March 2005

Using genome scans of DNA polymorphism to infer adaptive population divergence

Jay F. Storz
University of Nebraska - Lincoln, jstorz2@unl.edu

Published in *Molecular Ecology* **14**:3 (March 2005), pp. 671–688; doi 10.1111/j.1365-294X.2005.02437.x

http://www.blackwellpublishing.com/journal.asp?ref=0962-1083&site=1

Submitted September 16, 2004; revised November 18, 2004; accepted November 18, 2004.

INVITED REVIEW

Using genome scans of DNA polymorphism to infer adaptive population divergence

Jay F. Storz

Department of Biology, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA, 94132, USA

Abstract

Elucidating the genetic basis of adaptive population divergence is a goal of central importance in evolutionary biology. In principle, it should be possible to identify chromosomal regions involved in adaptive divergence by screening genome-wide patterns of DNA polymorphism to detect the locus-specific signature of positive directional selection. In the case of spatially separated populations that inhabit different environments or sympatric populations that exploit different ecological niches, it is possible to identify loci that underlie divergently selected traits by comparing relative levels of differentiation among large numbers of unlinked markers. In this review I first address the question of whether diversifying selection on polygenic traits can be expected to produce predictable patterns of allelic variation at the underlying quantitative trait loci (QTL), and whether the locus-specific effects of selection can be reliably detected against the genome-wide backdrop of stochastic variability. I then review different approaches that have been developed to identify loci involved in adaptive population divergence and I discuss the relative merits of model-based approaches that rely on assumptions about population structure vs. model-free approaches that are based on empirical distributions of summary statistics. Finally, I consider the evolutionary and functional insights that might be gained by conducting genome scans for loci involved in adaptive population divergence.

Keywords: adaptation, genomics, natural selection, neutral theory, population genomics, positive selection, QTL, speciation.

Introduction

According to the ecological theory of adaptive radiation, phenotypic divergence and speciation are the ultimate outcome of divergent natural selection between contrasting environments. Elucidating the genetic basis of adaptation to different environments therefore represents a goal of central importance in evolutionary biology. For example, insights into the genetic underpinnings of phenotypic divergence may shed light on long standing questions about the path of adaptive radiation (Simpson 1953; Schluter 2000): Why has phenotypic divergence proceeded in some directions and not others? And why has phenotypic divergence resulted in speciation in some instances and not others? The identification of specific loci that underlie divergently selected traits should also allow us to address fundamental questions about the genetic basis of adaptation (Fisher 1930; Kimura 1983; Orr 1998): How many genes are involved in the evolution of adaptive traits? What is the distribution of phenotypic effects among successive allelic substitutions? Is adaptation typically based on standing variation or new mutations? What is the relative importance of additive vs. nonadditive effects on adaptive trait variation? And what is the relative importance of structural vs. regulatory changes in phenotypic evolution?

Fortunately, it is now possible to infer the genetic basis of adaptive population divergence by measuring genome-wide associations between segregating variation and fitness-related traits (Lynch & Walsh 1998; Erickson *et al.* 2004). In cases where an identifiable phenotype is implicated in adaptive divergence, it is possible to locate the underlying genes by using a multilocus mapping approach such as quantitative trait locus (QTL) mapping

in an experimentally controlled population (e.g. F_2 progeny from a cross between inbred lines). This approach holds great promise for elucidating the genetic basis of adaptive population divergence. However, because it requires the use of phenotypic variation as a starting point, this approach is generally restricted to a consideration of measurable traits that have already been implicated as candidates for divergent selection by independent lines of evidence.

An alternative approach that appears to hold great promise involves screening genome-wide patterns of DNA polymorphism to detect the locus-specific signature of positive directional selection (Luikart *et al.* 2003; Schlötterer 2003). In principle, it should be possible to identify chromosomal regions that harbor one or more adaptive mutations by exploiting theoretical predictions about the effects of positive selection on patterns of variation at linked sites (Kim & Stephan 2002; Przeworski 2002). For example, the spread and fixation of adaptive mutations results in the joint fixation of linked neutral variants ("genetic hitch-hiking"; Maynard Smith & Haigh 1974; Kaplan *et al.* 1989). As an adaptive mutation is driven to fixation by positive selection, it may be repeatedly recombined against new genetic backgrounds. Although recombination is expected to randomize associations between the selected site and linked neutral variants, some fraction of the ancestral haplotype in which the mutation originated will also become fixed (Figure 1a). The strength of this hitch-hiking effect is determined by the ratio of the recombination rate to the selection coefficient, the initial frequency of the advantageous allele, and the time to fixation (Maynard Smith & Haigh 1974; Kaplan *et al.* 1989; Stephan *et al.* 1992; Wiehe & Stephan 1993). In general, genetic hitch-hiking results in a reduced level of variability and a skewed distribution of allele frequencies at linked neutral sites (Tajima 1989; Fu & Li 1993; Braverman *et al.* 1995; Simonsen *et al.* 1995; Barton 2000; Fay & Wu 2000; Kim & Stephan 2000, 2002; Kreitman 2000; Andolfatto 2001). An interpretative challenge associated with polymorphism-based neutrality tests is that the pattern of variation produced by genetic hitch-hiking can also be produced by demographic events, such as population expansion. It is therefore necessary to screen patterns of DNA variability at multiple, unlinked loci in order to disentangle the effects of demography and selection (Figure 1b). The premise of this multilocus approach is that demographic processes will have relatively uniform effects across the entire genome, whereas the effects of selection are generally expected to be locus-specific and can be inferred from patterns of variation at linked sites (Cavalli-Sforza 1966; Lewontin & Krakauer 1973).

In the case of spatially separated populations that inhabit different environments or sympatric populations that exploit different ecological niches, it is possible to identify chromosomal regions involved in adaptive divergence by comparing relative levels of differentiation among multiple, unlinked loci (Charlesworth *et al.* 1997; Stephan *et al.* 1998). For example, consider the effects of a geographically restricted selective sweep on patterns of nucleotide diversity at linked neutral sites (Figure 2). Levels of within-population diversity will be reduced by hitch-hiking with the locally adaptive allele, and levels of between-population diversity will be increased by recurrent selection against locally maladaptive alleles that are introduced by migration (Petry 1983; Barton & Bengsston 1986; Hilton *et al.* 1994; Charlesworth *et al.* 1997). Simultaneous changes in the within- and between-population components of genetic diversity can be measured by Wright's (1943, 1951) F_{ST}. This statistic was originally defined in terms of variance in allele frequencies, but it can also be expressed in terms of mean coalescence times (Slatkin 1991; Takahata 1991; Hudson *et al.* 1992; Charlesworth *et al.* 2003):

$$F_{ST} = (T_T - T_S) / T_T \quad (1)$$

where T_T is the expected coalescence time for a pair of alleles sampled randomly from the population as whole and T_S is the expected coalescence time for pairs of alleles sampled within local subpopulations. In the case of a geographically restricted selected sweep, F_{ST} values for the selected site and closely linked markers are expected to exceed the genome-wide average for neutral polymorphisms. The correlation in levels of differentiation between the selected site and linked neutral markers is expected to dissipate at a rate proportional to the recombinational distance between them (Figure 3; Charlesworth *et al.* 1997).

The basic approach of using genome-wide patterns of DNA polymorphism to locate genes under positive selection has been referred to as hitch-hiking mapping (Harr *et al.* 2002; Schlötterer 2003). In contrast to multilocus mapping approaches that are based on experimental crosses or known pedigrees, population-based genome scans are based on deep, but unknowable pedigrees that will typically include extensive amounts of historical recombination. Although the patterns and extent of linkage disequilibrium (LD) in the genome will strongly depend on demographic history and past episodes of selection, the potentially large number of meioses that have occurred since the most recent common ancestor of a sample means that population-based genome scans will typically make use of relatively small haplotype blocks and will therefore require much higher marker densities than mapping approaches that are based on experimental crosses. Despite the requirement of increased marker density, one advantage of using smaller blocks of LD for trait mapping is that marker–trait associations may indicate relatively tight linkage to the causative variants.

Compared to multilocus mapping approaches that are based on experimental crosses, population-based genome scans have several other important advantages.

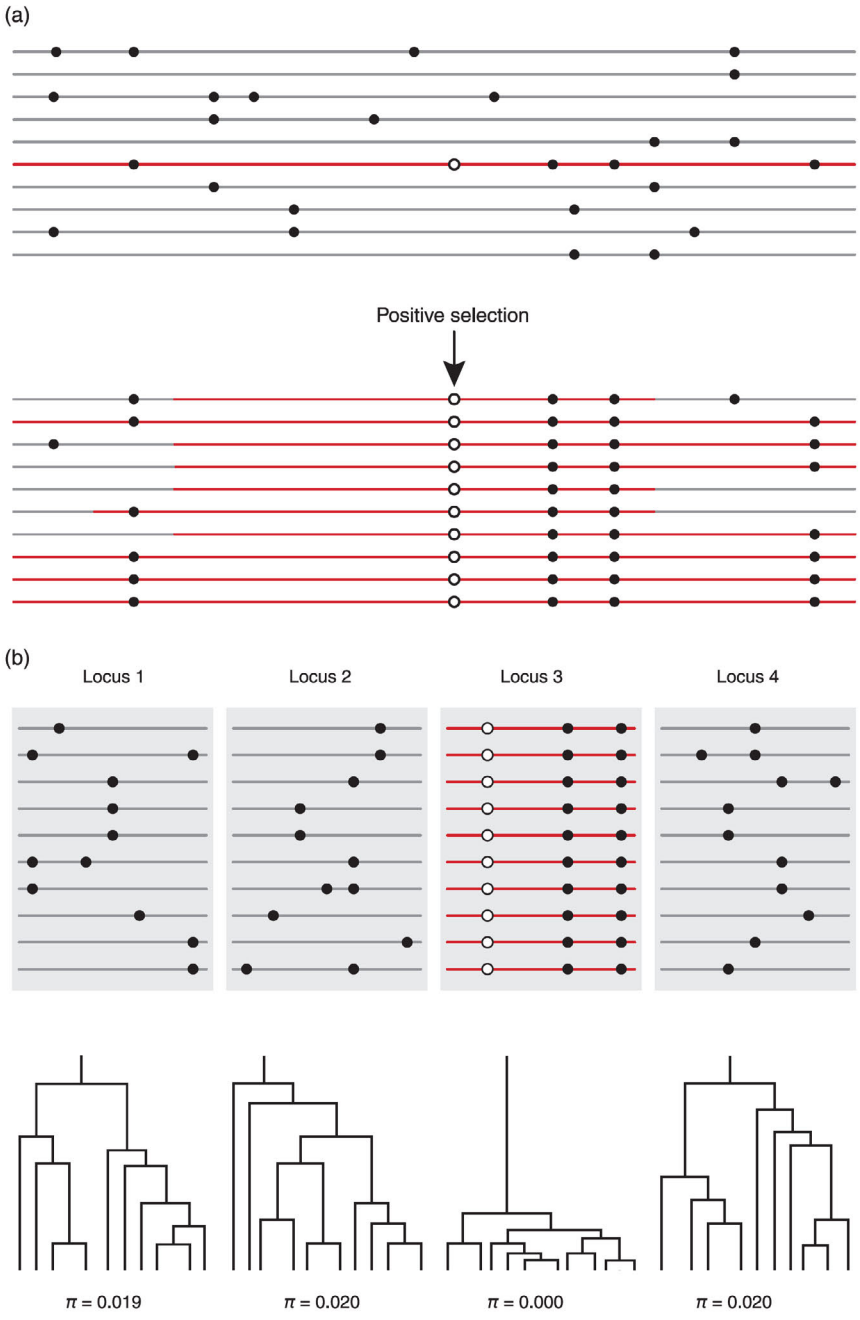

Figure 1. (a) Effects of genetic hitch-hiking along a recombining chromosome. Horizontal lines depict a population sample of homologous chromosomes, and filled symbols depict neutral mutations. In this example an advantageous mutation (open symbol) arises and is rapidly driven to fixation by positive selection. Although the mutation is recombined against new genetic backgrounds during the course of the selective sweep, a sizable fraction of the ancestral haplotype (shown in red) also becomes fixed. Consequently, neutral variants that were initially linked to the advantageous mutation undergo a dramatic increase in frequency as a result of hitch-hiking. **(b)** In this example, locus 3 has been rendered monomorphic by a selective sweep. Sampled gene copies (denoted by tips of the gene tree) share a very recent common ancestor, and $\pi = 0$ (where π= nucleotide diversity; Nei & Li 1979). By comparison, unlinked, neutrally evolving regions of the genome (loci 1, 2, and 4) are characterized by deeper genealogies, and higher levels of nucleotide diversity (π= 0.019–0.020). Note that the gene trees depict the true genealogies of the samples, not the genealogies inferred from observed variation.

First of all, the genome scan approach can be applied to natural populations of any species (provided that a high-density genetic map is available), whereas QTL mapping is generally restricted to species that can be crossed in the lab. Second, the approach should be capable of identifying loci that have experienced a history of weak selection. The fitness effects of many phenotypic variants may be far too subtle to detect experimentally, but over long periods of time, the cumulative effect of very small selection coefficients can be expected to produce a detectable signal in patterns of DNA polymorphism at the underlying loci (Lewontin 1974; Gillespie 1991). Third, the approach can be used to identify loci that underlie selected traits without having to identify the traits themselves at the outset. Thus, genome scans for selection may guide the identification of phenotypic traits whose adaptive significance was previously unanticipated. Although genome scans for selection do not require the use of phenotypic variation as a starting point, there are many situations where it might be useful to conduct genome scans between population samples that are grouped according to phenotype. For example, conducting genome scans of DNA polymorphism between sympatric morphs or closely related species that exploit

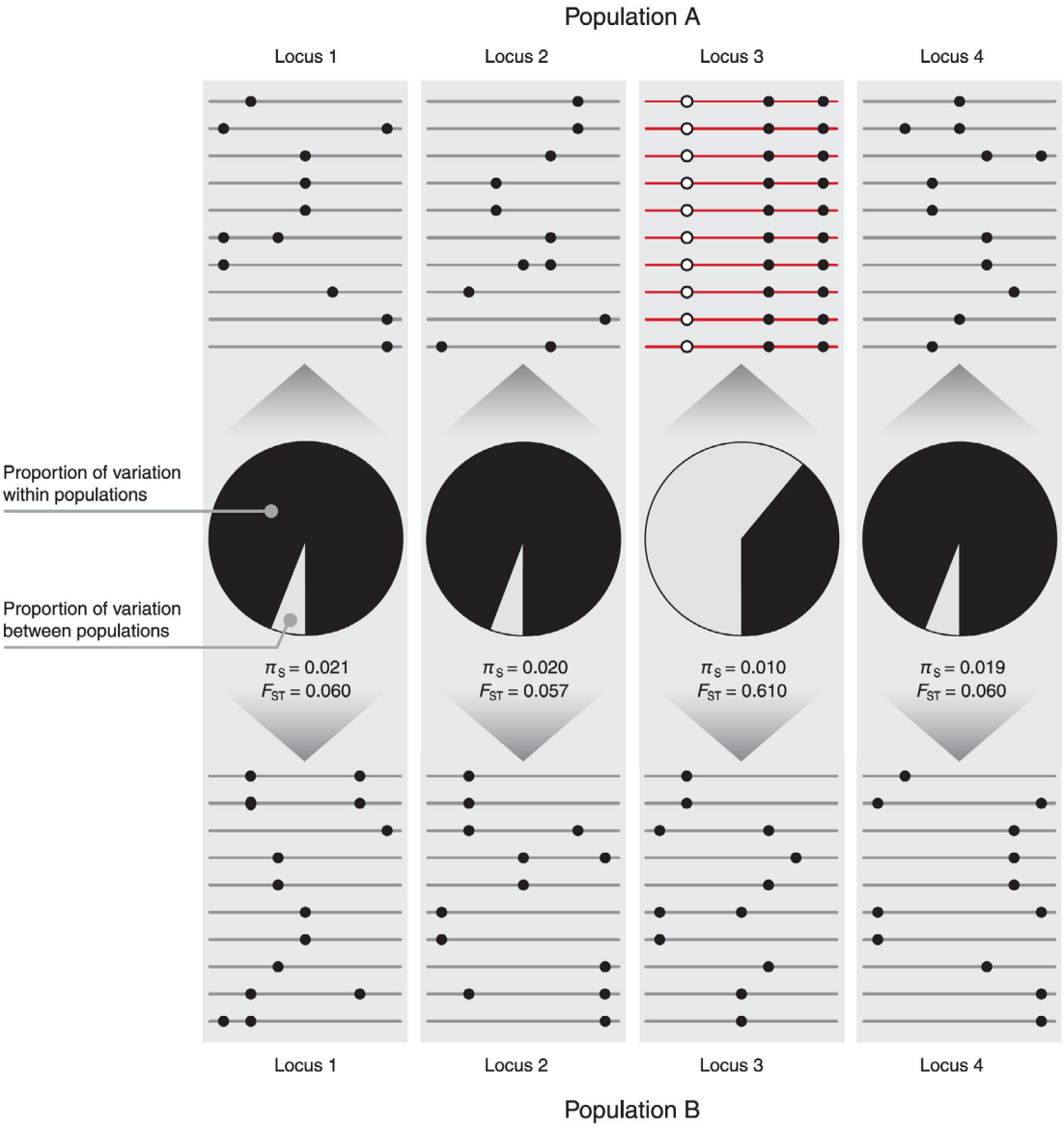

Figure 2. Effects of a geographically restricted selective sweep on patterns of nucleotide diversity at linked neutral sites. In this example, locus 3 has undergone a selective sweep that is restricted to population A. Relative to the other unlinked loci, locus 3 is characterized by a reduction in the average level of within-population nucleotide diversity, π_S (Nei & Kumar 2000, equation 12.72) and an elevated level of between-population nucleotide diversity, F_{ST} (=δ_{ST}; Nei & Kumar 2000, equation 12.74). The proportions of within- and between-population nucleotide diversities are calculated as $1 - (F_{ST}/\pi_T)$ and F_{ST}/π_T, respectively, where π_T is the nucleotide diversity for the pooled sample of gene copies from the two populations (Nei & Kumar 2000, equation 12.73). At locus 3, π_S is reduced and F_{ST} is elevated because of hitch-hiking with the locally adaptive allele in population A.

different ecological niches may reveal the chromosomal regions that contributed to the observed divergence in phenotype. Moreover, results of such an analysis could be used to verify the role of selection in producing the observed divergence in phenotype, and may identify additional loci that underlie traits that are part of the same adaptive syndrome.

A central tenet of neo-Darwinism is that the evolution of adaptive traits involves allelic substitutions of individually small effect at large numbers of loci (Fisher 1930; Lande 1983). Although genetic analysis of natural populations has provided a number of well-documented cases in which adaptations are attributable to a small number of genes of major effect (reviewed by Orr & Coyne 1992; Orr 1998, 1999), it is still not possible to draw any general conclusions about the genetic architecture of fitness-related traits. In some cases, such as the evolution of insecticide resistance in flies and mosquitoes (ffrench-Constant 1994; Raymond *et al.* 2001; Daborn *et al.* 2002) and drug resistance in malaria parasites

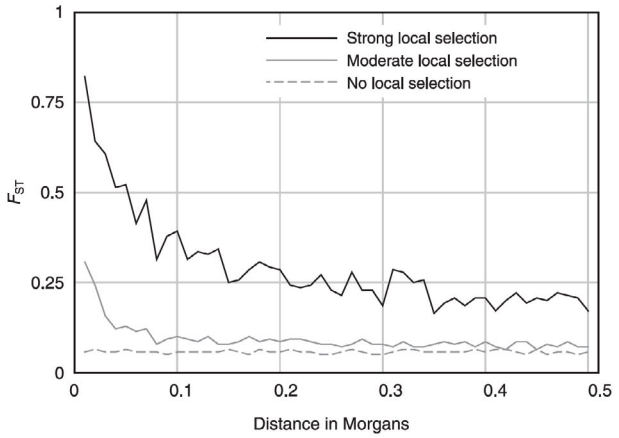

Figure 3. Simulation results showing the effects of spatially varying selection on levels of differentiation at linked sites [reproduced from Charlesworth *et al.* (1997)]. Local selection was modeled by assuming directional selection acting in opposite directions in two demes that exchange migrants. Heterozygotes and homozygotes at the selected locus were assigned fitnesses of $1 - (s/2)$ and $1 - s$, respectively, where $s = 0.5$ under "strong" selection and $s = 0.1$ under "moderate" selection. In the absence of local selection ($s = 0$), F_{ST} at linked markers is not correlated with map distance from the selected polymorphism. In the presence of local selection, elevated levels of differentiation are especially marked at sites that are closely linked to the selected polymorphism, and the rate of decay is inversely proportional to the strength of local selection.

(Wootton *et al.* 2002; Nair *et al.* 2003), response to selection may be attributable to adaptive substitutions at a small number of major genes. In the case of other ecologically important traits, such as body size of animals or flowering time of plants, response to selection probably involves simultaneous changes at many different loci. Because many (if not most) fitness-related traits are under polygenic control, it is important to move beyond genic selection models and consider how selection can be expected to shape patterns of allelic variances and covariances at QTL that underlie adaptive quantitative traits.

In this review I will first consider the following questions. Does diversifying selection on quantitative traits produce predictable patterns of allelic variation at the underlying QTL? And more specifically, can patterns of variation at QTL for divergently selected traits be distinguished from those at neutral markers and/or QTL for neutral traits? This question has important implications for the prospects of using genome scans to identify loci involved in adaptive population divergence. I will then review different approaches that have been developed to identify loci involved in adaptive population divergence. I discuss the relative merits of model-based approaches that rely on assumptions about population structure vs. model-free approaches that are based on empirical distributions of summary statistics. Finally, I consider the evolutionary and functional insights that might be gained by conducting genome scans for loci involved in adaptive population divergence.

Does diversifying selection on quantitative traits produce predictable patterns of allelic variation at the underlying QTL?

In general, directional selection toward different trait optima in different environments can be expected to increase the spatial heterogeneity of allele frequencies at the underlying loci (Barton 1999). If QTL for a divergently selected trait typically exhibit levels of allelic differentiation that exceed the genome-wide average for neutral polymorphisms, then it might seem reasonable to expect that such loci (or markers in LD with them) could be identified as outliers in a multilocus distribution of F_{ST} values. However, in the case of loci underlying quantitative traits, the efficacy of such an approach will depend on how much of the observed differentiation in trait values is attributable to the between-population variance in allele frequencies at individual QTL vs. the between-population covariance in allele frequencies among QTL. If adaptive divergence in trait values is primarily attributable to the between-population component of LD (Ohta 1982), then levels of allelic differentiation at the underlying QTL may not exhibit statistically detectable deviations from neutral expectations (Latta 1998, 2003; Le Corre & Kremer 2003).

To illustrate this point, consider an array of demes that are distributed across a linear ecological gradient where the phenotypic optimum for a polygenic trait, z, varies in a monotonic fashion from one end of the gradient to the other. If variation in the trait is influenced by n biallelic loci with additive effects, then the genetic variance of the trait can be expressed as:

$$\sigma_z^2 = \sum_i \sigma_i^2 + \sum_i \sum_{i \neq j} cov(i, j) \quad (2)$$

where σ_i^2 is the variance contributed by allelic variation at locus i, and $cov(i, j)$ is the covariance of allelic effects between loci i and j because of LD (Falconer & Mackay 1996; Latta 1998). If the trait is subject to stabilizing selection toward a spatially varying optimum, denoted z_x^* for population x, the contribution of the between-population component of LD to trait differentiation can be expressed as:

$$\sum_i \sum_{i \neq j} cov(i, j) = \sigma_{z^*}^2 - 2F_{ST}\sigma_0^2 \quad (3)$$

where $\sigma_{z^*}^2$ is the variance in trait optima, $2F_{ST}\sigma_0^2$ is the expected variance in trait values at migration–drift equilibrium, and σ_0^2 by itself is the additive genetic variance in trait values expected under panmixia (Wright 1951; Lande 1992). Equation 3 predicts that when the variance in trait optima across the gradient exceeds the expected between-population variance at migration–drift

equilibrium ($\sigma^2_{z^*} \gg 2F_{ST}\sigma^2_0$), diversifying selection on the trait will produce correlated shifts in allele frequencies among the underlying loci. The resultant LD across populations produces a positive covariance in allelic effects on the selected trait (Latta 1998; Barton 1999; Le Corre & Kremer 2003). Thus, when diversifying selection is strong and gene flow is high, adaptive divergence in phenotypic trait values may occur primarily as a result of covariance in allele frequencies among QTL even in the absence of appreciable shifts in allele frequencies at individual loci. Parallel differentiation of QTL allele frequencies will increase the level of trait divergence beyond that predicted by the additive effects of each locus considered separately, and the contributions of covariances to trait divergence will increase as a positive function of QTL number (Latta 1998, 2003; McKay & Latta 2002). Thus, in cases where a divergently selected trait exhibits clinal variation across an ecological gradient (and the between-population variance in trait values due to selection exceeds the between-population variance due to drift), the widths of allele frequency clines at the underlying QTL will increase as a positive function of QTL number. These theoretical results suggest that deviations from the expected level of differentiation at migration–drift equilibrium will be much more difficult to detect when large numbers of loci contribute to variation in a divergently selected trait (Lewontin 1984; Latta 1998, 2003).

Le Corre & Kremer (2003) extended the analysis of Latta (1998) and demonstrated that diversifying selection can be expected to produce substantial heterogeneity in levels of differentiation among QTL that code for the same trait. Not only does selection induce interlocus variance in levels of differentiation among QTL, it also causes loci to differentiate in their contribution to variance in the locally adaptive trait. When levels of gene flow are high ($Nm = 10$), allele frequency changes caused by diversifying selection produce a skewed distribution in the contributions of QTL to the between-population variance in trait values. A small fraction of highly differentiated loci end up contributing most of the between-population variance, and this remains true even if the distribution of phenotypic effects is uniform in the absence of selection (Le Corre & Kremer 2003). The same skew in the distribution of effect sizes is also predicted by models of directional selection toward a fixed optimum via sequential substitutions of beneficial mutations. Alleles that become fixed early in the course of adaptive evolution are expected to have larger phenotypic effects than those that become fixed later, with effect sizes trailing off as an approximate geometric sequence (Orr 1998, 1999). Regardless of the root cause, the skewed distribution of effect sizes leads to the prediction that most loci contributing to variation in a locally adaptive trait will be characterized by levels of differentiation that do not greatly exceed the neutral expectation (so average levels of differentiation at QTL and neutral markers will not be radically different; Latta 1998). However, the small number of QTL that contribute most of the between-population variance in trait values will be characterized by unusually high levels of allelic differentiation (Le Corre & Kremer 2003). These leading QTL, or markers in LD with them, are the loci that are most likely to be identified as outliers in genome scans of DNA polymorphism.

In summary, theory indicates that diversifying selection on quantitative traits should produce predictable patterns of allelic variation at the underlying QTL. The patterns to be expected depend on the genetic architecture of the trait, the intensity of selection on the trait, and the genetic structure of the population under consideration (Latta 1998, 2003; Barton 1999; McKay & Latta 2002; Le Corre & Kremer 2003). This body of theory also has implications for the replicated evolution of similar traits, and indicates that parallel or convergent evolution of genetic architecture may occur in the absence of parallelism or convergence in the effects of individual loci. According to the results of Le Corre & Kremer (2003), major QTL for locally adaptive traits will generally exhibit reduced diversity within populations and increased diversity between populations relative to neutral expectations. However, even if QTL for divergently selected traits generally exhibit levels of differentiation that exceed the genome-wide average, discrepancies in the expectations for selected and neutral loci may be very small relative to stochastic variance in levels of differentiation among unlinked neutral loci.

Using multilocus data to identify loci involved in adaptive population divergence

At loci that underlie fitness-related traits, adaptation to local conditions results in a reduction of within-population diversity (because of directional selection toward local phenotypic optima) as well as an increase in the between-population diversity (as a result of selection in favor of different alleles in different populations, as well as recurrent selection against maladaptive migrant alleles that pull populations away from their local optima; Petry 1983; Barton & Bengsston 1986; Charlesworth *et al.* 1997). Thus, methods for detecting diversifying selection can be divided into two classes of interlocus comparison: those based on levels of differentiation between populations, and those based on levels of diversity within populations. I will discuss each of these approaches in turn.

Methods based on levels of differentiation between populations

For the case of a linked neutral locus and symmetrical migration between two locally adapted populations, the effective migration rate is approximately $mr^*/(s + r^*)$,

where m is the expected migration rate in the absence of local selection, s is the selection coefficient against the locally maladaptive migrant allele, and r^* is the rate of recombination between the selected site and the neutral site (Charlesworth *et al.* 1997). At markers that are closely linked to the locally selected site, the reduced effective migration rate will result in an F_{ST} value that exceeds the genome-wide average for neutral polymorphisms. Thus, loci under strong diversifying selection can be expected to exhibit elevated levels of differentiation.

This insight was first formalized as a multilocus neutrality test by Lewontin & Krakauer (1973). In this test, the neutral expectation for the interlocus variance of F_{ST} is approximated by

$$\sigma^2 = \frac{2\bar{F}_{ST}^2}{n-1}, \quad (4)$$

where n is the number of sampled subpopulations, and the observed variance can be compared with σ^2 using a standard variance ratio test. This test was criticized on the grounds that the theoretical expectation for the interlocus variance in F_{ST} would be invalidated by certain modes of population structure that produce correlations in allele frequencies among subpopulations. For example, a spatial autocorrelation in allele frequencies could result from a stepping-stone pattern of migration (Nei & Maruyama 1975) and a phylogenetic autocorrelation in allele frequencies could result from variation in divergence times among hierarchically related subpopulations (Robertson 1975a,b).

A possible solution to this problem is to use simulations to generate a null distribution of a particular summary statistic (such as F_{ST}) under a neutral model of population structure. For example, in an analysis of 100 nuclear DNA polymorphisms in different continental populations of humans, Bowcock *et al.* (1991) simulated allele frequency distributions under a neutral model that incorporated phylogenetic information about the history of population divergence. The simulations were used to generate a null distribution of F_{ST} conditional on initial allele frequencies. By comparing observed F_{ST} values to the conditional distribution, it was possible to identify outlier loci that may have experienced a history of selection. The majority of polymorphisms conformed to expectations of the neutral model, but a subset of outlier loci exhibited lower-than-expected levels of differentiation (suggesting some form of spatially uniform selection) and a substantially larger subset of outlier loci exhibited higher-than-expected differentiation (suggesting diversifying selection among continental populations).

Beaumont & Nichols (1996) introduced a similar outlier-detection approach that used a structured coalescent model to generate null distributions of F_{ST} conditional on heterozygosity. Extensive simulation analyses revealed that null distributions generated under an island model with large numbers of demes were surprisingly robust to a range of different models of equilibrium and nonequilibrium population structure (Beaumont & Nichols 1996). For example, distributions generated by a nonequilibrium colonization model were indistinguishable from those generated by an equilibrium island model at expected F_{ST} values of less than 0.50. Simulation results also revealed that the null distribution was robust to interlocus variation in the rate and mode of mutation. Beaumont & Balding (2004) extended and refined this outlier-detection approach through the use of a hierarchical Bayesian model that is implemented via Markov chain Monte Carlo simulations. The model has two levels: a lower level model in which the likelihood for the allele counts is expressed as a function of F_{ST}, and a higher level model for the F_{ST} values. To model the mutational and demographic effects that give rise to locus-specific F_{ST} values, Beaumont & Balding (2004) evaluated the following logistic regression model:

$$\log\left(\frac{F_{ST}}{1-F_{ST}}\right) = \alpha_i + \beta_j + \gamma_{ij}, \quad (5)$$

where α_i is a locus-specific effect, β_j is a population-specific effect, and γ_{ij} is interpreted as a locus × population interaction term. Under this model, candidate loci for selection can be identified from the posterior distribution of locus-specific parameters: positive values of α_i are indicative of diversifying selection (higher-than-expected F_{ST}) and negative values of α_i are indicative of spatially uniform selection (lower-than-expected F_{ST}). In principle, a selective sweep that is restricted to a single subpopulation could be detected by a large positive value of γ_{ij}. Encouragingly, simulations that incorporated locus-specific selection revealed that the Bayesian regression method of Beaumont & Balding (2004) and the summary-statistic method of Beaumont & Nichols (1996) both successfully detected the effects of diversifying selection when the selection coefficient was roughly five times greater than the migration rate. However, neither method proved capable of reliably detecting spatially uniform selection unless migration rates were extremely low (Beaumont & Balding 2004).

Although the method of Beaumont & Nichols (1996) is robust to a range of nonequilibrium conditions, it appears to be sensitive to heterogeneity in demographic parameters among subpopulations. Thus, inclusion of samples from geographically distant or bottlenecked subpopulations may bias the method. The Bayesian method of Beaumont & Balding (2004) should be robust to this problem as the model explicitly accounts for variation in F_{ST} among subpopulations. Another possible solution to the problem is to restrict the analysis to pairs of subpopulations, thereby reducing the number of parameters in the model (Robertson 1975b; Tsakas & Krimbas 1976). Accordingly, Vitalis *et al.* (2001) introduced an outlier-detection approach that is based on estima-

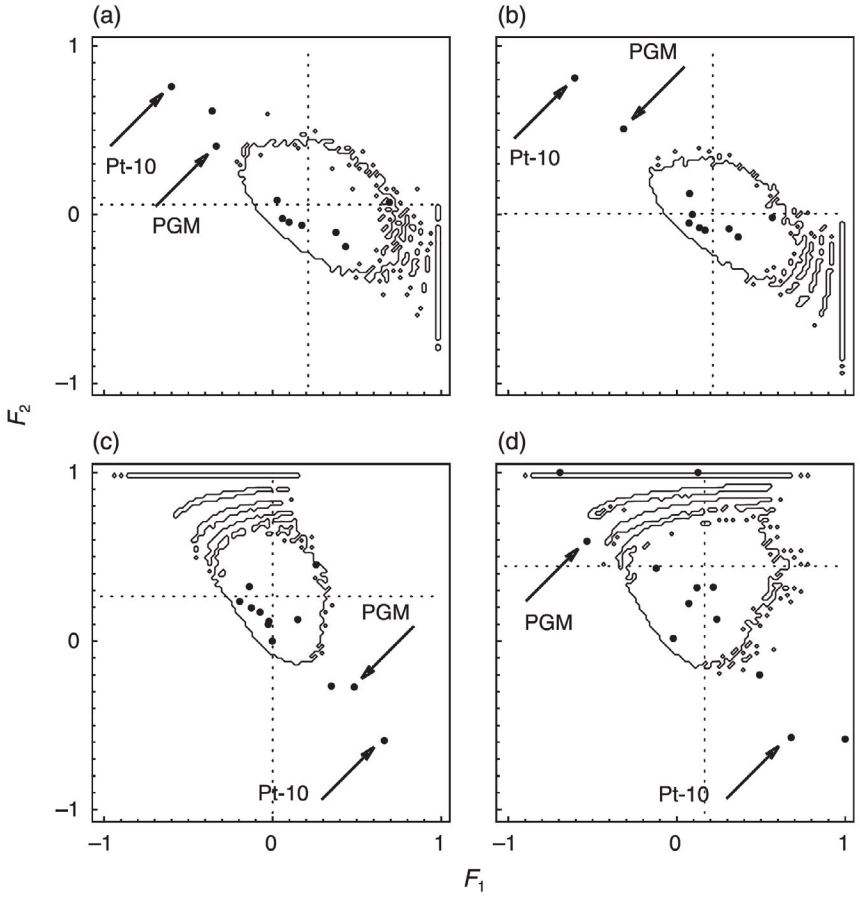

Figure 4. Joint distribution of branch length parameters estimated from pairwise comparisons between populations of *Drosophila simulans* ($n = 43$ loci; reproduced from Vitalis *et al.*[2001]). The branch-length parameters, F_1 and F_2, are defined as functions of identity probabilities for alleles sampled within or between the two populations in each comparison. Each distribution is from a pairwise comparison involving a population sample of *D. simulans* from the Congo and populations from **(a)** France, **(b)** Tunisia, **(c)** Cape Town, South Africa, and **(d)** Seychelle Island. All joint distributions of the branch length parameters are conditioned on $k = 4$ alleles. Solid lines enclose a region that is expected to enclose 95% of simulated data points. Observed values for each locus are denoted by filled symbols, and dotted lines denote the expected values for F_1 and F_2. In each conditional distribution, arrows indicate two loci, larval protein-10 (Pt-10) and phosphoglucomutase (PGM), that emerge as outliers in each of the four pairwise comparisons.

tors of branch-lengths for pairs of subpopulations (Figure 4). In this model, the branch-length parameters are defined as functions of identity probabilities for alleles sampled within or between the two subpopulations under consideration. These parameters are related to the ratio of divergence time to effective population size (N_e) in a pure drift model. The model considers the joint distribution of branch length estimates conditional on the total number of alleles in the pooled sample for each locus. The expected conditional joint distribution can then be used to identify outlier loci that may reflect a history of selection.

In model-based tests of selection that rely on assumptions about population structure, it is important to remember that the *P* value associated with any locus-specific departure from the neutral expectation is only relevant to the particular model used to generate the expectation. If polymorphism data are available from sufficient numbers of loci, it is also possible to use a model-free approach in which candidate loci are identified as outliers in an empirical genome-wide distribution of a summary statistic such as F_{ST} (Black *et al.* 2001; Luikart *et al.* 2003). This empirical approach was used by Akey *et al.* (2002) in an analysis of 26 530 single nucleotide polymorphisms (SNPs) with allele frequencies determined in three human populations: African American, East Asian, and European American. By contrasting F_{ST} values of individual SNPs against the genome-wide distribution of F_{ST}, this study identified 174 candidate genes for selection: 156 of the genes contained one or more SNPs that exhibited unusually high F_{ST} values, and 18 genes contained multiple SNPs that exhibited unusually low F_{ST} values. Although higher- or lower-than-expected F_{ST} values may be indicative of selection, F_{ST} values alone cannot identify the populations in which changes in allele frequency took place. An alternative approach is to assess the empirical distribution of locus-specific branch lengths after using a matrix of pairwise F_{ST} to construct a phylogenetic tree (Shriver *et al.* 2004). This approach effectively decomposes locus-specific F_{ST} values and permits inferences about the polarity of changes in allele frequency.

An interpretative problem associated with F_{ST}-based analyses relates to the fact that F_{ST} is defined as a ratio of within- and between-population diversity levels (Charlesworth 1998). Because hitch-hiking with a locally adaptive allele will produce elevated levels of locus-specific differentiation, local selective sweeps in *Drosophila* populations have been invoked to explain unusually high F_{ST} values in genomic regions of low recombination (Begun & Aquadro 1993, 1995; Stephan 1994). However, since an increased F_{ST} may result entirely from reduc-

tions in the within-population component of diversity, high F_{ST} values for loci in genomic regions of low recombination may be caused by any process that reduces local N_e (Charlesworth 1998). Hitch-hiking because of positive selection is one such process (Barton 1995), but so is purifying selection against linked deleterious mutations (background selection; Charlesworth *et al.* 1993; Hudson & Kaplan 1995). In principle, the effects of adaptive hitch-hiking and background selection in regions of low recombination can be distinguished by examining the distribution of allele frequencies within populations. Although models of adaptive hitch-hiking and purifying selection against mildly deleterious mutations both predict an excess of low frequency alleles at linked sites (Braverman *et al.* 1995; Charlesworth *et al.* 1995; Tachida 2000; Gordo *et al.* 2002; Williamson & Orive 2002), only adaptive hitch-hiking is expected to produce a transient excess of derived high-frequency alleles (Fay & Wu 2000). Inferences about the evolutionary forces responsible for elevated levels of locus-specific differentiation in regions of low recombination should be based on a joint consideration of within- and between-population patterns of variation.

Several recent empirical studies of functional polymorphisms have provided proof-of-principle that interlocus comparisons of F_{ST} values can be used to detect the signature of directional or balancing selection (Taylor *et al.* 1995; Bamshad *et al.* 2002; Fullerton *et al.* 2002; Hamblin *et al.* 2002; Rockman *et al.* 2002; Kohn *et al.* 2003; Hahn *et al.* 2004). Two particularly illustrative case studies involved surveys of variation at genes with well-documented effects on fitness: the Duffy blood group locus (*FY*) in humans and the warfarin-resistance locus (*Rw*) in rats. The *FY* locus, which encodes a chemokine receptor on the surface of red blood cells, is characterized by an unusually high variance in allele frequencies among human populations (Cavalli-Sforza *et al.* 1994). The derived *FY*O* allele is at or near fixation in sub-Saharan African populations, but is present at extremely low frequencies outside of Africa (Hamblin & Di Rienzo 2000; Hamblin *et al.* 2002). The unusually high frequency of this allele in sub-Saharan Africa is thought to reflect a history of geographically localized selection, as homozygosity for the *FY*O* allele confers resistance to *Plasmodium vivax* malaria. Consistent with this idea, F_{ST} at the site of the *FY*O* mutation far exceeded the upper range of values estimated from nucleotide polymorphisms at 10 unlinked, noncoding regions in comparisons between African and non-African populations. Patterns of variation among different sites within the *FY* gene region provided corroborative evidence that the *FY*O* mutation is the direct target of positive selection: F_{ST} was highest for the site of the *FY*O* mutation and F_{ST} values for linked polymorphisms decreased as a function of increasing distance from this site (Hamblin *et al.* 2002).

The *Rw* gene plays a well-documented role in resistance to anticoagulant rodenticides in European rat populations (Partridge 1979). LD mapping in an anticoagulant-resistant rat population was used to assign the *Rw* gene to a 2.2 cM interval on rat chromosome 1 (Kohn *et al.* 2000) and an association study identified a highly diagnostic marker for the resistance phenotype (Kohn *et al.* 2003). If *Rw* contributed to the past response to selection for anticoagulant resistance, levels of differentiation at the *Rw*-linked resistance marker should exceed the genome-wide average for neutral polymorphisms in comparisons between resistant and susceptible rat populations. As expected, Kohn *et al.* (2003) found that especially large disparities in levels of anticoagulant-resistance between populations were associated with correspondingly large disparities in levels of differentiation between the *Rw*-linked marker and unlinked neutral markers.

Methods based on comparisons of diversity within populations

Under a deterministic model of genetic hitch-hiking, the reduction in heterozygosity at linked neutral sites can be predicted by the product of the recombination rate, r, and the fixation time, t. Reduction of heterozygosity at a linked neutral locus can be described by the following formula:

$$\frac{H(t_1)}{H(t_0)} = 1 - \exp(-rt) \approx \min\{rt, 1\} \qquad (6)$$

where $H(t_0)$ and $H(t_1)$ denote levels of heterozygosity at the onset and completion of a selective sweep, respectively, and $t = t_1 - t_0$ (Maynard & Haigh 1974; Kaplan *et al.* 1989). This relationship applies to biallelic polymorphisms and can be generalized to predict the long-term equilibrium level of heterozygosity under recurrent selective sweeps. Slatkin (1995) extended models of genetic hitch-hiking to consider the effects of selective sweeps on the distribution of repeat numbers at a neutral microsatellite locus that is completely linked to a selected locus. Wiehe (1998) further generalized both deterministic and stochastic models of hitch-hiking at microsatellite loci, and demonstrated that the strength of the hitch-hiking effect depends strongly on mutation rates in addition to recombination rates and the selection coefficient. Thus, the effect of hitch-hiking on the variance in allele size (V) at a linked microsatellite locus can be described by a modified version of equation (6) that incorporates the mutation rate, μ, and the number of neutral alleles, n, as additional parameters:

$$\frac{V(t_1)}{V(t_0)} = 1 - \exp\left\{-\left(r + 4\frac{\mu}{n}\right)t\right\} \approx \min\left\{\left(r + 4\frac{\mu}{n}\right), 1\right\}. \qquad (7)$$

Wiehe (1998) demonstrated that selective sweeps at a linked microsatellite locus will reduce the variance in al-

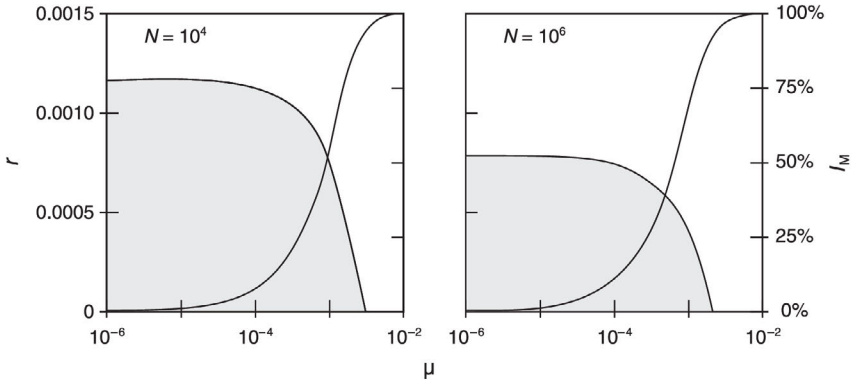

Figure 5. Predicted effect of genetic hitch-hiking on variance in allele size at linked microsatellite loci [modified from Schlötterer & Wiehe (1999)]. The graphs show the predicted effects of hitch-hiking with an advantageous mutation (s= 0.01) under two different population sizes: N= 10^4 (left panel) and N= 10^6 (right panel). If the recombination rate (r, left y-axis) and mutation rate (μ, x-axis) fall within the shaded area of the curves, variance in allele size is reduced ≥ 10% below the expectation at mutation-drift equilibrium. The right y-axis (I_M) and sigmoidal curve show the relative influence of mutation on the strength of the hitch-hiking effect in the case of complete linkage (r= 0). A value of 100% means that the mutation rate is too high to produce an observable hitch-hiking effect, while a value of zero means that the mutation rate is sufficiently low that the expected strength of the hitch-hiking effect is no different from that predicted by a deterministic model that only considers recombination rate and time to fixation of the adaptive mutation.

lele size relative to its equilibrium expectation provided that the mutation rate does not exceed $1/t_1$, the inverse of the fixation time of a linked adaptive mutation. If there is no mutational bias towards gains or losses of repeat units, the effect of a selective sweep will be obscured when the mutation rate is high and when the number of neutral alleles is small (Figure 5). This effect of mutation rate suggests that combining information from different classes of markers may provide information about the relative timing of hitch-hiking events. For example, as mutation rates of human microsatellites (3×10^{-6} – 6×10^{-4}; Ellegren 2000) are roughly four orders of magnitude higher than rates for single nucleotide changes (*c.* 2×10^{-8}; Nachman & Crowell 2000), Wiehe's (1998) theoretical results suggest that surveys of microsatellite variation are most appropriate for detecting selective sweeps that were very recent (and very strong), whereas surveys of nucleotide variation may be more appropriate for detecting selective sweeps that occurred in the more distant past. By contrast, in *Drosophila*, mutation rates for microsatellite loci and nucleotide sites are quite similar (Schug *et al.* 1997; Schlötterer 2000), suggesting that the two classes of marker may be informative over similar timescales.

Schlötterer *et al.* (1997) used theoretical expectations for the variance in allele size as the basis for a method to detect locus-specific deviations from mutation–drift equilibrium in a subdivided population. The premise of this approach is that population-specific selective sweeps will produce a transient departure from the expected equilibrium variance in allele size at linked microsatellite loci. For the case of k populations and l loci, the first step is to calculate v_{kl} the logarithm of the observed variance in repeat number for each locus in each population. This is followed by calculation of the mean variance among populations ($v_{k.}$), the mean variance among loci ($v_{.l}$), as well as the grand mean ($v_{..}$). At mutation–drift equilibrium the expected variance for a given locus in a given population is

$$u_{kl} = v_{k.} + v_{l.} - v_{..} \tag{8}$$

The deviation from predicted values is then calculated as

$$\frac{(v_{kl} - u_{kl})KL}{(K-1)(L-1)\sqrt{Var[v_{kl}]}} \tag{9}$$

where $Var[v_{kl}] \approx 0.85$ (Schlötterer *et al.* 1997; Schlötterer & Wiehe 1999). Deviations from predicted values result from violations of equilibrium assumptions, such as population-specific selection. Differences between population means, $v_{k.}$, and the grand mean, $v_{..}$, reflect influences specific to a given population (i.e., different N_es), whereas differences between locus means, $v_{.l}$, and $v_{..}$, reflect influences specific to a locus (i.e., differences in mutation rate and/or recombinational environment). Significant population × locus interactions may be attributable to positive directional selection that leads to the fixation of linked neutral variants (genetic hitch-hiking) or overdominant selection that maintains balanced polymorphism at linked sites (associative overdominance). The former case is implicated if significant population × locus combinations are characterized by unusually low variance, as would be expected under a model of local adaptation. The latter is implicated if significant population × locus combinations exhibit unusually high variance relative to other such combinations. Correlations of allele frequencies among populations because of gene flow or shared ancestry will reduce the variance of the log variances, resulting in a conservative

test. The sensitivity of this test to demographic assumptions has not yet been evaluated.

Genome scans of microsatellite variability are well suited to purely empirical approaches as it is now technically feasible to screen population-level variation at several hundreds of marker loci. Schlötterer (2002) developed an empirical outlier-detection approach that is based on pairwise population comparisons. Under the stepwise mutation model at mutation–drift equilibrium, both variance in allele size and expected heterozygosity can be used to estimate the neutral parameter $\theta = 4N_e\mu$, where $N_e\mu$ is the mutation rate scaled by effective population size (Ohta & Kimura 1973; Moran 1975). For two populations, the expected ratio of variance-based estimators of θ is

$$E[RV] = \frac{(2N_{ePop1})\mu}{(2N_{ePop2})\mu} \cong \frac{V_{pop1}}{V_{pop2}} \tag{10}$$

and the corresponding expression for heterozygosity is

$$E[RH] = \frac{(4N_{ePop1})\mu}{(4N_{ePop2})\mu} = \frac{\left(\left(\frac{1}{1-H_{pop1}}\right)^2 - 1\right)\frac{1}{8\mu}}{\left(\left(\frac{1}{1-H_{pop2}}\right)^2 - 1\right)\frac{1}{8\mu}} \cong \frac{\left(\frac{1}{1-H_{pop1}}\right)^2 - 1}{\left(\frac{1}{1-H_{pop2}}\right)^2 - 1} \tag{11}$$

Simulation results indicate that ln-transformed values of *RV* and *RH* both conform to normal distributions over a wide range of demographic conditions (Schlötterer 2002; Kauer *et al.* 2003b; Schöfl & Schlötterer 2004). Consequently, probabilities of single-locus ln *RV* and ln *RH* values can be estimated using the normal probability density function. Loci with outlying values can then be used to identify genomic regions that may have experienced a population-specific selective sweep. By considering ratios of θ values, it is possible to control for interlocus differences in levels of variability that are attributable to differences in mutation rate and/or recombinational environment. Under neutrality, these ratios are expected to be the same for all loci, and observed differences should simply reflect stochastic variation among independent realizations of the coalescent process. Within each population, all loci should have the same N_e because they have all experienced the same demographic history. However, the joint effects of linkage and selection can produce variation in N_e across different regions of the genome (Hill & Robertson 1966; Barton 1995). Thus, loci that have undergone a selective sweep in one of the two populations will exhibit an unusually large discrepancy in population-specific estimates of θ (relative to all other unlinked loci) and such loci will therefore appear as outliers in the genome-wide distributions of ln *RV* and/or ln *RH*. As heterozygosity is expected to return to its expected equilibrium value more rapidly than variance in allele size (Kimmel *et al.* 1998), ln *RH* should have maximal power to detect sweeps that have occurred during a relatively recent time interval, whereas tests based on ln *RV* should have relatively greater power to detect sweeps that occurred in the more distant past.

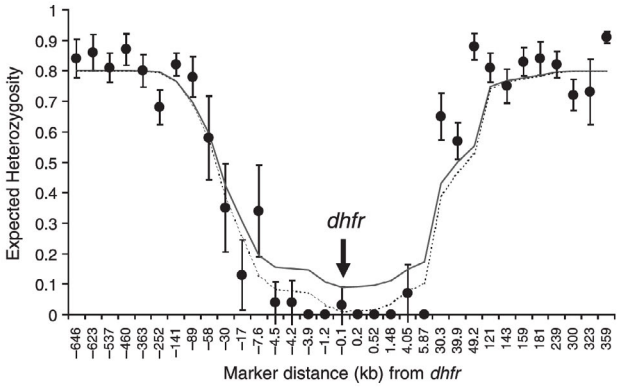

Figure 6. A multilocus scan of microsatellite variation in a southeast Asian population of the malaria parasite *Plasmodium falciparum* reveals evidence for a selective sweep on chromosome 4. Microsatellite variation was markedly reduced within an interval of *c.* 100 kb centered on *dhfr*, a gene involved in drug resistance [reproduced from Nair *et al.* (2003)].

Two recent studies of drug resistance in the human malaria parasite *Plasmodium falciparum* have provided proof-of-principle that pairwise comparisons based on relative levels of within-population diversity can be used to detect recent selective sweeps. Wootton *et al.* (2002) conducted a genome scan of microsatellite variation between chloroquine-resistant and chloroquine-sensitive isolates of *P. falciparum* from different parts of the world. They documented a dramatic reduction in variation and excess levels of LD in a *c.* 200-kb region of chromosome 7 that is centered on *pfcrt*, a gene that confers chloroquine resistance. Nair *et al.* (2003) conducted a multilocus scan of microsatellite variation across chromosome 4 of *P. falciparum* from Southeast Asia to test for evidence of a selective sweep in the region flanking *dhfr*, a gene that confers pyrimethamine resistance. They documented a dramatic reduction in microsatellite variation in a *c.* 100 kb region centered on *dhfr*, in addition to a skewed distribution of allele frequencies and excess levels of LD on chromosomes carrying the *dhfr*-resistance allele (Figure 6). These investigations of selective sweeps in populations of *P. falciparum* provide some indication of the marker density required to pinpoint the target of selection along a recombining chromosome. The selective sweeps documented on *P. falciparum* chromosomes 4 and 7 resulted in pronounced reductions in microsatellite variation over intervals of *c.* 100 kb and 200 kb, respectively (Wootton *et al.* 2002; Nair *et al.* 2003), suggesting that targets of selection for drug resistance in this species may be detectable using a marker spacing of *c.* 50 kb (3 cM; Anderson 2004).

Advantages and disadvantages of different multilocus tests of selection

Model-based vs. model-free approaches. Multilocus tests of selection can be divided into two classes: model-based approaches that rely on assumptions about population structure and model-free approaches that are based on empirical distributions of summary statistics. The advantage of empirical approaches is that outlier detection is not biased by model-based assumptions about population structure or history. However, choosing an empirical cut-off for identifying outliers in distributions of summary statistics may involve its own set of assumptions and biases. For example, if the normal probability density function is used to identify outlier loci in an empirical distribution of θ ratios (e.g. Harr *et al.* 2002; Kauer *et al.* 2003a, Kauer *et al.* 2003b; Schöfl & Schlötterer 2004), loci with values that fall more than |1.96| standard deviations (SDs) from the mean of the distribution are typically interpreted as significant outliers (i.e., candidates for selection) at a two-tailed α-level of 0.05. The problem is that if a given data set contains a large number of divergently selected loci, the empirical distribution will be characterized by an especially high SD. This will result in an overly conservative neutrality test because only the most extreme values would fall outside the 95% confidence interval. Conversely, a data set that contains only neutral loci will be characterized by a comparatively low SD, so outlier-detection tests based on θ-ratios would will be more likely to identify false positives. Thus, type I and type II error rates are strongly dependent on the true number of selected loci that are included in the analyzed data set. One partial solution to this problem is to standardize the test distribution for a set of markers using the mean and SD from a set of "control" markers that were typed in the same populations. Matched distributions for cross-standardization could involve comparisons between coding vs. noncoding sequence polymorphisms, comparisons between sets of markers that differ in genomic context (high vs. low gene density, high vs. low recombination rate, etc.), or comparisons between markers on different chromosomes. For example, Kauer *et al.* (2003b) and Schöfl & Schlötterer (2004) compared relative levels of microsatellite variation between X chromosomes and autosomes in populations of *Drosophila melanogaster* and *D. simulans*, respectively. Both studies found an excess of X-linked microsatellites that exhibited significantly reduced heterozygosity in European populations relative to African populations. To identify candidate regions of the X chromosome for selective sweeps outside of Africa, the authors standardized the distribution of θ ratios for X-linked markers with the mean and SD of θ ratios for markers that mapped to the third chromosome.

F_{ST}-based tests vs. θ-ratio tests. Multilocus tests of selection can also be divided into methods based on relative levels of differentiation between populations (e.g. F_{ST}-based tests; Lewontin & Krakauer 1973; Bowcock *et al.* 1991; McDonald 1994; Beaumont & Nichols 1996; Vitalis *et al.* 2001; Porter 2003; Beaumont & Balding 2004), and those based on relative levels of diversity within populations (e.g. θ-ratio tests; Schlötterer 2002; Vigouroux *et al.* 2002; Wootton *et al.* 2002). Empirical case studies that used one or both of these approaches to identify candidate loci for selection include surveys of DNA or protein polymorphism in populations of *Drosophila* (Harr *et al.* 2002; Kauer *et al.* 2003a, Kauer *et al.* 2003b; Schöfl & Schlötterer 2004), protozoan malaria parasites (Wootton *et al.* 2002; Nair *et al.* 2003), maize (Vigouroux *et al.* 2002), intertidal snails (Wilding *et al.* 2001), lake whitefish (Campbell & Bernatchez 2004), mice (Storz & Nachman 2003; Storz & Dubach 2004), and humans (Bowcock *et al.* 1991; Kayser *et al.* 2003; Storz *et al.* 2004).

Should we generally expect F_{ST}-based tests and θ-ratio tests to yield similar results? The tests may often identify the same outliers when applied to a common data set (Figure 7; Kayser *et al.* 2003; Storz *et al.* 2004), but there are many situations in which concordant results should not be expected. For example, consider the case of two isolated populations that are subject to independent selective sweeps involving the fixation of different alleles at the same locus. As levels of diversity at the selected locus would be reduced within each population, no discrepancy in population-specific θ values would be expected at linked microsatellites. However, if different neutral variants became fixed in the two populations as a result of random differences in associations with the selected site, linked loci would exhibit higher-than-expected F_{ST} values. This consideration suggests that θ-ratio tests may be most appropriate for pairwise comparisons in which only one of the two populations is subject to positive selection. Examples might include comparisons between an ancestral population and a derived population that has colonized a novel environment (e.g. Harr *et al.* 2002; Kauer *et al.* 2003a; Kauer *et al.* 2003b; Kayser *et al.* 2003; Schöfl & Schlötterer 2004; Storz *et al.* 2004), comparisons between affected vs. nonaffected populations in a case–control study design (Kohn *et al.* 2000, Wootton *et al.* 2002; Kohn *et al.* 2003; Nair *et al.* 2003), or comparisons between a domesticated species and its wild progenitor (Vigouroux *et al.* 2002).

Results of F_{ST}-based tests and θ-ratio tests may also differ if selection operates on standing variation rather than on newly arising mutations (as envisioned by classical hitch-hiking models), and the two approaches can be expected to differ in their power to detect selection over different timescales. In the case where a selective sweep is restricted to one member of a pair of populations, the discrepancy between population-specific θ values at linked microsatellites will be most pronounced in the immediate aftermath of the local sweep (so θ-ratio

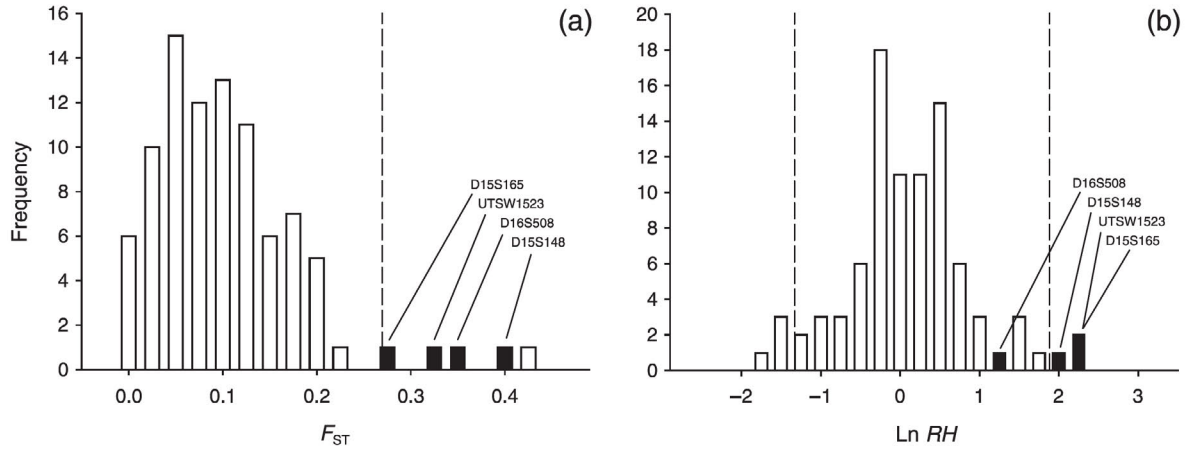

Figure 7. Identification of candidate loci for geographically restricted selective sweeps in humans [from the D2 data set analyzed in Storz *et al.* (2004)]. In simulation-based neutrality tests (Storz *et al.* 2004), four microsatellite loci (D15S148, D15S165, D16S508, and UTSW1523) were identified as statistically significant outliers in a three-way comparison between continental populations of humans (Mbuti pygmies, Italians, and Han Chinese; $n = 92$ microsatellite loci). (a) The same four loci were characterized by extreme values in the empirical distribution of F_{ST} values from the three-way comparison. The dashed vertical line denotes the upper 0.05 tail of the distribution. (b) The same four loci were also characterized by extreme values in the distribution of ln*RH* values from a pairwise comparison between African and non-African population samples. The dashed vertical lines denote the 95% confidence interval of the normal probability distribution. Because ln*RH* values were calculated using estimates of African gene diversity in the numerator of the ratio, loci with positive values indicate a reduction in relative levels of gene diversity in the non-African sample.

tests should have high power to identify selected loci). However, the input of new mutations after the selective sweep will gradually restore the equilibrium level of variability, thereby equalizing population-specific θ values (Wiehe 1998). If hitch-hiking results in the fixation of an initially rare allele, the stepwise mutation process will replenish variation around a new modal repeat number and the resultant shift in the frequency distribution of allelic length variants will persist long after mutation–drift equilibrium has been restored (Kayser *et al.* 2003). Compared to θ-ratio tests, this consideration suggests that F_{ST}-based tests may retain power to detect local selective sweeps over longer periods of time.

A comprehensive evaluation of the performance of different multilocus tests of selection would clearly be useful. To date, most efforts to evaluate the robustness of a given method have focused on how variation in demographic and mutational parameters can be expected to influence patterns of neutral variability (Beaumont & Nichols 1996; Vitalis *et al.* 2001; Schlötterer 2002). This is important because the distribution of test-statistics under neutrality typically provides the null expectation for tests of selection. The simulation study of Beaumont & Balding (2004) is unique in that the authors directly assessed the ability of their method to detect selected loci. More such studies are needed to determine which approaches are best suited to different situations.

Seeking confirmatory evidence of positive selection

Genome scans for detecting selection face the general problem of identifying and excluding false positives when multiple tests are conducted. It is therefore important to seek independent lines of evidence that positive selection has shaped patterns of variation at outlier loci. After using multilocus data from two or more populations to identify candidate loci for divergent selection, multilocus tests based on the frequency spectrum (Payseur *et al.* 2002; Storz & Beaumont 2002) or haplotype structure (Kohn *et al.* 2000; Sabeti *et al.* 2002) can be used to test for corroborative evidence of hitch-hiking effects within populations. For example, Vigouroux *et al.* (2002) used a genome scan of microsatellite variability in maize to identify gene regions that underwent selective sweeps during the process of domestication and subsequent crop improvement. Presumably, such regions would correspond to QTL for traits of agronomic importance. To identify candidate loci for selective sweeps, the authors used tests based on comparisons between domesticated maize and its wild progenitor (teosinte) in conjunction with tests based on the distribution of allele frequencies within domesticated maize. Loci that exhibit both reduced variability and a skew in the frequency spectrum are often considered good candidates for selection because these two properties are not correlated under neutral models of evolution. However, simulations under the stepwise mutation model and infinite-allele model have revealed that the excess of rare alleles predicted by hitch-hiking models is dependent on the mutation rate (scaled by N_e) and observed gene diversity (Schlötterer *et al.* 2004). For the case of DNA sequence data, one possible solution to this problem is to assess measures of the frequency spectrum that are jointly conditioned on

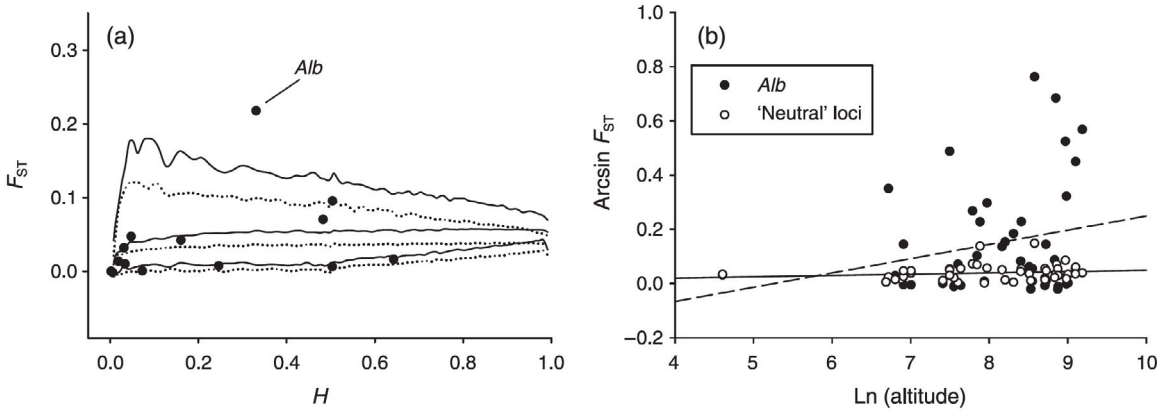

Figure 8. Evidence for diversifying selection on albumin polymorphism in deer mice, *Peromyscus maniculatus*. (a) Estimated F_{ST} values from 15 protein-coding genes are plotted as a function of heterozygosity in the deer mouse, *Peromyscus maniculatus*. Solid lines denote the 0.975, 0.500, and 0.025 quantiles of the conditional distribution obtained from coalescent simulations under an island model of population structure [using the method of Beaumont & Nichols (1996)]. Dotted lines denote the same quantiles of the null distribution that were recomputed after removing the outlying value for the albumin locus (*Alb*). (b) Linear regression of F_{ST} against altitudinal distance for pairwise comparisons of *P. maniculatus* samples taken from an altitudinal transect. The solid line denotes the linear regression line for transformed values of F_{ST} for neutral markers versus altitudinal distance, and the dashed line denotes the linear regression line for transformed values of F_{ST} for *Alb* versus altitudinal distance (modified from Storz & Dubach 2004).

observed nucleotide diversity and measures of interspecific divergence at silent sites.

Because a locus that has undergone a recent selective sweep is expected to exhibit aberrant patterns of variation relative to the rest of the genome (e.g. reduced polymorphism, a skewed distribution of allele frequencies, and excess LD), it is reasonable to expect tightly linked loci to exhibit similarly aberrant patterns of variation. Although hitch-hiking is expected to increase correlations in diversity levels among linked loci (Kim & Stephan 2002), correlations in the depths of neutral genealogies are expected even in the absence of selection at linked sites (Rosenberg & Nordborg 2002). To assess whether correlated patterns of variation at linked sites provide corroborative evidence of positive selection, it is important to compare the autocorrelation of coalescence times among linked markers to the expectations of a neutral model that accounts for variation in recombination rate. For example, in a genome-wide survey of nucleotide polymorphism in humans, Akey *et al.* (2002) reported a positive correlation between F_{ST} and intermarker distance that decayed to background levels over a distance of *c.* 200 kb. After using coalescent simulations to explore a range of different demographic scenarios, the authors concluded that F_{ST} values at linked loci were more highly correlated than expected under a neutral model.

Other sources of confirmatory evidence for selection include: (ii) parallel patterns of locus-specific variation among replicated population comparisons, and (ii) nonrandom associations between locus-specific variation and environmental variables. Several recent studies have revealed evidence for parallel divergence at the same loci in replicated population comparisons. A multilocus scan of amplified fragment length polymorphism (AFLP) between phenotypically distinct populations of intertidal snails revealed that the same 15 markers exhibited higher-than-expected levels of divergence in geographically replicated comparisons between the same two morphological types (Wilding *et al.* 2001). Likewise, a multilocus scan of AFLP markers between four sympatric pairs of lake whitefish ecotypes revealed that the same six markers exhibited higher-than-expected levels of divergence in each replicated comparison (Campbell & Bernatchez 2004). At the interspecific level, multilocus scans of protein polymorphism in natural populations of mice (genus *Peromyscus*) implicated the albumin locus as a candidate gene for local adaptation in four different species, suggesting that homologous polymorphisms may be subject to similar modes of selection in independent lineages (Storz & Nachman 2003). In one species, *Peromyscus maniculatus*, the albumin locus was also found to exhibit a highly nonrandom pattern of differentiation across an altitudinal gradient, in contrast to the spatial patterning of variation at unlinked loci (Figure 8; Storz & Dubach 2004). This latter study demonstrates how unlinked neutral loci can be used as an intragenomic control to test for environmental correlates of variation at candidate genes for selection.

The best confirmatory evidence for positive selection will ultimately come from functional studies. This requires making the transition from a static approach, in which selection is inferred from distributions of allele frequencies, to an experimental approach in which fitness-related variation among alternative genotypes

is measured directly. This transition to a functional approach requires identification of the specific substitution or combination of substitutions that confer the putative fitness advantage. Although high resolution mapping may provide a list of candidate genes within a particular marker interval, the identification of causative sequence variants represents a monumental challenge even in model organisms (Flint & Mott 2001). These challenges are illustrated by pioneering efforts to dissect the molecular basis of QTL for abdominal and sternopleural bristle number in *Drosophila melanogaster* (Mackay & Langley 1990; Lai *et al.* 1994; Long *et al.* 1996, 2000; Lyman *et al.* 1999). Despite the challenges, functional studies of putatively fitness-related sequence variants are ultimately required to make causal inferences about the genetic basis of adaptation.

Summary

In species that are distributed across ecologically heterogeneous landscapes, spatially separated populations that inhabit contrasting environments may be subject to different selection regimes. Similarly, competition for resources between sympatric morphs or closely related species may drive them to exploit new ecological niches where they become subject to different selection regimes. In both cases, divergent natural selection is expected to pull the population trait means toward different adaptive peaks. Results of population genetic theory indicate that it should be possible to detect QTL for divergently selected traits by screening genome-wide patterns of DNA polymorphism for the signature of positive directional selection. In contrast to other multilocus mapping approaches, genome scans for selection do not require identification of the affected traits at the outset. Because we know so little about the sources of fitness variation in natural populations of most organisms, it is important to have a means of identifying selected loci and their encoded phenotypes that is not constrained by a priori expectations about their adaptive significance. The real promise of the genome-scan approach lies in the possibility of identifying fitness-related phenotypes whose function and adaptive significance were previously unanticipated. Genome scans for selection can thus provide an important first step in establishing causal links between genotype, phenotype, and fitness in natural populations.

Acknowledgments

I thank M. A. Beaumont, L. Bernatchez, M. W. Hahn, R. G. Latta, J. K. McKay, M. W. Nachman, B. A. Payseur, M. D. Shriver, and three anonymous reviewers for helpful comments and suggestions, and T. J. C. Anderson, S. Nair, and R. Vitalis for providing figures.

References

Akey JM, Zhang G, Zhang K, Jin L, Shriver MD (2002) Interrogating a high-density SNP map for signatures of natural selection. Genome Research, 12, 1805– 1814.

Anderson TJC (2004) Mapping drug resistance genes in *Plasmodium falciparum* by genome-wide association. Current Drug Targets — Infectious Disorders, 4, 65– 78.

Andolfatto P (2001) Adaptive hitchhiking effects on genome variability. Current Opinion in Genetics and Development, 11, 635– 641.

Bamshad MJ, Mummidi S, Gonzalez E et al. (2002) A strong signature of balancing selection in the 5′-*cis*-regulatory region of *CCR5*. Proceedings of the National Academy of Sciences of the United States of America, 99, 10539– 10544.

Barton NH (1995) Linkage and the limits to natural selection. Genetics, 140, 821– 841.

Barton NH (1999) Clines in polygenic traits. Genetical Research, 74, 223– 236.

Barton NH (2000) Genetic hitchhiking. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 355, 1553– 1562.

Barton NH, Bengsston BO (1986) The barrier to genetic exchange between hybridizing populations. Heredity, 56, 357– 376.

Beaumont MA, Balding DJ (2004) Identifying adaptive genetic divergence among populations from genome scans. Molecular Ecology, 13, 969– 980.

Beaumont MA, Nichols RA (1996) Evaluating loci for use in the genetic analysis of population structure. Proceedings of the Royal Society of London. Series B, Biological Sciences, 263, 1619– 1626.

Begun DJ, Aquadro CF (1993) African and North American populations of *Drosophila melanogaster* are very different at the DNA level. Nature, 365, 548– 550.

Begun DJ, Aquadro CF (1995) Evolution at the tip and base of the X chromosome in an African population of *Drosophila melanogaster*. Molecular Biology and Evolution, 12, 382– 390.

Black WC, Baer CF, Antolin MF, DuTeau NM (2001) Population genomics: genome-wide sampling of insect populations. Annual Review of Entomology, 46, 441– 469.

Bowcock AM, Kidd JR, Mountain JL et al. (1991) Drift, admixture, and selection in human evolution: a study with DNA polymorphisms. Proceedings of the National Academy of Sciences of the United States of America, 88, 839– 843.

Braverman JM, Hudson RR, Kaplan NL, Langley CH, Stephan W (1995) The hitchhiking effect on the site frequency spectrum of DNA polymorphisms. Genetics, 140, 783– 796.

Campbell D, Bernatchez L (2004) Genomic scan using AFLP markers as a means to assess the role of directional selection in the divergence of sympatric whitefish ecotypes. Molecular Biology and Evolution, 21, 945– 956.

Cavalli-Sforza LL (1966) Population structure and human evolution. Proceedings of the Royal Society of London. Series B, Biological Sciences, 164, 362– 379.

Cavalli-Sforza LL, Menozzi P, Piazza A (1994) The History and Geography of Human Genes. Princeton University Press, Princeton, NJ.

Charlesworth B (1998) Measures of divergence between populations and the effect of forces that reduce variability. Molecular Biology and Evolution, 15, 538– 543.

Charlesworth B, Charlesworth D, Barton NH (2003) The effects of genetic and geographic structure on neutral variation. Annual Review of Ecology, Evolution, and Systematics, 34, 99– 125.

Charlesworth D, Charlesworth B, Morgan MT (1995) The pattern of neutral molecular variation under the background selection model. Genetics, 141, 1619– 1632.

Charlesworth B, Morgan MT, Charlesworth D (1993) The effect of deleterious mutations on neutral molecular variation. Genetics, 134, 1289– 1303.

Charlesworth B, Nordborg M, Charlesworth D (1997) The effects of local selection, balanced polymorphism and background selection on equilibrium patterns of genetic diversity in subdivided populations. Genetical Research, 70, 15D– 174.

Daborn PJ, Yen JL, Bogwitz MR et al. (2002) A single P450 allele associated with insecticide resistance in *Drosophila*. Science, 297, 2253– 2256.

Ellegren H (2000) Microsatellite mutations in the germline: implications for evolutionary inference. Trends in Genetics, 16, 551– 558.

Erickson DL, Fenster CB, Stenøien HK, Price D (2004) Quantitative trait locus analyses and the study of evolutionary process. Molecular Ecology, 13, 2505– 2522.

Falconer DS, Mackay TFC (1996) Introduction to Quantitative Genetics. Longman Science and Technology, Harlow, UK.

Fay JC, Wu C-I (2000) Hitchhiking under positive Darwinian selection. Genetics, 155, 1405– 1413.

ffrench-Constant RH (1994) The molecular and population genetics of cyclodiene insecticide resistance. Insect Biochemistry and Molecular Biology, 24, 335– 345.

Fisher RA (1930) The Genetical Theory of Natural Selection. Clarendon Press, Oxford.

Flint J, Mott R (2001) Finding the molecular basis of quantitative traits: successes and pitfalls. Nature Reviews Genetics, 2, 437– 445.

Fu Y-X, Li W-H (1993) Statistical tests of neutrality of mutations. Genetics, 133, 693– 709.

Fullerton SM, Bartoszewicz Ybazeta G et al. (2002) Geographic and haplotype structure of candidate type 2 diabetes-susceptibility variants at the Calpain-10 locus. American Journal of Human Genetics, 70, 1096– 1106.

Gillespie JH (1991) The Causes of Molecular Evolution. Oxford University Press, New York.

Gordo I, Navarro A, Charlesworth B (2002) Muller's ratchet and the pattern of variation at a neutral locus. Genetics, 161, 835– 848.

Hahn MW, Rockman MV, Soranzo N, Goldstein DB, Wray GA (2004) Population genetic and phylogenetic evidence for positive selection on regulatory mutations at the *factor VII* locus in humans. Genetics, 167, 867– 877.

Hamblin MT, Di Rienzo A (2000) Detection of the signature of natural selection in humans: evidence from the Duffy blood group locus. American Journal of Human Genetics, 66, 1669– 1679.

Hamblin MT, Thompson EE, Di Rienzo A (2002) Complex signatures of natural selection at the Duffy blood group locus. American Journal of Human Genetics, 70, 369– 383.

Harr B, Kauer M, Schlötterer C (2002) Hitchhiking mapping — a population-based fine mapping strategy for adaptive mutations in *Drosophila melanogaster*. Proceedings of the National Academy of Sciences of the United States of America, 99, 12949– 12954.

Hill WG, Robertson A (1966) The effect of linkage on the limits to artificial selection. Genetical Research, 8, 269– 294.

Hilton H, Kliman RM, Hey J (1994) Using hitchhiking genes to study adaptation and divergence during speciation within the *Drosophila melanogaster* species group. Evolution, 48, 1900– 1913.

Hudson RR, Boos DD, Kaplan NL (1992) A statistical test for detecting geographic subdivision. Molecular Biology and Evolution, 9, 138– 151.

Hudson RR, Kaplan NL (1995) Deleterious background selection with recombination. Genetics, 141, 1605– 1617.

Kaplan NL, Hudson RR, Langley CH (1989) The "hitchhiking effect" revisited. Genetics, 123, 887– 899.

Kauer M, Dieringer D, Schlötterer C (2003a) A microsatellite variability screen for positive selection associated with the "out of Africa" habitat expansion of *Drosophila melanogaster*. Genetics, 165, 1137– 1148.

Kauer M, Zangerl B, Dieringer D, Schlötterer C (2003b) Chromosomal patterns of microsatellite variability contrast sharply in African and non-African populations of *Drosophila melanogaster*. Genetics, 160, 247– 256.

Kayser M, Brauer S, Stoneking M (2003) A genome scan to detect candidate regions influenced by local natural selection in human populations. Molecular Biology and Evolution, 20, 893– 900.

Kim Y, Stephan W (2000) Joint effects of genetic hitchhiking and background selection on neutral variation. Genetics, 155, 1415– 1427.

Kim Y, Stephan W (2002) Detecting a local signature of genetic hitchhiking along a recombining chromosome. Genetics, 160, 765– 777.

Kimmel M, Chakraborty R, King JP, , Bamshad M, , Watkins WS, Jorde LB et al. (1998) Signatures of population expansion in microsatellite repeat data. Genetics, 148, 1921– 1930.

Kimura M (1983) The Neutral Theory of Molecular Evolution. Cambridge University Press, Cambridge, UK.

Kohn MH, Pelz H-J, Wayne RK (2000) Natural selection mapping of the warfarin resistance gene. Proceedings of the National Academy of Sciences of the United States of America, 97, 7911– 7915.

Kohn MH, Pelz H-J, Wayne RK (2003) Locus-specific genetic differentiation at *Rw* among warfarin-resistant rat (*Rattus norvegicus*) populations. Genetics, 164, 1055– 1070.

Kreitman M (2000) Methods to detect selection in populations with applications to the human. Annual Review of Genomics and Human Genetics, 1, 539– 559.

Lai C, Lyman RF, Long AD, Langley CH, Mackay TF (1994) Naturally occurring variation in bristle number and DNA polymorphisms at the scabrous locus of *Drosophila melanogaster*. Science, 266, 1697– 1702.

Lande R (1983) The response to selection on major and minor mutations affecting a metrical trait. Heredity, 50, 47– 65.

Lande R (1992) Neutral theory of quantitative genetic variance in an island model with local extinction and colonization. Evolution, 46, 381– 389.

Latta RG (1998) Differentiation of allelic frequencies at quantitative trait loci affecting locally adaptive traits. American Naturalist, 151, 283– 292.

Latta RG (2003) Gene flow, adaptive population divergence and comparative population structure across loci. New Phytologist, 161, 51– 58.

Le Corre V, Kremer A (2003) Genetic variability at neutral markers, quantitative trait loci and trait in a subdivided population under selection. Genetics, 164, 1205– 1219.
Lewontin RC (1974) The Genetic Basis of Evolutionary Change. Columbia University Press, New York.
Lewontin RC (1984) Detecting population differences in quantitative characters as opposed to gene frequencies. American Naturalist, 123, 115– 124.
Lewontin RC, Krakauer J (1973) Distribution of gene frequency as a test of the theory of the selective neutrality of polymorphisms. Genetics, 74, 175– 195.
Long AD, Lyman RF, Morgan AH, Langley CH, Mackay TF (2000) Both naturally occurring insertions of transposable elements and intermediate frequency polymorphisms at the achaete-scute complex are associated with variation in bristle number in *Drosophila melanogaster*. Genetics, 154, 1255– 1269.
Long AD, Mullaney SL, Mackay TF, Langley CH (1996) Genetic interactions between naturally occurring alleles at quantitative trait loci and mutant alleles at candidate loci affecting bristle number in *Drosophila melanogaster*. Genetics, 144, 1497– 1510.
Luikart G, England PR, Tallmon D, Jordon S, Taberlet P (2003) The power and promise of population genomics: from genotyping to genome typing. Nature Reviews Genetics, 4, 981– 994.
Lyman RF, Lai C, Mackay TF (1999) Linkage disequilibrium mapping of molecular polymorphisms at the scabrous locus associated with naturally occurring variation in bristle number in *Drosophila melanogaster*. Genetical Research, 74, 303– 311.
Lynch M, Walsh B (1998) Genetics and Analysis of Quantitative Traits. Sinauer Associates, Sunderland, MA.
Mackay TF, Langley CH (1990) Molecular and phenotypic variation in the achaete-scute region of *Drosophila melanogaster*. Nature, 348, 64– 66.
Maynard SJ, Haigh J (1974) The hitch-hiking effect of a favourable gene. Genetical Research, 23, 23– 35.
McDonald JH (1994) Detecting natural selection by comparing geographic variation in protein and DNA polymorphisms . In: Non-Neutral Evolution: Theories and Molecular Data (ed. Golding B) , pp. 88– 100. Chapman & Hall, New York.
McKay JK, Latta RG (2002) Adaptive population divergence: markers, QTL and traits. Trends in Ecology and Evolution, 17, 285– 291.
Moran PAP (1975) Wandering distributions and the electrophoretic profile. Theoretical Population Biology, 8, 318– 330.
Nachman MW, Crowell SL (2000) Estimate of the mutation rate per nucleotide in humans. Genetics, 156, 297– 304.
Nair S, Williams J, Brockman A et al. (2003) A selective sweep driven by pyrimethamine treatment in southeast Asian malaria parasites. Molecular Biology and Evolution, 20, 1526– 1536.
Nei M, Kumar S (2000) Molecular Evolution and Phylogenetics. Oxford University Press, Oxford.
Nei M, Li W-H (1979) Mathematical model for studying genetic variation in terms of restriction endonucleases. Proceedings of the National Academy of Sciences of the United States of America, 76, 5269– 5273.
Nei M, Maruyama T (1975) Lewontin–Krakauer test for neutral genes. Genetics, 80, 395.
Ohta T (1982) Linkage disequilibrium due to random genetic drift in finite subdivided populations. Proceedings of the National Academy of Sciences of the United States of America, 79, 1940– 1944.
Ohta T, Kimura M (1973) A model of mutation appropriate to estimate the number of electrophoretically detectable alleles in a finite population. Genetical Research, 22, 201– 204.
Orr HA (1998) The population genetics of adaptation: the distribution of factors fixed during adaptive evolution. Evolution, 52, 935– 949.
Orr HA (1999) The evolutionary genetics of adaptation: a simulation study. Genetical Research, 74, 207– 214.
Orr HA, Coyne JA (1992) The genetics of adaptation: a reassessment. American Naturalist, 140, 725– 742.
Partridge GG (1979) Relative fitness of genotypes in a population of *Rattus norvegicus* polymorphic for warfarin resistance. Heredity, 43, 239– 246.
Payseur BA, Cutter AD, Nachman MW (2002) Searching for evidence of positive selection in the human genome using patterns of microsatellite variability. Molecular Biology and Evolution, 19, 1143– 1153.
Petry D (1983) The effect on neutral gene flow of selection at a linked locus. Theoretical Population Biology, 23, 300– 313.
Porter AH (2003) A test for deviation from island-model population structure. Molecular Ecology, 12, 903– 915.
Przeworski M (2002) The signature of positive selection at randomly chosen loci. Genetics, 160, 1179– 1189.
Raymond M, Berticat C, Weill M, Pasteur N, Chevillon C (2001) Insecticide resistance in the mosquito *Culex pipiens*: what have we learned about adaptation? Genetica, 112– 113, 287– 296.
Robertson A (1975a) Remarks on the Lewontin–Krakauer test. Genetics, 80, 396.
Robertson A (1975b) Gene frequency distributions as a test of selective neutrality. Genetics, 81, 775– 785.
Rockman MV, Hahn MW, Soranzo N, Goldstein DB, Wray GA (2002) Positive selection on a human-specific transcription factor binding site regulating *IL4* expression. Current Biology, 13, 2118– 2123.
Rosenberg NA, Nordborg M (2002) Genealogical trees, coalescent theory and the analysis of genetic polymorphisms. Nature Reviews Genetics, 3, 380– 390.
Sabeti PC, Reich DE, Higgins JM et al. (2002) Detecting recent positive selection in the human genome from haplotype structure. Nature, 419, 832– 837.
Schlötterer C (2000) Evolutionary dynamics of microsatellite DNA. Chromosoma, 109, 365– 371.
Schlötterer C (2002) A microsatellite-based multilocus screen for the identification of local selective sweeps. Genetics, 160, 753– 763.
Schlötterer C (2003) Hitchhiking mapping — functional genomics from the population genetics perspective. Trends in Genetics, 19, 32– 38.
Schlötterer C. Kauer M. Dieringer D (2004) Allele excess at neutrally evolving microsatellites and the implications for tests of neutrality. Proceedings of the Royal Society of London. Series B, Biological Sciences, 271, 869– 874.
Schlötterer C, Vogl C, Tautz D (1997) Polymorphism and locus-specific effects on polymorphism at microsatellite loci in natural *Drosophila melanogaster* populations. Genetics, 146, 309– 320.

Schöfl G, Schlötterer C (2004) Patterns of microsatellite variability among X chromosomes and autosomes indicate a high frequency of beneficial mutations in non-African *D. simulans*. Molecular Biology and Evolution, 21, 1384– 1390.

Schlötterer C, Wiehe T (1999) Microsatellites, a neutral marker to infer selective sweeps . In: Microsatellites: Evolution and Applications (eds Goldstein DB, Schlötterer C) , pp. 238– 248. Oxford University Press, Oxford.

Schluter D (2000) The Ecology of Adaptive Radiation. Oxford University Press, Oxford.

Schug MD, Mackay TFC, Aquadro CF (1997) Low mutation rates of microsatellite loci in *Drosophila melanogaster*. Nature Genetics, 15, 99– 102.

Shriver MD, Kennedy GC, Parra EJ et al. (2004) The genomic distribution of population substructure in four populations using 8,525 autosomal SNPs. Human Genomics, 1, 274– 286.

Simonsen KL, Churchill GA, Aquadro CF (1995) Properties of statistical tests of neutrality for DNA polymorphism data. Genetics, 141, 413– 439.

Simpson GG (1953) The Major Features of Evolution. Columbia University Press, *New York*.

Slatkin M (1991) Inbreeding coefficients and coalescence times. Genetical Research, 58, 167– 175.

Slatkin M (1995) Hitchhiking and associative overdominance at a microsatellite locus. Molecular Biology and Evolution, 12, 473– 480.

Stephan W (1994) Effects of recombination and population subdivision on nucleotide sequence variation in *Drosophila ananassae* . In: Non-Neutral Evolution: Theories and Molecular Data (ed. Golding B) , pp. 57– 66. Chapman & Hall, New York.

Stephan W, Wiehe T, Lenz MW (1992) The effect of strongly selected substitutions on neutral polymorphism: analytical results based on diffusion theory. Theoretical Population Biology, 41, 237– 254.

Stephan W, Xing L, Kirby DA, Braverman JM (1998) A test of the background selection hypothesis based on nucleotide data from *Drosophila ananassae*. Proceedings of the National Academy of Sciences of the United States of America, 95, 5649– 5654.

Storz JF, Beaumont MA (2002) Testing for genetic evidence of population contraction and expansion: an empirical analysis of microsatellite DNA variation using a hierarchical Bayesian model. Evolution, 56, 154– 166.

Storz JF, Dubach JM (2004) Natural selection drives altitudinal divergence at the albumin locus in deer mice, *Peromyscus maniculatus*. Evolution, 58, 1342– 1352.

Storz JF, Nachman MW (2003) Natural selection on protein polymorphism in the rodent genus *Peromyscus*: evidence from interlocus contrasts. Evolution, 57, 2628– 2635.

Storz JF, Payseur BA, Nachman MW (2004) Genome scans of DNA variability in humans reveal evidence for selective sweeps outside of Africa. Molecular Biology and Evolution, 21, 1800– 1811.

Tachida H (2000) Molecular evolution in a multisite nearly neutral mutation model. Journal of Molecular Evolution, 50, 69– 81.

Tajima F (1989) Statistical method for testing the neutral mutation hypothesis by DNA polymorphism. Genetics, 123, 585– 595.

Takahata N (1991) Genealogy of neutral genes and spreading of selected mutations in a geographically structured population. Genetics, 129, 585– 595.

Taylor MFJ, Shen Y, Kreitman ME (1995) A population genetic test of selection at the molecular level. Science, 270, 1497– 1499.

Tsakas S, Krimbas CB (1976) Testing the heterogeneity of *F* values: a suggestion and a correction. Genetics, 84, 399– 401.

Vigouroux Y, McMullen M, Hittinger CT et al. (2002) Identifying genes of agronomic importance in maize by screening microsatellites for evidence of selection during domestication. Proceedings of the National Academy of Sciences of the United States of America, 99, 9650– 9655.

Vitalis R, Dawson K, Boursot P (2001) Interpretation of variation across marker loci as evidence of selection. Genetics, 158, 1811– 1823.

Wiehe T (1998) The effect of selective sweeps on the variance of the allele distribution of a linked multiallele locus: hitchhiking of microsatellites. Theoretical Population Biology, 53, 272– 283.

Wiehe T, Stephan W (1993) Analysis of a genetic hitchhiking model and its application to DNA polymorphism data from *Drosophila melanogaster*. Molecular Biology and Evolution, 10, 842– 854.

Wilding CS, Butlin RK, Grahame J (2001) Differential gene exchange between parapatric morphs of *Littorina saxatilis* detected using AFLP markers. Journal of Evolutionary Biology, 14, 611– 619.

Williamson S, Orive ME (2002) The genealogy of a sequence subject to purifying selection at multiple sites. Molecular Biology and Evolution, 19, 1376– 1384.

Wootton JC, Feng X, Ferdig MT et al. (2002) Genetic diversity and chloroquine selective sweeps in *Plasmodium falciparum*. Nature, 418, 320– 323.

Wright S (1943) Isolation by distance. Genetics, 16, 97– 159.

Wright S (1951) The genetical structure of populations. Annals of Eugenics, 15, 323– 354.

The main focus of the author's current research is molecular population genetics, with an emphasis on understanding the process of adaptive evolution in heterogenous environments. My empirical research in this area involves population genetic studies of the loci that underlie physiological and morphological adaptation in natural populations of deer mice (genus *Peromyscus*).