The multivariate Marginal Epistasis Test

Leveraging genetic correlation between traits improves the detection of epistasis in genome-wide association studies

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Epistasis could explain missing heritability^{1,2}

Genetic correlations between traits maintained by pleiotropy³

Multivariate modelling improves GWAS⁴

1 Manolio et al. (2009) 3 Chebib and Guillaume (2021) 4 Zhou and Stephens (2014)

Method

Model

$$\sum_{l \neq j} \beta_l \mathbf{x}_l^T$$

$$\mathbf{Y} = \mathbf{M}_j + \mathbf{Z}_j + \mathbf{E}$$

Interaction Effect Size α_1 Linear Effect Size β_1 Variant vectors **X**₁

$$\sum_{l \neq j} \alpha_l(\mathbf{x}_j \circ \mathbf{x}_l)^T$$

Normal Assumptions

$$\mathbf{M}_{j} \sim \mathrm{MN}\left(0, \mathbf{V}_{\beta}, \mathbf{K}\right)$$

 $\mathbf{Z}_i \sim \text{MN}\left(0, \mathbf{V}_{\alpha}, \sigma^2 \mathbf{G}\right)$

 $\mathbf{E} \sim \mathbf{MN} \left(0, \mathbf{V}_E, \mathbf{I} \right)$

Additive Variance Component

Pariwise Epistatic **Variance Component**

Error Term

Parameter Estimation

$$\widehat{\boldsymbol{\sigma}}_{j,(cd)}^2 = \mathbf{y}_c^T \mathbf{H}_j \mathbf{y}_d$$

$$\operatorname{Var}[\widehat{\boldsymbol{\sigma}}_{j,(cd)}^{2}] = \mathbf{y}_{c}^{T} \mathbf{H}_{j}^{T} \mathbf{V}_{j,(cd)} \mathbf{H}_{j} \mathbf{y}_{d} + \mathbf{y}_{c}^{T} \mathbf{H}_{j}^{T} \mathbf{V}_{j,(dd)} \mathbf{H}_{j} \mathbf{y}_{c}$$

Use MQS to find point estimates of parameters and compute z-scores.

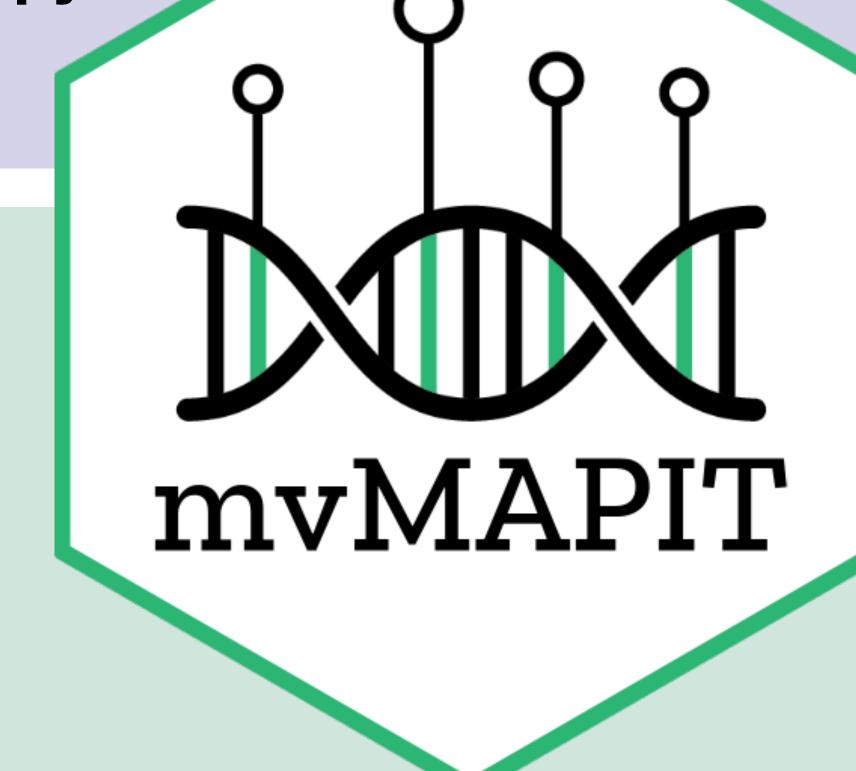
Hypothesis Testing

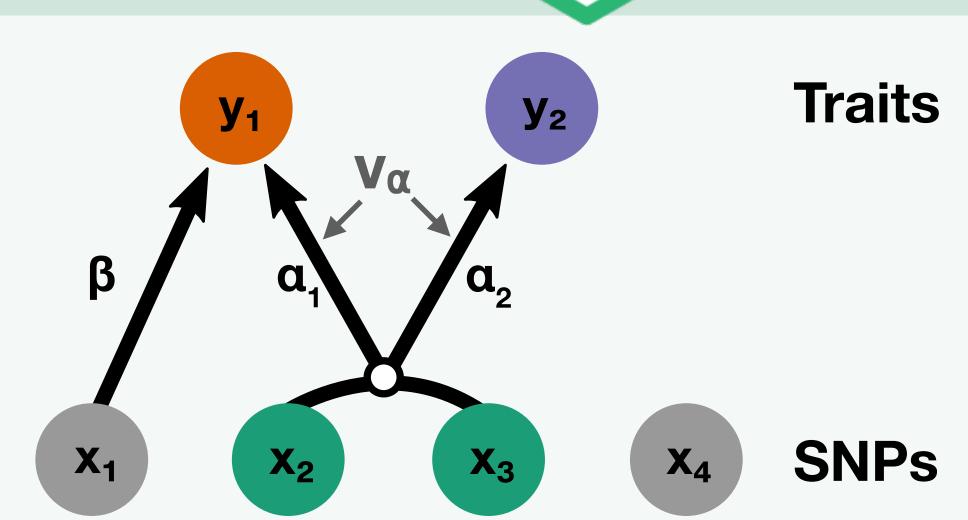
$$H_0: \mathbf{Z_j} = 0 \quad \Leftrightarrow \quad H_0: \sigma^2 = 0$$

Under H₀ nonlinear contributions to the trait are zero.

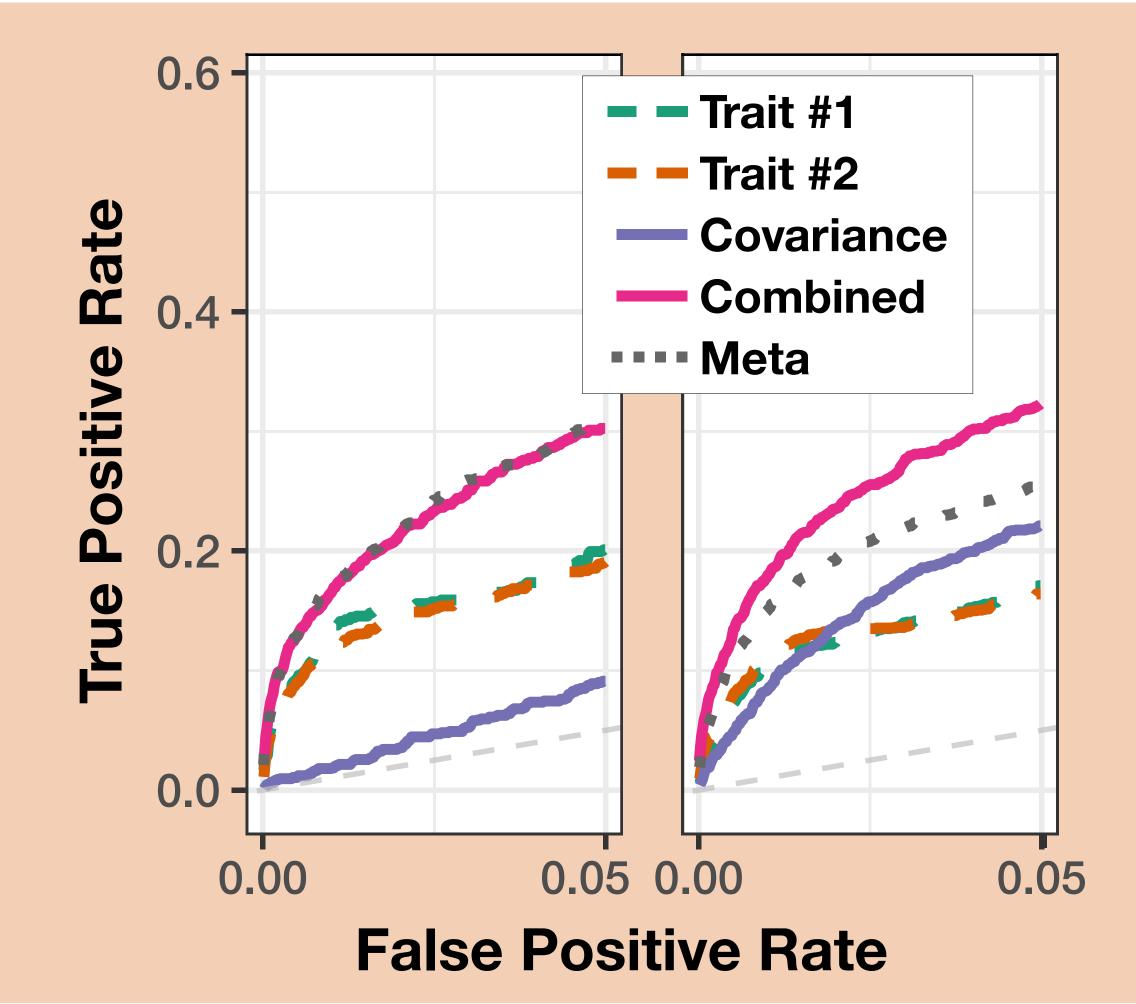
Compute z-scores for all variance and covariance components.

Combine P-values with Fisher's method.



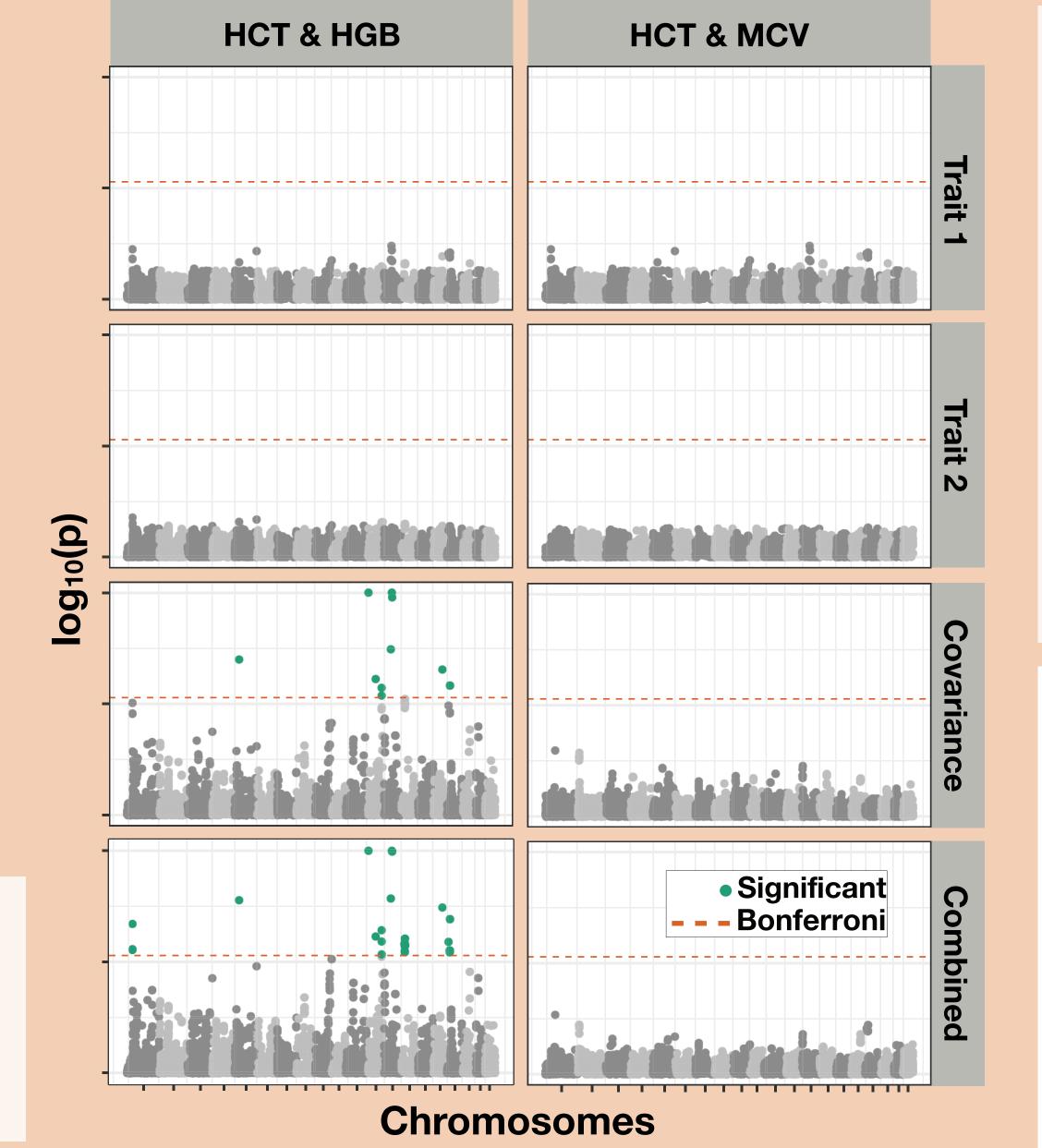


Multivariate MAPIT schematic. Illustration of the modeled genetic correlation v_{α} between the effect sizes α_1 and α_2 of the epistatic interaction $x_2 \circ x_3$ on the traits y_1 and y_2 .



Simulations

- Sensitivity of covariance statistic increases with correlation between effect sizes
- Combined statistic outperforms univariate and simple meta analysis



Hematology in Mice

- Covariance **statistic** reveals strong signal of pairwise epistasis
- Genetic correlations independent of trait correlations

R Package



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