Studies on inflation of GEBV in single-step GBLUP for type

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Status of single step

• Large data problem solved
  • APY G inverse + indirect computation of $A_{22}^{-1}$

• Convergence problem solved
  • Inbreeding in A
  • UPG formulas for H matrix
  • Cutting unneeded pedigrees

• Slow time/round solved
  • Extensive parallel processing

• Inflation of GEBV – not quite solved
  • No problem with broilers, beef and pigs (after QC)
Initial effort to reduce inflation

\[ H^{-1} = \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} + \lambda(G^{-1} - A_{22}^{-1}) \end{bmatrix} \]

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Aguilar et al., 2010
Parameter omega

\[ H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - \omega A_{22}^{-1} \end{bmatrix} \]

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Tsuruta et al., 2011
Why inflation and biases?

\[
A = \begin{bmatrix}
A_{11} & A_{12} \\
A_{21} & A_{22}
\end{bmatrix}
\]

1-ungotyped animals
2-genotyped animals

\[
H = A + \begin{bmatrix}
A_{12}A_{22}^{-1} & 0 \\
0 & I
\end{bmatrix}
\begin{bmatrix}
I & I
\end{bmatrix}
\begin{bmatrix}
G - A_{22}
\end{bmatrix}
\begin{bmatrix}
I & I
\end{bmatrix}
\begin{bmatrix}
A_{22}^{-1}A_{21} & 0 \\
0 & I
\end{bmatrix}
\]

Scales different

G - A_{22} 

Inflation/ deflation

Levels different

G - A_{22}

Bias

Incomplete pedigree

G - A_{22}

???
Properties of G and $A_{22}$

- **G** - “infinite” pedigree
  - depends on gene frequencies, arbitrary scaling, genotyping accuracy & errors

- **$A_{22}$** - depends on pedigree completeness, depth, errors
  - Typical heterogeneous base population

- **Adapt**
  - a) G to $A_{22}$?
  - b) $A_{22}$ to G?
  - c) Both?
Scaling G - gene frequencies

\[ G = \frac{(M - 2P)(M - 2P)'}{\sum_i 2p_i q_i} \]

M – gene content, P – gene frequencies

VanRaden (2008)

Different denominator (Gianola, 2009)

1. Use base population gene frequencies (Gengler, 2007; VanRaden, 2008; Christensen and Lund, 2010)
   - Hard to compute
   - Does not work if base population heterogeneous
Scaling G – fixed effects

2. Use a constant for phenotypes of genotyped animals

(Stranden and Christensen, 2010; Vitezica et al., 2011; Fernando et al., 2014)

\[
G_j = \frac{(M - 2P_j)(M - 2P_j)'}{\sum_i 2p_i q_i} \quad \text{Var}(u_1) = G_1, \text{Var}(u_2) = G_2
\]

\[
u_1 = u_2 + \mu \quad \text{Gene frequencies change the mean of EBV only}
\]

\[
y_{genot} = hys + u_1 + e \quad \equiv \quad y_{genot} = hys + \mu + u_2 + e
\]

Add a mean (or group effect) to model for genotyped animals
Works for means, not inflation
No effect for production if only bulls genotyped
Scaling G – compatibility with A

3. Scale G for compatibility with $A_{22}$ (VanRaden, 2008; Chen et al., 2011; Vitezica et al., 2011)

$$G = \alpha + (1 - \frac{\alpha}{2})G_0,$$

$\alpha$: $\text{avg}(a_{22,ij}) = \text{avg}(g_{ij})$
Computations

• Holstein type data up to 2014
• 18 traits
• 569k genotyped animals
• 1711 validation bulls with 50 daughters
• Single-step by blup90iod
• DYD2014=b_0 + b_1GEBV2010
$R^2$ and $b_1$ without and with inbreeding in A
\( R^2 \) and \( b_1 \) with omegas

\[
H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - \omega A_{22}^{-1} \end{bmatrix}
\]

Inbreeding in \( A \) reduces optimal omega.
GEBV Decomposition for Young Animals

\[
\begin{bmatrix}
X'X & X'Z \\
Z'X & Z'Z + \frac{\sigma_e^2}{\sigma_a^2}H^{-1}
\end{bmatrix}
\begin{bmatrix}
\hat{\beta} \\
\hat{u}
\end{bmatrix} =
\begin{bmatrix}
X'y \\
Z'y
\end{bmatrix}
\]

\[H^{-1} = A^{-1} + \begin{bmatrix}
0 & 0 \\
0 & G^{-1} - A_{22}^{-1}
\end{bmatrix}\]

GEBV = w1 PA + w2 DGV - w3 PI
GEBV Decomposition for Young Animals

Two parents known - no inbreeding in A

\[
\text{GEBV} = \frac{2}{2 + g_{ii} - a_{22}^{ii}} \cdot \text{PA} + \frac{g_{ii}}{2 + g_{ii} - a_{22}^{ii}} \cdot \text{DGV} - \frac{a_{22}^{ii}}{2 + g_{ii} - a_{22}^{ii}} \cdot \text{PI}
\]

Inbreeding \( F_i \)

\[
\text{GEBV} = \frac{2/(1-F_i)}{2/(1-F_i) + g_{ii} - a_{22}^{ii}} \cdot \text{PA} + \frac{g_{ii}}{2/(1-F_i) + g_{ii} - a_{22}^{ii}} \cdot \text{DGV} - \frac{a_{22}^{ii}}{2/(1-F_i) + g_{ii} - a_{22}^{ii}} \cdot \text{PI}
\]

\[
F_i = \frac{F_s}{2} + \frac{F_d}{2}
\]

Under inbreeding:
- Smaller weights of DGV and PI
- Larger share of PA

No inbreeding in A if at most 3 generations
Meaning of $\lambda$ parameter

$$H^{-1} = \begin{bmatrix} A^{11} & A^{12} \\ A^{21} & A^{22} + \lambda(G^{-1} - A^{-1}_{22}) \end{bmatrix}$$

$$\text{GEBV} = \frac{2/\lambda}{2/\lambda + g^{ii} - a^{ii}_{22}} \text{PA} + \frac{g^{ii}}{2/\lambda + g^{ii} - a^{ii}_{22}} \text{DGV} - \frac{a^{ii}_{22}}{2/\lambda + g^{ii} - a^{ii}_{22}} \text{PI}$$

$$\frac{2/\lambda}{2/\lambda + g^{ii} - a^{ii}_{22}} \equiv \frac{2}{1 - F_i}$$

$\lambda$ compensates for lack of inbreeding in A
Meaning of $\omega$ parameter

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - \omega A_{22}^{-1} \end{bmatrix}$$

$$\text{GEBV} = \frac{2/\omega}{2/\omega + g_{ii}/\omega - a_{22}^{ii}} \text{PA} + \frac{g_{ii}/\omega}{2/\omega + g_{ii}/\omega - a_{22}^{ii}} \text{DGV} - \frac{a_{22}^{ii}}{2/\omega + g_{ii}/\omega - a_{22}^{ii}} \text{PI}$$

Denominator larger
Fraction of PI down
Coefficient behind $A_{22}^{-1}$ more important
(Misztal et al., 2010)
Inbreeding and missing pedigree

• Inbreeding = f(pedigree depth)

• Options if incomplete pedigree:
  • Truncate
  • Nonzero inbreeding for unknown parents
    • Prediction by A – UPGs (VanRaden, 1992)
    • Prediction by G – metafounders (Legarra et al., 2015)
R² and b₁ with inbreeding for phantom parents (UPG)
Anything else to raise $b_1$ above 0.90? Why high $\text{corr}(b_1, h^2)$?

Reduction of $h^2$ -- Wiggans et al., 2011
Optimal reduction related to intensity of selection (Lawlor, 2017)
Reducing heritability for genotyped animals only?

\[ \mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & \tau \mathbf{G}^{-1} - \omega \mathbf{A}^{-1}_{22} \end{bmatrix} \]

Misztal et al. (2010)

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<th>( \omega )</th>
<th>( R^2 )</th>
<th>Regression</th>
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<td>0.6</td>
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<td>0.94</td>
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Optimal \( \tau = 1.5 \)

66% genetic variance for genotyped animals
Other factors influencing inflation

• Pedigree errors
• Foreign animals
• UPG definitions
• Chromosomes XY and 0
• Imputation

• Real inflation lower if DYD biased down
What if multibreed?

• Fixed effect for gene frequencies – does not eliminate inflation
• Possibly ignore, use avg gene frequencies (Simeone et al., 2011; Lourenco et al., 2016)
• Possibly, UPG sufficient (Swan et al., 2012)
• Match A to G using gene frequencies – metafounders (Legarra et al., 2015)

• How many breeds can share SNP60k without loss of accuracy?
Concept of Metafounders

We need to adjust the UPG theory to match A to G instead of viceversa.

In other words, we can infer the relationships across breeds from markers.

Compatibility of pedigree-based and marker-based relationship matrices for single-step genetic evaluation

Ancestral Relationships Using Metafounders:
Finite Ancestral Populations and Across Population Relationships

Ole F. Christensen

Genetic evaluation for three-way crossbreeding

Metafounders are related to $F_{st}$ fixation indices and reduce bias in single-step genomic evaluations

Ole F. Christensen, Andres Legarra, Mogens S. Lund, and Guosheng Su

Carolina A. Garcia-Baccino, Andres Legarra, Ole F. Christensen, Ignacy Misztal, Ivan Pocrnic, Zulma G. Vitezica, and Rodolfo J. C. Cantet

Legarra, AGBU 2017
Algorithm for Metafounders

• Construct $G$ using equal gene frequencies
• Call UPG metafounders
• Make metafounder effects random and calculate their covariances based on $G$
• Construct $A$ and $A_{22}$ using these covariances

\[ H^{\Gamma^{-1}} = \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{\Gamma^{-1}} \end{bmatrix} + A^{\Gamma^{-1}} \]
Parameters of $H^{-1}$ in blupf90

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 \\ 0 \end{bmatrix} \tau (\alpha G + \beta A_{22}^{-1} + \gamma I + \delta J)^{-1} - \omega A_{22}^{-1}$$

- Controls additive variance
- Blending for numerical stability
- Beta or gamma: 0.01-0.05
- Gamma better if causative SNPs
- Mainly controls inflation due to incomplete pedigree
- Default value 0.95
- Controls bias
Pretty good choice

\[ H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix} \]

If
* Truncated pedigree
* Inbreeding in A
* Inbreeding for UPG
* G slightly blended and scaled
Why inflation in dairy but not in other species?

- Dairy
  - Strong selection
  - Missing pedigrees particularly for grade cows
- Broilers (Cobb)
  - 3 generations of pedigree and phenotypes – no parents’ inbreeding
- Beef (Angus)
  - Data from breeding operations – nearly complete pedigrees
  - Less selection
- Pigs
  - Complete pedigrees – after truncation
Summary

- Incomplete relationships lead to inflation
  - Minimal impact on reliability
- Reducing heritability eliminates bias and increases reliability
- Possibly automatic multibreed scaling with “metafounders”
- Tuning parameters in ssGBLUP useful – now understood
DYD Regression coefficient as function of $\tau$ and $\omega$

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Optimal G if divided by 1.5