*POLYALLELIC RANDOM DRIFT IN RELATION TO EVOLUTION**

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The number of alleles that are maintained at a locus in a population of given size by a given mutation rate is important in evolutionary theory. The possible number of alleles is enormous. At a locus consisting of only 1000 nucleotide pairs, each with four alternatives, the number differing from the type gene by a single substitution is 3000 and by two substitutions, nearly 4.5×10^6. The total number from substitutions alone is 4^{1000}.

The actual number present at any given time in a population of size N obviously cannot exceed $2N$ and may be expected to be very much less. It is instructive to determine the steady-state distribution of frequencies of alleles under the simplifying assumption that all alleles, except perhaps one or more specified ones, have the same properties. The number of such similar alleles present at any time is the reciprocal of the mean frequency, multiplied by the portion of the total frequency which they constitute. The composition of this array is continually changing with turnover $2Nu$ where u is the mutation rate.

The first attempt at such estimates was for the case of self-incompatibility alleles (Wright[1]) in which it was known that rather large numbers actually occur in very small isolated populations.[2] Because of the peculiar mode of selection—inhibition of any pollen grain that carries the same allele as either of those in the cells of the style—any novel mutation is subject to maximum favorable selection. There is an equilibrium frequency toward which gene frequency tends to move from either direction.

Unfortunately this equilibrium frequency is not constant. It shifts especially with changes in the number of alleles. It was recognized that only an approximate solution could be obtained. Approximate relations between number of alleles (n), effective size of population (N), and rate of mutation from any allele (u) were presented which seemed adequate for most biological purposes. Discussion of the subject[3–7] has introduced rather more confusion than clarification, but some improvement of the formulas has emerged, and more is probably possible. The present paper will deal with simpler cases.

Method.—It will be assumed here that there is random mating within isolated populations of effective size N. The average rate of change (Δq) of any gene frequency (q) results from directed processes, dependent on the rates of mutation from, (u), and to, (v), the gene in question and in some cases selective differences. Balancing of opposed processes determines an equilibrium frequency ($\hat{q}$) at which $\Delta q = 0$. The opposition between these centripetal processes as a group and the scattering effects of random processes ($\sigma^2_{\Delta q}$) determine an almost continuous frequency distribution:

$$\varphi(q) = (C/\sigma_{\Delta q}{}^2) \exp\{2\textstyle\int(\Delta q/\sigma_{\Delta q}{}^2)dq\}, \qquad \textstyle\int \varphi(q)dq = 1.$$

The derivation[8, 9] involved the assumption that $(\Delta q)^2$, $(\delta q)^3$, $\Delta q(\delta q)^2$, and higher powers (where δq is a random deviation) are negligible.

The true distribution is, of course, a step distribution, with frequencies $F(q) = \varphi(q)/(2N)$ approximately, at intervals of $1/(2N)$. The frequency $F(0)$ of absence from the population is such that the frequency $2NvF(0)$ of recurrence in a population equals the frequency $(1/2)F(1/(2N)$ of loss.[10]

The same distribution, $F(q)$, applies to every allele in a set with identical properties. Since each is absent most of the time, $F(0)$ is very nearly 1. We may also, however, consider the frequency distribution of the array of n alleles present at any time, $f(q) = F(q)/[1 - F(0)]$, $\sum_{1/2N}^{1} f(q) = 1$, which by definition has no class at $q = 0$.

The probability of an increase to $(n + 1)$ alleles is $2Nu$, while that of a decrease to $(n - 1)$ alleles is $(n/2)f(1/2N)$. There is a steady state only if mutation and loss always occur simultaneously.

Actually, a distribution of values of n must be recognized. Distributions that are in a steady state except for the possibilities of gain or loss can be determined for each value of n separately and the frequencies of the values of n can then be determined by equating the chance of gain by mutation, starting from a given number (n) of alleles, with the chance of loss from the distribution for $(n + 1)$ alleles.[7] This is rather important[7] where $\hat{q}$ is a function of n as with self-incompatibility alleles but where not, it is enough for most purposes to put $2Nu = (n/2)f(1/2N)$ to find $\hat{n} = 4Nu/f(1/2N)$.

Multiple Isoalleles with No Selection.—The simplest case is that in which there is no selection and all alleles mutate at the same rate u. This was touched on in an encyclopedia article.[11] The distribution of existent alleles was expressed in discrete form $f(q) = Cq^{-1}(1 - q)^{4Nu-1}$ with $\sum_{1/2N}^{1} f(q) = 1$, and thus $C = 1/\sum_{1/2N}^{1}(q^{-1}(1 - q)^{4Nu-1})$. Since $f(1/2N) = 2NC$ approximately, $n = 2u\sum_{1/2N}^{1}(q^{-1}(1 - q)^{4Nu-1})$. "With $u = 10^{-6}$, a population of 250,000 may be expected to carry an average of 13.7 alleles. In larger populations, there should be a somewhat less than proportional increase, e.g., 132 alleles if N is increased tenfold."

Ewens[12] used the closely related continuous formula $n = 4Nu\int_{1/2N}^{1}(q^{-1}(1 - q)^{4Nu-1}dq)$ and gave results for $4Nu = 1$, 2, 3, or 4, varying either N or u. His result, $n = 12.4$ for $N = 250{,}000$, $u = 10^{-6}$, agrees fairly well with my figure 13.7.

Solution is simplified by introducing a finite, but very small, rate of recurrence of the same mutation, v.

The distribution of one allele as opposed to all others collectively is then:[10]

$$\varphi(q) = \frac{\Gamma(4Nu + 4Nv)}{\Gamma(4Nu)\Gamma(4Nv)} q^{4Nv-1}(1 - q)^{4Nu-1} \text{ with mean } \frac{v}{u + v},$$

$$F(1/2N) = \frac{\Gamma(4Nu + 4Nv)}{\Gamma(4Nu)\Gamma(4Nv)} (1/2N)^{4Nv} \text{ approximately,}$$

$$F(0) = F(1/2N)/4Nv.$$

Switching to the distribution of the array of existent alleles

$$\bar{q} = \frac{v}{u + v}\left[\frac{1}{1 - F(0)}\right],$$

$$n = 1/\bar{q} = \left(\frac{4Nu + 4Nv}{4Nv}\right)\left[1 - \frac{\Gamma(4Nu + 4Nv)}{4Nv\Gamma(4Nu)\Gamma(4Nv)}\left(\frac{1}{2N}\right)^{4Nv}\right].$$

This can also be derived by equating gains and losses.

Values of n can be calculated for given N and u, using the smallest value of $4Nv$ that the available table permits. It makes no appreciable difference whether $4Nv$ is taken as 0.0001 or 0.00001. The results agreed fairly well with those of Ewens,[12] but were on the average 5.7 per cent greater.

Table 1 gives the average turnover, $K = 2Nu$, and the average number of alleles, n, over a wider range.

TABLE 1

ISOALLELES WITH NO SELECTION AND MUTATION RATE u

	$u = 10^{-7}$		$u = 10^{-6}$		$u = 10^{-5}$		$u = 10^{-4}$	
N	K	n	K	n	K	n	K	n
10^4	0.002	1.04	0.02	1.4	0.2	4.7	2	32
10^5	0.02	1.5	0.2	5.7	2	41	20	318
10^6	0.2	6.6	2	51	20	410	200	3,170
10^7	2	60	20	503	200	4,100	2,000	31,700

Turnover, $K = 2Nu$, and number of alleles, n, for various values of N and u.

If the alleles all had the same frequency, the proportion of homozygotes would be given by the inbreeding coefficient, $F = 1/(4Nu + 1)$, and this would be the reciprocal of the number present. Kimura and Crow[13] define this as the effective number $n_e(=2K + 1)$. It may be seen that it is much smaller than the actual number present if this is large. The actual number is swelled by alleles with very few representatives.

Case of a Type Gene and Multiple Equivalent Deleterious Mutations.—Assume a type gene, A^+, and a class of equally unfavorable alleles, A^i, A^j, etc., that are maintained by mutation at the rate u from all alleles, including A^+. Assume first that there is semidominance with relative selective values of $(1 + 2s)$ for A^+A^+, $(1 + s)$ for A^+A^i, etc., and 1 for A^iA^i, A^iA^j, etc. It is again desirable to assume a very low rate, v, of mutation to each allele from any other. In this case, $\hat{q}_+ = 1 - (u/s)$ approximately,

$$\Delta q_i = v(1 - q_i) - uq_i + (1/2)q_i(1 - q_i)\frac{\partial \bar{w}}{\partial q_i}\Big/\bar{w},$$

where $\bar{w} = 1 + 2sq_+$ is the mean selective value,[14] $\dfrac{\partial \bar{w}}{\partial q_i} = 2s\dfrac{\partial q_+}{\partial q_i} = \dfrac{-2sq_+}{1 - q_i}$.

Taking $q_+ = \hat{q}_+$, $sq_+ = s - u$ with sufficient accuracy,

$$\Delta q_i = v(1 - q_i) - sq_i \text{ approximately,}$$

$$\sigma_{\Delta q}{}^2 = q_i(1 - q_i)/2N,$$

$$F(q_i) = \left(\frac{1}{2N}\right)\frac{\Gamma(4Ns + 4Nv)}{\Gamma(4Ns)\Gamma(4Nv)}\, q_i{}^{4Nv-1}(1 - q_i)^{4Ns-1}.$$

This distribution excludes q_+ and thus applies only to the portion u/s of the total. As A^i is usually absent, $F(0)$ is very nearly 1. The mean for q_i is $\dfrac{v}{s + v}$. In the distribution, $f(q)$, of existent alleles, the mean is $\bar{q} = \dfrac{v}{s + v}\left(\dfrac{1}{1 - F(0)}\right)$. The

number of mutant alleles present at any time is $u/(s\bar{q}) \approx \frac{u}{v}[1 - F(0)] = \frac{u}{v}[1 - F(1/2N)/4Nv]$

$$n \approx \frac{u}{v}\left[1 - \left(\frac{1}{4Nv}\right)\frac{\Gamma(4Ns + 4Nv)}{\Gamma(4Ns)\Gamma(4Nv)}(1/2N)^{4Nv}\right] \approx \frac{u}{v}\left[1 - \left(\frac{4Ns - 1}{2N}\right)^{4Nv}\frac{1}{\Gamma(1 + 4Nv)}\right]$$

A similar analysis in the case of completely recessive noncomplementary mutations, all with selective disadvantage t to type, leads to a similar formula except that the proportion of mutant alleles is $\sqrt{u/t}$, and $\sqrt{ut}$ is to be substituted for s. Both cases are illustrated in Table 2.

TABLE 2

NUMBER OF DELETERIOUS MUTATIONS MAINTAINED IN POPULATIONS OF 10^6 OR 10^5 BY MUTATION RATES OF 10^{-6} OR 10^{-5}

			Semidominant Alleles				Recessive Alleles		
N	u	K	$s = 0$	$s = 10^{-4}$	10^{-3}	10^{-2}	$t = 10^{-3}$	10^{-2}	10^{-1}
10^5	10^{-6}	0.2	5.7	3.2	2.3	1.3	3.7	3.2	2.7
10^5	10^{-5}	2	41	32	23	13	32	27	23
10^6	10^{-6}	2	51	32	23	13	36	32	27
10^6	10^{-5}	20	410	320	226	133	320	272	226

The case of semidominant and recessive mutations with various selection coefficients are compared with neutra mutations ($s = 0$).

The number of deleterious alleles present at any time depends most on the rate of turnover, but with given K it decreases with the amount of selective disadvantage.

Heterotic Loci.—Consider next a system of alleles in which all homozygotes are at the same selective disadvantage, s, with respect to all heterozygotes.[14] It is again assumed that all alleles mutate at the same rate, u.

$$\bar{w} = 1 - s\sum q^2, \qquad \frac{\partial \bar{w}}{\partial q_i} = -2s[q_i - \sum q^2]/(1 - q_i),$$

$$\Delta q_i = v(1 - q_i) - uq_i - sq_i(q_i - \sum q^2)/(1 - s\sum q^2),$$

$$\approx -uq_i - sq_i[q_i - \sum q^2(1 - sq_i^2)],$$

$$\varphi(q) = Ce^{4Ns(1+s\Sigma q^2)q}q^{-1}(1 - q)^{4Ns[1-\Sigma q^2(1-s)]+4Nu-1}.$$

Calculations have been made for various values of N and u, and for $s = 0.1$ or 1 (lethal homozygotes). Preliminary estimates were made of $\sum q^2$. Relative ordinates were derived from calculations of $\log_{10} \varphi(q)$. C was determined so as to make the sum of the frequencies, excluding $F(0)$, equal to 1. This permitted empirical estimation of $\bar{q}$ and hence $n(= 1/\bar{q})$ and of the losses of alleles, $(n/2)f(1/2N)$ for comparison with gains, $2Nu$. The estimate of $\sum q^2$ was revised and a second trial made. A third and usually final estimate was made by logarithmic interpolation. A check on the distribution was obtainable by empirical calculation of σ_q^2 and use of the formula $\sum q^2 = (1/n) + n\sigma_q^2$.

The estimate of total numbers of alleles (n) may be compared with estimates reported by Kimura and Crow[13] of effective number (n_e) taken here as the reciprocal

TABLE 3

TURNOVER (K), TOTAL AND EFFECTIVE NUMBERS OF ALLELES (n, n_e) IN POPULATIONS OF VARIOUS EFFECTIVE SIZES (N) AND MUTATION RATES (u), WITH NO SELECTION ($s = 0$) OR WITH EQUAL SELECTION AGAINST BOTH HOMOZYGOTES ($s = 0.1$, $s = 1$)

			$s = 0$		$s = 0.1$		$s = 1$	
N	u	K	n	n_e	n	n_e	n	n_e
10^3	10^{-7}	0.0002	1.0	1.0	5.0	4.6	14.8	13.1
	10^{-6}	0.002	1.0	1.0	5.8	5.3	16.7	14.7
	10^{-5}	0.02	1.3	1.0	7.4	6.3	19.8	17.0
	10^{-4}	0.2	3.8	1.4	11.9	11.2	27.4	21.4
10^4	10^{-7}	0.002	1.0	1.0	16.4	15.3	48.8	44.3
	10^{-6}	0.02	1.4	1.0	19.9	17.7	56.4	50.9
	10^{-5}	0.2	4.7	1.4	28.4	22.0	72.0	60.9
	10^{-4}	2	32.3	5.0	61.6	31.9	118	80
10^5	10^{-7}	0.02	1.5	1.0	56	51	163	151
	10^{-6}	0.2	5.7	1.4	73	62	198	175
	10^{-5}	2	41	5.0	126	81	282	218
	10^{-4}	20	318	41	418	137	619	315
10^6	10^{-7}	0.2	6.6	1.4	198	176	572	512
	10^{-6}	2	51	5	289	219	711	615
	10^{-5}	20	410	41	700	323	1183	803
	10^{-4}	200	3170	401	3447	689	4237	1333

of the equilibrium value for selection ($\hat{q} = \sum q^2$). Examples are given in Table 3. It may be seen that a large population may carry a great many heterotic alleles.

Discussion.—In actual cases, alleles would not have identical properties and the numbers maintained in populations of given size N, by an average mutation rate u and average selective disadvantages ($\bar{s}$, $\bar{l}$), would be much less. Nevertheless, species with really large numbers of individuals may be expected to carry a great many alleles at each locus. With an indefinitely large number of possible alleles, it is evident that no true equilibrium is ever reached even if the species lives for a very long period under the same conditions. There is what may be called an inevitable *polyallelic random drift*, based on accidental loss and random mutation.

Of primary interest are the implications of this sort of random drift for the Mendelian aspects of evolution (excluding here chromosome aberration and hybridization as factors). Various conditions for evolution and the extent to which each seemed favorable in 1929[15] were listed as follows, with items numbered here for convenience of reference.

(1) "In too small a population, there is nearly complete random fixation, little variation, little effect of selection and thus a static condition, modified occasionally by chance fixation of a new mutation, leading to degeneration and extinction.

(2) "In too large a freely interbreeding population, there is great variability but such a close approach of all gene frequencies to equilibrium that there is no evolution under static conditions.

(3) "Changed conditions cause a usually slight and reversible shift of gene frequencies to new equilibrium points.

(4) "With intermediate size of population, there is continual random shifting of gene frequencies and consequent alteration of all selection coefficients, leading to relatively rapid, indefinitely continuing, irreversible and largely fortuitous but not degenerative changes even under static conditions. The absolute rate, however, is slow, being limited by mutation pressure.

(5) "Finally, in a large but subdivided population, there is continually shifting differentiation among the local races, even under uniform static conditions, which,

through intergroup selection, brings about indefinitely continuing, irreversible, adaptive and much more rapid evolution of the species as a whole."

On further consideration[16] it was recognized that (2) yields "excessively slow" rather than "no" evolution, that in (3) "we undoubtedly have an important evolutionary process," and that in (4) "the rate of progress... is extremely slow...." Case (5) continued to be considered the most favorable.

There is one apparently glaring omission, the pure mutation theory which was widely favored at the time. It is, however, sufficiently obvious that mutation because of its randomness cannot be invoked as a cause, by itself, of progressive evolution. On the other hand, mutation has a fairly consistent destructive effect on characters. The elimination of useless processes and organs to make way for constructive change is, of course, an essential part of evolution, and it has often been suggested that mutation pressure is the principal agent. It certainly tends to act in this direction as far as it goes. It is probable, however, that selection pressure of one sort or another is always a more powerful agent even in this respect.[17, 18] Polyallelic random drift perhaps enhances somewhat the degenerative effect of mutation pressure if only because it leads to complete loss of alleles by accidents of sampling instead of mere reduction to an equilibrium value of 0.50 if there are only two alleles with equal mutation rates in both directions. No important upward revision of the estimate of its importance seems required, however. A comprehensive discussion leading to a somewhat more favorable view has been given by Haldane.[19]

The consideration of polyallelic random drift does not indicate any change in the evaluation of close inbreeding (1). It is obviously not a process that can be of appreciable evolutionary significance by itself although of the greatest importance in agriculture as a step, for example, in the production of hybrid corn.

Some further revision may seem to be indicated in case (2) (evolution in a large panmictic population under long, continued constant conditions), because of the continual turnover at each locus from a virtually inexhaustible array of possible alleles. This must be considerably discounted, however, because most of the turnover is in mutations that never reach appreciable frequencies. On the other hand, it must be recognized that no true equilibrium is ever arrived at and that there is always a chance, even though very small, for the appearance and establishment of a novel favorable mutation. Evolutionary change in this case is almost completely limited by the rate of this process. The only qualification is that the fixation of a novel mutation may unsettle somewhat the relative selective values at other loci and lead to readjustments. This must be considerably discounted because such a mutation cannot be favorable in the first place unless it fits very well into the interaction system that has been built up in the past.

The situation is very different under changing external conditions (3). The presence of a store of numerous diverse alleles at each locus makes possible a rapid adjustment to the new conditions, if not too severe. A succession of such changes is very unlikely to be reversible (contrary to the statement in the abstract above) because of the large number of peaks in the "surface" of selective values of the genes. This case, and case (2) as far as it goes, are those to which Haldane's papers in the 1920's, summarized in 1932,[20] and that of Fisher in 1930,[21] apply.

Polyallelic random drift at each locus should be somewhat more effective in pro-

viding material for evolutionary change than random drift among only two or a few alleles in a population of intermediate size (case 4) defined as one in which $1/(2N)$ is of the same order as u. In principle, random drift of any sort occurring simultaneously at all loci should lead to occasional passage across a two-factor saddle between two selective peaks, to act as a trigger for selection toward the higher peak (more favorable interaction system). This replaces the limitation by the rate of occurrence of favorable mutations of case (2), by an indefinitely extensive trial-and-error process, but the conditions are too severe in case (4) for this to be of appreciable importance.

Case (5), subdivision of the species into many local populations, sufficiently isolated to permit significant differentiation in gene frequencies, but not so isolated as to prevent excess diffusion of favorable systems from centers that have attained superior general adaptation, seems to be the most favorable for evolution whether under static or changing conditions. It permits a three-phase process: (*a*) relatively rapid, random local differentiation, if $(1/(2N))$ is of the order of the proportion of immigration from the species as a whole, that leads (*b*) to the crossing of two-factor saddles and mass selection toward control by the higher selective peaks, and (*c*) interlocality selection on the basis of differential population growth and diffusion. Polyallelic random drift greatly enhances the first phase.

The discussion of the number of alleles maintained in a population has been restricted here to random breeding populations. A subdivided species presents a much more favorable situation for maintaining a large number at high but ever-shifting frequencies. For example, a random breeding population of 500 with a mutation rate of 0.0002 was shown[1] to maintain about 22 self-compatibility alleles, but if subdivided into groups of 50, each receiving 0.1 per cent of its genes from the whole group per generation, the number within each group is only about 8, but about 50 alleles are maintained in the whole population. In other cases, slight differences in local conditions of selection may bring about considerable differences in the sets of alleles present in the local population, while small amounts of exchange maintain active random drift within each.

Under this theory (as well as under the preceding, as far as it goes), the elementary evolutionary step is not the incorporation of a novel favorable mutation but the occupation by the species of a new selective peak, the height of which depends on the harmonious interaction of many components of the genome. Since a small number of alleles at a small number of loci provide a virtually infinite number of different homozygous combinations (100^{100} from 100 alleles at each of 100 loci), there is no limitation under this process by the rate of occurrence of novel favorable mutations. An indefinitely great number of steps may occur, based on attainment of favorable new interaction systems, without the occurrence of a single mutation that could be considered favorable by itself.

Summary.—The number of alleles maintained in a population of given size by a given mutation rate, and the turnover from an indefinitely great possible number, are discussed in the cases of (1) neutral alleles, all with the same mutation rate; (2) equally deleterious alleles, semidominant or recessive, all with the same mutation rate; and (3) heterotic alleles for which all homozygotes are at the same selective disadvantage with respect to all heterozygotes and mutation rates are all the same.

The evolutionary implications of the polyallelic random drift that occurs in these cases is discussed.

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*GENE-SPECIFIC MRNA, II. REGULATION OF MRNA SYNTHESIS IN E. COLI AFTER INFECTION WITH BACTERIOPHAGE T4**

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Following infection of *E. coli* cells with a bacteriophage of the T-even series, enzymes needed for phage DNA synthesis are produced during the first few minutes. The structural components of the phage and enzymes concerned with their assembly do not appear until several minutes have elapsed and then continue to be synthesized up to the time of lysis of the host cell.[1] This temporal sequence of biochemical events, all specified by the phage genome, provides a unique opportunity to test some of the current concepts of how RNA and protein synthesis might be regulated. The regulation of protein synthesis is assumed to occur either at the level of transcription[2] or at the level of translation.[3, 4] These two alternatives should result in distinctly different patterns of RNA synthesis during phage development. If regulation occurs at the level of transcription, the sequential appearance of early and late proteins should be paralleled by a sequential production of early and late messages, i.e., the mRNA species present at early times after in-