

Analysis of genetic diversity in geographically structured populations: A Bayesian perspective

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Bayesian approaches have been widely applied to partitioning diversity within and among levels in many different multi-level modeling contexts. In spite of the structural similarities between these Bayesian models and hierarchical approaches to partitioning diversity in population genetics, population geneticists have not explored the use of hierarchical Bayesian models to provide estimates of Wright's F -statistics. In this paper I describe and illustrate the application of a simple multilocus, two-allele model sufficient for partitioning diversity within and among populations. Extensions of the model incorporate both fixed-effect and random-effect models of population sampling at multiple hierarchical levels with multiple alleles per locus. The Bayesian approach developed here is closely related to previously developed methods for likelihood analysis of the same problem. I illustrate the utility of the Bayesian approach with a reanalysis of previously published allozyme data from *Argania spinosa*.

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Biological diversity is inherently hierarchical. This is particularly evident at the level of species and above: closely related species are part of the same genus, closely related genera are part of the same family, closely related families are part of the same order, and so on. Similar hierarchical structure is often evident within species. Not only are there differences among individuals from the same population, there are differences among populations within a given geographical region and differences among geographical regions. For population geneticists this hierarchical structure is reflected in the extent to which genetic differences between individuals are the result of differences found between members of the same population, between members of different populations in the same geographical region, or between members of populations in different geographical regions.

WRIGHT (1951, 1965) introduced the use of F -statistics to describe this hierarchical structure. In a simple, two-level sampling hierarchy (individuals within populations within a given geographical region), F_{st} measures the proportion of genetic diversity in the entire sample that is due to allele frequency differences among populations. Because of this simple interpretation, estimates of F_{st} have been widely used to partition genetic diversity into within and among population components and to investigate the influence of life-history variables on that partitioning (see, for example, HAMRICK et al. 1979; NEVO et al. 1984; HAMRICK and GODT 1990). F_{st} estimates have also been widely used to infer patterns of gene flow

because F_{st} is closely related to the number of migrants per generation when populations have reached a drift-migration equilibrium (WRIGHT 1931; see, HAMRICK 1987 and GOVINDJARU 1989 for applications and SLATKIN and BARTON 1989 and COCKERHAM and WEIR 1993 for a discussion of theoretical issues).

Investigators in many other fields encounter hierarchically structured data and are interested in partitioning that variability in ways analogous to the partitioning of genetic diversity into within and among population components. An investigator might want to determine, for example, whether most of the variability in individual performance on standardized examinations is due to variation among the individuals taking the test or due to differences among the teachers to whom they were exposed. If each student has only one teacher, the hierarchical structure of this data is precisely analogous to the hierarchical structure of genetic data collected from geographically structured populations. Because of the frequency with which investigators encounter hierarchically structured data, statisticians have developed a variety of sophisticated methods for partitioning of variation among hierarchical levels (see SEARLE et al. 1992 for an overview). Indeed, many classic experimental designs are intended to produce reliable and efficient estimates of the hierarchically structured components of variance. Quantitative geneticists have made extensive use of many of these techniques for analysis of variance components (see, for example,

FALCONER and MACKAY 1996 or LYNCH and WALSH 1998), but population geneticists have used them less extensively (WEIR and COCKERHAM 1984 is an obvious exception; see also WEHRHAHN 1989, BALDING and NICHOLS 1995, and RANNALA and HARTIGAN 1995).

In recent years statisticians have increasingly made use of Bayesian methods for analysis of complex hierarchical data (see GOLDSTEIN 1995 for a recent comprehensive survey of statistical approaches to multilevel modeling), and Bayesian methods have recently been applied to the analysis of heterogeneity in genetic samples (for example, ROEDER et al. 1998). In this paper I describe a hierarchical Bayesian model for partitioning genetic diversity at biallelic loci within and among populations in a simple two-level hierarchy, and I show how it can be extended to incorporate multiple alleles at each locus and arbitrarily complex hierarchical structures. Inferring migration rates from F_{st} estimates normally involves neglecting the role of mutation in producing genetic diversity. I also illustrate that a straightforward extension of the basic approach can be used to make direct inferences about mutation rates ($4N_e\mu$) and migration rates ($4N_em$), at least in some simple cases. Finally, a reanalysis of allozyme data from *Argania spinosa* (Sapotaceae; PETIT et al. 1998) provides an example of how these techniques can be used in practice. I also use these data to demonstrate how patterns of genetic differentiation at selectively neutral loci may bear little resemblance to those at loci subject either to uniform or divergent directional selection.

ESTIMATING F_{st}

Wright defined F_{st} as "the correlation between random gametes within [populations], relative to gametes of the total [sample]" (WRIGHT 1969, p. 294). When considering one locus with two alleles, Wright's F_{st} is equal to the actual variance among populations divided by the maximum possible variance given the observed mean allele frequencies. NEI (1973) suggested using the expected panmictic heterozygosity in a sample as a measure of genetic diversity in that sample. Using this definition of genetic diversity the proportion of genetic diversity due to allele frequency differences among subpopulations is given by

$$G_{st} = \frac{H_t - H_s}{H_t},$$

where H_s is the average expected panmictic heterozygosity within subpopulations and H_t is the expected panmictic heterozygosity in the total sample (calculated from the mean allele frequencies across

populations). Nei's definition of G_{st} in terms of expected heterozygosity is equivalent to Wright's definition in terms of genetic correlations regardless of the number of alleles per locus (NEI 1973; compare HOLSINGER and MASON-GAMER 1996) when identity by type is equivalent to identity by descent.

Sources of sampling error

The definitions of the preceding paragraph assume, of course, that the allele frequencies are known without error. Applications of F -statistics to the interpretation of actual genetic data, however, must account for error associated with estimating allele frequencies from sample data. One source of error is immediately apparent to anyone who has had a basic course in statistics: sample allele frequencies from each population may differ from the actual allele frequencies in those populations. A second source of error may be less apparent: because the populations included in a study often represent only a portion of all populations that could have been included, the allele frequency distribution among populations for which allelic samples are available may be different from the allele frequency distribution among all populations of interest. Two widely used statistics, Nei's G_{st} (NEI and CHESSEY 1983) and Weir and Cockerham's θ (WEIR and COCKERHAM 1984), take different approaches to correcting for sampling error associated with estimates of F_{st} .

NEI and CHESSEY (1983) calculate the statistical bias associated with equating sample and population allele frequencies and use the calculated bias to produce formulas that allow unbiased estimation of H_s and H_t . For example, if \hat{p}_{ik} is the sample estimate for the frequency of allele A_i in subpopulation k , then $1 - \sum_i \hat{p}_{ik}^2$ is a biased estimate of the genetic diversity in subpopulation k because

$$E_k \left(1 - \sum_i \hat{p}_{ik}^2 \right) = \left(\frac{n_k - 1}{n_k} \right) \left(1 - \sum_i p_{ik}^2 \right),$$

where n_k is the sample size from population k and E_k represents the mathematical expectation across the process of sampling alleles from subpopulation k . To correct this bias, genetic diversity within subpopulation k is commonly estimated as

$$\hat{H}_{sk} = \left(\frac{n_k}{n_k - 1} \right) \left(1 - \sum_i \hat{p}_{ik}^2 \right).$$

This bias correction is equivalent to the bias correction usually applied to estimates of a population variance in which the sum of squared deviations about the mean is divided by $n - 1$ instead of by n , but it accounts only for sampling error associated with sampling alleles from within populations.

WEIR and COCKERHAM (1984) take a different approach to the problem of sampling error, an approach derived from the analysis of variance. For each allele sampled from population k , a set of indicator variables is defined:

$$x_{ik} = \begin{cases} 1, & \text{if it is allele } A_i \\ 0, & \text{if it is not allele } A_i \end{cases}$$

An analysis of variance on these indicator variables is performed, partitioning the sum of squares into within population and among population components. The sums of squares are converted to mean squares by dividing each by its associated degrees of freedom. Under a particular model of population divergence, COCKERHAM (1969) showed that the expected mean squares associated with such an ANOVA model are a function of coancestry coefficients that are equivalent to Wright's F statistics, assuming that the populations sampled are a random subset of all diverging populations. Estimates of the coancestry coefficients are derived by equating the observed and expected mean squares.

Estimates of population structure derived from Weir and Cockerham's θ can be quite different from those derived from Nei's bias-corrected G_{st} for two reasons:

1. the θ includes a correction for sampling error associated with differences between the allele frequency distribution the set of populations sampled and the actual allele frequency distribution of the entire set of populations.
2. Interpreting θ in terms of coancestry coefficients depends on a particular model of population divergence that may sometimes be a poor representation of the actual process.

Fortunately, G_{st} and θ typically differ little when the number of populations sampled is relatively large. Nonetheless, the current state of the art is unsatisfactory in two ways. First, in circumstances where the sampled populations are themselves regarded as a sample from all possible populations (the random-effect model of population sampling, WEIR 1996), it would be useful to have a method of partitioning genetic diversity into its within and among population components whose interpretation does not depend on a particular evolutionary model. Second, in circumstances where the sampled populations represent the entire set of populations in which investigators are interested (the fixed-effect model of population sampling, WEIR 1996), it would be useful if the conceptual framework used to make estimates of F_{st} were closely related to the one used make estimates in the random-effect population model. Likelihood methods (e.g., BARTON et al. 1983; WEHRHAHN and POWELL 1987;

SLATKIN and BARTON 1989; WEHRHAHN 1989; RANALA and HARTIGAN 1995) can be interpreted without reference to a particular evolutionary model, but they implicitly assume a random-effect model of population sampling. The Bayesian approach I describe below extends the existing framework of likelihood models and extends it by allowing for multiple levels in the sampling hierarchy and for either fixed-effect or random-effect population sampling (or both).

A Bayesian approach

Before describing the Bayesian approach to analysis of population structure, consider the simple case of estimating allele frequencies at a set of biallelic loci within a single population (compare WEIR 1996). The sample consists of data on genetic variation at I loci, each with 2 alleles A_1 and A_2 . Let a_{ik} be the number of A_1 alleles in the sample, and let n_{ik} be the sample size at locus i from population k . If we assume that alleles are sampled independently within each population and that we can ignore gametic disequilibrium, the probability of getting the observed sample from a population in which p_{ik} is the frequency of A_1 at locus in population k is just

$$L(a_{ik} | n_{ik}, p_{ik}) = \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{a_{ik}} p_{ik}^{a_{ik}} (1 - p_{ik})^{n_{ik} - a_{ik}}. \quad (1)$$

L is the likelihood of the sample (EDWARDS 1972). Maximum-likelihood estimates for the p_{ik} are those values of p_{ik} that maximize $L(a_{ik} | n_{ik}, p_{ik})$, in this case $\hat{p}_{ik} = a_{ik}/n_{ik}$. Bayesian estimates for the p_{ik} also depend on the likelihood, but they use it to refine prior beliefs about the p_{ik} . Specifically, if $\phi(p_{ik})$ is the probability we assign to the frequency of A_1 in population k prior to collecting the data (the prior probability for p_{ik}), then the posterior probability for p_{ik} is given by

$$P(p_{ik} | n_{ik}, a_{ik}) \propto \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{a_{ik}} p_{ik}^{a_{ik}} (1 - p_{ik})^{n_{ik} - a_{ik}} \phi(p_{ik}). \quad (2)$$

The choice of priors, i.e., the $\phi(p_{ik})$, is affected by many factors, and point estimates for p_{ik} can be derived from the posterior distribution, $P(p_{ik} | n_{ik}, a_{ik})$, in several ways (LEE 1989; O'HAGAN 1994). In the absence of any prior information about allele frequencies, a uniform distribution for $\phi(p_{ik})$ on $[0,1]$ is often chosen, suggesting that every possible allele frequency is equally likely. If we use the mean of the posterior distribution as a point estimate for p_{ik} , then $\hat{p}_{ik} = (a_{ik} + 1)/(n_{ik} + 2)$.*

* If we use the mode of the posterior distribution as a point estimate for p_{ik} , then $\hat{p}_{ik} = a_{ik}/n_{ik}$, and the Bayesian point estimate is equivalent to the maximum-likelihood estimate.

Table 1. Comparison of F_{st} Estimates¹

G_{st}	θ	G_{st}^B	θ^B
0.0911	0.1667(0.0372, 0.2844)	0.0877(0.0423, 0.1418)	0.1722(0.0460, 0.4068)

¹Data from *Aedes aegyptii* (J. Powell cited in WEIR 1996, p. 201). Reduced to two alleles per locus by combining least frequent alleles at each locus into a single, pseudo-allele class. G_{st} is from GENESTAT (LEWIS and WHITKUS 1989). θ is from GDA (LEWIS and ZAYKIN 1999). G_{st}^B and θ^B are from a Gibbs sampler implemented in WinBUGS (GILKS et al. 1994). Numbers in parentheses represent lower and upper bounds of the 95 % credibility interval.

Constructing a Bayesian model for inferring the partitioning of diversity within and among populations involves adding a hierarchical component to equation (2). Specifically, let the frequency distribution of p_{ik} in all populations (including those not sampled) be a beta distribution with parameters a_i and b_i , $Be(a_i, b_i)$. If we let $a_i = ((1 - \theta)/\theta)x_i$ and $b_i = ((1 - \theta)/\theta)(1 - x_i)$, then x_i corresponds with the mean allele frequency at locus i (averaged across all populations) and θ corresponds with F_{st} (calculated from the frequency distribution of allele frequencies across all populations; see ROEDER et al. 1998). Letting $X(x_i)$ be the prior distribution for the x_i and $T(\theta)$ be the prior distribution for θ , the posterior probability distribution for p_{ik} and θ is given by

$$P(p_{ik}, \theta | n_{ik}, a_{ik}) \propto \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{p_{ik}} p_{ik}^{a_{ik}} (1 - p_{ik})^{n_{ik} - a_{ik}} \times Be(a_i, b_i) X(x_i) T(\theta). \quad (3)$$

For a fixed-effect model of population sampling, corresponding with Nei's G_{st} , F_{st} can be estimated as

$$H_s = 1 - (1/K) \sum_{k=1}^K \sum_{i=1}^I \hat{p}_{ik}^2, \\ H_t = 1 - \sum_{i=1}^I \hat{p}_i^2, \\ F_{st} = \frac{H_t - H_s}{H_t}, \quad (4)$$

where \hat{p}_{ik} is the mean of the posterior distribution for p_{ik} and $\hat{p}_i = (1/K) \sum \hat{p}_{ik}$. I will refer to an estimate of F_{st} derived in this way as G_{st}^B . For a random-effect model of population sampling, corresponding with Weir and Cockerham's θ , F_{st} can be estimated as the mean of the posterior distribution for θ . I will refer to an estimate of F_{st} derived in this way as θ^B . Analytical expressions for the posterior distribution of G_{st}^B and θ^B are not available,[†] but they can be numerically approximated through the use of Gibbs sam-

pling (GELFAND and SMITH 1990). Gibbs sampling provides a numerical approximation of the full posterior distribution with which it is also easy to judge the reliability of point estimates.

The results in Table 1 illustrate that G_{st}^B and θ^B provide estimates of F_{st} quite comparable to G_{st} and θ , respectively.[‡] In this example as in others I have examined, the interval estimate for θ^B is substantially less symmetric than the interval estimate for θ , which is obtained by bootstrapping across loci. Differences in the degree of asymmetry appear to be smaller, however, in data sets consisting of samples from ten or more populations. This result is consistent with intuition suggesting that the reliability of F_{st} estimates may often be influenced as much by the number of populations sampled as by the number of loci sampled within each population (see LYNCH and CREASE 1990 for a quantitative demonstration of this point with DNA sequence data). This result also suggests that bootstrap intervals are likely to be overly narrow when the number of populations is small, because the sample distribution of allele frequencies will then provide a poor approximation to the actual distribution (compare EFRON and TIBSHIRANI 1993.)

Extending the approach

There are two obvious limitations to the approach I have just outlined. First, analyses are limited to data sets with only two alleles per locus. Second, analyses are limited to a simple, two-level hierarchy. Although there are some computational challenges to be faced in extending the approach to cover more complex and interesting cases, the conceptual framework I have just described accommodates them without difficulty.

Multiple alleles per locus. The extension to multiple alleles per locus is especially straightforward. Consider a sample of genetic variation at locus i having alleles A_1, A_2, \dots, A_{n_i} , where n_i is the number of alleles present at locus i in the sample. Let a_{ijk} be the

distribution for θ will be close to the maximum-likelihood estimate of θ provided the posterior distribution is close to symmetrical.

[‡] The prior for the x_i was uniform on $[0, 1]$, and the prior for θ was a $Be(1, 2)$ (compare ROEDER et al. 1998), but the results are quite insensitive to the choice of priors.

[†] The likelihood for this sampling model is a beta-binomial (WEHRHAHN 1989). Thus, if a uniform prior is chosen for θ , the mode of the posterior distribution for θ will correspond with the maximum-likelihood estimate of θ . The mean of the posterior

number of A_j alleles present in the sample at locus i and n_{ik} be the sample size at locus i from population k . Assuming that alleles are sampled independently within each population and ignoring gametic disequilibrium, the likelihood of the sample is

$$L(a_{ijk} | n_{ijk}, p_{ijk}) = \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{a_{i1k} a_{i2k} \dots a_{in_k k}} \times p_{i1k}^{a_{i1k}} p_{i2k}^{a_{i2k}} \dots p_{in_k k}^{a_{in_k k}}, \quad (5)$$

where p_{ijk} is the frequency of allele A_j at locus i in population k (compare with (1) above).

For multinomial samples, the Dirichlet distribution, $Dir(\alpha_{i1}, \alpha_{i2}, \dots, \alpha_{in_i})$ provides a natural prior for the allele frequencies at locus i (O'HAGAN 1994; LANGE 1995). If we let $\alpha_{ij} = ((1 - \theta)/\theta)x_{ij}$, then x_{ij} corresponds with the mean frequency of allele A_j at locus i (averaged across all populations) and θ corresponds with F_{st} (calculated from the frequency distribution of alleles across all populations; see ROEDER et al. 1998). Letting $X(x_{i1}, x_{i2}, \dots, x_{in_i})$ be the prior distribution for the x_{ij} and $T(\theta)$ be the prior distribution for θ , the posterior distribution for p_{ijk} and θ becomes

$$P(p_{ijk}, \theta | n_{ijk}, a_{ijk}) \propto \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{a_{i1k} a_{i2k} \dots a_{in_k k}} p_{i1k}^{a_{i1k}} p_{i2k}^{a_{i2k}} \dots p_{in_k k}^{a_{in_k k}} Dir(\alpha_{i1}, \alpha_{i2}, \dots, \alpha_{in_i}) X(x_{i1}, x_{i2}, \dots, x_{in_i}) T(\theta) \quad (6)$$

(compare with (3) above; see also WEHRHAHN 1989 and RANNALA and HARTIGAN 1995 for similar expressions in a likelihood context). Estimates for a fixed-effect model of population sampling, G_{st}^B , can be derived from the multiallelic analog of (4) where \hat{p}_{ijk} is the mean of the posterior distribution for p_{ijk} . Estimates for a random-effect model of population sampling, θ^B , can be obtained from the mean of the posterior distribution for θ .

Complex hierarchical structures. While the extension to more complex hierarchical structures becomes rotationally difficult, the principle involved is identical to that used to derive (3) from (2), namely we add levels to the hierarchy by adding appropriate hierarchical components to equation (6). To illustrate how this is accomplished, consider the following three-level sampling scheme: Alleles are sampled at random from subpopulations. Subpopulations are sampled (either randomly or completely) from populations. Populations are sampled (either randomly or completely) from geographical regions.

Let k_n be the number of subpopulations sampled from population n , let a_{ijkn} be the number of A_j alleles

present in the sample at locus i and n_{ikn} be the sample size at locus i from subpopulation k in population n . There are two options available in adding an additional level to the sampling hierarchy. Either we can assume that the partitioning of genetic diversity within and among subpopulations is the same in all populations (the assumption made in existing methods that use G_{st} or θ), or we can allow the partitioning of genetic diversity within and among subpopulations to differ among populations. I will refer to the first approach as the constant- θ_s approach (the subscript s refers to subpopulations) and to the latter as the variable- θ_s approach. Because the constant- θ_s approach is a special case of the variable- θ_s approach, I will describe the variable- θ_s approach in detail before showing how the constant- θ_s approach is derived from it.

Within population n the distribution of allele frequencies among subpopulations at locus i is given by

$$P(p_{ijkn} | x_{ijn}, \theta_n) = Dir(\alpha_{i1n}, \alpha_{i2n}, \dots, \alpha_{in_n n}) X(x_{i1n}, x_{i2n}, \dots, x_{in_n n}), \quad (7)$$

where $\alpha_{ijn} = ((1 - \theta_{s(n)})/\theta_{s(n)})x_{ijn}$. With this formulation x_{ijn} corresponds with the mean frequency of allele A_j at locus i (averaged across all subpopulations of n) and $\theta_{s(n)}$ corresponds with F_{st} calculated from the frequency distribution of alleles across all subpopulations of n . Similarly, the distribution of allele frequencies among populations at locus i is given by

$$P(x_{ijn} | x_{ij}, \theta) = Dir(\alpha_{i1}, \alpha_{i2}, \dots, \alpha_{in_i}) X(x_{i1}, x_{i2}, \dots, x_{in_i}), \quad (8)$$

where $\alpha_{ij} = ((1 - \theta)/\theta)x_{ij}$. With this formulation x_{ij} corresponds with the mean frequency of allele A_j at locus i (averaged across all populations) and θ corresponds with F_{st} calculated from the frequency distribution of alleles across all populations.

Combining (7) and (8) and assuming that allelic samples are independent across loci and populations, the posterior distribution for p_{ijkn} , x_{ijn} , $\theta_{s(n)}$, and θ is given by

$$P(p_{ijkn}, x_{ijn}, \theta_{s(n)}, \theta | n_{ijkn}, a_{ijkn}) \propto \prod_{i=1}^I \prod_{k=1}^K \prod_{n=1}^N \binom{n_{ikn}}{a_{i1kn} a_{i2kn} \dots a_{in_k kn}} p_{i1kn}^{a_{i1kn}} p_{i2kn}^{a_{i2kn}} \dots p_{in_k kn}^{a_{in_k kn}} P(p_{ijkn} | x_{ijn}, \theta_n) P(x_{ijn} | x_{ij}, \theta) X(x_{ij}) T(\theta_{s(n)}) T(\theta), \quad (9)$$

where $x(x_{ij})$, $T(\theta_{s(n)})$, and $t(\theta)$ are the priors for x_{ij} , $\theta_{s(n)}$, and θ , respectively. Fixed-effect estimates of F_{st} among subpopulations of population n ($G_{st(n)}^B$) can be derived from the multiallelic analog of (4) where \hat{p}_{ijkn}

is the mean of the posterior distribution for p_{ijkn} , and fixed-effect estimates of F_{st} among populations G_{st}^B can be similarly derived from the mean of the posterior distribution for x_{ijn} . Random-effect estimates of F_{st} among subpopulations of population n ($\theta_{s(n)}^B$) can be obtained from the mean of the posterior distribution for $\theta_{s(n)}$, and for F_{st} among populations from the mean of the posterior distribution for θ .

The constant- θ_s model is derived from the variable- $\theta_{s(n)}$ model by setting $\theta_{s(n)} = \theta_s$ for all populations. Fixed-effect estimates of F_{st} can be obtained from the posterior mean of p_{ijkn} and x_{ijn} as before. Random-effect estimates of F_{st} among subpopulations can be obtained from the posterior mean of θ_s and θ .

The flexibility this approach provides for describing the partitioning of diversity at each hierarchical level is an important advantage over existing methods. Rather than assuming that subpopulations are equally differentiated from one another regardless of which population in which subpopulations of one population may be relatively undifferentiated while those of another are markedly different. Moreover, it should also be possible to use Bayesian model choice criteria (for example, GELFAND and GHOSH 1998) to determine whether any differences among populations in the partitioning of genetic diversity (reflected in estimates of $\theta_{s(n)}$ that differ among populations) are statistically important.

F -statistics are also widely used to describe the departure of genotype frequencies from Hardy-Weinberg proportions within populations. When used in this way, however, the inbreeding coefficient F_{is} is assumed to be the same in all subpopulations. The same procedure used to extend this hierarchical approach to multiple levels above the subpopulation can also be used to extend the hierarchy downward to examine the relationship between allele frequencies and genotype frequencies within populations. With this approach F_{is} can be estimated separately for each population and Bayesian model choice criteria can be used both to determine whether there are detectable departures from Hardy-Weinberg within subpopulations and whether those departures are of a similar magnitude in all populations.

Estimating migration and mutation rates. It is also quite easy to extend the two-level hierarchy model to provide direct estimates of the migration rate ($4N_e m$) and the mutation rate ($4N_e \mu$) in the case of an island-type migration model (compare WRIGHT 1931; RANNALA and HARTIGAN 1995). N_e in this model corresponds to the effective size of local populations, and the migration process does not include local extinction and recolonization. WHTLOCK and BARTON (1997) and NUNNEY (1999) discuss the effective size of populations under much less restrictive models, but their analyses do not include the effects of mutation. If

we make the restrictive assumptions that mutation among all allelic classes is equally likely and that the frequency of allele A_i among migrants into a population is equal to $1/n_i$, then it can be shown that the stationary distribution of allele frequencies approached by a drift-migration-mutation process is given by a Dirichlet distribution in which all parameters are equal to $4N_e(u_i + m/n_i)/(n_i - 1)$ (see EWENS 1979 and compare CROW and KIMURA 1970; see also RANNALA and HARTIGAN 1995). This approach allows each locus to have a different mutation rate, μ_i , but the restrictive assumptions on mutation and migration rates imply that all alleles at a locus have the same expected frequency at stationarity and that this frequency matches the allele frequency in migrants. §

The posterior distribution for this model differs only a little from equation (6). Specifically, let $\alpha_{ij} = 4N_e(\mu_i + m/n_i)/(n_i - 1)$, let $M(4N_e m)$ be the prior distribution for $4N_e m$, and let $U(4N_e \mu)$ be the prior distribution for $4N_e \mu$ is given by

$$P(4N_e m, 4N_e \mu \mid n_{ijk}, a_{ijk}) \\ \propto \prod_{i=1}^I \prod_{k=1}^K \binom{n_{ik}}{a_{i1k}, a_{i2k}, \dots, a_{im_k}} p_{i1k}^{a_{i1k}} p_{i2k}^{a_{i2k}} \dots p_{im_k}^{a_{im_k}} \\ \text{Dir}(\alpha_{i1}, \alpha_{i2}, \dots, \alpha_{im_i}) M(4N_e m) U(4N_e \mu) \quad (10)$$

Estimates for $4N_e m$ and $4N_e \mu$ can then be obtained from their respective means in the posterior distribution. Notice that this approach implicitly assumes a random-effect model of population sampling. Because of the close relationship between the likelihood approach RANNALA and HARTIGAN (1995) present and the method described here, point estimates of $4N_e m$ and $4N_e \mu$ derived from (10) will be quite similar to their maximum-likelihood counterparts. Substantial differences between point estimates are likely only if strongly informative priors are used for $4N_e m$ and $4N_e \mu$, although the confidence intervals of likelihood estimates and the credibility intervals of Bayesian estimates may differ substantially when the number of populations sampled is relatively small.

An example comparing estimates of $4N_e m$ and $4N_e \mu$ derived from a two-allele version of (10) with estimates compared from inverting G_{st} or θ (and ignoring mutation) are provided in Table 2. ¶ Notice

§ If we restrict the model to two alleles at each locus, the restrictive assumption on migrant allele frequencies can be relaxed if mutation rates do not differ across loci (see CROW and KIMURA 1970). It should also be possible to extend this approach to more general models of mutation, migration, and population dynamics by direct simulation of the stationary distribution.

¶ The results presented are derived with use of a Gaussian prior (mean = 0, variance = 10) on $\log(4N_e m)$ and $\log(4N_e \mu)$. This corresponds to a lognormal prior on $4N_e m$ and $4N_e \mu$ with a mean 148 and 95 % of its density lying in the interval [0.002, 492].

that an analysis based on Weir and Cockherham's θ would conclude with some confidence that $4N_e m > 1$, the threshold commonly used to infer whether migration is sufficient to prevent neutral divergence (WRIGHT 1931). The Bayesian estimate, however, which includes the contribution of mutation to genetic diversity within populations, suggests that it cannot be reliably determined whether $4N_e m > 1$ or $4N_e m < 1$.

AN EXAMPLE

Conservation geneticists sometimes employ analyses of genetic diversity to identify areas for on-site conservation (RIGGS 1990; MILLAR and LIBBY 1991), to identify populations of endangered plants or animals that are particularly worthy of conservation concern (ALLENDORF and WAPLES 1996; HAMRICK and GODT 1996), or to identify populations of crop relatives that are particularly important for conservation of genetic resources (SCHOEN and BROWN 1993). An important part of such evaluations is often identifying those populations that contribute most to genetic diversity within the species being studied, either because they exhibit especially high levels of within population diversity or because they are markedly different from other populations of the species. PETIT et al. (1998) recently reported results from a survey of *Argania spinosa* (Sapotaceae) intended to identify populations important for conservation of this species. In addition to reporting F -statistics to describe the partitioning of genetic diversity within and among populations in their sample, they report statistics intended to reflect the contribution of each population to the genetic diversity of the entire sample.** These data provide an excellent example of how the Bayesian approach described above may lead to insights that other methods cannot provide.

Table 2. Comparison of $4N_e m$ Estimates¹

Parameter	Derived from		
	G_{st}	θ	Direct Bayesian approach
$4N_e m$	9.977	4.999(2.516, 25.88)	6.278(0.0245, 23.35)
$4N_e \mu$			0.3186(0.001801, 1.214)

¹Data from *Aedes aegyptii* (see note to Table 1). 95 % limits from θ were derived from inverting those reported in Table 1.

** PETIT et al. (1998) also report statistics based on allelic richness. Because these statistics are not directly comparable F -statistics, I do not discuss them in this paper.

Table 3. Analysis of genetic diversity in *Argania spinosa*¹

G_{st}	G_{st}^B	θ^B
0.18	0.1920(0.1768, 0.2063)	0.2677(0.2129, 0.3300)

¹ G_{st} from Table 3 of PETIT et al. (1998). G_{st}^B and θ^B are from a Gibbs sampler implemented in WinBUGS (GILKS et al. 1994). Numbers in parentheses represent lower and upper 95 % confidence limits. The data were reduced to two alleles per locus by combining least frequent alleles at each locus into a single, pseudo-allele class for Bayesian analyses.

The Data

PETIT et al. (1998) report data on variation at 15 polymorphic allozyme loci collected from 12 populations of *Argania spinosa*. Sample sizes range from 20 to 50 individuals, and 5 of the 12 polymorphic loci have more than 2 alleles. The main body of the species distribution extends for approximately 400 km along the Atlantic shore in central, western Morocco, and it extends inland no more than 200 km. Two populations, Oued Grou and Beni-Snassen, are widely separated from the main body of the species distribution. Oued Grou lies approximately 400 km north of the main body of the species distribution near the Atlantic shore. Beni Snassen is in the far northeastern corner of Morocco near the Mediterranean Sea. PETIT et al. (1998) regard the climate of three sites (Oued Grou, Tensift, and Tamanar) as semi-arid. They regard the climate of the remaining nine sites as arid.

Results

Results of a two-level analysis of genetic diversity for these data are presented in Table 3. Notice that fixed-effect estimates of F_{st} (G_{st} and G_{st}^B) are statistically indistinguishable. The random-effect estimate of F_{st} derived from θ^B is, however, substantially higher than that obtained from a fixed-effect model. One interpretation of this result might be that the sample of populations included significantly underestimates the amount of genetic differentiation among populations of *Argania spinosa*. Another interpretation might be that including outlier populations (Oued Grou and Beni-Snassen) leads to a substantial overestimate of genetic differentiation among populations in the main body of the species range. One way of distinguishing these possibilities is to examine the contribution that each population makes both to total diversity in the sample and to the proportion of diversity attributed to among population differences. Specifically, we can compare the total diversity in the sample, H_r , with total diversity remaining when population k is removed, $H_{r/k}$.††

†† See PETIT et al. (1998) for details.

Table 4 shows the result of such additional partitioning. Because the statistics reported concern the effect of deleting particular populations from a particular sample of populations, only statistics derived from a fixed-effect model are reported. When Beni-Snassen is deleted from the sample, the total diversity is reduced by about 5.5 %. This effect is almost entirely the result of a reduced amount of differentiation among populations remaining in the sample (G_{st}^B is reduced to 0.1556 from 0.1920). When any other population is deleted from the sample there is no detectable effect on the sample diversity. Thus, including the isolated population of Beni-Snassen in the analysis leads to a statistically detectable overestimate of the amount of genetic differentiation among populations in the main body of the species range.

The conservation implications of this result depend, in part, on what this pattern of differentiation can tell us about evolutionary processes in *Argania spinosa*. In particular, large values of F_{st} indicate that the time to common ancestry of alleles from different populations is substantially longer, on average, than the time to common ancestry of alleles from within the same populations (SLATKIN 1991). Thus, F_{st} can be regarded as a measure of the extent to which

populations are historically independent. In this case, the large contribution that Beni-Snassen makes to F_{st} and total genetic diversity in the sample suggests that it is the most historically independent of the remaining populations of *Argania spinosa*. In fact, Beni-Snassen is the only population for which there is evidence of a large, independent contribution to genetic diversity in this sample. As a result, Beni-Snassen may be a particularly important target for conservation efforts, because individuals within it may also have had the chance to diverge substantially at loci that contribute more directly to population persistence (HOLSINGER and VITT 1997).

While inverting the relationship between G_{st} and $4N_e\mu$ would suggest that $4N_e\mu = 4.56$, Using the model in (10) suggests that $4N_e\mu$ lies in the interval [1.95, 3.68] and that $4N_e\mu$ lies in the interval [0.00052, 0.107]. These estimates assume, of course, that the drift migration-mutation process among populations has reached stationarity and that the simple, island model of migration is an adequate representation of movement among populations. Given those caveats, the statistically detectable difference between $4N_e\mu$ estimates derived from G_{st} and those derived from the direct, Bayesian approach, has little impact on the qualitative conclusion: gene exchange among populations appears to be sufficient to prevent substantial divergence at neutral loci. It is important to note, however, that the same conclusion does not apply to loci subject even to moderate degrees of selection. Indeed, considerable divergence at loci subject to selection is possible.

Using the estimates just mutation and migration rate estimates just obtained ($4N_e\mu = 2.724$ and $4N_e\mu = 0.0374$), for example, it is possible to investigate the magnitude of differentiation expected at loci subject to different patterns of selection. Specifically, we can calculate F_{st} at a locus in which selection acts either uniformly across populations or divergently across populations (see the Appendix for details).

In the case of uniform selection, a selection coefficient as small as 0.01 would produce an F_{st} of only 0.052 in populations with an effective size of 1000. Conversely, a selection coefficient of 0.01 would produce an F_{st} of 0.76 in populations subject to divergent selection. Clearly, patterns of differentiation at loci subject even to weak selection may be quite different from those that are neutral. More generally, quantitative patterns of differentiation among populations at different sets of loci are likely to be similar only if the product of effective size and the selection coefficient is one or less at both sets of loci (compare CROW and KIMURA 1970). In populations with an effective size of 100, for example, F_{st} would be 0.25 in the case of uniform selection and 0.29 in the case of divergent

Table 4. Individual population contributions to diversity¹

Population	C_i	$G_{st/k}^B$
Aït Baba	-0.0033(-0.0306, 0.0238)	0.1787(0.1619, 0.1938)
Ademine	0.0041(-0.0235, 0.0311)	0.1974(0.1810, 0.2142)
Argana	0.0004(-0.0266, 0.0264)	0.1968(0.1823, 0.2150)
Beni-Snassen	0.0551(0.0288, 0.0806)	0.1556(0.1390, 0.1716)
Goulimine	0.0138(-0.0138, 0.0397)	0.1684(0.1531, 0.1837)
Mijji	-0.0035(-0.0304, 0.0234)	0.2044(0.1871, 0.2201)
Oued Grou	-0.0223(-0.0495, 0.0045)	0.1835(0.1668, 0.2002)
Sidi Ifni	-0.0167(-0.0444, 0.0108)	0.1973(0.1816, 0.2129)
Tafraout	0.0000(-0.0272, 0.0263)	0.2058(0.1902, 0.2230)
Tensift	-0.0191(-0.0474, 0.0091)	0.1963(0.1804, 0.2129)
Tamanar	0.0019(-0.0243, 0.0278)	0.1972(0.1815, 0.2137)
Tizint'est	0.0055(-0.0223, 0.0324)	0.2041(0.1871, 0.2227)

¹ $C_i = (H_i - H_{t/k})/H_t$ is the proportion of total diversity contributed by a population.

selection, both values much closer to the observed θ^B (0.27).

DISCUSSION

The method I describe here for analysis of genetic diversity produces estimates very similar to two existing approaches: Nei's biased-corrected diversity statistics (G_{st} ; NEI 1973; NEI and CHESSEY 1983) and Weir and Cockerham's ANOVA based diversity statistics (θ ; WEIR and COCKERHAM 1984). This similarity can be seen both as a strength and as a weakness. It is a strength because estimates of population structure derived from this method will be G_{st}^B , or to Weir and Cockerham's θ , in the case of θ^B . As a result, G_{st}^B and θ^B must be regarded as good summaries of population structure to exactly the same extent as G_{st} and θ themselves are so regarded. This similarity is a weakness because at first glance the similarity in results seems to make this new method superfluous. There are, however, several ways in which this method may represent a useful contribution to the tool box of population geneticists.

First, this approach provides a unified conceptual framework for fixed-effect model investigations of a specified set of populations and for random-effect model investigations of populations that are themselves regarded as a sample.^{‡‡} Because fixed-effect estimates are obtained from Bayesian estimates of allele frequencies in the populations *actually* sampled while random-effect estimates are obtained from a Bayesian estimate of allele frequencies in all populations *potentially* sampled this approach also helps to clarify the differences between these sampling models. Including these different sampling models within a single statistical framework may help investigators to choose the one most appropriate for analysis of their data.

Second, unlike Weir and Cockerham's θ statistics, interpretation of the random-effect estimates of population structure derived from the method proposed here do not depend on a particular model of population divergence. Instead they depend only on the assumption that a beta distribution, in the two-allele case, or a Dirichlet distribution, in the multiallele case, provides an adequate approximation to the actual distribution of allele frequencies among populations. While these distributions cannot describe all possible allele frequency distributions—a beta distribution cannot describe a distribution with three or

more modes, for example—they do accommodate a wide variety of possible distributions. Moreover, θ^B will depend only on the first two moments of the allele frequency distribution, regardless of what distribution is chosen to represent it. As a result, it seems unlikely that θ^B will depend strongly on the choice of allele-frequency distributions.

Third, when this approach is extended to more than one hierarchical level, fixed-effect estimates at one hierarchical level can be combined with random-effect estimates at other levels. While similar approaches are now commonplace in multilevel modeling in other contexts, I am not aware of methods that allow it in the context of F -statistics. It may estimates when samples are taken from the entire geographic range of a species, but only a sample of representative populations is available from different geographical regions. Variation among geographical regions might best be regarded as a fixed effect, for example, while variation among populations within those regions might be better regarded as a random effect.

Finally, this method can be extended to provide direct estimates of migration rates ($4N_e m$) and mutation rates ($4N_e \mu$). Estimates of $4N_e m$ are usually derived from F_{st} by ignoring the effect of mutational processes. As CHARLESWORTH (1998) has pointed out, however, evolutionary processes that affect the amount of diversity within populations may also have an effect on the partitioning of diversity within and among populations. Thus, estimates of $4N_e m$ derived from models that incorporate such evolutionary forces may be more reliable than those derived from models that neglect them. Of course the model of mutation and migration I used to illustrate the method is very restrictive. Nonetheless, it seems likely that this approach can be extended to more realistic models of migration and population dynamics using numerical methods to simulate the stationary distribution similar to those used by KUHNER et al. (1995, 1998) to solve a similar problem in a likelihood context.

If it is possible to extend the method I describe here to include more realistic models of migration and population dynamics, it will be straightforward to extend it further to accommodate models of mutation appropriate to sequence, restriction site, and microsatellite evolution. It will then be possible to analyze and compare the partitioning of genetic diversity within and among populations using the same conceptual framework, regardless of whether populations are regarded as fixed or random effects and regardless of the type of genetic data available for analysis. In short, the method I describe here pro-

^{‡‡} It would be possible, of course, to develop the fixed-effect model analogue of Weir and Cockerham's θ in an ANOVA framework. Indeed, WEIR (1996) provides an example of such an approach, but these possibilities have not been extensively explored.

vides a very flexible framework for the development of more sophisticated methods to analyze the hierarchical structure of genetic diversity in geographically structured populations. As important as this flexibility, however, is the close relationship between estimates provided through this method and those provided through methods with which population geneticists are already familiar.

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APPENDIX A: F_{st} AT A SELECTED LOCUS

The stationary distribution of allele frequencies for a pair of alleles subject to drift, selection, migration, and mutation is

$$\phi(x) = C e^{2N_e \bar{a}_x 4N_e(v + mx_f)^{-1}} (1-x)^{4N_e(\mu + m(1-x_f)) - 1}, \quad (\text{A.1})$$

where v is the rate of mutation from A_2 to A_1 , μ is the rate of mutation from A_1 to A_2 , m is the fraction of the population composed of migrants, x_f is the frequency of A_1 among migrants, and C is a normalizing constant (CROW and KIMURA 1970); \bar{a} reflects the effect of selection. If the relative fitnesses of A_1A_1 , A_1A_2 , and A_2A_2 are 1, $1+hs$, and $1+s$, respectively,

$$\bar{a} = 2x(1-x)hs + (1-x)^2s. \quad (\text{A.2})$$

Notice that genotypes are assumed to have the same relative fitnesses in all populations.

The value of F_{st} expected for any combination of parameters can be calculated numerically from (A.1) quite easily. By definition,

$$F_{st} = \frac{Var(x)}{\bar{x}(1-\bar{x})}, \quad (\text{A.3})$$

where $\bar{x} = \int_0^1 x\phi(x)$ and $Var(x) = \int_0^1 (x-\bar{x})^2\phi(x)$. The results quoted in the text assume $\mu = v$, $h = 1/2$, and $m_f = 1/2$.

When fitnesses vary among populations, the evolutionary dynamics are substantially more complex. There is, however, at least one circumstance in which it is possible to describe the stationary distribution of allele frequencies. Assume that there is directional selection in favor of A_1 in one set of populations and

directional selection of equal intensity selection in favor of A_2 in another set of populations and that the fitness of A_1A_2 is exactly intermediate between that of A_1A_1 and A_2A_2 in all populations. If there are many populations exchanging migrants and if each type of population makes up about half of the migrant pool, the mean allele frequency in migrants will be $1/2$. Then the stationary distribution of allele frequencies is given by

$$\begin{aligned} \phi(x) &= (1/2) \\ &\times (C_1 e^{2N_e \bar{a}_{1x} 4N_e(v+m/2)^{-1}} (1-x)^{4N_e(\mu+m/2)-1}) \\ &+ (1/2)(C_2 e^{2N_e \bar{a}_{2x} 4N_e(v+m/2)^{-1}} (1-x)^{4N_e(\mu+m/2)-1}), \end{aligned} \quad (\text{A.4})$$

where $\bar{a}_1 = x(1-x)s + x^2s = xs$ and $\bar{a}_2 = -xs$. Using (A.4), F_{st} can be calculated as before.

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