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Neutral additive genetic variance in a metapopulation

MICHAEL C. WHITLOCK
Department of Zoology, University of British Columbia, Vancouver, BC V6T 1Z4 Canada

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Summary

For neutral, additive quantitative characters, the amount of additive genetic variance within and among populations is predictable from Wright's F_{ST}, the effective population size and the mutational variance. The structure of quantitative genetic variance in a subdivided metapopulation can be predicted from results from coalescent theory, thereby allowing single-locus results to predict quantitative genetic processes. The expected total amount of additive genetic variance in a metapopulation of diploid individual is given by $2N_e\sigma_m^2(1+F_{ST})$, where F_{ST} is Wright's among-population fixation index, N_e is the eigenvalue effective size of the metapopulation, and σ_m^2 is the mutational variance. The expected additive genetic variance within populations is given by $2N_e\sigma_e^2(1-F_{ST})$, and the variance among demes is given by $4F_{ST}N_e\sigma_m^2$. These results are general with respect to the types of population structure involved. Furthermore, the dimensionless measure of the quantitative genetic variance among populations, Q_{ST}, is shown to be generally equal to F_{ST} for the neutral additive model. Thus, for all population structures, a value of Q_{ST} greater than F_{ST} for neutral loci is evidence for spatially divergent evolution by natural selection.

1. Introduction

Most species are subdivided into local populations. Often these populations become genetically differentiated through genetic drift, mutation and/or divergent selection, and this differentiation can be reduced by migration among populations or uniform selection. Moreover the dynamics of the interaction between these forces can be strongly affected by the demographic nature of the metapopulation. Factors such as distance-biased dispersal, extinction and colonization, population fission, and asymmetric or kurtotic migration can potentially give very different genetic patterns from the simpler models more often considered.

This note will concentrate on the genetic patterns expected with genes not subject to selection. Neutral models have proven of considerable value as null models which allow tests about the nature of selection (Lande, 1976, 1992; Lynch & Hill, 1986; Spitze, 1993; Lynch, 1994; Hey, 1999). In particular, neutral models of quantitative genetic divergence among populations are useful as a null model of the selective differentiation of populations (Spitze, 1993; Lynch *et al.*, 1999).

Lande (1992) derived results about the nature of neutral additive quantitative genetic variation expected under the island model and a simple of extinction and recolonization. For the island model he made the somewhat surprising discovery that the amount of additive genetic variance (V_A) expected within demes is the same as the total variance expected in an undivided population with a population size equal to the total size of the subdivided population (see also Lynch, 1988). Furthermore, for the island model and his extinction/colonization model, the amount of differentiation among populations, as measured by Wright's standardized index, F_{ST}, was the same for neutral quantitative genetic characters as for neutral single-locus results (Lande, 1992; compare with Whitlock & McCauley, 1990). This result has been used by many (Spitze, 1993; and see references in Lynch *et al.*, 1999) as the justification for using 'neutral' marker locus F_{ST} as a null expectation for the amount of differentiation among populations in quantitative genetic variance (termed Q_{ST} by Spitze, 1993; see the definition below). If this Q_{ST} is significantly greater than F_{ST}, then this stands as strong evidence that selection has been responsible for

differentiation among populations. One of the aims of this paper is to generalize this result about the correspondence between F_{ST} and Q_{ST} beyond the two models already considered.

More generally, we need to know more about how quantitative genetic variation is maintained. Genetic drift will, on average, remove genetic variance from a population or species; mutation acts to increase the genetic variance. If these are the only forces acting on a species, then an equilibrium between the effects of drift and mutation can be reached. Lynch & Hill (1986) have shown that in a single, undivided population, the amount of V_A expected at equilibrium between drift and mutation in a diploid population should be $2N_e\sigma_m^2$, where N_e is the effective population size and σ_m^2 is the mutational variance. To begin to understand the dynamics controlling genetic variation, we must understand the effects of more realistic demographics. This note will derive the amount of genetic variance expected in a quite general class of metapopulations, including the effects of all the factors listed above. We will see that the effective population size (as derived by Whitlock & Barton, 1997) for subdivided populations and the neutral F_{ST} predicted by standard theory allows us to predict the amount of genetic variance within and among populations at an equilibrium between drift and mutation.

To derive these results we can take advantage of several useful new results from the study of the coalescent. Single-locus models about the probability of identity by descent correspond to coalescent results; we will see that the coalescent has clear and easy interpretations in quantitative genetic terms.

2. Definitions

We can refer to the additive genetic variance V_A among all individuals that belong to a particular set i as $V_{A,i}$. These sets can be defined by location or genotype or more generally, such as 'all individuals in a species', 'all individuals in a deme', or even 'all individuals with a particular genotype at some locus'. This note will focus on diploid individuals, and it will be useful to refer to the variance in breeding values among haplotypes within set i as $V_{h,i}$. If the correlation of alleles within individuals in set i is given as f_i, then

$$V_{A,i} = 2(1+f_i)\,V_{h,i}. \tag{1}$$

The average time since coalescence of two randomly chosen alleles from set i (i.e. the average amount of time since their most recent common ancestor) will be called t_i. Other terms are defined as:

σ_m^2 mutational variance per generation,
γ_j the fraction of σ_m^2 due to locus j,
n number of loci affecting the trait,
d number of demes,
N_i number of individuals in deme i,
$V_{T(0)}$ the amount of V_A in a randomly mated population with the same allele frequencies as the species in question,
N_e the effective population size of the species,
V_{within} the average additive genetic variance within demes,
V_{among} the additive genetic variance among demes.

3. The coalescent and the additive genetic variance

Coalescent theory can be used to address simple questions of quantitative genetics (Lynch, 1994). Assuming a character without dominance or epistasis effects and without linkage disequilibrium, the amount of additive genetic variance at any given level is the sum across loci of the V_A contributed by each locus. Thus we can investigate the amount of additive genetic variance contributed by a single locus to fully understand the dynamics of the trait.

We can proceed by realizing that the total variance in a population is the expected value of the variance among a pair of individuals chosen at random from this population. We can use coalescent theory to determine the expected variance among the effects of two alleles. Two alleles from set i have diverged on average for t_i generations since their most recent common ancestor. Assuming that mutational variance is independent of the current state of the individual, for each generation after coalescence the amount of V_A between a pair of alleles increases by the amount of mutational variance due to that locus, $\gamma_j\sigma_m^2/2$. Thus the expected amount of genetic variance among two alleles from set i at locus j is given by

$$V_{h,ij} = t_i\sigma_m^2\gamma_j/2. \tag{2}$$

Summed across loci, the additive genetic variance among haplotypes expected in set i is therefore given by

$$V_{h,i} = t_i\sigma_m^2/2. \tag{3}$$

Therefore, by (1) above, we get

$$V_{A,i} = (1+f_i)\,t_i\sigma_m^2. \tag{4}$$

The values for the variances in these equations are expectations; any particular population could deviate from these expectations as a result of history or of linkage disequilibrium induced by drift. This linkage disequilibrium is on average zero, so correlations among loci do not appear in these equations.

Two useful and interesting properties of a subdivided population are $V_{T(0)}$, the amount of V_A in a randomly bred population with the same allele

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frequencies as the subdivided population in question, and V_{within}, the average amount of V_A within demes. $V_{T(0)}$ can be determined simply by finding the average coalescence time of pairs of alleles chosen at random from the species and setting f_i to zero to account for the random mating:

$$V_{T(0)} = t_{\text{species}}\,\sigma_m^2. \tag{5}$$

Since the mean coalescence time of two randomly chosen alleles is $2N_e$ (Hartl & Clark, 1997), we can predict $V_{T(0)}$ from a knowledge of the effective size of subdivided populations (see below).

By similar logic, the amount of V_A within a deme can also be determined by the coalescence time of alleles within demes:

$$V_{\text{within}} = t_{\text{within}}\,\sigma_m^2. \tag{6}$$

4. Partitioning of variance for neutral, additive characters

Wright's *F*-statistics can be used to describe the partitioning of genetic variance within and among populations, as described by Wright (1969) and Lande (1992). The *F*-statistic that we will be most concerned with for our present purposes is F_{ST}, a measure of the correlation of alleles within populations. F_{ST} has been used in a variety of ways; for this paper I will use it to mean a parametric description of the expected state of the population, not as an estimate of that state. F_{ST} is defined in terms of the probabilities of identity in state, where f_0 is the probability that two alleles chosen at random from the same deme are identical and $\bar{f}$ is the probability that two alleles chosen at random from the whole metapopulation are identical. Then $F_{ST} = (f_0 - \bar{f})/(1 - \bar{f})$.

Denoting the amount of additive genetic variance within and among population by subscripts, I follow Spitze (1993) in defining

$$Q_{ST} = \frac{V_{\text{among}}}{V_{\text{among}} + 2V_{\text{within}}}, \tag{7}$$

where Q_{ST} is the quantitative genetic analogue of F_{ST}. As the variance components for quantitative characters can be affected by many evolutionary processes, and in different ways perhaps compared with neutral single-locus allele frequencies, it is convenient to refer to this quantity by a different name. In this section, I show generally that the Q_{ST} expected for a neutral additive trait is expected to be the same as the F_{ST} for a neutral locus in the low mutation limit. Therefore we can use single-locus results to predict the pattern of neutral differentiation of quantitative traits. This has been shown before for several special cases, but this analysis will show that the result is general.

By the formulae given in Wright (1969), we can see that, under the additivity assumptions used in this paper,

$$V_{T(0)} = V_{\text{within}} + \frac{V_{\text{among}}}{2}. \tag{8}$$

Thus,

$$Q_{ST} = \frac{V_{T(0)} - V_{\text{within}}}{V_{T(0)}}. \tag{9}$$

Substituting from (5) and (6) in the previous section, we find

$$Q_{ST} = \frac{t_{\text{species}} - t_{\text{within}}}{t_{\text{species}}}. \tag{10}$$

Slatkin (1991) showed that, in the limit of low mutation, the coalescent approach gives a value of

$$F_{ST} = \frac{t_{\text{species}} - t_{\text{within}}}{t_{\text{species}}}. \tag{11}$$

In neither case has any assumption been made about the types of population structure considered. Therefore, for neutral additive quantitative characters and neutral marker loci, we see that $Q_{ST} = F_{ST}$.

With this information, we can derive the amount of genetic variance within and among demes. The amount of genetic variance within demes on average is $(1 - Q_{ST})\,V_{T(0)}$ (see equation 9) and the amount of genetic variance among demes is given by $2Q_{ST}\,V_{T(0)}$ (from equations 8 and 9). Substituting from above, the expected neutral additive genetic variance within and among demes is

$$V_{\text{within}} = 2N_e(1 - F_{ST})\,\sigma_m^2 \tag{12}$$

and

$$V_{\text{among}} = 4N_e\,F_{ST}\,\sigma_m^2, \tag{13}$$

respectively. Note that in these two equations the effective size and the F_{ST} are both the same as determined by the coalescent for a single locus with mutation rate vanishingly small. Slatkin (1991) has shown that the value of F_{ST} derived in a coalescent model is equivalent to that derived by identity by descent (IBD) methods, in the limit of low mutation (see also Wilkinson-Herbots, 1998). In the next section we will see that the effective size appropriate to the coalescent is equivalent in the limit to that already derived by IBD for generalized subdivided population models (Whitlock & Barton, 1997).

5. The effective population size of metapopulations

The effective size of a subdivided population has been examined a number of times (Wright, 1939; Slatkin, 1977; Maruyama & Kimura, 1980; Ewens, 1989; Nei & Takahata, 1993; Hedrick & Gilpin, 1997; Wang,

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1997*a*, *b*, 1998; Whitlock & Barton, 1997; Wang & Caballero, 1999; Nunney, 1999). Wright (1939) found that the effective size of a species subdivided by the island model had an effective size equivalent to $Nd(1-F_{ST})$. Further analysis by Whitlock & Barton (1997) has confirmed that this is the effective size of any subdivided population where each deme is equal in size, equal in contribution to migration, and equal in receipt of migrants. Therefore, for example, populations following the stepping stone models have an effective size that is also equal to $Nd/(1-F_{ST})$, although the value of F_{ST} will in general differ for the same total rate of migration.

Whitlock & Barton (1997) also derived a more general view of the effective size of subdivided populations, accounting for any population structure in which the distribution of deme types remained constant over time. This analysis is showed that a very important parameter in determining N_e is the variance among demes in reproductive success. For example, for the special case when deme is equal across all demes, but the contribution of each deme to the migrant pool varies without temporal autocorrelation, the effective size of a species is given by

$$N_e = \frac{Nd}{(1+V)(1-F_{ST})+2NF_{ST}\,Vd/(d-1)}, \tag{14}$$

where V is the variance among demes in their total contribution to the next generation. (More general equations are given in Whitlock and Barton (1997), which allow for variable deme size and correlations across generations in reproductive success.) In this context, the island model and stepping stone models are extremes, because in these models the variance among demes in reproductive success is at its minimum value, $V = 0$. As a result, most realistic population structures cause the effective size of species to be lower than would be predicted by the census size. Certainly the island model result is not general; the effective size of realistic species is much less than $Nd/(1-F_{ST})$. Wang & Caballero (1999), in an excellent review on effective size, extended these results to include factors affecting local effective size.

The effective size given in (14) was determined by an identity by descent approach, finding the size of an ideal population which changed in the probability of common ancestry at the same rate as the real population in question. This was shown to be equivalent to the eigenvalue effective size and nearly equal to the mutation effective size (Whitlock & Barton 1997; see also Pannell & Charlesworth, 1999). For our current purposes, we require the effective size that determines the probability of IBD, which is directly and exactly related to the mean time of coalescence (Barton & Wilson 1995); this is provided by the eigenvalue effective size in the Whitlock & Barton (1997) approach.

Seemingly paradoxically, the eigenvalue effective size works better for the quantitative genetic problem with mutation every generation than it does for the problem of finding whether two alleles are identical in state. For this latter question, the effective size is accurate for low values of the mutation rate (and approximately so for reasonable mutation rates) but not for rapid mutation (see below).

6. Examples

(i) *Island model*, *stepping stone model*

For population structures in which demes are not changing in size and for which migration is conservative (*sensu* Nagylaki, 1980), each deme contributes the same number of individuals to the next generation and there is no variance in reproductive success among demes. Examples of these models include the island model and basic stepping stone models. For these types of models, the effective population size is given by $N_e = Nd/(1-F_{ST})$, as discussed above. As a result, at equilibrium the expected amount of variance within demes is

$$V_{within} = 2N_e(1-F_{ST})\,\sigma_m^2 = 2Nd\,\sigma_m^2. \tag{15}$$

Thus the amount of variance within demes in this restricted class of population structure models is equal to the amount of variance expected in an undivided population of the same total size, Nd (as found by Lande (1992) for the island model). This result is not general, as more realistic population structures do not give this equivalence.

The variance among demes for these conservative population structures is $V_{among} = 4NdF_{ST}\,\sigma_m^2/(1-F_{ST})$, also in accordance with Lande's results. The same result will hold for stepping stone models, although of course the F_{ST} will be different for the different models.

(ii) *Extinction and colonization*

The population structure effects of local extinction and colonization of demes have been investigated in detail in a series of models. Slatkin (1977) derived the effective population size for two versions of this model (see also Maruyama & Kimura, 1980), generalized later by Whitlock & Barton (1997). The effective size of a species with local extinction and colonization at rate e and island model migration among demes at rate m is given approximately by

$$N_e \cong \frac{Nd}{4N(m+e)\,F_{ST}} \tag{16}$$

(Slatkin, 1977; Whitlock & Barton, 1997; with F_{ST} in this case derived in Whitlock & McCauley, 1990). With $e > 0$, this is typically much lower than the census size, Nd, in contrast to the island model. Thus

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the expected average amount of additive genetic variance within demes under this model is expected to be:

$$V_{\text{within}} \cong \frac{2Nd(1-F_{\text{ST}})\,\sigma_{\text{m}}^2}{4N(m+e)\,F_{\text{ST}}}. \tag{17}$$

As a result, the genetic variance in this metapopulation is likely to be less than in an undivided population. The reproductive success of demes is highly variable as a result of the extinction/colonization process, which reduces N_{e} and therefore reduces the equilibrium variance. Similarly, the amount of V_{A} within demes is expected to be much less than under an initial model and much less would be expected in an undivided species.

Equation (17) gives a value slightly different from the value predicted by Lande (1992). In the derivation in that paper, the approximation is made that the variance among demes is expected to be (in the current notation)

$$(1-e)[V_{\text{among}}+V_{\text{within}}/N]+e[V_{\text{among}}/k+V_{\text{c}}/K],$$

where V_{c} is the variance among individuals in the colonizing pool, k is the number of demes from which colonists are drawn and K is the number of colonists per new deme. This approximation drops a term associated with the loss of variance among demes because of the sampling caused by extinction. As a result the variance among demes is reduced by approximately eV_{among}/d each generation relative to Lande's model. Adding this small term to the derivation results in equations that are in agreement with those above.

7. Partitioning of variance with epistasis

Non-additive genetic variance can, for some characters, be a substantial component of the total genetic variance (Crnokrak & Roff 1995; Whitlock *et al.*, 1995). With the inbreeding associated with population subdivision, this non-additive variance can behave differently from that in a single panmictic population (Whitlock *et al.*, 1993; Goodnight, 1995, 1999). Here let us briefly consider the effects of additive-by-additive epistasis on the partitioning of genetic variance among populations.

The additive genetic variance within a population is expected to be approximately

$$(1-F_{\text{ST}})\,V_{\text{A}}+4F_{\text{ST}}(1-F_{\text{ST}})V_{\text{AA}}$$

where these variance components are those that would obtain in a panmictic population with the same alleles and allele frequencies as the metapopulation in question (Cockerham & Tachida, 1988; Whitlock *et al.*, 1993). By similar calculations, the total genetic variance among demes is given by $2F_{\text{ST}}\,V_{\text{A}}+4F_{\text{ST}}\,V_{\text{AA}}$ (see Goodnight, 1995). Thus the genetic variance among populations is increased by the presence of epistatic variance, relative to the case considering additive genetic variance alone. However, the effect on Q_{ST} is the reverse; the Q_{ST} as calculated by the traditional common garden experiment uses the total genetic variance among populations, or

$$Q_{\text{ST}} = \frac{F_{\text{ST}}\,V_{\text{A}}+2F_{\text{ST}}^2\,V_{\text{AA}}}{V_{\text{A}}+2F_{\text{ST}}(2-F_{\text{ST}})\,V_{\text{AA}}} \leqslant F_{\text{ST}}. \tag{18}$$

With only additive-by-additive epistasis, $Q_{\text{ST}} = F_{\text{ST}}/(2-F_{\text{ST}})$. Hence the effect of epistatic variance for the trait is to increase the variance among demes, but decrease the expected Q_{ST}. Hence epistasis cannot be an alternative explanation for the result $Q_{ST} > F_{\text{ST}}$. However, epistasis can complicate the interpretation of low Q_{ST} as evidence for uniform selection and can potentially mask some of the effects of divergent selection.

8. Molecular diversity, mutation rates and their effects on F_{ST}

The eigenvalue effective size as calculated by Whitlock & Barton (1997) predicts the rate of divergence of quantitative genetic variation, as seen above. Furthermore, under some circumstances, this effective size does well at calculating molecular diversity. This eigenvalue effective size approximates the 'mutation effective size' which predicts the rate of change of diversity at the molecular level (Whitlock & Barton 1997; Pannell & Charlesworth, 1999), so long as the mutation rate is small relative to inverse total population size. With higher mutation rates, the number of mutation events in the coalescent paths between two individuals is expected to be high enough that the probability of differences is no longer well predicted by the product of the mutation rate per generation and the time of divergence. The discrepancies between the eigenvalue and mutation effective sizes are due to errors in the standard calculations of the diversity with high mutation rates, not to a fundamental difference between the drift processes involved. As a result, population structure measures calculated from molecular markers with high mutation rates can be subject to bias, such that the identity by state measures do not give a good measure of the identity by descent relationships.

9. Conclusions

This note has three main intentions: to illustrate the relationship between the coalescent and quantitative genetic models, to derive the expected genetic variance at equilibrium between mutation and drift in a metapopulation, and to generalize the expected relationship between F_{ST} and Q_{ST} for neutral traits and characters. Neutral additive genetic variances follows

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patterns that are easily predicted from single-locus theory about the identity by descent and coalescence of homologous alleles. In particular, we have seen that the expected genetic variance in a subdivided population is easily related to the $2N_e\sigma_m^2$ predicted in an undivided population (Lynch & Hill, 1986) with recourse to well-known results about F_{ST} and a new derivation of the effective size of subdivided populations (Whitlock & Barton, 1997). Furthermore, we have seen that the Q_{ST} predicted for neutral additive characters should be predicted by F_{ST} generally, not just for the island model.

The total genic diversity in a subdivided population is predictable from the eigenvalue effective size and the mutational variance. Lynch & Hill (1986) showed that the total additive genetic variance expected at an equilibrium between mutation and drift in an undivided population would be $2N_e\sigma_m^2$, and this is also the expectation in a subdivided population for the amount of genic diversity, i.e. the V_A which would be obtained in a panmicitic population with the same allele frequencies. This N_e, although larger than the census size for the island model and many other simplified models of population structure, is likely to be much lower than the census size in realistic populations when populations are variable in their reproductive success (Whitlock & Barton, 1997). Thus the total quantitative genetic diversity maintained in a metapopulation at equilibrium between mutation and drift is likely to be less than in an undivided population of the same size.

Furthermore, we can use the predictions derived from single-locus models to predict the partitioning of this genetic variance. Neutral single-locus population differentiation measures, in the limit of low mutation rates, are expected to be equal to the neutral additive quantitative genetic differentiation measures; that is, $F_{ST} = Q_{ST}$. We have seen that this result should hold quite generally, regardless of the model of population structure. As a result, the use of the difference between Q_{ST} and F_{ST} as a test of spatially divergent selection has more general support. The consensus of these studies us that quantitative genetic variance among populations is always equal to or greater than that expected from neutral models (Lynch *et al*., 1999).

There are two caveats that deserve mention about the overconfident application of this technique. First, F_{ST} and Q_{ST} must be estimated, and the statistical properties of these estimates are not well known. Given that both are ratios of variances, the error in their estimation is very large. Secondly, as pointed out by Lynch *et al*. (1999), variation in the local breeding system can result in variation in mean phenotype due to different inbreeding depression. Mean phenotypes can vary among populations but not due to variance in breeding values or variable environmental effects. This is unlikely to be a major problem for most morphological traits, as inbreeding depression is not large for most of these traits. A third difficulty suggested by Lynch *et al*. (1999), that epistasis can cause an increase in Q_{ST}, appears not to be a problem in the direction they envisioned.

As suggested by the inbreeding depression point in the previous paragraph, dominance can potentially affect the value of Q_{ST} even for neutral characters. The effects of dominance on the among population variance have not been fully explored to my knowledge, but preliminary results with biallelic loci suggest that dominance can either increase or decrease Q_{ST} even with neutral differentiation. If genetic variance is due to rare recessive alleles, then Q_{ST} will be less than F_{ST} even for neutral traits. With rare dominant alleles, Q_{ST} will be greater than F_{ST}. Averaged over a uniform distribution of allele frequencies, the contribution of dominance to Q_{ST} approaches zero. Overdominance tends to cause Q_{ST} to be greater than F_{ST}, again even with neutral differentiation. The overall pattern expected by combinations across loci with varying allele frequencies and dominance relationships is complex and deserves further study.

The extension of Q_{ST} results to metapopulations allows a possible means of measuring the strength of divergent selection. It is often to identify the age of extant demes within metapopulations (Whitlock, 1992); in most cases the neutral divergence (as measured by a age-class specific F_{ST}) is greatest in youngest populations. The Q_{ST} among recently colonized populations should be equal to F_{ST}, for selection will not have had much opportunity to act. Older populations will diverge more from the equivalence between Q_{ST} and F_{ST}. The rate at which the difference between the two measures increases will reflect the strength of selective differentiation among populations.

Finally, it is useful to recognize that the predictions made by these models about the change in variation among demes can be quite different depending on whether one is looking at the absolute or relative scale. For example, with epistatic variance the amount of variance among demes is expected to increase on an absolute scale, but Q_{ST} is actually predicted to be lower, relative to the case without the epistatic variance.

Applying simple results from coalescent theory to quantitative genetics has great promise in providing further results. Here we have seen that such quantitative genetic questions such as the maintenance of genetic variance, the partitioning of variance among populations, and the selective divergence of populations can be addressed by a coalescent approach, even with the complications of subdivided populations. Further work could use the strengths of the coalescent in providing moments of the distribution of allele frequencies to infer the variances of these

parameters and in providing more insight into the effects of direct and indirect selection. We need stronger models of the joint effects of selection, drift, migration and mutation to further our understanding of real populations. The combination of approaches from different subdisciplines holds real promise in achieving this.

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