# permGWAS: Efficient Permutation-based Genome-wide Association Studies for Skewed Phenotypic Distributions

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## Motivation

- Genome-wide association studies (GWAS) are a key tool to analyze relationship between genotypes and phenotypes
- Linear mixed models (LMMs) test whether a single genetic marker is associated with a given phenotype via the model

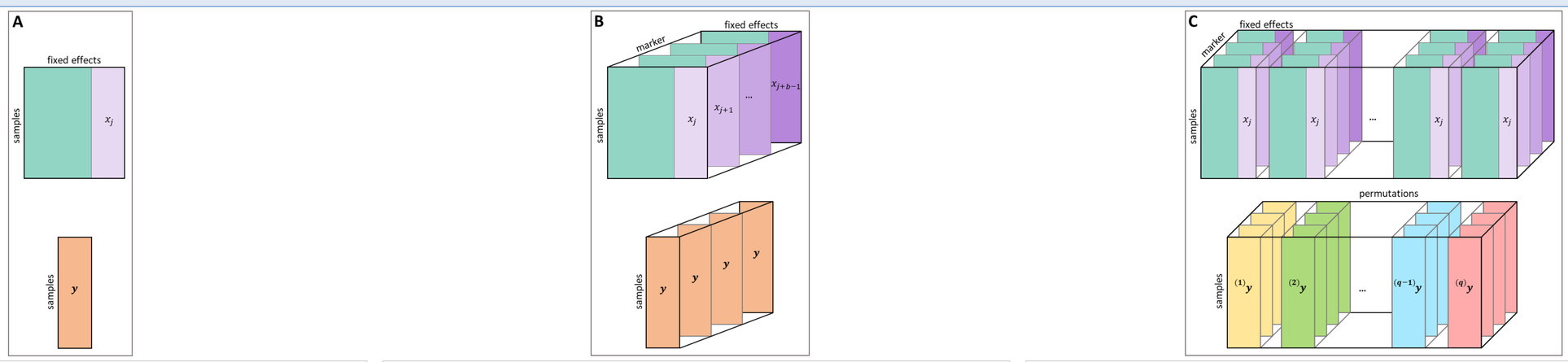
$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{u} + \boldsymbol{\epsilon} \qquad \boldsymbol{\epsilon} \sim \mathcal{N}(0, \sigma_e^2 \boldsymbol{I}),\ \boldsymbol{u} \sim \mathcal{N}(0, \sigma_g^2 \boldsymbol{K})$$

phenotype | fixed effects | random effects | noise | variance components | genetic similarity matrix

- Variance components are estimated by maximizing the likelihood function $L(\boldsymbol{\beta}, \sigma_g^2, \sigma_e^2)$

- Assumptions of Gaussian distribution and independent genetic markers are often violated in real-world data
- Commonly used Bonferroni significance threshold [1] often too conservative for normally distributed phenotypes or not stringent enough for phenotypes with skewed distributions
- Idea: permutation-based threshold via *maxT* method [2]:
  Permute phenotype $q$ times and compute minimal p-value for each permutation
  The adjusted threshold is the $\alpha^{th}$ percentile
- Problem: enormous computational complexity
- Solution: permGWAS, an efficient reformulation of LMMs using 3D and 4D tensors that can provide permutation-based thresholds

## permGWAS Architecture




**Basic Linear Mixed Model**
Estimate the effect of a single genetic marker:

$$L(\boldsymbol{\beta}, \sigma_g^2, \sigma_e^2) = \mathcal{N}(\boldsymbol{y}|\boldsymbol{X\beta}; \sigma_g^2\, \boldsymbol{K} + \sigma_e^2 \boldsymbol{I})$$

**Batch-wise Linear Mixed Model**
Estimate the effects of several genetic markers simultaneously using 3D-tensors:

$$L(\boldsymbol{\beta}_j^b, \sigma_g^2, \sigma_e^2) = \mathcal{N}(\boldsymbol{y}|\boldsymbol{X}_j^b \boldsymbol{\beta}_j^b; \sigma_g^2\, \boldsymbol{K} + \sigma_e^2 \boldsymbol{I})$$

**Permutation-based Linear Mixed Model**
Estimate the effects of several genetic markers and permutations simultaneously using 4D-tensors:

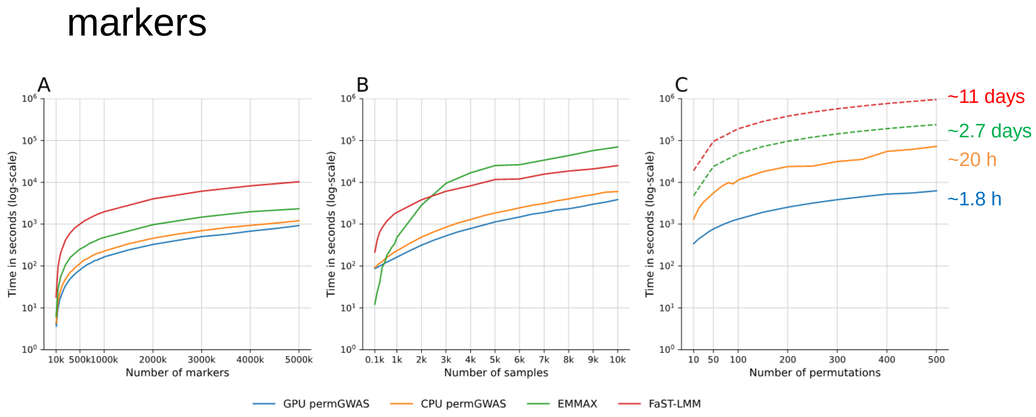
$$L({}^q\boldsymbol{\beta}_j^b, \sigma_g^2, \sigma_e^2) = \mathcal{N}(\boldsymbol{y}|{}^q\boldsymbol{X}_j^b\, {}^q\boldsymbol{\beta}_j^b; \sigma_g^2\, \boldsymbol{K} + \sigma_e^2 \boldsymbol{I})$$

## Results

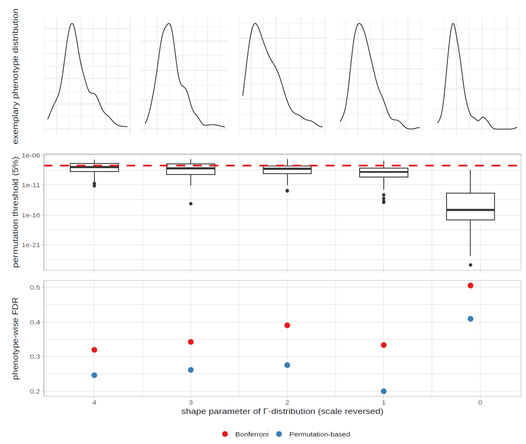
### Runtime comparison to state-of-the-art

Comparison of the runtime of permGWAS to EMMAX [3] and FaST-LMM [4] with respect to

A. Number of **markers** with fixed number of $1000$ samples
B. Number of **samples** with fixed number of $10^6$ markers
C. Number of **permutations** with $1000$ samples and $10^6$ markers



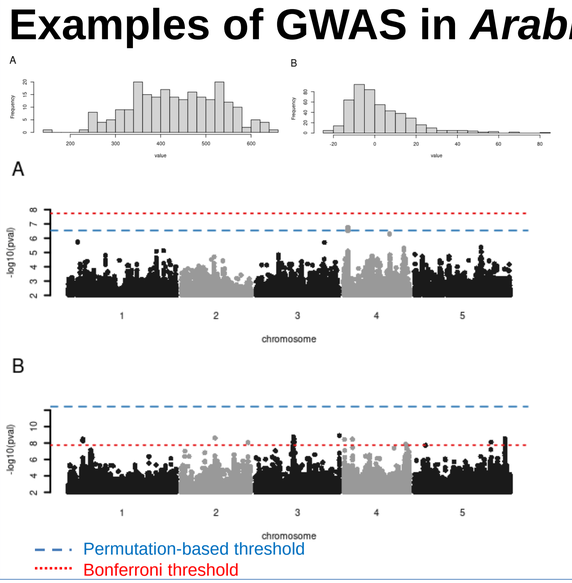

### False Discovery Rate for skewed phenotypes




Comparison of False Discovery Rate (FDR) of permutation-based thresholds and Bonferroni threshold for synthetic phenotypes with gamma-distributed noise:

- ➢ FDR increases when phenotypes become more skewed
- ➢ Permutation-based thresholds become more stringent for skewed phenotypes
- ➢ Permutation-based thresholds have lower FDR for skewed phenotypes than Bonferroni threshold

### Examples of GWAS in *Arabidopsis thaliana*




Analysis of GWAS results for real phenotypes from model plant *Arabidopsis thaliana [5,6]:*

A. For normally distributed phenotypes the permutation-based threshold is less conservative
B. For non-normally distributed phenotypes the permutation-based threshold is more stringent

## References

**Publication:**
John, M., Ankenbrand, M. J., Artmann, C., Freudenthal, J. A., Korte, A., & Grimm, D. G. (2022). Efficient Permutation-based Genome-wide Association Studies for Normal and Skewed Phenotypic Distributions. bioRxiv. **Accepted at ECCB 2022**

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**Website:**
http://bit.cs.tum.de

**GitHub:**
https://github.com/grimmlab/permGWAS

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