

EAAP 2015 - Genetics commission early career scientist competition

A new model for an imprinting analysis of Brown Swiss slaughterhouse data

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FOR FARM ANIMAL BIOLOGY

What is genomic imprinting?

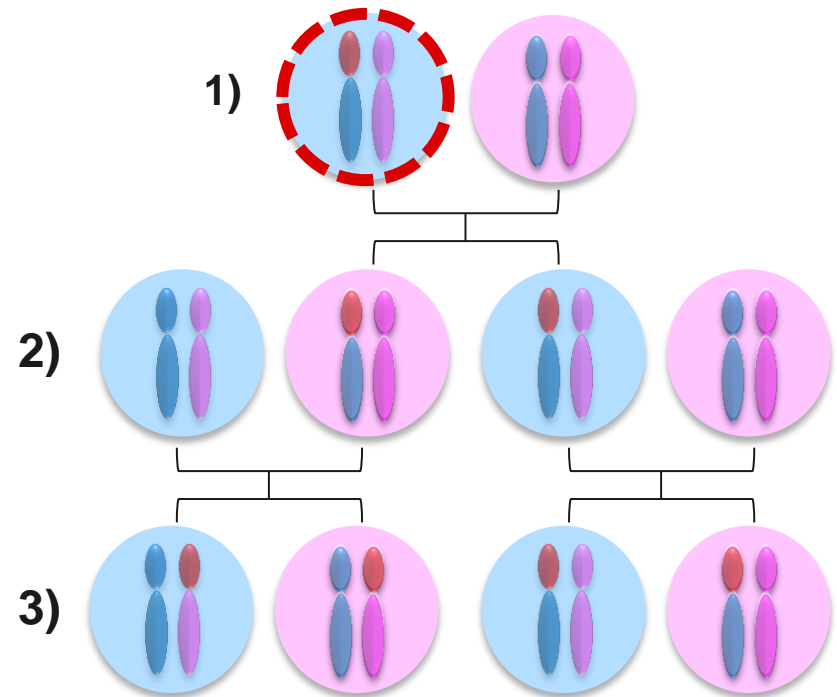


 Callipyge phenotype

What is genomic imprinting?



 Callipyge phenotype



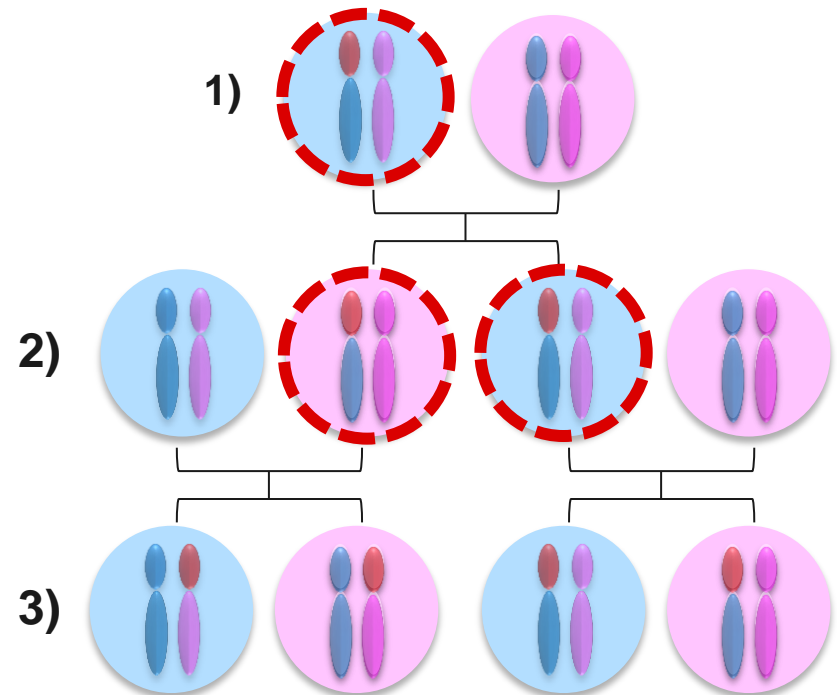
 Female animals

 Male animals

What is genomic imprinting?



 Callipyge phenotype



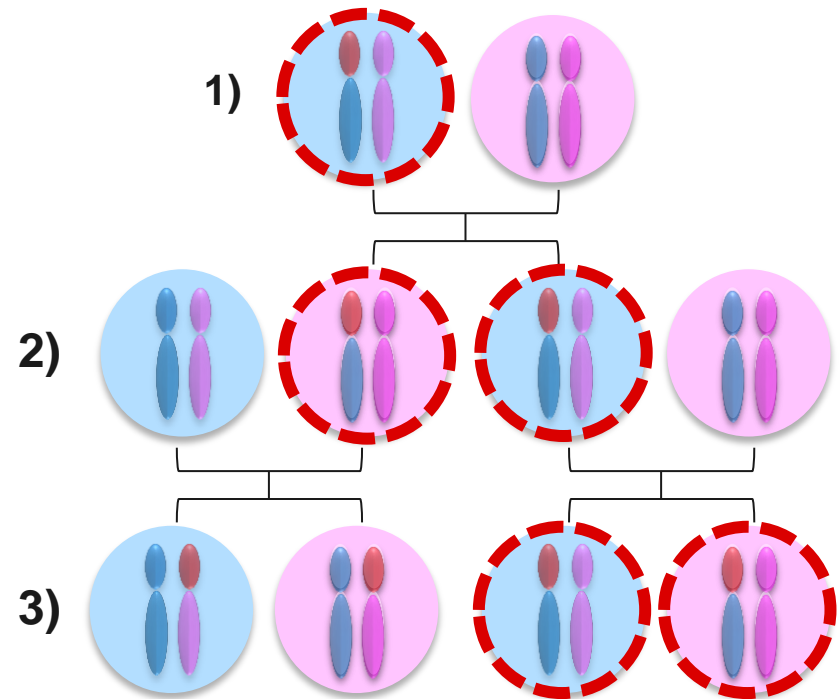
 Female animals

 Male animals

What is genomic imprinting?



 Callipyge phenotype



 Female animals

 Male animals

Motivation

- Effects on agricultural traits, e.g.:
 - Meat percentage, %
 - Carcass beefiness
 - Body composition traits
 - ...
- Potential application in animal breeding!



<http://www.agrarhandel-kornhochheim.de/Bilder/Imagemap/Bullenh%E4lfte.jpg>

Motivation

Neugebauer model:

$$Y = X\beta + Z_s a_s + Z_d a_d + e$$



a_s = EBV of sires as **sire**

a_d = EBV of dams as **dam**

$$i = a_s - a_d$$

imprinting effect

Motivation

Neugebauer model:

$$Y = X\beta + Z_s a_s + Z_d a_d + e$$



a_s = EBV of sires as **sire**

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$$i = a_s - a_d$$

imprinting effect

$$\text{Var} \begin{bmatrix} a_s \\ a_d \end{bmatrix} = A \otimes \begin{bmatrix} 1/2 \sigma_s^2 & 1/2 \sigma_{sd} \\ 1/2 \sigma_{sd} & 1/2 \sigma_d^2 \end{bmatrix}$$

A = additive genetic relationship matrix

$$\sigma_i^2 = \sigma_s^2 + \sigma_d^2 - 2\sigma_{sd}$$

imprinting variance

Problems and Goals

Practical problem:

- High effort to determine the **standard errors** of imprinting effects for a large number of animals

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Goals

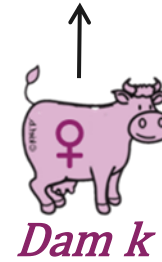
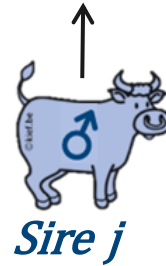
- Introducing an equivalent **imprinting model**
- Applying this model to **slaughter data** in **Brown Swiss**

Introduction of a new imprinting model

Neugebauer: $y_{ijk} = \mu + a_{s_j} + a_{d_k} + e_{ijk}$

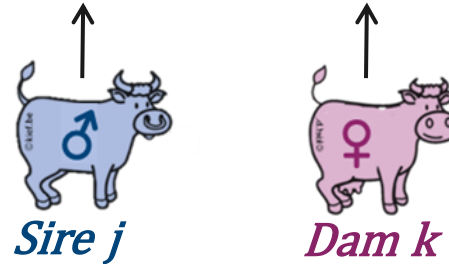
a_{s_j} = EBV of **sire j** as **sire**

a_{d_k} = EBV of **dam k** as **dam**



Introduction of a new imprinting model

Neugebauer: $y_{ijk} = \mu + a_{s_j} + a_{d_k} + e_{ijk}$



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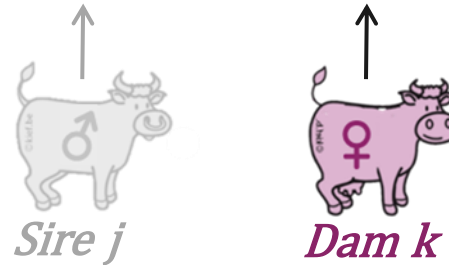
Imprinting effect: $i_d = a_d - a_s \Rightarrow a_{d_k} = a_{s_k} + i_{d_k}$

Introduction of a new imprinting model

Neugebauer: $y_{ijk} = \mu + a_{s_j} + a_{d_k} + e_{ijk}$

a_{s_j} = EBV of *sire j* as sire

a_{d_k} = EBV of *dam k* as dam



Imprinting effect: $i_d = a_d - a_s \Rightarrow$

$$a_{d_k} = a_{s_k} + i_{d_k}$$

New model: $y_{ikl} = \mu + a_{s_j} + a_{s_k} + i_{d_k} + e_{ijk}$

Introduction of a new imprinting model

$$y_{ikl} = \mu + a_{s_j} + a_{s_k} + i_{d_k} + e_{ijk}$$

a_{s_j} = EBV of **sire j** as **sire**

a_{s_k} = EBV of **dam k** as **sire**



Introduction of a new imprinting model

$$y_{ikl} = \mu + \underbrace{a_{s_j} + a_{s_k}} + i_{d_k} + e_{ijk}$$

a_{s_j} = EBV of **sire j** as **sire**

a_{s_k} = EBV of **dam k** as **sire**

i_{d_k} = imprinting effect of **dam k**

$$Y = X\beta + Z_s a_s + Z_i i_d + e$$

Introduction of a new imprinting model

$$y_{ikl} = \mu + \underbrace{a_{s_j} + a_{s_k}} + i_{d_k} + e_{ijk}$$

a_{s_j} = EBV of **sire j** as **sire**

a_{s_k} = EBV of **dam k** as **sire**

i_{d_k} = imprinting effect of **dam k**

$$Y = X\beta + Z_s a_s + Z_i i_d + e$$

- Z_s contains entries for **sires** and **dams** (coded as „1“)
- Z_i contains an entry for **dams** (coded as „1“)

Benefits of the new imprinting model

Mixed model equation for the new model:

$$\begin{bmatrix} X'W^{-1}X & X'W^{-1}Z_s & X'W^{-1}Z_i \\ Z_s'W^{-1}X & Z_s'W^{-1}Z_s + A^{-1}\lambda_1 & Z_s'W^{-1}Z_i + A^{-1}\lambda_2 \\ Z_i'W^{-1}X & Z_i'W^{-1}Z_s + A^{-1}\lambda_2 & \boxed{Z_i'W^{-1}Z_i + A^{-1}\lambda_3} \end{bmatrix} \begin{bmatrix} \beta \\ a_s \\ \mathbf{i} \end{bmatrix} = \begin{bmatrix} X'W^{-1}y \\ Z_s'W^{-1}y \\ Z_i'W^{-1}y \end{bmatrix}$$

- **Standard errors** derived from diagonal elements
- Direct estimation of **imprinting effects**

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- **Standard errors** derived from diagonal elements
- Direct estimation of **imprinting effects**
- Direct estimation of the **imprinting variance**

$$\text{Var} \begin{bmatrix} a_s \\ i \end{bmatrix} = \mathbf{A} \otimes \begin{bmatrix} \frac{1}{2}\sigma_s^2 & \frac{1}{2}(\sigma_{sd} - \sigma_s^2) \\ \frac{1}{2}(\sigma_{sd} - \sigma_s^2) & \frac{1}{2}\sigma_i^2 \end{bmatrix}$$

Application to slaughter data in Brown Swiss

Traits	Observations	Pedigree size
Net BW gain (g/d)	173,051	428,710
EUROP class	133,671	420,626
Fat score (1-5)	133,671	420,626
Killing out percentage (%)	3,226	24,347



http://www.krankykids.com/cows/cow_wall_country/switzerland/switzerland_sBreed_dName.html



Application to slaughter data in Brown Swiss



Step 1

- Using the **Neugebauer model** $Y = X\beta + Z_s a_s + Z_d a_d + e$
- Estimating the **imprinting variance** σ_i^2
- Significance test via RLRT

Application to slaughter data in Brown Swiss



Step 1


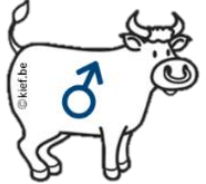
- Using the **Neugebauer model** $Y = X\beta + Z_s a_s + Z_d a_d + e$
- Estimating the **imprinting variance** σ_i^2
- Significance test via RLRT

Step 2

- Using the **new model** $Y = X\beta + Z_s a_s + Z_i i_d + e$
- Estimating the **imprinting effects** i
- Evaluation of the reliabilities

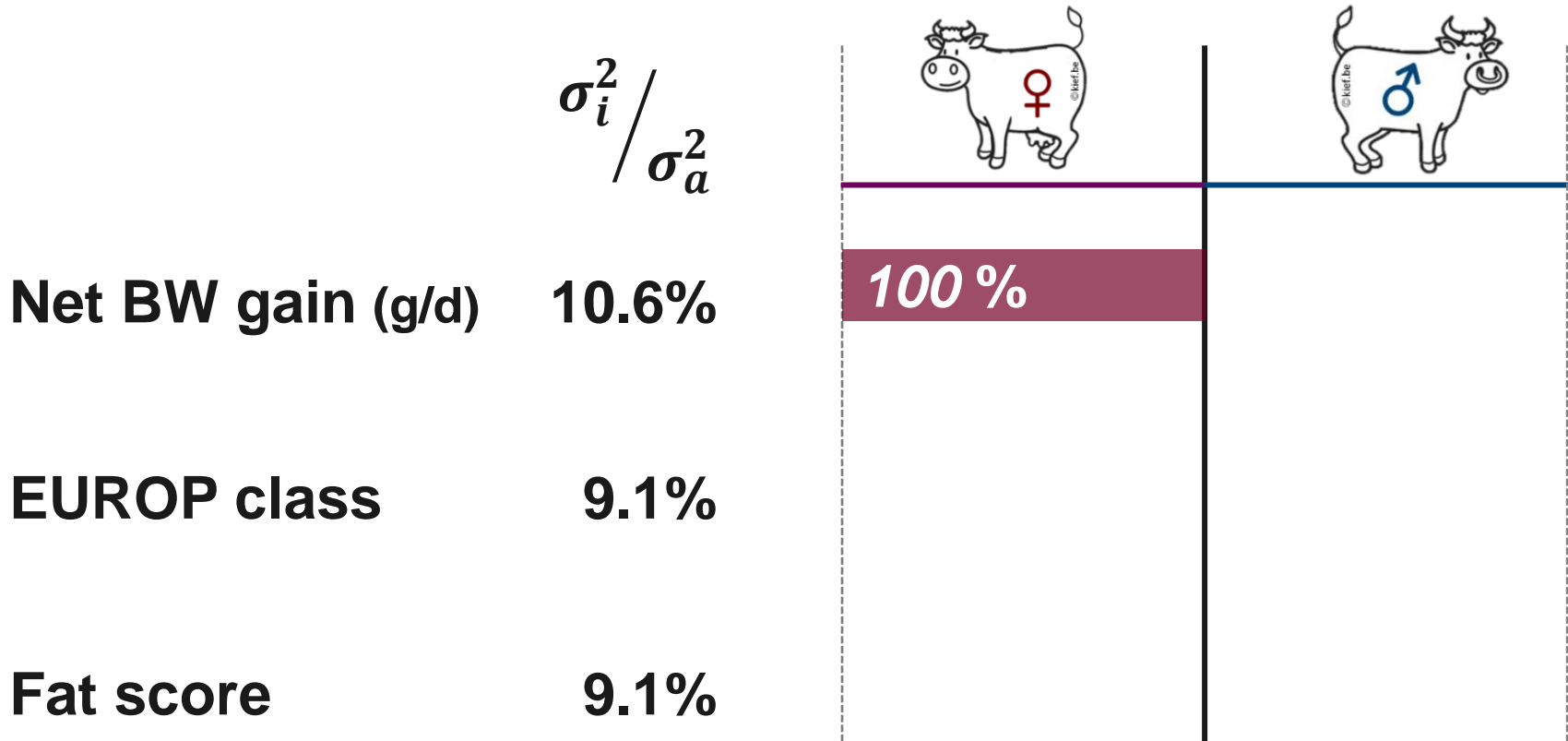
Results of Step 1



	σ_i^2 / σ_a^2		
Net BW gain (g/d)	10.6%		
EUROP class	9.1%		
Fat score	9.1%		

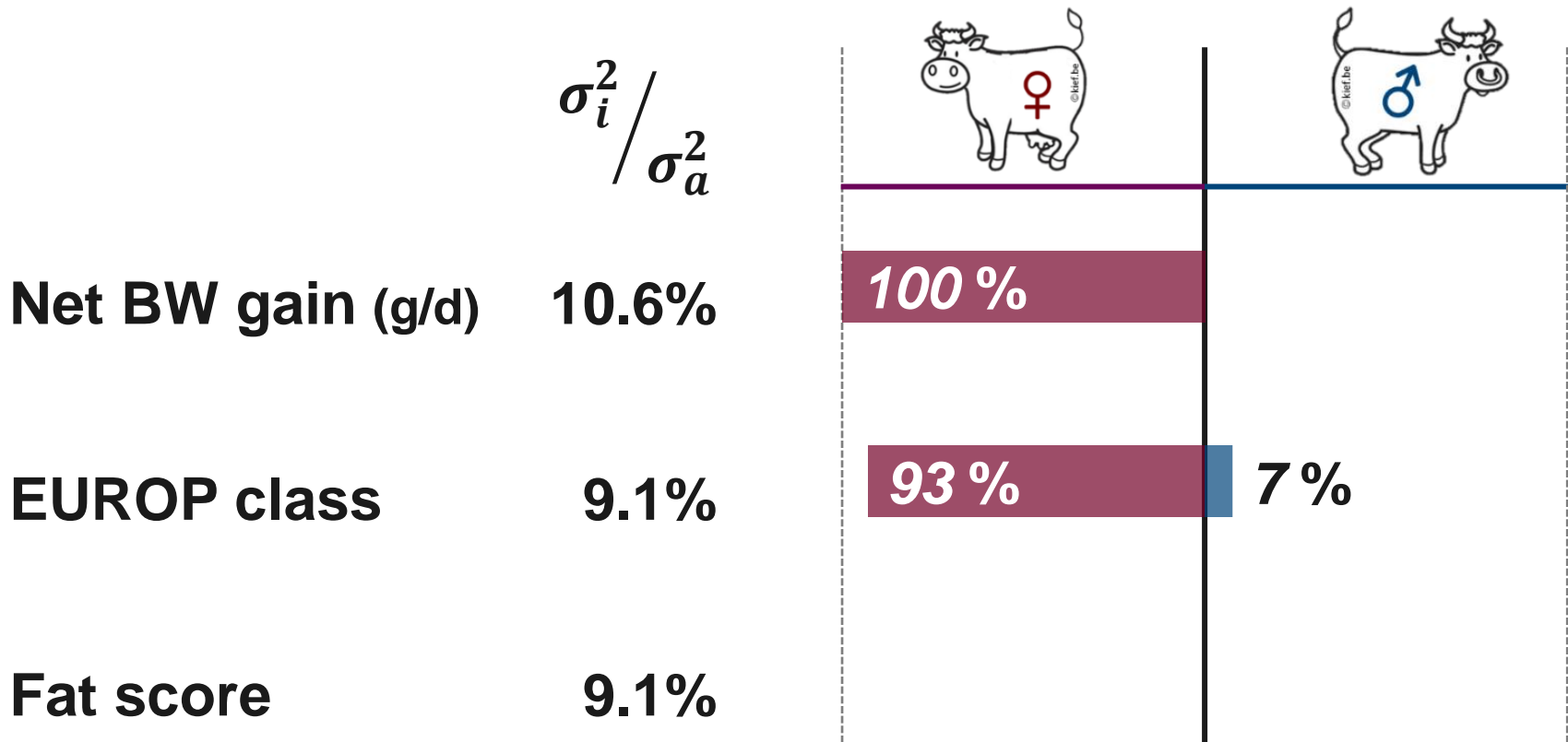
p-value < 10⁻⁵

Results of Step 1



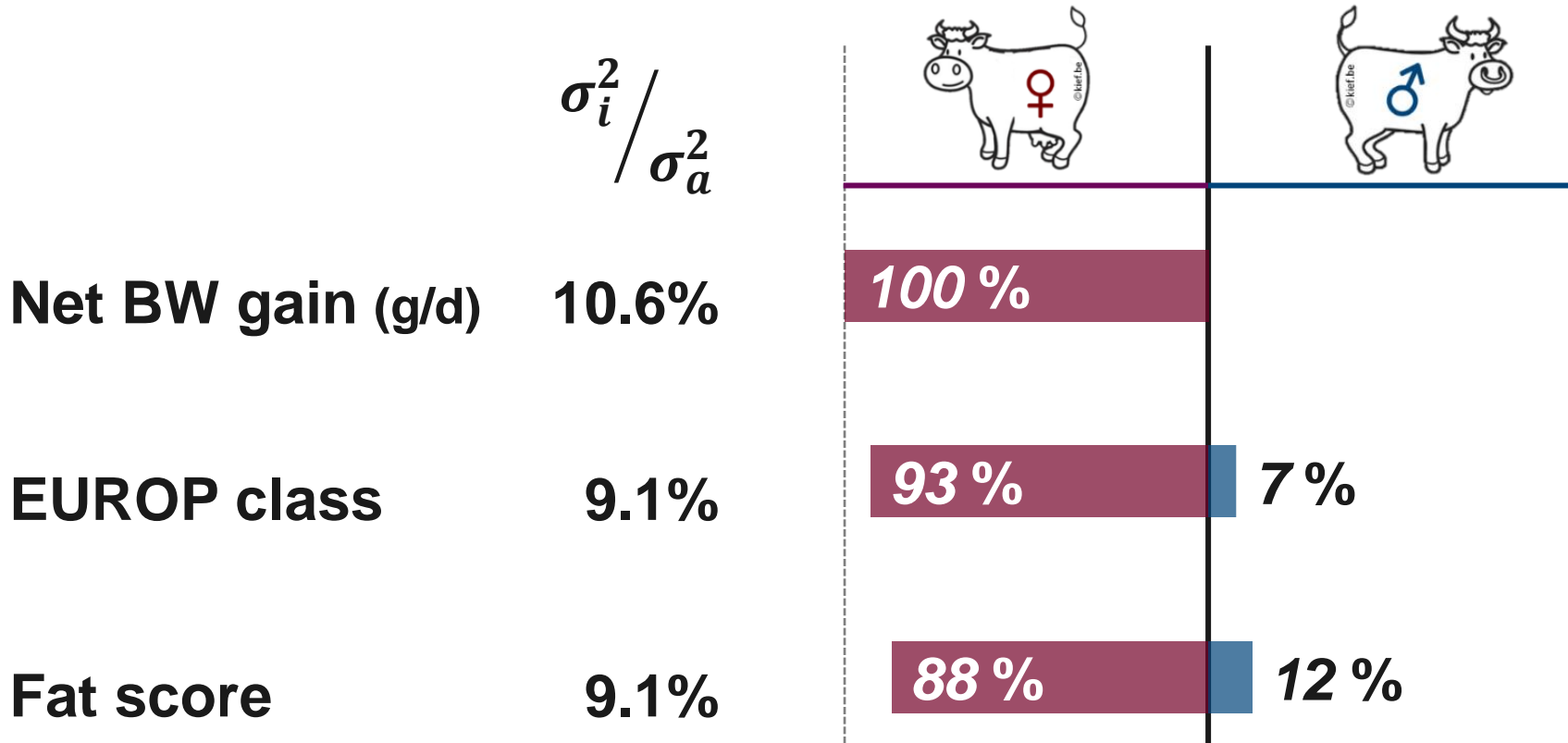
$p\text{-value} < 10^{-5}$

Results of Step 1



$p\text{-value} < 10^{-5}$

Results of Step 1

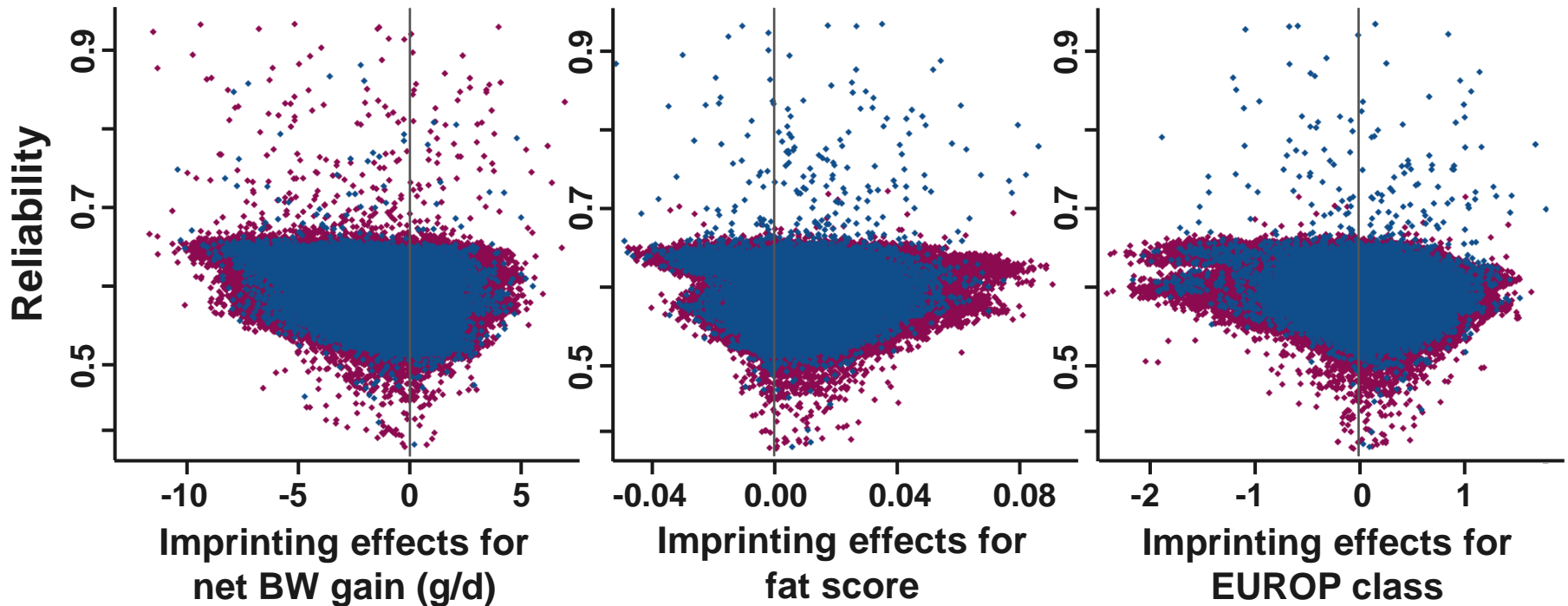


$p\text{-value} < 10^{-5}$

Results of Step 2



Estimated imprinting effects applying the new imprinting model:



Summary

We developed a new equivalent imprinting model

- Easy determination of standard errors for a large number of animals using existing software

$$\begin{bmatrix} X'W^{-1}X & X'W^{-1}Z_s & X'W^{-1}Z_i \\ Z_s'W^{-1}X & Z_s'W^{-1}Z_s + A^{-1}\lambda_1 & Z_s'W^{-1}Z_i + A^{-1}\lambda_2 \\ Z_i'W^{-1}X & Z_i'W^{-1}Z_s + A^{-1}\lambda_2 & Z_i'W^{-1}Z_i + A^{-1}\lambda_3 \end{bmatrix} \begin{bmatrix} \beta \\ a_s \\ i \end{bmatrix} = \begin{bmatrix} X'W^{-1}y \\ Z_s'W^{-1}y \\ Z_i'W^{-1}y \end{bmatrix}$$

Summary

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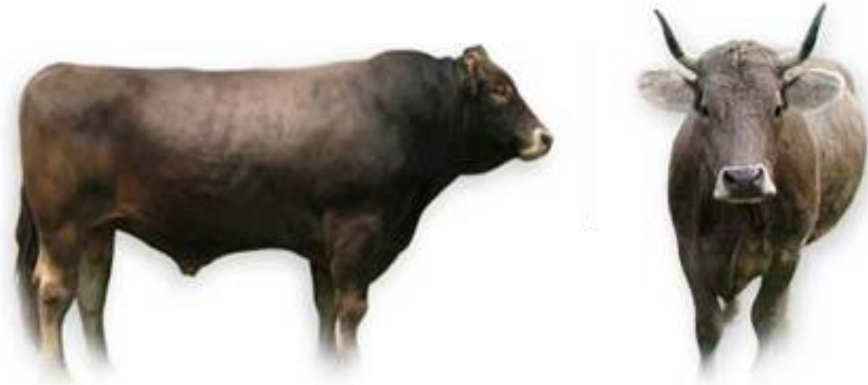
$$\begin{bmatrix} X'W^{-1}X & X'W^{-1}Z_s & X'W^{-1}Z_i \\ Z_s'W^{-1}X & Z_s'W^{-1}Z_s + A^{-1}\lambda_1 & Z_s'W^{-1}Z_i + A^{-1}\lambda_2 \\ Z_i'W^{-1}X & Z_i'W^{-1}Z_s + A^{-1}\lambda_2 & Z_i'W^{-1}Z_i + A^{-1}\lambda_3 \end{bmatrix} \begin{bmatrix} \beta \\ a_s \\ i \end{bmatrix} = \begin{bmatrix} X'W^{-1}y \\ Z_s'W^{-1}y \\ Z_i'W^{-1}y \end{bmatrix}$$

We detected imprinting effects in Brown Swiss

- Average relative imprinting variance of 9.6%
- Maternal gametes contributed $\geq 88\%$



Thank you for your attention!



H. Wilhelm Schaumann-Foundation Hamburg European Federation of Animal Science

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- Neugebauer, N., Luther, H. and Reinsch, N. (2010a). Parent-of-origin effects cause genetic variation in pig performance traits. *Animal*. 4: 672-681.
- Neugebauer, N., Räder, I., Schild H.J., et al. (2010b). Evidence for parent-of-origin effects on genetic variability of beef traits. *J. Anim. Sci.* 88: 523-532.

http://www.krankykids.com/cows/cow_wall_country/switzerland/switzerland_sBreed_dName.html



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Appendix

The Neugebauer model:

$$Y = X\beta + \mathbf{Z}_s \mathbf{g}_s + \mathbf{Z}_d \mathbf{g}_d + e$$

$$\mathbf{g}_s = \mathbf{g}_b + \mathbf{g}_p = \text{paternal gametic effect}$$

$$\mathbf{g}_d = \mathbf{g}_b + \mathbf{g}_m = \text{maternal gametic effect}$$

The imprinting effect:

$$\begin{aligned} i &= (\mathbf{g}_b + \mathbf{g}_p) - (\mathbf{g}_b + \mathbf{g}_m) \\ &= \mathbf{g}_p - \mathbf{g}_m \end{aligned}$$

Appendix

The imprinting variance:

$$\text{Var} \begin{bmatrix} g_s \\ g_d \end{bmatrix} = G \otimes \begin{bmatrix} \sigma_s^2 & \sigma_{sd} \\ \sigma_{sd} & \sigma_d^2 \end{bmatrix}$$

$$\sigma_s^2 = \sigma_b^2 + \sigma_p^2 + 2\sigma_{bp}$$

$$\sigma_d^2 = \sigma_b^2 + \sigma_m^2 + 2\sigma_{bm}$$

$$\sigma_{sd} = \sigma_b^2 + \sigma_{bp} + \sigma_{bm} + \sigma_{pm}$$

$$\sigma_i^2 = (\sigma_s^2 - \sigma_{sd}) + (\sigma_d^2 - \sigma_{sd})$$

$$\sigma_i^2 = \sigma_s^2 + \sigma_d^2 - 2\sigma_{sd}$$

Appendix

The imprinting effect is given by: $i = a_s - a_d$

The PEV of the imprinting effects is given by:

$$Var(\hat{i} - i) = Var(\hat{a}_s - a_s) + Var(\hat{a}_d - a_d) - \underbrace{2Cov(\hat{a}_s - a_s, \hat{a}_d - a_d)}_{\uparrow}$$

Off-diagonal elements of the inverted coefficient matrix are needed:

$$\begin{bmatrix} \beta \\ a_s \\ a_d \end{bmatrix} = \begin{bmatrix} X'W^{-1}y \\ Z_s'W^{-1}y \\ Z_d'W^{-1}y \end{bmatrix} \begin{bmatrix} X'W^{-1}X & X'W^{-1}Z_s & X'W^{-1}Z_d \\ Z_s'W^{-1}X & Z_s'W^{-1}Z_s + A^{-1}\alpha_1 & \mathbf{Z_s'W^{-1}Z_d + A^{-1}\alpha_2} \\ Z_d'W^{-1}X & \mathbf{Z_d'W^{-1}Z_s + A^{-1}\alpha_2} & Z_d'W^{-1}Z_d + A^{-1}\alpha_3 \end{bmatrix}^{-1}$$

Appendix

Equivalence between the Neugebauer model and our new model

As stated by Henderson (1985), equivalent models generate a class of covariance estimates that are identical to those generated with the original model after **linear transformation**:

Possibility 1 of linear transformation:

$$\begin{bmatrix} \sigma_s^2 \\ \sigma_i^2 \\ (\sigma_{sd} - \sigma_s^2) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & -2 \\ -1 & 0 & 1 \end{bmatrix} \begin{bmatrix} \sigma_s^2 \\ \sigma_d^2 \\ \sigma_{sd} \end{bmatrix}$$



Possibility 2 of linear transformation:

$$\begin{bmatrix} \sigma_s^2 \\ \sigma_d^2 \\ \sigma_{sd} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & +2 \\ 1 & 0 & 1 \end{bmatrix} \begin{bmatrix} \sigma_s^2 \\ \sigma_i^2 \\ (\sigma_{sd} - \sigma_s^2) \end{bmatrix}$$

Appendix

$$y_{ijkl} = \mu + \underbrace{a_{s_j} + a_{s_k}} + i_{d_k} + e_{ijk}$$



$$Y = X\beta + Z_s a_s + Z_i i_d + e$$

The correlation between a_{s_j} and a_{s_k} is constrained to 1 using an overlay procedure in ASReml (Gilmour *et al.* (2006)).

Appendix

Z_s has the dimension $n \times q$

Z_i has the dimension $n \times q$

n = # of observations

q = # of animals within the pedigree

#	F	M	FB	F	M
1	0	0	10	9	8
2	0	0	11	5	7
3	1	0	12	9	8
4	1	0	13	5	7
5	3	4			
6	0	4			
7	6	4			
8	3	2			
9	0	2			

$$Z_s = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \end{bmatrix}$$

$$Z_i = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{bmatrix}$$

Appendix

W is a diagonal matrix with the elements: $w_{ii} = \left[\frac{1/2\sigma_s^2(1-F_{s_i}) + 1/2\sigma_d^2(1-F_{d_i}) + \sigma_e^2}{1/2\sigma_s^2 + 1/2\sigma_d^2 + \sigma_e^2} \right]^{-1}$

It is a weighting which corrects the **error variance** of each observation due to the **Mendelian sampling component** with regard to the respective **inbreeding coefficient** of the parents.

Appendix

- $H_0: \sigma_i^2 = 0$ Imprinting arises when the **correlation** between both parental effects is imperfect and/or the **variances are different**
- $H_1: \sigma_i^2 > 0$ leading to an imprinting variance greater zero.

Two models were fitted per trait:

The first corresponds to the *imprinting model*. The second to an equivalent animal model (*Mendelian model*).

Which model fits the data best and thus whether significant imprinting effects exist was tested by comparing REML log-likelihoods of both models using a REML likelihood ratio test (RLRT):

$$RLRT = 2(l_{R2} - l_{R1})$$

Appendix

The RLRT is asymptotically distributed as a 1:1 mixture of two χ^2 distributions with one and two degrees of freedom (Self and Liang, 1987).

However, this only holds for the assumption of between-subject independence and under the null hypothesis. Because these requirements are not satisfied, we followed the suggestions of Neugebauer *et al.* (2010a and 2010b) and applied a χ^2 -distribution with two degrees of freedom to achieve a more conservative test.

Number of d.f.:

- 3 covariance parameters for the imprinting model
- 1 covariance parameter for the Mendelian model

→ 2 d.f.



Appendix

Beef trait data

Fattening bulls were slaughtered between 1994 and 2013. 4 slaughter traits observed in context of the unconducted progeny field test are provided by the genetic evaluation center of the LGL (Landesamt für Geoinformation und Landentwicklung).

Net body weight gain (g/d): Slaughter weight/age at slaughter. Average is 650g/d. Average age at slaughter is 629 days. Live weight at time of slaughter is ca. 500kg thus in accord. to KOP slaughter weight is ca. 200-250kg.

Carcass conformation: European muscle conformation system EUROP (E = excellent to P = poor). They were replaced by monetary values (670-655-635-585-525). Those reflect the fact that although prices differ over time, price differences between classes remain stable.

We treated carcass fatness as a trait rather than an effect. In this regard, this trait was available in form of scores ranging from 1 (lean) to 5 (very fat).



Appendix

Trait	\hat{h}^2	$\hat{\sigma}_a^2$	$\hat{\sigma}_s^2$	$\hat{\sigma}_d^2$	$\hat{\sigma}_{sd}$	$\hat{\sigma}_e^2$	r	RLRT ¹	$\frac{\hat{\sigma}_i^2}{\hat{\sigma}_a^2}$	$\frac{(\hat{\sigma}_s^2 - \hat{\sigma}_{sd})}{\hat{\sigma}_i^2}$	$\frac{(\hat{\sigma}_d^2 - \hat{\sigma}_{sd})}{\hat{\sigma}_i^2}$
Net BW gain (g/d)	0.279 (0.011)	804.960 (34.870)	359.660 (18.48)	445.300 (25.468)	359.890 (18.074)	2071.200 (27.362)	0.899 (0.020)	122.8***	10.58 (2.1)	-0.27 (16.8)	100.27 (16.8)
EUROP class	0.155 (0.009)	58.614 (3.900)	27.027 (1.98)	31.587 (2.850)	26.634 (1.980)	320.080 (3.289)	0.912 (0.029)	27.6***	9.12 (2.8)	7.35 (28.3)	92.65 (28.3)
Fat score	0.229 (0.012)	0.044 (0.002)	0.021 (0.001)	0.024 (0.002)	0.020 (0.001)	0.149 (0.002)	0.910 (0.022)	69.2***	9.17 (2.2)	12.31 (22.2)	87.69 (22.2)
Killing out percentage (%)	0.516 (0.092)	1.348 (0.267)	0.701 (0.138)	0.648 (0.201)	0.672 (0.135)	1.262 (0.221)	0.998 (0.096)	0.7	-	-	-

¹REML likelihood ratio test; $RLRT=2(\log \text{likelihood}_{\text{Imprinting model}} - \log \text{likelihood}_{\text{Mendelian model}})$

*** $P < 0.001$

Appendix

$$y_{ijklmn} = SD_i + PN_j + BT_k + b_1x + b_2x^2 + b_3x^3 + a_{s_l} + a_{d_m} + e_{ijklmn}$$

y_{ijklmn} beef trait record

SD_i fixed effect of i^{th} comparison group (fattening farm x date of slaughter)

PN_j fixed effect of the j^{th} parity number (first, second and more calvings)

BT_k fixed effect of the k^{th} birth type (singleton or twin)

b the linear (b_1), quadratic (b_2) and cubic (b_3) regression on slaughter age x

a_{s_l} random additive genetic effect as sire l

a_{d_m} random additive genetic effect as dam m

e_{ijklmn} random residual