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Evolution

Evolution and maintenance of quantitative genetic variation by mutations

(founder populations/drift/equilibria/multiple alleles/additive effects)

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ABSTRACT **The genotypic variance within, σ_w^2, and between, σ_b^2, random mating populations and rates and times for convergence to equilibrium values from different founder populations are formulated for an additive genetic model with an arbitrary number of alleles k, number of loci m, population size N, and mutation rate u, with unequal mutation rates for alleles. As a base of reference, the additive variance σ_a^2 in an infinite equilibrium population is used. σ_a^2 increases as k increases and decreases with variation in the mutation rates. Both transitional and equilibrium values of the variance within populations could be expressed as $\sigma_w^2 = (1 - \theta)\sigma_a^2$, where θ is the coancestry with mutations of individuals within populations. Thus, rates of convergence and evolutionary times are a function of those for θ, which involves both N and u. When the founder population is fixed, very long times are required to obtain a perceptible increase in σ_w^2 and equilibrium values of σ_w^2 are very small when $4Nu \leq 10^{-1}$. The variance between populations can be expressed as $\sigma_b^2 = 2\theta\sigma_a^2$ when the founder population is an infinite equilibrium population, and as $\sigma_b^2 = 2(\theta - \varphi)\sigma_a^2$ when the founder population is fixed, where φ is a function only of u. In this latter case, rates of divergence, while affected by both N and u, are dominated by u and asymptotically a function of u only. With $u = 10^{-5}$, very long times (10^3 generations) are required for any perceptible divergence, even for $N = 1$–10. At equilibrium, most of the variance is between small populations and within very large populations. Migration increases the variance within populations and decreases the variance between populations.**

A theory for the evolution of quantitative characters when the only driving forces are drift and mutation is important as a basis for comparing the consequences of additional forces. There are also practical considerations for plant and animal breeding.

We formulate the genotypic variance within and between populations and the rates and times for convergence within populations and for divergence among populations from different founder populations, for an additive genetic model with an arbitrary number of alleles, number of loci, population size, and mutation rates. The effects of migration are also considered.

The results are different from most of those in the literature, which is reviewed later and compared.

Population, Quantitative, and Mutation Models

We envision independent replicate random mating (including selfing) monoecious diploid populations, each consisting of N individuals in each distinct generation, all stemming from the same founder population. Our purpose is to develop transitional and equilibrium values for genotypic components of variance for individuals within populations σ_w^2, among populations σ_b^2, and among independent individuals $\sigma_\tau^2 = \sigma_b^2 + \sigma_w^2$, for a quantitative character contributed to by genes, which are otherwise neutral, undergoing mutation.

Only additive effects of genes within and between loci are considered. Thus, we may treat a single locus and, except for linkage disequilibrium, add over loci. The genotypic value for a genotype with alleles A_i and A_j is $G_{ij} = x_i + x_j$ where the xs are considered to be from some distribution with mean zero and variance σ_x^2. The genotypic variance among individuals within populations is $\varepsilon G^2 - \varepsilon GG'$ where ε denotes expectation and G and G' are for a random pair of individuals in the same population. This is actually the difference between the variance of unrelated individuals $\varepsilon G^2 - (\varepsilon G)^2$ and the covariance of individuals in the same population, $\varepsilon GG' - (\varepsilon G)^2$. We expand the expectation $\varepsilon = \varepsilon_x\varepsilon_b\varepsilon_w$ to include the expectation ε_w within populations, ε_b over replicate populations, and ε_x with respect to the xs. Let $\mathring{p}_i$ be the expected frequency of allele A_i in gametes at reproduction within a population. Then, with random union of gametes as in our mating system $\varepsilon G^2 = \varepsilon_x\varepsilon_b \sum\sum_{ij} \mathring{p}_i\mathring{p}_j(x_i + x_j)^2 = \varepsilon_x\varepsilon_b [2\sum_i(\mathring{p}_i + \mathring{p}_i^2)\, x_i^2 + 2\sum\sum_{i\neq j} \mathring{p}_i\mathring{p}_j x_i x_j]$. Continuing the expectation for the xs $\varepsilon G^2 = \varepsilon_b\,(1 + \Sigma_i \mathring{p}_i^2)2\sigma_x^2$ since the xs have mean zero and are uncorrelated. For two random members in the population, the expectation is $\varepsilon GG' = \varepsilon_x\varepsilon_b \Sigma_i\Sigma_j \mathring{p}_i\mathring{p}_j\,(x_i + x_j)\,\Sigma_k\Sigma_l \mathring{p}_k\mathring{p}_l(x_k + x_l) = 4\varepsilon_b\Sigma_i \mathring{p}_i^2\sigma_x^2$, again making use of the lack of correlation of the xs. The genotypic variance within populations is then $\sigma_w^2 = (1 - Q)2\sigma_x^2$, where $Q = \varepsilon_b\Sigma_i \mathring{p}_i^2$ and the factor of 2 simply shows that the genotypic variance for diploids is twice the genic variance with only additive effects of genes.

The component of variance for differences among populations is the difference between the covariance of individuals within populations and that of individuals in distinct populations—i.e., $\sigma_b^2 = \varepsilon GG' - \varepsilon G_1G_2$, where G_1 and G_2 are in different replicate populations. If we substitute the expected gene frequency, $p_i = \varepsilon_b\mathring{p}_i$ for $\mathring{p}_i$ in $\varepsilon GG'$, we obtain $\varepsilon G_1G_2 = 4\Sigma_i p_i^2\sigma_x^2$ and letting $q = \Sigma_i p_i^2$, $\sigma_b^2 = 2(Q - q)2\sigma_x^2$ with a total variance of $\sigma_\tau^2 = \sigma_w^2 + \sigma_b^2 = (1 + Q - 2q)2\sigma_x^2$.

Mutation is of the form that a random gene mutates to the ith allele with probability v_i each generation, including no change in the state of the gene. The total mutation rate for the locus is $u = \Sigma_i v_i$, $i = 1, 2, \ldots, k$, for k alleles.

Background

Before incorporating mutation into the results, it is helpful to review the situation when the only forces operating are population size and mating system. Let the initial population be an infinite random mating population with additive variance $\sigma_a^2 = (1 - q)2\sigma_x^2$ for our model since $q = Q$ initially. The components of variance over time for a monoecious population (1, 2) are $\sigma_w^2 = (1 - \theta)\sigma_a^2$, $\sigma_b^2 = 2\theta\sigma_a^2$, $\sigma_\tau^2 = (1 + \theta)\sigma_a^2$, where θ is the coancestry coefficient between individuals in the same population and is the same as the inbreeding coefficient. For the tth generation of random mating in a monoecious population, $\theta_t = 1 - (1 - 1/2N)^t$. The additive vari-

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ance within populations as a proportion of the total is $\sigma_w^2/\sigma_\tau^2 = (1 - \theta)/(1 + \theta)$. However, of more interest is the variance maintained within finite populations relative to that for an infinite population, $\sigma_w^2/\sigma_a^2 = 1 - \theta$, and the relative variance among populations, $\sigma_b^2/\sigma_a^2 = 2\theta$. Wright (2) commented that these relationships also hold when a steady state has been reached with respect to mutation or migration.

Transitional and Equilibrium Results

We extend the probability θ of two random genes being identical by descent to include that neither gene has mutated, as did Malécot (3). For θ_{t+1} the probability that a random pair of genes descended from the same gene in the previous generation is $1/2N$ and from different genes is $1 - 1/2N$, but these are identical by descent with probability θ_t. The probability that neither gene has mutated is $(1 - u)^2$. Consequently, $\theta_{t+1} = (1 - u)^2[1/2N + (1 - 1/2N)\theta_t]$. At equilibrium, θ has a value of $\theta_* = \rho^2/2N(1 - \lambda)$; $\rho = 1 - u$, $\lambda = \rho^2\gamma$, $\gamma = 1 - 1/2N$, $1 - \theta_* = (1 - \rho^2)/(1 - \lambda)$. Before equilibrium, $\theta_t = \theta_* + (\theta_0 - \theta_*)\lambda^t$, where θ_0 is the initial value. For values of N and u often encountered in practice, good approximations are $\theta_* \cong 1/(1 + 4Nu)$, $\lambda \cong 1 - 2u - 1/2N \cong 1 - 1/2N\theta_*$.

The terms q and Q, the frequencies with which genes are alike between and within populations, respectively, were studied in detail (4). We briefly repeat the results essential to this study and develop the relationship between θ and Q.

The equilibrium frequency from mutation of the ith allele is $p_{i*} = v_i/u$ with a transitional value of $p_{it} = p_{i*}(1 - \rho^t) + p_{i0}\rho^t$, where p_{i0} is the initial frequency. The frequency with which genes from distinct replicate populations are alike is $q_t = \sum_i p_{it}^2$ and at equilibrium $q_* = \sum_i p_{i*}^2 = (1 + c^2)/k$, where c is the coefficient of variation of the mutation rates or of the p_*s. The transitional value of q can be put into the form

$$q_t = q_*(1 - \varphi_t) + q_0\varphi_t + (q_{*0} - q_*)2\rho^t(1 - \rho^t),$$

where $q_{*0} = \sum_i p_{i*}p_{i0}$ and $\varphi_t = \rho^{2t}$ is the probability that a random pair of genes from different populations have not mutated, $\varphi_* = 0$.

We develop $Q_t = \varepsilon_b\mathring{p}_{it}^2$ in a different manner and with none of the approximations used in ref. 4. The expected frequency, $\mathring{p}_i$, is expressed in terms of the actual frequency, $\hat{p}_i$, of the parents allowing for mutation, $\mathring{p}_{it+1} = \hat{p}_{it}(1 - u) + up_{i*}$ and $Q_{t+1} = \varepsilon_b\Sigma_i\mathring{p}_{it+1}^2 = \varepsilon_b\varepsilon_w\Sigma_i\hat{p}_{it}^2(1 - u)^2 + u^2\Sigma_i p_{i*}^2 + 2u(1 - u)\varepsilon_b\Sigma_i p_{i*}\hat{p}_{it}$. Pursuing expected values further $\varepsilon_w\Sigma_i\hat{p}_{it}^2 = \Sigma_i\mathring{p}_{it}^2 + \Sigma_i\mathring{p}_{it}(1 - \mathring{p}_{it})/2N = \Sigma_i\mathring{p}_{it}^2(1 - 1/2N) + 1/2N$ since $\mathring{p}_{it}(1 - \mathring{p}_{it})/2N$ is the variance of $\hat{p}_{it}$ from random sampling of $2N$ genes. Using $\varepsilon_b\hat{p}_{it} = p_{it}$, $\varepsilon_b\Sigma_i p_{i*}\hat{p}_{it} = q_* + (q_{*0} - q_*)\rho^t$. With these substitutions, $Q_{t+1} = Q_t\lambda + \rho^2/2N + (1 - \rho^2)q_* + 2u(1 - u)(q_{*0} - q_*)\rho^t$. At equilibrium, the rightmost term is zero and $Q_* = \rho^2/2N(1 - \lambda) + (1 - \rho^2)q_*/(1 - \lambda) \equiv \theta_* + (1 - \theta_*)q_*$, a feature overlooked in ref. 4. From the relationship $Q_t - Q_* = (Q_{t-1} - Q_*)\lambda + 2u(1 - u)(q_{*0} - q_*)\rho^{t-1}$ and utilizing $\Sigma_j \rho^j\lambda^{t-1-j} = (\rho^t - \lambda^t)/(\rho - \lambda)$, $j = 0, 1, \ldots, t - 1$, the solution to the difference equation is

$$Q_t = Q_* + (Q_0 - Q_*)\lambda^t + 2\rho(1 - \rho)(q_{*0} - q_*)(\rho^t - \lambda^t)/(\rho - \lambda).$$

Founder Populations

We shall consider different initial or founder populations. For all initial populations $q_0 = Q_0$. For an initial infinite equilibrium population, $q_0 = Q_0 = q_t = q_{*0} = q_*$, $\theta_0 = 0$; $\theta_t = \theta_*(1 - \lambda^t)$, $Q_t = q_* + \theta_*(1 - \lambda^t)(1 - q_*)$. Only Q and θ change with time. Consequently, $\sigma_{wt}^2 = (1 - Q_t)2\sigma_x^2 = (1 - \theta_t)\sigma_a^2$ and $\sigma_{bt}^2 = 2(Q_t - q_t)2\sigma_x^2 = 2\theta_t\sigma_a^2$, where $\sigma_a^2 = (1 - q_*)2\sigma_x^2$ is the additive variance in an infinite equilibrium population equivalent to the initial population. Thus, the components of variance over time in this situation may be phrased in terms of θ and σ_a^2.

When the initial population is fixed for one allele, the evolution of q and Q is complex with unequal mutation rates (4). We avoid this complexity by assuming that the initial population is fixed for allele i with probability p_{*i} and refer to this as a random fixed population. Then as an average over these initial fixed populations, or for equal mutation rates or for an infinite allele model, $q_0 = Q_0 = \theta_0 = 1$, $q_{*0} = q_*$; $q_t = q_* + (1 - q_*)\varphi_t$, $\theta_t = \theta_* + (1 - \theta_*)\lambda^t$, $Q_t = Q_* + (1 - Q_*)\lambda^t = q_* + (1 - q_*)\theta_t$. Consequently, the genetic variance components are $\sigma_{wt}^2 = (1 - \theta_t)\sigma_a^2$ and $\sigma_{bt}^2 = 2(\theta_t - \varphi_t)\sigma_a^2$. The component of variance within populations again involves only θ and σ_a^2, while that between populations involves φ in addition. If $N = \infty$, $\theta_t = \varphi_t$, $Q_t = q_t$ and $\sigma_{wt}^2 = (1 - \varphi_t)\sigma_a^2$, $\sigma_{bt}^2 = 0$.

Nei (5) assumed an initial finite equilibrium population with size equal to that of the replicate populations. More precisely, it is a random finite equilibrium population and expectations are taken over such initial populations. For these $q_0 = Q_0 = Q_t = Q_*$, $q_{*0} = q_*$, $\theta_0 = \theta_t = \theta_*$ and the only change is in q, $q_t = q_* + (Q_* - q_*)\varphi_t$. The component of genetic variance within populations remains the same, σ_{w*}^2, and that between populations, $\sigma_{bt}^2 = 2\theta_*(1 - \varphi_t)\sigma_a^2$, increases in response to mutations over time to that for equilibrium populations.

Effects of Multiple Alleles

The additive variance for a particular locus $\sigma_a^2 = [1 - (1 + c^2)/k]2\sigma_x^2$ increases as k increases to a maximum when $k = \infty$ and decreases as c^2 increases if k is finite. This latter effect can be substantial for few alleles. With mutation rates 10^{-5}, $10^{-5.5}$, 10^{-6}, $10^{-6.5}$ for four alleles $c^2 \cong 1.12$, and $1 - q_* = 0.47$, which is about 63% of that with equal mutation rates and about half of that for an infinite number of alleles. With mutation rates 10^{-5}, 10^{-6} for two alleles $1 - q_* = 0.17$.

The assumption that the effects are random with respect to the alleles may not be too far off when viewed over loci. Of course, σ_x^2 may vary among loci so that some loci with fewer alleles will have greater variance than others with more alleles. The number of alleles does not have to be very large, $k \geq 10$, for the infinite allele model to be a good approximation.

Multiple Loci and Linkage

For m loci the total variance within populations is $\sigma_W^2 = \Sigma_l\sigma_{wl}^2 = \Sigma_l(1 - \theta_l)\sigma_{al}^2$, $l = 1, \ldots, m$. If the mutation rate is the same at all loci, then $\theta_l = \theta$. If not, $\sigma_W^2 = (1 - \bar{\theta})\sigma_A^2$, $\bar{\theta} = \Sigma_l\theta_l\sigma_{al}^2/\sigma_A^2$ where $\Sigma_l\sigma_{al}^2 = \sigma_A^2$, the total additive variance in the infinite equilibrium population. Consequently, the total additive variance within populations is $1 - \bar{\theta}$ of that in the infinite equilibrium population.

For all equilibrium populations and for transient populations from an initial infinite equilibrium population, the component of variance among populations is $\sigma_B^2 = 2\Sigma_l\theta_l\sigma_{al}^2 = 2\bar{\theta}\sigma_A^2$. For transient populations from a finite equilibrium population, $\sigma_B^2 = 2\Sigma_l\theta_{*l}(1 - \varphi_l)\sigma_{al}^2 = 2\overline{\theta_*(1 - \varphi)}\sigma_A^2$, where the function $\overline{\theta_*(1 - \varphi)}$ is a complicated weighted average. For an initial random fixed population $\sigma_B^2 = 2\Sigma_l(\theta_l - \varphi_l)\sigma_{al}^2 = 2(\bar{\theta} - \bar{\varphi})\sigma_A^2$.

While mutations will lead to linkage disequilibrium, temporarily but for some time with tight linkage within a population, the average effect over pairs of loci or over populations will be of little consequence as long as mutational events at different loci are independent. It would take some unusual mutational structure to lead to covariances.

Variations in the Mating System

Selfing is included in the formulations by letting $N = 1$. Then, σ_w^2 is the genotypic variation among individuals from the same parent, σ_τ^2 is the genotypic variation among individuals from different initial parents, and $\sigma_b^2 = \sigma_\tau^2 - \sigma_w^2$. Since drift is almost entirely a function of the effective number N_e, we may substitute N_e for N to accommodate circumstances where the effective number is larger or smaller than the census number.

With separate sexes and no mutations, $\sigma_w^2 = (1 + F - 2\theta)\sigma_a^2$, $\sigma_b^2 = 2\theta\sigma_a^2$, $\sigma_\tau^2 = (1 + F)\sigma_a^2$, where F is the inbreeding coefficient. Thus, for exact results we would need to incorporate F into the development. However, with random mating, $\theta_t = F_{t+1}$, and with mutations, $\rho^2\theta_t = F_{t+1}$. Also, the greatest difference in θ_t and F_t occurs in the initial generations and for full sibbing, $N = 2$. Even then a reasonable approximation is obtained by letting $2N = 5$ in the monoecious formulations. Consequently, we may use $N_e = 4N_{em}N_{ef}/(N_{em} + N_{ef})$ where N_{em} and N_{ef} are the effective numbers for males and females, respectively (6, 7), and then substitute $2N_e + 1$ for $2N$ in the monoecious formulation for a good approximation.

The frequency, q, with which genes are alike between replicate populations is independent of the mating system.

Evolutionary Rates of Convergence and Divergence

The rate at which the variation within populations converges to the equilibrium state and the rate at which populations or lines diverge from each other are not necessarily the same, although they can be. We treat rates for a single locus with the understanding that an average value over loci is implied.

The rate of convergence or divergence is defined as the fraction of the distance to equilibrium that is accomplished in the transition from one generation to the next. The rate of convergence for θ is $(\theta_{t+1} - \theta_t)/(\theta_* - \theta_t) = 1 - \lambda \cong 2u + 1/2N \cong 1/2N\theta_*$. The rate is a constant, $1 - \lambda$, whether from an initial value of 1 or 0, and involves both the mutation rate and population size.

The rate of convergence of σ_w^2 is strictly a function of the transition rate of θ when the founder population is an infinite equilibrium population or a random fixed population. Consequently, the rate is $1 - \lambda$. When the founder population is a finite equilibrium population, there is no change in θ and σ_w^2, $\theta_t = \theta_*$, $\sigma_{wt}^2 = \sigma_{w*}^2$.

For the divergence among populations, measured by σ_b^2, the rates depend on the founder population. For an initial infinite equilibrium population the rate is again $1 - \lambda$, the same as for θ. If the initial population is a finite equilibrium population, the rate $1 - \rho^2 \cong 2u$ is the same as that for φ. It is also a constant but now strictly a function of the mutation rate. Recall that population size plays no role in the transition of q or φ, and in this case the transition of σ_b^2 is strictly a function of the transition of q or φ.

When the initial population is a random fixed population the transition of σ_b^2 involves both that in θ and φ, and the rate $1 - \rho^2 - \rho^2(1 - \theta_*)\gamma^t/2N[1 - (1 - \theta_*)\gamma^t]$ is not constant. Recall that $\gamma = 1 - 1/2N$ is a function of N. While population size affects the rate for some time, asymptotically the rate is $1 - \rho^2$ and just a function of the mutation rate. Lynch and Hill (8) also found the asymptotic rate to be independent of population size for a somewhat different model. The effect of finite population size on the early rates is to make them less than for mutation alone.

Evolutionary Time

The rate of approach to equilibrium in many cases is a constant $1 - \lambda$. In these cases, the number of generations required to progress a fraction z of the distance to equilibrium is given by equating $1 - \lambda^t = z$. For $u < 10^{-1}$ and $N > 5$, a very good approximation is given by $t_z \cong \theta_* N K_z$ where $K_z = -2\log_e(1 - z) = 1.39$ for $z = 0.5$, 6.00 for $z = 0.95$, and 9.21 for $z = 0.99$.

Since $\lambda = \rho^2\gamma$ the relative roles of mutation and drift in the progress to equilibrium depend on the relative values of ρ^2 and γ, respectively. Each has equal weight in determining λ^t when $\rho^2 = \gamma$—i.e., $4Nu \cong 1$, $\theta_* \cong 1/2$. When N is small relative to u^{-1}, $Nu \leq 10^{-2}$, which with $u = 10^{-5}$ means that N is 1,000 or less, then population size dominates the transition and $t_z \cong NK_z$. This is the transition time found by Robertson (9) for selection advance and by Lynch and Hill (8) for mutational advance with N small in both cases. On the other hand, if N is considerably larger than u^{-1}, $Nu \geq 10$, or N is 1 million or more for $u = 10^{-5}$, then the process is dominated by the mutation rate $\theta_* N \cong 1/4u$, $t_z \cong K_z/4u$, which is the result for N infinite.

When the rate of divergence among populations is $1 - \rho^2$, as for the initial finite equilibrium population, then also $t_z = K_z/4u$ since divergence is entirely a function of mutations. With an initial random fixed population, the rate of divergence among populations is not constant and we have the relationship, $\rho^{2t}[1 + 4Nu(1 - \gamma^t)] = 1 - z$. For N not too large and for the range of ts of interest, $t_z \cong (K_z - 2\log_e \theta_*)/4u$, which is somewhat longer than with mutations alone.

Migration

We briefly check Wright's (2) comment that F statistics should also correctly apportion the genotypic variance within and among populations at equilibrium with migration. From what we have demonstrated, this must be the case since mutations maintain the total equilibrium variance and mutation, migration, and population size determine the variances within and among populations.

We consider gametic migration with rate m occurring at the time of reproduction in an infinite island model. Let $\alpha = 1 - m$. Then, $\theta_{t+1} = \rho^2[\alpha^2(1/2N + \gamma\theta_t) + (1 - \alpha^2)\varphi_t\theta_0]$, where the last term is for genes from different populations. We find the relationship $\theta_t = \theta_* + (\theta_0 - \theta_*)\lambda^t\alpha^{2t} + (1 - \alpha^2)\theta_0\rho^{2t}(1 - \gamma^t\alpha^{2t})/(1 - \gamma\alpha^2)$, where $\theta_* = \rho^2\alpha^2/2N(1 - \lambda\alpha^2) \cong 1/(1 + 4Nu + 4Nm)$ for small m. If the initial population is an infinite equilibrium population, $\theta_0 = 0$, then the rate of convergence of θ is constant $1 - \lambda\alpha^2$ (faster than without migration) and at all stages $\sigma_{wt}^2 = (1 - \theta_t)\sigma_a^2$, $\sigma_{bt}^2 = 2\theta_t\sigma_a^2$. In any case, at equilibrium $\sigma_{w*}^2 = (1 - \theta_*)\sigma_a^2$, $\sigma_{b*}^2 = 2\theta_*\sigma_a^2$. With fixed initial populations, the rates are more complex than for mutation alone. Of course, the effect of migration is to maintain more variation within populations and less between populations.

Discussion

With unequal mutation rates and a fixed initial population, the transitions of Q and q are gene-frequency-composition dependent. An example is given in ref. 4, in which the allele that is fixed has the smallest mutation rate. Values obtained by q and Q over time are less than the equilibrium values and finally return to the equilibrium values, although each started with a value of 1. However, for our purposes, the main issues are clarified by considering random fixed initial populations.

It is difficult to relate many other studies to this one because of the differences involving number of alleles, dominance, mutation model, population size or $4Nu$, and selection. We review only those that include results for neutral genes with additive effects.

Wright (10) found the equilibrium variance within populations for two alleles with additive effects. Let v_1 and v_2 be

the two mutation rates with $u = v_1 + v_2$. The equilibrium gene frequencies are $p_{1*} = v_1/u$ and $p_{2*} = v_2/u$. Then his variance can be put into the form $(1 - \theta_*)\sigma_a^2$, where $1 - \theta_* = 4Nu/(1 + 4Nu)$ and $\sigma_a^2 = 2p_{1*}p_{2*}a^2$, a being one-half the difference between the two homozygotes. Thus, σ_a^2 is the variance in an infinite equilibrium population. Nei and Imaizumi (11) also found this result in a study involving dominance and selection.

Chakraborty and Nei (12) studied an additive genetic model similar to ours but with a stepwise mutation model. They found the equilibrium variance within populations to be $\sigma_{W*}^2 = 2Nnmva^2$, where n is the number of loci, m is the maximum number of steps in the mutation model, v is the mutation rate, and a is the effect of the mutation for a single step. They assumed a binomial distribution for the number of steps for each mutation, which has a variance of $ma^2/2$ that is equivalent to $2\sigma_x^2$ in our model. With this interpretation, $\sigma_{W*}^2 = n4Nv(2\sigma_x^2) \cong n(1 - \theta_*)\sigma_a^2$. The latter approximation rests on $4Nv$ being very small and on σ_a^2 being for an infinite number of alleles in an infinite equilibrium population. The authors do not mention any constraints on N and v but a very small $4Nv$ is implied in their derivation of σ_{Wt}^2, which has a constant rate, $1/2N$, of approach to equilibrium. The variance between populations is $\sigma_{Bt}^2 = 2nmva^2\ [t - 2N(1 - e^{-t/2N})]$ for monomorphic initial populations when $\sigma_{W0}^2 = 0$, and $\sigma_{Bt}^2 = 2nmva^2t$ when $\sigma_{W0}^2 = \sigma_{W*}^2$, both being linear in t in time. The variance between finite populations becomes infinite over time.

Lynch and Hill (8) restricted their results to $4Nu < 1$ and argued that in small populations there will be only two alleles segregating at a locus at any particular time. They also treated dominance for two allele models but we compare only the results for additive effects. Their equilibrium variance within populations is $\sigma_{W*}^2 = [2N - (2N - 1)/2N]\ 2n\mu\ \varepsilon(a^2) \cong n4N\mu\varepsilon a^2$ where n is the number of loci, μ is the mutation rate, and a is half the difference between the two homozygotes. They considered only fixed initial populations and the rate of approach to equilibrium for the additive model is a constant $1/2N$. In their model, a corresponds to half the difference between the two homozygotes so that $\varepsilon a^2 = 2\sigma_x^2$ in our model. Consequently, $\sigma_{W*}^2 \cong n\ 4N\mu(2\sigma_x^2) \cong n\ (1 - \theta_*)\sigma_a^2$ by restricting $4N\mu$ to be much smaller than $4N\mu < 1$. Their variance between populations, like that in ref. 12, becomes infinite in time. They also studied separate sexes and concluded that neither separate sex nor dominance appreciably altered conclusions based on additive effects with monoecy.

These results (8, 12) are considerably different from ours. Utilizing our interpretation, their σ_w^2s are similar to each other and similar to ours for an infinite alleles model and very small $4Nu$—that is, $4Nu/(1 + 4Nu) \cong 4Nu$. Also, the σ_B^2s of refs. 8 and 12 are similar in that mutations accumulate differences among populations that are ever increasing. This is in sharp contrast to our variance among populations, which increases to a finite equilibrium value $2\theta_*\sigma_a^2$.

The most pleasing aspect of our study is that we can formulate the variance σ_a^2 or σ_A^2 for an infinite equilibrium population and use this as a base of reference in expressing the variance within and among finite populations. While we may disagree or argue about the appropriate value for σ_A^2, it seems reasonable to assume that it is finite. If this is accepted, then a new perspective is provided on the time required to obtain and the amount of variance that can be maintained within and among finite populations. The generality of the results is enhanced by having no restraints placed on N or u or their combination.

As expected, Wright's conjectures (2) were correct. Not so obvious was the exact form of the F statistic. Fortunately, Malécot's (3) identity by descent measure with mutation can be utilized in the same manner as without mutation for equilibrium populations and for elaborating the transitional values of the variance within populations. The transitional values for the variance among populations from fixed founder populations require an additional but simple identity parameter φ.

One of the main results of interest is that for many situations the variation within finite populations relative to that in infinite populations is $(1 - \theta)$. The transitional values of $1 - \theta$ for $u = 10^{-5}$ and different population sizes, starting with $\theta = 0$ and $\theta = 1$, are plotted against $\log_{10}t$ in Fig. 1. These provide a pictorial view of rates, times to equilibrium, and the equilibrium values. At equilibrium, there is little variation within populations relative to an infinite population when $N \leq 10^3$, but it is about 80% for $N = 10^5$ and practically 100% for $N \geq 10^6$.

While we do not address selection directly, Fig. 1 depicts little opportunity for short-term selection within populations evolving from a fixed base and little opportunity ever in small populations ($N \leq 10^3$).

One can also relate the heritability within populations, h_w, to that in an infinite equilibrium population, $h_* = \sigma_A^2/(\sigma_A^2 + \sigma_E^2)$, where σ_E^2 is the environmental variance among individuals. Then, $h_w = (1 - \theta)\sigma_A^2/[(1 - \theta)\sigma_A^2 + \sigma_E^2] = (1 - \theta)h_*/(1 - \theta h_*) = (1 - \theta)/(h_*^{-1} - \theta)$. With $h_* = 0.5$ and $u = 10^{-5}$, the heritability in an equilibrium population is 0.037 for $N = 10^3$ and 0.004 for $N = 10^2$. Thus, observations on heritability correspond very closely to those on σ_w^2.

Another main result of interest is σ_b^2 representing the differentiation among populations. When starting from an initial infinite equilibrium population, the divergence between populations proceeds at the same rate as the convergence within populations and $\sigma_b^2 = 2\theta$ times the variance within an infinite equilibrium population. The rate is very fast, particularly for small populations, in contrast to an initial fixed population, because all of the variance is present in the initial population, and it is just a matter of apportioning the variance within and between populations by drift while mutations maintain the total variance. The curves for θ in this case are the reverse image, $1 - (1 - \theta)$, of the dashed lines in Fig. 1.

With a fixed initial population, variation arises entirely by mutational events and divergence among populations is governed to a great extent by the mutation rate. The function $\theta_t - \varphi_t$ for $u = 10^{-5}$ is plotted against $\log_{10}t$ in Fig. 2, σ_{bt}^2 being proportional to twice this value. Long times are required—10^3 generations even for the smallest Ns ($N = 1, 10, 100$)—for there to be any perceptible variation among populations.

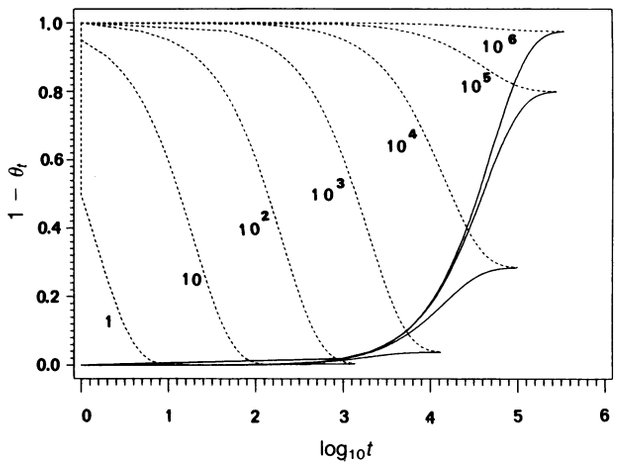

FIG. 1. Values of $(1 - \theta_t)$ for $u = 10^{-5}$ and several values of N are plotted against $\log_{10}t$ starting with initial values of $\theta_0 = 0$ (dashed lines) and $\theta_0 = 1$ (solid lines). Values of N are noted beside each curve. The two lines converge to the equilibrium value.

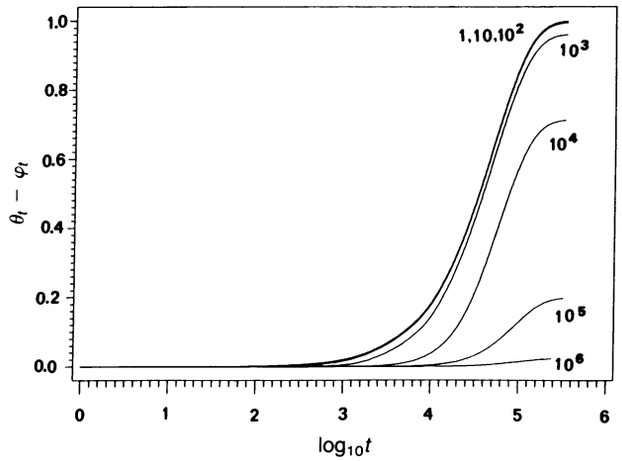

FIG. 2. Values of $\theta_t - \varphi_t$ for $u = 10^{-5}$ and several values of N are plotted against $\log_{10} t$ for $\theta_0 = 1$. Values of N are noted beside each curve. $N = 1$, 10, and 10^2 are not distinguishable.

There is little prospect of short-term advance from selecting among even the smallest lines or populations.

At equilibrium σ^2_{b*} is proportional to $2\theta_*$. With $u = 10^{-5}$, $2\theta_* > 1.9$ for $N \leq 10^3$, while $2\theta_* < 0.05$ for $N \geq 10^6$ with intermediate values between these two ranges. Consequently, most of the variation is between modest to small populations and most of the variation is within very large populations.

We have only superficially treated migration, the main thrust being on the interplay of drift and the production of new variation. Also, an infinite island model is less realistic than a finite island or other migration models considered by Crow and Aoki (13). The obvious effect of migration is to oppose the effect of drift by maintaining more variation within populations and less between populations than would otherwise be obtained. Migration plays a significant role in natural populations but little or no role in plant and animal improvement except in the context of contamination or purposefully crossbreeding or hybridization.

We have not addressed dominance and epistasis. No one seems to have treated a general multiple allele model with dominance and mutations. Even without mutations, multiple allele models with dominance and drift are very complex (14), requiring several components of genetic variance and descent measures. Dominance being an interaction of alleles often just adds noise to the system unless there is overdominance and does not alter qualitative conclusions. This conclusion was reached by Lynch and Hill (8), although they considered only two gene models for pairs of alleles. First-order interactions of nonalleles, additive by additive epistasis, have implications different from dominance and the potential of increasing the total variance tremendously. Yet, relative to the total variance in an infinite equilibrium population, the effects of mutation and drift are probably not qualitatively different from those based on an additive model.

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1. Wright, S. (1951) *Ann. Eugen.* **15,** 323–354.
2. Wright, S. (1952) *Genetics* **37,** 312–321.
3. Malécot, G. (1948) *Les mathématiques de l'hérédité* (Masson, Paris).
4. Cockerham, C. C. (1984) *Proc. Natl. Acad. Sci. USA* **81,** 530–534.
5. Nei, M. (1972) *Am. Nat.* **106,** 283–292.
6. Kimura, M. & Crow, J. F. (1963) *Evolution* **17,** 279–288.
7. Cockerham, C. C. (1967) *Genetics* **56,** 89–104.
8. Lynch, M. & Hill, W. G. (1986) *Evolution* **40,** 915–935.
9. Robertson, A. (1960) *Proc. R. Soc. Lond. Ser. B* **153,** 234–249.
10. Wright, S. (1931) *Genetics* **16,** 97–159.
11. Nei, M. & Imaizumi, Y. (1966) *Genetics* **54,** 763–782.
12. Chakraborty, R. & Nei, M. (1982) *Genet. Res. Camb.* **39,** 303–314.
13. Crow, J. F. & Aoki, K. (1984) *Proc. Natl. Acad. Sci. USA* **81,** 6073–6077.
14. Cockerham, C. C. (1984) in *Human Population Genetics: The Pittsburgh Symposium,* ed. Chakravarti, A. (Van Nostrand Reinhold, New York), pp. 195–208.