AGRICULTURE VICTORIA

Meta-analysis of GWAS to estimate SNP effects and breeding values

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Economic Development, Jobs, Transport and Resources

Introduction

What is a meta-analysis?

Why do we need it?

How good is it?

Examples

Proposal for Interbull

What is a meta-analysis

Combining the results from >1 analysis rather than combining the raw data

Why do we need it?

To increase power

To increase robustness

Cant combine raw data

How good is it?

Very widely used to combine information from medical trials

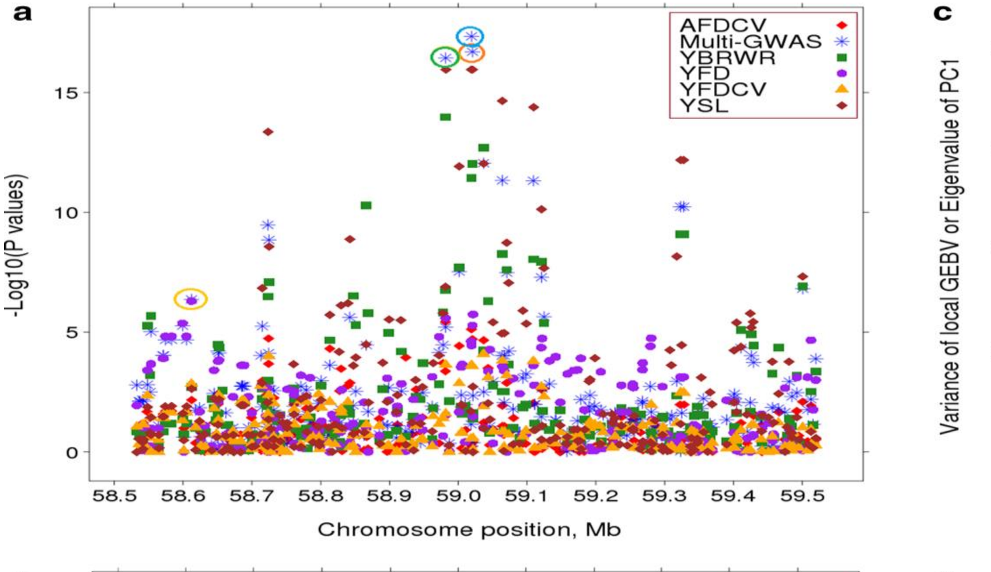
Some information is lost

- Covariances between estimates
- OLS vs GLS

Example 1- Multi-trait GWAS

Bolormaa et al(2017)

Combine single trait GWASs on correlated traits



Example 2- Multi-country GWAS of Stature

Bouwman et al (2018)

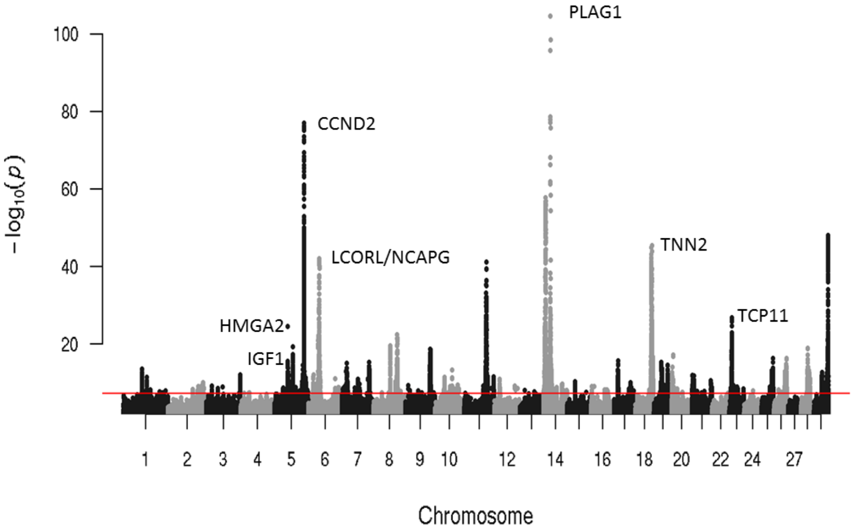
Combine GWASs on stature from different breeds and countries

58,000 bulls from 17 countries-breeds

163 lead variants with $p<5*10^{-8}$

Explaining 13% of variance

Example 2- Multi-country GWAS of Stature



Example 3- LD score regression in humans

Uses summary data ie chi-square from GWAS and LD r^2 to estimate h^2 (Bulik-Sullivan et al 2015)

Can be used to estimate r_g

Assess the importance of prior information (Finucane et al 2015)

eg H3K4me3 sites enriched 2 fold for effect on 27 disease traits

Less accurate than raw data?

Example 4- Joint and conditional GWAS in humans

Yang et al (2012)
Simultaneously estimating the effect of many SNPs on a trait
Least squares equation for multiple regression
X’X b = X’y

b from published data
X’X from reference sample
X’Xb → X’y for sample

Bayesian multiple regression (Zhu and Stephens 2016)

Example 5- Combining eQTL and GWAS summary statistics

Zhu et al 2017

Regression of expression on phenotype for individual SNP associations

Opportunities in cattle

Many countries and breeds have genotypes and phenotypes but raw data cannot be combined.

Opportunities in cattle

Sale of semen increasing based on genomic EBVs

We want them to be as accurate as possible

(for all traits in all breeds and countries and between breeds)

i.e. We want estimated SNP effects to be as accurate as possible

High accuracy ← high N, non-linear estimation, one-step, sequence data, functional information

Opportunities in cattle

High N

Human genetics

- meta-analysis of 270,000 people for height → more SNPs, increased accuracy
- in UK 500,000 people with WGS
- in USA 1M people with WGS

Dairy cattle

- 1,000,000s world wide if we collaborate
- not within-breed, within-country for all traits

Interbull SNPMace

Interbull combines progeny test EBVs from different countries

→ more accurate EBVs which are comparable regardless of country of origin

Selection of bulls now largely on genomic EBVs

Lose information if you combine GEBVs from different countries

Better to combine SNP solutions

Interbull SNPMace

Lose information if you combine GEBVs from different countries

Options

- Convert GEBVs from country A to country B as for progeny test EBVs
  - GEBVs are regressed back by r_g

- Put genotype from country A through prediction equation of country B
  - Limited accuracy due to size of reference population in country B

- Combine estimates of SNP effects, allowing for r_g, to get most accurate estimate of SNP effects in country B

Interbull SNPMace

Single country equations to estimate SNP effects (g)

$(Z_1'Z_1 + \lambda I)\ g_1 = Z_1'y_1$

Two countries

$(Z_1'Z_1 + Z_2'Z_2 + \lambda I)\ g = Z_1'y_1 + Z_2'\ y_2$

If individual countries provide g_i and $Z_i'Z_i$ we can construct the multi-country BLUP and solve for g

Extensions: include r_g <1 between countries and weights for records

Extensions for SNPMace model

$$\begin{bmatrix} Z_1'\mathbf{Z}_1 + \mathbf{G}^{1} & \boldsymbol{\Psi}_{12} + \mathbf{G}^{12} \\ \boldsymbol{\Psi}_{12} + \mathbf{G}^{12} & Z_2'\mathbf{Z}_2 + \mathbf{G}^{2} \end{bmatrix} \times \begin{bmatrix} \hat{\mathbf{g}}_1 \\ \hat{\mathbf{g}}_2 \end{bmatrix} = \begin{bmatrix} Z_1' y_1 \\ Z_2' y_2 \end{bmatrix}$$

Common daughter information

$$\mathbf{B} = \frac{1}{\sum_j 2p_i(1-p_i)}\mathbf{I}$$

(VanRaden 2008)

$$G = \operatorname{var}\begin{bmatrix} g_1 \\ g_2 \end{bmatrix}^{-1} = \begin{bmatrix} \sigma_1^2\mathbf{B}_1 & r_{12}\sqrt{\sigma_1^2\mathbf{B}_1 \times \sigma_2^2\mathbf{B}_2} \\ r_{12}\sqrt{\sigma_1^2\mathbf{B}_1 \times \sigma_2^2\mathbf{B}_2} & \sigma_2^2\mathbf{B}_2 \end{bmatrix}^{-1}$$

A general SNPMace model

$$\begin{bmatrix} \ddots & \cdots & \cdots & \cdots & \iddots \\ \vdots & \left[Z_i^{'}\mathbf{Z}_i + \mathbf{G}^{ii}\right] & \cdots & \left[\boldsymbol{\Psi}_{ii^+} + \mathbf{G}^{ii^+}\right] & \vdots \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & \left[\boldsymbol{\Psi}_{ii^+} + \mathbf{G}^{ii^+}\right] & \cdots & \left[\mathbf{Z}_{i^+}^{'}\mathbf{Z}_{i^+} + \mathbf{G}^{i^+i^+}\right] & \vdots \\ \iddots & \cdots & \cdots & \cdots & \ddots \end{bmatrix} \times \begin{bmatrix} \cdots \\ \left[\hat{\mathbf{g}}_i\right] \\ \vdots \\ \left[\hat{\mathbf{g}}_{i^+}\right] \\ \cdots \end{bmatrix} = \begin{bmatrix} \cdots \\ \left[Z_i^{'}\mathbf{y}_i\right] \\ \vdots \\ \left[\mathbf{Z}_{i^+}^{'}\mathbf{y}_{i^+}\right] \\ \cdots \end{bmatrix}$$

Interbull SNPMace Project

2018-2019

We will write software to do SNPMace and deliver it to Interbull

We will test method on Brown Swiss

- Interbull have individual records for all countries and can calculate GEBV
- We will use SNPMace to calculate SNP effects and hence GEBVs
- Compare the two sets of GEBVs

Based on 50k SNP genotypes

Interbull Data

- $Z'R^{-1}Z$ matrices were calculated for six countries:

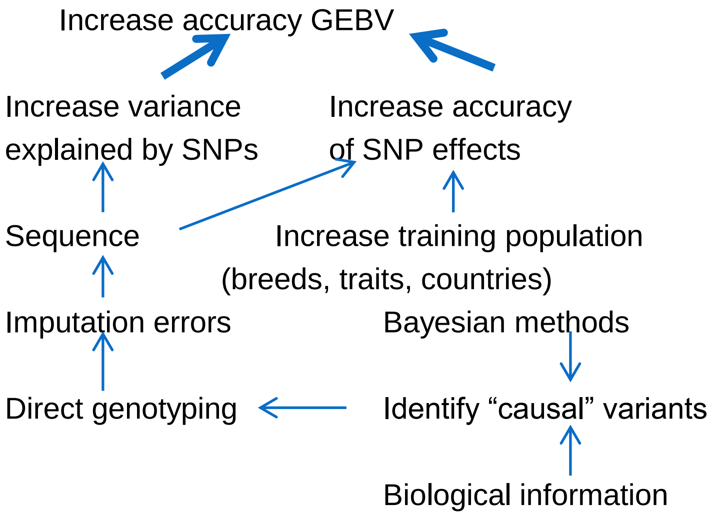
Country	No bulls
CHE	1922
DEA	2578
FRA	171
ITA	1418
SVN	227
USA	796

Interbull SNPMace Project

Possible extension of project

Use all sequence variants and Bayesian method instead of BLUP.

Medium term



Increase accuracy GEBV

Increase variance explained by SNPs

Increase accuracy of SNP effects

Sequence

Increase training population (breeds, traits, countries)

Imputation errors

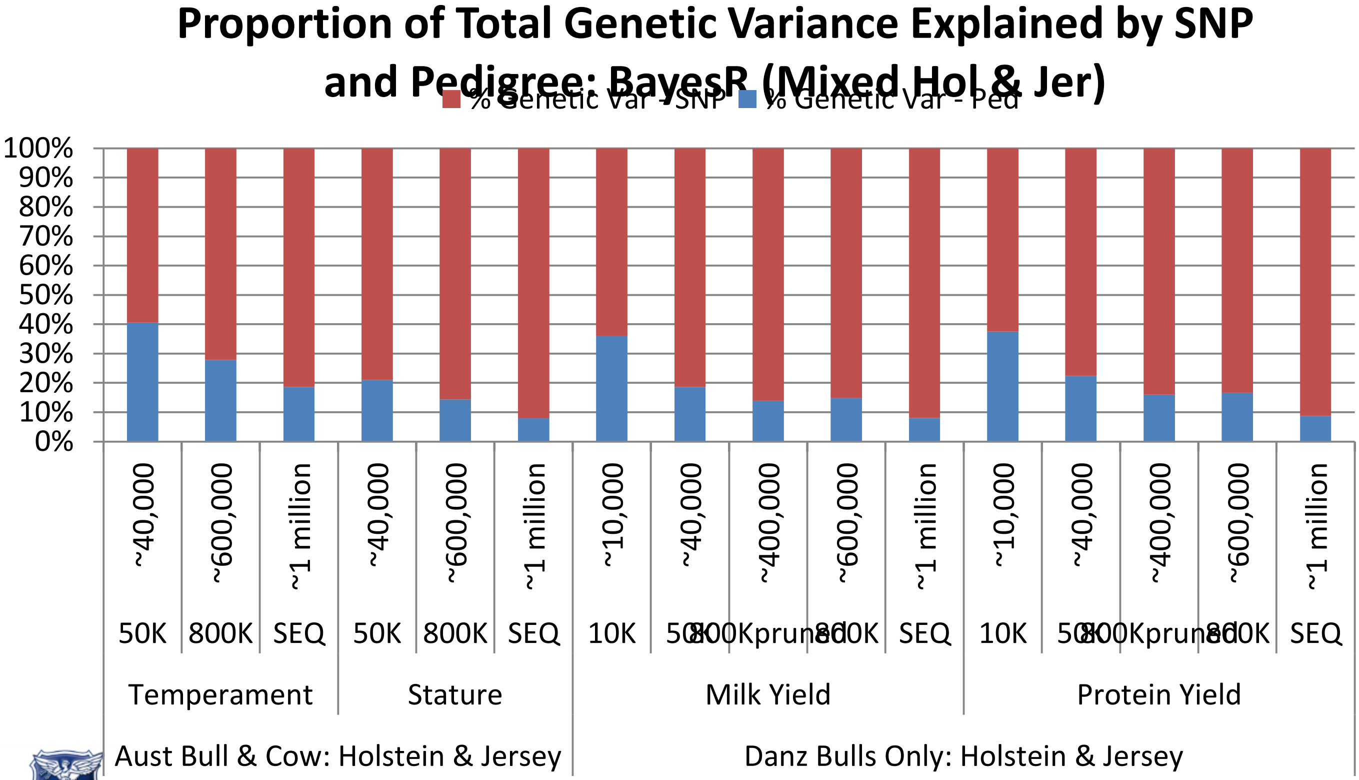
Bayesian methods

Direct genotyping

Identify “causal” variants

Biological information

Variance explained by SNPs and sequence (Iona Macleod)


Proportion of Total Genetic Variance Explained by SNP and Pedigree: BayesR (Mixed Hol & Jer)

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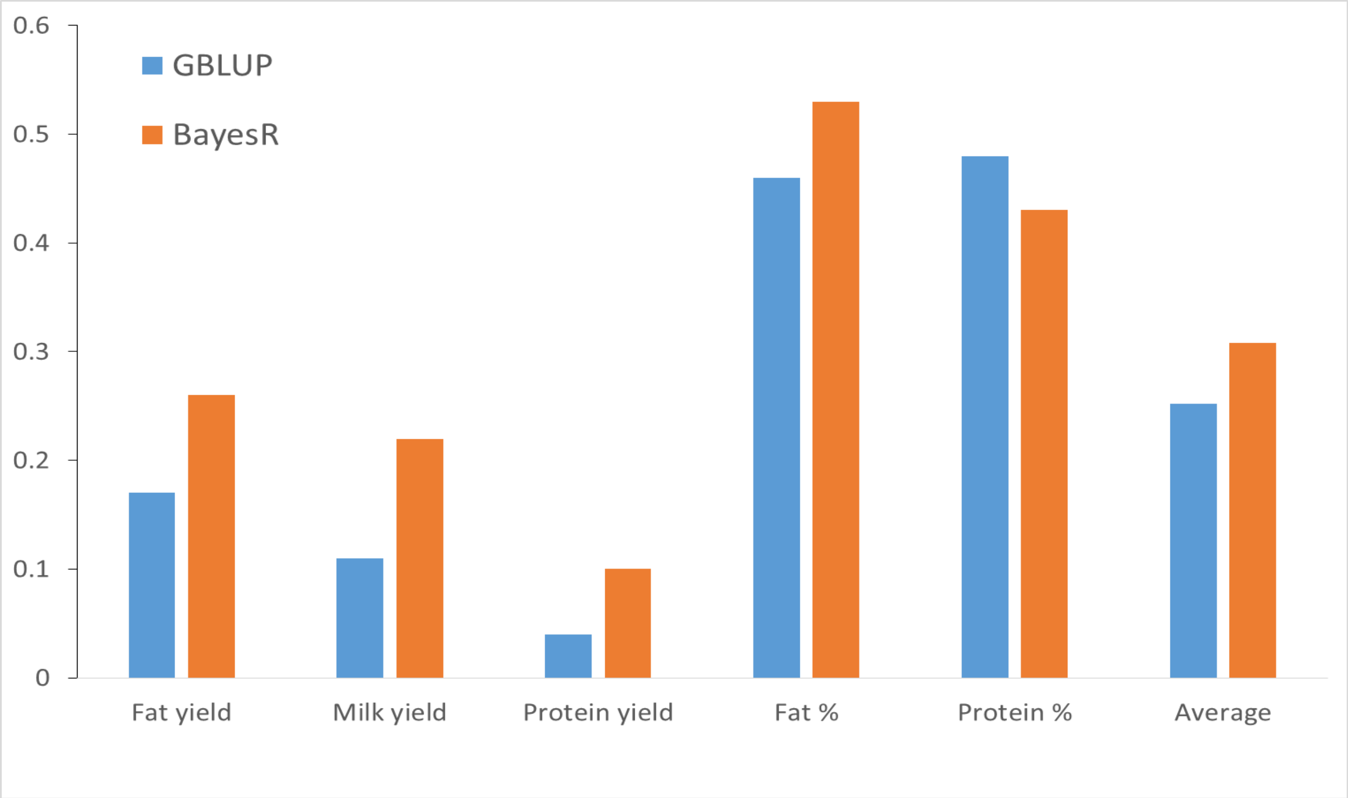
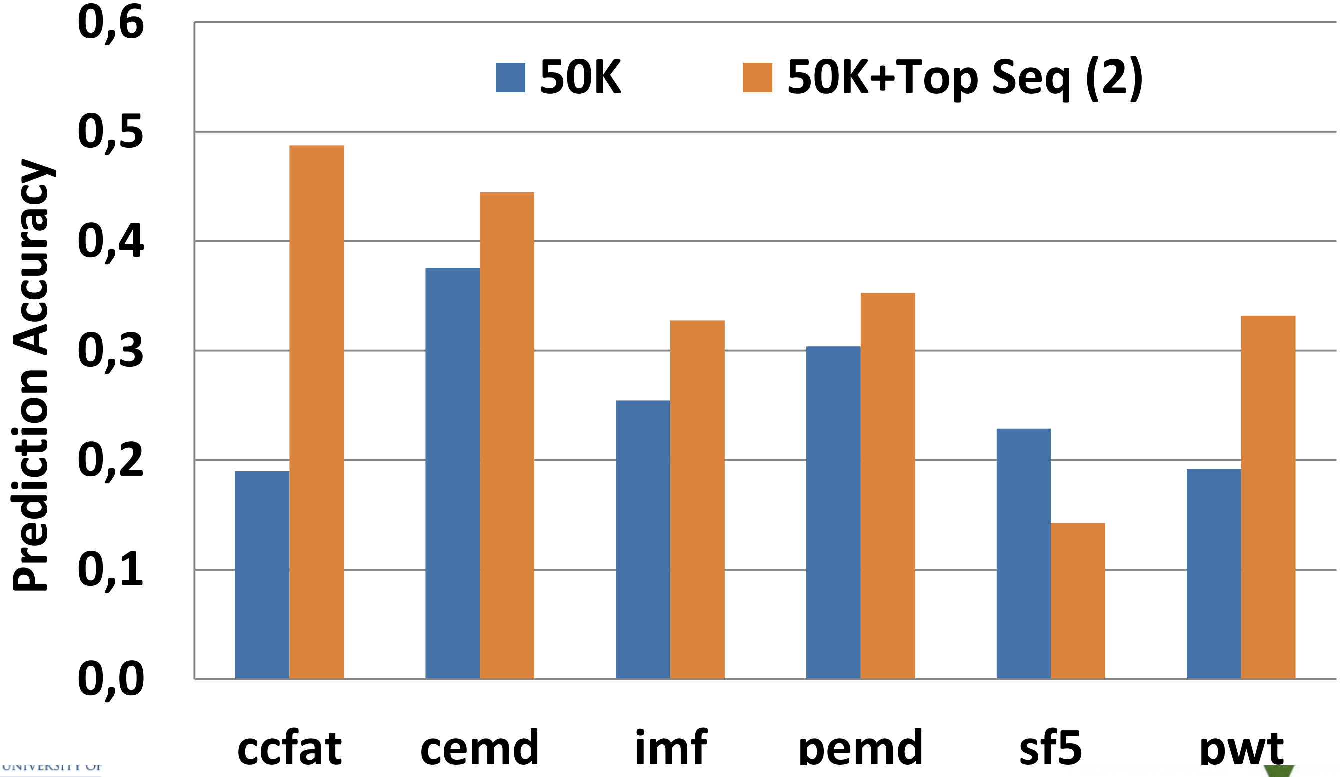
Accuracy r(DGV,DTD) in Aussie Red Bulls (Iona MacLeod)



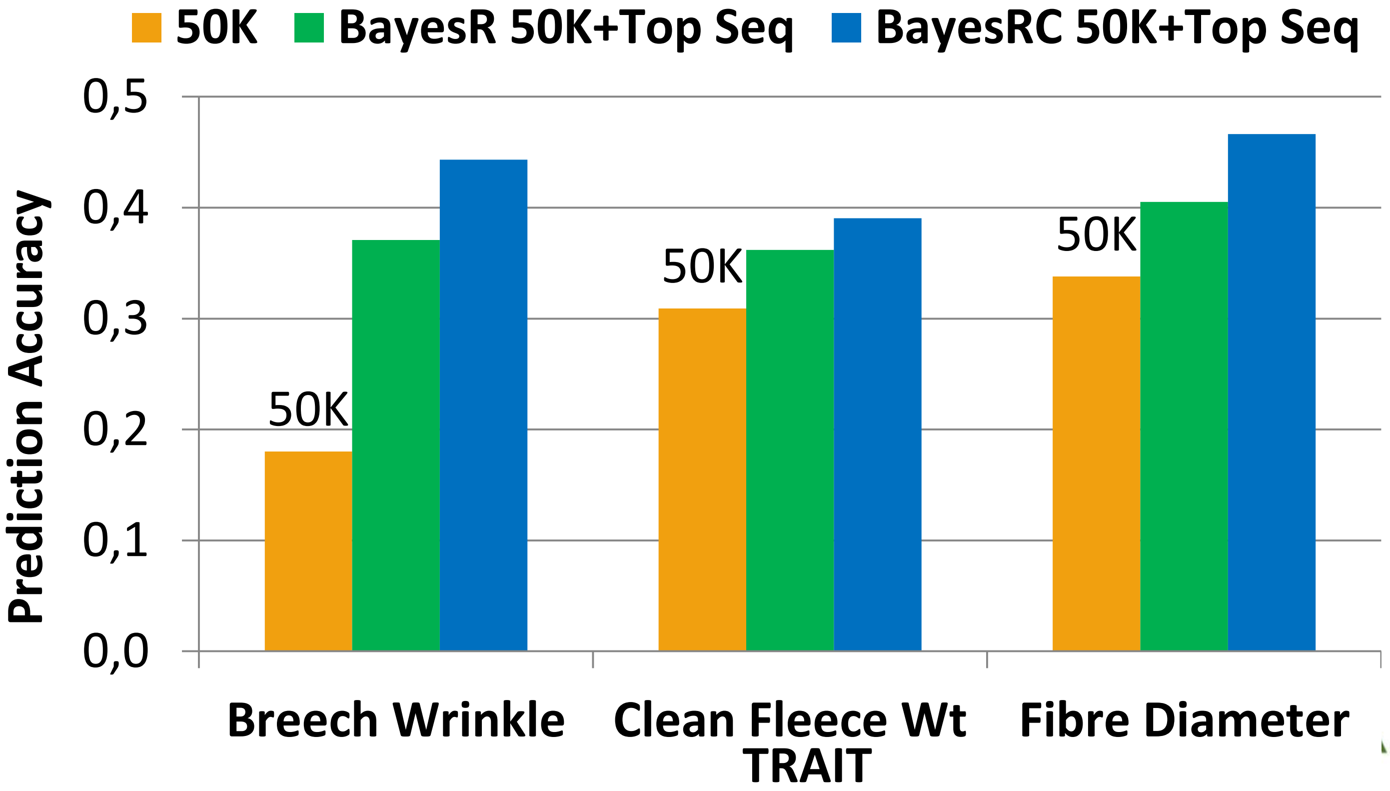
Meat Traits:

GBLUP Accuracy - Merino x Border Leicester

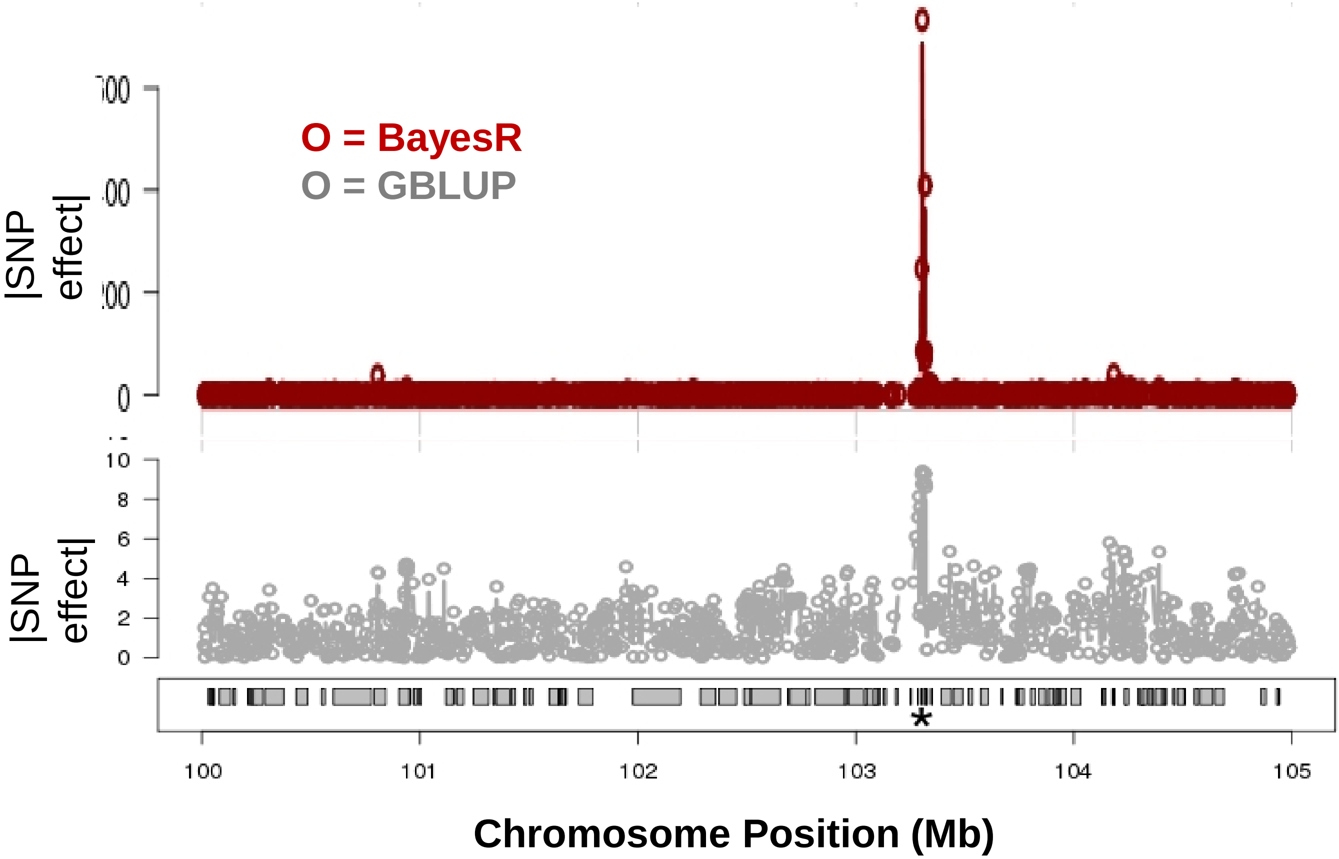


Wool Traits:

Prediction Accuracy in Merinos

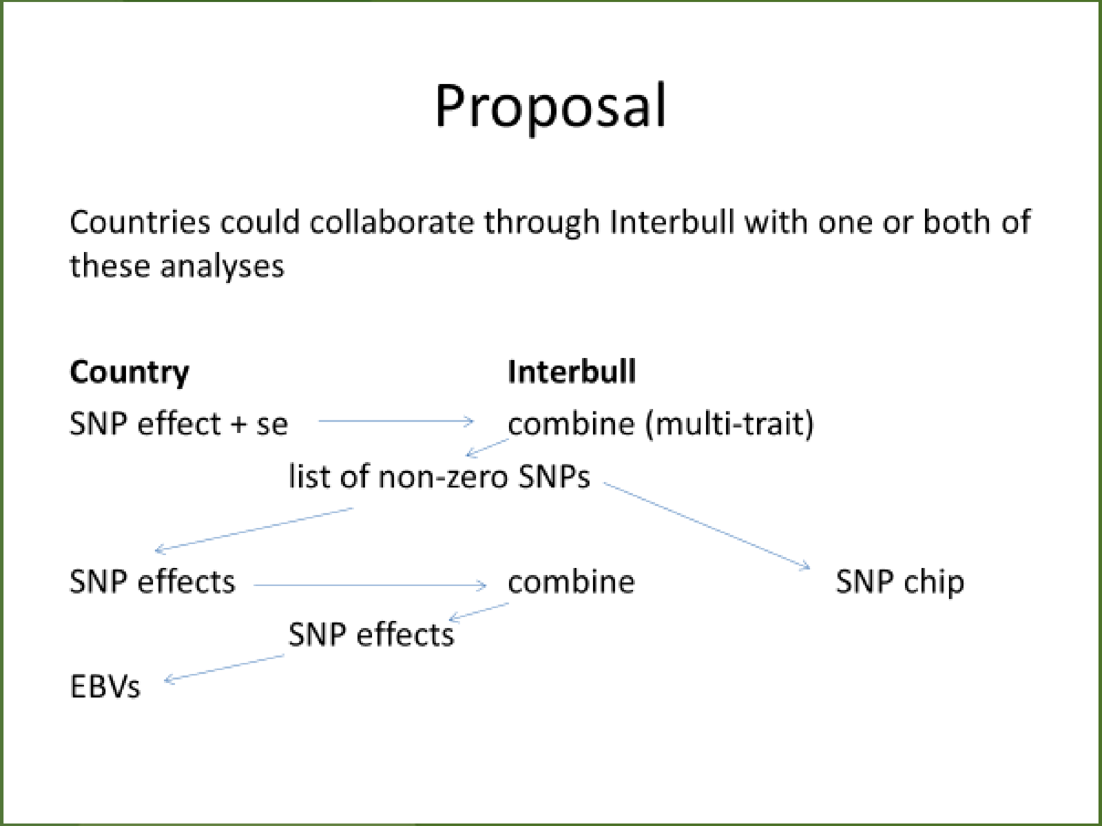


BayesR vs BLUP (BTA11)



Cattle stature (Aniek Bouwman, Ben Hayes et al)

Annotation class	Number
intergenic_variant	83
upstream_gene_variant	11
5_prime_UTR_variant	1
intron_variant	55
missense_variant	5
downstream_gene_variant	8
ChiP-SEQ peaks*	8
WBC eQTL	10



Proposal

Countries could collaborate through Interbull with one or both of these analyses

Country **Interbull**

SNP effect + se → combine (multi-trait)

list of non-zero SNPs

SNP effects → combine SNP chip

SNP effects

EBVs

Breaker

Conclusions

Meta-analysis could be used more to collaborate between countries

Interbull project is an example

Acknowledgements

Thank you to the
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Section Breaker