So far:
* Using predicted breeding values as selection criteria to find parents of future generations using all available phenotypic information together with pedigree relationships.
* Used linear mixed effect models to get to predicted breeding values

Traditional approach

no marker

2006 /7

use marker information on a large scale to predict breeding values

Genomic Selection

Peter von Rohr

2022-12-02

Making selection decisions to find parents of future generation based on genomic breeding values.

Shift in paradigm, mainly in cattle breeding

Introduction

* Meuwissen et al. (2001): How to use total genotypic values for prediction of breeding values.
* Genotypic values (V_{ij}) for a single locus model: with values

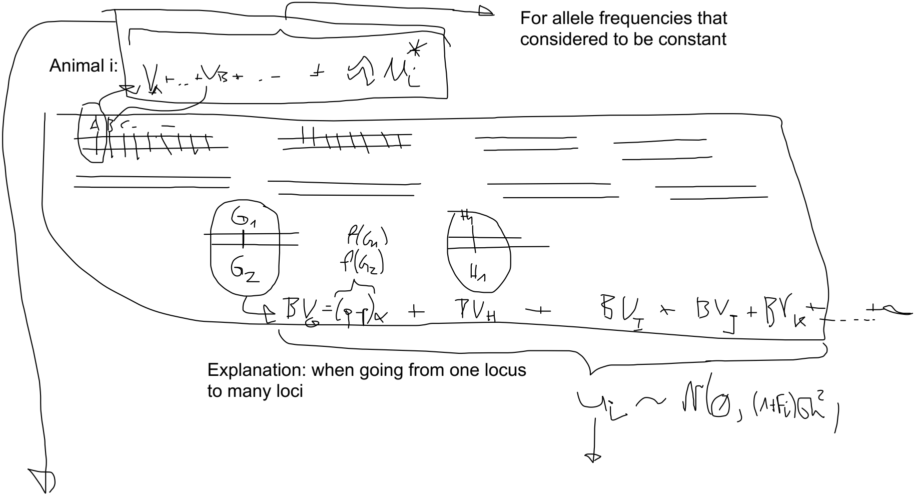
$$\begin{array}{c|c} & V_{ij} \\ G_1G_1 & +a \\ G_1G_2 & +d \\ G_2G_2 & -a \end{array}$$

- 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

By consequently basing selection decisions on genomics breeding values, costs of a cattle breeding program could be reduced by about 90%

accurate predictions at very young ages

Cattle: As soon as calf is born, a hair sample taken and is sent to the lab and after 2-4 weeks, genomic breeding values are available. Reliabilities range between 30-50%


$V_A + \dots + V_B + \dots + a_i^*$
A B C ...
G_1
G_2
$f(G_1)$
$f(G_2)$
H_1
H_1
$BV_G = (p-q)\alpha + BV_H + BV_I + BV_J + BV_K + \dots + a$
$u_i \sim N(0, (1+F_i)\sigma_a^2)$

For allele frequencies that considered to be constant

Animal i:

Explanation: when going from one locus to many loci

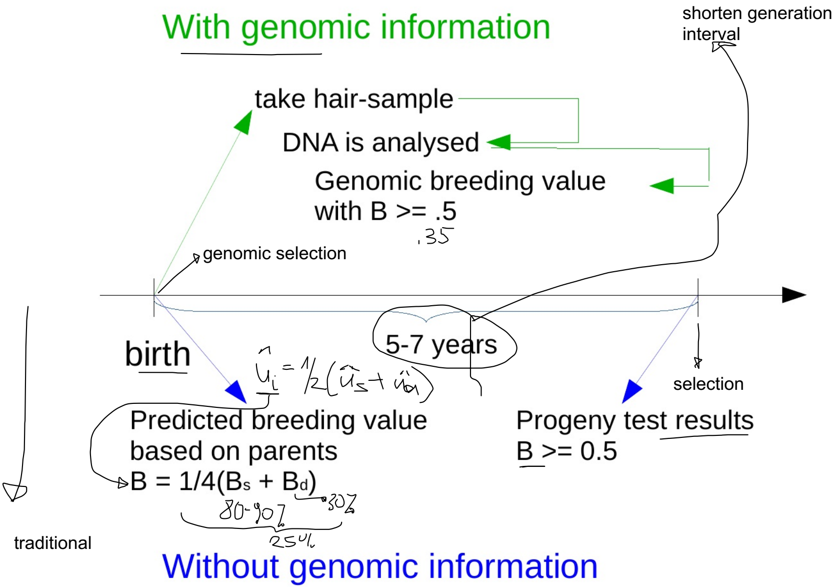
Reason for linear mixed effect models

The idea of Meuwissen allows to use fixed linear effect models

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

shorten generation interval

take hair-sample

DNA is analysed

Genomic breeding value
with B >= .5

.35

genomic selection

birth

5-7 years

selection

$\hat{u}_i = 1/2(\hat{u}_s + \hat{u}_d)$

Predicted breeding value
based on parents
$B = 1/4(B_s + B_d)$

80-90%

30%

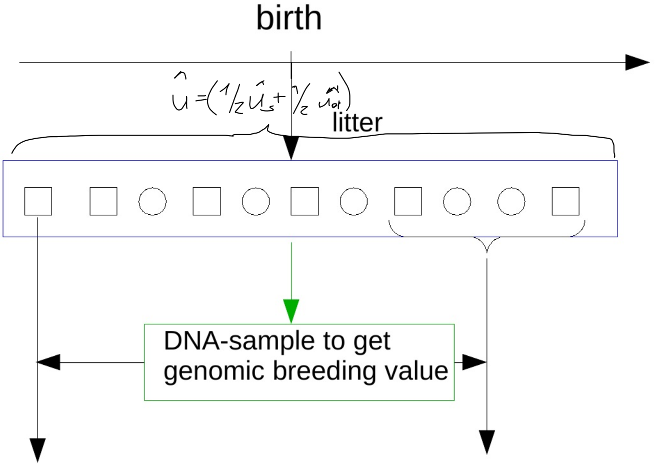
25%

Progeny test results
B >= 0.5

traditional

Without genomic information

Benefits in Pigs



birth

$\hat{u} = (1/2\, \hat{u}_s + 1/2\, \hat{u}_d)$

litter

DNA-sample to get genomic breeding value

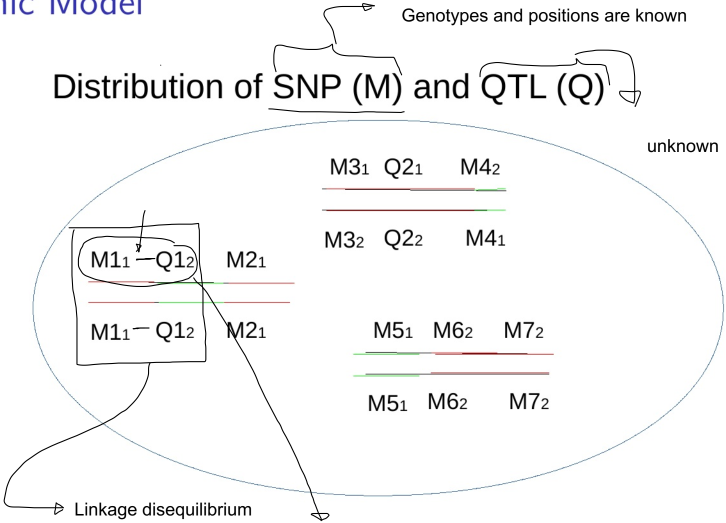
selection candidate own performance test

litter mates for station test

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



Genotypes and positions are known

Distribution of SNP (M) and QTL (Q)

unknown

Linkage disequilibrium

Pairs of Marker-QTL alleles that are more frequent than expected by random

🟥 Non-Coding region

🟩 Coding region

$$f(M1_1 - Q1_2) \neq f(M1_1) \cdot f(Q1_2)$$

Statistical Models

$$\begin{array}{c|c|c} Ani & SNP_1 \cdot - \quad - SNP_k & y_i \\ \hline 1 & & y_1 \\ 2 & & y_2 \\ \vdots & & \vdots \\ N & & y_N \\ & \underbrace{\qquad\qquad\qquad\qquad}_{k = 150'000} & \end{array}$$

800'000 — HD

$Seq: 2 \cdot 10^7$

Two types of models are used

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

MEM

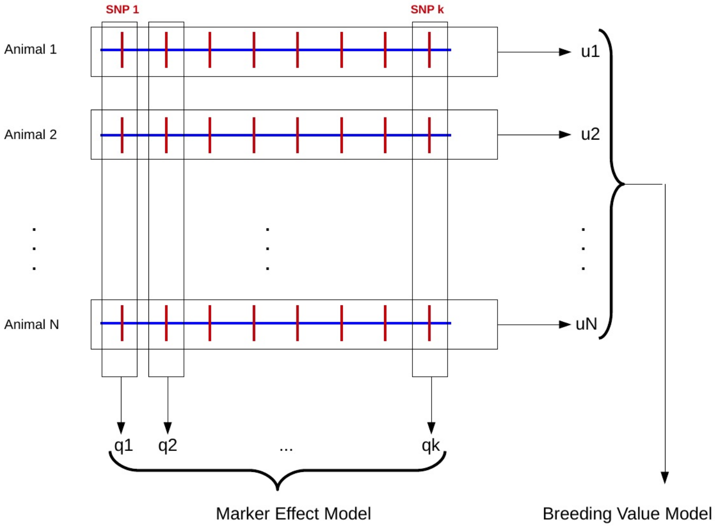
$$\overbrace{y_i = \mu + \underbrace{\beta_1 \cdot a_1 + \beta_2 \cdot a_2 + \dots + \beta_k \cdot a_k}_{} + e_i}^{\text{fixed effect}}$$

- marker effects (*a*-values) are fitted using
  - a simple linear model → marker effects are fixed
  - a linear mixed effects model → 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)

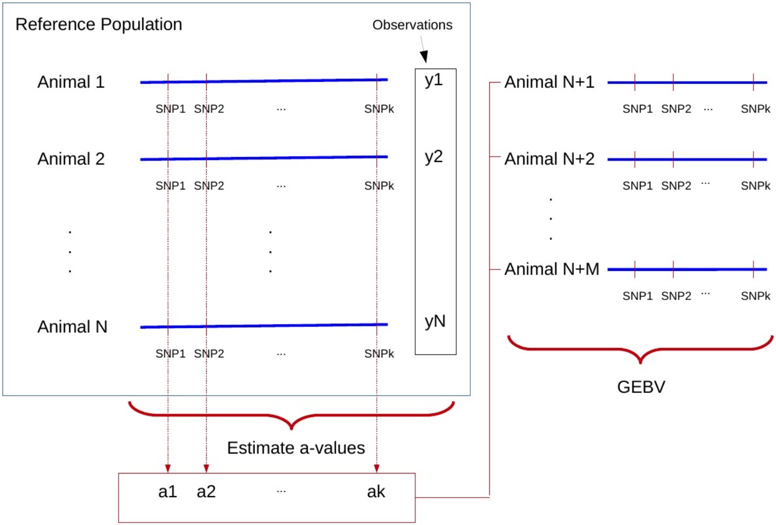
MEM versus BVM



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

- $E(e) = 0,\ var(e) = I * \sigma_e^2$
- $E(g) = 0,\ var(g) = G * \sigma_g^2$
- 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 $\lambda = 1$)

$$\left[\begin{array}{lll} X^TX & X^TZ & 0 \\ Z^TX & Z^TZ + G^{(11)} & G^{(12)} \\ 0 & G^{(21)} & G^{(22)} \end{array}\right] \left[\begin{array}{c} \hat{b} \\ \hat{g}_1 \\ \hat{g}_2 \end{array}\right] = \left[\begin{array}{c} X^Ty \\ Z^Ty \\ 0 \end{array}\right]$$

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

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

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

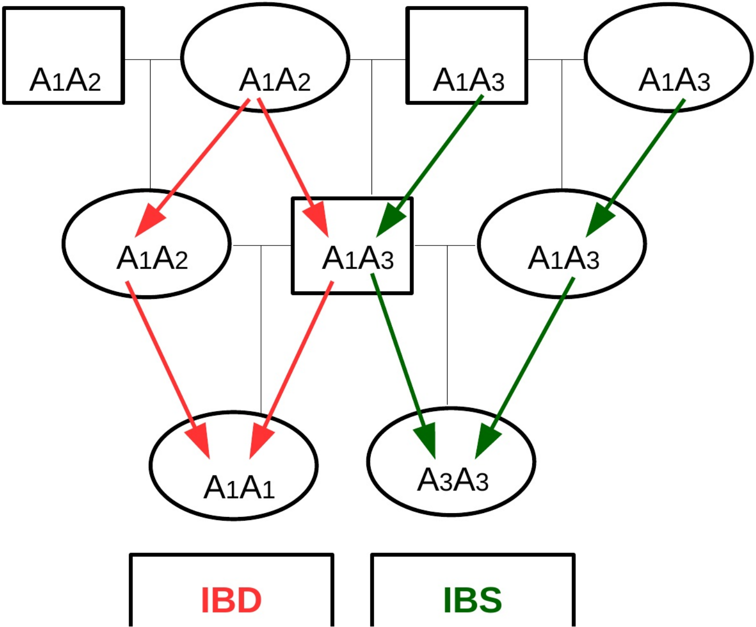
Properties of G

- 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:

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

$\rightarrow E(w_i)$: 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 $s_i = E(w_i) = 2p - 1$

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

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

- From earlier: $g = U \cdot q$

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

- Combining

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

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