Genetic Variability at Neutral Markers, Quantitative Trait Loci and Trait in a Subdivided Population Under Selection

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ABSTRACT

Genetic variability in a subdivided population under stabilizing and diversifying selection was investigated at three levels: neutral markers, QTL coding for a trait, and the trait itself. A quantitative model with additive effects was used to link genotypes to phenotypes. No physical linkage was introduced. Using an analytical approach, we compared the diversity within deme (H_S) and the differentiation (F_{ST}) at the QTL with the genetic variance within deme (V_W) and the differentiation (Q_{ST}) for the trait. The difference between F_{ST} and Q_{ST} was shown to depend on the relative amounts of covariance between QTL within and between demes. Simulations were used to study the effect of selection intensity, variance of optima among demes, and migration rate for an allogamous and predominantly selfing species. Contrasting dynamics of the genetic variability at markers, QTL, and trait were observed as a function of the level of gene flow and diversifying selection. The highest discrepancy among the three levels occurred under highly diversifying selection and high gene flow. Furthermore, diversifying selection might cause substantial heterogeneity among QTL, only a few of them showing allelic differentiation, while the others behave as neutral markers.

A S concern for conserving and managing natural populations in the face of environmental changes has increased, it is of urgent need to assess whether the most widely used method for describing genetic variability within and among populations, *e.g.*, molecular genetic markers, does provide information about genetic variability at adaptive traits. Several recent experimental studies (reviewed in BUTLIN and TREGENZA 1998; LYNCH *et al.* 1999; MCKAY and LATTA 2002) and two meta-analyses (MERILÄ and CRNOKRAK 2001; REED and FRANKHAM 2001) have demonstrated that there is no, or only weak, correlation between the two measures. In the case of outcrossing species, surveys conducted with molecular markers indicate that most of the variation resides within population whereas much higher population differentiation occurs for complex traits. A striking example illustrating this pattern is given by tropical and temperate forest trees (WRIGHT 1976; ADAMS *et al.* 1992; MORGENSTERN 1996). This discrepancy has traditionally been interpreted as the consequence of different evolutionary forces acting on the different classes of traits (BUTLIN and TREGENZA 1998). In addition to their different modes of evolution, the two classes of traits differ in their structure. Gene markers are usually analyzed as single-locus traits, even though multiple loci are investigated. However, quantitative traits are controlled by multiple loci and quantitative genetic variation includes

also covariances introduced by disequilibria among loci (MCKAY and LATTA 2002). As considerable progress has now been made toward identifying quantitative trait loci (QTL) or candidate genes responsible for trait variation, studies of the allelic variation underlying quantitative variation in natural populations should become more common (BARTON and KEIGHTLEY 2002). The objective of this article is to evaluate the impact of the contrasting properties of genetic markers and quantitative traits on the structure of their genetic diversity. We compare the level and distribution of genetic diversity at (i) neutral genetic markers, (ii) the QTL contributing to an adaptive trait, and (iii) the adaptive trait *per se*. This can be seen as an attempt to bridge the gap between population and quantitative genetics. Comparative analyses of genetic diversity at different integrative levels of the same trait have only seldom been addressed (LATTA 1998; BOST *et al.* 1999; KREMER *et al.* 2000). By applying the classical model of quantitative genetics in simulation studies, LATTA (1998) and KREMER *et al.* (2000) showed that population differentiation is in most cases expected to be different at these different levels. Our investigations extend this approach in two additional directions. First, we compare both within-deme variability and between-deme differentiation and estimate the impact of disequilibria on these two parameters. As shown by KREMER *et al.* (1997), the larger the disparity between within- and between-deme disequilibria, the higher the disparity between differentiation at multilocus and single-locus traits. Second, we address the variation from locus to locus.

Our investigations will help determine whether the

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use of QTL can complement or even replace phenotypic evaluation involving complex crossing schemes or common garden experiments. This approach implies identifying the more important genes from QTL detection studies and functional genomic data and then identifying within each gene the sequence polymorphisms that affect the phenotype (quantitative trait nucleotides, QTN). While this requires a great investment and is still out of reach in many species, it is already possible, using *in silico* simulations, to test whether describing the underlying allelic frequencies is sufficient to describe the distribution of genetic variability of an adaptive trait. We have reassembled earlier work on multilocus systems (LATTA 1998; KREMER *et al.* 2000) to provide approximate relationships between diversity and differentiation at a trait and at its underlying loci. In a second step, we have considered the effects of various evolutionary scenarios generated by simulations. The evolution of genetic parameters for a trait, its QTL, and neutral markers was modeled in a subdivided population undergoing different selection pressures. We have focused on the impact of selection within and between demes and compared simulations of outcrossing *vs.* predominantly self-fertilizing species with varying levels of gene flow among demes.

ANALYTIC DERIVATIONS

We considered a quantitative trait determined by n loci (QTL) acting additively, so that the genetic value of any individual was the sum over loci of the effects of the two parental alleles at each locus. All QTL had the same variance in allelic effects α^2 and the same mutation rate μ. There was no physical linkage among QTL. We then considered a set of d identical demes of constant size N. Migration occurred at a rate m and was supposed to be conservative, as in the island and stepping-stone models (WHITLOCK 1999).

The total allelic diversity at QTL was separated according to NEI (1987) into the within-deme expected diversity H_S and the between-deme expected diversity D_{ST}. The allelic differentiation among demes was measured by $G_{ST} = D_{ST}/(H_S + D_{ST})$. For diallelic loci, G_{ST} measures the fixation index F_{ST} as defined by WRIGHT (1951). In the text we use F_{ST} for diallelic loci and G_{ST} for multiallelic loci. The total amount of genetic variance for the trait was separated into its within-deme component V_W and its between-deme component V_B. A measure of differentiation for the trait analogous to the differentiation for allelic frequencies is

$$Q_{ST} = V_B(1 + F_{IS})/[V_B(1 + F_{IS}) + 2V_W]$$

(PROUT and BARKER 1989; SPITZE 1993; BONNIN *et al.* 1996), where F_{IS} is the within-deme inbreeding coefficient as defined by WRIGHT (1951).

For a neutral additive trait the quantitative differentia-

tion Q_{ST} is equal to the allelic differentiation F_{ST} (WHITLOCK 1999). No simple general relationships exists, however, that relates the within-deme component of variance V_W to the within-deme diversity H_S (FOLEY 1992).

As selection creates gametic disequilibrium among loci, the value of Q_{ST} no longer equals that of F_{ST} (WHITLOCK 1999). Two distinct components of genetic variance have to be considered: first, the contribution of allelic variation at each locus or genic variance and second, the covariance of allelic effects among loci. Considering first-order gametic disequilibrium only,

$$V = \sum_i \sigma_i^2 + \sum_i \sum_{j \neq i} \text{Cov}_{ij},$$

where σ_i^2 is the genic variance at locus i and Cov_{ij} is the covariance between locus i and locus j. Following GAVRILETS and HASTINGS (1995), we introduced the parameter $\theta = \sum_i \sum_{j \neq i} \text{Cov}_{ij} / \sum_i \sigma_i^2$ to simplify the previous expression to

$$V = (1 + \theta)\sum_i \sigma_i^2. \tag{1}$$

θ represents the part of the trait's variance due to the *effects of allelic associations* among QTL, relative to the part of the variance due to *individual allelic effects* at each QTL. Hence θ can be interpreted as a measure of disequilibrium of allelic effects among QTL, in contrast to disequilibrium measuring association of allelic states (KREMER *et al.* 1997). As shown by GAVRILETS and HASTINGS (1995) for a population under stabilizing selection, θ is approximately constant and, if loci are unlinked, depends only on the intensity of selection.

Most of the difficulties linked with the analytical treatment of selection on a multilocus trait in a subdivided population arise from the presence of genetic covariances among loci, at both the within- and the between-deme level. The multiallelic model is untractable analytically and was analyzed using simulations (see COMPUTER SIMULATIONS below), but some analytical results could be derived for a diallelic model. We considered n loci, each with two alleles having symmetrical additive genetic effects $-a/2$ and $+a/2$ (FALCONER and MACKAY 1996). The within- and between-deme components of the genic variance at each locus i have the relationship

$$\sigma_{Wi}^2 = (1 + F_{ISi})(1 - F_{STi})\sigma_{0i}^2$$
$$\sigma_{Bi}^2 = 2F_{STi}\sigma_{0i}^2 \tag{2}$$

(WRIGHT 1951; LANDE 1992), where σ_{0i}^2 is the variance expected at locus i in a single panmictic population with the same allele frequencies as the subdivided population (LATTA 1998; WHITLOCK 1999).

The diallelic model has the convenient property that, at each locus i, the genic variance is proportional to the expected genetic diversity (FALCONER and MACKAY 1996, Equation 8.5), so that

$$\sigma_{0i}^2 = a^2 H_{Ti},$$

which, by replacing into (2), leads to
$$\sigma_{Wi}^2 = a^2(1 + F_{ISi})H_{Si}$$

$$\sigma_{Bi}^2 = 2a^2 D_{STi}. \qquad (3)$$

If inbreeding is due only to the properties of the mating system, the F_{ISi} values have the same expectation, F, at each locus. Thus for a trait controlled by n loci, the within (V_W) and between (V_B) variance of the trait can be obtained after summing genic variances over loci:

$$V_W = na^2(1 + \theta_W)(1 + F)H_S$$

$$V_B = 2na^2(1 + \theta_B)D_{ST}. \qquad (4)$$

These results lead to the following relationship between Q_{ST} and F_{ST}:

$$Q_{ST} = V_B(1 + F)/(V_B(1 + F) + 2V_W)$$

$$= (1 + \theta_B)F_{ST}/[(\theta_B - \theta_W)F_{ST} + 1 + \theta_W]. \qquad (5)$$

Under the diallelic model, the differentiation for the selected trait Q_{ST} will therefore take the same value as the allelic differentiation F_{ST} at QTL in two cases:

1. There is linkage equilibrium among QTL (ROGERS and HARPENDING 1983; LATTA 1998) at the within-deme level and at the between-deme level ($\theta_B = \theta_W = 0$).
2. Linkage disequilibrium among QTL contributes equally to the within- and between-deme variances for the trait ($\theta_B = \theta_W$).

Consequently, Q_{ST} is equal to F_{ST} not only for a neutral phenotypic trait, but also for traits under selection and for which the disequilibrium among QTL is of the same amount at the within- and between-deme levels. Q_{ST} will be greater than F_{ST} if between-deme disequilibrium is dominant, which is expected when diversifying selection drives demes to different phenotypic optima. Q_{ST} will be smaller than F_{ST} if within-deme disequilibrium is dominant, which is expected under uniform selection, or when genetic drift or selection intensity is high (KREMER *et al.* 2000). The build-up of negative covariance within a population subjected to stabilizing selection is well known as the Bulmer effect and has been described analytically. BULMER (1974, 1989) considered an n-locus, continuum-of-alleles model and derived an approximation under weak selection, whereas GAVRILETS and HASTINGS (1994) derived exact equations for the value of θ_W in a two-locus, diallelic model. The occurrence of between-deme covariance in a subdivided population subjected to stabilizing and diversifying selection has been demonstrated by LATTA (1998) using simulations, but to our knowledge has never been investigated theoretically. In the following, we present results from computer simulations that describe in more detail the effects of stabilizing selection on covariance at both the within- and the between-deme levels.

COMPUTER SIMULATIONS

The simulation model and simulation procedures: We used *Metapop* (LE CORRE *et al.* 1997), a program designed to study the genetic evolution of a subdivided

TABLE 1

A summary of simulation parameters used and their values

s	Selfing rate	0; 0.9
d	No. of demes	25
N	No. of individuals per deme	500
m	Migration rate (island model)	0.0002; 0.002; 0.02
n	No. of QTL	10
μ	Mutation rate per locus	10^{-5}
α^2	Variance of allelic effects at each QTL	1
$V_M = 2n\mu\alpha^2$	Mutational variance per generation	2×10^{-4}
V_E	Environmental variance	1
ω^2	Intensity of stabilizing selection	10^9; 100; 50; 10; 5; 1
$V_{Z_{OPT}}$	Variance of phenotypic optima across demes	0; 1; 10; 50; 100

population of a diploid species under natural selection. The simulation model can be divided into three parts.

The genetic model: The phenotypic value of a given genotype was the sum of independent genetic and environmental contributions, $Y = G + E$, where E had a Gaussian distribution with mean zero and variance set to 1. The genetic value G was determined by summing the allelic effects over all QTL. In this study (Table 1) we considered 10 independent QTL with allelic effects drawn at random from a Gaussian distribution with mean zero and variance 1. The mutation rate was set to 10^{-5} for each QTL. Ten additional loci with no effect on the trait and unlinked to each other and to the QTL served as neutral genetic markers.

The population model: We considered 25 demes each of size 500, connected according to an island migration model. The number of migrants per generation, Nm, took the value 0.1, 1, or 10. The mating system was set to either complete allogamy or predominant selfing (selfing rate = 0.9).

Simulation of natural selection: At the within-deme level, stabilizing Gaussian selection toward a local optimum $Z_{OPT}(k)$ for deme k determined the relationship between individual phenotypic values and fitness (TURELLI 1984):

$$W_k(Z) = \exp[-(Z - Z_{OPT}(k))^2/2\omega^2].$$

The selection intensity ω^2 was set to vary from 1 to 100. In the absence of selection, the variance within deme under an island model is $2NdV_M$ (WHITLOCK 1999), which, after replacing with our parameter values (Table 1), gives $V_W = 5$. Therefore, values of $\omega^2 < 5$ are strong selection pressures, while a value of 100 is a weak selection pressure. Furthermore, a compilation and comparison of experimental data with mutation-selection models has shown that for most traits ω^2/V_E falls between 5 and 50 (ROFF 1997).

At the between-deme level, either uniform or diversifying selection was introduced by defining a separate

phenotypic optimum $Z_{OPT}(k)$ for each deme k. The diversifying action of selection was scaled by $V_{Z_{OPT}}$, the variance of $Z_{OPT}(k)$ over demes. In this study, $Z_{OPT}(k)$ varied according to a one-dimensional linear gradient on a grid of 5×5 demes by taking values $-x$, $-x/2$, 0, $x/2$, x, so that $V_{Z_{OPT}} = x^2/2$. The linear gradient was adopted for simplicity. As migration followed an island model, this had no effect on the genetic structure of the subdivided population. Five different values were chosen for $Z_{OPT}(k)$ in order to have an equal number of demes for each value. $V_{Z_{OPT}}$ was set to vary between 0 (uniform selection) and 10 (diversifying selection). In the absence of selection, the between-deme variance under an island model is $(d-1)V_M/m$ (WHITLOCK 1999; McKAY and LATTA 2002), which, after replacing with our parameter values (Table 1), gives $V_B = 24$, 2.4, or 0.24, for $Nm = 0.1$, 1, or 10, respectively. For $Nm = 0.1$, the between-deme variance expected in the simulations due to drift thus always exceeded the between-deme variance expected due to selection ($V_{Z_{OPT}}$, set to be at most 10). This was designed to model species with low gene flow, for which a similar high level of differentiation is observed at both neutral markers and traits (HENDRY 2003). By contrast, for $Nm = 10$, the between-deme variance expected due to drift was less than the between-deme variance expected due to selection for most simulated selection schemes. This was designed to model high gene flow species such as forest trees (McKAY and LATTA 2002). Simulations with $Nm = 1$ represented an intermediate case.

The starting point of each simulation was a population of 12,500 individuals homozygous at each locus. This population underwent random mating during 100,000 generations, during which new alleles were created by mutation and mutation-drift equilibrium was reached. Twenty-five demes were generated by sampling at random without replacement from this base population and evolved during 3000 generations under different evolutionary scenarios. Twenty-five different selection patterns were considered, corresponding to the combination of five levels of diversifying selection and five levels of selection intensities (see Table 1). In addition, a neutral scenario was also considered by setting ω^2 to 10^9 (Table 1). These 26 selection patterns were simulated for each combination of the number of migrants per generation and the selfing rate, thus generating 156 different scenarios. Within each scenario, 10 replicated simulations were run. In what follows, we compare the values of diversity and differentiation that were reached after 3000 generations.

Effects of selection parameters on genetic covariance among QTL: The extent of genetic covariance at the within-deme level, as measured by the parameter θ_W, depended primarily on the intensity of selection (Figure 1). Under complete allogamy, no or low linkage disequilibrium was maintained at the within-deme level, except when selection intensity was strong, *i.e.*, when $\omega^2 < 5$.

The variance of phenotypic optima had also an effect on the extent of within-deme covariance, but less important. When selection was highly diversifying (large $V_{Z_{OPT}}$), there was on average less negative covariance. This was because demes located at both ends of the gradient of phenotypic optima were selected toward extreme values, leading to a large reduction in variance and thus in the amount of covariance within them. As expected, under predominant selfing (10% allogamy), much larger amounts of negative linkage disequilibrium were maintained at the within-deme level, as recombination was then less effective. Under very strong selection ($\omega^2 \leq 5$), values of θ_W were close to -1, indicating that nearly all the within-deme genic variance was absorbed by negative covariance among loci.

The extent of between-deme covariance depended primarily on $V_{Z_{OPT}}$ (Figure 1). Theory predicts that positive covariance is generated at the between-deme level when $V_{Z_{OPT}}$ is much larger than the neutral between-deme variance and that negative covariance is generated when $V_{Z_{OPT}}$ is much smaller than this variance (LATTA 1998). The expected neutral variance between demes, 24, 2.4, or 0.24, for $Nm = 0.1$, 1, or 10, provided reliable estimates of threshold values of $V_{Z_{OPT}}$ when selection was weak, in which case the phenotypic differentiation among demes to match $V_{Z_{OPT}}$ was due mainly to between-deme covariance (Figure 1). However, when selection was strong, it also modified allele frequencies at QTL, so that the between-deme genic variance increased and response to diversifying selection could be achieved with less positive covariance or even negative disequilibrium between demes, as can be seen from Figure 1, especially for $Nm = 10$. Similar patterns were observed for 100% allogamy and 10% allogamy.

Figure 1 shows that, whatever the selfing rate, the disparity between covariance among QTL at the within- and between-deme levels is maximal in the following two circumstances: first, weak uniform selection on a species having a low migration rate (then $\theta_B \ll \theta_W$) and second, weak but highly diversifying selection on a species having a high migration rate (then $\theta_B \gg \theta_W$).

Comparison of simulation results with predictions of the diallelic model: From Equation 4 above, the genetic variance within deme is a function of the allelic diversity H_S at QTL, weighted by the term $1 + \theta_W$, where θ_W represents the covariance among QTL. Figure 2 shows simulation values for the within-deme variance for the trait as a function of the within-deme allelic diversity at QTL across the 25 selection patterns. An approximately linear relationship was observed on a log-log scale. This was in agreement with Equation 4 and with the parallel variation in θ_W and H_S as a function of the intensity of selection (Figures 1 and 5). The slope of the linear relationship between V_W and H_S did not vary with the migration rate.

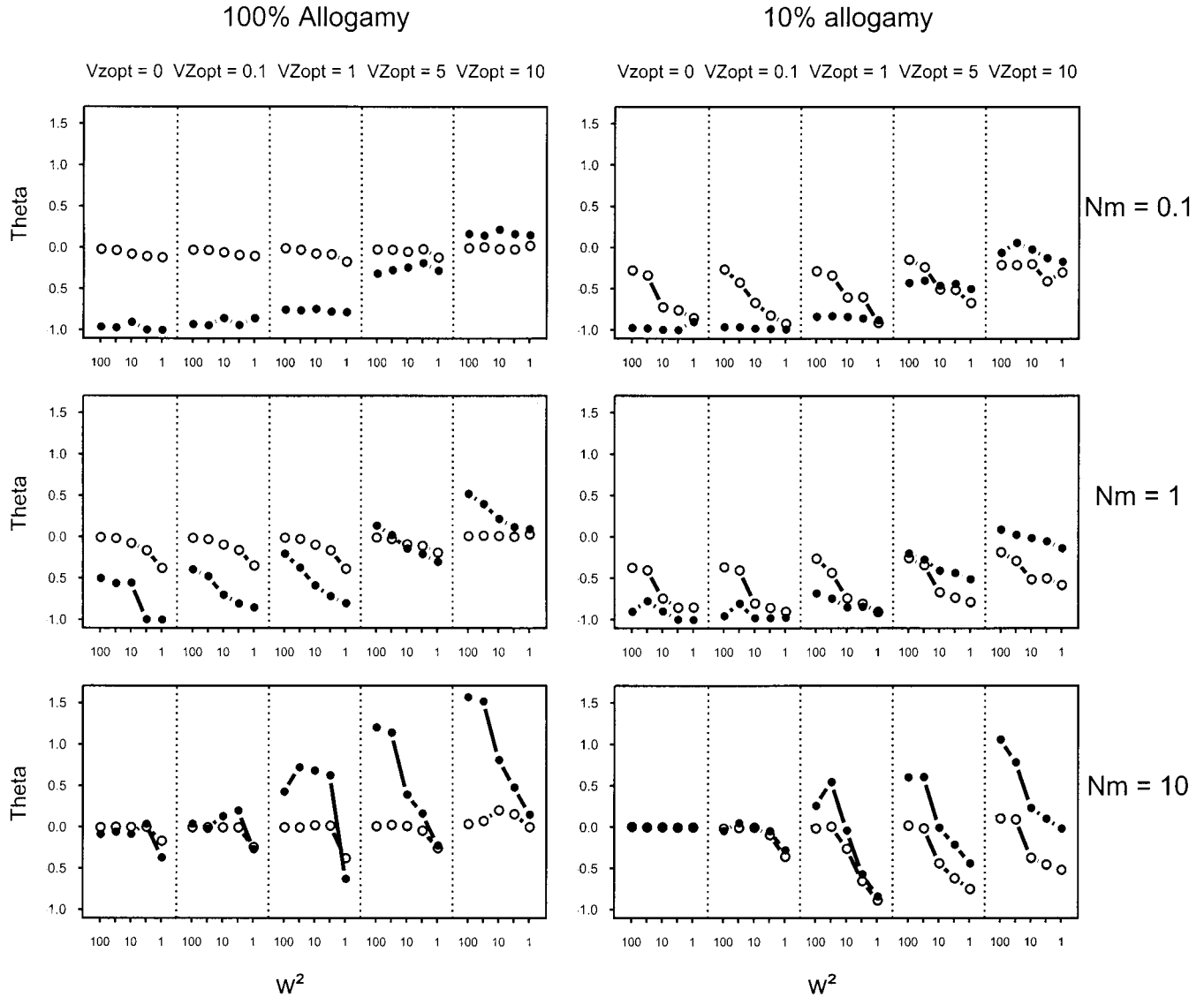Figure 3 shows simulation and expected values of Q_{ST} over the 25 stabilizing selection patterns. Expected

FIGURE 1.—The effect of variance of phenotypic optima ($V_{Z_{OPT}}$) and intensity of stabilizing selection (ω^2) on the genetic covariance among QTL at the ($\bigcirc$) within- and ($\bullet$) between-deme levels, θ_W and θ_B. On each graph, the different subplots correspond to varying degrees of diversifying selection among demes, from uniform ($V_{Z_{OPT}} = 0$) on the left to highly diversifying ($V_{Z_{OPT}} = 10$) on the right. Within each subplot, the x-axis represents the intensity of selection within deme, from weak ($\omega^2 = 100$) on the left to strong ($\omega^2 = 1$) on the right.

values were derived from the diallelic model according to Equation 5. They were calculated from observed values of G_{ST} at the QTL and θ_B and θ_W values. The diallelic model underestimated Q_{ST} values for most selection patterns. One explanation for the lack of adequacy of the diallelic model may come from the fact that we considered first-order gametic disequilibrium only, whereas gametic disequilibria of higher orders may also be present and will be all the more important as more alleles are maintained. However, Figure 4 shows that despite that the diallelic model was quantitatively erroneous, it was qualitatively well verified by the simulations results. As predicted by Equation 5, Q_{ST} values were greater or smaller than G_{ST} values at the QTL depending on the kind of selection simulated. For most selection patterns

tested, Q_{ST} was greater than G_{ST} at the QTL when covariance for the trait was higher at the between-deme level than at the within-deme level (Figure 4, solid symbols).

Comparison of within-deme genetic variability at neutral markers, QTL, and trait across different selection patterns: Figure 5 shows the genetic variability at the within-deme level, measured either by allelic diversity H_S at markers (neutral or QTL) or by the heritability h^2 for the trait, for the different selection patterns. Under complete allogamy, H_S at neutral markers remained close to its value in the absence of selection (respectively 0.155, 0.286, and 0.326 for $Nm = 0.1$, 1, and 10) and decreased only under very strong and diversifying selection. As expected, this indirect effect of selection on unlinked neutral markers was more pronounced under
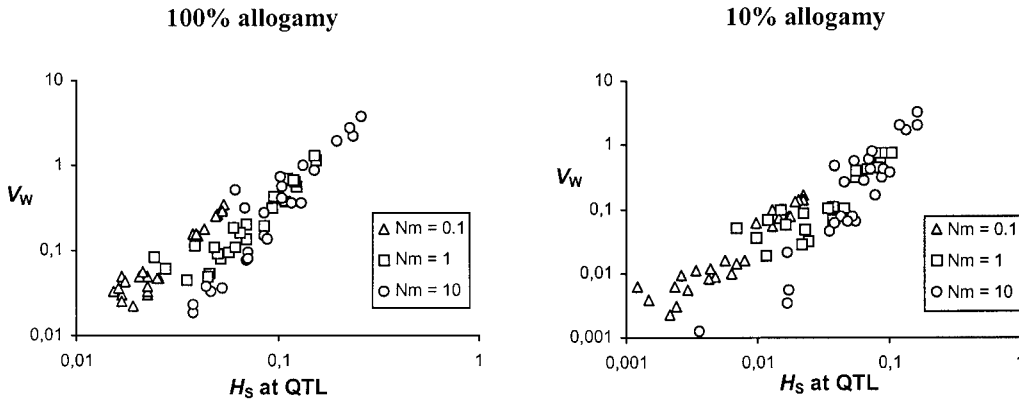
100% allogamy 10% allogamy

FIGURE 2.—Within-deme variance for the trait, V_W, as a function of H_S, the allelic diversity at QTL, over the different selection patterns simulated and for three different migration rates. Scale is logarithmic on both axes.

selfing, because of fewer recombination events between the neutral markers and the QTL. The allelic diversity at QTL was always lower than the allelic diversity at the neutral markers and decreased as selection intensity increased. However, it also varied as a function of the variance of phenotypic optima among demes. Under high gene flow ($Nm = 10$) and highly diversifying but weak selection ($V_{Z_{OPT}} \geq 5$ and $\omega^2 \geq 10$), an increase in H_S at the QTL was observed, which was probably due to the mixing by gene flow of the different alleles selected for in demes having different phenotypic optima. In contrast to molecular markers, the amount of within-deme genetic variability for the trait, measured by the heritability, showed a complex pattern in response to the simulation parameters tested. In general, the trend of variation was parallel but more amplified to the allelic diversity at the QTL. Under low to moderate gene flow, within-deme heritability depended only on the intensity of selection. Under large gene flow ($Nm = 10$), it depended on the interacting effects of both the selection intensity and the variance of phenotypic optima among demes. It was then lowest for strong uniform selection and highest for weak, highly diversifying selection. Strong selection depleted genetic variation in each deme, while under diversifying selection, gene flow could restore variation by mixing individuals with different phenotypic values.

The correlation between H_S at markers (neutral and

QTL) and heritability for the trait was quantified by calculating Spearman's rank coefficient across the 25 different combinations of selection parameters. All correlations were significant except between neutral markers and trait when gene flow was high ($Nm = 10$). The correlations between neutral markers and trait were always smaller than the correlations between QTL and trait. Furthermore, the significant correlations between neutral markers and trait were caused entirely by the genetic drift effect associated with the strongest selection intensities simulated ($\omega^2 \leq 5$). Under weak to moderate selection ($\omega^2 > 5$), no significant correlations were found between neutral markers and trait, whereas H_S at QTL was highly and significantly correlated with the heritability for the trait (Spearman's ρ varied from 0.936 for $Nm = 0.1$ to 0.975 for $Nm = 10$ under 100% allogamy and from 0.83 for $Nm = 0.1$ to 0.976 for $Nm = 10$ under 10% allogamy). However, as can be seen from Figure 5, the allelic diversity at the QTL did not perfectly track the heritability for the trait across the different selection patterns. Both parameters decreased with increasing selection intensity, but the allelic diversity at QTL was much less affected by the variance of phenotypic optima than was the heritability. As noted above, under diversifying selection, gene flow has a large effect on the within-deme variance for the trait because migrant alleles may carry an additive effect very different from that of resident alleles. But, as those migrant alleles are in low frequency, they have only a small effect on H_S at the QTL.
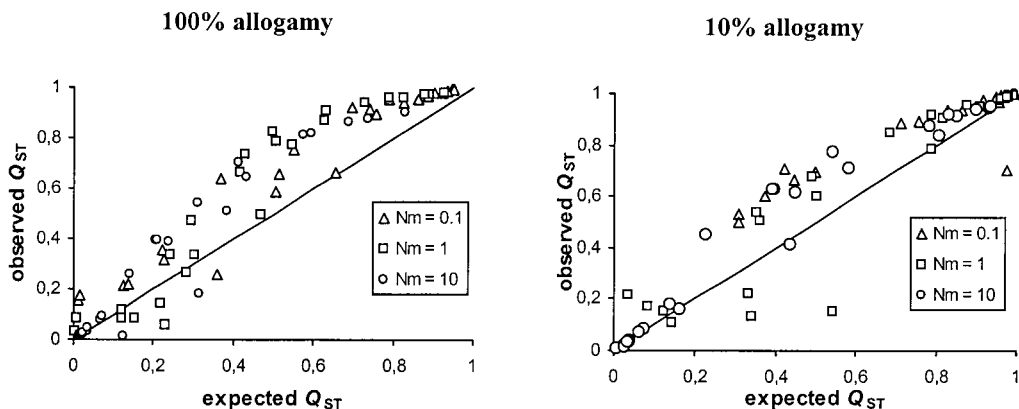
100% allogamy 10% allogamy

FIGURE 3.—Differentiation at the trait (Q_{ST}) over the different selection patterns simulated, as a function of its expected value in the diallelic case $(1 + \theta_B) G_{ST} / [(\theta_B - \theta_W) G_{ST} + 1 + \theta_W]$ (see Equation 5).
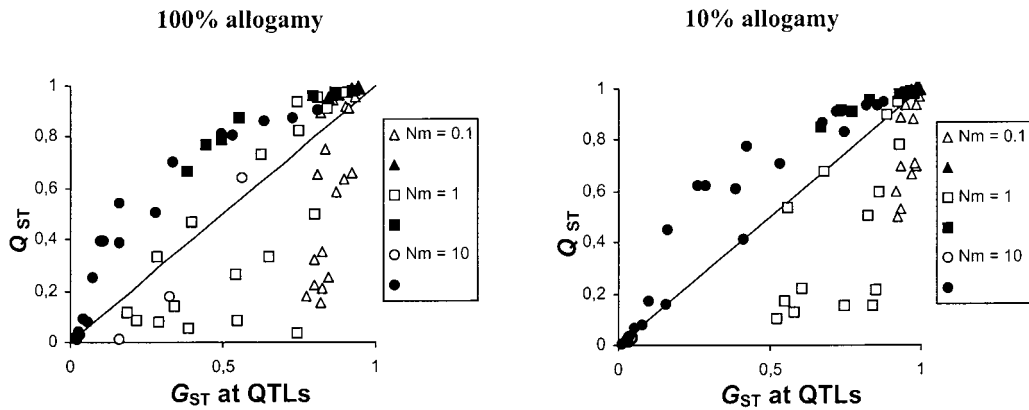
FIGURE 4.—Differentiation at the trait, Q_{ST}, as a function of G_{ST}, the allelic differentiation at QTL, over the different selection patterns simulated and for three different migration rates. Selection patterns generating more genetic covariance at the between-deme level than at the within-deme level (*i.e.*, $\theta_B > \theta_W$) are plotted with solid symbols. Selection patterns generating less genetic covariance at the between-deme level than at the within-deme level (*i.e.*, $\theta_W > \theta_B$) are plotted with open symbols.

Comparison of genetic differentiation at neutral markers, QTL, and trait across different selection patterns: Figure 6 shows the between-deme differentiation, G_{ST} for neutral markers and QTL, and Q_{ST} for the trait, for the different selection patterns simulated. Differentiation at neutral markers increased when selection intensity and variance of phenotypic optima increased. Thus, whereas G_{ST} at neutral markers is unaffected by weak or moderate selection, it can be substantially increased by strong and highly diversifying selection. Genetic differentiation at the QTL was always equal to or higher than genetic differentiation at the neutral markers, even under uniform selection. Under the set of selection parameters tested, G_{ST} at QTL increased mainly with increasing intensity of selection and also, but in a less dramatic manner, with increasing variance of phenotypic optima. Q_{ST} varied as a function of both selection intensity and variance of phenotypic optima, being smallest under weak uniform selection and highest under strong diversifying selection. The between-deme component of selection ($V_{Z_{OPT}}$) had less effect on the allelic differentiation at the QTL than on the differentiation for the trait. As before, the reason was that G_{ST} at QTL reflected differences in the frequencies of alleles among populations, whereas the Q_{ST} value also took into account the effect of alleles on the trait's value.

Spearman's rank correlation was calculated between G_{ST} at neutral markers or QTL and Q_{ST} across the different selection patterns simulated. Correlations varied between 0.72 and 0.98 and all were highly significant. However, Figure 6 shows that under diversifying selection, G_{ST} at neutral markers was always much smaller than Q_{ST}, whereas G_{ST} at QTL approached Q_{ST} values more closely. By contrast, under uniform selection and reduced gene flow, QTL were misleading, as they showed a high level of allelic differentiation, whereas no differentiation was present for the trait.

Heterogeneity of the response to selection among QTL coding for a same trait: Until now, we have compared Q_{ST} with G_{ST}, the mean allelic differentiation at all loci affecting the trait's value. However, identifying every locus underlying a given trait is hardly achievable in practice. Essentially, a few loci showing the highest contributions to the trait's variance can be identified and used for population genetics studies. The QTL coding for a same selected trait may differ in their allelic variability and contribution to the trait's variance because they differed in their genetic effects on the trait before selection took place. We have not considered this in this study. Instead, we have considered QTL having identical effects on a trait initially (except for the stochastic variation associated with the sampling of additive values of alleles in a Gaussian law) and questioned whether they would differentiate in their allelic variability and contribution to the trait's variance in response to selection.

A polymorphic locus was defined as a locus having its most frequent allele in frequency <0.95 over the subdivided population. The number of polymorphic neutral markers varied between 7.9 and 8.3 and was unaffected by selection (data not shown). Table 2 shows how many QTL were polymorphic at the end of the simulations. Under diversifying selection, the number of polymorphic QTL was almost identical to the number of polymorphic neutral markers. By contrast, most QTL became fixed or nearly fixed under uniform selection as gene flow increased. In other cases, between one-half and two-thirds of the QTL retained allelic polymorphism. Thus the allelic richness at QTL, which represents the short- to mid-term potential for adaptation, differed greatly according to an interaction between the type of selection acting on the trait (uniform or diversifying) and the amount of gene flow. In the following, we consider only polymorphic QTL, since fixed or nearly fixed QTL are likely to show erratic, noninformative patterns of genetic differentiation. Furthermore, if not known as candidate genes or from interspecific crosses, fixed or nearly fixed QTL have only a few chances to be detected in segregation studies.

The heterogeneity of G_{ST} values among loci was measured using the statistic k defined by LEWONTIN and
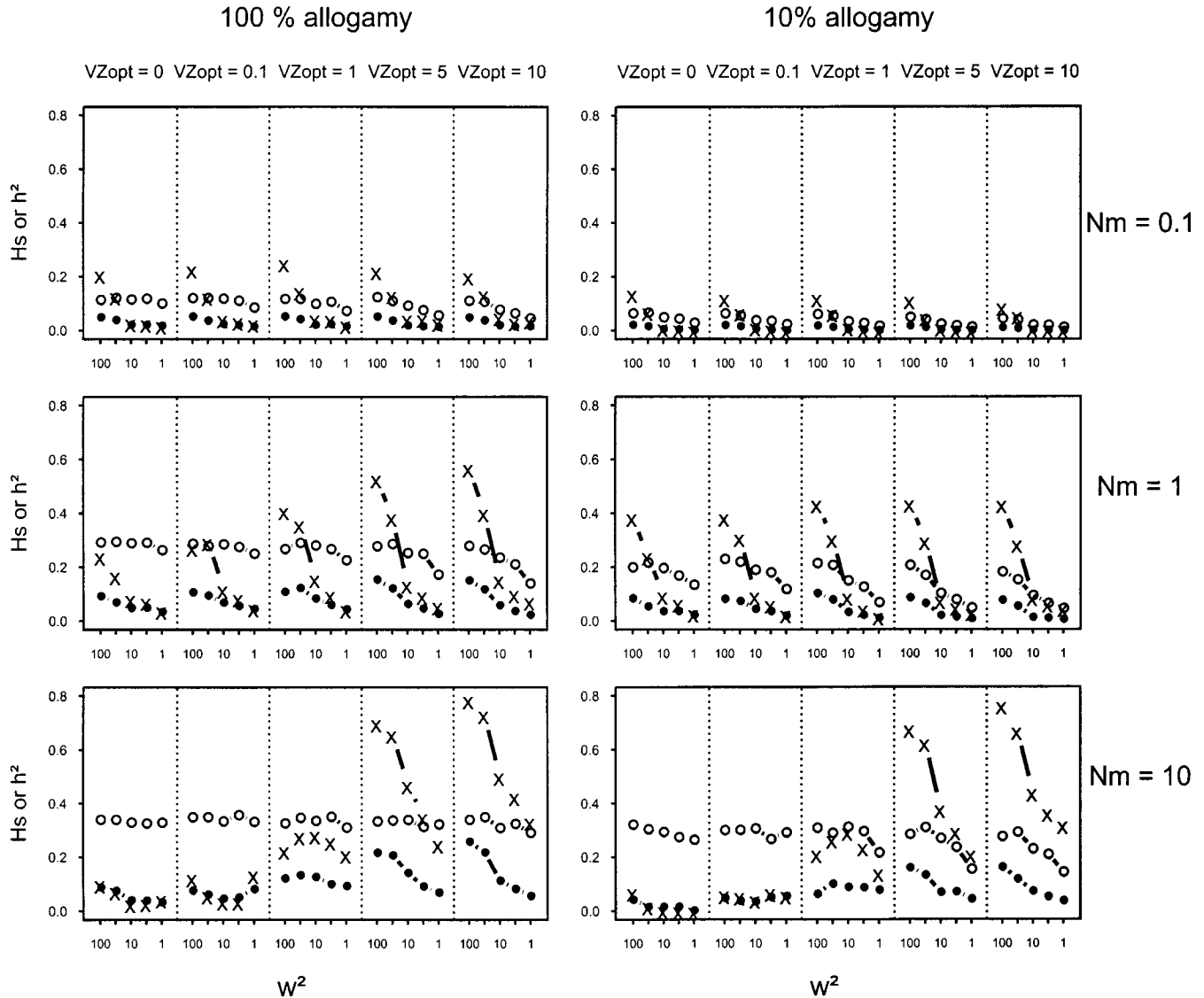
FIGURE 5.—The effect of variance of phenotypic optima ($V_{Z_{OPT}}$) and intensity of selection (ω^2) on the within-deme genetic diversity (H_S) at (○) neutral markers and (●) QTL and on the within-deme heritability for the (X) trait (h^2). The different graphs are arranged as in Figure 1.

KRAKAUER (1973). This statistic was originally defined to provide a test for neutrality, since for neutral loci, k is expected to be ≤ 2 (LEWONTIN and KRAKAUER 1973). k was calculated as

$$k = (d - 1)\text{var}(G_{ST})/\overline{G_{ST}}^2$$

(BAER 1999), where d is the number of demes and var(G_{ST}) and $\overline{G_{ST}}$ are, respectively, the variance and the mean of G_{ST} across loci.

The heterogeneity of G_{ST} values among neutral markers was unaffected by selection (data not shown) but increased with gene flow. The average values of k were 0.41, 1.21, and 1.56 for $Nm = 0.1$, 1, and 10, respectively, under complete allogamy, and 0.13, 0.62, and 1.61 under predominant selfing. Table 3 shows the heterogeneity of G_{ST} values among polymorphic QTL. For each selection pattern, we compared the k values obtained

at QTL with the k values obtained at neutral markers from 10 replicated simulations using a Wilcoxon signed rank test for paired data. Under strong, uniform selection with low gene flow and selfing, polymorphic QTL had high G_{ST} values and displayed significantly less heterogeneity than neutral markers did. By contrast, under weak diversifying selection with high gene flow and no selfing, polymorphic QTL displayed significantly more heterogeneity in allelic differentiation than neutral markers did. They behaved as a mix of neutral and selected loci, having either a low G_{ST} value due to large gene flow or a high G_{ST} value due to diversifying selection.

The heterogeneity among QTL was explored more in detail for a case of moderate diversifying selection, when $V_{Z_{OPT}} = 5$ and $\omega^2 = 50$ (Figure 7). The contribution of each polymorphic QTL to the between-deme genetic variance of the trait has two components: first, the be-
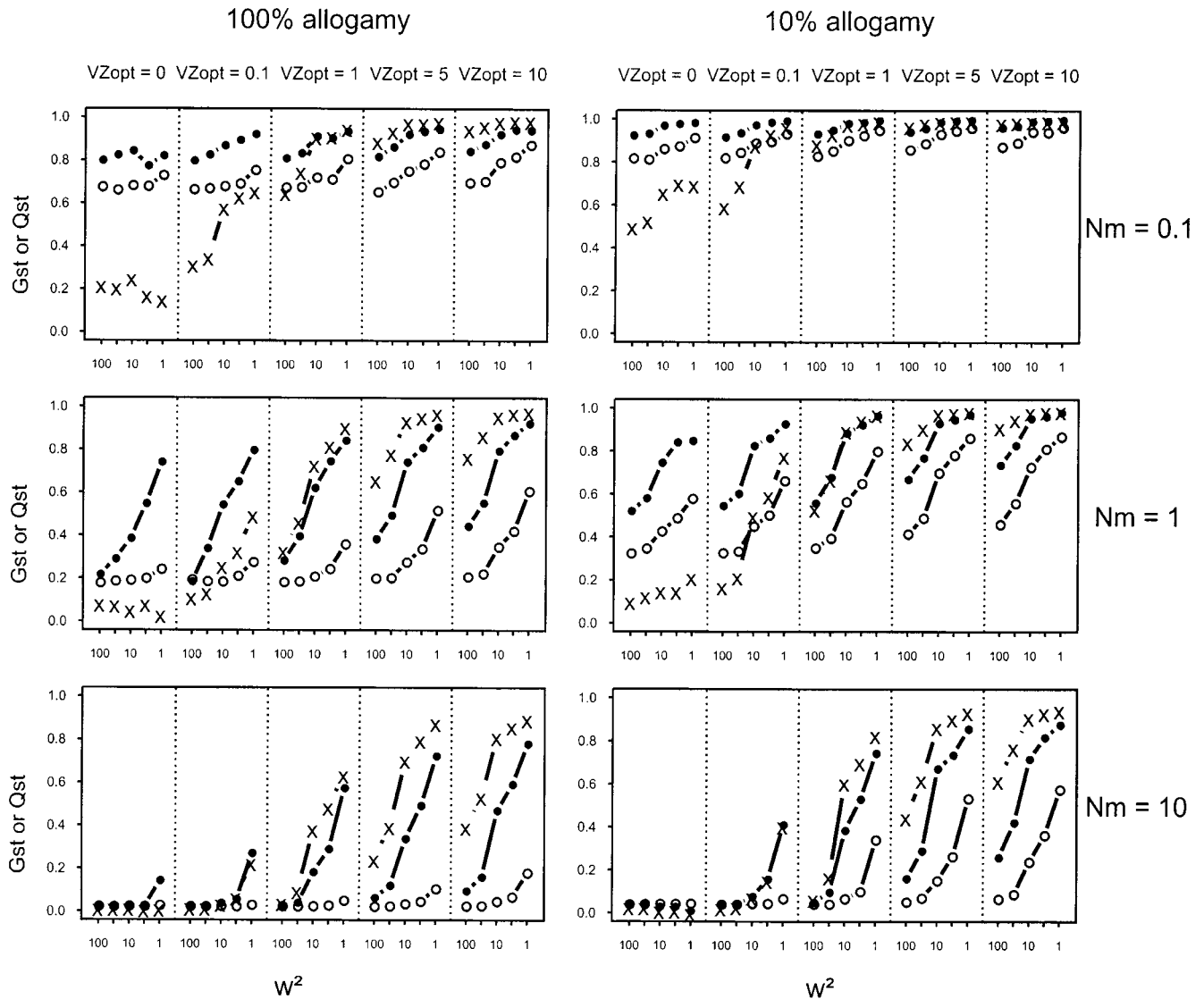
FIGURE 6.—The effect of variance of phenotypic optima ($V_{Z_{OPT}}$) and intensity of selection (ω^2) on the genetic differentiation G_{ST} at (○) neutral markers and (●) QTL and on the quantitative differentiation (X) Q_{ST}. The different graphs are arranged as in Figure 1.

tween-deme genic variance at the locus and second, the between-deme genetic covariance with other QTL. These two contributions have been studied as a function of the allelic differentiation, by grouping QTL into several class intervals of G_{ST} values (Figure 7). Under low gene flow ($Nm = 0.1$), most polymorphic QTL fell in the class of highest G_{ST} values (between 0.8 and 1) and displayed a high between-deme genic variance, compensated for by negative genetic covariance with other QTL. For an intermediate level of gene flow ($Nm = 1$), the complete range of G_{ST} values, from low (0–0.20) to high (0.80–1), was found among the polymorphic QTL. The highest between-deme genic variance was displayed by highly differentiated QTL, which were also negatively correlated with most other QTL. Under high gene flow ($Nm = 10$), most polymorphic QTL fall in the class of lowest G_{ST} values (between 0 and 0.20) and contributed very little to the between-deme genic variance of the

trait. Response to diversifying selection was achieved by allele frequency changes at a few loci that displayed a high G_{ST} value together with a high between-deme genic variance and positive covariance with one another.

Thus, notably, when a trait is experiencing diversifying selection under intermediate to high gene flow, the underlying QTL seem to have an L-shaped distribution of their contribution to the between-deme genetic variance. Most QTL contribute little to the variance, while a few contribute a lot. Such an L-shaped distribution has indeed been frequently observed in QTL detection studies (FALCONER and MACKAY 1996; KEARSEY and FARQUHAR 1998).

DISCUSSION

Analytic approach *vs.* simulations: The study of variation in adaptive traits has been recognized as a major

TABLE 2

Number of polymorphic QTL under the different selection patterns simulated

	$V_{Z_{OPT}}$									
	100% allogamy					10% allogamy				
ω^2	0	0.1	1	5	10	0	0.1	1	5	10
					$Nm = 0.1$					
1	6.1	5.8	6.0	6.7	6.9	7.2	7.4	7.1	7.5	7.2
5	5.1	5.3	6.4	6.0	6.7	6.8	7.2	6.8	7.3	7.5
10	5.1	5.6	5.9	5.9	6.7	6.5	6.7	6.7	7.2	7.3
50	5.9	6.1	6.5	6.8	6.9	6.7	6.6	7.2	7.0	7.2
100	6.6	6.9	6.9	7.2	7.5	7.4	6.8	7.3	7.5	7.7
					$Nm = 1$					
1	4.3	6	6.2	6.2	6.7	6.5	6.7	7.3	7	7.4
5	4.1	4.8	5.7	5.8	6.3	6.4	6.5	6.3	7.5	6.9
10	3.1	4.4	5.7	5.6	6.6	5.5	6.6	6.8	6.8	6.9
50	2.9	4.1	5.2	5.3	6.2	4.6	5.7	6.2	7.2	7.2
100	3.3	3.8	4.5	5.9	6.4	5.2	4.7	6.2	6.3	6.4
					$Nm = 10$					
1	1.6	2.3	5	5.6	6.5	0.1	2.5	6.5	7.1	6.8
5	1.2	1.7	3	4.9	5.9	0.4	1.8	4.1	6.3	6.3
10	1.4	1.9	3.8	4.4	4.9	0.6	1.0	3.2	5.1	5.5
50	2.7	2.6	3.7	5.8	5.8	0.7	1.4	3.0	4.1	4.5
100	3.0	2.8	3.5	5.3	6.4	1.5	1.3	2.1	4.3	4.9

A QTL was considered as polymorphic when the frequency of its most common allele over the subdivided population was <0.95. Means over 10 replicates for each set of selection parameters are given for each case.

topic in conservation biology and the management of genetic resources (STORFER 1996; FRANKHAM 1999; BOOY *et al.* 2000), and a number of experimental investigations have recently studied the genetic differentiation of populations using both marker loci and quantitative traits (see McKAY and LATTA 2002 for a review of published data for 29 species). By contrast, analytical models for the evolution of selected traits in subdivided populations have only rarely been proposed. Their complexity usually requires simplifying assumptions such as infinite number of loci and linkage equilibrium (see NARAIN and CHAKRABORTY 1987; TACHIDA and COCKERHAM 1987; NAGYLAKI 1994). Even fewer studies (LATTA 1998) have focused on the theoretical basis of the discrepancy observed between genetic variability at a trait *vs.* that at the loci coding for the trait. The diallelic model we used clarified the effects of within- and between-deme gametic disequilibria at QTL on the difference between the two measures of differentiation, Q_{ST} and F_{ST}. However, when compared to simulations based on multiallelic loci, the diallelic model was found to underestimate the difference between Q_{ST} and F_{ST}. Because of the limits of analytical approaches, computer simulations are a promising tool for the investigation of the dynamics of adaptive traits in subdivided populations. In his simulation study, LATTA (1998) pointed out that selection results in linkage disequilibrium between QTL rather than in allele frequency changes at the between-deme level, thus decoupling the differentiation at QTL from

the differentiation for the trait. Our simulations have extended Latta's results to the within-deme level. We also examined the relationship between differentiation for the trait and differentiation at QTL on a locus-per-locus basis.

Discrepancy between diversity and differentiation at an adaptive trait and its underlying QTL: H_S and G_{ST} are basically single-locus measures, even though they are averaged over all QTL. On the other hand, V_W and Q_{ST} are multilocus measures, since they also include covariances generated by gametic disequilibria (Equation 1). Therefore the discrepancies observed between the two kinds of measures are a direct consequence of their properties. These discrepancies were more pronounced for differentiation than for within-deme diversity, because disequilibria at both the within- and the between-deme levels contributed to Q_{ST} whereas only θ_W contributes to V_W. The equilibrium value of V_W and H_S decreased as the intensity of stabilizing selection got stronger. This parallel evolution contributed to the positive correlation between V_W and H_S as shown by Figure 2. However, the combined effect of gene flow and diversifying selection can contribute to maintaining higher levels of within-deme variability for the adaptive trait than for the QTL. This is because migrant alleles in the case of strong diversifying selection may only slightly change allele frequencies, but can have larger effect on the additive value of the trait.

At the between-deme level, our results indicate that

TABLE 3

Heterogeneity of G_{ST} values among polymorphic QTL as measured by Lewontin and Krakauer's k statistic, for the different selection patterns simulated

	$V_{Z_{OPT}}$									
	100% allogamy					10% allogamy				
ω^2	0	0.1	1	5	10	0	0.1	1	5	10
					$Nm = 0.1$					
1	0.35	0.19*	0.17	0.16	0.10	0.00**	0.00**	0.00**	0.01*	0.00**
5	1.08	0.29	0.23	0.09*	0.17	0.01**	0.01**	0.03*	0.03	0.01**
10	0.25*	0.29	0.15**	0.17	0.21	0.03**	0.02**	0.01**	0.02*	0.03
50	0.38	0.26	0.44	0.40	0.26	0.13	0.13	0.07**	0.09	0.04**
100	0.38	0.77	0.25	0.39	0.28	0.07**	0.10*	0.10	0.09	0.05
					$Nm = 1$					
1	1.94	1.24	1.09	0.40	0.20*	0.04**	0.05**	0.03**	0.10	0.04
5	3.83*	2.32	1.57	1.27	0.48*	0.71	0.17**	0.10*	0.07	0.08
10	—	3.02*	3.84**	2.34	1.44	0.28	0.70	0.15**	0.07**	0.04**
50	—	4.16*	5.31**	6.24**	5.22**	1.08	1.34	1.65	1.02	0.52
100	—	—	4.08*	6.57**	5.14**	3.02*	1.72*	2.72**	1.62**	1.05
					$Nm = 10$					
1	—	—	6.22*	2.88	1.24**	—	—	0.24**	0.11**	0.11**
5	—	—	—	10.77**	6.20**	—	—	3.91	0.97*	0.31**
10	—	—	—	15.99**	6.20**	—	—	—	1.40	1.92
50	—	—	—	27.84**	20.44**	—	—	—	12.35**	9.67**
100	—	—	—	22.61**	19.56**	—	—	—	21.23**	12.63**

Lewontin and Krakauer's k was not calculated when less than four QTL were polymorphic on average (see Table 2). Means over 10 replicates of each selection pattern are given. Asterisks represent the significance of the difference of k between QTL and neutral markers as determined by a paired signed-rank Wilcoxon test; two-sided probability values were calculated. *$0.01 \leq P < 0.05$; **$P < 0.01$.

the difference between the gametic disequilibria within and between demes (*e.g.*, between θ_B and θ_W) is the key factor involved. Under diversifying selection, if θ_B and θ_W reach similar values, G_{ST} and Q_{ST} are expected to be equal. Whatever the selection scenario considered, when $\theta_B > \theta_W$ then $Q_{ST} > G_{ST}$ of the QTL and vice versa as predicted by Equation 5 and as shown on Figures 4 and 6. As the difference between both disequilibria increased, the difference between G_{ST} and Q_{ST} also increased. These results confirm earlier comparative analyses of mono- and multitrait systems, which also outlined the role of the disparity between disequilibria in population differentiation (KREMER *et al.* 1997).

Comparative dynamics of variability at neutral markers, QTL, and adaptive traits, and inferences on selection patterns: Neutral markers, QTL, and adaptive traits responded very differently to different selection scenarios and gene flow as shown by Figures 5 and 6. Contrasting patterns can be identified corresponding to whether there is congruence or discrepancy for diversity and differentiation at the three levels considered (neutral markers, QTL, and traits), leading to some practical recommendations for assessing adaptive variation within and between natural populations.

The most peculiar pattern appears when there is complete congruence among the three levels for diversity and differentiation. This is the case when there is low gene flow and diversifying selection. Both factors act toward high differentiation and extremely low diversity within deme. In this case, measures at the three levels are congruent and assessment done with neutral markers would be sufficient for genetic surveys.

A second less trivial case occurs when congruence for differentiation coexists with a discrepancy for diversity. This occurs when uniform selection is associated with high gene flow. In this case extremely low differentiation occurs at all three levels, but diversity is strikingly higher at neutral markers than at QTL or the trait. Due to uniform selection the same alleles are selected in all demes and diversity of QTL and the trait reaches low values. In this case the use of neutral markers for measuring adaptive diversity within deme would be misleading; however, assessments at the QTL would be reliable.

A third case occurs when there is congruence for diversity but discrepancy for differentiation. This occurs when gene flow is low and there is uniform selection. Diversity is depleted for all three levels, and differentiation is strikingly low for the trait but high for the QTL and neutral markers. This discrepancy is due to a large negative covariance between QTL. This covariance ensures a very low differentiation at the trait in spite of a
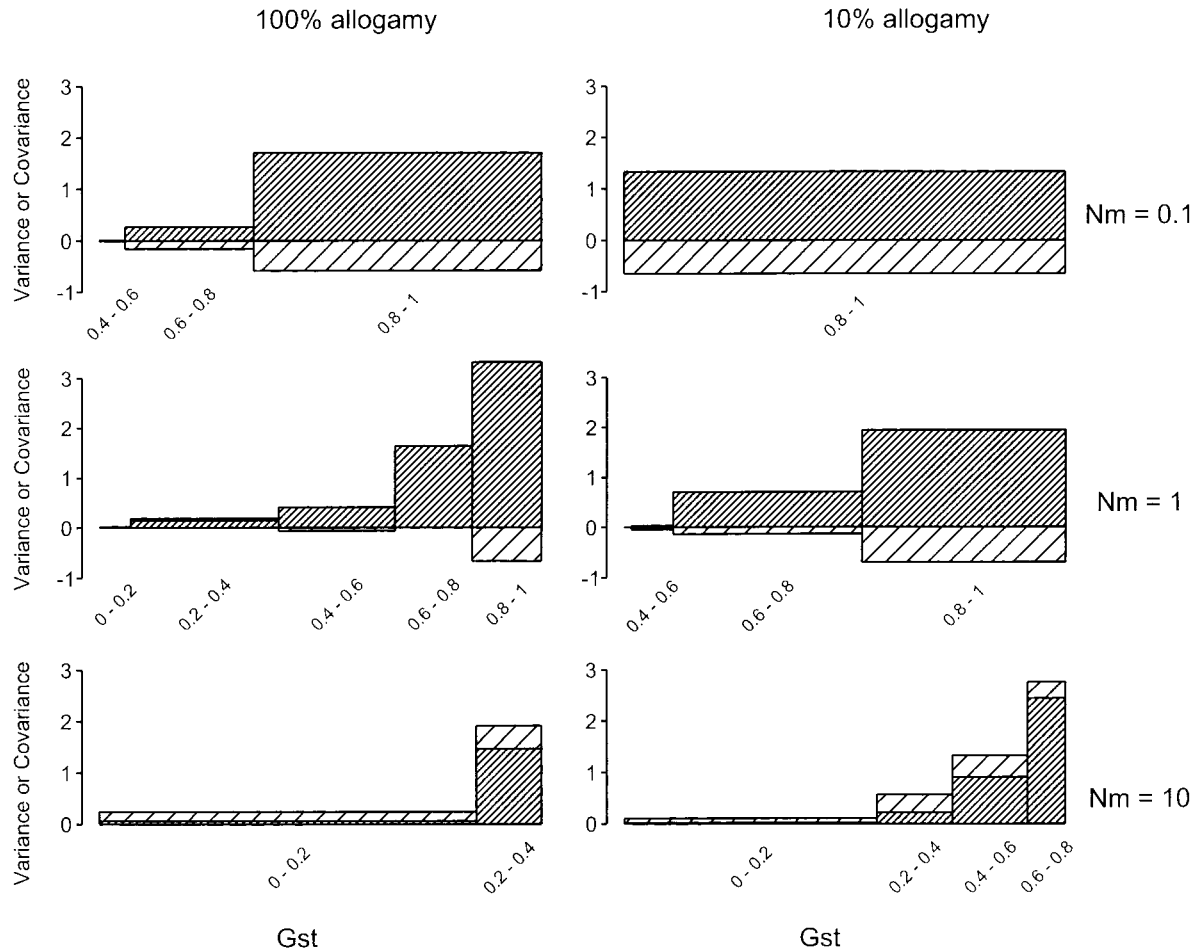
FIGURE 7.—Contribution of each polymorphic QTL to the between-deme (▨) genic variance and (▨) genetic covariance for the trait under weak diversifying selection. Simulation parameters were $V_{Z_{OPT}} = 5$ and $\omega^2 = 50$. Polymorphic QTL were classified into six groups according to their G_{ST} value (0–0.2; 0.2–0.4; 0.4–0.6; 0.6–0.8; 0.8–1). Height of hatched bars represents the contribution to the genic variance or to the genetic covariance of each QTL, averaged over all QTL in a given class of G_{ST} values. Width of hatched bars is proportional to the number of QTL found in the class.

high level of differentiation at each QTL. Neither neutral markers nor QTL would be recommended for assessing differentiation of present adaptive traits. However, the allelic differentiation at the QTL, which is offset by disequilibria, may be relevant from the point of view of future adaptation.

Finally, the last case arises when there is an important discrepancy between the three levels for both diversity and differentiation. This situation occurs when there is highly diversifying selection and important gene flow. As already mentioned, higher within-deme diversity for traits than for QTL can be maintained due to the more pronounced effect of migrant alleles on the additive values than on the allelic frequency. The difference between θ_B and θ_W is expected to be larger, increasing the discrepancy between Q_{ST} and G_{ST} of the QTL. As the contribution of covariances among QTL represents the largest component of the variance of the adaptive trait, a suggested option would be to assess disequilibria between QTL (association between alleles at QTL), even though the allelic effects are not known.

These peculiar dynamics may in turn be used to interpret the existing data and infer conclusions on selection occurring in natural populations, which is usually difficult to assess. The several recent studies that have focused on the comparison of differentiation at quantitative traits *vs.* biochemical or molecular markers may highlight which evolutive scenarios are more likely among the several described in our study. The general lack of association found between neutral marker and quantitative genetic variation within population (REED and FRANKHAM 2001) suggests, if not due to a bias toward allogamous species with high gene flow, that natural stabilizing selection is generally of moderate intensity. A comparison of experimental data with mutation-selection models indeed suggests that for most traits ω^2/V_E falls between 5 and 50 (ROFF 1997). In several tree species (*Pinus contorta*, YANG *et al.* 1996; *P. sylvestris*, HURME *et al.* 2000; *Quercus petraea*, KREMER *et al.* 2000; *Salix viminalis*, LASCOUX 1996), Q_{ST} values were found to be much higher than G_{ST} values for neutral markers, with the highest values being observed for bud

burst (in *Q. petraea* and *P. sylvestris*). Since temperate forest trees occupy large areas with contrasting ecological conditions, one would anticipate strong diversifying selection for fitness-related traits such as bud burst. If selection is weak, however, important gametic disequilibria may be maintained between demes. Conversely, because forest trees are mostly random-mating species with large deme sizes, no positive θ_W is expected. An important disparity between θ_B and θ_W may therefore exist, leading to a discrepancy between G_{ST} at QTL and Q_{ST}, although a few QTL should be much more differentiated than neutral markers. In the annual plant *Scabiosa columbaria* (WALDMANN and ANDERSSON 1998), Q_{ST} values were also found to be higher than G_{ST} values at markers, but varied greatly among traits, with values ranging from 0.15 (leaf number) to 0.75 (stem height). A large variation was also observed among 17 traits (values ranging from 0.005 to 1) in the annual plant *Clarkia dudleyana* (PODOLSKY and HOLTSFORD 1995). In *Daphnia pulex* (LYNCH *et al.* 1999), 12 traits among 18 studied showed a higher differentiation than that for molecular markers, as well as a reduced variation within population, a pattern consistent with strong diversifying selection. The two other traits, which measured age at reproduction, showed low variation and low differentiation and were likely to be subject to strong uniform selection. According to these experimental data, diversifying selection seems to be the most common form of selection in natural populations (LYNCH *et al.* 1999), but selection parameters are also likely to vary from trait to trait, so that no general conclusion can be drawn.

Impact of selection on the distribution of genetic variability among QTL: A notable result of our simulations was that diversifying selection could generate an L-shaped distribution of the contributions of QTL to the between-deme variance for the trait, when the initial contributions of the QTL differed only due to random sampling in the same Gaussian distribution. These results are similar to those that were obtained for the contribution of QTL to the variance of segregating populations, as illustrated by various experimental results (KEARSEY and FARQUHAR 1998; BOST *et al.* 1999), including QTL analyses in wild species. In Drosophila, two major QTL have been found to be associated with bristle number variation and to have large effects relative to standing natural variation in the trait (LONG *et al.* 2000). In Scots pine, two QTL were found in a study of bud burst timing from a cross involving two natural populations from different latitudes (HURME *et al.* 2000). In *Arabidopsis thaliana*, a large number of small-effect alleles and a small number of larger-effect alleles have been found to account for natural variation in seed weight and several other life-history traits (ALONSO-BLANCO *et al.* 1999). The comparison of the L-shaped distribution for the contribution of QTL to the between-deme variance should, however, be taken with caution, as the detection of the number of QTL is underestimated in crossing experiments in comparison to natural

populations. On the other hand, the L-shaped pattern may not be general, as other studies of natural populations have found several QTL each explaining a small fraction of the variation in adaptive traits (see, *e.g.*, JERMSTAD *et al.* 2001) and also because a statistical bias may be present in some studies, which reduces the number of QTL detected and amplifies their estimated effects (BARTON and KEIGHTLEY 2002). Our simulations indicated that the distribution should be more L-shaped when populations undergo strong diversifying selection and are connected by important gene flow. In this case, most of the loci contributing to the trait would exhibit G_{ST} values of similar magnitude to neutral markers, whereas only a few would exhibit important allelic differentiation and important contribution to the between-deme variance of the trait. In our simulations, this pattern was caused by allele frequency changes at the QTL under both selection and population subdivision. Other explanations have, however, been proposed to account for an L-shaped distribution of QTL effects. Evolution of a population toward a fixed optimum via sequential susbstitution of favorable mutations generally leads to such a pattern (ORR 1998); linkage or the intrinsic properties of enzymatic pathways are other explanations (BOST *et al.* 1999). Whatever its underlying causes, an L-shaped distribution of gene effects may be a serious obstacle to a complete genetic analysis of all QTL for a trait, including the estimation of linkage disequilibria. The most easily detected QTL (*i.e.*, those showing allelic differentiation) being those that have responded to selection, they are also the most informative regarding present adaptive variability; however, they may not respond to future selection pressures. Identifying and assessing the genetic variability that may be adaptive in the future remains a challenging issue, since QTL that exhibit low G_{ST} values today ("silent" QTL) may actually be "turned on" as a result of new or recent mutations and may be important for future adaptation.

Future research needs: In this study, we have considered a fairly simple genetic architecture for the trait: a moderate number of genes having identical and additive effects, with no physical linkage. Increasing the number of QTL would, as shown by LATTA (1998), increase the amount of gametic disequilibrium and thus inflate the discrepancy between Q_{ST} and G_{ST}. Physical linkage is also expected to maintain higher levels of gametic disequilibria (GAVRILETS and HASTINGS 1995) and thus may increase also the discrepancy between Q_{ST} and G_{ST}. Furthermore, more allelic variability is maintained under stabilizing selection when loci tend to be tightly linked (BÜRGER and GIMELFARB 1999), which should lower the G_{ST} value. Unequal contributions to the trait of the different QTL before selection would probably just accentuate the degree of final heterogeneity among them. The consequences of nonadditive effects at QTL, *i.e.*, dominance or epistasis, are much more difficult to envisage and have only rarely been considered in theoretical analyses. In the presence of

epistasis, higher degrees of within-deme variance are maintained under stabilizing selection than that for a purely additive trait (Gimelfarb 1989). On the other hand, since a given allele may have a small additive effect, but nevertheless a large effect on the trait via its interaction with alleles at other loci, we expect that the allelic variability at QTL will be more disconnected from the variance at the trait in the presence of epistasis. As several recent experimental studies have indicated the presence of epistatic interactions among loci coding for adaptive traits (see, *e.g.*, Routman and Cheverud 1997; Shook and Johnson 1999; Fenster and Galloway 2000), there is clearly a need for more theoretical or simulation-based studies that consider the consequences of epistasis on the dynamics of genetic variability under natural selection.

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