Theoretical Study of Near Neutrality. II. Effect of Subdivided Population Structure With Local Extinction and Recolonization

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ABSTRACT

There are several unsolved problems concerning the model of nearly neutral mutations. One is the interaction of subdivided population structure and weak selection that spatially fluctuates. The model of nearly neutral mutations whose selection coefficient spatially fluctuates has been studied by adopting the island model with periodic extinction-recolonization. Both the number of colonies and the migration rate play significant roles in determining mutants' behavior, and selection is ineffective when the extinction-recolonization is frequent with low migration rate. In summary, the number of mutant substitutions decreases and the polymorphism increases by increasing the total population size, and/or decreasing the extinction-recolonization rate. However, by increasing the total size of the population, the mutant substitution rate does not become as low when compared with that in panmictic populations, because of the extinction-recolonization, especially when the migration rate is limited. It is also found that the model satisfactorily explains the contrasting patterns of molecular polymorphisms observed in sibling species of *Drosophila*, including heterozygosity, proportion of polymorphism and fixation index.

A T the molecular level, mutations with very small effects are abundant, and both random genetic drift and natural selection influence their behavior. For example, results of DYKHUIZEN and HARTL (1980) suggest that many naturally occurring enzyme polymorphisms in *Escherichia coli* are nearly neutral, and SAWYER, DYKHUIZEN and HARTL (1987) estimated that the selection coefficient of a typically polymorphic locus of this species is very small. Several theoretical models for treating the population dynamics of such mutants have been investigated. Two main formulations are the fixed model and the shift model. In the former, the distribution of selection coefficient of new mutations is fixed regardless of allelic state of the population, whereas in the latter, the distribution is assumed to shift after mutant substitution, since the population fitness remains at unity. In formulating the behavior of nearly neutral mutations at the molecular level, the shift model has been studied extensively (OHTA 1977; KIMURA 1979; LI 1979). By considering adaptation at the molecular level, OHTA and TACHIDA (1990) and TACHIDA (1991) introduced the fixed model into the study of molecular evolution, since the population fitness gradually increases in this model. Another problem concerning near neutrality is whether or not the weak selection is constant in space and in time. OHTA and TACHIDA (1990) have studied the case where the selection coefficient spatially varies with two extreme situations, *i.e.*, a panmictic population and a structured population with low migration rate, and found that the rate of mutant substitution is only slightly different between the two situations, but that the level of polymorphism is differs greatly. TACHIDA (1991) ignored spatial fluctuation, but investigated the properties of near neutrality in more detail, and has shown that several statistics under this model become indistinguishable from those under strict neutrality. In the present report, analyses are extended to a more realistic population structure where migration rate is intermediate, with local extinction and recolonization. The results will be useful for understanding various data on molecular evolution and polymorphisms.

MODEL AND SIMULATION STUDIES

As in the previous simulation study (OHTA and TACHIDA 1990), the selection coefficient of a new mutant in a local colony is assumed to follow the normal distribution with mean μ_s and variance σ_s^2. Since we assume that they are independently chosen, the selection coefficients independently fluctuate in space. Let N be the size of a local colony, and l colonies are assumed, with total size, $N_T = lN$. Unlike the previous study, the island model with an intermediate migration rate is used. In addition, local extinction is introduced. This is based on the consideration that natural populations often pass through bottlenecks, such that current populations have been formed from small initial populations through rapid expansion (CARSON 1976). Thus, in the simulations, at specified intervals, a single, randomly chosen colony replaces all other colonies in one generation *i.e.*, periodic ex-

tinction-recolonization. Such a population structure has been thought to be rather common in nature in relation to frequent fixation of chromosome inversions and translocations (LANDE 1979).

The sudden expansion of a single colony may seem unrealistic; however, note the following situation. The period in generations of the extinction-recolonization event is assumed to be of the order of reciprocal of mutation rate, a very long time interval. We are concerned here with the evolution of a small segment of DNA that corresponds to an exon or a region even smaller (OHTA and TACHIDA 1990). Since the mutation rate of an exon is $10^{-6} \sim 10^{-7}$ per year from the molecular evolution data (KIMURA 1983), the reciprocal becomes $1 \sim 10$ million generations, provided that 1 generation corresponds to 1 year. In such a long period, speciation often occurs more than once (GINGERICH 1991), and is often accompanied by a bottleneck (MAYR 1963). The present extinction-recolonization corresponds to the speciation event. Actually, extinction-recolonization is more frequent in nature, but takes place gradually, i.e., one or a few colonies become extinct and are replaced by neighboring colonies. Thus I include another model of extinction-recolonization in which one colony periodically becomes extinct and is replaced by another colony randomly chosen (MARUYAMA and KIMURA 1980). I shall call it one colony-extinction model, against the sudden-expansion model. The effective size of the total population becomes smaller by such extinction-recolonization, and various quantities of interest are examined in simulations. Here the migration rate also plays an important role in mutants' behavior, and let m be the migration rate of the island model. Thus, in this model, the mutants' behavior is influenced by the interaction of weak selection spatially varying, random genetic drift, migration and extinction-recolonization.

Let v be the mutation rate per gene per generation under the 100-allele model. Here the product of population size and mutation rate, Nv, is important, and was chosen to be 0.01. As before, each experiment was continued for $11/v$ generations, so that the expected number of mutant substitution is 11, if the mutant is completely neutral. Note again that $1/v$ generations correspond to a very long period of $10^6 \sim 10^7$ years. Also notice that the small value of N and the large value of v are used in simulations so that $Nv = 0.01$. Actually, when the frequency of a mutant reaches 90% or more, the mutant is counted as a substitution. The selection coefficient of the kth mutant in the ith colony, $s_{k,i}$ was determined by sampling from a normal distribution with mean μ_s and variance σ_s^2. For a set of parameter values, 40 replications were performed.

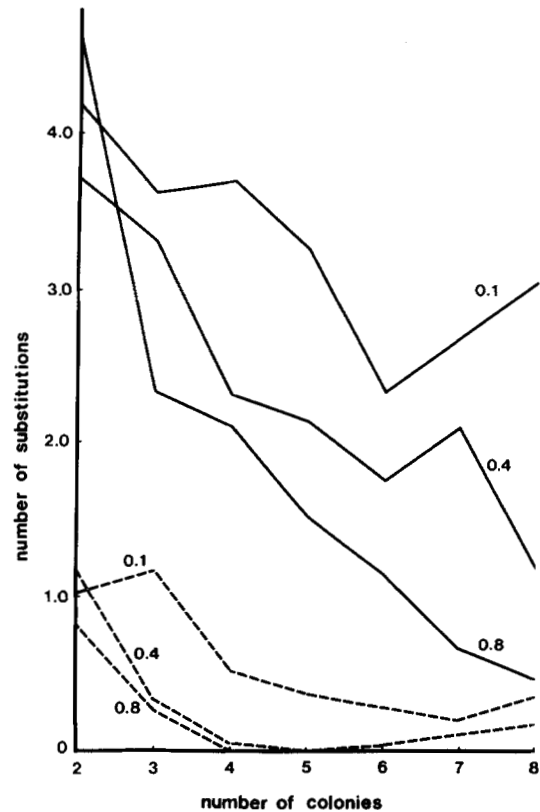Various quantities of evolutionary interest have

FIGURE 1.—Number of mutant substitutions as functions of the number of colonies. Solid lines are for $-\mu_s = \sigma_s$ and broken lines for $-\mu_s = 2\sigma_s$. Parameters are $2Nv = 0.02$, $2N\sigma_s = 1$, the interval of the extinction-recolonization is $1/v$, and $2N = 20$. Figures beside lines are values of $2Nm$.

been computed, and the results will be given in the next section. We examine the number of substitutions, heterozygosity, actual number of alleles, probability of polymorphism, and dispersion index.

RESULTS AND DISCUSSION

For nearly neutral, but slightly deleterious mutations, the mutant substitution stops with increase in the population size, and the theory of slightly deleterious mutations (OHTA 1973, 1976) has been criticized because of this prediction (NEI 1987). Our studies on nearly neutral mutations on the fixed model have shown that the evolution does not stop but simply slows down for large populations (OHTA and TACHIDA 1990; Tachida 1991). Here, I present data in which the effect of large population size on the substitution rate becomes even smaller by incorporating extinction-recolonization.

Figure 1 shows how the average number of substitutions in the whole period of simulation experiments becomes smaller by increasing the total size (number of colonies). We specify the parameters as follows: the interval of extinction is $1/v$ generations, the intensity of selection is $2N\sigma_s = 1.0$, $2N\mu_s = -2.0$ (solid line) or -1.0 (broken line), and the migration rate is $2Nm =$
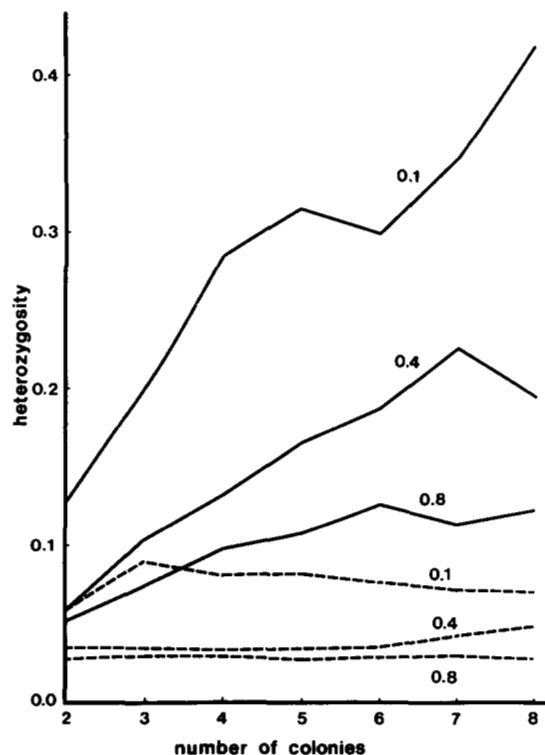
FIGURE 2.—Average heterozygosity as functions of the number of colonies. Parameters are the same as in Figure 1.

0.1, 0.4 and 0.8 as indicated beside each line. By comparing the present results with those of the previous study, it can be seen that periodic extinction is effective for increasing the number of substitutions. Note that, without periodic extinction, there is no substitution when $2N\mu_s = -2$ and $l \geq 4$ and only a few substitutions when $2N\mu_s = -1$ and $l \geq 4$ (see Table 2 of OHTA and TACHIDA 1990). The figure also indicates that limited migration enhances such a tendency. A higher migration rate has an effect similar to larger population size, and selection becomes more effective as the rate increases. However, note that when $l = 2$, the effect of migration is not obvious. This is because, in addition to slightly deleterious mutations, slightly advantageous mutations occur when the total population size is small (see TACHIDA 1991), and their fixation would be enhanced by migration. When l is 3 or more, such mutations become rare and do not violate the general pattern.

Figure 2 gives the average heterozygosity of the total population in the interval from the $(1/v)$th generation to the end of experiments as functions of the number of colonies. Again, the periodic extinction inflates the heterozygosity, as does the number of substitutions. In general, by increasing the population size, the substitution rate becomes lower, and the heterozygosity, higher, for nearly neutral mutations, and this prediction is again verified, but the stable mutation-selection balance is not reached. The rate of migration again influences heterozygosity.

We shall now examine more quantities of evolutionary interest. Table 1 gives the results for the number of substitutions, heterozygosity, actual number of alleles, probability of polymorphism, and dispersion index. Except for the number of substitutions, the values are the averages in the period from the $(1/v)$th generation to the end of experiments. The two cases, $l = 2$ and 8, each with two levels of $2N\mu_s = -1$ and -2, are shown. In the table, the ratio is the variance to the mean of the number of substitutions, which has been much discussed in recent years [GILLESPIE (1987), for review]. The actual data show that it is often $2 \sim 3$, occasionally 10 or more, indicating that the process of mutant substitution is not simple Poisson. The results in Table 1 show that the ratio is mostly larger than unity under the present model. This is because, by chance, a slightly deleterious mutation may fix in the population, followed by slightly advantageous mutant substitutions. I have checked the pattern of mutant substitution in some simulations, and found that slightly deleterious mutant substitution is followed by slightly advantageous one. The pattern is somewhat similar to the "episodic" process (GILLESPIE 1987). The details of this process has been studied by Y. IWASA (personal communication).

Other quantities examined concern polymorphism. Data tell us that the quantities fluctuate considerably. Note that the standard deviation is obtained from 40 replications, and that the value of a single replication is the average of $10/v$ generations. The probability of polymorphism $(P_{0.95})$ is on a stringent criterion (95%). It increases with an increase in the population size, or a decrease in the migration rate. However, when $2N\mu_s = -2.0$, the increase of population size has only a small effect. The dispersion index, G_{ST}, was obtained from the average heterozygosities of 40 replications by using the formula, $G_{ST} = (H_T - H_C)/H_T$, where H_T and H_C are the average heterozygosity of the total population and that of a colony (NEI 1987). The expected value has been shown to be,

$$E(G_{ST}) = \frac{1}{4Nma + 1} \tag{1}$$

where $a = \{l/(l - 1)\}^2$ (CROW and AOKI 1982). From the table it can be seen that G_{ST} becomes almost the same in our model as in the strictly neutral case.

Another model of the extinction-recolonization is the one adopted by MARUYAMA and KIMURA (1980), in which one colony randomly chosen becomes extinct, and is replaced by another colony again randomly chosen (one colony-extinction model). This type of extinction-recolonization would be more frequent in natural populations than the previous one. As mentioned before, the sudden-expansion model is intended to treat speciation, and the one colony-extinction model may apply to the more stable state.

TABLE 1

Results of simulation experiments on gene substitution and polymorphism

Model	Period	l	$-\mu_s$	$2Nm$	No. of substitution[a]	Ratio[b]	Heterozygosity[a]	Actual No. of Alleles[a]	$P_{0.95}$[a]	$G_{ST}/E(G_{ST})$
Sudden-expansion model	$\dfrac{1}{v}$	2	0.05	0.1	4.18 ± 2.02	0.98	0.126 ± 0.063	1.39 ± 0.13	0.31 ± 0.12	1.16
				0.2	4.18 ± 2.68	1.72	0.075 ± 0.026	1.28 ± 0.07	0.21 ± 0.06	1.21
				0.3	4.73 ± 2.06	0.90	0.079 ± 0.028	1.29 ± 0.07	0.23 ± 0.06	1.34
				0.4	3.90 ± 2.71	1.88	0.061 ± 0.023	1.25 ± 0.06	0.19 ± 0.05	1.38
				0.5	4.53 ± 2.74	1.65	0.058 ± 0.017	1.25 ± 0.05	0.18 ± 0.04	1.40
		2	0.1	0.1	1.00 ± 1.50	2.26	0.057 ± 0.042	1.22 ± 0.10	0.17 ± 0.08	0.95
				0.2	0.95 ± 1.81	3.45	0.045 ± 0.026	1.20 ± 0.06	0.15 ± 0.05	1.05
				0.3	1.45 ± 2.00	2.76	0.041 ± 0.021	1.20 ± 0.06	0.14 ± 0.05	1.07
				0.4	1.00 ± 1.68	2.82	0.037 ± 0.017	1.18 ± 0.05	0.13 ± 0.04	1.17
				0.5	0.98 ± 2.19	4.92	0.031 ± 0.016	1.17 ± 0.04	0.12 ± 0.04	1.00
		8	0.05	0.1	2.73 ± 1.34	0.66	0.404 ± 0.092	3.39 ± 0.44	0.81 ± 0.11	1.03
				0.2	2.35 ± 2.19	2.04	0.315 ± 0.108	2.88 ± 0.44	0.72 ± 0.15	1.08
				0.3	1.80 ± 2.04	2.31	0.247 ± 0.122	2.56 ± 0.45	0.61 ± 0.18	1.13
				0.4	1.08 ± 1.42	1.88	0.196 ± 0.091	2.34 ± 0.35	0.53 ± 0.15	1.14
				0.5	1.08 ± 1.75	2.83	0.168 ± 0.097	2.22 ± 0.34	0.47 ± 0.17	1.16
		8	0.01	0.1	0.20 ± 0.56	1.59	0.083 ± 0.072	1.86 ± 0.34	0.27 ± 0.13	0.87
				0.2	0.35 ± 1.08	3.30	0.077 ± 0.098	1.82 ± 0.42	0.22 ± 0.17	0.92
				0.3	0.15 ± 0.80	4.29	0.049 ± 0.042	1.69 ± 0.19	0.17 ± 0.08	0.84
				0.4	0.03 ± 0.16	1.00	0.037 ± 0.008	1.64 ± 0.06	0.14 ± 0.03	0.80
				0.5	0.00		0.033 ± 0.006	1.61 ± 0.04	0.12 ± 0.02	0.77
One colony-extinction model	$\dfrac{1}{(l\text{-}1)v}$	8	0.05	0.1	0.40 ± 0.71	1.26	0.377 ± 0.123	3.20 ± 0.56	0.87 ± 0.09	1.03
				0.2	0.40 ± 0.59	0.87	0.300 ± 0.128	2.79 ± 0.51	0.80 ± 0.11	1.08
				0.3	0.50 ± 0.82	1.34	0.238 ± 0.118	2.50 ± 0.40	0.74 ± 0.12	1.12
				0.4	0.28 ± 0.51	0.93	0.182 ± 0.088	2.28 ± 0.29	0.68 ± 0.10	1.12
				0.5	0.18 ± 0.81	3.65	0.145 ± 0.068	2.16 ± 0.24	0.63 ± 0.08	1.12
	$\dfrac{1}{10(l\text{-}1)v}$	8	0.05	0.1	2.55 ± 2.33	2.13	0.242 ± 0.096	2.45 ± 0.36	0.73 ± 0.12	1.00
				0.2	1.75 ± 2.24	2.87	0.197 ± 0.073	2.30 ± 0.27	0.68 ± 0.09	1.00
				0.3	1.83 ± 2.29	2.87	0.183 ± 0.080	2.24 ± 0.29	0.66 ± 0.11	1.07
				0.4	0.90 ± 1.61	2.88	0.139 ± 0.069	2.08 ± 0.23	0.60 ± 0.09	1.06
				0.5	0.78 ± 1.46	2.73	0.126 ± 0.047	2.02 ± 0.16	0.57 ± 0.07	1.09
	$\dfrac{1}{20(l\text{-}1)v}$	8	0.05	0.1	4.78 ± 3.53	2.61	0.198 ± 0.060	2.25 ± 0.23	0.66 ± 0.09	0.92
				0.2	2.80 ± 3.03	3.28	0.163 ± 0.065	2.13 ± 0.25	0.61 ± 0.10	0.95
				0.3	1.65 ± 2.67	4.32	0.124 ± 0.058	1.98 ± 0.20	0.56 ± 0.09	0.98
				0.4	1.63 ± 2.67	4.37	0.124 ± 0.055	1.97 ± 0.19	0.56 ± 0.09	1.00
				0.5	0.98 ± 1.82	3.38	0.110 ± 0.050	1.92 ± 0.19	0.53 ± 0.08	0.92

Parameters: $2Nv = 0.02$, $2N\sigma_s = 1.0$ with $N = 10$.
[a] Average ± standard deviation of 40 replications.
[b] Ratio of the mean to the variance of the number of substitution.

Intuitively, one extinction-recolonization under the sudden-expansion model would correspond to $(l - 1)$ events of the one colony-extinction model, because a colony would be replaced once on the average. However, the one-colony-extinction model is less effective than that. Table 1 includes results under various periods of extinction-recolonization with the one colony-extinction model. The effect on the number of substitutions seems to be $1/10$ that expected, whereas that on heterozygosity is just about as predicted by the intuitive argument.

Simulations of Table 1 were performed under the assumption that the interval of the extinction-recolonization is $1/v$, for the sudden expansion model. Thus, 10 extinction-recolonizations occur in one simulation. The next simulations were done to find out the effect of the interval. Table 2 gives the results. The interval was changed from $1/v$ to more than $11/v$ (i.e., from 10 to 0 extinction-recolonizations in one simulation), and three levels of migration rate were chosen. Results in the table show that the number of substitution is influenced by the interval when the migration rate is low. Heterozygosity is relatively insensitive to the interval. It should be noted that the present extinction-recolonization is not equivalent to the ordinary model of bottle neck in which the small population size continues for certain generations. In the present study, extinction-recolonization occurs in a single generation and the expected heterozygosity is not much reduced. It seems that the extinction-recolonization in natural species is often similar to the present one rather than the ordinary model of bottle neck (CARSON 1971). Also note that the number of the extinction-recolonization is not so important for the number

TABLE 2

Results of simulations on the effect of the interval of extinction-recolonization

Interval	2Nm					
	0.1		0.5		4	
	No. of substitutions	heterozygosity	No. of substitutions	heterozygosity	No. of substitutions	heterozygosity
$1/v$	2.98 ± 1.80	0.383 ± 0.104	1.18 ± 1.67	0.192 ± 0.105	0.18 ± 0.59	0.055 ± 0.013
$2/v$	2.08 ± 1.40	0.480 ± 0.120	0.63 ± 1.33	0.180 ± 0.080	0.33 ± 0.83	0.064 ± 0.020
$3/v$	1.25 ± 1.15	0.488 ± 0.130	0.33 ± 0.57	0.167 ± 0.066	0.38 ± 1.13	0.069 ± 0.024
$4/v$	1.05 ± 1.06	0.506 ± 0.128	0.53 ± 0.85	0.182 ± 0.082	0.55 ± 1.66	0.066 ± 0.022
$5/v$	1.25 ± 1.01	0.684 ± 0.168	0.55 ± 1.22	0.239 ± 0.135	0.20 ± 0.46	0.079 ± 0.010
$6/v$	0.60 ± 0.63	0.506 ± 0.121	0.25 ± 0.49	0.181 ± 0.087	0.28 ± 0.99	0.060 ± 0.017
$11/v$	0.23 ± 0.53	0.456 ± 0.121	0.30 ± 0.65	0.145 ± 0.069	0.38 ± 0.95	0.060 ± 0.021

Parameters: $2Nv = 0.02$, $2N\sigma_s = 1$, $2N\mu_s = 1$ and $l = 8$. Average $\pm$ standard deviation of 40 replications is given.

TABLE 3

Contrasting pattern of protein and DNA polymorphism between _D. melanogaster_ and _D. simulans_ (modified from AQUADRO _et al._ 1988)

Assay	D. melanogaster	D. simulans
Protein		
Proportion of polymorphism	0.42	0.29
Heterozygosity	0.102	0.096
G_{st}	0.091	0.025
DNA: heterozygosity per nucleotide site	0.003	0.019

of substitutions in the present model as predicted by the model of FOLEY (1987).

Polymorphism at the molecular level has been studied in _Drosophila_ species in most detail. Especially noteworthy is the observation that the two sibling species, _D. melanogaster_ and _D. simulans_, show a contrasting pattern (AQUADRO _et al._ 1988; SINGH 1989). Although the heterozygosity at the protein level is about the same in the two species, that at the DNA level differ considerably. We have mentioned the possibility that protein variation is nearly neutral, but that DNA variation is strictly neutral (AQUADRO _et al._ 1988, Ohta and TACHIDA 1990). Let us examine this hypothesis in more detail. The contrasting levels of polymorphism summarized by AQUADRO _et al._ (1988) is given in Table 3. It is likely that _D. melanogaster_ has a smaller but more highly structured population than _D. simulans_ as suggested by AQUADRO _et al._ (1988). Here I shall revise the possible set of parameter values in Table 6 of OHTA and TACHIDA (1990).

Table 4 gives the results of simulations done with the sets of plausible parameter values for the protein variation. The set for $l = 2$ is for _D. melanogaster_, and that for $l = 4$ is for _D. simulans_. The value of $2N_Tv$ is 0.04 for the former and 0.08 for the latter. The expected heterozygosity under strict neutrality and sufficient migration becomes 0.074 and 0.138 for these sets. Two classes of selection intensity were chosen; $2N\sigma_s = 0.5$ (nearly neutral) and $2N\sigma_s = 4$ (deleterious), by considering that there exist molecu-

lar variants of different intensities of selection. Actually the value of $2N\sigma_s$ changes continuously from zero to definitely deleterious, but for simplicity, the two classes were set. Simulation study of TACHIDA (1991) indicates that, for nearly neutral mutations, the average fitness of the population stays in the range of $\sigma_s \sim 2\sigma_s$ for quite a long time. Therefore, $-\mu_s$ was chosen to be equal to σ_s. As to the migration rate, low rate was chosen for _D. melanogaster_, and high rate, for _D. simulans_. Again the interval of extinction-recolonization is $1/v$.

Suppose that the mutation responsible for protein polymorphism is expressed by the sum of nearly neutral and deleterious classes. Also assume that $2Nm$ is $0.4 \sim 0.5$ for _D. melanogaster_ and $4 \sim 8$ for _D. simulans_. Then it can be seen from the table that the rate of protein evolution is considerably lower but that the heterozygosity is not so much lower than the strictly neutral prediction. In particular, note that both the evolutionary rate and heterozygosity take similar values in the two species in spite of difference of total population size. For DNA variation that is primarily strictly neutral, heterozygosity is expected to be higher in _D. simulans_ than in _D. melanogaster_. This pattern is just as found in natural populations. The proportion of polymorphism has been examined on 99% and 95% criterions. For nearly neutral class, it becomes similar in the two sets, but for deleterious class, it is higher in the _D. melanogoster_ set than in the _simulans_ set, again agreeing with real data. The dispersion index appears to be slightly too high, but the general pattern of higher G_{ST} in the _D. melanogaster_ set than in the _D. simulans_ set is compatible with the observation. As for the extinction-recolonization, only the cases for $1/v$ generations are presented. Simulations have been done for several other periods of extinction-recolonization, and it was found that the extinction-recolonization has a relatively small effect on the heterozygosity and polymorphism, and the contrasting pattern may be explained under various intervals of the extinction-recolonization.

TABLE 4

Results of simulations for examining the contrasting pattern of polymorphism

l	N	$2N\sigma_s$	$2Nm$	No. of substitutions[a]	Ratio	Heterozygosity[a]	Actual no. of alleles[a]	$P_{0.95}$[a]	$P_{0.99}$[a]	G_{ST}	$E(G_{ST})$
D. melanogaster											
2	40	0.5	0.1	2.43 ± 1.57	1.01	0.138 ± 0.070	1.78 ± 0.17	0.34 ± 0.14	0.44 ± 0.13	0.55	0.56
			0.2	2.08 ± 1.65	1.32	0.110 ± 0.047	1.73 ± 0.13	0.29 ± 0.10	0.39 ± 0.10	0.39	0.38
			0.3	2.38 ± 1.82	1.40	0.098 ± 0.047	1.70 ± 0.13	0.27 ± 0.11	0.38 ± 0.10	0.31	0.29
			0.4	2.63 ± 1.89	1.36	0.096 ± 0.030	1.71 ± 0.09	0.27 ± 0.07	0.38 ± 0.07	0.23	0.24
			0.5	2.33 ± 2.10	1.91	0.086 ± 0.026	1.68 ± 0.08	0.25 ± 0.06	0.36 ± 0.06	0.21	0.20
		4	0.1	0.08 ± 0.27	0.94	0.075 ± 0.127	1.50 ± 0.26	0.16 ± 0.25	0.24 ± 0.24	0.83	
			0.2	0.15 ± 0.36	0.87	0.068 ± 0.122	1.49 ± 0.25	0.15 ± 0.25	0.22 ± 0.23	0.78	
			0.3	0.08 ± 0.27	0.94	0.052 ± 0.100	1.45 ± 0.22	0.11 ± 0.20	0.19 ± 0.19	0.69	
			0.4	0.18 ± 0.45	1.11	0.051 ± 0.087	1.46 ± 0.19	0.12 ± 0.18	0.19 ± 0.17	0.59	
			0.5	0.28 ± 0.51	0.91	0.058 ± 0.109	1.47 ± 0.24	0.13 ± 0.23	0.21 ± 0.21	0.59	
D. simulans											
4	20	0.5	4	2.40 ± 2.46	2.52	0.084 ± 0.026	1.57 ± 0.09	0.26 ± 0.06	0.39 ± 0.054	0.09	0.07
			8	2.80 ± 2.36	1.98	0.082 ± 0.024	1.53 ± 0.09	0.25 ± 0.06	0.37 ± 0.053	0.06	0.03
		4	4	0.0		0.009 ± 0.014	1.40 ± 0.04	0.02 ± 0.03	0.12 ± 0.03	0.13	
			8	0.0		0.006 ± 0.001	1.38 ± 0.04	0.01 ± 0.00	0.11 ± 0.01	0.04	

Parameters: $2Nv = 0.02$, $\mu_s = -\sigma_s$, and the interval of extinction-recolonization $= 1/v$.
[a] Average $\pm$ standard deviation of 40 replications.

TABLE 5

Effect of population structure on behavior of nearly neutral mutations

Effect	No. of colony	Migration	Extinction/ recolonization
No. of substitution	−	−	+
Heterozygosity (total population)	+	−	−

Key: + and − are positive and negative correlations.

The extinction-recolonization is significant in enhancing fixation of slightly deleterious mutations (see Table 2). Thus, one problem of the nearly neutral theory such that the evolution stops when the population size becomes large (see NEI 1987) may be accounted for by incorporating the extinction-recolonization. As pointed out before, the present parameters of the extinction-recolonization is rather conservative, *i.e.*, one bottleneck or even less in $10^6 - 10^7$ years is a minimum number, and one can safely conclude that the evolutionary rate by nearly neutral mutations is not so sensitive to population size as the previous theories suggest.

The present study shows that the fixed model of weak selection may explain various observed facts on protein evolution and polymorphisms. On the other hand, the majority of DNA variation are thought to be strictly neutral. The model also explains the gradual adaptation of protein function, and appears to be more appropriate than the shift model, in which the population fitness shifts to unity once any mutant substitutes the other and hence no improvement of function occurs. Table 4 summarizes the effect of population structure on nearly neutral mutations. In the table, + and − mean positive and negative correlations, respectively.

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