BIOL 502 Population Genetics Spring 2017

Week 9 Population Structure and Migration

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Table of contents

1. Population Structure
2. Wahlund Effect
3. Population subdivision and F coefficients
4. Migration
5. Migration and Differentiation
6. Methods to estimate population structure
7. Methods to estimate migration

Population Structure

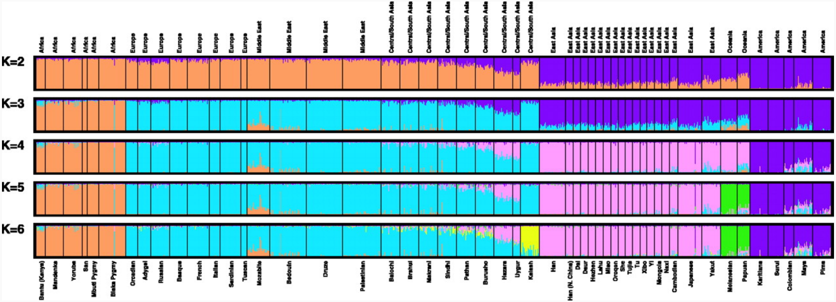
Population Structure

Most populations are grouped into smaller subpopulations within which mating usually takes place.

- Ubiquitous across species.
- Genetic differentiation between subpopulations.
- i.e. allele frequencies among subpopulations maybe different.
- This genetic differentiation (change in allele frequency within each subpopulation) can be due to what?
- Extreme case of subpopulation structure?

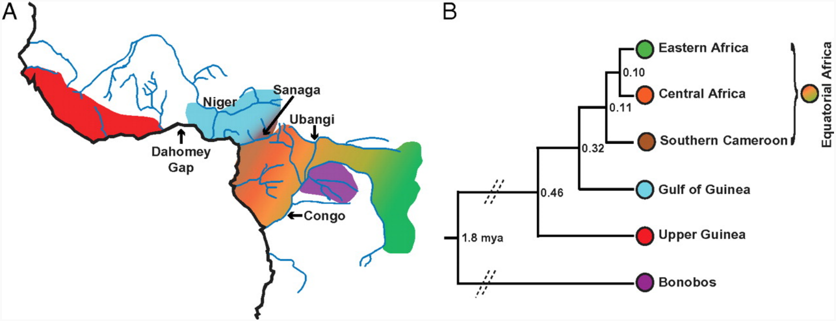
Rosenberg et al. 2002 Science DOI:10.1126/science.1078311

Human population structure - isolation by distance



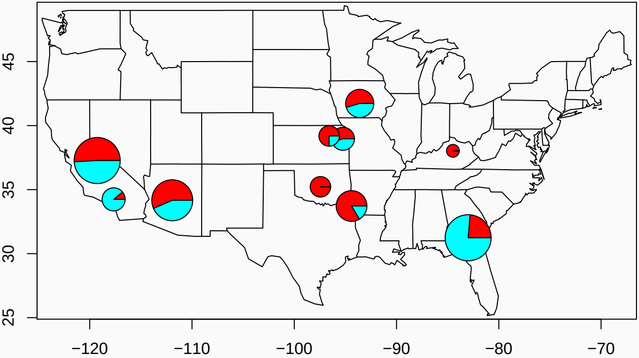
Gonder et al. 2011 PNAS DOI:10.1073/pnas.1015422108

Chimpanzee population structure - isolation by geography



Sethuraman et al. 2015 DOI:10.1016/j.biocontrol.2015.01.002

Convergent lady beetles - homogenization by augmentation



Wahlund Effect

Problems in sampling

What is the effect of sampling what appears to be a single population, but is actually two or more subpopulations with limited gene flow between them?

- Consider a population that is divided into two subpopulations of equal size, randomly mating within each subpopulation, but individuals from one subpopulation don't mate with individuals from the other.
- Sample 100 individuals from each, obtaining:
- Genotype *AA Aa aa*
- Subpop 1 64 32 4
- Subpop 2 4 64 64
- Total 68 64 68
- What are the allele frequencies in each population?
- How about genotype frequencies? Are they in HWE?
- How about if you lumped them all together? What are allele frequencies and genotype frequencies?

Wahlund Effect

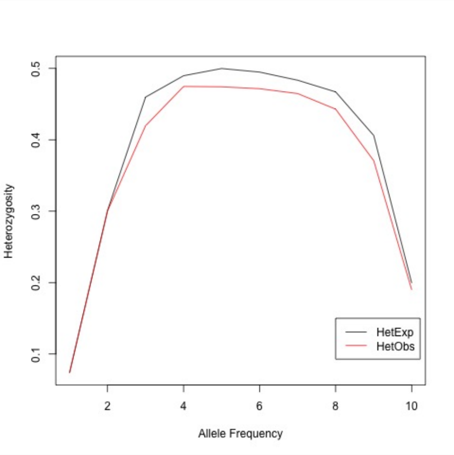
Wahlund Effect

The *perceived* deficiency of heterozygotes in a population compared to Hardy-Weinberg expectations due to population structure. Conversely, if population structure were eliminated, there would be an increase in heterozygosity, and corresponding decrease in homozygosity.

- Let the two subpopulations have allele frequencies p_1, q_1, p_2, q_2 respectively, such that $p_1 + q_1 = 1$, and $p_2 + q_2 = 1$.
- Expected genotype frequencies are then $p_1^2, 2p_1q_1, q_1^2$ and $p_2^2, 2p_2q_2, q_2^2$.
- Allele frequencies in the total (fused) population are $\bar{p} = \frac{p_1+p_2}{2}$ and $\bar{q} = \frac{q_1+q_2}{2}$.
- Genotype frequencies in the fused population are $\frac{p_1^2+p_2^2}{2}$, $p_1q_1 + p_2q_2, \frac{q_1^2+q_2^2}{2}$.
- Hence difference in heterozygosity due to population structure = ?

Observed vs Expected Heterozygosities

```
#define observed and expected heterozygosities
hetexp<-function(x,y)
{(x*(1-x)+y*(1-y)+(1-x)*y+(1-y)*x)/2}
hetobs<-function(x,y)
{x*(1-x)+y*(1-y)}
#simulate some frequencies
p1<-sort(runif(20,0,1))
p2<-sort(runif(20,0,1))
#plot heterozygosity
plot(hetexp(p1,p2),type=’l’,
ylab="Heterozygosity",xlab="Allele Frequency")
points(hetobs(p1,p2),type=’l’,col="red")
#Add a legend
legend(8,0.15,c("HetExp","HetObs"),
lty=c(1,1),col=c("black","red"))
#compare heterozygosities
hetexp(p1,p2)>hetobs(p1,p2)
```



Population subdivision and F coefficients

Extending Wahlund Effect

- Generalizing the Wahlund Effect to K subpopulations, where N_k is the size of the k^{th} subpopulation, such that $N = \sum_k N_k$ is the size of the total population.
- Let $w_k = \frac{N_k}{N}$ be the proportion of individuals in the total population that are in subpopulation k.
- Expected genotype frequencies in subpopulation k are then $p_k^2, 2p_k q_k, q_k^2$.
- Frequency of the A allele in the total population is the weighted average of p_k across all K subpopulations, such that $\bar{p} = \sum w_k p_k$.
- So if there were no subdivision, the observed genotype frequencies in the fused population would be $\bar{p}^2, 2\bar{p}\bar{q}, \bar{q}^2$.
- But with subdivision, the expected genotype frequencies in the total fused population would be $P(AA) = \sum_{k=1}^{K} w_k p_k^2, P(Aa) = \sum_{k=1}^{K} 2w_k p_k q_k, P(aa) = \sum_{k=1}^{K} w_k q_k^2$

Another definition of F

- By definition, the variance in allele frequency across subpopulations is $\sigma_p^2 = Var(p) = \sum_{k=1}^{K} w_k(p_k - \bar{p})^2 = \sum_{k=1}^{K} w_k p_k^2 - \bar{p}^2 = \sum_{k=1}^{K} w_k(\bar{q} - q_k)^2 = \sum_{k=1}^{K} w_k q_k^2 - \bar{q}^2$
- Hence $P(AA) = \bar{p}^2 + \sigma_p^2$
- $P(aa) = \bar{q}^2 + \sigma_p^2$
- $P(Aa) = 1 - P(AA) - P(aa) = 1 - \bar{p}^2 - \bar{q}^2 - 2\sigma_p^2 = 2\bar{p}\bar{q} - 2\sigma_p^2 = 2\bar{p}\bar{q}(1 - \frac{\sigma_p^2}{\bar{p}\bar{q}})$

F_{ST}

$F_{ST} = \frac{2\sigma_p^2}{2\bar{p}\bar{q}} = \frac{H_T - H_S}{F_T}$, the proportionate reduction in heterozygosity in the total population due to population structure, where S represents the subpopulation, T is the total population.

- As before, $P(AA) = \bar{p}^2 + \bar{p}\bar{q}F_{ST}$
- $P(Aa) = 2\bar{p}\bar{q}(1 - F_{ST})$
- $P(aa) = \bar{q}^2 + \bar{p}\bar{q}F_{ST}$

Inbreeding and Population Structure

- What if the K subpopulations themselves were also inbreeding, with an inbreeding coefficient $F_{IS} = \frac{H_S - H_I}{H_S}$, where I represents the individual, and S is the subpopulation.
- Recall our previous derivation: $P(AA) = p_k^2 + p_k q_k F_{IS}$.
- $P(Aa) = 2p_k q_k(1 - F_{IS})$
- $P(aa) = q_k^2 + p_k q_k F_{IS}$
- Now in the total population, the genotype frequency of AA becomes $P(AA) = \sum_{k=1}^{K} w_k \bar{p}^2 + F_{IS} \sum_{k=1}^{K} w_k p_k q_k$
- $= \bar{p}^2 + \sigma_p^2 + F_{IS} \sum_{k=1}^{K} w_k(p_k - p_k^2)$
- $= \bar{p}^2 + \sigma_p^2 + F_{IS}(\bar{p} - \bar{p}^2 - \sigma_p^2)$
- $= \bar{p}^2 + \bar{p}\bar{q}(F_{ST} + F_{IS}(1 - F_{ST}))$
- Set $F_{IT} = F_{ST} + F_{IS}(1 - F_{ST})$

F_{IT}

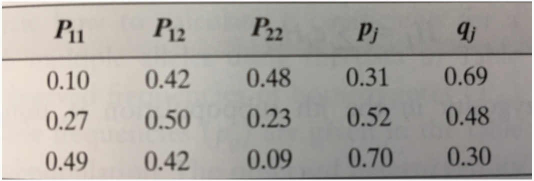
$F_{IT} = \frac{H_T - H_I}{H_T}$ such that $(1 - F_{IS})(1 - F_{ST}) = 1 - F_{IT}$, also defined as the proportionate reduction in heterozygosity due to inbreeding, relative to the total population.

Interpreting F_{ST}

- F_{ST} defines the degree of differentiation between subpopulations, so the greater the F_{ST}, greater the differentiation.
- When is $F_{ST} = 0$?
- When is $F_{ST} = 1$?
- Caution - this does NOT make a statement about the cause of differentiation between subpopulations.
- What causes differentiation?

Calculate F coefficients

Consider a total population comprised of three subpopulations, with equal number of individuals in each, i.e. $w_k = 0.333$. Given the following genotype and allele frequencies, compute the F coefficients. What can you say about the subpopulations?



P_{11}	P_{12}	P_{22}	p_j	q_j
0.10	0.42	0.48	0.31	0.69
0.27	0.50	0.23	0.52	0.48
0.49	0.42	0.09	0.70	0.30

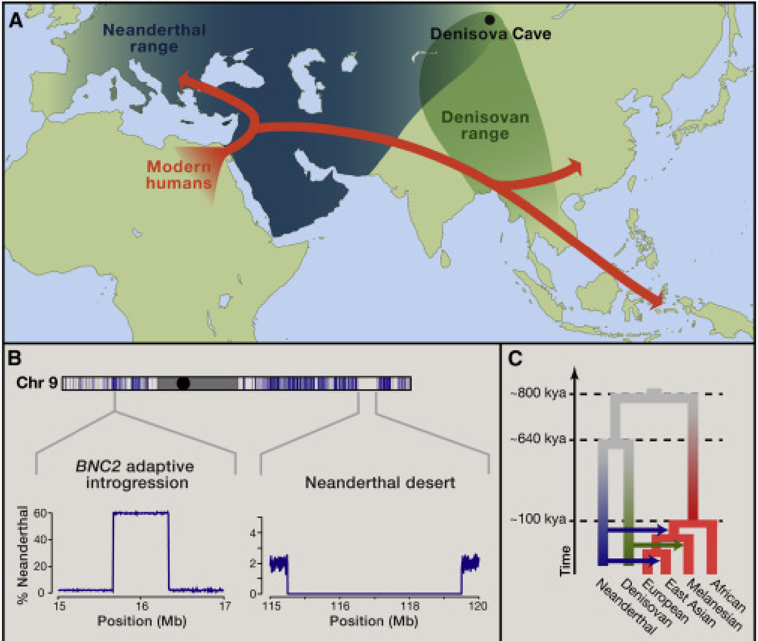
Migration

Gene Flow

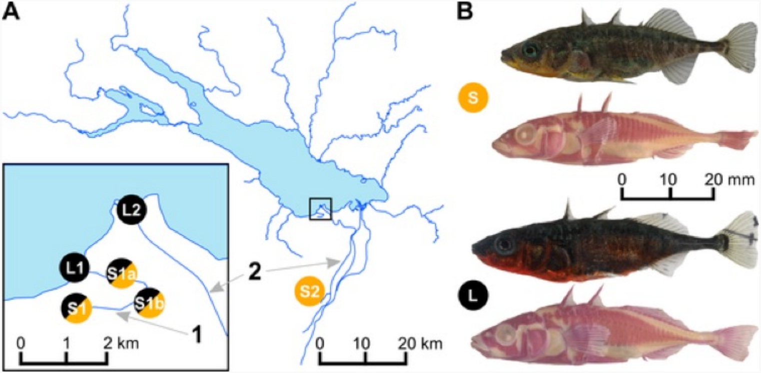
Migration

Migration refers to the movement of some organisms (or their gametes) among subpopulations and subsequent breeding, also referred to as gene flow, or admixture. Migration acts to homogenize populations, or reduce differences between populations.

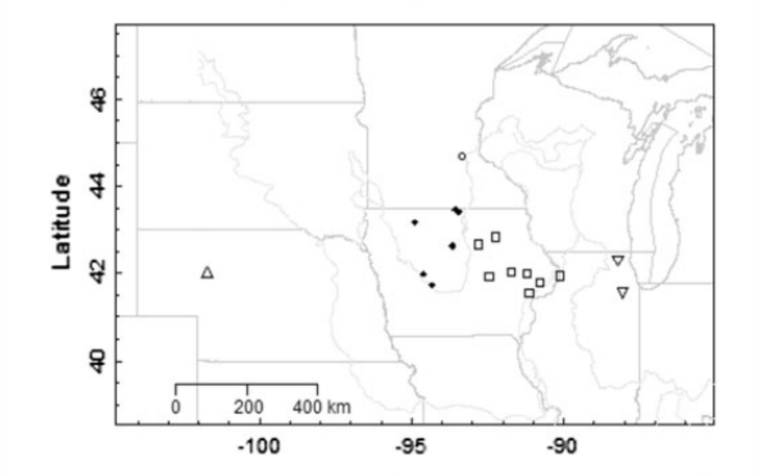
Vattathil and Akey 2015 Cell DOI:10.1016/j.cell.2015.09.042



Marques et al. 2016 DOI:10.1371/journal.pgen.1005887



Sethuraman et al. 2014 DOI:10.1007/s10592-013-0521-8



Migration - contd.

- Migration occurs over space and time.
- Migration is expected to be homogenizing, unless there is selection against migration (or migrant alleles).
- How would F_{ST} vary with increased or decreased migration?
- What does migration do to allele frequencies?

Continent-Island Model

- Consider the simplest model, where migration is unidirectional from a large mainland population, called the *continent* to a smaller population, called the *island*.
- Consider a single, biallelic genetic locus, such that p_c is the frequency of an allele A on the continent, and p_t is the frequency of the same allele in the island in generation t.
- Let m be the migration rate, or rate of gene flow, the proportion of alleles on the island that have come from the continent in each generation.
- Then in one generation, on the island, a proportion m of individuals would have just come from the continent, and a proportion of $1 - m$ would be from the island.
- Allele frequency, $p_{t+1} = (m)p_c + (1 - m)p_t = p_t + m(p_c - p_t)$
- Therefore $\Delta p = p_{t+1} - p_t = m(p_c - p_t)$

Equilibrium frequencies

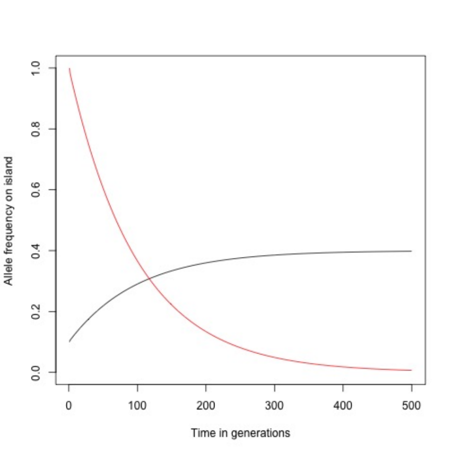
- At equilibrium, setting $\Delta p = 0$ we get $\hat{p} = p_c$.
- Recursively, $p_t = p_c + (1 - m)^t (p_0 - p_c)$, where p_0 is the initial allele frequency on the island.
- As t increases, $(1 - m)^t$ goes to 0, and p_t approaches p_c.

Equilibrium frequencies

```
#Scenario 1
pc=0.4
p0=0.1
m=0.01
pt1<-c(1:500)
pt1[1]=p0
for (i in 2:500){
pt1[i]=pc+(1-m)^i*(p0-pc)
}

#Scenario 2
p0=1.0
pc=0.0
m=0.01
pt2<-c(1:500)
pt2[1]=p0
for (i in 2:500){
pt2[i]=pc+(1-m)^i*(p0-pc)
}

jpeg("contisland.jpeg")
plot(pt1,type=’l’,xlab="Time in generations",ylab="Allele frequency on island",ylim=c(0:1))
points(pt2,type=’l’,col="red")
dev.off()
```



Island Model

- Consider a large population, split into many subpopulations dispersed geographically.
- Let each subpopulation comprise an equal proportion m of migrants from each other.
- Consider a single island - with respect to this island, the remaining islands together form a *continent* with allele frequency $\bar{p}$.
- So allele frequency in this island after one generation is $p_{t+1} = m\bar{p} + (1 - m)p_t$, which is very similar to the continent-island model.

Equilibrium frequencies - Homework

Consider four islands in an island model with gene flow, such that $m = 0.1$. If initial allele frequencies in these islands are $0, 0.3, 0.7, 1.0$ respectively, plot the allele frequency trajectories under an island model. What is the equilibrium frequency?

Other models

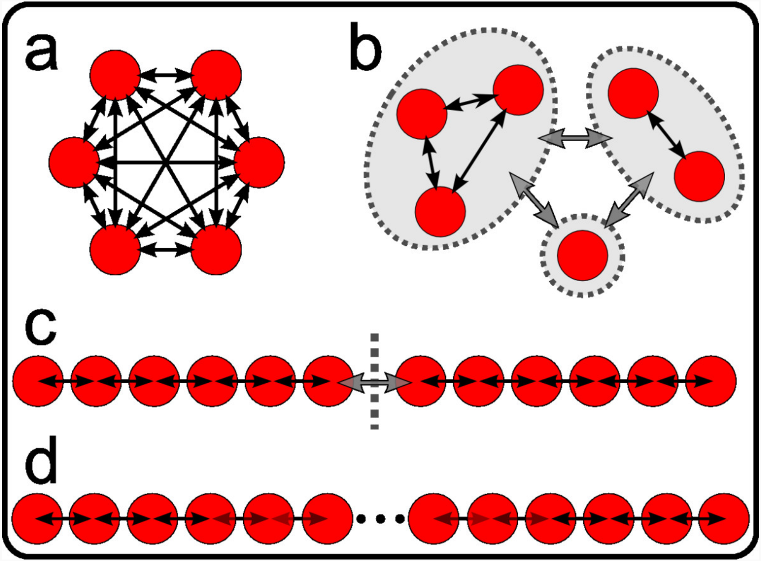


Image courtesy Jombart et al. 2010 DOI:10.1186/1471-2156-11-94

Isolation by Distance

- Direct extension of stepping-stone models, where two subpopulations that are far apart will experience little of the homogenizing effects of gene flow, and thus will be more different than two subpopulations that are close to each other.
- What would you predict under this model if you were to plot genetic differentiation measured as F_{ST} against geographical distance?

Isolation by Distance contd.

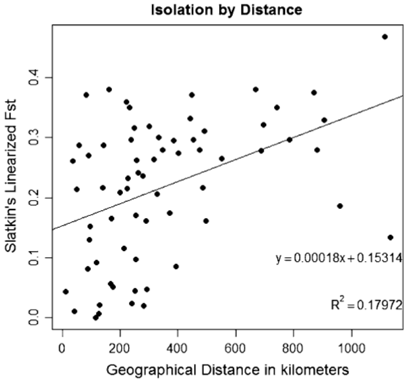


Fig. 2 Plot of linear geographic distance between sampled populations of *Emys blandingii* vs. Slatkin's linearized F_{st} genetic distance between these same sampled populations to estimate the presence of isolation by distance. This plot was derived from a Mantel test performed in GenAlex v.6.2 with 1000 permutations

Image from Sethuraman et al. 2014 Conservation Genetics DOI:10.1007/s10592-013-0521-8

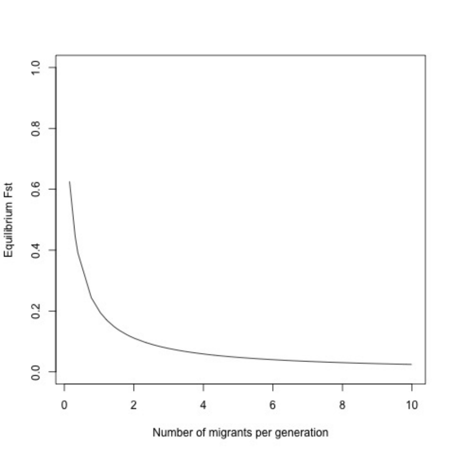
Migration and Differentiation

Let's redefine F (again!)

- How much migration is required to prevent differentiation/divergence among finite subpopulations as measured by F_{ST}?
- Let two alleles be drawn at random from a subpopulation in generation t from generation $t-1$.
- Probability of IBD from one generation to the next is simply $\frac{1}{2N}$.
- If m is the rate of migration, the probability that both alleles are IBD, and from the same population is $\frac{1}{2N}(1-m)^2$.
- Alternately, two alleles can be not IBD, and not be migrants, and IBD in some previous generation with probability $(1-\frac{1}{2N})(1-m)^2F_{t-1}$.
- Hence $F_t = \frac{1}{2N}(1-m)^2 + (1-\frac{1}{2N})(1-m)^2F_{t-1}$
- Look familiar?
- Therefore, setting $F_t = F_{t-1}$, at equilibrium, $\hat{F} = \frac{1}{1+4Nm}$.
- Nm can be interpreted as the total number of immigrant individuals per generation, or $2Nm$ is the total number of immigrant alleles per generation.

Equilibrium F_{ST}

```
Nm<-sort(runif(100,0,10))
F<-1/(1+4*Nm)
jpeg("eqfst.jpeg")
plot(Nm,F,type='l',
xlab="Number of migrants per generation",
ylab="Equilibrium Fst",ylim=c(0,1))
dev.off()
```



Methods to estimate population structure

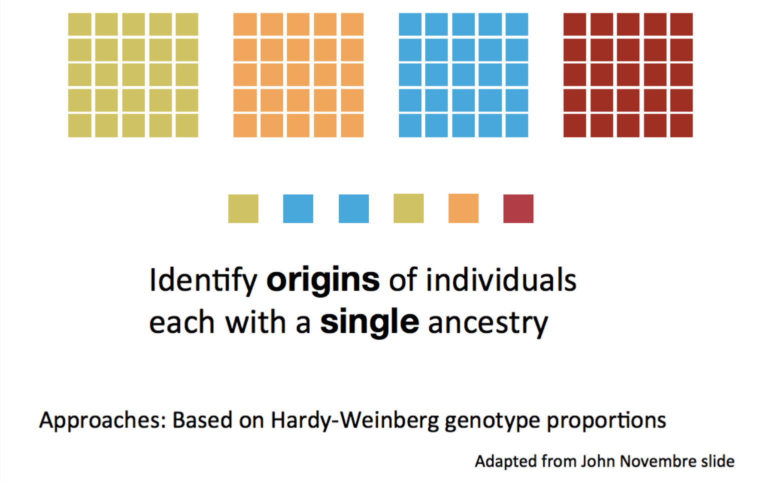
Summary Statistics

- Population differentiation, measured as F_{ST}, or variants of it - for example, use `F_ST.stats` function in `PopGenome` package in R.
- Also see `mmod` package in R, function `diff_stats`.
- AMOVA - Analysis of MOlecular VAriance - see function `amova` in `pegas` package in R.
- Isolation By Distance analyses - see function `mantel.randtest` in `adegenet` package to perform Mantel Tests between genetic distances, and geographic distances.
- DAPC - Discriminant Analyses of Principle Components - built into the `adegenet` package in R, function `dapc`.
- More information: http://popgen.nescent.org/2015-12-15-microsatellite-differentiation.html

Model-based methods

- STRUCTURE - Pritchard et al. 2000 http://www.genetics.org/content/155/2/945
- ADMIXTURE - Alexander et al. 2009 DOI:10.1101/gr.094052.109
- MULTICLUST - Sethuraman 2013 http://lib.dr.iastate.edu/etd/13332

Mixture Model - courtesy Graham Coop, UC Davis

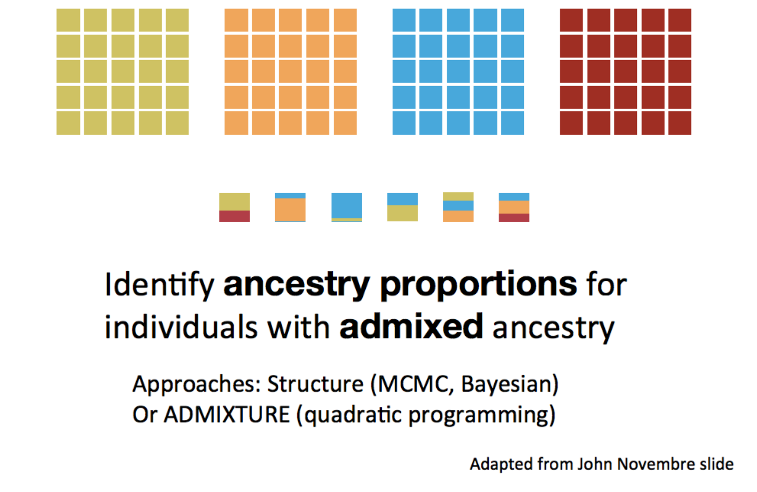


Identify **origins** of individuals
each with a **single** ancestry

Approaches: Based on Hardy-Weinberg genotype proportions

Adapted from John Novembre slide

Admixture Model - courtesy Graham Coop, UC Davis



Identify **ancestry proportions** for individuals with **admixed** ancestry

Approaches: Structure (MCMC, Bayesian)
Or ADMIXTURE (quadratic programming)

Adapted from John Novembre slide

Methods to estimate migration

Summary Statistics

Recall that equilibrium $F_{ST} = \frac{1}{1+4N_e m}$, so in theory, if you were able to estimate F_{ST}, and the effective population size, N_e, you should be able to estimate m.

Model-based methods

- MIGRATE - Beerli and Felsenstein 2001 http://evolution.genetics.washington.edu/lamarc/download/beerli-felsenstein-2001.pdf
- IMa2, IMa2p - Hey and Nielsen 2007 DOI:10.1073/pnas.0611164104, Sethuraman and Hey 2016 DOI:10.1111/1755-0998.12437