Modelling Parent-Of-Origin-Effects For Traits With Both Direct And Maternal Genetic Variation

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Introduction

Genomic imprinting refers to an epigenetic marking of genes, which are differentially expressed when they are maternally or paternally transmitted. The molecular mechanism is a parent-specific methylation of DNA, established during gametogenesis. Evidence for the relevance of genomic imprinting for genetic variation in livestock comes from QTL-studies, known mutations (Cockett et al., 1994; Jeon et al., 1999; Nezer et al., 1999) and quantitative analyses (de Vries et al., 1994). Recently models have been proposed (Neugebauer et al., 2010) with two genetic effects per animal: the genetic effect as sire accounts for gene action under a paternal expression pattern, while the genetic effect as dam accounts for the same genotype with a maternal expression pattern. The main advantage compared to previous approaches is, that all possible combinations of paternal imprinting, maternal imprinting and full and partial imprinting are covered by this kind of model. The imprinting variance σ_i^2 can be expressed as the variance of the difference between the two types of genetic effects. When maternal genetic effects are involved separation of the imprinting variance becomes, however, more difficult. Therefore we demonstrate how this can be achieved by applying a special kind of gametic model and present an example analysis of birth weight and gestation length data from German Holsteins.

Material and methods

Statistical analyses. For our purposes we employ a gametic model, since under genomic imprinting breeding values and genetic values do not coincide. Further, both the direct and the maternal genetic effect are split up into genetic effects as dam and as sire. Thus the model in matrix notation becomes

$$y = X\beta + Z_{ds}g_{ds} + Z_{dd}g_{dd} + Z_{ms}g_{ms} + Z_{md}g_{md} + e \qquad (1)$$

where y is the vector of observations, X is the design matrix for fixed effects with the corresponding vector β; Z_{ds} and Z_{dd} are the design matrices for direct random gametic effects with the vectors g_{ds} (paternal expression pattern) and g_{dd} (maternal expression pattern) for parental gametic effects; Z_{ms} and Z_{md} are the design matrices for maternal random gametic effects with the vectors g_{ms} (paternal expression pattern) and g_{md} (maternal expression

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pattern) for parental gametic effects of the dam and e is the vector of random residuals. The covariance of random effects is assumed as

$$Var\begin{bmatrix} g_{ds} \\ g_{dd} \\ g_{ms} \\ g_{md} \\ e \end{bmatrix} = \left[\begin{array}{cccc|c} G\sigma^2_{ds} & G\sigma_{ds,d} & G\sigma_{ds,ms} & G\sigma_{ds,md} & 0 \\ G\sigma_{ds,d} & G\sigma^2_{dd} & G\sigma_{dd,ms} & G\sigma_{dd,md} & 0 \\ G\sigma_{ds,ms} & G\sigma_{dd,ms} & G\sigma^2_{ms} & G\sigma_{ms,d} & 0 \\ G\sigma_{ds,md} & G\sigma_{dd,md} & G\sigma_{ms,d} & G\sigma^2_{md} & 0 \\ \hline 0 & 0 & 0 & 0 & I\sigma^2_e \end{array}\right] = \left[\begin{array}{c|c} S \otimes G & 0 \\ \hline 0 & I\sigma^2_e \end{array}\right] \quad (2)$$

The 4×4 matrix S contains all genetic covariances and G is the gametic relationship matrix (Schaeffer et al., 1989). In the standard case without genomic imprinting there are only three different parameters in S, and S_{00}, representing the null hypothesis of no imprinting both for the direct and maternal trait, becomes

$$S_{00} = \left[\begin{array}{cc|cc} \sigma^2_d & \sigma^2_d & \sigma_{dm} & \sigma_{dm} \\ \sigma^2_d & \sigma^2_d & \sigma_{dm} & \sigma_{dm} \\ \hline \sigma_{dm} & \sigma_{dm} & \sigma^2_m & \sigma^2_m \\ \sigma_{dm} & \sigma_{dm} & \sigma^2_m & \sigma^2_m \end{array}\right] \quad (3)$$

The alternative is a situation, where genomic imprinting affects the direct as well as the maternal trait, as represented by S_{11}

$$S_{11} = \left[\begin{array}{cc|cc} \sigma^2_{ds} & \sigma_{ds,d} & \sigma_{ds,ms} & \sigma_{ds,md} \\ \sigma_{ds,d} & \sigma^2_{dd} & \sigma_{dd,ms} & \sigma_{dd,md} \\ \hline \sigma_{ds,ms} & \sigma_{dd,ms} & \sigma^2_{ms} & \sigma_{ms,d} \\ \sigma_{ds,md} & \sigma_{dd,md} & \sigma_{ms,d} & \sigma^2_{md} \end{array}\right] \quad (4)$$

Further hypotheses - and their corresponding S-matrices - with genomic imprinting only for either the direct (S_{10}) or the maternal (S_{01}) trait can easily be derived. It can be demonstrated (Neugebauer, 2010) that the variance components from this gametic model can be separated.

Data set and linear model. As an example we analysed birth weight and gestation-length data collected between 1998 and 2007/2008 on three dairy farms in Northern Germany. Only observations from the first lactation and singletons were included, gestation lengths between 265 and 295 days were considered as plausible (Philipsson, 1979). The proportion of male calves was 52% and the number of observations was 8375 for birth weight and 8116 for gestation length.

The fixed effects of the linear model for observations $y_{ijklmno}$ were adopted from Junge et al. (2003):

$$y_{ijklmno} = HYS_i + S_j + b_1x + b_2x^2 + b_3x^3 + ds_k + dm_l + ms_m + mm_n + e_{ijklmno} \quad (5)$$

where HYS_i is the fixed effect of the barn year season (in months) interaction, S_j is the fixed effect of sex, b_1, b_2, b_3 are linear, quadratic and cubic regressions on calving age (x), ds_k is the random direct gametic effect as sire, dm_l the random direct gametic effect as dam, ms_m and mm_n are the random maternal gametic effects as sire and as dam and $e_{ijklmno}$ is the random residual.

Since convergence could not be obtained within a reasonable time for all submodels desired for hypothesis testing, we fitted also simplified models, where maternal genetic effects were modelled as uncorrelated maternal grandsire effects, allowing only hypothesis testing for the presence of a direct imprinting variance. Analyses were done with the REMLF90 (Misztal et al. 2002) and ASReml (Gilmour *et al.*, 2004) programs.

Results and discussion

Estimates (REMLF90) for the genetic covariances from the full gametic direct and maternal effects imprinting model are shown in Table 1.

Table 1: Estimates of the gametic direct (d) and maternal (m) effects imprinting model.

	Birth weight				Gestation length			
	As sire (d)	As dam (d)	As sire (m)	As dam (m)	As sire (d)	As dam (d)	As sire (m)	As dam (m)
As sire (d)	5.914	8.384	-0.969	-0.114	12.65	10.63	-0.015	-1.494
As dam (d)	0.733	22.150	-4.402	-1.785	0.616	23.52	-2.646	-5.866
As sire (m)	-0.036	-0.839	1.244	0.854	-0.003	-0.433	1.589	1.630
As dam (m)	-0.004	-0.307	0.620	1.523	-0.246	-0.708	0.757	2.919

Variances in the diagonal, covariances above and correlations below the diagonal.

For both traits the estimated direct genetic variance ($\sigma^2_{ds} + \sigma^2_{dd}$) was considerably larger than the maternal genetic variances ($\sigma^2_{ms} + \sigma^2_{md}$), estimates for the direct genetic variances were 21.75 kg^2 for birth weight and 22.98 $days^2$ for gestation length, with corresponding direct heritabilities of 68% and 72%, which compare to maternal heritabilities of 11% and 17%. Similar estimates were reported in the literature Philipsson et al., 1979; Meijering, 1984; Eriksson et al., 2004). For the direct trait differences between gametic variances as sire and as dam seemed to be large, but no formal significance test could be obtained from the full model. Estimates for the direct imprinting variance in absolute numbers were 4.38 kg^2 and 2.66 $days^2$ ($\sigma^2_i = \sigma^2_{ds} + \sigma^2_{dd} - 2\sigma_{ds,d}$), translating into relative imprinting variances of 20% and 12% ($\sigma^2_i \big/ \sigma^2_a$). The latter values are in the upper range of estimates found for slaughter traits in cattle and pigs (Neugebauer et al., 2010 a, b, c).

Estimates from the simplified models (Table 2) showed also large differences between direct gametic variances as sire and as dam and here they were significant at the 5%-level for both traits.

Table 2: Estimates of the simplified model with gametic direct (d) effects and an uncorrelated maternal grandsire effect.

	Birth weight			Gestation length		
	As sire (d)	As dam (d)	Grandsire (m)	As sire (d)	As dam (d)	Grandsire (m)
As sire (d)	6.064	8.686	0	10.306	10.161	0
As dam (d)	0.891	15.690	0	0.889	12.676	0
Grandsire (m)	0	0	0.000	0	0	0.292

Variances in the diagonal, covariances above and correlations below the diagonal.

Conclusion

As a conclusion, it could be demonstrated that, at least in principle, imprinting variances can be estimated for traits being affected by maternal genetic effects. Further research can therefore be expected to give insight into the relative importance of genomic imprinting for this class of traits in livestock.

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