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Genetics

Effect of temporal fluctuation of selection coefficient on gene frequency in a population

(population genetics/diffusion model/protein polymorphism/molecular evolution/neutral theory)

NAOYUKI TAKAHATA, KAZUSHIGE ISHII, AND HIROTSUGU MATSUDA*

Department of Biology, Faculty of Science, Kyushu University, Fukuoka, Japan

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ABSTRACT **The diffusion equations describing the change of gene frequencies are extended to include the effect of temporal fluctuation of selection coefficient that may persist for some generations. The equilibrium distribution of gene frequencies and the fixation probability of a mutant gene are obtained from the extended equations. Comparison is made with the experimental data on protein polymorphism. A possible bearing of the fluctuation of selection coefficient on the problem of molecular evolution is discussed in relation to the neutral theory.**

Dobzhansky (1) has remarked: "Mathematical models usually assume, and experimental studies endeavor to provide, uniform and constant environments in which the selection can take place. This convention is convenient, because the Darwinian fitness of a genotype in a constant environment is also constant. Unfortunately, it is also an oversimplification. Not only a species or a population but even a single individual faces a variety of environments in its lifetime."

Recent developments of experimental techniques such as electrophoresis and sequence analysis have revealed (2) that the protein polymorphism is a phenomenon of common occurrence. Thus, the existence of many different proteins with no appreciable physiological functional difference is indicated. This fact strongly suggests that there are many alleles whose selective advantages over the others are very small. In view of this and also to understand the observed nearly constant rate of molecular evolution, Kimura (3, 4) went as far as to assume that the selective advantages of most alleles are effectively zero in the process of molecular evolution, that is, selectively neutral, so that the difference of homologous proteins of different species should be understood rather as a result of random fixation of one of selectively neutral alleles than as a result of natural selection. King and Jukes (5) pointed out that the frequency of an amino acid, averaged over a large number of proteins, is approximately proportional to the number of synonymous codons, and that this is in accord with Kimura's neutral theory of molecular evolution.

Although there have been many arguments (2–8) for and against the neutral theory and the problem is still open, one must note that if the selective advantage of an allele is very small, the gene substitution in a population or in a species should occur very slowly. Therefore, for such a long time process the assumption that the environment remains constant becomes all the more questionable. Moreover, for a constant amount of fluctuation of the selection coefficient from its time average, its ratio to the latter increases as the time average approaches zero; this indicates the relative importance of the fluctuation.

Now, let T be the time in which the gene frequency significantly changes, and let τ be the time duration beyond which the selection coefficient has almost no correlation. Throughout this paper we take one generation as a unit of time. Wright (9) and Kimura (10) considered a mathematical model corresponding to the stationary stochastic process of a selection coefficient with $\tau = 1$. Kimura (10) and Ohta (11) used the Wright–Kimura model when discussing the effect of a random fluctuation of the selection coefficient on the fixation probability. Recently, Jensen (12) and Gillespie (13) reconsidered this model, pointed out that the diffusion equation previously derived by Wright and Kimura has to be modified, and obtained more accurate fixation probabilities for somewhat special cases. Karlin and Levikson (14) generalized the above results and pointed out some salient consequences of random environmental changes.

However, for a practical application to a problem such as protein polymorphism or molecular evolution, in which selection coefficients of very small values are mostly involved, the effect of the fluctuation is only of the second order of magnitude of the selection coefficient so long as $\tau = 1$. On the other hand, if $\tau \gg T$, then the process may be regarded as if proceeding essentially under a constant environment. Thus, in this paper we derive the diffusion equation for the case $1 \ll \tau \ll T$, and discuss possible bearings of our results on the problem of molecular evolution by comparing them with experimental data on protein polymorphism.

DIFFUSION EQUATION

Let us start from the Kolmogorov backward equation (15) for semidominant alleles in a diploid population with effective number N:

$$-\frac{\partial\phi(x,t;x',t')}{\partial t} = \frac{1}{4N}x(1-x)\frac{\partial^2\phi}{\partial x^2} + s(t)x(1-x)\frac{\partial\phi}{\partial x} \quad [1]$$

where $\phi(x, t; x', t')$ is the probability density for the frequency x' of the mutant at time t' under the condition that the frequency was x at time t, while $s(t)$ is the selection coefficient at time t as a Malthusian parameter. When $s(t)$ is a constant, this equation has been extensively studied by Wright and Kimura and others. It has been found to be a good approximation to the discrete model in which the effect of natural selection and random sampling is taken into account. We may naturally expect that even when $s(t)$ varies with time, [1] remains a good approximation as long as the time variation of $s(t)$ is sufficiently slow, that is, as long as $\tau \gg 1$.

To include the effect of random fluctuation of the selection coefficient, we assume that $s(t)$ is a bounded random

* Also at Research Institute for Fundamental Physics, Kyoto University, Kyoto, Japan.

variable with a duration time τ such as

$$\int_0^t < [s(t_1 + t_2) - \bar{s}][s(t_1) - \bar{s}] > dt_2 \simeq V \quad \text{for } t \geqslant \tau \quad [2]$$

Here, $\bar{s} = \langle s(t) \rangle$ and V are constants, and the bracket denotes the ensemble average.

We note that [1] can be written in the form

$$\frac{\partial f(t)}{\partial t} = [A + \sigma(t)B]f(t) \quad [3]$$

where

$$f(t) = \phi(x, -t; x', t') \quad [4]$$

$$A = \frac{1}{4N} x(1 - x)\frac{\partial^2}{\partial x^2} + \bar{s}x(1 - x)\frac{\partial}{\partial x} \quad [5]$$

$$B = x(1 - x)\frac{\partial}{\partial x} \quad [6]$$

$$\sigma(t) = s(-t) - \bar{s} \quad [7]$$

Putting $f(t) = e^{At}\tilde{f}(t)$, and $\tilde{B}(t) = e^{-At}Be^{At}$, we have

$$\frac{\partial \tilde{f}(t)}{\partial t} = \sigma(t)\tilde{B}(t)\tilde{f}(t) \quad [8]$$

Hence

$$\tilde{f}(t) = \int_0^t dt'\sigma(t')\tilde{B}(t')\tilde{f}(t') + \tilde{f}(0) \quad [9]$$

$$= \left[1 + \int_0^t dt'\sigma(t')\tilde{B}(t') + \int_0^t dt'\sigma(t')\tilde{B}(t') \times \int_0^{t'} dt''\sigma(t'')\tilde{B}(t'') + \ldots\right]\tilde{f}(0)$$

If we assume that for odd n $\langle \sigma(t_1)\sigma(t_2) \ldots \sigma(t_n) \rangle = 0$ and remember the assumption about $s(t)$, we have for $t \gg \tau$:

$$\langle \tilde{f}(t) \rangle \simeq \left[1 + V\int_0^t dt'\tilde{B}^2(t') + V^2\int_0^t dt'\tilde{B}^2(t')\int_0^{t'} dt''\tilde{B}^2(t'') + \ldots\right]\tilde{f}(0) \quad [10]$$

Therefore, we obtain

$$\frac{\partial \langle \tilde{f}(t) \rangle}{\partial t} \simeq V\tilde{B}^2(t)\langle \tilde{f}(t) \rangle \quad [11]$$

which reduces to

$$\frac{\partial \langle f(t) \rangle}{\partial t} = (A + VB^2)\langle f(t) \rangle \quad \text{for } t \gg \tau \quad [12]$$

In deriving [12] from [3] no specification of the operators A and B was necessary, so that the result [12] is rather general. If we specify the operators by [5] and [6], we at once reach the Kolmogorov backward equation for the average probability density $\langle \phi(x, x', t) \rangle = \langle \phi(x, t'; x', t' + t) \rangle$:

$$\frac{\partial \langle \phi(x,x',t) \rangle}{\partial t} = \nu(x)\frac{\partial^2 \langle \phi \rangle}{\partial x^2} + \mu(x)\frac{\partial \langle \phi \rangle}{\partial x} \quad [13]$$

where

$$\nu(x) = \frac{1}{4N}x(1 - x) + Vx^2(1 - x)^2 \quad [14]$$

and

$$\mu(x) = \bar{s}x(1 - x) + Vx(1 - x)(1 - 2x) \quad [15]$$

Similarly, we obtain the corresponding forward equation

$$\frac{\partial \langle \phi(x', x, t) \rangle}{\partial t} = \frac{\partial^2}{\partial x^2}\{\nu(x)\langle \phi \rangle\} - \frac{\partial}{\partial x}\{\mu(x)\langle \phi \rangle\} \quad [16]$$

An equation similar to [12] has also been derived by Kubo (16) and Lax (17) by somewhat different methods.

EQUILIBRIUM DISTRIBUTION

Let v be a mutation rate per generation from the wild type to the mutant and u be the mutation rate from the mutant to the wild type. Then by a standard method of population genetics (15) we obtain from [16] the equilibrium probability density

$$\phi(x) \propto x^{4Nv-1}(1 - x)^{4Nu-1}(\alpha_+ - x)^{4NA_+} \times (x - \alpha_-)^{4NA_-} \quad [17]$$

where

$$\alpha_\pm = \frac{1}{2}\{1 \pm \sqrt{1 + 1/(NV)}\} \quad [18]$$

$$A_\pm = \{-\bar{s}/(4NV) - u\alpha_\pm + v\alpha_\mp\}/(\alpha_\pm - \alpha_\mp) \quad [19]$$

To simplify [17] we consider two extreme cases: (I) $NV \ll 1$ and (II) $NV \gg 1$.

Case (I) $NV \ll 1$

In this case [17] reduces to

$$\phi(x) \propto x^{4Nv-1}(1 - x)^{4Nu-1}e^{4N\bar{s}x} \quad [20]$$

This is nothing but the equilibrium distribution for a constant selection coefficient $\bar{s}$.

Case (II) $NV \gg 1$

In this case we have asymptotically

$$\phi(x) \propto x^{4Nv-1}(1 - x)^{4Nu-1}\{x + 1/(4NV)\}^{-4Nv+w/V} \times \{1 - x + 1/(4NV)\}^{-4Nu-w/V} \quad [21]$$

where $w = \bar{s} + v - u$.
Further, [21] becomes

$$\phi(x) \propto \begin{cases} x^{4Nv-1} & [x \ll 1/(4NV)] \quad [22] \\ (1 - x)^{4Nu-1} & [1 - x \ll 1/(4NV)] \quad [23] \\ x^{w/V-1}(1 - x)^{-w/V-1}\exp[-v/(Vx) - u/\{V(1 - x)\}] & [x, 1 - x \gg 1/(4NV)] \quad [24] \end{cases}$$

FIXATION PROBABILITY

Let $u(x, t; t')$ be the fixation probability by time t' of a mutant introduced into the population at time t with an initial frequency x. The average fixation probability $\langle u(x, t' - t) \rangle = \langle u(x, t; t') \rangle$ satisfies the backward Eq. [13]:

$$\frac{\partial \langle u(x,t) \rangle}{\partial t} = \nu(x)\frac{\partial^2 \langle u \rangle}{\partial x^2} + \mu(x)\frac{\partial \langle u \rangle}{\partial x} \quad [25]$$

The ultimate fixation probability $\langle u(x) \rangle = \langle u(x, \infty) \rangle$ is obtained as the solution of [25] in which the right side is equat-

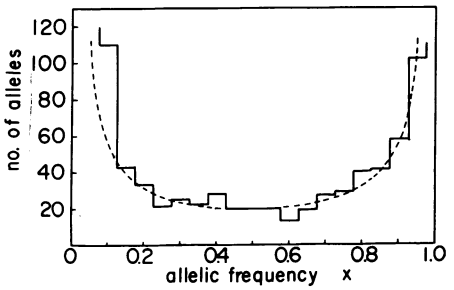

FIG. 1. The histogram of frequencies of alleles. The ordinate denotes a number of alleles in the frequency interval of width 0.05. The broken line is proportional to $\{x(1-x)\}^{-1}$.

ed to zero, under the boundary condition

$$\langle u(0)\rangle = 0, \qquad \langle u(1)\rangle = 1 \qquad [26]$$

The result is

$$\langle u(x)\rangle = \begin{cases} \dfrac{1-\left|\dfrac{1-x/\alpha_+}{x/\alpha_- - 1}\right|^{\lambda}}{1-|\alpha_-/\alpha_+|^{2\lambda}} & (\bar{s}\neq 0) \\ \dfrac{\log\left|\dfrac{1-x/\alpha_+}{x/\alpha_- - 1}\right|}{2\log|\alpha_-/\alpha_+|} & (\bar{s}=0) \end{cases} \qquad [27]$$

where $\lambda = \bar{s}/\{V\sqrt{1+1/(NV)}\}$.

To simplify [27] we consider the two extreme cases as before.

Case (I) $NV \ll 1$

$$\langle u(x)\rangle \simeq \begin{cases} (1-e^{-4N\bar{s}x})/(1-e^{-4N\bar{s}}) & (\bar{s}\neq 0). \\ x & (\bar{s}=0). \end{cases} \qquad [28]$$

This is nothing but the fixation probability for a constant selection coefficient $\bar{s}$.

Case (II) $NV \gg 1$

$$\langle u(x)\rangle \simeq \begin{cases} \dfrac{1-\left|\dfrac{1-x\{1-1/(4NV)\}}{x+1/(4NV)}\right|^{k}(4NV)^{-k}}{1-(4NV)^{-2k}} & (\bar{s}\neq 0), \\ \dfrac{\log(4NV)+\log\left|\dfrac{x+1/(4NV)}{1-x\{1-1/(4NV)\}}\right|}{2\log(4NV)} & (\bar{s}=0). \end{cases} \qquad [29]$$

Here, we have put $k = \bar{s}/V$.

To further simplify [29], we consider three frequency regions separately.

For $1/(4NV) \ll x, 1-x$,

$$\langle u(x)\rangle \simeq \begin{cases} 1-(4NV)^{-k}\{(1-x)/x\}^{k} & (\bar{s}>0) \\ \dfrac{1}{2}+\dfrac{\log\{x/(1-x)\}}{2\log(4NV)} & (\bar{s}=0) \\ (4NV)^{-|k|}\{x/(1-x)\}^{|k|} & (\bar{s}<0) \end{cases} \qquad [30]$$

For $x \ll 1/(4NV)$,

$$\langle u(x)\rangle \simeq \begin{cases} \dfrac{4N\bar{s}}{1-(4NV)^{-2k}}\,x & (\bar{s}\neq 0) \\ \dfrac{2NV}{\log(4NV)}\,x & (\bar{s}=0) \end{cases} \qquad [31]$$

Especially when $|k\log(4NV)| \ll 1$, we have

$$\langle u(x)\rangle \simeq 2NVx/\log(4NV) \qquad [32]$$

Here the fixation probability is proportional to x, but it depends on NV.

For $1-x \ll 1/(4NV)$, we can obtain $\langle u(x)\rangle$ from [31] or [32] by using the relation

$$\langle u(x;\bar{s})\rangle = 1 - \langle u(1-x;-\bar{s})\rangle \qquad [33]$$

where $\langle u(x;\bar{s})\rangle$ denotes the fixation probability of a mutant with a fluctuating selection coefficient characterized by $\bar{s}$ and V. The Eq. [33] is easily verified from [25] and [26].

DISCUSSION

Allelic frequencies, or more exactly frequencies of a set of alleles coding for peptides with equal charge, have been measured by electrophoresis at various loci for various populations of *Drosophila*, *Mus*, and *Limulus* (2, 8). Fig. 1 illustrates a histogram of frequencies of 1366 different sets of such alleles. The histogram can be well fitted by a curve proportional to $[x(1-x)]^{-1}$ except for the region of x close to 0. On the other hand, from [24] the equilibrium probability density in our model is approximately proportional to $[x(1-x)]^{-1}$ if

$$V \gg \mathrm{Max}[|\bar{s}|, v, u, 1/N] \qquad [34]$$

in the region of x such as

$$x, 1-x \gg \mathrm{Max}[v/V, u/V, 1/(4NV)] \qquad [35]$$

Note that the right side of [35] is close to 0 when [34] holds.

Thus, in Fig. 1 the experimental histogram is in accord with the hypothesis that in natural populations almost every allele is under the influence of a fluctuating selection pressure satisfying [34], except for some of those alleles whose frequencies are close to 0. Such alleles are supposed to be more or less permanently deleterious in the sense that $-\bar{s} \gg V$ or $NV \ll 1 \ll -N\bar{s}$.

Let us consider the case [34] in our model a little more closely. In this case $\phi(x)$ can be approximated as

$$\phi(x) \simeq 1/\{|\log(x_1x_2)|x(1-x)\} \qquad \text{for } x_1 < x < 1-x_2 \qquad [36]$$

where x_1 and x_2 are small positive numbers of the order of the right side of [35]. Let H be the probability that two randomly chosen alleles from the population are different. This probability is given by

$$H = 2\int_0^1 \phi(x)x(1-x)dx \simeq 2/|\log(x_1x_2)| \qquad [37]$$

If we call a locus with an allele whose frequency is between

Table 1. H versus x_1 in [37] ($x_1 = x_2$)

x_1	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}
H	0.217	0.145	0.109	0.087	0.072	0.062

$1 - q$ and 1 ($0 < q \ll 1$) monomorphic (with index q), and if we call the other loci polymorphic, we obtain the proportion of the polymorphic loci as

$$P_q = \int_q^{1-q} \phi(x)dx \simeq 2|\log\ q/\log(x_1x_2)| \quad [38]$$

From [37] and [38] we have

$$P_q \simeq |\log\ q|H \quad [39]$$

In Fig. 2 we compare the theoretical relation [39] with the observed values (2) shown by dots.

Previously, Kimura and Ohta (18) obtained the expressions for H and P_q under a neutral model. When there are infinitely many possible neutral allelic states for a given locus they are given by

$$H \simeq 4Nv/(4Nv + 1) \quad [40]$$

$$P_q \simeq 1 - q^{4Nv} \quad [41]$$

Thence

$$P_q = 1 - q^{H/(1-H)} \quad [42]$$

This relation coincides with [39] for small H. The relation [42] is shown in Fig. 2 by a broken line. Both [39] and [42] are in fair agreement with experiments.

However, we note that the prediction of the neutral theory is very sensitive to the value of Nv as pointed out by several authors (2, 8). According to [40] the value Nv must be in a narrow range between 0.014 and 0.057 to obtain the experimental values of H, which are all between 0.056 and 0.185. Since H is strongly dependent on Nv in [40], this requirement seems to be too stringent to be realistic.

On the other hand, in [37] H is insensitive to the value of x_1 and x_2. When x_1 is set equal to x_2 we show values of H for some typical values of x_1 in Table 1. If we suppose that $v \simeq 10^{-6}$ and $x_1 \simeq v/V$, the values of V that correspond to those in Table 1 cover the range 10^{-4}–10. In view of the definition of V in [2] they are not unreasonable values.

Now, the rate γ of so-called molecular evolution can be given as the mutation rate v times the fixation probability of a mutant summed over all the individuals of a population. For the case [34] we have from [32]

$$\gamma \simeq 2NVv/\log(4NV) \quad [43]$$

This rate depends on NV. However, to calculate the rate of molecular evolution we must regard the value of $s(t)$ as an average over the fitness of individuals of a species living in diverse environments. It is then possible that the value of V becomes smaller as N increases due to the smoothing out by averaging. Thus, the rate γ, though not just v as in the neutral theory, may be restricted to some narrow range of values. Here, we note that detailed analyses of homologous proteins of different species have shown that the observed constancy is only an approximate one with nonnegligible deviation from the prediction of the neutral theory (19, 20).

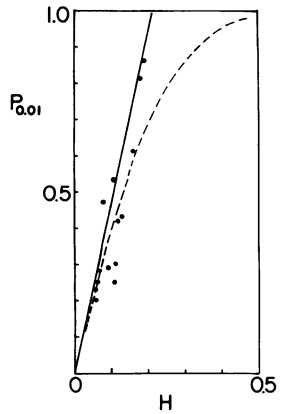

FIG. 2. The relation between the average heterozygosity H and the proportion of polymorphic loci with index 0.01 denoted by $P_{0.01}$. Dots are experimental data according to (2). The solid line represents [39], whereas the broken line represents [42].

For the neutral theory we must assume that

$$|s(t)| \ll 1/N \quad [44]$$

This assumption seems very restrictive if N has to be of the order of the number of individuals of a species. As we have discussed, it is sufficient only to assume [34] for the gross understanding of experiments. Here, the time average of the selection coefficient need only be small in the sense

$$|\bar{s}| \ll 1/V \quad [45]$$

This is also a kind of near neutrality hypothesis. We may call [45] the *average* neutrality hypothesis in contrast to the *classical* neutrality hypothesis [44]. The *average* neutral theory predicts how polymorphisms and rates of molecular evolution depend on the parameters N, V, and v. However, the *average* neutral theory *per se* does not predict an interpopulation or interlocus quantity as in the *classical* neutral theory, since $s(t)$ for different populations and for different loci may be correlated any way. In this sense, it could be immune from criticisms raised against the neutral theory based on the experimental data for such quantities (2, 8).

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