Genetic Evaluation

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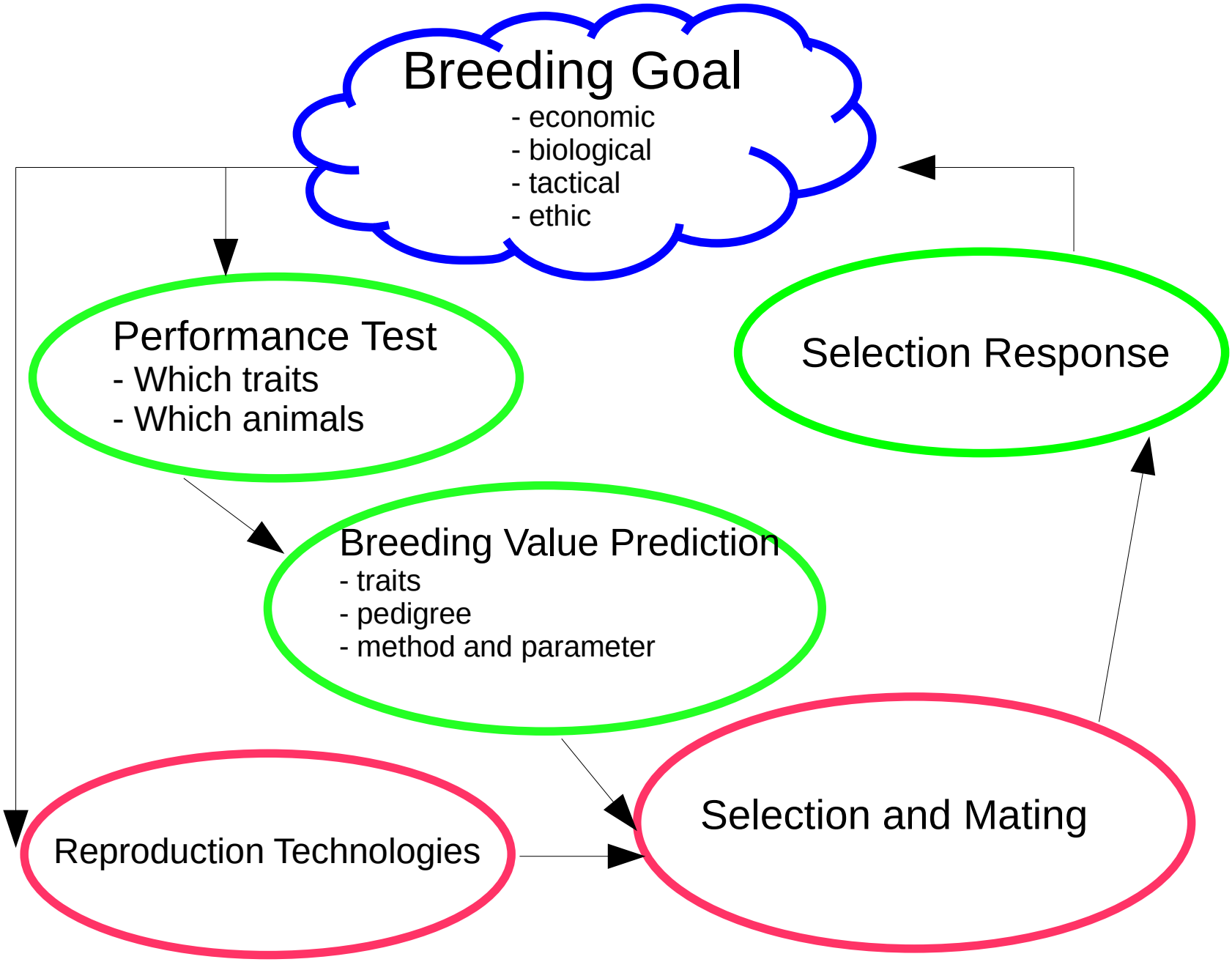
Breeding Program



New Trait

- New trait to be considered in breeding program
- Why? $\rightarrow$ Trait is of economic importance
- Want to improve average level of trait in a given population
- How is this done?
- What do we have to do?

Background and Context

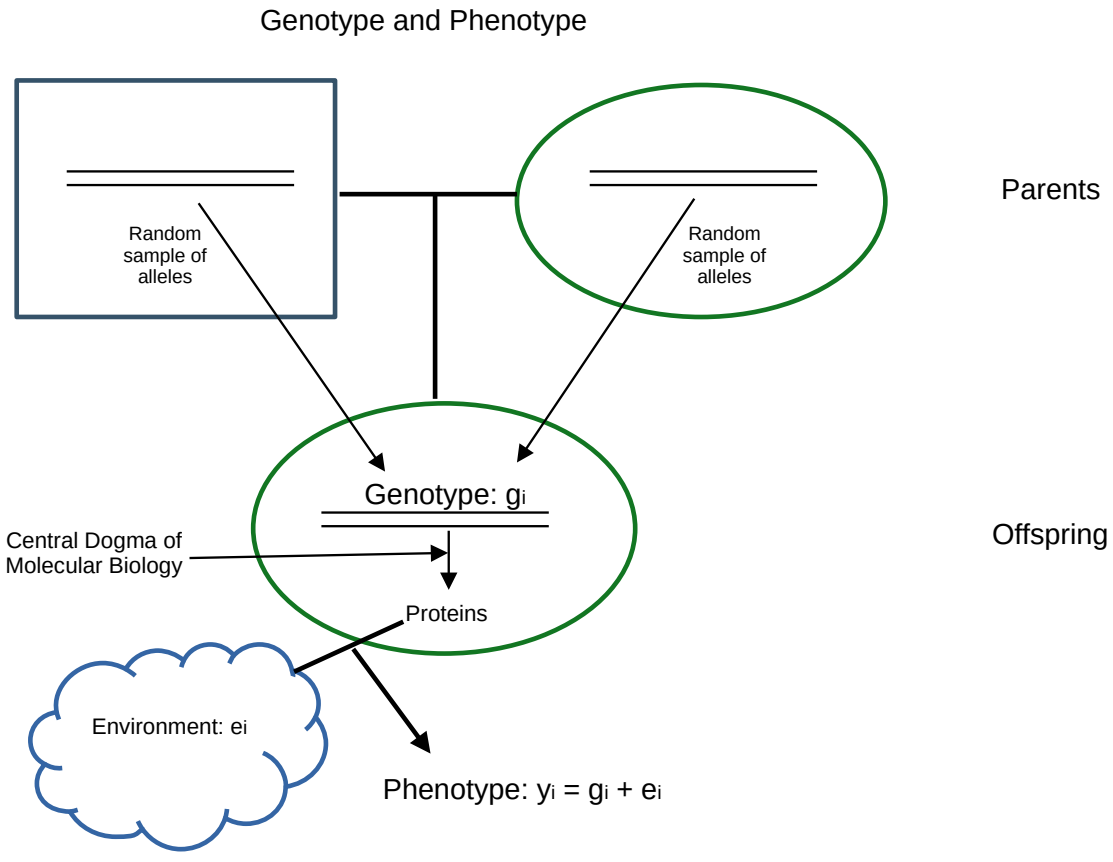
- Farms/Enterprise use livestock products as base for economic existence
- Improvements of production efficiency improves sustainability
- Short-term:
  - improve management and environment
  - select optimal livestock breed / population for given environment
- Long-term:
  - improve population at genetic level
  - define breeding goal
  - select parents such that offspring are “closer” to goal compared to parents

Genetic Improvement

- Genetic improvement happens between parents and offspring
- Parents pass random sample of alleles to offspring
- Goal: select parents that have many "good" alleles to pass to offspring
- Value of alleles quantified by breeding value
- How to find parents with "good" alleles without knowing which genes are important?

$\rightarrow$ Predict breeding value using **Statistical Modeling**

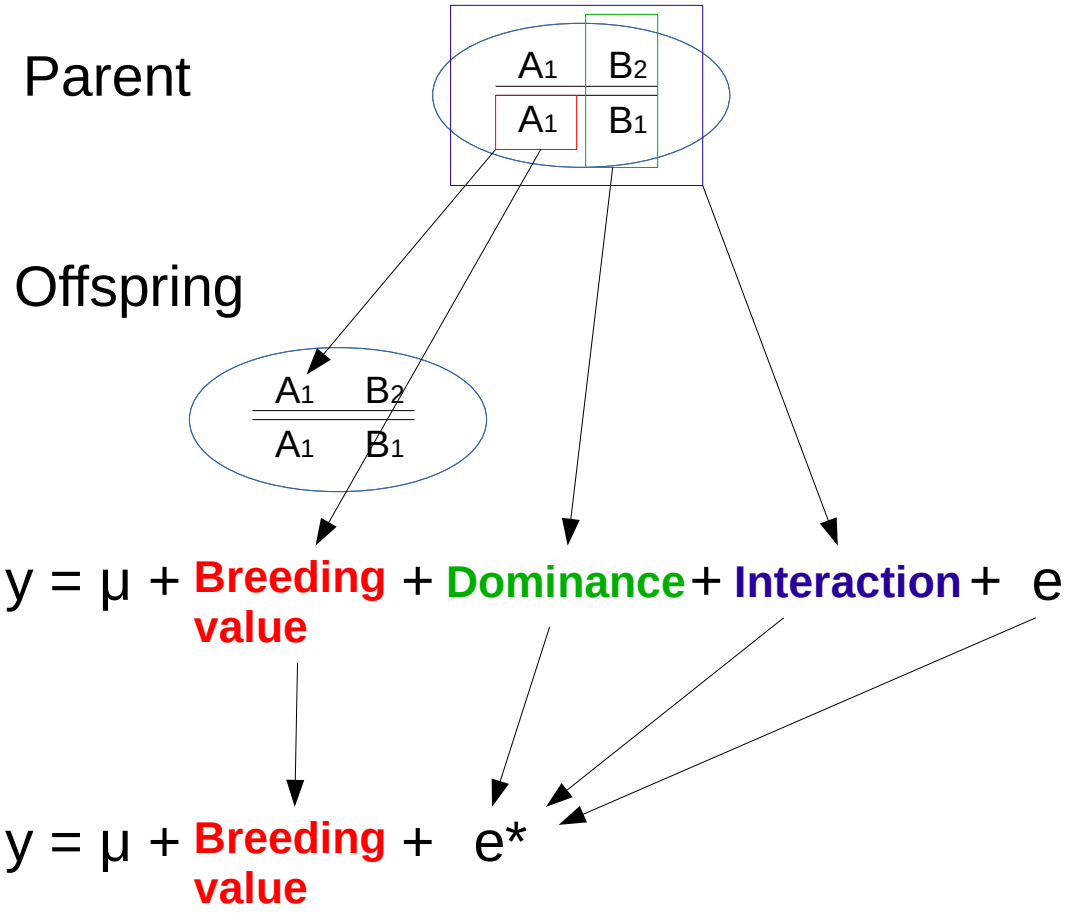
Genotype and Phenotype



- Selection based on phenotypes: in-efficient
- Instead: use statistical model to predict breeding value

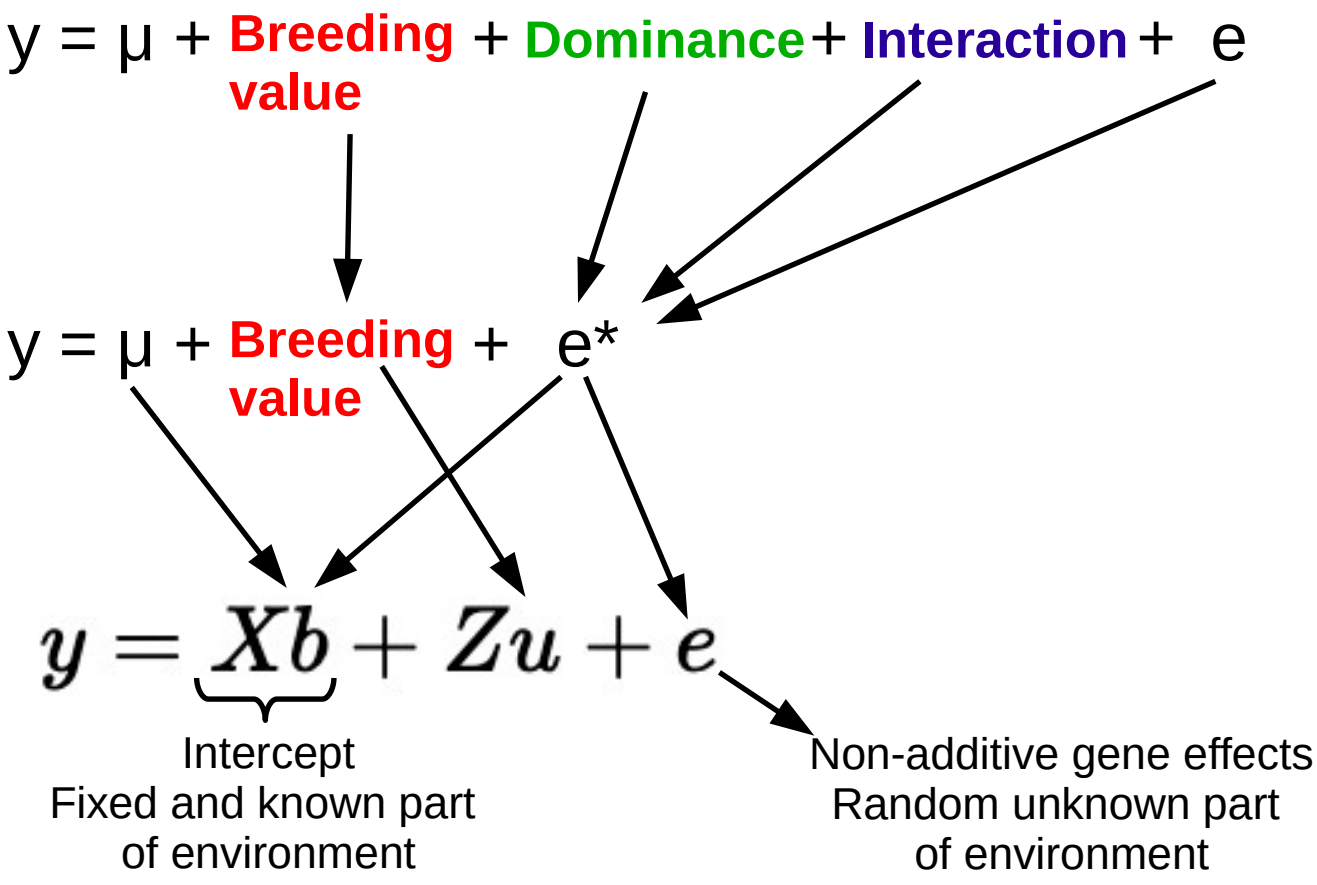
Selection Criterion

- Quantify value of alleles passed from parent to offspring
- Requires decomposition of effect of genotype on phenotype



Model Based on Decomposition of Genotype

- Genotype is decomposed



Statistical Model

- stochastic systems contains many sources of uncertainty
- statistical models can handle uncertainty
- components of a statistical model
  - response variable y
  - predictor variables $x_1, x_2, \ldots, x_k$ (fixed), u (random)
  - error term e
  - function $m(x)$

How Does A Statistical Model Work?

- predictor variables $x_1, x_2, \ldots, x_k$ are transformed by function $m(x)$ to explain the response variable y
- uncertainty is captured by error term.
- as a formula, for observation i

$$y_i = m(x_i) + e_i$$

Which function $m(x)$?

- class of functions that can be used as $m(x)$ is infinitely large
- restrict to linear functions of model parameter (b_0 and b_1), e.g.

$$y_i = b_0 + b_1 * x_i + e_i$$

Which predictor variables?

- In genetic evaluation a large variety of information is available which could be used as predictors
- Question, about which predictor variables to use is answered by model selection

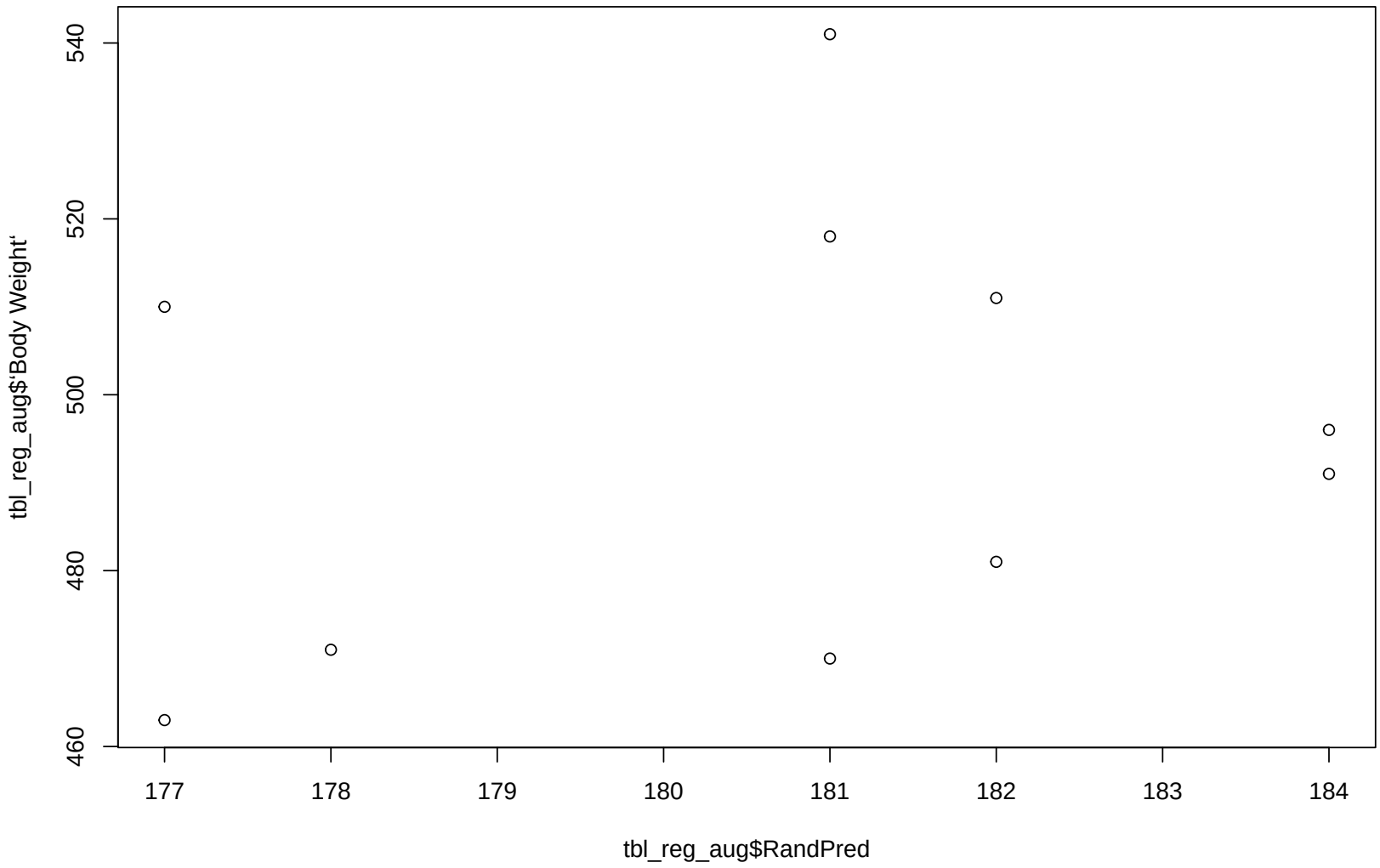
Why Model Selection

- Many predictor variables are available
- Are all of them `relevant`?
- What is the meaning of `relevant` in this context?

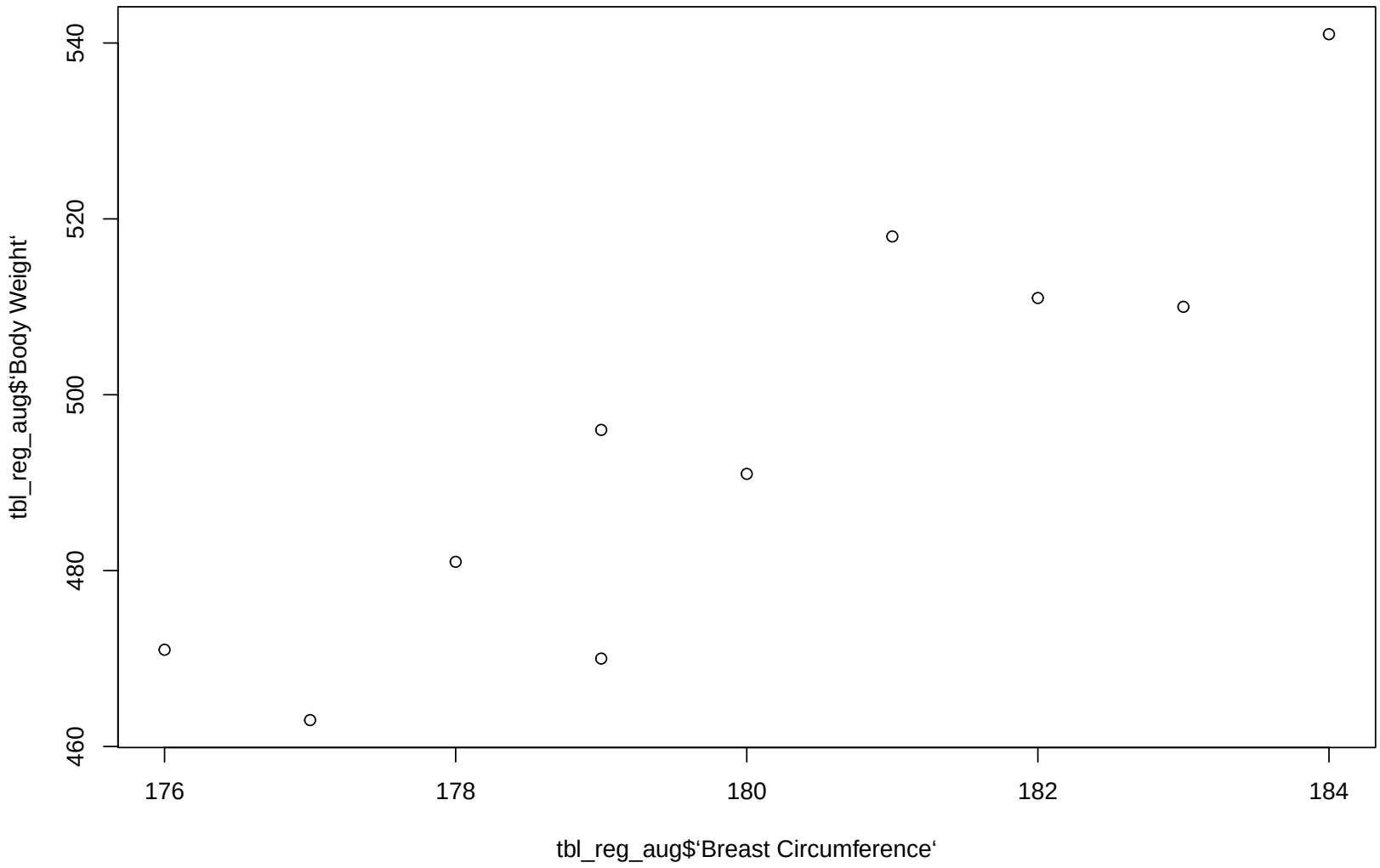
Example Dataset

Animal	Breast Circumference	Body Weight	RandPred
1	176	471	178
2	177	463	177
3	178	481	182
4	179	470	181
5	179	496	184
6	180	491	184
7	181	518	181
8	182	511	182
9	183	510	177
10	184	541	181

No Relevance of Predictors



Relevance of Predictors



Fitting a Regression Model

```
##
## Call:
## lm(formula = `Body Weight` ~ RandPred, data = tbl_reg_aug)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -25.867 -17.921  -9.036  19.827  45.133
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   93.511    598.111   0.156    0.880
## RandPred       2.223      3.310   0.672    0.521
##
## Residual standard error: 25.66 on 8 degrees of freedom
## Multiple R-squared:  0.05338,    Adjusted R-squared:  -0.06495
## F-statistic: 0.4511 on 1 and 8 DF,  p-value: 0.5207
```

Fitting a Regression Model II

```
##
## Call:
## lm(formula = `Body Weight` ~ `Breast Circumference`, data = tbl_reg_aug)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -17.3941  -6.5525  -0.0673   9.3707  13.2594
##
## Coefficients:
##                          Estimate Std. Error t value Pr(>|t|)
## (Intercept)             -1065.115    255.483  -4.169 0.003126 **
## `Breast Circumference`      8.673      1.420   6.108 0.000287 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 11.08 on 8 degrees of freedom
## Multiple R-squared:  0.8234, Adjusted R-squared:  0.8014
## F-statistic: 37.31 on 1 and 8 DF,  p-value: 0.000287
```

Multiple Regression

```
##
## Call:
## lm(formula = `Body Weight` ~ `Breast Circumference` + RandPred,
##     data = tbl_reg_aug)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -17.817  -6.946  -1.337   9.196  13.118
##
## Coefficients:
##                          Estimate Std. Error t value Pr(>|t|)
## (Intercept)             -1218.2339   352.3805  -3.457 0.010588 *
## `Breast Circumference`      8.5321     1.4885   5.732 0.000711 ***
## RandPred                    0.9879     1.4983   0.659 0.530785
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 11.5 on 7 degrees of freedom
## Multiple R-squared:  0.8337, Adjusted R-squared:  0.7862
## F-statistic: 17.55 on 2 and 7 DF,  p-value: 0.001874
```

Which model is better?

Why not taking all predictors?

- Additional parameters must be estimated from data
- Predictive power decreased with too many predictors (cannot be shown for this data set, because too few data points)
- Bias-variance trade-off

Bias-variance trade-off

- Assume, we are looking for optimum prediction

$$s_i = \sum_{r=1}^{q} \hat{\beta}_{j_r} x_{ij_r}$$

with q relevant predictor variables

- Average mean squared error of prediction s_i

$$MSE = n^{-1} \sum_{i=1}^{n} E\left[(m(x_i) - s_i)^2\right]$$

where $m(.)$ denotes the linear function of the unknown true model.

Bias-variance trade-off II

- MSE can be split into two parts

$$MSE = n^{-1} \sum_{i=1}^{n} \left(E\left[s_i\right] - m(x_i) \right)^2 + n^{-1} \sum_{i=1}^{n} var(s_i)$$

where $n^{-1} \sum_{i=1}^{n} \left(E\left[s_i\right] - m(x_i) \right)^2$ is called the squared **bias**

- Increasing q leads to reduced bias but increased variance ($var(s_i)$)
- Hence, find s_i such that MSE is minimal
- Problem: cannot compute MSE because $m(.)$ is not known

$\rightarrow$ estimate MSE

Mallows C_p statistic

- For a given model $\mathcal{M}$, $SSE(\mathcal{M})$ stands for the residual sum of squares.
- MSE can be estimated as

$$\widehat{MSE} = n^{-1} SSE(\mathcal{M}) - \hat{\sigma}^2 + 2\hat{\sigma}^2 |\mathcal{M}|/n$$

where $\hat{\sigma}^2$ is the estimate of the error variance of the full model, $SSE(\mathcal{M})$ is the residual sum of squares of the model $\mathcal{M}$, n is the number of observations and $|\mathcal{M}|$ stands for the number of predictors in $\mathcal{M}$

$$C_p(\mathcal{M}) = \frac{SSE(\mathcal{M})}{\hat{\sigma}^2} - n + 2|\mathcal{M}|$$

Searching The Best Model

- Exhaustive search over all sub-models might be too expensive
- For p predictors there are $2^p - 1$ sub-models
- With $p = 16$, we get 6.5535×10^4 sub-models

$\rightarrow$ step-wise approaches

Forward Selection

1. Start with smallest sub-model $\mathcal{M}_0$ as current model
2. Include predictor that reduces SSE the most to current model
3. Repeat step 2 until all predictors are chosen

$\rightarrow$ results in sequence $\mathcal{M}_0 \subseteq \mathcal{M}_1 \subseteq \mathcal{M}_2 \subseteq \ldots$ of sub-models

4. Out of sequence of sub-models choose the one with minimal C_p

Backward Selection

1. Start with full model $\mathcal{M}_0$ as the current model
2. Exclude predictor variable that increases SSE the least from current model
3. Repeat step 2 until all predictors are excluded (except for intercept)

$\rightarrow$ results in sequence $\mathcal{M}_0 \supseteq \mathcal{M}_1 \supseteq \mathcal{M}_2 \supseteq \ldots$ of sub-models

4. Out of sequence choose the one with minimal C_p

Considerations

- Whenever possible, choose **backward** selection, because it leads to better results
- If $p \geq n$, only forward is possible, but then consider LASSO

Alternative Model Selection Criteria

- AIC or BIC, requires distributional assumptions.
- AIC is implemented in `MASS::stepAIC()`
- Adjusted R^2 is a measure of goodness of fit, but sometimes is not conclusive when comparing two models
- Try in exercise

Genetic Variation

- Concerns random effects of model, usually given as breeding values
- Requirement for trait to be considered in breeding goal
- Breeding means improvement of next generation via selection and mating
- Only genetic (additive) components are passed to offspring
- Selection should be based on genetic component of trait
- Selection only possible with genetic variation

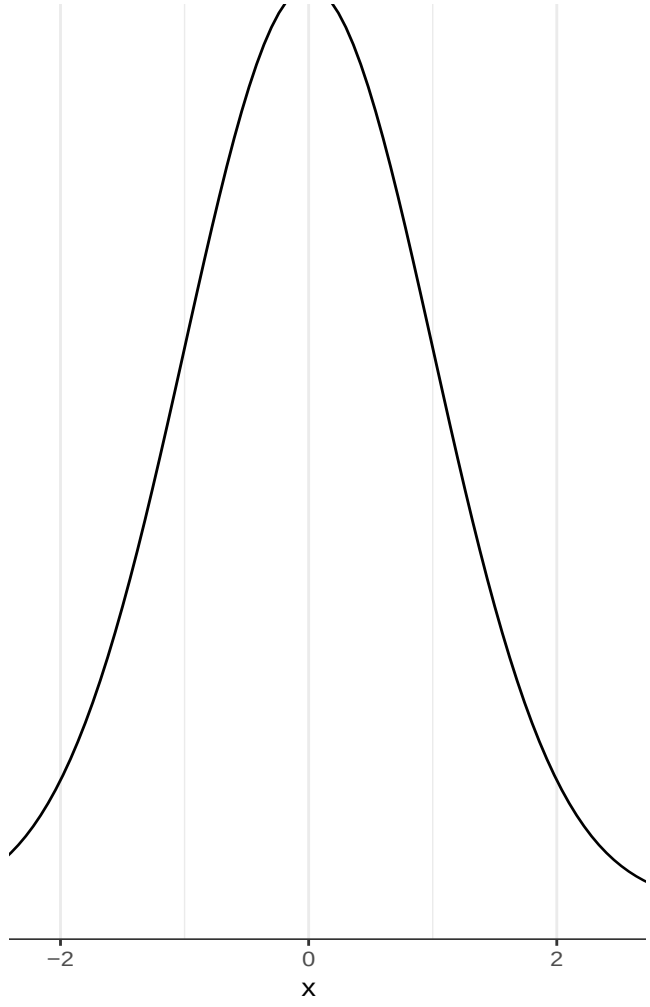
$\rightarrow$ genetic variation indicates how good characteristics are passed from parents to offspring

$\rightarrow$ measured by **heritability** $h^2 = \frac{\sigma_a^2}{\sigma_p^2}$

Two Traits

no variation

with variation



Problems

- Genetic components cannot be observed or measured
- Must be estimated from data
- Data are mostly phenotypic

$\rightarrow$ topic of variance components estimation

- Model based, that means connection between phenotypic measure and genetic component are based on certain model

$$p = g + e$$

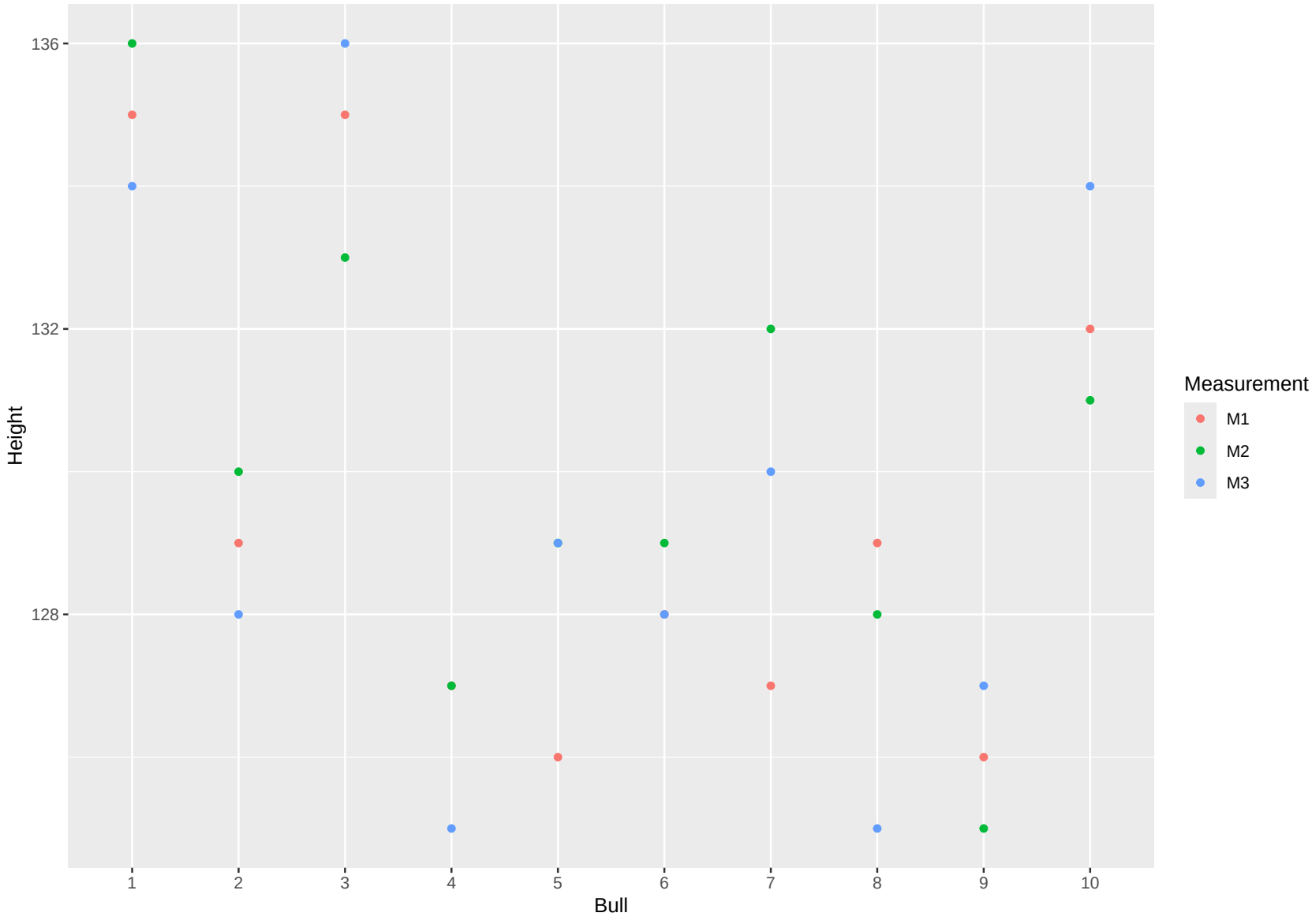
with $cov(g, e) = 0$

- **Goal**: separate variation due to g (σ_a^2) from phenotypic variation

Example of Variance Components Separation

- Estimation of repeatability
- Given repeated measurements of same trait at the same animal
- Repeatability means variation of measurements at the same animal is smaller than variation between measurements at different animals

Repeatability Plot



Model

$$y_{ij} = \mu + t_i + \epsilon_{ij}$$

where

y_{ij}	measurement j of animal i
μ	expected value of y
t_i	random deviation of y_{ij} from μ attributed to animal i
ϵ_{ij}	measurement error

Animal Model

- trait of interest as response variable (y)
- fixed effects (b) as known part of environment
- random animal effect, corresponds to breeding values (u)

$$y = Xb + Zu + e$$

with

- vector e as random residuals and
- matrices X and Z as design matrices

Estimates and Predictions

- solution leading to estimates of fixed effects

$$\hat{b} = (X^T V^{-1} X)^- X^T V^{-1} y$$

- predictions for random effects

$$\hat{u} = U Z^T V^{-1} (y - X\hat{b})$$

with

- $U = var(u)$
- $V = var(y)$

Mixed Model Equations

Equivalent solutions are obtained via

$$\begin{bmatrix} X^T R^{-1} X & X^T R^{-1} Z \\ Z^T R^{-1} X & Z^T R^{-1} Z + U^{-1} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{u} \end{bmatrix} = \begin{bmatrix} X^T R^{-1} y \\ Z^T R^{-1} y \end{bmatrix}$$

with

- $U = A * \sigma_u^2$

where A is pedigree-based relationship matrix and σ_u^2 the genetic additive variance

Single-Step Genomic Breeding Values

- Assume all animals have genotypes

$$y = Xb + Zg + e$$

$$\begin{bmatrix} X^T R^{-1} X & X^T R^{-1} Z \\ Z^T R^{-1} X & Z^T R^{-1} Z + H^{-1} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{g} \end{bmatrix} = \begin{bmatrix} X^T R^{-1} y \\ Z^T R^{-1} y \end{bmatrix}$$

- $H = G * \sigma_u^2$

where G is the genomic relationship matrix and σ_u^2 the genetic additive variance

Genomic Relationship

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

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

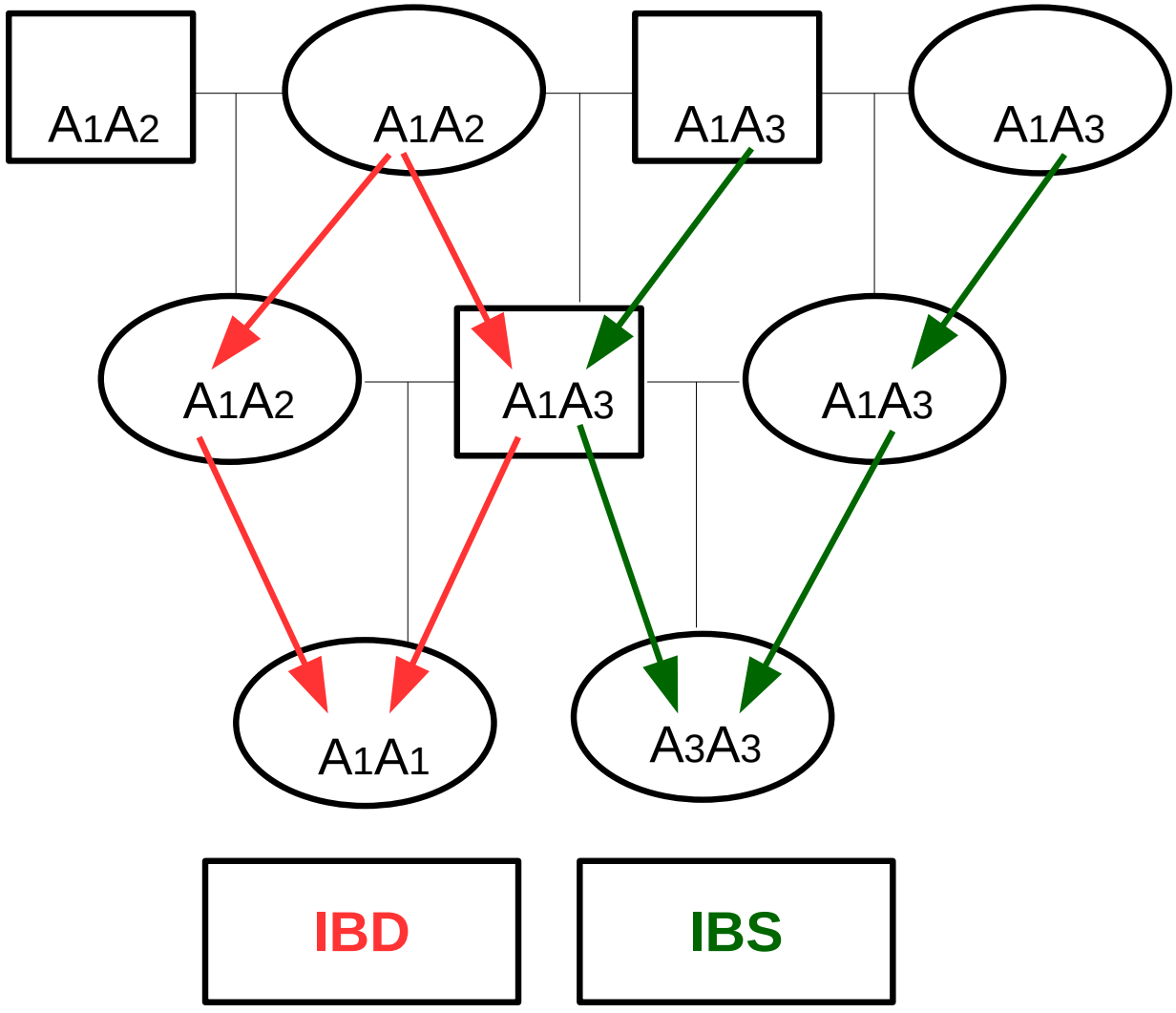
where G is called **genomic relationship matrix** (GRM)

Desired Properties of G

- genomic breeding values g are linear combinations of SNP-effects q: $g = Z_{SNP} \cdot q$
- 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

G based on IBS, where A is based on IBD



Result

Combining all properties:

- Linear combination

$$var(g) = var(W \cdot q) = W \cdot var(q) \cdot W^T = WW^T\sigma_q^2$$

with $W = Z_{SNP} - S$ where S contains corrections of $2p - 1$ and p is the minor allele frequency

- Genetic variance $var(g)$ explained by marker effects

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

- Solve for G

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