F_{ST} generalized for arbitrary population structures

ICAhN Think & Drink

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2016-03-02

F_{ST} and "island" models

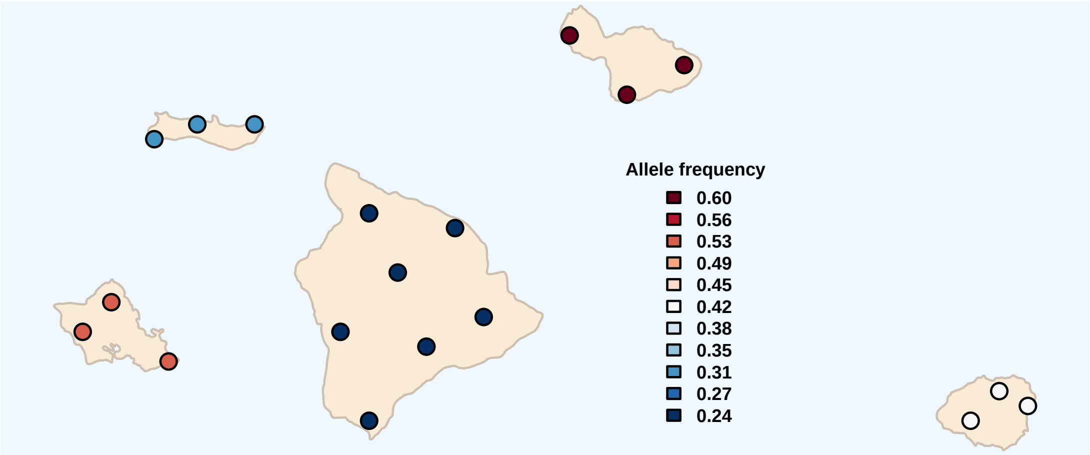
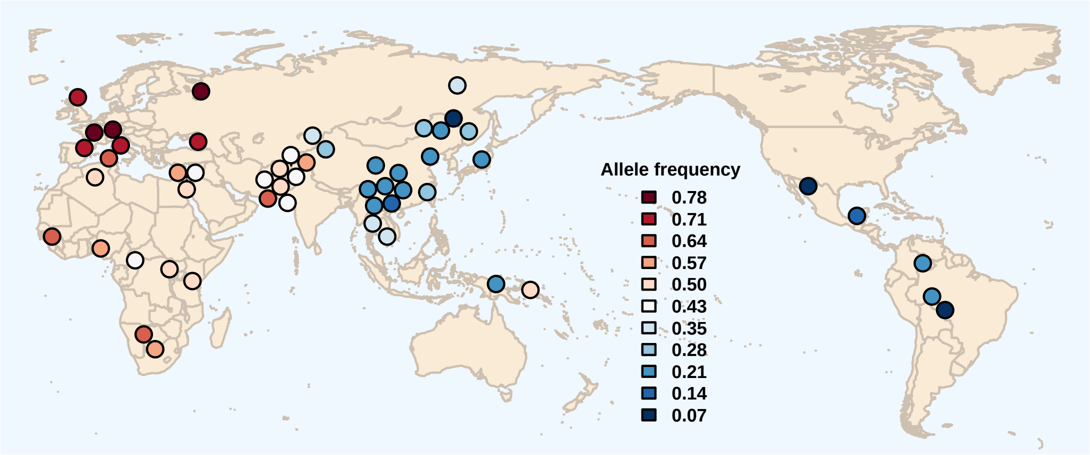
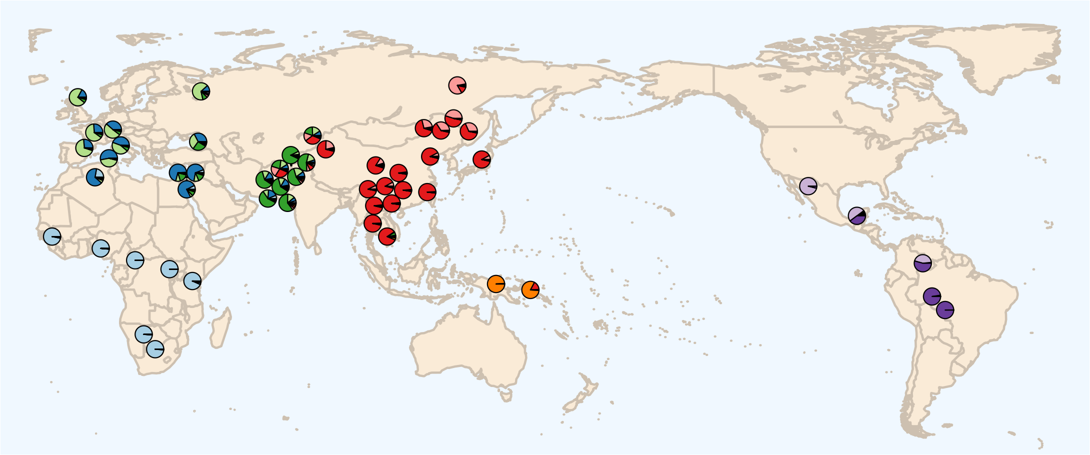


Illustration (not real data)

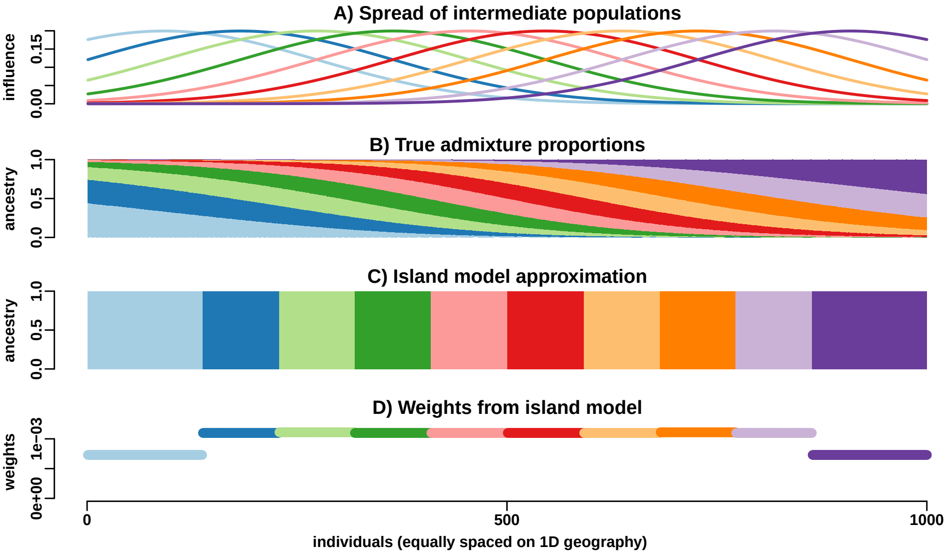
Allele frequencies in human populations



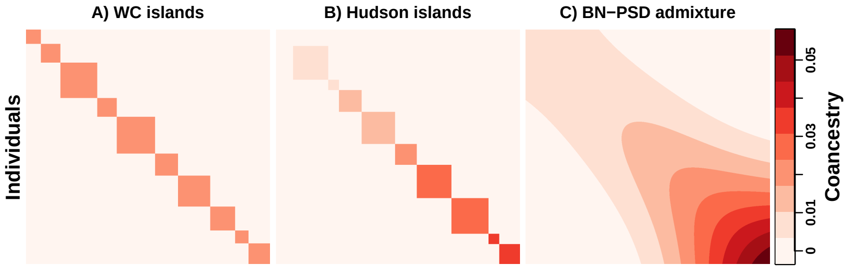
Admixture in human populations



Our admixture simulation



Our contribution



Previous F_{ST} definitions/estimators assume subdivided, independent populations.

We generalize F_{ST} for **arbitrary populations**, in terms of **individuals**, using **inbreeding** and **kinship** coefficients.

We characterize the **bias** of popular **estimators**, through theory and simulations.

An unstructured population

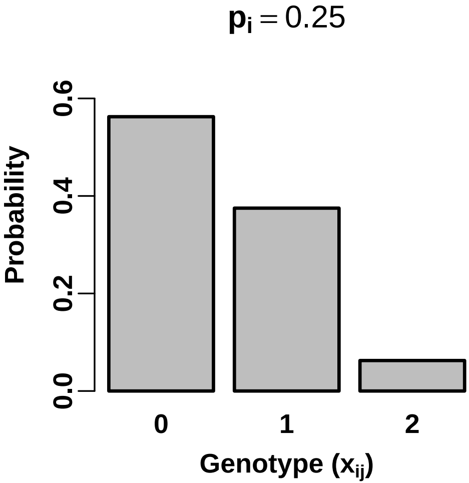
Individuals mate randomly.

In a large population, genotypes

$$x_{ij} \sim \text{Binomial}(2, p_i),$$

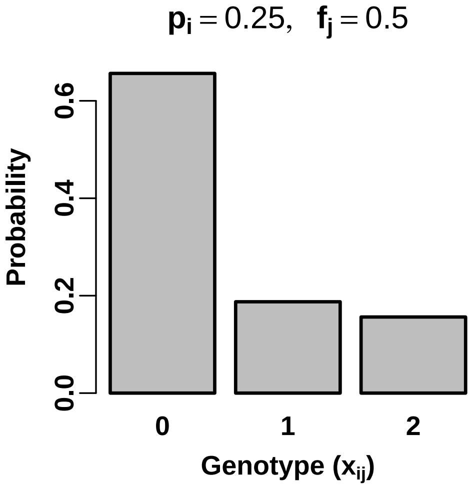
at SNP i with reference allele frequency p_i, for any individual j.

This is “Hardy-Weinberg Equilibrium”.



Inbreeding coefficient f_j

Probability that the two alleles of individual j at a random SNP are "identical by descent" (IBD) **given** an ancestral population.



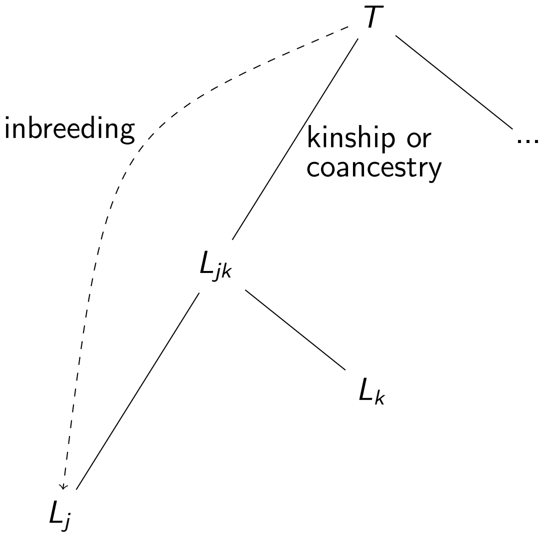
Kinship coefficients φ_{jk}

Local kinship,
given **unrelated founders**

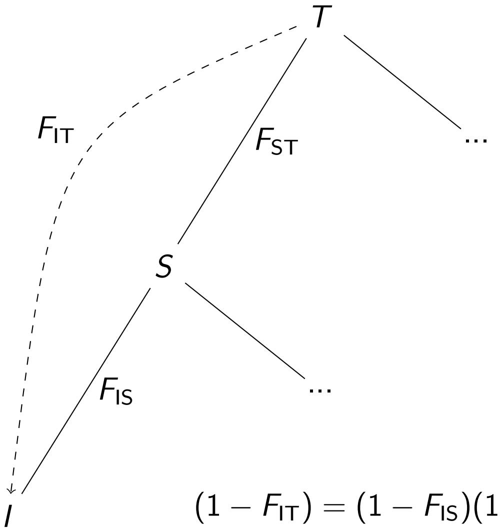
j, k relation	φ_{jk}
self	$1/2$
child	$1/4$
sibling	$1/4$
half sibling	$1/8$
uncle or nephew	$1/8$
first cousins	$1/16$
second cousins	$1/64$
unrelated	0

Probability that one allele of individual j and one of individual k, at a random SNP, are IBD, **given** an ancestral population.

Populations related by a tree

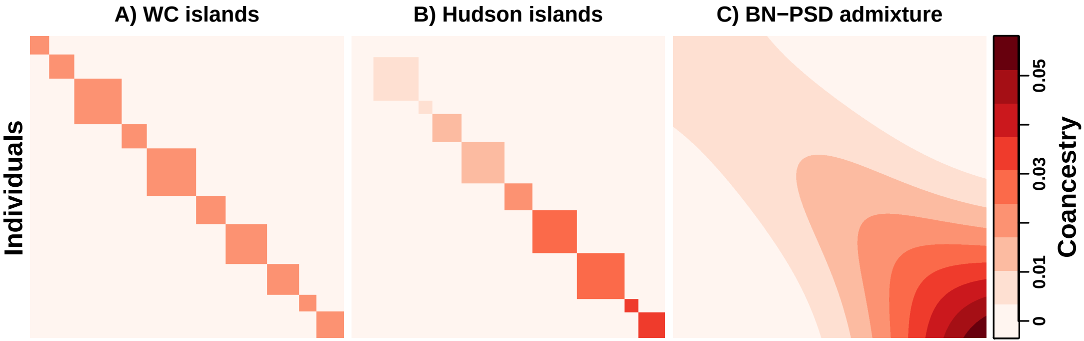


F_{ST} in a subdivided population: Wright (1951)



$$(1 - F_{\mathrm{IT}}) = (1 - F_{\mathrm{IS}})(1 - F_{\mathrm{ST}})$$

Comparison of models assumed for F_{ST} estimation



Kinship model for genotypes

Let T be the ancestral population. In the absence of selective pressures, allele frequencies drift randomly from the ancestral frequency p_i^T, with covariances modulated by the kinship coefficients:

$$\begin{aligned} \mathrm{E}[x_{ij} | T] &= 2p_i^T, \\ \mathrm{Var}(x_{ij} | T) &= 2p_i^T(1 - p_i^T)(1 + f_j^T), \\ \mathrm{Cov}(x_{ij}, x_{ik} | T) &= 4p_i^T(1 - p_i^T)\varphi_{jk}^T. \end{aligned}$$

Note that $\varphi_{jj}^T = \frac{1}{2}(1 + f_j^T)$.

(Wright 1921, Malécot 1948, Wright 1951, Jacquard 1970).

Individual-level analogs of F_{IT}, F_{IS}, F_{ST}

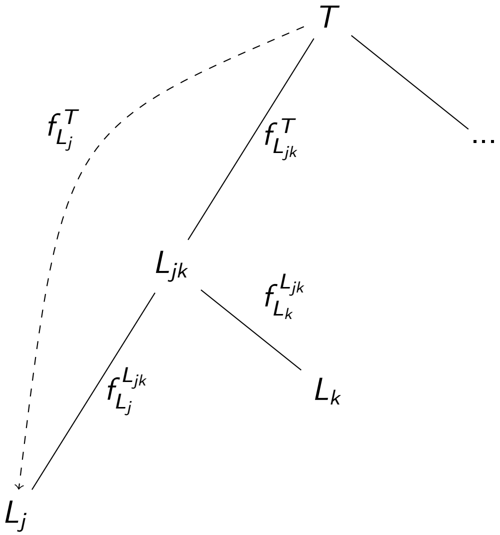
"Total" coef., analogous to F_{IT}:
f_j^T and φ_{jk}^T are relative to T.

"Local" coef., analogous to F_{IS}:
$f_j^{L_j}$ is relative to L_j,
$\varphi_{jk}^{L_{jk}}$ is relative to L_{jk}.

"Structural" coef., analogous to F_{ST}:

$$f_{L_j}^T = \frac{f_j^T - f_j^{L_j}}{1 - f_j^{L_j}},$$

$$f_{L_{jk}}^T = \frac{\varphi_{jk}^T - \varphi_{jk}^{L_{jk}}}{1 - \varphi_{jk}^{L_{jk}}}.$$



F_{ST} for arbitrary population structures

We propose

$$F_{\mathrm{ST}} = \sum_{j=1}^{n} w_j f_{L_j}^{T},$$

where $\sum_{j=1}^{n} w_j = 1$ are non-negative weights.

Backward compatible with island models (needs specific weights), and coherent with Wright's original definition.

Local inbreeding is removed on an **individual** basis!

“Coancestry” model and individual allele frequencies

This restricted model assumes the existence of “individual-specific allele frequencies” π_{ij}, modulated by “coancestry” coefficients θ_{jk}^T:

$$\begin{aligned} x_{ij} | \pi_{ij} &\sim \text{Binomial}(2, \pi_{ij}), \\ \text{E}[\pi_{ij} | T] &= p_i^T, \\ \text{Cov}(\pi_{ij}, \pi_{ik} | T) &= p_i^T (1 - p_i^T) \theta_{jk}^T. \end{aligned}$$

This model excludes local relationships. Given these assumptions, coancestry and kinship coefficients are the same:

$$\theta_{jk}^T = \begin{cases} \varphi_{jk}^T & \text{if} \quad j \neq k, \\ 2\varphi_{jj}^T - 1 = f_j^T & \text{if} \quad j = k. \end{cases}$$

F_{ST} estimation under the island model

Weir-Cockerham and Hudson F_{ST} estimators using π_{ij}'s reduce to

$$\begin{aligned} \hat{p}_i &= \frac{1}{n} \sum_{j=1}^{n} \pi_{ij}, \\ s_i^2 &= \frac{1}{n-1} \sum_{j=1}^{n} (\pi_{ij} - \hat{p}_i)^2, \\ \hat{F}_{\text{ST}}^{\text{island}} &= \frac{\sum_{i=1}^{m} s_i^2}{\sum_{i=1}^{m} \hat{p}_i(1-\hat{p}_i) + \frac{1}{n} s_i^2} \\ &\xrightarrow[m\to\infty]{\text{a.s.}} F_{\text{ST}}. \end{aligned}$$

Under the island model, F_{ST} can be solved for:

$$\mathrm{E}\left[\frac{1}{m} \sum_{i=1}^{m} s_i^2 \right] = \overline{p(1-p)} F_{\text{ST}},$$

$$\mathrm{E}\left[\frac{1}{m} \sum_{i=1}^{m} \hat{p}_i(1-\hat{p}_i) \right] = \overline{p(1-p)} \left(1 - \frac{F_{\text{ST}}}{n} \right)$$

F_{ST} estimation under arbitrary coancestry

Weir-Cockerham and Hudson F_{ST} estimators using π_{ij}'s reduce to

$$\hat{p}_i = \frac{1}{n} \sum_{j=1}^{n} \pi_{ij},$$

$$s_i^2 = \frac{1}{n-1} \sum_{j=1}^{n} (\pi_{ij} - \hat{p}_i)^2,$$

$$\hat{F}_{\text{ST}}^{\text{island}} = \frac{\sum_{i=1}^{m} s_i^2}{\sum_{i=1}^{m} \hat{p}_i(1-\hat{p}_i) + \frac{1}{n} s_i^2}$$

$$\xrightarrow[m \to \infty]{\text{a.s.}} \frac{n\left(F_{\text{ST}} - \bar{\theta}\right)}{n - 1 + F_{\text{ST}} - n\bar{\theta}}$$

Under the general coancestry model, system is underdetermined:

$$\mathrm{E}\left[\frac{1}{m} \sum_{i=1}^{m} s_i^2\right] = \overline{p(1-p)} \frac{n(F_{\text{ST}} - \bar{\theta})}{n-1},$$

$$\mathrm{E}\left[\frac{1}{m} \sum_{i=1}^{m} \hat{p}_i(1-\hat{p}_i)\right] = \overline{p(1-p)}(1-\bar{\theta}).$$

$\bar{\theta} =$ mean coancestry.

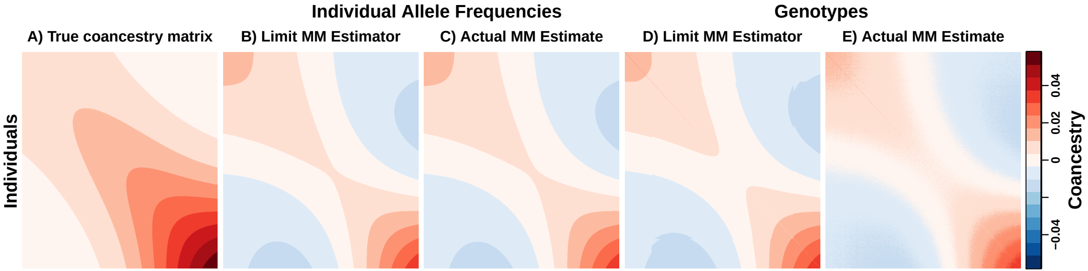
In islands, $\bar{\theta} = \frac{1}{n} F_{\text{ST}}$.

Bias estimating kinship/coancestry coefficients

The popular kinship estimator from genotypes, and its limit as $m \to \infty$, are

$$\hat{\varphi}_{jk} = \frac{\sum_{i=1}^{m} \left(x_{ij} - 2\hat{p}_i\right)\left(x_{ik} - 2\hat{p}_i\right)}{4\sum_{i=1}^{m} \hat{p}_i(1 - \hat{p}_i)} \xrightarrow[m\to\infty]{\text{a.s.}} \frac{\varphi_{jk} - \bar{\varphi}_j - \bar{\varphi}_k + \bar{\varphi}}{1 - \bar{\varphi}},$$

where $\bar{\varphi}_j$ and $\bar{\varphi}$ are weighted mean kinships. Bias in our admixture simulation:

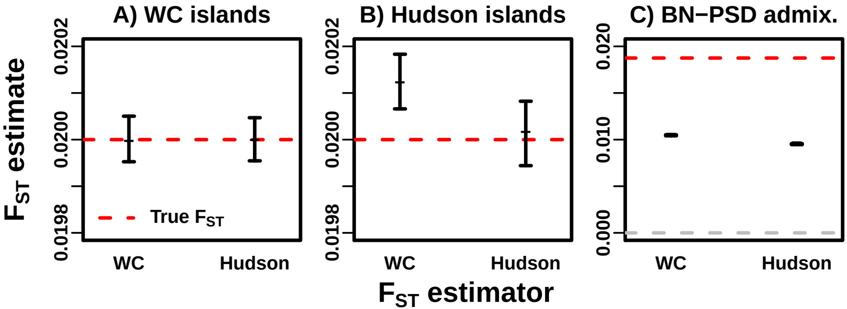


Bias estimating the generalized F_{ST}

A “simple” F_{ST} estimator, derived from $\hat{\theta}_{jj}$, is also biased as $m \to \infty$:

$$\hat{F}_{\text{ST}} = \frac{\sum_{i=1}^{m} \sum_{j=1}^{n} w_j (\pi_{ij} - \hat{p}_i)^2}{\sum_{i=1}^{m} \hat{p}_i (1 - \hat{p}_i)} \xrightarrow[m \to \infty]{\text{a.s.}} \frac{F_{\text{ST}} - \bar{\theta}}{1 - \bar{\theta}}.$$

WC and Hudson F_{ST} estimators are similarly biased in our admixture simulation:



In this work, we...

...generalized F_{ST} using IBD probabilities for individuals.

...connected F_{ST}, kinship coefficients, and admixture models.

...proved almost sure convergence of simple estimators to biased quantities.

...used an admixture simulation to illustrate biases.

Our models could lead to more robust estimators.

Thanks!

John D. Storey
Andrew Bass
Irineo Cabreros
Chee Chen
Sean Hackett
Wei Hao
Emily Nelson

Neo Christopher Chung
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