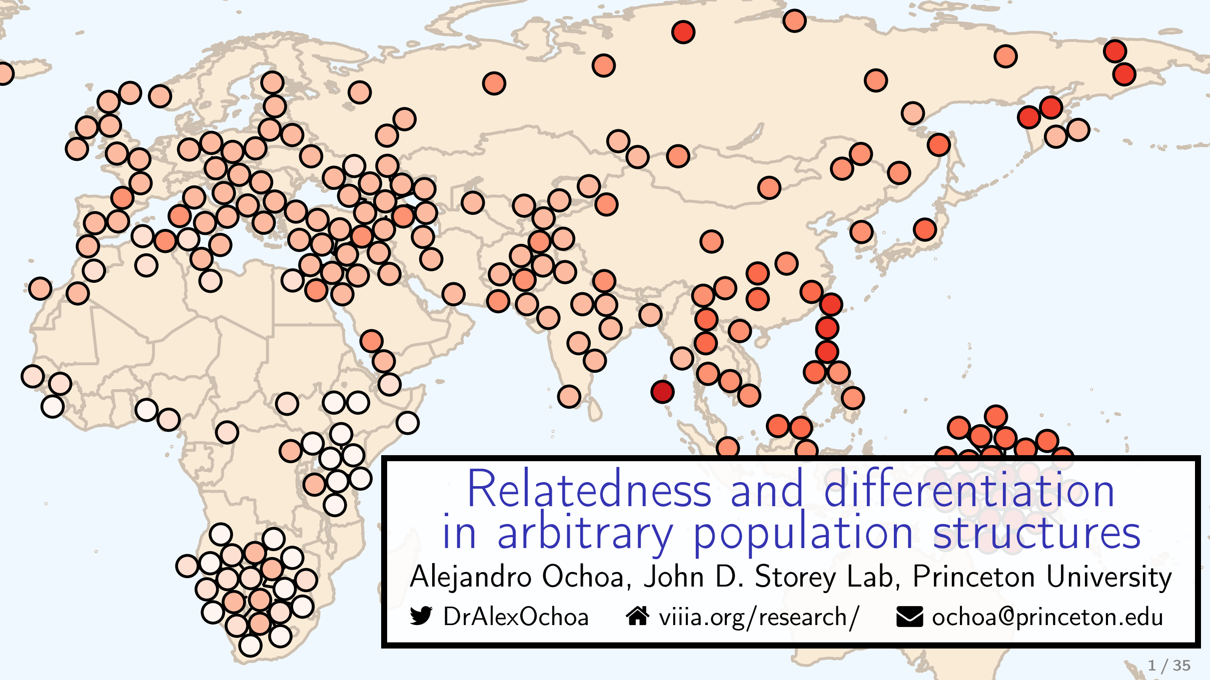

Relatedness and differentiation in arbitrary population structures

Alejandro Ochoa, John D. Storey Lab, Princeton University

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My research areas / Contributions

1. Stratified False Discovery Rate (FDR)
    - Finding: per-stratum local FDR maximizes power controlling overall FDR
    - Improved power in protein domain prediction
    - Identified protein classes with problematic statistics

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3. **Kinship and F_{ST} for arbitrary population structures**
    - Motivation: world-wide human population structure
    - Generalized definitions and models
    - Novel bias calculations validated by simulations
    - Novel non-parametric estimator with greatly improved accuracy

Why study relatedness?

Human genetics
is fascinating!

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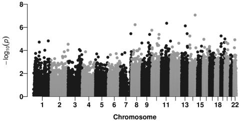

Pop. structure confounds association studies (GWAS)

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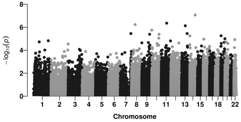

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Heritability of complex traits

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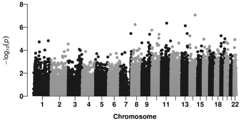
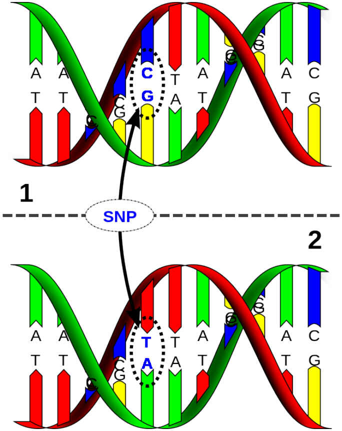


Pop. structure confounds association studies (GWAS)

Heritability of complex traits

Animal and plant breeding

Single Nucleotide Polymorphism (SNP) data



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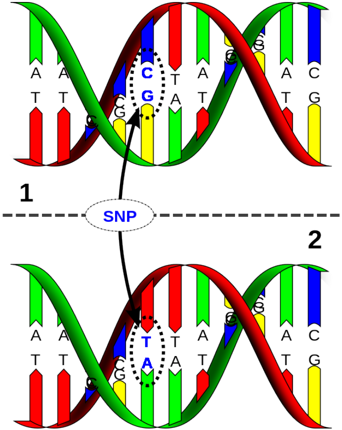

⇒

Genotype	x_{ij}
CC	0
CT	1
TT	2

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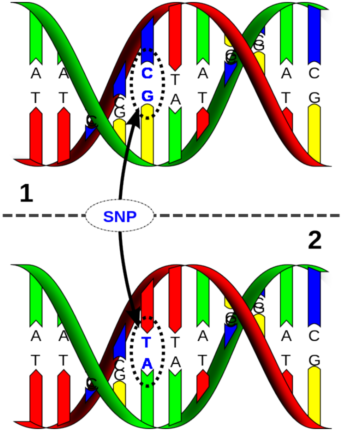

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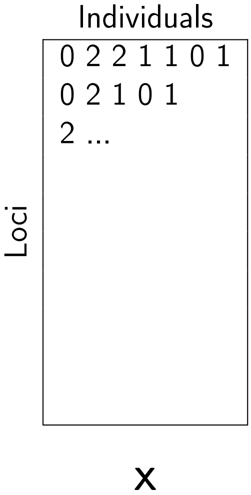

0 2 2 1 1 0 1
0 2 1 0 1
2 ...

$\mathbf{X}$

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:

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\Pr(x_{ij} = 2 | p_i^T) &= \left(p_i^T\right)^2, \\
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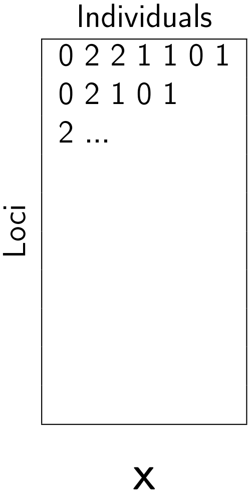
$$

HWE not valid under population structure!

Goal: measure dependence structure of genotype matrix columns



Individuals

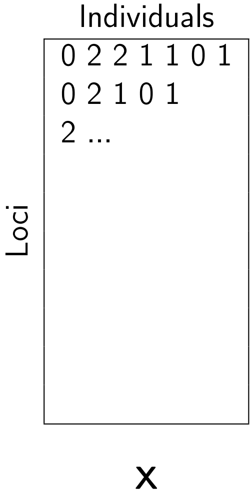
Loci

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

X

High-dimensional binomial data

Goal: measure dependence structure of genotype matrix columns



High-dimensional binomial data

Population structure
⇒ dependence between individuals (columns)

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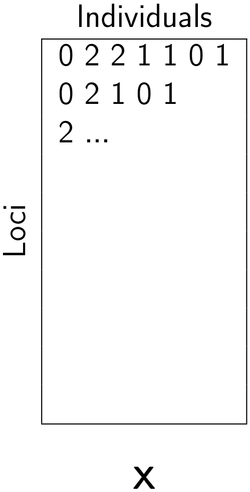

High-dimensional binomial data

Population structure
⇒ dependence between individuals (columns)

Linkage disequilibrium
⇒ dependence between loci (rows)

Model parameters

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

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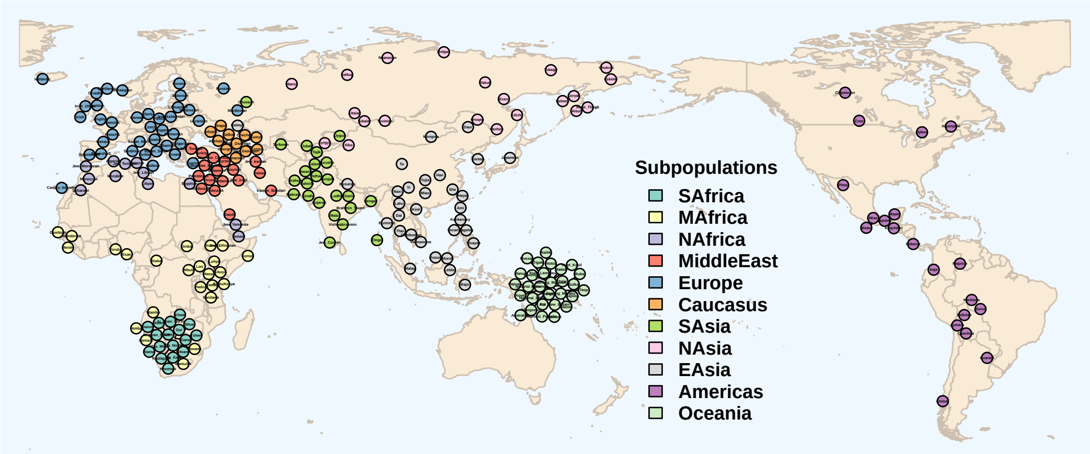
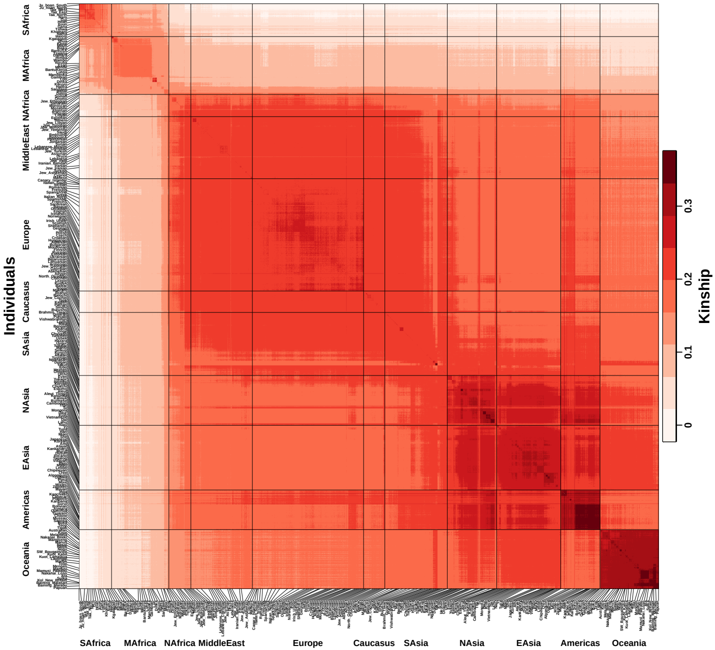
2. Kinship estimation
   - "Standard" kinship estimator (1950s)
     - Used by most modern GWAS approaches that control for population structure (PCA, LMM, adj. χ^2; top paper 6K citations)
     - GCTA heritability estimation (2 papers: 4K citations)
   - Our novel finding: accuracy requires unstructured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

Dataset: Human Origins

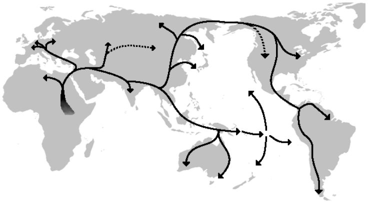


2,922 indivs. from 244 locs. — 593,124 loci — SNP chip
Lazaridis *et al.* (2014), (2016); Skoglund *et al.* (2016)



Our new kinship estimates

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



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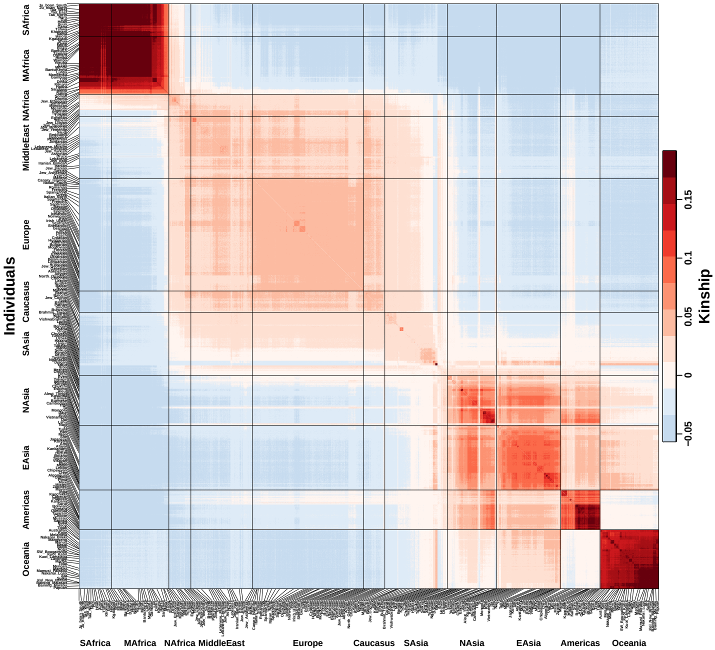
*Inbreeding coeffs. on diagonal



Standard kinship estimates

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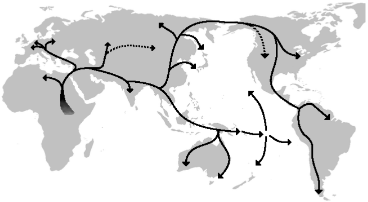

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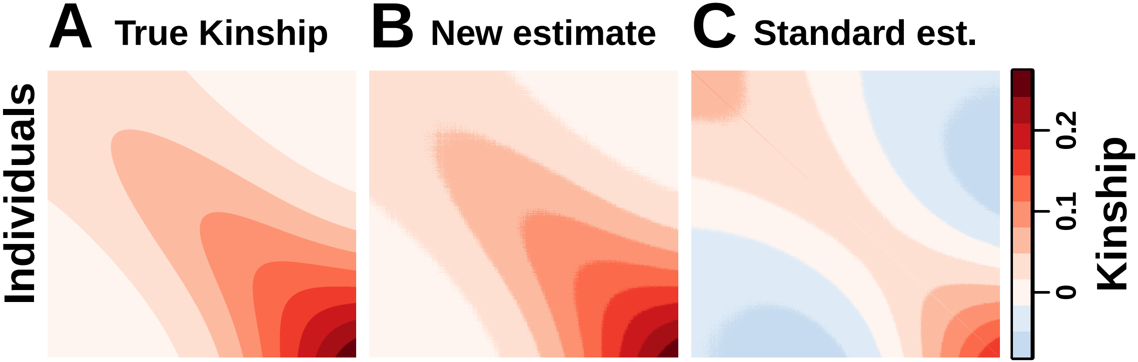
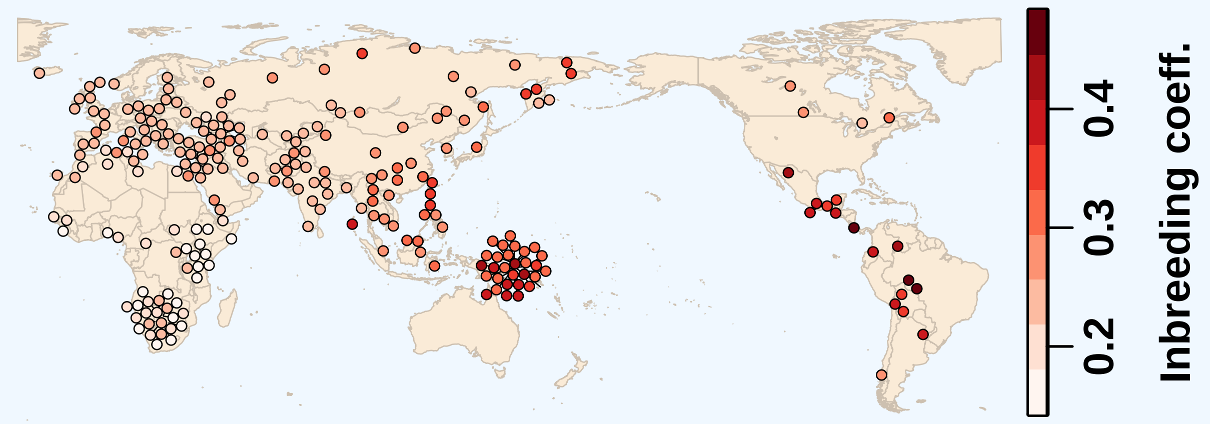
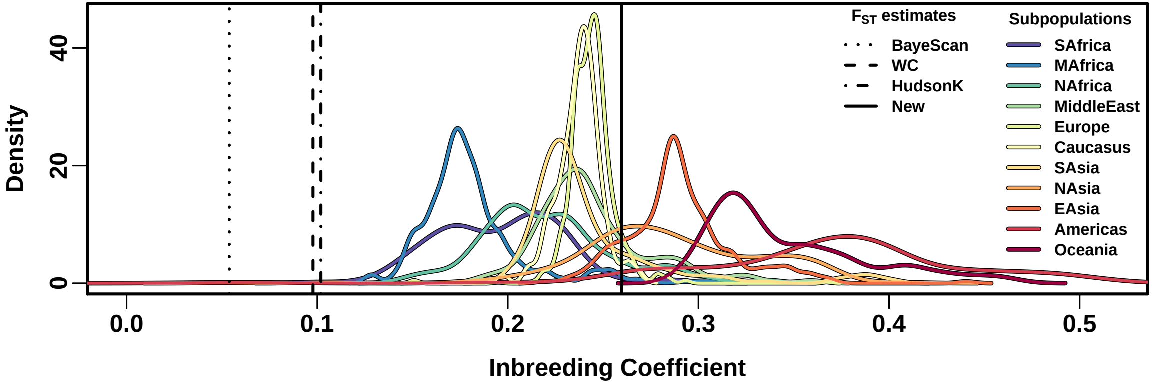
Only our new estimator is accurate in simulations



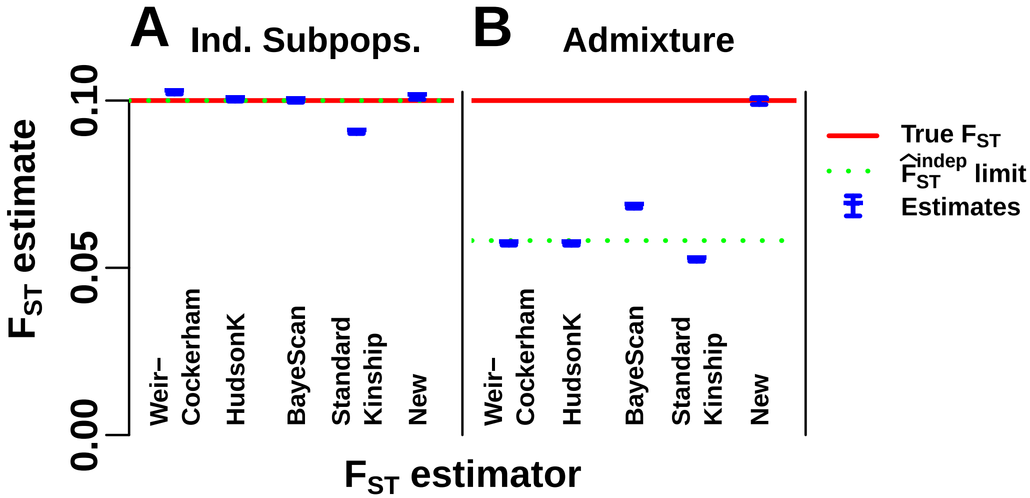
Population-level inbreeding increases with distance from Africa



Differentiation (F_{ST}) previously underestimated

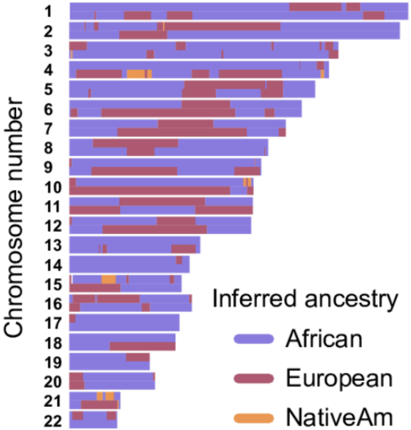


Only our new method estimates generalized F_{ST} accurately



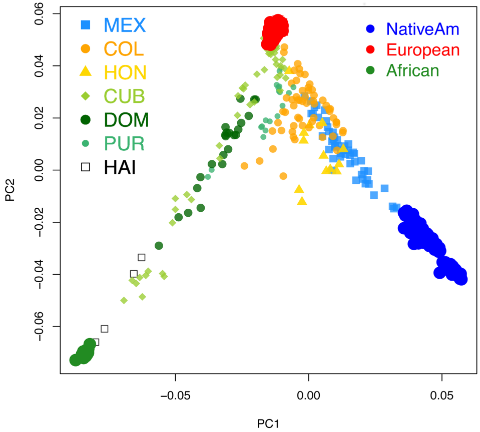
Recently-admixed populations

African-Americans



Baharian *et al.* (2016)

Hispanics



Moreno-Estrada *et al.* (2013)

Admixed siblings from different populations?

Lucy and Maria, UK

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Ochoa brothers, MX

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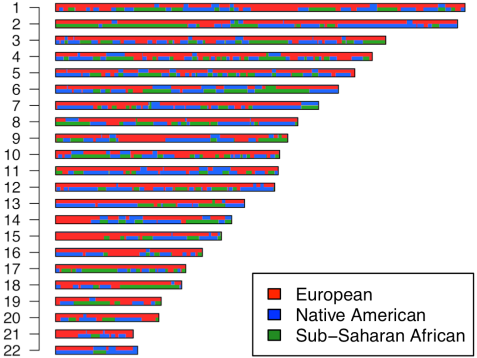
High Admixture LD:



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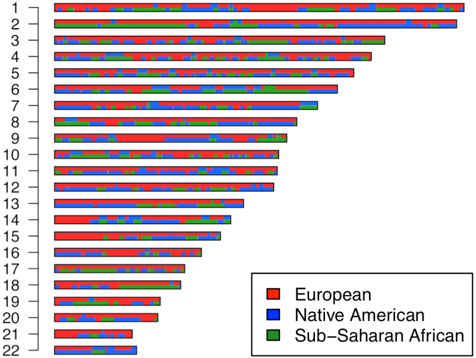
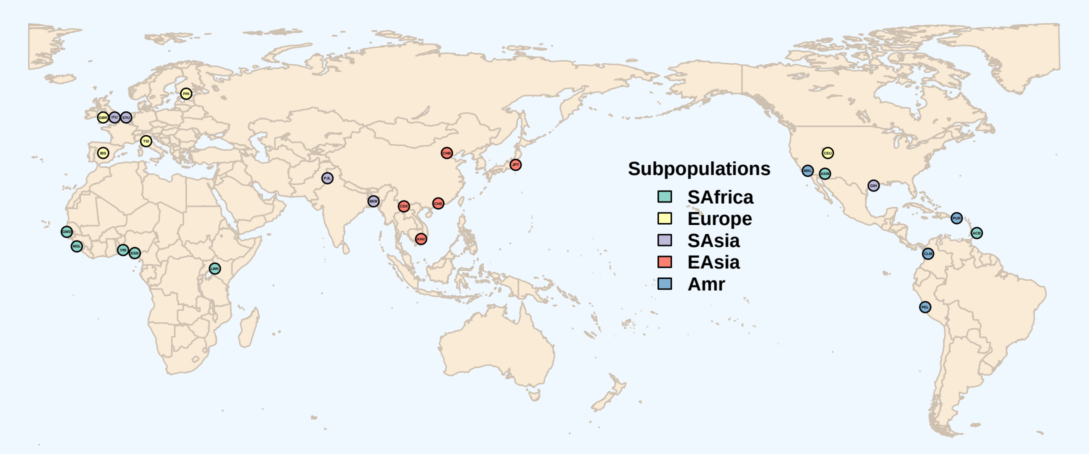


Moreno-Estrada *et al.* (2013)

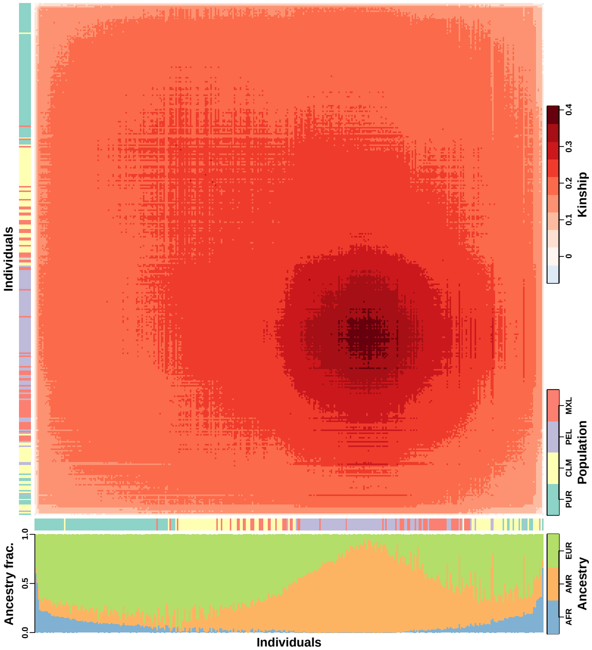
Solution: treat every individual as its own population!

Dataset: 1000 Genomes Project (2013)



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

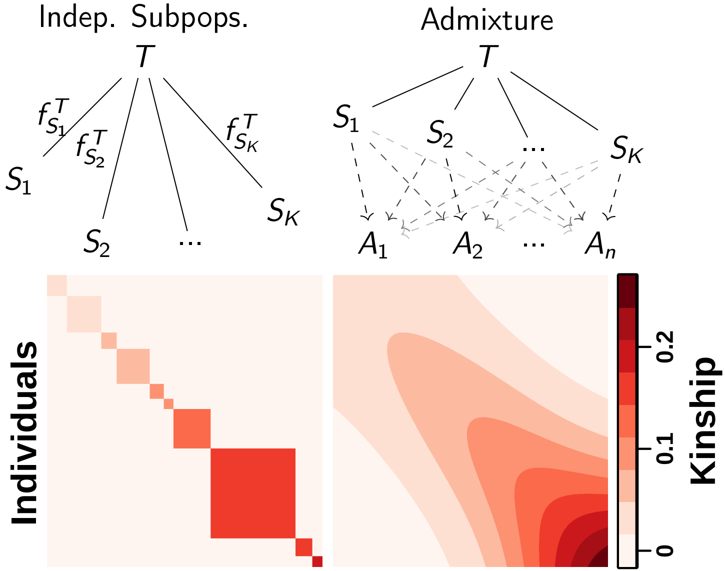
Kinship driven by admixture in Hispanics



Our new kinship estimates

Genotypes from the 1000 Genomes Project (2013)

Comparison of population structures in simulation



F_{ST} in the independent subpopulation model

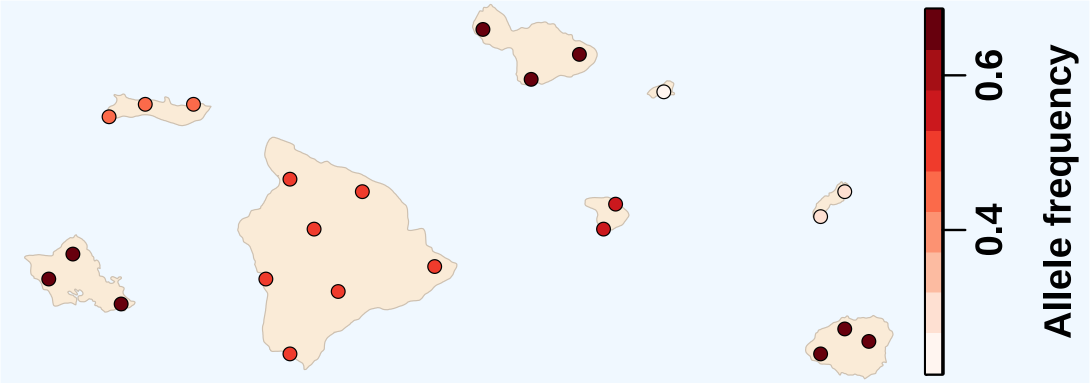


Illustration.

F_{ST} in the independent subpopulation model

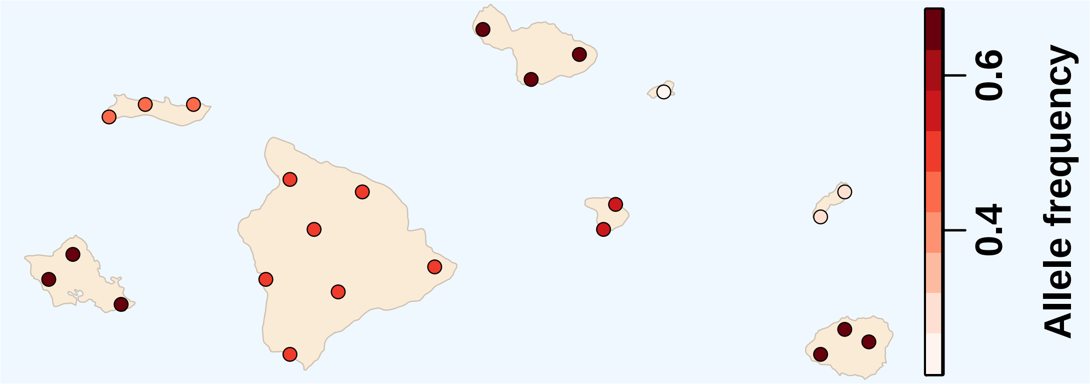


Illustration.

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

Here F_{ST} = 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):

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

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

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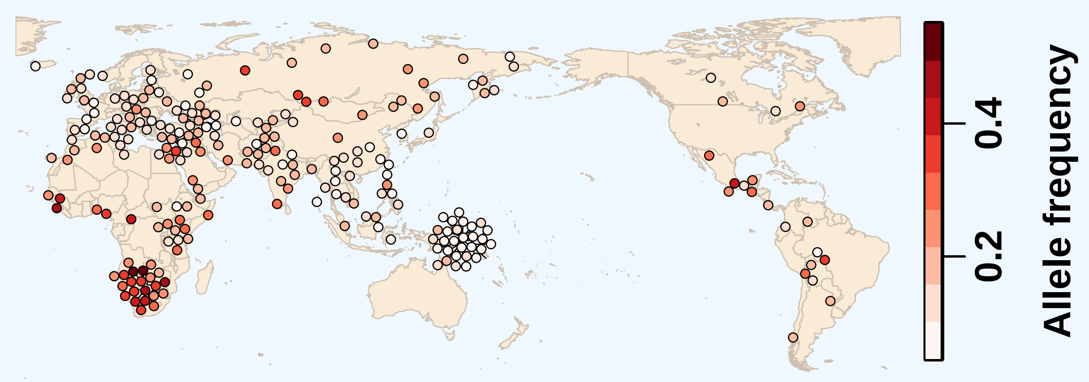
$$F_{\mathrm{ST}} = \sum_{j=1}^{n} w_j f_{L_j}^T.$$

Mean heterozygosity in a structured population:

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

F_{ST} measures population structure / differentiation



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

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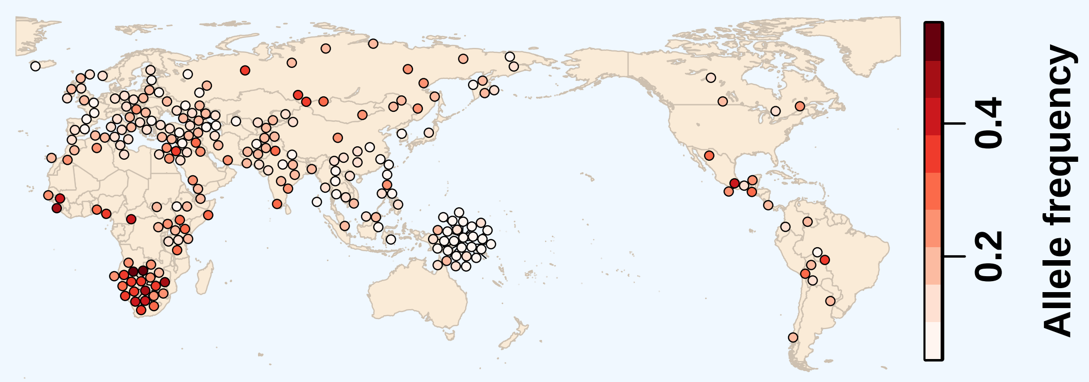

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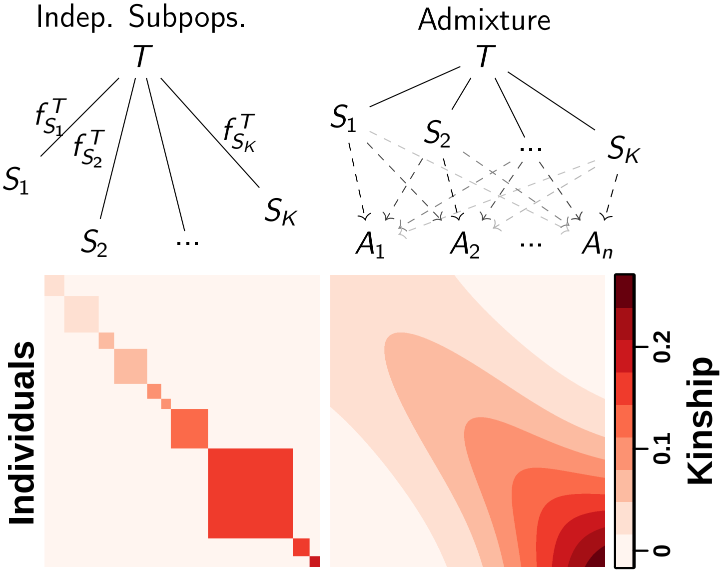
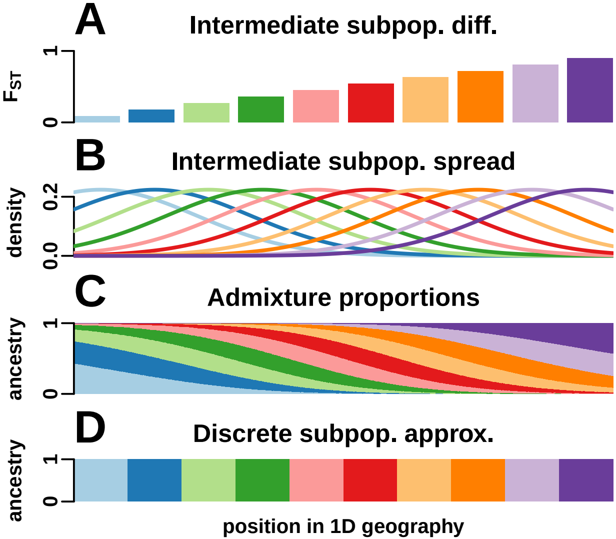
$\hat{F}_{\mathrm{ST}}^{\mathrm{WC}} \approx 0.0961$ using Weir-Cockerham estimator and $K = 244$.

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:

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

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 non-zero 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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(for independent individuals $\bar{\varphi}^T = \frac{1}{2n}(1 + F_{\mathrm{ST}})$. $\Rightarrow n_{\mathrm{Eff}} \approx 4$ in Human Origins!)

Therefore, 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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Bias varies by j, k:

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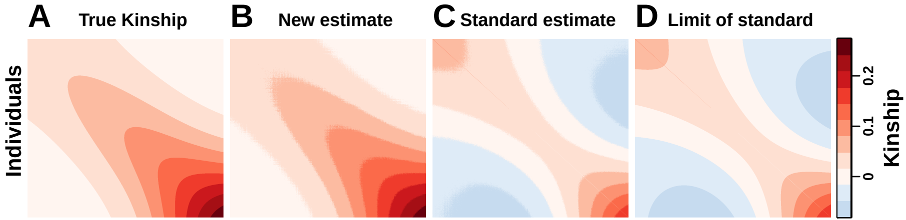

Our new estimator (R package ‘popkin’ on CRAN)

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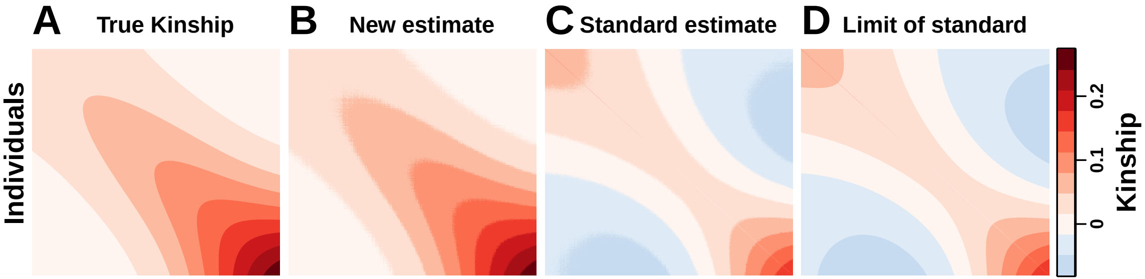
Step 2: Estimate minimum kinship, use to unbias “step 1” estimates.

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

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}):

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

$$\hat{p}_i^T = \frac{1}{n} \sum_{j=1}^{n} \pi_{ij}, \qquad \hat{\sigma}_i^2 = \frac{1}{n-1} \sum_{j=1}^{n} \left(\pi_{ij} - \hat{p}_i^T\right)^2.$$

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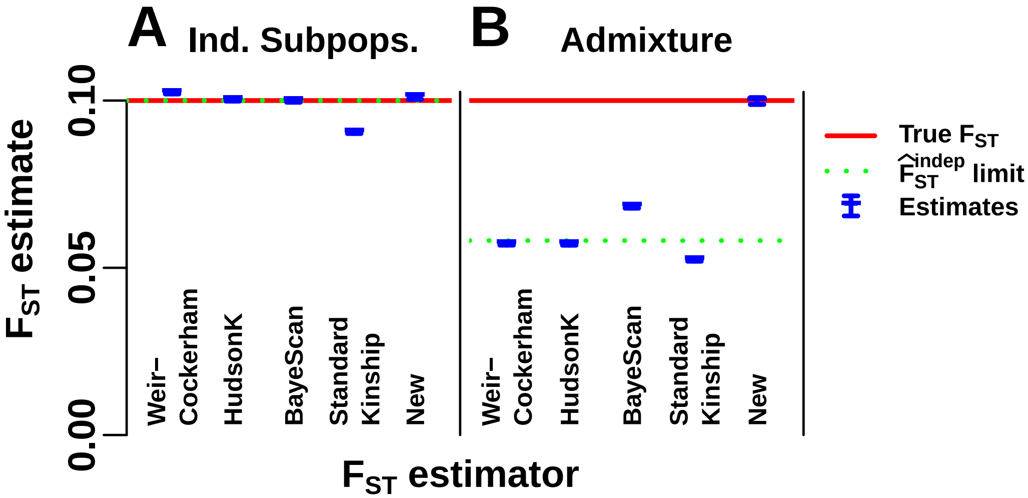
Estimator is biased in dependent subpopulations:

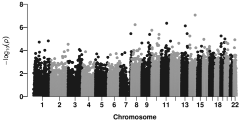
$$\hat{F}_{\text{ST}}^{\text{indep}} \xrightarrow[m\to\infty]{\text{a.s.}} \frac{F_{\text{ST}} - \frac{1}{n-1}\left(n\bar{\theta}^T - F_{\text{ST}}\right)}{1 - \frac{1}{n-1}\left(n\bar{\theta}^T - F_{\text{ST}}\right)}.$$

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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