Proc. Natl. Acad. Sci. USA
Vol. 77, No. 1, pp. 522–526, January 1980
Genetics

Average time until fixation of a mutant allele in a finite population under continued mutation pressure: Studies by analytical, numerical, and pseudo-sampling methods

(population genetics/evolution/stochastic process/degeneration of character/Monte Carlo simulation)

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Contributed by Motoo Kimura, October 9, 1979

ABSTRACT **We consider a single locus, and denote by A the wild-type allele and by A' the mutant allele that is produced irreversibly in each generation from A at the rate v. Let $1 + s$, $1 + h$, and 1 be, respectively, the relative fitnesses of mutant homozygote $A'A'$, mutant heterozygote $A'A$, and wild-type homozygote AA. Then, it is shown, on the basis of the diffusion equation method, that the average time until fixation of the mutant allele (A') in a randomly mating population of effective size N_e, given that the initial frequency is p, is**

$$\bar{T}(p) = 4N_e \int_p^1 e^{-B(y)} y^{-V} dy \int_0^y \frac{e^{B(x)} x^{V-1}}{1-x} dx,$$

in which $B(x) = (S/2)x^2 + Hx(1-x)$, $S = 4N_e s$, $H = 4N_e h$, and $V = 4N_e v$. Of particular interest are the cases in which the mutant allele is deleterious ($s = -s'$, $s' > 0$). Three cases are considered; the mutant is: (*i*) completely dominant $s = h = -s'$, (*ii*) completely recessive $s = -s'$, $h = 0$, and (*iii*) semidominant $s = -s'$, $h = -s'/2$, in which s' is the selection coefficient against the mutant homozygote. It is shown that the average time until fixation is shorter when the deleterious mutant allele is dominant than when it is recessive if $4N_e v$ is larger than 1. On the other hand, the situation is reversed if $4N_e v$ is smaller than 1. It is also shown that for a mutant allele for which $N_e s' > 10$, it takes such a long time until fixation that we can practically ignore the occurrence of random fixation of a deleterious allele under continued mutation pressure. To supplement the analytical treatment, extensive simulation experiments were performed by using a device called the pseudo-sampling variable, which can enormously accelerate the process of simulation by a computer. This method simulates the diffusion process itself rather than the binominal sampling process (in population genetics the diffusion model is usually regarded as an approximation of the discrete binomial sampling process).

It is a well-known observation in evolution that organs and characters that are no longer in use tend to degenerate with time. A good example is the loss of eyes and pigmentation in cave animals. A plausible explanation for this phenomenon is that amorphic or hypomorphic mutations, which were previously deleterious, become harmless (neutral) or only slightly deleterious after the character is no longer in use. Then the mutant alleles tend to accumulate by mutation pressure (see ref. 1 and p. 418 of ref. 2) and finally become fixed in the species with the help of random genetic drift. The loss of vitamin C-synthesizing ability in some vertebrate species whose diets are rich in ascorbic acid has similarly been explained by Jukes and King (3). They claim that, under such diets, mutant alleles that caused loss of ability to synthesize vitamin C became neutral (or only very slightly deleterious) and such alleles were fixed by random drift under mutation pressure.

The purpose of the present paper is to investigate this type of problem by determining the average length of time required for a mutant allele to become fixed (i.e., to reach 100% frequency) in the population when such an allele is produced irreversibly from the normal wild-type allele in each generation. In their study on persistence of common alleles in two related populations, Li and Nei (4) investigated the same problem for the case of no dominance. In this paper, we consider a more general situation, assuming an arbitrary degree of dominance. We also present a method to simulate the diffusion process involved.

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Analytical treatment by diffusion equation method

Throughout this paper we assume a randomly mating population consisting of N diploid individuals and having an effective size N_e (for the meaning of the effective population size, see refs. 5 and 6; roughly speaking, N_e is equal to the number of breeding individuals in one generation).

Consider a particular locus, and let A be the normal wild-type allele. We assume that A mutates irreversibly to its allele A' at the rate v per generation. In reality, the mutant allele A' is usually not a single entity (particularly at the molecular level), but a set of mutant alleles; however, we designate them collectively as A'. Let us denote the relative fitnesses of the three genotypes AA, AA', and $A'A'$ as 1, $1 + h$, and $1 + s$, so that s and h are the selection coefficients for the mutant homo- and heterozygotes. Because we mainly consider, in the present paper, the situation in which A' is deleterious, we also use the symbol s' to represent the selection coefficient *against* the mutant homozygote. Thus, if the mutant allele A' is completely dominant and deleterious, we have $s = h = -s'$. If A' is completely recessive and deleterious, we have $s = -s'$ and $h = 0$; finally, if A' is semidominant (i.e., the case of "no dominance"), $s = -s'$ and $h = -s'/2$.

We now consider the stochastic process of change of the mutant allele frequency and make use of the diffusion equation method (or "diffusion model", see ref. 7) to treat the process. We shall denote by p the frequency of A' in the population. Let $u(p, t)$ be the probability that the mutant allele becomes fixed in the population by the tth generation, given that its initial frequency (at time $t = 0$) is p. Then, $u(p, t)$ satisfies the Kolmogorov backward equation,

$$\frac{\partial u(p,t)}{\partial t} = \frac{1}{2} V_{\delta p} \frac{\partial^2 u(p,t)}{\partial p^2} + M_{\delta p} \frac{\partial u(p,t)}{\partial p}, \qquad [1]$$

in which $M_{\delta p}$ and $V_{\delta p}$ stand for the mean and variance of the change of allele frequency p per generation (see refs. 5–7).

If p is the frequency of A' in the population, then the change (δp) in one generation by selection is

$$\delta p = p(1-p)[sp + h(1-2p)]/\bar{w}, \qquad [2]$$

in which $\bar{w} = 1 + 2hp(1-p) + sp^2$. Also, the change by mutation is

Abbreviation: PSV, pseudo-sampling variable.

$$\delta p = v(1-p). \quad [3]$$

Combining these two changes, and assuming that the selection coefficients are small, we may put

$$M_{\delta p} = p(1-p)[sp + h(1-2p)] + v(1-p). \quad [4]$$

Also, from the assumption of the effective size N_e, we have

$$V_{\delta p} = p(1-p)/(2N_e). \quad [5]$$

Now, let $\overline{T}(p)$ be the average time until fixation of the mutant allele given that its initial frequency is p, so that

$$\overline{T}(p) = \int_0^\infty t \frac{\partial u(p,t)}{\partial t} dt. \quad [6]$$

Note that if a population is finite in size, the deleterious allele eventually becomes fixed in the population under irreversible mutation, although the time required for such fixation may be extremely long unless the deleterious effect is very small.

In order to derive an equation for $\overline{T}(p)$, we differentiate both sides of Eq. 1 with respect to t, followed by multiplying each term through by t, and then integrate with respect to t from 0 to ∞. Note that the left-hand side of the resulting equation becomes

$$\int_0^\infty t \frac{\partial u^2(p,t)}{\partial t^2} dt = \left[t \frac{\partial u(p,t)}{\partial t}\right]_{t=0}^{t=\infty} - \int_0^\infty \frac{\partial u(p,t)}{\partial t} dt$$
$$= -[u(p,t)]_{t=0}^{t=\infty} = -1.$$

In this derivation we assume that $t\partial u(p,t)/\partial t$ is 0 at the limit $t = \infty$. Note also that $u(p,\infty) = 1$ and $u(p,0) = 0$.

Thus, we obtain the required equation for $\overline{T}(p)$:

$$\frac{1}{2} V_{\delta p} \frac{d^2\overline{T}(p)}{dp^2} + M_{\delta p} \frac{d\overline{T}(p)}{dp} + 1 = 0. \quad [7]$$

The appropriate boundary conditions are

$$\overline{T}'(0) = \text{finite, and } \overline{T}(1) = 0, \quad [8]$$

in which the prime denotes differentiation. Letting

$$\overline{T}(p) = 4N_e y(p) \quad [9]$$

and substituting Eqs. 4 and 5 for $M_{\delta p}$ and $V_{\delta p}$ in Eq. 7, we obtain

$$p(1-p)\frac{d^2y(p)}{dp^2} + (1-p)[4N_e sp^2 + 4N_e hp(1-2p) + 4N_e v]\frac{dy(p)}{dp} + 1 = 0. \quad [10]$$

Note that $y(p)$ depends on the products $N_e s$, $N_e h$, and $N_e v$ but not on N_e, s, h, and v separately. The solution of this equation that satisfies the conditions $y'(0) =$ finite and $y(1) = 0$, is as follows.

$$y(p) = \int_p^1 e^{-B(\eta)}\eta^{-V} d\eta \int_0^\eta \frac{e^{B(\xi)}\xi^{V-1}}{1-\xi} d\xi, \quad [11]$$

in which

$$B(\xi) = (S/2)\xi^2 + H\xi(1-\xi), \quad [12]$$

$S = 4N_e s$, $H = 4N_e h$, and $V = 4N_e v$.

We are particularly interested in the average number of generations until fixation starting from a population consisting exclusively of the wild-type allele (see Fig. 1). This is given by

$$\overline{T}(0) = 4N_e y(0) = 4N_e \int_0^1 e^{-B(\eta)}\eta^{-V} d\eta \int_0^\eta \frac{e^{B(\xi)}\xi^{V-1}}{1-\xi} d\xi. \quad [13]$$

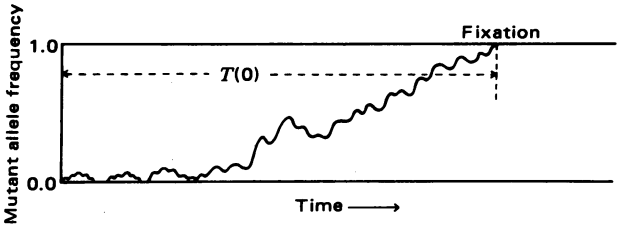

FIG. 1. Illustration of the meaning of the length of time until fixation, $T(0)$, of the mutant allele under irreversible mutation, starting from a population free of the mutant allele. Eq. 13 gives the average value of $T(0)$.

For a selectively neutral mutant allele, the formula for $y(0)$ can be much simplified. Assuming that $4N_e v \neq 1$, we have

$$y(0) = \frac{1}{V-1}\int_0^1 \frac{1-\xi^{V-1}}{1-\xi} d\xi = \frac{1}{V-1}[\gamma + \psi(V)], \quad [14]$$

in which $V = 4N_e v$, and $\psi(\cdot)$ stands for the digamma function (see ref. 8) and $\gamma = 0.577\ldots$ is Euler's constant. For $4N_e v = 1$, we have $y(0) = \pi^2/6 \approx 1.64$. When V is a positive integer, the relationship

$$y(0) = [1 + 1/2 + \ldots + 1/(V-1)]/(V-1) \quad [15]$$

is convenient to compute $y(0)$. In particular, if $V = 4N_e v = 2$, we get $y(0) = 1$. In other words, it takes $4N_e$ generations on the average until fixation of the mutant allele if one mutant gene is fed into the population in each generation (assuming $N = N_e$). When V is small, the following formula is useful to compute the average time until fixation:

$$y(0) = \frac{1}{1-V}\left(\frac{1}{V} - \frac{\pi^2}{6}V + \frac{\pi^3}{25.79}V^2 - \frac{\pi^4}{90}V^3 + \ldots\right). \quad [16]$$

Thus, if $4N_e v$ is very small, we have

$$\overline{T}(0) = 4N_e y(0) \approx 1/v. \quad [17]$$

In Fig. 2, the average time until fixation $\overline{T}(0)$ is illustrated for various values of $4N_e s'$ (deleterious case) ranging from 0 to 30, and also for $4N_e s$ (advantageous case) ranging from 0 to 10, assuming several values of $4N_e v$. These results are obtained by numerically integrating Eq. 13 by a computer. It is interesting to note that, if $4N_e v > 1$, the average time taken for the mutant allele to reach fixation is shorter when the mutant is deleterious in both the heterozygous and homozygous states (dominant) than when it is deleterious only in the homozygous state (recessive). The situation is reversed if $4N_e v < 1$.

When $4N_e v = 1$ exactly, it can be shown analytically that the average time until fixation is the same for the dominant and recessive mutations. In this case, the average fixation time for semidominant mutations becomes shorter than the dominant or recessive ones, contrary to what one might expect intuitively, for one would expect that if the degree of dominance is intermediate, the time until fixation would also be intermediate. Furthermore, numerical studies suggest that, in general, the fixation time is prolonged when the mutant allele is either overdominant or underdominant, but is shortened when it is partially dominant. From Fig. 2 we can also see that for a mutant allele having appreciable deleterious effect such that $4N_e s' > 30$, the time taken for fixation is so long that we can practically ignore the occurrence of fixation in evolution. This means that deleterious mutants that have an effect on fitness of 1% or more in homozygous condition, whether dominant, recessive,

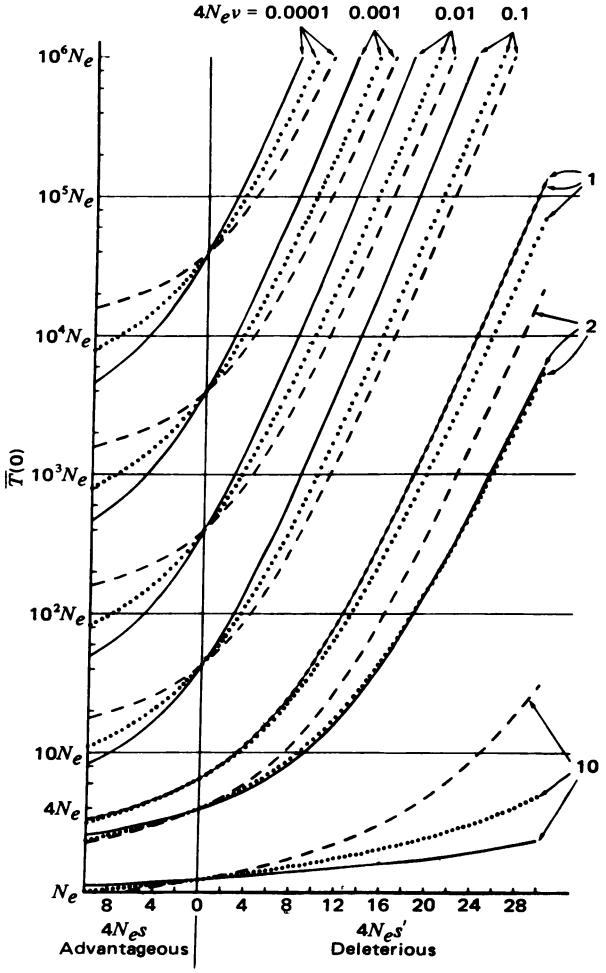

FIG. 2. Average number of generations until fixation, $\overline{T}(0)$, is illustrated as a function of the selection coefficient (s or s') multiplied by $4N_e$, assuming the values of $4N_e v$ shown for each family of curves. The solid curves represent the case in which the mutant allele is completely dominant, the broken curves the case in which it is completely recessive, and the dotted curves the case in which it is semidominant (the case of no dominance).

or intermediate, are too deleterious to become fixed in an ordinary population. Many, if not the great majority, of Mukai's (9) "viability polygenes" would be in this category (for the fitness of minor viability mutants, see refs. 10 and 11). Eq. 13 was also used to construct Table 1, in which semidominance is assumed.

Table 1. Time until fixation of semidominant deleterious mutation, taking N_e generations as the unit length of time

S' *	V† 0.01	0.1	1.0	10.0
10	1.2×10^4	1.0×10^3	4.0×10^1	1.9
20	8.6×10^5	6.8×10^4	1.1×10^3	2.7
30	8.4×10^7	6.4×10^6	6.8×10^4	5.1
40	9.4×10^9	6.9×10^8	5.4×10^6	1.8×10^1
50	1.1×10^{12}	8.0×10^{10}	5.0×10^8	1.4×10^2
60	1.4×10^{14}	9.7×10^{12}	5.1×10^{10}	2.1×10^3
80	2.3×10^{18}	1.6×10^{17}	6.2×10^{14}	1.5×10^6
100	4.0×10^{22}	2.7×10^{21}	8.6×10^{18}	2.4×10^9
200	1.0×10^{44}	6.5×10^{42}	1.1×10^{40}	4.8×10^{27}

Note: $-S$ in table 3 of ref. 4 corresponds to $S'/2$ in this table.
* $S' = 4N_e s' = -4N_e s$.
† $V = 4N_e v$.

Numerical treatment by the finite Markov chain method

In order to corroborate the treatment in the previous section and particularly to confirm the result that, if $4N_e v > 1$, the deleterious allele reaches fixation more quickly when it is dominant than when it is recessive, the process of fixation was treated as a finite Markov chain. Let us assume that the population consists of N breeding individuals (more precisely, let $N = N_e$), and let $F_t(i)$ be the probability that the population contains i mutant genes and $(2N - i)$ wild-type genes in the tth generation, in which $i = 0, 1, \ldots, 2N$ and $t = 0, 1, 2, \ldots$. Then the transformation of the gene frequency distribution from one generation to the next can be expressed by the following equation.

$$\begin{bmatrix} F_{t+1}(0) \\ F_{t+1}(1) \\ \vdots \\ F_{t+1}(2N) \end{bmatrix} = \begin{bmatrix} a(0,0) & a(0,1) & \ldots & a(0,2N) \\ a(1,0) & a(1,1) & \ldots & a(1,2N) \\ \vdots & \vdots & & \vdots \\ a(2N,0) & a(2N,1) & \ldots & a(2N,2N) \end{bmatrix} \begin{bmatrix} F_t(0) \\ F_t(1) \\ \vdots \\ F_t(2N) \end{bmatrix}, \quad [18]$$

in which the matrix element $a(j, i)$, $j = 0, 1, \ldots, 2N$ is

$$a(j,i) = \frac{(2N)!}{j!\,(2N-j)!} (P_i')^j (1 - P_i')^{2N-j}, \quad [19]$$

in which $P_i' = p + p(1-p)[sp + h(1-2p)]/\overline{w}$, $p = P_i + v(1 - P_i)$, and $P_i = i/(2N)$.

Then, the average number of generations until fixation is computed by

$$\overline{T}(0) = \sum_{t=0}^{\infty} (t+1)[F_{t+1}(2N) - F_t(2N)], \quad [20]$$

starting from a population consisting exclusively of the wild-type allele [$F_0(0) = 1$]. By using a computer, the values of $\overline{T}(0)$ were evaluated numerically for various values of $4Ns'$, assuming $N = 20$ and $4Nv = 2$, for both recessive and dominant mutations. In Fig. 3, these values are plotted together with the corresponding values derived by the diffusion equation method. The agreement between the results obtained by these two methods is satisfactory. The small discrepancies for the cases $4N_e s' > 8$ must have come from the larger selection coefficients that had to be assumed because of a small population size ($N = 20$) used in the matrix multiplication.

Simulation experiments using pseudo-sampling variable

The results obtained by the diffusion equation method were also checked by Monte Carlo experiments using a device called the "pseudo-sampling variable" (PSV), which can enormously speed up the simulation process. The gist of this method is that instead of sampling in each generation $2N$ gametes to produce the population in the next generation, as is usually done in the Monte Carlo experiments simulating a diploid population of size N, a single uniform random number is generated with a suitable mean and a variance to produce the gene frequency after sampling drift. Specifically, if p is the frequency of the mutant allele in the present generation (but after mutation and selection), then the frequency in the next generation (at fertilization) is given by

$$p' = p + \xi_{PSV}, \quad [21]$$

in which ξ_{PSV} is a uniform random variable with mean 0 and

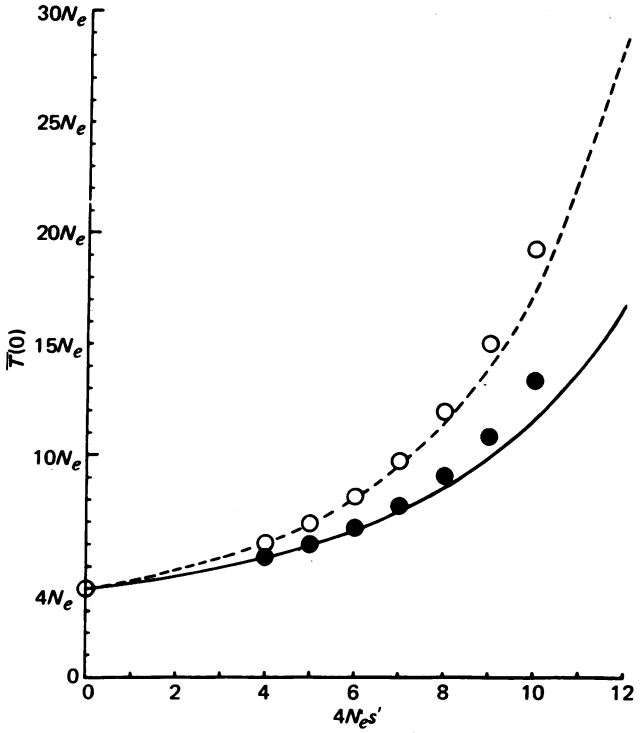

FIG. 3. $2N_e v = 1$. Results obtained by a discrete treatment (finite Markov chain method), assuming a population of 20 individuals, are shown by ● for the dominant deleterious mutation and by ○ for the recessive deleterious mutation. The corresponding results obtained by a continuous treatment (diffusion equation method) are also plotted by solid and broken curves. The ordinate represents the average number of generations until fixation and the abscissa the selective disadvantage multiplied by $4N_e$.

variance $p(1-p)/(2N)$. If p' happens to become negative by chance, which may sometimes happen when p is very near to 0, then p' is set to 0 to continue the experiment. On the other hand, if p' becomes larger than $1 - 1/(2N)$, then p' is set to unity, and the experiment is ended [no significant differences were found when the criterion $p' > 1$ rather than $p' > 1 - 1/(2N)$ was used]. In terms of the standard random number that follows uniform distribution in the range between 0 and 1, which we denote *rnd* in this paper, PSV in Eq. 21 may be expressed as

$$\xi_{PSV(a)} = \sqrt{3\sigma^2}\,(2rnd - 1), \qquad [22]$$

in which $\sigma^2 = p(1-p)/(2N)$. This pseudo-random number is illustrated in Fig. 4*a*. The rationale of substituting $\xi_{PSV(a)}$, rather than a more realistic-looking variable (such as a normal variate) for the binomial variate comes from the nature of the continuous stochastic process (see p. 374 of ref. 5). In the diffusion equation method, only the mean and variance of the change (δp) in gene frequency determine the process as long as the higher moments of the change are negligible. Because the third

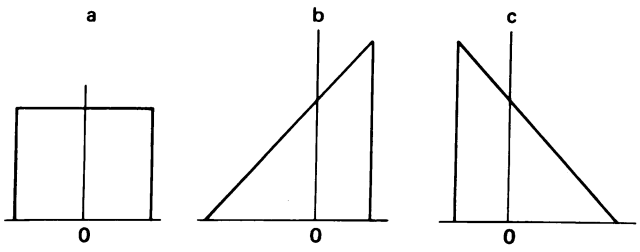

FIG. 4. Three types of pseudo-sampling variables (PSV) used in the simulation experiments.

and in general the $(2n+1)$th moment is zero, and the fourth and in general the $2n$th moment is of the order of $(2N)^{-n}$ for $\xi_{PSV(a)}$, this is satisfied if N is large (where $n = 1, 2, \ldots$). The merit of the PSV method is that it makes it possible to perform simulation experiments assuming a very large population size, or to try many replicate trials without prohibitive computing time, or both. Note that the PSV method simulates the diffusion process itself rather than the discrete binominal sampling process ("Fisher–Wright model") for which the diffusion model is usually regarded as an approximation.

In Fig. 5, the results of Monte Carlo simulation experiments using $\xi_{PSV(a)}$ are plotted as squares, assuming that the mutant allele is semidominant—that is, $s = -s'$ and $h = -s'/2$. The solid curve represents the corresponding values obtained by the diffusion equation method, assuming semidominance. In order to demonstrate that only the mean and the variance and not the detailed shape of the distribution of the change δp really matter, we also tried PSV with a negatively skewed triangular distribution as depicted in Fig. 4*b*, and with a positively skewed one in Fig. 4*c*. They are given respectively by

$$\xi_{PSV(b)} = \sqrt{18\sigma^2}\,(\sqrt{rnd} - 2/3) \qquad [23]$$

and

$$\xi_{PSV(c)} = -\xi_{PSV(b)}, \qquad [24]$$

in which $\sigma^2 = p(1-p)/(2N)$ and *rnd* is a random variable which follows a uniform distribution between 0 and 1. Results of simulation experiments using these two types of skewed

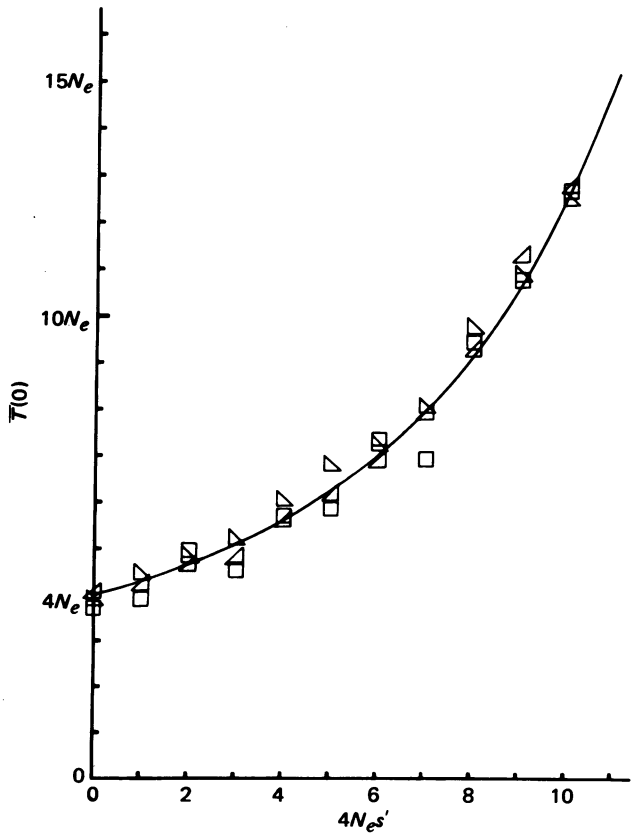

FIG. 5. $2N_e v = 1$. Results of simulation experiments using three types of PSVs, as depicted in Fig. 4, are plotted together with the corresponding result (solid curve) obtained by the diffusion equation method. For example, a □ is a result of an experiment using PSV(*a*) in Fig. 4. Each symbol is the average of 100 replicate trials with $N = 100$. The mutant allele is assumed to be semidominant. Ordinate: the average time until fixation $\overline{T}(0)$; abscissa: selective disadvantage multiplied by $4N_e$.

distributions are plotted as triangles in Fig. 5 corresponding to the shapes in Fig. 4. It is clear that the agreement between the experimental results and the analytical solutions is excellent, and that the detailed shape of the PSV distribution does not matter.

Discussion

We investigated the time taken for a slightly deleterious mutant allele to reach fixation by random drift under continued mutation pressure, starting from a population initially consisting exclusively of the wild-type allele. The results show that, for $4N_e v$ of about 1 or less, the time until fixation is extremely long unless $4N_e s'$ is less than about 20. If $4N_e s'$ is larger, particularly beyond 40, the time until fixation is so long that we can neglect the occurrence of fixation in evolution. For example, assuming $4N_e v = 1$, if $4N_e s' = 80$, it takes about $6.2 \times 10^{14} N_e$ generations (see Table 1) until fixation, which is an enormously long time, considering the fact that the earth is only some 4.6×10^9 years old. Thus, for fixation of a deleterious mutant allele to occur, its deleterious effect must usually be extremely small. However, in a small isolated population, accumulation of mildly detrimental mutant alleles may occur, leading to deterioration and eventual extinction of the species. A biologically more interesting situation is that, through change of environment, mutations at a certain locus become no longer harmful. Then, a mutant allele becomes fixed in the population, taking on the average $4N_e y(0)$ generations with $y(0)$ given by Eq. 14. If $4N_e v$ is small, as is likely in an isolated population living in a specialized environment, such as a fish population in an underground cave, the average time until fixation of a mutant allele is roughly $1/v$ generations, the reciprocal of the mutation rate. This means hundreds of thousands of generations for a given locus. This problem is also discussed by Li and Nei (4). In addition, as pointed out by Muller (1), gene mutations often have deleterious pleiotropic effects and this may prolong the fixation time. For example, the white-eyed flies are less viable as larvae (before they have eyes), and thus, degeneration of eyes in a cave may take longer time than expected merely from the mutation rate considerations. However, under the alternative hypothesis that the loss of eyes is adaptive and occurred by positive natural selection, it may take much less time.

The problem of the time until fixation of a slightly deleterious allele might have some bearing on "Muller's ratchet" mechanism, which Felsenstein (12) considers important in promoting recombination in evolution (see also refs. 13 and 14). For this to work, $4N_e s'$ values must be very small. But then the effect of random fixation of mutant alleles on the population fitness may be quite small.

Finally, I would like to remark on the PSV method. Although we treated a single variable case in this paper, the method can be extended to treat cases with more than one variable. For example, to treat the three-variable case (such as arises when we consider four chromosome types involving two loci, or four nucleotide bases at a single site), we can generate three correlated PSVs, $\xi_{PSV(1)}$, $\xi_{PSV(2)}$, and $\xi_{PSV(3)}$, as follows:

$$\begin{aligned}\xi_{PSV(1)} &= \sigma_1 U_1 \\ \xi_{PSV(2)} &= \sigma_2(c_{21}U_1 + c_{22}U_2) \\ \xi_{PSV(3)} &= \sigma_3(c_{31}U_1 + c_{32}U_2 + c_{33}U_3). \end{aligned} \quad [25]$$

In these equations, σ_i is the standard deviation of $\xi_{PSV(i)}$, $(i = 1, 2, 3)$, and the U_is are mutually independent, uniformly distributed, random numbers each with mean 0 and unit variance: $U_i = \sqrt{3}[2rnd(i) - 1]$. The coefficients c_{ij}s, $(j = 1, 2, 3)$, are given in terms of correlation coefficient ρ_{ij} between $\xi_{PSV(i)}$ and $\xi_{PSV(j)}$ as follows: $c_{21} = \rho_{12}$, $c_{22} = \sqrt{1 - c_{21}^2}$, $c_{31} = \rho_{13}$, $c_{32} = (\rho_{23} - \rho_{12}\rho_{13})/c_{22}$, $c_{33} = \sqrt{1 - c_{31}^2 - c_{32}^2}$.

I thank Dr. N. Takahata and, particularly, Dr. Thomas Nagylaki for many helpful comments in composing the manuscript. Thanks are also due to Dr. J. F. Crow, who read the first draft and made many useful suggestions to improve the presentation. This is contribution no. 1276 from the National Institute of Genetics, Mishima, Shizuoka-Ken 411, Japan.

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