SOME GENETIC PROBLEMS IN NATURAL POPULATIONS

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1. Introduction

This article deals with the theory of genetic changes in natural populations. It does not review the extensive and rapidly growing body of experimental and observational data, but is restricted to the mathematical theory.

Natural selection differs from that in populations under human control in two important respects. (1) The plant or animal breeder can select his stocks on the basis of any character he chooses; in nature the only criterion is the probability of surviving and leaving descendants. (2) The plant or animal breeder can select on the basis of performance of relatives as well as on individual traits; natural selection (insofar as it is intrapopulational) is typically on an individual basis.

The process of genetic change from generation to generation is stochastic, since the factors directing the change (selection, migration, mutation) are usually not constant and because of the process of random sampling of gametes in reproduction. However, it is much simpler to treat the process as deterministic, and for large populations with constant environmental factors this model is satisfactory. Under other conditions a more realistic stochastic model must be introduced. We shall deal here first with deterministic models (J. C.) and, in the second part, introduce mathematically more involved stochastic models (M. K.).

The deductive theory of population genetics and microevolution is due almost entirely to three men: J. B. S. Haldane, R. A. Fisher and Sewall Wright. Haldane has dealt mainly with deterministic processes, especially the rate of change of gene frequencies with natural selection under a wide variety of circumstances. Most of his early work is summarized in the mathematical appendix to his book, "The Causes of Evolution" [10], where references to this work are given. See also [12]. Work on stochastic processes is due mainly to Wright and Fisher. Fisher has been especially concerned with the theory of natural selection and his earlier results are summarized in his book, "The Genetical Theory of Natural Selection" [5]. He has dealt with a stochastic process in connection with the probability of persistence of a mutant gene in a population. After earlier work on the consequences of various mating systems, Wright has been especially concerned with the steady state distribution of gene frequencies under increasingly general conditions [25], [28], [30].

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PART I. DETERMINISTIC PROCESSES

2. Measurement of fitness or selective value

From the standpoint of evolution, fitness is measured by the number of descendants in future generations. Thoday [23] has argued that the descendants should be counted after a long period of time and the "unit of evolution" should be the entire body of individuals that have common descendants; this may range from a single individual in nonsexual organisms to the entire species in sexual organisms or even larger units where hybridization followed by polyploidy or introgression is possible. But, in practice one is constrained by both experimental and mathematical limitations to take a narrower view. We consider fitness as measured by representation in the next generation. This is misleading for some characters (for example, the mutant "grandchildless" in *Drosophila obscura* which renders the daughters sterile), but usually is reasonably satisfactory. Furthermore our unit is the individual and we shall deal mainly with intrapopulation selection.

Wright has measured fitness by the coefficient, w, the selective value, defined (in his words) as follows: "the selective value of a given type of zygote (fertilized egg) is assumed to be measured by its average contribution under the prevailing conditions to the array of zygotes produced a generation later in such a way that $\bar{w}$ is the ratio of the effective size of the population in the following generation to that in the one under consideration." Haldane [10] has used a similar definition. Fisher [5], [8] has measured fitness in terms of the "Malthusian parameter," m, defined by the relation

$$\int_0^\infty e^{-mx} l_x b_x dx = 1 , \tag{2.1}$$

where l_x is the probability of surviving to age x and b_x is the probability of reproducing at age x. In populations with overlapping generations and unstable age distributions it is convenient to weight each age group by its reproductive value [5]; otherwise it makes relatively little difference what system is used. Overlapping generations have been studied specifically by Haldane ([10], and earlier references given there).

3. Effect of deterministic factors on individual genes

This problem has been considered by Haldane, Fisher and Wright. In a series of early papers Haldane discussed in detail the course of selection acting on genes of various types (sex-linked, autosomal, dominant, recessive, heterotic, favored in one sex, etc.) and under various assumptions ([10] and earlier references given here). In general the problems are not difficult in principle, though the actual process may involve some tedious algebra.

The most comprehensive formula for the rate of change in frequency x_i of a gene A_i is Wright's equation (see [30], p. 378), which includes mutation to and from a series of alleles, migration, and genotypic selection with variable coefficients. In our terminology, the formula for a locus with k alleles is

$$\frac{dx_i}{dt} = \sum_{j=1}^{k} (u_{ij}x_j) - \left(\sum_{j=1}^{k} u_{ji}\right) x_i - m(x_i - x_{iI}) + \frac{x_i(1 - x_i)}{2\bar{w}} \left[\frac{\partial \bar{w}}{\partial x_i} - \left(\frac{\overline{\partial w}}{\partial x_i}\right)\right] , \tag{3.1}$$

where x_i is the proportion of A_i among the alleles at this locus, u_{ij} is the rate of mutation from A_j to A_i, m is the immigration coefficient, x_{iI} is the frequency of gene A_i among the immigrants, and w is the genotypic selective value.

4. Effect of selection on population fitness

In nature, as well as in the laboratory, we are often concerned with the aggregate effect of a number of genes on some measurable character. In the theory of natural selection the character of most interest is the selective value or fitness. In this section we consider the effect of selection on the average fitness of the population.

Let P_{ii} be the frequency of the homozygous genotype A_iA_i and $2P_{ij}$ be the frequency of the heterozygous type A_iA_j $(i \neq j)$. No distinction is made between A_iA_j and A_jA_i. Let y_{ij} be the average phenotypic measure of genotype A_iA_j in the population under consideration. Then the average measure of the population will be

$$\bar{y} = \sum_{ij} P_{ij}y_{ij} . \tag{4.1}$$

It is convenient to express the genotype frequencies in terms of gene frequencies and Wright's coefficient of inbreeding, F [24], [33]. Letting x_i be the frequency of the gene A_i, we have

$$\begin{aligned} P_{ij} &= x_ix_j(1 - F) , \qquad i \neq j , \\ P_{ii} &= x_i^2(1 - F) + x_iF . \end{aligned} \tag{4.2}$$

This introduces some restrictions when there are more than two alleles since a single parameter F, together with the gene frequencies, is insufficient to specify all the genotype frequencies. This could be especially troublesome if there were assortative mating. However, with any system of inbreeding the *expected* frequencies of all genotypes are expressible with a single value of F.

If the population is large and with overlapping generations it is reasonable to regard the change in average phenotype as continuous. Then the change in mean measure with selection may be written by differentiating the expression for $\bar{y}$. Since $\bar{y}$ is a function of the x_i's, of F, and of the y_{ij}'s,

$$\frac{d\bar{y}}{dt} = \sum_i \left(\frac{\partial \bar{y}}{\partial x_i}\right)_y \frac{dx_i}{dt} + \frac{\partial \bar{y}}{\partial F}\frac{dF}{dt} + \sum_{ij} \frac{\partial \bar{y}}{\partial y_{ij}}\frac{dy_{ij}}{dt} , \tag{4.3}$$

where $\left(\frac{\partial \bar{y}}{\partial x_i}\right)_y$ means that the derivative is taken as if the y_{ij}'s were constants. But, $\partial\bar{y}/\partial y_{ij} = P_{ij}$ [from (4.1)] and

$$\sum_{ij} P_{ij}\frac{dy_{ij}}{dt} = \overline{\left(\frac{dy}{dt}\right)} . \tag{4.4}$$

Hence, we arrive at the fundamental equation for the change in the average phenotypic measure,

$$\frac{d\bar{y}}{dt} = \sum_i \left(\frac{\partial \bar{y}}{\partial x_i}\right)_y \frac{dx_i}{dt} + \frac{\partial \bar{y}}{\partial F}\frac{dF}{dt} + \overline{\left(\frac{dy}{dt}\right)} . \tag{4.5}$$

In (4.5) the three terms on the right measure the change in average phenotype due to, respectively, changes in gene frequencies, changes in inbreeding coefficient, and changes in the phenotypic measure of individual genotypes. Explicit expressions for the quantities $\partial\bar{y}/\partial x_i$ and $\partial y/\partial F$ can be obtained by differentiating the expression for $\bar{y}$ [see (4.1) and (4.2)], dF/dt is determined by the mating system and $\overline{(dy/dt)}$ depends on the way the phenotypic values of the various genotypes change with time. The value of dx_i/dt depends on the system of selection as shown below.

Equation (4.5) is true for any measured character. In a natural population we wish especially to consider the character fitness. Following Fisher [5], [6], we measure fitness by the Malthusian parameter, m. This is the rate of geometric increase such that, if m is the fitness of a particular class, its contribution to the next generation is proportional to e^m. We obtain an explicit formula for dx_i/dt as follows.

Let N stand for the population number, and n_i stand for the number of A_i genes. The increment of increase in population size in one generation due to the contribution from A_iA_i parents is $NP_{ii}m_{ii}$, which is therefore also a measure of the increase in A_i genes due to contributions from A_iA_i parents. Likewise for any genotype A_iA_j, the increase in A_i genes due to contributions from this genotype is $NP_{ij}m_{ij}$. (Only half the total frequency of A_iA_j and A_jA_i genotypes is used, since only half the contributed genes are A_i.) Thus, $dn_i = \sum_j NP_{ij}m_{ij}dt$ and, since $\sum_j P_{ij} = x_i$ (and $N\sum_j P_{ij} = n_i$),

$$\frac{1}{n_i}\frac{dn_i}{dt} = \frac{\sum_j P_{ij}m_{ij}}{x_i} = a_i', \quad \text{say},$$

$$\frac{dx_i}{dt} = \frac{d(n_i/N)}{dt} = \frac{N\dfrac{dn_i}{dt} - n_i\dfrac{dN}{dt}}{N^2}. \tag{4.6}$$

Substituting from (4.6) and noting that $dN/N = \bar{m}\,dt$,

$$\frac{dx_i}{dt} = \frac{Nn_ia_i' - n_iN\bar{m}}{N^2} = x_i(a_i' - \bar{m}) = x_ia_i. \tag{4.7}$$

Following Fisher [5], [6], we call the quantity a_i $(= a_i' - \bar{m})$ the *average excess* in fitness of the gene A_i. Fisher used the term average excess to designate the excess due to substituting one allele for another, whereas we measure the excess of an allele from the average for the population. The quantity a_i' has also been used by Kempthorne (personal communication).

We may now rewrite (4.5) specifically for the character fitness (measured in Malthusian parameters) as follows:

$$\frac{d\bar{m}}{dt} = \sum_i x_ia_i\left(\frac{\partial\bar{m}}{\partial x_i}\right)_m + \frac{\partial\bar{m}}{\partial F}\frac{dF}{dt} + \overline{\left(\frac{dm}{dt}\right)}. \tag{4.8}$$

The total rate of change in fitness is given by summing the above equation over all relevant loci.

The first term measures the effect on fitness of gene frequency changes, holding constant the fitness coefficients and the inbreeding coefficient. The second term measures the effect due to the change in inbreeding coefficient. This may be written, by differentiation of (4.1) using (4.2), and replacing y_{ij} with m_{ij},

$$\frac{\partial \bar{m}}{\partial F} = \sum_i m_{ii}x_i(1 - x_i) - \sum_{i \neq j} m_{ij}x_ix_j \tag{4.9}$$

$$= \sum_{i<j} (m_{ii} - 2m_{ij} + m_{jj})x_ix_j \, .$$

When $m_{ii} - 2m_{ij} + m_{jj} = 0$ for all i, j (that is, no dominance) the above expression becomes zero as it should; in the absence of dominance, inbreeding has no effect on mean fitness.

The last term in (4.8) represents the effects of changes in the selective value of the genotypes with time. This may be due to changes in the environment. For example, the rise of a competing species might lower the adaptive value of all the genotypes, or a change in climate might increase the fitness of some genotypes and decrease that of others. Even with a stable environment, the fitness of the different genotypes may change with their frequency.

For two alleles (4.8) reduces to

$$\frac{d\bar{m}}{dt} = x_1a_1\left(\frac{\partial \bar{m}}{\partial x_1}\right)_m + x_2a_2\left(\frac{\partial \bar{m}}{\partial x_2}\right)_m + x_1x_2(m_{11} - 2m_{12} + m_{22})\frac{dF}{dt} + \overline{\left(\frac{dm}{dt}\right)} \, , \tag{4.10}$$

or

$$\frac{d\bar{m}}{dt} = x(1-x)(a_1' - a_2')\left(\frac{\partial \bar{m}}{\partial x}\right)_m + x(1-x)(m_{11} - 2m_{12} + m_{22})\frac{dF}{dt} + \overline{\left(\frac{dm}{dt}\right)} \, , \tag{4.11}$$

where $x = x_1$ and $1 - x = x_2$. The quantity $(a_1' - a_2')$ is the average excess of the gene substitution, A_1 for A_2, as used by Fisher.

Equation (4.8) is considerably simplified when random mating can be assumed. When $F = 0$, $P_{ij} = x_ix_j$ and $\partial \bar{m}/\partial x_i = 2\sum_j x_jm_{ij} = 2a_i'$. Thus (4.8) becomes,

$$\frac{d\bar{m}}{dt} = 2\sum_i x_i(a_i' - \bar{m})a_i' + \overline{\left(\frac{dm}{dt}\right)} \, , \tag{4.12}$$

and, since $\bar{m} = \sum_i x_ia_i'$, $2\sum_i x_i(a_i' - \bar{m})a_i' = 2\left(\sum_i x_ia_i'^2 - \bar{m}^2\right) = 2\sum_i x_i(a_i' - \bar{m})^2$.

This quantity is clearly a measure of the variance in fitness due to gene differences at the A locus, since a_i' is the average fitness of the A_i-containing genotypes weighted in accordance with the frequency with which A_i enters into these genotypes. It can also be shown, by the usual least-squares methods, to be the (additive) genetic variance at this locus. Thus we obtain, for a randomly mating population

$$\frac{d\bar{m}}{dt} = V_m + \overline{\left(\frac{dm}{dt}\right)} \, , \tag{4.13}$$

where V_m is the genetic variance in fitness. As before, this can be extended by summing over all independent relevant loci.

Wright [34] has independently derived an analogous formula for the change in fitness in one generation

$$\Delta\bar{w} = \frac{V_w}{w} + \overline{\left(\frac{dw}{dt}\right)}, \tag{4.14}$$

where w is the selective value as defined in section 2. Roughly, $w = e^m$. If the fitnesses of the genotypes are constant, (4.13) reduces to

$$\frac{d\bar{m}}{dt} = V_m, \tag{4.15}$$

which is Fisher's elegant "Fundamental Theorem of Natural Selection." In his words, "The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time" [5].

Although Fisher's theorem depends on the constancy of the fitnesses of the various genotypes, it does not, as the previous section might imply, depend on random mating. Fisher measures the extent of departure from random mating genotype frequencies by a quantity λ, defined as

$$\lambda = \frac{P_{ij}^2}{P_{ii}P_{jj}} \qquad (i \neq j). \tag{4.16}$$

The necessary condition that the rate of change in fitness be equal to the genetic variance is that λ be constant as Fisher has shown explicitly for the two-allele case [6]. Extension to more than two alleles has been made by Kempthorne (personal communication). The theorem holds as long as the population changes in such a way as to maintain constant λ's.

A difficulty in the utility of λ is that, except for random mating ($\lambda = 1$), λ is not invariant with changes in gene frequency. In this respect Wright's F is more useful, for it is a function of the mating system and independent of gene frequencies. For example, one generation of sib mating in a previously randomly mating population leads to $F = .25$. But it leads to a value of λ of 9/25 when $x = .5$ and 27/91 when $x = .75$.[1]

The Fundamental Theorem of Natural Selection would imply, since the variance must always be positive, that fitness can never decrease. Usually the direction of gene frequency change under natural selection is such as to increase the fitness, but this is not necessarily so. If the system is such that the most fertile organisms produce progeny of lowest fitness, the average fitness of the population will be lowered. An examination of the terms in equation (4.8) shows that decrease in fitness can happen either by a change in the level of inbreeding or by a change in the value of the selection coefficients.

The following example illustrates that average fitness can decrease under selection. Consider for simplicity a single pair of alleles in a haploid organism. Gene A_1 is progressively less favored as it becomes more common as might happen, for example, in a heterogeneous environment.

[1] The λ referred to here is the symbol used in Fisher's 1941 paper. The remarks do not apply to the λ introduced in his 1949 book [7] as the dominant latent root of the generation matrix for a specific inbreeding plan and which, like F, is independent of the gene frequency.

GENE	FREQUENCY	FITNESS
A_1	x	$m_1 = s(1 - 2x)$
A_2	$1 - x$	$m_2 = 0$

$$\bar{m} = xm_1$$

$$\left(\frac{\partial \bar{m}}{\partial x}\right)_m = m_1 = s(1 - 2x)$$

$$\frac{dx}{dt} = x(1 - x)(a_1' - a_2'), \quad a_1' = s(1 - 2x), \quad a_2' = 0$$

$$\left(\frac{d\bar{m}}{dt}\right) = \left(x\frac{dm_1}{dx} + (1 - x)\frac{dm_2}{dx}\right)\frac{dx}{dt} = -2s^2x^2(1 - x)(1 - 2x) .$$

Then, from the relevant terms in (4.11)

$$\frac{d\bar{m}}{dt} = s^2x(1 - x)(1 - 2x)(1 - 4x) , \tag{4.17}$$

which is negative when $1/4 < x < 1/2$. In this range natural selection acts so as to lower the population fitness. Other examples have been given by Wright ([30], and personal communication).

Fisher [6] has considered selection of a hypothetical mating habit gene that, although changing frequency under selection, has no influence on population fitness. An actual example, similar in some respects, has been studied by Crosby [1]. In his case a gene that is disadvantageous to the species spreads because of its immediate advantage to the individual. Haldane [10] and Wright [30] have considered several other possibilities, such as selection for characters useful in intraspecies competition but lowering the average fitness of the species, intrabrood competition, self sterility factors in plants, and models that lead to cyclic changes in gene frequencies.

The general conclusion is that natural selection always acts in such a way as to increase those factors that cause the greatest probability of leaving progeny. Usually this results in increased fitness of the species, but not necessarily. When interpopulation selection is included the situation is, of course, more complicated.

5. The effect of mutation on fitness

The formulas given previously may be modified to include the effects of mutation and migration by using the appropriate terms from (3.1). Since migration and mutation can both be regarded as linear pressures on the gene frequency, they are interchangeable in the theory and we shall consider only mutation.

As long as the effects of mutation and selection are both small, we may write

$$\frac{dx_i}{dt} = x_ia_i - \left(\sum_j u_{ji}\right)x_i + \sum_j (u_{ij}x_j) , \tag{5.1}$$

which for two alleles reduces to

$$\frac{dx}{dt} = x(1 - x)(a_1' - a_2') - ux + v(1 - x) , \tag{5.2}$$

where $x = x_1$, $1 - x = x_2$, $u = u_{21}$ and $v = u_{12}$. These formulas may then be substituted into (4.5).

The effect of recurrent mutation on fitness may then be measured by comparing the average fitness, $\bar{m}$, of a population at equilibrium with and without mutation. By setting (5.2) equal to zero the equilibrium frequencies may be found, and by omitting the mutation terms the equilibrium in the absence of mutation is obtained. Then by substituting these values in (4.1) we find the effect of mutation on fitness.

The interesting result is that the effect of recurrent mutation on fitness is dependent almost solely on the mutation rate and hardly at all on the fitness of the mutant genotype. This was first pointed out by Haldane in 1937 [11].

We shall illustrate this for the case of two alleles. For this purpose there is no loss of generality in assuming that one genotype has fitness zero, measured in Malthusian parameters.

GENOTYPE	FREQUENCY	FITNESS
A_1A_1	$x^2(1-F) + xF$	0
A_1A_2	$2x(1-x)\,(1-F)$	$-h$
A_2A_2	$(1-x)^2\,(1-F) + (1-x)F$	$-m$.

Assume that the rate of mutation from A_1 to A_2 is u per generation. Assume that the reverse mutation rate, v, is zero. (Mutation acting in the same direction as selection has a very minor effect.)

Then, from (4.6) $a_1' = -h(1-x)(1-F)$ and $a_2' = -hx(1-F)-m[(1-x)(1-F) + F]$. Substituting these values into (5.2) and setting the expression equal to zero gives the equilibrium value of the gene frequency, $\hat{x}$. Examination of the region around the point of equilibrium shows that it is stable. In this example, the average fitness if there were no mutation would clearly approach 0. The average fitness with mutation is given by $\bar{m}$, which is therefore a measure of the effect of mutation on fitness. If we designate this reduction in fitness due to mutation by $\Delta\bar{m}$, we obtain

$$(5.3)\qquad \begin{aligned}\Delta\bar{m} &= -2\hat{x}(1-\hat{x})(1-F)h - [(1-\hat{x})^2(1-F) + (1-\hat{x})F]m \\ &= -u - h(1-F)(1-\hat{x})\,.\end{aligned}$$

We shall consider four genetically interesting cases:

(a) Deleterious factor recessive, $h = 0$. $\Delta\bar{m} = -u$

(b) Deleterious factor dominant, $h = m$. $\Delta\bar{m} \cong -u(2-F)$

With random mating; $F = 0$. $\Delta\bar{m} \cong -2u$

(c) Complete homozygosity, $F = 1$. $\Delta\bar{m} = -u$

(d) Incomplete dominance. $\Delta\bar{m} = -u\left[1 + \frac{h(1-F)}{mF+h-hF} - \frac{uh(1-F)^2(m-2h)}{(mF+h-hF)^3} + \cdots\right]$

With random mating; $F = 0$. $\Delta\bar{m} \cong -2u\left[1 - \frac{u(m-2h)}{2h^2}\right]$.

As long as $2h^2 \gg u(m-2h)$, the effect on fitness is approximately twice the mutation rate. Hence the effect of mutation to any gene which is not almost completely recessive is as if the gene were dominant. Only when h is small enough that h^2 is of the order of the mutation rate and m is large does the gene act effectively as a recessive, unless there is considerable departure from random mating.

The total effect of mutation at all loci is the sum of the mutation rates weighted by a factor of 2 if the mutant is not recessive, or (as Haldane has shown) by 3/2 if the factor is sex linked. If fitness is measured in Malthusian parameters this is exactly the weighted sum, because the Malthusian parameter is additive in this respect.

This fact has been used in three ways:

(1) Haldane [11] has noted that $\sum ku$, where k is a weighting constant between 1 and 2 inclusive, is the loss in fitness that a species suffers because of mutation. Prevailing estimates of gene number and average mutation rate would lead to a value of 5 or 10 per cent for this figure, and Haldane suggests that this is "the price paid by a species for its capacity for further evolution."

(2) Muller [20], using a somewhat different approach, likewise concludes that the total genetic damage due to mutation is proportional to the total mutation rate and warns against the dangers of increasing this by unnecessary exposure to radiations. This problem has also been discussed by Wright [32].

(3) Crow [2] has used this as an argument against the assumption that much heterosis in fitness can result from the removal of deleterious recessives during inbreeding. If heterosis were due entirely to concealment of recessives, crosses between inbred lines should not on the average exceed the equilibrium populations from which they were derived by more than the total mutation rate. He has suggested that, although inbreeding decline and recovery on outcrossing probably depend largely on loci with deleterious recessive alleles, differences between various hybrids and variance in randomly mated populations are principally due to genes of intermediate frequency, of which the simplest explanation is overdominance. The applicability of this analysis to yield characters depends on the extent to which yield can be equated to fitness, which in turn depends on the extent to which these characters have had a long history of selection so that approximate equilibrium has been reached.

PART II. STOCHASTIC PROCESSES

In Part I we have treated the process of change in gene frequency as deterministic, but only as a simplification. The process of organic evolution, which proceeds over enormous periods of time under ever fluctuating natural conditions is likely to be stochastic rather than deterministic. Furthermore, in a finite population the segregation of genes intrinsic to the Mendelian mechanism of inheritance introduces a random element into the process even when everything else is constant.

We classify the factors which cause the random fluctuation in gene frequency into two groups: (1) Random sampling of gametes in reproduction in finite populations. (2) Random fluctuation of systematic pressures (that is, intensity of selection, rate of migration and the rate of mutation). The first is prominent in smaller populations, while the second is important in larger ones (Kimura, [13]). The biological significance of these factors, Wright [25], [29], [31] has advocated, consists in adding a trial and error mechanism to the process of change of the genetic constitution of local populations, thus making the process of evolution less shortsighted.

Corresponding to each of these factors listed above, we can associate various factors with directional effect such as mutation, selection and migration. Our chief task is to investigate how the population undergoes genetical changes with the

passage of time. As will be seen in the following treatments, the solution of each problem is often rather difficult and our results are not general enough to cover all cases. It is hoped however that the presentations cover some important cases and stimulate mathematicians to work further so that more powerful techniques will be introduced.

6. Fundamental differential equations

In natural populations, the number of individuals is usually large and the process of gradual change covers enormous periods of time. This enables us to regard the process of the change in gene frequency as a continuous stochastic process. Then we can apply the Kolmogorov equations [17].

Consider n loci each containing an arbitrary number of alleles such that the lth locus has m_l alleles, say $A_1^{(l)}, A_2^{(l)}, \cdots, A_{m_l}^{(l)} (l = 1, 2, \cdots, n)$. Let $x_i^{(l)}$ be the frequency of ith allele in the lth locus, i.e., $A_i^{(l)}$, and let $\delta x_i^{(l)}$ be the amount of change of $x_i^{(l)}$ per generation. Here $\sum_{i=1}^{m_l} x_i^{(l)} = 1$ for all l.

If we denote by $\phi(x_1^{(1)}, \cdots, x_{m_1-1}^{(1)}, \cdots, x_1^{(n)}, \cdots, x_{m_n-1}^{(n)}; p_1^{(1)}, \cdots, p_{m_1-1}^{(1)}, \cdots, p_1^{(n)}, \cdots, p_{m_n-1}^{(n)}; t)$ the probability density that the frequencies of $A_i^{(l)}$'s lie between $x_i^{(l)}$ and $x_i^{(l)} + dx_i^{(l)}$ after t generations, given that the initial frequencies of $A_i^{(l)}$'s are $p_i^{(l)}$ (where $i = 1, \cdots, m_l - 1$), then ϕ should satisfy the following partial differential equation:

$$\frac{\partial \phi}{\partial t} = \frac{1}{2} \sum_{l,l'} \sum_{i,i'} \frac{\partial^2}{\partial x_i^{(l)} \partial x_{i'}^{(l')}} \{E[(\delta x_i^{(l)} - E(\delta x_i^{(l)}))(\delta x_{i'}^{(l')} - E(\delta x_{i'}^{(l')}))]\}\phi - \sum_l \sum_i \frac{\partial}{\partial x_i^{(l)}} \{E(\delta x_i^{(l)})\phi\} \tag{6.1}$$

where i and i' go from 1 to $m_l - 1$ and l, l' go from 1 to n. (6.1) is a direct application of Kolmogorov's second (or forward) fundamental differential equation giving the law of forward progression of the state of gene frequencies. In applying this, of course, we must be careful that the assumptions underlying (6.1) are met in the actual situation.[2]

In our case $x_i^{(l)}$ takes on values from 0 to 1 and

$$E\{(\delta x_i^{(l)} - E(\delta x_i^{(l)}))(\delta x_{i'}^{(l')} - E(\delta x_{i'}^{(l')}))\}$$

vanishes at the boundaries (singularity at boundaries) and ϕ should be defined on the domain $I: 0 < x_i^{(l)} < 1$ $(i = 1, \cdots m_l, l = 1, \cdots, n)$. If the nontrivial steady state distribution exists, as in the case of reversible mutations and selection in finite populations, the distribution at the steady state should satisfy $\partial\phi/\partial t = 0$, $\int_I \phi dx$'s $= 1$ and (6.1) seems to be sufficient. Unfortunately, if the processes of fixation and loss are irreversible, the information from (6.1) may be insufficient to describe the whole processes and additional devices are necessary. In such a simple case as random genetic drift in a triallelic locus, the probability density of the classes containing two alleles when the third is lost does not satisfy the Kolmogorov equa-

[2] The effect of the previous generation has been studied by Patlak [21] for some simple cases.

tion, as will be seen later. If the only factor causing random fluctuation is random sampling of the gametes,

$$E\{(\delta x_i^{(l)} - E(\delta x_i^{(l)}))(\delta x_i^{(l')} - E(\delta x_i^{(l')}))\} = 0, \quad \text{for } l \neq l' .$$

Let us now consider the simplest case of one locus ($n = 1$) containing only a pair of alleles denoted by A_1 and A_2. Then we have

$$\frac{\partial \phi}{\partial t} = \frac{1}{2}\frac{\partial^2}{\partial x^2}\{V_{\delta x}\phi\} - \frac{\partial}{\partial x}\{M_{\delta x}\phi\} , \tag{6.2}$$

where $M_{\delta x} = E(\delta x)$, $V_{\delta x} = E(\delta x)^2 - (E(\delta x))^2$ and x is the frequency of A_1. This equation was first introduced in population genetics by Wright [28] and is equivalent to the Fokker-Planck equation in physics. When random sampling of gametes is the only source of the random fluctuation, $V_{\delta x} = x(1 - x)/2N$. If the systematic pressures are linear (that is, mutation, migration) $M_{\delta x}$ has the form $\beta - (\alpha + \beta)x$. For this case (6.2) has been studied by Malécot [18]. Also it has been investigated by Feller [3] and Goldberg [9] from pure mathematical interest. From the standpoint of population genetics, the solution of (6.2) for a steady state ($\partial\phi/\partial t = 0$) in which recurrent mutation, migration, selection and random factors balance each other, is quite important and was obtained by Wright [26] before he introduced (6.2). This is

$$\phi(x) = \frac{C}{V_{\delta x}} \exp\left[2\int \frac{M_{\delta x}}{V_{\delta x}}\, dx\right] \tag{6.3}$$

in our terminology. The constant C is chosen such that $\int_0^1 \phi(x)dx = 1$. In the present paper, however, we will not be especially concerned with this steady state distribution.

7. Random sampling of gametes as a factor causing random fluctuation

In the following discussion, we assume that the mating is at random and generations do not overlap.

(1) *Pure "random drift" with a pair of alleles.*—This was first studied by Fisher [4], who called it the Hagedoorn effect. The correct solution for the probability distribution of frequency classes at the state of steady decay was first obtained by Wright [25]. The complete solution has been obtained very recently [15] and will be summarized briefly.

Let A_1 and A_2 be a pair of alleles and let $p(0 < p < 1)$ be the initial frequency of A_1 in the population with N breeding individuals mating at random. Under the assumption that mutation, migration and selection are absent, the frequency of gene A_1, denoted by x, fluctuates from generation to generation until the gene is irreversibly fixed or lost.

The probability $f(1, t)$ of the gene A_1 being fixed in the population by the tth generation is

$$f(1, t) = p + \sum_{i=1}^{\infty} (-1)^i \frac{(2i + 1)}{2i(i + 1)} (1 - r^2)\, T_{i-1}^1(r) \exp\left[-\frac{i(i + 1)t}{4N}\right] , \tag{7.1}$$

where $r = 1 - 2p$ $(-1 < r < 1)$, and $T^1_{i-1}(r)$ is the Gegenbauer polynominal [19] which is related to the hypergeometric function F by

$$T^1_{i-1}(r) = \frac{i(i+1)}{2} F\left(i+2, 1-i, 2, \frac{1-r}{2}\right), \tag{7.2}$$

so that

$$T^1_0(r) = 1,\ T^1_1(r) = 3r,\ T^1_2(r) = 3(5r^2 - 1)/2,\ T^1_3(r) = 5(7r^3 - 3r)/2,$$

etc. The probability of the gene A_1 being lost from the population by the tth generation, $f(0, t)$, can be obtained by replacing p with q and r with $-r$ in the above formula (7.1).

Next let us consider the probability distribution of unfixed classes. Let $\phi(x; p; t)$ be the probability density that the gene frequency in the tth generation is between x and $x + dx(0 < x < 1)$, given that the initial frequency of A_1 is p. Since $V_{\delta x} = x(1 - x)/2N$ and $M_{\delta x} = 0$ in this case (6.2) becomes

$$\frac{\partial \phi}{\partial t} = \frac{1}{4N} \frac{\partial^2}{\partial x^2} \{x(1-x)\phi\}. \tag{7.3}$$

The pertinent solution of this equation with the initial condition of $\phi(x; p; 0) = \delta(x - p)$ is

$$\phi(x; p; t) = \sum_{i=1}^{\infty} \frac{(2i+1)(1-r^2)}{i(i+1)} T^1_{i-1}(r) T^1_{i-1}(z) \exp\left[-\frac{i(i+1)t}{4N}\right], \tag{7.4}$$

where T represents the Gegenbauer polynomial as before, and $z = 1 - 2x$ $(-1 < z < 1)$. The series is uniformly convergent for $t > 0$, and for large t we have the well known formula

$$\phi(x; p; t) \sim C \exp\left[-\frac{1}{2N} t\right], \quad (t \to \infty) \tag{7.5}$$

where the constant C is equal to $6pq$.

We shall next consider the process of random drift in a multi-allelic locus. Though the complete solution has not been obtained, the asymptotic behavior of this process has been investigated successfully [16]. Especially in the case of a tri-allelic locus a detailed analysis of this process has been carried out and we can construct graphs illustrating the process of change after about N generations.

(2) *Random drift with three alleles.*—Consider the random mating population containing three alleles A_1, A_2, and A_3 with frequencies x, y and z $(x + y + z = 1)$. Let $\mu'^{(t)}_{m,n}$ be the m, nth moment of distribution of x and y at the tth generation such that $\mu'^{(t)}_{m,n} = E(x_t^m y_t^n)$, then we obtain a system of differential equations:

$$\frac{d\mu'^{(t)}_{m,n}}{dt} = -\frac{(m+n)(m+n-1)}{4N} \mu'^{(t)}_{m,n} + \frac{m(m-1)}{4N} \mu'^{(t)}_{m-1,n} + \frac{n(n-1)}{4N} \mu'^{(t)}_{m,n-1} \tag{7.6}$$

$$(m, n = 1, 2, 3, \cdots),$$

where N is the number of breeding individuals in the population which is assumed

to be sufficiently large that terms of order $1/N^2$, $1/N^3$, etc., can be neglected without serious error.

If the initial frequencies of A_1, A_2 and A_3 in the population are p_1, p_2, and p_3 respectively ($p_1 + p_2 + p_3 = 1$), $\mu'^{(0)}_{m,n} = p_1^m p_2^n$ and the asymptotic formula for the moment $\mu'^{(t)}_{m,n}$ is obtained from (7.6). From this moment formula, we can obtain the asymptotic formulas for various probability distributions of all classes.

First consider the classes which contain three alleles ($0 < x, y, z < 1$). Let $\phi(x, y; p_1, p_2; t)$ be the probability density that the frequency of A_1 lies between x and $x + dx$ and at the same time A_2 lies between y and $y + dy$ in the tth generation, given that they start from $x = p_1$ and $y = p_2$ at $t = 0$, then

$$
\begin{aligned}
(7.7)\quad \phi(x, y; p_1, p_2; t) &= 5!p_1p_2p_3 \exp\left[-\frac{3t}{2N}\right] + \frac{7!}{2!}p_1p_2p_3\left\{\left(p_1 - \frac{1}{3}\right)x\right. \\
&\left. + \left(p_2 - \frac{1}{3}\right)y + \left(p_3 - \frac{1}{3}\right)z\right\}\exp\left[-\frac{6t}{2N}\right] + \frac{9!}{3!2!}p_1p_2p_3\left\{\left(p_1^2 - \frac{3}{4}p_1 + \frac{3}{28}\right)x^2\right. \\
&+ \left(p_2^2 - \frac{3}{4}p_2 + \frac{3}{28}\right)y^2 + \left(p_3^2 - \frac{3}{4}p_3 + \frac{3}{28}\right)z^2 + 3\left(p_1p_2 - \frac{p_1+p_2}{4} + \frac{1}{14}\right)xy \\
&+ 3\left(p_1p_3 - \frac{p_1 + p_3}{4} + \frac{1}{14}\right)xz + 3\left(p_2p_3 - \frac{p_2 + p_3}{4} + \frac{1}{14}\right)yz\Big\} \\
&\cdot \exp\left[-\frac{10t}{2N}\right] + \cdots .
\end{aligned}
$$

It can be shown by direct substitution that (7.7) satisfies the following partial differential equation derived from (6.1):

$$
(7.8)\qquad \frac{\partial\phi}{\partial t} = \frac{1}{4N}\frac{\partial^2}{\partial x^2}\{x(1-x)\phi\} - \frac{2}{4N}\frac{\partial^2}{\partial x\partial y}\{xy\phi\} + \frac{1}{4N}\frac{\partial^2}{\partial y^2}\{y(1-y)\phi\} .
$$

Figure 1 illustrates the distributions given by (7.7) in triangular coordinates. Figure 2 illustrates the state of steady decay in the distribution of gene frequencies.

Next, we can also obtain the probability density $\phi_{12}(x; t)$ in the tth generation, that the frequency of gene A_1 lies between x and $x + dx$ ($0 < x < 1$), with A_1 and A_2 coexisting but with A_3 lost from the population. The explicit expression of ϕ_{12} has been obtained but it does not satisfy the Fokker-Planck equation since a contribution to the probability distribution also comes from the classes where three alleles coexist. Also, using (7.1) we can obtain the probability that gene A_1 has become fixed in the population by the tth generation.

(3) *Arbitrary number of alleles.* We shall merely state the following theorem.

If we start from the population which contains m alleles, say, $A_1, A_2, \cdots$ *and* A_m *with frequencies* $p_1, p_2, \cdots$ *and* p_m $\left(\sum_1^m p_i = 1\right)$, *the probability density that it contains k of them, say,* $A_1, A_2, \cdots$ *and* A_k *with respective frequencies* $x_1, x_2, \cdots$ *and* x_k $\left(\sum_1^k x_i = 1\right)$ *in the* tth *generation is given asymptotically by*

$$(7.9)\quad \phi_{1,2,\cdots,k}(x_1, x_2, \cdots, x_{k-1}; t) \sim (2k-1)!\left(\prod_{j=1}^{k} p_j\right)\exp\left[-\frac{k(k-1)t}{4N}\right], \qquad (t \to \infty),$$

where $k < m$. The validity of this formula depends on the assumption that the population size N is sufficiently large as compared with m, the number of the alleles in question.

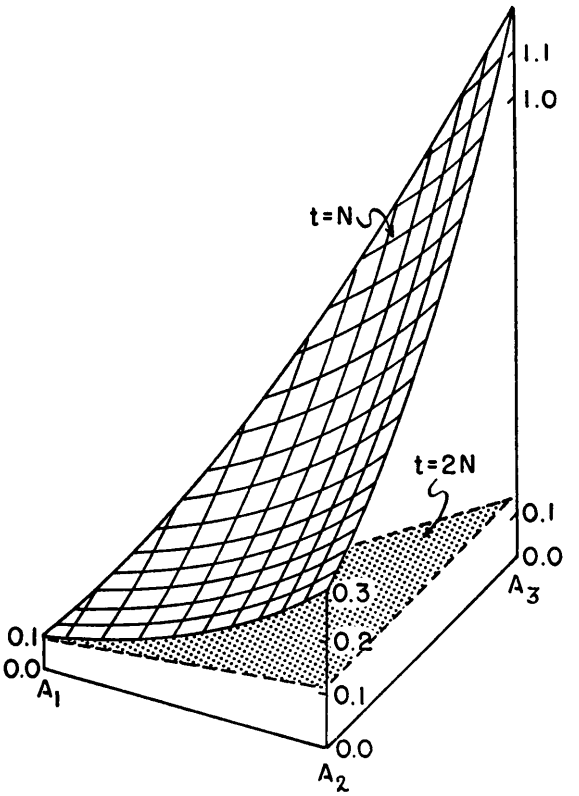

FIGURE 1

The distribution of unfixed classes in a tri-allelic system. The frequency of the three alleles, A_1, A_2, and A_3, are given in triangular coordinates on the abscissa; for example, the corner labeled A_2 represents fixation of gene A_2. The ordinate is the probability density, ϕ. The distribution surface is given for two values of time measured in generations, $t = N$, and $t = 2N$. The initial gene frequencies are $p_1 = 0.1$, $p_2 = 0.3$, and $p_3 = 0.6$.

Here it will be noted that amount of heterozygosis decreases exactly at the rate of $1/2N$:

$$(7.10)\quad H_t = H_0 \exp\left[-\frac{t}{2N}\right],$$

where H_t is the frequency of heterozygotes in the population at the tth generation.

(4) *Transformation of the population under linear pressures.*—Under the term linear pressure, we include the pressures of gene mutation and migration. Usually the rate of mutation is so low that although supplying the raw material for evolu-

tion, it can hardly determine the course of change of gene frequency. On the other hand, migration between subdivided populations may be of considerable significance for determining the gene frequency as will be found in Wright's theory. Consider a population of size N. If we suppose that this population exchanges individuals with a random sample taken from the total species at the rate m per generation,

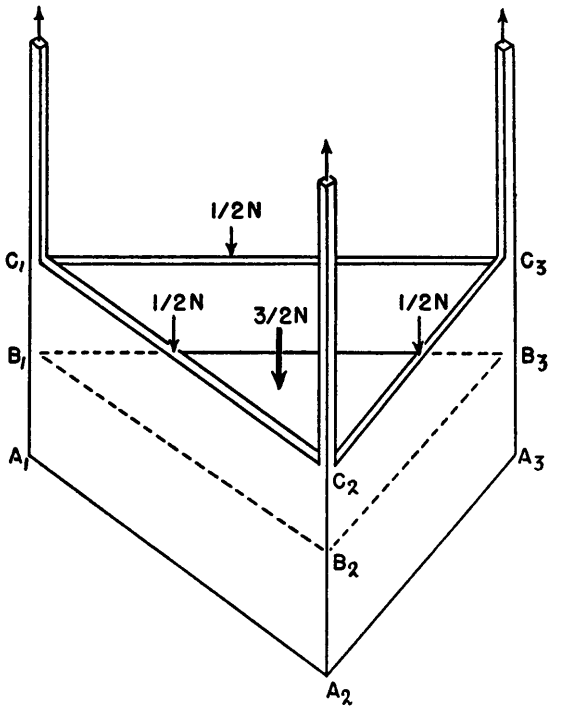

FIGURE 2

Diagram illustrating the distribution when a state of steady decay has been reached. In the center is the surface where the three alleles coexist; the three margins illustrate classes where one allele has been lost; and the corners represent states of fixation of one of the allelels. As indicated, the distribution surface where three alleles coexist is reduced by $3/2N$ per generation. The margins, which are equivalent to a di-allelic population, have a rate of decay of $1/2N$ per generation. The relative proportion of areas and the volume are not exact in the drawing.

then the amount of change of the frequency of gene A_1 per generation is $\delta x = m(\xi - x)$ where ξ is the frequency of A_1 in the immigrants.[3] Using the system of differential equations, as in the case of random genetic drift, we can obtain the moments of the distribution about the origin at the tth generation. The general formula is

$$(7.11)\qquad \mu_n'^{(t)} = \sum_{i=0}^{\infty} \binom{n}{i} \frac{\Gamma(B+n)\Gamma(A+2i)\Gamma(A-B+i)\Gamma(A+i-1)}{\Gamma(A+n+i)\Gamma(B+i)\Gamma(A-B)\Gamma(A+2i-1)}$$

$$\cdot F(A+i-1, -i, A-B, 1-p) \exp\left[-i\left(m + \frac{i-1}{4N}\right)t\right],$$

[3] If mutation rates are not negligible, we replace m by $m + u + v$ and $m\xi$ by $m\xi + v$, where u and v are respectively the mutation rates of A_1 to and from its allele A_2.

where $A = 4Nm$, $B = 4Nm\,\xi\,(1 > \xi > 0)$ and p is the initial frequency of A. Putting $n \to \infty$, we obtain $\lim \mu_n'^{(t)} = 0$, showing that under this continuous model there are no fixed classes in the distribution. The partial differential equation for the probability distribution of gene frequencies is

$$\frac{\partial \phi}{\partial t} = \frac{1}{4N}\frac{\partial^2}{\partial x^2}\{x(1-x)\phi\} - m\frac{\partial}{\partial x}\{(\xi - x)\phi\}\,. \tag{7.12}$$

Equation (7.11) suggests that (7.12) must have the solution of the form:

$$\phi(x; p; t) = \sum_{i=0}^{\infty} X_i(x)\exp\left[-i\left(m + \frac{i-1}{4N}\right)t\right]. \tag{7.13}$$

By comparing $\int_0^1 \phi x^n dx$ with (7.11), we can show that pertinent solution of (7.12) is given by (7.13) with

$$X_i(x) = x^{B-1}(1-x)^{(A-B)-1}F(A + i - 1, -i, A - B, 1 - x) \tag{7.14}$$

$$\cdot\, F(A+i-1, -i, A-B, 1-p)\,\frac{\Gamma(A-B+i)\Gamma(A+2i)\Gamma(A+i-1)}{i!\,\Gamma^2(A-B)\Gamma(B+i)\Gamma(A+2i-1)}\,.$$

It must be noted that this agrees with Goldberg's [9] "fundamental solution with flux zero boundary condition," ($A = \alpha + \beta$, $B = \beta$, $t = 4Nt$ in Goldberg's formula) while his "absorbing barrier solution" has no genetical meaning under recurrent mutations.

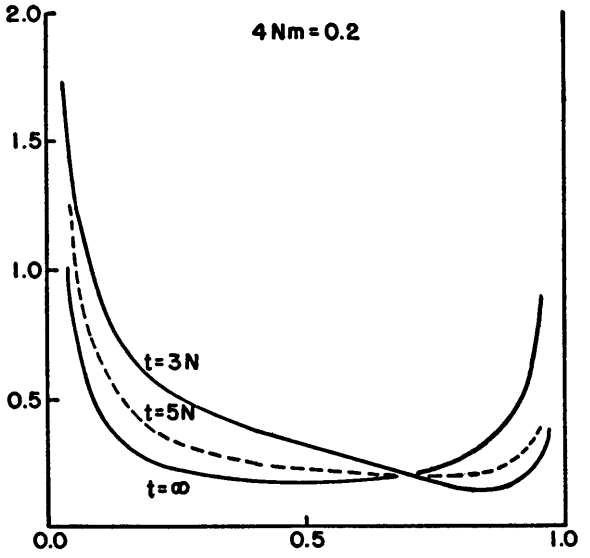

FIGURE 3

Distribution curves for a finite population with migration or other linear pressure. The gene frequency of the immigrants is assumed to be 0.5, and the initial frequency in the population, 0.2. The abscissa is the gene frequency, x; the ordinate is the probability density, ϕ. $4Nm = 0.2$.

At $t \to \infty$, our formula (7.13) converges to Wright's well known formula which can be derived from (6.3). Figures 3, 4 and 5 show the asymptotic behavior of the distribution curve for three different cases: $4Nm = .2$, $4Nm = 2$, and $4Nm = 6$. In

all these cases the gene frequency, ξ, of the immigrants is .5 and the initial gene frequency, p, of the population is .2.

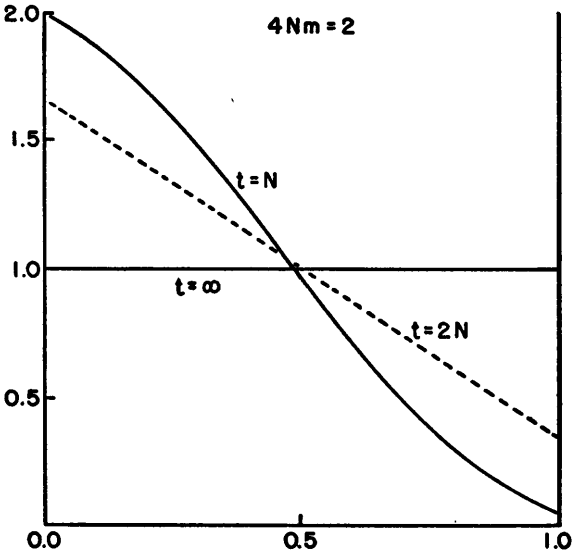

FIGURE 4
Distribution curves for $4Nm = 2$

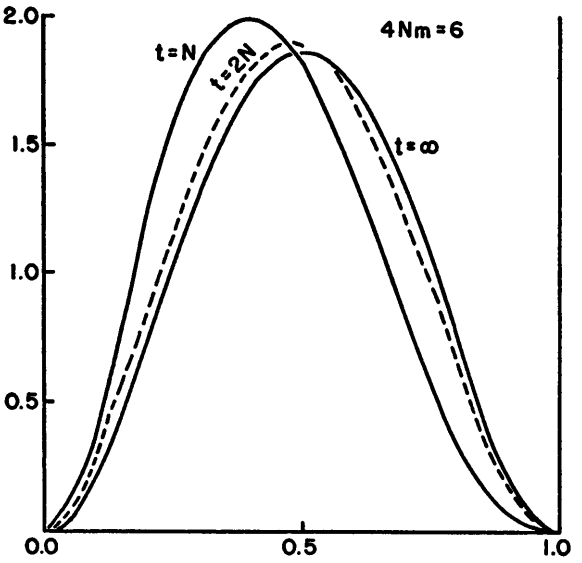

FIGURE 5
Distribution curves for $4Nm = 6$

We should like to point out here that from the genetical point of view the present treatment leading to solution (7.13) is not completely satisfactory, because the present solution gives $\int_0^1 \phi(x; p; t)dx = 1$, while fixed classes must exist if the population size is very small or the mutation rates are extremely low. In other words, if

$4Nm \ll 1$, fixation of the genes dominates mutation and migration so that the population contains only one of the alleles A_1 or A_2 most of the time.[4] Mathematically speaking, the present treatment regards $x = 0$ and $x = 1$ as reflecting barriers, while they should act as elastic barriers under the actual situation.

(5) *Process of genic selection in a finite population.*—This process has been studied recently by Wright and Kerr [35] in connection with the selection experiment done in very small populations of Drosophila. The partial differential equation in this case is

$$\frac{\partial \phi}{\partial t} = \frac{1}{4N} \frac{\partial^2}{\partial x^2} \{x(1 - x)\phi\} - s \frac{\partial}{\partial x} \{x(1 - x)\phi\} , \tag{7.15}$$

where s is the average excess in fitness of the gene substitution A_1 for A_2. Using an ingenious method of his own, Wright successfully analyzed this process assuming the state of steady decay. Recently the junior author has found that the problem can be solved completely. Since the details will be published elsewhere, only a brief report will be given here.

Putting $\phi = e^{2cx} V_l(x) e^{-\lambda_l t}$, (7.15) yields

$$(1 - z^2) \frac{d^2 V_l}{dz^2} - 4z \frac{dV_l}{dz} + [(4N\lambda_l - 2 - c^2) + c^2 z^2] V_l = 0 , \tag{7.16}$$

where $c = Ns$ and $z = 1 - 2x$ $(-1 < z < 1)$. The crucial point is that (7.16) is the oblate spheroidal wave equation [22].

$$(1 - z^2)V'' - 2(m + 1)zV' + (b_l + c^2 z^2)V = 0 , \tag{7.17}$$

with $m = 1, b_l = 4N\lambda_l - 2 - c^2$.

We need the solution V_{1l} which is finite at $z = \pm 1$ and reduces to the Gegenbauer polynomial if there is no selection, that is, if $s = 0$ and therefore $c = 0$. This is because if there is no selection the process should reduce to the process of pure random drift studied in section 7 and $V_{1l}(z)$ should reduce to $T_l^1(z)$. In fact such expansion of V_{1l} into the Gegenbauer polynomials has been studied by Stratton and others [22],

$$V_{1l}(z) = \sum_{n=0,1}^{\infty}{}' f_n^l T_n^1(z) . \tag{7.18}$$

Here the primed summation is over even values of n if l is even, over odd values if l is odd. Coefficients f_n^l and eigenvalues $4N\lambda_l$ can be obtained from the tables of spheroidal wave functions [22]. In the table quoted here $B_{1,l} = c^2 - 4N\lambda_l$ is listed for various values of c from 0 to 5.0 [22, p. 107].

We can write the solution of (7.15) in the form

$$\phi(x; p; t) = \sum_{l=0}^{\infty} C_l e^{2cx} V_{1l}(z) e^{-\lambda_l t} . \tag{7.19}$$

[4] It is interesting to note how Wright [25] managed this problem in his studies of gene frequency distribution at a steady state. He calculated the frequency of fixed classes by the relations:

$$f(0) = \frac{1}{4Nv} f\left(\frac{1}{2N}\right), f(1) = \frac{1}{4Nu} f\left(1 - \frac{1}{2N}\right) \quad \text{and} \quad \sum_{i=0}^{2N} f\left(\frac{i}{2N}\right) = 1 ,$$

where $f(i/2N)$ is the frequency of classes with gene frequency $i/2N$ and is put proportional to $\phi(i/2N)/2N$ if i is neither 0 nor $2N$.

The coefficients C_l can be obtained from the initial condition, $\phi(x; p; 0) = \delta(x - p)$ by using the orthogonal relations of the eigenfunctions $\{V_{1l}\}$.

As $t \to \infty$, the distribution curve decreases its height at a constant rate,

$$\phi(x; p; t) \sim C_0 e^{2cx} V_{10}(z) e^{-\lambda_0 t} . \tag{7.20}$$

So λ_0 gives the rate of constant decay which is denoted by K in Wright and Kerr's paper [35]. In this paper Wright found empirically the following formula giving $2NK$

$$2NK = 1 + \frac{(2Ns)^2}{10} - \frac{(2Ns)^4}{7000} - \frac{(2Ns)^6}{1{,}050{,}000} - .000{,}000{,}004(2Ns)^8 . \tag{7.21}$$

It is impressive that $2N\lambda_0 = (c^2 - B_{1,0})/2$, which should be equal to $2NK$, gives a very good numerical fit to the results obtained from (7.21), as is shown below:

$c = Ns$	$2N\lambda_0 = (c^2 - B_{1,0})/2$	$2NK = 1 + \frac{(2c)^2}{10} + \cdots$
0	1.00000	1.00000
1	1.39765	1.39770
2	2.55927	2.55926
3	4.36529	4.36370

8. Random fluctuation of systematic evolutionary pressures

In order to compare the effect due to random fluctuation of the systematic pressures with that due to random sampling of gametes discussed above, we assume here that the population is sufficiently large that the random sampling variation is negligible. In the following, random fluctuation of selection intensity and of migration rate will be investigated separately.

(1) *Random fluctuation of selection intensities.*—Let A_1 and A_2 be a pair of alleles and assume that there is no dominance. If s is the selective advantage of A_1, defined as before, $\delta x = sx(1 - x)$.

Consider the simplest case in which the gene A_1 is selectively neutral on the average such that the mean value of s over a very long period is zero. The Fokker-Planck equation becomes

$$\frac{\partial \phi}{\partial t} = \frac{V_s}{2} \frac{\partial^2}{\partial x^2} \{x^2(1 - x)^2 \phi\} , \tag{8.1}$$

where V_s is the variance of s.

Putting

$$u = \frac{1}{2} \exp\left[\frac{V_s}{8} t\right] x^{3/2}(1 - x)^{3/2} \phi \quad \text{and} \quad \xi = \log \frac{x}{1 - x}$$

we get the heat conduction equation

$$\frac{\partial u}{\partial t} = \frac{V_s}{2} \frac{\partial^2 u}{\partial \xi^2} \qquad (-\infty \leqq \xi \leqq \infty) , \tag{8.2}$$

and we can obtain the solution of (8.1),

$$(8.3)\qquad \phi(x; p; t) = \frac{1}{\sqrt{2\pi V_s t}} \exp\left\{ -\frac{V_s}{8} - \frac{\left[\log \frac{x(1-p)}{(1-x)p}\right]^2}{2V_s t} \right\} \frac{[p(1-p)]^{1/2}}{[x(1-x)]^{3/2}},$$

where p is the initial frequency of A_1 in the population [14].

The maximum of the distribution shifts towards the two terminals of the distribution as time goes on. The striking difference from the case of random drift due to random sampling of gametes is that in the present case no fixation is possible in the strict sense. In this connection the process of the change in the terminal part of the distribution is important and precise investigation has been made [14]. For large t the distribution curves appear to be U-shaped, since the classes with the highest probability shift toward the terminals indefinitely with time. But it is not a true U-shaped curve since its value at the terminal is always 0.

Here we shall merely state the properties of the change without giving the proofs:

(1) Let $x_{max_1}(<1/2)$ be the gene frequency giving the relative maximum of ϕ near 0, then $x_{max_1} \to 0$, $\phi_{max_1} \to \infty$ as $t \to \infty$.

(2) Let A be the probability that the gene frequency in the population is lower than x_{max_1}, then $A \to 0$ as $t \to \infty$.

(3) Let B stand for the probability that the gene frequency in the population is larger than x_{max_1} but smaller than ϵ, where ϵ is an arbitrarily chosen gene frequency larger than x_{max_1}, then

$$B \to (1-p) - 0\left(\frac{e^{-V_s t/8}}{\sqrt{t}}\right) \to (1-p) \quad \text{as} \quad t \to \infty .$$

Similar relations hold for the other terminal part of the distribution where the gene frequency is close to 1.

(4) Let x_{min} be the gene frequency giving the relative minimum of this pseudo-U-shaped distribution curve, then $x_{min} \to 1/2$ as $t \to \infty$, irrespective of the initial gene frequency.

(5) $\phi_{min} \to 0$ as $t \to \infty$. Finally,

$$(6)\qquad \lim_{\epsilon \to 0+} \int_{\epsilon}^{1-\epsilon} \phi(x; p; t)dx = 1 ,$$

showing that the random fluctuation of selection intensity by itself cannot lead to complete fixation or loss, in the strict sense, contrary to the case of random drift. But as shown above there exists a strong tendency for the gene frequency to move toward either terminus with increasing time. In other words, after a sufficient number of generations almost all populations will be in such a situation that the gene is either almost fixed in the population or almost lost from it. To distinguish this from the fixation or loss in the case of drift due to random sampling of gametes in finite populations, the terms "quasifixation" and "quasiloss" have been proposed.

(2) *Random fluctuation of the migration rate.*—Consider a pair of alleles A_1 and A_2 and let x be the frequency of A_1. If ξ is the frequency of A_1 in the immigrants, then $\delta x = -m(x - \xi)$ where m is the rate of migration. Suppose m fluctuates

randomly from generation to generation with mean $\bar{m}$ and the variance V_m ($=E(m^2) - \bar{m}^2$), then we have

$$\frac{\partial \phi}{\partial t} = \frac{V_m}{2} \frac{\partial^2}{\partial x^2} \{(x - \xi)^2 \phi\} + \bar{m} \frac{\partial}{\partial x} \{(x - \xi)\phi\} . \tag{8.4}$$

By applying the method which Kolmogorov [17] gave in his paper (the second example of section 17), we can solve (8.4) easily. If the initial gene frequency of the population denoted by p is higher than that of the immigrants, that is, $p \geqq \xi$,

$$\phi(x; p; t) = \frac{1}{(x - \xi)\sqrt{\pi V_m t/2}} \exp\left\{ - \frac{\left[\log \frac{x - \xi}{p - \xi} + \left(\frac{V_m}{2} + \bar{m}\right)t\right]^2}{2V_m t} \right\} \tag{8.5}$$

$$(x \geqq \xi) .$$

Thus

$$\lim_{t \to \infty} \phi(x; p; t) = \delta(x - \xi), \text{ where } \delta \text{ represents the delta function.} \tag{8.6}$$

This shows that the frequency of the gene A_1 in the population finally becomes the same as that in the gene pool from which the immigrants come and no frequency distribution, in the usual sense, exists at this state. This seems obvious on intuitive grounds.

Wright [29] studied the steady state distribution of gene frequency when there is selection and random fluctuation in the rate of migration. His formula, however, does not reduce to (8.6) when $s = 0$, since it becomes

$$\phi(x) = C/\left\{(x - \xi)^{2\bar{m}/V_m^2}\right\} \tag{8.7}$$

in our terminology. This discrepancy must be investigated now.

If we seek the steady state distribution by putting $M_{\delta x} = -\bar{m}(x - \xi)$ and $V_{\delta x} = V_m(x - \xi)^2$ in (6.3), we at once obtain (8.7). So this satisfies $\partial\phi/\partial t = 0$. But this does not guarantee that $\phi(x; p; t) \to \phi(x)$ at the limit of $t \to \infty$. This may serve as a warning against the mechanical application of Wright's formula (6.3) though it is very useful and applicable to a wide variety of important cases.

For the other case of $p \leqq \xi$, a formula similar to (8.5) can be obtained easily.

REFERENCES

[1] J. L. Crosby, "Selection of an unfavorable gene-complex," Evolution, Vol. 3 (1949), pp. 212–230.

[2] J. F. Crow, "Dominance and overdominance," *Heterosis*, edited by J. W. Gowen, Ames, Iowa State College Press, 1952, pp. 282–297.

[3] W. Feller, "Diffusion processes in genetics," *Proceedings of the Second Berkeley Symposium on Mathematical Statistics and Probability*, Berkeley and Los Angeles, University of California Press, 1951, pp. 227–246.

[4] R. A. Fisher, "On the dominance ratio," *Proc. Roy. Soc. Edin.*, Vol. 42 (1922), pp. 321–341.

[5] ———, *The Genetical Theory of Natural Selection*, Oxford, The Clarendon Press, 1930.

[6] ———, "Average excess and average effect of a gene substitution," *Annals of Eugenics*, Vol. 11 (1941–42), pp. 53–63.

[7] R. A. FISHER, *The Theory of Inbreeding*, Edinburgh, Oliver and Boyd, 1949.
[8] ———, "Population genetics," *Proc. Roy. Soc. London*, Ser. B., Vol. 141 (1953), pp. 510–523.
[9] S. GOLDBERG, "On a singular diffusion equation." Unpublished Ph.D. thesis, Cornell University, 1950.
[10] J. B. S. HALDANE, *The Causes of Evolution*, New York, Harper and Brothers, 1932.
[11] ———, "The effect of variation on fitness," *Amer. Naturalist*, Vol. 71 (1937), pp. 337–349.
[12] ———, "The statics of evolution," *Evolution as a Process*, London, Allen and Unwin, 1954, pp. 109–121.
[13] M. KIMURA, "Effect of random fluctuation of selective value on the distribution of gene frequencies in natural populations," *Annual Report of the National Inst. of Genetics (Japan)*, Vol. 1 (1951), pp. 45–47.
[14] ———, "Process leading to quasi-fixation of genes in natural populations due to random fluctuation of selection intensities," *Genetics*, Vol. 39 (1954), pp. 280–295.
[15] ———, "Solution of a process of random genetic drift with a continuous model," *Proc. Nat. Acad. Sci.*, Vol. 41 (1955), pp. 144–150.
[16] ———, "Random genetic drift in a multi-allelic locus," *Evolution*, Vol. 9 (1955), pp. 419–435.
[17] A. KOLMOGOROV, Über die analytischen Methoden in der Wahrscheinlichkeitsrechnung," *Math. Annalen*, Vol. 104 (1931), pp. 415–458.
[18] G. MALÉCOT, *Les Mathématiques de l'Hérédité*, Paris, Masson et Cie, 1948.
[19] P. M. MORSE and H. FESHBACH, *Methods of Theoretical Physics*, New York, McGraw-Hill Book Co., 1953.
[20] H. J. MULLER, "Our load of mutations," *Amer. Jour. of Human Genetics*, Vol. 2 (1950), pp. 111–176.
[21] C. S. PATLAK, "The effect of the previous generation on the distribution of gene frequencies in populations," *Proc. Nat. Acad. Sci.*, Vol. 39 (1953), pp. 1063–1068.
[22] J. A. STRATTON, P. M. MORSE, L. J. CHU, and R. A. HUTNER, *Elliptic Cylinder and Spheroidal Wave Functions*, New York, John Wiley and Sons, 1941.
[23] J. M. THODAY, "Components of fitness," *Evolution, Symposium of the Society for Experimental Biology*, No. 7, New York, Academic Press, 1953, pp. 96–113.
[24] S. WRIGHT, "Coefficients of inbreeding and relationship," *Amer. Naturalist*, Vol. 56 (1922), pp. 330–338.
[25] ———, "Evolution in Mendelian populations," *Genetics*, Vol. 16 (1931), pp. 97–159.
[26] ———, "The distribution of gene frequencies under irreversible mutation," *Proc. Nat. Acad. Sci.*, Vol. 24 (1938), pp. 253–259.
[27] ———, "Statistical genetics and evolution," *Bull. Amer. Math. Soc.*, Vol. 48 (1942), pp. 223–246.
[28] ———, "The differential equation of the distribution of gene frequencies," *Proc. Nat. Acad. Sci.*, Vol. 31 (1945), pp. 382–389.
[29] ———, "On the roles of directed and random changes in gene frequency in the genetics of populations," *Evolution*, Vol. 2 (1948), pp. 279–294.
[30] ———, "Adaptation and selection," *Genetics, Paleontology, and Evolution*, Princeton, Princeton University Press, 1949, pp. 365–389.
[31] ———, "Population structure as a factor in evolution," *Moderne Biologie (Festschrift für H. Nachtsheim)*, Berlin, F. W. Peters, 1950, pp. 275–287.
[32] ———, "Discussion on population genetics and radiation," *Symposium on Radiation Genetics, Jour. of Cellular and Comparative Physiol.*, Vol. 35 (1950), Suppl. 1, pp. 187–205.
[33] ———, "The genetical structure of populations," *Annals of Eugenics*, Vol. 15 (1951), pp. 323–354.
[34] ———, "Variable selective values of genotypes," (mimeographed notes on lectures at Edinburgh, 1950).
[35] ———, and W. E. KERR, "Experimental studies of the distribution of gene frequencies in very small populations of *Drosophila melanogaster*, II. *Bar*," *Evolution*, Vol. 8 (1954), pp. 225–240.