Multivariate MAPIT

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

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Outline

Introduction

Methods

Simulated Data

Real Data

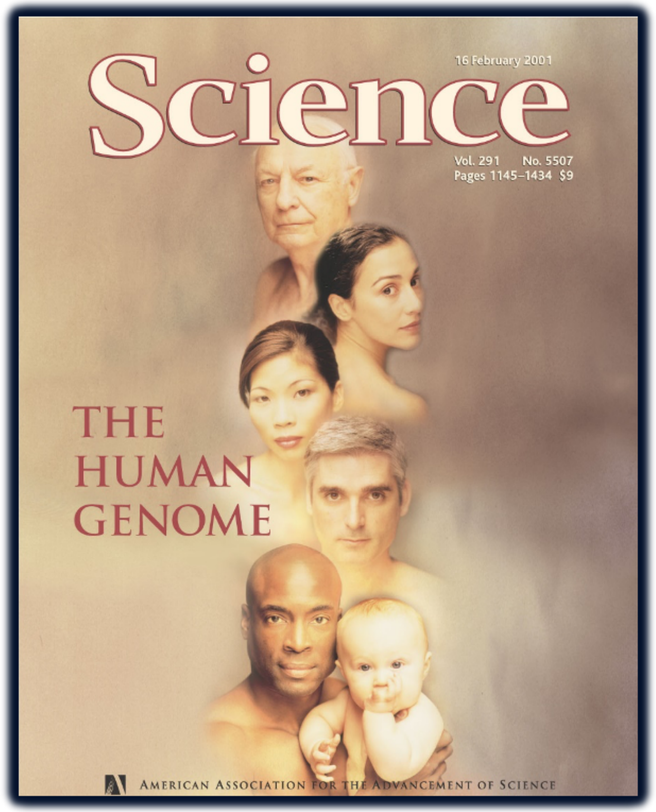
Summary

Genome Wide Association Studies

- Genotype large cohorts
- Map traits through statistical tests

20 years later & many open problems:

- Rare variants
- Inaccurate predictions
- Missing heritability



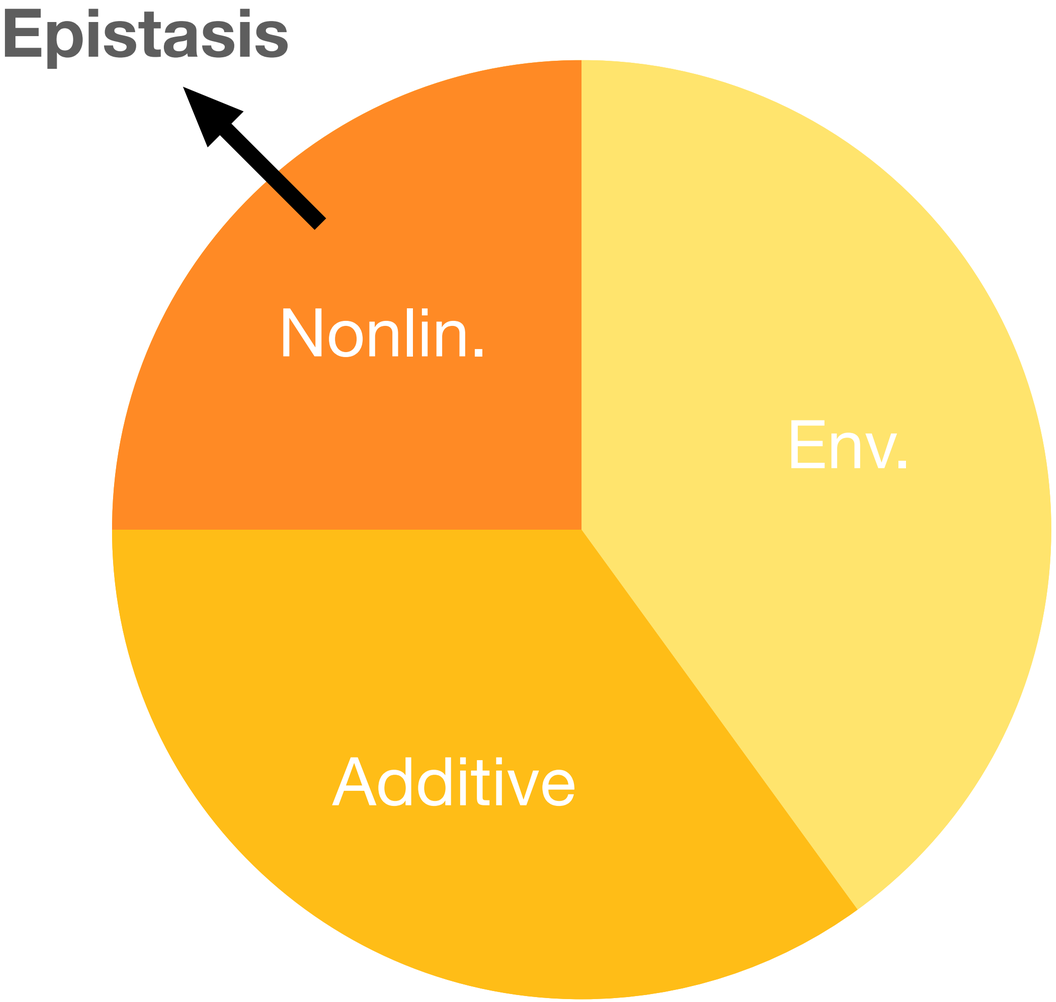
Phenotypic Variance

Genetic & Environmental Factors

$$P = G + E$$

Broad sense Heritability

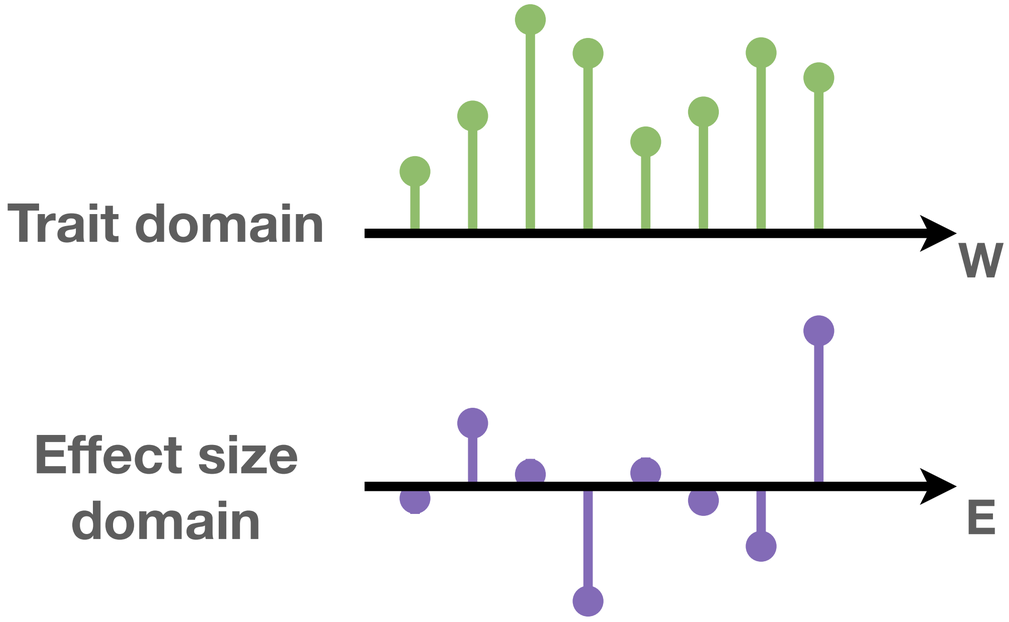
$$H^2 = \frac{\mathrm{Var}[G]}{\mathrm{Var}[P]}$$



Hadamard-Walsh Transform

- For combinatorially complete data transform linearly from trait to epistatic effects
- Rows are mapped to genotypes

$$\frac{1}{2^L}\Psi\vec{W} = \vec{E}_W$$



$$\frac{1}{2^L} \cdot \underbrace{\begin{pmatrix} +1 & +1 & +1 & \cdots & +1 \\ +1 & -1 & +1 & \cdots & -1 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ +1 & -1 & -1 & \cdots & -1 \end{pmatrix}}_{\text{Hadamard matrix}} \cdot \underbrace{\begin{pmatrix} 1.07 \\ 2.54 \\ \vdots \\ 0.41 \end{pmatrix}}_{\text{Trait values}} = \underbrace{\begin{pmatrix} 2.28 \\ 0.0857 \\ \vdots \\ -0.1051 \end{pmatrix}}_{\text{Effect size of interactions}}$$

Biobank Scale Data

- ~ 10^5 to 10^6 variants
- ~ 10^4 to 10^5 samples
- ~ 3^{100000} genotype combinations*

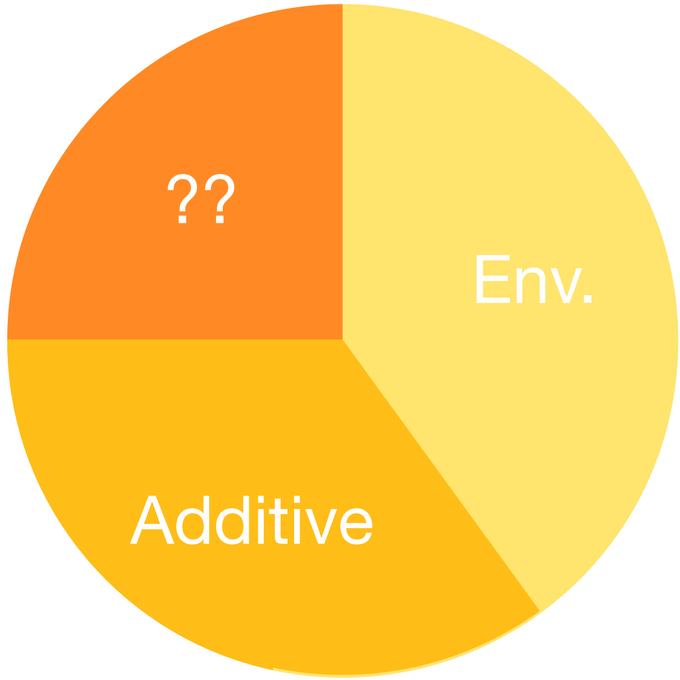
$\Longrightarrow$ underdetermined & combinatorially incomplete

*Number of atoms in the universe: ~ 10^{80}

Motivation

Multivariate approach to studying non-linear contributions in complex traits

- More than 11 million SNPs in human genome[1], ∼400k trait associations[2]
- Majority of the heritability of complex traits “missing”[3]
- Epistasis could explain missing heritability
- Computational methods to detect epistasis are underpowered or computationally resource intensive[4]

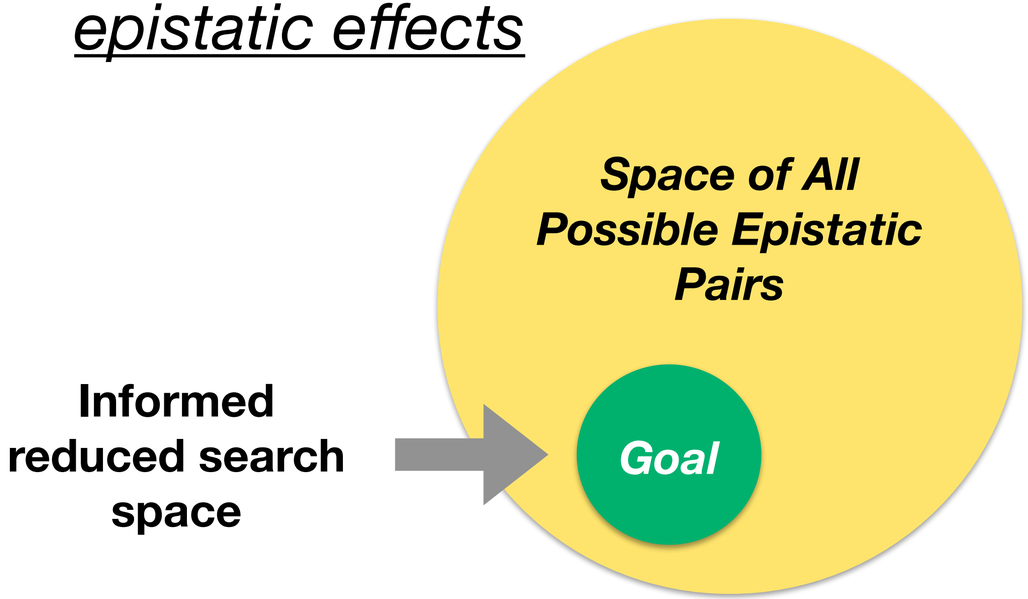


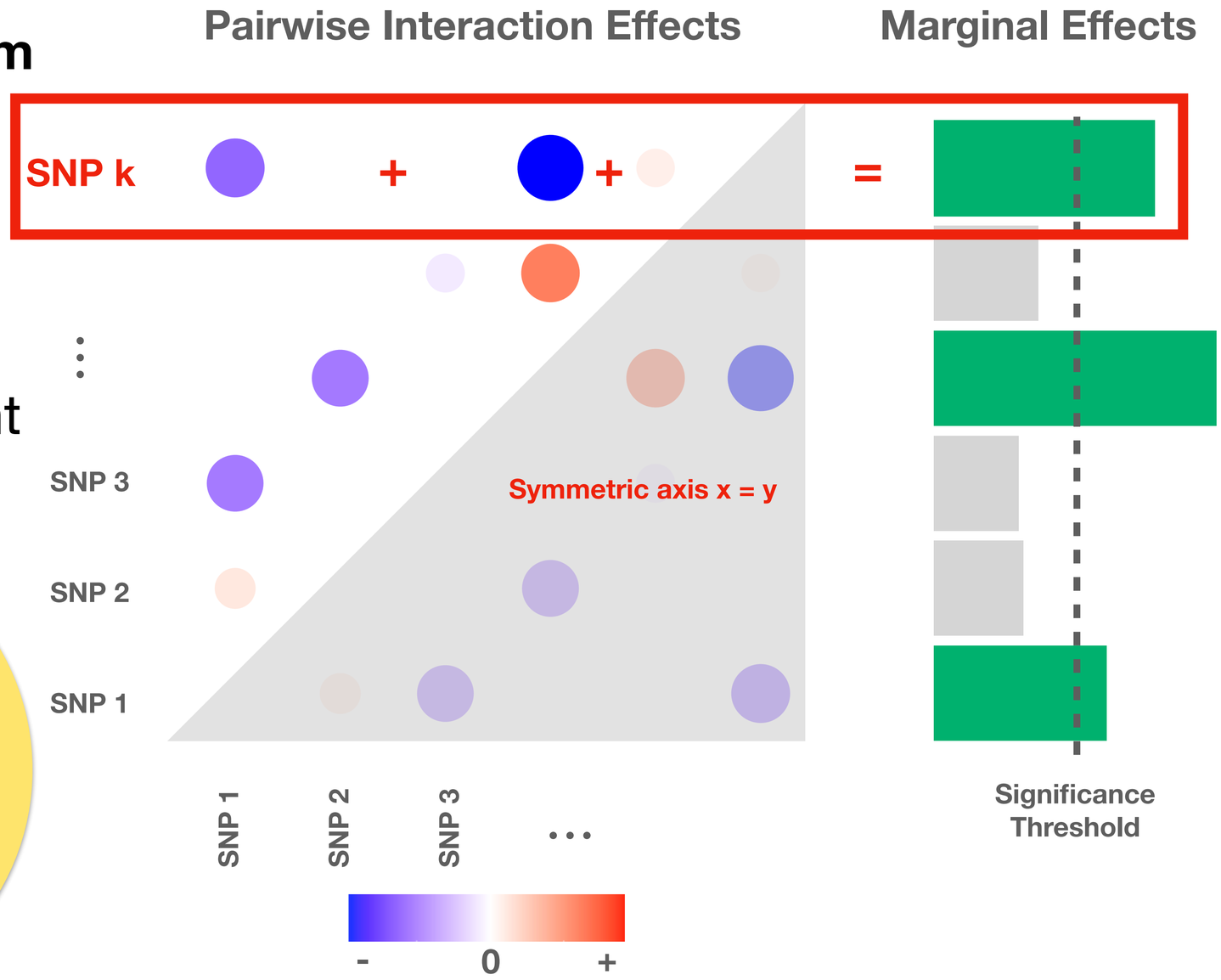
1 Madsen et al. (2007), *Genome Research*
2 Sollis et al. (2022), *Nucleic Acids Research*
3 Young (2019), *PLOS Genetics*
4 Crawford et al. (2017), *PLOS Genetics*

Explicit search space

Epistasis as combinatorial problem

- There are $p(p-1)/2$ possible interacting pairs for p SNPs
- **Idea:** Prioritize search for variant interactions using *marginal epistatic effects*

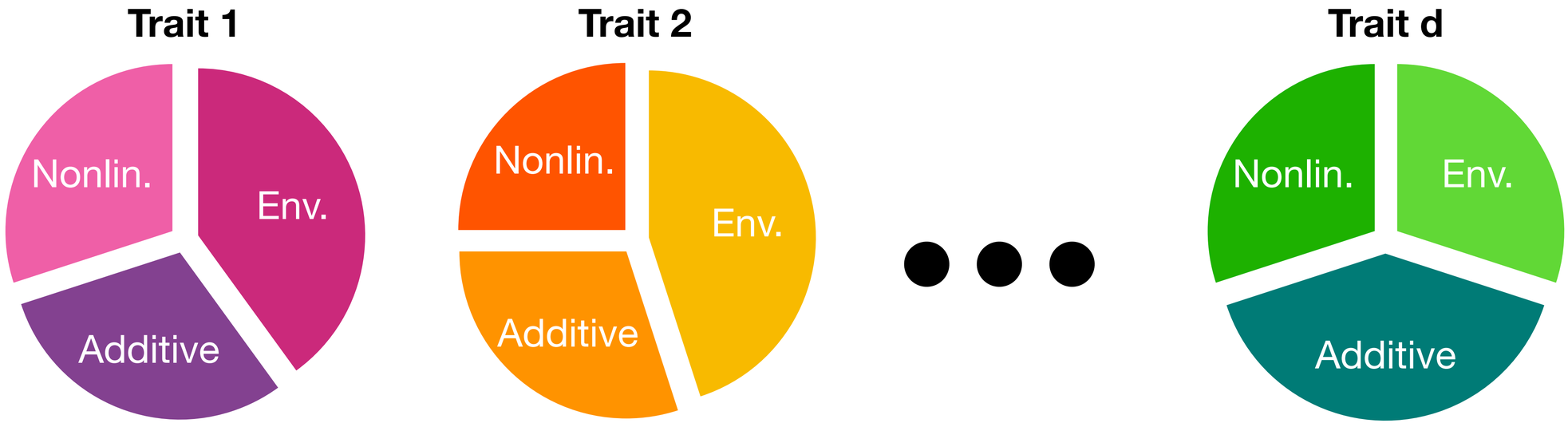




Multivariate LMM

- Genetic correlations between traits maintained by pleiotropy[1]
- Multivariate modelling improves GWAS[2]

⇒ Can we leverage **genetic correlations** to improve detection of epistasis?



1 Chebib and Guillaume (2021), *Genetics*
2 Zhou and Stephens (2014), *Nature*

Approach

Starting point: The Marginal Epistasis Test (MAPIT)

Population mean

Variant vectors

Error

$$\mathbf{y} = \mu + \beta_k \mathbf{x}_k + \sum_{l \neq k} \beta_l \mathbf{x}_l + \sum_{l \neq k} \alpha_l (\mathbf{x}_k \circ \mathbf{x}_l) + \varepsilon, \quad \varepsilon \sim \mathbf{MVN}\left(\mathbf{0}, \tau^2 \mathbf{I}\right)$$

Quantitative Trait

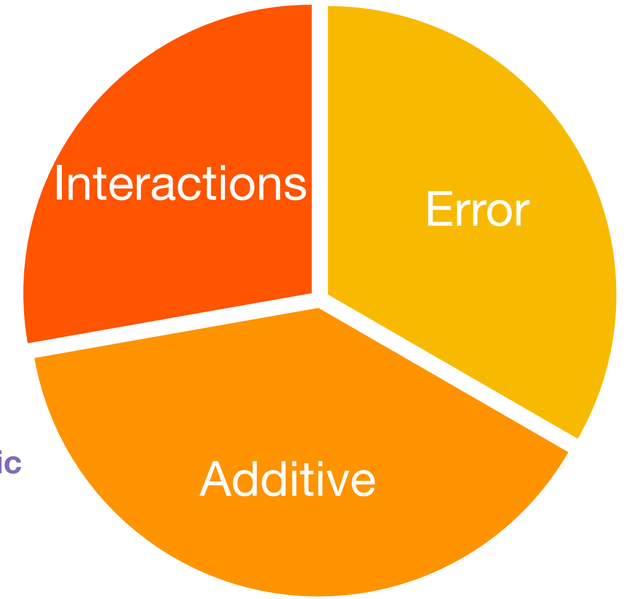
Linear Effect Sizes

Interaction Effect Size

$$= \mu + \beta_k \mathbf{x}_k + \mathbf{m}_k + \mathbf{g}_k + \varepsilon$$

Additive Variance Component

Pariwise Epistatic Variance Component



Crawford et al. (2017), *PLOS Gen*

Approach

Normal assumption for effect size trick for underdetermined data

$$\mathbf{y} = \mu + \beta_k \mathbf{x}_k + \mathbf{m}_k + \mathbf{g}_k + \varepsilon$$

- Genetic Relatedness Matrix
  $\mathbf{K} = \mathbf{X}_{-k}\mathbf{X}_{-k}^T$
- Covariance of the interaction of SNP *k* with it's background
  $\mathbf{G} = \mathbf{D}_k\mathbf{K}\mathbf{D}_k$ with
  $\mathbf{D}_k = \mathrm{diag}(\mathbf{x}_k)$
- Estimate variance parameters jointly using MQS

$$\mathbf{m}_k \sim \mathbf{MVN}\left(\mathbf{0}, \omega^2\mathbf{K}\right)$$

$$\mathbf{g}_k \sim \mathbf{MVN}\left(\mathbf{0}, \sigma^2\mathbf{G}\right)$$

$$\varepsilon \sim \mathbf{MVN}\left(\mathbf{0}, \tau^2\mathbf{I}\right)$$

Crawford et al. (2017), *PLOS Gen*

Approach

Multivariate extension of MAPIT (mvMAPIT)

MAPIT

- One trait $\mathbf{y} = (y_1, \ldots, y_n)^{\mathsf{T}}$
- Only covariance between samples $\mathbf{g}_k \sim \mathbf{MVN}\left(\mathbf{0}, \sigma^2\mathbf{G}\right)$
- Estimate variance components $\hat{\sigma}^2 = \mathbf{y}^T\mathbf{A}_k\mathbf{y}$

Crawford et al. (2017), *PLOS Gen*

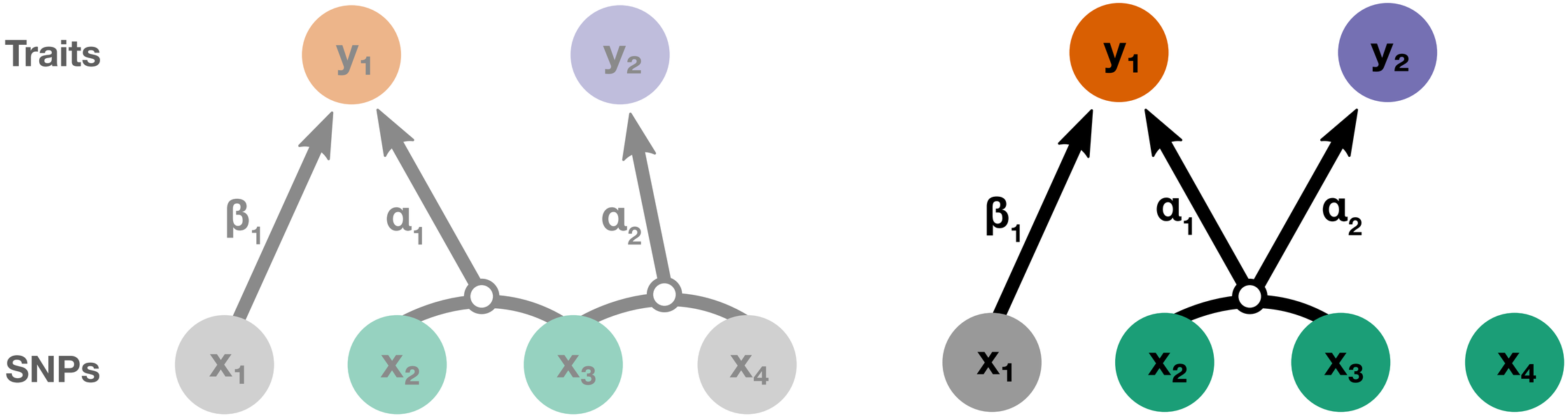
mvMAPIT

- Many traits $\mathbf{Y} = \begin{pmatrix} y_{11} & \cdots & y_{1d} \\ \vdots & \ddots & \vdots \\ y_{n1} & \cdots & y_{nd} \end{pmatrix}$
- Covariance between samples and variance components $\mathbf{g}_k \sim \mathrm{MN}_{n\times d}\left(0, \mathbf{V}_G, \sigma^2\mathbf{G}\right)$
- Estimate d choose 2 variance and covariance components $\hat{\sigma}^2_{12} = \mathbf{y}_1^T\mathbf{A}_k\mathbf{y}_2$

Stamp et al. (2023), *G3*

mvMAPIT

Modelling cross-trait genetic correlations of interaction effects



Stamp et al. (2023), *G3*

MAPIT

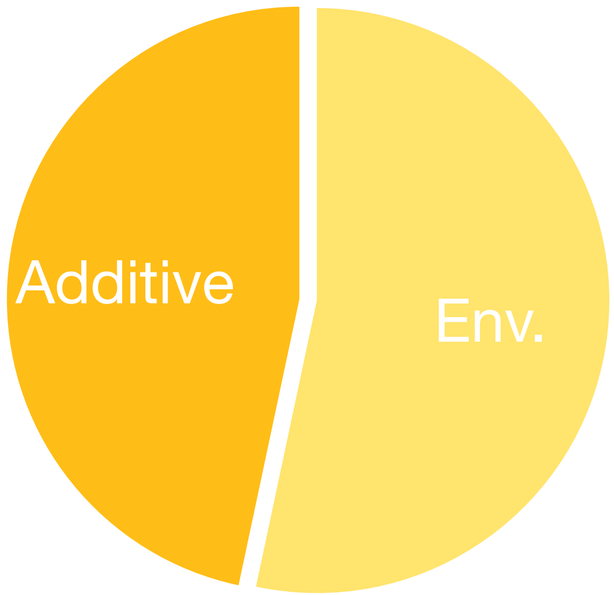
Simulations of complex traits

Scenarios

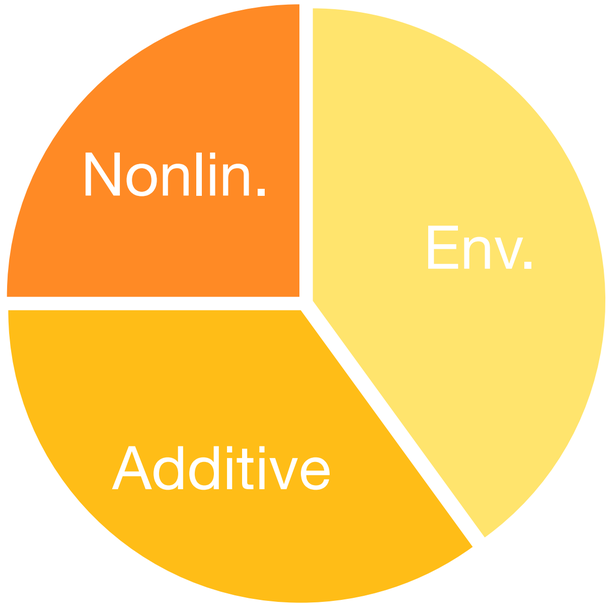
- Null Hypothesis true: no epistasis
- Epistasis with varying parameters

Parameters

- Broad sense heritability H^2
- Proportion of heritable variance due to epistasis $H^2(1-\rho)$



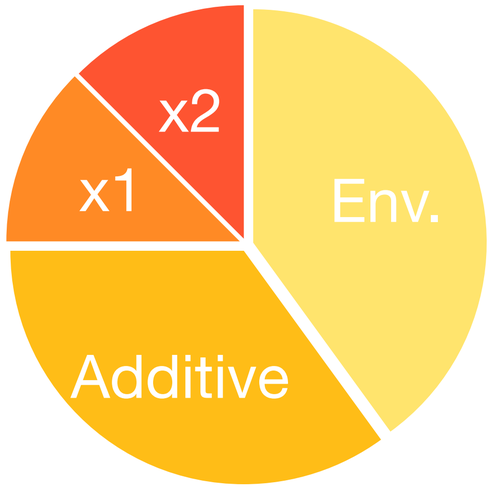
$H_0 : \sigma^2 = 0$



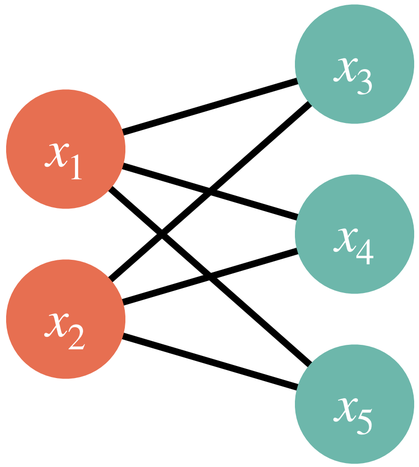
$H_1 : \sigma^2 \neq 0$

MAPIT

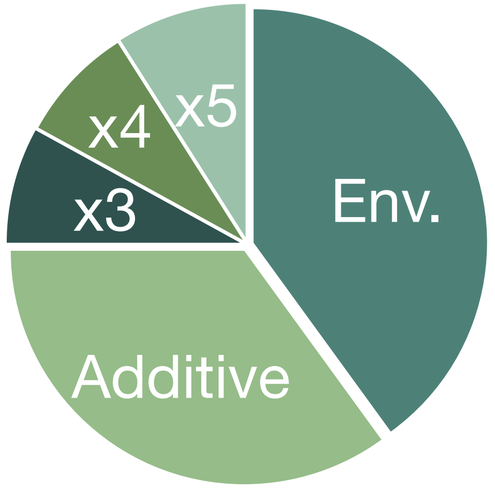
Simulations of complex traits



Group 1



Group 2



Additive SNPs

Epistatic Group 1

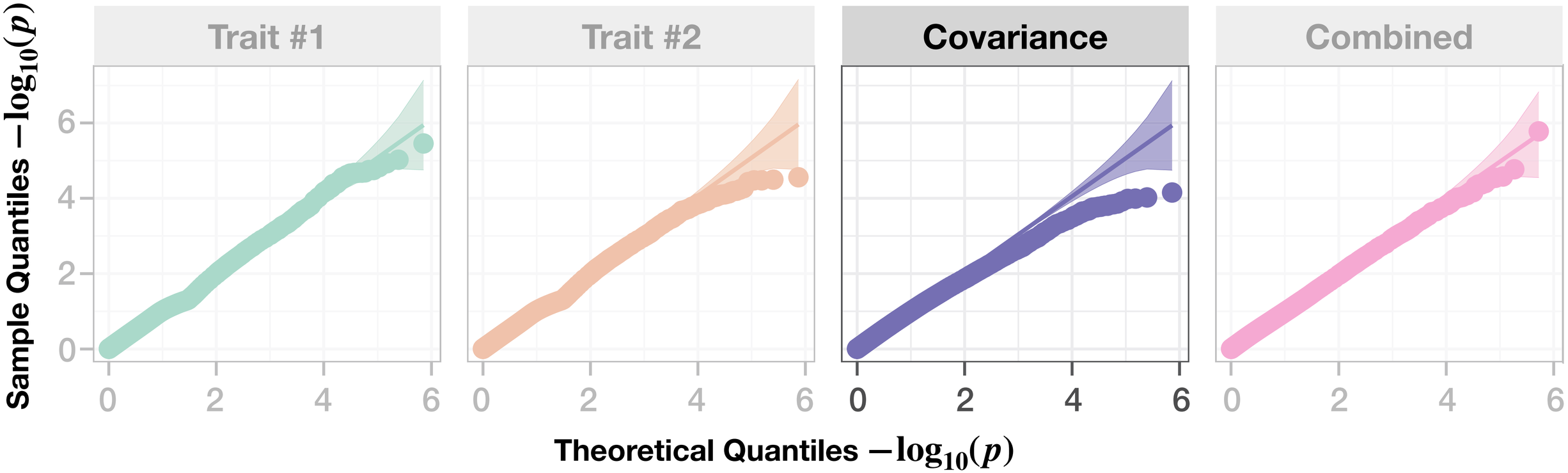
Epistatic Group 2

Marginal epistasis e.g.

- $\mathbf{g}_{x_1} = (\mathbf{x}_1 \circ \mathbf{x}_3) \cdot \alpha_{13} + (\mathbf{x}_1 \circ \mathbf{x}_4) \cdot \alpha_{14} + (\mathbf{x}_1 \circ \mathbf{x}_5) \cdot \alpha_{15}$
- $\mathbf{g}_{x_3} = (\mathbf{x}_1 \circ \mathbf{x}_3) \cdot \alpha_{13} + (\mathbf{x}_2 \circ \mathbf{x}_3) \cdot \alpha_{23}$

QQ-Plots*

mvMAPIT is well calibrated

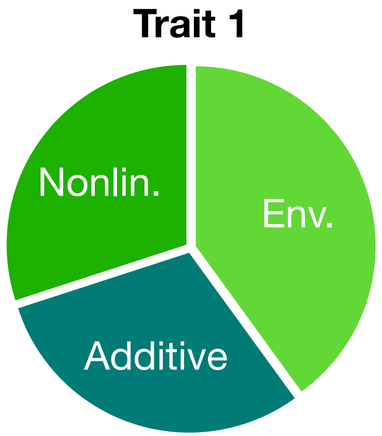


* Simulated data with null hypothesis true

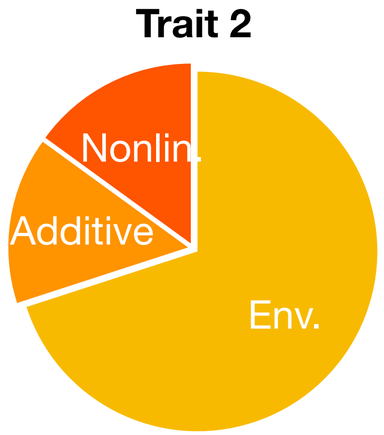
Stamp et al. (2023), *G3*

Empirical Power

Genetic correlations improve power of mvMAPIT

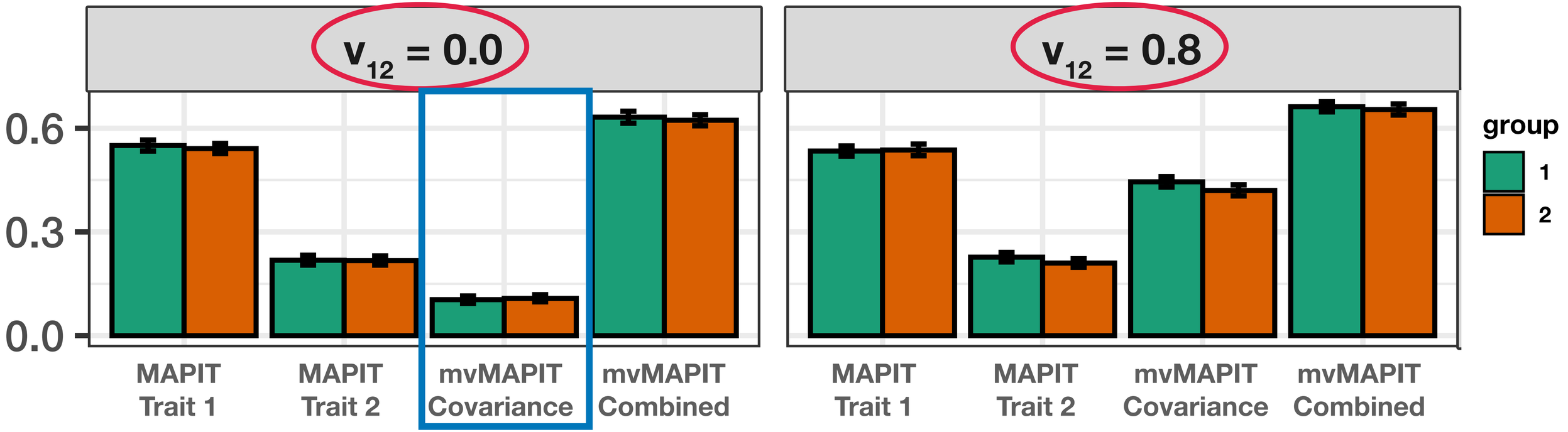


$H^2 = 0.6$



$H^2 = 0.3$

Correlation between epistatic effect sizes V_{12}



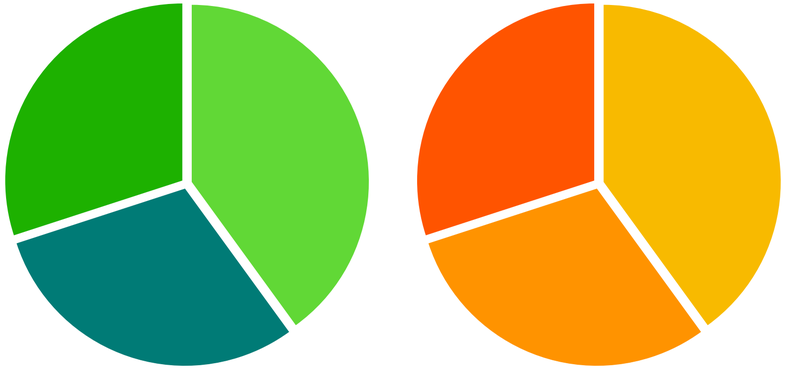
*significance threshold $\alpha = 0.05; \rho = 0.5$

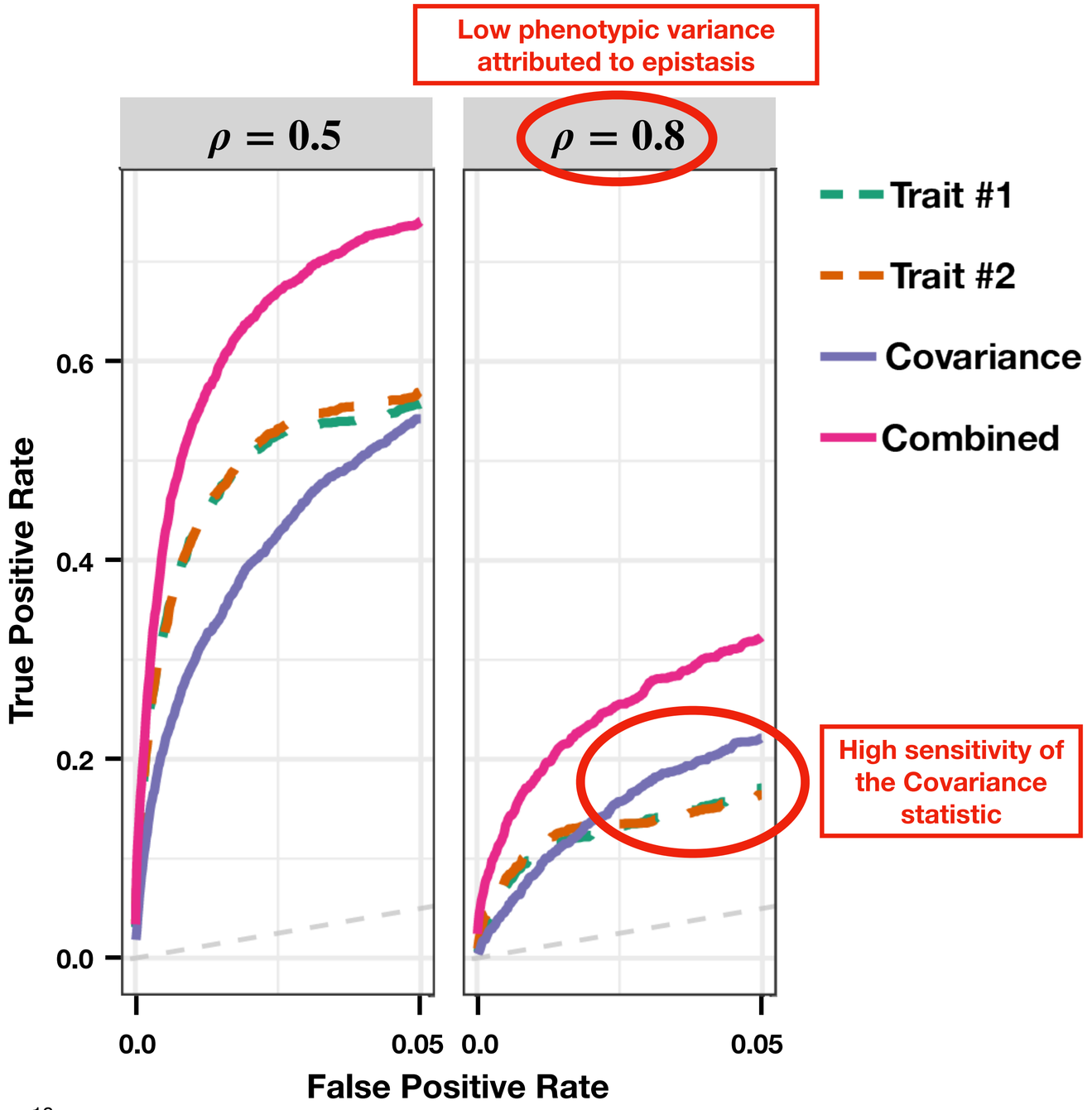
Stamp et al. (2023), *G3*

ROC Curves

Genetic correlations increase sensitivity of mvMAPIT

- Heritability $H^2 = 0.6$
- High correlation $v_{12} = 0.8$
- Steeper curves indicate higher sensitivity

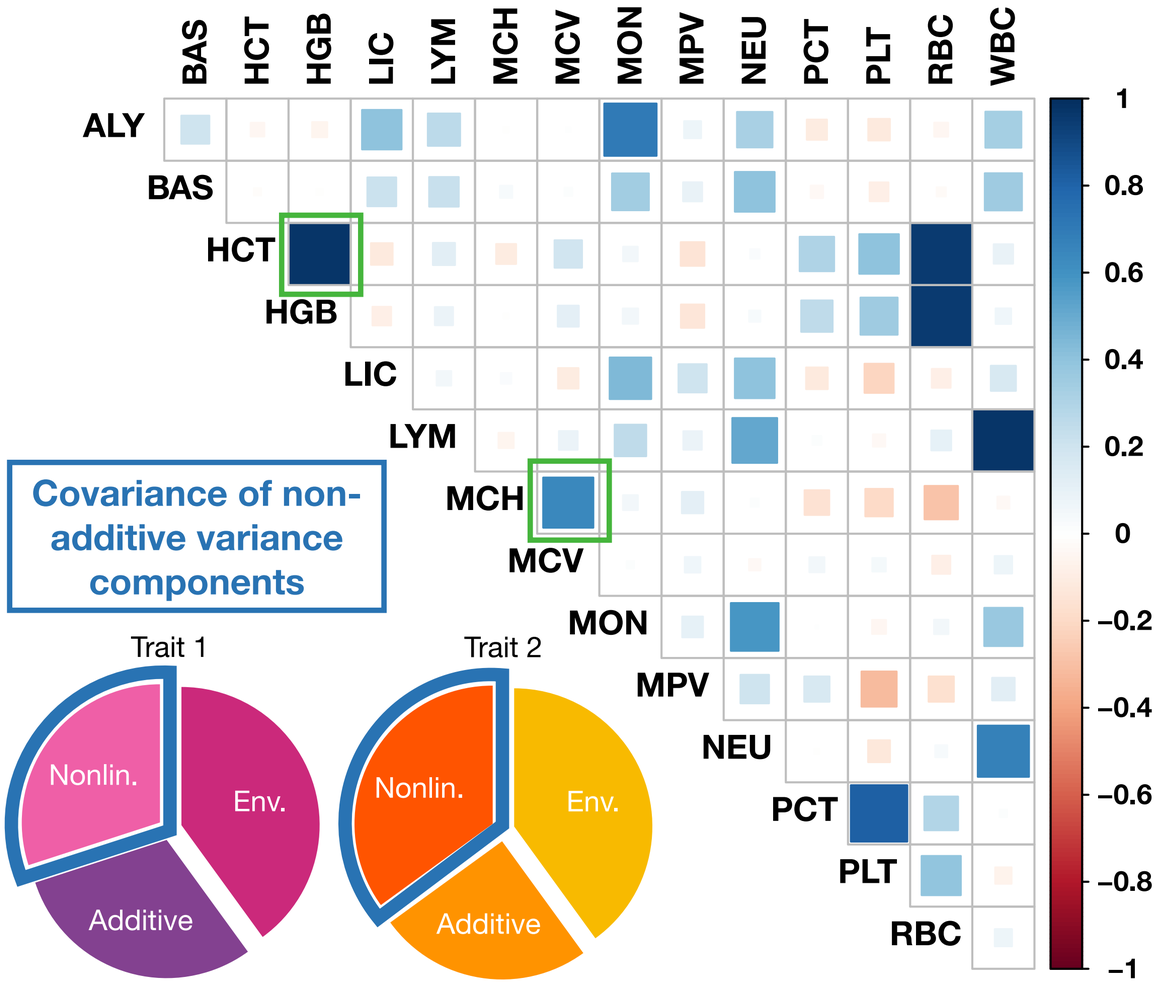




*Trait 1 & Trait 2 correspond to baseline (MAPIT)

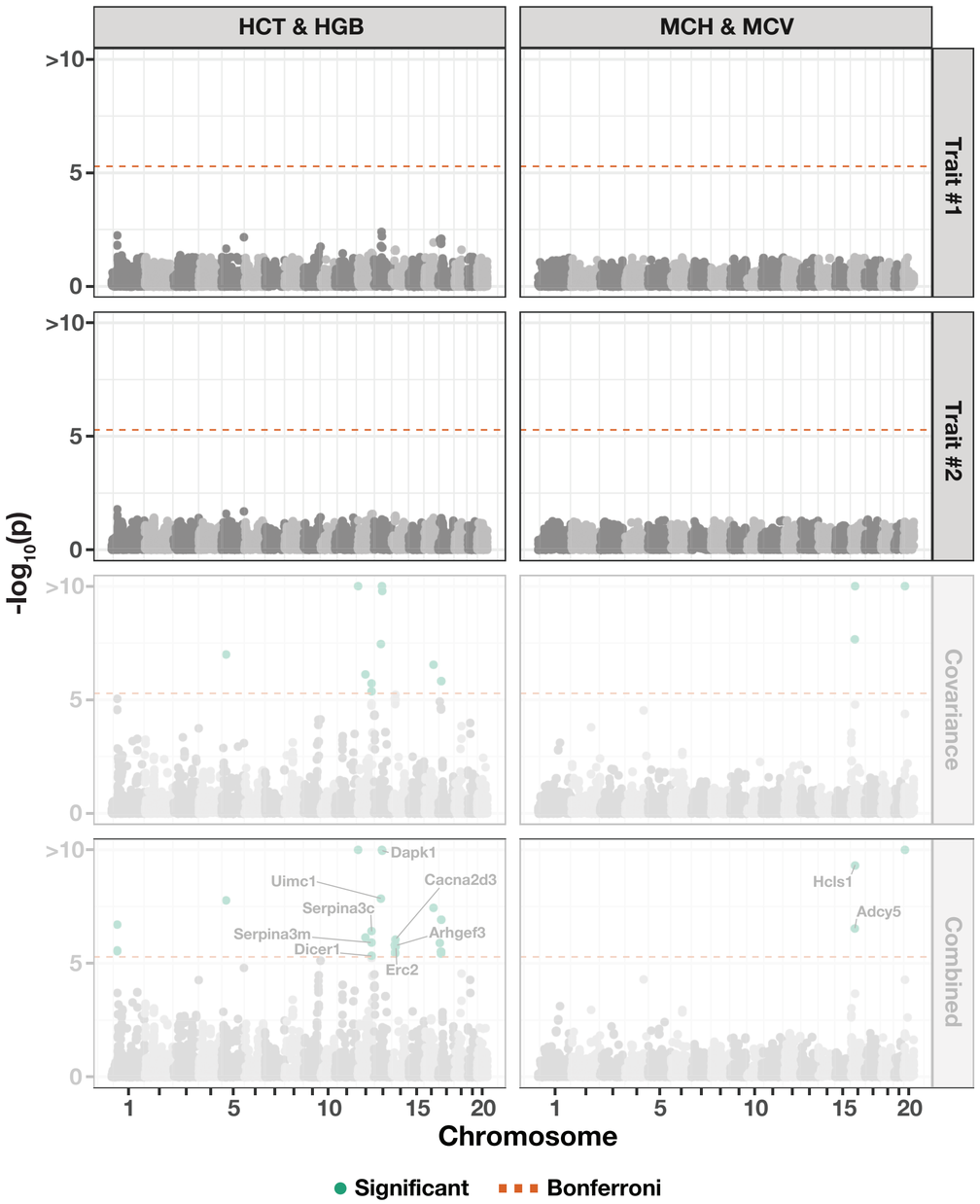
Real Data*

Genetic correlations reveal strong signal of epistasis



Covariance of non-additive variance components

* Hematology traits of WTCCC Mice



MAPIT
Trait 1

MAPIT
Trait 2

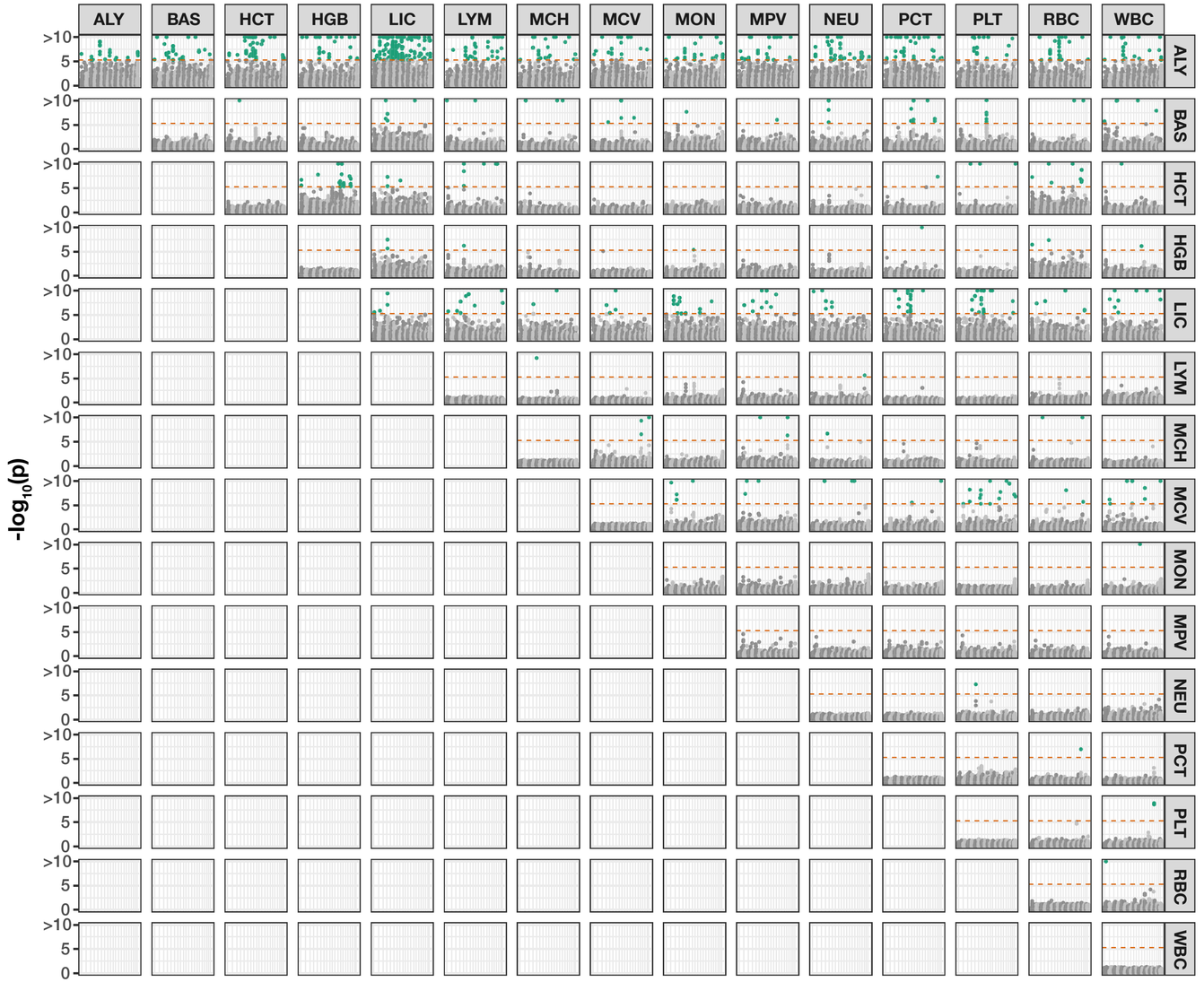
mvMAPIT
Covariance
Trait 1 & Trait 2

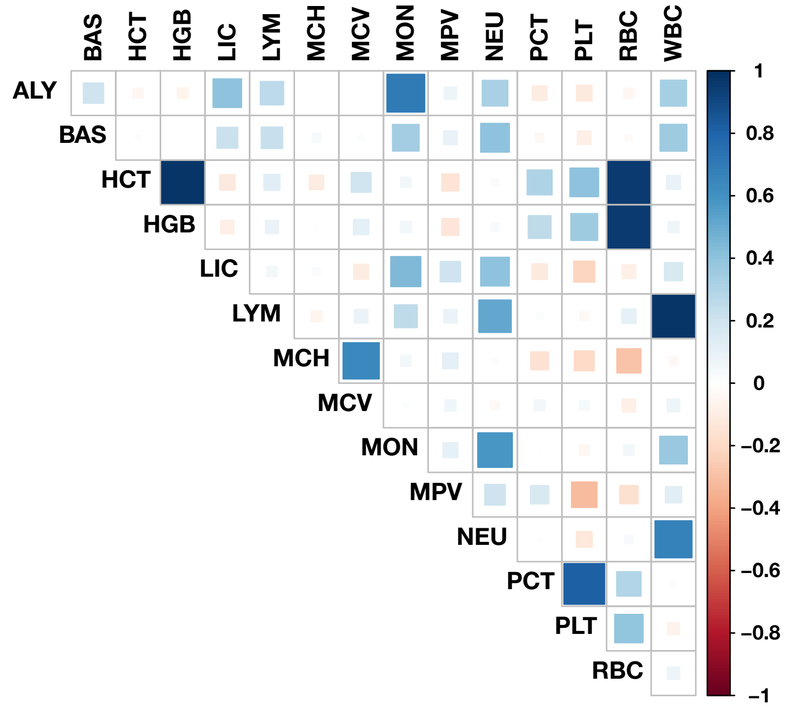
mvMAPIT
Combined
Trait 1 & Trait 2 & Covariance

Stamp et al. (2023), *G3*

Real Data*

New significant associations across many trait pairs



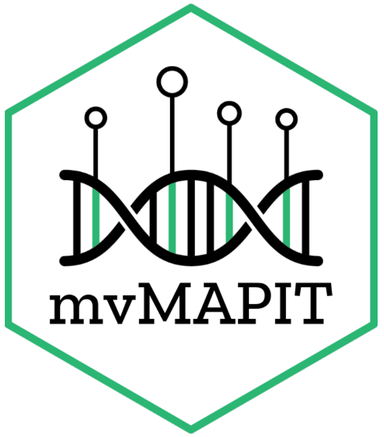


* Hematology traits of WTCCC Mice

Stamp et al. (2023), *G3*

Weaknesses

- Time complexity scaling with sample size
- Unknown interaction partner
- Meta analysis p-value interpretability



Strengths

- Analysis of shared genetic architecture of traits
- Correlation between effects improves sensitivity
- Marginalisation accumulates weak effects to strong signal
- Marginalisation reduces search space

Acknowledgements

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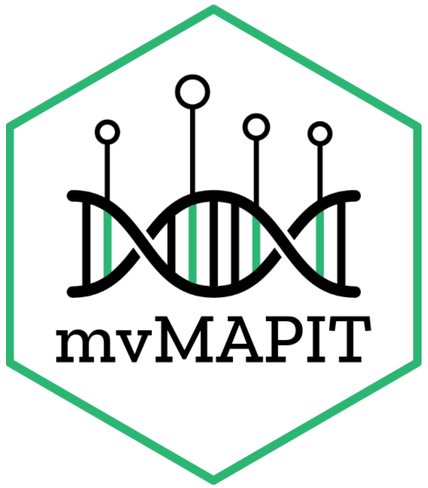
Wai Shing Tang
Whitney Sloneker
Yu Zhong
Collin Small
Ryan Huang

mvMAPIT

- Code and documentation on GitHub: https://lcrawlab.github.io/mvMAPIT/
- R package published on CRAN: https://cran.r-project.org/package=mvMAPIT

```
install.packages('mvMAPIT')
```



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Relevant References

Variance Component Estimation

- X. Zhou. "A unified framework for variance component estimation with summary statistics in genome-wide association studies." Ann. Appl. Stat. 11 (4) 2027 - 2051, December 2017. https://doi.org/10.1214/17-AOAS1052

Marginal Epistasis Detection

- L. Crawford, P. Zeng, S. Mukherjee, & X. Zhou, (2017). Detecting epistasis with the marginal epistasis test in genetic mapping studies of quantitative traits. PLOS Genetics, 13(7), e1006869. https://doi.org/10.1371/journal.pgen.1006869
- **J. Stamp**, A. DenAdel, D. Weinreich, & L. Crawford, (2023). Leveraging the Genetic Correlation between Traits Improves the Detection of Epistasis in Genome-wide Association Studies. G3 Genes|Genomes|Genetics, jkad118. https://doi.org/10.1093/g3journal/jkad118

Related Software/Source Code:

- mvMAPIT: https://lcrawlab.github.io/mvMAPIT/