PROBABILITY OF FIXATION OF A MUTANT GENE IN A FINITE POPULATION WHEN SELECTIVE ADVANTAGE DECREASES WITH TIME[1]

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PROBABILITY of gene fixation, that is to say, the probability by which a mutant allele becomes eventually established in a population is a subject of considerable interest both in population and evolutionary genetics.

In his pioneering work, HALDANE (1927) showed that in an infinite population an individual mutant gene having selective advantage s can reach fixation with the probability of about $2s$. Later, more general results were obtained by KIMURA (1957) for finite populations based on diffusion models (see also KIMURA 1964). His formulae were used by ROBERTSON (1960) to develop a theory of limits in artificial selection. A still more general but quite simple formula for the probability of fixation was also obtained by KIMURA (1962) as a function of the mean ($M_{\delta x}$) and the variance ($V_{\delta x}$) of the rate of change in gene frequency per generation. The formula is quite general, and as far as a single locus with a pair of alleles is concerned, it can cope with any degree of dominance and also random fluctuation in selection intensity. However, there are still restrictions in using the formula, the most serious of which is that the process of change in mutant gene frequency must be time homogeneous. In other words, the selection coefficients of mutant homo- and heterozygotes have to remain constant with time.

When we consider the fate of a new mutant (including chromosome mutant) in natural populations, there are numerous situations for which time nonhomogeneity has to be taken into account because of changing environment as well as alteration of genetic background with time. For example, consider the fate of a chromosome with a new inversion. If it happens to have a good combination of genes at the beginning, it will spread in the population reaching fixation or leading to inversion polymorphism. The fitness of the inverted chromosome segment in such a process can best be expressed by the exponential function of time, since deleterious mutants will accumulate in the inverted segment with time as shown by MUKAI (1964). This may also apply to a mutant gene that is itself neutral but happens to be included in a chromosome segment which does not contain deleterious genes. It is also possible that a mutant gene which is originally advantageous gradually loses its advantage due to deterioration of environment.

The fixation probability in such a time nonhomogeneous process was investi-

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gated by OHTA and KOJIMA (1968) and also by POLLAK (1966). They used the method of branching process that was applicable to an infinite population. However, in an infinite population, the probability of fixation of a mutant turns out to be zero if the selective advantage decreases with time and if its sum over infinite time converges, however great its initial advantage may be. Such a theoretical conclusion is unrealistic and cannot be applied to the treatment of such phenomena as the establishment of a new inversion in natural populations.

In the present paper, we will present a new theory based on diffusion models which enables us to calculate the probability of fixation of a mutant in a finite population when its selective advantage decreases at a constant rate with time. In other words, we will elaborate the case of exponentially decreasing selective advantage. Actually, the theory can be extended to cover more general cases in which selective advantage is a function of the exponential function of time.

The present treatment is essentially an approximation which is valid when the initial frequency of the mutant is low. Therefore, in order to check the accuracy of the analytical treatment, extensive computations were carried out using the method of multiplying transition probability matrices. We believe that this is the first time in the literature of population genetics theory that the probability of gene fixation in a finite population under nonhomogeneous time process was determined.

BASIC THEORY

Consider a particular moment of time (present generation) and let $u(p,s)$ be the probability of ultimate fixation of a mutant allele having the frequency p and the selective advantage s at that moment. Let $g(p,p+\xi;\tau)$ be the probability density that the frequency changes from p to $p+\xi$ during the succeeding short time interval of length τ. We will assume that the selective advantage decreases at a constant rate k per unit time (per generation) so that the selective advantage becomes $e^{-k\tau}$ of the present value after τ generations.

Then we have

$$u(p,s) = \int g(p,p+\xi;\tau)u(p+\xi,se^{-k\tau})d\xi \ , \qquad (1)$$

where the integral is over all possible values of ξ. This equation may be derived from the consideration that the probability of ultimate fixation starting from frequency p is equal to a sum total of the probabilities of cases in which the frequency changes from p to $p+\xi$ during the succeeding time interval of length τ and then reaches fixation afterward. Note that in the integrand we have $u(p+\xi,se^{-k\tau})$, since the selective advantage after time τ is $se^{-k\tau}$.

If we expand $u(p+\xi,se^{-k\tau}) \approx u(p+\xi,s-sk\tau)$ around (p,s) in terms of ξ and τ, equation (1) becomes

$$u(p,s) = \int g(p,p+\xi;\tau)\left(u + \xi\frac{\partial u}{\partial p} - sk\tau\frac{\partial u}{\partial s} + \frac{\xi^2}{2}\frac{\partial^2 u}{\partial p^2} + \dots\right)d\xi, \qquad (2)$$

where u on the right-hand side stands for $u(p,s)$.

Neglecting higher order terms containing $\tau\xi$, τ^2, ξ^3 etc., and noting that

$$\int g(p,p+\xi;\tau)d\xi = 1,$$

we get

$$sk\frac{\partial u}{\partial s}=\frac{1}{2}V(p,\tau)\frac{\partial^2 u}{\partial p^2}+M(p,\tau)\frac{\partial u}{\partial p}\ , \tag{3}$$

where

$$M(p,\tau)=\frac{1}{\tau}\int \xi g(p,p+\xi;\tau)\,\mathrm{d}\xi$$

and

$$V(p,\tau)=\frac{1}{\tau}\int \xi^2 g(p,p+\xi;\tau)\,\mathrm{d}\xi.$$

Then, taking the limit $\tau\to 0$, and, substituting the mean ($M_{\delta p}$) and the variance ($V_{\delta p}$) of the change of the mutant frequency per generation, respectively, for $\lim_{\tau\to 0} M(p,\tau)$ and $\lim_{\tau\to 0} V(p,\tau)$, we obtain our basic diffusion equation equation

$$sk\frac{\partial u(p,s)}{\partial s}=\frac{V_{\delta p}}{2}\frac{\partial^2 u(p,s)}{\partial p^2}+M_{\delta p}\frac{\partial u(p,s)}{\partial p}. \tag{4}$$

Note that $u(p,s)$ in this equation has a different meaning from a similar function $u(p,t)$ previously used for the time homogeneous case (KIMURA 1957, 1962, 1964) where it denoted the probability of a mutant allele reaching fixation by the t-th generation, given that the process starts from $t=0$ with initial frequency p. On the other hand, u(p,s) in the above equation denotes the probability of ultimate fixation of a mutant having the initial frequency p and the initial selective advantage s.

In the following treatments, we shall assume that the "variance" effective number of the population (KIMURA and CROW 1963) is N_e such that

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

Also, we shall restrict our consideration to the case of semidominance in fitness so that

$$M_{\delta p}=sp(1-p)$$

at the start. With these expressions for $V_{\delta p}$ and $M_{\delta p}$, equation (4) becomes

$$ks\frac{\partial u}{\partial s}=\frac{p(1-p)}{4N_e}\frac{\partial^2 u}{\partial p^2}+sp(1-p)\frac{\partial u}{\partial p}\ . \tag{5}$$

In order to solve this equation, and especially, to obtain an approximate solution which is valid when p is small, we try a solution of the form

$$u(p,s)=\frac{1-\mathrm{e}^{-4N_e\gamma p}}{1-\mathrm{e}^{-4N_e\gamma}}\ , \tag{6}$$

where $\gamma=\gamma(s)$ is a function of s but not of p. This expression for $u(p,s)$ satisfies the necessary boundary conditions

$$u(0,s)=0 \qquad \text{and} \qquad u(1,s)=1,$$

and also gives the exact solution for the time homogeneous case ($k=0$) by setting $\gamma(s)=s$, since for this case we have

$$u(p,s)=(1-\mathrm{e}^{-4N_e sp})/(1-\mathrm{e}^{-4N_e s})$$

(KIMURA 1957).

Let us now assume that the initial frequency p of the mutant allele is so low that $|4N_e\gamma p|$ is much smaller than unity even if $|4N_e\gamma|$ may be large.

For example, if the mutant allele is represented only once at the moment of its appearance in a population of actual size N, $p=1/(2N)$ and $|4N_e\gamma p| = (2N_e/N)|\gamma| \leqq (2N_e/N)|s|$ is much smaller than unity provided that $|s|$ is small. So, the assumption is realistic if the initial frequency of the mutant is very low and its selective advantage is not very large. With this assumption, we have approximately (neglecting small terms)

$$\frac{\partial u}{\partial s} = 4N_e p \frac{1-(1+4N_e\gamma)e^{-4N_e\gamma}}{(1-e^{-4N_e\gamma})^2}\left(\frac{d\gamma}{ds}\right),$$

$$\frac{\partial u}{\partial p} = \frac{4N_e\gamma}{1-e^{-4N_e\gamma}}$$

and

$$\frac{\partial^2 u}{\partial p^2} = \frac{-(4N_e\gamma)^2}{1-e^{-4N_e\gamma}}.$$

Substituting these in equation (5) and also replacing $p(1-p)$ in the equation by p since p is very small by assumption, we obtain the following ordinary differential equation for γ;

$$\frac{d\gamma}{ds} = \frac{\gamma(s-\gamma)(1-e^{-4N_e\gamma})}{sk\{1-(1+4N_e\gamma)e^{-4N_e\gamma}\}} \tag{7}$$

Note that this equation does not contain p so that γ can be determined as a function of s only, in agreement with the assumption made in (6).

Let $S=4N_es$, $K=4N_ek$ and $Y=4N_e\gamma$, then the above equation is expressed as

$$\frac{dY}{dS} = \frac{Y(S-Y)(1-e^{-Y})}{KS\{1-(1+Y)e^{-Y}\}} \tag{8}$$

This is a nonlinear first order differential equation and can be solved numerically without much difficulty. Namely, for each given value of K, values of Y may be tabulated as a function of S. Then the probability of eventual fixation for a rare mutant allele may be given approximately by

$$u(p) = \frac{1-e^{-Yp}}{1-e^{-Y}} \approx \left(\frac{Y}{1-e^{-Y}}\right)p. \tag{9}$$

Numerical integration of (8) was performed by using the method of step-by-step integration starting from the neighborhood of $S=Y=0$. Note that

$$\lim_{S\to 0}(Y/S) = \lim_{S\to 0}(dY/dS) = 1/(1+K/2). \tag{10}$$

The results of integration are presented in Table 1 and also in Figure 1. In the table, values of Y are tabulated as a function of K and S for $K=0.1\sim10$ and $S=1\sim20$. It may be seen from the table that as K gets large, the probability of fixation drops considerably. For example, if $S=10$ and $p=0.1$, the probability of fixation is 0.63 for $K=0$, while it reduces to 0.31 for $K=5$ and to 0.21 for $K=10$. Figure 1 illustrates the relationship between Y and S mainly for larger values of K and S. For still larger values of K and S, we may use the following formulae;

(i) If S is much larger than K, the approximate solution of (8) is

$$Y = S - K. \tag{11}$$

TABLE 1

Values of Y *for various combinations of values of* S *and* K, *where* $Y=4N_e y$, $S=4N_e s$ *and* $K=4N_e k$

S \ K	0.1	1	2	3	4	5	6	7	8	9	10
1	0.885	0.699	0.507	0.410	0.343	0.292	0.255	0.226	0.203	0.184	0.169
2	1.894	1.417	1.054	0.838	0.697	0.596	0.519	0.460	0.412	0.374	0.342
3	2.897	2.181	1.648	1.307	1.068	0.916	0.795	0.703	0.629	0.570	0.521
4	3.897	3.037	2.286	1.798	1.480	1.251	1.084	0.955	0.854	0.772	0.704
5	4.898	3.962	2.976	2.338	1.898	1.606	1.386	1.219	1.087	0.981	0.894
6	5.898	4.865	3.725	2.900	2.367	1.983	1.705	1.595	1.330	1.198	1.090
7	6.899	5.839	4.536	3.548	2.851	2.384	2.042	1.784	1.583	1.423	1.292
8	7.899	6.835	5.408	4.214	3.394	2.813	2.399	2.089	1.849	1.659	1.502
9	8.899	7.848	6.334	4.939	3.952	3.275	2.779	2.410	2.127	1.903	1.821
10	9.899	8.861	7.307	5.754	4.598	3.771	3.185	2.751	2.419	2.159	1.948
11	10.899	9.872	8.314	6.625	5.270	4.308	3.619	3.113	2.728	2.427	2.185
12	11.899	10.881	9.345	7.548	5.982	4.887	4.085	3.498	3.054	2.708	2.433
13	12.899	11.887	10.390	8.516	6.787	5.512	4.585	3.908	3.400	3.005	2.692
14	13.900	12.890	11.441	9.520	7.643	6.186	5.124	4.347	3.766	3.318	2.964
15	14.900	13.892	12.493	10.552	8.548	6.912	5.704	4.817	4.155	3.648	3.249
16	15.900	14.891	13.543	11.604	9.500	7.688	6.327	5.321	4.570	3.997	3.550
17	16.900	15.890	14.589	12.667	10.486	8.514	6.993	5.860	5.013	4.369	3.867
18	17.900	16.887	15.631	13.737	11.512	9.389	7.708	6.460	5.486	4.763	4.201
19	18.900	17.885	16.669	14.810	12.560	10.312	8.468	7.054	5.989	5.181	4.656
20	19.900	18.883	17.703	15.881	13.630	11.275	9.275	7.713	6.527	5.626	4.930

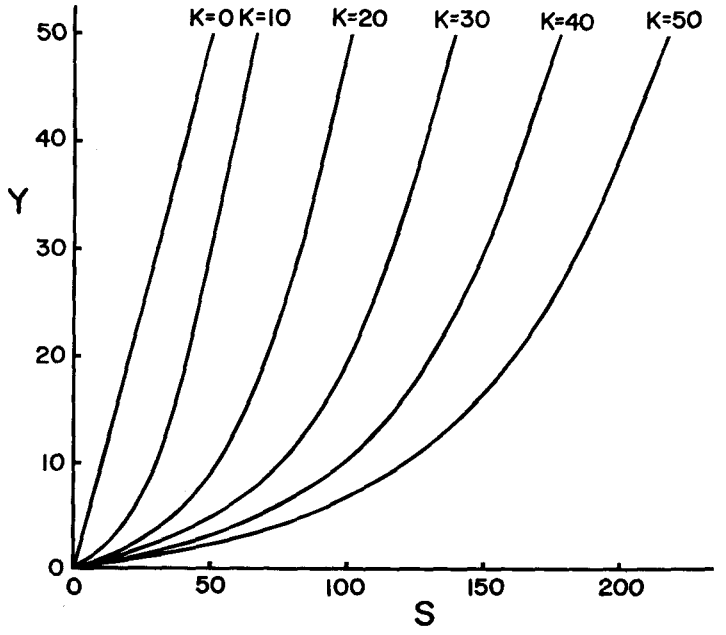

FIGURE 1.—Graphs showing the relationship between Y and S for $K = 0, 10, 20, 30, 40$ and 50.

Validity of this approximation may be evident in the lower left corner of Table 1, particularly for $S \geqq 10$ and $K \leqq 1$.

(ii) On the other hand, if S is of the same order of magnitude as K or smaller, we have

$$\frac{Y}{1-e^{-Y}} = e^{S/(K+2)} , \tag{12}$$

with good approximation. Actually, this formula is quite satisfactory for S up to about $2K$.

NUMERICAL CHECK OF THE BASIC THEORY

In order to check the validity of the foregoing treatments, the exact probability of fixation was computed based on the discrete model of generation time by multiplying the transition probability matrices. The method is essentially the same as the one used by EWENS (1963) except that in the present case the transition matrix changes each generation since the selective advantage decreases with time.

All the calculations were performed by using computer IBM 360 with "double precision."

In these calculations, a haploid population with 50 breeding individuals was assumed. The results are given in Table 2, where the probabilities of fixation computed by multiplying the probability matrices (P.M.) are listed together with those obtained by diffusion approximation formula (6) (D.A.) by setting $2N=50$.

The agreement between these two sets of values is sufficiently close to demonstrate the essential validity of the present theory based on diffusion models.

DISCUSSION

Although the present theory was developed originally to treat the case of exponentially decreasing selective advantage, it can be extended to cover a more general case in which the selective advantage is a function of an exponentially decreasing term.

In such a general case, the equation corresponding to (4) or (5) becomes

$$sk\frac{\partial u}{\partial s} = \frac{p(1-p)}{4N_e}\frac{\partial^2 u}{\partial p^2} + f(s)p(1-p)\frac{\partial u}{\partial p} , \tag{13}$$

where $f(\cdot)$ denotes a function such that $f(se^{-kt})$ is the selective advantage of the mutant at the t-th generation.

Then, assuming the same form of solution as (6), the differential equation corresponding to (7) becomes

$$\frac{d\gamma}{ds} = \frac{\gamma\{f(s)-\gamma\}(1-e^{-4N_e\gamma})}{ks\{1-(1+4N_e\gamma)e^{-4N_e\gamma}\}} , \tag{14}$$

from which γ may be solved as a function of s. With this γ, the probability of fixation may be obtained using formula (9), provided that the initial frequency p of the mutant is very low. In particular, if the mutant is represented only once at the moment of its appearance in a population consisting of N individuals, we may put $p=1/(2N)$. If, in addition, $4N_e\gamma$ is sufficiently large so that $e^{-4N_e\gamma}$ is negligibly small, equation (14) may be replaced by

TABLE 2

The probability of fixation calculated by multiplying the transition probability matrices (P.M.) and the probability obtained by diffusion approximation (D.A.)

s	k	Method	p=0.02	p=0.04	p=0.06	p=0.08	p=0.1
0.16	0.0	P.M.	0.255	0.443	0.583	0.687	0.765
		D.A.	0.274	0.473	0.617	0.722	0.798
0.16	0.001	P.M.	0.253	0.441	0.580	0.684	0.762
		D.A.	0.272	0.470	0.615	0.719	0.796
0.16	0.01	P.M.	0.238	0.418	0.554	0.657	0.736
		D.A.	0.259	0.449	0.592	0.696	0.774
0.16	0.1	P.M.	0.067	0.127	0.183	0.234	0.282
		D.A.	0.068	0.130	0.191	0.248	0.299
0.08	0.0	P.M.	0.139	0.259	0.362	0.450	0.525
		D.A.	0.148	0.274	0.382	0.473	0.551
0.08	0.001	P.M.	0.138	0.256	0.357	0.445	0.520
		D.A.	0.144	0.267	0.368	0.462	0.546
0.08	0.01	P.M.	0.116	0.218	0.307	0.385	0.454
		D.A.	0.127	0.238	0.336	0.422	0.494
0.08	0.1	P.M.	0.037	0.073	0.108	0.141	0.174
		D.A.	0.038	0.075	0.111	0.145	0.179
0.04	0.0	P.M.	0.074	0.143	0.207	0.266	0.321
		D.A.	0.078	0.151	0.217	0.279	0.336
0.04	0.001	P.M.	0.073	0.140	0.202	0.260	0.314
		D.A.	0.077	0.147	0.212	0.270	0.330
0.04	0.01	P.M.	0.058	0.112	0.163	0.211	0.256
		D.A.	0.060	0.116	0.169	0.220	0.267
0.04	0.1	P.M.	0.027	0.053	0.080	0.105	0.131
		D.A.	0.028	0.054	0.082	0.108	0.134

Calculations were performed assuming a population of 50 haploid individuals and taking 3 levels of s (0.16, 0.08 and 0.04), 4 levels of k and 5 levels of p.

$$\frac{d\gamma}{ds} = \frac{1}{ks}\gamma\{f(s)-\gamma\} \ , \tag{15}$$

and the probability of eventual fixation $u \equiv u(1/2N)$ may be given approximately by

$$u = 2(N_e/N)\gamma. \tag{16}$$

OHTA and KOJIMA (1968) investigated the ultimate survival probability of a new inversion assuming that its selective advantage decreases with time. They used the method of branching processes that is applicable to an infinitely large population, and they showed that this probability is zero unless the inversion has a unique advantage, permanently maintaining some selective superiority.

They also worked out the ultimate survival probability for the case in which the selective advantage of the inversion at the t-th generation may be expressed in the form

$$f(se^{-kt}) = c_0 + \frac{c_1 se^{-kt}}{1+se^{-kt}}, \tag{17}$$

where c_0 and c_1 are constants. Actually, they treated a more restricted case in

which c_0, c_1 and k are given by $c_0=c/2$, $c_1=nc/2$, and $k=c/2$, where c is a positive constant and n is the number of loci influencing fitness. The ultimate survival probability they obtained was, in our notation,

$$u = (n+1)cr_0/\{1-(1-r_0)^{n+1}\}, \tag{18}$$

where $r_0=s/(1+s)$.

We can now show that this satisfies our equation (15) in which $f(s)$ is given by (17): Assuming that the actual and the effective sizes of the population are equal ($N_e=N$), we have $u=2y$ from (16). But, from (18), $du/ds=(u/cs)\{c+ncs/(1+s)-u\}$, so that we have

$$\frac{dy}{ds} = \frac{y}{(c/2)s}\left\{\frac{c}{2} + \frac{(nc/2)s}{1+s} - y\right\}. \tag{19}$$

On the other hand, from (17), noting that in OHTA and KOJIMA's case $c_0=c/2$ and $c_1=nc/2$, we have $f(s)=(c/2)+(nc/2)s/(1+s)$. In addition, $k=c/2$ in their case. Therefore, (19) agrees with (15), as was to be shown.

It is reassuring that the previous result obtained by OHTA and KOJIMA (1968) by an entirely different method has now turned out to be a special case of the present treatment based on the diffusion models.

Finally, we will consider briefly the fate of a new inversion which happens to contain an unusually small number of deleterious genes. Let us assume that at each locus within the inverted segment, the deleterious allele (a) produced by mutation lowers fitness by hs_1 in the heterozygote and s_1 in the homozygote as compared with its normal allele (A). If the mutation rate from A to a is μ and if n such loci are contained in the segment, then, assuming that the mutant alleles have enough dominance so that the selection against them is mainly through the heterozygous state, the selective advantage of the inverted segment at the t-th generation having initially no deleterious genes is approximately

$$f(se^{-kt}) = n\mu e^{-hs_1 t}$$

(NEI, KOJIMA and SCHAFFER 1967). Thus the theory developed in the present paper can be applied to the evaluation of the probability of fixation by putting $s=n\mu$ and $k=hs_1$.

If the inversion covers 1,000 loci, then referring to CROW (1968), MUKAI (1964) and others, we may take $n\mu=0.01\sim0.05$ and $hs_1=0.02\sim0.05$. In this case, s and k are roughly equal. So we will consider the case $s=k=1/50$, assuming $N_e=N$. In a very small population with effective size $N_e=50$, we obtain $Y=4N_ey=1.48$ corresponding to $S=4N_es=4$ and $K=4N_ek=4$ in Table 1. Then from equation (9), taking $p=1/(2N)=0.01$, the probability of eventual fixation is $u=0.019$. In a population ten times as large ($N_e=500$), $S=K=40$ and from Figure 1 we get roughly $Y=2.5$. Taking $p=1/(2N)=0.001$, this gives $u=2.6\times10^{-3}$. Note that the corresponding value of Y derived from formula (12) is approximately $Y=2.4$, in good agreement with the value obtained using Figure 1. In a still larger population of $N_e=5{,}000$, we have $S=K=400$. These are outside the range covered by Figure 1, but we can obtain the value of Y from formula (12), namely, $Y=2.72$. The probability of fixation of a single inversion turns out to be $u=2.72\times10^{-4}$. Note that at the limit of $S=K\to\infty$, the ultimate fixation of a single inversion in a very large population of size N ($=N_e$) is $e/(2N)$ or $1.36/N$, as may be seen by

combining formulae (12) and (9). Since the corresponding probability is $1/(2N)$ for a completely neutral inversion, we may conclude that in a large population the fixation probability becomes only about 3 times as large by having selective advantage s which decreases at a rate s per generation (i.e., $k=s$). If the rate of decrease is half as large (i.e., $k=s/2$), the fixation probability becomes about 7.5 times as large as that for the case of complete neutrality.

The above treatment of the fixation probability for a new inversion is but one application of the present theory. More generally, the theory may be used to obtain the fixation probability of a mutant in a finite population when the environmental condition or the genetic constitution changes with time, as long as the resulting change in selective advantage can be expressed as a continuous function of an exponentially decreasing term.

SUMMARY

A theory was developed which enables us, for the first time, to obtain the probability of fixation of a mutant in a finite population when its selective advantage decreases at a constant rate with time. The theory is based on diffusion models and it can be extended to cover a more general case in which the selective advantage can be expressed as a function of the exponential function of time.

Let $u(p)$ be the probability of ultimate fixation of a mutant allele with initial frequency p and having selective advantage se^{-kt} at time t. Then, assuming that p is small, the fixation probability in a population of effective size N_e is given approximately by

$$u(p) = \{Y/(1-e^{-Y})\}p,$$

where Y is the solution of the differential equation

$$\frac{dY}{dS} = \frac{Y(S-Y)(1-e^{-Y})}{KS[1-(1+Y)e^{-Y}]},$$

in which $S=4N_es$ and $K=4N_ek$. The numerical solution (Y) of this differential equation was tabulated in Table 1 and also given graphically in Figure 1. For larger values of S and K not covered by the graphs, the following approximation formulae were found useful to estimate Y: (i) if $K<<S$, we have $Y\approx S-K$, while (ii) if $S\leqq 2K$, we have $Y/(1-e^{-Y})\approx e^{S/(K+2)}$.

In order to check the validity of the theory, an extensive computation was carried out by using the method of multiplying the transition probability matrices, and the result turned out to be satisfactory.

Finally, as an application of the present theory, the probability of establishing a new inversion initially containing an exceptionally small number of deleterious genes was worked out.

LITERATURE CITED

CROW, J. F., 1968 Some analysis of hidden variability in Drosophila populations. pp. 71–86. In: *Population Biology and Evolution.* Edited by R. C. LEWONTIN. Syracuse Univ. Press, New York.

EWENS, W. J., 1963 Numerical results and diffusion approximations in a genetic process. Biometrika **50**: 241–249.

HALDANE, J. B. S., 1927 A mathematical theory of natural and artificial selection. Part IV. Proc. Cambridge Phil. Soc. **23**: 607–615.

KIMURA, M., 1957 Some problems of stochastic processes in genetics. Ann. Math. Statist. **28**: 882–901. ——, 1962 On the probability of fixation of mutant genes in a population. Genetics **47**: 713–719. ——, 1964 Diffusion models in population genetics. J. Appl. Probability **1**: 177–232.

KIMURA, M. and J. F. CROW, 1963 The measurement of effective population number. Evolution **17**: 279–288.

MUKAI, T., 1964 The genetic structure of natural populations of *Drosophila melanogaster*. I. Spontaneous mutation rate of polygenes controlling viability. Genetics **50**: 1–19.

NEI, M., K. KOJIMA and H. E. SCHAFFER, 1967 Frequency changes of new inversions in populations under mutation-selection equilibria. Genetics **57**: 741–750.

OHTA, T. and K. KOJIMA, 1968 Survival probabilities of new inversions in large populations. Biometrics **24**: 501–516.

POLLACK, E., 1966 Some effects of fluctuating offspring distributions on the survival of a gene. Biometrika **53**: 391–396.

ROBERTSON, A., 1960 A theory of limits in artificial selection. Proc. Royal Soc. London B **153**: 234–249.