MASTER

Annual Progress Report

A Study of Mathematical Models of Mutation
and Selection in Multi-locus Systems.

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Abstract

Findings of this year's work include: 1) linkage materially affects the gene frequency clines that result from a cline in selection; 2) migration and gene flow produces substantial linkage disequilibrium; 3) there is a significant time lag in the response of populations to gene migration so that equilibration under migration is very slow; 4) in a fluctuating environment with selection for an intermediate optimum, selection will favor loss of variance unless fluctuation is large; 5) large amounts of genetic variation can be held by recurrent mutation with optimizing selection; and 6) under a broad variety of conditions, selection on quantitative characters selects a population distribution of phenotypes that maximizes mean fitness.

General Remarks

This progress report covers a short and unusual period in the history of this long standing research program. Because the principle investigator moved from the University of Chicago to Harvard University during the previous grant year, there was a complete dislocation both in research and in administrative arrangements. A protracted period of relocation of laboratories and offices (we did not move into our new quarters until November, 1974) caused a delay in even beginning research at Harvard. A combination of lateness on the submission of the new contract proposal together with administrative delays resulting from the necessity of transferring the contract to Harvard meant that, although the starting date of this year's contract is shown as April 1, 1974, the notification of the award of the contract was not received until June 15, 1974! Thus the effective period of the present progress report is only a little over 6 months.

Because of the confusion and delays in the first year's contract at Harvard, none of the considerable progress made during the last six months was the direct result of work by the principle investigator and virtually none of the funds appropriated were expended. Thus, the principle investigator did not take any of the \$3000 salary appropriated since he would not have been justified in doing so. Moreover, only about \$1500 of the \$6000 appropriated for computing was actually used. Indeed, the only substantial expenditures have been the acquisition of the computer terminal (after a wait of four months for delivery) and the well-justified consultants fee to M. Slatkin, who is responsible for more than half the progress reported during the last contract period. Thus, of the 18,500 direct costs appropriated for this contract last year, about \$11,000 will remain unexpended on March 31, 1975, the official termination date of the current year's contract.

In view of these unusual circumstances, our request for renewal will ask for only about \$8000 in new funds for 1975-76 and will also propose that the starting date of the new contract be June 1, 1975 in keeping with the actual period of work involved in the present year.

Despite all the delays and confusions, a good deal of progress has actually been made during the last six months, due chiefly to M. Slatkin, who was formerly a co-principal investigator on the contract at Chicago, but who appears technically as a "consultant" this year; and to Russell Lande, a graduate student of R. Lewontin's at Harvard.

Travel and Consultation

M. Slatkin spent the summer as a visiting scientist in the Population Genetics Department of the National Institute of Genetics in Misima, Sizuoka-ken, Japan. He worked with Drs. M. Kimura, T. Maruyama and T. Ohta on problems relating to the stochastic changes in gene frequencies in natural populations. The members of the Population Genetics Department are some of the world's leading authorities on mathematical population genetics. He used his time there to learn the techniques they have developed and to apply those techniques to problems arising in his research on the effect of spatial and temporal variation in selection intensities on the genetic structure of natural populations. He visited no other laboratories and attended no scientific meetings related to his research on population genetics while he was in Japan.

R.C. Lewontin again spent a month with T. Prout at the University of California, Riverside, working on problems of the estimation of fitness and migration. In addition, short visits of one or two days were made for discussions with Marc Feldman, R. Selander, John Gillespie, T. Maruyama (while he visited Seattle) and J. Felsenstein.

Visits of one day to two weeks were made to Harvard by M. Feldman (Stanford), S. Karlin (Stanford), B. Charlesworth (Sussex), and R. Levins (Chicago), and these were largely devoted to technical discussions on linkage and selection.

Research Accomplished

The research carried out this year has concentrated on two main issues. The first is the buildup of linkage disequilibrium in the presence of geographical clines in selection. The other is the amount of genetic variation for quantitative characters that is maintained by mutation pressure when there is stabilizing selection.

A. Spatial and temporal variation in gene frequencies.

I. Slatkin continued his main research on the effect of spatial and temporal variation in selection pressures on the genetic structure of natural

populations. A paper on the structure of a cline in gene frequencies at two linked loci was completed and submitted to Genetics. The manuscript was accepted for publication and has been returned to the journal with the necessary revisions. In this paper, it was shown that linkage between loci could either increase or decrease a population's ability to respond to local selection pressures. If the selection on the two loci changes at the same location, then linkage would produce a steeper cline in frequencies at both of the loci. If the selection changes at different locations, then linkage will interfere with the population's response to the selection and the gene frequencies will not reflect the spatial pattern in selection. According to the general theory of Karlin and McGregor (1974), there would be selection for or against an allele which decreased the recombination fraction between the two loci depending on the spatial pattern of the selection intensities.

It is also shown in this paper that gene flow and selection can produce a significant amount of linkage disequilibrium even in the absence of epistasis. When the recombination fraction between the two loci is of the same order of magnitude as the selection coefficient for either of the loci or less, then there would be expected to be a measurable amount of linkage disequilibrium in the middle of the cline. The degree of epistasis between the loci would be relatively unimportant in determining the general properties of the system. This is in contrast to the results from the model of linkage and epistasis in a single panmictic population (Lewontin and Kojima, 1960) in which there could be linkage disequilibrium maintained only if the recombination fraction were less than the epistatic deviation from additive fitness. When the fitnesses between the loci were multiplicative, this would require that the recombination fraction be less than the square of the selection coefficients, while with gene flow only the first power of the selection coefficient is important. Thus, Lewontin's (1974) statement that the presence or absence of linkage disequilibrium in a population is quite a sensitive test of epistasis is true only in a panmictic population.

II. The most important new work of the project grew out of Slatkin's visit to the National Institute of Genetics in Misima, Japan. While there, he worked with M. Kimura, T. Maruyama, and J.F. Crow (who was visiting from the Department of Genetics at the University of Wisconsin, Madison). Slatkin learned several techniques for analyzing stochastic changes in gene frequencies and applied these techniques to several problems of interest. He analyzed the rate of response of

one population to gene flow from a neighboring population and found that there is always a time lag associated with gene flow. Although the two populations would be genetically identical at equilibrium, for a period of several hundred generations or more, they could be genetically distinct. Slatkin points this out in a letter to the Editor of Nature and argues that when the expected time until extinction of local populations is on the same order of magnitude as the time lag, then the equilibrium might never be reached. If there was a large number of such populations, genetic differences could accumulate between them even though there were sufficient gene flow to prevent divergence at equilibrium.

There was a fruitful collaboration on related problems with T. Maruyama. One is on the effect of genetic drift in a cline. Slatkin and Maruyama, in a paper submitted to Genetics, show that genetic drift will always tend to reduce the slope of a cline, sometimes by as much as $1/2$, but that the selection in the cline makes little change in the correlation in gene frequencies predicted in the absence of selection by Kimura and Weiss (1964). In a second paper, submitted to the American Naturalist, Slatkin and Maruyama analyzed the effect of a small amount of gene flow on measures of genetic distance between the populations. They show that even a small amount of gene flow is sufficient to significantly change the estimates of divergence times of two populations based on genetic distance. The most important part of their result is that the error in the estimate of divergence times does not depend strongly on the number of steps separating the two populations. They suggest that a comparison of the estimated and actual divergence times of two populations would provide an estimate of the average level of gene flow between them since divergence.

B. Mutation and phenotypic variation.

Slatkin has continued his work on the determination of the variance of phenotypic characters subject to temporally varying selection. In a paper with Russell Lande of the Department of Biology at Harvard University, the evolutionarily stable equilibrium variance of a character subject to temporally varying, density independent, optimizing selection was found. Slatkin and Lande find the effect of different amplitudes of environmental fluctuation and different degrees of autocorrelation in the environment. They find that only if the variance in the optimal phenotype is above a certain threshold will selection favor a non-zero variance of the character. Also, they find that autocorrelation in the changes in the optimal phenotype tends to reduce the variance, indicating

that a species could afford to specialize more in a more predictable environment. This paper has been accepted for publication in the American Naturalist, and the final copy is being prepared.

Slatkin, in collaboration with Jonathan Roughgarden of Stanford University, has used the same type of analysis on density dependent optimizing selection to find the evolutionarily stable variance when intraspecific competition is a factor. Slatkin and Roughgarden have shown that selection on a modifier would tend not to maximize the total population size but rather to equalize the fitnesses in each of the phenotypic classes. They show that, in general, the total population size is not maximized at equilibrium. The manuscript describing this work is now being written.

R. Lande has investigated the effect of selecting for an intermediate phenotype value (stabilizing selection) when there is a constant input of new variation from mutation. In this and subsequent work, Lande has been able to show that, to a first order of approximation, most of the behavior of the distribution of phenotypes can be predicted without recourse to a detailed genetic model. It is assumed that a character under stabilizing selection is determined genetically by n linked, mutable loci with additive effects and a range of many possible allelic effects at each locus. A general qualitative feature of such systems is that the genetic variance for the character is independent of the linkage map of the loci, provided linkage is not very tight. A particular detailed model shows that certain aspects of the genetic system are molded by stabilizing selection, while others are selectively neutral. With reference to experimental data on characters of Drosophila flies, maize and mice, it is concluded that large amounts of genetic variation can be maintained by mutation in polygenic characters even when there is strong stabilizing selection. This work has been submitted to Genetical Research for publication.

Using a similar approach involving the moments of the distribution of phenotypes, Lande has made an analysis of the deterministic and stochastic forces affecting the mean value of phenotypic characters. Many evolutionary arguments have been weakened by the finding of Moran that deterministic changes in gene frequencies caused by natural selection do not necessarily increase the level of adaption or the average fitness of a population. Lande derived an alternative principle showing that under certain conditions with respect to changes in the average phenotypes of a set of correlated characters, evolution does maximize the average fitness of individuals in the population. These conditions are: 1) the phenotype

variance must be independent of the mean and 2) no density or frequency dependence of the fitness values. These conditions also apply to Fisher's Fundamental Theorem. He also has developed a simple model of random genetic drift which applies to phenotypic characters under stabilizing selection. He has shown that considerable change in the mean value of a character can be produced by genetic drift in populations with effective size in the tens or hundreds, within a timespan typical for speciation. Random genetic drift may thus play an important role in the differentiation of populations in the process of geographic speciation. Unlike in Wright's theory of random genetic drift in gene frequencies, this conclusion is valid even for completely isolated populations.

Papers Produced

- Feldman, M., Lewontin, R.C., Franklin, I., and F.B. Christiansen. 1975.
Selection in complex genetic systems. III. An effect of allele multiplicity with two loci. Theoretical Population Biology: in press.
- Lande, R. 1974. The maintenance of genetic variability by mutation in a polygenic character with linked loci under stabilizing selection. Submitted to Genetical Research.
- Lewontin, R.C. 1974. The analysis of variance and the analysis of causes. Amer. J. of Human Genetics 26:400-411.
- Slatkin, M. 1973. Gene flow and selection in a cline. Genetics 75:733-756.
- Slatkin, M. 1974. Competition and regional coexistence. Ecology 55: 128-134.
- Slatkin, M. 1974. Cascading speciation. Nature: in press.
- Slatkin, M. 1975. Gene flow and selection in a two locus system. Genetics: in press.
- Slatkin, M. and R. Lande. 1975. Niche width in a fluctuating environment - density independent model. Amer. Nat.: in press.
- Slatkin, M. and T. Maruyama. 1975. Genetic drift in a cline. Submitted to Genetics.