

## STABLE EQUILIBRIA UNDER OPTIMIZING SELECTION\*

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*Communicated by Sewall Wright, June 9, 1966*

The rate of evolution in both natural populations and artificially selected lines is dependent upon the amount of genetic variation present. Any form of selection that helps to maintain genetic variation, rather than destroying it, is then of special interest to the evolutionist and the breeder. A common form of selection that would seem at first sight to favor the maintenance of variation is "optimizing" selection, in which the probability of survival and reproduction of individuals is smaller the greater their deviation from some intermediate optimum phenotype.

Some form or other of optimizing selection has been the object of theoretical investigation for many years, with the purpose of finding the requirements that such selection maintain genetic variation in stable equilibrium. Wright<sup>6</sup> examined a quadratic model in which fitness of genotypes falls off as the square of the deviation of the genotype from an optimum. He showed that there could be no stable equilibrium of gene frequencies if dominance was complete or if there was no dominance. Robertson<sup>5</sup> considered a variety of optimum models and also concluded that for no dominance or complete dominance, no stable equilibrium of gene frequency existed. Kojima,<sup>2</sup> on the other hand, showed that at intermediate levels of dominance, the quadratic deviation model could lead to stable gene frequency equilibrium provided a certain relationship holds between the level of dominance and the location of the optimum in the phenotypic scale. The range of values of dominance and optimum phenotype for which stable gene frequency equilibrium occurs was calculated and given graphically by Kojima<sup>2</sup> on the assumption that the gene loci involved are at perfect linkage equilibrium. This result was advanced slightly farther by Lewontin,<sup>3</sup> who showed that for a variety of numerical cases predicted to be stable by Kojima, the presence of linkage was not a disturbing factor. That is, stable equilibrium existed for the more realistic models that allowed for the effect of linkage.

It was with some interest, then, that we encountered in these PROCEEDINGS an article by Jain and Allard<sup>1</sup> reporting that the introduction of linkage even at a recombination level of 0.50 resulted in a smaller region of stability than that given by Kojima<sup>2</sup> and Lewontin,<sup>3</sup> so that ignoring linkage disequilibrium leads to a substantial overestimation of the region of stability. In view of the fact that the region of stability given by Jain and Allard was too small for the case of one locus for which an exact solution is known, we thought it would be worthwhile to examine their report in general, using a somewhat more exact numerical method.

This paper will show that for the quadratic deviations model, the introduction of linkage *increases* the region of stability over that given by Lewontin<sup>3</sup> and Kojima<sup>2</sup> rather than decreasing it as more recently reported by Jain and Allard.<sup>1</sup> While this increase is small for free recombination, it is quite marked for tight linkage. The region of stability obtained with the assumption of linkage equilibrium is perhaps at its minimum. Disregarding linkage disequilibrium may be considered as a case of linkage with a very high recombination value, such that in every generation

crossing-over occurs to such a large extent that the product of coupling gametes equals the product of repulsion gametes. Tight linkage increases the region of stability and results in greater linkage disequilibrium.

Wright's quadratic deviation model for two loci was considered, in which the fitness of a phenotype falls off as the square of the deviation of that phenotype from an optimum. We assume that each of the two loci has two alleles, that the contribution from each locus is equal, that there is random mating among the selected individuals, that they are linked with a recombination value of  $R$ , and that for the  $j$ th locus, the phenotypes of the three zygotic types are:

$$\begin{array}{lll} B_j B_j & B_j b_j & b_j b_j \\ 2a & (1+h)a & 0 \end{array}$$

where  $a$  is the contribution of a favorable allele, and  $h$  is degree of dominance.

It should be clearly understood that the phenotype and the optimum referred to in this paper are not absolute, but relative as determined by two loci. In other words, we are assuming that all other loci are fixed and that their contribution to the phenotype is zero.

The fitness,  $W$ , of an individual is determined by the expression:

$$W = 1 - K(P - O)^2,$$

where  $K$  is a constant whose value for convenience is taken to be equal to the reciprocal of maximum value of  $(P - O)^2$ ,  $P$  is the phenotype of an individual, and  $O$  is optimum phenotype.

The equations for change of frequency of the four gametic types each generation are given by Lewontin and Kojima.<sup>4</sup> For each parameter set examined, we began at linkage equilibrium and with gene frequencies equal to 0.37 and 0.79 at the two loci. The gene frequencies and gametic frequencies in successive generations were calculated using a Fortran program for the IBM 7094 until no change in gametic frequency was observed in the seventh decimal place. This often required several thousand generations. The point reached by the process was considered an equilibrium value.

*Test for Stability.*—The equilibrium frequencies of the three types of gametes (AB, Ab, aB) were disrupted in the following eight ways. The disrupted frequency of the fourth type (ab) was found by difference.

$$\begin{array}{llll} +++ & +-+ & +-- & --+ \\ ++- & -++ & -+- & --- \end{array}$$

Here plus indicates an addition and minus a subtraction of 10 per cent of the equilibrium frequency to and from itself. In those cases where the equilibrium frequency was too close to fixation to be perturbed by 10 per cent, perturbation was 1 per cent. In some cases perturbation could be done in only four of the above eight ways because of the closeness of the frequencies to 0 or 1. The equilibrium frequency was considered as stable if in all of the above eight (four) cases, optimizing selection, starting with the disrupted frequencies, led to the same original equilibrium values.

The other method used for the stability test was to disrupt the equilibrium gene frequencies at both the loci in four ways: ++, +-, -+, --. Equilibrium

was considered stable if disrupted gene frequencies in all four cases returned to the same equilibrium frequencies.

Recombination values of 0.50 and 0.01 were considered. As optimizing selection continued, linkage disequilibrium was generated. In cases where the equilibrium gene frequency was close to fixation, linkage disequilibrium was very small but never zero.

Combinations of values of optimum and degree of dominance at which equilibrium was reached under the quadratic deviation model for two loci are given in Figure 1. Values of the optimum scaled in the units of gene effect,  $a$ , are shown along the ordinate. Values of the levels of dominance are represented along the abscissa. The shaded region represents the region of stability where both the loci are segregating.

For recombination of 50 per cent, the points of stability lie in the region  $BCD$ . This region lies within the band of width  $a$  formed by two dashed lines. At lower levels of dominance, the region is narrower and becomes wider as the value of  $h$  approaches but does not reach 1.0. For  $0 \leq h \leq 0.20$  and  $h = 1.0$ , there is no value of the optimum which gives stable equilibrium. The upper bound of the region coincides exactly with that found by Kojima<sup>2</sup> and Lewontin,<sup>3</sup> but is quite different from that shown by Jain and Allard.<sup>1</sup> As regards the lower bound of the region, Jain and Allard<sup>1</sup> agreed with Kojima<sup>2</sup> and Lewontin.<sup>3</sup> In our study the lower bound is similar to that reported by these workers for  $0.20 < h < 0.90$ , but markedly differs for values of  $h$  between approximately 0.90 and 1.0. These workers showed that as  $h$  increases beyond about 0.90 and approaches 1.0, the region of stability disappears rapidly. In our study the region continued to exist even at  $h = 0.99$ . Stable equilibrium was reached at  $3.0 \leq \text{optimum} \leq 3.9$  with  $h = 0.99$ . The region  $BCD$  is slightly larger than that shown by Kojima<sup>2</sup> and Lewontin,<sup>3</sup> and much larger than that reported by Jain and Allard.<sup>1</sup> Ignoring linkage disequilibrium does not lead to substantial overestimation of the region of stability as reported by Jain and Allard,<sup>1</sup> but would result in a slight underestimation. The amount of underestimation increases as the recombination value decreases.

Recombination of 1 per cent greatly increases the region of stability, resulting in the maintenance of greater genetic variation. In Figure 1, extension of the region of stability toward the lower levels of dominance represents the additional region of stability due to tight linkage. The lower limits of the degree of dominance at which no stable equilibrium is reached now lie between 0.0 and 0.03, inclusive. At  $R = 0.50$ , the optimum of  $2.9a$  gave no stable equilibrium, whereas at  $R = 0.01$  the optimum of  $2.5a$  had several stable points. The upper bound is the same as with  $R = 0.50$ . The lower bound has changed considerably, and stretches even below the dashed line which forms a lower boundary of the band of width  $a$ . The additional region of stability due to tight linkage lies near the lower boundary where the

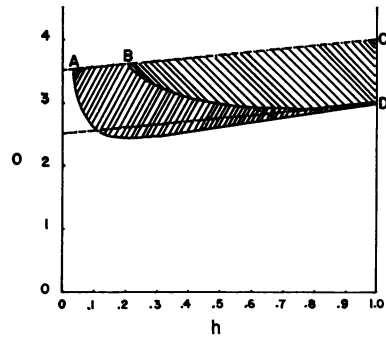


FIG. 1.—Region of stability. The ordinate is the value of the optimum scaled in units of gene effect,  $a$ . The abscissa is the dominance,  $h$ . Region  $BCD$  is for 50 per cent recombination, and region  $ACD$  is for 1 per cent recombination. At  $h = 1.0$  there is no equilibrium.

TABLE 1  
LIMITS OF OPTIMUM VALUES IN THE REGION OF STABILITY WITH SOME PARAMETERS AT  
STABLE EQUILIBRIUM

1 Per Cent Recombination					50 Per Cent Recombination				
<i>h</i>	<i>O</i>	<i>D</i>	$\bar{W}$	$p_1 = p_2$	<i>h</i>	<i>O</i>	<i>D</i>	$\bar{W}$	$p_1 = p_2$
0.05	3.0	-0.0544	0.9750	0.7545	0.22	3.5	-0.0001	0.9881	0.9635
	3.5	-0.0002	0.9875	0.9883		3.6	*	0.9920	0.9965
0.10	2.6	-0.1577	0.9812	0.5785	0.30	3.3	-0.0011	0.9812	0.8869
	3.5	-0.0005	0.9877	0.9773		3.6	*	0.9921	0.9843
0.20	2.5	-0.1862	0.9852	0.5376	0.35	3.2	-0.0018	0.9777	0.8484
	3.5	-0.0015	0.9881	0.9576					
0.30	2.5	-0.1919	0.9848	0.5260	0.40	3.1	-0.0026	0.9739	0.8102
	3.6	-0.0003	0.9921	0.9810					
0.40	2.6	-0.1856	0.9815	0.5321	0.45	3.1	-0.0025	0.9736	0.8064
	3.6	-0.0009	0.9924	0.9660		3.7	*	0.9955	0.9932
0.50	2.6	-0.1885	0.9785	0.5213	0.50	3.0	-0.0033	0.9689	0.7682
	3.7	-0.0001	0.9956	0.9859					
0.60	2.7	-0.1785	0.9733	0.5302	0.60	3.0	-0.0029	0.9668	0.7636
	3.7	-0.0003	0.9957	0.9766		3.7	*	0.9957	0.9781
0.70	2.8	-0.1609	0.9674	0.5479	0.70	3.0	-0.0025	0.9638	0.7631
	3.8	*	0.9980	0.9915		3.8	*	0.9980	0.9918
0.80	2.9	-0.1254	0.9612	0.5804	0.85	3.0			
	3.8	*	0.9980	0.9883		3.9	*	0.9995	0.9980
0.90	3.0	-0.0532	0.9566	0.7095	0.90	3.0	-0.0006	0.9550	0.5965
	3.9	*	0.9995	0.9973		3.9	*	0.9995	0.9973
0.98	3.0	-0.0032	0.9510	0.5417	0.99	3.0	*	0.9510	0.5156
	3.9	*	0.9995	0.9990		3.9	*	0.9995	0.9995

Blank cells indicate that the given combinations of *h* and *O* were not tried.  
\* Indicates very small negative values.

equilibrium gene frequencies are near 0.5. This leads to fewer chances for the equilibrium frequencies to go to fixation by drift, and thus results in the maintenance of greater genetic variation for a longer time.

Table 1 gives the values of optimum (*O*) and levels of dominance (*h*) which represent some stable equilibrium points near the boundary of the region of stability, together with the gene frequencies at equilibrium ( $p_1$  and  $p_2$ ), the linkage disequilibrium (*D*), and mean fitness ( $\bar{W}$ ). It is to be understood that the upper and lower values of the optimum resulting in stable equilibrium at a given level of dominance are not the exact limits. They represent the limits tried closest to the boundary. For example, at  $R = 0.50$  and  $h = 0.30$ , the upper and lower values of the optimum are given as 3.6*a* and 3.3*a*, respectively. These are not the exact limits. From Figure 1 it is clear that the exact limits are between 3.6*a* and 3.7*a* for upper limit and between 3.2*a* and 3.3*a* for lower limit.

*Summary.*—The conditions for stability of gene frequency equilibrium have been investigated for natural selection favoring an intermediate optimum phenotype with the so-called "quadratic deviations" model. We find, contrary to the report of Jain and Allard, that tightening the linkage between the genes controlling the character *increases* the region of stability of equilibrium over that given by Lewontin and Kojima, on the assumption of no linkage. When recombination is about 1 per cent, almost any value of dominance can lead to stable gene frequency equilibrium.

\* This work was performed under Atomic Energy Commission contract AT(11-1)-1437.

<sup>1</sup> Jain, S. K., and R. W. Allard, these PROCEEDINGS, 54, 1436-1443 (1965).

<sup>2</sup> Kojima, K., these PROCEEDINGS, 45, 989-993 (1959).

<sup>3</sup> Lewontin, R. C., *Genetics*, 50, 757-782 (1964).

<sup>4</sup> Lewontin, R. C., and K. Kojima, *Evolution*, 14, 458-472 (1960).

<sup>5</sup> Robertson, A., *J. Genet.*, 54, 236-248 (1956).

<sup>6</sup> Wright, S., *J. Genet.*, 30, 257-266 (1935).