Analyzing the Genetic Structure of Populations: Individual Assignment

Introduction

Although $F$-statistics are widely used and very informative, they suffer from one fundamental limitation: We have to know what the populations are before we can estimate them. They are based on a conceptual model in which organisms occur in discrete populations, populations that are well mixed within themselves (so that we can regard our sample of individuals as a random sample from within each population) and clearly separate from others. What if we want to use the genetic data itself to help us figure out what the populations actually are? Can we do that?\footnote{Would I be asking this question if the answer were “No?”}

A little over 15 years ago a different approach to the analysis of genetic structure began to emerge: analysis of individual assignment. Although the implementation details get a little hairy,\footnote{OK, to be fair. The get very hairy.} the basic idea is fairly simple. Suppose we have genetic data on a series of individuals. Label the data we have for each individual $x_i$. Suppose that all individuals belong to one of $K$ populations and let the genotype frequencies in population $k$ be represented by $\gamma_k$. Then the likelihood that individual $i$ comes from population $k$ is just

$$P(i|k) = \frac{P(x_i|\gamma_k)}{\sum_k P(x_i|\gamma_k)}.$$  

So if we can specify prior probabilities for $\gamma_k$, we can use Bayesian methods to estimate the posterior probability that individual $i$ belongs to population $k$, and we can associate that assignment with some measure of its reliability.\footnote{You can find details in [6]. If you think about that equation a bit, you can begin to see why the details get very hairy. First, we’re trying to get the data to tell us what the populations are, so we don’t even know how many populations there are. Then we have to find a way of estimating allele frequencies (and genotype frequencies) in populations when we don’t even know which populations individuals in our sample belong in.}
### Table 1: Mean log probability of the data for $K = 2, 3, 4, 5$ in the *Berberis thunbergii* data (adapted from [3]).

<table>
<thead>
<tr>
<th>$K$</th>
<th>Mean L($K$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-2553.2</td>
</tr>
<tr>
<td>3</td>
<td><strong>-2331.9</strong></td>
</tr>
<tr>
<td>4</td>
<td>-2402.9</td>
</tr>
<tr>
<td>5</td>
<td>-2476.3</td>
</tr>
</tbody>
</table>

**Applying assignment to understand invasions**

We’ll use Structure to assess whether cultivated genotypes of *Berberis thunbergii* contribute to ongoing invasions in Connecticut and Massachusetts [3]. The first problem is to determine what $K$ to use, because $K$ doesn’t necessarily have to equal the number of populations we sample from. Some populations may not be distinct from one another. There are a couple of ways to estimate $K$. The most straightforward is to run the analysis for a range of plausible values, repeat it 10-20 times for each value, calculate the mean “log probability of the data” for each value of $K$, and pick the value of $K$ that is the biggest, i.e., the least negative (Table 1). For the barberry data, $K = 3$ is the obvious choice.

Having determined that the data support $K = 3$, the results of the analysis are displayed in Figure 1. Each vertical bar corresponds to an individual in the sample, and the proportion of each bar that is of a particular color tells us the posterior probability that the individual belongs to the cluster with that color.

Figure 1 may not look terribly informative, but actually it is. Look at the labels beneath the figure. You’ll see that with the exception of individual 17 from Beaver Brook Park, all the individuals that are solid blue are members of the cultivated *Berberis thunbergii* var. *atropurpurea*. The solid red bar corresponds to *Berberis thunbergii* 'Atropurpurea', another modern cultivar. You’ll notice that individuals 1, 2, 18, and 19 from Beaver Brook Park and individual 1 from Bluff Point State Park fall into the same genotypic cluster as this cultivar. *Berberis ×ottawensis* is a hybrid cultivar whose parents are *Berberis thunbergii* and *Berberis vulgaris*, so it makes sense that individuals of this cultivar would be half blue and half red. The solid green bars are feral individuals from long-established populations. Notice that the cultivars are distinct from all but a few of the individuals in the long-established feral populations, suggesting that contemporary cultivars are doing relatively little to maintain the invasion in areas where it is already established.
Genetic diversity in human populations

A much more interesting application of Structure appeared a little over a decade ago. The Human Genome Diversity Cell Line Panel (HGDP-CEPH) consisted at the time of data from 1056 individuals in 52 geographic populations. Each individual was genotyped at 377 autosomal loci. If those populations are grouped into 5 broad geographical regions (Africa, Europe, the Middle East, and Central/South Asia, East Asia, Oceania, and the Americas), we find that about 93% of genetic variation is found within local populations and only about 4% is a result of allele frequency differences between regions [7]. You might wonder why Europe, the Middle East, and Central/South Asia were grouped together for that analysis. The reason becomes clearer when you look at a Structure analysis of the same data (Figure 2).

A non-Bayesian look at individual-based analysis of genetic structure

Structure has a lot of nice features, but you’ll discover a couple of things about it if you begin to use it seriously: (1) It often isn’t obvious what the “right” K is.\(^4\) (2) It requires a

\(^4\)In fact, it’s not clear that there is such a thing as the “right” K. If you’re interested in hearing more about that, feel free to ask.
lot of computational resources, especially with datasets that include a few thousand SNPs, as is becoming increasingly common. An alternative is to use principal component analysis directly on genotypes. There are technical details associated with estimating the principal components and interpreting them that we won’t discuss, but the results can be pretty striking. Figure 3 shows the results of a PCA on data derived from 3192 Europeans at 500,568 SNP loci. The correspondence between the position of individuals in PCA space and geographical space is remarkable.

Jombart et al. [2] describe a related method known as discriminant analysis of principal components. They also provide an R package, dapc, that implements the method. I prefer Structure because its approach to individual assignment is based directly on population genetic principles, and as of a few months ago, I don’t have to worry so much about how long it takes to run an analysis on large datasets. A few months ago Gopalan et al. [1] released teraStructure, which can analyze data sets consisting of 10,000 individuals scored at a million SNPs in less than 10 hours.

References


See [5] for details
Figure 3: Principal components analysis of genetic diversity in Europe corresponds with geography (from [4]). Panel b is a close-up view of the area around Switzerland (CH).


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