

Genomic Selection

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Introduction

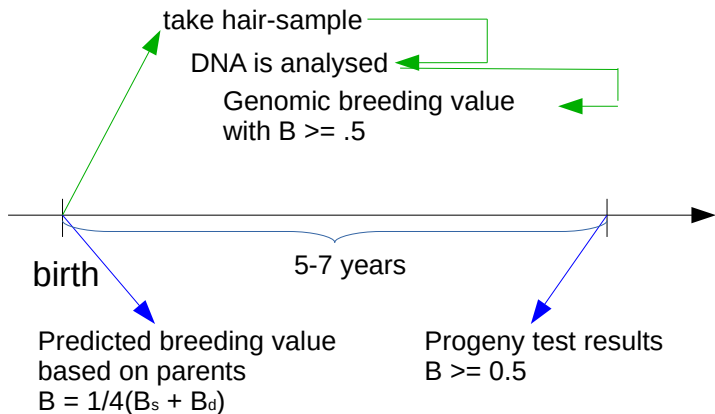
- ▶ Proposed in 2001
- ▶ Widely adopted in 2007/2008
- ▶ Costs of breeding program reduced due to shorter generation intervals
- ▶ In cattle: young sire selection versus selection based on sire proofs
- ▶ In pigs: early selection among full sibbs
- ▶ Inbreeding must be considered

Terminology

- ▶ **Genomic Selection:** use of genomic Information for selection decisions
- ▶ Genomic Information is used to predict **genomic breeding values**

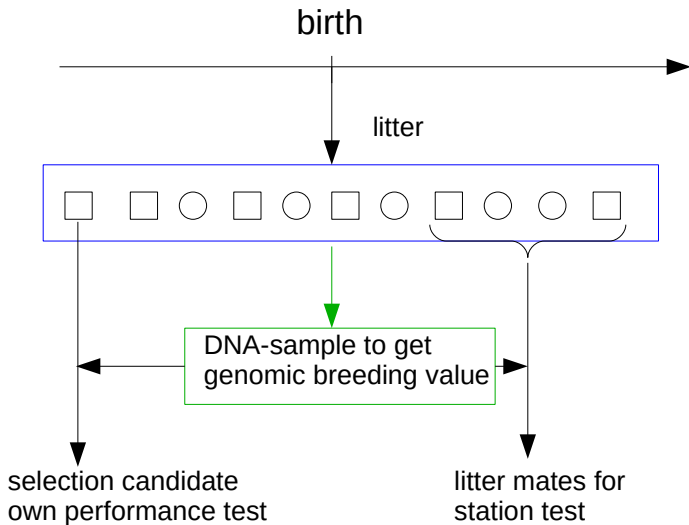
Benefits in Cattle

With genomic information



Without genomic information

Benefits in Pigs

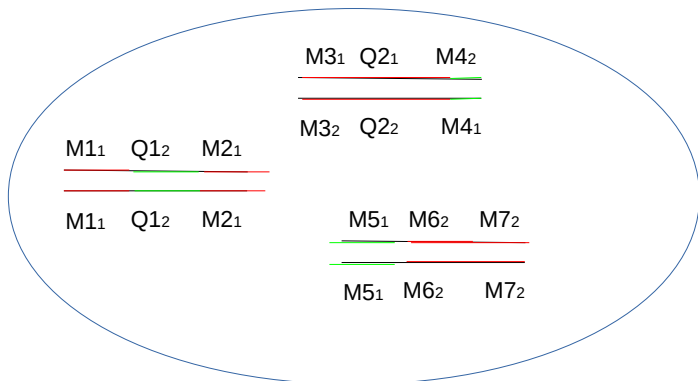


Genetic Model

- ▶ Recall: BLUP animal model is based on infinitesimal model
- ▶ Prediction of genomic breeding values is based on **polygenic model**
- ▶ In polygenic model: **Single Nucleotide Polymorphisms** (SNP) are used as markers
- ▶ Marker genotypes are expected to be associated with genotypes of **Quantitative Trait Loci** (QTL)

Polygenic Model

Distribution of SNP (M) and QTL (Q)



— Non-Coding region

— Coding region

Statistical Models

Two types of models are used

1. marker-effect models (MEM)
2. genomic-breeding-value based models (BVM)

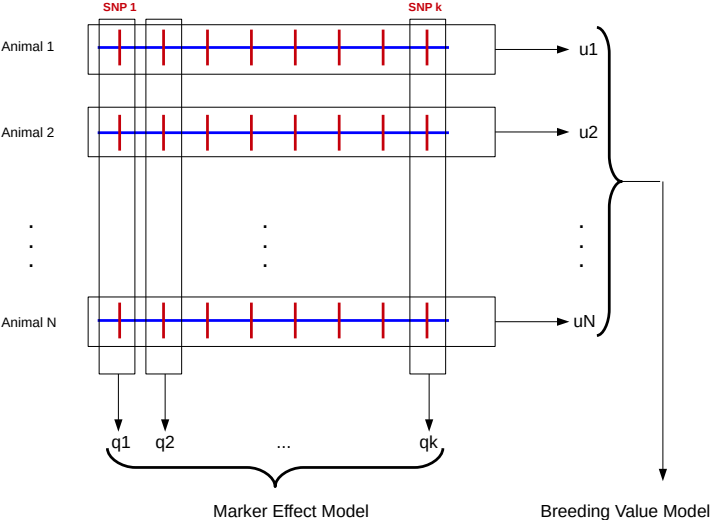
MEM

- ▶ marker effects (a -values) are fitted using
 - ▶ a simple linear model \rightarrow marker effects are fixed
 - ▶ a linear mixed effects model \rightarrow marker effects are random
- ▶ Problem of finding which markers are associated to QTL
- ▶ With high number of SNP compared to number of genotyped animals: very large systems of equations to solve

BVM

- ▶ genomic breeding values as random effects
- ▶ similar to animal model
- ▶ genomic relationship matrix (G) instead of numerator relationship matrix (A)

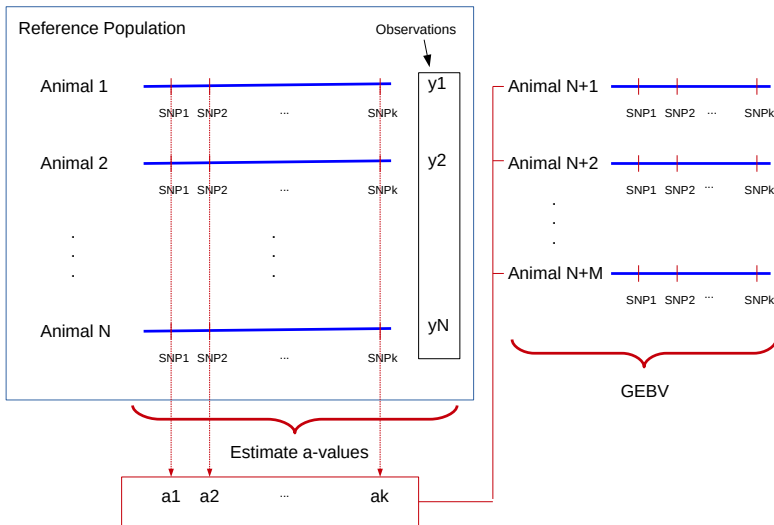
MEM versus BVM



Logistic Procedures

- ▶ Two Step:
 - ▶ use reference population to get marker effects using MEM
 - ▶ use marker effects to get to genomic breeding values
- ▶ Single Step
 - ▶ MEM or BVM in a single evaluation
 - ▶ difficulty how to combine animals with and without genotypes

Two Step Procedure



Single Step GBLUP

- ▶ Use a mixed linear effect model
- ▶ Genomic breeding values g are random effects

$$y = Xb + Zg + e$$

with

- ▶ $E(e) = 0, \text{var}(e) = I * \sigma_e^2$
- ▶ $E(g) = 0, \text{var}(g) = G * \sigma_g^2$
- ▶ Genomic relationship matrix G

Solution Via Mixed Model Equations

- ▶ All animals have genotypes and observations

$$\begin{bmatrix} X^T X & X^T Z \\ Z^T X & Z^T Z + \lambda * G^{-1} \end{bmatrix} \begin{bmatrix} \hat{b} \\ \hat{g} \end{bmatrix} = \begin{bmatrix} X^T y \\ Z^T y \end{bmatrix}$$

with $\lambda = \sigma_e^2 / \sigma_g^2$.

Animals Without Observations

- ▶ Young animals do not have observations
- ▶ Partition \hat{g} into
 - ▶ \hat{g}_1 animals with observations and
 - ▶ \hat{g}_2 animals without observations
- ▶ Resulting Mixed Model Equations are (assume $\lambda = 1$)

$$\begin{bmatrix} X^T X & X^T Z & 0 \\ Z^T X & Z^T Z + G^{(11)} & G^{(12)} \\ 0 & G^{(21)} & G^{(22)} \end{bmatrix} \begin{bmatrix} \hat{b} \\ \hat{g}_1 \\ \hat{g}_2 \end{bmatrix} = \begin{bmatrix} X^T y \\ Z^T y \\ 0 \end{bmatrix}$$

Predicted Genomic Breeding Values

- ▶ Last line of Mixed model equations

$$G^{(21)} \cdot \hat{g}_1 + G^{(22)} \cdot \hat{g}_2 = 0$$

Solutions

- ▶ Solving for \hat{g}_2

$$\hat{g}_2 = -(G^{(22)})^{-1} \cdot G^{(21)} \cdot \hat{g}_1$$

Genomic Relationship Matrix

- ▶ Breeding value model uses genomic breeding values g as random effects
- ▶ Variance-covariance matrix of g are proposed to be proportional to matrix G

$$\text{var}(g) = G * \sigma_g^2$$

where G is called **genomic relationship matrix** (GRM)

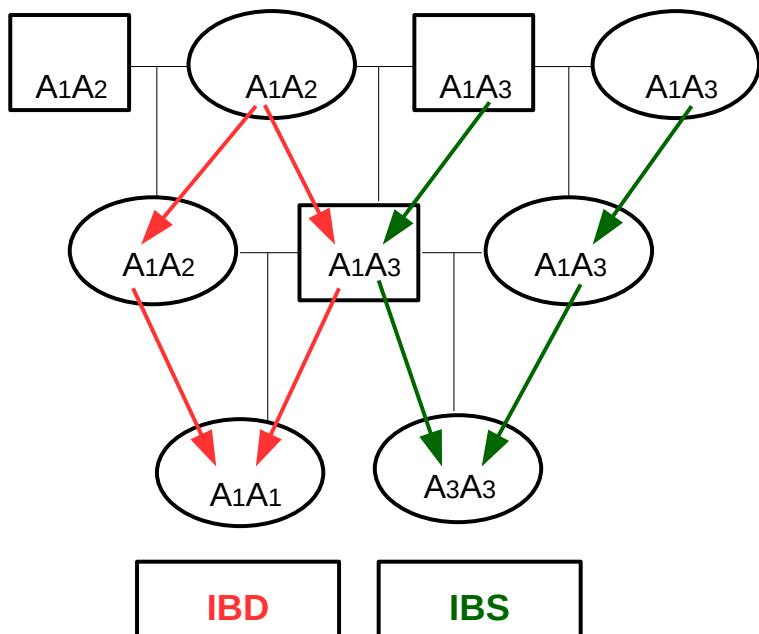
Properties of G

- ▶ genomic breeding values g are linear combinations of q
- ▶ g as deviations, that means $E(g) = 0$
- ▶ $var(g)$ as product between G and σ_g^2 where G is the genomic relationship matrix
- ▶ G should be similar to A

Change of Identity Concept

- ▶ A is based on identity by descent
- ▶ G is based on identity by state (including ibd), assuming that the same allele has the same effect
- ▶ IBS can only be observed with SNP-genotype data

Identity



Linear Combination

- ▶ SNP marker effects (a values) from marker effect model are in vector q
- ▶ Genomic breeding values from breeding value model are determined by

$$g = U \cdot q$$

- ▶ Matrix U is determined by desired properties of g

Deviation

- ▶ Genomic breeding values are defined as deviation from a certain basis

$$\rightarrow E(g) = 0$$

- ▶ How to determine matrix U such that $E(g) = 0$

Equivalence Between Models

Decomposition of phenotypic observation y_i with

- ▶ Marker effect model

$$y_i = w_i^T \cdot q + e_i$$

- ▶ Breeding value model

$$y_i = g_i + e_i$$

- ▶ g_i and $w_i^T \cdot q$ represent the same genetic effects and should be equivalent in terms of variability

Expected Values

- ▶ Required: $E(g_i) = 0$
- ▶ But: $E(w_i^T \cdot q) = q^T \cdot E(w_i)$
- ▶ Take q as constant SNP effects
- ▶ Assume w_i to be the random variable with:

$$w_i = \begin{cases} 1 & \text{with probability } p^2 \\ 0 & \text{with probability } 2p(1-p) \\ -1 & \text{with probability } (1-p)^2 \end{cases}$$

→ $E(w_i)$: For a single locus

$$E(w_i) = 1 * p^2 + 0 * 2p(1-p) + (-1)(1-p)^2 = p^2 - 1 + 2p - p^2 = 2p - 1 \neq 0$$

Specification of g

- ▶ Set

$$g_i = (w_i^T - s_i^T) \cdot q$$

with $s_j = E(w_j) = 2p_j - 1$

- ▶ Resulting in

$$g = U \cdot q = (W - S) \cdot q$$

with matrix S having columns j with all elements equal to $2p_j - 1$ where p_j is the allele frequency of the SNP allele associated with the positive effect.

Genetic Variance

- ▶ Requirement: $\text{var}(g) = G * \sigma_g^2$
- ▶ Result from Gianola et al. (2009):

$$\sigma_g^2 = \sigma_q^2 * \sum_{j=1}^k (1 - 2p_j(1 - p_j))$$

- ▶ From earlier: $g = U \cdot q$

$$\text{var}(g) = \text{var}(U \cdot q) = U \cdot \text{var}(q) \cdot U^T = UU^T \sigma_q^2$$

- ▶ Combining

$$\text{var}(g) = UU^T \sigma_q^2 = G * \sigma_q^2 * \sum_{j=1}^k (1 - 2p_j(1 - p_j))$$

Genomic Relationship Matrix

$$G = \frac{UU^T}{\sum_{j=1}^k (1 - 2p_j(1 - p_j))}$$

How To Compute G

- ▶ Read matrix W
- ▶ For each column j of W compute frequency p_j
- ▶ Compute matrix S and $\sum_{j=1}^k (1 - 2p_j(1 - p_j))$ from p_j
- ▶ Compute U from W and S
- ▶ Compute G