Statistical Genetics Research: Kinship, Bias, Admixture

Alejandro Ochoa

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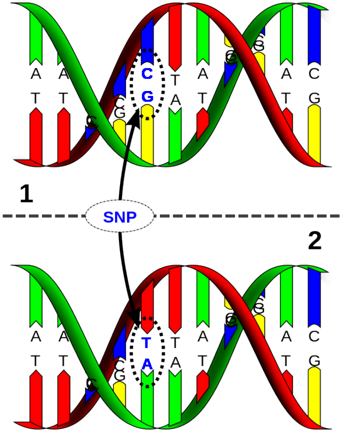
2021-08-19 — B&B Orientation

Single Nucleotide Polymorphism (SNP) data



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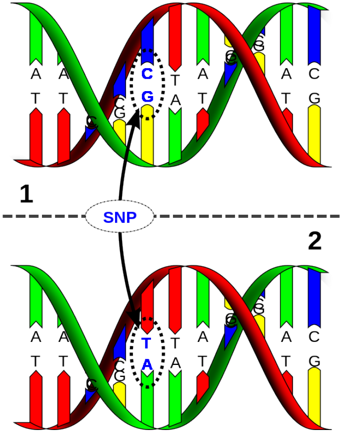

⇒

Genotype	x_{ij}
C/C	0
C/T	1
T/T	2

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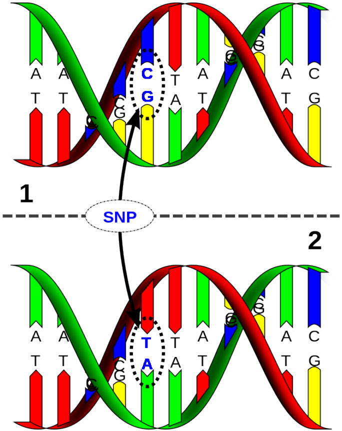

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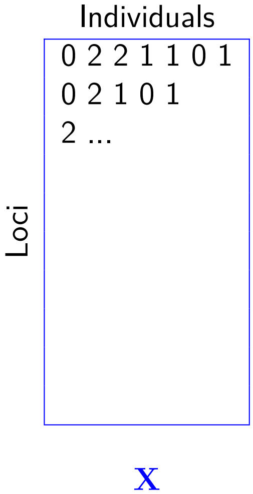
Individuals

Loci

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

$\mathbf{X}$

Dependence structure of genotype matrix



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0 2 2 1 1 0 1

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Loci

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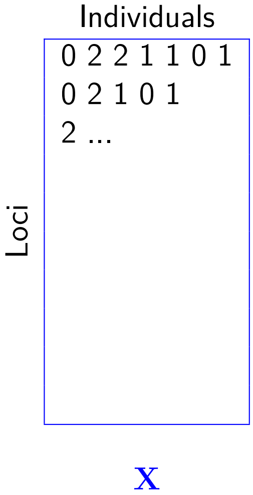
High-dimensional binomial data

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

Dependence structure of genotype matrix



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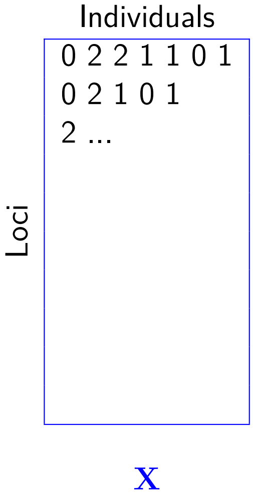
Relatedness / Population structure

- Dependence between individuals (columns)

Dependence structure of genotype matrix



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$\mathbf{X}$

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Relatedness / Population structure

- Dependence between individuals (columns)

Linkage disequilibrium

- Dependence between loci (rows)

New kinship estimator for general relatedness

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

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

New kinship estimator for general relatedness

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Standard estimator is **biased**:

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

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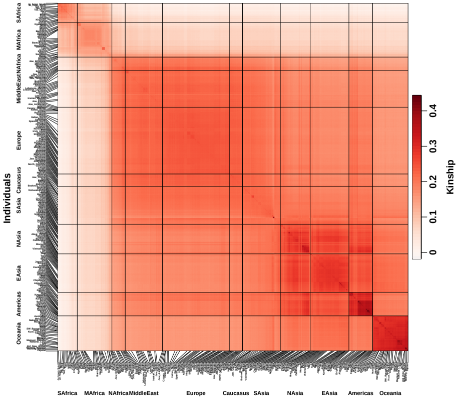
`popkin`: first unbiased kinship estimator! R package (Ochoa and Storey, 2021)

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

https://github.com/StoreyLab/popkin

Kinship bias: Consequences? Applications?



New "popkin"
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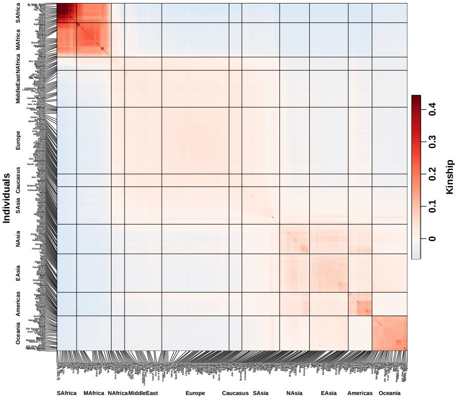
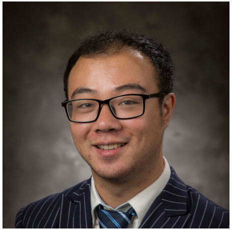


Biased "standard"
kinship estimator

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

Principal components vs mixed effects in genetic association



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MB 2020

BenHealth
Shanghai

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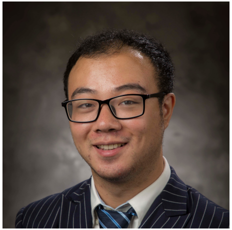

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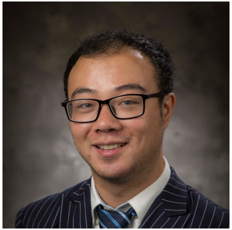
Association with Principal Components Analysis (PCA) and Linear Mixed-effects Model (LMM):

Principal components vs mixed effects in genetic association



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

$$\begin{aligned} \text{PCA}: \quad & \mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{U}_d\boldsymbol{\gamma}_d + \epsilon, \\ \text{LMM}: \quad & \mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{s} + \epsilon. \end{aligned}$$

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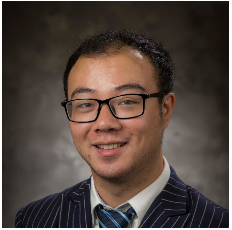

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$\mathbf{U}_d$ are top d eigenvectors of kinship matrix Φ.

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

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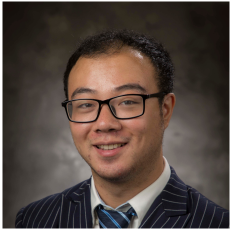

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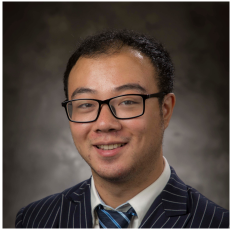
- PCA is faster but low-dimensional
- LMM is slower but can model families
- Both depend on estimated kinship matrix

Principal components vs mixed effects in genetic association



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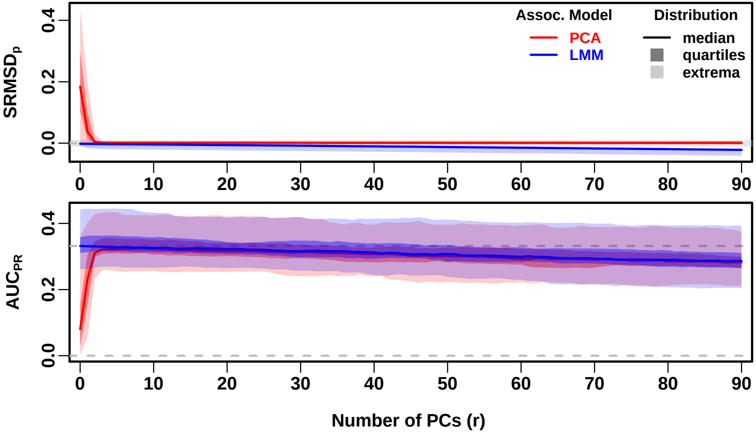
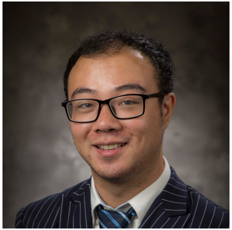


Simulated admixed individuals

Principal components vs mixed effects in genetic association



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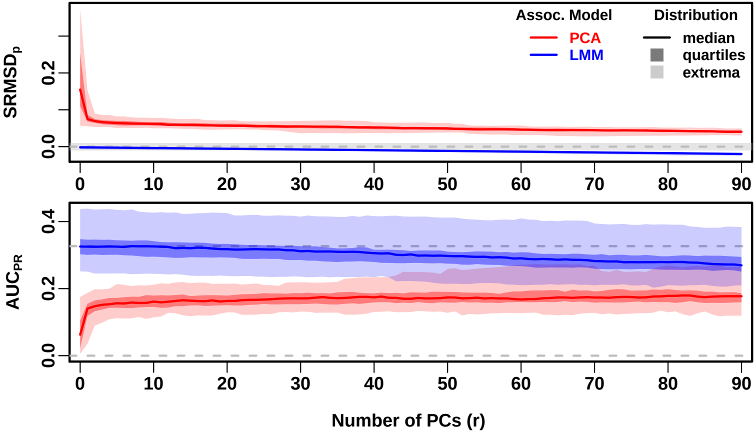
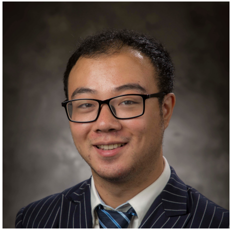


Simulated admixed family

Principal components vs mixed effects in genetic association



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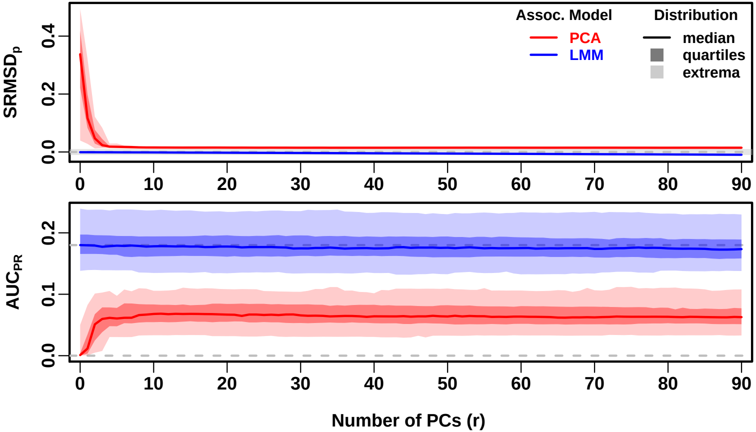

1000 Genomes Project

Kinship bias does not affect genetic associations

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MB 2021

Now: B&B PhD

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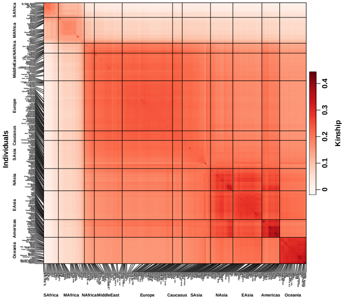
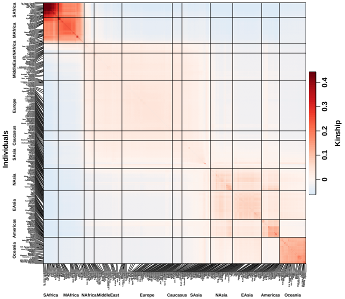


New popkin
kinship estimator



Standard
kinship estimator

Kinship bias does not affect genetic associations

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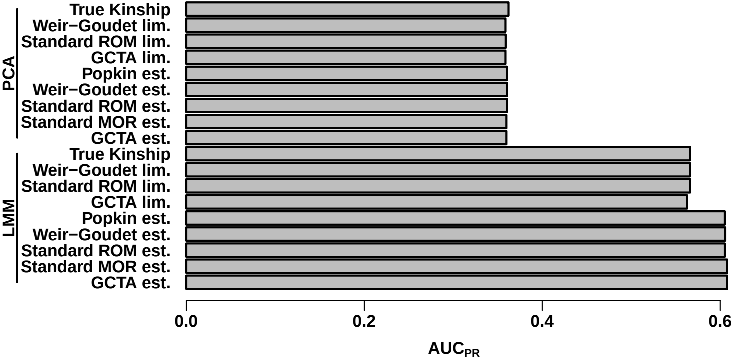

Kinship bias doesn't matter?

Kinship bias does not affect genetic associations

Zhuoran Hou
MB 2021

Now: B&B PhD

Proved with linear algebra!

$$\Phi' = \frac{1}{1-\bar{\varphi}} \mathbf{C} \Phi \mathbf{C}, \qquad \mathbf{C} = \mathbf{I} - \frac{1}{n}\mathbf{J}.$$

Kinship bias does not affect genetic associations

Zhuoran Hou
MB 2021

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$$\Phi' = \frac{1}{1 - \bar{\varphi}} \mathbf{C} \Phi \mathbf{C}, \qquad \mathbf{C} = \mathbf{I} - \frac{1}{n} \mathbf{J}.$$

In LMM and PCA, the bias is compensated by the scale and intercept coefficients:

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

Kinship bias affects heritability estimation

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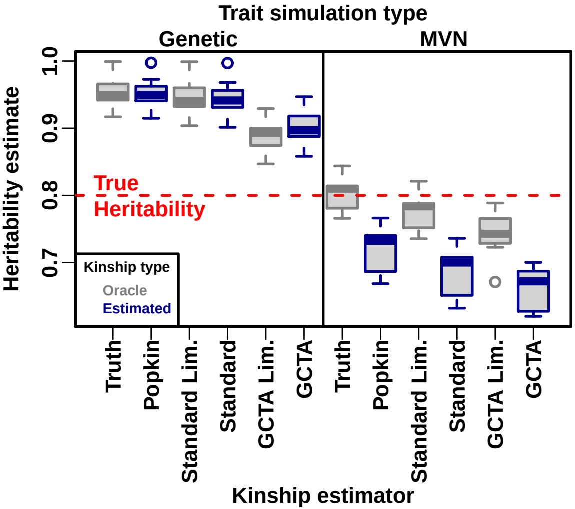

LIGERA: light genetic robust association

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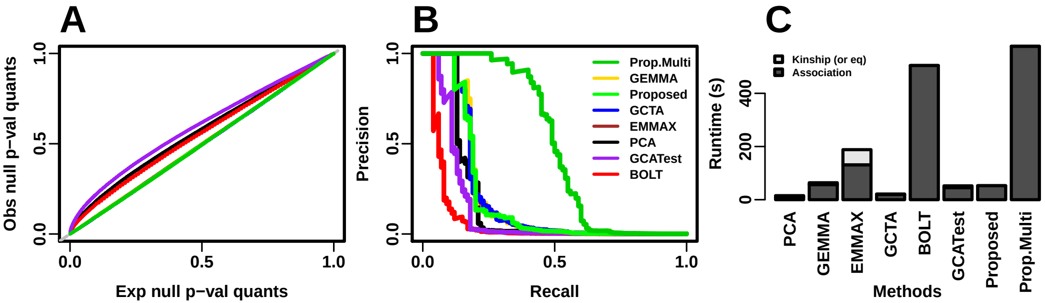
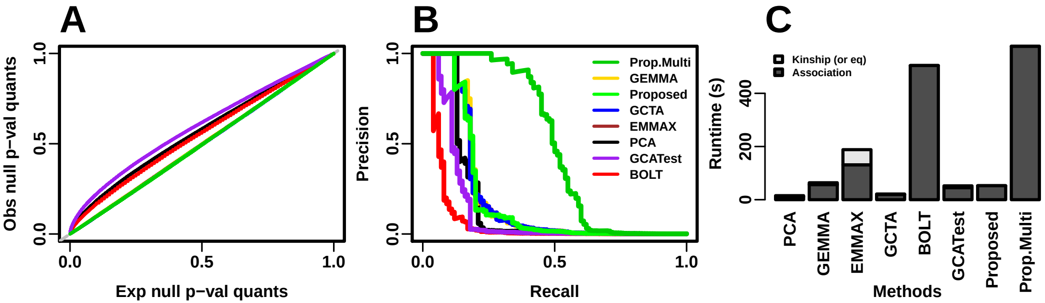
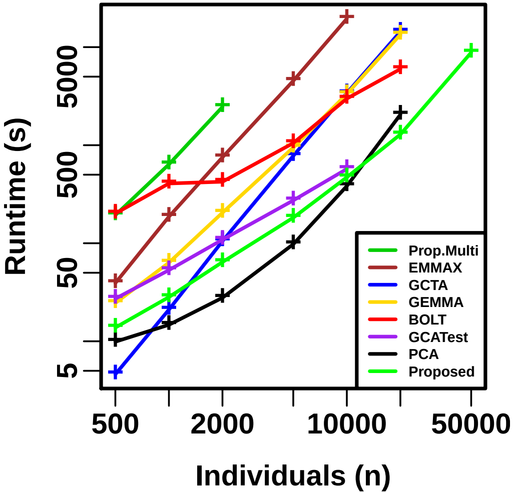


LIGERA: light genetic robust association



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

LIGERA: light genetic robust association: scalability



Admixture: kinship driven by admixture in Hispanics

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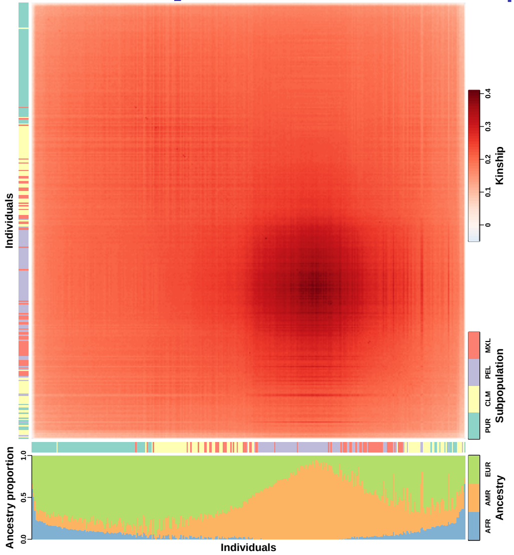

Ochoa and Storey (2019b) doi:10.1101/653279

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Kinship under the admixture model

Amika Sood
Postdoc

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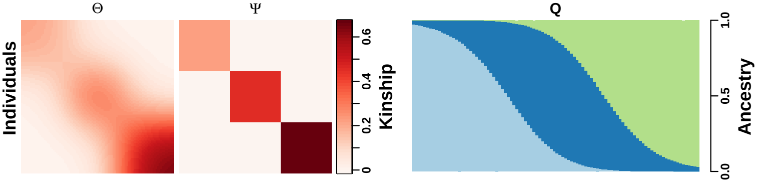

Kinship under the admixture model

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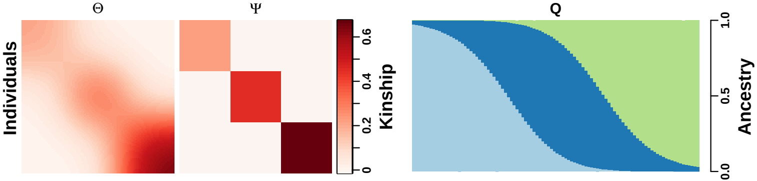

$$\Theta = \mathbf{Q}\Psi\mathbf{Q}^\top$$

Kinship under the admixture model

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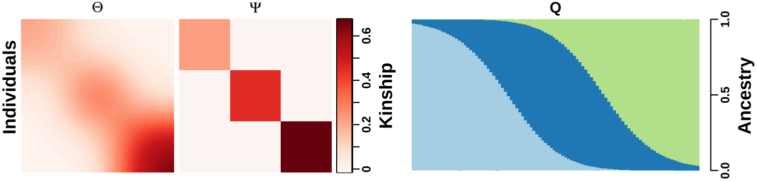

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Can we reverse this formula?

Kinship under the admixture model

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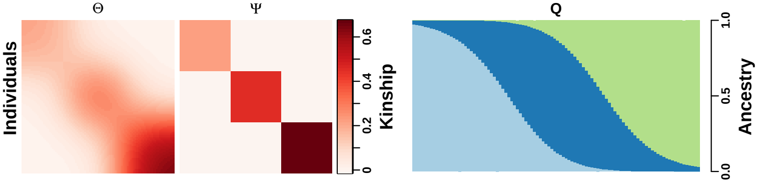


$$\Theta = \mathbf{Q}\Psi\mathbf{Q}^\top$$

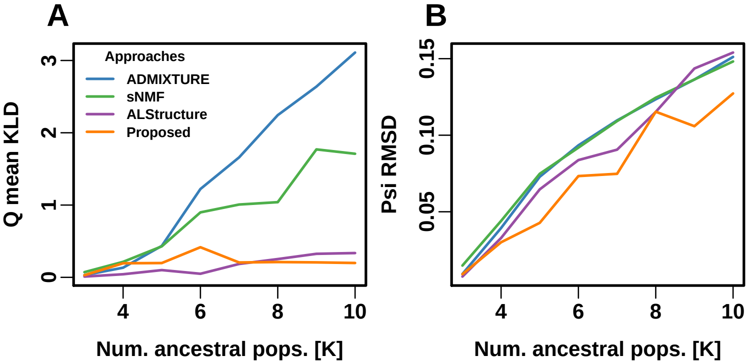
Can we reverse this formula?

Constrained optimization, regularized objective:

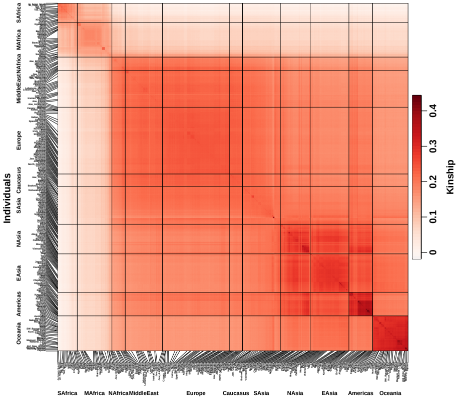
$$F = \left|\left|\hat{\Theta} - \mathbf{Q}\Psi\mathbf{Q}^\top\right|\right|^2 + \gamma\,\mathrm{tr}(\Psi).$$

AdmixCor: accuracy

Amika Sood
Postdoc



Unbiased kinship estimates: new models, opportunities



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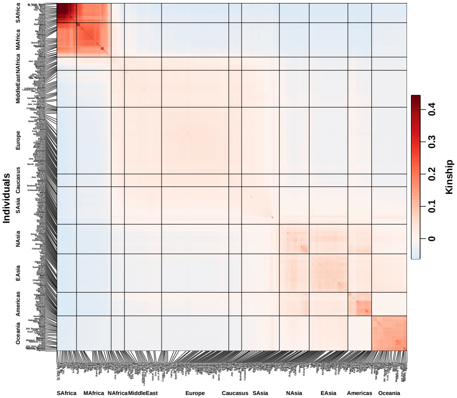

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Acknowledgments

Ochoa Lab

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GCB
Duke Center for Genomic and Computational Biology

Department of Biostatistics & Bioinformatics
Duke University School of Medicine

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