Genealogy of Neutral Genes and Spreading of Selected Mutations in a Geographically Structured Population

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ABSTRACT

In a geographically structured population, the interplay among gene migration, genetic drift and natural selection raises intriguing evolutionary problems, but the rigorous mathematical treatment is often very difficult. Therefore several approximate formulas were developed concerning the coalescence process of neutral genes and the fixation process of selected mutations in an island model, and their accuracy was examined by computer simulation. When migration is limited, the coalescence (or divergence) time for sampled neutral genes can be described by the convolution of exponential functions, as in a panmictic population, but it is determined mainly by migration rate and the number of demes from which the sample is taken. This time can be much longer than that in a panmictic population with the same number of breeding individuals. For a selected mutation, the spreading over the entire population was formulated as a birth and death process, in which the fixation probability within a deme plays a key role. With limited amounts of migration, even advantageous mutations take a large number of generations to spread. Furthermore, it is likely that these mutations which are temporarily fixed in some demes may be swamped out again by non-mutant immigrants from other demes unless selection is strong enough. These results are potentially useful for testing quantitatively various hypotheses that have been proposed for the origin of modern human populations.

IN this paper I attempt to provide a theoretical basis for understanding the origin of modern humans (*Homo sapiens*). The study of human paleontology appears always to revolve around this enigma. Although a variety of hypotheses have been put forward (*e.g.*, see SMITH and SPENCER 1987; LEWIN 1988; MELLARS and STRINGER 1989), they have one feature in common: based on fossil evidence the first demonstrable migration of *Homo erectus* from Africa to Europe, Asia and Australia took place 1.0–1.5 million years ago. What has been extensively debated is whether all living populations had a recent origin in the Late Pleistocene, some hundred thousand years ago, or whether they evolved in many different regions from local archaic populations of *H. erectus*. There are two extreme hypotheses, the candelabra and the Noah's Ark (HOWELLS 1976). The candelabra assumes no migration and parallel evolution of modern *H. sapiens* in several regional localities at the same time. The Noah's Ark, on the other hand, assumes the complete replacement of populations in the Old World by anatomically modern *H. sapiens* from Africa. There can be many possibilities between the two extremes. One such is a modified version of the candelabra, called the multiregional hypothesis (WOLPOFF, ZHI and THORNE 1987; WOLPOFF 1989), which allows continuous but presumably infrequent gene exchanges between different populations. In short, the existing hypotheses for the origin of modern *H. sapiens* differ essentially in the role and extent of migration which might have occurred during the Middle and Upper Pleistocene. The problem thus appears to be the one that can be quantified by population genetics. In this paper I shall derive several mathematical formulas which I believe are relevant to the problem.

The model of population structure used in this paper is WRIGHT's (1931) island model, except that the population consists of a finite number of demes or colonies (MARUYAMA 1970a; CROW and MARUYAMA 1971). In the first part, the ancestral relationships of neutral genes at a locus sampled from such a structured population is studied. The total coalescence time (or the time to an ancestral gene from which all in the sample are descended) is of particular interest in relation to intrapopulational gene genealogy inferred from DNA sequences (*e.g.*, CANN, STONEKING and WILSON 1987; SATTA and TAKAHATA 1990; HORAI 1991; VIGILANT *et al.* 1991). Recently, the study of coalescence in a subdivided population was initiated (TAKAHATA 1988) and the general mathematical framework is now available (NOTOHARA 1990). Yet, it appears very difficult to derive explicit solutions except for some special cases. It is therefore

important to develop appropriate approximation methods. Such an approach, as it turns out, leads to a simple but surprisingly accurate description of the ancestry of neutral genes in a structured population.

In the second part, the fixation process of a favorable mutation is studied. Of interest is the probability that a new mutation fixed in one deme will spread through the whole population and the time this requires. For such genes to be important in modern human evolution, they must spread within a reasonably short time period. Since the human population was to some extent structured, it is worth investigating how rapidly fixation can take place in a subdivided population. Although some indirect approaches to this problem was developed by SLATKIN (1981) (see also LANDE 1979; SLATKIN 1976), the present formulas seem to be in better agreement with simulation results.

COALESCENCE OF NEUTRAL GENES

The population considered here consists of L demes each of which has effective size N (WRIGHT 1931; MARUYAMA 1970a). There are NL diploid individuals in total. The per generation migration rate is denoted by m, and when emigration occurs from one deme, the $L-1$ remaining demes receive immigrants equally likely. The average fraction of immigrants in a recipient deme from a donor is $m/(L-1)$ every generation. Assume that n_i genes are sampled from the ith deme, but n_i may be 0 for some demes (no samples). The total numbers of demes and genes sampled are r ($r \leq L$) and $n = \sum_{i=1}^{L} n_i$. In this section, two situations, low and high migration limits, are treated separately.

Generations are measured backward in time, and accordingly evolutionary events are so described. Throughout this paper coalescence always refers to an event at which a pair of sampled genes trace back to the most recent common ancestral gene.

Low migration limit: When migration is limited, it is most likely that orthologous genes within each deme coalesce to or are descended from a common ancestor within the deme. It follows that as time goes back there must be a time (T_{ni}) at which all genes sampled from the ith deme are descended from a single ancestral gene that existed also in this deme (Figure 1). By definition, $T_{ni} = 0$ if only one gene is sampled from the ith deme ($n_i = 1$), and immediately before T_{ni} there was a single lineage. Denote by T_n the maximum value of T_{ni} among the sampled demes. Then, T_n generations ago, there were r distinct lineages of all sampled genes, each of which is represented singly in a deme. Such an ancestral lineage is called a singleton and r specifies the previous coalescence. A key assumption is that T_n is much shorter than the waiting time for a migration to occur. In fact, the inequality $4N \ll 1/m$ must hold for the low migration limit ($4Nm \ll 1$), since the expected coalescence time in an isolated deme is bounded by $4N$ (KINGMAN 1982) and the mean waiting time for a migration is $1/m$ (TAKAHATA 1988; NOTOHARA 1990): the coalescence and migration processes are decoupled.

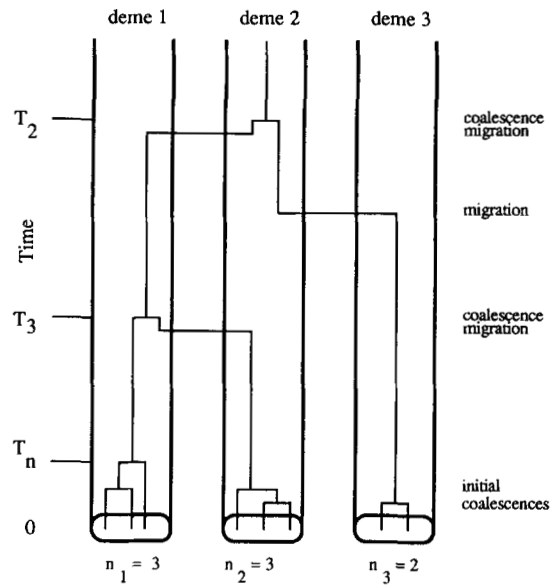

FIGURE 1.—Coalescence process in a structured population with limited migration. Horizontal lines crossing thick lines (deme boundaries) indicate migration events. T_n is the maximum value of coalescence times for n genes sampled from r ($\leq L$) demes without any migration. Immediately before T_n, there are r (= 3) ancestral lineages for the sample. In further tracing back their ancestors, migration is necessarily involved. If there are j ($2 \leq j \leq r$) genes singly represented in demes, two of them must come from the same deme in which they diverged. This waiting time T_j is given approximately by Equation 2 with $r = j$. When m (migration rate) is small, the waiting time for a coalescence within a deme can be ignored.

Once r singletons for the ancestry of sampled genes are achieved, it takes a long time for them to change their residing demes by gene migration and makes further coalescences possible. Denote by T_r the waiting time at which r singletons change their residence and a pair of r singletons came from the same deme for the first time (Figure 1). If this happens, the coalescence of these two lineages is assured in that deme, reducing the number of distinct ancestral lineages by one. Denote by K_r the number of migration events during T_r generations. The value of K_r is a random variable and the probability of $K_r = k$ ($k = 1, 2, \ldots$) follows a geometric distribution

$$P\{K_r = k\} = (1 - a_r)^{k-1} a_r \qquad (1)$$

in which $a_r = (r-1)/(L-1)$. Since a_r is the probability that a pair of genes come from the same deme by a single migration event, K_r is geometric with parameter a_r. As mentioned, the waiting time for migration of a gene is exponentially distributed with mean $1/m$. For r genes, the time until the kth migration occurs is gamma distributed with mean $1/rm$ (COX 1962; FELLER 1970). However, since not all migrations result in a pair of genes (a doublet), it is necessary to

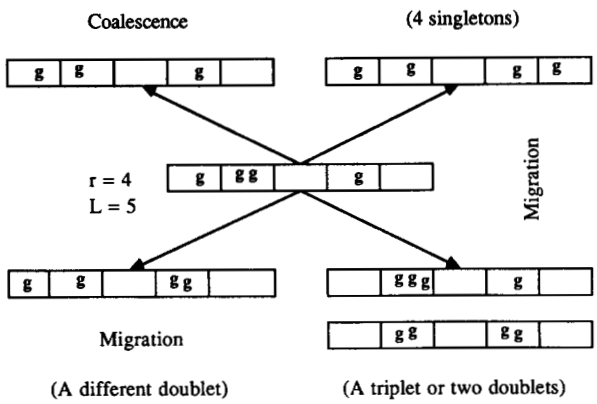

FIGURE 2.—An illustration of r gene lineages (center) indicated by g, two of which reside in a single deme (box) and the remaining $r - 2$ are represented singly in different demes. The four possible events by coalescence and migration are shown by arrows. In the text, P_c, P_s, P_d and P_o designate the probabilities of these events.

take the expectation of this gamma distributed time with respect to the distribution in Equation 1. This leads to the probability of $T_r = t$ being exponentially distributed with mean $(L - 1)/r(r - 1)m$, or

$$P\{T_r = t\} = \frac{r(r-1)m}{L-1} \exp\left\{-\frac{r(r-1)mt}{L-1}\right\}. \quad (2)$$

To confirm that the most likely ancestral pattern is their coalescence once a pair of ancestral genes reside in a deme, it may be instructive to evaluate the probabilities of (a) coalescence before further migration, P_c, and of migration, without coalescence, that leads to (b) a different distribution of r singletons, P_s, (c) a single pair in a different deme (a doublet), P_d, or (d) two doublets or one triplet, P_o (Figure 2). The results in TAKAHATA (1988) and NOTOHARA (1990) (see also TAKAHATA and SLATKIN 1990) show that

$$P_c = \frac{1/(2N)}{1/(2N) + rm} = \frac{1}{1 + rM}$$

in which $M = 2Nm$. Case (b) occurs when one of the two genes in the same deme migrates to one of the unoccupied demes $L - 1 - (r - 2)$ before coalescing. This probability becomes

$$P_s = \frac{2(L-r+1)}{r(L-1)} \frac{rM}{1+rM} = \frac{2(L-r+1)M}{(L-1)(1+rM)}.$$

In this case the process starts over (*i.e.*, there are again r singletons). Case (c) occurs when one of the two genes in the same deme migrates to form another pair with one of the $r - 2$ singletons or when one of the $r - 2$ singletons migrates to an unoccupied deme. This probability is given by

$$P_d = \left\{\frac{2(r-2)}{r(L-1)} + \frac{(r-2)(L-r+1)}{r(L-1)}\right\} \frac{rM}{1+rM}$$

$$= \frac{(r-2)(L-r+3)M}{(L-1)(1+rM)}.$$

The last possibility occurs when there is one deme in which three genes reside or when there are two demes each of which contains two genes. This probability becomes

$$P_o = \left\{\frac{(r-2)(r-3)}{r(L-1)} + \frac{(r-2)}{r(L-1)}\right\} \frac{rM}{1+rM}$$

$$= \frac{(r-2)^2 M}{(L-1)(1+rM)}.$$

Clearly, P_s, P_d, and P_o are of the order of M, and for them to be much smaller than 1, $rM \ll 1$, a sufficient condition for the low migration limit. Once again, the waiting time for a sample of size n to include $r - 1$ singletons is mainly determined by the slow migration process among the r singletons (*i.e.*, $T_n \ll T_r$). Time $T_r + T_n$ is therefore approximated by T_r in Equation 2.

As time goes back further in the past, the ancestral lineages are usually represented as singletons in the population. However, occasional migration occurs to form a pair of lineages in a single deme. This coalescence time is very short ($2N$ generations on average) relative to the time between successive migration events. By the same token, therefore, the waiting time for $r - 2$ singletons since the first establishment of $r - 1$ singletons is given by Equation 2 with r replaced by $r - 1$. In this way, the coalescence process continues backward in time until there remains only one common ancestral lineage for the sample. Thus the probability density of the total waiting time ($T = \sum_{j=2}^{r} T_j$) can be approximated by the convolution of $P\{T_j = t\}$ ($j = 2, 3, \ldots, r$). The explicit representation of this probability density was derived in TAKAHATA and NEI (1985), but in a different context. It is simpler to use the Laplace transform (Q_T) of T and the probability generating function (Q_K) of the total number of migration events ($K = \sum_{j=2}^{r} K_j$) during the whole process. They are

$$Q_T(z) = \int_0^\infty P\{T = t\} e^{-zt}\, dt = \prod_{j=2}^{r} \frac{j(j-1)m}{j(j-1)m + (L-1)z} \quad (3)$$

and

$$Q_K(z) = \sum_{k=1}^{\infty} P\{K = k\} z^k = \prod_{j=2}^{r} \frac{(j-1)z}{L - 1 - (L-j)z} \quad (4)$$

in which z stands for a dummy variable relevant to

each transformation. The mean and variance of T and K become

$$E\{T\} = \frac{L-1}{m}\left(1 - \frac{1}{r}\right),$$
$$V\{T\} = \left(\frac{L-1}{m}\right)^2 \sum_{j=2}^{r} \frac{1}{\{j(j-1)\}^2} \tag{5}$$

and

$$E\{K\} = (L-1)\sum_{j=1}^{r-1}\frac{1}{j},$$
$$V\{K\} = (L-1)^2 \sum_{j=1}^{r-1}\frac{1}{j^2} - E\{K\}. \tag{6}$$

In the above and subsequently, $E\{\ \}$ and $V\{\ \}$ stand for mean and variance.

It is clear that the number (r) of sampled demes is an important parameter to determine the total coalescence time T, *i.e.*, the total length of ancestry (see also TAKAHATA 1988). For example, if a sample is taken from a single deme (*e.g.*, $r = 1$), the time to the most recent common ancestor is so short that $E\{T\}$ is bounded by $4N$ generations, which is $E\{T_n\}$. If, on the other hand, a sample includes two different demes ($r = 2$), T can be very long, depending on the extent of gene migration. Note, however, that further increasing the number of sampled demes does not greatly increase T in an island model. The total number (L) of demes in the model also affects the above results, but T is very weakly dependent of L, if time is measured in units of $2NL$ or $4NL$ generations. This time unit is convenient to see to what extent population structure affects the coalescence process relative to that in a panmictic population with the same number of breeding individuals (NL).

High migration limit: When migration occurs frequently, there must be a number of gene migrations before sampled genes coalesce to a common ancestor. In this case, the ancestral lineages are expected to be distributed at random over L demes even before the first coalescence for the sample occurs. Therefore the distribution is obtained similarly as for the case where n "balls" are thrown at random in L "cells." What matters is how n such balls are distributed in L cells, because the rate of the coalescence is in proportion to $H_n = \sum_{i=1}^{L} n_i(n_i - 1)/(4N)$ where n_i is the number of balls in the ith cell and $n = \sum_{i=1}^{L} n_i$ as before. The value of H_n is a random variable, but from the above argument, the expectation can immediately be computed from the multinomial distribution of $\{n_i\}$. That is $(n - 1)/4NL$, which, as expected, provides the same coalescent rate as in a panmictic population of size NL. Since migration occurs with rate $n \times m$, the expected probability of coalescence is

$$P_c = \frac{n(n-1)}{n(n-1) + 4NLnm} = \frac{n-1}{n-1+2LM}$$

while the probability of migration is

$$P_m = 1 - P_c = \frac{2LM}{n-1+2LM}.$$

Define a random variable K_n as the number of migration events until the first coalescence takes place in a sample of size n. The probability of $K_n = k$ is then given by the geometric distribution

$$P\{K_n = k\} = P_c P_m^k, \qquad (k = 0, 1, \ldots) \tag{7}$$

with the probability generating function

$$Q_n(z) = \frac{n-1}{n-1+2LM(1-z)}. \tag{8}$$

The first coalescence time T_n can be approximated by the exponential distribution with mean rate $n(n-1)/4NL$, *or*

$$P\{T_n = t\} = \frac{n(n-1)}{4NL}\exp\left\{-\frac{n(n-1)t}{4NL}\right\} \tag{9}$$

and the Laplace transform is

$$Q_n^*(z) = \frac{n(n-1)}{n(n-1) + 4NLz}. \tag{10}$$

Since the same arguments can be applied after the first coalescence or to T_i and K_i ($i = 2, 3, \ldots, n-1$), the distributions of $T = \sum_{i=2}^{n} T_i$ and $K = \sum_{i=2}^{n} K_i$ can be found in the same manner as that for the low migration limit, but of importance here is the coalescence process.

Note in the above that it does not matter how the initial sample is taken from the demes, and the initial sample size n does not greatly change the distributions of T and K. These can be seen from their means and variances, which are given by

$$E\{T\} = 4NL\left(1 - \frac{1}{n}\right), \quad E\{K\} = 2LM\sum_{i=1}^{n-1}\frac{1}{i}, \tag{11}$$

and

$$V\{T\} = (4NL)^2 \sum_{i=2}^{n} \frac{1}{\{i(i-1)\}^2},$$
$$V\{K\} = E\{K\} + (2LM)^2 \sum_{i=1}^{n-1}\frac{1}{i^2}. \tag{12}$$

There is no r dependence in Equations 11 and 12 in sharp contrast to the low migration limit.

Table 1 compares Equations 5, 6, 11 and 12 with simulation results, showing their excellent agreement for the range of $2M = 4Nm \leq 0.1$ or ≥ 10 (see also

TABLE 1

Theoretical and simulation results on the mean and standard deviation of the coalescence time (T) and the number of migration events (K) in an island model of L demes

$M = 2Nm$		Case A		Case B	
		T	K	T	K
0.0001	Sim	4773 ± 2681	219 ± 62	3901 ± 2582	103 ± 57
	Exp	4802 ± 2638	220 ± 61	3920 ± 2626	102 ± 57
0.0005	Sim	960 ± 534	220 ± 61	774 ± 526	102 ± 57
	Exp	960 ± 528	220 ± 61	784 ± 525	102 ± 57
0.005	Sim	97 ± 53	221 ± 61	79 ± 54	105 ± 59
	Exp	96 ± 53	220 ± 61	78 ± 53	102 ± 57
0.05	Sim	10 ± 5.8	241 ± 67	8.9 ± 5.7	108 ± 59
	Exp	9.6 ± 5.3	220 ± 61	7.8 ± 5.3	102 ± 57
5	Sim	1.0 ± 0.6	2523 ± 713	1.0 ± 0.6	2330 ± 710
	Exp	1.0 ± 0.5	2234 ± 636	1.0 ± 0.5	2234 ± 636
10	Sim	1.0 ± 0.6	4803 ± 1349	1.0 ± 0.6	4589 ± 1340
	Exp	1.0 ± 0.5	4378 ± 1270	1.0 ± 0.5	4378 ± 1270

The mean ± standard deviation of T are measured in units of $4NL$ generations and similarly those of K are given in column K. In both case A and B, $L = 50$ and n (the sample size) = 50. The initial configuration is, however, different: there are 50 singletons ($r = 50$) in case A while there are only five such demes ($r = 5$), each containing 10 sampled genes in case B. Each simulation result (Sim) is obtained by a method similar to that described in TAKAHATA (1988): the number of replicates is 5000. Theoretical expectations (Exp) are based on Equations 5 and 6 for $4Nm \leq 0.1$ and Equations 11 and 12 for $4Nm \geq 10$.

Figure 3). Figure 3 further suggests that, for intermediate values of M, a simple interpolation for the mean coalescence time

$$E\{T\} = \frac{(r-1)(L-1)}{rm} + 4NL\left(1 - \frac{1}{n}\right) \quad (13)$$

or

$$\frac{E\{T\}}{4NL} = \frac{(r-1)(L-1)}{2rLM} + 1 - \frac{1}{n}$$

can make a reasonably accurate prediction. The relevance of Equation 13 to the global effective population size (*e.g.*, EWENS 1979) is discussed elsewhere. To show effects of a limited migration rate on the total coalescence time, a histogram of T is presented in Figure 4, which was obtained by computer simulation. The shape is similar to that of the distribution of fixation time (see Figure 1 in KIMURA 1970), but the time scale of the histogram is enlarged greatly as expected from Equations 3 and 5.

SPREADING OF SELECTED MUTATIONS

Let us begin this section by recalling the mean fixation time (T_s) of an advantageous mutation when it appears singly in a panmictic population of size N and it is subjected to genic selection with selection coefficient s. The approximate formula of $E\{T_s\}$ is given by

$$E\{T_s\} = \frac{2}{s}\log(2N) \quad (14)$$

for large Ns (EWENS 1979; NEI 1987; TAKAHATA 1991; see also KIMURA and OHTA 1969). The variance of T_s is 0 under the approximation which leads to Equation 14. The dependence of $E\{T_s\}$ on N is very weak, and the process takes only some hundreds of generations if s is a few percent. For simplicity, first assume that fixation in each deme occurs rapidly and almost surely. Under this assumption, each deme is fixed most of the time for either mutant or non-mutant genes, so that each deme can be designated by qualifiers, mutant and non-mutant. Subsequently, the possibility that even advantageous mutations are lost by genetic drift and migration will be taken into account.

Approximation by a birth process: Of interest is the probability that a mutant gene already fixed in one deme spreads over the entire population and the time this requires. The establishment of a mutant gene in the first deme is a different problem. In such a case, not only migration and genetic drift but also mutation plays an important role. For instance, the age of an advantageous allele in a panmictic population is exponentially distributed with mean $1/8Nsv$ (TAKAHATA 1991) where v is the per generation mutation rate under the infinitely many allele model of mutations (KIMURA and CROW 1964) and $Ns \gg 1$ is assumed. When v is small, the age of allele can of course be much longer than the mean fixation time in Equation 14.

Now suppose that at a given generation, there are i mutant and $L - i$ non-mutant demes ($i = 1, 2, \ldots, L - 1$). Under this circumstance, each of the mutant demes receives a fraction of $(L - i)m/(L - 1)$ non-mutant immigrants while each of the non-mutant demes receives a fraction of $im/(L - 1)$ mutant immi-

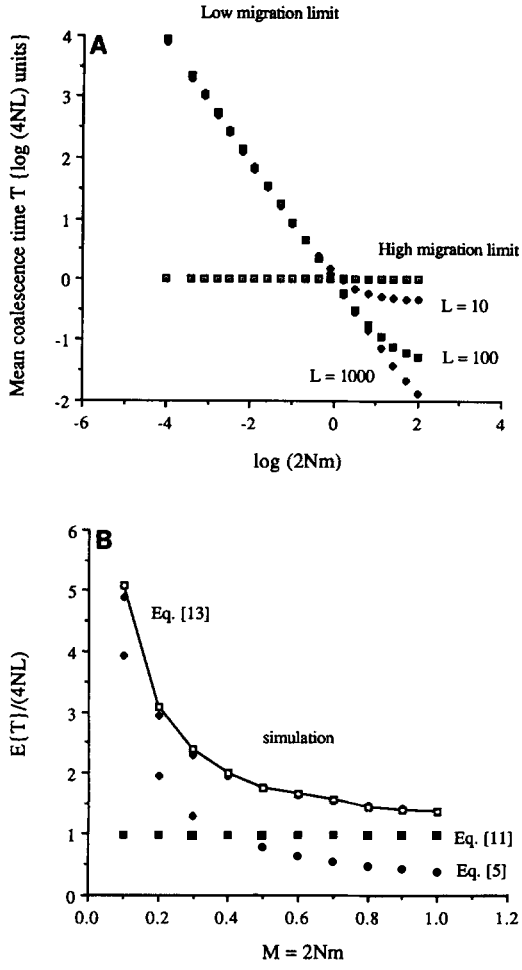

FIGURE 3.—(A) Mean coalescence time $E\{T\}$ of neutral genes sampled from r demes for a wide range of $M = 2Nm$. There are L demes in the population. The ordinate is $\log_{10}[E\{T\}/(4NL)]$ obtained from Equation 5 and the abscissa is $\log_{10} M$: the sample size is 100, 10 from each of ten demes (*i.e.*, $n = 100$ and $r = 10$). (B) Mean coalescence time $E\{T\}$ for $L = 50$ and M ranging from 0.1 to 1.0. The number of genes sampled from 5 demes is 50 (10 from each of five deme). The formula (5) (solid diamonds) underestimates the simulation result (connected open squares), but more accurate figures can be obtained from Equation 13. The number of replicates in the simulation is 5000.

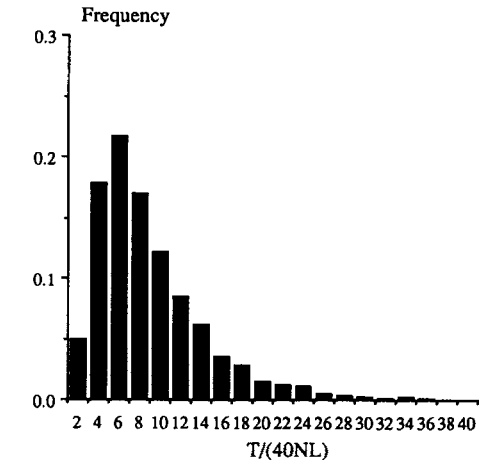

FIGURE 4.—Computer-generated histogram of the total coalescence time T in a finite island model of population structure ($L = 50$, $n_i = 10$ for 5 demes and $4Nm = 0.01$). The number of replicates is 5000. The mean and standard deviation of T in this simulation are 79.4 and 54.3 in units of $4NL$ generations. Note that the abscissa is measured in units of $40NL$ generations.

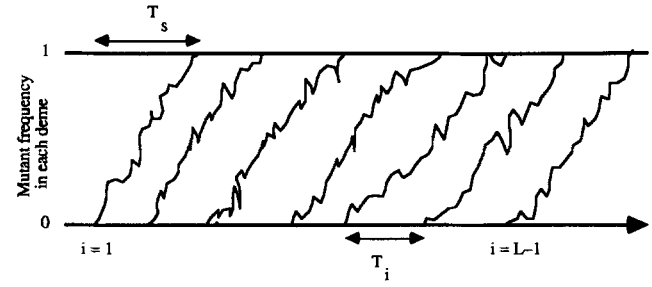

FIGURE 5.—Schematic representation of the fixation process in an island model with L demes. $E\{T_s\}$, $E\{T_i\}$, and $E\{T\} = \sum_{i=1}^{L-1} E\{T_i\}$ are given by Equations 14, 15 and 17, respectively. The total fixation time T_c is the sum of T and T_s. It should be noted that when selection is weak, T_s may be significantly long so that Equation 17 for the time T until the last non-mutant deme starts to be fixed underestimates the value of $T_c = T + T_s$.

grants. It is assumed that mutant demes never return to nonmutant ones, and in fact this assumption can be verified by an extremely small value of the extinction probability under the condition specified later. Thus once a deme becomes mutant, it remains in this state forever: the fixation process in each deme is irreversible so that the whole process can be treated as a pure birth process (*e.g.*, EWENS 1979). In contrast, a nonmutant deme receiving a small fraction of mutant immigrants does not necessarily have a high probability of fixing them. This is so particularly when migration rate is small, and the loss of mutant immigrants occurs rapidly. Hence, in addition to irreversibility, it is assumed that the chance of build-up of mutants solely due to immigration is small. When these assumptions are approximately met, the seemingly complicated process is greatly simplified mathematically.

Consider a particular deme consisting of a fraction of $im/(L-1)$ mutant and $1 - im/(L-1)$ non-mutant genes. The fixation probability $u(x)$ of a mutant gene in this deme is denoted by u_i when the initial frequency (x) is $im/(L-1)$, or $u_i = u(im/L - 1)$. Under the assumption of no build-up of immigrants, the probability that this deme does not become entirely mutant for t generations is given by $(1 - u_i)^t$. There are, however, $L - i$ non-mutant demes altogether, so the probability that none of them becomes mutant is $(1 - u_i)^{(L-i)t}$. Hence the probability that one or more non-mutant demes start to become mutant after t generations is given by

$$G_i(t) = (1 - u_i)^{(L-i)(t-1)} - (1 - u_i)^{(L-i)t}. \quad (15a)$$

Define a random variable T_i whose distribution is given by $G_i(t)$ (Figure 5). The T_i is the waiting time until one or more non-mutant demes go to fixation

by mutant genes that emigrated from the i mutant demes. In the above treatment, time is discrete. In a time-continuous approximation in which only one deme transition is allowed per unit-time with small values of u_i, the corresponding formula for T_i becomes an exponential function

$$G_i(t) \approx (L - i)u_i \exp\{-(L - i)u_i t\}. \quad (15b)$$

For simplicity, it is therefore assumed that formula (15a) gives essentially the waiting time distribution that only one non-mutant deme goes to fixation. In short, the model captured by Equations 15a and 15b is as follows. When there are $L - i$ non-mutant demes, one and only one of them begins to be replaced (fixed) by mutant immigrants with the waiting time T_i. This distribution is $G_i(t)$ with mean $\{1 - (1 - u_i)^{L-i}\}^{-1}$. When this happens, the number of mutant demes after T_s generations increases by one, and the process proceeds further. Therefore starting at state $i = 1$, the process ends up at $i = L - 1$ at which the last non-mutant deme starts to become fixed (Figure 5). The total time for the completion of this pure birth process is designated by $T = \sum_{i=1}^{L-1} T_i$ while the fixation time in the last non-mutant deme is T_s. It is immaterial whether $T_i > T_s$ or $T_i < T_s$.

It is easy to compute the moments of the total fixation time ($T_c = T + T_s$) in the entire population, since the distribution is given by the convolution of $G_i(t)$ for $i = 1, 2, \ldots, L - 1$ and the distribution of T_s. Unfortunately, however, the distribution of T_s is unsolved so that only the distribution of T is examined below. The probability generating function ($R(z)$) of T is given by the product of generating function $R_i(z)$ of T_i for $i = 1, 2, \ldots, L - 1$, or

$$R_i(z) = \sum_{t=1}^{\infty} G_i(t)z^t = \frac{z\{1 - (1 - u_i)^{L-i}\}}{1 - z(1 - u_i)^{L-i}}$$
$$R(z) = \prod_{i=1}^{L-1} R_i(z) = z^{L-1} \prod_{i=1}^{L-1} \frac{1 - (1 - u_i)^{L-i}}{1 - z(1 - u_i)^{L-i}}. \quad (16)$$

From Equation 16, the mean and variance of T become

$$E\{T\} = \sum_{i=1}^{L-1} \frac{1}{1 - (1 - u_i)^{L-i}} \quad (17)$$

and

$$V\{T\} = \sum_{i=1}^{L-1} \frac{(1 - u_i)^{L-i}}{\{1 - (1 - u_i)^{L-i}\}^2}. \quad (18)$$

As an example, consider the semidominant case where $u_i = \frac{4Nms'i}{L - 1}$ approximately ($s' = \frac{s}{2}$, see KIMURA 1962; MARUYAMA 1970b; CROW and KIMURA 1970). Then Equation 17 becomes $E\{T\} = \frac{L - 1}{2Nms'L} \sum_{i=1}^{L-1} \frac{1}{i} \approx \frac{L - 1}{2Nms'L} \{0.5771 + \log(L - 1)\}$. This mean fixation time is of course much shorter than that for neutral genes. Nonetheless, it is clear that for small values of m, it takes a large number of generations for an advantageous gene to become fixed in the whole population. Table 2 shows the mean and variance of T_c approximated by Equations 17, 18, $E\{T_s\} = -\frac{2}{s'} \log(m)$, and $V\{T_s\} = 0$ in comparisons of simulation results.

When migration occurs frequently, the mean fixation time in a panmictic population should provide an accurate figure. For the initial frequency of $1/L$ and the case of semidominance, $E\{T_c\} \approx E\{T_s\} = 2/s' \log(L)$ approximately (Table 2).

Approximation by a birth and death process: It may be necessary to extend the above analysis to the case where selection is relatively weak so that fixation of mutant genes in a deme is not necessarily assured. That is, there is a possibility that a deme once fixed by a mutant gene may be swamped out again by non-mutant immigrants from other demes. Such a process may be approximated by a birth and death process, provided that either "fixation" in one of the $L - i$ non-mutant demes or "extinction" in one of the i mutant demes can happen in a generation. SLATKIN (1981) considered a similar process under a general setting of population structure. Noticing the equivalence of the process to that in the haploid MORAN (1962) model, he used the formula of the mean fixation time obtained by the diffusion approximation. The equivalence is based on the assumption that the initial frequency of a mutant gene in a non-mutant deme is always $1/2N$, independent of m, L and the number of mutant demes (i). Unfortunately, however, this assumption may oversimplify the situation, because the initial frequency of a mutant gene depends on these parameter values and affects the fixation process greatly. A more accurate expression for the rate of fixation in the $L - i$ non-mutant demes can be written as

$$r_i = u\left(1 - \frac{(L - i)m}{L - 1}\right)^i \left[1 - \left\{1 - u\left(\frac{im}{L - 1}\right)\right\}^{L-i}\right],$$

since the first term on the right is the probability of no change in the i mutant demes and the second is the probability of transition in the $L - i$ non-mutant demes to mutant. Likewise, the rate of extinction in one of the i mutant demes can be given by

$$q_i = \left\{1 - u\left(\frac{im}{L - 1}\right)\right\}^{L-i} \left\{1 - u\left(1 - \frac{(L - i)m}{L - 1}\right)^i\right\}.$$

Thus the transition that either increases or decreases the number of mutant demes by one occurs with a waiting time whose distribution is exponential with mean rate $r_i + q_i$.

The ultimate fixation and extinction probabilities

TABLE 2

Theoretical (Exp) and simulation (Sim) results on the mean and standard deviations of fixation time of semidominant advantageous mutations

		m				
s		0.00001	0.0001	0.001	0.01	0.1
0.1	Sim	54,300 (±8,038)	5,754 (±874)	876 (±108)	300 (±15)	218 (±10)
	Exp	51,740 (±9,218)	5,544 (±923)	841 (±92)	308 (±9)	192 (±[a])
0.05	Sim	109,200 (±13,180)	11,450 (±1,910)	1,629 (±194)	549 (±36)	419 (±27)
	Exp	103,400 (±18,430)	11,040 (±1,847)	1,629 (±185)	534 (±18)	285 (±[a])
0.01	Sim	517,700 (±81,150)	53,270 (±9,022)	6,801 (±1,028)	2,440 (±335)	1,993 (±262)
	Exp	451,900 (±82,650)	47,960 (±7,959)	7,237 (±797)	2,337 (±80)	1,039 (±[a])

s, selection coefficient; h, the degree of dominance, and the per generation increment of mutant frequency x is given by $sx(1-x)\{h+(1-2h)x\}$. Equations 17 and 18 for $h = 0.5$ and the fixation probability $u(x) = \dfrac{1-\exp(-4Ns'x)}{1-\exp(-4Ns')}$ are used ($2s' = s$). $N = 100$ and $L = 100$. The simulation for each parameter set was carried out until the number of fixed cases reaches 100. During such repeats that the value of s was specified as small as 0.01, there were 20, 17, 10, and 6 cases of extinction for $m = 0.0001$, 0.001, 0.01, and 0.1, respectively, while no extinction occurred for $s = 0.05$ and 0.1.

[a] The variance formula (18) cannot predict accurate figures.

of a mutant gene which is initially fixed in one of L demes provide the condition for the validity of Equation 16. This computation is not as difficult as might be expected, since the matrix in the present birth and death process is a continuant (*i.e.*, tridiagonal) for which several useful formulas are available (*e.g.*, EWENS 1979). Let V_i be the fixation probability in the entire population when there are i demes fixed by mutant genes initially. Of main concern is the case of $i = 1$, V_1, since initially there is only one such deme in the present model, but the formula of V_i for any i ($1 \leq i \leq L-1$) is known. Define w_k as $w_0 = 1$ and

$$w_k = \frac{q_1 q_2 \cdots q_k}{r_1 r_2 \cdots r_k} \quad \text{for} \quad k > 0.$$

Then V_i becomes

$$V_i = \frac{\sum_{k=0}^{i-1} w_k}{\sum_{k=0}^{L-1} w_k}$$

and the extinction probability becomes $1 - V_i$. For $i = 1$, the formula reduces to

$$V_1 = \frac{1}{\sum_{k=0}^{L-1} w_k}. \tag{19}$$

In the case of genic selection, $u(x) = \dfrac{1-e^{-2Sx}}{1-e^{-2S}}$ in which $S = 2Ns$ so that for small values of $2Si(L-i)m$

$$r_i \approx \frac{2Si(L-i)m}{(L-1)(1-e^{-2S})},$$

and

$$q_i \approx \frac{2Si(L-i)me^{-2S}}{(L-1)(1-e^{-2S})}.$$

The ratio of q_i to r_i is thus e^{-2S} approximately and w_k becomes e^{-2Sk}. Substituting this value of w_k for V_i yields

$$V_i = \frac{1-e^{-2Si}}{1-e^{-2SL}}, \qquad (i = 1, 2, \ldots, L-1)$$

and hence

$$V_1 = \frac{1-e^{-2S}}{1-e^{-2SL}}. \tag{20}$$

Equation 20 is the same as the fixation probability in a panmictic population of size L when a mutant gene is favored by $2S$ and the initial frequency is $1/L$. If S is small, V_1 approaches $1/L$ as for a neutral mutation (KIMURA 1962). Although Equation 20 is independent of m, a more rigorous expression of V_i is not so simple and shows that it is actually an increasing function of m. It is intuitively clear that for given values of N and s, the more migration, the higher the fixation probability of a favorable mutant gene. In any case, the formula for V_1 specifies the extent of S in order for Equation 16 to be valid. Comparison of simulation results shows that for a wide range of Nm values,

Equation 16 is sufficiently accurate if $Ns \geqslant 5$ (Table 2). It is still accurate even if Ns is as small as 1, but if $Nm < 1$. Underestimates of $V\{T_c\}$ are mostly due to the assumption of $V\{T_s\} = 0$, where T is small relative to T_s.

Equation 20 or a more accurate expression of V_1 may also be used as a criterion for Wright's three-phase shifting balance theory to work (WRIGHT 1931; 1932; 1988). Roughly speaking, unless values of S for favorable genotypes are sufficiently large (*e.g.*, $S \geqslant 10$), they are likely to be lost by genetic drift and migration before they go to fixation. Hence the third phase of WRIGHT's theory appears to require a fairly strong protection of such genotypes. This is particularly so when L is large and m is small. Under such protection, small amounts of immigration can upgrade the fitness of recipient demes against undesirable effects of recombination on favorable gene combinations (CROW, ENGELS and DENNISTON 1990; CROW 1990).

Equations 16, 17 and 18 can be used even when there is dominance. Dominance has somewhat unexpected effects on T. When migration is frequent, $E\{T\}$ for $s = 0.1$ and semidominant case ($h = 0.5$) is shorter than that for either completely recessive ($h = 0$) or dominant ($h = 1$) case. For instance, numerical and simulation results show that $E\{T\} = 633$, 218, and 701 generations for $h = 0$, 0.5, and 1, respectively, when $m = 0.1$, $N = 100$ and $L = 100$. However, as m decreases, this trend becomes more conspicuous; when $m = 0.0001$ ($s = 0.1$), $E\{T\} = 20360$ for $h = 0$, 738 for $h = 0.5$ and 3383 for $h = 1$. The reason for this retardation effect of the degree of dominance h is that selection is relatively inefficient for rare recessive mutations and for abundant dominant ones (*cf.* KIMURA 1980).

Finally, it is useful to recall that the mean and variance of T and those conditioned on fixation can be derived also from the birth and death process. For example, the mean sojourn time of the process at state j, starting at i, is given by

$$E\{T_{ij}\} = \frac{1 - V_i}{w_{j-1}q_j} \sum_{k=0}^{j-1} w_k \quad \text{for} \quad j = 1, 2, \ldots, i$$

$$= \frac{V_i}{w_j r_j} \sum_{k=j}^{L-1} w_k \qquad \text{for} \quad j = i + 1, \ldots, L - 1.$$

Therefore the mean time starting at state i is given by $E\{T_i\} = \sum_{j=1}^{L-1} E\{T_{ij}\}$ and the variance by $V\{T_i\} = 2\sum_{j=1}^{L-1} E\{T_{ij}\}E\{T_j\} - E\{T_j\} - E\{T_i\}^2$, etc. (*e.g.*, EWENS 1979).

DISCUSSION

The above study for the island model provides an extreme case with respect to effects of population subdivision. If a stepping-stone model (KIMURA 1953) is more appropriate, some obvious modifications are required, but very similar approaches can be taken. One immediate consequence in such a highly structured population is that the number of demes becomes a more important parameter than in an island model [see HALDANE (1948); FISHER (1958); NAGYLAKI (1975, 1983); FELSENSTEIN (1975); SLATKIN and MARUYAMA (1975) and SLATKIN (1976) for studies on cline and isolation by distance]. This is intuitively clear since, other things being equal, both coalescence and spreading times must become much longer without long-range migrations. Notwithstanding such apparent differences in models of population structure, the present treatment is sufficient in the sence that if anything is unlikely in an island model, it is more unlikely in other highly structured populations. It is this conservatism that makes study of an island model valuable for testing various hypotheses for the origin of modern human populations.

In what follows, some implications of the formulas are discussed with a special reference to the human mitochondria (mt) DNA ancestry constructed by CANN, STONEKING and WILSON (1987), HORAI (1991) and VIGILANT *et al.* (1991). For mtDNA, it is necessary to modify the theory because of the differences in inheritance and ploidy. The modification is, however, straightforward by interpreting m as female migration rate and by replacing $2N$ by N_f (the number of breeding females in a generation). First, note that, when there is no migration ($m = 0$) as assumed in the candelabra hypothesis, Equations 3 and 5 cannot be used. However, if genes are sampled from demes that have long been isolated, the genealogy must reflect the mode of isolation. The exhaustive sampling of mtDNA from worldwide human populations failed to find such a shape as candelabra, and no pairs of gene lineages have lasted for one million years. Despite some uncertainty in the calibrated substitution rate in mtDNA, the deepest branch length appears to be as short as 200,000 years (CANN, STONEKING and WILSON 1987; HORAI 1991; VIGILANT *et al.* 1991). Therefore the mtDNA data are certainly inconsistent with the candelabra hypothesis.

For the present model of population structure to be able to account for such mtDNA data, one of the following two conditions must be met. The first is based on the assumption of $N_f m < 1$. In this case, the ancestry of mtDNA is mainly determined by rare migration events. It is then necessary that Equation 3 does not predict branch lengths longer than 200,000 years, or 10^4 generations if one generation amounts to 20 years. This requirement can be expressed roughly by $N_f L < L/m < 10^4$. The second condition is derived for the case of $N_f m > 1$ in which intensity of random genetic drift within demes is a main determinant of the length of ancestry. It is then necessary

that drift is so strong (small N_f) as to be $L/m < N_fL < 10^4$ (see Equations 9, 10 and 11). Hence, in either case, the total number of breeding females (N_fL) must be limited to $N_fL < 10^4$ and migration cannot be particularly infrequent, or $m/L > 10^{-4}$. It is interesting to note that KOCHER and WILSON (1991) estimated the value of N_fL as about 6,000 (see also NEI and GRAUR 1984). If this were the case during the Late Pleistocene, the mtDNA data become irrelevant either to the multiregional hypothesis or to the Noah's Ark hypothesis (the latter suggests literally that modern *H. sapiens* was founded by a small number of individuals or experienced a severe bottleneck): the mtDNA simply do not have any power to distinguish between them. But if $N_fL > 10^4$ turns out to be valid (KLEIN, GUTKNECHT and FISCHER 1990; TAKAHATA 1990), then the mtDNA data require a fairly severe bottleneck that took place around 200,000 years ago. Such an abrupt bottleneck changes the shape of gene genealogy, and in an extreme situation it looks like a star phylogeny rather than a random bifurcation tree. In any case, without more information about the size of the recent human population, it is inevitable to conclude that both the multiregional and Noah's Ark hypotheses are consistent with the mtDNA data (*cf.* STRINGER 1990). Detailed examination of nuclear DNA loci, including such extraordinary polymorphic loci as major histocompatibility complex, should be very informative in this respect (*e.g.*, KLEIN, GUTNECHT and FISCHER 1990; TAKAHATA 1990).

Estimating the value of N_fm or Nm is also an important task to understand the evolution of *H. sapiens*. STONEKING *et al.* (1990) used the F_{ST} statistic (measuring the genetic variation among different demes) and applied it to the New Guinea population. Their F_{ST} value was 0.31, leading to $N_fm = 1.1$ for the model of island population. A very similar estimate ($Nm = 2.3$) was obtained by using protein polymorphisms (NEI and ROYCHOUDHURY 1982) under neutrality (KIMURA 1968) and the assumption that the sex ratio is one and migration is sexually unbiased. These estimates imply that there has been enough migration that the human population has been nearly panmictic. One may therefore assert that this extent of gene flow is inconsistent with the multiregional hypothesis. A problem in this argument is that F_{ST} equilibrates rather rapidly (NEI, CHAKRAVARTI and TATENO 1977; CROW and AOKI 1984; TAKAHATA and NEI 1984). When mutation rate is negligibly small relative to migration rate, L is large and selection is absent, this can be shown from the explicit non-equilibrium solution of $F_{ST}(t)$:

$$F_{ST}(t) = \frac{1 - \exp\{-(2m + 1/N_f)t\}}{1 + 2N_fm}$$

with $F_{ST}(0) = 0$ initially. From $N_fm = 1.1$ and $N_fL < 10^4$, it is clear that $t = 10^4$ generations are sufficiently long for F_{ST} to reach its equilibrium value. In other words, it is unlikely that F_{ST} of neutral genes provides useful information about the population structure during the Middle and Upper Pleistocene. Nevertheless, the estimated value of $N_fm = 1.1$ or $Nm = 2.3$ suggests that racial differentiation, if it actually occurred during the Late Pleistocene [see NEI and LIVSHITS (1990) for review], must invoke local selection which could overcome the moderate level of gene flow revealed by protein and mtDNA polymorphisms. If on the other hand mutant genes, that might be responsible for the evolution of *H. sapiens*, were favored in any deme, they could spread over the entire population with high probability (see Equation 20 and SLATKIN 1981). However, the required time depends strongly on the interplay among various population parameters (Table 2), and if the multiregional hypothesis assumes a large number of demes and $Nm \leq 0.1$, it is unreasonable to think that even such favorable mutations could spread over the entire human population during the Pleistocene.

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