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Segregation variance after hybridization of isolated populations

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Summary

We develop a model to predict the increase in genetic variance of a quantitative character in a hybrid population produced by crossing two previously isolated populations of the same species. The increase in variance in the F_2 hybrids, the 'segregation variance', is caused by differences in the average allelic effects at each locus and by linkage disequilibrium among loci. We focus on the case in which the character is additively based and the average value of the character does not differ in the two populations. In that case the predicted segregation variance depends strongly on what is assumed about the genetic basis of the character. If the genetic variance of the character in each population is attributable to loci with numerous alleles of small effect that are in moderate frequency, as in Lande's (1975) model, the segregation variance should increase linearly with time since the populations were isolated, at a rate determined by the inverse of the effective population size. If the genetic variance is attributable to loci with alleles in very low frequency, as in Turelli's (1984) house-of-cards model or in Barton's (1990) model of pleiotropic, deleterious alleles, then the segregation variance in the hybrid population increases at a much lower rate.

1. Introduction

In different populations, genes that determine the distribution of a quantitative character may differ even though the means and variances of the character are the same. Selection may constrain the mean of a character but that mean value can be achieved by a large variety of genetic combinations. Genetic drift and mutation may result in very different combinations of genes in different isolated populations and those differences will be manifest in the segregation variance in an F_2 hybrid population obtained by crossing two isolates. How much segregation variance there is in a hybrid population depends on the genetic basis of the character. In this paper we will consider three different models of the maintenance of genetic variability and show that they lead to different predictions about the segregation variance. The essential difference between the models is in whether variation is attributable to numerous alleles in moderate frequency at each locus or only to very rare alleles.

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2. Mathematical models

(i) *Variance in a hybrid population*

Throughout, we will be concerned with a diploid species and a single quantitative character that is determined by additive effects at k loci. We assume throughout that the variance in the character is maintained by a balance between selection and mutation. Let $\bar{x}_i$ and σ_i^2 be the mean and variance of the additive effects of alleles at locus i in a population. If the character is at an equilibrium under symmetric mutation and stabilizing selection, then the mean of the character will be at the optimum, which we can arbitrarily set to 0, and the variance is determined by the balance achieved between mutation and selection. Lande (1975) showed that in such a model the $\bar{x}_i$ are constrained to sum to 0

$$\sum_{i=1}^{k} \bar{x}_i = 0, \tag{1}$$

but otherwise may take any values. Thus, there is only one constraint on the average allelic effects at the k loci. The total genetic variance of the character is,

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ignoring linkage disequilibrium, the sum of the variances in additive effects at individual loci

$$\sigma_A^2 = 2\sum_{i=1}^{k} \sigma_i^2. \quad (2)$$

The actual values of the σ_i^2 depend on the relative strengths of mutation and selection. We will assume that the loci are not tightly linked and that the isolated populations are sufficiently close to an equilibrium that linkage disequilibrium can be ignored (Lande, 1975; Turelli, 1984).

If two populations are subject to the same stabilizing selection, then at equilibrium the mean of the character will be 0 in both and the genetic variance will be σ_A^2 in both, yet the average effect at each locus may differ because of genetic drift or other factors. Let $\bar{y}_i$ be the average effect at the ith locus in a second population. We are concerned with the additive genetic variance in a population that is formed by first hybridizing the two populations to form an F_1 population and then allowing the resulting hybrid population to breed randomly to form an F_2 population. The additive genetic variance in the F_2 generation of the hybrid population is

$$\sigma_A'^2 = \sigma_A^2 + \Delta\sigma_A^2 = \sigma_A^2 + \frac{1}{2}\sum_{i=1}^{k} (\bar{x}_i - \bar{y}_i)^2 + \frac{1}{2}\sum_{i \neq j}^{k} (1 - 2r_{ij})(\bar{x}_i - \bar{y}_i)(\bar{x}_j - \bar{y}_j), \quad (3)$$

where r_{ij} is the recombination rate between locus i and j. Equation (3) assumes either that there is no stabilizing selection on the character in the hybrid population or that it is sufficiently weak that the values of $\bar{x}_i$ and $\bar{y}_i$ do not change significantly. It also ignores the effect of mutation during the formation of the F_1 and F_2 populations.

The term $\Delta\sigma_A^2$, which is the sum of the second and third terms of the right hand side of (3), is the segregation variance in the F_2, following the usage of Lande (1981). The second term on the right-hand side represents the contribution of the differences in the average effects of each locus and the third term represents the contribution of linkage disequilibrium. The third term is probably less important than the second. Terms in the sum representing unlinked loci ($r_{ij} = 1/2$) will be 0, and even for linked loci the terms in the sum would not tend to be of one sign unless the means of the character differed in the two populations, which is not the case we are concerned with here. The second term is always positive and will be the focus of our interest.

(ii) *Multivariate normal model*

The magnitude of the increase in the segregation variance when two populations are hybridized will depend on how variability in the character is maintained and on how long the populations have been isolated from each other. We will consider three models of the maintenance of quantitative genetic variability and predict the magnitude of the segregation variance in each. The first model is the multivariate normal model analysed by Lande (1975). In this model, as in Turelli's (1984) house-of-cards model discussed next, the variance of a quantitative character is determined by a balance between mutation at loci affecting that character and selection acting directly on that character. This assumption differs from the model of Barton (1990), the third model we consider, in which the character is neutral but is affected by numerous pleiotropic loci influencing both overall fitness and the character. As discussed by Turelli (1984), Lande's model assumes in effect that mutation at each locus is stronger than stabilizing selection felt by each locus, which implies that the genetic variance at each locus is attributable to numerous alleles in moderate frequency.

Assume that the two populations of interest were identical at time $t = 0$ and have diverged after that because of genetic drift and mutation only. The force of stabilizing selection is the same in both and is sufficiently strong that the mean of the character remains near 0 in both populations and that the variance remains at σ_A^2. Because we have assumed that the $\bar{x}_i$ are constrained only by (1), i.e. they are not constrained by the mutation process itself, each $\bar{x}_i$ can change because of drift. Under drift alone the sampling variance in $\bar{x}_i$ is $\sigma_i^2/(2N)$, where σ_i^2 is the additive component of the variance attributable to locus i and N is the effective population size (Lande, 1976). Selection returning the overall mean to 0 will then reduce the sampling variance in proportion to the contribution of locus i to the total. Hence, the asymptotic rate of divergence per generation under drift and selection is

$$E[(\bar{x}_i - \bar{y}_i)^2] = \frac{\sigma_i^2}{2N}\left(1 - \frac{\sigma_i^2}{\Sigma\sigma_i^2}\right) \quad (4)$$

(cf. Kendall & Stuart (1973, §27.14)).

This is the variance in the average effects at the ith locus in one generation. After t generations of isolation, the variance in $\bar{x}_i$ over independent replicates would be t times this value. Substituting into eqn (3) and treating each of the two populations of interest as independent replicates, we obtain

$$E(\Delta\sigma_A^2) = \frac{t\sigma_A^2}{4N}\left(1 - \frac{1}{n_E}\right), \quad (5)$$

where σ_A^2 is the additive genetic variance of the character and $n_E = (\Sigma\sigma_i^2)^2/\Sigma\sigma_i^4$ is the effective number of loci (Lande, 1981). The expected value of the third term on the right-hand side of (3) is zero because the expected value of the linkage disequilibrium created by drift alone is zero for each pair of loci.

On a longer time scale, our assumptions will not be satisfied. It seems unlikely that the average effect of

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each locus can be increased or decreased by an arbitrary amount. Instead, we can imagine that there are bounds on the average effect at each locus that are caused by some intrinsic limitation in what it can do. As drift carries some $\bar{x}_i$ to their limits, increments to the segregation variance would decrease. After a longer time we would expect the segregation variance to reach a plateau. The exact location of that plateau would depend on what limits were assumed for each locus. Nevertheless, the multivariate normal model would not be a reasonable approximation unless the average effects at each locus could be changed by a few standard deviations, so that we can assume that the overall limit on the segregation variance is at least several times the initial genetic standard deviation.

(iii) *House-of-cards model*

Turelli (1984) noted that Lande's (1975) multivariate normal model is actually an approximation to a more general model of mutation-selection balance. Turelli posed an alternative approximation, which is called the 'house-of-cards' model. In the house-of-cards model, as in the multivariate normal model, there are a large number of allelic states at each locus with each state differing in its additive effect on the character of interest. In the multivariate normal model, no one allele is very common, but in the house-of-cards model, one allele at each locus is in high frequency and the other alleles are maintained in very low frequency. Turelli (1984) shows that the house-of-cards approximation is valid if the additive effect of each mutation is relatively large. In the house-of-cards model, then, there is a constraint on the changes in average effect at each locus. The value of $\bar{x}_i$ will not be able to change steadily under drift because the same allele will tend to remain in high frequency. Instead, there will be only slight but non-cumulative variation in the value of $\bar{x}_i$ with the possibility of an occasional large change as a result of the fixation of one of the previously low frequency alleles. Thus, it seems likely that segregation variance may increase much more slowly between isolated populations under the assumptions of the house-of-cards model than under the multivariate normal model.

We can obtain an approximate expression for the segregation variance under the house-of-cards model as follows. Assume that at each locus there is one common allele, which we can assume without loss of generality to have additive effect 0, and one or more alleles in low frequency. Let α be the additive effect of one of these alleles and V_s be the strength of stabilizing selection on the character. Turelli (1984) shows that the frequency of this allele in an infinite population is approximately $\hat{p} = \mu/s$, where μ is the mutation rate to this allele and $s = \alpha^2/(2V_s)$ is the intensity of selection against individuals heterozygous for this allele. At each locus there may be several such alleles, each with its own value of μ and α. For the allele frequencies to remain small, μ and α are constrained to values for which $\mu/s \ll 1$, that is $\alpha^2 \gg 2\mu V_s$.

In a finite population, the expected frequency is still μ/s but there is some variation because of genetic drift. We can find the net effect of genetic drift before there is a replacement of one of the common alleles by considering each low frequency allele separately, taking advantage of the fact that while they are all rare, their frequencies are nearly independent of one another. The change in the mean effect of each locus will be caused by changes in frequencies of rare alleles. Consider one such allele and assume, for simplicity, that its frequency in the ancestral population is $\hat{p} = \mu/s$. For $t > 0$, its frequency is a random variable that changes according to

$$p_{t+1} = p_t + \mu(1-p_t) - sp_t(1-p_t) + \xi_t, \tag{6}$$

where ξ_t is a random variable with mean 0 and variance $p_t(1-p_t)/(2N)$. If p_t is small, then (6) can be approximated by the linear equation

$$p_{t+1} = p_t + \mu - sp_t + \xi_t, \tag{7}$$

where the mean of ξ_t is 0 and the variance of ξ_t is approximately $p_t/(2N)$. The third term on the right hand side of (6) would be different for mutant alleles with other degrees of dominance, but for such alleles the linear approximation in (7) would still be valid provided that the frequency is small and that they are not completely recessive.

Taking the expectation of (7) we conclude that $E(p_t) = \hat{p}$. To find the variance, we let $\delta_t = p_t - \hat{p}$ to obtain

$$\delta_{t+1} = (1-s)\,\delta_t + \xi_t. \tag{8}$$

Squaring both sides and taking the expectation, we find

$$E(\delta_{t+1}^2) = (1-s)^2 E(\delta_t^2) + \frac{\hat{p}}{2N}. \tag{9}$$

Therefore,

$$E(\delta_t^2) = \frac{\hat{p}}{2N}\frac{1-(1-s)^{2t}}{1-(1-s)^2} \approx \frac{\hat{p}}{4Ns}[1-e^{-2st}]. \tag{10}$$

This would be the increase in $E(\sigma_t^2)$ if selection did not constrain the overall mean of the character. With that constraint and the assumption that all alleles have the same selection coefficient, s, and same mutation rate, μ, $E(\delta_t^2)$ is reduced by a factor of $(1-1/n)$, where n is the number of loci.

Equation (10) predicts the variance in the frequency of a particular allele subject to selection of strength s and with an equilibrium frequency $\hat{p}$. The variance increases to an asymptotic value of $2\alpha^2(1-1/n)\hat{p}/(4Ns)$. The approach to this asymptote will be on a time scale of $1/(2s)$ generations. We are concerned here not with one allele but with a potentially large number of such alleles, at the same or at different loci,

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each of which could have different values of μ and s. The segregation variance in a hybrid population will be attributable to variance in the frequencies of all the low frequency alleles. The segregation variance will then approach an asymptotic value that is the sum of $(1-1/n)\hat{p}/(4Ns)$ across alleles, which is $(1-1/n)V_G/4Ns$. Under this model, the segregation variance will not increase in proportion to time but will instead reach an asymptotic value and, if $Ns \gg 1$, the segregation variance will be a small fraction of the equilibrium genetic variance. That is in contrast to the multivariate normal model, in which an asymptote is not likely to be reached for a much longer time. The difference is caused by the constraint on possible mutational effects that is implicit in the house-of-cards model.

On a longer time scale, there will be additional segregation variance because low frequency alleles will occasionally become fixed. That will occur at a rate determined by the probability of fixation of deleterious mutants. The process is the same as that described by Barton (1989). Barton (1989) showed that when $Ns \gg 1$, which is the case we are concerned with here, the fixation probability is very small.

The picture that emerges of the increase in the segregation variance in a hybrid population as a function of time in this model is quite different from that in the multivariate normal model. The segregation variance would increase relatively quickly to a plateau that will be quite small if N is large. Then on a much longer time scale, there would be a slow increase with time as low-frequency alleles occasionally become fixed.

(iv) *Pleiotropic mutation model*

The two previous models assumed that selection directly affects the quantitative character of interest. Another possibility, discussed by Hill & Keightley (1988) and modeled in more detail by Barton (1990), is that the character itself is neutral but that its value is determined by the pleiotropic effects of alleles at loci that are themselves selected. In Barton's model, there are a number of loci affecting overall fitness and each locus is at an equilibrium under selection against alleles that lower fitness and mutation to those alleles. Each allele has an additive effect, α_i, on a neutral character, where the value of α_i is drawn from a known probability distribution with mean 0 and variance α^2. Barton assumes that the fitness of each deleterious allele is $1-s$ and fitnesses are multiplicative across loci. He also assumes that the mutation rate μ is much less than s. That implies that in an infinite population, deleterious alleles are rare and that the number of deleterious alleles carried by any individual follows a Poisson distribution with mean $2k\mu/s$, where k is the number of loci.

Our concern here is with the amount of segregation variance after t generations of isolation if both populations are of effective size N. Although the genetic assumptions differ substantially from those in the house-of-cards model, the amount of segregation variance that would accumulate is the same. The reason is that both models have the property that the genetic variance of the quantitative character is determined by the frequencies of alleles that are each governed by a separate mutation–selection balance. The cause of the selection is different in the two models but its effect is the same. As a consequence, the results for the house-of-cards model can be used here with the one modification that the value of s here is the selection intensity caused by pleiotropic effects on fitness rather than as a result of selection directly on the quantitative character itself. Genetic evidence reviewed by Barton (1990) shows that a value of s of 0·01 to 0·001 is reasonable so Ns is likely to be quite large in most species. Hence, in this model we would expect a very small initial plateau for the segregation variance and a very slow increase later caused by the fixation of deleterious mutations.

3. Simulations

To test the accuracy of the approximations made above, we developed a simulation model. The model was of a single randomly mating population containing N diploid individuals. There were k unlinked loci that contributed equally to the value z of a quantitative character. For each individual, the value of z was $\Sigma_{i=1}^{k}(a_i+a_i')+E$, where a_i and a_i' are the additive effects of the two alleles at the ith locus, and E is the environmental component. We assumed that E was drawn from a normal distribution with mean 0 and variance 1. Selection was imposed at the mating stage. For each of the N offspring making up the next generation, an individual was chosen as a potential parent. Then its relative fitness, $w(z) = \exp[-z^2/(2V_s)]$, was used to determine its chance of being rejected, thus modeling viability selection. After parents were chosen for each offspring, gametes were formed and then subject to mutation. Each locus had the same probability μ of mutating. If an allele mutated, the additive effect of the descendant allele differed by an amount δa that was drawn from a normal distribution with mean 0 and variance V_m. Thus the net effect of mutation is $\sigma_m^2 = 2k\mu V_m$.

Each replicate simulation began with each locus initially fixed for an $a = 0$ allele. Then the population evolved under the above assumptions until the variance of z reached an apparent equilibrium. We found that waiting 1000 generations was more than sufficient and that waiting longer did not affect our results. The program saved a copy of the population after 1000 generations (the initial population) and then proceeded to let the population evolve for 1000 more generations, saving copies of the population at times $t = 100, 200, \ldots, 1000$.

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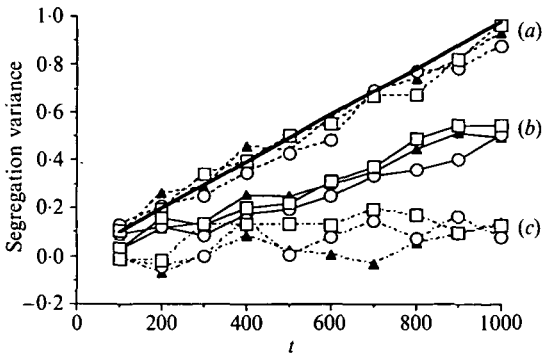

Fig. 1. Average values of the segregation variance in F_2 populations formed as described in the text. In each replicate, a copy of the population was saved at $t = 0$, after a stochastic equilibrium was reached, and then hybridized with copies of the population saved at $t = 100, 200, \ldots, 1000$. The values plotted are the averages over 100 replicate simulations. In all cases, $N = 128$ and $V_s = 20$. Nine sets of replicates were run: three each with $k = 8$ (▲), $k = 16$ (○), and $k = 32$ (□), with values of V_m: (*a*) 0·1; (*b*) 1; (*c*) 10. Cases with the same values of V_m are connected by lines of similar types. In each case, the value of μ was adjusted so that the equilibrium additive genetic variance was approximately 1. The values of μ used in each case are as follows: $\mu = 0{\cdot}006$ ($k = 8$, $V_m = 0{\cdot}1$), $\mu = 0{\cdot}002$ ($k = 8$, $V_m = 1$), $\mu = 0{\cdot}0016$ ($k = 8$, $V_m = 10$), $\mu = 0{\cdot}0025$ ($k = 16$, $V_m = 0{\cdot}1$), $\mu = 0{\cdot}0009$ ($k = 16$, $V_m = 1$), $\mu = 0{\cdot}0008$ ($k = 16$, $V_m = 10$), $\mu = 0{\cdot}0011$ ($k = 32$, $V_m = 0{\cdot}1$), $\mu = 0{\cdot}00044$ ($k = 32$, $V_m = 1$), $\mu = 0{\cdot}0004$ ($k = 32$, $V_m = 10$). The solid line shows the expectation, $t/(8N) = t/(1024)$, which is based on eqn (5) with $\sigma_A^2 = 1$, $n_E = \infty$. The expectation takes account of the factor of 2 which must be present because populations separated by time t in the simulation represent two populations descended from a common ancestral population at a time $t/2$ in the past.

The populations saved were each hybridized with the initial population according to the procedure for forming an F_2. Then we found the increase in the segregation variance by subtracting the variance in z in the F_2 from the average of the variances in the two parent populations. That would give a single estimate of the segregation variance between two populations separated by time t and so is equivalent to the segregation variance between two populations that were isolated for a time $t/2$. Each replicate yielded 10 estimates of the segregation variance, one for each time at which copies of the population were saved. The program then repeated the process for a different replicate with the same parameter values and produced a table of average segregation variances at the end of a set of 100 replicates.

Some results are shown in Figure 1. The results for nine cases are shown, with all combinations of $k = 8$, 16 and 32, and $V_m = 0{\cdot}1$, 1 and 10. In all the results presented in Figure 1, $N = 128$ and $V_s = 20$. For each set of parameter values, the value of μ was adjusted by trial and error so that the equilibrium additive genetic variance was approximately 1 (in all cases $0{\cdot}95 < V_G < 1{\cdot}05$). The mutation rates used are in the figure caption.

We can see that the number of loci, k, does not significantly affect the results. For a given value of V_m, the results for $k = 8$, 16 and 32 overlap and are not consistently different. They do however depend strongly on V_m and confirm the predictions based on the analytic theory. For $V_m = 0{\cdot}1$, each mutation has a relatively small effect on the character and hence is weakly selected, and the results fit the analytic predictions of the multivariate normal model, which is shown as the solid line. For $V_m = 10$, each mutation has a relatively large effect and hence is strongly selected. In that case, the segregation variance is relatively small. The case with $V_m = 1$ is intermediate.

4. Empirical studies

There are few empirical studies in which characters not closely related to fitness have been analysed in the way we need. Characters such as viability and fertility cannot be usefully compared with our predictions because of the evident non-additivity. In fact, finding the causes of heterosis in such characters has been an important research program in genetics. One study that is relevant is of leaf number in tobacco. Wright (1968, p. 377) cites the data of Hayes, East & Beinhart (1913) in which the means in two parent populations were 19·9 and 19·8, the mean in the F_1 was 19·8 and the mean in the F_2 was 20·9. The variances in the parent populations were 2·25 and 1·90. The variance in the F_1 was 1·46 and the variance in the F_2 was 10·96. Thus the segregation variance was 8·88 and is considerably larger than the initial variances. In the absence of other information about these populations, we cannot test the quantitative predictions of our model but it does appear that we can reject the hypothesis that variation in leaf number was maintained only by low frequency alleles if the populations diverged under the effects of genetic drift.

5. Discussion

We have shown that the kind of genetic variation underlying a quantitative character strongly affects the segregation variance expected between two populations that have been isolated for some time if divergence was because of drift. If variation is maintained by numerous alleles of moderate or small effect, then the segregation variance increases roughly linearly with the time of separation. Selection imposes only a single constraint on the mean of the character so alleles at the underlying loci are free to drift. In contrast, if variation is maintained primarily by low-frequency alleles, either under the house-of-cards model of Turelli (1984) or the pleiotropy model analysed by Barton (1990), then the increase in segregation variance is likely to be small. In both models, each allele contributing significantly to the genetic variance of the character is effectively in a

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separate mutation–selection balance and hence can be only slightly affected by drift.

At present, there are few data that allow us to distinguish the two possibilities other than the study cited above. Our analysis does not, of course, account for non-additivity and additional theory will undoubtedly be needed in the analysis of experimental data. Nevertheless, our results do not depend as much on the assumption of additivity as on the extent to which each allele frequency is separately constrained by selection. We would expect similar results for multivariate stabilizing selection. If the number of loci is much larger than the number of characters under stabilizing selection, the qualitative nature of our conclusions will still be true. The extent of the segregation variance that accumulates under drift depends primarily on the constraints on allele frequencies, and not on the details of the selection process. The question is whether a character is overdetermined, meaning that there are more constraints on its value than there are independent allele frequencies, or underdetermined.

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