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RANDOM GENETIC DRIFT IN MULTI-ALLELIC LOCUS [1]

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Introduction

In the theory that evolution is an irregularly shifting state of balance, especially that of a subtle balance between the evolutionary pressures of mutation, immigration and selection as a group and random or stochastic processes which give rise to processes of trial and error (Wright, 1950), the process of random genetic drift is one of the problems first to be clarified.

Actually the problem of the random drift has been discussed by various authors. As early as 1921, Hagedoorn and Hagedoorn pointed out that the group of organisms destined to become the parents of the next generation is usually considerably smaller than the number of individuals of their species so that some genes will be lost by chance. According to their opinion, reduction of potential variability is automatic, being independent of any sort of selection. They considered that this is the most important gain in knowledge that we owe to Mendel's work and to the biomechanical interpretation of it.

The first mathematical treatment of this so-called "Hagedoorn Effect" was carried out by Fisher (1922). It was rather unfortunate that an abbreviation of a term in his differential equation led him to the erroneous result that the rate of decrease of the variance in the population is 1/4n per generation, where n is the number of individuals in the population. Independently, Wright worked on this problem and obtained the correct answer of 1/2N for the first time, where N is the effective population number (see Wright, 1931). Using an integral equation he also arrived at the flat distribution of unfixed classes for the state of steady decay. This stimulated Fisher to re-examine his results and he found himself in entire agreement with Wright's results. Furthermore, Fisher elaborated the terminal part of the distribution for the case of steady decay by his method of a functional equation (Fisher, 1930a, b). This method was followed by Haldane (1939) to treat the more general case where the number of descendants does not necessarily follow the Poisson distribution. Until now, Fisher's method remains as an unique and powerful tool to find the exact distribution at the terminal part.

In 1945, Wright introduced the Fokker-Planck equation to solve the problem of the gene frequency distribution and applied the equation to the case of steady decay. The problem of random drift was also treated as a problem of a finite Markov chain by Malécot (1944), who got the asymptotic formula for a very large number of generations which is essentially the same as the previously known formula for steady decay. His result on the characteristic roots was later corrected by Feller (1951), who succeeded in getting all characteristic values of the matrix of transition probabilities.

In spite of all these works, the theoretical results have been largely at the level of asymptotic formulae, and no complete solution has been published until the present

author reported the complete solution with a continuous model (Kimura, 1955), of which brief exposition will be made in the first part of this paper.

The problem of random drift due to small population number has also attracted much attention from experimental geneticists and many model experiments have been performed to verify the mathematical deductions or to demonstrate the phenomenon in the classroom. Among them, Dubinin and Romashov (1932) (cited from Dobzhansky, 1951), Bonnier (1947), Moody (1947) and House (1953) may be cited. Recently studies on this phenomenon using laboratory populations of Drosophila melanogaster have been done by several authors; namely by Merrell (1953) using several recessive sex-linked and autosomal genes, by Kerr and Wright (1954) using the gene *forked*, and by Prout (1954) using lethal genes.

In natural populations, some evidence has been found that may suggest the effectiveness of random drift in determining the genetic structure of the population. Among them Lamotte's works (1951, 1952) on *Cepaea nemoralis* and Haga and Kurabayashi's work (1954) on *Trillium kamtschaticum* may be especially interesting. The later authors found, through their ingenious application of the phenomenon known as the differential reactivity of the chromosomes, that in natural populations of this plant high homozygosity correlates with the smallness of population size and high heterozygosity with largeness.

In most of the experimental works mentioned above, however, selection was the predominating factor for determining the genetic change of the populations.

The theoretical treatment of the problem of the random genetic drift has been confined so far to the case where only a pair of alleles exists. This restriction, however, seems to be not only unnatural but also undesirable in some cases. In fact, Haga and Kurabayashi's work suggests the necessity of the extension to the multi-allelic case. The purpose of the present paper is therefore to give the general treatment of the problem in the case of a multi-allelic locus. It will be convenient, however, to give first the brief explanation on the case of two alleles and proceed from the special case to the general.

Summary of the Results Obtained in the Case of a Pair of Alleles

Consider a random mating population of N breeding individuals of diploid organism and let A and A' be a pair of alleles whose frequencies in the population are x and $1 - x$ respectively.

To simplify the discussion, we assume an idealized situation where selection, migration and mutation are absent and generations do not overlap. In this finite population, the gene frequency changes fortuitously from generation to generation due to random sampling of gametes in reproduction. This stochastic process of the change in gene frequency is adequately described by giving the transition probability $f(x;p;t)$ that the frequency of A in the tth generation will be x when it started from the frequency p in the 0th generation. Here x is a discrete random variable which takes values between 0 and 1 in steps of $1/2N$.

In natural populations, however, the number of breeding individuals will usually be large enough such that x can be treated as a continuous random variable with good approximation. This assumption of the continuous model simplifies the mathematical treatment tremendously. The only point we must take care of is that the process of random fixation or loss of an allele is irreversible and the probability distribution has definite discontinuities at both termini, x = 0 and 1. So we must essentially specify 3 probabilities denoted by $f(1;p;t)$, $f(0;p;t)$ and $\phi(x;p;t)dx$ giving respectively the probabilities that A becomes fixed in the population by the tth

generation, that A is lost by the same generation and that the frequency of A lies between x and x + dx ($0 < x < 1$) in the tth generation. The last expression has real meaning for x between 0 and 1 exclusive and will be used as a good approximation of f(x;p;t) with dx being substituted for $1/2N$.

The first probability f(1;p;t) can be obtained by using a moment formula for the distribution and only the results will be presented here:

$$f(1;p;t) = p + \sum_{i=1}^{\infty} (2i + 1)pq(-1)^i F(1-i,i+2,2,p)e^{-[i(i+1)/4N]t}, \qquad (1)$$

where p is the initial frequency of A and q = 1 − p. F in this expression represents the hypergeometric function which is defined by

$$F(1-i,i+2,2,x) = 1 + \frac{(1-i)(i+2)}{1\cdot 2}x + \frac{(1-i)(2-i)\cdot(i+2)(i+3)}{1\cdot 2\cdot 2\cdot 3}x^2 + \cdots$$

$$(i = 1, 2, 3\cdots)$$

For i = 1, 2, 3, 4 etc., it is 1, 1 − 2x, 1 − 5x + 5x², 1 − 9x + 21x² − 14x³ etc. respectively. Putting p = (1 − r)/2, (1) can be expressed also by

$$f(1;p;t) = p + \sum_{i=1}^{\infty} \frac{(-1)^i}{2}\{P_{i-1}(r) - P_{i+1}(r)\}e^{-[i(i+1)/4N]t}, \qquad (2)$$

where $P_n(r)$ represents Legendre polynomials: $P_0 = 1$, $P_1 = r$, $P_2 = \frac{1}{2}(3r^2 - 1)$, $P_3 = \frac{1}{2}(5r^3 - 3r)$ etc.

The second probability f(0;p;t) of A being lost or A' being fixed by the tth generation is obtained simply by replacing p with q, and r with −r in the above expressions.

The third probability f(x;p;t) is expressed by ϕ(x;p;t)dx under the continuous model. It can be shown that the probability density ϕ(x;p;t) satisfies the partial differential equation (Wright 1945, Kimura 1954);

$$\frac{\partial \phi}{\partial t} = \frac{1}{4N}\frac{\partial^2}{\partial x^2}\{x(1 - x)\phi\} \qquad (3)$$

with an initial condition of

$$\phi(x;p;0) = \delta(x - p),$$

where δ represents the delta function. The solution

$$\phi(x;p;t) = \sum_{i=1}^{\infty} pqi(i + 1)(2i + 1)F(1-i,i+2,2,p)F(1-i,i+2,2,x)e^{-[i(i+1)/4N]t} \qquad (4)$$

gives the probability density that A lies between x and x + dx in the tth generation ($0 < x < 1$). The series is shown to be uniformly convergent for t > 0, and for large t the exponential terms decrease very rapidly, so we have an asymptotic formula:

$$\phi(x;p;t) \sim 6pqe^{-(1/2N)t} + 30pq(1 - 2p)(1 - 2x)e^{-(3/2N)t} + \cdots \qquad (5)$$

(Kimura, 1954). It is interesting to note that Malécot's (1944) result

$$\theta_{rt}^{(n)} \sim (3/N)(r/2N)(1 - r/2N)k^n$$

is the first term of the above expansion.

Figure 1a illustrates the process of change in the distribution of unfixed classes when the initial gene frequency is 50% ($p = \frac{1}{2}$). It will be seen that after 2N generations the distribution curve becomes almost flat and still the genes are unfixed in about 50% of the cases. In fig. 1b the initial gene frequency is assumed to be 10% ($p = 0.1$). In this case it takes 4N or 5N generations before the distribution curve becomes practically flat. By that time, however, the genes are fixed in more than 90% of the cases. So the simplest asymptotic formula $\phi \sim Ce^{-(1/2N)t}$ may not be as useful as previously thought.
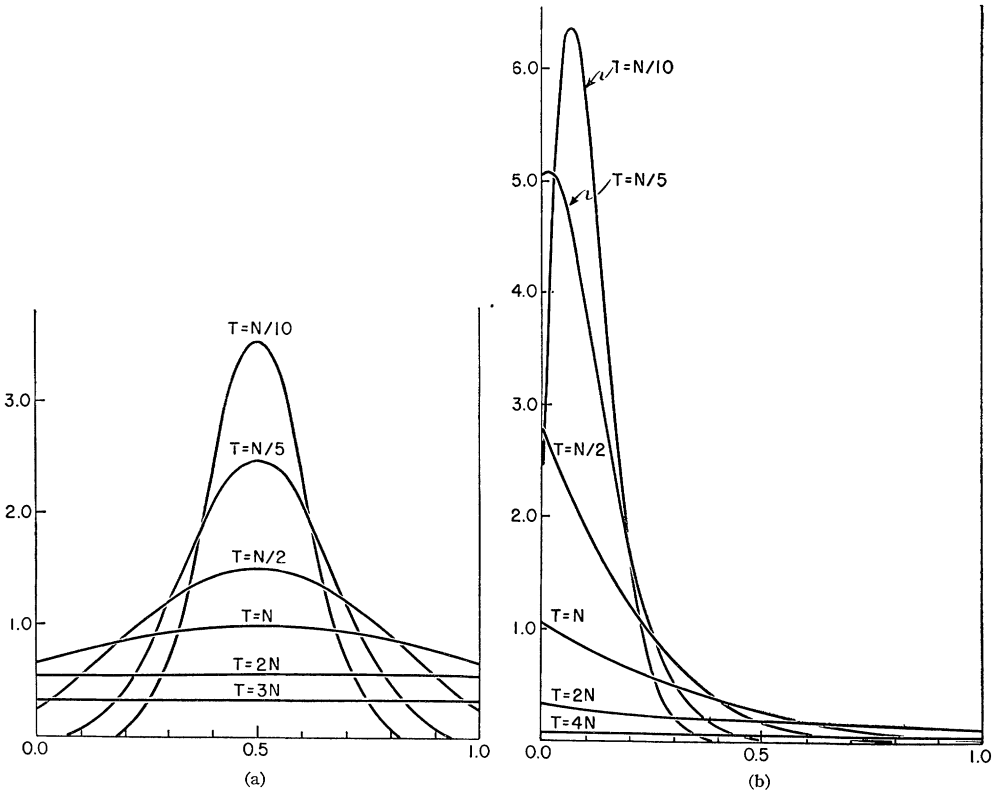

FIG. 1a and 1b. Graphs showing the process of change in the frequency distribution of unfixed classes due to random genetic drift. In this case a pair of alleles is assumed to exist. In *1a* the initial gene frequency is 50%, while in *1b* it is 10%. N is effective population size; t; number of generations elapsed, ordinates; probability densities, abscissae; the gene frequencies.

The probability that A and A' still co-exist in the population after t generations is easily calculated from the above formula (4);

$$\Omega_t = \int_0^1 \phi(x,p;t)dx = \sum_{j=0}^{\infty} \{P_{2j}(r) - P_{2j+2}(r)\}e^{-[(2j+1)(2j+2)/4N]t}. \qquad (6)$$

For $t > 0$ the series is easily seen to be convergent and as $t \to \infty$, Ω_t goes to zero, giving an asymptotic formula;

$$\Omega_t \sim 6pqe^{-(1/2N)t}. \qquad (7)$$

For $t = 0$ it can be proved that Ω_t converges to 1. Furthermore from (2) and (6)

we can verify the relation:

$$f(1;p;t) + \Omega_t + f(0;p,t) = 1.$$

The probability that a randomly chosen individual is heterozygous can be calculated from (4):

$$H_t = \int_0^1 2x(1 - x)\phi(x,p;t)dx = 2pqe^{-(1/2N)t} = H_0e^{-(1/2N)t}, \tag{8}$$

showing that the heterozygosis decreases exactly at the rate of $1/2N$ per generation. This fact was already shown by Wright (1931) by his method of path coefficients. It is also confirmed by the following calculation. Let p be the frequency of A in the population where the frequency of heterozygotes is 2pq. The amount of heterozygosis to be expected after one generation of random mating is

$$E\{2(p + \delta p)(q + \delta q)\} = 2pq - 2E(\delta p)^2$$
$$= 2pq\left(1 - \frac{1}{2N}\right),$$

since $\delta q = - \delta p$, $E(\delta p) = 0$ and $E(\delta p)^2 = pq/2N$.

A Note on the Effect of Population Structure

In the present paper, in order to avoid unnecessary complications, an extremely simple population structure is assumed; mating is at random and the mode of reproduction is such that N male gametes and N female gametes are drawn as a random sample from the whole population and the resulting N individuals form the next generation. Also selection, migration and mutation are assumed to be absent and generations do not overlap.

In nature, population structures are not so simple, and the concept of effective size must be introduced. The main results on this problem may be found in Wright (1931 and many of his later papers), Crow (1954), Crow and Morton (1955) and Kimura (1952). Therefore only few remarks will be made here.

1) If the population size N changes gradually from generation to generation in a deterministic way such that N_t can be represented as a continuous function of t (still $N \gg 1$), t/N in the exponential term of the previous formulas must be replaced by $\int_0^t (dt/N_t)$. For example (7) and (8) become

$$\Omega_t \sim 6pq \exp\left(-\int_0^t \frac{dt}{2N_t}\right) \tag{9}$$

and

$$H_t = 2pq \exp\left(-\int_0^t \frac{dt}{2N_t}\right) \tag{10}$$

respectively.

Thus a necessary and sufficient condition that for a growing population, H_t and Ω_t to vanish at the limit when t becomes ∞ is that the integral $\int_0^\infty (dt/N_t)$ diverges, i.e. N_t must be at most of the order of t at the limit. If the population increases

more rapidly, heterozygosis can not be eliminated entirely.   This agrees with the results obtained by Malécot (1948) who used a different method.

2) If N changes stochastically around its mean $\overline{N}$ with sufficiently small deviations (compared with $\overline{N}$) and if these deviations are mutually independent, N in the previous formulas should be replaced by $\overline{N} - (V_N/\overline{N})$, where V_N is the variance of N.

RANDOM GENETIC DRIFT IN A TRI-ALLELIC LOCUS

In a randomly mating population of effective size N, let x_t, y_t and z_t $(=1-x_t-y_t)$ be the frequencies of three alleles denoted by A_1, A_2 and A_3 respectively in the tth generation. As in the case of two alleles, we define a function $f(x,y;p_1,p_2;t)$ giving the probability that the frequencies of A_1 and A_2 are respectively x and y at the tth generation when they start with $x = p_1$ and $y = p_2$ at the 0th generation.

Let δx_t and δy_t be the amount of change in x_t and y_t due to the random sampling of gametes to form the next generation where frequencies of A_1 and A_2 will be x_{t+1} and y_{t+1}, then

$$x_{t+1} = x_t + \delta x_t, \qquad y_{t+1} = y_t + \delta y_t.$$

In order to find the recurrence formula which gives the law of change in the moments of distribution, we note that x_{t+1} and y_{t+1} are random variables from a trinomial distribution.

If we denote by $\mu'^{(t)}_{m,n}$ the m, n^{th} moment of distribution about zero at the tth generation such that $\mu'^{(t)}_{m,n} = E(x_t^m y_t^n)$, then

$$\mu'^{(t+1)}_{m,n} = E\{(x_t + \delta x_t)^m (y_t + \delta y_t)^n\}.$$

Expanding the right side and noting that

$$E(\delta x_t) = E(\delta y_t) = 0, \qquad E(\delta x_t)^2 = x_t(1 - x_t)/2N,$$
$$E(\delta y_t)^2 = y_t(1 - y_t)/2N, \qquad E(\delta x_t \delta y_t) = -x_t y_t/2N,$$

we obtain the following recurrence formula, under the assumption that the population number N is sufficiently large that the terms of order $1/N^2$, $1/N^3$ etc., can be neglected without serious error:

$$\mu'^{(t+1)}_{m,n} = \left\{1 - \frac{m(m-1)}{4N} - \frac{mn}{2N} - \frac{n(n-1)}{4N}\right\} \mu'^{(t)}_{m,n}$$
$$+ \frac{m(m-1)}{4N} \mu'^{(t)}_{m-1,n} + \frac{n(n-1)}{4N} \mu'^{(t)}_{m,n-1} \quad (m, n \geq 1).$$

Under this assumption, the moments change very slowly per generation and we can replace the above equation by a system of differential equations:

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

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

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 first few moments are obtained directly.

$$\mu'^{(t)}_{1,1} = p_1p_2e^{-(1/2N)t}$$

$$\mu'^{(t)}_{1,2} = \tfrac{1}{2}p_1p_2e^{-(1/2N)t} + (p_1p_2{}^2 - \tfrac{1}{2}p_1p_2)e^{-(3/2N)t}$$

$$\mu'^{(t)}_{1,3} = \tfrac{3}{10}p_1p_2e^{-(1/2N)t} + (p_1p_2{}^2 - \tfrac{1}{2}p_1p_2)e^{-(3/2N)t}$$
$$+ (p_1p_2{}^3 + \tfrac{1}{5}p_1p_2 - p_1p_2{}^2)e^{-(6/2N)t}$$

$$\mu'^{(t)}_{1,4} = \tfrac{1}{5}p_1p_2e^{-(1/2N)t} + (6/7)(p_1p_2{}^2 - \tfrac{1}{2}p_1p_2)e^{-(3/2N)t}$$
$$+ \tfrac{3}{2}(p_1p_2{}^3 + \tfrac{1}{5}p_1p_2 - p_1p_2{}^2)e^{-(6/2N)t}$$
$$+ (p_1p_2{}^4 - \tfrac{3}{2}p_1p_2{}^3 + (9/14)p_1p_2{}^2 - (1/14)p_1p_2)e^{-(10/2N)t}$$

$$\mu'^{(t)}_{2,2} = \tfrac{1}{5}p_1p_2e^{-(1/2N)t} + \tfrac{1}{3}(-p_1p_2p_3)e^{-(3/2N)t}$$
$$+ \left(p_1{}^2p_2{}^2 + \frac{p_1p_2p_3}{3} - \frac{p_1p_2}{5} \right)e^{-(6/2N)t}$$

$$\mu'^{(t)}_{2,3} = \tfrac{1}{10}p_1p_2e^{-(1/2N)t} + (1/7)(2p_1p_2{}^2 + p_1{}^2p_2 - \tfrac{3}{2}p_1{}^2p_2{}^2)e^{-(3/2N)t}$$
$$+ \tfrac{1}{4}(\tfrac{3}{5}p_1p_2 + p_1p_2{}^3 - 2p_1p_2{}^2 - p_1{}^2p_2 + 3p_1{}^2p_2{}^2)e^{-(6/2N)t}$$
$$+ (p_1{}^2p_2{}^3 - \tfrac{3}{4}p_1{}^2p_2{}^2 - \tfrac{1}{4}p_1p_2{}^3 + (3/14)p_1p_2{}^2$$
$$+ (3/28)p_1{}^2p_2 - (1/28)p_1p_2)e^{-(10/2N)t}.$$

$$(12)$$

By virture of symmetry, $\mu'^{(t)}_{2,1}$, $\mu'^{(t)}_{3,1}$, etc. can be obtained simply by interchanging p_1 and p_2 with each other. These formulas· may be used for treating observational results on natural populations. The same type of formulas have been derived by Robertson (1952, p. 205) for the case of a pair of alleles.

From the above derivation it will be seen that the general moment formula must have the form:

$$\mu'^{(t)}_{m,n} = C^{(1)}_{m,n}e^{-(1/2N)t} + C^{(2)}_{m,n}e^{-(3/2N)t} + \cdots + C^{(m+n-1)}_{m,n}e^{-[(m+n)(m+n-1)/4N]t}. \quad (13)$$

Substituting this back in (11) and solving the resulting finite difference equations with respect to these coefficients, we obtain the following expressions:

$$C^{(1)}_{m,n} = \frac{6 \cdot m!n!}{(m+n+1)!}\, C^{(1)}_{1,1}$$

$$C^{(2)}_{m,n} = \frac{60 \cdot m!n!}{(m+n+2)!}\, \{(m-1)C^{(2)}_{2,1} + (n-1)C^{(2)}_{1,2}\}$$

$$C^{(3)}_{m,n} = \frac{420 \cdot m!n!}{(m+n+3)!}\, \{(m-1)(m-2)C^{(3)}_{3,1}$$
$$+ 3(m-1)(n-1)C^{(3)}_{2,2} + (n-1)(n-2)C^{(3)}_{1,3}\}$$

$$C^{(4)}_{m,n} = \frac{9!}{3!4!}\frac{m!n!}{(m+n+4)!}\, \{(m-1)(m-2)(m-3)C^{(4)}_{4,1}$$
$$+ 6(m-1)(m-2)(n-1)C^{(4)}_{3,2} + 6(m-1)(n-1)(n-2)C^{(4)}_{2,3}$$
$$+ (n-1)(n-2)(n-3)C^{(4)}_{1,4}\} \text{ etc.,}$$

where the coefficients in the right side are the coefficients of the moment formulas given in (12). For example, $C^{(1)}_{1,1}$ is the first coefficient in $\mu'^{(t)}_{1,1}$ which is p_1p_2. As t gets large the exponential terms in (13) soon become very small so that only the first few terms are important.

First let us find the probability that the gene A_1, A_2 or A_3 becomes fixed in the population by the tth generation. For this purpose we need only put $p = p_1$, p_2 or p_3 in the formula $f(1;p;t)$ in (1) which gives the same kind of probability for the case of two alleles. The function $f(1;p;t)$ tells us more about the process of the change

in the triallelic case. Let $P_t(A_1)$ be the probability of A_1 being fixed in the population by the tth generation, $P_t(A_1A_2)$ the probability that A_1 and A_2 coexist in the population but A_3 is lost from it, and $P_t(A_1A_2A_3)$ be the probability that 3 genes A_1A_2 and A_3 still coexist in the population in the tth generation. Then

$$P_t(A_1) = f(1;p_1;t), \quad P_t(A_2) = f(1;p_2;t), \quad P_t(A_3) = f(1;p_3;t)$$

$$P_t(A_1A_2) = f(1;p_1 + p_2;t) - f(1;p_1;t) - f(1;p_2;t)$$

$$P_t(A_1A_2A_3) = 1 - P_t(A_1) - P_t(A_2) - P_t(A_3) - P_t(A_1A_2) - P_t(A_1A_3) - P_t(A_2A_3).$$

From these relations we obtain

$$P_t(A_1A_2) = 6p_1p_2e^{-(1/2N)t} - 30p_1p_2p_3e^{-(3/2N)t}$$
$$+ 14p_1p_2\{1 - 5(1 - p_1)(1 - p_2) + 10p_3^2\}e^{-(6/2N)t} + \cdots \quad (14)$$

$$P_t(A_1A_2A_3) = 60p_1p_2p_3e^{-(3/2N)t}$$
$$+ 90p_1p_2p_3\{7(p_1^2 + p_2^2 + p_3^2) - 3\}e^{-(10/2N)t} + \cdots. \quad (15)$$

These formulas tell us that at the final state of steady decay, the frequency of the classes in which only two alleles coexist decreases at the rate of $1/2N$, while that of classes in which the 3 alleles coexist decreases at the rate of $3/2N$ per generation.

This fact suggests that the moment formula (13) contains contributions from these heterogeneous classes. So we shall start our consideration from the distribution of gene frequencies among the classes where the 3 alleles coexist. As in the case of a pair of alleles, the gene frequencies x and y are discrete random variables which take on values between 0 and 1 with steps of size $1/2N$, but we introduce a simplifying assumption that N is sufficiently large that we can treat x and y as continuous random variables with good approximation. Of course, we must assume discontinuity of the distribution at the terminal part because of the irreversible process by which alleles become fixed or lost by chance.

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 $(0 < x < x + y < 1)$, given that one starts from $x = p_1$ and $y = p_2$ at $t = 0$. The probability $\phi(x,y;p_1,p_2;t)dxdy$ is a substitute for $f(x,y;p_1,p_2;t)$ with dx and dy each being substituted for $1/2N$. In order to obtain this, we need the moment for this distribution which does not contain the classes where any one of the alleles has been lost. Actually we need only to remove from (13) the contribution from the classes where the gene A_3 has been lost, since (13) vanishes automatically for other cases of $x = 0$ (A_1 lost) and $y = 0$ (A_2 lost). For this purpose consider the quantity:

$$\nu_{m,n,k}^{(t)} = \sum_{x=0}^{1} \sum_{y=0}^{1} x^m y^n (x + y)^k f(x,y;p_1,p_2;t), \quad (16)$$

by letting x and y discrete variables in the right side.

(16) can be calculated by (13) through the relation:

$$\nu_{m,n,k}^{(t)} = E\{x^m y^n (x + y)\}^k = \sum_{i=0}^{1} \frac{k!}{i!(k-i)!} \mu_{m+i,n+k-i}^{\prime(t)}.$$

What we are going to use is the property of (16) that by letting $k \to \infty$, terms in the right hand side of (16) vanish except for the case when $x + y = 1$ i.e., $z = 0$. Thus

$$\lim_{k\to\infty} \nu_{m,n,k}^{(t)} = \sum_{x+y=1} x^m y^n f(x,y;p_1,p_2;t) \quad (17)$$

is the part to be removed from (13). The explicit expression of (17) is as follows;

$$\lim_{k \to \infty} \nu_{m,n,k}^{(t)} = D_{m,n}^{(1)} e^{-(1/2N)t} + D_{m,n}^{(2)} e^{-(3/2N)t} + D_{m,n}^{(3)} e^{-(6/2N)t} + D_{m,n}^{(4)} e^{-(10/2N)t} + \cdots, \quad (18)$$

where

$$D_{m,n}^{(1)} = \frac{6 \cdot m!n!}{(m+n+1)!} C_{1,1}^{(1)}$$

$$D_{m,n}^{(2)} = \frac{60 \cdot m!n!}{(m+n+2)!} \{(m+1)C_{2,1}^{(2)} + (n+1)C_{1,2}^{(2)}\}$$

$$D_{m,n}^{(3)} = \frac{420 \cdot m!n!}{(m+n+3)!} \{(m+1)(m+2)C_{3,1}^{(3)}$$
$$+ 3(m+1)(n+1)C_{2,2}^{(3)} + (n+1)(n+2)C_{1,3}^{(3)}\}$$

$$D_{m,n}^{(4)} = \frac{9!}{3!4!} \frac{m!n!}{(m+n+4)!} \{(m+1)(m+2)(m+3)C_{4,1}^{(4)}$$
$$+ 6(m+1)(m+2)(n+1)C_{3,2}^{(4)} + 6(m+1)(n+1)(n+2)C_{2,3}^{(4)}$$
$$+ (n+1)(n+2)(n+3)C_{1,4}^{(4)}\} \text{ etc.}$$

Thus the required moment is obtained by subtracting (18) from (13):

$$\int_0^1 \int_0^{1-y} x^m y^n \phi(x,y;p_1,p_2;t)dxdy = \mu_{m,n}'^{(t)} - \lim_{k \to \infty} \nu_{m,n,k}^{(t)}$$
$$= E_{m,n}^{(1)} e^{-(1/2N)t} + E_{m,n}^{(2)} e^{-(3/2N)t} + E_{m,n}^{(3)} e^{-(6/2N)t} + E_{m,n}^{(4)} e^{-(10/2N)t} + \cdots, \quad (19)$$

where

$$E_{m,n}^{(1)} = 0$$

$$E_{m,n}^{(2)} = -\frac{120 \cdot m!n!}{(m+n+2)!} \{C_{2,1}^{(2)} + C_{1,2}^{(2)}\}$$

$$E_{m,n}^{(3)} = -\frac{7!}{2!} \frac{m!n!}{(m+n+3)!} \{m(C_{3,1}^{(3)} + C_{2,2}^{(3)}) + n(C_{2,2}^{(3)} + C_{1,3}^{(3)})\}$$

$$E_{m,n}^{(4)} = -\frac{9!}{3!2!} \frac{m!n!}{(m+n+4)!} \{(m^2+1)C_{4,1}^{(4)} + (3mn+m^2+2)C_{3,2}^{(4)}$$
$$+ (3mn+n^2+2)C_{2,3}^{(4)} + (n^2+1)C_{1,4}^{(4)}\} \text{ etc.}$$

Applying the relations:

$$\frac{m!n!}{(m+n+2)!} = \int_0^1 \int_0^{1-y} x^m y^n dxdy$$

$$\frac{m!n!}{(m+n+3)!} = \int_0^1 \int_0^{1-y} x^m y^n z dxdy$$

$$\frac{m!n!}{(m+n+4)!} = \frac{1}{2} \int_0^1 \int_0^{1-y} x^m y^n z^2 dxdy$$

etc. to (19), we arrive at the desired formula which gives the simultaneous frequency distribution of A_1 and A_2:

$$\phi(x,y;p_1,p_2;t) = 5!\,p_1p_2p_3e^{-(3/2N)t}$$

$$+ \frac{7!}{2!}\,p_1p_2p_3\{(p_1 - \tfrac{1}{3})x + (p_2 - \tfrac{1}{3})y + (p_3 - \tfrac{1}{3})z\}e^{-(6/2N)t}$$

$$+ \frac{9!}{3!2!}\,p_1p_2p_3\left\{(p_1{}^2 - \tfrac{3}{4}p_1 + 3/28)x^2 + (p_2{}^2 - \tfrac{3}{4}p_2 + 3/28)y^2\right.$$

$$+ (p_3{}^2 - \tfrac{3}{4}p_3 + 3/28)z^2 + 3\left(p_1p_2 - \frac{p_1 + p_2}{4} + \frac{1}{14}\right)xy$$

$$+ 3\left(p_1p_3 - \frac{p_1 + p_3}{4} + \frac{1}{14}\right)xz$$

$$\left. + 3\left(p_2p_3 - \frac{p_2 + p_3}{4} + \frac{1}{14}\right)yz\right\}e^{-(10/2N)t} + \cdots, \quad (20)$$

where $z = 1 - x - y$ and $p_3 = 1 - p_1 - p_2$. The final rate of decay is $3/2N$ per generation as was inferred from (15). By direct integration we can verify that

$$P_t(A_1A_2A_3) = \int_0^1 \int_0^{1-y} \phi(x,y,p_1,p_2;t)dxdy.$$

For the purpose of illustrating the process of change in the frequency distribution of various classes, triangular coordinates will be convenient. If we start from a population that contains 3 alleles A_1, A_2 and A_3 with frequencies $p_1 = 0.1$, $p_2 = 0.3$ and $p_3 = 0.6$ respectively, the initial population is expressed as a point Q in figure 2. After N generations, the gene frequency distribution given by $\phi(x,y;0.1,0.3;N)$ form a surface on the triangular coordinate $A_1A_2A_3$ as illustrated by the cross-hatched surface in figure 3. In this case after 2N generations the surface becomes very nearly flat as is seen in the same figure (dotted surface). Volumes under these surfaces give probabilities $P_t(A_1A_2A_3)$ that 3 alleles coexist in the population at $t = N$ and $t = 2N$ respectively.

With the continuous model, it can be shown that $\phi(x,y;p_1,p_2;t)$ must satisfy the following partial differential equation:

$$\frac{\partial\phi}{\partial t} = \frac{1}{4N}\frac{\partial^2}{\partial x^2}\{x(1 - x)\phi\} - \frac{1}{2N}\frac{\partial^2}{\partial x\partial y}\{xy\phi\} + \frac{1}{4N}\frac{\partial^2}{\partial y^2}\{y(1 - y)\phi\}. \quad (21)$$

By the direct substitution of (20) into (21), it has been verified that (20) satisfies this equation.[2]

Next, let us designate by $\phi_{12}(x;t)$ the probability density 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 A_3 has been lost from the population.

This probability density can be obtained from (18) since

$$\int_0^1 x^m(1 - x)^n\phi_{12}(x;t)dx = \lim_{k\to\infty} \nu_{m,n,k}^{(t)}.$$

By using the relation:

$$\frac{m!n!}{(m + n + 1)!} = \int_0^1 x^m(1 - x)^ndx,$$

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[2] Since this paper was written, the complete solution of (21) has been obtained. The result confirmed formula (20). The detailed solution is to be published in Biometrics: Kimura, M. "Random genetic drift in a tri-allelic locus: Exact solution with a continuous model."
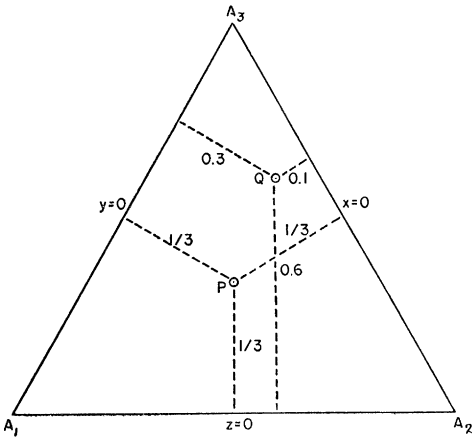
FIG. 2. Expression of the gene frequencies of the populations on the triangular coordinate.
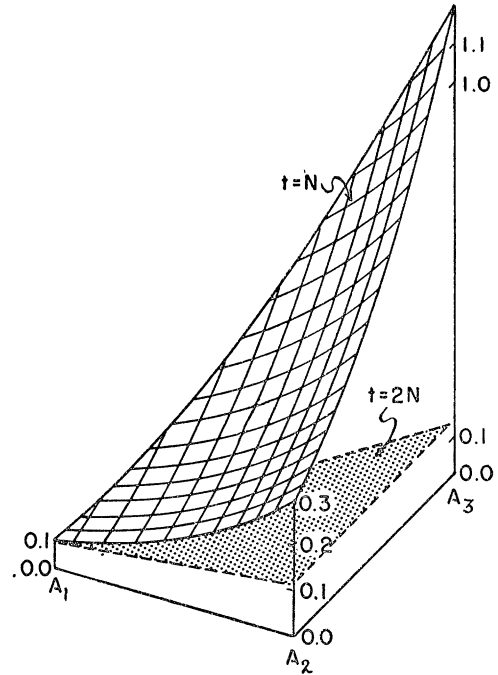

FIG. 3. Surfaces on the triangular coordinate, showing the frequency distributions of the classes where all the three alleles A_1, A_2 and A_3 coexist. In this case the initial gene frequencies are $p_1 = 0.1$, $p_2 = 0.3$ and $p_3 = 0.6$, i.e. the population starts from the point Q in the fig. 2. The cross-hatched and the dotted surfaces show respectively the distributions after N and 2N generations, where N is the effective population size.

we obtain

$$\phi_{12}(x;t) = 3!C^{(1)}_{1,1}e^{-(1/2N)t} + \frac{5!}{2!}\{C^{(2)}_{2,1}x + C^{(2)}_{1,2}(1-x)\}e^{-(3/2N)t}$$

$$+ \frac{7!}{3!2!}\{C^{(3)}_{3,1}x^2 + 3C^{(3)}_{2,2}x(1-x) + C^{(3)}_{1,3}(1-x)^2\}e^{-(6/2N)t}$$

$$+ \frac{9!}{4!3!}\{C^{(4)}_{4,1}x^3 + 6C^{(4)}_{3,2}x^2(1-x)$$

$$+ 6C^{(4)}_{2,3}x(1-x)^2 + C^{(4)}_{1,4}(1-x)^3\}e^{-(10/2N)t} + \cdots. \quad (22)$$

In this case the final rate of decay is $1/2N$ per generation as was inferred from (14). By direct integration of (22), we can verify that

$$P_t(A_1A_2) = \int_0^1 \phi_{12}(x;t)dx.$$

The probability density, $\phi_{23}(y;t)$, $(0 < y < 1)$, giving the frequency distribution of the gene A_2 when A_1 is lost can be obtained from (22) by replacing p_1, p_2 and p_3 with p_2, p_3 and p_1 respectively. Similarly the density, $\phi_{31}(z;t)$, $(0 < z < 1)$, giving

the frequency distribution of the gene A_3 when A_2 is lost can be obtained from (22) by replacing p_1, p_2 and p_3 with p_3, p_1 and p_2 respectively. These formulas together with (20) and (1) in which p is replaced by p_1, p_2 and p_3 successively can completely describe the process of random genetic drift in a tri-allelic locus.

Some examples are illustrated in fig. 4 and fig. 5. In fig. 4 the population starts from the gene frequency corresponding to P in fig. 2, while in fig. 5, the population starts from the point Q. It is interesting to observe that though $\phi(x,y,p_1,p_2;t)$ becomes practically flat in both cases after 2N generations, distributions given by $\phi_{12}(x,t)$, $\phi_{23}(y,t)$ etc., are widely different in both cases depending on the starting point in gene frequency. All distributions, however, become finally flat after a sufficient time.
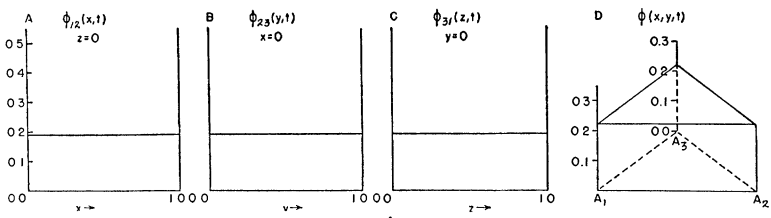

FIG. 4 A–D. Various frequency distributions for different classes after 2N generations assuming that the initial composition of the population is $p_1 = p_2 = p_3 = \frac{1}{3}$, i.e. the population starts from the point P in the fig. 2. For example, A shows the frequency distribution of the classes where A_1 and A_2 coexist but A_3 is lost from the population. Also, D shows the frequency distribution of the classes where all three alleles coexist. x, y and z denote respectively the frequencies of A_1, A_2 and A_3. The probabilities of the various states at t = 2N are as follows:

$$P(A_1) = P(A_2) = P(A_3) \doteqdot 10.7\%,$$
$$P(A_1A_2) = P(A_2A_3) = P(A_3A_1) \doteqdot 19.0\%,$$
$$P(A_1A_2A_3) = 11.0\%.$$
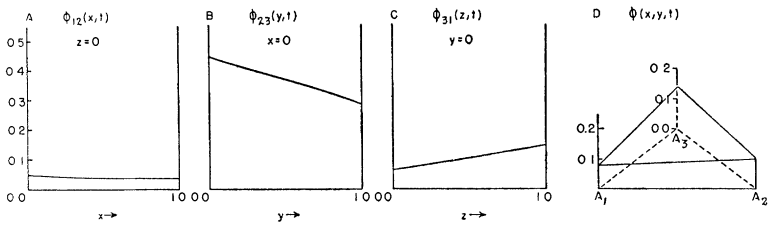

FIG. 5 A–D. Same as the fig. 4 except for the population starts from $p_1 = 0.1$, $p_2 = 0.3$ and $p_3 = 0.6$, i.e. from the point Q in the fig. 2. The probabilities of the various states at t = 2N are:

$$P(A_1) = 1.8\%, \qquad P(A_2) = 8.9\%, \qquad P(A_3) = 32.4\%,$$
$$P(A_1A_2) = 4.1\%, \qquad P(A_2A_3) = 36.8\%, \qquad P(A_1A_3) = 10.6\%,$$
$$P(A_1A_2A_3) = 5.4\%, \quad \text{approximately.}$$

To summarize the process of steady decay, fig. 6 has been constructed.

The 3 columns standing on the apexes A_1, A_2 and A_3 represent the frequencies of 3 fixed classes and increase in height as fixation of alleles proceeds. The plane $B_1B_2B_3$ represents the distribution of the classes where 3 alleles coexist and this plane declines at the rate of 3/2N per generation. The 3 surrounding walls each of which represents the distribution of two alleles when the third is lost, decreases in height at the rate of 1/2N per generation. The upper edge of each of them is flat but their heights are not necessarily the same.
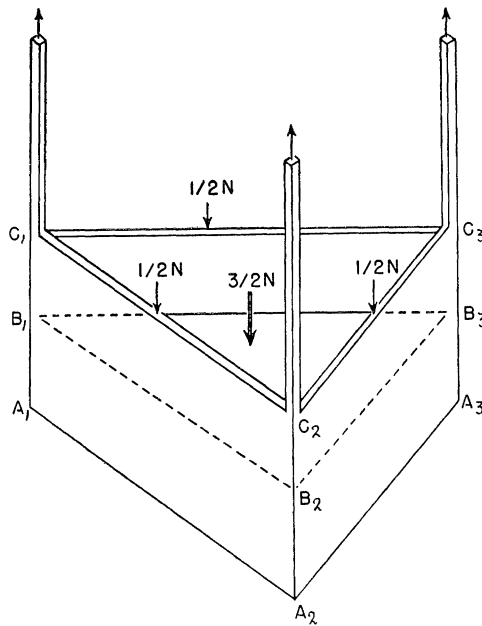
FIG. 6. Explanatory figure to summarize the results obtained for the triallelic case. The relative proportion of areas and the volume in the figure are not exact.

Any population which is located in an interior point of the co-ordinate triangle $A_1A_2A_3$ (see fig. 2) may wander randomly from generation to generation and if it happens to reach one of the edges, say A_1A_2, then it can wander only along it. Finally the point may reach one of its terminal points, say A_1, and stop moving, which means that gene A_1 is fixed.

The decrease of heterozygosis is a different matter. As in the case of a pair of alleles, the heterozygosis decreases exactly at the rate of $1/2N$ per generation from the beginning, as is easily demonstrated by a procedure similar to that employed in the case of a pair of alleles: Let p_1, p_2 and p_3 be the frequencies of A_1, A_2 and A_3 in the population where the frequency of heterozygotes is $\sum_{j>i} 2p_ip_j$ $(i, j = 1, 2, 3)$. After one generation of random mating, the frequency of heterozygosis in the next generation is expected to be

$$E\{2 \sum_{i>j} (p_i + \delta p_i)(p_j + \delta p_j)\} = 2 \sum_{i>j} E(p_ip_j) + 2 \sum_{i>j} E(\delta p_i \delta p_j)$$

$$= 2 \sum E(p_ip_j) + 2 \sum E\left(\frac{-p_ip_j}{2N}\right) = \{2 \sum_{i>j} p_ip_j\}\left(1 - \frac{1}{2N}\right).$$

Therefore

$$H_t = H_0 e^{-(1/2N)t}.$$

GENERAL CASE OF MULTIPLE ALLELES

From the foregoing treatment one might infer that in the general case of m alleles, also the "flat" distribution of heterallelic classes will be realized after sufficiently many generations. At this state of steady decay, the probability density $\phi(x_1, \cdots, x_{m-1}; p_1, \cdots, p_{m-1}; t)$ that all the original m alleles coexist in the population will decrease at the rate of $m(m-1)/4N$ per generation, where x_i is the frequency

of the ith allele whose initial frequency is p_i ($\sum p_i = 1$). This can be verified from the Fokker-Planck equation for the case of the m alleles:

$$\frac{\partial \phi}{\partial t} = \frac{1}{4N} \sum_{i=1}^{m-1} \frac{\partial^2}{\partial x_i^2} \{x_i(1 - x_i)\phi\} - \frac{2}{4N} \sum_{i>j} \frac{\partial^2}{\partial x_i \partial x_j} \{x_i x_j \phi\}$$
$$(i, j = 1, 2, \cdots, m - 1), \quad (23)$$

which is satisfied by

$$\phi = C \cdot e^{-[m(m-1)/4N]t}. \tag{24}$$

The constant C is determined as follows: Let $H_t^{(m)}$ be the probability that m randomly chosen genes are all different. For large N, this probability is proved to decrease at the rate of approximately $\binom{m}{2}/2N$ per generation, which is independent of t. To prove this we let p_i ($i = 1, \cdots, m$) be the frequency of the gene A_i in the population. Then the same probability in the next generation is expected to be proportional to

$$E\{(p_1 + \delta p_1)(p_2 + \delta p_2) \cdots (p_m + \delta p_m)\}$$

$$= E\left\{ \prod_{i=1}^m p_i + \sum_{j=1}^m (\prod_{i \neq j} p_i)\delta p_j + \sum_{(j \neq k),} (\prod_{i \neq j,k} p_i)\delta p_j \delta p_k + \text{etc.} \right\}$$

$$= \prod_{i=1}^m p_i + \sum_{(j \neq k)} (\prod_{i \neq j,k} p_i)E(\delta p_j \delta p_k) + O(1/N^2) \doteq \{1 - \binom{m}{2}/2N\} \prod_{i=1}^m p_i.$$

Hence

$$H_t^{(m)} = \left\{1 - \frac{m(m - 1)}{4N}\right\} H_{t-1}^{(m)},$$

if we neglect the terms of $O(1/N^2)$. Thus

$$H_t^{(m)} = m! \, (\prod_{i=1}^m p_i) e^{-[m(m-1)/4N]t}, \tag{25}$$

since $H_0^{(m)} = m! \prod p_i$.

On the other hand, this probability is also obtained by

$$m! \underset{x_1+x_2+\cdots+x_m=1}{\iint \cdots \int} (\prod_{i=1}^m x_i)\phi(x_1, \cdots, x_{m-1}; p_1, \cdots, p_{m-1}; t) \prod_{i=1}^{m-1} dx_i.$$

Using (24), we obtain the asymptotic relation:

$$H_t^{(m)} \sim C \cdot \frac{m!}{(2m - 1)!} e^{-[m(m-1)/4N]t}. \tag{26}$$

By comparing this with (25), we find $C = (2m - 1)! \prod_{i=1}^m p_i$ so that

$$\phi(x_1, \cdots, x_{m-1}; p_1, \cdots, p_{m-1}; t) \sim (2m - 1)! (\prod_{i=1}^m p_i) e^{-[m(m-1)/4N]t}. \tag{27}$$

The probability that the m alleles coexist in the population at the tth generation is obtained by

$$\Omega_t^{(m)} = \underset{x_1+x_2+\cdots+x_m=1}{\iint \cdots \int} \phi(x_1, \cdots, x_{m-1}; p_1, \cdots, p_{m-1}; t) \prod_{i=1}^{m-1} dx_i$$

which is asymptotically

$$\Omega_t^{(m)} \sim \frac{(2m-1)!}{(m-1)!} (\prod_{i=1}^{m} p_i) e^{-[m(m-1)/4N]t}. \tag{28}$$

In the case of the distributions of heteroallelic classes where some alleles have been lost, the Fokker-Planck equation does not hold exactly since contributions may also come from other classes containing additional unfixed alleles. The equation is applicable only asymptotically and we have the following general result:

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

$$\phi_{1, 2, \ldots k}(x_1, x_2, \cdots, x_{k-1}, t) \sim (2k-1)! (\prod_{j=1}^{k} p_j) e^{-[k(k-1)/4N]t}, \tag{29}$$

where $k \leq m$. 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.

On the other hand the amount of heterozygosis always decreases at the rate of 1/2N:

$$H_t = H_0 e^{-(1/2N)t}, \tag{30}$$

which can easily be shown by exactly the same method employed in the case of 3 alleles.

The effectiveness of random genetic drift as an evolutionary factor in natural populations is still a problem of much dispute (Fisher and Ford, 1947; Wright, 1948; Fisher and Ford, 1950; Wright, 1951). Since the purpose of this paper is to present theoretically the general picture of the process of random genetic drift in an idealized situation, the present writer has no intention to join this discussion. It must be noted, however, that as the number of the coexisting alleles increases, the rate at which the probability of coexistence is reduced increases rapidly as (29) indicates. In this sense, the effect of the random genetic drift might have an important bearing on the genetic structure of natural populations by keeping down the number of coexisting alleles in the population.

The causes of random fluctuation of gene frequency in natural populations are not restricted to the random sampling of gametes in reproduction to which exclusive attention has been paid in this paper. Another important factor is the random fluctuation of the selection intensity. The process of the change in gene frequency due to the latter factor in an idealized condition was investigated earlier (Kimura, 1954). The steady state gene frequency distribution involving this factor was first worked out by Wright (1948).

In natural populations, these two factors must be working simultaneously, and, in conjunction with mutation, selection and migration, constitute a main factor in evolution.

SUMMARY

After the short review of the theoretical as well as experimental results so far obtained on the problem of the random genetic drift due to small population number,

the complete solution of the process of the random genetic drift for the case of a pair of alleles is illustrated.

From this it is pointed out that the well known steady decay solution; $\phi = Ce^{-t/2N}$, though useful when the initial gene frequency is near 50%, decreases in usefulness as the initial gene frequency deviates from this value (fig. 1a and 1b).

The main purpose of this paper, however, is to present the general treatment of the problem of random drift for a multiallelic locus. First the asymptotic solutions are elaborated for the triallelic system. They show that as the number of generations becomes large, the rate of decay of the frequencies of the classes where only two alleles coexist approaches 1/2N per generation, while that of the classes where the 3 alleles coexist approaches 3/2N per generation.

The most general result obtained is as follows: If we start from a population which contains m alleles say $A_1, A_2, \cdots$ and A_m with frequencies $p_1, p_2, \cdots$ and p_m respectively ($\sum p_i = 1$), 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 ($\sum_1^k x_i = 1$) in the tth generation is given asymptotically by

$$\phi_{1, 2, \ldots, k}(x_1, x_2, \cdots, x_{k-1}; t) \sim (2k - 1)! (\prod_{j=1}^{k} p_j) \exp \{- k(k - 1)t/4N\},$$

where $k < m$. This indicates that as the number of coexisting alleles increases, the rate by which that state is eliminated increases with rapid progression. In this sense, random drift might be effective in keeping down the number of coexisting alleles in the population.

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