Efficient Estimation of Polygenic Effects via Multivariate Ridge Regression

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Outline

1. **Introduction**
   - Rationale and statistical model
2. **Coefficients**
   - Univariate
   - Multivariate
3. **Variances**
   - Univariate
   - Multivariate
4. **Simulations**
   - Study 1: Comparison to REML in small balanced data
   - Study 2: Performance in large unbalanced data
   - Limitations and other considerations
5. **Conclusion**

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Rationale

- Single-trait models for genomic prediction in plant breeding are well-stablished (e.g. GBLUP and BayesB)

- Phenotypes come from multiple locations, years, and quantitative traits; and most traits have genetically correlated breeding values

Rationale

- **Complex GxE / multi-trait patterns** (= higher accuracy)
- **Assess new phenomic traits** (*e.g.* canopy coverage in soy)
- **Computationally PROHIBITIVE***

* Zhou, X., & Stephens, M. (2014). Efficient multivariate linear mixed model algorithms for genome-wide association studies. *Nature methods*, *11*(4), 407-409.

Why would multivariate be any better?

Simple (bivariate) model:

INFORMATION GAIN

$$\mathbf{y} = \mathbf{g} + \mathbf{e}$$

$$Var\begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} \sigma^2_{a_1} & \sigma_{a_{12}} \\ \sigma_{a_{12}} & \sigma^2_{a_2} \end{bmatrix} + \begin{bmatrix} \sigma^2_{e_1} & \sigma_{e_{12}} \\ \sigma_{e_{12}} & \sigma^2_{e_2} \end{bmatrix}$$

Why marker ridge regression?

1. Regression-type models are easy to store and use for prediction
2. Compatible with the multi-stage[1,2] framework
3. Well-known properties: Gaussian, additive, and equivalent to GBLUP
4. No need to build and invert G matrix (which is not always positive definite)
5. Provides covariance components for meaningful statistics:
   - Heritability, reliability, accuracy, genetic correlations, selection indexes, correlated response

1. Smith, A., Cullis, B., and Gilmour, A. (2001). Applications: the analysis of crop variety evaluation data in Australia. Australian & New Zealand Journal of Statistics, 43(2), 129-145.
2. Mohring, J, and H-P Piepho, (2009) Comparison of weighting in two-stage analysis of plant breeding trials. Crop Sci. 49: 1977–1988.

Statistical model

$$\mathrm{y} = \mu + \mathbf{Z}\beta + \mathrm{e} \qquad (1)$$

- Where $\mathrm{y} = \{\mathrm{y}_1, \mathrm{y}_2, \ldots, \mathrm{y}_K\}$, $\mu = \{\mu_1, \mu_2, \ldots, \mu_K\}$, $\beta = \{\beta_1, \beta_2, \ldots, \beta_K\}$,
  $\mathrm{e} = \{\mathrm{e}_1, \mathrm{e}_2, \ldots, \mathrm{e}_K\}$, $\mathrm{Z} = \mathrm{BlockDiag}\{\mathbf{Z}_1, \mathbf{Z}_2, \ldots, \mathbf{Z}_K\}$
- Variances:

$$\Sigma_\beta = \begin{bmatrix} \sigma^2_{\beta(1)} & \cdots & \sigma_{\beta(1,K)} \\ \vdots & \ddots & \vdots \\ \sigma_{\beta(K,1)} & \cdots & \sigma^2_{\beta(K)} \end{bmatrix} \text{ and } \Sigma_e = \begin{bmatrix} \sigma^2_{e(1)} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma^2_{e(K)} \end{bmatrix}$$

Corresponding mixed model equation

Under the traditional framework, the mixed-model equations required to solve the multivariate ridge regression (eq. 1) can be written as follows:

$$\begin{bmatrix} \mathbf{1}_1'\mathbf{1}_1\sigma_{e_1}^{-2} & \dots & \mathbf{0} & \mathbf{1}_1'\mathbf{Z}_1\sigma_{e_1}^{-2} & \dots & \mathbf{0} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ \mathbf{0} & \dots & \mathbf{1}_K'\mathbf{1}_K\sigma_{e_K}^{-2} & \mathbf{0} & \dots & \mathbf{1}_K'\mathbf{Z}_K\sigma_{e_K}^{-2} \\ \mathbf{Z}_1'\mathbf{1}_1'\sigma_{e_1}^{-2} & \dots & \mathbf{0} & \mathbf{Z}_1'\mathbf{Z}_1\sigma_{e_1}^{-2} + \mathbf{I}_m\sigma_\beta^{11} & \dots & \mathbf{I}_m\sigma_\beta^{1K} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \dots \\ \mathbf{0} & \dots & \mathbf{Z}_K'\mathbf{1}_K'\sigma_{e_K}^{-2} & \mathbf{I}_m\sigma_\beta^{K1} & \vdots & \mathbf{Z}_K'\mathbf{Z}_K\sigma_{e_K}^{-2} + \mathbf{I}_m\sigma_\beta^{KK} \end{bmatrix} \begin{bmatrix} \hat{\mu}_1 \\ \vdots \\ \hat{\mu}_k \\ \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_K \end{bmatrix} = \begin{bmatrix} \sigma_{e1}^{-2}\mathbf{1}_1'\mathbf{y}_1 \\ \vdots \\ \sigma_{e_K}^{-2}\mathbf{1}_k'\mathbf{y}_K \\ \sigma_{e1}^{-2}\mathbf{Z}_1'\mathbf{y}_1 \\ \vdots \\ \sigma_{e_K}^{-2}\mathbf{Z}_k'\mathbf{y}_K, \end{bmatrix} \quad (2)$$

where σ_β^{ij} is the element at position ij of $\mathbf{\Sigma}_\beta^{-1}$. This setup involves storing K times the cross-product or marker scores ($\mathbf{Z}_k'\mathbf{Z}_k$), each with dimension $m \times m$.

Moreover, this **huge** matrix must be **inverted** for the estimation of covariance components: $\hat{\Sigma}_{\beta(i,j)} = m^{-1}[\hat{\boldsymbol{\beta}}_i'\hat{\boldsymbol{\beta}}_j + \mathrm{tr}(\mathbf{C}^{ij})]$

Computing very large multivariate models is **impossible**

unless…

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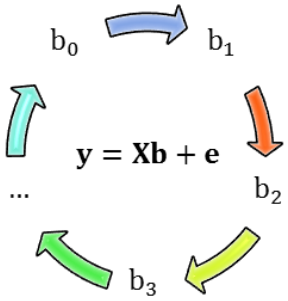
Coefficients for univariate model

1. Whole-genome regression (*e.g.* BayesA) rely on the *Gauss-Seidel* method [1]
2. GS has only two steps, whereas coordinate descent has three [2]
3. It avoids building the systems of equations altogether!!
4. Estimates one marker effects, then uses residuals to update the next effect

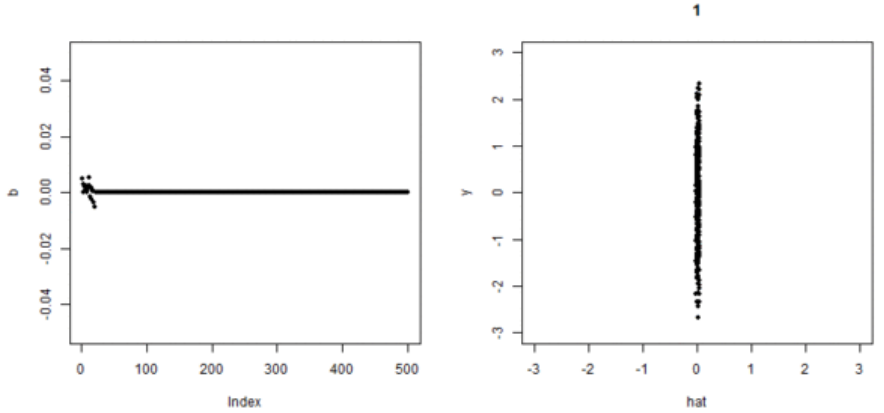


for j in 1:p {

$$\hat{b}_j^{t+1} = \frac{x_j'\hat{e}^t + x_j'x_j\hat{b}_j^t}{x_j'x_j + \lambda}$$

$$\hat{e}^{t+1} = \hat{e}^t - x_j\left(\hat{b}_j^{t+1} - \hat{b}_j^t\right)$$

}



1 Legarra, A., & Misztal, I. (2008). Computing strategies in genome-wide selection. *Journal of dairy science*, *91*(1), 360-366.
2 Xavier, A. (2021). Technical nuances of machine learning. *Crop Breeding and Applied Biotechnology*, 21.

Coefficients for multivariate model

For updating estimated marker effects we define, $\hat{\boldsymbol{\beta}}_j^{'(t)} = [\hat{\beta}_{j1}^{(t)}\ \hat{\beta}_{j1}^{(t)}\ \ldots\ \hat{\beta}_{jK}^{(t)}]$ to be the vector of estimated marker effects for marker j and all K environments, $\mathbf{Z}_j = \oplus_{k=1}^{K} \boldsymbol{z}_{jk}$ to be a matrix containing marker scores at marker j, and $\hat{\boldsymbol{\Sigma}}_e^{(t)} = Diag\{\hat{\sigma}_{e1}^{2(t)}, \hat{\sigma}_{e2}^{2(t)}, \ \ldots\ , \hat{\sigma}_{ek}^{2(t)}\}$ to be a diagonal matrix of estimated residual variances. Effects for marker j are initialized with zero and updated as

$$\hat{\boldsymbol{\beta}}_j^{(t+1)} = (\hat{\boldsymbol{\Sigma}}_e^{-1(t)}\mathbf{Z}_j'\mathbf{Z}_j + \hat{\boldsymbol{\Sigma}}_\beta^{-1(t)})^{-1}\mathbf{Z}_j'\hat{\boldsymbol{\Sigma}}_e^{-1(t)}(\mathbf{Z}_j\hat{\boldsymbol{\beta}}_j^{(t)} + \hat{\boldsymbol{e}}^{(t)}), \tag{5}$$

and before moving to the next marker, the residual vector is updated as

$$\hat{\boldsymbol{e}}^{(t+1)} = \hat{\boldsymbol{e}}^{(t)} - \mathbf{Z}_j'(\hat{\boldsymbol{\beta}}_j^{(t+1)} - \hat{\boldsymbol{\beta}}_j^{(t)}). \tag{6}$$

Note that the computation of Kronecker products are not necessary for the multivariate Gauss-Seidel formulation (eq. 5) as long as the residual covariance $\hat{\boldsymbol{\Sigma}}_e$ is a diagonal matrix.

NO KRONECKER PRODUCTS!!!!

For(j in 1:p) {

These genetic covariances are the whole key for the MRR model

1st solve for beta

$$\begin{bmatrix} \hat{\Sigma}_{\beta}^{11} + \mathbf{z}'_{j(1)}\mathbf{z}_{j(1)}\sigma_{e(1)}^{-2} & \hat{\Sigma}_{\beta}^{12} \\ \hat{\Sigma}_{\beta}^{21} & \hat{\Sigma}_{\beta}^{22} + \mathbf{z}'_{j(2)}\mathbf{z}_{j(2)}\sigma_{e(2)}^{-2} \end{bmatrix} \begin{bmatrix} \hat{\beta}_{j(1)}^{t+1} \\ \hat{\beta}_{j(2)}^{t+1} \end{bmatrix} = \begin{bmatrix} \sigma_{e(1)}^{-2}\left(\mathbf{z}'_{j(1)}\mathbf{z}_{j(1)}\hat{\beta}_{j(1)}^{t} + \mathbf{z}'_{j(1)}\hat{e}_{1}^{t}\right) \\ \sigma_{e(2)}^{-2}\left(\mathbf{z}'_{j(2)}\mathbf{z}_{j(2)}\hat{\beta}_{j(2)}^{t} + \mathbf{z}'_{j(2)}\hat{e}_{2}^{t}\right) \end{bmatrix}$$

2nd update residuals

$$\begin{bmatrix} \hat{e}_{j(1)}^{t+1} \\ \hat{e}_{j(2)}^{t+1} \end{bmatrix} = \begin{bmatrix} \hat{e}_{1}^{t} + \mathbf{z}'_{j(1)}(\hat{\beta}_{j(1)}^{t+1} - \hat{\beta}_{j(1)}^{t}) \\ \hat{e}_{2}^{t} + \mathbf{z}'_{j(2)}(\hat{\beta}_{j(2)}^{t+1} - \hat{\beta}_{j(2)}^{t}) \end{bmatrix}$$

}

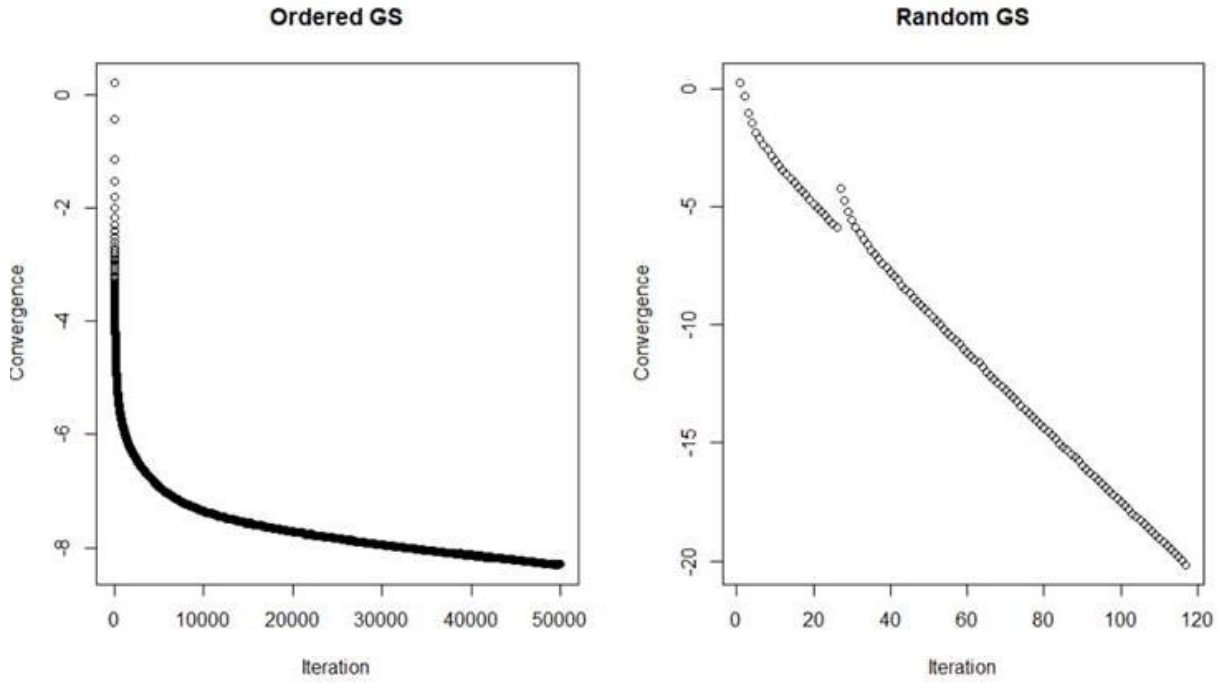
Color code

- **Computed only once, before the loop starts (ZpZ)**
- **Computed once every iteration**
- **Computed for each marker in every iteration**

What is in memory?

- Z (n x m)
- B (m x k)
- E (n x k)
- ZpZ (m x k)
- $\hat{\Sigma}_{\beta}^{-1}$ (k x k)
- $\hat{\Sigma}_{e}^{-1}$ (k)

Side note: Updating markers in random order can speed up convergence



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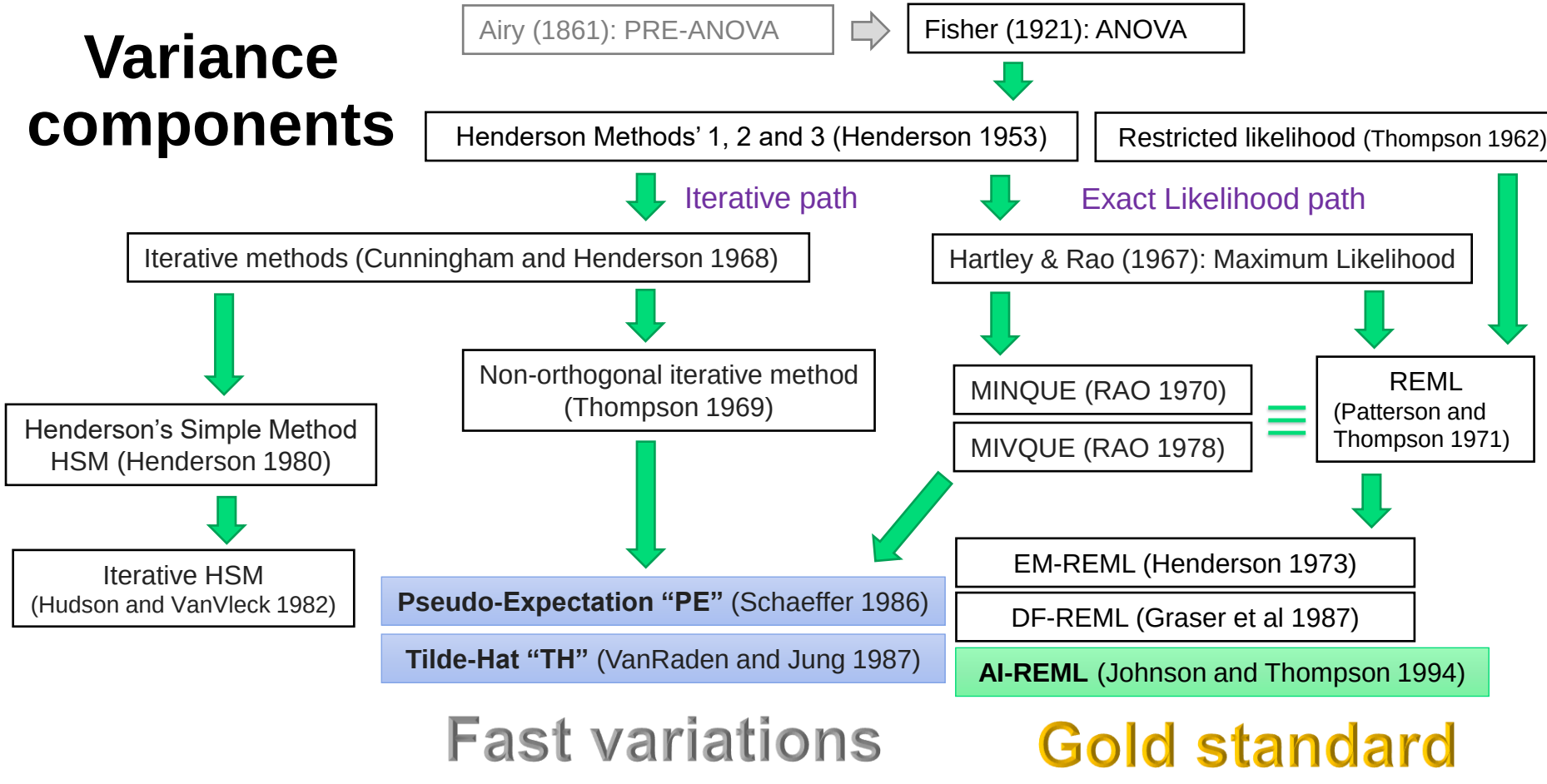
Variance components



Univariate case: Variance components

- REML

$$\hat{\sigma}^2_{\beta} = \frac{y'P'V_iPy}{tr(PV_i)} = \frac{y'S'V^{-1}ZZ'V^{-1}Sy}{tr(V^{-1}SZZ')} = \frac{\hat{\beta}\hat{\beta}}{tr(V^{-1}\tilde{Z}'\tilde{Z})}$$

"Let's get rid of this V^{-1}!"

All methods yield the same residual variance:

$$\hat{\sigma}^2_e = \frac{y'e}{n-1}$$

V is a pain to compute

- Schaffer's (Thompson's) Pseudo-Expectation

$$\hat{\sigma}^2_{\beta} = \frac{y'S'\cancel{V^{-1}}ZZ'V^{-1}Sy}{tr(\cancel{V^{-1}}SZZ')} = \frac{\tilde{y}'Z\hat{\beta}}{tr(\tilde{Z}'\tilde{Z})}$$

"Let's replace this V^{-1} by something similar, but easier to compute!"

$$\mathbf{V = ZZ'\sigma^2_{\beta} + I\sigma^2_{\beta}}$$

$$S = I - (X'X)^{-1}X'; \quad P = V^{-1}S$$

$$P = V^{-1} - V^{-1}(X'V^{-1}X)^{-1}X'V^{-1}$$

$$PX = SX = 0$$

$$Sy = \text{Centralized } y = \tilde{y}$$

$$SZ = \text{Centralized } Z = \tilde{Z}$$

- VanRaden's Tilde-Hat

$$\hat{\sigma}^2_{\beta} = \frac{y'S'D^{-1}ZZ'V^{-1}Sy}{tr(D^{-1}SZZ')} = \frac{\tilde{y}D^{-1}Z\hat{\beta}}{tr(D^{-1}\tilde{Z}'\tilde{Z})} = \frac{\tilde{\beta}\hat{\beta}}{tr(D^{-1}\tilde{Z}'\tilde{Z})}$$

$\tilde{\beta}$

$$D = Diag(Z'Z\hat{\sigma}^{-2}_e + I\hat{\sigma}^{-2}_{\beta})$$

Multivariate case: (co)variance components

$$\hat{\sigma}^2_{\beta(k)} = \frac{\tilde{\beta}_k \hat{\beta}_k}{\mathrm{tr}(D_k^{-1} \tilde{Z}_k{}' \tilde{Z}_k)}$$

$$\hat{\sigma}_{\beta(k,k')} = \frac{\tilde{\beta}_k \hat{\beta}_{k'} + \tilde{\beta}_{k'} \hat{\beta}_k}{\mathrm{tr}(D_k^{-1} \tilde{Z}_k{}' \tilde{Z}_k) + \mathrm{tr}(D_{k'}^{-1} \tilde{Z}_{k'}{}' \tilde{Z}_{k'})}$$

$$\hat{\sigma}^2_{e(k)} = \frac{y_k' \hat{e}_k}{n_k - 1}$$

Note: Schaffer's is obtained by assuming $\mathbf{D} = \mathbf{I}$

No V, No C, No LHS,
No determinants,
No dense inversions

Color code

- Computed only once, before the loop starts (ZpZ)
- Computed once every iteration
- Computed once for PE, and every iteration for TH

What is in memory?

- Z (n x m)
- Bhat (m x k)
- Btilde (m x k)
- E (n x k)
- Y (n x k)
- Ytilde (n x k)
- ZpZ (m x k)
- ZpZtilde (m x k)
- $\hat{\Sigma}_{\beta}$ (k x k)
- $\hat{\Sigma}_{e}$ (k)
- N (k)

An intuitive derivation for Schaeffer's method?

The genetic covariance is simply estimated as the cross-prediction between traits A and B normalized by mean squared genotypes (MSX)!!

Centered phenotype of **A** | **A** predicted from **B** | Centered phenotype of **B** | **B** predicted from **A**

$$\widehat{\sigma}_{\beta(A,B)} = \frac{(y_A - \mu_A)'(Z_A\beta_B) + (y_B - \mu_B)'(Z_B\beta_A)}{\mathrm{MSX_A} + \mathrm{MSX_B}}$$

$$*\mathrm{MSX} = \mathrm{Tr}\left(\tilde{\mathbf{Z}}'\tilde{\mathbf{Z}}\right) = \mathrm{n}\sum_{\mathrm{j}=1}^{\mathrm{P}}\widehat{\sigma}^2_{\mathrm{Z_j}}$$

The key parameters from multivariate models

- Genetic variance

$$\hat{\sigma}^2_{a(k)} = \hat{\sigma}^2_{\beta(k)} \mathrm{tr}(\mathbf{D}_k^{-1} \tilde{\mathbf{Z}}_k{}' \tilde{\mathbf{Z}}_k)$$

- Heritability

$$\hat{h}^2_{(k)} = \frac{\hat{\sigma}^2_{a(k)}}{\hat{\sigma}^2_{a(k)} + \hat{\sigma}^2_{e(k)}}$$

- Genetic correlations

$$\hat{\rho}_{(k,k')} = \frac{\hat{\sigma}_{\beta(k,k')}}{\sqrt{\hat{\sigma}^2_{a(k)} \hat{\sigma}^2_{a(k')}}}$$

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Metrics

1. Breeding values:

$$\text{Accuracy} = \text{cor}(\text{GEBV}, \text{TBV})$$

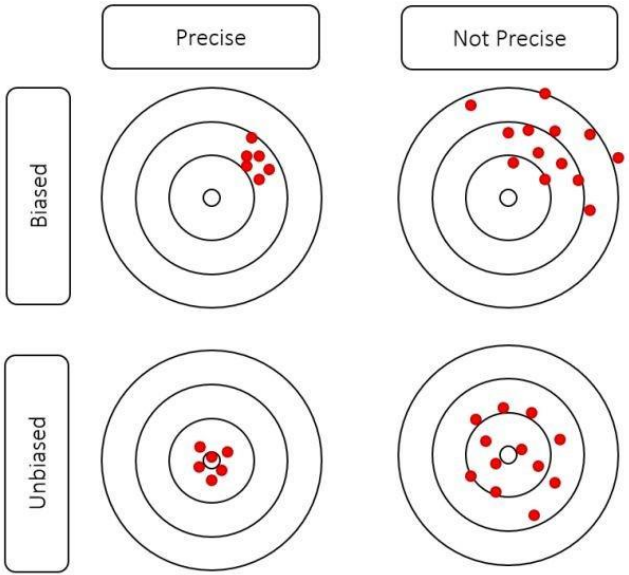
2. Heritability (h^2) and genetic correlations (ρ):

$$\text{Bias} = \text{E}(\hat{\theta} - \theta)$$

$$\text{Precision} = \text{SD}(\hat{\theta} - \theta)$$

3. Computation efficiency:

Elapsed time to fit the model



Picture source

Study 1

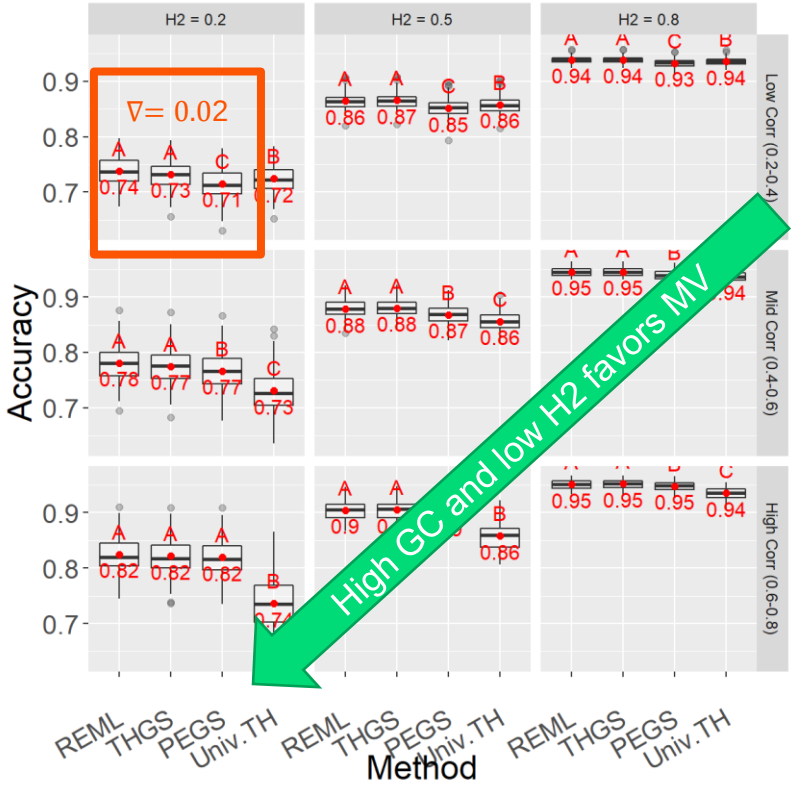
- Wheat data (CYMMIT)
- 599 Individuals
- 1299 Markers
- Scenario: 10 environments, all individuals observed in all locations
- Methods: REML, PEGS, THGS, Univariate

Elapsed time

Method	Time in minutes (SD)	
REML	**256.9 (60.57)**	= 4 hours and 17 minutes
PEGS	0.27 (0.02)	= 16 seconds
THGS	0.27 (0.02)	
Univariate	0.23 (0.03)	= 13 seconds

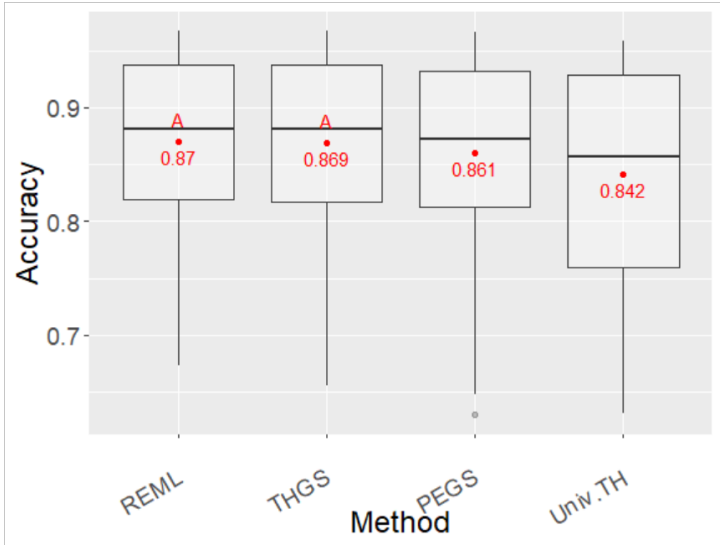
Wheat dataset: 10 traits, 599 individuals, 1299 markers
(available in the BGLR package)

Accuracy of breeding values

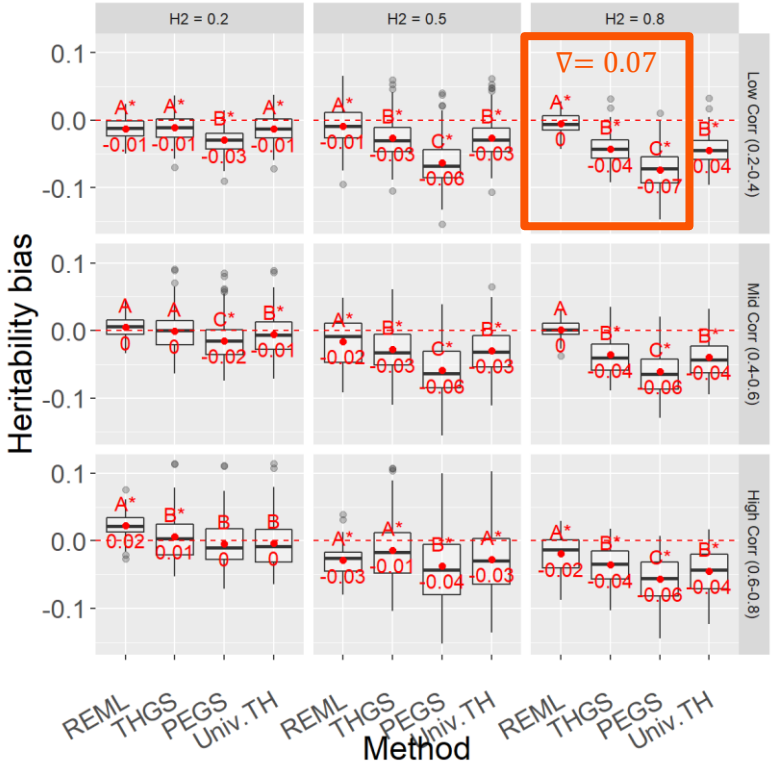


$$Acc = cor(GEBV, TBV)$$

(Higher is better)



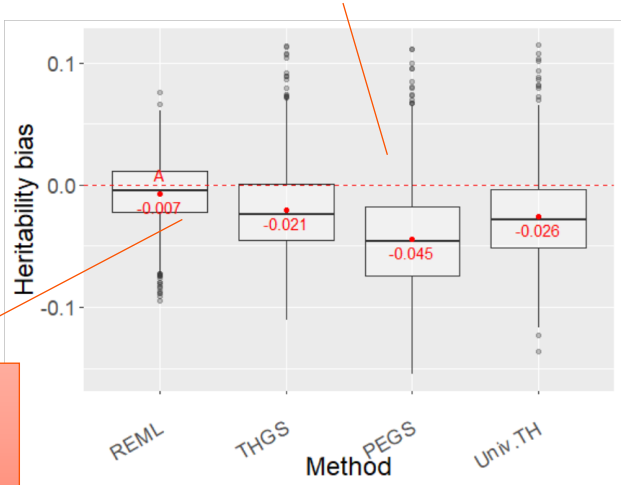
Bias of heritability estimates



$$\text{Bias } h^2 = E(\hat{h}^2 - h^2)$$

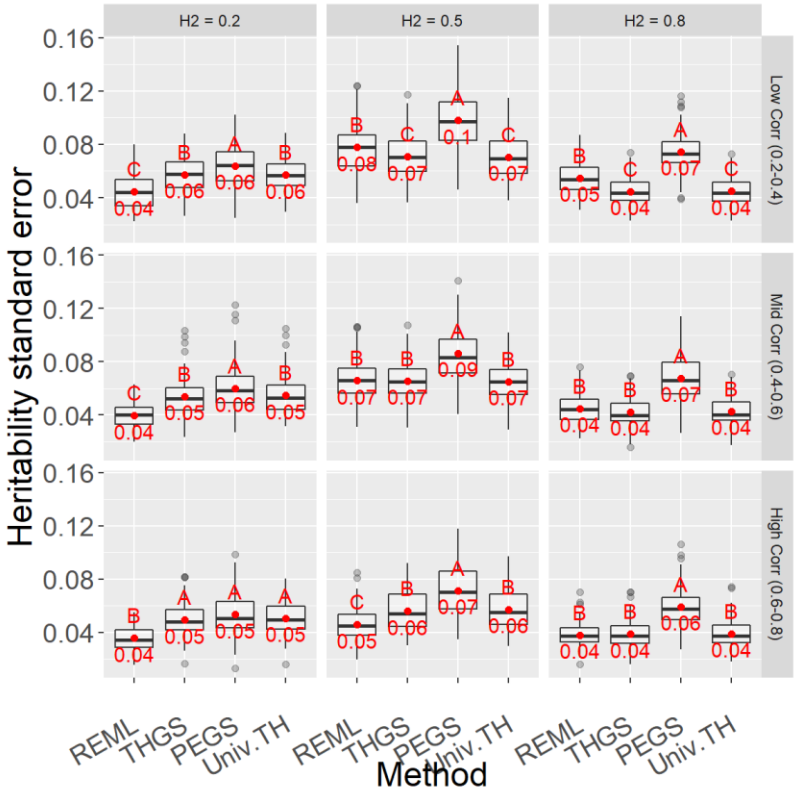
(Closer to zero is better)

PEGS underestimated h2 when true h2 was mid-high



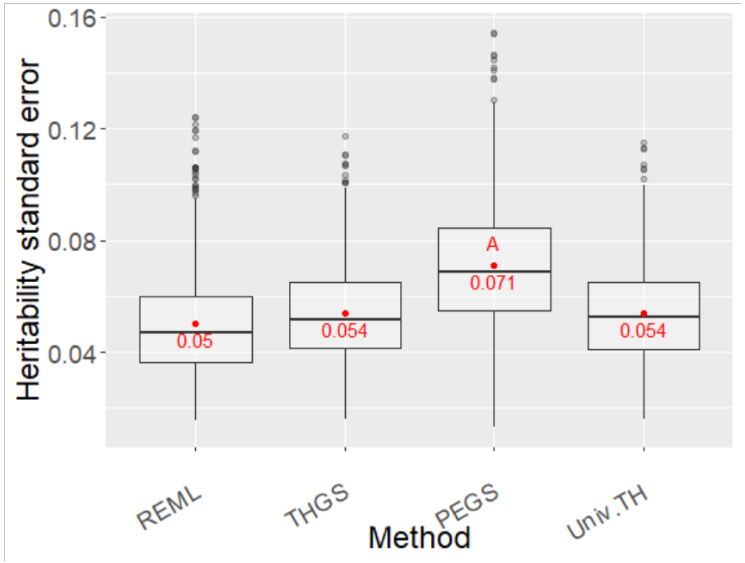
REML also shows large variation…

Precision of heritability estimates



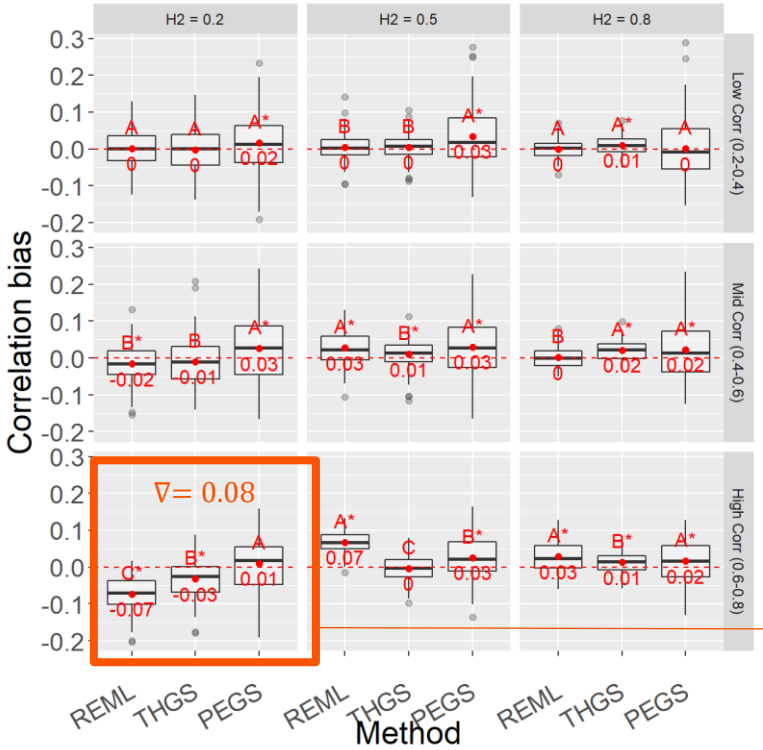
$$\text{Prec } h^2 = SE(\hat{h}^2 - h^2)$$

(Lower is better)



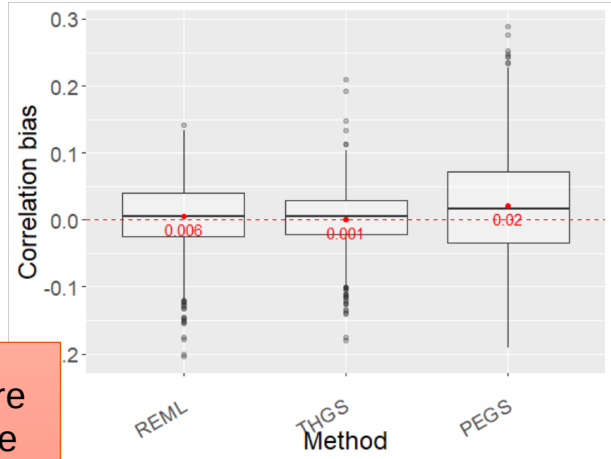
REML / THGS / Univ > PEGS

Bias of genetic correlation estimates



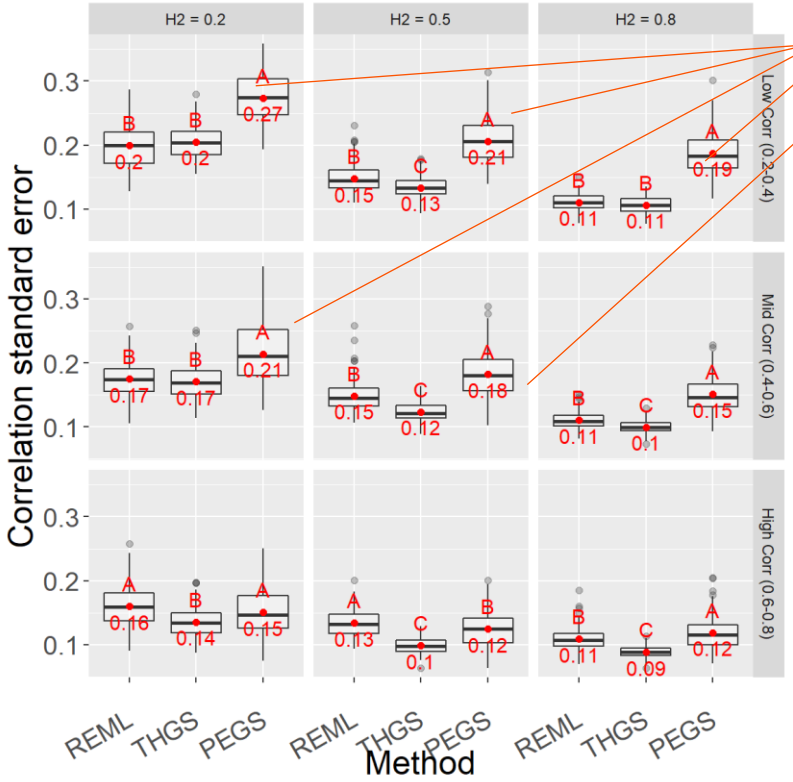
$$\text{Bias } \rho = \mathrm{E}(\hat{\rho} - \rho)$$

(Closer to zero is better)



Differences are large because REML is doing a poor job

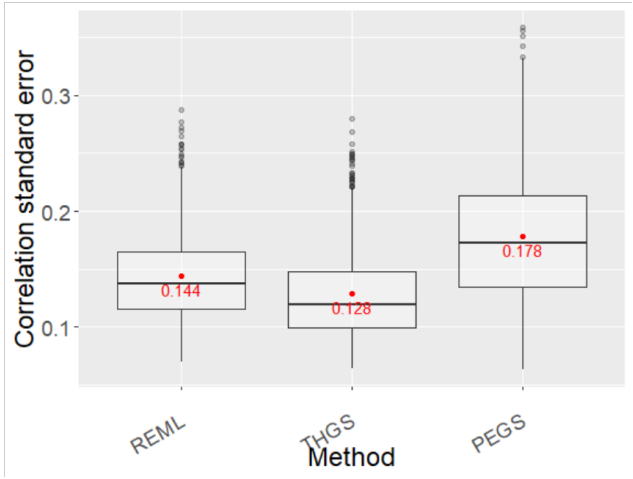
Precision of genetic correlation estimates



PEGS has a hard time to estimate **correlations** when heritability is low, possibly because it **underestimates Genetic Variances**

$$\text{Precision } \rho = \text{SE}(\hat{\rho} - \rho)$$

(Lower is better)



THGS > REML > PEGS

Summary of the smaller & balanced (wheat) dataset

Method	Accuracy	Bias H2	Precision H2	Bias GC	Precision GC
REML	**0.88 (0.01)**	-0.00 (0.03)	0.04 (0.02)	0.01 (0.05)	0.15 (0.03)
PEGS	0.87 (0.02)	-0.03 (0.02)	0.04 (0.01)	0.01 (0.08)	**0.18*** (0.04)
THGS	**0.88 (0.01)**	-0.01 (0.01)	**0.03 (0.01)**	**-0.01 (0.04)**	**0.13 (0.02)**
Univariate	0.85 (0.03)	-0.01 (0.01)	**0.03 (0.01)**	-	-

* PEGS correlations were less precise than THGS, but not statistically different than REML in small balanced datasets

Study 2

- Soybean data (SoyNAM)
- 5000 Individuals
- 4300 Markers
- Scenario: 10 environments, no overlapping individuals
  - **Each individual is observed in a single environment!**
- Methods: PEGS, THGS, Univariate

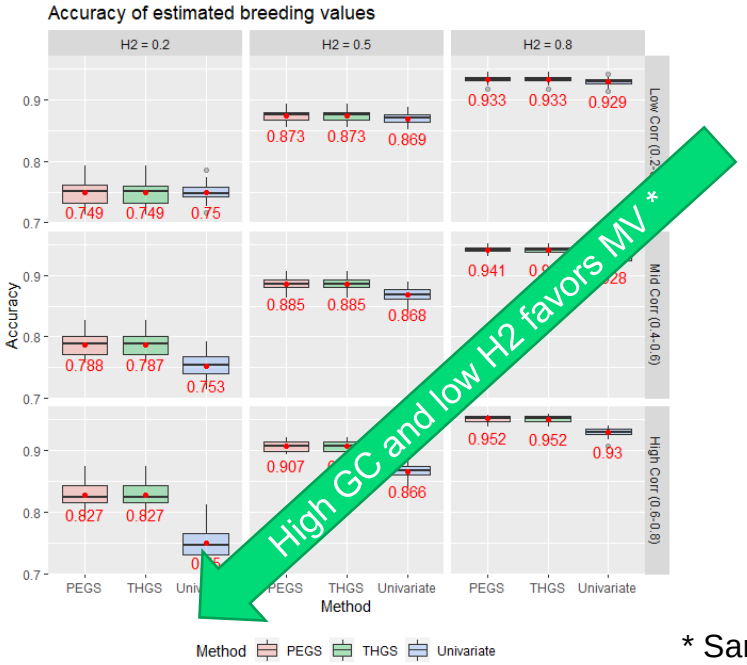
Elapsed time

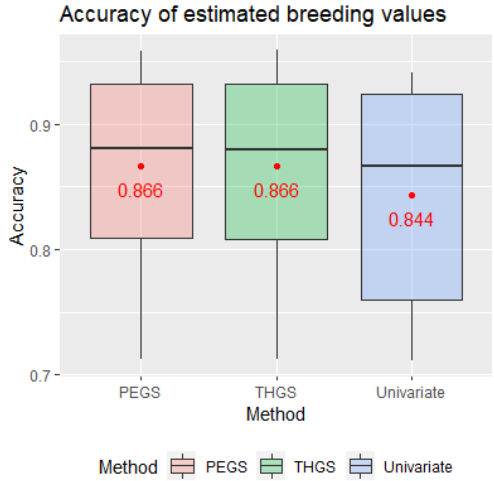
No. of environments		PEGS	THGS	Univariate-THGS
10		0.7 (0.2)	0.7 (0.2)	0.2 (0.0)
50		12 (3)	12 (3)	1.0 (0.1)
100		43 (13)	44 (14)	2.0 (0.3)
200	~3h	168 (48)	165 (44)	4.0 (0.4)
400	~10h	568 (47)	560 (53)	8.0 (1.9)
500	~14h	807 (39)	832 (49)	10.0 (0.6)

(Time in minutes)

Accuracy of breeding values

$$Acc = cor(GEBV, TBV)$$

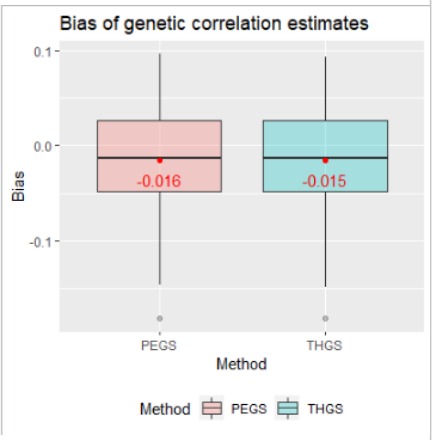


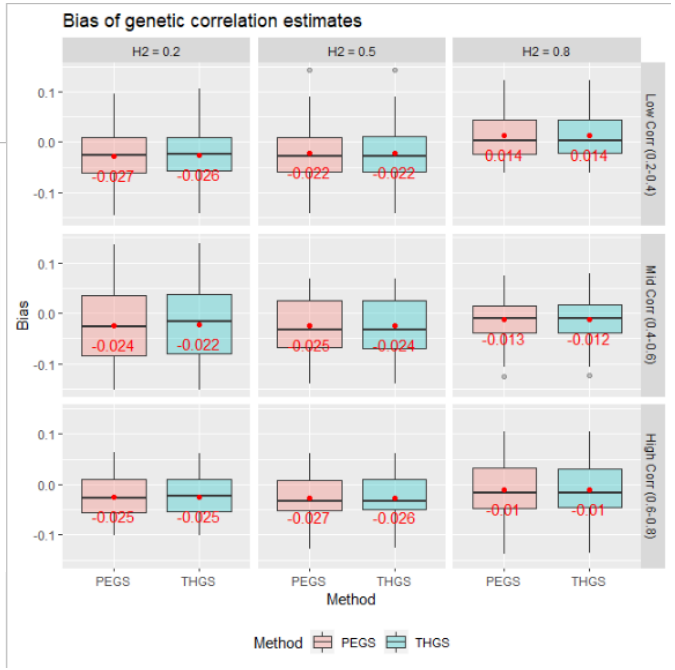


* Same trend observed in wheat

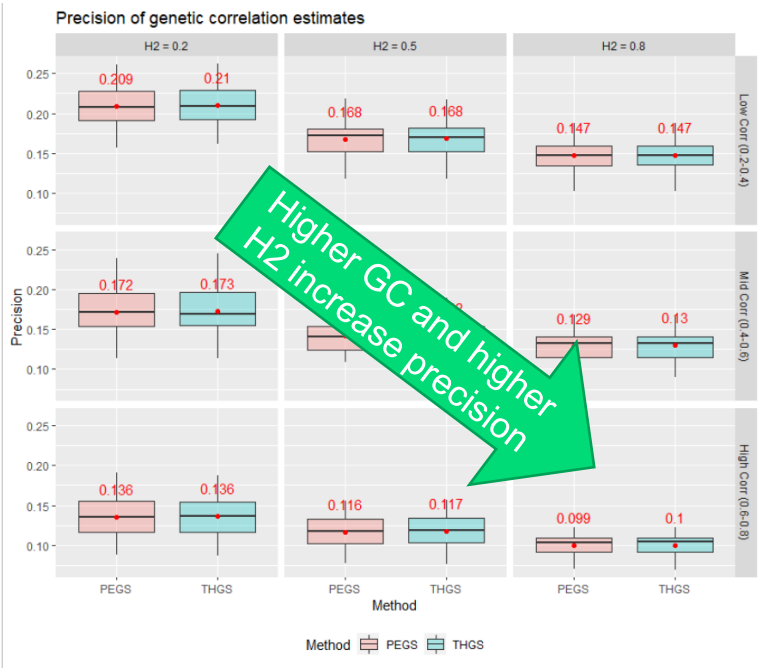
Bias of genetic correlation estimates

$$\text{Bias } \rho = \mathrm{E}(\hat{\rho} - \rho)$$



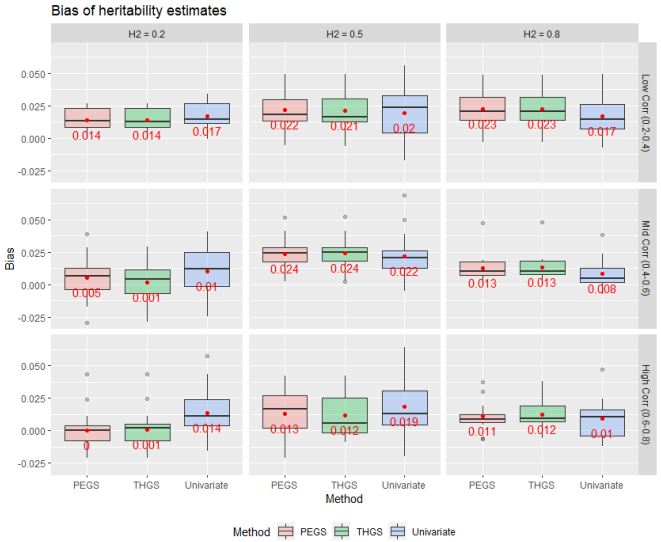


$$\text{Precision } \rho = \mathrm{SE}(\hat{\rho} - \rho)$$

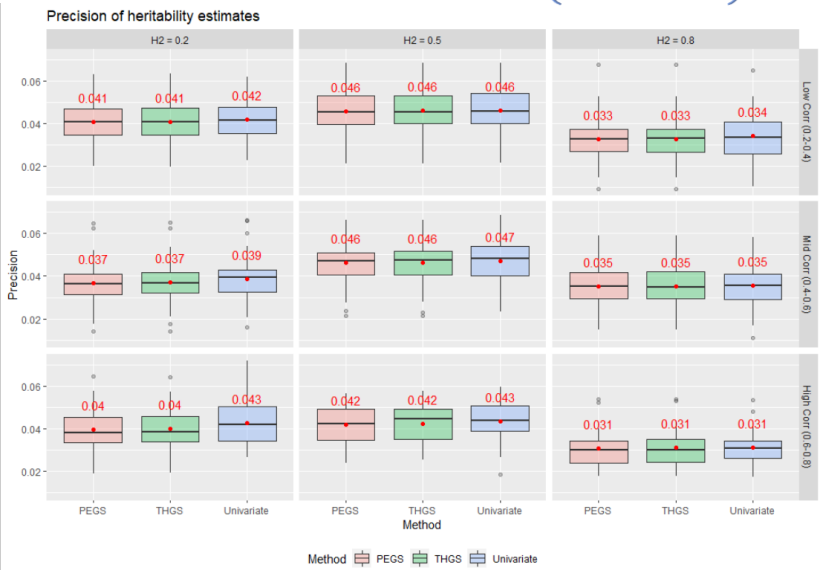


Bias of heritability estimates

$$\text{Bias } h^2 = \mathrm{E}(\widehat{h}^2 - h^2)$$



$$\text{Precision } h^2 = \mathrm{SE}(\widehat{h}^2 - h^2)$$



All roughly the same ~ bias 0.01, S.E. 0.04

Summary in smaller balanced dataset (wheat)

Method	Time (in min.)	Accuracy	Bias H2	Precision H2	Bias GC	Precision GC
REML	256.90 (60.57)	0.88 (0.01)	-0.00 (0.03)	0.04 (0.02)	0.01 (0.05)	0.15 (0.03)
PEGS	0.27 (0.02)	0.87 (0.02)	-0.03 (0.02)	0.04 (0.01)	0.01 (0.08)	0.18 (0.04)
THGS	0.27 (0.02)	0.88 (0.01)	-0.01 (0.01)	0.03 (0.01)	-0.01 (0.04)	0.13 (0.02)
Univariate	0.23 (0.03)	0.85 (0.03)	-0.01 (0.01)	0.03 (0.01)	-	-

THGS ≥ REML ≥ PEGS > Univ

Summary in larger unbalanced dataset (soy)

Method	Accuracy	Bias H2	Prec. H2	Bias GC	Prec. GC
PEGS	0.87 (0.01)	-0.01 (0.01)	0.04 (0.01)	-0.02 (0.06)	0.14 (0.02)
THGS	0.87 (0.01)	-0.01 (0.01)	0.04 (0.01)	-0.02 (0.06)	0.14 (0.02)
Univariate	0.85 (0.02)	-0.02 (0.02)	0.04 (0.01)	-	-

PEGS≅THGS > Univ

Limitations and other considerations

- **More fixed effects?** The absorption of fixed effects beyond the intersect can create a large computational burden. But it is OK to work with pre-adjusted phenotypes like BLUEs, BLUPs and deregressed BLUPs[1].
- **Correlated residuals**: Modeling residual covariances may offset most saving in computation time because of the need for $n \times n$ Kronecker products.
- **Kernels & SVD**: When P>>N, Gauss-Seidel may be costly. When feasible, a solution comes from regress Eigenvectors[2] instead (Z=UDV, solve the MRR using Z*=UD, back solve coefficients β= β*V).
- **Bending[3]**: The covariance $\hat{\Sigma}_\beta$ may not be inversible with too many correlated traits. One may need to shrink the covariance until $\hat{\Sigma}_\beta$ can be inverted. Alternatively, use of simpler covariances: CS and XFA.
- **Balanced data**: REML can be efficiently computed when all phenotypes are collected in all individuals using *canonical transformation*[4] or *kernel diagonalization via eigendecomposition*[5]

1 Garrick et al (2009). Deregressing estimated breeding values and weighting information for genomic regression analyses. Genetics Selection Evolution, 41(1), 1-8.
2 Ødegård et al (2018). Large-scale genomic prediction using singular value decomposition of the genotype matrix. Genetics Selection Evolution, 50(1), 1-12.
3 Jorjani et al (2003). A simple method for weighted bending of genetic (co) variance matrices. Journal of dairy science, 86(2), 677-679.
4 Meyer, K. (1985). Maximum likelihood estimation of variance components for a multivariate mixed model with equal design matrices. Biometrics, 153-165.
5 Lee and Van der Werf (2016). MTG2: an efficient algorithm for multivariate linear mixed model analysis based on genomic information. Bioinformatics, 32(9), 1420-1422.

1. **Introduction**
   - Rationale and statistical model
2. **Coefficients**
   - Univariate
   - Multivariate
3. **Variances**
   - Univariate
   - Multivariate
4. **Simulations**
   - Study 1: Comparison to REML in small balanced data
   - Study 2: Performance in large unbalanced data
   - Limitations and other considerations
5. **Conclusion**

Thank you for your attention!

Remarks:

1) Multivariate models are valuable, but these have been computationally unfeasible
2) Efficient estimation of coefficients (RGS) and variances (PE/TH) enable large MRR
3) THGS & PEGS have some limitations but are suitable replacements to REML

Questions??

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