Statistical models and methods for human genetic data

Alejandro Ochoa

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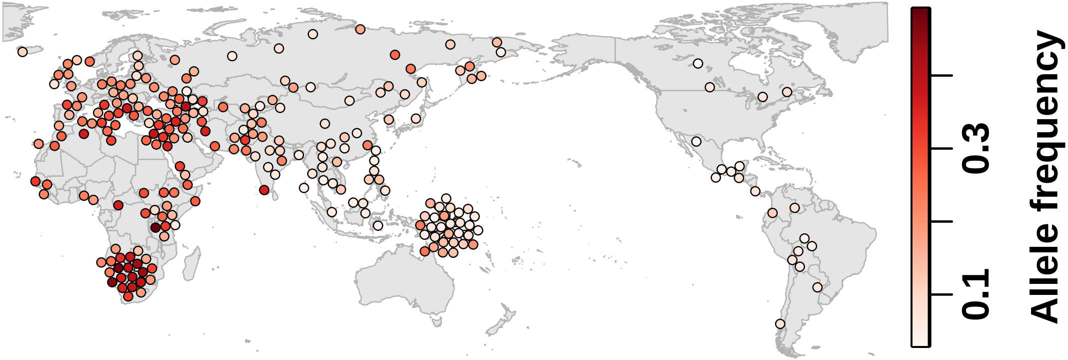
2021-03-10 — WSU Mathematics and Statistics

Human genetic structure



Ochoa and Storey (2019a) doi:10.1101/653279

rs17110306; median differentiation among loci with minor allele frequency $\geq$ 10%

Why? Migration and isolation, admixture, family structure

Overview

New population kinship and F_{ST} estimates

- Human Origins dataset
- Simulation validations

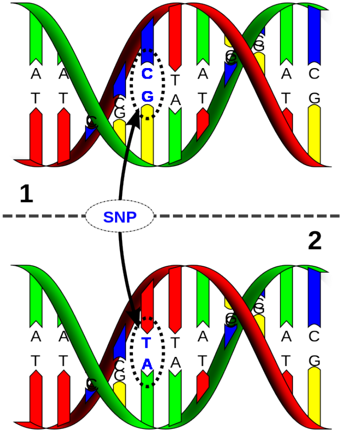
Genetic association models

- Robustness of PCA and LMM approaches
- Biases in heritability estimation
- LIGERA: Light Genetic Robust Association

Admixture model

- Hispanics in 1000 Genomes Project
- Joint inference of admixture and population history from genetic covariance

Single Nucleotide Polymorphism (SNP) data



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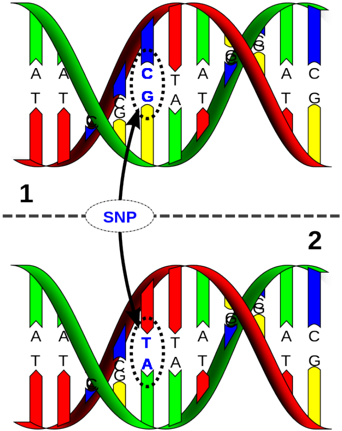

⇒

Genotype	x_{ij}
CC	0
CT	1
TT	2

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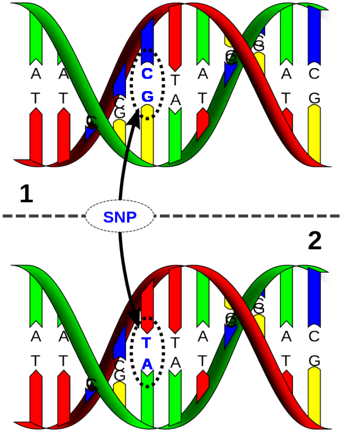

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Individuals

Loci

0 2 2 1 1 0 1
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2 ...

$\mathbf{X}$

Hardy-Weinberg Equillibrium (HWE): Binomial draws

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

p_i = frequency of reference allele at locus i.

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Under HWE:

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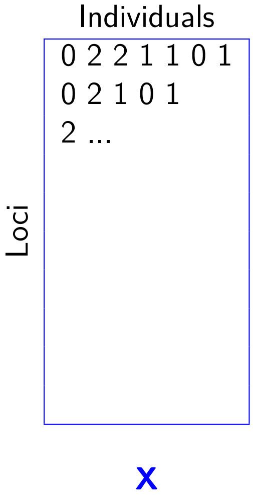
HWE not valid under genetic structure!

Goal: measure dependence structure of genotype matrix columns



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High-dimensional binomial data

- No general likelihood function
- My work: method of moments

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Relatedness / Population structure

- Dependence between individuals (columns)

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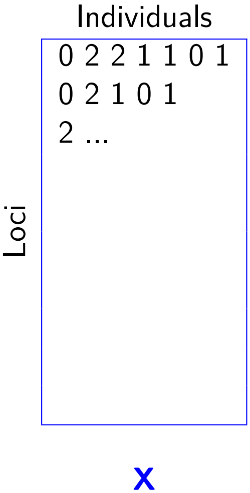
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Linkage disequilibrium

- Dependence between loci (rows)

Model parameters

IBD: “Identical By Descent” (given implicit ancestral pop.) — shared coin flips

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F_{ST}: **Fixation index**

Pr. that two random alleles in a **subpopulation** at a random locus are IBD

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New kinship estimator for general relatedness

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Kinship model for neutral genotypes $x_{ij} \in \{0, 1, 2\}$:

$$\mathrm{E}[x_{ij}] = 2p_i, \qquad \mathrm{Cov}(x_{ij}, x_{ik}) = 4p_i(1-p_i)\varphi_{jk}.$$

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Standard estimator is **biased**:

$$\hat{p}_i = \frac{1}{2n}\sum_{j=1}^{n} x_{ij}, \qquad \hat{\varphi}_{jk}^{\text{std}} = \frac{1}{m}\sum_{i=1}^{m} \frac{(x_{ij} - 2\hat{p}_i)(x_{ik} - 2\hat{p}_i)}{4\hat{p}_i(1 - \hat{p}_i)} \approx \frac{\varphi_{jk} - \bar{\varphi}_j - \bar{\varphi}_k + \bar{\varphi}}{1 - \bar{\varphi}}.$$

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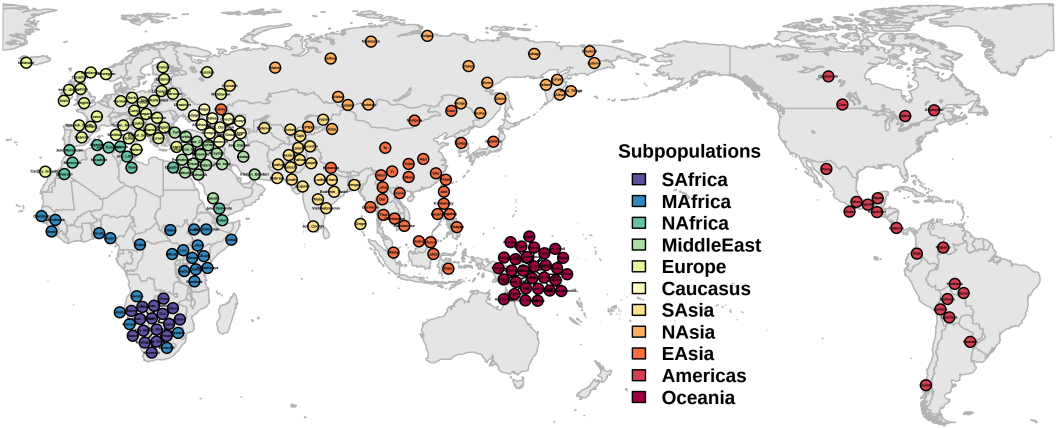
`popkin`: first unbiased kinship estimator! R package (Ochoa and Storey, 2021)

$$A_{jk} = \frac{1}{m}\sum_{i=1}^{m}(x_{ij} - 1)(x_{ik} - 1) - 1, \qquad \hat{A}_{\min} = \min_{u \neq v} \frac{1}{|S_u||S_v|}\sum_{j \in S_u}\sum_{k \in S_v} A_{jk},$$

$$\hat{\varphi}_{jk}^{\mathrm{new}} = 1 - \frac{A_{jk}}{\hat{A}_{\min}} \xrightarrow[m \to \infty]{\text{a.s.}} \varphi_{jk}.$$

https://github.com/StoreyLab/popkin

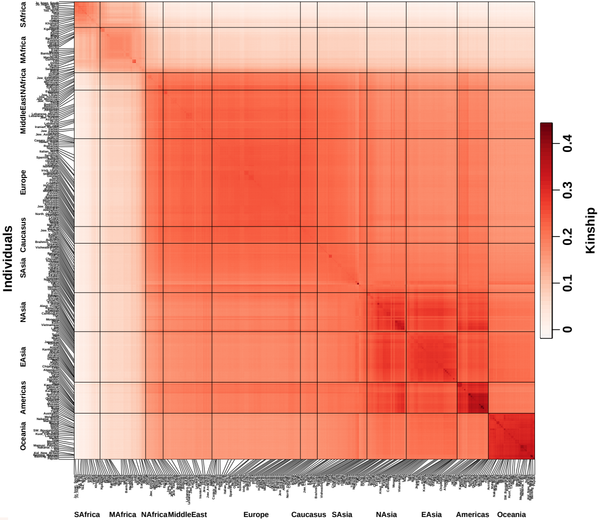
Dataset: Human Origins

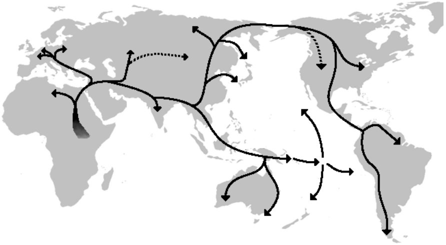


Lazaridis *et al.* (2014), (2016); Skoglund *et al.* (2016)

2,922 indivs. from 243 locs. — 588,091 loci — SNP chip

Kinship matrix of world-wide human population





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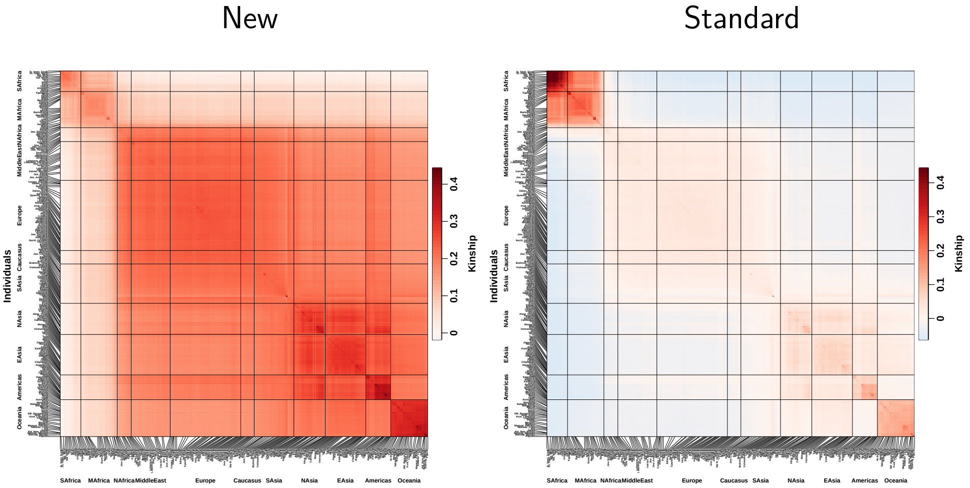
Standard kinship estimator is severely biased



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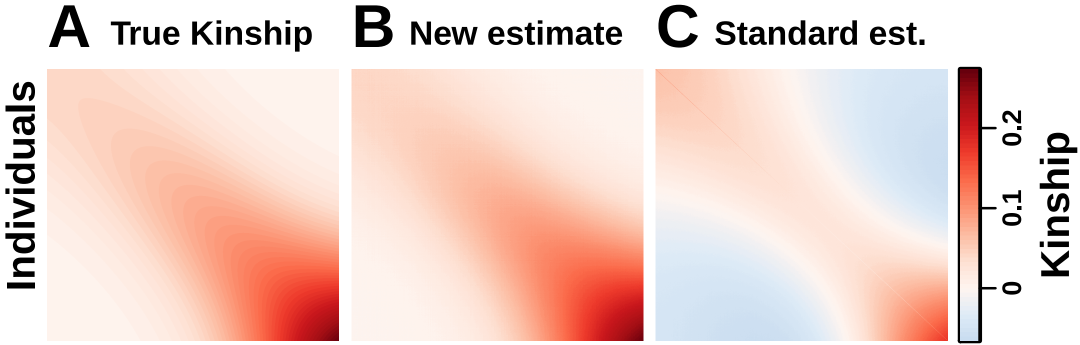
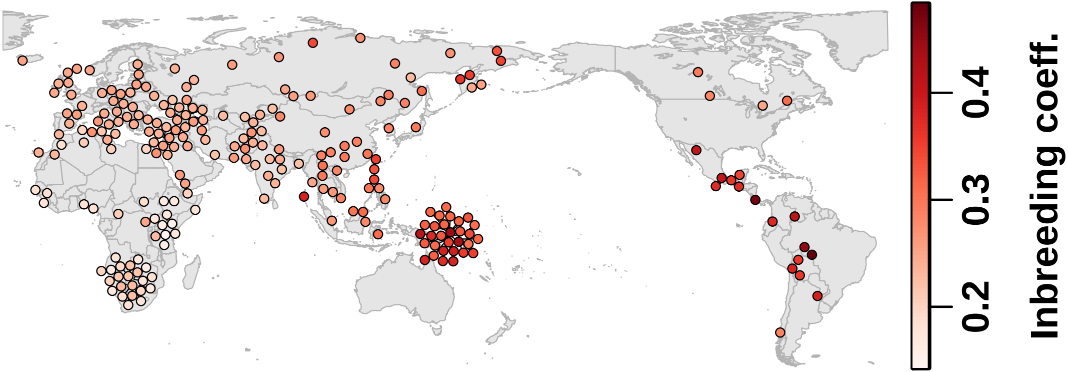
Validation in simulation



Ochoa and Storey (2021) doi:10.1371/journal.pgen.1009241

Population-level inbreeding increases with distance from Africa



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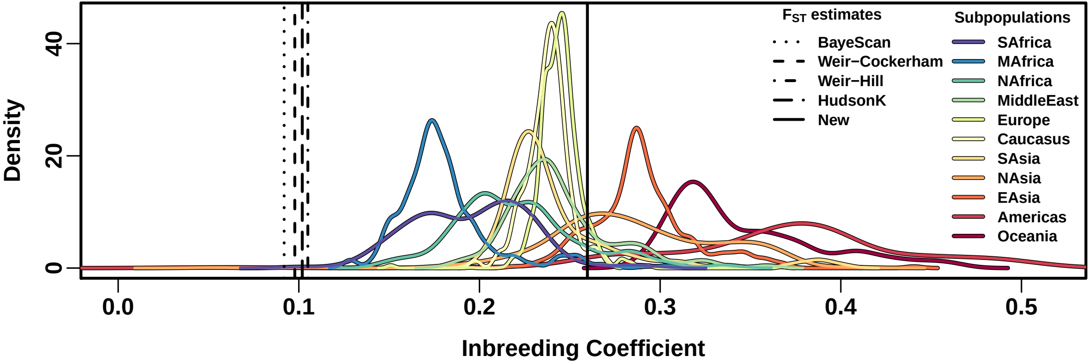
Differentiation (F_{ST}) previously underestimated



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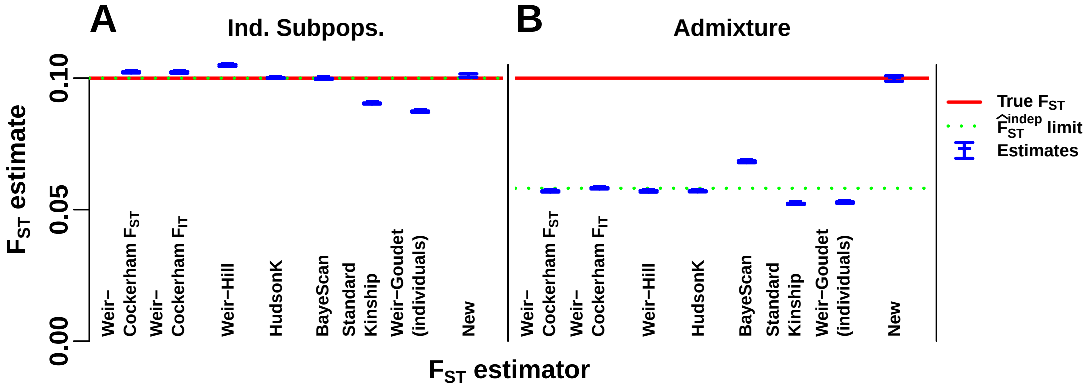

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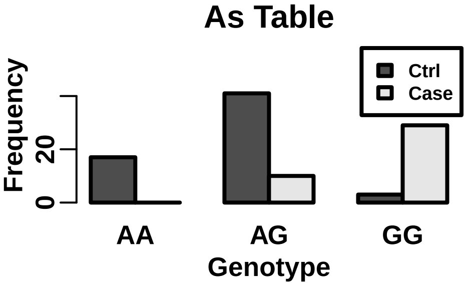

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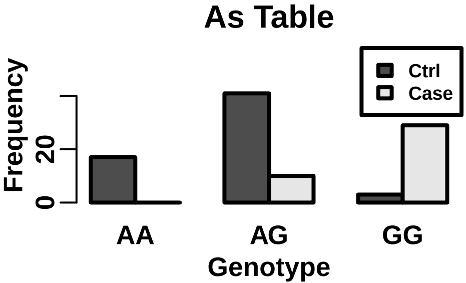

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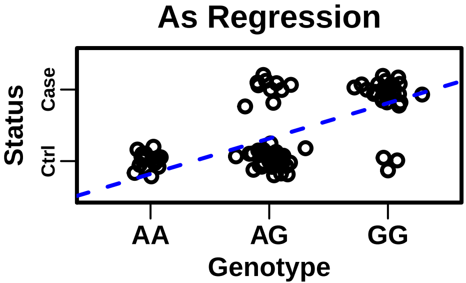

As Regression

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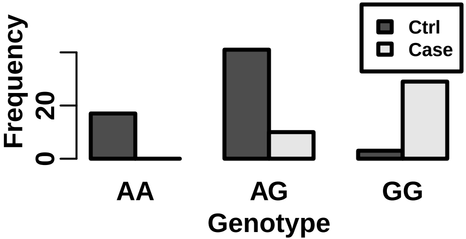

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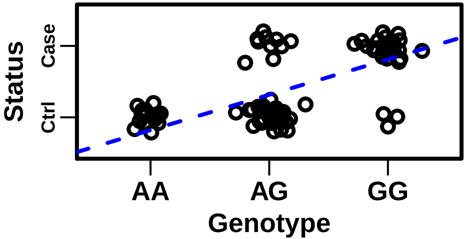
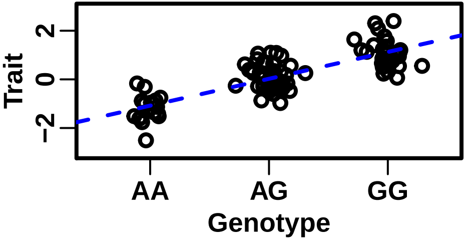


Continuous trait



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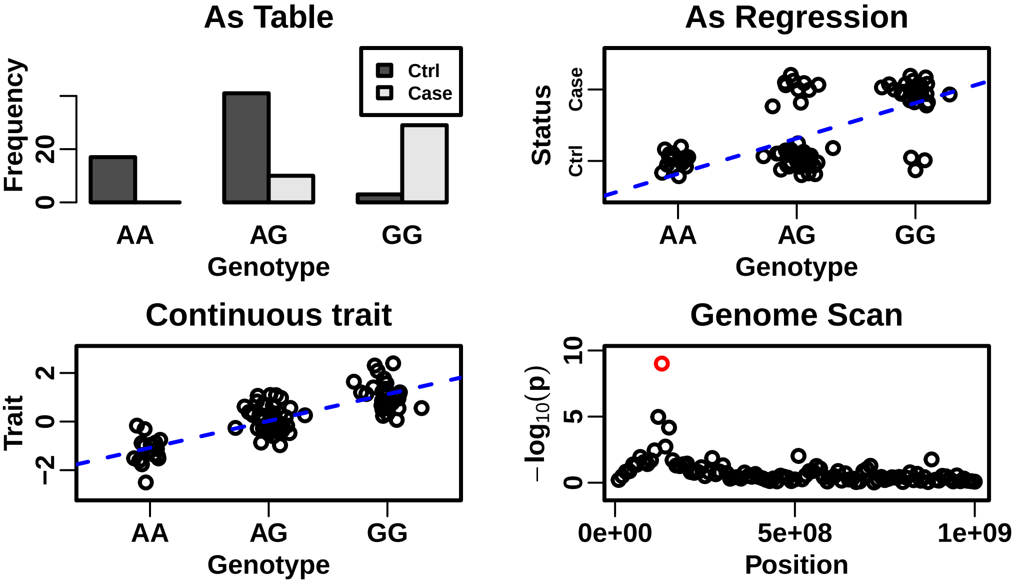

Why is this problem so hard?

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- Millions of tests
- Polygenicity
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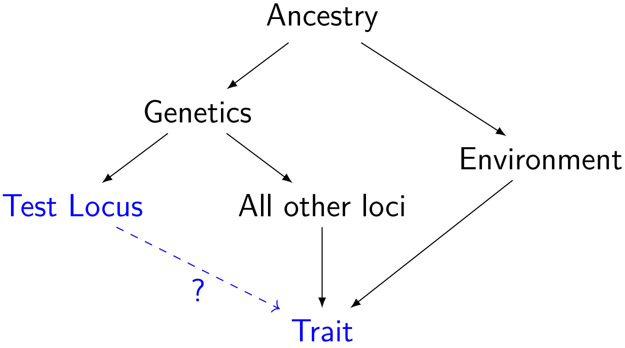
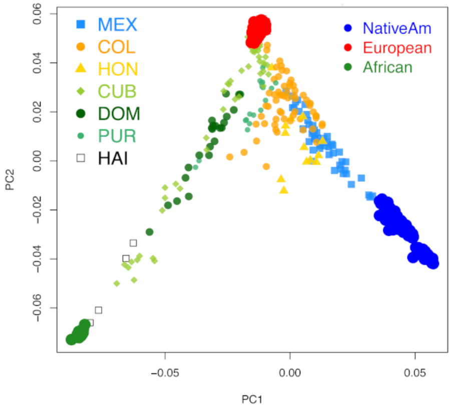


PCA: Principal Component Analysis



Moreno-Estrada *et al.* (2013)

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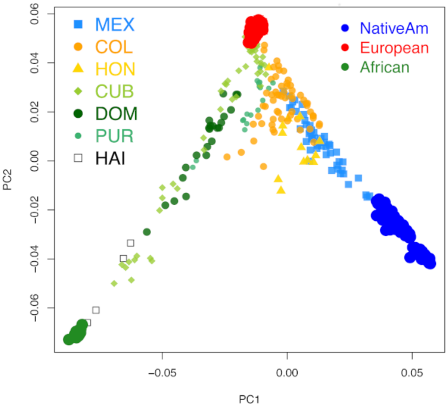

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PCs map to ancestry.

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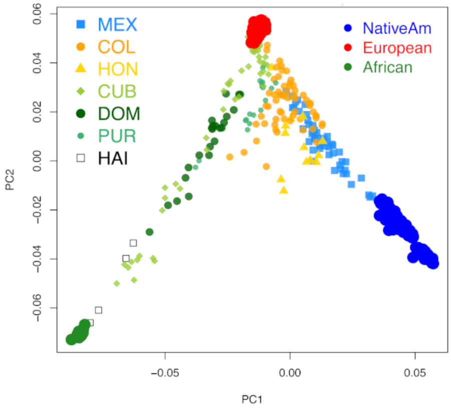

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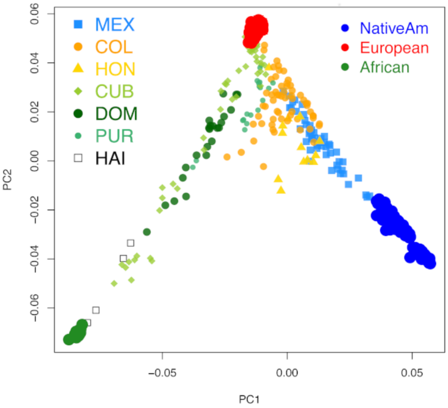

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Pros: Fast!

Cons: Fails on family data.

Genetic association methods: PCA and LMM

Principal components analysis (PCA) association model: fixed-effects regression:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{U}_d\gamma_d + \epsilon.$$

- $\mathbf{U}_d$ are top d eigenvectors of kinship matrix $\mathbf{\Phi}$.

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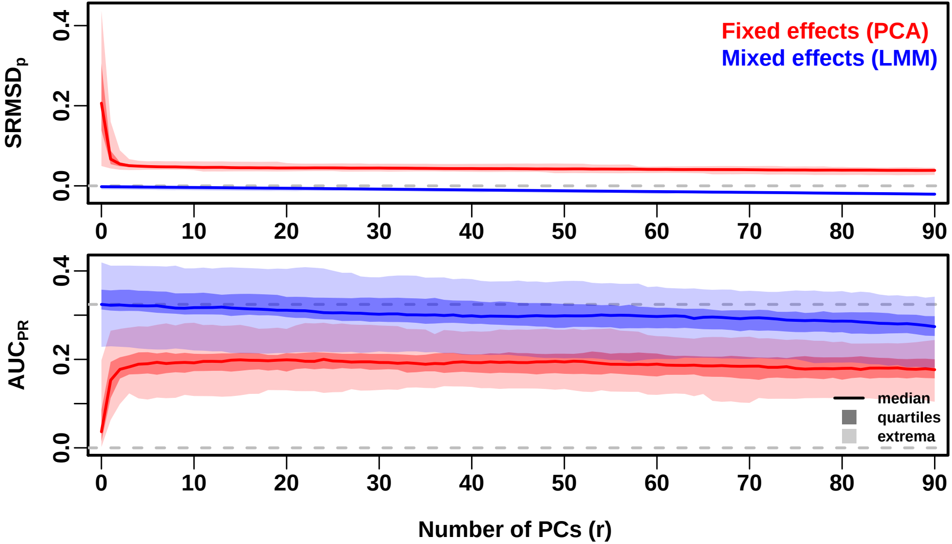
Linear mixed-effects model (LMM):

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{s} + \epsilon.$$

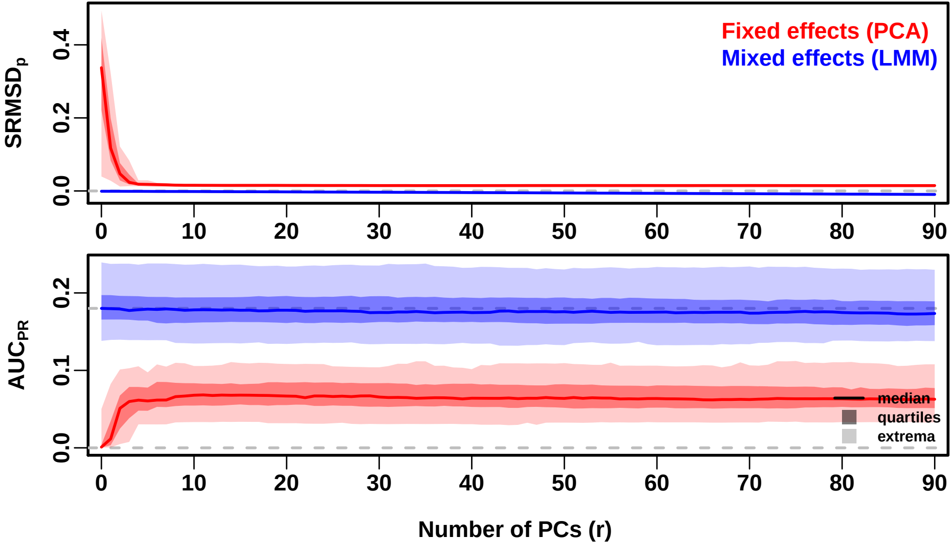
- Random effect has covariance structure from kinship matrix $\mathbf{\Phi}$:

$$\mathbf{s} \sim \text{Normal}\left(\mathbf{0}, \sigma^2\mathbf{\Phi}\right).$$

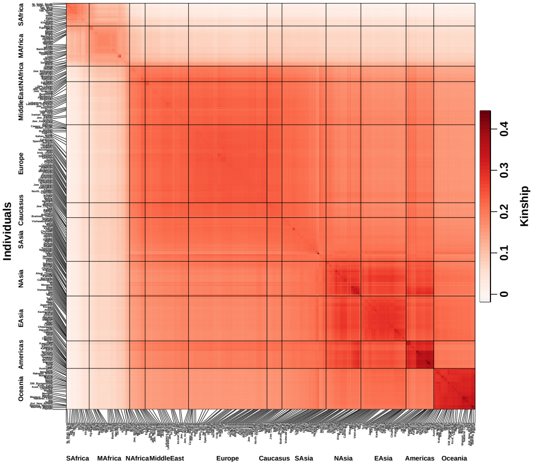
LMM outperforms PCA: Simulated admixture + family structure



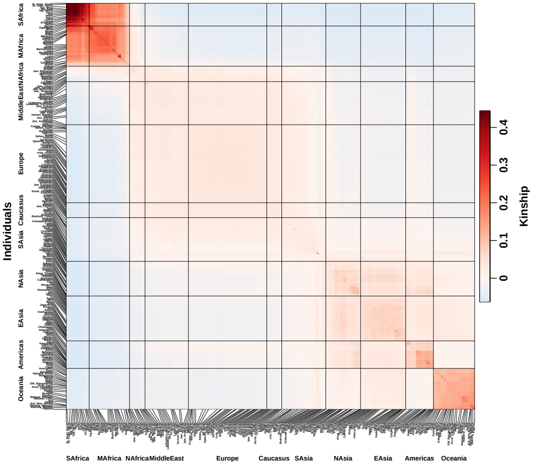
LMM outperforms PCA: 1000 Genomes Project + sim trait



Kinship bias does not affect genetic associations



New popkin
kinship estimator



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Standard kinship bias as a transformation of true kinship by centering:

$$\mathbf{\Phi}' = \frac{1}{1 - \bar{\varphi}}\mathbf{C}\mathbf{\Phi}\mathbf{C}.$$

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Matrix square root also centered:

$$(\mathbf{\Phi}')^{\frac{1}{2}} = \frac{1}{\sqrt{1 - \bar{\varphi}}}\mathbf{C}\mathbf{\Phi}^{\frac{1}{2}}.$$

Kinship bias does not affect genetic associations

LMM equivalent models:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{s} + \epsilon, \qquad \mathbf{s} \sim \text{Normal}\left(\mathbf{0}, \sigma^2\mathbf{\Phi}\right),$$

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Fit under true kinship ($\mathbf{\Phi}$) vs biased limit ($\mathbf{\Phi}'$) is equally good (algebra depends on centering matrix properties):

$$\begin{aligned} \mathbf{y} &= \mathbf{1}\alpha + \mathbf{x}_i\beta + \sigma \mathbf{\Phi}^{\frac{1}{2}} \mathbf{r} + \epsilon \\ &= \mathbf{1}\alpha' + \mathbf{x}_i\beta' + \sigma' \left(\mathbf{\Phi}'\right)^{\frac{1}{2}} \mathbf{r}' + \epsilon', \end{aligned}$$

$$\beta' = \beta, \quad \epsilon' = \epsilon, \quad \mathbf{r}' = \mathbf{r}, \quad \sigma' = \sigma\sqrt{1 - \bar{\varphi}}, \quad \alpha' = \alpha + \sigma \frac{1}{n} \mathbf{1}^\intercal \mathbf{\Phi}^{\frac{1}{2}} \mathbf{r}.$$

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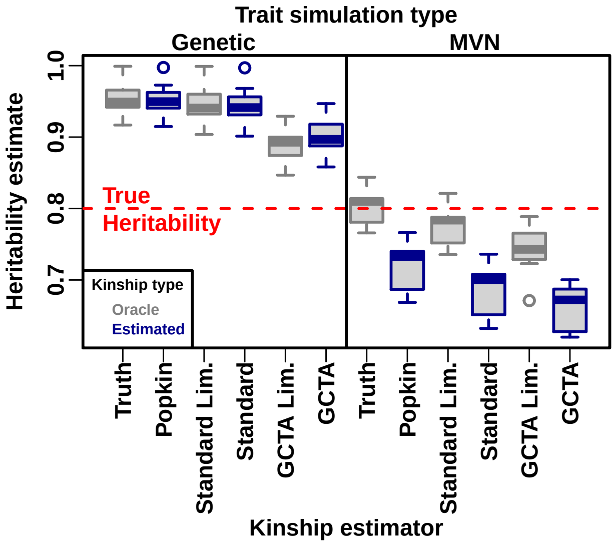
Similar argument holds approximately for PCA regression.

Kinship bias affects heritability estimation



Future work: Tuning elastic nets for genetic association

$$\hat{\beta} \equiv \underset{\beta}{\mathbf{argmin}}(\|y - X\beta\|^2 + \lambda_2\|\beta\|^2 + \lambda_1\|\beta\|_1).$$

- Validate existing PCA extension
- How to model higher-dimensional relatedness?

Genetic association models: forward vs reversed

(Forward) linear mixed-effects model	Reverse model

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$\mathbf{y} = \alpha_i + \mathbf{x}_i \beta_i + \mathbf{F}\gamma_i + \mathbf{r}_i$	

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Models trait (complicated, unknowns)	

Genetic association models: forward vs reversed

(Forward) linear mixed-effects model	Reverse model
$\mathbf{y} = \alpha_i + \mathbf{x}_i \beta_i + \mathbf{F}\gamma_i + \mathbf{r}_i$	$\mathbf{x}_i = \alpha'_i + \mathbf{y}\beta'_i + \epsilon'_i$
Models trait (complicated, unknowns)	Models genotype (kinship).

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Random effects are slow!	Fast!

LIGERA: light genetic robust association

Objective function: move genetic structure to residuals:

$$G = \left(\mathbf{Y} \beta_i - \mathbf{x}_i \right)^\intercal \mathbf{\Phi}^{-1} \left(\mathbf{Y} \beta_i - \mathbf{x}_i \right).$$

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Variance under null hypothesis has closed form:

$$\mathrm{Cov}\left(\hat{\beta}_i \middle| \mathbf{Y}\right) = 4p_i\left(1 - p_i\right)\left(\mathbf{H}^\intercal \mathbf{\Phi} \mathbf{H}\right), \qquad \left(\mathbf{H}^\intercal \mathbf{\Phi} \mathbf{H}\right) = \left(\mathbf{Y}^\intercal \mathbf{\Phi}^{-1}\mathbf{Y}\right)^{-1}.$$

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This is fast! Bottleneck is calculating $\mathbf{\Phi}^{-1}\mathbf{Y}$.
Solve efficiently with “conjugate gradient” algorithm!

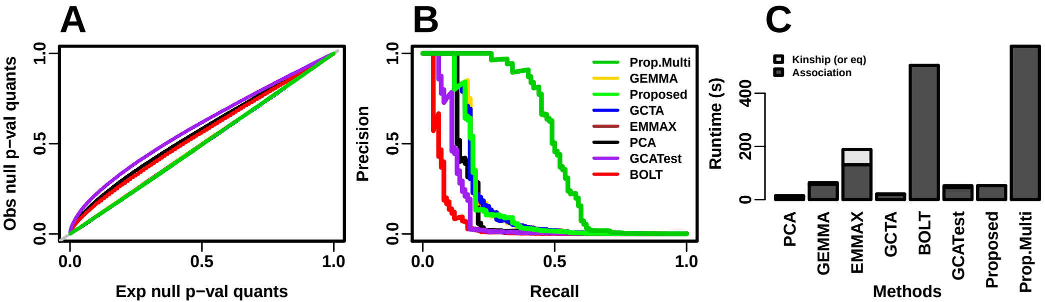
LIGERA: light genetic robust association

“Multiscan”: forward variable selection.

At each iteration:

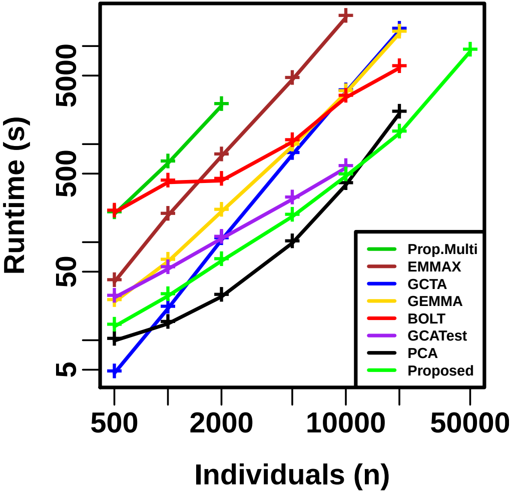
- Calculate p-values
- Estimate q-values
- Select all loci with $q < 0.05$, add as covariates in following iteration
- Stop if no new loci are selected.

LIGERA: light genetic robust association



- Control of type-I error
- Increased power with multiscan
- Great runtime for single scan (enables multiscan)

LIGERA: light genetic robust association: scalability



Overview

New population kinship and F_{ST} estimates

- Human Origins dataset
- Simulation validations

Genetic association models

- Robustness of PCA and LMM approaches
- Biases in heritability estimation
- LIGERA: Light Genetic Robust Association

Admixture model

- Hispanics in 1000 Genomes Project
- Joint inference of admixture and population history from genetic covariance

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