THE DISTRIBUTION OF GENE FREQUENCIES UNDER
IRREVERSIBLE MUTATION

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Communicated June 13, 1938

Under reversible mutation, the frequency \( q \) of a gene, subject to systematic evolutionary pressure \( \Delta q \) and to the accidents of sampling in a limited population \( N \) diploid individuals), varies according to a certain distribution \( \varphi(q) \) discussed in previous papers.\(^1\)\(^2\)\(^3\) If mutation is irreversible, the distribution curve for such genes should attain constancy of form, but all class frequencies should fall off at a uniform rate \( K \) as genes drift irreversibly into fixation. The purpose of the present paper is to broaden somewhat the treatment in this latter case.

As previously shown\(^2\) the rate of fixation is approximately half the frequency, \( f(1 - 1/2N) \), in the subterminal class. Thus with

\[
\int_0^1 \varphi(q) dq = 1
\]

\[
K = 1/2 f(1 - 1/2N) = \frac{\varphi(1 - 1/2N)}{4N}
\]

approximately. \(^1\)

The changes in the mean \( \bar{q} = \int_0^1 q \varphi(q) dq \) and the variance \( \sigma_q^2 = \int_0^1 (q - \bar{q})^2 \varphi(q) dq \) of gene frequencies, due to fixation in one generation, may be expressed as follows in terms of the systematic evolutionary pressure, \( \Delta q \), and the variation due to sampling, \( \sigma_{\Delta q}^2 \)

\[
\int_0^1 \Delta q \varphi(q) dq = K(1 - \bar{q}). \tag{2}
\]

\[
\int_0^1 (q + \Delta q - \bar{q})^2 \varphi(q) dq + \int_0^1 \sigma_{\Delta q}^2 \varphi(q) dq = (1 - K) \sigma_q^2 + K(1 - \bar{q})^2. \tag{3}
\]

The latter can be reduced to following, ignoring a negligible term in \((\Delta q)^2\)
If the conditions are such that under equilibrium, with reverse mutation at an indefinitely low rate, there is no important accumulation of genes in the class $q = 1$, complete irreversibility of mutation should make no appreciable difference in the form of distribution. The demonstration of the formula for this case ($K = 0$) can be put in a very simple form.

Let $\int \Delta q \varphi(q) dq = \chi(q)$. (5)

Equations (2) and (4) can be written as follows, putting $K = 0$,

$$\chi(1) - \chi(0) = 0. \quad (6)$$

$$\int_0^1 \chi(q) dq - [\bar{q} \chi(0) + (1 - \bar{q}) \chi(1)] - \frac{1}{2} \int_0^1 \sigma_{\Delta q}^2 \varphi(q) dq = 0. \quad (7)$$

Equation (7) is obviously satisfied by the following

$$\chi(q) - [\bar{q} \chi(0) + (1 - \bar{q}) \chi(1)] - \frac{1}{2} \sigma_{\Delta q}^2 \varphi(q) = 0. \quad (8)$$

This means little, until it is shown that (8) also satisfies (6).

As there can be no sampling variance in homallelic populations, $\sigma_{\Delta q}^2 = 0$ if $q = 0$ or $q = 1$. Equation (8) reduces to (6) if $q = 0$ or $q = 1$ and both $\varphi(0)$ and $\varphi(1)$ are finite. Equation (8), therefore, satisfies the condition of constancy of the mean as well as that of constancy of the variance.

$$\varphi(q) = 2[\chi(q) - \chi(1)] / \sigma_{\Delta q}^2. \quad (9)$$

$[\chi(q) - \chi(1)]$ can be evaluated as follows, using (5) and (9),

$$d \log [\chi(q) - \chi(1)] = \frac{d \chi(q)}{\chi(q) - \chi(1)} = \frac{2 \Delta q \varphi(q) dq}{\sigma_{\Delta q}^2 \varphi(q)}, \quad (10)$$

$$\chi(q) - \chi(1) = \frac{C}{2} e^{\frac{2 q \Delta q}{\sigma_{\Delta q}^2}}, \quad (11)$$

$$\varphi(q) = \frac{Ce^2}{\sigma_{\Delta q}^2}. \quad (12)$$

This is the desired expression for the distribution in terms of $\Delta q$ and $\sigma_{\Delta q}^2$.

Putting $\sigma_{\Delta q}^2 = \frac{q(1 - q)}{2N}$, its value in a population of $N$ diploid indi-
individuals, it is the same as the formula given previously (except for the value of the coefficient $C$).

If $K$ is not zero, this method does not appear to lead to a usable general expression which satisfies (1), (2) and (4). An expression for the rate of decay can, however, be obtained from (2). Let $v$ be the rate of mutation, and let $\bar{W}$ be the mean selective value of genotypes. As shown previously

$$\Delta q = v (1 - q) + q (1 - q) \frac{d \log \bar{W}}{2dq}. \quad (13)$$

From (2)

$$K = v + \frac{1}{2 (1 - q)} \int_0^1 q (1 - q) \phi(q) d \log \bar{W}. \quad (14)$$

If there is no selection ($\bar{W} = 1$)

$$K = v. \quad (15)$$

The condition that the frequency of any class of gene frequencies, $q_c$, be reconstructed after each generation, except for a uniform decay at rate $K$ can be represented as follows, using $p = 1 - q$ for brevity.

$$(1 - K) \varphi(q_c) = A \int_0^1 (q + \Delta q)^{2Nq_c} (p - \Delta q)^{2Np_c} \phi(q) dq$$

where

$$A = \frac{\Gamma(2N)}{\rho_d q_c \Gamma(2Np_c) \Gamma(2Nq_c)}. \quad (18)$$

If $v$ is so small that practically all genes are fixed in the class $f(0)$, $K$ may be ignored in determining the form of the distribution for unfixed genes. Substituting the value of $\Delta q$ from (17)

$$\varphi(q_c) = A \int_0^1 q^{2Nq_c} p^{2Np_c} \left[1 + p(s + tq)\right]^{2Nq_c} \left[1 - q(s + tq)\right]^{2Np_c} \phi(q) dq. \quad (19)$$

The following approximations may be used

$$[1 + p(s + tq)]^{2Nq_c} = e^{2Nq_c \rho (s + tq)} \left[1 - N q_c p^2 (s + tq)^2\right]. \quad (20)$$
\[ [1 - q(s + tq)]^{2N p_c} = e^{-2N p_c(q(s + tq))} [1 - N p_c q^2(s + tq)^2]. \] (21)

The product of expressions (20) and (21) is approximately
\[ e^{2N s (q_c - q) + N t (q_c - q)^2 - N t (q_c - q)^2} \left\{ 1 - N (s + tq)^2 [p_c q_c + (q_c - q)^2] \right\}. \] (22)

Since the random deviations of \( q \) have the variance, \( \sigma_{2q}^2 = \frac{pq}{2N} (q_c - q)^2 \)
is of the order 1/2N. The term \( N (s + tq)^2 (q_c - q)^2 \) is thus negligibly small compared with \( N (s + tq)^2 p_c q_c \) which itself is as small a term as it is necessary to consider. The former may thus be ignored. The constant and variable gene frequencies are separable in the exponential term in (22) except in the term \( e^{-N t (q_c - q)^2} \). The exponent in this case is smaller than \( -t \) and the term can be written \( [1 - N t (q_c - q)^2] \) with sufficient accuracy. Equation (19) can now be written as follows:

\[ \varphi(q_c) = A e^{2N s q_c + N t q_c} \int_0^1 q^{2N p_c - 1} p^{2N p_c - 1} e^{-2N s q - N t q^2} [1 - N (s + tq)^2 p_c q_c - N t (q_c - q)^2] \varphi(q) dq. \] (23)

Let
\[ \varphi(q) = \frac{e^{2N s q + N t q^2}}{q (1 - q)} \left( C_0 + C_1 q + C_2 q^2 + \ldots \right). \] (24)

This entirely eliminates the exponential terms, leaving (23) in a form which can be solved, using the following sufficiently accurate formula in which terms of the order \( \frac{1}{N^2} \) are ignored.

\[ \frac{\Gamma(2N)}{\Gamma(2N p_c) \Gamma(2N q_c)} \int_0^1 q^{2N p_c - 1 + x} p^{2N p_c - 1} dq = q_c^2 \left[ 1 - \frac{x(x - 1)}{4N} \right] + q_c^{x-1} \left[ \frac{x(x - 1)}{4N} \right]. \] (25)

The resulting coefficients of the powers of \( q_c \) on the right side may be equated to those on the left side leading to the following general expression (in which \( C_{-1} = C_{-2} = C_{-3} = 0 \)).

\[ C_m = \frac{m(m + 1)}{4N} C_{m+1} + C_m - \frac{C_{m-1}}{2} (2N s^2 + t) \]
\[ - C_{m-2} (2N s t) - C_{m-3} N t^2. \] (26)

The higher coefficients can all be expressed in terms of \( C_0 \) and \( C_1 \) and substituted in (24). By letting \( C_1 = 2N s C_0 + D \) the terms for which \( C_0 \) is the coefficient can be condensed into exponential form. It will be convenient to substitute \( C \) for \( C_0 \).
\[ \varphi(q) = \frac{e^{2Nsq + Ntq^2}}{q(1 - q)} \left[ Ce^{2Nsq + Ntq^2} + Dq\psi(q) \right], \quad (27) \]

where

\[ \psi(q) = 1 + \frac{(2Nsq)^2}{3} + \frac{(2Nsq)^4}{5} + \frac{(2Nsq)^6}{7} \ldots \quad (28) \]

\[ + (2Ntq^2) \left( \frac{1}{3} + \frac{(2Nsq)^2}{3} + \frac{2(2Nsq)^2}{5} + \frac{2(2Nsq)^3}{5} + \frac{3(2Nsq)^4}{7} \ldots \right) \]

\[ + (2Ntq^2)^2 \left( \frac{7}{5} + \frac{2(2Nsq)}{5} + \frac{69(2Nsq)^2}{7} \ldots \right) \]

\[ + (2Ntq^2)^3 \left( \frac{27}{7} \ldots \right) + \ldots \]

If \( D = 0 \)

\[ \varphi(q) = \frac{Ce^{4Nsq + 2Ntq^2}}{q(1 - q)}. \quad (29) \]

This is the case of equilibrium under reversible mutation or irreversible mutation opposed by sufficiently strong selection as can be seen by substituting \( \Delta q = (s + tq)q(1 - q) \), \( \sigma_q^2 = \frac{q(1 - q)}{2N} \) in (12). They agree except in the coefficient.

The case of irreversible mutation with fixation occurring at a low rate, can be found from (1) and (2), assuming that nearly all genes are in one of the homallelic classes. It should be noted that the formula for \( \varphi(q) \) only applies where \( K \) is of lower order than \( 1/2N, 2N^2 + t \) in (26). Mutations to the class \( q = 1/2N \) contribute the amount \( 2Nt\varphi(0) = \frac{1}{2}f(1/2N) \) and these contribute to the change of mean by the amount \( f(1/2N)/4N \). The mean, however, must be so low that the term \( K(1 - \bar{q})/4N \) may be written \( K \) sufficiently accurately. The following relations are all approximate:

\[ \int_0^1 \Delta q\varphi(q)dq + \frac{f(1/2N)}{4N} = K = \frac{f(1 - 1/2N)}{2}. \quad (30) \]

\[ f(1/2N) = C \left[ 1 + \frac{1}{2N} + 2s \right] + \frac{D}{2N}. \quad (31) \]

\[ f(1 - 1/2N) = C[e^{4Ns + 2Nt}(1 + 1/2N - 2s - 2t)] + \]

\[ D[e^{2Ns + Nt}(1 - s - t)\psi(1 - 1/2N)] . \quad (32) \]
\[ \int_0^1 \Delta q \phi(q) dq = C \left[ \frac{e^{4Ns} + 2Nt}{4N} - \frac{1}{4N} \right] + \frac{Ds}{2} + \frac{Dt}{3}. \] (33)

Substituting (31), (32), (33) in (30) and substituting \( \psi(1) \) for \( \psi(1 - 1/2N) \) (leading terms in difference, \( t/3, \frac{2Ns^2}{3} \))

\[ D = - \frac{Ce^{2Ns + Nt}}{\psi(1)}. \] (34)

With practically all genes in the class \( q = 0 \), \( f(0) = 1 = \frac{f(1/2N)}{4Nv} = \frac{C}{4Nv} \).

Thus \( C = 4Nv \) approximately.

\[ \varphi(q) = \frac{4Nv e^{4Ns} + 2Ntq^2}{q(1 - q)} \left[ 1 - \frac{e^{2Ns(1-q)} + Nt(1-q)q\psi(q)}{\psi(1)} \right]. \] (35)

For sufficiently small values of \( Ns \) and \( Nt \) we may take \( \psi(q) = 1 + 1/3Ntq^2 \) and represent the exponentials by the first two terms of their expansions. The following shows how the hyperbolic distribution \( 4Nv/q \) is modified by weak selection (\( s \) positive for favorable mutation, negative for unfavorable mutation).

\[ \varphi(q) = \frac{4Nv}{q} [1 + 2Ns + 2/3Ntq(2q - 1)]. \] (36)

The rate of fixation \( (K) \) of genes can be found from the left member of (30) (in which inaccuracies in the evaluation of \( D \) have less effect than in the right member).

\[ K = v \left[ e^{4Ns} + 2Nt - \frac{(2Ns + 4/3Nt)e^{2Ns + Nt}}{\psi(1)} \right]. \] (37)

This reduces to \( v(1 + 2Ns + 2/3Nt) \) for such small values of \( Ns \) and \( Nt \) as implied in (36). It is to be noted that irreversible mutation should ultimately lead to fixation of the mutant even when opposed by selection (\( s \) negative) but the rate is exceedingly slow unless \( Ns \) and \( Nt \) are small.

In the special case of genic selection \( (t = 0) \)

\[ \psi(q) = \frac{e^{2Ns} - e^{-2Nsq}}{4Ns}. \] (38)

\[ \varphi(q) = \frac{4Nv}{(1 - e^{-4Ns})} \left[ 1 - e^{-4Ns(1-q)} \right]. \] (39)

An essentially similar derivation of this formula has been given previously by the author and a different one by Fisher. In this case \( K = \frac{4Nvs}{1 - e^{-4Ns}} \) approaching \( v(1 + 2Ns) \) as \( 4Ns \) decreases.
The question of the chance of fixation of an individual mutation must be distinguished from the rate of fixation \((K)\) under recurrent mutation. The chance of fixation is given by the ratio \(f(1 - 1/2N)/f(1/2N) = K/2Nv\). In the case of no dominance, this gives \(2s/(1 - e^{-4Ns})\) or approximately \(2s\) for favorable mutations occurring in a large population, in agreement with Fisher.\(^4\) For indifferent factors it is \(1/2N\). Unfavorable mutations have a chance of fixation \(2s/(e^{4Ns} - 1)\) but this is small unless \(4Ns\) is small.

The results presented here bear on the possibility of a course of evolutionary change determined by mutation pressure, a process which at first sight seems the most obvious implication of modern genetics. The possibility does indeed exist but requires either an almost complete indifference of the mutation with respect to adaptive value or else a very small effective size of population over a long period of time. The most important case in which mutation pressure seems likely to be a major factor is that of extreme degeneration or elimination of organs that have ceased to be useful.\(^5,6\)

The degeneration of the eyes and loss of pigment of cave forms is an example of a case in which the conditions make it especially probable that mutation pressure is a real factor. In all of these cases, however, the likelihood that various direct and indirect effects of selection may also play a rôle should not be ignored.\(^5\)

It should be noted that while the average rate of fixation of irreversible mutations is low, the large element of chance with respect to which mutations become fixed in each particular case makes this a greater factor in the diversification of small isolated populations than is at first apparent. Indeed there may be much diversification of gene frequencies among such populations under conditions in which there is no appreciable systematic tendency toward fixation of the sort investigated here.