Genet. Res. Camb. (1991), **58**, *pp.* 243–251 *With 2 text-figures Printed in Great Britain*

Fixation probability in spatially changing environments

HIDENORI TACHIDA[1]* AND MASARU IIZUKA[2]

[1] *National Institute of Genetics, Mishima, Shizuoka-ken 411, Japan*

[2] *General Education Course, Chikushi Jogakuen Junior College, Ishizaka 2-12-1, Dazaifu-shi, Fukuoka-ken 818-01, Japan*

(*Received 22 April 1991 and in revised form 18 July 1991*)

Summary

The fixation probability of a mutant in a subdivided population with spatially varying environments is investigated using a finite island model. This probability is different from that in a panmictic population if selection is intermediate to strong and migration is weak. An approximation is used to compute the fixation probability when migration among subpopulations is very weak. By numerically solving the two-dimensional partial differential equation for the fixation probability in the two subpopulation case, the approximation was shown to give fairly accurate values. With this approximation, we show in the case of two subpopulations that the fixation probability in subdivided populations is greater than that in panmictic populations mostly. The increase is most pronounced when the mutant is selected for in one subpopulation and is selected against in the other subpopulation. Also it is shown that when there are two types of environments, further subdivision of subpopulations does not cause much change of the fixation probability in the no dominance case unless the product of the selection coefficient and the local population size is less than one. With dominance, the effect of subdivision becomes more complex.

1. Introduction

The fixation probability of a mutant gene in a population has been of great interest for evolutionary study. If we regard evolution as substitutions of genes, this process always starts from a single mutant. Rates of evolution measured by the substitution rates of genes are computed using the fixation probability of a mutant gene. Let v, u and N be the mutation rate per gamete per generation, the probability of a single mutant ultimately reaching fixation in the population and the population size, respectively. Then, the rate, k, per generation of mutant substitutions in the population is approximately expressed as (see Kimura, 1983)

$$k = 2Nvu.$$

A method to compute the fixation probability in a random mating population was developed by Kimura (1962) using Kolmogorov's backward equation. For the genic selection model, it is

$$u = \frac{1-\exp(-2N_e s/N)}{1-\exp(-4N_e s)} \qquad (1)$$

where N_e and s are the effective population size and the selection coefficient of the mutant gene, respectively. Maruyama (1970*a*) extended this result to the case of a geographically structured population. He showed that under genic selection the fixation probability does not depend on the population structure and is computed by (1) using the total population size for N in the formula. Although this result is very general with regard to the geographical structure, this property holds only for uniform selection. Hence, the result can not be applied to cases where selection coefficients differ from one subpopulation to another.

However, the situation in nature may not be so simple and selection coefficients might differ from one place to another. For example, the selection coefficients of naturally occurring alleles of the *gnd* locus in chemostats in which limiting resource was glucose are different from those in chemostats in which limiting resource was gluconate in *E. coli* (Dykhuizen & Hartl, 1980). Similar observations are made for other loci in chemostats with different resources (Hartl & Dykhuizen, 1984). Other observations which also suggest different selection coefficients in varying environments were made by Drosophila workers (Dobzhansky & Levene, 1955; Tachida & Mukai, 1985; Takano, Kusakabe & Mukai, 1988). They reared flies in various cultures and measured viability

* Corresponding author.

of the flies in respective environments. They found that viability differs from one environment to another and there is genotype-environment interaction for viability. Although various environments in those experiments are artificially created and thus the results do not necessarily indicate that fitness varies from one place to another in nature, they show the possibility of it. Thus, it is worthwhile to examine the fixation probability in spatially changing environments.

One interesting question in such a situation is whether the fixation probability increases or decreases in a spatially varying environment compared to that in a uniform environment in which the selection coefficients are the average of those in the varying environment. Pollak (1966) used an approximation to compute the fixation probability in varying environments for a haploid model. The fixation probability is expressed as [equation (4·6) of Pollak, 1966]

$$\frac{1-\pi_1^{z_1}\dots\pi_K^{z_K}}{1-\pi_1^{N_1}\dots\pi_K^{N_K}} \tag{2}$$

where z_i and N_i are the initial number of mutants and the size of the ith subpopulation. π_i is approximated by e^{-2s_i} where s_i is the selection coefficient of the mutant in the ith subpopulation. This shows that the fixation probability does not depend on the migration rate. However, he did not justify the approximation used in the derivation of (2).

Here, we investigate the fixation probability of a mutant gene in an island model with varying environments. For cases with small migration rate, we use the approximation developed by Lande (1979, 1985) and Slatkin (1981). First we checked the validity of the approximation with numerical methods in the two subpopulation case. Then using the approximation, we find that the fixation probability increases significantly in some cases if the environmental variability is introduced and if the migration rate is very small, which contradicts the conclusion drawn from (2). Also we consider some simple cases with more than two subpopulations using this approximation.

2. Model

We assume a diploid finite island model. There are n subpopulations with an equal size N. At first, the entire population is fixed with an allele A. A mutant allele a appears in one of the subpopulations. We are interested in the probability of the ultimate fixation of this gene in the entire population. We assume the Wright–Fisher model with multiple subpopulations. First selection operates within the gamete pool of each subpopulation. Relative fitness of genotypes AA, Aa and aa are 1, $1+s_i$ and $1+2s_i$, respectively, in the ith subpopulation. Next migration occurs. A portion m of the gamete pool of each subpopulation is exchanged with that of the entire population. Finally, $2N$ genes are sampled from the gamete pool of each subpopulation to form the next generation.

Let x_i be the frequency of the allele a in the ith subpopulation and X be the frequency of the allele a in the entire population. We assume that s and $1/N$ are small compared to one so that we can use the diffusion approximation. Nagylaki (1980) showed that the process X converges weakly to a diffusion process of the gene frequency in a panmictic population with size N_e (in our case nN) and the selection coefficient being the average of those in the subdivided population if N becomes large keeping the migration rates constant. Thus, for $m \gg 1/N$, the fixation probability is very close to that in a corresponding panmictic population in which the selection coefficient of the a allele is the average of selection coefficients over the varying environments.

Next we consider a case where $s_i, 1/N$ and m are small compared to one. Then, neglecting higher order terms of $s_i, 1/N$ and m, the first and the second moments of the change of gene frequency, Δx_i, in one generation are

$$\left.\begin{aligned} &E[\Delta x_i] = s_i x_i(1-x_i)+m(X-x_i) \\ &E[(\Delta x_i)^2] = \frac{x_i(1-x_i)}{2N} \\ &E[\Delta x_i \Delta x_j] = 0 \quad (i \neq j). \end{aligned}\right\} \tag{3}$$

Measuring time in unit of $2N$ generations, the dynamics of the gene frequency is approximately described by a system of stochastic differential equations,

$$\begin{aligned} dx_i = {} & [x_i(1-x_i)]^{\frac{1}{2}} dB_i(t) \\ & + [2Ns_i x_i(1-x_i)+2Nm(X-x_i)]\,dt, \end{aligned} \tag{4}$$

where $B_i(t)$ are mutually independent Brownian motions. Any exact analysis of this multi-dimensional diffusion process seems very difficult.

However, when the product Ns_i is small compared to one, the fixation probability can be obtained approximately. As shown in Appendix, the fixation probability is

$$u = E[X]_{t=\infty} = \left(\frac{1}{n}\sum_{i=1}^{n} s_i\right) + \frac{1}{2nN}. \tag{5}$$

Thus, the fixation probability in varying environments is the same as that of a panmictic population whose selection coefficients are the averages over the varying environments, if Ns_i is small compared to one.

In summary, the fixation probability in varying environments is the same as that in the corresponding panmictic population with an uniform environment if either migration is strong or selection is very weak. Thus, we shall look at the cases where selection is modest to strong and migration is weak hereafter.

3. Weak migration with modest to strong selection

If the migration rate is very small, we can use the Markov chain approximation developed by Lande (1979) and Slatkin (1981). They used this approxi-

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

mation in their study of fixation probabilities in cases involving dominance. In this Markov chain, a state is defined by an n-dimensional vector whose elements take one or zero depending on whether the ith subpopulation is fixed with the a or A allele, respectively. The approximation assumes that if an allele is to be fixed in a subpopulation, it becomes so immediately upon introduction into that subpopulation. First we consider a simple case of two subpopulations.

(i) *Two Subpopulations*

Since this case is simple, we consider a more general situation where sizes of the first and the second subpopulations are N_1 and N_2, respectively, and the migration rate from the first to the second and from the second to the first are m_2 and m_1, respectively. We assume that migration is so weak that it does not affect the fixation probability of an allele in each subpopulation. Let u_{ai} and u_{Ai} be the fixation probabilities of the a and the A alleles, respectively, starting from a single gene in the ith subpopulation when there is no migration. These probabilities can be computed from eqn (1). In the low migration rate limit, there are two ways for the a allele to be fixed in the total population. If the mutant first appears in the first subpopulation, the probability of its fixation in the first subpopulation is u_{a1}. After the fixation in the first subpopulation, there are two possibilities for the fate of the a allele, i.e., fixation in the second subpopulation or loss in the first subpopulation. Since the first subpopulation provides the a allele to the second subpopulation at a rate of $2N_2m_2$ per generation, the waiting time, T_2, for the first appearance of the a gene to be fixed in the second subpopulation is distributed exponentially with a mean $1/(2N_2m_2u_{a2})$. Similarly, the waiting time, T_1, for the first appearance of the A gene to be fixed in the first subpopulation is distributed exponentially with a mean $1/(2N_1m_1u_{A1})$. If T_1 is larger than T_2, the fixation of the a allele in the second subpopulation results. Otherwise the loss of the a allele from the first subpopulation results. Thus, the a allele is fixed in the second subpopulation with a probability

$$\frac{2N_2m_2u_{a2}u_{a1}}{2N_1m_1u_{A1}+2N_2m_2u_{a2}}$$

if a mutant first appears in the first subpopulation. If a mutant first appears in the second subpopulation, the probability of the a allele being fixed in the whole population is similarly computed to be

$$\frac{2N_1m_1u_{a1}u_{a2}}{2N_2m_2u_{A2}+2N_1m_1u_{a1}}.$$

Since the probability of the first mutant appearing in the first or the second subpopulation is $N_1/(N_1+N_2)$ or $N_2/(N_1+N_2)$, respectively, the probability of fixation of the a allele in the entire population starting from a single mutant is

$$u=\left(\frac{N_1N_2u_{a1}u_{a2}}{N_1+N_2}\right)\left(\frac{m_2}{N_1m_1u_{A1}+N_2m_2u_{a2}}+\frac{m_1}{N_2m_2u_{A2}+N_1m_1u_{a1}}\right). \tag{6}$$

This is considered to be the low migration limit of the fixation probability.

Also we can compute the average time for the fixation of the a allele using this approximation (Slatkin, 1981). The average time for the fixation of the a allele given it is fixed in the whole population is computed to be

$$\frac{N_1}{(2N_2m_2u_{a2}+2N_1m_1u_{A1})(N_1+N_2)}+\frac{N_2}{(2N_1m_1u_{a1}+2N_2m_2u_{A2})(N_1+N_2)}. \tag{7}$$

For the derivation, consult Slatkin (1981).

In order to see the applicability of the low migration limit approximation, we numerically computed the fixation probability using Kolmogorov's backward equation. The fixation probability $u(p_1,p_2)$ of an allele whose initial frequencies in the first and the second subpopulations are p_1 and p_2, respectively, satisfies (see Crow & Kimura, 1970)

$$\frac{p_1(1-p_1)}{4N_1}\frac{\partial^2u}{\partial p_1^2}+\frac{p_2(1-p_2)}{4N_2}\frac{\partial^2u}{\partial p_2^2}+[s_1p_1(1-p_1)+m_1(p_2-p_1)]\frac{\partial u}{\partial p_1}+[s_2p_2(1-p_2)+m_2(p_1-p_2)]\frac{\partial u}{\partial p_2}=0 \tag{8}$$

with the boundary conditions

$$u(0,0)=0,\quad u(1,1)=1.$$

The partial differential equation was numerically solved using the Gauss–Seidel method (see for example, Ortega & Poole, 1981). Though computations are carried out for small population sizes, the results can be extended to cases of larger population sizes with the same N_is_i and N_im_i. The reason is that the difference is only in the initial frequencies and an approximate linearity of the fixation probability holds for a small initial frequency since a small number of initial mutants do not influence their fates each other.

Fixation probabilities in a subdivided population with two environments are computed using the low migration limit (6) and numerically solving the partial differential equations. The number of meshes used in the numerical computation of the partial differential equation was 100. They are presented in Table 1.

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

Table 1. *Fixation probabilities in a subdivided population with varying environments computed by the Gauss–Seidel method and by the approximate formula. Probabilities multiplied by 100 are tabulated. Parameters are* $N_1 = N_2 = 50$, $m_1 = m_2 = 0{\cdot}0005$

	Case 1*		Case 2*		Case 3*	
s	A†	B†	A†	B†	A†	B†
0·005	0·54	0·54	0·80	0·80	0·32	0·30
0·01	0·65	0·65	1·21	1·22	0·21	0·17
0·02	1·01	1·02	2·25	2·26	0·18	0·04
0·03	1·46	1·46	3·34	3·30	—	—
0·04	1·92	1·92	4·36	4·28	—	—
0·05	2·38	2·38	5·33	5·21	—	—

* Case 1: $s_1 = -s_2 = s$; Case 2: $s_1 = s, s_2 = 0$; Case 3: $s_1 = -s, s_2 = 0$.
† A: computed by solving the partial differential equation (8).
B: approximation computed from (6).

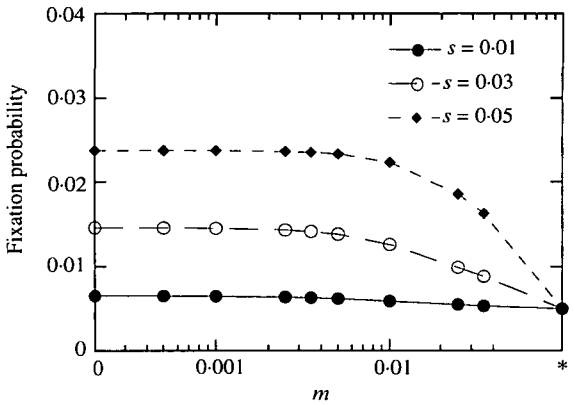

Fig. 1. The fixation probability when the migration rate is changed. Values are computed by numerically solving the partial differential equation (8). The value at $m = *$ is for the case with complete mixture (a panmictic population). There are two subpopulations with equal size $N = 50$. Other parameters are $s_1 = -s_2 = s$.

Three cases are considered. In Case 1, selection coefficients have opposite signs in different environments. In Case 2 and Case 3, the mutant allele is advantageous and disadvantageous, respectively, in the first subpopulation and it is neutral in the second subpopulation. For larger s ($> 0{\cdot}03$), the probabilities become very small in Case 3. Since it takes very long to compute small probabilities accurately using the Gauss–Seidel method, we have not carried out numerical computations for larger values of s in Case 3. As shown in the table, except for the cases where the probability is small (for larger s in Case 3), the agreement between the low migration limit and the values obtained by the numerical method is quite good when the migration rate is very small.

The effect of migration was investigated in Case 1 and the result is shown in Fig. 1. From this figure, we can see that the fixation probability is close to the low migration limit until the migration rate becomes 0·005 ($4Nm = 1{\cdot}0$). In the figure, the fixation probability of the panmictic population is plotted at $m = *$. As the selection coefficient becomes larger, the approach of the fixation probability to the value of that in a panmictic population becomes slower if we measure the approach by the ratio of the difference between the fixation probabilities in the subdivided and the panmictic population to that between the low migration limit and the fixation probability in the panmictic population. This is because the fixation process within a subpopulation becomes quicker as s becomes larger and this makes the assumption of the weak migration approximation to be satisfied more easily.

Since the low migration limit was shown to give fairly accurate values for cases with small migration rates, we will investigate the difference between subdivided populations and panmictic populations using this approximation. Consider a special case where $N_1 = N_2, m_1 = m_2$ and $s_1 = -s_2 = s$ ($s > 0$). The formula (6) is simplified approximately as,

$$u = \frac{u_{a1} + u_{a2}}{4}.$$

This can be also derived by a simpler reasoning. With a probability 1/2, the mutant appears in the first subpopulation and it is fixed in this subpopulation with a probability u_{a1}. Once this state is achieved, the fixation of the mutant is 1/2 because of the symmetry. Thus, in this case, the fixation probability of the mutant is $u_{a1}/4$. Similarly, if the mutant appears in the second subpopulation, the fixation probability of the mutant is $u_{a2}/4$. Hence, we obtain the above expression. In an extreme case where $Ns \gg 1$, it is further simplified to be

$$u = \frac{s}{2}. \tag{9}$$

Note that this special case is an average neutral case where the average selection coefficient of the mutant gene is zero. In the neutral case, the fixation probability is $1/4N$. Comparing this with (9), we can see that changing environments increases the fixation probability in this case. The conclusion differs from that of Pollak (1966) which predicts that both fixation probabilities have the same value. We will discuss this discrepancy in the Discussion.

We numerically computed fixation probabilities in subdivided populations using the low migration limit approximation and those in corresponding panmictic populations in other cases and some of the results are shown in Table 2. The selection coefficient in the panmictic population is the average of those in the subpopulations. Results for the case of $s_1 = -s_2$ are also shown for comparison. Except for the case where mutants are advantageous in both subpopulations (Case F in Table 2), fixation probabilities are higher in

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

Table 2. *Comparison of fixation probabilities in subdivided populations and those in corresponding panmictic populations. Probabilities multiplied by 100 are tabulated. Population size is N = 50. Sub. and Pan. are abbreviations for subdivided and panmictic populations, respectively. Seven cases are: A,* $s_1 = -s_2 = s$; *B,* $s_1 = -2s_2 = s$; *C,* $2s_1 = -s_2 = s$; *D,* $s_1 = s$, $s_2 = 0$; *E,* $s_1 = 0$, $s_2 = -s$; *F,* $s_1 = s$, $s_2 = s/2$; *G,* $s_1 = -s/2$, $s_2 = -s$

	$s = 0{\cdot}0005$		$s = 0{\cdot}005$		$s = 0{\cdot}05$	
Case	Sub.	Pan.	Sub.	Pan.	Sub.	Pan.
A	0·5004	0·5000	0·5397	0·5000	2·3793	0·5000
B	0·5127	0·5125	0·6620	0·6346	4·7054	2·4858
C	0·4879	0·4877	0·4035	0·3859	0·0333	0·0172
D	0·5253	0·5253	0·8023	0·7890	5·2085	4·8773
E	0·4758	0·4755	0·2981	0·2917	0·0003	0·0002
F	0·5381	0·5382	0·9637	0·9618	7·2040	7·2257
G	0·4638	0·4636	0·2183	0·2162	0·0000	0·0000

subdivided populations than in corresponding panmictic populations. This tendency is pronounced when selection coefficients have different signs in different populations. If selection coefficients have the same sign, there is not much difference between the two types of populations.

(ii) *More than two populations*

Next we consider cases with more than two subpopulations using the low migration limit approximation. For simplicity, we assume that there are two symmetric types of environments, 1 and 2. The fitnesses of the allele a and A are $1+s$ and 1, respectively, in the environment 1 and vice versa in the environment 2. The numbers of subpopulations in the environments 1 and 2 are K and L, respectively, and the size of each subpopulation is N. Because of the symmetry assumption, a state of the Markov chain in the low migration limit is characterized by two numbers, k and l, of the numbers of subpopulations fixed with the a allele in the environment 1 and 2, respectively. Thus, we represent the state of the Markov chain by a vector (k, l). First we consider the transition rate, $t_{(k,l)(k+1,l)}$ per generation from (k, l) to $(k+1, l)$. For this event to happen, a fixation of the allele a in one of the $K-k$ subpopulations in the environment 1 which are previously fixed with the allele A must occur. For each such subpopulation, $2Nm$ migrants are coming in among which $(k+l)/(K+L)$ are a genes. Let u_{Zi} be the fixation probability of a Z allele introduced into a population of size N which is fixed with the other type allele and is in the environment i. Then, the rate at which a fixation of the allele a occurs in one such subpopulation is $2Nm(k+l)u_{a1}/(K+L)$. Since there are $K-k$ such subpopulations,

$$t_{(k,l)(k+1,l)} = \frac{2Nm(K-k)(k+l)u_{a1}}{K+L}. \tag{10}$$

Similarly,

$$t_{(k,l)(k-1,l)} = \frac{2Nmk(K+L-k-l)u_{A1}}{K+L} \tag{11}$$

$$t_{(k,l)(k,l+1)} = \frac{2Nm(L-l)(k+l)u_{a2}}{K+L} \tag{12}$$

$$t_{(k,l)(k,l-1)} = \frac{2Nml(K+L-k-l)u_{A2}}{K+L}. \tag{13}$$

Probabilities to all other states are zero. Let $u_{(k,l)}$ be the ultimate fixation probability of the allele a in the total population starting from the state (k, l). By considering the fixation probabilities in the next generation, we can show that u's satisfy

$$\begin{aligned} u_{(k,l)} = {} & (1 - t_{(k,l)(k+1,l)} - t_{(k,l)(k-1,l)} - t_{(k,l)(k,l+1)} \\ & - t_{(k,l)(k,l-1)})u_{k,l} + t_{(k,l)(k+1,l)}u_{(k+1,l)} \\ & + t_{(k,l)(k-1,l)}u_{(k-1,l)} + t_{(k,l)(k,l+1)}u_{(k,l+1)} \\ & + t_{(k,l)(k,l-1)}u_{(k,l-1)}, \end{aligned} \tag{14}$$

with the boundary condition

$$u_{(0,0)} = 0 \tag{15}$$

$$u_{(K,L)} = 1. \tag{16}$$

Since the probability of the first mutant gene appearing in the environment 1 and the environment 2 are $K/(K+L)$ and $L/(K+L)$, respectively, the fixation probability of a mutant gene is

$$u = \frac{Ku_{a1}u_{(1,0)} + Lu_{a2}u_{(0,1)}}{K+L}. \tag{17}$$

We numerically solved equation (14) with the boundary conditions (15) and (16) and computed the fixation probability using equation (17). Some of the results are shown in Table 3. For simplicity, cases with an equal number of subpopulations are considered. In order to see the effect of subdivision, the total population size was kept constant ($N_T = 1000$ in the table) and effects of various levels of subdivision are investigated. For comparison, the fixation probability in the neutral case is also tabulated. When selection is weak ($s = 0{\cdot}001$), the fixation probability is close to that in the neutral case and further subdivision does not change the fixation probability. When selection is strong ($s = 0{\cdot}01$ and $0{\cdot}02$), the fixation probability becomes much larger than that in the neutral case. The fixation probability is almost the same in all cases ($K = 1-10$ in the table). Thus, the probability in the multi-subpopulation case can be computed using eqn (9) in this case. For medium values of selection coefficients ($s = 0{\cdot}005$), intermediate behaviour is observed. As long as the local population size is large

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

Table 3. *Fixation probability in an island model computed from the low migration limit approximation. There are two environments. The total population size is kept constant and it is 1000 in the computation. The population is divided into 2K subpopulations of equal size, K for each environment. Selection coefficients of the mutant allele are* $s_1 = -s_2 = s$ *and the size of a subpopulation is N. Probabilities multiplied by 1000 are tabulated*

K	N	$s = 0{\cdot}0$	$s = 0{\cdot}001$	$s = 0{\cdot}005$	$s = 0{\cdot}01$	$s = 0{\cdot}02$
1	500	0·50	0·66	2·49	4·95	9·80
2	250	0·50	0·61	2·46	4·95	9·80
4	125	0·50	0·57	2·26	4·92	9·80
6	83·3	0·50	0·55	1·98	4·79	9·79
8	62·5	0·50	0·54	1·72	4·58	9·75
10	50	0·50	0·53	1·51	4·33	9·65

($Ns > 1$), the fixation probability is large compared to that in the neutral case and further subdivision does not cause change in the fixation probability. However, if the subpopulation size becomes smaller, the probability becomes smaller as we further divide the population. Eventually, the probability becomes the same as that in the neutral case (data not shown). In conclusion, if $4Ns$ is large, further subdivision of the population does not affect the fixation probability in this case.

4. Discussion

In the present paper, we investigated the fixation probability of a mutant gene in spatially changing environments. We found that the fixation probability in a spatially varying environment is different from that in a uniform environment in which the selection coefficients are the average of those in the varying environment. Specifically, if selection is fairly strong ($Ns > 1$) and the migration rate is small, the fixation probability increases as the environmental variation is introduced in most cases. This can be typically seen in the average neutral case where the selection coefficients in two subpopulations have the same magnitude and opposite signs [see (9)]. In most of the other cases, this tendency holds although it is not as pronounced as in the average neutral case. So we cannot compute the fixation probability simply by assigning the average fitness of a gene as its fitness. In many cases, the fixation probability could be more than that computed using the average fitness. Accordingly, the substitution rate becomes larger in these cases.

As stated in the introduction, our observation contradicts the result of Pollak (1966). For the average neutral case, eqn (2) shows that the fixation probability is the same as that of the neutral case when s is much smaller than one. In the derivation, he approximated a linear equation of a finite number of variables with that of an infinite number of variables (see p. 149 of Pollak, 1966). Although his formula leads to the same answer as that obtained by the diffusion method in the single population case, this approximation has not been justified mathematically as far as we know. Our derivation seems intuitively correct when the migration rate is very small and we justified the approximation by solving the partial differential equation for the diffusion process. Furthermore, we obtained similar values using simulation (data not shown). Thus, we think that his approximation used to derive (2) is not valid and we can not use his formula in cases with variable environments.

Our observation can be compared to those made for the fixation probability in temporally changing environments. If the average selection coefficient is zero or positive, the fixation probability of a mutant gene increases as the environmental variation is increased in many cases (Ohta, 1972; Jensen, 1973; Karlin & Levikson, 1974; Takahata, Ishii & Matsuda, 1975). However, we can construct a simple model in which this is not true (Karlin & Levikson, 1974). Thus, we cannot state generally that environmental variation increases the fixation probability.

We have considered only the island model without dominance thus far. However, the same method can be applied to investigate other models. We considered some of them and results are shown in Table 4. For comparison, we also tabulated the case of the island model with no dominance.

In the linear stepping stone model (Maruyama, 1970*b*) with the left half in the first environment and the right half in the second environment, we can index the states of the Markov chain by a vector (i,j), where i and j are the left- and the right-most subpopulations, respectively, in which the mutant allele is fixed. The equation for the fixation probability in this Markov chain was solved in a similar way as in the previous section. Compared to the island model, the effect of subdivision is smaller (Table 4). This is because the left half and the right half are behaving like a single population, respectively. If the environment changes alternately, the behaviour will be different. Slatkin (1981) observed that changes of the migration pattern do not affect the fixation probability in the uniform selection case if migration is symmetric. Our result shows that when environmental variation is introduced, this invariant property no longer holds.

We also considered cases with dominance. The method explained in the previous section uses fixation probabilities in a single population to compute the transition rate [see eqns (10)–(13)]. Thus, we can use the same method to compute the fixation probability by just replacing u_{zi}'s for the no dominance case with those for dominance cases. To make the selection scheme for two alleles symmetric, we computed the fixation probability when the favourable allele in each environment is dominant or recessive. The behaviour is quite different from that in the no dominance case.

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

Table 4. *Fixation probability in various models computed from the low migration limit approximation. There are two environments. The total population size is kept constant and it is 1000 in the computation. The population is divided into 2K subpopulations of equal size, K for each environment. Selection coefficients of the mutant allele are* $s_1 = -s_2 = 0{\cdot}01$ *and the size of a subpopulation is N. Probabilities multiplied by 1000 are tabulated*

		No dominance			
				Dominant	Recessive
K	*N*	Island	Stepping stone	Island	Island
1	500	4·95	4·95	9·54	1·26
2	250	4·95	4·95	9·24	1·78
4	125	4·92	4·94	8·36	2·49
6	83·3	4·79	4·93	7·35	2·91
8	62·5	4·58	4·91	6·50	3·11
10	50	4·33	4·89	5·80	3·16

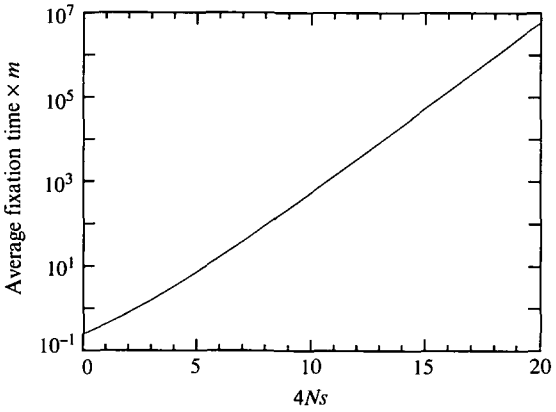

Fig. 2. The average time for fixation in the two subpopulation case when $4Ns$ is changed. The values are computed using (18). The average time multiplied by the migration rate m is plotted.

When the favourable allele is dominant, the fixation probability decreases as subdivision proceeds. However, when the favourable allele is recessive, it increases as subdivision proceeds. Thus, the effect of subdivision becomes complex if dominance is introduced.

If we increase s, the fixation probability becomes large in the average neutral case [see (9)]. However, there is a practical limit for this increase because the average time for the fixation of a mutant given the mutant is fixed in the whole population becomes very large. In a symmetric case where $N_1 = N_2 = N$, $m_1 = m_2 = m$ and $s_1 = -s_2 = s > 0$, the average time for fixation becomes [see (7)]

$$\frac{\exp(4Ns) - 1}{16Nms} \qquad (18)$$

ignoring the small second term. Numerical evaluations of this formula are shown in Fig. 2. The average time for fixation multiplied by the migration rate m is plotted. The average fixation time increases very quickly as the selection coefficient increases. Recall that the fixation probability is increased with the introduction of environmental variability when the migration rate is very small ($Nm < 1$). Thus, we should multiply the values shown in Fig. 2 by a large value. This means that for larger $4Ns$ the average fixation time becomes very long, i.e., the population stays polymorphic for very long time. However, the environments may change over long periods of time and thus equation (9) would no longer hold. Thus, our conclusion that the fixation probability increases in spatially changing environments has a practical implication for evolutionary theory when selection is intermediate, say, when $4Ns$ is less than 10.

In the case of weak migration, we used a Markov chain approximation which was developed by Lande (1979) and Slatkin (1981). This approximation is similar to those used by Gillespie (1983), Walsh (1985), Li (1987), Zeng, Tachida & Cockerham (1989), Tachida (1990) and Takahata (1990) for cases of weak mutation or weak gene conversion in finite populations. These approximations were used heuristically and they propose a mathematical conjecture that some diffusion processes associated with population genetics converge to Markov chains in the weak mutation, the weak gene conversion or the weak migration limit. This conjecture provides us with a new type of limit theorem for the theory of stochastic processes since a jump process appears as a limit of stochastic processes with continuous paths (diffusion processes). Iizuka & Ogura (1991) have proved the conjecture for the one-dimensional case (see also Ogura, 1989). The proof of this conjecture seems to be difficult in general cases such as ours with more than one dimension. However, at least in the parameter range used in our study, the agreement between the approximation and the numerical solution to the partial differential equation is pretty good.

We thank C. Basten, T. Ohta, F. Tajima and two anonymous reviewers for helpful comments on the earlier draft of the manuscript. This research was partially supported by NIG Cooperative Research Program ('90-35) and a grant-in-aid from the Ministry of Education, Science and Culture of Japan. This is contribution no. 1889 from the National Institute of Genetics, Mishima, Japan.

References

Crow, J. F. & Kimura, M. (1970). *An Introduction to Population Genetic Theory*. New York: Harper & Row.

Dobzhansky, T. J. & Levene, H. (1955). Genetics of natural populations. XXIV. Developmental homeostasis in natural populations of *Drosophila pseudoobscura*. *Genetics* **40**, 779–808.

Dykhuizen, D. E. & Hartl, D. L. (1980). Selective neutrality of 6PGD allozymes in *E. coli* and the effects of genetic background. *Genetics* **96**, 801–817.

Gillespie, J. H. (1983). Some properties of finite populations experiencing strong selection and weak mutation. *American Naturalist* **121**, 691–708.

Hartl, D. L. & Dykhuizen, D. E. (1984). The population genetics of *Escherichia coli*. *Annual Review of Genetics* **18**, 31–68.
Iizuka, M. & Ogura, Y. (1991). Convergence of one-dimensional diffusion processes to a jump process related to population genetics. *Journal of Mathematical Biology* **29**, 671–687.
Jensen, L. (1973). Random selection advantages of genes and their probability of fixation. *Genetical Research* **21**, 215–219.
Karlin, S. & Levikson, B. (1974). Temporal fluctuations in selection intensities: Case of small population size. *Theoretical Population Biology* **6**, 383–412.
Karlin, S. & Taylor, H. M. (1981). *A Second Course in Stochastic Processes*. New York: Academic Press.
Kimura, M. (1962). On the probability of fixation of mutant genes in a population. *Genetics* **47**, 713–719.
Kimura, M. (1983). *The Neutral Theory of Molecular Evolution*. Cambridge: Cambridge University Press.
Lande, R. (1979). Effective deme sizes during long-term evolution estimated from rates of chromosomal rearrangement. *Evolution* **33**, 234–251.
Lande, R. (1985). The fixation of chromosomal rearrangements in a subdivided population with local extinction and colonization. *Heredity* **54**, 323–332.
Li, W.-H. (1987). Models of nearly neutral mutations with particular implications for nonrandom usage of synonymous codon. *Journal of Molecular Evolution* **24**, 337–345.
Maruyama, T. (1970*a*). On the fixation probability of mutant genes in a subdivided population. *Genetical Research* **15**, 221–225.
Maruyama, T. (1970*b*). Analysis of population structure. I. One-dimensional stepping-stone models of finite length. *Annals of Human Genetics, London* **34**, 201–219.
Maruyama, T. (1972). Some invariant properties of a geographically structured finite population: distribution of heterozygotes under irreversible mutation. *Genetical Research* **20**, 141–149.
Nagylaki, T. (1980). The strong-migration limit in geographically structured populations. *Journal of Mathematical Biology* **9**, 101–114.
Ogura, Y. (1989). One-dimensional bi-generalized diffusion processes. *Journal of Mathematical Society of Japan* **41**, 213–242.
Ohta, T. (1972). Fixation probability of a mutant influenced by random fluctuation of selective intensity. *Genetical Research* **19**, 33–38.
Ortega, J. M. & Poole Jr., W. G. (1981). *An Introduction to Numerical Methods for Differential Equations*. Marshfield, Massachusetts: Pitman Publishing Inc.
Pollak, E. (1966). On the survival of a gene in a subdivided population. *Journal of Applied Probability* **3**, 142–155.
Slatkin, M. (1981). Fixation probabilities and fixation times in a subdivided population. *Evolution* **35**, 477–488.
Tachida, H. (1990). A population genetic model of selection that maintains specific trinucleotides at a specific location. *Journal of Molecular Evolution* **31**, 10–17.
Tachida, H. & Mukai, T. (1985). The genetic structure of natural populations of *Drosophila melanogaster*. XIX. Genotype-environment interaction in viability. *Genetics* **111**, 43–55.
Takahata, N. 1990. A simple genealogical structure of strongly balanced allelic lines and trans-species evolution of polymorphism. *Proceedings of the National Academy of Sciences, U.S.A.* **87**, 2419–2423.
Takahata, N., Ishii, K. & Matsuda, H. (1975). Effect of temporal fluctuation of selection coefficient on gene frequency in a population. *Proceedings of the National Academy of Sciences, U.S.A.* **72**, 4541–4545.
Takano, T., Kusakabe, S.-I. & Mukai, T. (1987). The genetic structure of natural populations of *Drosophila melanogaster*. XX. Comparison of genotype-environment interaction in viability between a northern and a southern population. *Genetics* **117**, 245–254.
Zeng, Z. B., Tachida, H. & Cockerham, C. C. (1989). Effects of mutation on selection limits in finite populations with multiple alleles. *Genetics* **122**, 977–984.

Appendix

First note that the fixation probability u is computed from the mean of X at $t = \infty$ as

$$E[X]_{|t-\infty} = u \times 1 + (1-u) \times 0 = u \tag{A 1}$$

since fixation or loss of the allele a occurs with probability one. The moment equations can be derived from (4) using the Ito's formula and taking expectations (see Karlin & Taylor, 1981),

$$\frac{dE[x_i]}{dt} = S_i E[x_i(1-x_i)] + ME[X-x_i] \tag{A 2}$$

$$\frac{dE[x_i^2]}{dt} = 2S_i E[x_i^2(1-x_i)] + 2ME[x_i(X-x_i)] + E[x_i(1-x_i)] \tag{A 3}$$

$$\frac{dE[x_i x_j]}{dt} = S_i E[x_i x_j(1-x_i)] + S_j E[x_i x_j(1-x_j)] + ME[x_j(X-x_i) + x_i(X-x_j)], \tag{A 4}$$

where $S_i = 2Ns_i$ and $M = 2Nm$. The initial conditions are

$$E[x_i]_{|t=0} = \frac{1}{2nN}, \quad E[x_i^2]_{|t=0} = \frac{1}{4nN^2}, \quad E[x_i x_j]_{|t=0} = 0.$$

Since these equations are not closed by themselves, we can not solve them in general. In order to compute the first moment, we need the second moments and to get these, third moments are necessary. However, if we assume that S_i's are of the order of ϵ ($\epsilon \ll 1$), the third moments in the latter two equations can be truncated approximately and we can obtain the first moments with an error of the order of ϵ^2. In fact, from (A 2), the dynamics of $E[X]$ is described by

$$\frac{dE[X]}{dt} = \frac{1}{n}\sum_{i=1}^{n} S_i E[x_i(1-x_i)]. \tag{A 5}$$

Integrating both sides from $t = 0$ to $t = \infty$, we obtain

$$E[X]_{|t-\infty} = \frac{1}{n}\sum_{i=1}^{n} S_i \int_0^\infty E[x_i(1-x_i)]\,dt + \frac{1}{2nN}. \tag{A 6}$$

To get the left-hand side with an error of the order of ϵ^2 or less, it is necessary to compute $\int_0^\infty E[x_i(1-x_i)]\,dt$ with an error of the order of ϵ or less. From equations (A 2)–(A 4), it can be shown that this amounts to computing the quantity under neutrality. Maruyama

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press

(1972) has shown that under neutrality the total number of heterozygotes which appeared in the population is invariant in any geographical structures and it is $2N_T$ if the total population size is constant. Randomizing the subpopulation in which the mutant first appeared, the total number of the heterozygotes which appeared in one subpopulation becomes $2N_T/n = 2N$. Since the integral is the total number of heterozygotes which appeared in one subpopulation divided by $2N$, the integral is calculated to be $1/(2N)$ noting that we measure time in units of $2N$ generations. Thus, we obtain

$$u = E[X]_{t=\infty} = \left(\frac{1}{n}\sum_{i=1}^{n} s_i\right) + \frac{1}{2nN}. \qquad \text{(A 7)}$$

This means that if selection is very weak, so that $2Ns_i$ is much smaller than one, the fixation probability is the same as that in a uniform panmictic population where the selection coefficient of the a allele is the average of those in varying environments.

https://doi.org/10.1017/S0016672300029992 Published online by Cambridge University Press