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SNPs explaining
genotype by environment interaction
in German Holstein dairy cattle

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Introduction

- **Reaction norm** – performance of a genotype as a function of a gradually changing environment

- **Environmental sensitivity** – first derivative of a reaction norm, describes the sensibility of animals to changes in the environment

- Genetic variation in environmental sensitivity → **genotype by environment interaction** (GxE)

- **GxE-analysis** by multi-trait models or reaction norm models

- **Reaction norm** appropriate if the environment changes gradually

Random Regression Sire Model
to study reaction norms

- 2279 sires (German Holstein)
- total number of daughters: 1.3 million (50 to 74842 daughters per sire)

- 12 million first lactation test day records for
 - protein (g)
  - fat (g)
  - milk (kg)

  observations are corrected for: herd test day, days in milk, age at calving, calving season, permanent environment effect (animal test day model)

Random Regression Sire Model
to study reaction norms

- For each observation from cows the corresponding herd test day solution from routine genetic evaluation system was available

- Herd test day solutions for milk traits were combined in herd test day solution for milk energy yield

- Herd test day solution for milk energy yield is used as a continuous descriptor of the environment in that the cow produced the milk

- low herd test day solution: poor environment, e.g. poor feeding level
- high herd test day solution: good environment

Random Regression Sire Model
to study reaction norms
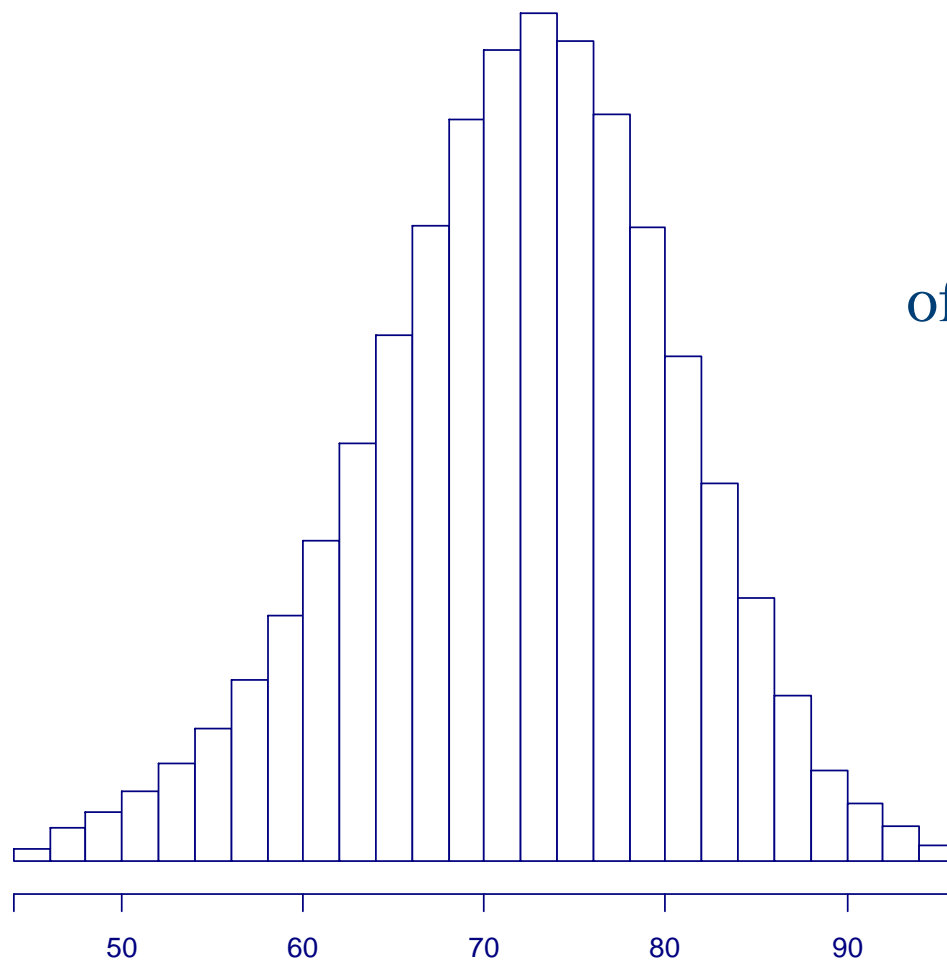
Histogram

of herd test day solutions

for milk energy yield

Linear Random Regression Sire Model

$$Yc_{ijk} = \mu + b * htds_k + \sum_{m=0}^{1} S_{jm} * htds_k^m + \sum_{m=0}^{1} D_{jm} * htds_k^m + e_{ijk}$$

according to Lillehammer et al., 2009

- Y_C precorrected observation of daughter i of sire j at herd test day k

- μ mean

- $htds$ herd test day solution at day k

- b regression coefficient

- S sire

- D daughter

- e residual, modelled heterogeneous

$$Var\begin{bmatrix} S_0 \\ S_1 \end{bmatrix} = A \otimes \begin{bmatrix} \sigma_{S_0}^2 & \sigma_{S_0 S_1} \\ \sigma_{S_0 S_1} & \sigma_{S_1}^2 \end{bmatrix}$$

$$Var\begin{bmatrix} D_0 \\ D_1 \end{bmatrix} = I \otimes \begin{bmatrix} \sigma_{D_0}^2 & \sigma_{D_0 D_1} \\ \sigma_{D_0 D_1} & \sigma_{D_1}^2 \end{bmatrix}$$

models were solved using ASReml 3.0

Results from Random Regression Sire Model

	σ_I^2	σ_S^2	σ_{IS}	$r_{(I,S)}$
protein / milk energy (g)	2379.37	17.02	158.16	0.79
fat / milk energy (g)	7883.41	46.76	561.60	0.93
milk / milk energy (kg)	1.30	0.01	0.09	0.72

- Significant slope variance: presence of GxE
  (also if observations were log-transformed)

- High genetic correlation between intercept and slope: selection for milk increases environmental sensitivity (Kolmodin et al. 2002, Lillehammer et al. 2009).

- Can we find genes that are responsible for GxE and suitable to breed for less sensitive animals?

For a full non-linear analysis see Streit et al. 2012, JABG

A sample of sires reaction norms

protein

fat

milk
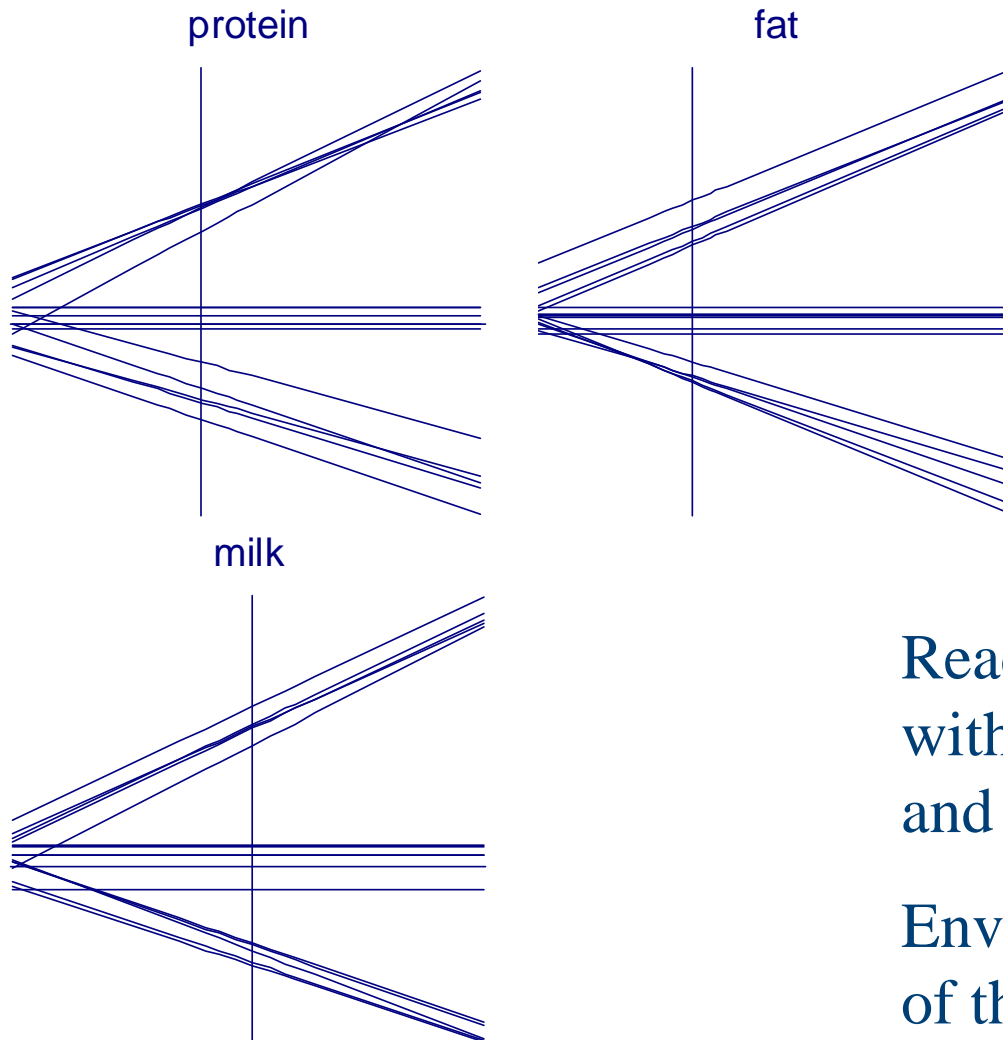
Reaction norms of a sample of 15 sires with a steep positive, a steep negative, and a flat slope

Environmental sensitivity is the slope of the reaction norm

GWAS to find SNPs associated with environmental sensitivity

- Sires were genotyped with Illumina 50 K SNP-chip
- SNPs were filtered, 41K used in this study

- Phenotypes: Sire solutions from linear random regression sire models for intercept and slope

GWAS – validation

- total: 2279 sires, split in two datasets
- discovery dataset: 1797 sires
- validation dataset: 500 sires

- SNP significant in the discovery dataset: $p \leq 0.001$
- Significant SNP validated: $p \leq 0.01$ in the validation dataset and same sign as in the discovery dataset

GWAS – model

$$Y = \mu + bx + u + e$$

- y sire solution from random regression analysis for intercept and slope (two univariate analyses)
- μ mean
- x number of copies of allele 1 for the SNP
- b regression coefficient
- u effect of the animal
- e residual

$$Cov[u] = A \otimes \sigma_u^2$$

models were solved using ASReml 3.0

Results – detected loci

	protein		fat		milk	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
(1)	450	351	465	385	415	416
(1) ∩ (2)	69	44	118	99	104	98

(1) $p \leq 0.001$ (discovery dataset)

(2) $p \leq 0.01$ (validation dataset)

Results – Correlation between intercept and slope for validated SNPs

Protein - milk energy environment

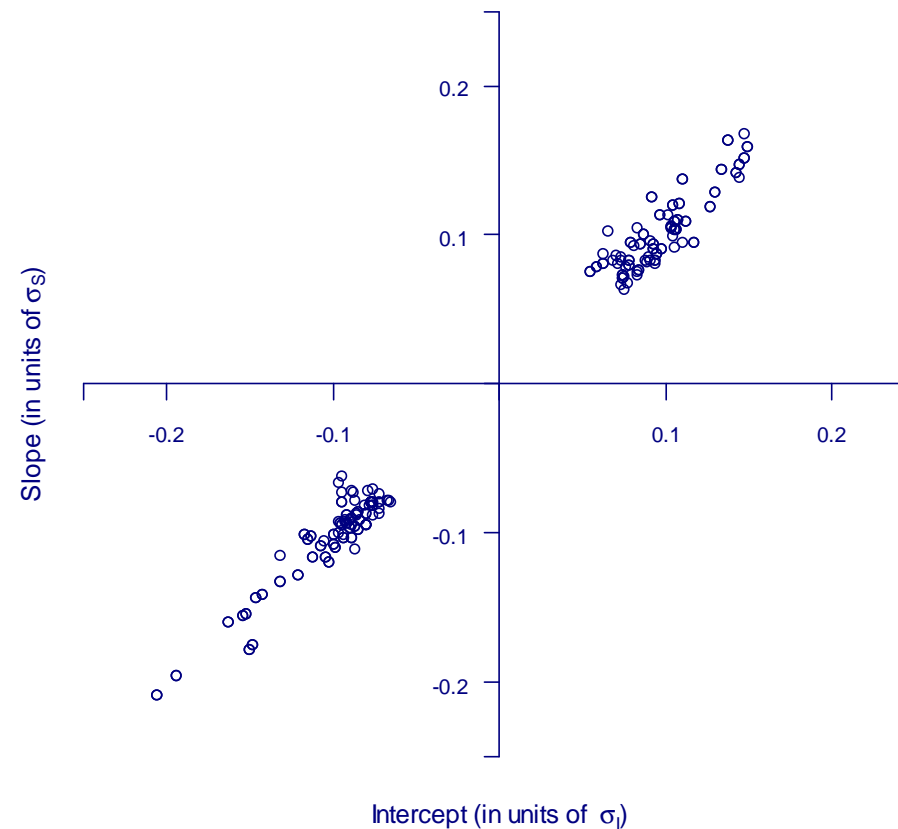Slope (in units of σ_S)

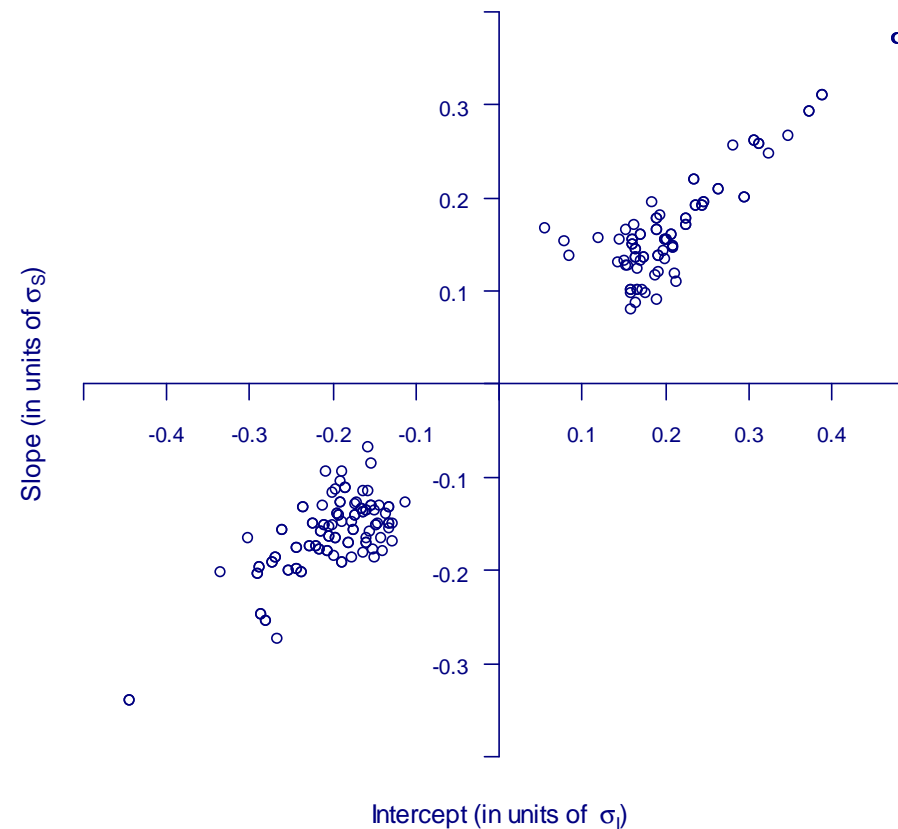Intercept (in units of σ_I)
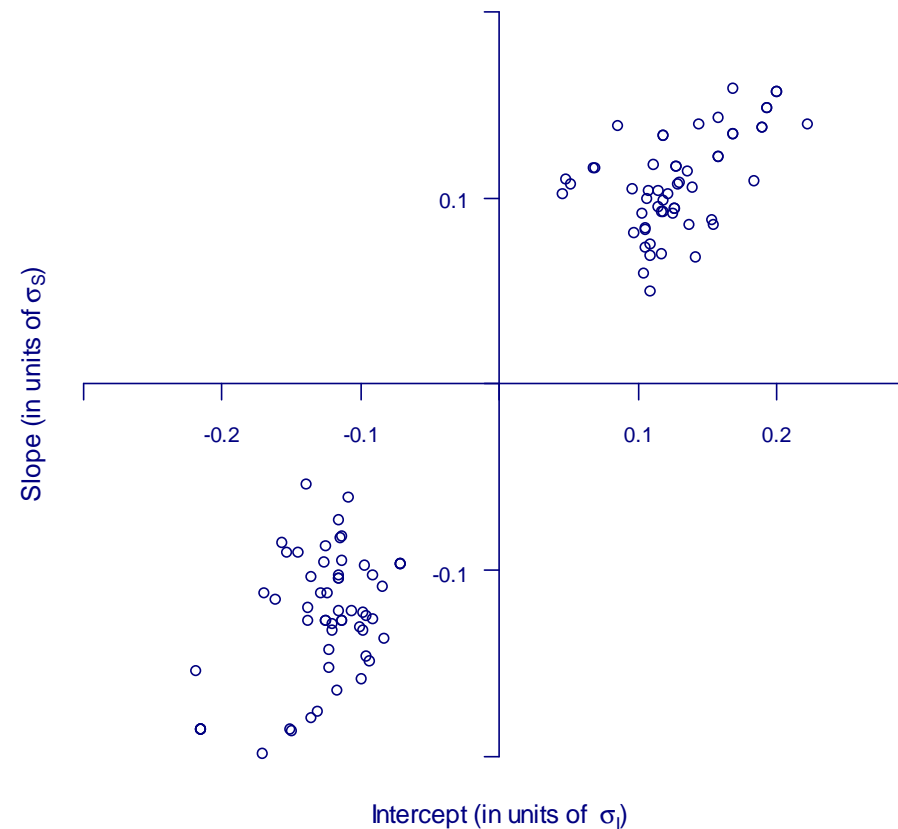
Results – Correlation between intercept and slope for validated SNPs

Fat - milk energy environment

Results – Correlation between intercept and slope for validated SNPs

Milk - milk energy environment

Slope (in units of σ_S)

Intercept (in units of σ_I)

Conclusions

Highly significant GxE in German Holsteins found (see also Streit et al., JABG, 2012). Almost no re-ranking effects (in agreement with König et al., 2005).

Modeling heterogeneous residual variance was important.

Intercept and slope positive correlated, selection for production resulted in correlated selection response in environmental sensitivity.

Robust animals (i.e. showing a flat reaction norm) were genetically inferior in 'good' environments.
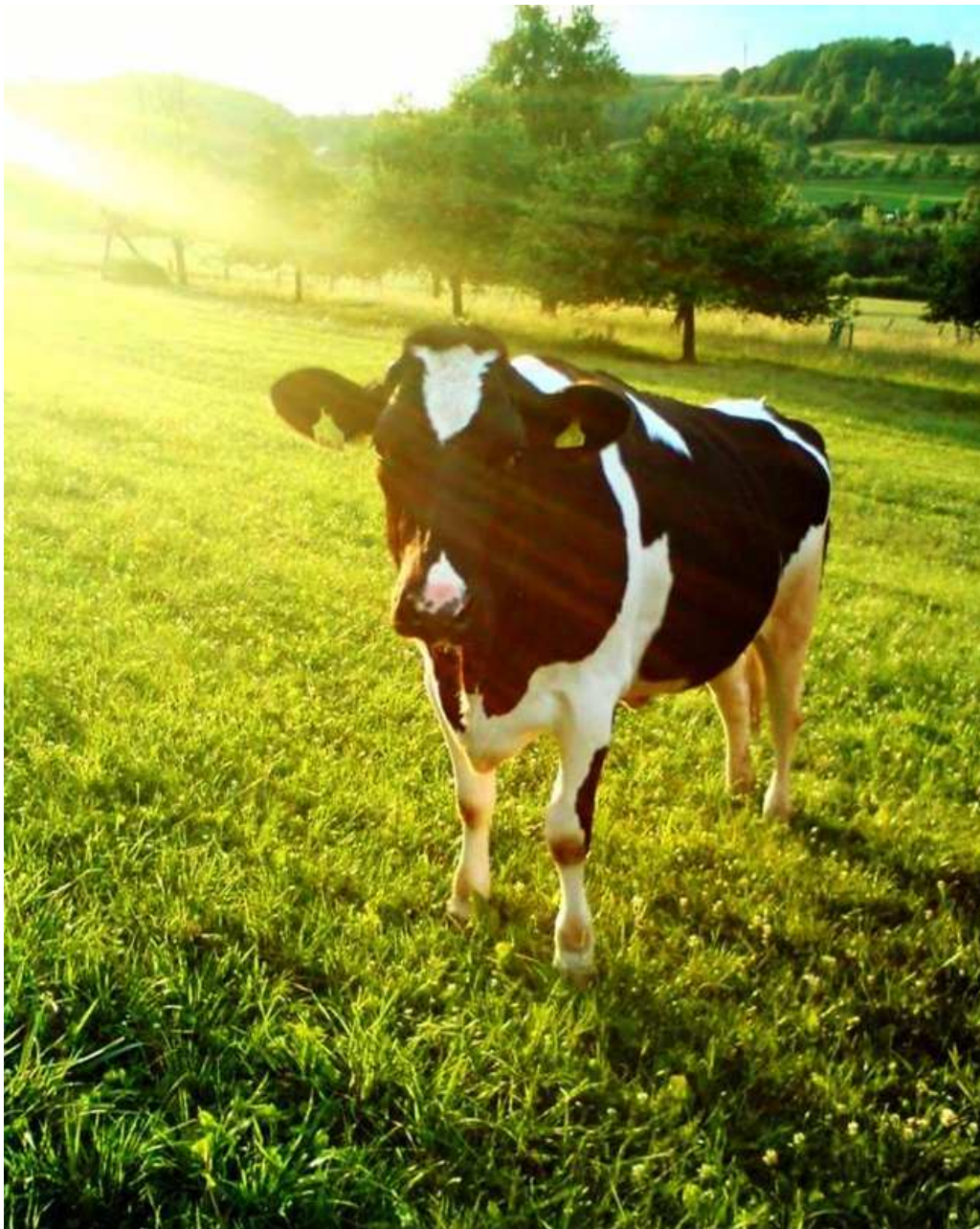
Conclusions

Several SNPs found and confirmed explaining the environmental sensitivity.

Environmental sensitivity seems to be a 'typical' quantitative trait (many SNPs distributed along the genome).

Validated SNP effects for intercept and slope were highly correlated (as expected from quantitative results).

Hard to find SNPs that are suited for breeding for robustness, i.e. showing a high intercept and a low slope effect.

Breeding for robustness (i.e. animals with a flat reaction norm) does come at a cost of general production level.

Thanks
for your
attention!