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Genetics

Genetic variability and effective population size when local extinction and recolonization of subpopulations are frequent

(population genetics/protein polymorphism/periodic selection/neutral mutation-random drift hypothesis)

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ABSTRACT **If a population (species) consists of n haploid lines (subpopulations) which reproduce asexually and each of which is subject to random extinction and subsequent replacement, it is shown that, at equilibrium in which mutational production of new alleles and their random extinction balance each other, the genetic diversity (1 minus the sum of squares of allelic frequencies) is given by $2N_e v/(1 + 2N_e v)$, where**

$$N_e = \tilde{N} + n/(2\lambda) + n\tilde{N}v/\lambda,$$

in which $\tilde{N}$ is the harmonic mean of the population size per line, n is the number of lines (assumed to be large), λ is the rate of line extinction, and v is the mutation rate (assuming the infinite neutral allele model). In a diploid population (species) consisting of n colonies, if migration takes place between colonies at the rate m (the island model) in addition to extinction and recolonization of colonies, it is shown that effective population size is

$$N_e = \tilde{N} + n/[4(v + \lambda + m)] + n\tilde{N}(v + m)/(v + \lambda + m).$$

If the rate of colony extinction (λ) is much larger than the migration rate of individuals, the effective population size is greatly reduced compared with the case in which no colony extinctions occur (in which case $N_e = n\tilde{N}$). The stepping-stone type of recolonization scheme is also considered. Bearing of these results on the interpretation of the level of genetic variability at the enzyme level observed in natural populations is discussed from the standpoint of the neutral mutation-random drift hypothesis.

The concept of effective population size, introduced by Wright (1), has played a fundamental role in treating the process of random gene frequency drift in finite populations. Useful formulae have been derived by him and others (2–6) to compute the effective sizes for various situations such as unequal numbers of males and females, different parents contributing widely different numbers of young, the population size fluctuating from time to time, and overlapping generations (see refs. 7–9 for reviews).

It is known that most species in nature have subdivided population structure, and extinction and recolonization of local populations may occur rather frequently in some groups of organisms such as insects (see refs. 10 and 11). This will greatly reduce the effective population size of the species.

Wright (12) pointed out that if local populations are liable to frequent extinction with restoration from the progeny of a few stray immigrants, the species may pass repeatedly through extremely reduced state of effective population size even though the species include at all times "countless millions of individuals in its range as a whole." He suggested that mutations such as reciprocal translocations that are very strongly selected against until half-fixed may require some such mechanism to become established.

A pioneering study of the effect of local extinction and recolonization of subpopulations on genetic variability of the species was made by Slatkin (11) using two models termed "propagule pool" and "migration pool." By pursuing the same problem further, we obtained some results which we report in this paper. Our model is similar to Slatkin's propagule pool model, but we use both "island model" (1) and "stepping-stone model" (13) of population structure. We shall also discuss some implication of the results for our interpretation of the amount of genetic variability observed in natural populations in the light of the neutral mutation-random drift hypothesis [the neutral theory, for short (14, 15)].

Random replacement of haploid lines (island model)

Let us consider a population (species) of haploid organisms consisting of a finite number, n, of subpopulations which we refer to as lines. All the results in this section, however, hold equally well if the term "line" is replaced by "local colony" or "deme." Let us assume that each line is subject to extinction with rate λ and that whenever a line is extinct it is immediately replaced by a line derived from individuals chosen from a single line in the population. In this section, we assume that, whenever extinction occurs, every existing line has an equal chance of becoming a donor, so that the geographical distance is irrelevant in the replacement (island model). We present the treatment using the stepping-stone model (where donors are chosen from neighboring colonies) in the next section. Throughout this paper, we assume the infinite allele model of Kimura and Crow (16)—that is, we assume that whenever a mutation occurs at a locus it represents a new, not a preexisting, allele.

Let P_t be the probability that two randomly chosen homologous genes from a single line at time t are identical by descent and therefore identical in allelic states. Similarly, let Q_t be the probability of two randomly chosen genes, one each from two different lines at time t, being identical. Consider the species as a whole and ask what is the probability that two randomly chosen lines have descended from a single line a short time (Δt) ago. Since the probability of extinction of a line during Δt is $\lambda\Delta t$, and since there are n lines as a whole, the probability of two randomly chosen lines at time t having descended from a single line Δt ago is $2\lambda\Delta t/(n - 1)$. The factor 2 in the numerator comes from the consideration that, when two lines (tentatively called the first and the second lines) happen to have descended from a single colony Δt ago, there are two possibilities—that is, either the first line is the donor (case A in Fig. 1) or the first line is the recipient (case B in Fig. 1). The probability that two lines at time $t + \Delta t$ have descended from two lines which are separate at time t is therefore $1 - 2\lambda\Delta t/(n - 1)$.

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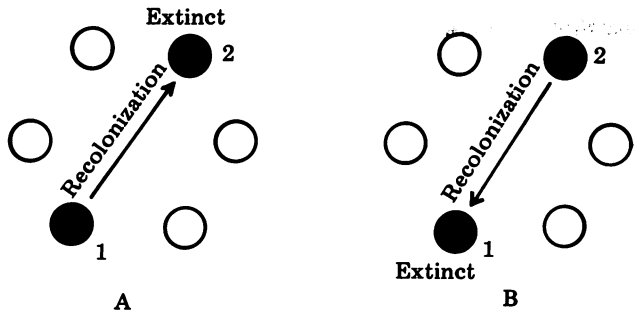

FIG. 1. Diagram illustrating extinction and recolonization for the case $n = 6$.

Let v be the mutation rate per haploid individual per generation, then we have

$$Q_{t+\Delta t} = (1 - v\Delta t)^2 \left\{\left(1 - \frac{2\lambda\Delta t}{n-1}\right) Q_t + \frac{2\lambda\Delta t}{n-1} P_t + o(\Delta t)\right\} \quad [1]$$

where $o(\Delta t)$ stands for terms of higher order than Δt. Note that $(1 - v\Delta t)^2$, or $(1 - 2v\Delta t)$ if we neglect $o(\Delta t)$, represents the probability that no mutations occur during the time interval Δt in two lines. An important assumption made in deriving Eq. 1 is that there is no exchange of individuals between lines. In other words, there is no exchange of genetic material (recombination) between asexual lines. If "lines" represent local colonies, within which random matings occur, this means no migration between colonies.

At equilibrium in which the identity coefficients remain constant with time so that $Q_{t+\Delta t} = Q_t$ and $P_{t+\Delta t} = P_t$, writing the equilibrium values of P_t and Q_t as P and Q, we get from Eq. 1,

$$-\left(2v + \frac{2\lambda}{n-1}\right) Q + \frac{2\lambda}{n-1} P = 0, \quad [2]$$

where we neglect terms of higher order than Δt. Thus, we obtain

$$Q/P = \frac{1}{1 + (n-1)v/\lambda}. \quad [3]$$

An analogous formula giving the relationship between two identity coefficients—that is, identity coefficients of gene members between and within chromosomes—was obtained by Ohta (17) in her theoretical study on genetic variation in a multigene family.

In order to derive a formula for P_t, let N_t (>0) be the effective population size of a single line at time t. Consider random sampling of individuals within the line, still assuming no immigration of individuals from other lines. Then, we have

$$P_{t+\Delta t} = (1 - 2v\Delta t)\left\{\left(1 - \frac{\Delta t}{N_t}\right) P_t + \frac{\Delta t}{N_t}\right\}. \quad [4]$$

This is a continuous generation analogue of a more familiar expression

$$P_{t+1} = (1 - 2v)\left\{\left(1 - \frac{1}{N_t}\right) P_t + \frac{1}{N_t}\right\}, \quad [5]$$

which holds when generations are discrete [i.e., $t = 0, 1, 2, \ldots$ (see ref. 7, page 323)]. From Eq. 4, neglecting terms involving $(\Delta t)^2$ and letting $\Delta P_t = P_{t+\Delta t} - P_t$, and substituting dP_t/dt for $\Delta P_t/\Delta t$, we obtain

$$\frac{dP_t}{dt} = -\left(2v + \frac{1}{N_t}\right) P_t + \frac{1}{N_t}. \quad [6]$$

Let $h_t = 1 - P_t$; then h_t gives the probability that two randomly chosen homologous genes within a line are distinct in allelic states. From Eq. 6, we have

$$\frac{dh_t}{dt} = 2v - \left(2v + \frac{1}{N_t}\right) h_t. \quad [7]$$

This can be integrated to give

$$h_t = h_0 \exp\left\{-2vt - \int_0^t \frac{d\xi}{N_\xi}\right\} + 2v \int_0^t \exp\left\{-2v(t-\theta) - \int_\theta^t \frac{d\xi}{N_\xi}\right\} d\theta. \quad [8]$$

Also, in Eq. 6, if we take expectations over all generations and if we assume (as an approximation) that the harmonic mean of N_t and the arithmetic mean of P_t are independent, we get

$$-(2v + 1/\tilde{N})P + 1/\tilde{N} = 0,$$

where $\tilde{N}$ is the harmonic mean of N_t and P is the average probability at equilibrium of two randomly chosen genes within a line being identical. This leads to

$$P = \frac{1}{1 + 2\tilde{N}v}. \quad [9]$$

Substituting this in Eq. 3, we get

$$Q = \frac{1}{(1 + 2\tilde{N}v)[1 + (n-1)v/\lambda]}. \quad [10]$$

Let $\overline{H}_0$ be the probability of two homologous genes randomly extracted from the whole population being identical. Then,

$$\overline{H}_0 = (1 - 1/n)Q + (1/n)P \quad [11]$$

so that we obtain

$$\overline{H}_0 = \frac{1 + (n-1)k/n}{1 + (n-1)k} \cdot \frac{1}{1 + 2\tilde{N}v}, \quad [12]$$

where $k = v/\lambda$. The effective number of alleles, n_e, as defined by Kimura and Crow (16) is $1/\overline{H}_0$. If n is large but k is much smaller than unity, we have $n_e \approx (1 + nk)(1 + 2\tilde{N}v)$. This may be compared with the situation in which all the individuals in the population are panmictic rather than grouped into isolated lines which are subject to extinction and replacement. In such a situation $n_e = 1 + 2n\tilde{N}v$.

More generally, if N_e is the effective size of a haploid population, then $n_e = 1 + 2N_e v$. Thus, equating this with $1/\overline{H}_0$ where $\overline{H}_0$ is given by Eq. 12, and assuming $n \gg 1$ and $k \ll 1$, we obtain $1 + 2N_e v = (1 + nk)(1 + 2\tilde{N}v)$ or

$$N_e = \tilde{N} + n/(2\lambda) + n\tilde{N}v/\lambda. \quad [13]$$

Similarly, for a diploid population consisting of a large number, n, of local colonies each with the effective size $\tilde{N}$, if exchange of individuals between colonies is extremely rare and if extinction and recolonization occur frequently, $n_e = (1 + nk)(1 + 4\tilde{N}v)$. Equating this with $1 + 4N_e v$, we obtain

$$N_e = \tilde{N} + n/(4\lambda) + n\tilde{N}v/\lambda. \quad [14]$$

Note that this is much smaller than the effective size of a corresponding population which is completely panmictic, in which case we have $N_e = n\tilde{N}$.

Stepping-stone model with local extinction and recolonization

We consider a one-dimensional stepping-stone model with n subpopulations arranged on a circle. Because of geographical structure, we refer to subpopulations as "colonies," although the term "lines" could still be used for them. We assume that

every existing colony is subject to extinction with rate λ per generation and that, whenever extinction of a colony occurs, it is replaced by individuals from either one of two adjacent colonies.

Let $g_{k,t}$ be the probability that two different colonies which are k steps apart do not share a common ancestor during the past t generations—that is, they are kept separate at least for the last t generations. In what follows, although we treat t as a continuous variable, it is convenient to measure time required for one generation as the unit. Then

$$g_{k,t+\Delta t} = (1 - 2\lambda\Delta t)g_{k,t} + \lambda\Delta t(g_{k-1,t} + g_{k+1,t}) + o(\Delta t). \quad [15]$$

Neglecting the terms $o(\Delta t)$ and substituting $dg_{k,t}/dt$ for $\Delta g_{k,t}/\Delta t$ where $\Delta g_{k,t} = g_{k,t+\Delta t} - g_{k,t}$, we obtain the following set of differential equations:

$$\frac{dg_{k,t}}{dt} = \lambda(g_{k-1,t} - 2g_{k,t} + g_{k+1,t}), \quad [16]$$

where $k = 1, 2, \ldots, n-1$, and

$$g_{0,t} = g_{n,t} = 0.$$

The solution of Eq. 16 which satisfies the initial condition $g_{k,0} = 1$ for $k = 1, 2, \ldots, n-1$ is as follows:

$$g_{k,t} = \frac{2}{n}\sum_{i=1}^{n-1} c_i e^{-2\lambda(1-\cos\frac{\pi i}{n})t}\sin\frac{k\pi i}{n}, \quad [17]$$

where

$$c_i = \sum_{k=1}^{n-1}\sin\frac{k\pi i}{n}.$$

Because $1 - g_{k,t}$ is the probability of two colonies that are k steps apart sharing a common ancestral colony some time during the past t generations, $d(1 - g_{k,t})/dt$ or $-dg_{k,t}/dt$ represents the probability density that these two colonies are derived from a common colony t generations back. Thus, the probability Q_k of two genes chosen from colonies which are geographically k steps apart being identical is given by

$$Q_k = -P\int_0^\infty e^{-2vt}\frac{dg_{k,t}}{dt}dt,$$

where e^{-2vt} represents the probability of two gene lineages remaining identical in allelic states after they diverged t generations ago. Noting Eq. 17, we obtain

$$Q_k = \frac{2P}{n}\sum_{i=1}^{n-1}\frac{c_i\sin(k\pi i/n)}{1 + v/\{\lambda[1 - \cos(\pi i/n)]\}}. \quad [18]$$

Then, the average probability of identity for two homologous genes each chosen randomly from two different colonies is

$$Q = \frac{2P}{n(n-1)}\sum_{i=1}^{n-1}\frac{{c_i}^2}{1 + v/\{\lambda[1 - \cos(\pi i/n)]\}}. \quad [19]$$

This corresponds to Eq. 3 in the island model.

Effects of migration

In the preceding analyses, we assumed that there is no migration (equal exchange of individuals) among different subpopulations. Such an assumption is realistic if local extinction and recolonization occur much more frequently than exchange of individuals between existing subpopulations. It is obviously desirable to extend these models to allow migration.

We consider an island model with the entire population consisting of n haploid colonies and assume that migrations among different colonies occur at a constant rate. Thus, every colony receives a fraction $m\Delta t$ of individuals from the entire population during a short time interval Δt. Using the same notations as before, we obtain

$$P_{t+\Delta t} = (1 - v\Delta t)^2\left\{(1 - m\Delta t)^2\left[P_t + \frac{1 - P_t}{N_t}\Delta t\right] + 2m\Delta t Q_t\right\} + o(\Delta t) \quad [20]$$

and

$$Q_{t+\Delta t} = (1 - v\Delta t)^2(1 - \lambda\Delta t)^2(1 - m\Delta t)^2 Q_t + 2(\lambda + m)\Delta t\left(\frac{1}{n}P_t + \frac{n-1}{n}Q_t\right) + o(\Delta t), \quad [21]$$

where P_t and Q_t are the identity probabilities within and between lines, and v, m, λ, N_t, and n are, respectively, the mutation rate, the migration rate, the colony extinction rate, the colony size, and the number of colonies.

From these equations we get

$$dP_t/dt = -2(v + m)P_t + (1 - P_t)/N_t + 2mQ_t \quad [22]$$

and

$$dQ_t/dt = -2(v + \lambda + m)Q_t + 2(\lambda + m)\{P_t + (n-1)Q_t\}/n. \quad [23]$$

At equilibrium in which $dP_t/dt = 0$ and $dQ_t/dt = 0$, we get

$$P = 1/[1 + 2\tilde{N}v + 2n\tilde{N}mv/(nv + \lambda + m)] \quad [24]$$

and

$$Q = 1/\{(1 + 2\tilde{N}v)[1 + nv/(\lambda + m)] + 2n\tilde{N}mv/(\lambda + m)\} \quad [25]$$

so that

$$Q/P = 1/[1 + nv/(\lambda + m)]. \quad [26]$$

For $m = 0$ (no migration), Eqs. 24 and 25 reduce, respectively, to Eqs. 9 and 10 except that n in Eq. 25 has to be replaced by $n - 1$. This discrepancy arises because we ignored the difference between n and $n - 1$ in deriving equations in this section.

The probability of identity of two randomly chosen homologous genes from the whole population is $\bar{H}_0 = [P + (n-1)\cdot Q]/n$, and if we equate $1/\bar{H}_0$ with $1 + 2N_e v$, we get

$$N_e = \tilde{N} + n/[2(v + \lambda + m)] + n\tilde{N}(v + m)/(v + \lambda + m). \quad [27]$$

For a diploid population, the corresponding formula is

$$N_e = \tilde{N} + n/[4(v + \lambda + m)] + n\tilde{N}(v + m)/(v + \lambda + m). \quad [28]$$

Monte Carlo experiments

To test the validity of the above analyses, simulation experiments were carried out. An outline of the experiments is as follows. At the beginning, 10 lines each with 20 haploid individuals are assumed; and at the beginning, all the individuals have identical alleles. The first operation in each generation is to test if extinctions occur to the lines. For each line, a random number that is distributed uniformly in the interval (0, 1) is drawn, and this is compared with a given λ. If the drawn random number happens to be less than λ, that particular line is terminated and it is replaced by a certain number (N_0) of individuals randomly drawn from a single line which is chosen according to the model. For the island model, the donor line is chosen randomly from the remaining $n - 1$ lines. For the stepping-stone model the donor line is chosen from one of the two neighboring lines with equal probability. However, if the

drawn random number is greater than λ, that line remains unchanged. The second operation in the simulation is the production of mutation. For each gene a random number is drawn and it is compared with a given value of v. If the random number happens to be less than v, mutation to a new allele occurs. Otherwise, the gene remains unchanged. The third operation is to increase the line size. Every line which is less than 20 individuals is increased by 1. The last operation is random sampling of gametes to form individuals in the next generation within each line.

These four operations constitute one generation for each line, and this cycle is repeated for a large number of times. The first $2/v$ generations were discarded to eliminate initial effects, and then data for Q, P, and Q/P were taken at an interval of 10 generations. In Table 1, the averages of these quantities over 30 observations are presented, and they are compared with corresponding theoretical values. In these simulations rather high mutation and extinction rates and small population sizes were assumed to save computing time.

Discussion

From the above analyses, it is clear that, when local extinction and recolonization occur frequently, not only the effective size of the total population (species) is much reduced but also divergence of subpopulations is largely prevented. As an example, let us consider a haploid population (species) consisting of 100,000 lines ($n = 10^5$). Let us assume that each line starts from a single individual and, although it may grow into a line (subpopulation) comprising an immense number of individuals, it then becomes extinct on the average in 1000 generations ($\lambda = 10^{-3}$) with the result that its harmonic size is only $\tilde{N} = 100$. Let us also assume that mutation rate per generation is $v = 10^{-8}$. Then, from Eq. **13**, we get the effective size of the population of about 50 million—i.e., $N_e \approx 5 \times 10^7$.

The sum of squares of allelic frequencies for the total population is $\overline{H}_0 \approx 0.5$. This means that the genetic diversity (1 minus sum of squares of allelic frequencies) is only 50%. Yet, at any moment, this species may comprise an immense number, say 10^{20}, of individuals. From Eqs. **9** and **10**, we have $P \approx 1$, $Q \approx 0.5$, which means that genetic variability is almost entirely due to line differences. Such a situation most likely may be met by lower organisms which reproduce almost exclusively by asexual means and which can increase rapidly in number when conditions become favorable but then easily become extinct when conditions become unfavorable.

A remarkable example of this type of population structure is represented by *Escherichia coli* as revealed by recent studies by Levin (B. R. Levin, personal communication) and Selander and Levin (18). According to Levin (B. R. Levin, personal communication), "periodic selection" (i.e., appearance of a clone with a high fitness followed by its rapid expansion) occurs frequently, but gene exchange between clones through plasmid and phage-mediated mechanisms is extremely rare; its rate appears to be lower than the mutation rate. This is consistent with the finding by Selander and Levin (18), who surveyed electrophoretic variation at 20 enzyme loci in 109 clones of *E. coli* from natural populations, that the number of distinctive *E. coli* genotypes is rather limited; electrophoretically identical clones were obtained from unassociated hosts. They obtained an estimate of mean genetic diversity of 0.4718.

The genetic structure of *E. coli* population can most easily be understood by regarding it as a collection of asexual lines. Random sampling of such lines occurs frequently through periodic selection. We can think of each line being derived from a single individual (bacterium) in which a mutation that endows higher competitive ability happens to occur followed by rapid expansion of its progeny by asexual means to form countless individuals. Eventually such a line may become extinct to be replaced by a new "periodic" line. We may regard intestines of mammals as a sort of chemostat in which periodic selection goes on continuously. Thus, the effective size of *E. coli* is not really very large, contrary to the claim of Milkman (19) who considers that his observations on allozyme variation in *E. coli* (20, 21) are inconsistent with the neutral theory. It is now clear that Milkman's criticism against the neutral theory is not warranted, as pointed out by Levin (personal communication). In this respect, Nei (22) had a remarkable insight when he suggested in 1976 that the effective size of *E. coli* in the long evolutionary history must be much smaller than 10^{10}, contrary to Milkman's (19) claim that *E. coli* has been at a population size well over 10^{10} for at least 4×10^{10} generations. "This is because an *E. coli* colony rapidly grows under certain circumstances, while in other circumstances it easily becomes extinct" (22).

A similar criticism of the neutral theory of protein polymorphisms was made by Ayala *et al.* (23) on the ground that, in the neotropical fruit fly *Drosophila willistoni* which has immense population size (which they think has at least the ef-

Table 1. Comparisons of Monte Carlo simulation results (Sim.) with the theoretical expectations (Theo.)

			P		Q/P	
v	λ	$\tilde{N}$	Sim.	Theo.	Sim.	Theo.
			Island model			
0.05	0.1	10.4	0.599	0.510	0.154	0.182
0.02	0.1	10.4	0.759	0.706	0.295	0.357
0.01	0.1	10.4	0.872	0.828	0.507	0.526
0.001	0.1	10.4	0.987	0.980	0.853	0.917
0.002	0.05	13.2	0.958	0.951	0.735	0.735
0.005	0.05	12.6	0.907	0.888	0.566	0.526
			Stepping-stone model			
0.002	0.05	13.4	0.951	0.949	0.683	0.593
0.005	0.05	13.4	0.889	0.883	0.316	0.386
0.01	0.01	—	—	—	0.077	0.081
0.01	0.1	—	—	—	0.415	0.386

In these simulation experiments listed, the initial line size after extinction (N_0) is assumed to be 2. Letters v, λ, and $\tilde{N}$ denote mutation rate, extinction rate, and harmonic mean of the population size per line, respectively. Ten lines ($n = 10$) each with the maximum of 20 haploid individuals are assumed.

fective size $N_e = 10^9$, with geographical distribution encompassing several million square kilometers), the observed heterozygosity is roughly 18%. They pointed out that, even if we assume a very low neutral mutation rate such as $v = 10^{-7}$, we still have $4N_ev = 400$ and, from the neutral theory, the predicted heterozygosity should practically be 100%, contrary to their observation. In this case, however, if we assume that the rate of local extinction (λ) of subpopulations is much higher than that of equal exchange of individuals (m) between subpopulations, the effective size of the species N_e is much smaller than $n\tilde{N}$, the product of the number of colonies (n) and the effective size of individual colony ($\tilde{N}$). In fact, if m/λ is small, $N_e \approx n\tilde{N}(m/\lambda)$ from Eq. **28**. In *D. willistoni*, it is possible that the effective size is 2 orders of magnitude less than what Ayala *et al.* claim and that their criticism of the neutral theory is unwarranted.

It is known that the average heterozygosity among loci per individual in diverse species, including those with apparently immense population sizes, is mostly restricted to the range 0–20% and seldom exceeds 30% (24). This observation has been used repeatedly as evidence against the neutral theory (see ref. 25). It is likely that local extinction and recolonization of subpopulations occur commonly in many species having very large apparent population sizes, and effective population sizes are therefore greatly reduced. In conjunction with the model of effectively neutral mutations (26) in which selective constraint is incorporated, such a difficulty of the neutral theory seems to be resolved.

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