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Efficient Estimation of Polygenic Effects via Multivariate Ridge Regression

Presentation for the 2021 ASA, CSSA, SSSA INTERNATIONAL ANNUAL MEETING, session “Complex Method Integration for Genomic Selection and their Implementation in the Private and Public Sectors”

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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

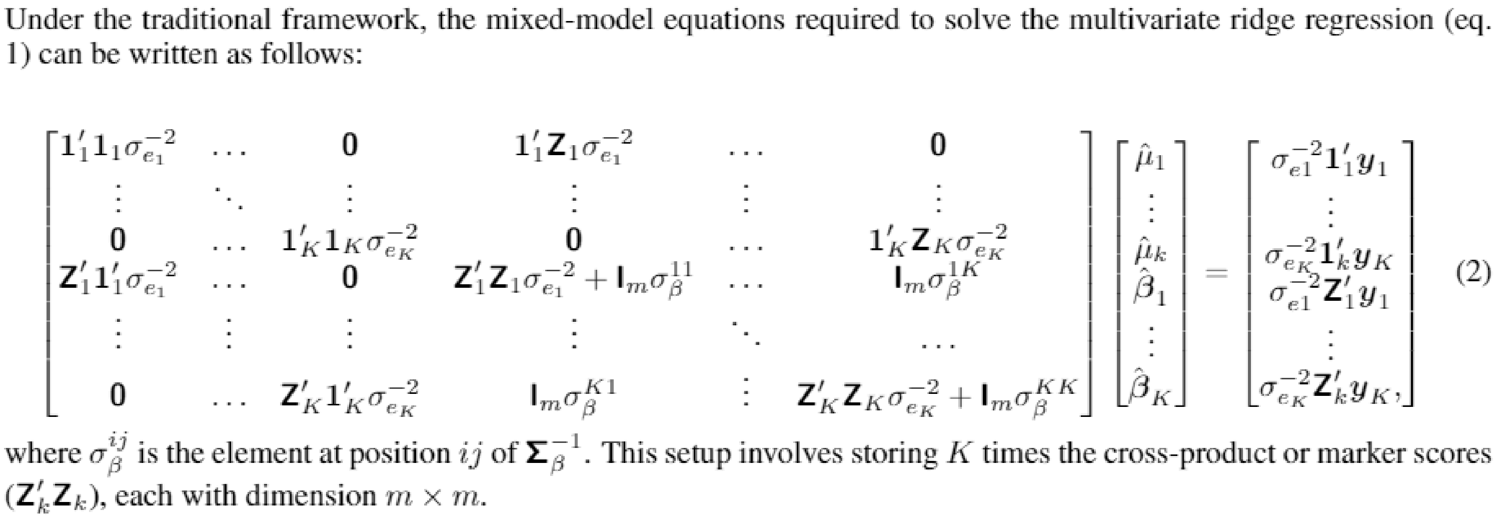
$$y = \mu + \mathbf{Z}\beta + e \tag{1}$$

- Where $y = \{y_1, y_2, \dots, y_K\}$, $\mu = \{\mu_1, \mu_2, \dots, \mu_K\}$, $\beta = \{\beta_1, \beta_2, \dots, \beta_K\}$,

  $e = \{e_1, e_2, \dots, e_K\}$, $Z = \text{BlockDiag}\{\mathbf{Z}_1, \mathbf{Z}_2, \dots, \mathbf{Z}_K\}$
- 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:

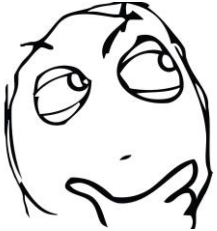
$$\begin{bmatrix} \mathbf{1}_1'\mathbf{1}_1\sigma_{e_1}^{-2} & \dots & \mathbf{0} & \mathbf{1}_1'\mathbf{Z}_1\sigma_{e_1}^{-2} & \dots & \mathbf{0} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ \mathbf{0} & \dots & \mathbf{1}_K'\mathbf{1}_K\sigma_{e_K}^{-2} & \mathbf{0} & \dots & \mathbf{1}_K'\mathbf{Z}_K\sigma_{e_K}^{-2} \\ \mathbf{Z}_1'\mathbf{1}_1'\sigma_{e_1}^{-2} & \dots & \mathbf{0} & \mathbf{Z}_1'\mathbf{Z}_1\sigma_{e_1}^{-2} + \mathbf{I}_m\sigma_\beta^{11} & \dots & \mathbf{I}_m\sigma_\beta^{1K} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \dots \\ \mathbf{0} & \dots & \mathbf{Z}_K'\mathbf{1}_K'\sigma_{e_K}^{-2} & \mathbf{I}_m\sigma_\beta^{K1} & \vdots & \mathbf{Z}_K'\mathbf{Z}_K\sigma_{e_K}^{-2} + \mathbf{I}_m\sigma_\beta^{KK} \end{bmatrix} \begin{bmatrix} \hat{\mu}_1 \\ \vdots \\ \hat{\mu}_k \\ \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_K \end{bmatrix} = \begin{bmatrix} \sigma_{e1}^{-2}\mathbf{1}_1'y_1 \\ \vdots \\ \sigma_{e_K}^{-2}\mathbf{1}_k'y_K \\ \sigma_{e1}^{-2}\mathbf{Z}_1'y_1 \\ \vdots \\ \sigma_{e_K}^{-2}\mathbf{Z}_k'y_K, \end{bmatrix} \qquad (2)$$

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: $\hat{\Sigma}_{\beta(i,j)} = m^{-1}[\widehat{\boldsymbol{\beta}}_i'\widehat{\boldsymbol{\beta}}_j + \mathrm{tr}(\mathbf{C}^{ij})]$

Computing very large multivariate models is **impossible**

unless…



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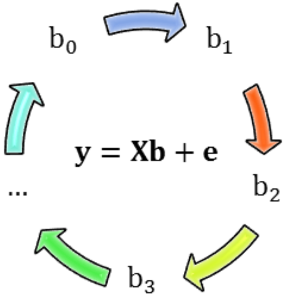
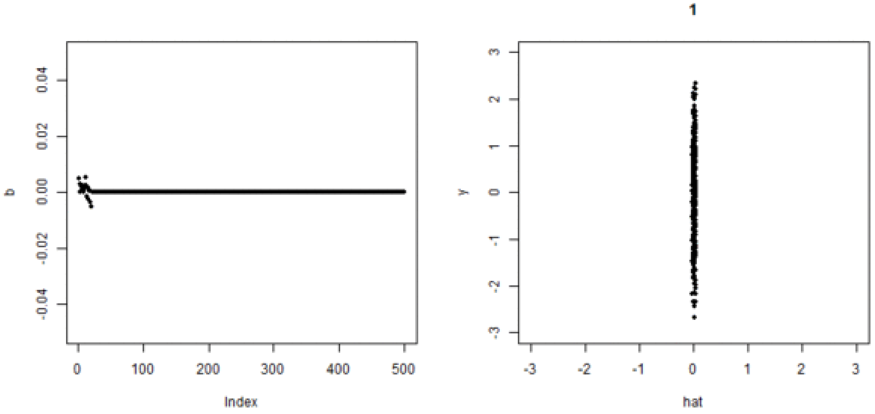
Coefficients for univariate model

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

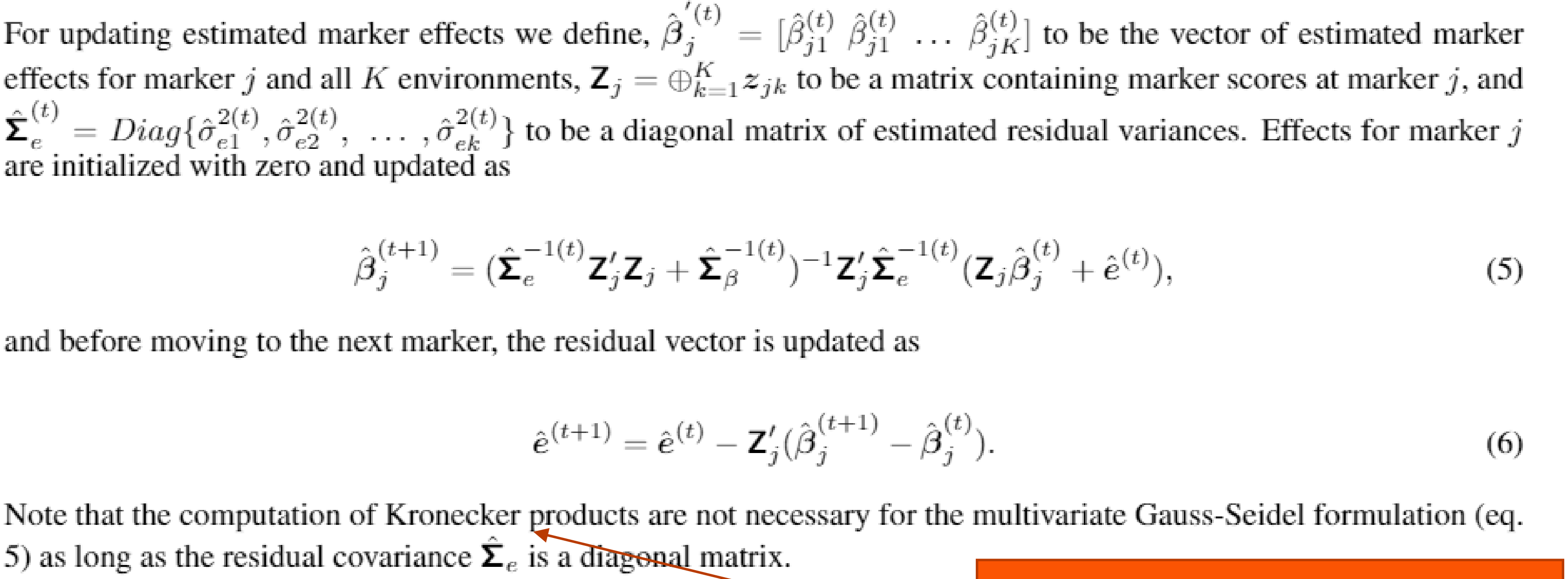


```
for j in 1:p {
    $\hat{b}_j^{t+1} = \frac{x_j'\hat{e}^t + x_j'x_j\hat{b}_j^t}{x_j'x_j + \lambda}$
    $\hat{e}^{t+1} = \hat{e}^t - x_j\left(\hat{b}_j^{t+1} - \hat{b}_j^t\right)$
}
```



[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, $\hat{\beta}_j^{\prime(t)} = [\hat{\beta}_{j1}^{(t)}\ \hat{\beta}_{j1}^{(t)}\ \ldots\ \hat{\beta}_{jK}^{(t)}]$ to be the vector of estimated marker effects for marker j and all K environments, $\mathbf{Z}_j = \oplus_{k=1}^{K} z_{jk}$ to be a matrix containing marker scores at marker j, and $\hat{\mathbf{\Sigma}}_e^{(t)} = Diag\{\hat{\sigma}_{e1}^{2(t)}, \hat{\sigma}_{e2}^{2(t)},\ \ldots\ , \hat{\sigma}_{ek}^{2(t)}\}$ to be a diagonal matrix of estimated residual variances. Effects for marker j are initialized with zero and updated as

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

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

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

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

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

2nd update residuals

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

}

Color code

➢ **Computed only once, before the loop starts (ZpZ)**

➢ **Computed once every iteration**

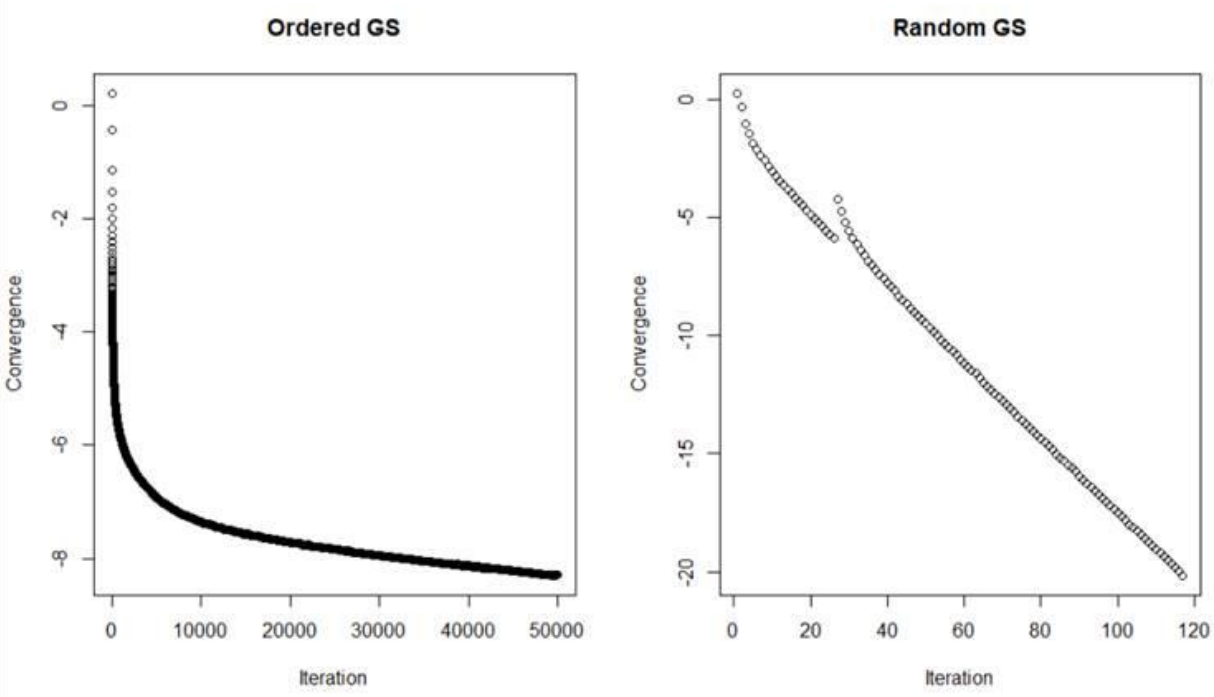
➢ **Computed for each marker in every iteration**

What is in memory?

- Z (n x m)
- B (m x k)
- E (n x k)

- ZpZ (m x k)
- $\hat{\boldsymbol{\Sigma}}_{\beta}^{-1}$ (k x k)
- $\hat{\boldsymbol{\Sigma}}_{e}^{-1}$ (k)

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



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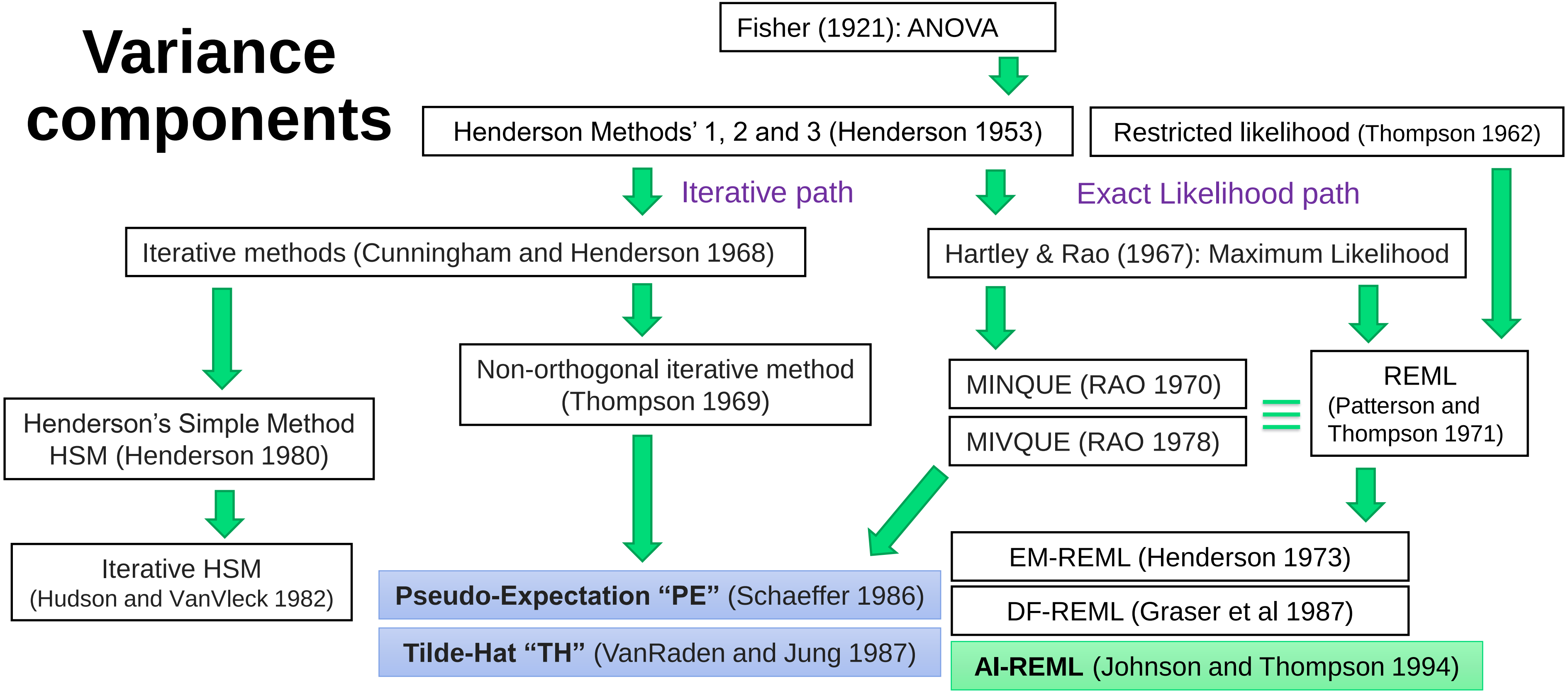
Variance components



Fisher (1921): ANOVA

Henderson Methods' 1, 2 and 3 (Henderson 1953)

Restricted likelihood (Thompson 1962)

Iterative path

Exact Likelihood path

Iterative methods (Cunningham and Henderson 1968)

Hartley & Rao (1967): Maximum Likelihood

Henderson's Simple Method HSM (Henderson 1980)

Non-orthogonal iterative method (Thompson 1969)

MINQUE (RAO 1970)

MIVQUE (RAO 1978)

≡

REML (Patterson and Thompson 1971)

Iterative HSM (Hudson and VanVleck 1982)

Pseudo-Expectation "PE" (Schaeffer 1986)

Tilde-Hat "TH" (VanRaden and Jung 1987)

EM-REML (Henderson 1973)

DF-REML (Graser et al 1987)

AI-REML (Johnson and Thompson 1994)

Fast variations

Gold standard

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}!"

- 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!"

- VanRaden's Tilde-Hat

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

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

All methods yield the same residual variance:

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

V is a pain to compute

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

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

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

$$PX = SX = 0$$

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

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

Multivariate case: (co)variance components

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

$$\hat{\sigma}_{\beta(k,k')} = \frac{\tilde{\boldsymbol{\beta}}_k \hat{\boldsymbol{\beta}}_{k'} + \tilde{\boldsymbol{\beta}}_{k'} \hat{\boldsymbol{\beta}}_k}{\mathrm{tr}\left(\mathbf{D}_k^{-1} \tilde{\mathbf{Z}}_k{}' \tilde{\mathbf{Z}}_k\right) + \mathrm{tr}\left(\mathbf{D}_{k'}^{-1} \tilde{\mathbf{Z}}_{k'}{}' \tilde{\mathbf{Z}}_{k'}\right)}$$

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

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)

- $\hat{\boldsymbol{\Sigma}}_{\boldsymbol{\beta}}$ (k x k)
- $\hat{\boldsymbol{\Sigma}}_{\boldsymbol{e}}$ (k)
- N (k)

An intuitive derivation for Schaeffer’s method?

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

$$\hat{\sigma}_{\beta(A,B)} = \frac{\overset{\text{Pheno of A}}{(y_A - \mu_A)'}\overset{\text{A pred from B}}{(Z_A\beta_B)} + \overset{\text{Pheno of B}}{(y_B - \mu_B)'}\overset{\text{B pred from A}}{(Z_B\beta_A)}}{\mathrm{MSX_A} + \mathrm{MSX_B}}$$

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

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:

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

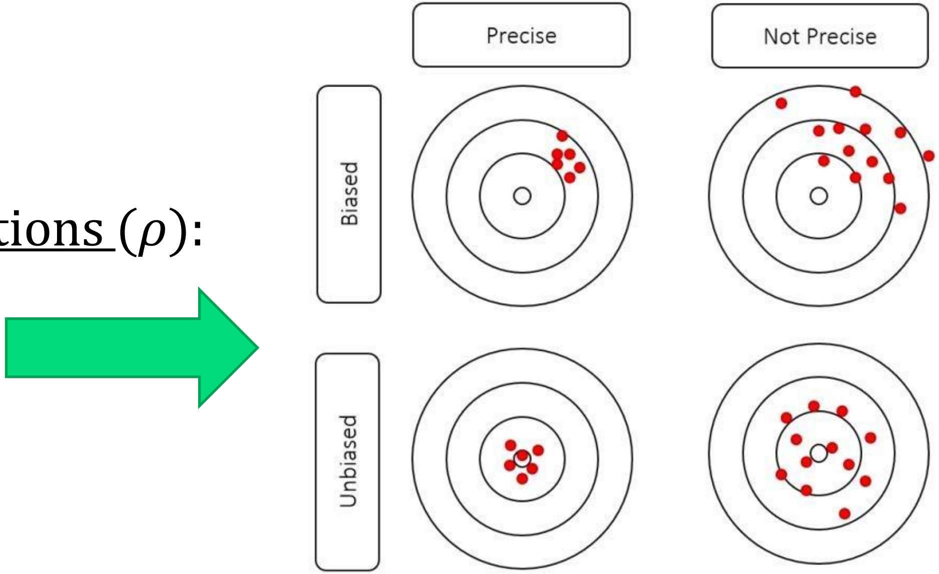
2. Heritability (h^2) and genetic correlations (ρ):

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

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

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

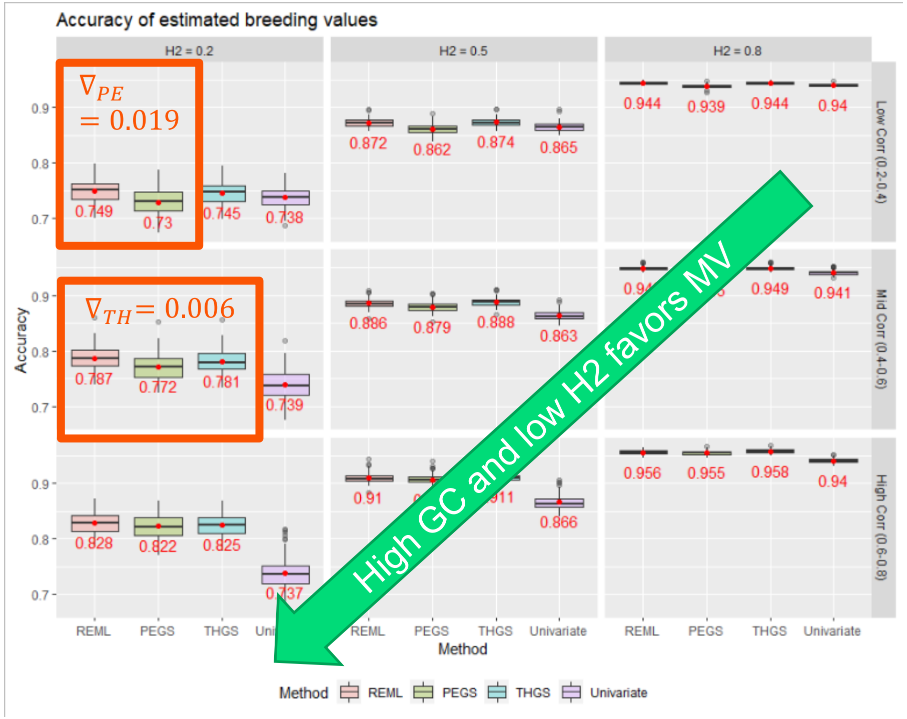
Method	Time in minutes (SD)	
REML	**256.9 (60.57)**	= 4 hours and 17 minutes
PEGS	0.27 (0.02)	= 16 seconds
THGS	0.27 (0.02)	
Univariate	0.23 (0.03)	= 13 seconds

Wheat dataset: 10 traits, 599 individuals, 1299 markers

Accuracy of breeding values

$$\mathrm{Acc} = \mathrm{cor}(\mathrm{GEBV}, \mathrm{TBV})$$

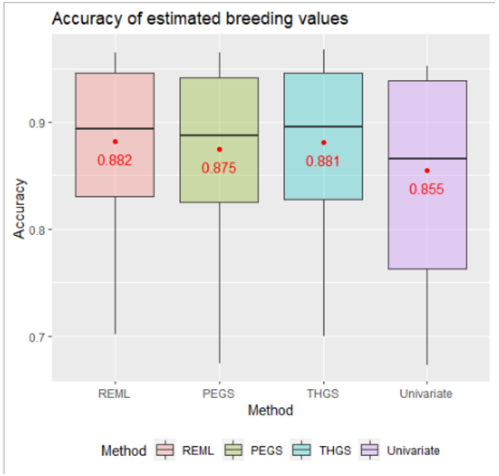
(Higher is better)



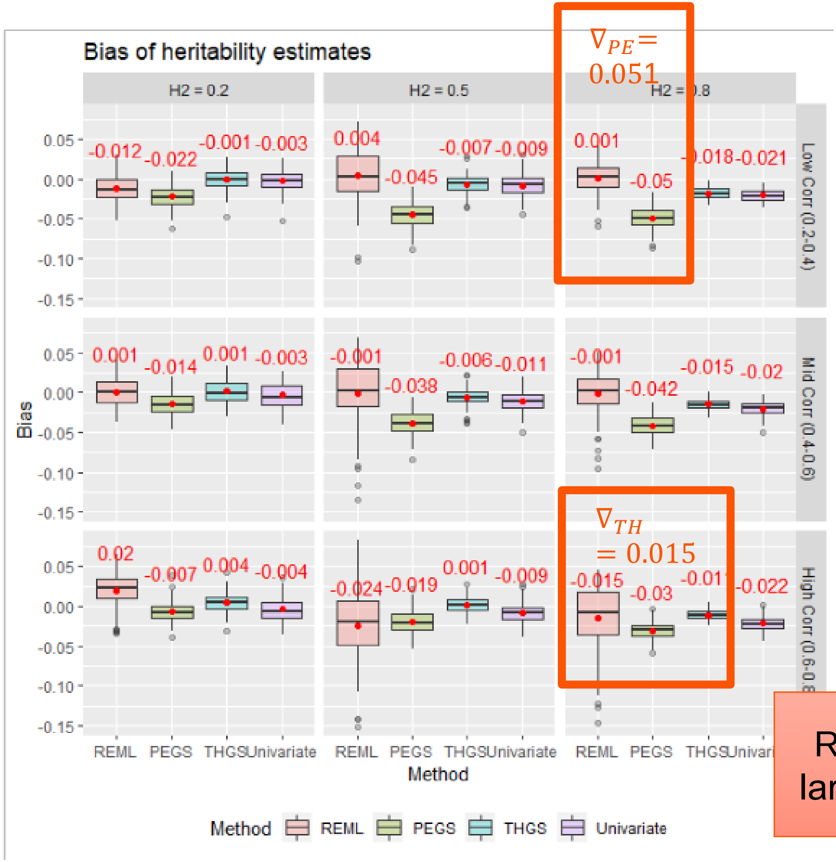
$\nabla_{PE} = 0.019$

$\nabla_{TH} = 0.006$

High GC and low H2 favors MV



Bias of heritability estimates



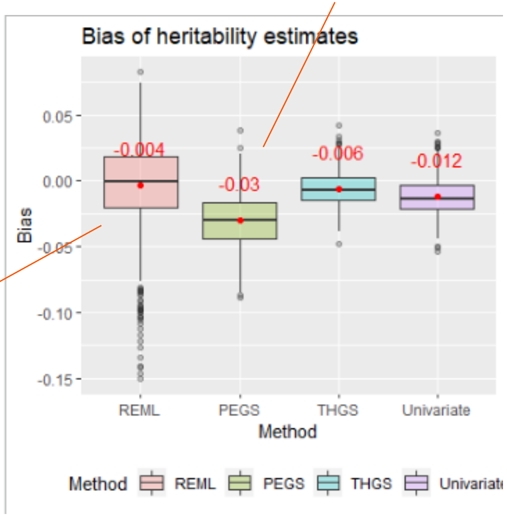
$\nabla_{PE} = 0.051$

$\nabla_{TH} = 0.015$

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

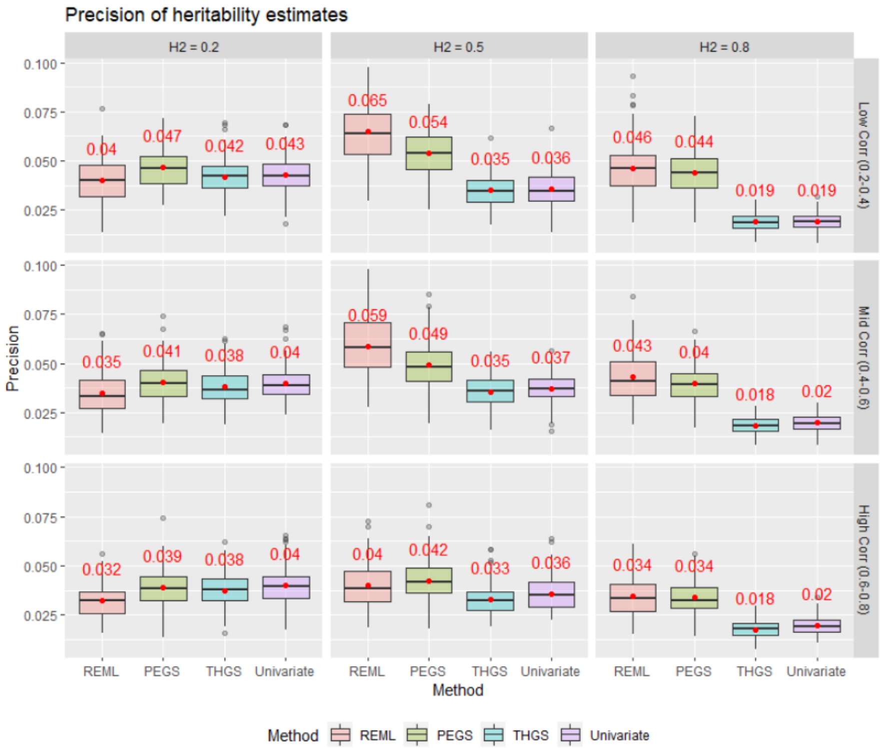
(Closer to zero is better)

PEGS underestimated h2 when true h2 was mid-high



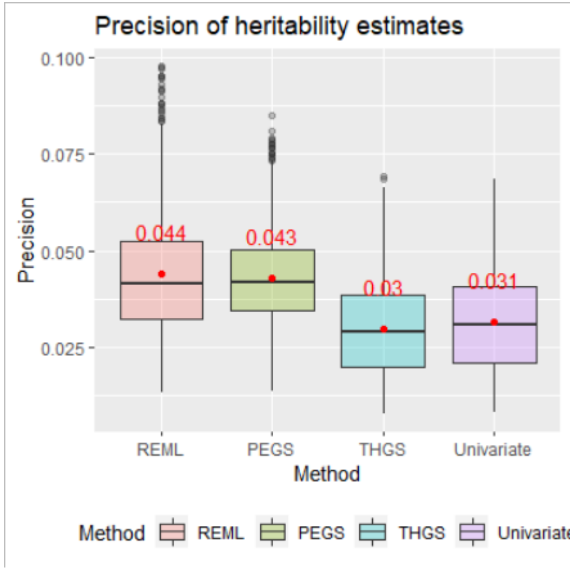
REML showed large variation…

Precision of heritability estimates



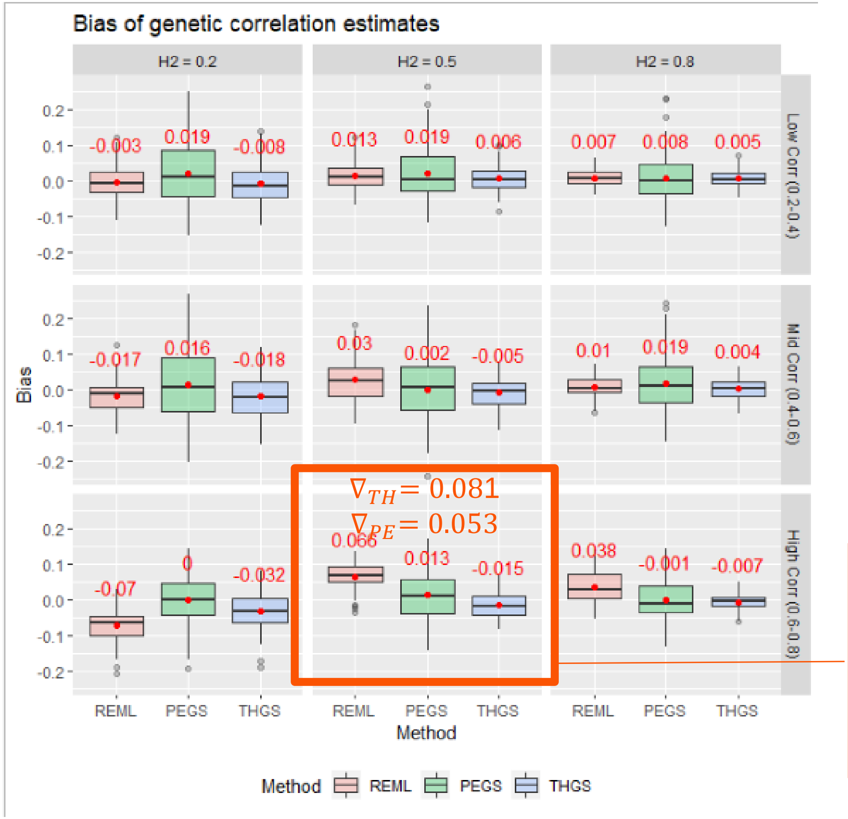
$$\text{Prec } h^2 = SD(\hat{h}^2 - h^2)$$

(Lower is better)



THGS ≅ Univ > PEGS ≅ REML

Bias of genetic correlation estimates

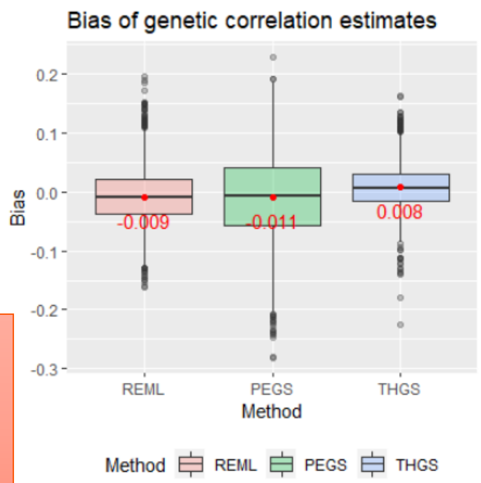


$\nabla_{TH} = 0.081$

$\nabla_{PE} = 0.053$

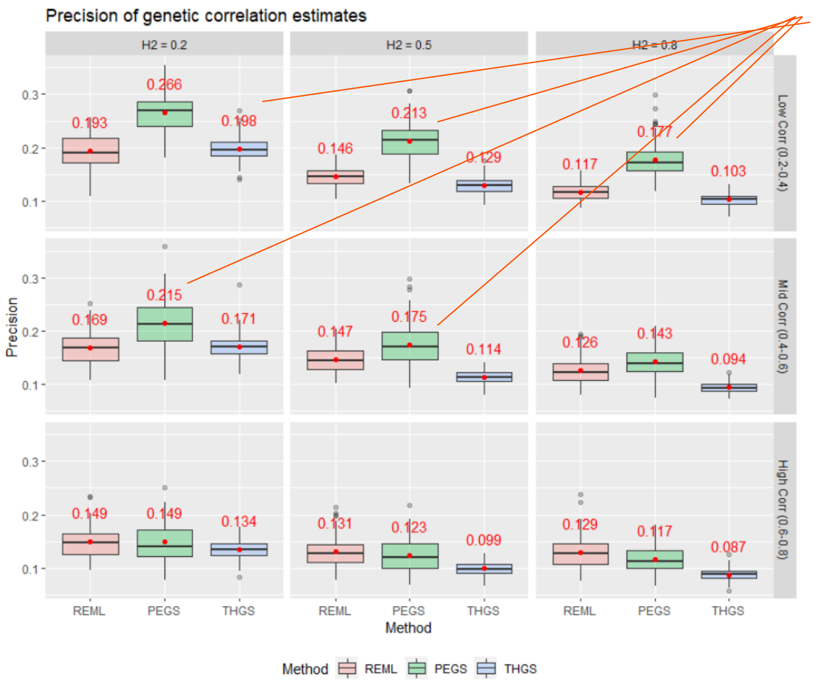
$$\text{Bias } \rho \; = \mathrm{E}(\hat{\rho} - \rho)$$

(Closer to zero is better)



Differences are large because REML is doing a poor job (overestimating)

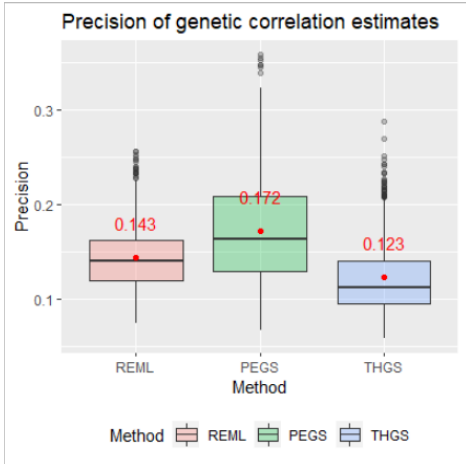
Precision of genetic correlation estimates



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

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

(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
- Methods: PEGS, THGS, Univariate

Elapsed time

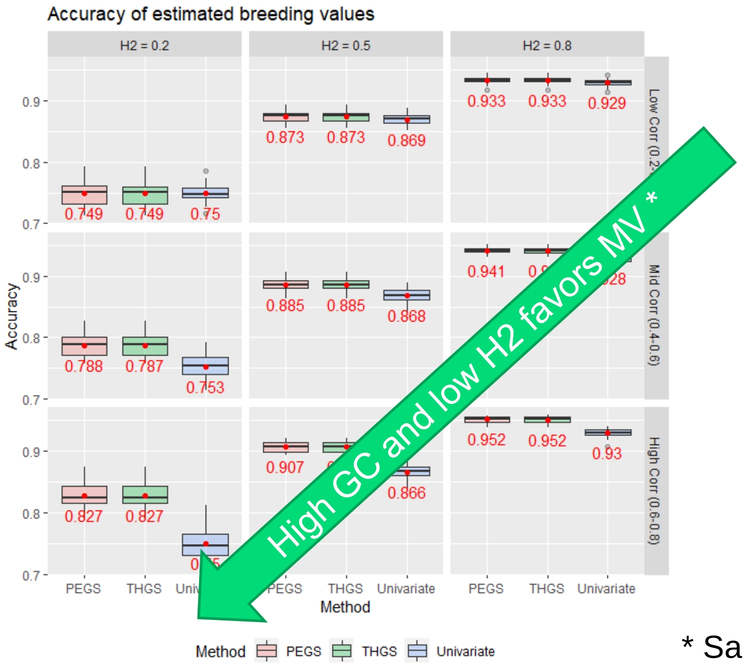
# Traits	Scale	PEGS	THGS	Univariate
10	min.	4.5 (0.1)	4.5 (0.1)	7.5 (0.0)
50	min.	30.7 (0.3)	30.8 (0.3)	37.6 (0.4)
100	min.	63.1 (0.5)	67.7 (8.1)	77.6 (7.6)
200	hrs.	2.9 (0.5)	2.7 (0.3)	2.5 (0.2)
400	hrs.	9.3 (0.8)	9.4 (1.3)	4.7 (0.6)
500	hrs.	13.6 (0.8)	13.2 (0.6)	5.6 (0.3)

MV is faster

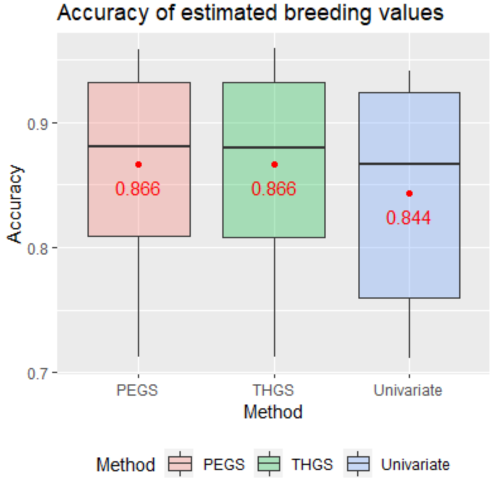
UV is faster

Accuracy of breeding values

$$\mathrm{Acc} = \mathrm{cor}(\mathrm{GEBV}, \mathrm{TBV})$$



High GC and low H2 favors MV *

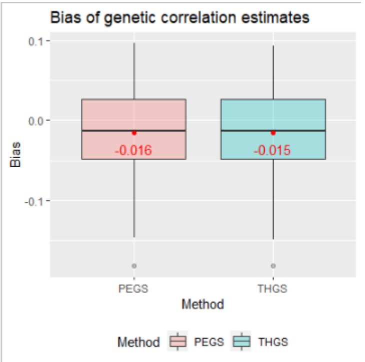


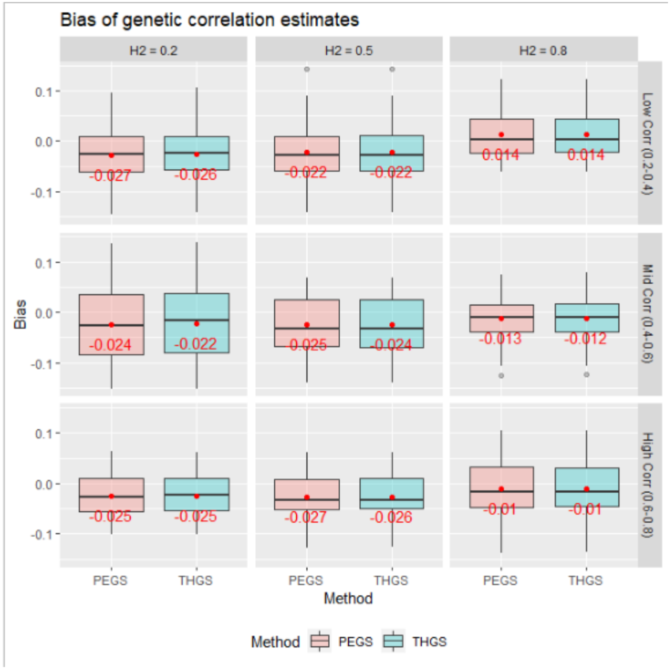
* Same trend
observed in wheat

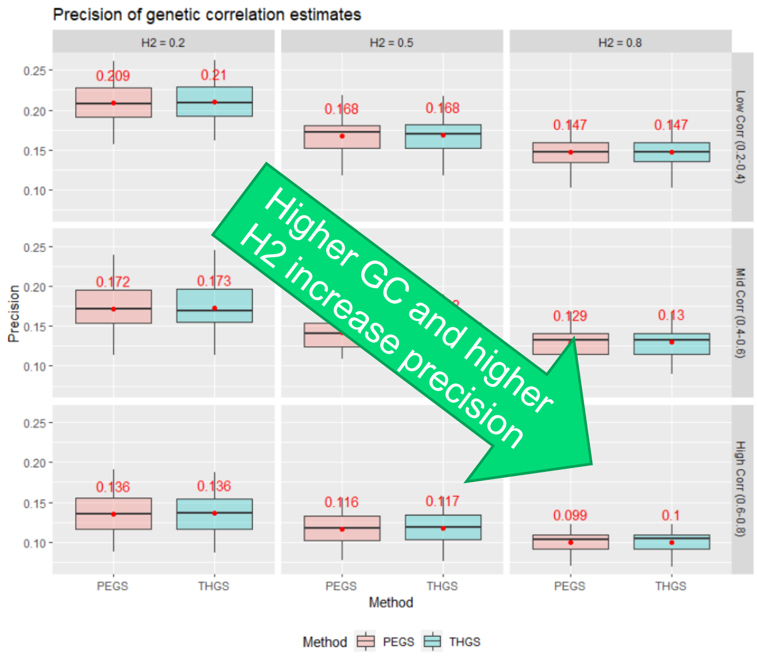
Bias of genetic correlation estimates

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

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



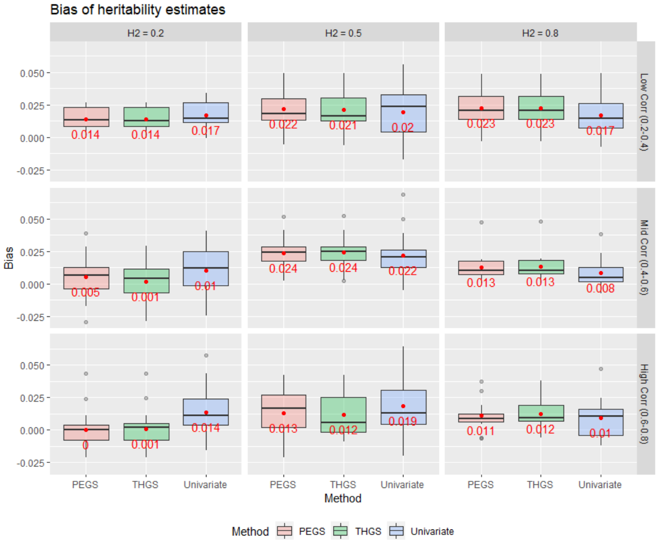




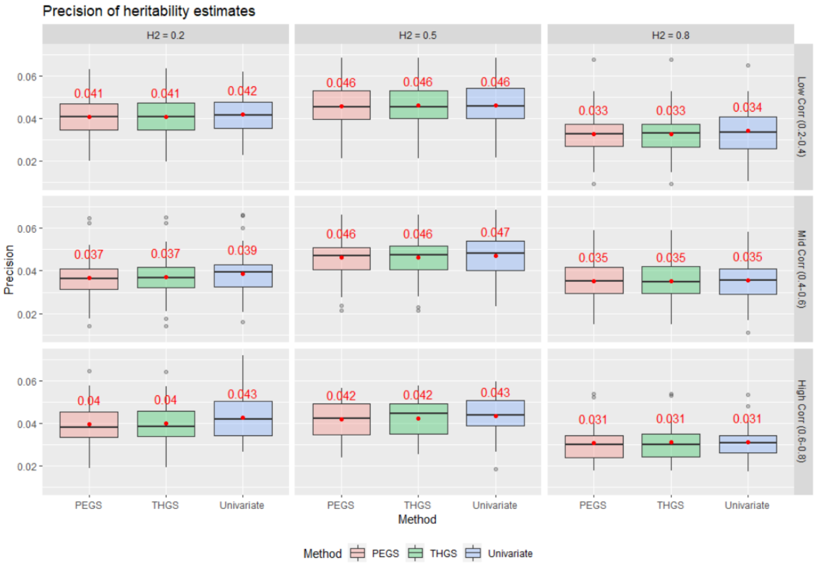
Higher GC and higher H2 increase precision

Bias of heritability estimates

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



$$\text{Precision } h^2 = \text{SD}(\hat{h}^2 - h^2)$$



All roughly the same ~ bias 0.01, prec. 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 Kronecker products.
- **High-dimensionality**: 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]: With too many trait, or highly correlated traits, the covariance $\hat{\Sigma}_\beta$ may not be inversible. When that happens, we may need to shrink the covariance until $\hat{\Sigma}_\beta$ can be inverted. Alternatively, use of simpler covariance structures: compound symmetry and XFA.
- **Balanced data**: We can get a very efficient REML when all phenotypes were collected in all individuals by using canonical transformation[4] or 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 unfeasible under traditional settings
2) Efficient estimation of coefficients (GS) and variances (PE/TH) enable big MRR
3) THGS & PEGS have some limitations but are suitable replacements to REML

Questions??

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