AdjHE: An efficient way to estimate heritability

Christian Coffman

Advised by: Dr. Saonli Basu
University of Minnesota Twin Cities
Division of Biostatistics

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General influences on traits

Traits are determined by different contributions of genetics and environmental influencers.
Which traits are dictated by which set of influencers?

Image credit:

https://blogs.kcl.ac.uk/editlab/2019/05/07/if-something-is-genetic-it-can-still-be-influenced-by-the-environment/

GWAS

- Genome Wide Association studies (GWAS)

$$Y' = X_c\alpha + X_g\beta + \epsilon$$

- X_g: genotype
- X_c: other covariates
- Inference done on the β (sometimes millions)
- Pro: Great for highly influential SNP's
- Low: Low power for causality spread across multiple SNP's

Gene effects as random

- Consider $\beta \sim N(0, \sigma_g^2 I)$
- Then $X_g\beta \sim N(0, \sigma_g^2 X_g X_g')$
- Redefined as $N(0, \sigma_G^2 A)$
- Where A is called the **Genetic Relatedness Matrix**
- Model becomes

$$Y' = X_c\alpha + \epsilon, \epsilon \sim (0, \sigma_G^2 A + \sigma_e^2 I)$$

GRM based heritability estimation

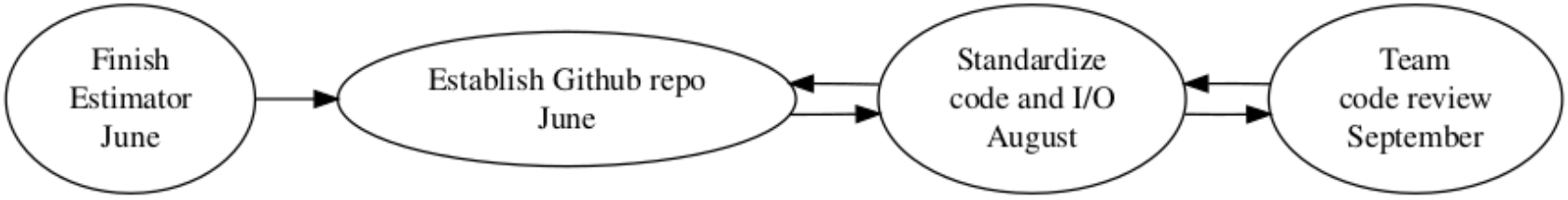
- Describe variation in phenotype as random effect (LMM)

$$Y' = \epsilon, \epsilon \sim N(0, \sigma_g^2 A + \sigma_e^2 I)$$

- Gain: power for dispersed genetic effects
- Loss: resolution on genome
- GCTA uses REML which can be slow with large studies (n x n matrix)
- Not efficient for exploration of mildly heritable traits (large sample sizes)
- Can solve via MOM, but what about when there is population substructure?

New tool: AdjHE

- Two-stage Method of Moments approach
- Accounts for ethnicity as PC's of GRM
- Key assumption: $X_c \perp A$
- Closed form $\therefore$ Much more efficient
- Benchmarked: 2x faster with 4000 subjects
- 10x faster with 45k subjects



Dealing with population substructure

- Now relatedness contains family relations A as well as structure from ethnic groups G

$$GRM = A + G$$

- PCA on GRM

$$GRM = \sum \lambda_i VV' = \sum \lambda_i A_i A_i' + \sum \lambda_i G_i G_i'$$

- Suppose G_i contribute more to variance
- First k PC's define G

Dealing with covariates

- Project away covariates ("Residualize")

$$Q = I - X_c(X_c'X_c)^{-1}X_c'$$

$$QY' = Y = QX_c + Q\epsilon = Q\epsilon$$

$$Y \sim N(0, \sigma_G^2 A + \sum \delta_i G_i G_i' + \sigma_e^2 I)$$

- 2nd moment

$$EYY' = Var(Y) + EYEY' = Var(Y)$$

$$= \sigma_G^2 A + \sum \delta_i G_i G_i' + \sigma_e^2 I$$

- Solve via OLS

Properties of OLS estimator

$$EYY' = \begin{bmatrix} A & G_1 G_1' & \vdots & G_k G_k' & I \end{bmatrix} \begin{bmatrix} \sigma_G^2 \\ \delta_1 \\ \dots \\ \delta_k \\ \sigma_e^2 \end{bmatrix}$$

$$EYY' - G\delta = \begin{bmatrix} A & I \end{bmatrix} \begin{bmatrix} \sigma_G^2 \\ \sigma_e^2 \end{bmatrix}$$

$$\begin{bmatrix} \hat{\sigma}_G^2 \\ \hat{\sigma}_e^2 \end{bmatrix} = \begin{bmatrix} A & I \end{bmatrix} \left(\begin{bmatrix} trA^2 & trA \\ trA & n \end{bmatrix} \right)^{-1} \begin{bmatrix} A \\ I \end{bmatrix} (YY' - G\hat{\delta})$$

Problem with multi-site estimation

- More studies using consortia to study smaller effects
- The Adolescent Brain Cognitive Development (ABCD) has $+$10,000 subjects $>$ 20 sites
- Measures brain features
- Brain features sensitive to machine used (i.e. depends on site)
- Adding fixed effect blows up SE (coming up in a few slides)
- So treat it as random effect

$$Y \sim N(X_c\alpha, \sigma_G^2 A + \sum G_i\delta_i + S\sigma_s^2 + I\sigma_e^2)$$

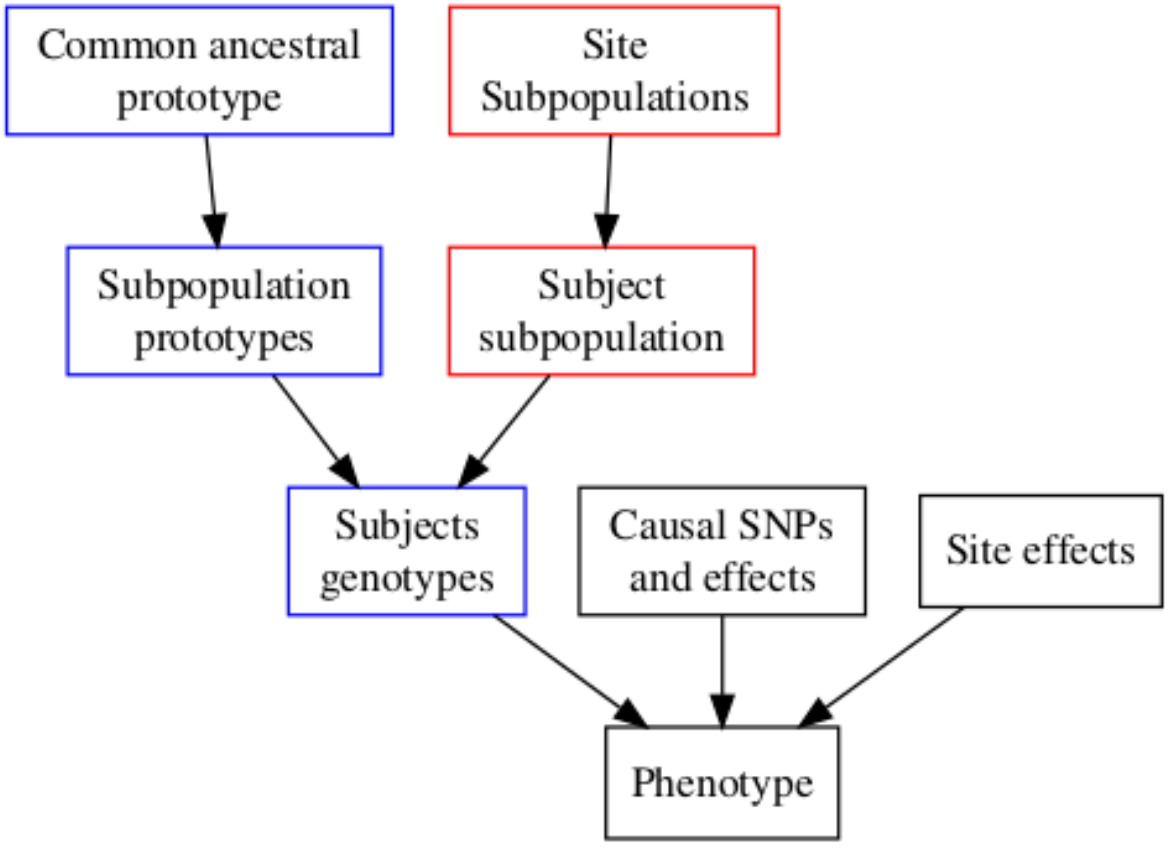
AdjHE site extension

- Assume $X_c \perp X_s, A, G$

$$EYY' - G\Delta G' = \begin{bmatrix} A & QSQ & I \end{bmatrix} \begin{bmatrix} \sigma_G^2 \\ \sigma_s^2 \\ \sigma_e^2 \end{bmatrix}$$

- OLS solution not closed form
- Only involves inverson of 3x3 matrix

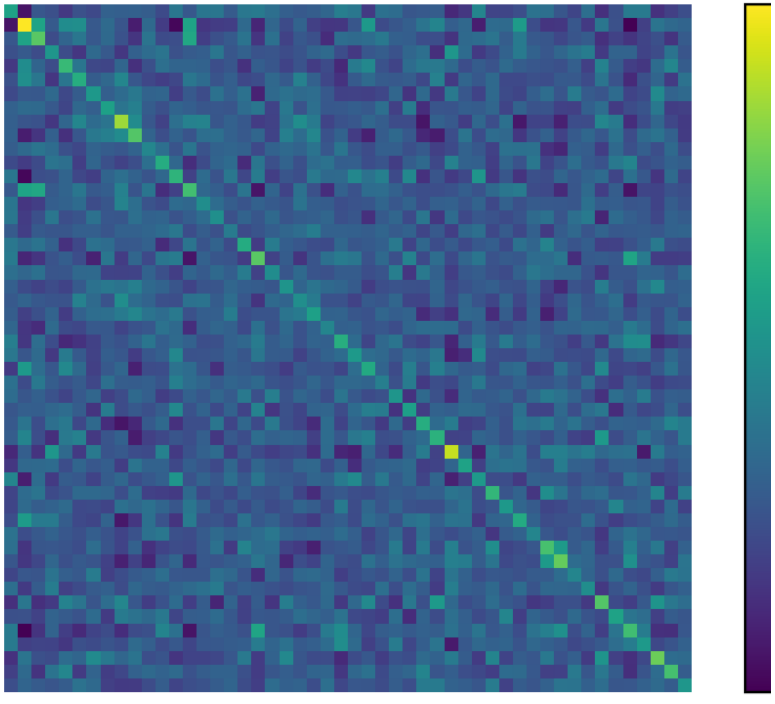
Simulation tool



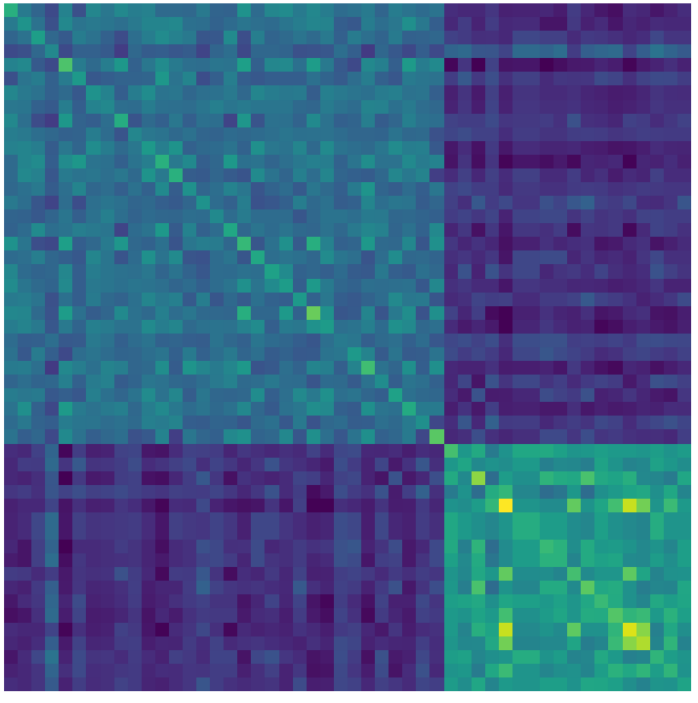
- Simulate realistically structured GRM's and phenotypes
- Determine what scenarios fit within AdjHE model

Simulating population structures

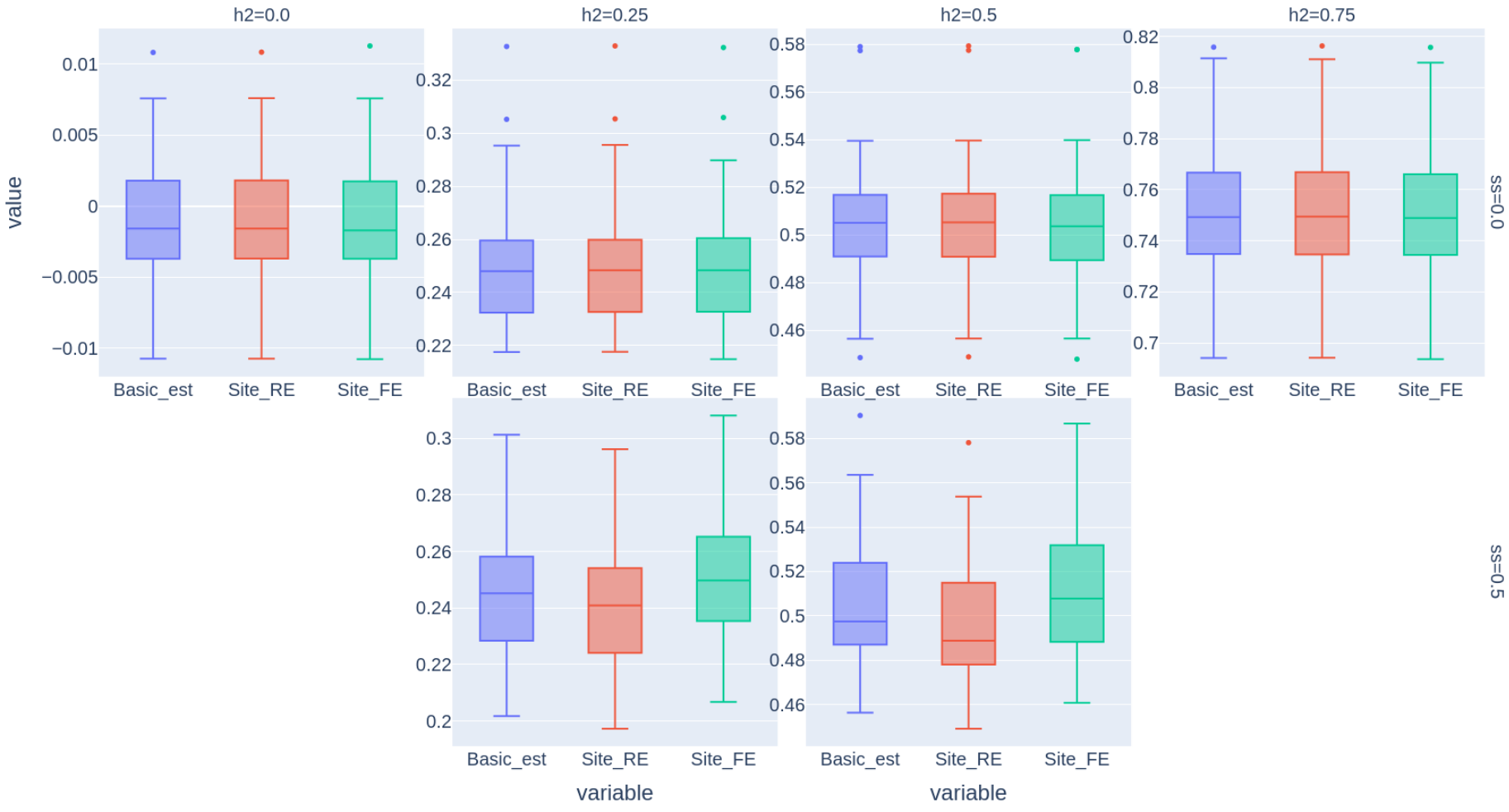
GRM: clusters = 1, Site pops = Homo



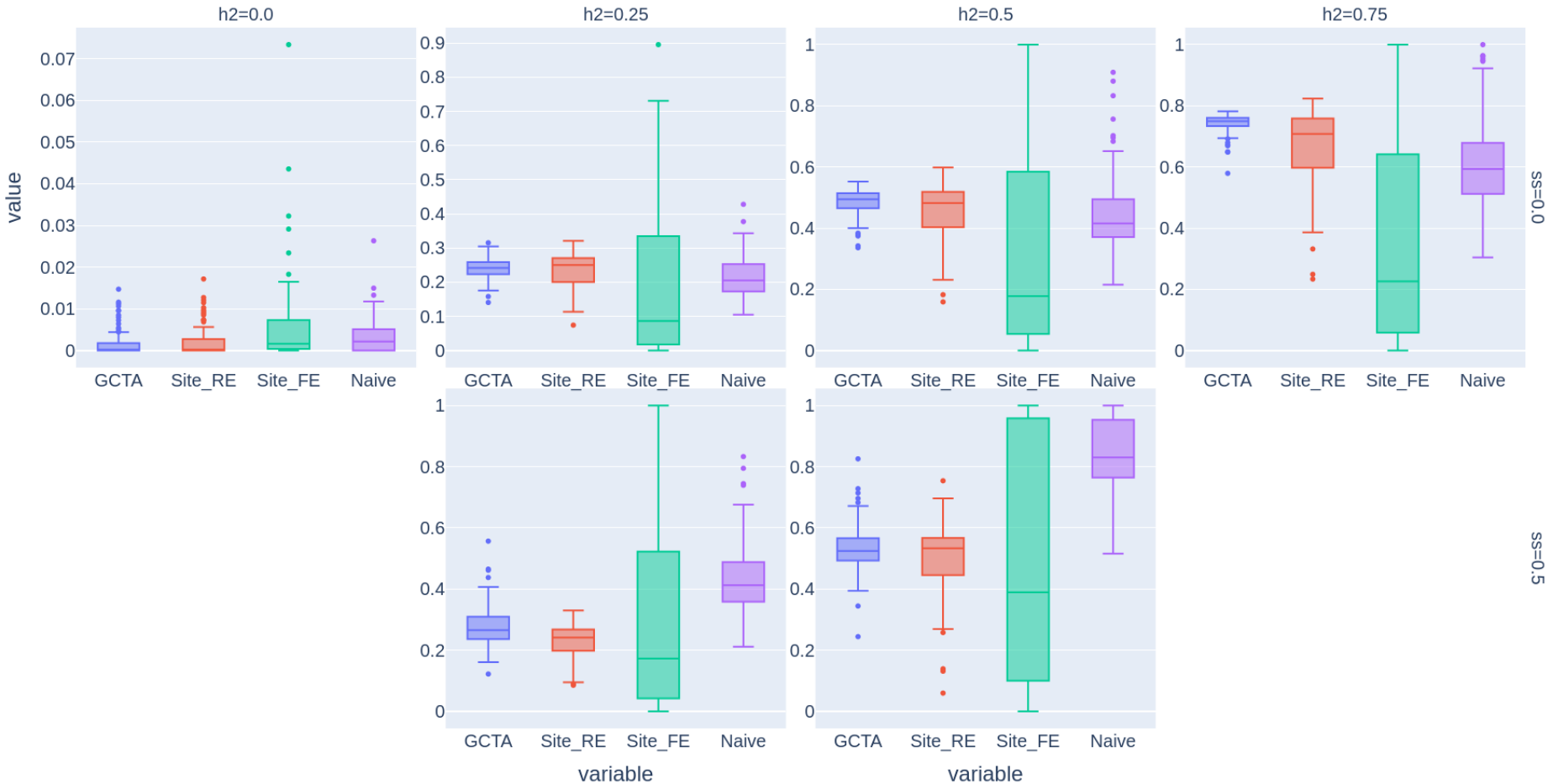
GRM: clusters = 2, Site pops = IID



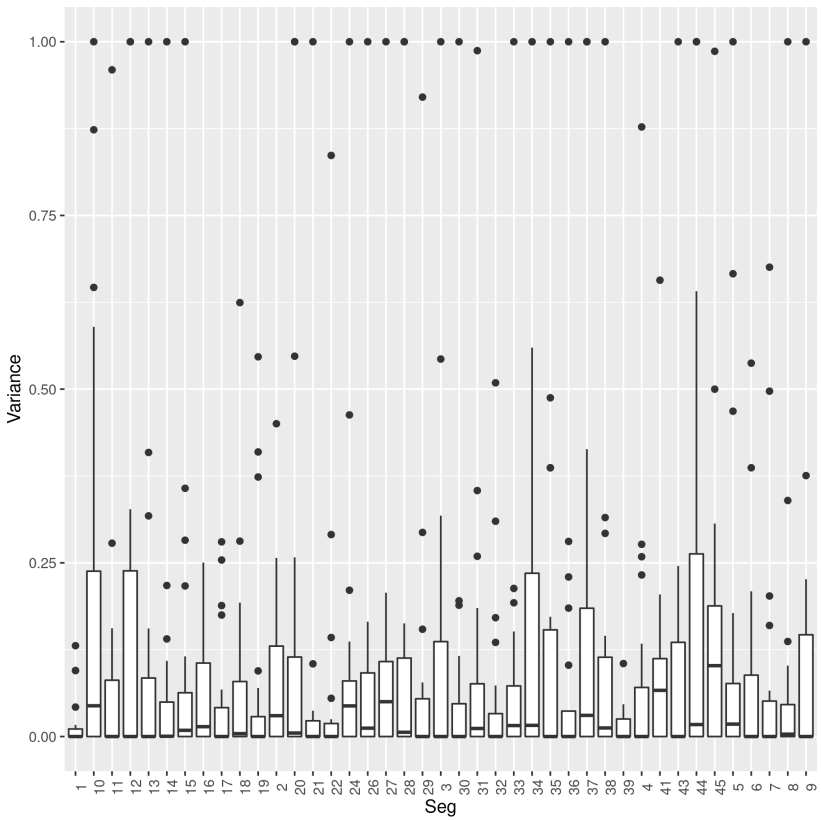
Estimation on Homogeneous

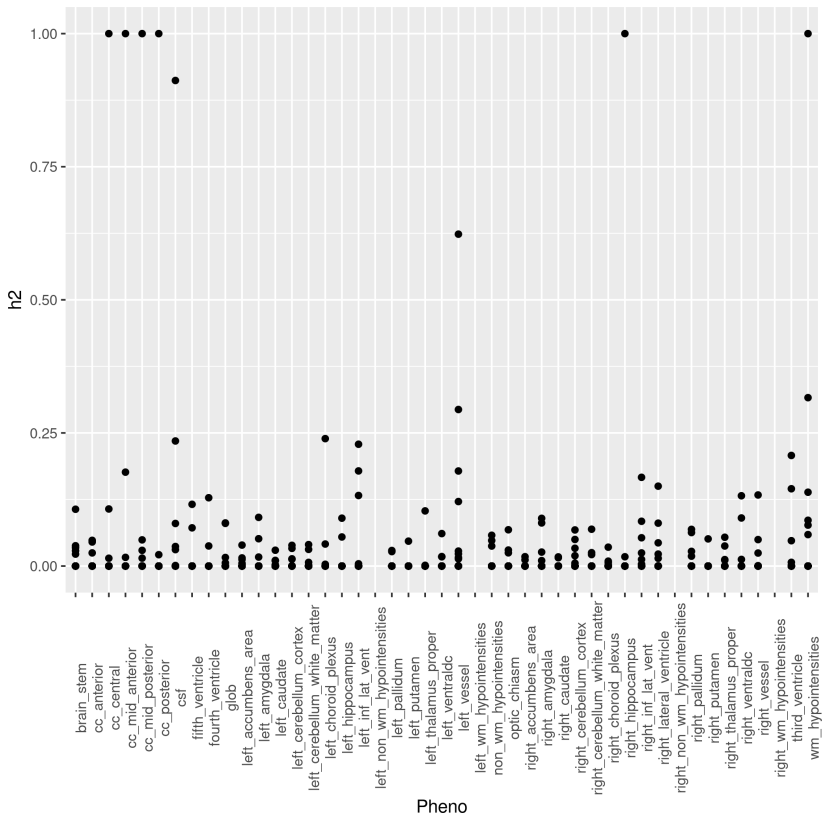


Estimation on Sites with IID composition

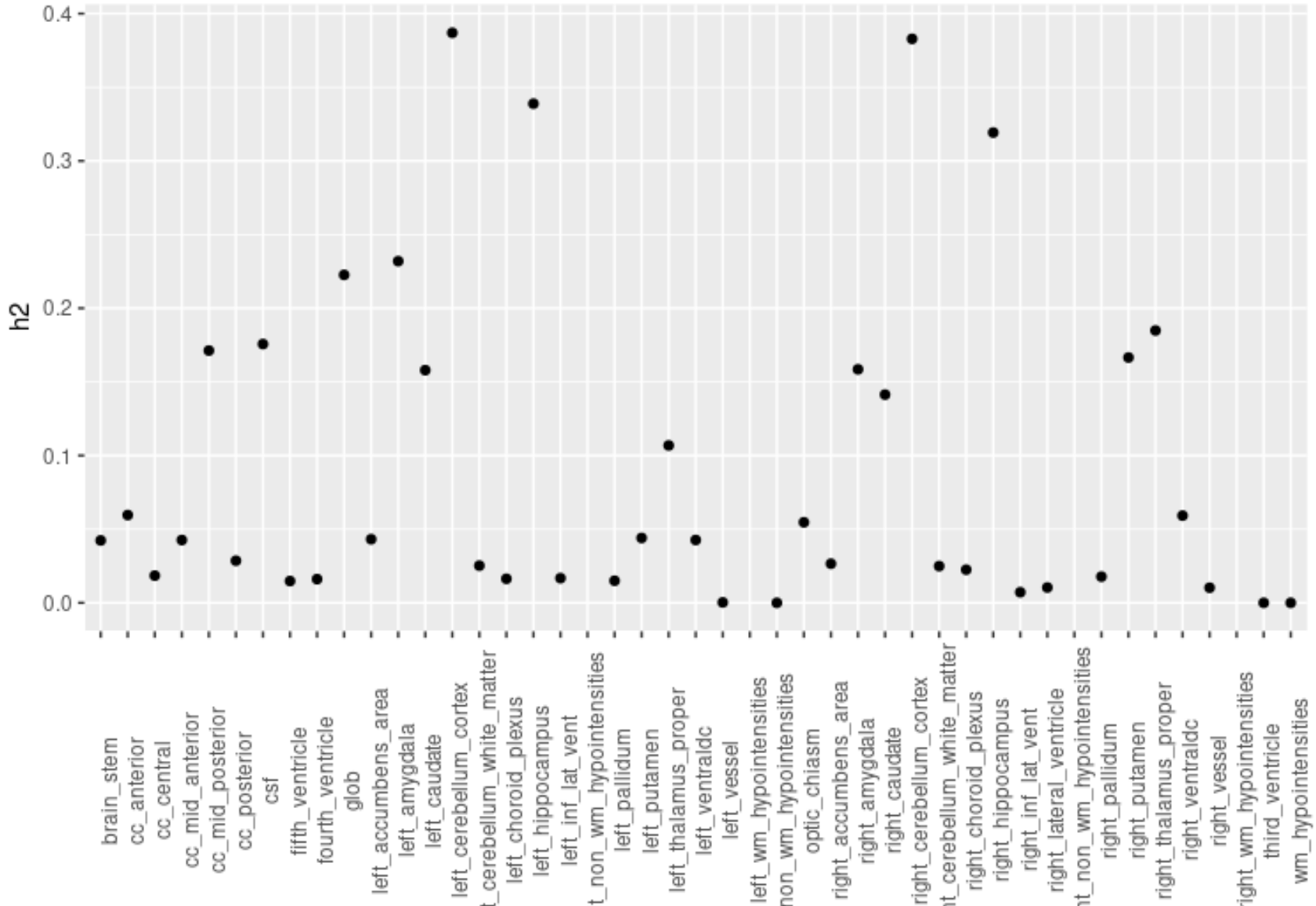


Naive estimates on Asegs data



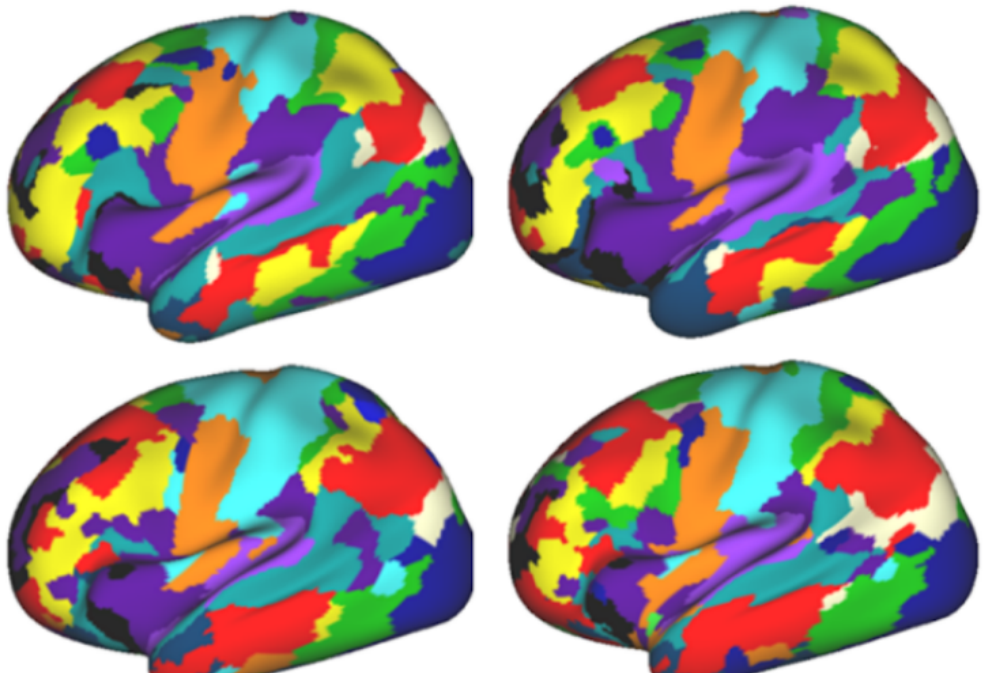


Controlling for Site AdjHE



Conclusions and future aims

- AdjHE is efficient estimator and accounts for basic effect from site
- Early analysis suggests volumes in adolescent brains are heritable
- Consistent with ADNI results where
- Applications to functional topology

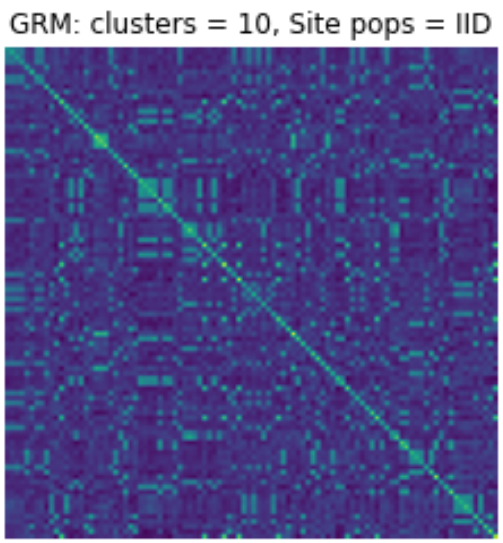


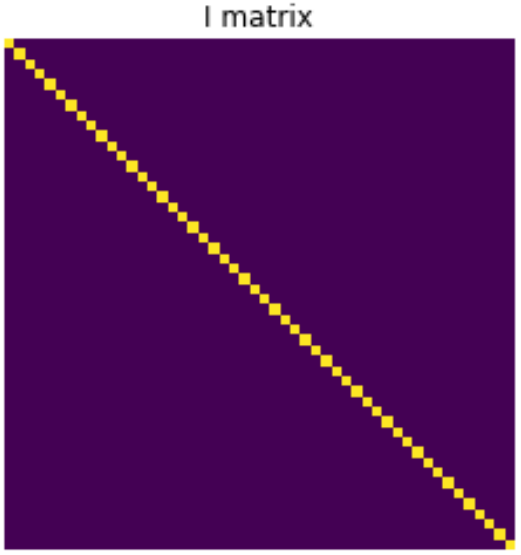
Thank you for listening
Questions?

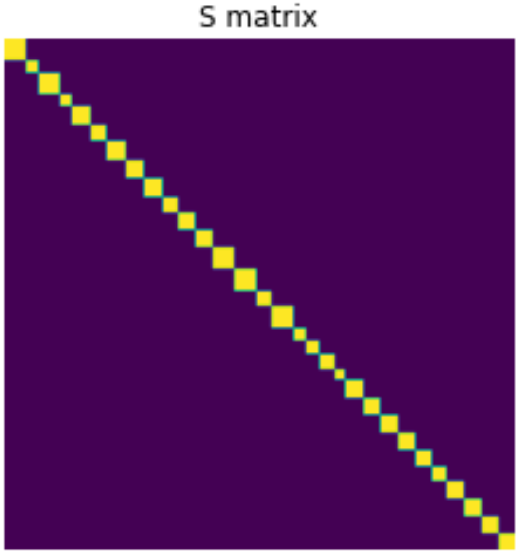
References

Lin, Seal, and Basu. "Estimating SNP Heritability in Presence of Population Substructure in Biobank-Scale Datasets." Genetics 2022
Hermosillo et al. "A Precision Functional Atlas of Network Probabilities and Individual-Specific Network Topography." 2022 bioRxiv
Zhao et al., 2019 "Heritability of Regional Brain Volumes in Large-Scale Neuroimaging and Genetic Studies."

Source Identifiability problem







Zhao paper results (ADNI)