

Mandel (1959) found that a modified form of overdominance appears necessary for an equilibrium to be established, namely,

$$\tfrac{1}{2}h_1(a_2+b_2) > a_1a_2, \quad b_1b_2 . \qquad . \qquad . \qquad . \quad (4.1)$$

which do not imply and are not implied by $h_1 > a_1$, b_1 or simple overdominance in the females.

If we put $h_1 = 1$, $a_1 = 1-\alpha_1$, $a_2 = 1-\alpha_2$, $b_1 = 1-\beta_1$ and $b_2 = 1-\beta_2$ as before, and ignore terms of order $\alpha\beta$ then the conditions for an equilibrium become

$$2\beta_1+\beta_2-\alpha_2 > 0 \qquad . \qquad . \qquad . \qquad . \quad (4.2)$$

$$2\alpha_1+\alpha_2-\beta_2 > 0 \qquad . \qquad . \qquad . \qquad . \quad (4.3)$$

the first being identical to the inequality (3.6) given as the condition for gene A to increase. Thus the relation between the condition for a gene to increase and the conditions for an equilibrium is striking. The second inequality (4.3) is in fact the condition for gene a to increase in a population initially all A. These inequalities also show that a degree of overdominance is implied in the formation of an equilibrium, for to take an extreme case, if $\alpha_1 = \beta_1 = 0$ and $\alpha_2 \neq \beta_2$ then only one of the two inequalities (4.2) and (4.3) would hold, and either the new gene would not become established, or would completely replace the old gene.

In conclusion, only those mutants with heterozygote advantage will become established if there is no inbreeding. In some cases, heterozygote advantage may be a product of the background genotype. It is possible that the degree of heterozygote advantage needed might be modified by linked loci, for example a mutation arising near a locus which shows over-dominance may become established more readily than a mutant arising further from the overdominant locus or on a different chromosome. With some inbreeding, those mutants with heterozygote advantage are, on the whole, more likely to be established than those without heterozygote advantage, but this depends on the degree of inbreeding. Finally, with sex linkage the necessity of heterozygote advantage in the homogametic females depends on the relative viabilities of the heterogametic males.

5. SUMMARY

The conditions for the establishment of newly occurring genes are examined for two genetic systems. One is where viabilities of genotypes differ between sexes, and the other is for sex-linked genes. In the former situation, heterozygote advantage in one sex must exceed any possible heterozygote disadvantage in the other sex for the initial increase of a new gene, and in the latter situation, the necessity of heterozygote advantage in the homogametic females is dependent on the relative viabilities of the genotypes in the heterogametic males.

6. REFERENCES

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Note added in proof:

The condition (4.1), namely

$$\tfrac{1}{2}h_1(a_2+b_2)>b_1b_2$$

can be derived directly from equation (3.5) without further approximations. The approximations, however, permit easier interpretation of the meaning of the results.