Genetic association and heritability estimation in structured populations

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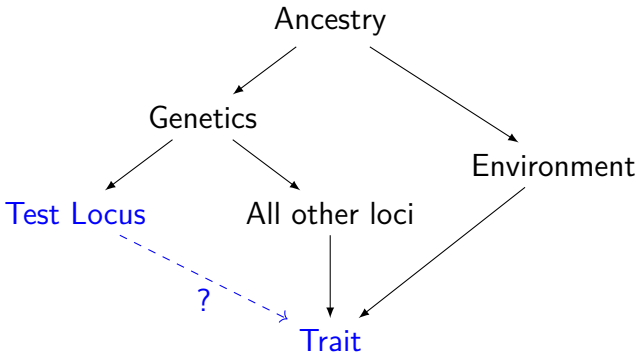
Part 1: Cryptic relatedness matters a lot in genetic association studies ... or: how I learned to love Linear Mixed-effects Models

Association studies are hard

- Millions of tests
- Polygenicity (many causal variants)
- Incorrect assumptions: independence / additivity
- **Confounders**



PCA vs LMM in association

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

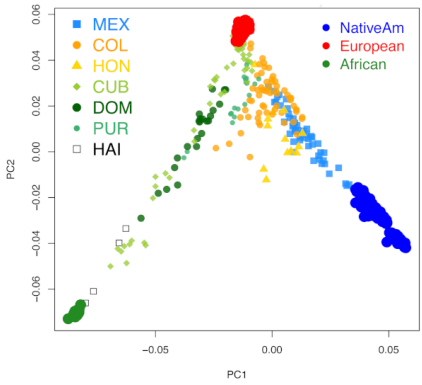
$$\text{PCA}: \quad \mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta + \mathbf{U}_d\gamma_d + \epsilon,$$

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

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

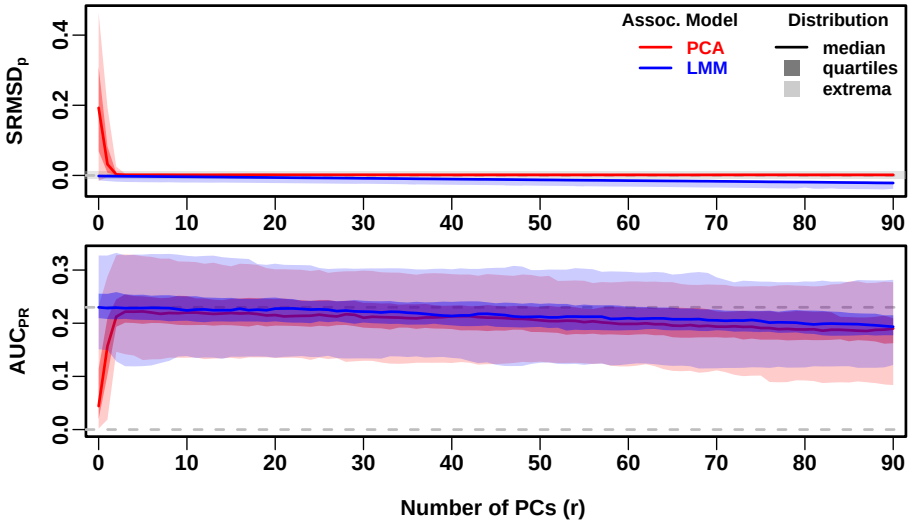
$$\mathbf{s} \sim \text{Normal}\left(\mathbf{0}, \sigma_G^2\Phi\right).$$

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



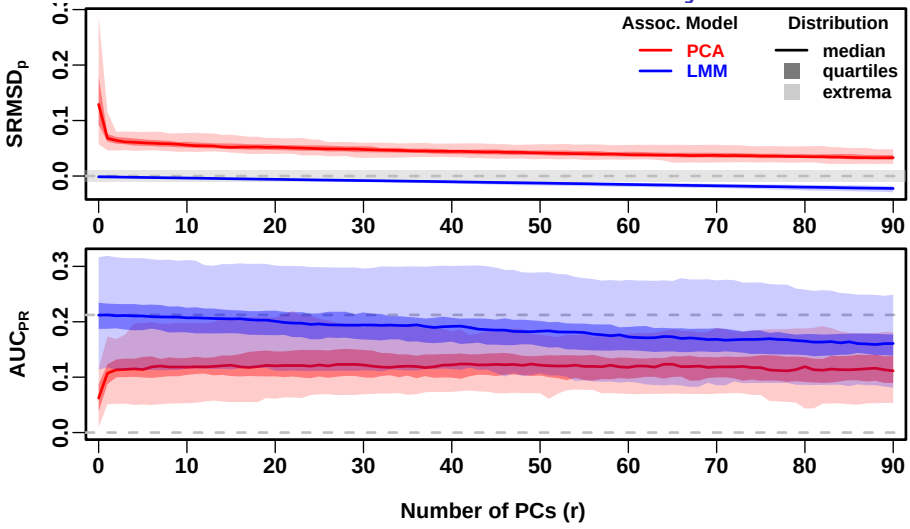
Moreno-Estrada *et al.* (2013)

PCA < LMM in association: simulated admixture



Yao and Ochoa (2023) doi:10.7554/eLife.79238

PCA < LMM in association: simulated family structure



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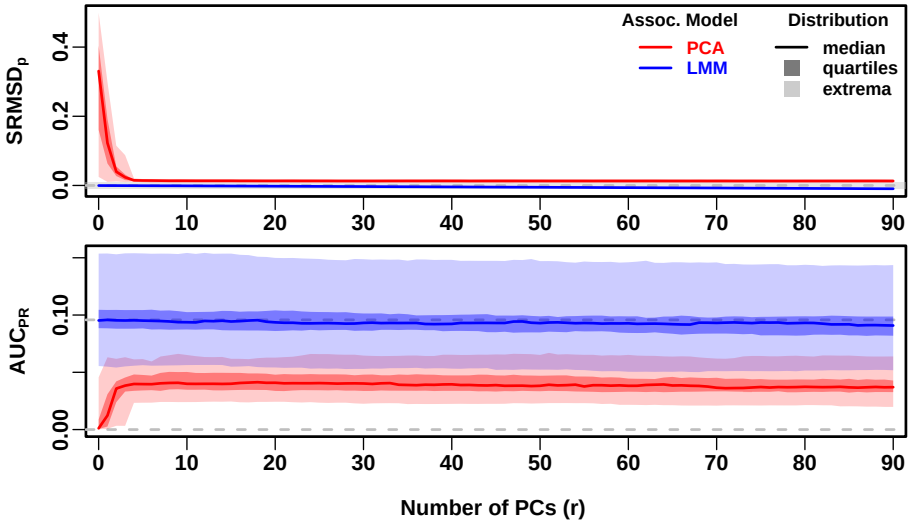
PCA < LMM in association: 1000 Genomes



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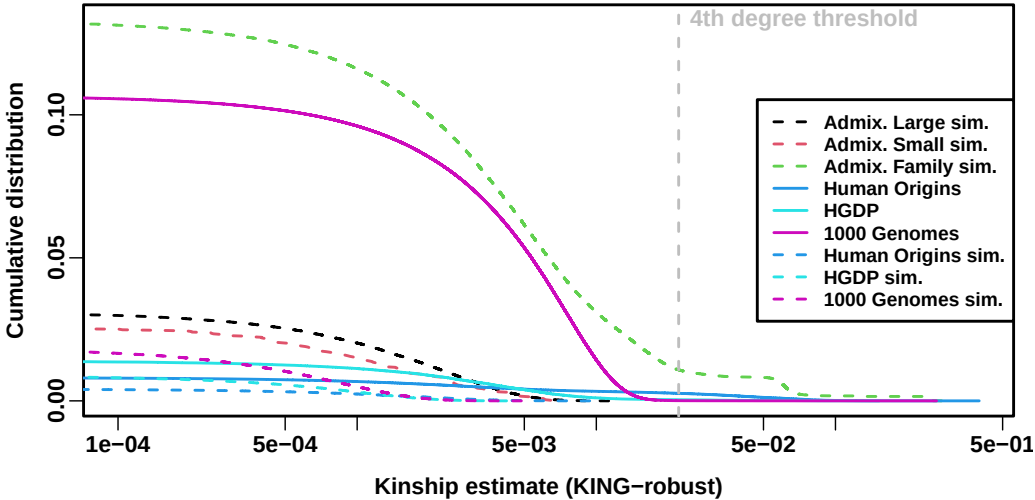
Numerous distant relatives in real datasets



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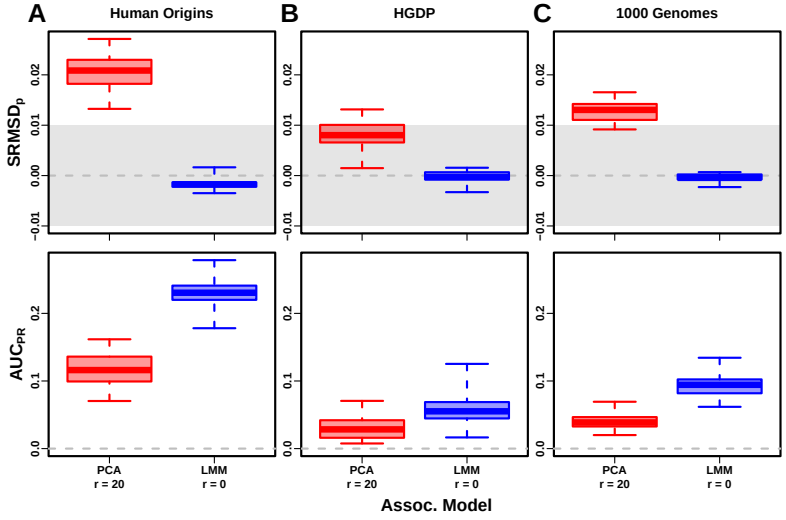
Numerous distant relatives in real datasets explain PCA < LMM



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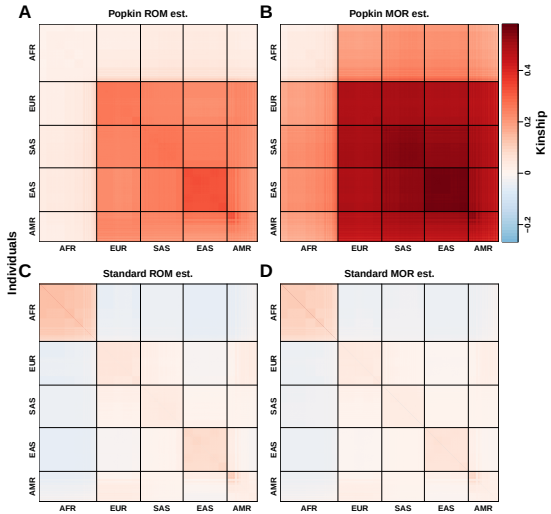
Part 2: Kinship bias carries over to heritability, but not association!

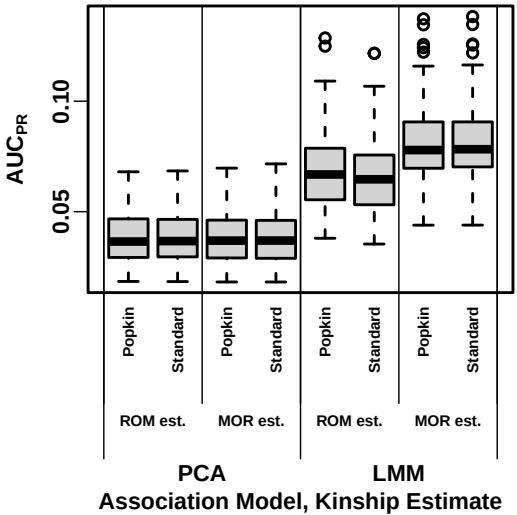
Standard kinship estimator is severely biased



- ROM: Ratio of Means
  - Upweighs common variants
  - Behaves well statistically
- MOR: Mean of Ratios
  - Upweighs rare variants
  - Introduces additional bias

Hou and Ochoa (2023) doi:10.1093/genetics/iyad030

Kinship bias does not affect genetic associations



Hou and Ochoa (2023) doi:10.1093/genetics/iyad030

Kinship bias does not affect genetic associations

Linear algebra proof!

Transforming true to biased kinship matrices:

Φ : Unbiased kinship matrix,

Φ' : Biased kinship matrix,

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

$\mathbf{C} = \mathbf{I} - \frac{1}{n}\mathbf{1}\mathbf{1}^\top$: Centering matrix.

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Association test is a regression with correlated residuals:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta_i + \mathbf{s} + \epsilon,$$
$$\mathbf{s} \sim \text{Normal}\left(\mathbf{0}, 2\sigma^2_G\Phi\right),$$
$$\epsilon \sim \text{Normal}\left(\mathbf{0}, \sigma^2_E\mathbf{I}\right).$$

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Kinship bias compensated by intercept!

$$\mathbf{s}' = \mathbf{C}\mathbf{s} \sim \text{Normal}\left(\mathbf{0}, 2\sigma^{2\prime}_G\Phi'\right),$$
$$\sigma^{2\prime}_G = (1-\bar{\varphi})\sigma^2_G,$$
$$\mathbf{s}' = \mathbf{s} - \mathbf{1}\bar{s},$$
$$\alpha' = \alpha + \bar{s}$$

Hou and Ochoa (2023) doi:10.1093/genetics/iyad030

Kinship bias affects heritability estimation

Model:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{s} + \epsilon,$$
$$\mathbf{s} + \epsilon \sim \text{Normal}\left(\mathbf{0}, 2\sigma_G^2\Phi + \sigma_E^2\mathbf{I}\right).$$

Heritability definition:

$$h^2 = \frac{\sigma_G^2}{\sigma_G^2 + \sigma_E^2}.$$

Variance is estimated with bias:

$$\sigma_G^{2\prime} = (1 - \bar{\varphi})\sigma_G^2.$$

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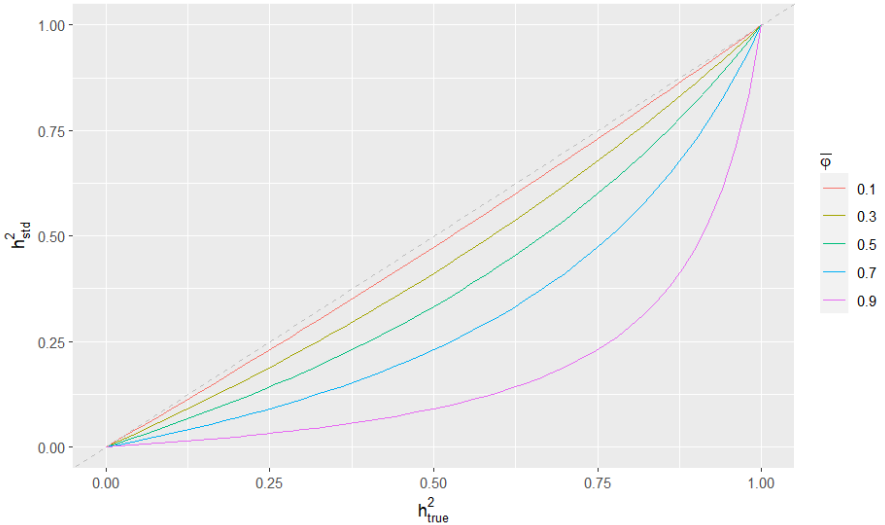
Heritability is estimated with bias that depends on mean kinship $\bar{\varphi}$ and the true heritability h^2:

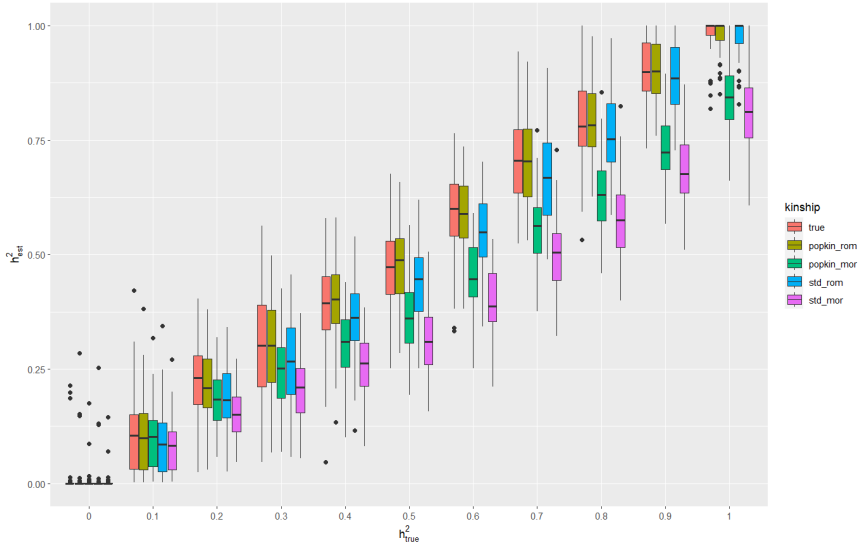
$$\begin{aligned} h^{2\prime} &= \frac{\sigma_G^{2\prime}}{\sigma_G^{2\prime} + \sigma_E^{2\prime}} \\ &= h^2 \frac{1 - \bar{\varphi}}{1 - \bar{\varphi}h^2}. \end{aligned}$$

Kinship bias affects heritability estimation

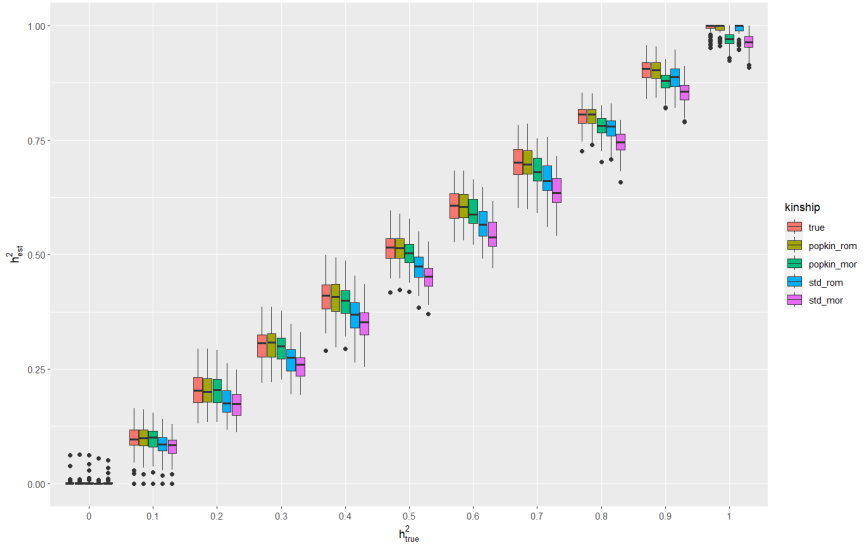
$$h^{2\prime} = h^2 \frac{1-\bar{\varphi}}{1-\bar{\varphi}h^2}$$



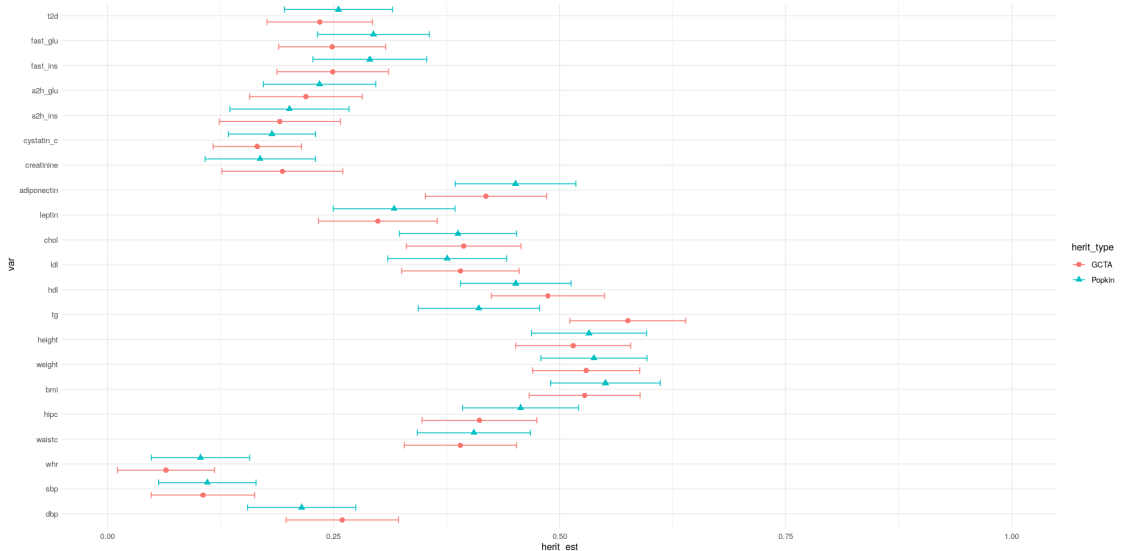
Simulated admixture (high mean kinship)



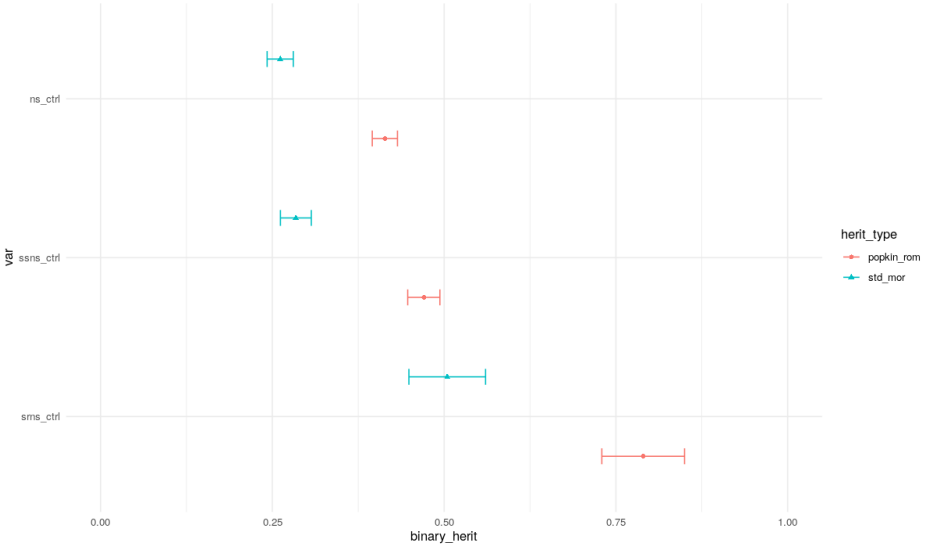
Simulated family structure (reduced mean kinship)



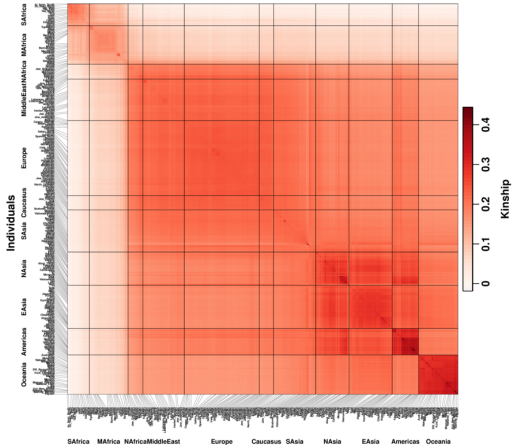
San Antonio Family Study: Type 2 Diabetes (low mean kinship)



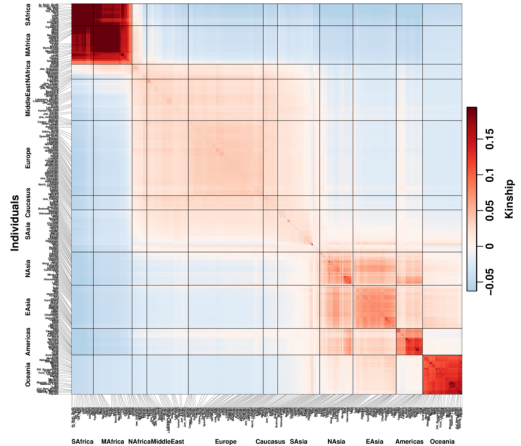
Nephrotic Syndrome: multiethnic cohort (high mean kinship)



Unbiased kinship estimates: new models, opportunities



New "popkin"
kinship estimator



Biased "standard"
kinship estimator

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New kinship/GRM estimator

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

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

Standard estimator is **biased**:

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

`popkin`: first unbiased kinship estimator! R package

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

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

https://github.com/StoreyLab/popkin