Accounting for Discovery Bias in Genomic Prediction

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Genomic Enhanced EPDs (GE-EPDs)

- Enhance response to selection in traits:
  - Difficult to measure
  - Low heritability
  - Measured late in life
  - Sex-limited
- Current methods of genomic selection being used by many breed associations
  - Angus, Hereford, Simmental, Charolais, Red Angus, Limousin, Gelbvieh, Brangus, Santa Gertrudis, etc.

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Alternative Models Underlying Genomic Selection

Unweighted	Weighted
• Every marker given equal emphasis ▫ Realistic	• Marker emphasis weighted by [illegible] trait of [illegible]
• Works well [illegible] candidates are closely related to phenotyped and genotyped animals ▫ Accuracy diminishes rapidly with relationships	[illegible]tion candidates are closely related to phenotyped and genotyped animals ▫ Accuracy is less dependent upon relationships

Unweighted analyses not believed to be subject to discovery bias

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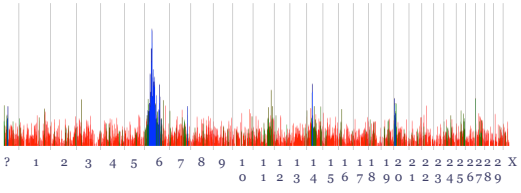
What is Weighting?

- Emphasis given to markers believed to have greater effect on traits of interest
  - Based on training population
  - Different weights for different traits



What is Discovery Bias?

- Occurs because of double counting
  - Same data is used to estimate SNP effects as is used for prediction of breeding values
    - "Winners Curse" (Goddard et al., 2009; Xu et al., 2011)
- Not only a bias of the predictions
  - Also a bias of the accuracy (usually overstated)
    - Difference between model-derived and true accuracies

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Model Derived Accuracy

- Computed from the inverse of the Mixed Model Equations
  - Prediction Error Variances (PEV)
- Requires that discovery data is analyzed simultaneously with prediction (Single-Step or One-Step)

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Effect of Discovery Bias

- Accuracy is overstated
  - MBV appear more accurate than they actually are
  - Blending methods of calculating GE-EPD weight genomic portion by its accuracy
    - Too little emphasis placed on phenotypic information
    - Inflation of genomic variance can cause genomic effects to be reported on an inflated scale relative to information derived directly from phenotypes

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Why Use Weighted Analyses?

- Generally obtain greater true accuracy than from unweighted
  - Especially when animals to be predicted are not closely related to those in training
    - At least partly due to the model matching the underlying biology more closely
- Discovery bias is the price we pay for greater true accuracy
  - How do we account for it?

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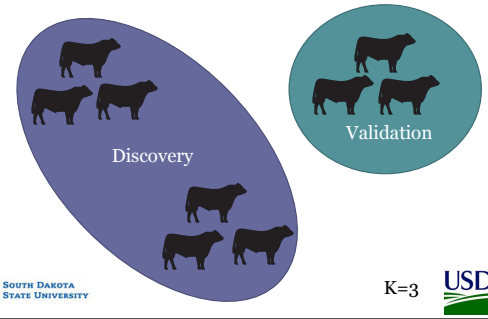
K-Means Validation



K=3

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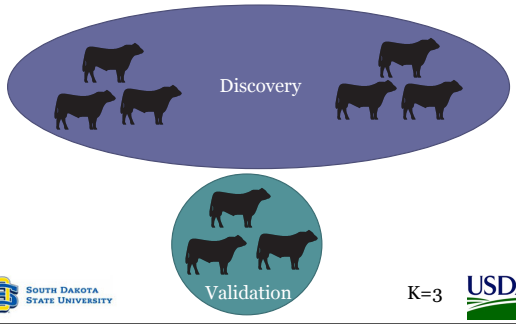
K-Means Validation



K=3

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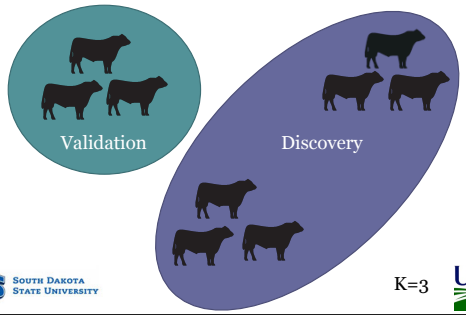
K-Means Validation



K=3

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Objective

- Investigate the topic of discovery bias and propose a way in which to partially account for it
  - Determine whether removing groups of animals from a pedigree, with their phenotypes, during training would reduce discovery bias resulting from their records being used in training

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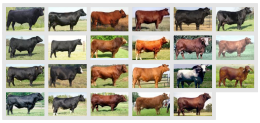
Taking K-Means Validation to the Limit



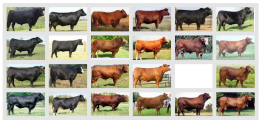
Discovery

- Each animal is its own group.

- Estimate marker effects conditional on Discovery subset of the population
- Apply those effects to the Prediction Animal's marker data.

k = n

Cycle Through Each Animal in the Population



Discovery

- Each animal is its own group.

- This results in a Corrected Molecular Breeding Value (CMBV)
  - own information was not used in estimation of the marker effects.

k = n

Molecular Breeding Value (MBV)

- Summary of the genetic merit of an individual as measured by genomic effects
- Computed as a sum of SNP effects

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SNP Analysis Model

- One random effect per SNP, each with its own variance parameter
  - i.e. Weighting
- BLUP predictions of SNP effects and REML estimates of SNP variances
  - Deterministic algorithm (not MCMC)

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Correcting for Discovery Bias

- Step 1: Estimate marker effects conditional on the entire population (only once)
  - Results in an MBV for each individual
- Step 2: Adjust the effects for each individual for dropping its information from the data set
  - Results in a Corrected MBV (CMBV)
  - This latter step requires minimal computational effort, even though it is applied to each individual in the population

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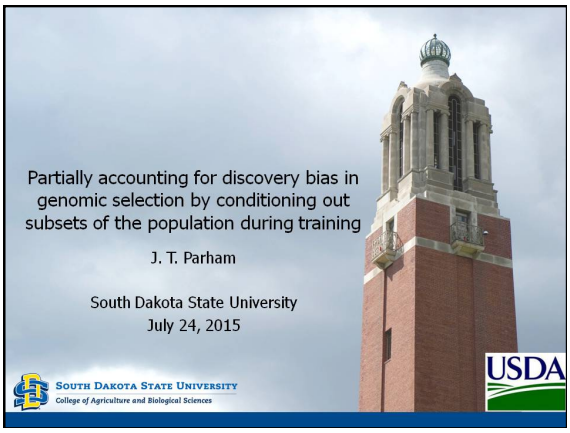

Materials and Methods

- Animals
  - Cattle in the GPE population at USMARC
    - Cycle VII of GPE (Snelling et al., 2010)
    - Represented 18 industry breeds
  - Used 2,600 animals with BovineSNP50 genotypes
    - 107 sire groups (1-107 animals per group)
    - Simulated phenotypes for non parents only
      - Resulted in 107 non overlapping paternal half sib groups
      - Population structure simplified computations for replicated data

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Simulated Phenotypes

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

y = vector of simulated phenotypes
Q = matrix of Quantitative Trait Nucleotide (QTN) genotypes
q = vector of simulated QTN effects
e = vector of simulated residuals

True Breeding Value (TBV) = **u** = **Qq**

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SNP and QTN Selection

- Used real data from the BovineSNP50 chip
- Total of 2,500 SNP used as markers for MBVs
  - Selected regions of 250 nearly contiguous SNP on each of 10 chromosomes (2,500 total SNP)
  - Monomorphic SNP were removed
- Total of 35 SNP selected as QTN
  - Moderate frequency (q = 0.29-0.30)
  - Located within regions of the 2,500 marker SNP

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Analysis of Simulated Data

- Step 1: Estimate marker effects conditional on the entire population (only once)
- Step 2: Adjust the effects for each paternal half sib group by dropping their information from the data set
  - Removed closest relatives for each individual

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Realized vs. Model Derived Accuracy

Comparison of Accuracies of Simulation (n_r = 105)

	Realized Accuracy		Model Derived Accuracy		Discovery Bias
	Mean	SE	Mean	SE	Mean
MBV	0.687	0.006	0.960	7.11e-5	0.273
CMBV	0.620	0.007	0.954	7.59e-5	0.334

MBV = Uncorrected Molecular Breeding Value; CMBV = Corrected MBV

- Realized Accuracy is the correlation between MBV and TBV
- Model derived accuracy computed from PEV

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Problem…

- Dropping phenotypes of each individual and their closest relatives had a negative effect on the realized accuracy
- Challenge to incorporate phenotypes without influencing the estimation of SNP effects

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A Solution: Two Trait Post-Analysis

- Used to reintroduce phenotype into the analysis
- Trait 1: simulated phenotype
  - GE-EPD are predictions of trait 1
- Trait 2: MBV/CMBV from analysis excluding paternal half sib group

Realized vs. Model Derived Accuracy

Comparison of Accuracies of Simulation (n_s = 105)

	Realized Accuracy		Model Derived Accuracy		Discovery Bias
	Mean	SE	Mean	SE	Mean
MBV	0.687	0.006	0.960	7.11e-5	0.273
CMBV	0.620	0.007	0.954	7.59e-5	0.334
GE-EPD	0.716	0.006	0.942	6.85e-5	0.226
★CGE-EPD	0.721	0.007	0.865	5.84e-5	0.144

MBV = Uncorrected Molecular Breeding Value; CMBV = Corrected MBV;
GE-EPD = Uncorrected Genomic Enhanced Expected Progeny
CGE-EPD = Corrected GE-EPD

Conclusions from Thesis

- Method of accounting for bias decreased gap between model derived and realized accuracy
  - Believed to partially account for bias
- True accuracies of genomic prediction were higher when accounting for bias than when not accounting for it
- Accounting separately for polygenic effects improved accuracy for uncorrected predictions
  - Using the two trait model
- Overall, promising "first step" method

Moving Forward

- Removing paternal half sib groups was an expedient proof of principle
  - Not a final solution
- Optimal correction for each individual in a general pedigree is yet to be determined

The Traditional Genetic Prediction Paradigm

- A single analysis conducted for an entire population
  - Optimized to predict differences among all members of the population simultaneously
  - Results in an unnecessary constraint on optimization

A New Genetic Prediction Paradigm

- Individual analyses conducted to optimize prediction for each animal within a population
  - Excluded data customized for each individual
  - Predicts the individual relative to population
    - Rather than directly to specific individuals
  - May require small base adjustment for each individual
- Requires thinking outside of the traditional "box"

Conclusion

- Weighted and Unweighted analyses differ
  - Weighted analyses subject to discovery bias, but can result in more accurate predictions
    - Improvement in accuracy especially important for beef cattle populations
- Although we may not be able to eliminate the effects of discovery bias, we can mitigate them
  - Results of thesis research promising and supportive

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Questions?

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