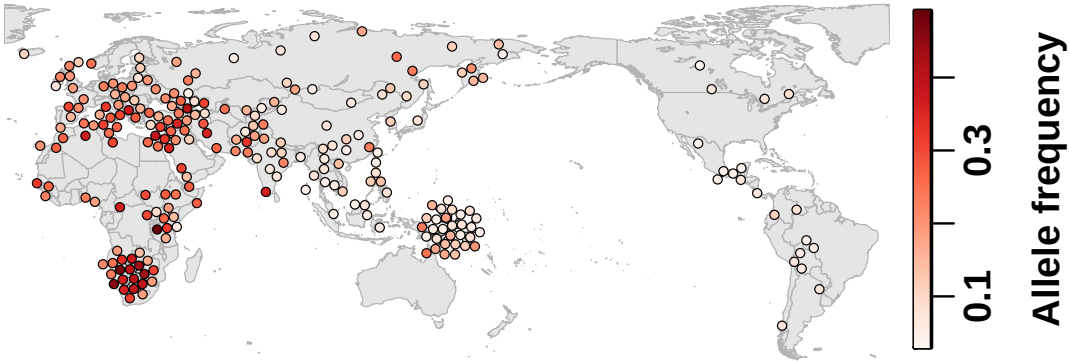
Statistical Genetics Research: Kinship, Bias, Admixture

Alejandro Ochoa

StatGen, Biostatistics & Bioinformatics — Duke University

2022-06-11 — UPGG retreat

Human genetic structure

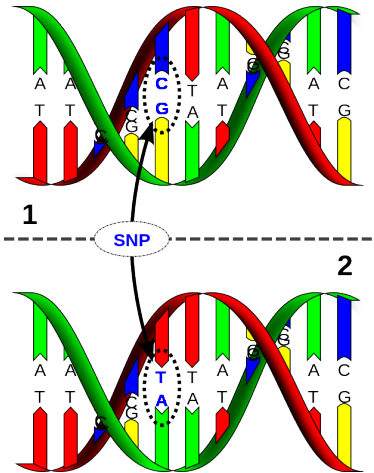


Ochoa and Storey (2019a) doi:10.1101/653279

rs17110306; median differentiation given MAF $\geq 10\%$

Why? Migration and isolation, admixture, family structure

Single Nucleotide Polymorphism (SNP) data



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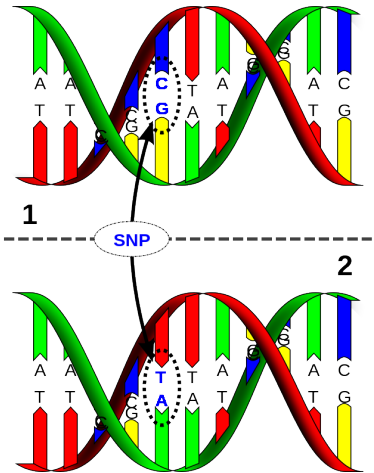

$\Rightarrow$

Genotype	x_{ij}
CC	0
CT	1
TT	2

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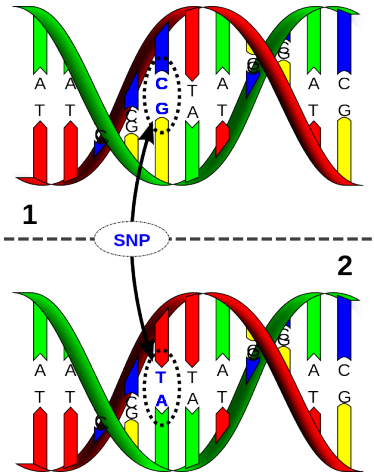

$\Rightarrow$

Genotype	x_{ij}
CC	0
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$\Rightarrow$

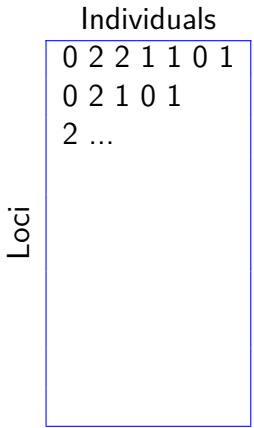
Individuals

Loci

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

$\mathbf{X}$

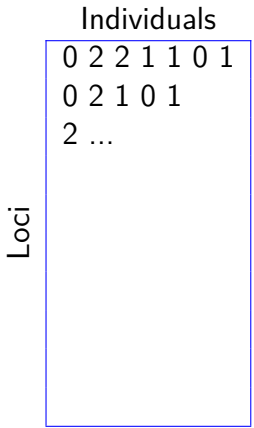
Dependence structure of genotype matrix



High-dimensional binomial data

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

Dependence structure of genotype matrix



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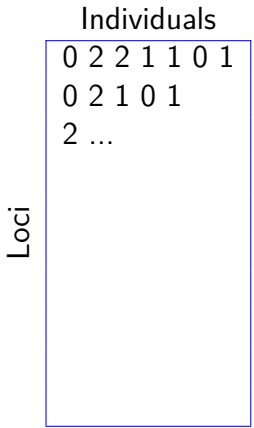
Relatedness / Population structure

- Dependence between individuals (columns)

Dependence structure of genotype matrix



High-dimensional binomial data

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

Relatedness / Population structure

- Dependence between individuals (columns)

Linkage disequilibrium

- Dependence between loci (rows)

New kinship/GRM estimator for general relatedness

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

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

New kinship/GRM estimator for general relatedness

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Standard estimator is **biased**:

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

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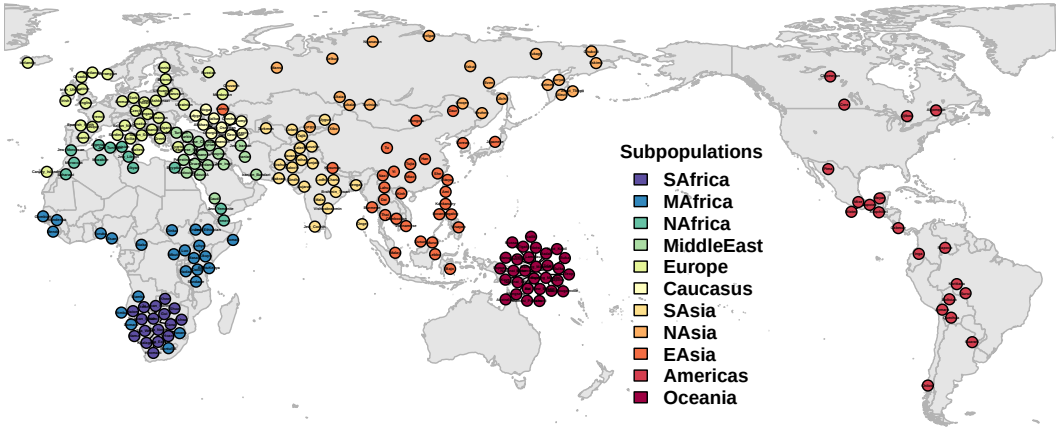
popkin: first unbiased kinship estimator! R package (Ochoa and Storey, 2021)

$$A_{jk} = \frac{1}{m}\sum_{i=1}^{m}(x_{ij} - 1)(x_{ik} - 1) - 1, \qquad \hat{\varphi}_{jk}^{\text{new}} = 1 - \frac{A_{jk}}{\hat{A}_{\text{min}}} \xrightarrow[m\to\infty]{\text{a.s.}} \varphi_{jk}.$$

https://github.com/StoreyLab/popkin

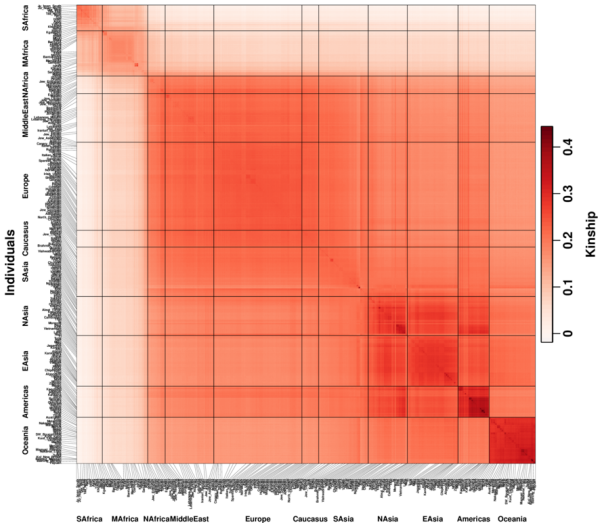
Dataset: Human Origins

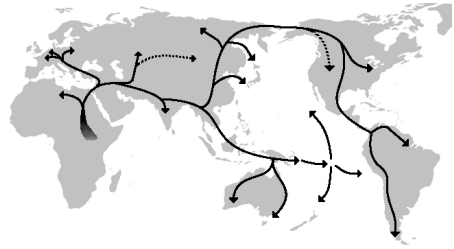


Lazaridis *et al.* (2014), (2016); Skoglund *et al.* (2016)

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

Kinship matrix of world-wide human population

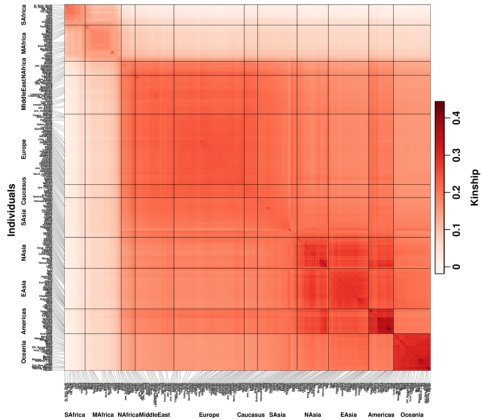




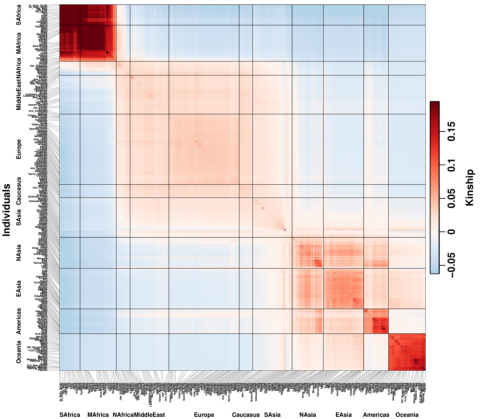
Ochoa and Storey (2019) doi:10.1101/653279

Standard kinship estimator is severely biased

New



Standard



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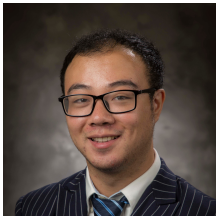
Kinship bias: Consequences? Applications?

- Genetic association studies
- Heritability estimation
- Admixture inference

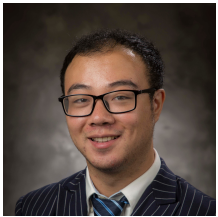
PCA vs LMM in association



Yiqi Yao
MB 2020

BenHealth
Shanghai

PCA vs LMM in association



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Association with Principal Components Analysis (PCA) and Linear Mixed-effects Model (LMM):

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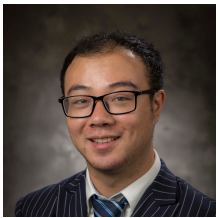

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Association with Principal Components Analysis (PCA) and Linear Mixed-effects Model (LMM):

$$\text{PCA}: \quad \mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{U}_d\gamma_d + \epsilon,$$

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

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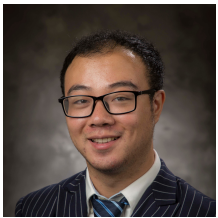

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$\mathbf{U}_d$ are top d eigenvectors of kinship matrix Φ.

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

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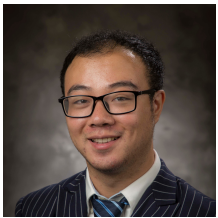

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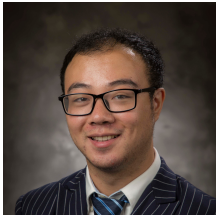
- PCA is faster but low-dimensional
- LMM is slower but can model families

Yao and Ochoa (2022) doi:10.1101/2022.03.25.485885

PCA < LMM in association for real datasets



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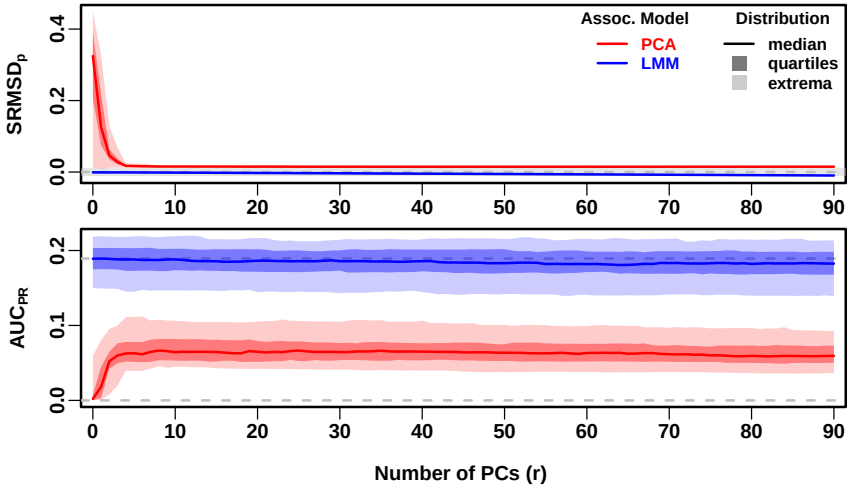
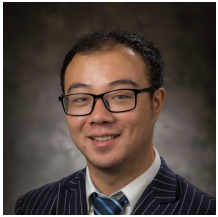


1000 Genomes Project

Yao and Ochoa (2022) doi:10.1101/2022.03.25.485885

Numerous distant relatives in real datasets



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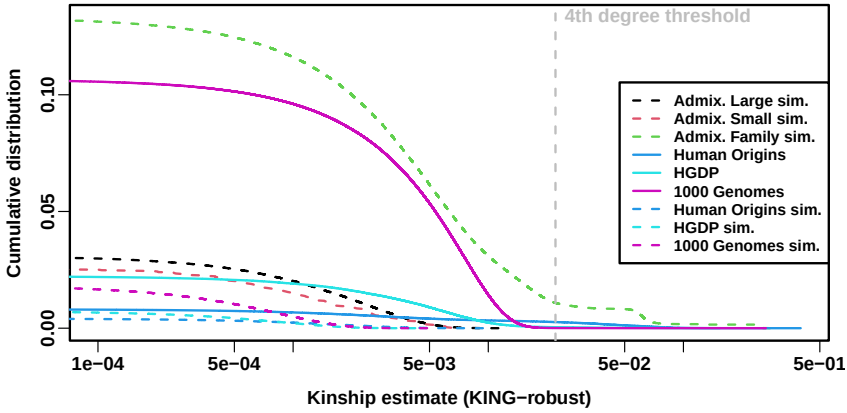

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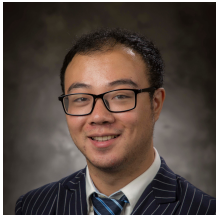
Numerous distant relatives in real datasets explain PCA < LMM



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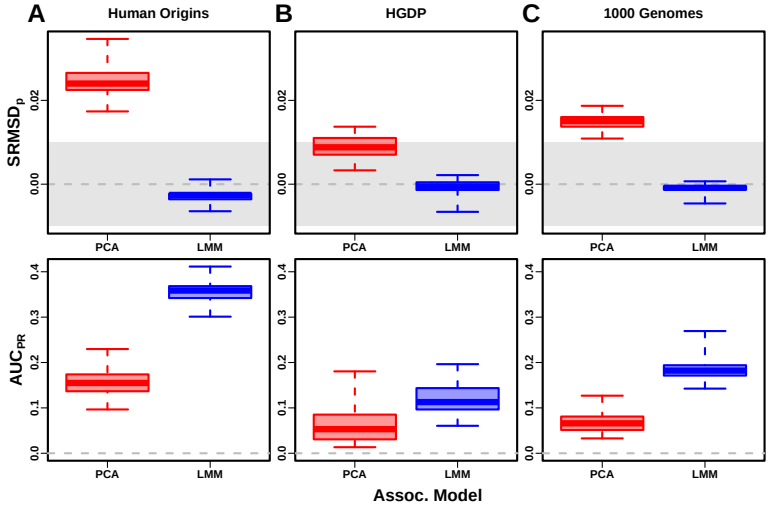

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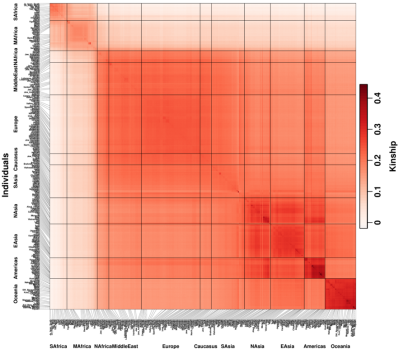
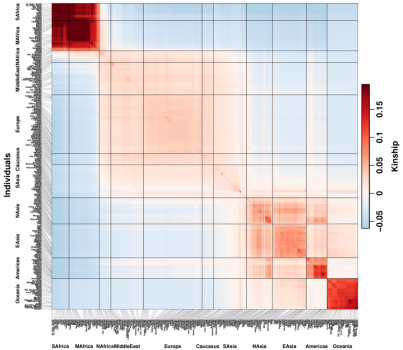
Kinship bias does not affect genetic associations

Zhuoran Hou
MB 2021

Now: B&B PhD student



New popkin kinship estimator



Standard kinship estimator

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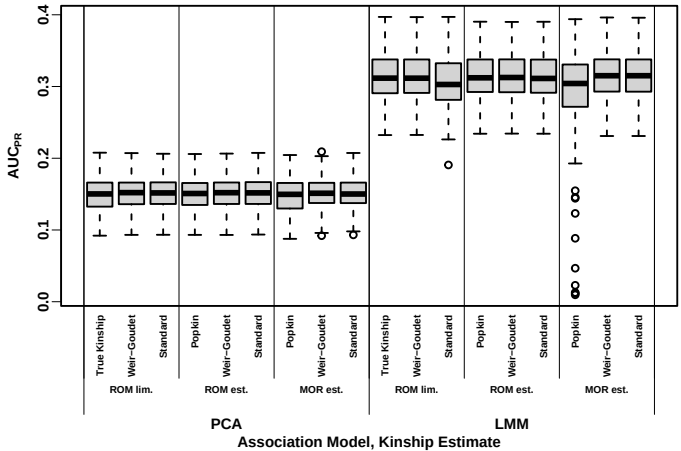
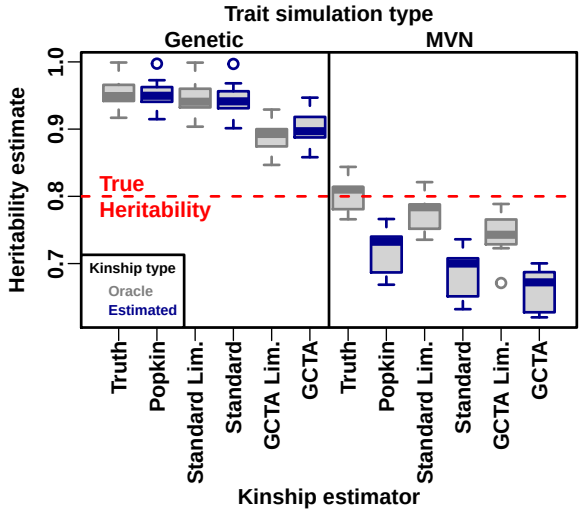


Kinship bias doesn't matter? Proved with linear algebra!

Kinship bias affects heritability estimation

Zhuoran Hou
MB 2021

Now: B&B PhD student



Nephrotic Syndrome association study

Tiffany Tu
CBB PhD student

With
Gbadegesin lab
(Pediatrics)

Severe pediatric kidney disease. 1000 cases/1000 controls; multiethnic; LMM association

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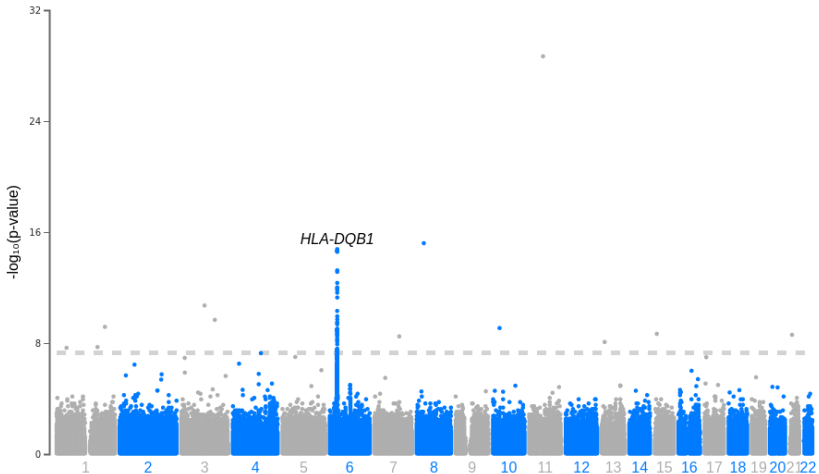

LIGERA: light genetic robust association

Tiffany Tu
CBB PhD
student

- Enabled by unbiased kinship
- Like LMM but reverses trait and genotype
  - Faster by avoiding costly “variant component” fitting

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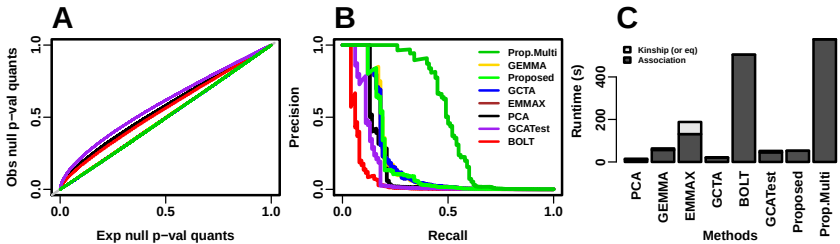

- Control of type-I error
- Increased power with multiscan: polygenic model!

LIGERA: light genetic robust association: scalability

Tiffany Tu
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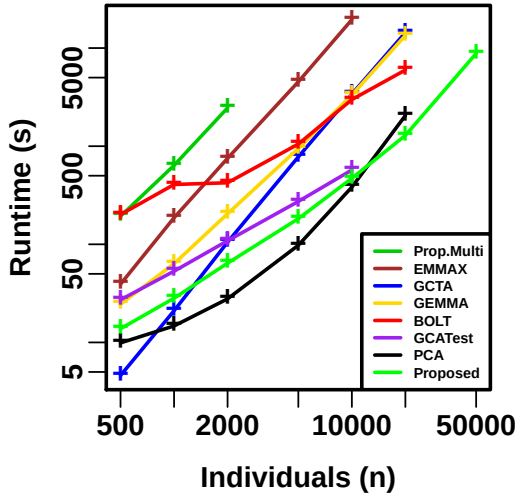
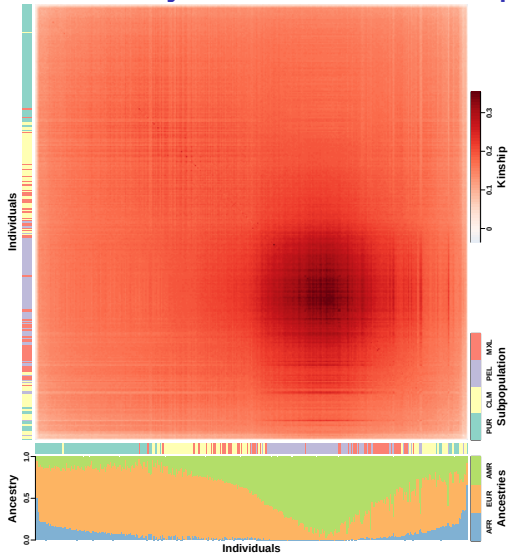


Population kinship driven by admixture in Hispanics



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Kinship under the admixture model

Amika Sood
Postdoc

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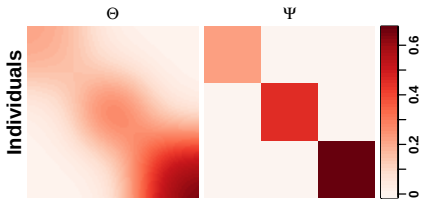

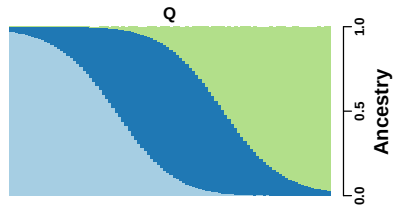

Kinship under the admixture model

Amika Sood
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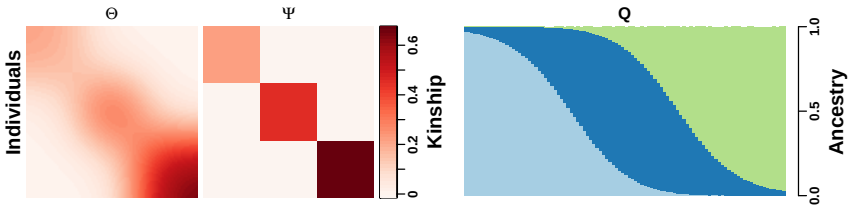
UGA



$$\Theta = \mathbf{Q}\Psi\mathbf{Q}^\top$$

(Only for unbiased kinship)

Kinship under the admixture model

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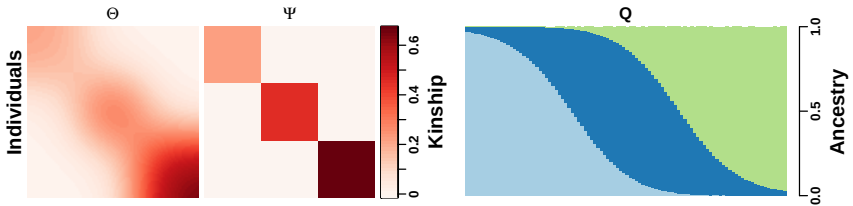

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(Only for unbiased kinship)

Can we reverse this formula?

AdmixCor: accuracy

Amika Sood
Postdoc

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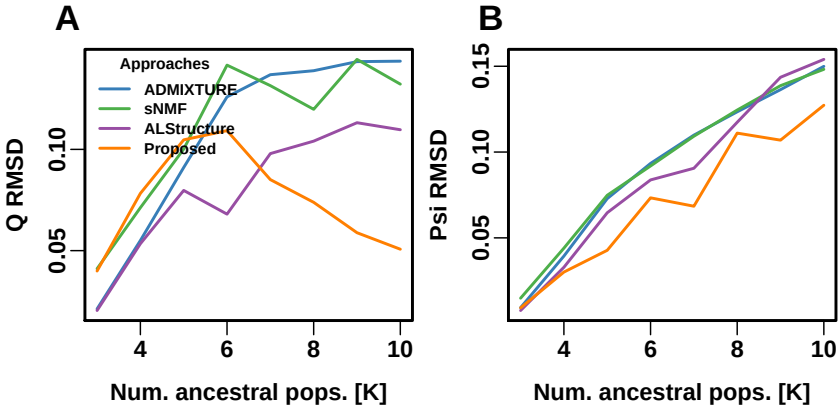
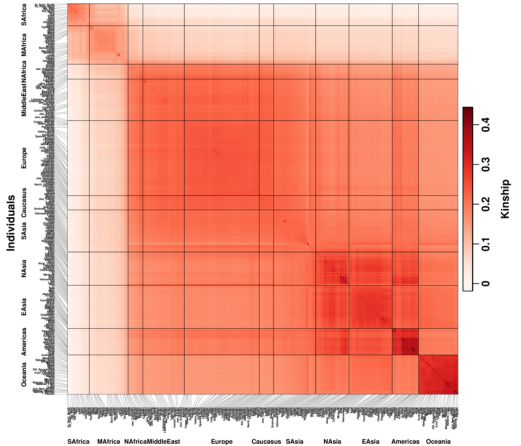
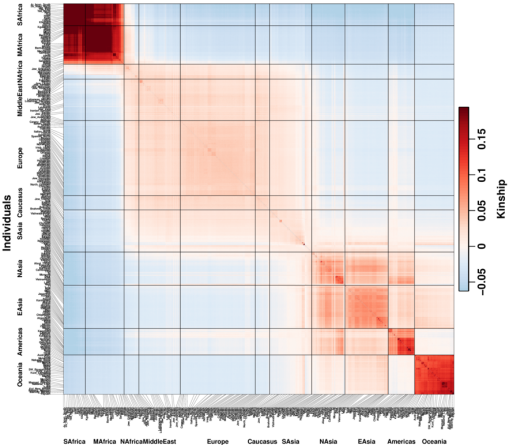
UGA



Unbiased kinship estimates: new models, opportunities



New "popkin"
kinship estimator



Biased "standard"
kinship estimator

Acknowledgments

Ochoa Lab
Amika Sood
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Emmanuel Mokel
RP Pornmongkolsuk

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Duke University
Rasheed Gbadegesin
Kouros Owzar
Beth Hauser
Yi-Ju Li
Andrew Allen
Amy Goldberg

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Whitehead Scholars

Duke Center for Statistical Genetics and Genomics
Department of Biostatistics & Bioinformatics
Duke University School of Medicine

DrAlexOchoa
ochoalab.github.io
alejandro.ochoa@duke.edu