Fixed Linear Effects Models

Peter von Rohr
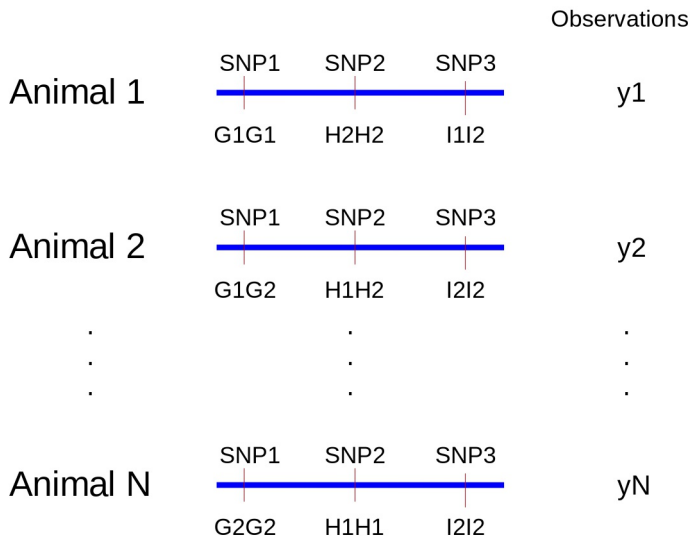
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Background
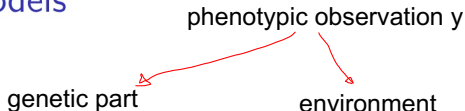

Animal	Genotypes			Observations
	G	H	I	y
1	G1G2	H2H2	I1I1	y1

Available information for animal 1

- ▶ Given a population of N animals
- ▶ Each animal has information on genotypes at loci G, H and I
- ▶ Each animal has an observation for one quantitative trait of interest y
- ▶ **Goal**: Predict genomic breeding values

Data

Observations

Animal 1

SNP1   SNP2   SNP3

y1

G1G1   H2H2   I1I2

Animal 2

SNP1   SNP2   SNP3

y2

G1G2   H1H2   I2I2

.   .   .
.   .   .
.   .   .

Animal N

SNP1   SNP2   SNP3

yN

G2G2   H1H1   I2I2

Two Types Of Models

phenotypic observation y

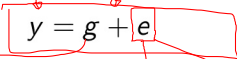genetic part

environment

1. **Genetic** Model: How can we decompose the <u>phenotype</u> into genetic part and non-genetic environmental part
2. **Statistical** Model: How to estimate unknown parameters from a dataset

Goals:

1. Use genetic model to show how observations and genetic information can be used to predict breeding values.
2. Use statistical techniques to do the prediction

Genetic Model

- ▶ simple model from quantitative genetics to split phenotypic observation into
  - ▶ genetic part g and
  - ▶ environmental part e

$$y = g + e$$

- ▶ environment: split into
  - ▶ known environmental factors: herd, year, ... (β)
  - ▶ unknown random error (ϵ) $E(\epsilon) = 0$, $var(\epsilon)$
- ▶ polygenic model: use a finite number of loci to model genetic part of phenotypic observation
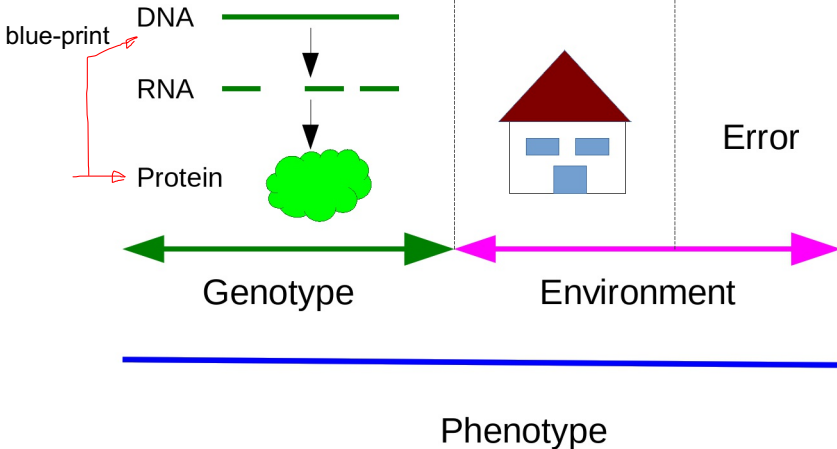
why do all phenotypes have g? ==> y = e?

Genetic Model (II)

Why are all phenotypes influenced by genetics?

Central Dogma Of Molecular Biology

known

unknown

blue-print

DNA

RNA

Protein

Error

Genotype

Environment

Phenotype

Polygenic Model

Simple version: only additive contributions of single loci to the genetic part (g) of a given trait

▶ Component g can be decomposed into contributions g_j of single loci

$$g = \sum_{j=1}^{k} g_j$$

genetic contribution of single locus, e.g. in our dataset: loci G, H and I

▶ Assume that loci are additive, hence genotypic values g_j depends on a_j with $d_j = 0$ Marker effect
▶ Genotypic values at locus j can either be $-a_j$, 0 or a_j
▶ Breeding values based on locus j depends on a_j.

Example: locus G: Genotypes G1G1, G1G2 and G2G2

$$g = \sum_{j=1}^{k} g_j$$

Assuming only additive effects ==> gj is either -a, 0 or +a

* Sum over gj is replaced by a Matrix-Vector multiplication ==> g = M * a

Genotypic Value

▶ Genotypic value g_i for animal i over all loci

$$g_i = M_i \cdot a$$

where M_i is a row vector with elements -1, 0 and 1 and a is the vector of all genotypic values of the positive homozygous genotypes of all loci.

Phenotypic Value

► Collecting all components for an observation y_i for animal i

$$y_i = \overbrace{W_i \cdot \beta}^{\text{known envireonment}} + \underbrace{M_i \cdot a}_{\text{genetic part}} + \epsilon_i \longrightarrow \text{random error}$$

► all animals in the population

$$y = W \cdot \beta + M \cdot a + \epsilon$$

► combining $b^T = \begin{bmatrix} \beta & a \end{bmatrix}$ and $X = \begin{bmatrix} W & M \end{bmatrix}$

$$y = X \cdot b + \epsilon$$

Fixed linear effects model

Statistical Model

- genetic model from statistics point of view
- phenotypic observation as response y
- vector b (known environment and genotypic values) as unknown parameter
- fixed predictor variales in matrix X
- vector ϵ as random error terms

$\rightarrow$ Fixed Linear Effects Model

Parameter Estimation

Simple version of Fixed Linear Effects Model

▶ use regression model

y

X

▶ regression means both response and predictors are continuous
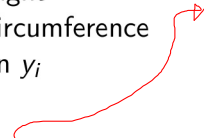
▶ example dataset: body weight on breast circumference

Regression Dataset

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

Regression Model

- response y: body weight
- predictor x: breast circumference
- model for observation y_i

Body weight for animal i can be expressed as the product of an unknown parameter b times the breast circumference of animal i plus a random error

$$y_i = x_i * b + \epsilon_i$$

- meaning of b: change x_i by one unit $\to y_i$ changes on average by b units.
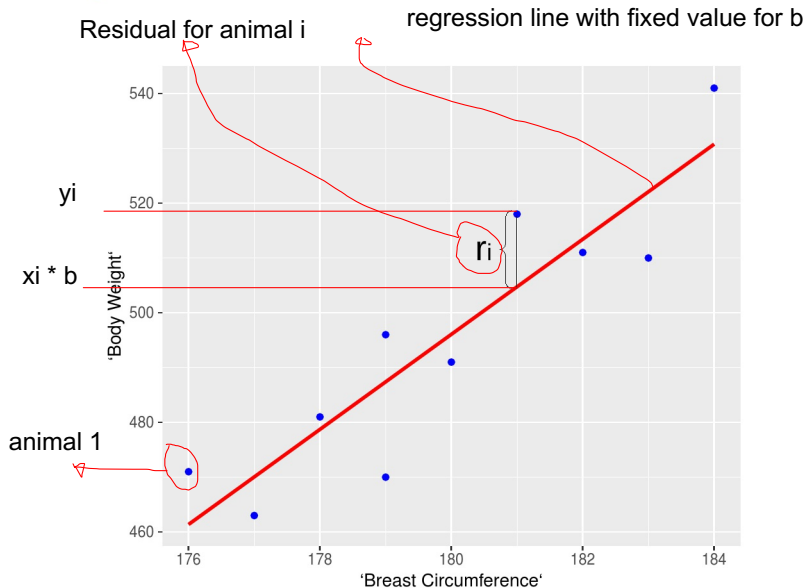- use case: measure x_{N+1} for animal $N+1$ with unknown weight and use b to predict y_{N+1}

Goal

Least Squares

- How to find b such that y is best approximated by x
- Residuals $r_i = y_i - x_i * \hat{b}$
- Minimization of sum of squared residuals (LS)
- Use $\hat{b}$ at minimal LS as estimate

LSQ Diagram

Residual for animal i

regression line with fixed value for b

yi

xi * b

animal 1

r_i

Sum of squared residuals

$$LS = \sum_{i=1}^{n} r_i^2$$

- In matrix-vector notation with r denoting the vector of all residuals

$$LS = ||r||^2 = r^T r$$

where $||.||$ stands for the norm ("length in 2D") of a vector

▶ Replacing r with $r = y - X\hat{b}$

$$LS = (y - X\hat{b})^T (y - X\hat{b}) = y^T y - y^T X\hat{b} - \hat{b}^T X^T y + \hat{b}^T X^T X\hat{b}$$

Minimization

▶ Set partial derivative of LS with respect to $\hat{b}$ to 0

$$\frac{\partial LS}{\partial \hat{b}} = -X^T y - X^T y + 2X^T X\hat{b} = 0$$

▶ Take the $\hat{b}$ that satisfies the above equation as the least squares estimate $\hat{b}_{LS}$

$$X^T X\hat{b}_{LS} = X^T y$$

▶ Solution

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

Variance of Error Terms

- Least Squares Procedure does not yield an estimate for σ^2
- The estimator based on the residuals

$$\hat{\sigma^2} = \frac{1}{n-p} \sum_{i=1}^{n} r_i^2$$

Different Types of Regressions

▶ Regression through the origin

$$y_i = x_i * b + e_i$$

▶ Regression with intercept

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

Predictions

- One of the use-cases for regression is **prediction**
- Prediction means that given a regression model with estimated regression coefficients based on a data set, values of responses are to be predicted for new predictor values (x_{new})

$$\hat{y} = x_{new} * \hat{b}$$

- No predictions outside of the range of x used to estimate $\hat{b}$

Multiple Linear Regression

▶ Use more than one predictor variable
▶ Example: Conformation traits `BCS` and `HEI` besides `BC`
▶ New model:

$$y_i = b_0 + BC_i * b_1 + BCS_i * b_2 + HEI_i * b_3 + e_i$$

▶ In matrix vector notation:

$$y = Xb + e$$

with $b^T = \begin{bmatrix} b_0 & b_1 & b_2 & b_3 \end{bmatrix}$

New data set

Table 2: Dataset for Multiple Linear Regression

Animal	Breast Circumference	Body Weight	BCS	HEI
1	176	471	5.0	161
2	177	463	4.2	121
3	178	481	4.9	157
4	179	470	3.0	165
5	179	496	6.8	136
6	180	491	4.9	123
7	181	518	4.4	163
8	182	511	4.4	149
9	183	510	3.5	143
10	184	541	4.7	130

Goal

- Find solution for $\hat{b}_{LS}$
- Same principle of least squares as with simple linear regression
- Different dimensions for X and b

$\rightarrow$ Problem 1 in Exercise 2
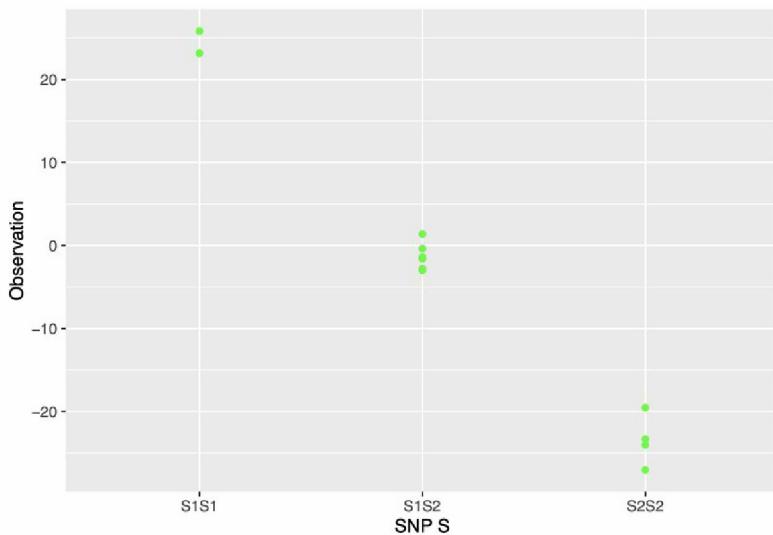
Regression on Dummy Variables

- What happens when predictor variables X are no longer continuous
- Examples: SNP-Genotypes
- X can only take a few discrete values, e.g., $0, 1$ or $-1, 0, 1, \ldots$

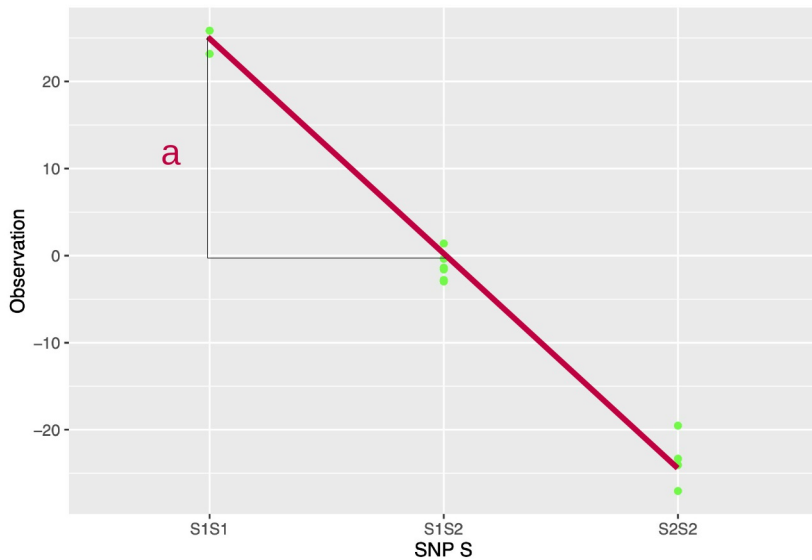$\rightarrow$ regression on dummy variables or just general fixed linear model.

Example: SNP-Data

Goal

- ▶ Same as in linear regression: fit line through points such that least squares criterion holds
- ▶ Interpretation: Difference between effect levels
- ▶ For SNP-data: differences correspond to marker effects

Dummy Regression Line

Problem

- In many datasets X does not have full column-rank
- That means some columns of X show linear dependence
- As a consequence of that $(X^T X)$ cannot be inverted

Solution

- ▶ Use a generalised inverse $(X^T X)^-$ to get a solution $\hat{b}_{LS}$ for least squares normal equations
- ▶ Use estimable functions of $\hat{b}_{LS}$ which are independent of the choice of $(X^T X)^-$
- ▶ One example for estimable functions are differences between effect levels
- ▶ For example of SNP-data these correspond to marker effects.

Generalised Inverse

- ▶ Reminder: the (ordinary) inverse A^{-1} of A is given by $A^{-1}A = I$, but A^{-1} exists only, if A is of full rank.
- ▶ A generalised inverse G of matrix A satisfies: $AGA = A$
- ▶ For the system of equations $Ax = y$, the vector $x = Gy$ is a solution, if $AGA = A$
- ▶ For a generalised inverse G of A, the system of equation $Ax = y$ has solutions

$$\tilde{x} = Gy + (GA - I)z$$

for an arbitrary vector z.

Estimable Functions

- linear function of the parameter (b) that is identical to linear function of expected values of observations y, i.e.,

$$q^T b = t^T E(y)$$

- estimable functions are invariant (do not change) with different generalised inverses.