A GENERAL MODEL TO ACCOUNT FOR ENZYME VARIATION IN NATURAL POPULATIONS[1,2]

JOHN H. GILLESPIE

Department of Biology, University of Pennsylvania, Philadelphia, Pennsylvania 19174

and

CHARLES H. LANGLEY[3]

University of Wisconsin, Department of Medical Genetics, Madison, Wisconsin 53706

Manuscript received May 9, 1973
Revised copy received December 17, 1973

ABSTRACT

Approximate conditions for genetic polymorphism in temporally and spatially varying environments are presented for loci which are intermediate at the level of fitness or at the level of gene function. The conditions suggest that polymorphism will be more likely in more variable environments while unlikely in constant environments. Biochemical evidence is presented to justify the assumption of heterozygote intermediacy. Observations on natural populations are cited which substantiate the claim that allozymic polymorphism is primarily due to selection acting on environmental variation in gene function.

ELECTROPHORETIC analyses of natural populations have shown that there is a considerable amount of genetic variation in the mobility of soluble enzymes. This variation could be maintained by the opposing forces of mutation and genetic drift, and/or by various forms of balancing selection. To what extent this variation is due to each of these causes is completely unknown at the present time.

Heterosis is the simplest form of selection which can account for variation, yet observations on enzymes at the molecular level have repeatedly shown heterozygotes to be intermediate in most parameters of enzyme function (see DISCUSSION). While this does not necessarily imply that heterozygotes will be intermediate with respect to fitness, it does necessitate the adoption of a general biochemical mechanism for elevating the fitnesses of heterozygotes if heterosis at the fitness level is to explain the observed polymorphism. As yet no such mechanism has been demonstrated. This problem does not arise, however, when the environment changes at random. In fact, in both temporally and spatially varying environments heterozygote intermediacy can lead to genetic polymorphism, providing the variance in the environment is large enough. This argument is developed in this paper and supporting experimental evidence is presented.

[1] This is paper No. 1717 of the Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin.
[2] Supported by NIH grant GM 15422.
[3] Present address: Mutagenesis Branch, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Theoretical Considerations

In this section we introduce two models of the relationship between gene function and fitness and examine their consequences in spatially and temporally fluctuating environments. The mathematical treatment is straightforward but tedious, so it has been relegated to an appendix.

The point of departure is a very large diploid population where finite population effects can be ignored. Let p be the frequency of allele A_1 and let the absolute fitnesses of the genotypes A_1A_1, A_1A_2, and A_2A_2 be $1 + S_1(i)$, $1 + S_2(i)$, and $1 + S_3(i)$, where $S(i)$, $S_1(i)$, $S_2(i)$, $S_3(i)$ is a discrete-parameter, stationary stochastic process with continuous state space. The parameter i will represent the i^{th} generation in models of temporally varying environments and the i^{th} subpopulation in models of spatially varying environments. The two models to be developed differ in their assumptions about the dominance relationships of the two alleles.

Model I: No dominance. If the heterozygote is intermediate in fitness,

$$S_2(i) = \tfrac{1}{2}(S_1(i) + S_3(i)).$$

An approximate condition for polymorphism in a temporally fluctuating environment is that the absolute value of the difference of the geometric mean fitnesses of the two homozygotes, $\Delta\Gamma$, be less than one-quarter the variance of the selection differential, $S_1(i) - S_3(i)$:

$$|\Delta\Gamma| < \tfrac{1}{4}\,\sigma^2. \tag{1}$$

This result is obtained by a simple application of the theorem that polymorphism occurs in a temporally fluctuating environment if the geometric mean fitness of the heterozygote exceeds both homozygotes (GILLESPIE 1973a and APPENDIX). The assumption that the heterozygote is intermediate in each environment implies that the variance in fitness of the heterozygote is less than that of both homozygotes. Since the geometric mean is a decreasing function of the variance, it is possible for this lowering of the variance to elevate the geometric mean of the heterozygote above both homozygotes. The arithmetic mean fitness of the heterozygote, however, will always be half-way between the two homozygotes. Such a phenomenon is obviously impossible in haploids, and, not surprisingly, polymorphism has been shown to be impossible in these organisms in temporally changing environments (GILLESPIE 1972, 1973b).

The situation in spatially changing environments is similar. Consider first a species which mates at random and then distributes itself onto a large number of spatially separate localities where selection takes place. This structure was first discussed by LEVENE (1953). In this situation the change in the frequency of the allele A_1 for the whole population will equal the expected change in any subpopulation (see APPENDIX). The approximate condition for polymorphism in this case is

$$|\Delta\Gamma| < \tfrac{1}{2}\,\sigma^2, \tag{2}$$

where the means and variances are now calculated spatially rather than temporally.

As a final case, we will consider a one-dimensional stepping stone model (see CROW and KIMURA (1970), page 469, for a description of the structure of stepping stone models) in which the fitnesses of the two homozygotes are assigned at random in each stone and migration is allowed between stones. In this model, an approximate condition for polymorphism is that

$$|\Delta\Gamma| < \tfrac{1}{2}\,\sigma^2 - \frac{4m}{1-2m} \tag{3}$$

where $2m$ is the fraction of the population in each stone which is exchanged with the two neighboring stones each generation (see APPENDIX).

Comparison of (1), (2), and (3) shows a striking similarity in the conditions for polymorphism. Collectively they imply that polymorphism can always occur providing the variance in the selection differential is large enough to override the mean differences between homozygote genotypes. Or, to be less precise, polymorphism will occur if the environmental variance is large enough.

The approximate conditions for polymorphism are arrived at by assuming that the fitnesses of the homozygotes are very close to one. They should not be regarded as necessary or sufficient, but only as suggestive. The degree of approximation improves as the homozygote fitnesses approach unity, and in certain cases, for example the case of a temporally fluctuating non-autocorrelated environment, the condition becomes exact for an appropriate limiting model (see GILLESPIE (1973c) for such a case). The conditions are not meant to deal with genotypes experiencing large fitness deviations, such as lethals.

The results presented can be made more useful if some effort is made to relate the fitness of an individual to a measurable parameter of the environment. Toward this end let ξ_n be a stochastic process representing such a parameter and let the fitnesses of the three genotypes be expressed as functions of this parameter,

$$S_i(j) = S_i(\xi_j)$$

(see Figure 1). If the variance in the environment, σ_ξ^2 ,

is small, the functions, $S_i(\xi_j)$ may be approximated by their Taylor series near the mean value of the environment. If we arbitrarily set this mean at zero, we can write

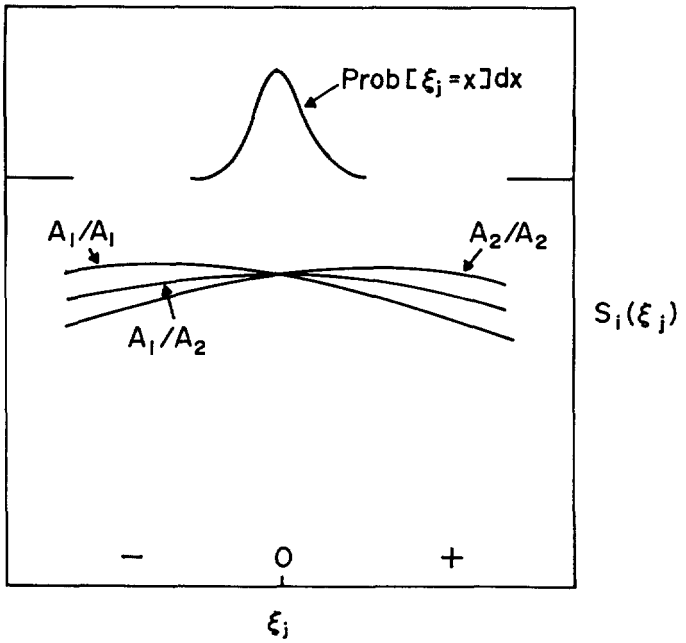
$$S_i(\xi_j) \simeq S_i(E\xi_j) + \xi_j\, S_i'\,(E\xi_j) = S_i(0) + \xi_j\, S_i'\,(0)$$

and express the conditions for polymorphism (1), (2), and (3), in terms of this expansion. This is accomplished in the temporal case, for example, by writing down the first two moments of $S_i\,(\xi_j)$, using the approximation for the geometric mean given in the APPENDIX, and applying the theorem of geometric means. With this approach and analogous efforts for the other cases we get the following conditions for polymorphism:

Temporal fluctuations

$$\sigma_\xi^2\,(S_1'(0)^2 - \tfrac{1}{4}\,(S_1'(0) + S_3'\,(0))^2) > S_1(0) - S_3(0)$$

$$\sigma_\xi^2\,(S_3'(0)^2 - \tfrac{1}{4}\,(S_1'(0) + S_3'\,(0))^2) > S_3(0) - S_1(0)$$



Spacial fluctuations—LEVENE *model*

$$\sigma_\xi^2 (S'_1(0)^2 - S'_1(0)S'_3(0)) > S_1(0) - S_3(0)$$

$$\sigma_\xi^2 (S'_3(0)^2 - S'_1(0)S'_3(0)) > S_3(0) - S_1(0)$$

Spacial fluctuations—Stepping stone model

$$\sigma_\xi^2 (S'_1(0)^2 - S'_1(0)S'_3(0)) > S_1(0) - S_3(0) + \frac{4m}{1-2m}$$

$$\sigma_\xi^2 (S'_3(0)^2 - S'_1(0)S'_3(0)) > S_3(0) - S_1(0) + \frac{4m}{1-2m}$$

In these inequalities the mean and variance effects of the environment have been isolated on either side so we can now judge the role of environmental variance in the maintenance of variation.

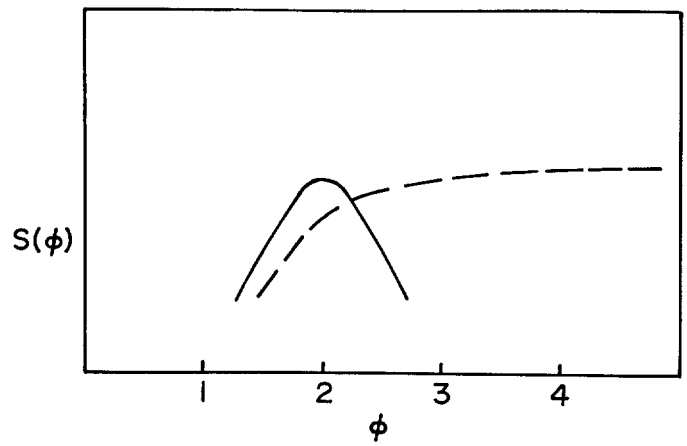
The representation suggests the following model: Of all the mutational varieties of a gene, natural selection will quickly sort out those whose geometric mean fitnesses are largest in the region of the environmental mean. In this early phase of selection the variance effects are less important than the mean effects. Due to the quantum nature of the mutation process, it is unlikely that any single allele will be optimal; rather it is likely that there will be some that do better in an environment slightly larger than zero, and others in an environment with a mean slightly lower than zero (as in Figure 1). In the former group $S_i'(0)$ will be positive; in the latter, $S_i'(0)$ will be negative. It is this situation which we feel leads to genetic polymorphism. Examination of the conditions for polymorphism in the spatial model shows that the left side will always be positive

and directly proportional to the variance in the environment. Thus, as the environmental variance goes to zero, the population goes monomorphic; if it increases enough, the population goes polymorphic. The situation in temporal environments is similar, although the conditions for polymorphism are more restrictive. The rightmost term on the right side of the inequality will generally be quite small, since $S_1'(0)$ and $S_3'(0)$ have different signs, making polymorphism likely if σ_ξ^2 is large enough. The only condition where polymorphism cannot occur by increasing σ_ξ^2 is if one $S_1'(0)$ or $S_3'(0)$ is very much larger than the other.

Model II: The role of dominance. In this model we will assume that the heterozygote is intermediate at the level of gene function but that fitness is a non-linear (mathematical) function of the level of gene function. As before, let the environment be represented by the process ξ_j. Let the levels of gene function be functions of the state of the environment, $\phi_i\ (\xi_j)$ with the assumption of heterozygote intermediacy entering by the relationship

$$\phi_1(\xi_j) = \tfrac{1}{2}(\phi_1(\xi_j) + \phi_3(\xi_j)).$$

Finally, let the fitness of a genotype be determined by a function of ϕ, $S(\phi)$. Thus the fitness of the i^{th} genotype is $S(\phi_i(\xi_j))$. Two possible forms for $S(\cdot)$ are illustrated in Figure 2.



The conditions for polymorphism may now be written in terms of these two functions. For conciseness we will only consider the temporal case since it illustrates well the role of dominance in polymorphism. The spatial models may be modified analogously. For the temporal case polymorphism will occur if

$$\sigma_\xi^2\,(a_1^2 - a_2^2) > S(\phi_1(0)) - S\left(\frac{\phi_1(0) + \phi_3(0)}{2}\right)$$

$$\sigma_\xi^2\,(a_3^2 - a_2^2) > S(\phi_3(0)) - S\left(\frac{\phi_1(0) + \phi_3(0)}{2}\right)$$

$$a_i = S'\,(\phi_i(0))\,\phi_i'(0),\ i = 1,3$$

$$a_2 = \tfrac{1}{8}\,S'\,(\tfrac{1}{2}\,\phi_1(0) + \phi_3(0))\,(\phi_1'(0) + \phi_3'(0)).$$

A comparison of these conditions with those for Model I shows that the most important difference lies in the comparison of

$$S\left(\frac{\phi_1(0) + \phi_3(0)}{2}\right),$$

with

$$\frac{S(\phi_1(0)) + S(\phi_3(0))}{2}.$$

If $S(\cdot)$ is concave (as in either case in Figure 2), the effect of dominance is to make polymorphism more likely (i.e., the conditions are easier to satisfy). If $S(\cdot)$ were convex, the opposite would be true. We feel that $S(\cdot)$ is much more likely to be concave, although there is no evidence one way or the other.

The results from Models I and II all point to the case with which polymorphism can occur in spatially and temporally fluctuating environments. The conditions imply that polymorphism will be more likely to occur in more variable environments. At this point it should be emphasized, however, that the variability of the environment for a particular gene, such as an enzyme, will be a function of the genetic background as well as the external environment. An esterase in a homeothermic organism, for example, will see a less variable environment with respect to temperature than will a analogous esterase in a poikilotherm.

Experimental Considerations

Several experimental observations support the assumptions and results of the theoretical considerations alone. In the following several sections we describe the various observations and point out their relevance.

1. *Gene function and heterozygote intermediacy.* The magnitude of the allelic differences in gene function, with which we are concerned, is small. Many kinds of gene products (including enzymes) function as single molecules or in small assemblages (e.g., dimers). If we assume as is reasonable and commonly observed that the monomers associate into multimers at random then we can see that the activity of the heterologous associations will have to deviate considerably above or below that of the homologous associations in order to bring the heterozygote gene function outside the range of the two homozygotes.

Although heterozygote intermediacy seems reasonable from such theoretical considerations we will present experimental evidence in order to better justify this most critical of our assumptions. The evidence is divided into two catagories: biochemical properties associated with heterozygotes for rare deficiencies in various enzymes and biochemical properties associated with heterozygotes for polymorphic variation in enzymes. The evidence from non-polymorphic variation does not apply directly to the concerns of this paper. It is, however, indirect substantiation of the generality of additive gene dosage.

In man, the following five enzymes have been shown to exhibit dosage effect for *in vitro* catalytic activity. The mutants in these studies are rare and characterized by large reductions in activity: phosphohexose isomerase (DETTER *et al.* 1968), catalase (AEBI and SUTER 1969), diaphorase (JAFFÉ 1969), pyruvate kinase (TANAKA 1969), and triosephosphate isomerase (SCHNEIDER 1969). Simi-

lar dosage effects in enzyme activity are observed in other organisms: in Drosophila (GRELL 1962) and in jimson weed (CARLSON 1972). The general impression from these studies is that dosage compensation, i.e., some mechanism for the maintenance of a certain level of gene function, is not common for structural genes. Thus, we can expect allelic effects to be additive for gene function.

Gene function difference for polymorphic variation is more difficult to observe since the magnitude is often small. The following seven enzymes exhibit polymorphic variation in humans (frequency of the common allele < 0.99), in these various properties have been ascertained for the several phenotypes, and the heterozygote intermediacy is consistently observed: red cell acid phosphatase, activity (SPENCER, HOPKINSON and HARRIS 1964) and thermostability (LUFFMAN and HARRIS 1967); placental alkaline phosphatase, thermostability (THOMAS and HARRIS 1971); cholinesterase, activity (SIMPSON 1966); galactose-1-phosphate uridyltransferase, activity (BEUTLER 1969; glutamic-pyruvic transaminase, activity (CHEN *et al.* 1972); 6-phosphogluconate dehydrogenase, inhibition by urea and iodoacetate (DAVIDSON 1967); and glutathione reductase, activity (LONG 1967, personal communication).

Similarly in *Drosophila melanogaster* heterozygote intermediacy is observed (specific activity, substrate specificity and heat stability) at the electrophoretically polymorphic locus: alcohol dehydrogenase (VIGUE and JOHNSON 1973; GIBSON 1970; RASMUSON, NILSON and RASMUSON 1966). Activity and thermostability of glucose-6-phosphate dehydrogenase (STEELE, YOUNG and CHILDS 1968) also show heterozygote intermediacy. We know of no well-documented incidence of the heterozygote demonstrating biochemical properties outside the range of the homozygotes.

Although this substantial and consistent evidence does not rule out the possibility of exceptions, we feel that it justifies the assumption of heterozygote intermediacy.

2. *Gene function and polymorphism.* It has been demonstrated in Drosophila that enzymes in glycolysis and the citric acid cycle (Group I) tend to be less variable than such non-specific enzymes (Group II) as esterases, phosphotases and alcohol and aldyhyde dehydrogenoses (GILLESPIE and KOJIMA 1968; KOJIMA, GILLESPIE and TOBARI 1970). These particular enzymes can be characterized more generally based on the uniqueness or diversity as well as the sources of their physiological substrates. We can thereby re-define Group I as those enzymes characterized by a singular physiological substrate which is usually generated and utilized intracellularly. The Group II enzymes are re-defined as enzymes with multiple physiological substrates which reflect environmental diversity. This more general re-definition has little effect on the previous analysis of Drosophila allozymic variation. It does, however, alter the analysis of the vertebrate data summarized by SELANDER and JOHNSON (1973). Table 1 is an analysis along the lines proposed above. Many enzymes not involved with glucose metabolism are now included in to Group 1, such as glutamate-oxaloacetate transaminase and xanthine dehydrogenase. We have also included enzymes such as nonspecific phosphatases and peptidases into Group II. With this breakdown of the data, the difference between Group I and Group II is evident and consistent

TABLE 1

*Group I and Group II analysis of the electrophoretic variation in enzymatic proteins in single populations of humans, mice and Drosophila**

		Number of loci	Percent loci polymorphic	Mean number of alleles per locus	Heterozygosity Mean	Heterozygosity Group I / Group II
Man	Group I	45	24	1.2	0.05	0.38
	Group II	20	45	1.6	0.13	
Mouse	Group I	18	22	1.2	0.08	0.65
	Group II	9	44	1.8	0.13	
Drosophila	Group I	11	27	1.4	0.04	0.17
	Group II	10	70	2.6	0.24	

* The human data are taken from HARRIS and HOPKINSON (1972). Utilizing the numbers in Tables 1 and 2 of HARRIS and HOPKINSON (1972), the enzymes are grouped as follows: Group I—from Table 1 numbers 2,3,4,8,9,12,13,14,18,19,20; from Table 2 numbers 5,8,9,10,11,13,20,21,23, 24,25,26,27,28,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,49,50,51; Group II—from Table 1 numbers 1,5,6,7,10,11,15,16,17; from Table 2 numbers 1,2,6,7,14,15,16,17,18,19,29. Numbers 3,4, 22,47, and 48 from Table 1 are excluded because of ambiguity in classification. Number 12 from Table 2 is excluded (serum cholinesterase E_2) because it is unclear whether this is a structural locus or not. Because some of the gene frequencies for nonpolymorphic ($p>0.99$) loci are not available we have computed the average heterozygosity (human) assuming no contribution from these loci (European population).

The mouse data are taken from SELANDER and YANG (1969). Group II enzymes are alkaline phosphotase, esterases 1, 2, and 3, plasma esterases A, B, and C, erythrocyte esterase D, and alcohol dehydrogenase. Group I enzymes are aldolase, lactate dehydrogenase (loci A and B), the three different malate dehydrogenases, xanthine dehydrogenase, hexose-6-phosphate dehydrogenase, glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, two isocitrate dehydrogenases, two phosphoglucomutases, and fumarase. Lactate dehydrogenase regulator and esterase 5 were not included because it is unclear whether these are structural loci or not. Indophenol oxidase was not included because the physiological substrate and role of this enzyme is not apparent (Hallowell Farm population).

The Drosophila data are taken from LANGLEY, TOBARI and KOJIMA (1974). Group I enzymes are α-glycerophosphate dehydrogenase, malate dehydrogenase, phosphoglucomutase, isocitrate dehydrogenase, xanthine dehydrogenase, aldolase, fumarase, glutamicoxaloacetate transaminase, hexokinase, malate enzyme, and phosphoglucoisomerase. Group II enzymes are alcohol dehydrogenase, α-amylase, esterase 6, esterase C, octonal dehydrogenase, aldehyde oxidase, leucylaminopeptidase A and D, and alkaline phosphotases 1 and 2 (Brownsville, Texas population).

over a wide range of species, as demonstrated in Table 1 for humans, mice and Drosophila. We feel the theory developed in this paper goes a long way toward explaining this phenomenon.

The heterozygosity of the Group I enzymes is very constant at approximately 0.05. This variation may be due to several factors such as variability in temperature, pH, salt concentrations, etc. It may reflect a balance between the force of mutation and random drift or perhaps some form of biochemical heterosis. The increased heterozygosity of the Group II enzymes suggests that *roughly* 80% of the heterozygosity in Group II enzymes in Drosophila could be due environmental fluctuations in the amounts and types of substrates. These are, of course, very *crude* estimations. But they do suggest that a large portion of the observed allozymic variation is due to a rather specific type of phenomenon: *substrate variability*.

The consideration of these differences between Groups I and II points out that all loci should not be assumed equivalent when extrapolating electrophoretic data to whole genomes. Because of the generalized function of Group II enzymes, the expected number of genes in the category in the whole genome is small. Structural proteins, ribosomal proteins, and regulatory proteins as well as most enzymes involved in biosynthesis, intermediary metabolism, glycolysis, and citric acid cycle are classified in Group I. We feel it is perhaps grossly misleading to extrapolate from an average heterozygosity of allozymic variations to a total genomic heterozygosity since Group II enzymes are disproportionately represented in survey studies so far conducted.

3. *Environmental variation and allozymic polymorphism.* POWELL (1971) has recently reported a remarkable experiment in which Drosophila populations were maintained under several different environmental regimes for many generations. Those maintained in temporally and spatially fluctuating environments retained more allozymic variation than those maintained in constant environments. Similar evidence can be found in the report of LEVINTON (1973) that related environmental variation to allozymic polymorphism in clams. Heterozygosity and number of alleles per locus showed strong negative correlation with depth of habitat in the sediment. This, in turn, is known to correlate negatively with environmental variation in salinity and presumably other significant ecological parameters. Both of these studies indicate that the amount of allozymic polymorphism is an increasing function of environmental variation.

4. *Homeostasis: ecological and physiological.* SELANDER and KAUFMAN (1973) have noted the correlation between genetic variability as measured by electrophoretic techniques and various indices of environmental grain. They note that heterozygosity correlates negatively with body size and the amount of physiological and behavioral homeostatic control. SELANDER and KAUFMAN interpret this correlation in terms of the adaptive strategy concept of LEVINS (1968). This correlation can also be understood in light of the results of this paper. Larger, more homeostatic organisms provide a more buffered and less variable environment for the enzymes studied in electrophoretic surveys. As was pointed out above, the likelihood of polymorphism is an increasing function of environmental variation in gene function. Thus, analogous genes should be less polymorphic in the more homeostatic species.

Our major debt is to DR. PEPPER who was present at the inception of this paper and provided constant stimulation during its development.

APPENDIX

If X_n is a stationary stochastic process, the Ergodic theorem allows the geometric mean of the process to be uniquely defined by

$$\gamma = \lim_{n\to\infty} [\Pi X_i]^{\frac{1}{n}} = \lim_{n\to\infty} e^{\frac{1}{n}\sum \ln X_i} = e^{E(\ln X)},$$

providing the usual conditions for convergence are satisfied by the associated process, $\ln X_n$. If the mean and variance of X_n are small and of the same order, and all higher order moments are

vanishingly small, the geometric mean may be approximated by the mean of X_n minus one-half its variance:

$$\gamma \simeq \mu - \tfrac{1}{2}\sigma^2$$

This approximation allows condition (1) to be written immediately from the result of GILLESPIE (1973a) on the conditions for polymorphism in diploids.

To arrive at condition (2) begin with LEVENE's (1953) model, assigning an equal fraction of the population into each of n subpopulations. This done, the difference equation given by LEVENE is

$$\Delta p = 1/n\, \Sigma \Delta p_i$$

$$\Delta p_i = \tfrac{1}{2}\frac{p(1-p)(S_1(i) - S_3(i))}{1 + pS_1(i) + (1-p)S_2(i)} .$$

In the present context $S(i)$ is a spacially varying stochastic process. If the $S(i)$ are mutually independent, the law of large numbers allows that

$$\lim_{n\to\infty} \Delta p = E\Delta p_i .$$

Disregarding higher order moments

$$E\Delta p_i = \tfrac{1}{2}\, p(1-p)[\Delta\Gamma + \sigma^2(\tfrac{1}{2} - p)], \quad \hat{p} = \tfrac{1}{2} + \frac{\Delta\Gamma}{\sigma^2} .$$

In order for $0 < \hat{p} < 1$,

$$|\Delta\Gamma| < \frac{\sigma^2}{2} ,$$

must hold, which is condition (2).

For condition (3) consider a circular stepping stone configuration made up of n subpopulations each of which is large enough to ignore finite population effects. Let $P(j) = (p_1(j), p_2(j) \ldots, p_n(j))$ be a vector giving the frequency of allele A_1 in each of the n subpopulations. Changes in the $p_i(j)$ result from the action of selection and migration, in that order. Random mating is assumed to occur within each subpopulation after migration is accomplished by exchanging a fraction, $2m$, of the individuals of one subpopulation with a fraction, m, from each of the two neighboring subpopulations.

There are two states for the entire population which we will call monomorphic states. These occur when all of the $p_i(j)$ are zero, or all are one. If these fixed points are both unstable, then polymorphism will occur.

Sufficient conditions for instability of the origin, given the fitnesses of the genotypes in the n subpopulations, $(S(i), i = 1, \ldots n)$, may be found by linearization of the appropriate difference equations and examination of the eigenvalues of the associated matrix. Toward this end note that, after selection, $p_i(j)$ becomes

$$p_i(j) = \frac{p_i(j)\,\{1 + (p_i(j) + q_i(j))S_1(i) + \tfrac{1}{2}\, q_i(j)S_3(i)\}}{1 + p_i(j)S_1(i) + q_i(j)S_3(i)}$$

$$q_i(j) = 1 - p_i(j)$$

and, after migration, we get

$$p_i(j+1) = (1-2m)\, p'_i(j) + m(p'_{i-1}(j) + p'_{i+1}(j))$$

Linearization of $p_i\ (j+1)$ near the origin leads to the following matrix

$$A = \begin{bmatrix} (1-2m)\alpha_1 & m\alpha_2 & 0 & \cdots & m\alpha_n \\ m\alpha_1 & (1-2m)_2 & m\alpha_3 & \cdots & 0 \\ 0 & m\alpha_2 & (1-2m)\alpha_3 & \cdots & 0 \\ \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & & \cdot \\ m\alpha_1 & 0 & 0 & \cdots & (1-2m)\alpha_n \end{bmatrix}$$

which operates on $P(j)$ near the origin. The first two terms of the characteristic equation of A are

$$\lambda^n - \lambda^{n-1}(1-2m)\sum_{i=1}^{n} \alpha_i$$

$$\alpha_i = \frac{1 + 1/2(S_1(i) + S_3(i))}{1 + S_3(i)}$$

As is well known (BURNSIDE and PANTON 1912), the sum of the eigenvalues of A equals the negative of the coefficient of λ^{n-1} in the characteristic equation:

$$\sum_{i=1}^{n} \lambda^i = (1-2m) \sum_{i=1}^{n} \alpha_i$$

Instability will occur if one or more of the eigenvalues is larger than one in absolute value. This will certainly occur if

$$(1-2m) \sum_{i=1}^{n} \alpha_i > n$$

or

$$(1-2m) \frac{\sum_{i=1}^{n} \alpha_i}{n} > 1 \ .$$

As $n \to \infty$ we approach the description of a linear habitat and also arrive at a *sufficient* condition for polymorphism:

$$(1-2m)\, E(\alpha_i) > 1 \ .$$

This condition holds equally well for autocorrelated and uncorrelated environments. Using the same assumption of small effects as we did in the previous sections to approximate $E\alpha_i$, the condition for polymorphism becomes

$$| \Delta\Gamma | < \tfrac{1}{2}\, \sigma^2 - \frac{4m}{1-2m} \ .$$

LITERATURE CITED

AEBI, H. and H. SUTER, 1969 Catalase. Pp. 255–288. In: *Biochemical Methods in Red Cell Genetics*. Edited by J. J. YUNIS. Academic Press, New York.

BEUTLER, E., 1969 Galactose-1-phosphate uridyl transferase. Pp. 289–305. In: *Biochemical Methods in Red Cell Genetics*. Edited by J. J. YUNIS. Academic Press, London.

BURNSIDE, W. S. and A. W. PANTON, 1912 The *Theory of Equations*. Dover Edition, 1960, New York.

CARLSON, P. S., 1972 Locating genetic loci with aneuploids. Molec. Gen. Genetics **114**: 273–280.

CHEN, S., E. R. GIBLETT, J. E. ANDERSON and B. L. G. FOSSUM, 1972 Genetics of glutamic-pyruvic transaminase: its inheritance, common and rare variants, population distribution, and differences in catalytic activity. Ann. Hum. Genet. **35**: 401–409.

CROW, JAMES F. and MOTOO KIMURA, 1970 *An Introduction to Population Genetics Theory*. Harper and Row, Publishers, Inc., New York City, New York.

DAVIDSON, R. G., 1967 Electrophoretic variants of human 6-phosphogluconate dehydrogenase: population and family studies and description of a new variant. Ann. Hum. Genet. **30**: 355–361.

DETTER, J. C., P. O. WAYS, E. R. GIBLETT, M. A. BAUGHAN, D. A. HOPKINSON, S. POVEY and H. HARRIS, 1968 Inherited variation in human phophohexose isomerase. Ann. Hum. Genet. **31**: 329–338.

GIBSON, J., 1970 Enzyme flexibility in *Drosophila melanogaster*. Nature **227**: 959–960.

GILLESPIE, J. H. and K. KOJIMA, 1968 The degree of polymorphism in enzymes involved in energy production compared to that in non-specific enzymes in two *Drosophila ananassae* populations. Proc. Natl. Acad. Sci. U.S. **61**: 582–585. ——, 1972 The effect of stochastic environments on allele frequencies in natural populations. Theoret. Pop. Biol. **3**: 241–248. ——, 1973a Polymorphism in random environments. Theoret. Pop. Biol. **4**: 193–195.

——, 1973b Natural selection with varying selection coefficients—a haploid model. Genet. Res. **21**: 115–120. ——, 1973c Polymorphism in patchy environments. Am. Naturalist (In press.)

GRELL, E. H., 1962 The dose effect of *ma-l*+ and *ry*+ on xanthine dehydrogenase activity in *Drosophila melanogaster*. Z. Vererb. **93**: 371–377.

HARRIS, H. and D. A. HOPKINSON, 1972 Average heterozygosity per locus in man: an estimate based on the incidence of enzyme polymorphisms. Ann. Hum. Genet. **36**: 9–20.

JAFFÉ, E. R., 1969 DPNH—Methemoglobin Reductase (Diaphorase). Pp. 231–253. In: *Biochemical Methods in Red Cell Genetics*. Edited by J. J. YUNIS. Academic Press, New York.

KOJIMA, K., J. GILLESPIE and Y. N. TOBARI, 1970 A profile of Drosophila species' enzymes assayed by electrophoresis. 1. number of alleles, heterozygosities, and linkage disequilibrium in glucose-metabolizing systems and some other enzymes. Biochem. Genet. **4**: 627–637.

LANGLEY, C. H., Y. N. TOBARI and K. KOJIMA, 1974 Linkage disequilibrium in natural populations of *Drosophila melanogaster*. Genetics (In press.)

LEVENE, H., 1953 Genetic equilibrium when more than one ecological niche is available. Am. Naturalist **87**: 311–313.

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

LEVINTON, J., 1973 Genetic variation in a gradient of environmental variability: marine Bivalvia (Mollusca). Science **180**: 75–76.

LONG, W. K., 1967 Glutathione reductase in red blood cells: Variant associated with gout. Science **155**: 712–713.

LUFFMAN, J. E. and H. HARRIS, 1967 A comparison of some properties of human red cell acid phosphatase in different phenotypes. Ann. Hum. Genet. **30**: 387–401.

POWELL, J. R., 1971 Genetic polymorphisms in varied environments. Science **174**: 1035–1036.

RASMUSON, B., L. R. NILSON and M. RASMUSON, 1966 Effects of heterozygosity on alcohol dehydrogenase (ADH) activity in *Drosophila melanogaster*. Hereditas **56**: 313–316.

SCHNEIDER, A. S., 1969 Triosephosphate isomerase deficiency. Pp. 189–200. In: *Biochemical Methods in Red Cell Genetics*. Edited by J. J. YUNIS. Academic Press, New York.

SELANDER, R. K. and S. Y. YANG, 1969 Protein polymorphism and genic heterozygosity in a wild population of the house mouse. Genetics **63**: 653–667.

SELANDER, R. K. and W. E. JOHNSON, 1973 Genetic variation among vertebrate species. Ann. Rev. Ecol. Syst. **4**: (In press.)

SELANDER, R. K. and D. W. KAUFMAN, 1973 Genic variability and strategies of adaption. Proc. Natl. Acad. Sci. **70**: 175–177.

SIMPSON, N. E., 1966 Factors influencing cholinesterase activity in Brazilian populations. Am. J. Hum. Genet. **18**: 243–252.

SPENCER, N. HOPKINSON, D. A. and H. HARRIS, 1964 Quantitative differences and gene dosage in the human red cell acid phosphatase polymorphism. Nature **201**: 299–300.

STEELE, M. W., W. J. YOUNG and B. CHILDS, 1968 Glucose-6-phosphate dehydrogenase in *Drosophila melanogaster*: starch gel electrophoretic variation due to molecular instability. Biochem. Genet. **2**: 159–175.

TANAKA, K. R., 1969 Pyruvate Kinase. Pp. 167–188. In: *Biochemical Methods in Red Cell Genetics*. Edited by J. J. YUNIS. Academic Press, New York.

THOMAS, D. M. and H. HARRIS, 1971 Comparison of thermostability of different human placental alkaline phosphatase X phenotypes. Ann. Hum. Genet. **35**: 221–224.

VIGUE, C. L. and F. M. JOHNSON, 1973 Isozyme variability in species of the genus *Drosophila*. VI. Frequency-property-environment relationships of allelic alcohol dehydrogenases in *D. melanogaster*. Biochem. Genet. **9**: 213–227.

Corresponding editor: R. C. LEWONTIN