GENE FLOW AND SELECTION IN A CLINE

MONTGOMERY SLATKIN

Department of Theoretical Biology, The University of Chicago, Chicago, Illinois 60637

Manuscript received March 22, 1973
Revised copy received July 9, 1973

ABSTRACT

A model of the effect of gene flow and natural selection in a continuously distributed, infinite population is developed. Different patterns of spatial variation in selective pressures are considered, including a step change in the environment, a "pocket" in the environment and a periodically varying environment. Also, the problem of the effect of a geographic barrier to dispersal is analyzed. The results are: (1) there is a characteristic length scale of variation of gene frequencies, $l_c = l/\sqrt{s}$. The population cannot respond to changes in environmental conditions which occur over a distance less than the characteristic length. The result does not depend either on the pattern of variation in selective pressures or on the exact shape of the dispersal function. (2) The reduction in the fitness of the heterozygote causes a cline in gene frequencies to become steeper. (3) A geographic barrier to dispersal causes a drastic change in the gene frequencies at the barrier only when almost all of the individuals trying to cross the barrier are stopped.

SPATIAL variation in the intensity of natural selection can play an important part in determining the genetic structure of natural populations. The difference between the allopatric speciation theory proposed by MAYR (1963) and the sympatric speciation theories of PIMENTEL and STONE (1967) and others is the amount of flow which is necessary to prevent the genetic differentiation of two populations. In the allopatric theory a small amount of gene flow is enough to prevent the evolution of reproductive isolating mechanisms. The assumption for the theory of sympatric speciation is that if differences in selection pressures are large enough, then reproductive isolating mechanisms can evolve even in the presence of a large amount of gene flow. A quantitative analysis of gene flow and selection is necessary to determine the amount of divergence that can result from spatially varying selective forces.

A second and perhaps more practical reason for developing a model of gene flow and selection is to increase our understanding of the causes of the observed spatial patterns of gene frequencies. One of the ways to measure the strength of selection in nature is to measure the rate of change in gene frequencies in a cline. HALDANE's (1948) original work on this subject was motivated by the problem of measuring selection in *Mus musculus* and has been used by others to estimate the strength of selection in other natural populations (KETTLEWELL and BERRY 1961).

In this paper, I develop a model from a simplified set of assumptions about

gene flow and selection and relate the implications of the model to the theoretical work which has been done previously on the subject. Then, I go on to consider cases which have not been previously analyzed—specifically, the effect of reduced or increased heterozygote fitness and the effect of a geographic barrier to migration. The last two topics will be discussed in relation to some observational data from the literature.

ASSUMPTIONS

The basic assumptions for the model are as follows:

(1) A population is continuously distributed in a region and is allowed to vary in only one spatial direction.

(2) The effects of genetic drift are ignored so that the gene frequencies after mating are given by the HARDY-WEINBERG relation.

(3) Generations in the population are discrete and non-overlapping.

(4) A single generation is made up of three separate steps: mating and the production of offspring, natural selection, and the movement of individuals to other locations to find mates and begin the next generation.

(5) Mating and selection of the offspring take place at each location independently before the offspring disperse.

(6) There are no genetic differences in dispersal patterns of individuals, and no mortality occurs during dispersal.

(7) Only density-independent selection is being considered.

The validity of assumption (1) depends on the particular population under consideration. This assumption would be true for organisms which are relatively evenly distributed in their habitat, such as animals in the intertidal community or grasses in a field. It is not likely to be true for organisms which have a very patchy distribution, such as insects living only in fallen logs in a forest. The restriction to one spatial dimension is strictly for convenience and the extension of the model to two or even three spatial dimensions is simple and straightforward. Assumption (2) is certainly untrue although it may be nearly valid when the effective population size is great enough at each location in the habitat so that drift is relatively weak. Certainly, the first extension of this model must be to include the effects of genetic drift.

Assumptions (3) and (4) are the usual ones made in the development of population genetic models. Assumption (5) is equivalent to the assumption that the location of birth of an individual determines the selective forces which will act on it before it mates. This assumption is valid if most of the selection is acting at an early stage in the life cycle. If selection on the character of interest is also acting late in the life cycle, possibly affecting the choice of mates (sexual selection), then a different assumption must be made. The selection acting would depend both on the initial and final locations of an individual.

Assumption (6) will be valid when there is no difference in the ability of the different genotypes to disperse and when there is no differential habitat preference by the different genotypes.

Also, I assume the region is infinite in extent. This is done for mathematical convenience and in any applications of the model the possible effects of the boundaries of the region have to be considered. The justification for this assumption is that it allows the examination of the effects of gene flow and selection without other complicating factors.

THE MODEL

We consider a single locus with two possible alleles (A and a), and describe the population by the frequency of A at every location, x, and at every time, t, $p(x,t)$. This description is sufficient since we are ignoring the effects of density (assumption 7). Initially, let us consider relative viabilities of the form

$$\begin{aligned} AA &: 1+s\gamma(x) \\ Aa &: 1 \\ aa &: 1-s\gamma(x) \end{aligned} \tag{1}$$

where s is a measure of the strength of selection and $\gamma(x)$ is a function which describes the spatial variation in selection intensity. We will not consider the possibility of γ varying in time. We chose s so that the maximum of $\gamma(x)$ is 1. At this point, s is not necessarily small, although most measured selective differences between genotypes are on the order of 5–10% or less, except for lethals.

Since we have assumed that mating and selection take place at each location independently, we can use the usual formulae of population genetics for this part of the generation (CROW and KIMURA 1970). Therefore

$$p'(x,t) = \frac{p(x,t) + s\gamma(x)p^2(x,t)}{1 + s\gamma(x)(p(x,t) - q(x,t))} \tag{2}$$

where $p'(x,t)$ is the frequency of A after mating and selection but before dispersal.

We describe the dispersal stage by a conditional probability distribution, $M(x,x')$, the probability that an individual moves from x' to x during the dispersal stage. Since $M(x,x')$ is a probability distribution in x, $M(x,x')$ must be normalized in x. Also, since there is no mortality during dispersal, $M(x,x')$ must be normalized in x'.

$$\int M(x,x')dx' = 1, \quad \int M(x,x')dx = 1 \tag{3}$$

where the range of integration is over the region of interest.

The contribution to $p(x,t+h)$ (where h is the generation time) of location x' is $M(x,x')p'(x',t)dx'$ so

$$p(x,t+h) = \int_{-\infty}^{\infty} M(x,x')p'(x',t)dx' \tag{4}$$

Combining (2) and (4) we get the final equation for the model

$$p(x,t+h) = \int_{-\infty}^{\infty} M(x,x') \frac{p(x',t) + s\gamma(x')p^2(x',t)}{1 + s\gamma(x')(p(x') - q(x'))} dx' . \tag{5}$$

In this model $p(x,t)$ is the frequency of A after dispersal and before mating.

An alternative formulation of this model can be made in terms of discrete variables (x_i) which represent discrete locations in the region of interest. The resulting model will be in terms of a sum rather than an integral over all of the locations of interest but it is essentially the same model. The latter formulation has been used by HANSON (1966) and by JAIN and BRADSHAW (1966) to calculate results in some special cases.

In this paper, we will be concerned with the equilibrium solution to (5) where $p(x,t+h) = p(x,t)$. The question of the stability of the equilibrium solution will be taken up elsewhere (SLATKIN, in preparation). Here, it is sufficient to say that in all the cases of biological interest there is a stable equilibrium solution. This is verified in the several examples by direct numerical computation. For convenience, we can write the equation for $q(x)$ equivalent to (5) and subtract that equation from (5) to get a new equation for the introduced variable $A(x) = p(x) - q(x)$.

$$A(x) = \int_{-\infty}^{\infty} M(x,x')A(x')dx' + \frac{s}{2}\int_{-\infty}^{\infty} M(x,x')\gamma(x')\frac{1-A^2(x')}{1+sA(x')\gamma(x')}dx' \quad (6)$$

The possible range of A is -1 to 1, corresponding to $p = 0$ and $p = 1$. The first term on the right-hand side of (6) represents the effect of dispersal alone on gene frequencies. The second term represents the effect of selection after the dispersal stage.

The simplest assumption we can make about the dispersal function, $M(x,x')$, is that it is a function of x-x' only. This form for M is reasonable when there is no habitat selection and when there is no barrier to dispersal. Later, I will consider the effect of a barrier to dispersal and will have to introduce another form for M. Migration functions of this type have been used by MALECÓT (1968) and by KIMURA and WEISS (1964) in models of genetic drift in spatially distributed populations.

We can assume that $M(x)$ has certain simple properties which can enable us to find the approximate solution to (6), at least in some cases:

(1) $M(x)$ is an even function of x which is equivalent to assuming that there is no preferential direction for dispersal.
(2) $M(x)$, considered as a probability distribution, should have finite moments of all order.
(3) For mathematical reasons, it is also necessary to assume that $M(x)$ is analytic (has derivatives of all orders) except at $x = 0$.

For any M which satisfies the above conditions, it is possible to reduce (6) to a differential equation (see APPENDIX). In addition, when the selection acting is weak (small s) it is possible to approximate the differential equation by the following equation:

$$-\frac{d^2A}{dx^2} = \frac{-s}{l^2}\gamma(x)(1-A^2(x)) \quad (7)$$

where $l^2 = \int x^2M(x)dx$, the second moment of M. Equation (7) is correct to order

s. That is, the difference between the exact solution obtained from (6) and the approximate solution obtained from (7) is not larger than s or some small multiple of s.

Another way to derive equation (7) is to assume that random dispersal of individuals is effectively a diffusion process with a diffusion constant equal to the second moment of M. FISHER (1937) first analyzed a similar problem in this way. Also, equation (7) can be derived by expanding M in a Taylor series about $x = 0$ in (6) and assuming that the first terms in the expansion must be approximately equal. HALDANE (1948) used this approach in considering the effect of a step change in selective intensities. The purpose of the discussion in the APPENDIX is to show that equation (7) is approximately correct under a wide variety of conditions. In particular, it is not necessary to assume anything about the form of the spatial variation in selective intensities. Nor is it necessary to assume any functional form for M, as long as it satisfies the assumptions listed above.

We can rewrite equation (7) in terms of another variable, $\xi = \sqrt{s}\, x/l$, to get

$$-\frac{d^2A(\xi)}{d\xi^2} = \frac{1}{2}\gamma(\xi)(1 - A^2(\xi)) \,. \tag{8}$$

By introducing the variable ξ, we can see that the appropriate description of the problem is not in terms of the average distance traveled at the dispersal stage, l, but $l/\sqrt{s}$. Since the coefficients on each side of (8) are of order unity, it appears that the balance between gene flow and selection is most easily seen in terms of ξ. From the form of (8) we could guess that if $\gamma(\xi)$ varies significantly over distances less than $\xi = 1$, then $A(\xi)$ will not reflect those variations. On the other hand, $A(\xi)$ should respond to changes in $\gamma(\xi)$ which occur over a distance greater than $\xi = 1$. We will verify our intuition about the expected properties of the solution to (8) in the examples treated below.

Based on the above discussion, we can define a length $l_c = l/\sqrt{s}$ (correspond to $\xi = 1$), as the *characteristic length* for the spatial variation in the frequencies of alleles. Regardless of the pattern of spatial variation in the selection intensities, we would not expect the gene frequencies to vary significantly over a distance less than the characteristic length. Therefore, the population could not respond to changes in selection which occur over distances less than the characteristic length, while it could respond to or "track" changes which occur over distances greater than the characteristic length. We will test this prediction by analyzing several examples in which particular forms for $\gamma(x)$ are chosen.

The existence of a characteristic length scale of variation for the population is related to LEVINS' (1968) concept of "environmental grain." A fine-grained environment is one for which the spatial variation in the environment is over a short enough length scale that the population is unable to respond. For a coarse-grained environment, the population can respond to the local variations. The importance of the result here is that the grain of the environment depends not only on the mobility of the species (as measured by l) but also on the strength of the selection being applied to the character. Therefore, it is possible to have a

situation in which the environment is coarse-grained with respect to one character, on which strong selection is acting, and fine-grained with respect to another, on which relatively weak selection is acting.

EXAMPLES

Solutions to (8) can be found for special functional forms for $\gamma(x)$. In each case, we must determine the relevant boundary conditions on $A(\xi)$ which are consistent with the biological problem, because of the loss in information in going from the integral to the differential equation. In this section, a few of these simple cases are treated in order to illustrate the behavior of systems which are governed by equation (8). The main point in all the examples is the importance of the characteristic length, $\xi = 1$ in this rescaled equation.

In order to test the validity of the approximations made in obtaining equation (8), numerical iterations of equation (5), the original equation for the model, were carried out, and the results compared with solutions to (8). To perform the numerical calculations, the model had to be reformulated in terms of a finite number of discrete locations, rather than an infinite continuum. The probability of an individual moving from location i to location j in a single generation is $M(i,j)$. $M(i,j)$ is a matrix and has been called the "migration matrix" by KIMURA and WEISS (1964) and others when analyzing problems involving genetic drift. At each of the locations, the same equations from population genetics apply between the dispersal stages. Therefore, the allelic frequencies at each location in the next generation are given by

$$p(i) = \sum_j M(i,j)p'(j) \tag{9}$$

where the $p'(j)$ are obtained from equation (2). The calculations are carried out by choosing initial values for the $p(i)$ and iterating according to (9) until an equilibrium is approached.

In each of the examples below I compare the numerical solution of (9) with the solution to (8). In the numerical calculation, we might expect that the boundaries introduced by having a finite number of locations would have a significant effect on the results. That possibility was tested by running the same examples with different locations of the boundaries. It was found that when the boundary was placed sufficiently far from the region of interest, moving the boundary had no effect on the results. It is reasonable to assume that the results from the calculations made when the boundary location is determined in this way are a good approximation to the exact solution in an infinite region.

The first example is the so-called step environment which is modeled by $\gamma(\xi) = \theta(\xi)$ where $\theta(\xi) = +1$ for $\xi > 0$ and $\theta(\xi) = -1$ for $\xi < 0$. This form for γ represents an abrupt change in some environmental factor which would reverse the relative advantage of the homozygotes. The necessary boundary conditions are that $A(\xi)$ approaches $+1$ as ξ approaches $\pm\infty$. Since $\gamma(\xi)$ is an odd function, the solution to (8) is also odd and is the same as the solution to

$$-\frac{d^2}{d\xi^2}A(\xi) = \frac{1}{2}(1-A^2(\xi)) \tag{10}$$

in $0 < \xi < \infty$ with the boundary conditions that $A(0) = 0$ and $A(\infty) = 1$. The condition that A and A' be continuous at 0 are automatically satisfied. There is a discontinuity in $A''(\xi)$ at $\xi = 0$ caused by the discontinuity in $\gamma(\xi)$. The solution to (10) is

$$A(\xi) = -2 + 3\tanh^2(\xi/2 + \tanh^{-1}\sqrt{2/3}) \,. \tag{11}$$

The maximum slope of the cline, at $\xi = 0$, is $\sqrt{2/3}$ in the scaled variables or $1/l\sqrt{2s/3}$ in the unscaled variables. This is often the only number that can be measured.

The analytic solution (11) was compared to the results from the numerical calculations made in the manner described above. Two different choices for M were chosen, exponential and normal. Thus, we can determine whether the particular functional form of M has very much effect on the results. The results are shown in Table 1. In each of the three sections, the first column was obtained by evaluating (11) at the various points; the second and third columns and the values from the equilibrium solution were obtained by using the normal and

TABLE 1

A comparison of the actual values of A(x) *obtained by using the numerical iteration of the integral equation with gaussian* M (b) *and exponential* M (c) *and the values for* A(x) *from equation (10)* (a)

x/l	(a)	(b)	(c)
		$s = 0.05$	
0.5	.1159	.1133	.0888
1.5	.3158	.3197	.2470
2.5	.4759	.4857	.3817
4.5	.6991	.7128	.5892
6.5	.8303	.8427	.7308
8.5	.9053	.9147	.8251
10.5	.9475	.9540	.8869
		$s = 0.1$	
0.5	.1225	.1512	.1225
1.5	.3320	.4157	.3297
2.5	.4971	.6085	.4931
4.5	.7215	.8890	.7894
6.5	.8487	.9803	.9369
8.5	.9186	.9963	.9790
		$s = .5$	
0.5	.4574	.2633	.2408
1.5	.8581	.6626	.5661
2.5	.9649	.8597	.7552
3.5	.9914	.9424	.8632
4.5	.9979	.9765	.9242

exponential migration functions. These results are in agreement with the predictions based on the analytic techniques. The error made in the cases when s is small (.1 and .05) is of order s. Furthermore, the difference between the calculations using the normal and the exponential migrations functions are of the same order of magnitude. We would expect that the approximations not be valid for larger values of $s(s = 0.5)$, and this is the case. These results allow us to use the approximate differential equation with some confidence.

Although the question of the uniqueness and stability of the equilibrium solution will not be considered here, it is worth mentioning that in the above example, several different sets of initial conditions were tried and the same solutions were always obtained at equilibrium. That suggests that our intuition is correct and that the equilibrium solution is unique and stable. The mathematical aspects of the problem will be analyzed in a later paper (SLATKIN, in preparation).

HALDANE (1948) was the first to treat the case of the step environment. He derived an equation analogous to (10) and he applied the model to examples with varying degrees of dominance. While the exact shape of the cline depends on the degree of dominance at the locus, the general character of the solution does not change. Therefore, the definition of the characteristic length does not depend on the degree of dominance at the locus.

An example similar to the step environment above is one for which the change in selective values is more gradual. This situation is modeled by

$$\begin{aligned} \gamma(\xi) &= -1 \quad \xi < -k \\ \gamma(\xi) &= \xi/k \quad -k < \xi < k \\ \gamma(\xi) &= +1 \quad \xi > k \end{aligned} \tag{12}$$

The equation for this new problem will have the same boundary conditions as in the previous case and the solution is still an odd function of ξ. Thus, $A(\xi)$ satisfies

$$-\frac{d^2}{d\xi^2} A(\xi) = \frac{\xi}{2k} (1-A^2(\xi)) \quad 0 < \xi < k \tag{13a}$$

$$-\frac{d^2}{d\xi^2} A(\xi) = \frac{1}{2} (1-A^2(\xi)) \quad k < \xi < \infty \tag{13b}$$

with $A(0) = 0$ and $A(\infty) = 1$. In addition, A and A' must be continuous at $\xi = k$. The solution to (13b) is

$$A(\xi) = -2 + 3\tanh^2 \left(\frac{\xi - k}{2} + \tanh^{-1} \frac{2 + A_k}{3} \right) \tag{14}$$

where $A_k = A(\xi = k)$. There is no analytic solution to (13a), so a numerical method was used. In Figure 1, $A(\xi)$ is plotted against ξ for different values of k. For $k < 1$, the solutions are quite similar. In fact, it would be difficult to distinguish them on the basis of any observations. For $k > 1$, $A(\xi)$ is different for different values of k, so for more gradual changes in the selective values, the rate of change in the frequencies of the alleles is more gradual.

FISHER (1950) considered the problem of the effect of gradual environmental

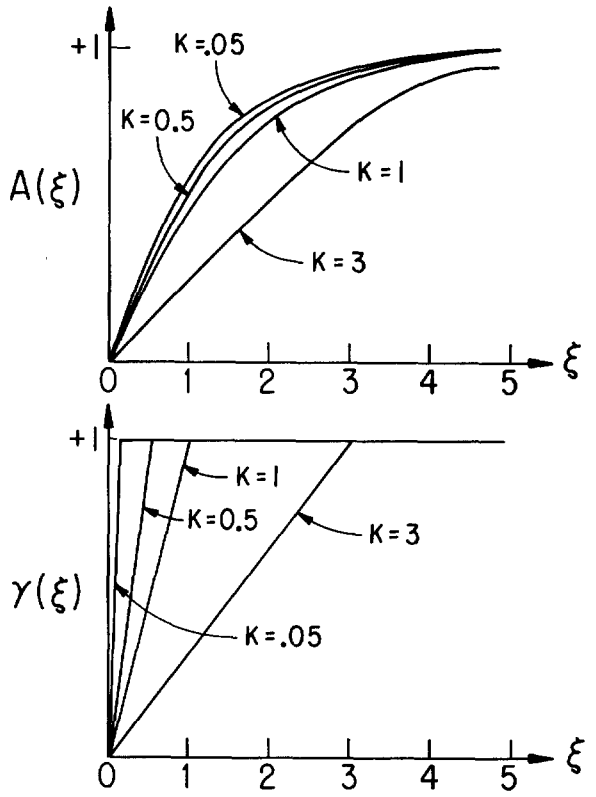

FIGURE 1.—Graphs of $A(x)$ *vs.* x for the case of a gradual change in the environment. These graphs were obtained using the approximate differential equation (13).

change of gene frequencies. In that paper, he ignored the fact that the linear change in the fitness of the genotypes could not apply over an indefinitely large range. FISHER's argument, that the slope of the fitnesses function, γ, is unimportant and can be absorbed into the rest of the analysis, is incorrect. There are two significant length scales in the problem—the length scale associated with the change in the fitnesses, k, and the characteristic length scale of variation for the population, l_c. A comparison of these two lengths is needed to provide an understanding of the results. In one extreme, when the slope of the environmental change is small, large k, the gene frequencies closely follow the change in fitnesses, and in these cases, FISHER's argument is valid, as long as it is applied only to the interior region of the cline.

ENDLER (1973) discusses several models of gene flow and selection, including effect of a gradual change in the selective values of the homozygotes (the gradient model). He calculates the effect of different amounts of gene flow (different values of l) for a particular selection function (constant k). To compare ENDLER's results to those given above, we plot $A(x)$ against x for $k = 5$ (Figure 2). We can see that when l is much less than k, the cline is very steep, in agreement

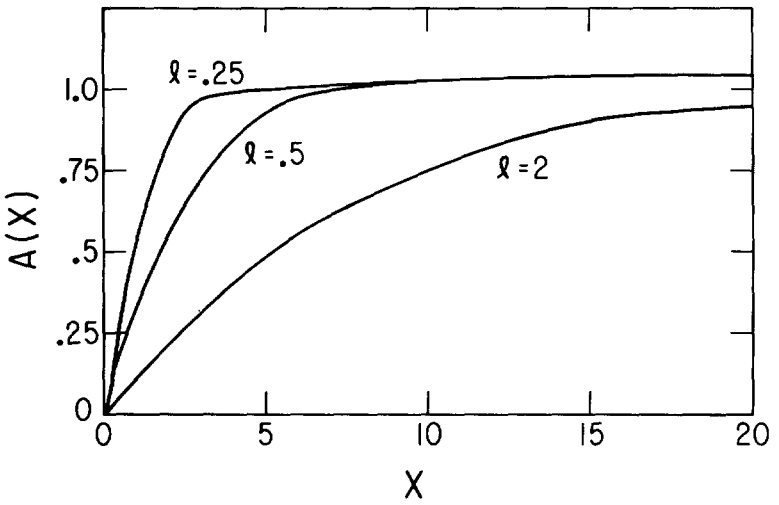

FIGURE 2.—$A(x)$ *vs.* x for a gradual change in the selection intensities. The selection was held constant and the migration distance, l, was changed. The curves were obtained from (13).

with ENDLER's results obtained from a direct iteration of the basic equation. However, as l increases, the steep cline is rapidly smoothed over. On the basis of his computations, ENDLER concluded that the effect of gene flow on this model is small. From Figure 2 we can see that the conclusion depends on how much gene flow is allowed. In ENDLER's study, gene exchange is possible only between adjacent demes, so even with the maximum amount of gene flow, l could not be greater than the interdeme distance. If longer distance dispersal is permitted, the effects of gene flow can be much greater.

If γ has the form

$$\begin{aligned} \gamma(\xi) &= +1 \qquad |\xi| > l_o \\ &= -1 \qquad |\xi| < l_o \end{aligned} \tag{15}$$

then we have a model of a situation in which there is a region of finite size, or a "pocket" in the environment (HANSON 1966), where one homozygote is favored, surrounded by a region where the other homozygote has the selective advantage. In this example, $A(\xi)$ is an even function and the boundary conditions are that $A(\xi)$ approaches 1 as ξ approaches $\pm\infty$. Thus we want the solution to the system

$$\frac{d^2}{d\xi^2} A(\xi) = \frac{1}{2}(1 - A^2) \qquad 0 < \xi < l_o \tag{16a}$$

$$\frac{d^2}{d\xi^2} A(\xi) = -\frac{1}{2}(1 - A^2) \quad l_o < \xi < \infty\ . \tag{16b}$$

The solution to (16a) and (16b) can be found directly. A quantity of interest is the maximum difference in gene frequencies, which is measured by $A(0)$. Figure 3 shows a plot of $A(0)$ against l_o, the size of the region measured in units of l_c. Notice that if $l_o < .5$ (i.e., the size of the region is less than the critical

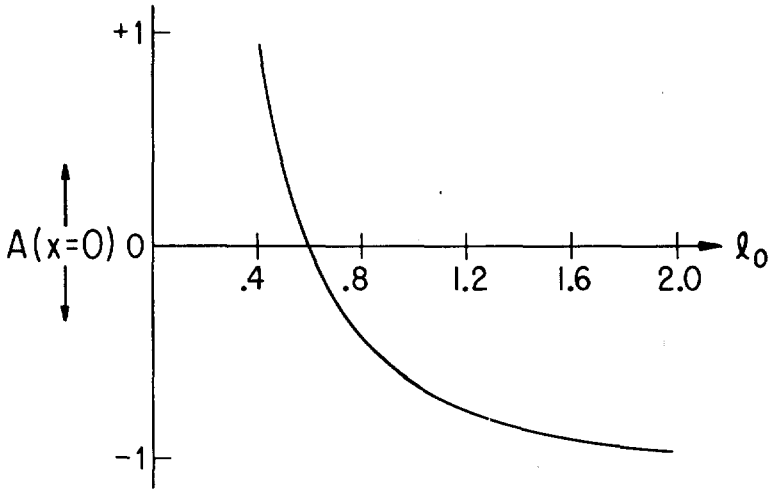

FIGURE 3.—Graph of the minimum of A, $A(0)$, as a function of the size of the "pocket" in the environment, l_0. These values were obtained using the approximate differential equation (16).

length), then $A(0)$ is nearly 1 and dispersal masks the presence of such a region. This is in agreement with HANSON's (1966) results, which were obtained using a computer model similar to the one described previously in this paper.

Another example will further illustrate the importance of the critical length of the system. If $\gamma(x)$ is defined to be the periodic function

$$\begin{aligned} \gamma(\xi) &= -1 \qquad 0 < \xi < 2l_2 \\ &= +1 \qquad 2l_2 < \xi < 2l_1 + 2l_2 \end{aligned} \tag{17a}$$

$$\gamma(\xi + 2l_1 + 2l_2) = \gamma(\xi) \tag{17b}$$

then we would expect the equilibrium solution to be also periodic in x. We want the solution to

$$\frac{d^2}{d\xi^2} A(\xi) = \frac{1}{2}(1 - A^2(\xi)) \quad -0 < \xi > 2l_2 \tag{18a}$$

$$\frac{d^2}{d\xi^2} A(\xi) = -\frac{1}{2}(1 - A^2(\xi)) \quad 2l_2 < \xi < 2l_1 + 2l_2 \tag{18b}$$

with the additional condition that A and A' be continuous $x = 0$ and $x = 2l_2$ and that

$$A(2l_1 + 2l_2) = A(0) \, . \tag{19}$$

The numbers of real interest are maximum and minimum values of A and some estimate of the average value of A. A sample solution is shown in Figure 4. Figure 5 shows plots of $A_0 = A(l_1)$, $A_1 = A(2l_1)$, and $A_2 = A(2l_1 + l_2)$, as functions of l_2 for fixed l_1 (measured in units of l_c). Notice that when $l_1 = .5$, there is little difference between the maximum and minimum frequencies. In this case, the population is not able to respond to the variation in the selective values. Except

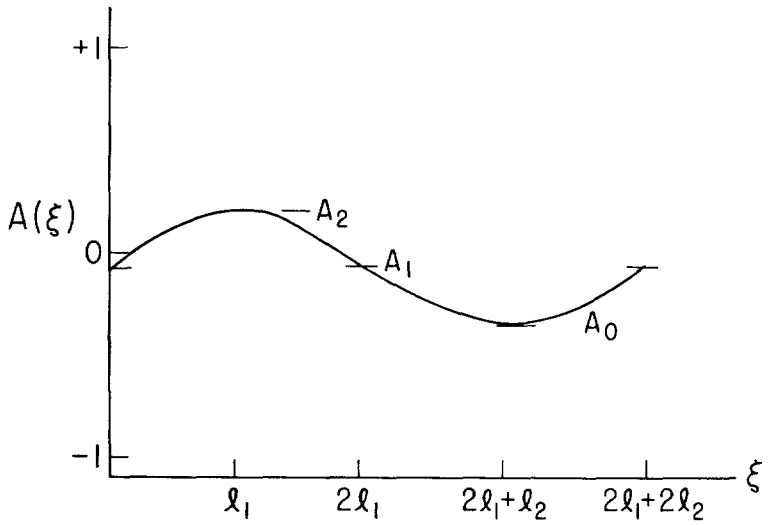

FIGURE 4.—A representative solution in the case of a periodically varying environment.

when l_1 and l_2 are nearly equal, one or the other allele is eliminated. This result is the same as one derived by LEVINS (1968) using his fitness set argument on fine-grained and coarse-grained environments. In the case of coarse-grained environments, the prediction of the fitness set model is that the species would adopt an intermediate strategy with both alleles present. While one genotype is common in one habitat type and the other in the other habitat type, in a sample taken from a large enough area, a mixture of genotypes would be found. The area sampled must be a large enough area for the "intermediate" strategy to be observed.

REDUCED HETEROZYGOTE FITNESS

In the previous section, various examples have been considered in which the fitness of the heterozygote is the average of the fitnesses of the homozygotes. If the fitness of the heterozygote is less than 1, then the clines predicted in the previous sections should be steepened. To illustrate this effect, I will show the change in the spatial pattern in the step environment model. The fitnesses of the three genotypes are now assumed to be

$$AA\colon 1+s\gamma(x) \qquad Aa\colon 1-u \qquad aa\colon 1-s\gamma(x) \tag{20}$$

where u is a constant—for the moment, positive. The equilibrium equation for this model is

$$A(x)=\int_{-\infty}^{\infty}A(x')M(x-x')dx'+\frac{1}{2}\int_{-\infty}^{\infty}\frac{(uA(x')+s\gamma(x'))(1-A^2(x'))}{1-\frac{u}{2}(1-A^2(x'))+s\gamma(x')A(x')}dx'. \tag{21}$$

We consider the case in which

$$1>u>>s$$

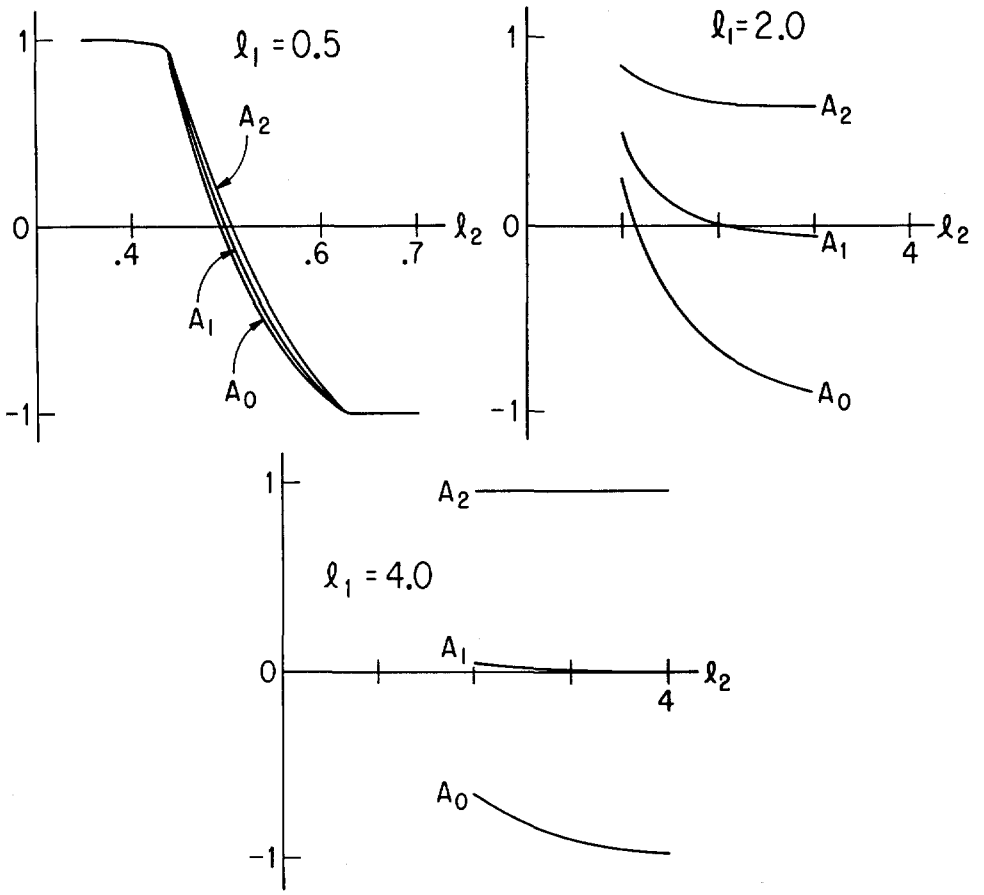

FIGURE 5.—Graphs of the maximum, minimum, and average values of $A(x)$ as a function of length of intervals, of the periodic environment, for given values of the other l_1. These values were obtained using the approximate differential equation (18).

Following the procedure in the APPENDIX, the basic equation is

$$-\frac{d^2}{dx^2}A(x) = \frac{u}{2l^2}\frac{A(x)(1-A^2(x))}{1-\frac{u}{2}(1-A^2(x))}. \tag{22}$$

Equation (22) is correct to order s/u, which we have assumed to be small. With sufficient effort equation (22) could be integrated to give A as an implicit function of x. The only quantity found here is the maximum slope of the cline.

$$A'(0) = \frac{1}{l}\left[1-2\left(1-\frac{1}{u}\right)\log\left(1-\frac{u}{2}\right)\right]^{1/2} \tag{23}$$

Therefore, when the fitness of the heterozygote is much less than the fitnesses of either of the homozygotes, then the structures of the cline is independent of the

exact values of the homozygote fitnesses. The selection on the homozygotes determines the location of the cline but the selection of the heterozygote determines the slope.

The analysis carried out above can just as well be applied to the system where there is a gradual change in the environmental conditions affecting the fitness of the homozygotes, i.e., where $\gamma(x)$ has the form given in equation (12). With $u >> s$, $\gamma(x)$ acts only to determine the boundary conditions for $A(x)$. Therefore, a relatively steep cline could be present even when there is no sudden change in the environment. The so-called "area effects" in *Cepaea nemoralis* and *C. hortensis* which have been extensively described and discussed in the literature (FORD 1964, and *Studies in Cepaea*, 1968, provide the most comprehensive review of this subject) might be the result of this kind of balance between selection and gene flow. The purpose of the discussion here is not to try to provide an explanation for the area effects, which involve many factors outside the scope of this model, but to illustrate some of the implications of the model for problems of practical interest.

The European land snails, *C. nemoralis* and *C. hortensis*, have distinctive color and banding patterns of the shell which have been found to be under relatively simple genetic control. Furthermore, the different morphs have, in many cases, been found to have a selective advantage in different habitats by being more or less visible to the potential avian predators. For example, the brown, unbanded form is cryptic in grass. Much of the geographic variation in Cepaea can be accounted for by this mechanism. However, some cases cannot be so explained. There are regions which have populations in which different banding and color patterns are dominant and between which there is a relatively rapid change in the frequency of the different morphs. In these regions, such as the chalk downs of England, none of the morphs present seem to have any cryptic value. This phenomenon has been called the area effect.

There are two explanations which have been put forward for the area effects. First, CAIN and CURRAY (1963) suggest that the color and banding patterns are indications of some other physiological adaptation to selection which is not apparent to human observers. In this case, the area effects are a reflection of the adaptations to local changes in the habitat. In support of this hypothesis, CAIN and CURRAY have found a strong correlation of some morphs with particular microhabitats. For example, the brown color morph is closely associated with frost hollows. However, such correlations are not always found, particularly with the different banding forms, and it is difficult to apply this hypothesis to all observations of area effects. GOODHARDT (1963) has suggested that some area effects are historical in origin. Small, genetically different, founder populations began in different parts of a region. As these populations grew, coadapted gene complexes formed which prevented the interbreeding of the populations when they came into contact. With the explanation, the area effects are non-adaptive. The difficulty with GOODHARDT's hypothesis is that there is evidence that the area effects have persisted for thousands of years (CURRAY and CAIN 1968). Therefore the different coadapted gene complexes must be identical in fitness.

There is another explanation for the maintenance of area effects which is a compromise between the two given above. If coadapted gene complexes did have the chance to evolve in the different isolated populations, then it is likely that this would serve to reduce the fitness of the heterozygotes created by crosses between the individuals from the two populations. If, in addition, some character which is controlled by part of the coadapted gene complex is subject to selective forces which gradually change with distance, then these two mechanisms could produce the area effects. The region of change in the selection on the homozygotes could be much longer than the size of the habitat under consideration. Using the argument based on the model, the cline in gene frequencies could be much steeper than the rate of change in the selective values. It is possible, then, to maintain the area effects with relatively weak selection against some physiological character which is linked to the banding and color patterns and a reduction in the fitness of the heterozygote.

Some calculations, using the numerical method described earlier, were carried out to illustrate this idea. $\gamma(x)$ had the form given by (11). The results of the calculations are shown in Figure 6. For comparison, the case with $u = 0$ is also shown. CLARKE (1966) has proposed a different type of model of area effects based on the effect of modifier genes.

If the fitness of the heterozygotes is only slightly smaller than unity, then we can write $u = \alpha s$ where α is of order one. The basic equation is

$$\frac{-d^2A}{d\xi^2} = \frac{1}{2}(\alpha A(\xi) + \gamma(\xi))(1 - A^2(\xi)) \tag{24}$$

with the boundary conditions that $A(0) = 0$ and $A(+\infty) = 1$. The first integral of (24) is

$$-\left(\frac{dA}{d\xi}\right)^2 = \frac{\alpha}{2} A^2(\xi)(1 - \frac{1}{2}A^2) + A - \frac{1}{3}A^3 + C \tag{25}$$

where C must be chosen so that $A' = 0$ when $A = 1$. Therefore

$$C = -\frac{2}{3} - \frac{\alpha}{4} \tag{26}$$

The slope of the cline at the origin is $\sqrt{-C}$. In terms of the unscaled variables, the effect of the reduced fitness of the heterozygote on the maximum slope of the cline is

$$\frac{dA(0)}{dx} = \sqrt{\frac{s}{l}}\sqrt{\frac{2}{3} + \frac{1}{4}\frac{u}{s}}. \tag{27}$$

For the third range of values of u, $u \ll s$, there is no effect on the lowest order solution.

If $-s < u < 0$, the equation (27) for the maximum slope of the cline is still valid. An increase in the heterozygote fitness reduces the slope of the cline. For $u < -s$, there is overdominance at every location. Therefore the boundary conditions at $x = \pm\infty$ must be changed to $A(\pm\infty) = \pm s/u$ (corresponding to $p =$

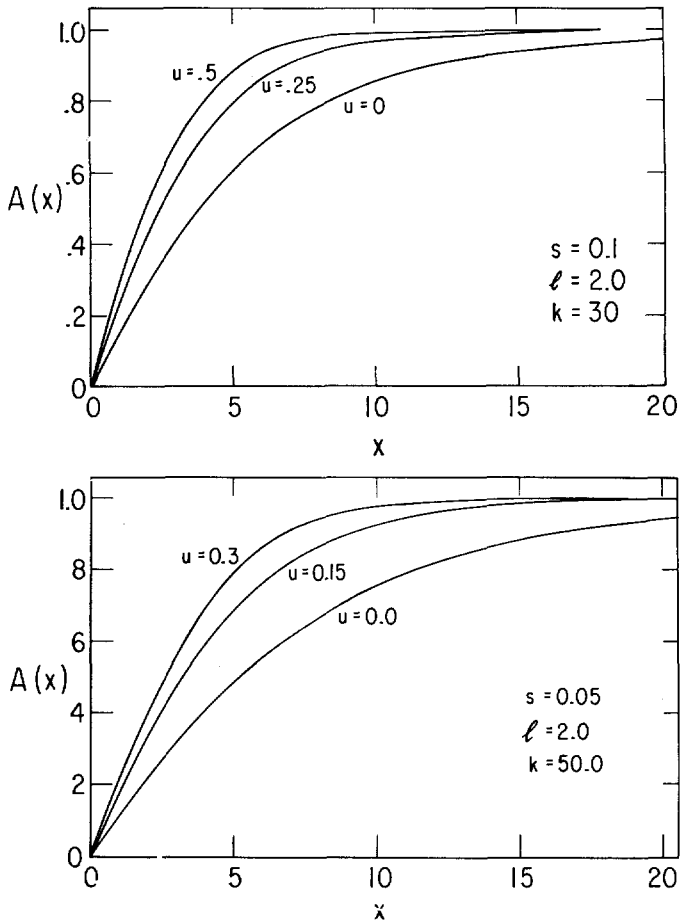

FIGURE 6.—Graphs of $A(x)$ *vs.* x obtained by using the numerical iteration of the exact equation (5) for the model, carried out as described in the text. In each case, the boundaries of the model were set at ± 50. The fitnesses of the three genotypes were

AA: $1+s\gamma(x)$
Aa: $1-u$
aa: $1-s\gamma(x)$

where $\gamma(x) = +1\ x > k$
$= x/k\ |x| < k$
$= -1\ x < -k$

$(u+s)/2u$ and $p = (u-s)/2u$)). In this case, the condition for determining C in (25) is $A' = 0$ when $A = u/s$, where $\alpha < -1$. The result is that the maximum slope of the cline is

$$\frac{dA(0)}{dx} = \sqrt{\frac{s}{l}}\sqrt{-\frac{s}{u}\left(\frac{1}{2}-\frac{s^2}{12u^2}\right)} \tag{28}$$

which decreases as u becomes larger in absolute value. Therefore as the fitness of the heterozygote increases, the cline becomes less steep.

GEOGRAPHIC BARRIER TO DISPERSAL

So far, we have considered examples for which the probability of dispersal between two points depends only on the distance between the points. That assumption could not be true if there were a physical barrier to dispersal at some location. There are several possible dispersal functions which could model the effect of a geographic barrier. A particularly simple one is found by assuming that all dispersing individuals travel the same distance as they would in the absence of the barrier, but that a certain fraction of the individuals which reach the barrier turn around and proceed in the other direction, traveling the same total distance. I will call this a "reflecting barrier". Mathematically, it can be described by a dispersal function $M(x,x')$ of the form

$$\begin{aligned} M(x,x') &= (1-k)M(x-x') && xx' < 0 \\ &= M(x-x') + kM(x+x') && xx' > 0 \end{aligned} \tag{29}$$

where $M(x\text{-}x')$ is the dispersal function of the type used in the previous sections and k is a measure of the strength of the barrier. It is convenient to use (29) because the normalization properties of M are preserved. The effect of a barrier to dispersal can be illustrated by considering the example of a step environment. With (29) the basic equation (6), becomes

$$\begin{aligned} A(x) = &\int_{-\infty}^{\infty} M(x-x')A(x')dx' + 2k\int_{0}^{\infty} M(x+x')A(x')dx' \\ &+\frac{s}{2}\int_{-\infty}^{\infty} M(x-x')\gamma(x')\frac{1-A^2(x')}{1+sA}dx' \\ &+ sk\int_{0}^{\infty} M(x+x')\gamma(x')\frac{(1-A^2(x'))dx'}{1+sA(x)}dx' \end{aligned} \tag{30}$$

for $x > 0$. We can still assume that $A(x)$ is an odd function but A is not necessarily continuous at $x = 0$. In fact, $A(0+)$ is found to be non-zero by letting x approach 0 from the positive direction. Equation (30) becomes

$$A(0+) = 2k\int_{0}^{\infty} M(x')A(x')dx' + sk\int_{0}^{\infty} M(x')\frac{1-A^2(x')}{1+sA(x')}dx'. \tag{31}$$

We can reduce (30) by the method described in the APPENDIX and find that the approximate equation is

$$-\frac{d^2A}{d\xi^2} = \gamma(\xi)(1-A^2(\xi)) \tag{32}$$

which is the same equation as in the case without the barrier. The difference is that $A(0)\neq 0$ in the present case. In other words, the balance between gene flow and selection on either side of the barrier is unchanged by the barrier. The barrier changes the boundary condition at the origin by reducing the number of individuals which cross that point. The solution to (32) is

$$A(x) = -2 + 3\tanh^2\left(\frac{\sqrt{s}\,x}{2l} + \tanh^{-1}\sqrt{\frac{2+3A(0+)}{3}}\right) \tag{33}$$

where $A(0+)$ must be determined from (32). We can find $A(0+)$ approximately by using the fact that the length scales of change of $A(x)$ and $M(x)$ are different. In (31), $A(x)$ can be replaced by $A(0+)+xA'(0+)$ to lowest order. From (33)

$$A'(0+) = \frac{\sqrt{s}}{l}\,\frac{2+A(0+)}{3} \tag{34}$$

and (31) becomes

$$A(0+) = kA(0+) + \frac{2\sqrt{sk}}{l}(1-A(0+))\int_0^\infty xM(x)dx\,: \tag{35}$$

The integral in (35) is proportional to l with the constant of proportionality dependent on the functional form of M. Therefore, $A(0+)$ is independent of l. The general dependence of $A(0+)$ on k can be easily found by rewriting (35) and observing that

$$(1-k)A(0+) = 0(\sqrt{s})$$

where $0(\sqrt{s})$ means of the order of magnitude of $\sqrt{s}$. For this condition to be satisfied, either $A(0+)$ or $1\text{-}k$ must be $0(\sqrt{s})$. Therefore, unless the barrier is very strong and almost all of the individuals trying to cross are stopped ($1\text{-}k \ll 1$), the effect of the barrier on the equilibrium gene frequencies is small. This result is valid, of course, only if the relative selection coefficient, s, is small. Figure 7 shows the results of numerical evaluation of the equilibrium solution which was

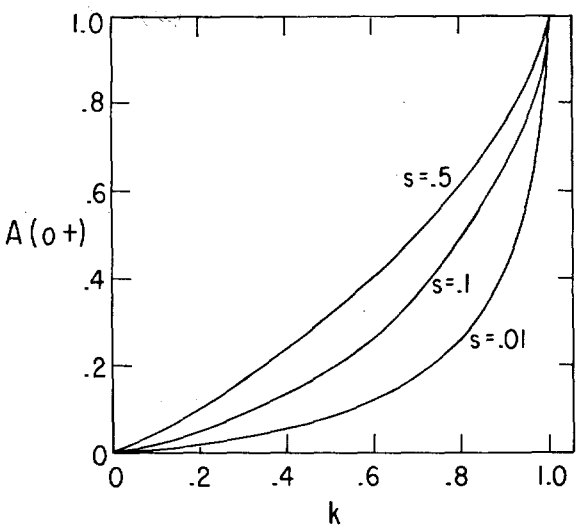

FIGURE 7.—A graph of $A(0+)$ obtained from the numerical iteration in the case of a geographic barrier to dispersal. In this case k is a measure of the strength of the barrier and $A(0+)$ of its effect.

carried out in the manner described earlier. $M(x\text{-}x')$ was assumed to have a normal form in these calculations.

A barrier to dispersal is much less effective in producing a steep cline than reduction in fitness of the heterozygote. A barrier alters the "effective fitness" of an individual in a region of width l about the barrier while the reduction of fitness of the heterozygote changes the effective fitness throughout the region of the cline. By effective fitness I mean the probability of survival of the offspring of an individual averaged over future generations, not simply the individual's chance of surviving to mate and produce offspring. This is similar to HAMILTON's (1964) "inclusive fitness".

A field study on the effect of a geographic barrier to dispersal on gene frequencies has been done by KETTLEWELL and BERRY (1968) on the Caradrinid moth, *Amethes glareosa*, in the Shetland islands. The darker form (*f. edda*) is produced by a single dominant gene which decreases in frequency from 98% in the north of the island to 1% in the south (KETTLEWELL 1961a,b; KETTLEWELL and BERRY 1961). KETTLEWELL (1961c) has shown that *f. edda* has a selective advantage of approximately 5% on the most northern island (Unst) because of differential predation by certain gulls. In a later study of this cline, KETTLEWELL and BERRY (1968) concentrated on the central part of the South Mainland where the frequency of *f. edda* decreases by 50% in 15 miles. They were especially interested in the effect of a potential geographic barrier to dispersal, the Tingwall Valley, which crosses the entire island in the middle of the area of maximum slope of the cline. The valley is two to three miles wide and is what KETTLEWELL and BERRY describe as a wind tunnel driven by the prevailing winds. Therefore, it should be a great hindrance for individual moths which would attempt to cross.

KETTLEWELL and BERRY measured the frequencies of the two forms in the immediate neighborhood of the Tingwall Valley. They also released marked individuals on either side of the valley to measure the average dispersal distance and the probability of crossing the valley. The results they obtained are: (1) The maximum slope of the cline does not occur across the valley but in a region two or three miles north, where the frequency of *f. edda* decreases from 35% to 20% in approximately one mile. (2) The frequency of *f. edda* is the same on either side of the valley. (3) The average distance between release and recapture of marked individuals was ½ mile. (4) Of the 65 moths which were recaptured, only one crossed the valley. On the basis of these results, they concluded that "fairly intensive selective pressures must be occurring to maintain the observed gene frequencies." In other words, they are proposing that there is relatively strong heterosis acting to maintain the gene frequencies at their observed levels. The cline in gene frequencies results from the gradual change in the selective intensities rather than from a balance between selection and gene flow.

In order to distinguish between these two hypotheses, it would be necessary to show that the Tingwall Valley is a sufficiently good barrier to dispersal that the gene frequencies on either side would not be the same unless they were maintained so by selection. While there are not sufficient data to provide conclusive evidence, there are enough to investigate the consequences of the model.

If the maximum change in the cline is 15% in one mile, then from equation (11), $s = .015$ is sufficient to maintain the cline. Since the gene causing the melanic form is dominant, this value is only approximate but of the correct order of magnitude. In equation (35), we can use $A(0+)$ as an estimate of the maximum discontinuity in a cline which could be produced by a geographic barrier. In fact, this is an overestimate of the size of the expected discontinuity because the geographic barrier is not located at the point of maximum slope of the cline. If we use the above estimate for s and assume that a discontinuity of 5% or less would be masked by the sampling of gene frequencies, then we can conclude from (35) that k would have to be at most .22, for $A(0+)$ to be less than .05. In making this calculation, we assume that

$$\int_0^\infty xM(x)dx = l$$

which would be exactly true only for an exponential form for M. Therefore, if as many as 20% of the individuals which would otherwise cross the barrier do not, then the discontinuity in gene frequencies would be appreciable. If we assume that nearly half of the individuals released by KETTLEWELL and BERRY would have tried to cross the valley, and if we assume that individuals which did cross the valley would be as likely to be recaptured as those that did not cross, then the results of the experiment provide evidence in favor of their hypothesis that there is strong heterotic selection acting. Since only one of the 65 recaptured individuals had crossed the valley, we could conclude that more than 20% were turned back by the barrier. While this argument is hardly conclusive, the orders of magnitude of the estimates involved are sufficiently different, that the alternative hypothesis, that the frequencies are maintained by gene flow, seems less likely to be correct.

CONCLUSIONS

The general results which have been derived from the analysis on gene flow and selection can be summarized as follows:

1) There is a characteristic length scale of variation, l_c, which determines the equilibrium pattern of gene frequencies in a spatially distributed population. If the environment changes on a scale less than the characteristic length, then the gene frequencies will not respond to the local variations but to the selection intensities averaged over the characteristic length. When the scale of variation in the environment is larger than the characteristic length, the gene frequencies can respond to the local variations resulting in genetically differentiated populations with clines between them. The result does not depend on the exact form for the dispersal function, M, but only on the average distance between the initial final locations of an individual.

2) The effect of a reduction of the heterozygote fitness is a steepening of the cline. If the reduction in fitness of the heterozygote is sufficiently large, then the maximum slope of the cline is determined mainly by the heterozygote fitness. Therefore a steep cline can result even when there is no abrupt change in environ-

mental conditions. An increase in the heterozygote fitness will reduce the maximum slope of the cline.

3) A geographic barrier to dispersal can cause an abrupt change in gene frequencies or a very steep cline only if the barrier stops most of the dispersing individuals who try to cross it.

4) For the same order of magnitude of selection coefficients and dispersal distances, a geographic barrier will permit much less differentiation in a spatially distributed population than will a reduction in heterozygote fitness.

There are some general conclusions we can reach based on the above results. The effect of gene flow and selection on a spatially distributed population cannot always be anticipated. The possibility of local differentiation depends on the quantitative analysis of the two mechanisms. The fact that a barrier to dispersal is relatively ineffective in isolating the populations on either side of the barrier, except in the case of very strong selection or an almost complete restriction of gene flow, might also not be anticipated. We have found that even a fairly large reduction in ability of individuals to cross a barrier, say by 50% or 75%, would probably not be detectable by measuring gene frequencies. That conclusion, in addition to the result that a sufficient reduction in the heterozygote fitness can produce a relatively steep cline, suggests that we would not necessarily expect to find a rapid change in gene frequencies or area effects associated with sudden changes in environmental conditions.

In a recent paper, ENDLER (1973) has argued that in many cases the effect of gene flow may be negligible on the amount of differentiation in a spatially distributed population. In one of his examples, he models a cline maintained by heterosis at each location (deme) with the relative fitness of the two homozygotes varying linearly with location. The resulting cline in gene frequencies is approximately linear with distance and ENDLER shows that the cline in gene frequencies does not change in the presence of some gene exchange between populations. In his system he allowed 40% gene exchange between adjacent populations and he showed that with this amount of gene flow, there was no effect on the cline, either in the computer model or in a series of population cages of *Drosophila melanogaster* where a cline was maintained in the *Bar* gene. The computer model predicted quite accurately the results from the population cages. Based on these results, ENDLER argues that gene flow has no effect because the averaging of gene frequencies on either side of a deme will produce the same gene frequencies as in the deme. That would still be true if longer distance dispersal were allowed. However, that result and the conclusion that gene flow has no effect on the cline depends strongly on the linearity of the selection pressures. In fact gene flow will tend to product a linear cline in gene frequencies whether or not the selection intensities are linear functions of distance. The actual outcome does depend on the quantitative balance between the two mechanisms.

I wish to thank G. F. CARRIER, W. H. BOSSERT, E. O. WILSON, E. MAYR, S. JONES, R. LANDE, J. SOHN, M. FELDMAN and R. LEVINS for helpful discussion and criticism during the course of this work. This research was supported in part by NSF grant number GP:8666 and by the Division

of Engineering and Applied Physics, Harvard University, and in part by U.S. AEC contract AT(11-1)-1437 to the University of Chicago.

LITERATURE CITED

ABROMOWITZ, M. and I. A. STEGUN, 1965 *Handbook of Mathematical Function.* Dover.

CAIN, A. J. and J. D. CURRAY, 1963 Area effects in *Cepaea.* Phil. Trans. B. **246:** 1–81.

CLARKE, B. C., 1966 The evolution of morph cline ratios. Am. Naturalist **100:** 389–402.

COLE, J. D., 1968 *Perturbation Methods in Applied Mathematics.* Blaisdell.

CROW, J. F. and M. KIMURA, 1970 *An Introduction to Population Genetics Theory.* Harper and Row, New York.

CURRAY, J. D. and A. J. CAIN, 1968 Climate and selection of banding morphs in *Cepaea* from the climatic optimum to the present. Phil. Trans. B. **253:** 483.

ENDLER, J. A., 1973 Gene flow and population differentiation. *Science* **179:** 243–250.

FISHER, R. A., 1937 The wave of advance of advantageous genes. Ann. Eugenics **7:** 355–369. ——, 1950 Gene frequencies in a cline determined by selection and diffusion. Biometrics **6:** 353–361.

FORD, E. B., 1964 *Ecological Genetics.* Methuen and Co., London.

GOODHARDT, C. B., 1963 "Area effects" and non-adaptive variation between populations of *Cepaea (mullusca).* Heredity **18:** 459–465.

HALDANE, J. B. S., 1948 The theory of a cline. J. Genet. **48:** 277–284.

HAMILTON, W. D., 1964 The genetical evolution of social behavior. J. Theoret. Biol. **7:** 1–16.

HANSON, W. D., 1966 Effects of partial isolation (distance) migration, and fitness requirements among environmental pockets upon steady state gene frequencies. Biometrics **22:** 453–468.

HIRSCHMAN, I. I. and D. V. WIDDLER, 1955 *The Convolution Transform.* Princeton University Press, Princeton, New Jersey.

JAIN, S. K. and A. D. BRADSHAW, 1966 Evolutionary divergence among adjacent plant populations. I. The evidence and its theoretical analysis. Heredity **21:** 407–441.

KETTLEWELL, H. B. D., 1961a The phenomenon of industrial melanism in the lepidoptera. Ann. Rev. Ent. **6:** 246–262. ——, 1961b Geographic melanism in the lepidoptera of Shetland. Heredity **16:** 393–402. ——, 1961c Selection experiments on melanism in *Amathes glareosa.* Heredity **16:** 415–434.

KETTLEWELL, H. B. D. and R. J. BERRY, 1961 The study of a cline. Heredity **16:** 403–414. ——, 1968 Gene flow in a cline. Heredity **24:** 1.

KIMURA, M. and G. H. WEISS, 1964 The stepping stone model of population structure and the decrease in genetic correlation with distance. Genetics **49:** 561–576.

LEVINS, R., 1968 *Evolution in a Changing Environment.* Princeton University Press, Princeton, New Jersey.

MALECÓT, G., 1968 *The Mathematics of Heredity.* Freeman.

MAYR, E., 1963 *Animal Species and Evolution.* Harvard University Press, Cambridge.

PIMENTEL, D. and F. C. STONE, 1967 A population model of sympatric speciation. Am. Naturalist **101:** 493–503.

SLATKIN, M., An analysis of a non-linear integral equation from population genetics. (In preparation.)

Studies on Cepaea, 1968 *Phil. Trans. B.* ***253:***, May.

Corresponding editor: R. LEWONTIN

APPENDIX

In the main text, equation (6) was derived from the assumptions about the mechanisms of gene flow and natural selection. As indicated, (6) can be approximated by a differential equation, (7), which is adequate for many purposes. The mathematical development of that approximation is complicated enough that it is presented here rather than in the main part of the paper. What follows is not a rigorous mathematical proof but an argument based on commonly used techniques in applied mathematics. The results must be checked for consistency and plausibility. In the present paper, the system is simple enough that spurious results do not appear. As is mentioned in the text, the reduction of the integral equation by that technique described below is equivalent to making certain assumptions about the balance of gene flow and selection (HALDANE 1948; FISHER 1937). The agreement with previous work on this problem also supports the use of the mathematical techniques. The purpose of the analysis is to show what assumptions are necessary for making the approximations and what changes we would expect when those assumptions are not satisfied.

We have assumed that $M(x)$ is an even, normalized function of $x (M(x) = M(x)$ and $\int M(x)dx = 1)$, has finite moments of all order ($\int x^n M(x)dx < \infty$ for all n) and is analytic except possibly at $x = 0$. For such a function, we can find a linear differential operator L_x which satisfies

$$L_x M(x) = \delta(x) \tag{A1}$$

where $\delta(x)$ is the Dirac delta function. $M(x)$ is the Green's function for L_x which satisfies the boundary conditions $M(x) \to 0$ as $x \to \pm 0$. L_x can be found by using Fourier transforms to be

$$L_x = 1/\bar{M}\left(i\frac{d}{dx}\right) \tag{A2}$$

where

$$\bar{M}(k) = \int_{-\infty}^{\infty} e^{ikx} M(x)dx .$$

Two examples might clarify the general result. If $M(x) = \frac{1}{2l} e^{-|x|/l}$ then L_x calculated using (A2) is

$$L_x = 1 - l^2 \frac{d^2}{dx^2} . \tag{A3}$$

That (A3) satisfies (A1) can be seen by direct substitution. If

$$M(x) = \frac{1}{\sqrt{4\pi l^2}} e^{-x^2/2l^2}$$

then

$$L_x = e^{-\frac{l^2}{2}\frac{d^2}{dx^2}}$$

where we must interpret the infinite order operator operating on a function f as

$$\left(e^{-\frac{l^2}{2}\frac{d^2}{dx^2}}\right) f(x) = \sum_{n=0}^{\infty} \left(-\frac{l^2}{2}\right)^n \frac{1}{n!} \frac{d^{2n} f(x)}{dx^{2n}} . \tag{A4}$$

Equation (A1) is satisfied for this choice of M because

$$\sum_{n=0}^{\infty} \left(\frac{-l^2}{2}\right)^n \frac{1}{n!} \frac{d^{2n}}{dx^{2n}} \frac{1}{\sqrt{4\pi l^2}} e^{-x^2/2l^2} = \delta(x) \tag{A5}$$

reduces to a statement of completeness of the Hermite polynomials (ABRAMOWITZ and STEGUN 1965). Similar results can be derived for other choices of M, although with less ease.

I shall always assume that the function $A(x)$ is in the region of function space for which an expansion of the form (A4) is valid. It is at this point where a formal proof would be required. The mathematical aspects of the problem are far from simple but will not be discussed here. HIRSCHMANN and WIDDER (1955) consider the general problem in detail.

Because $M(x)$ is assumed to be even and normalized, the form for L_x is always

$$1 - l^2 \frac{d^2}{dx^2} + \sum_{i=2}^{\infty} M_{2i} \frac{d^{2i}}{dx^{2i}} \tag{A6}$$

where l^2 is the second moment of M and M_{2i} are the higher even moments. l is usually the only thing which can be measured in a field situation from the release-recapture experiments. It will be argued that under many conditions, l is the essential parameter and the detailed form of M is unnecessary.

We can now apply L_x to equation (5) to reduce the integral equation to a differential equation.

$$(L_x - 1)A(x) = \frac{s}{2}\gamma(x) \frac{1 - A^2(x)}{1 + sA(x)\gamma(x)} \tag{A7}$$

As mentioned above, in many cases of interest s is small. In these cases, it is reasonable to look for a solution to (A7) in the form of a power series in s.

$$A(x) = \sum_{n=0}^{\infty} A_n(x)s^n \tag{A8}$$

In practice, only the first term in the series, A_0, would be of any interest. If this is attempted, it is found that the solution is not in terms of x, but in terms of another independent variable, which we can call ξ, where $\xi = \sqrt{s}\,x/l$. Therefore, the required solution to (A7) is in the form

$$A(\xi) = \sum_{n=0}^{\infty} s^n A_n(\xi) \tag{A9}$$

where the series must be interpreted as meaning that the error made by including only the first n terms in the series is $0(x^{n+1})$. This is the usual requirement for an asymptotic series and must be used here because we cannot consider the limit of (A9) as $s \to 0$ to be the solution to (A7) with $s = 0$. The model with $s = 0$ is fundamentally different. We want to find an approximate solution to (A7) for a *given value* of s.

We could show that (A9) represents the only possible form of the solution to (A7) by using the method of multiple scaling (COLE 1968, Chapter 3) but this is not necessary for our purposes. This will be taken up in a mathematically oriented paper on this problem (SLATKIN, in preparation). It will be sufficient to show that (A9) provides us with a good approximation to the exact solution, found numerically, and enables us to understand the basic nature of the balance between gene flow and selection.

When we substitute (A9) into (A7), the resulting equation is in the form

$$\frac{d^2A(\xi)}{d^2} = \frac{1}{2}\gamma(\xi)\,(1 - A^2(\xi)) + s\,\{\ldots\} \tag{A10}$$

where all of the terms in the braces are of the order of unity or smaller. Therefore, we conclude that equation (7) is correct to order s. We have assumed that M_4 is not too large as compared with l^2. That is, M_4/l^4 is not much greater than 1. This assumption is valid for all reasonable, unimodal forms for M, including all that have been measured in natural populations.