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Comparison of Bayesian Models for genomic selection using real dairy data

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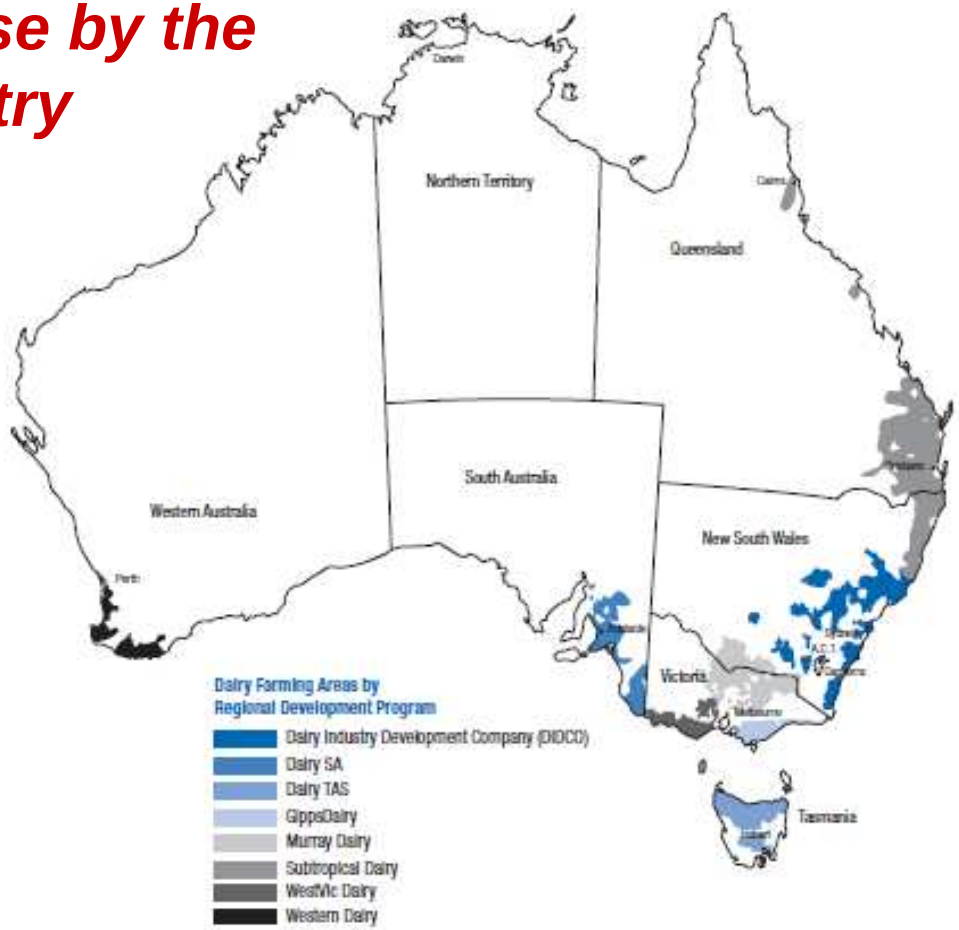
Project Aim:
To find the best method for GENOMIC SELECTION for implementation and use by the Australian dairy industry



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Generally, the methods to predict of GEBV face 2 statistical issues:

- Number of SNP (p) is greater than the number of individuals or records (n) i.e **p>n** problem
  - oversaturated or overparameterised model
- Large number of SNP effects that are zero or close to zero (need a sparse model).

WHAT APPROACH SHOULD BE USED??

- Dimension Reduction (PCA, PLS)
- Machine learning (SVM)
- Shrinkage models – penalised methods exploring sparsity (LASSO)
- Variable Dimension Model approaches (SSVS)
- Variable Selection (reduced set of SNPs)

Project: Tested 20 Methods!

→ **Bayesian Inference**

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Data

Reference Population

• 1098 Holstein Friesian bulls progeny tested ≤ 2003

Validation Population

• 400 Holstein Friesian bulls progeny tested > 2003

Phenotypes

• deregressed breeding values for protein, fat, milk volume, protein%, fat%, fertility, ASI (Australian Selection Index), APR (Australian Profit Ranking) and Overall type.

Genotypes

•39,048 markers

Evaluate methods on

• r(GEBV,ABV)

Correlation of Predicted GEBV with Australian breeding value (ABV)

•MSE

•Regression Coefficient

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Bayesian Models

Statistical Model:

$$y = \mu 1_n + \sum_j^p X_j \beta_j + Zu + e$$

- y is the vector of phenotypes of the trait for n individuals
- μ is the mean
- 1_n is a vector of ones of length n
- X_j is a vector of indicator variables representing the genotypes of the jth marker for all individuals (x_{ij}=0,1,2)
- β_j is the size of the SNP effect associated with marker j
- u is the vector of random polygenic effects of length n (Z is the associated design matrix)

$$u \sim N\left(0, \sigma_u^2 A\right)$$

- e is the residual error

$$e \sim N\left(0, \sigma_e^2 \mathbf{I}_n\right)$$

$$\boldsymbol{GEBV} = \hat{\boldsymbol{u}} + \boldsymbol{X}\hat{\boldsymbol{\beta}}$$

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Bayes A

Prior Distributions
SNP effects

$$\beta_i \mid \sigma_i^2 \sim N\left(0, \sigma_i^2\right)$$

$$\sigma_i^2 \sim \chi^{-2}(r, S) \sim \gamma^{-1}\left(\frac{r}{2}, \frac{rS}{2}\right)$$

r degrees of freedom and
scale parameter S

SNP EFFECTS
- Normal-inverse scaled chi square (t distribution)
- unequal variance
- assumes that all SNPs have an effect
- Gibbs Sampler

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Bayes BLUP

Prior Distributions
SNP effects

$$\beta_i \mid \sigma_\beta^2 \sim N\left(0, \sigma_\beta^2\right)$$

$$\sigma_\beta^2 \sim \chi^{-2}(r, S) \sim \gamma^{-1}\left(\frac{r}{2}, \frac{rS}{2}\right)$$

r degrees of freedom and
scale parameter S

SNP EFFECTS
- Normal
- equal variance
- Infinitesimal assumptions
- assumes that all SNPs have an effect
- Gibbs Sampler

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Bayes C
Stochastic Search Variable Selection (SSVS)

(George and McCulloch, 1993)

Use latent variable γ_i (0,1)

SAME ASSUMPTIONS AS BAYES B

Prior Distributions
SNP effects

$$\beta_i \mid \gamma_i, \sigma_i^2 \sim (1-\gamma_i) N\left(0, \sigma_i^2/100\right) + \gamma_i N\left(0, \sigma_i^2\right)$$

$$\sigma_i^2 \sim \chi^{-2}(\boldsymbol{r}, \boldsymbol{S})$$

$$\gamma_i \sim \boldsymbol{bernoulli}(\boldsymbol{p}_i)$$

$$1 - \boldsymbol{p}(\gamma_i = 0) = \boldsymbol{p}(\gamma_i = 1) = \boldsymbol{p}_i$$

SNPs with γ_i=0, posterior values limited to values close to 0 (but not removed from the model- NO changing dimensionality) – GIBBS SAMPLER

SNP EFFECTS
- Mixture of two Normal-inverse scaled chi square distributions (t distributions)
- unequal variance
- assumes that a few SNP have an significant effect

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Methods

- Bayes A
  - All SNPs
  - Selected SNPs with weights
  - Selected SNPs without weights
- Bayes BLUP
  - All SNPs
  - Selected SNPs with weights
  - Selected SNPs without weights
- Bayes C
  - All SNPs

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SNP Pre-selection

Single SNP analysis (ASReml)

$$y = 1_n \mu + X\beta + Z_1 u_1 + Z_2 u_2 + e$$

- X is a vector of indicator variables representing the genotypes of the current SNP marker for all individuals (X_n=0,1,2) and β is the associated effect of the SNP
- u_1 is the random sire effect (Z_1 associated design matrix)

$$u_1 \sim N(0, \sigma^2_{u_1} I)$$

- u_2 is the random maternal grand sire effect (Z_2 associated design matrix)

$$u_2 \sim N(0, \sigma^2_{u_2} A)$$

Fitted with and without weights

-Weights = Number of Effective Records

-SNPs with p-value <0.1 included in predictive set.

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Results r(GEBV,ABV)

Method	*Fat*	*Fat%*	*Milk*	*Protein*	*Protein%*
Bayes BLUP - All SNPs	0.528	0.630	0.648	0.613	0.660
Bayes BLUP - Selected SNPs (Unweighted)	0.527	0.689	0.646	0.596	0.678
Bayes BLUP - Selected SNPs (Weighted)	0.543	0.643	0.659	0.610	0.661
Bayes A - All SNPs	0.538	0.700	0.631	0.572	0.645
Bayes A - Selected SNPs - (Unweighted)	0.543	0.712	0.639	0.579	0.667
Bayes A - Selected SNPs - (Weighted)	0.538	0.704	0.635	0.583	0.648
Bayes C	0.557	0.728	0.644	0.588	0.670

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Fat % - DGAT1

Table 1. Effect of the *DGAT1 K232A* Mutation on Sires' Daughter Yield Deviations (DYDs) for Milk Yield and Composition

Trait	$\alpha/2 \pm$ 2std.err.	r^2_{QTL}	P value$_{QTL}$	$r^2_{polygenic}$	r^2_{error}
Milk yield (kgs)	−158 ± 24.5	0.18	5.00E − 35	0.49	0.32
Fat yield (kgs)	5.23 ± 0.9	0.15	1.57E − 29	0.55	0.30
Protein yield (kgs)	−2.82 ± 0.7	0.08	1.70E − 15	0.65	0.26
Fat (%)	0.17 ± 0.012	0.51	4.33E − 122	0.29	0.19
Protein (%)	0.04 ± 0.006	0.14	5.05E − 28	0.66	0.20

(i) $\alpha/2$: QTL allele substitution effect on DYD (≈ halve breeding value), corresponding in the mixed model to the regression coefficient on the number of *K* alleles in the *DGAT1 K232A* genotype, and to $\alpha/2$, where α is defined according to Falconer and Mackay 1996. (ii) r^2_{QTL}: proportion of the trait variance explained by the *DGAT1 K232A* polymorphism. (iii) P value$_{QTL}$: statistical significance of the *DGAT1 K232A* effect. (iv) $r^2_{polygenic}$: proportion of the trait variance explained by the random, polygenic effect in the mixed model. (v) r^2_{error}: proportion of the trait variance unexplained by the model.

- QTL explains > 50% of genetic variance in fat%
- QTL allele is common and acts additively

→ Major violation of BLUP assumptions

Grisart et al. (2002)

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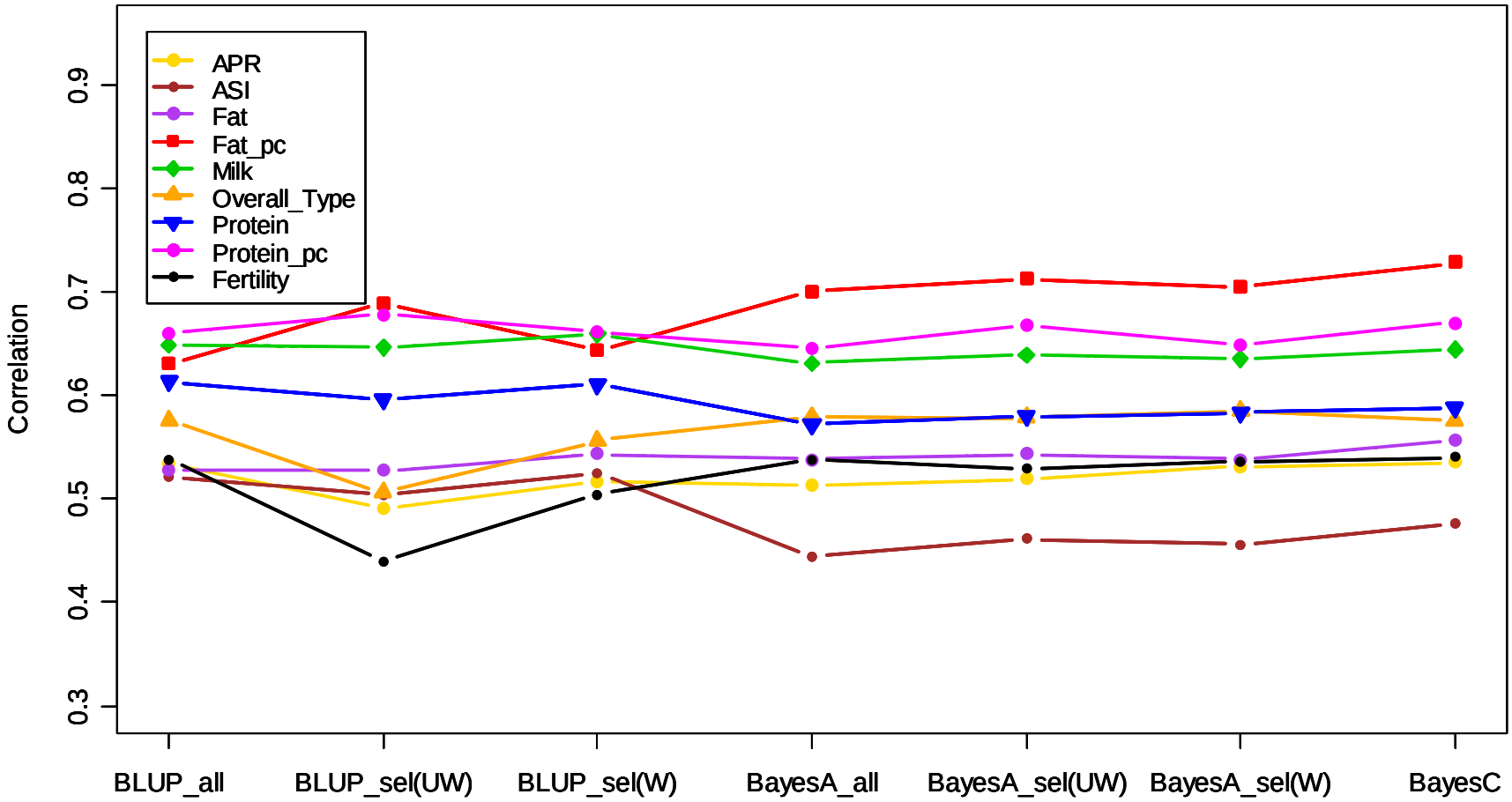
Results r(GEBV,ABV)



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RESULTS - IN CONTEXT:

A SUBSET OF ALL METHODS USING ALL SNPs

Method	*Average Correlation Across all traits*
Bayes BLUP	*0.589*
Bayes A	*0.578*
Bayes C	*0.597*
LASSO	0.595
SVR	0.587
GBLUP	0.588
PLS	0.592

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Conclusions

- Only small differences in accuracy and bias of GEBV from different methods
- Method by trait interaction. Better results when priors matched “real” distribution of QTL effects

  → *best method is trait dependent!*
- Pre-selection of SNP neither reduces or increases the accuracy of predicted GEBV
- Bayesian BLUP performs as well as or better than the other methods EXCEPT for traits with QTL that explain large amount of genetic variance eg. Fat % with DGAT1
- Still a need to find a method that produces equally accurate GEBV across traits with different genetic architecture.

Recognitions

Personally:

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Project:

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All other people involved in the project