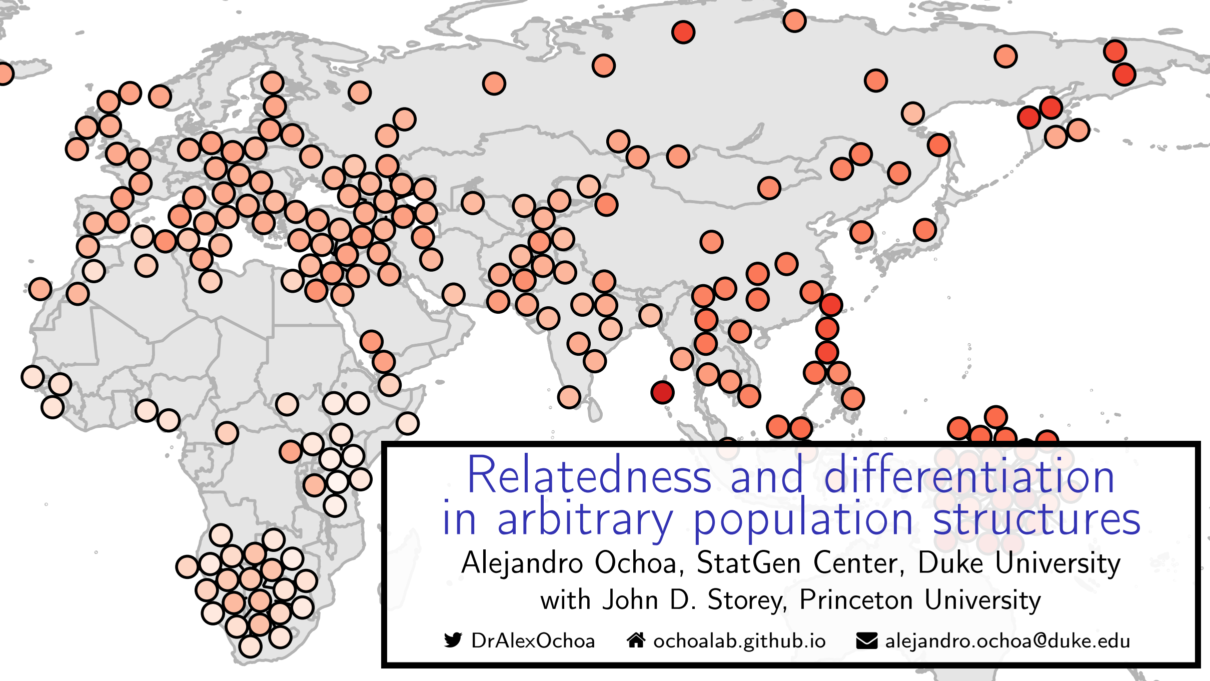

Relatedness and differentiation in arbitrary population structures

Alejandro Ochoa, StatGen Center, Duke University

with John D. Storey, Princeton University

🐦 DrAlexOchoa 🏠 ochoalab.github.io ✉ alejandro.ochoa@duke.edu

Why study relatedness?

Human genetics
is fascinating!

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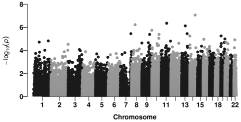

Pop. structure confounds association studies (GWAS)

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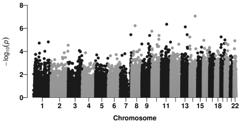
Human genetics is fascinating!



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Heritability of complex traits

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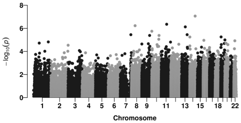
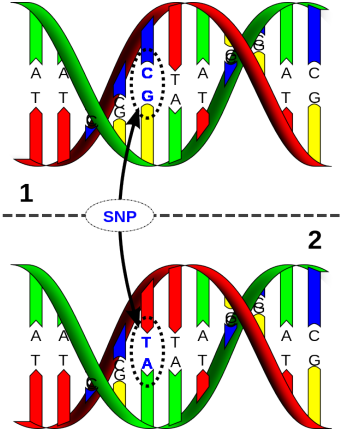


Pop. structure confounds association studies (GWAS)

Heritability of complex traits

Animal and plant breeding

Single Nucleotide Polymorphism (SNP) data



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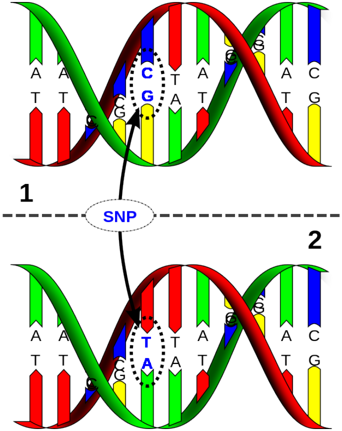
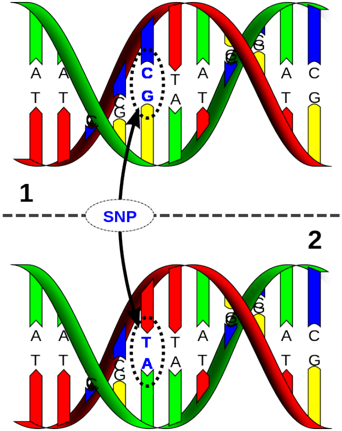


$\Rightarrow$

Genotype	x_{ij}
CC	0
CT	1
TT	2

Single Nucleotide Polymorphism (SNP) data



⇒

Genotype	x_{ij}
CC	0
CT	1
TT	2

⇒

Individuals

Loci

0 2 2 1 1 0 1
0 2 1 0 1
2 ...

X

Hardy-Weinberg Equillibrium (HWE): Binomial draws

x_{ij} = genotype at locus i for individual j.

p_i^T = frequency of reference allele at locus i, (ancestral) population T.

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Under HWE:

$$\begin{aligned}
\Pr(x_{ij} = 2|p_i^T) &= \left(p_i^T\right)^2, \\
\Pr(x_{ij} = 1|p_i^T) &= 2p_i^T\left(1 - p_i^T\right), \\
\Pr(x_{ij} = 0|p_i^T) &= \left(1 - p_i^T\right)^2.
\end{aligned}$$

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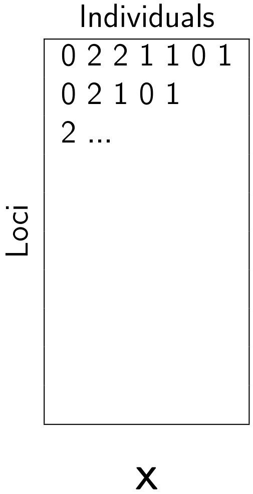
\end{aligned}$$

HWE not valid under population structure!

Goal: measure dependence structure of genotype matrix columns



Individuals

Loci

0 2 2 1 1 0 1

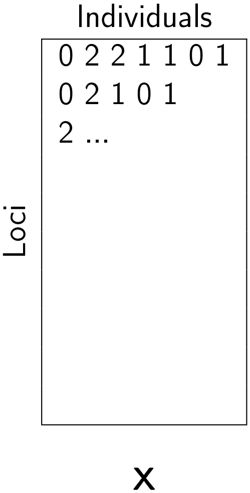
0 2 1 0 1

2 ...

$\mathbf{X}$

High-dimensional binomial data

Goal: measure dependence structure of genotype matrix columns



Individuals

Loci

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0 2 1 0 1

2 ...

X

High-dimensional binomial data

Population structure
⇒ dependence between individuals (columns)

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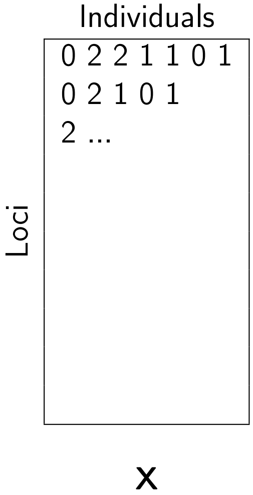


Individuals

Loci

0 2 2 1 1 0 1

0 2 1 0 1

2 ...

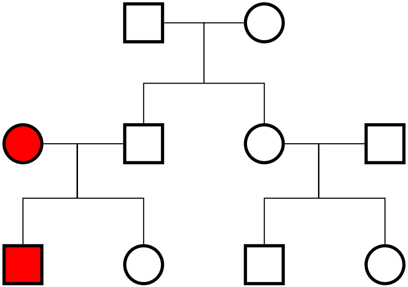
X

High-dimensional binomial data

Population structure
⇒ dependence between individuals (columns)

Linkage disequilibrium
⇒ dependence between loci (rows)

The kinship coefficient for parent-child: $\frac{1}{4}$



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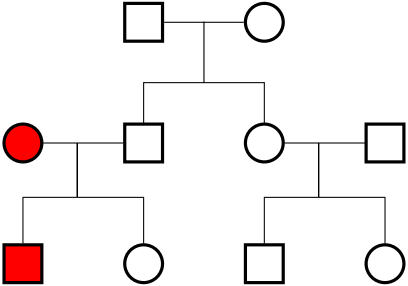

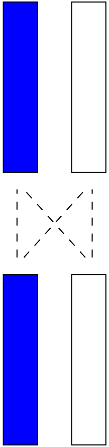

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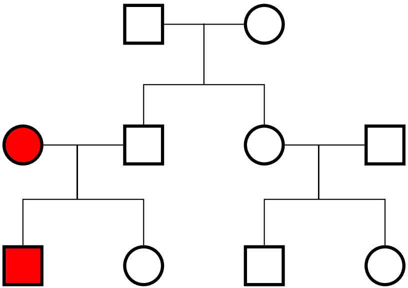
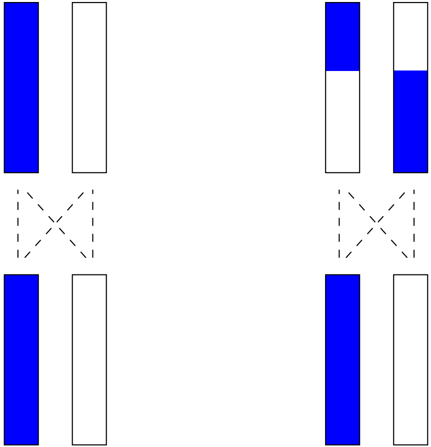
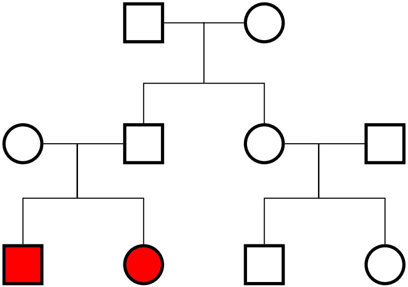




The kinship coefficient for siblings: $\frac{1}{4}$ on average



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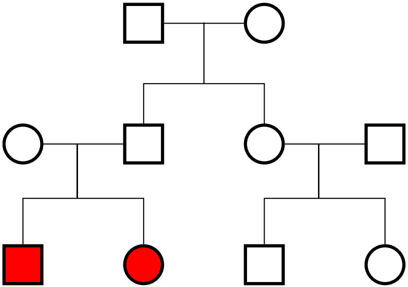

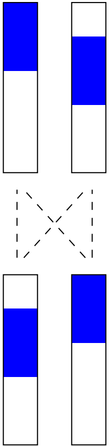

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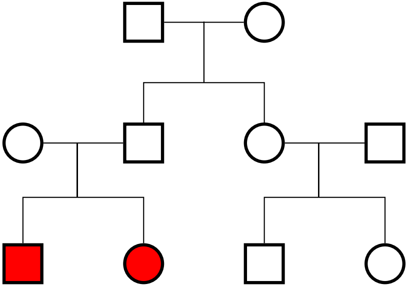
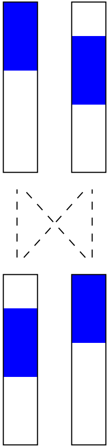
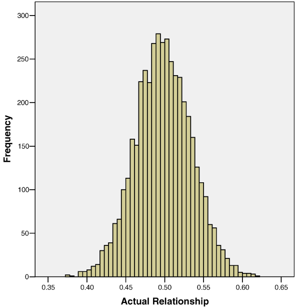
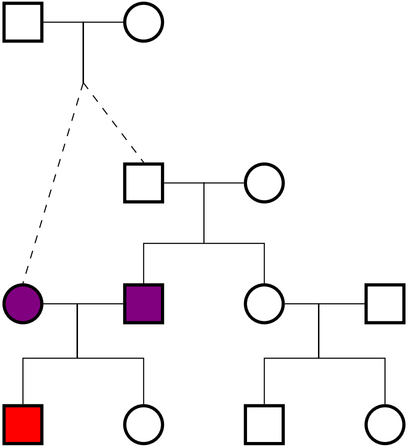






Visscher *et al.* (2006)

The inbreeding coefficient in populations



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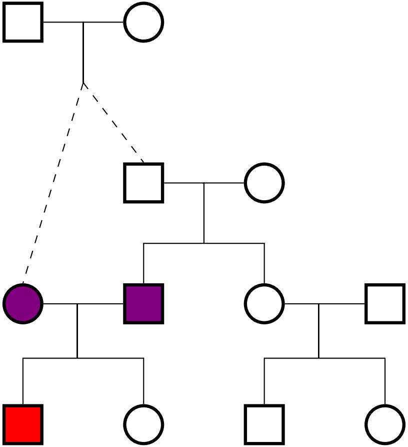

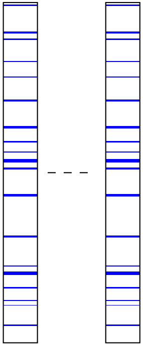

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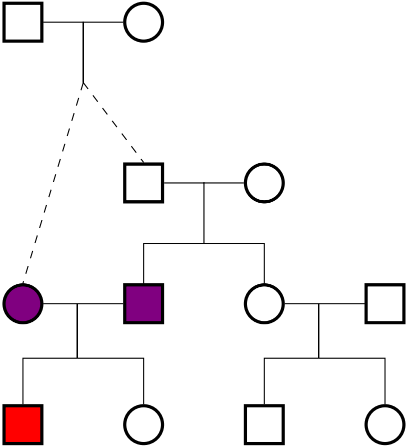

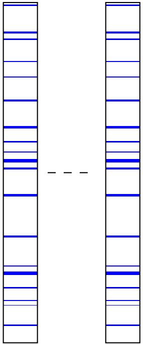

Measurements relative to a reference pop.:

Inbreeding $= 0$ in the local population

Inbreeding ≥ 0 relative to a distant ancestral population

Better measured using covariance

Model parameters

IBD(T): “Identical By Descent” for ancestral population T — shared coin flips

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f_j^T: **Inbreeding coefficient**
Pr. that the two alleles at a random locus of individual j are IBD(T)

$$\mathrm{Var}(x_{ij}|T) = 2p_i^T\left(1 - p_i^T\right)\left(1 + f_j^T\right)$$

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$$\mathrm{Cov}(x_{ij}, x_{ik}|T) = 4p_i^T \left(1 - p_i^T\right)\varphi_{jk}^T$$

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$$\mathrm{Cov}(x_{ij}, x_{ik} | T) = 4p_i^T \left(1 - p_i^T\right) \varphi_{jk}^T$$

F_{ST}: **Fixation index**
Pr. that two random alleles in a subpopulation at a random locus are IBD(T)

Existing approaches

1. F_{ST} estimation
   - *For independent subpopulations only!*
   - Weir-Cockerham (WC) estimator (1984) — 15K citations!
   - “Hudson” pairwise estimator (2013) tweaks WC
   - BayeScan (2008) — 1.2K citations

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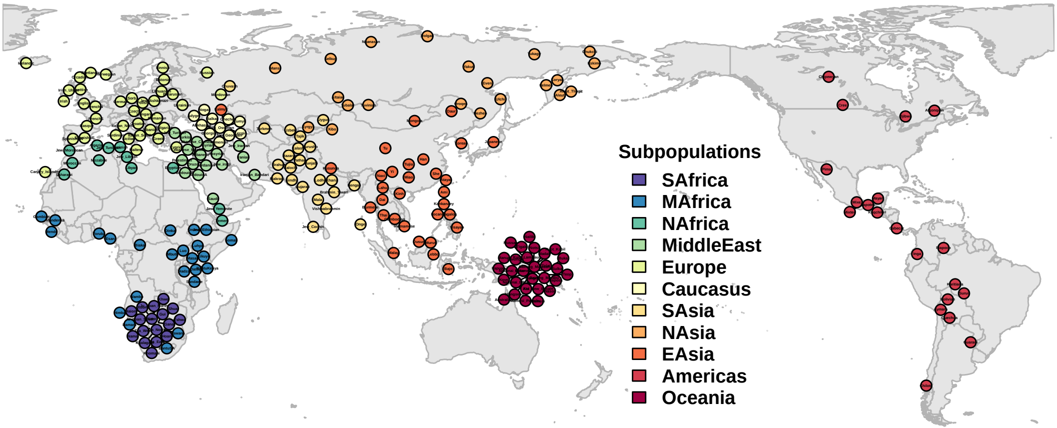
   - BayeScan (2008) — 1.2K citations

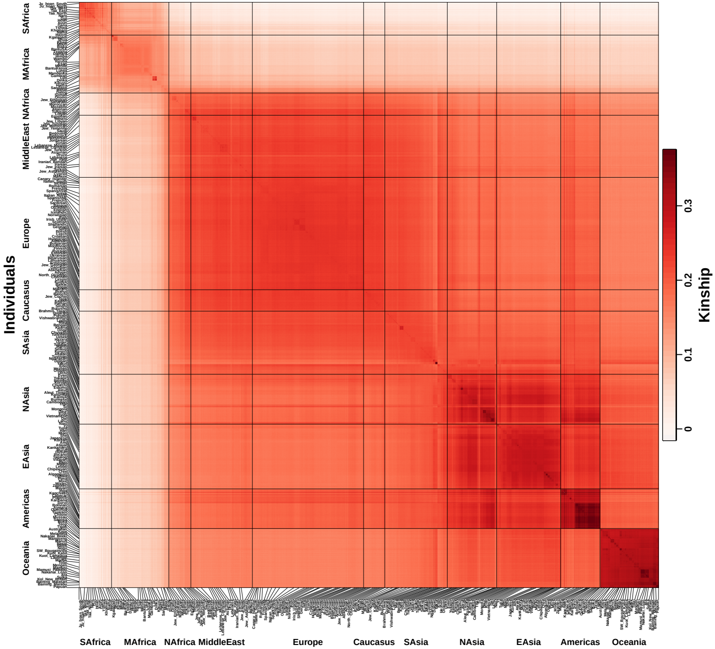
2. Kinship estimation
   - "Standard" kinship estimator (1950s)
     - Used by most modern GWAS approaches that control for population structure (PCA, LMM, adj. χ^2; top paper 6K citations)
     - GCTA heritability estimation (2 papers: 4K citations)
   - Our novel finding: accuracy requires unstructured population (a minority of closely-related individuals)

Dataset: Human Origins



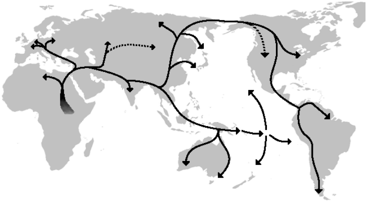
2,922 indivs. from 244 locs. — 593,124 loci — SNP chip

Lazaridis *et al.* (2014), (2016); Skoglund *et al.* (2016)



Our new kinship estimates

Genotypes from "Human Origins" (Lazaridis *et al.* 2014, 2016; Skoglund *et al.* 2016)



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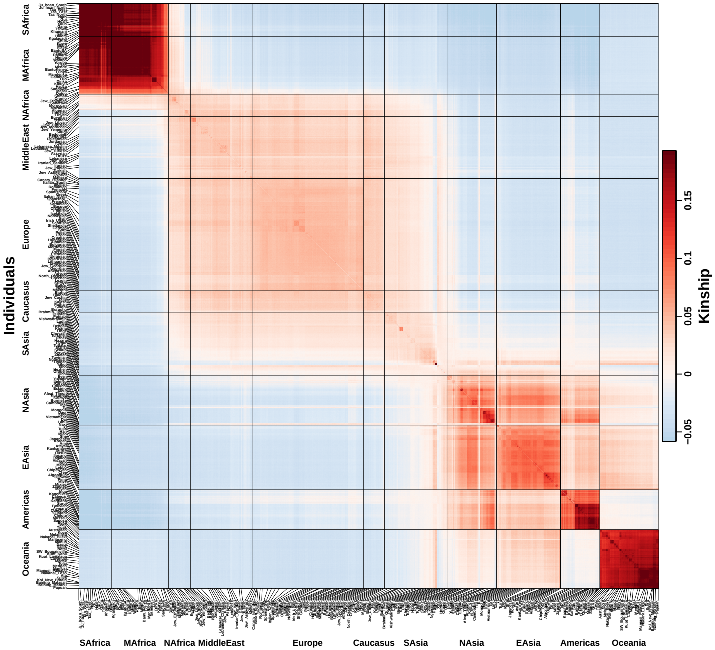
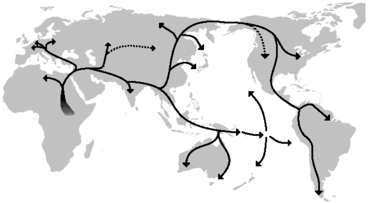
*Inbreeding coeffs. on diagonal



Standard kinship estimates

Genotypes from "Human Origins" (Lazaridis *et al.* 2014, 2016; Skoglund *et al.* 2016)



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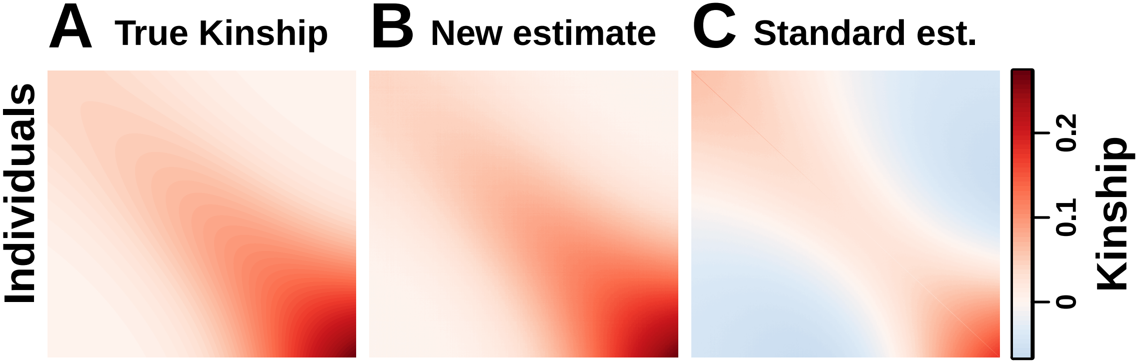
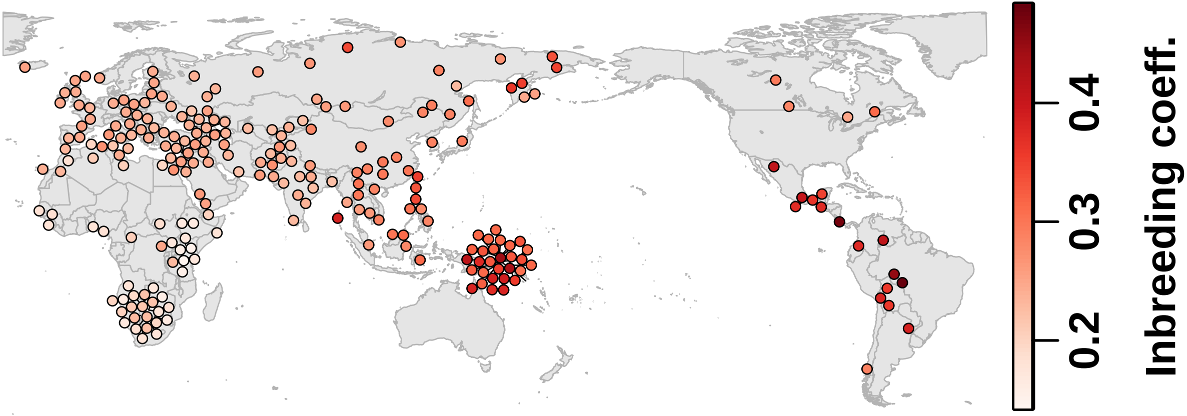
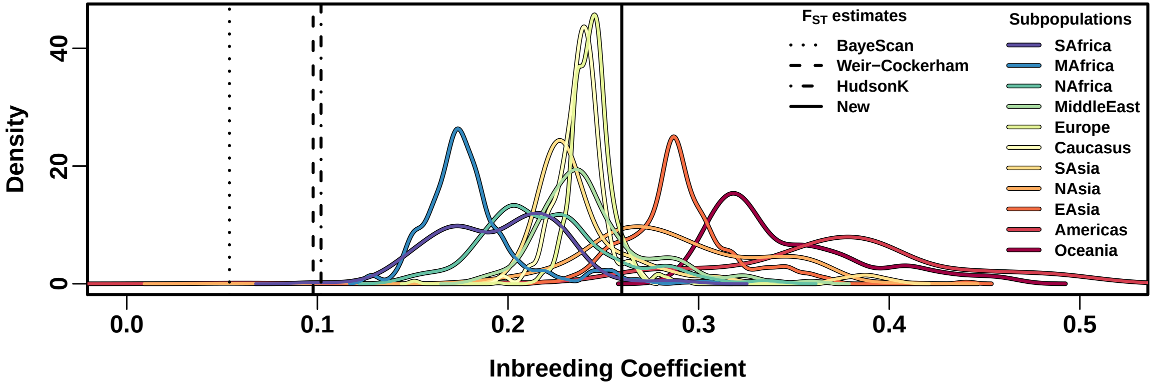
Only our new estimator is accurate in simulations



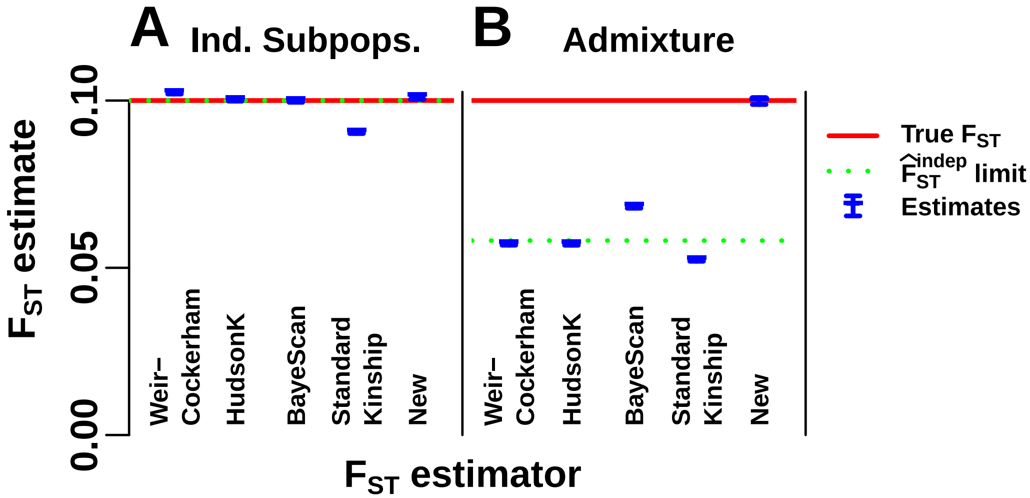
Population-level inbreeding increases with distance from Africa



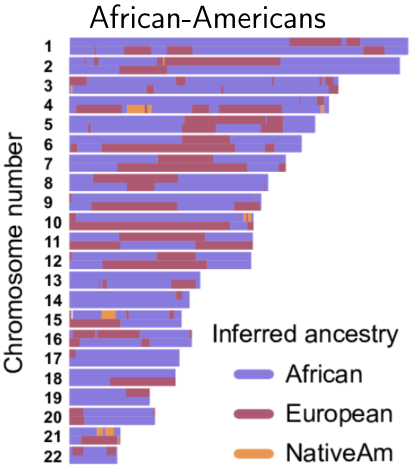
Differentiation (F_{ST}) previously underestimated



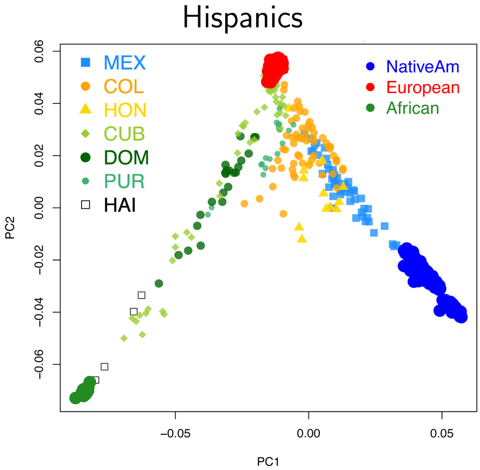
Only our new method estimates generalized F_{ST} accurately



Recently-admixed populations

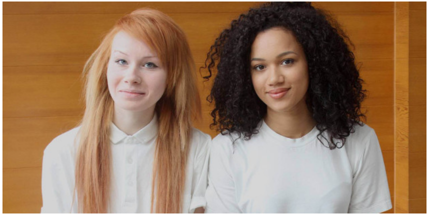


Baharian *et al.* (2016)



Moreno-Estrada *et al.* (2013)

Admixed siblings from different subpopulations?



Lucy and Maria, UK

Admixed siblings from different subpopulations?

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Ochoa brothers, MX

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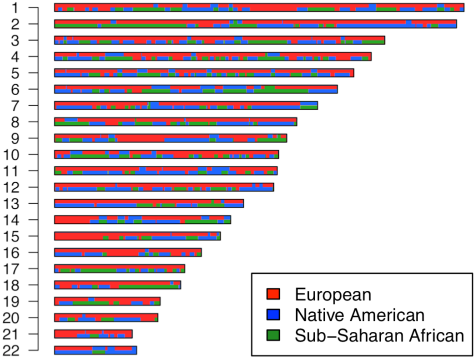
High Admixture LD:



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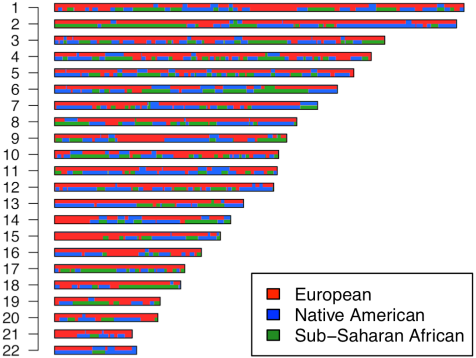
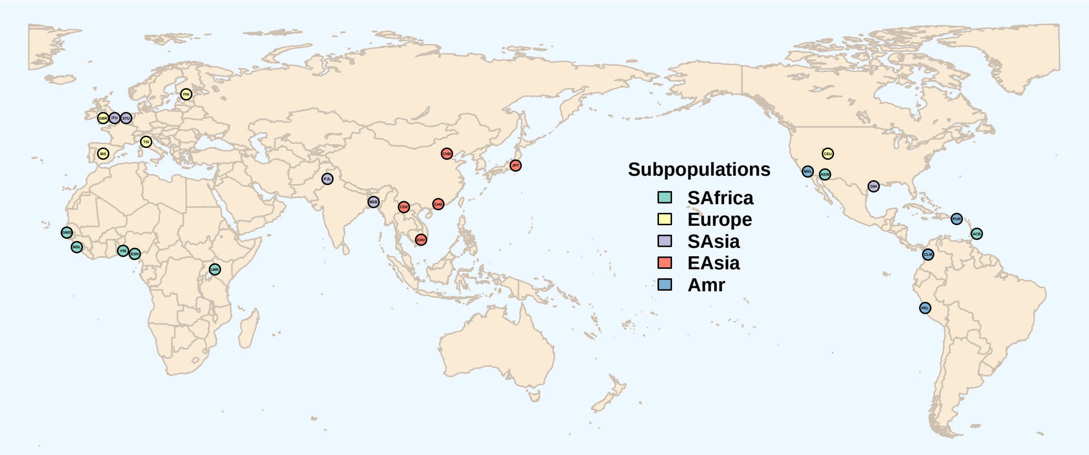


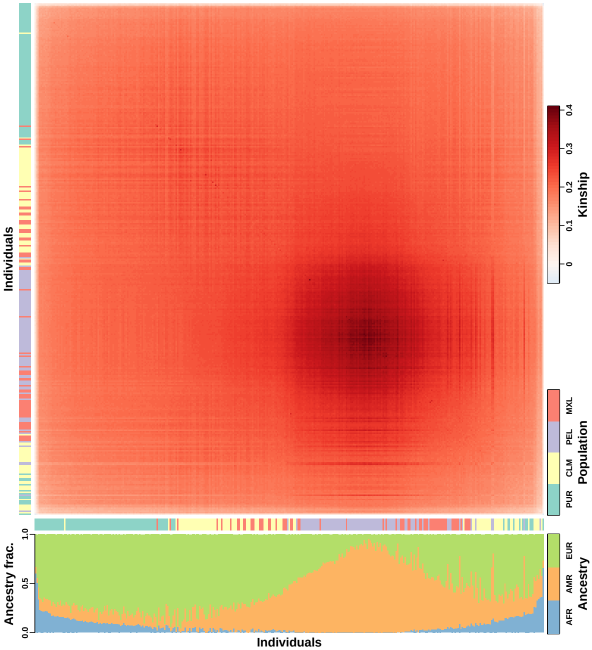
Moreno-Estrada *et al.* (2013)

Solution: treat every individual as their own subpopulation!

Dataset: 1000 Genomes Project (2013)



2,504 indivs. from 26 locs. — 20,417,698 loci (asc. in YRI) — WGS trios, etc.

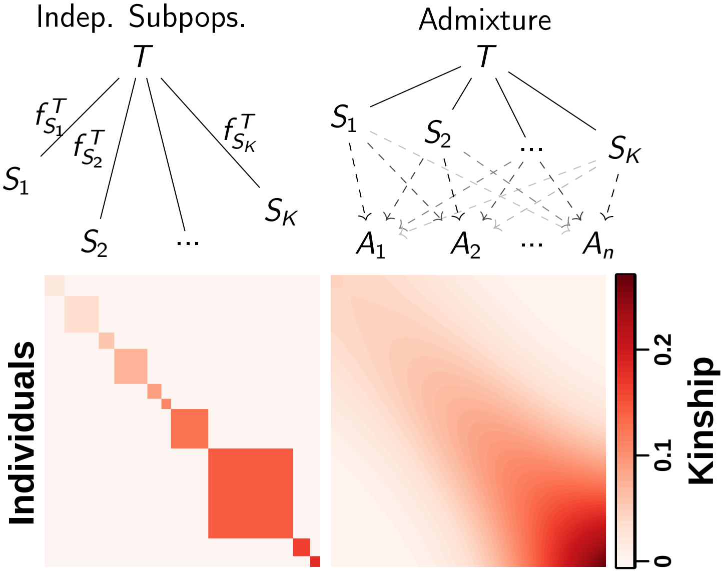


Kinship driven by admixture in Hispanics

Our new kinship estimates

Genotypes from the 1000 Genomes Project (2013)

Comparison of population structures in simulation



F_{ST} in the independent subpopulation model

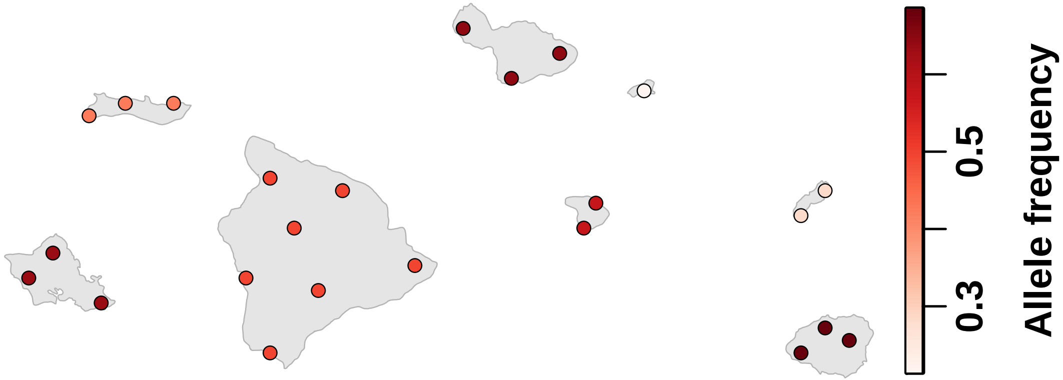


Illustration.

F_{ST} in the independent subpopulation model

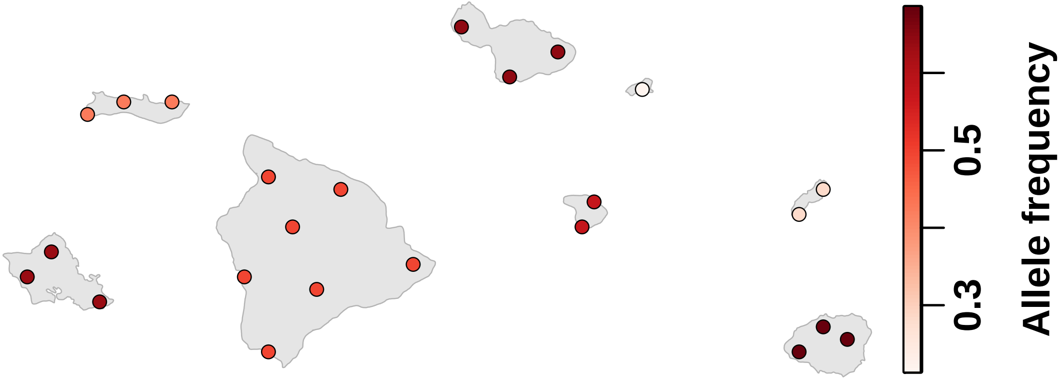


Illustration.

$$F_{\mathrm{ST}} = \frac{\mathrm{Var}\left(p_i^S \middle| T\right)}{p_i^T\left(1 - p_i^T\right)}.$$

Here F_{ST} relates to proportion of variance explained by pop. structure

Wright's F_{ST}

T = Total, S = Subpopulation, I = Individual.

Total inbreeding:
$$F_{\mathrm{IT}} = \frac{1}{|S|} \sum_{j \in S} f_j{}^T,$$

Local inbreeding:
$$F_{\mathrm{IS}} = \frac{1}{|S|} \sum_{j \in S} f_j^S,$$

Structural inbreeding:
$$F_{\mathrm{ST}} = \frac{F_{\mathrm{IT}} - F_{\mathrm{IS}}}{1 - F_{\mathrm{IS}}}.$$

Our generalized F_{ST}

Need new “local” subpopulations L_j (separates total from local inbreeding):

$$\left(1 - f_j^T\right) = \left(1 - f_j^{L_j}\right)\left(1 - f_{L_j}^T\right).$$

Our generalized F_{ST}

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Generalized F_{ST}: applicable to arbitrary population structures, equals previous definition for subpopulations:

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

Our generalized F_{ST}

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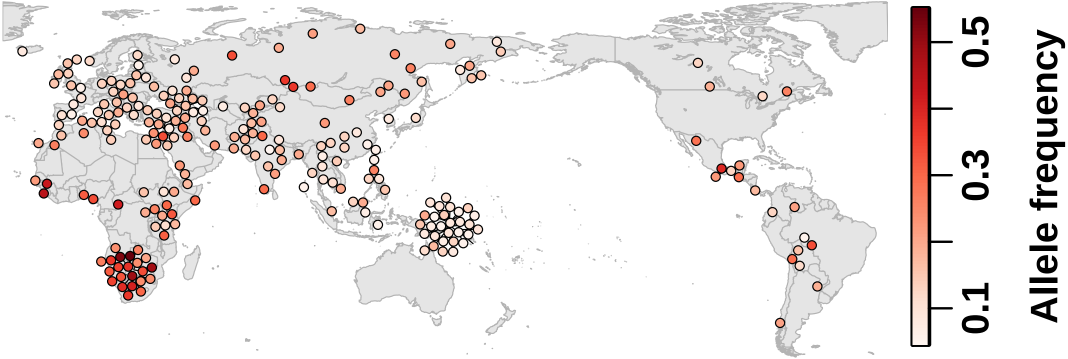
Generalized F_{ST}: applicable to arbitrary population structures, equals previous definition for subpopulations:

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

Mean heterozygosity in a structured population:

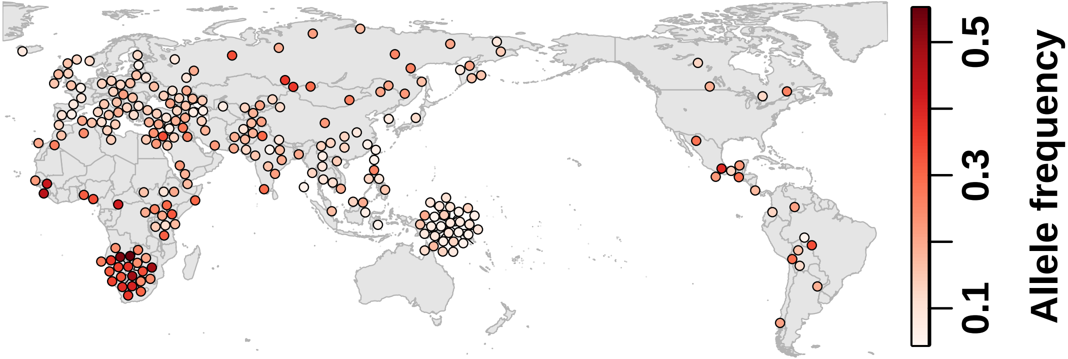
$$\bar{H}_i = \frac{1}{n}\sum_{j=1}^{n} \Pr(x_{ij} = 1 | T) = 2p_i^T\left(1 - p_i^T\right)\left(1 - F_{\mathrm{ST}}\right).$$

F_{ST} measures population structure / differentiation



Median diff. SNP in Human Origins (rs2650044; given MAF $\geq$ 10%).

F_{ST} measures population structure / differentiation



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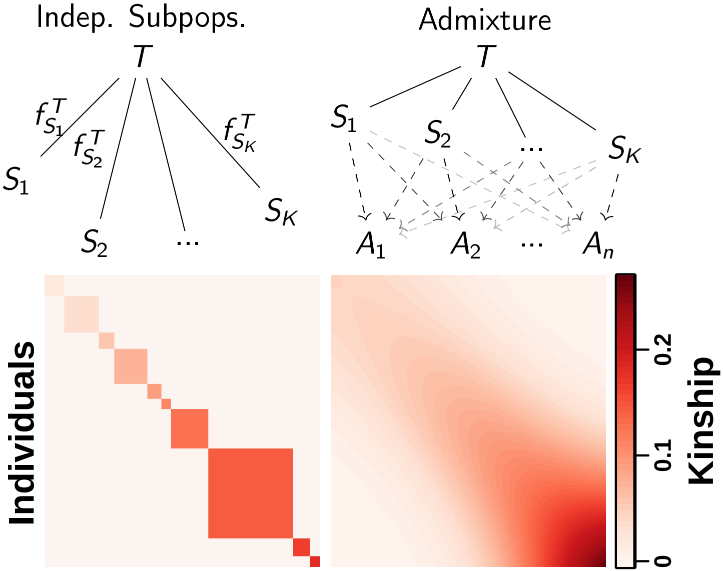
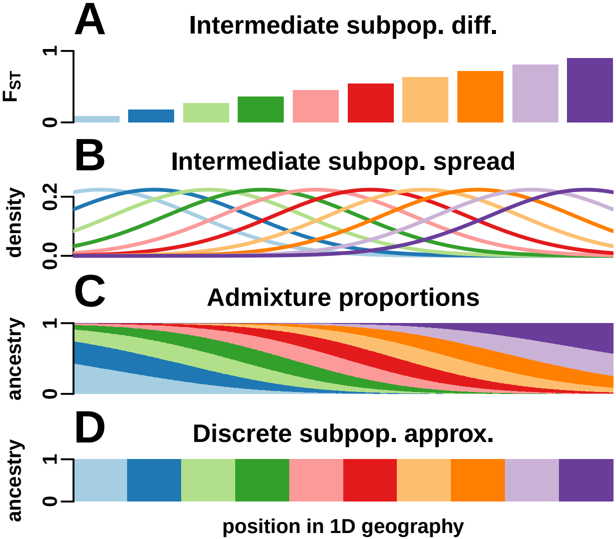
$\hat{F}_{\text{ST}}^{\text{WC}} \approx 0.0961$ using Weir-Cockerham estimator and $K = 244$.

Comparison of population structures in simulation



Our admixture simulation (R package `bnpsd` on CRAN)



Kinship model for genotypes

symbol	meaning
T	ref ancestral population
i	locus index
j, k	individual indexes
p_i^T	ref allele frequency
x_{ij}	genotype (num ref alleles)
φ_{jk}^T	kinship of j, k
f_j^T	inbreeding of j

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

Statistical model:

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

Problem: common estimators not consistent under structure

Estimate of ancestral allele frequency:

$$\hat{p}_i^T = \frac{1}{2} \sum_{j=1}^{n} w_j x_{ij}$$

Variance asymptotically > 0 under population structure:

$$\mathrm{Var}\left(\hat{p}_i^T \middle| T \right) = p_i^T \left(1 - p_i^T \right) \bar{\varphi}^T$$

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Naive estimators that use $\hat{p}_i^T$ (next) are not consistent!

Bias in standard kinship estimator

$$\hat{\varphi}_{jk}^{T,\text{std}} = \frac{\sum_{i=1}^{m} \left(x_{ij} - 2\hat{p}_i^T \right) \left(x_{ik} - 2\hat{p}_i^T \right)}{4 \sum_{i=1}^{m} \hat{p}_i^T \left(1 - \hat{p}_i^T \right)}, \qquad \hat{p}_i^T = \frac{1}{2} \sum_{j=1}^{n} w_j x_{ij}.$$

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Bias varies by j, k:

$$\hat{\varphi}_{jk}^{T,\text{std}} \xrightarrow[m \to \infty]{\text{a.s.}} \frac{\varphi_{jk}^T - \bar{\varphi}_j^T - \bar{\varphi}_k^T + \bar{\varphi}^T}{1 - \bar{\varphi}^T}.$$

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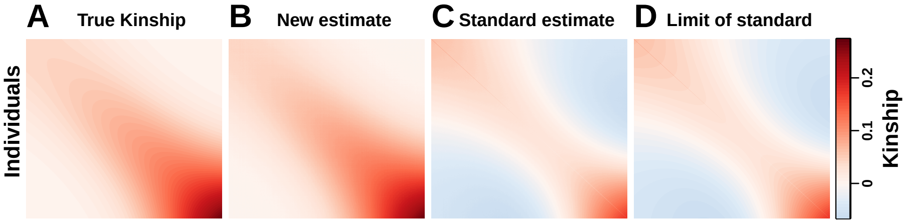

Our new estimator (R package `popkin` on CRAN)

Step 1: “pre-adjusted” kinship estimator with uniform bias.

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

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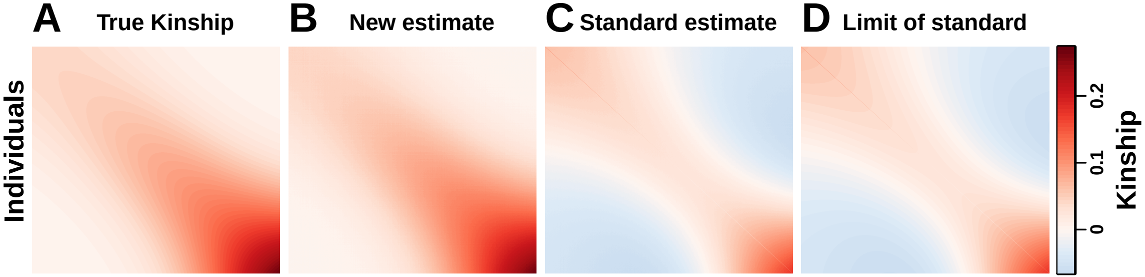
Step 2: Estimate minimum kinship, use to unbias “step 1” estimates.

$$\hat{\varphi}_{\text{min}}^{T,\text{preadj}} \xrightarrow[m \to \infty]{\text{a.s.}} -\frac{\bar{\varphi}^T}{1 - \bar{\varphi}^T}, \qquad \hat{\varphi}_{jk}^{T,\text{new}} = \frac{\hat{\varphi}_{jk}^{T,\text{preadj}} - \hat{\varphi}_{\text{min}}^{T,\text{preadj}}}{1 - \hat{\varphi}_{\text{min}}^{T,\text{preadj}}} \xrightarrow[m \to \infty]{\text{a.s.}} \varphi_{jk}^T.$$

This yields consistent $\hat{f}_j^{T,\text{new}}$, $\hat{F}_{\text{ST}}^{\text{new}}$ estimators!

Performance of new estimator



Bias in F_{ST} estimators for independent subpopulations

Previous estimator for n subpopulations, simplified for known AFs (π_{ij}):

$$\hat{F}_{\text{ST}}^{\text{indep}} = \frac{\sum_{i=1}^{m} \hat{\sigma}_i^2}{\sum_{i=1}^{m} \hat{p}_i^T \left(1 - \hat{p}_i^T\right) + \frac{1}{n}\hat{\sigma}_i^2},$$

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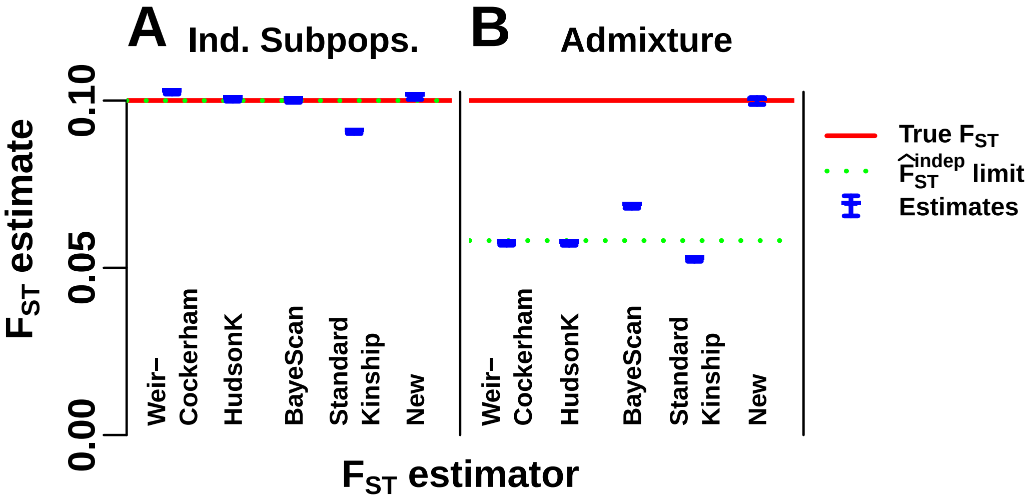
Estimator is biased in dependent subpopulations:

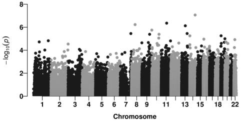
$$\hat{F}_{\text{ST}}^{\text{indep}} \xrightarrow[m \to \infty]{\text{a.s.}} \frac{F_{\text{ST}} - \frac{1}{n-1}\left(n\bar{\theta}^T - F_{\text{ST}}\right)}{1 - \frac{1}{n-1}\left(n\bar{\theta}^T - F_{\text{ST}}\right)}.$$

Only our new method estimates generalized F_{ST} accurately



The future: improved kinship has repercussions across genetics!

Accurate and efficient estimation, admixture modeling



Association studies, selection tests

Bias in heritability of complex traits

Animal and plant breeding

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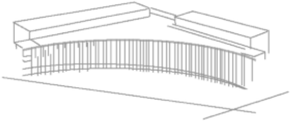
PRINCETON UNIVERSITY



Lewis-Sigler Institute for Integrative Genomics