IT-Solutions for
Animal Production

Large Scale Genomic Evaluation in Dairy Cattle

Zengting Liu
F. Seefried, F. Reinhardt, and R. Reents
vit w.V., Heideweg 1, 27283 Verden, Germany

OUTLINE

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Introduction: genetic evaluation models

- Conventional genetic evaluation in dairy cattle
  - Using phenotypic data and pedigree
  - Henderson's mixed model (BLUP) methodology
  - Indirect setup of A^{-1} and iteration on data techniques
    - 292 million test-day records from 16 million cows (German Holstein)
    - Total # equations: 370 millions for each of milk, fat, protein and SCS
  - Reliabilities of (multi-trait) EBV reasonably accurately approximated
  - Very successful for breeding, BUT
    - reliable EBV available late
    - low reliability for cows or pedigree index
- Genomic model contrasting the animal model
  - Small *n* large *p* problem of the genomic SNP model
  - Realised genomic (**G**) vs. expected relationship (**A**)
  - No algorithm yet for indirect setup of $\mathbf{G}^{-1}$
  - Direct inversion of **G** becoming increasingly infeasible

A BLUP SNP genomic model (German Holsteins)

- A BLUP SNP model for bulls (no cows in training set)

$$q_i = \mu + v_i + \sum_{j=1}^{p} z_{ij} u_j + e_i$$

  - Phenotypic record: bull deregressed EBV (similar to DYD)
  - $\mathrm{var}(q_i) = \sigma_a^2 + \sigma_e^2 / \varphi_i$ where φ_i is effective # daughters of bull
  - Deregressed EBV (DPRF) easier to obtain than DYD from international conventional evaluation MACE
  - Residual polygenic effect with trait-specific variance
    - Validation showing candidates' GEBV with too high variance
    - SNP markers may not explain all genetic variation
    - SNP effects depend too much on pedigree (Habier et al. 2007)
    - SNP effects less biased and more persistent (Solberg et al. 2009)
    - Polygenic effect also in French QTL model (Guillaume et al. 2008)

1) Deregressed EBV for genomic evaluation

- Genomic evaluation using national genotypes and phenotypes
  - Genotyped foreign calves may have sires without daughters in Germany
- EuroGenomics / North-American / IGenoP projects
  - Multiple country SNP model is a better approach (sharing genotypes?)
  - Use international MACE EBV for genomic evaluation
- Best possible choice for dependent variable
  - EBV should be avoided, due to double counting phenotypic info
  - DYD preferred, but not available for all traits / countries
  - Sub-optimal deregression on an animal by animal basis
    - $DPRF = (EBV - PA)/R^2_{dau} + \mu$
  - Deregressing MACE EBV using full pedigree
    - Loop over pedigree sorted by birth years
    - Keep EBV constant for bulls with daughters
    - Iterative process until deregressed EBV converged

1) The MACE EBV deregression method

- MACE EBV and equivalent effective daughter contribution (EDC)
  - Required for all bulls on a given country scale
  - Even for bulls without local daughters
- Calculation of equivalent EDC for every bull
  - Using multi-trait EDC method (Liu et al. 2004)
  - National EDCs from all countries $\varphi_i\,(i=1,\cdots,27)$
  - Genetic correlations between all country pairs
  - Sire variances for all countries
  - National heritability values
- Same software as for deregressing national EBV

1) Results: deregressed with original EBV

Birth year	MACE Evaluation Aug 2009			National Evaluation Aug 2009		
	No. Bulls	Corr. x 100	Difference	No. Bulls	Corr. X 100	Difference
1990	5685	95.8	-10.3	911	99.3	0.6
1991	5809	95.7	-9.3	924	99.3	-3.0
1992	6156	95.8	-7.1	986	99.5	-1.7
1993	5937	95.1	3.5	1063	99.4	3.2
1994	6206	96.0	6.1	1191	99.4	4.2
1995	6438	95.7	-14.5	1283	98.9	4.1
1996	6661	96.0	-16.6	1330	99.5	-1.2
1997	6816	95.5	-16.9	1381	99.3	-1.6
1998	6459	95.7	-2.7	1214	99.4	1.0
1999	6156	95.5	3.0	1192	99.5	1.2
2000	5940	95.7	-20.2	1176	99.4	1.6
2001	5963	96.0	-11.4	1140	99.5	-1.9
2002	5977	96.0	-7.3	1081	99.6	-4.0
2003	6009	95.1	-10.8	1140	99.3	-0.0
2004	4089	93.8	23.0	793	97.6	28.8
2005	387	90.2	97.0	15	90.9	7.8

all Holstein bulls included with EDC>0

Milk yield

1) Discussion: MACE EBV deregression

- Deregression very fast and well converged (milk yield)
  - 114,003 Holstein bulls with daughters worldwide
  - 212,181 Holstein animals in pedigree
  - 4494 rounds reached convergence (10^{-10}) in 2.3 minutes
- Many more bulls considered than national data (110,000 vs 24,000)
- Deregressed MACE reasonably highly correlated with MACE proofs
- The lower correlations of MACE than German national data:
  - Lower reliabilities of daughter info on German scale than national German proofs (0.75 vs 0.93)
- Larger difference between proofs and deregressed proofs for MACE than German national data
  - Pedigree difference between deregression (sire+dam) and MACE Aug'09 evaluation (sire+MGS+MGD group)
  - Unofficial bulls were missing in MACE result files

2) SNP effect estimation: Data materials

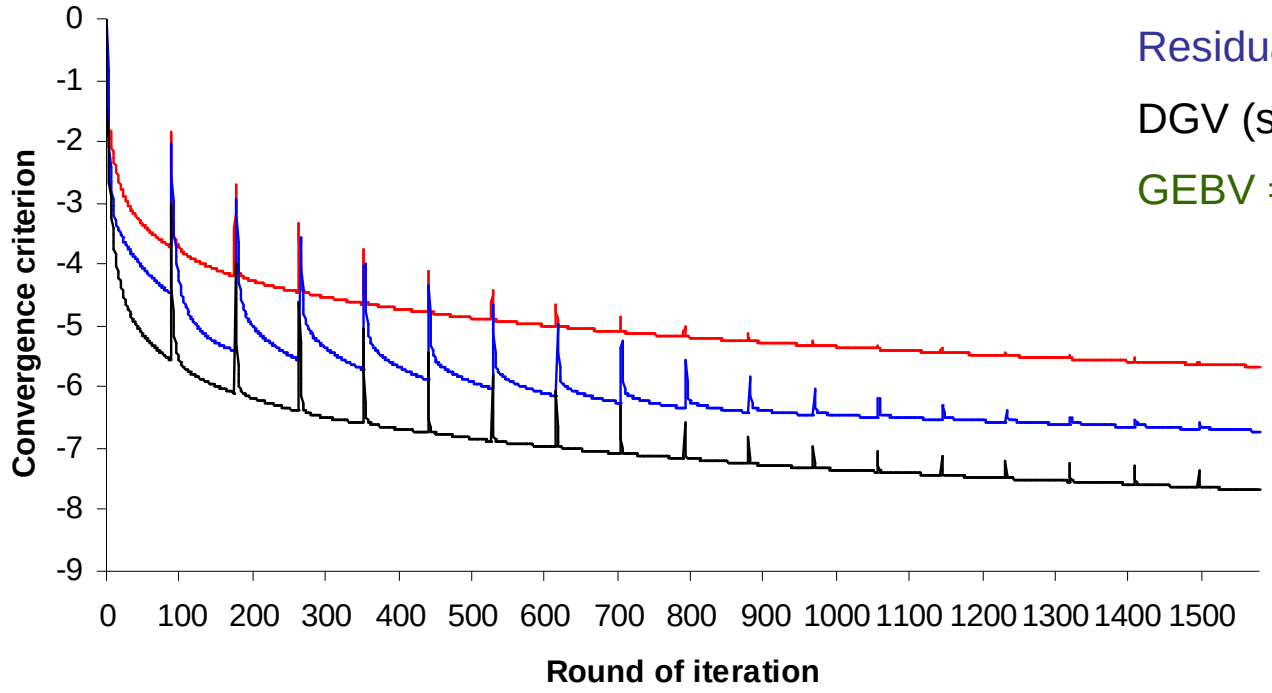
- Genotyped animals (June'10)
  - 27,721 genotyped animals in total
  - 17,477 Holstein bulls (5,477 DEU + 12,000 EuroGenomics)
    - 50,516 ancestors for estimating residual polygenic effect (RPG)
    - 107 phantom parent groups of RPG
    - Representing 21.4 million cows
- Phenotypes from April'10 conventional evaluation
  - Deregressed MACE or national proofs for 44 traits
  - 24,405 bulls with daughters in national evaluation
  - 114,003 bulls with daughters in international evaluation
- Combining genomic and conventional evaluation
  - 128,126 animals with (genomic) data
  - Including reference bulls, bulls with phenotype only, and candidates
  - 236,873 animals in pedigree and 330 phantom parent groups

2) SNP effect estimation: Computing resources

Evaluation	No. training bulls	No. animals in pedigree	CPU (snds) per round
German national Aug'09	4339	24,478	16
German national Jan'10	5025	27,041	17
EuroGenomics Apr'10	17,429	50,385	99
EuroGenomics Jun'10	17,477	50,516	103

- CPU time increased linearly with no. of training bulls
- RAM usage increased also nearly linearly (2.9 Gb)
- Estimating residual polygenic effects required little CPU
- Convergence criteria: DGV > RPG > SNP effects
- Model with higher residual polygenic variance converged better
- SNP model feasible for very large reference population

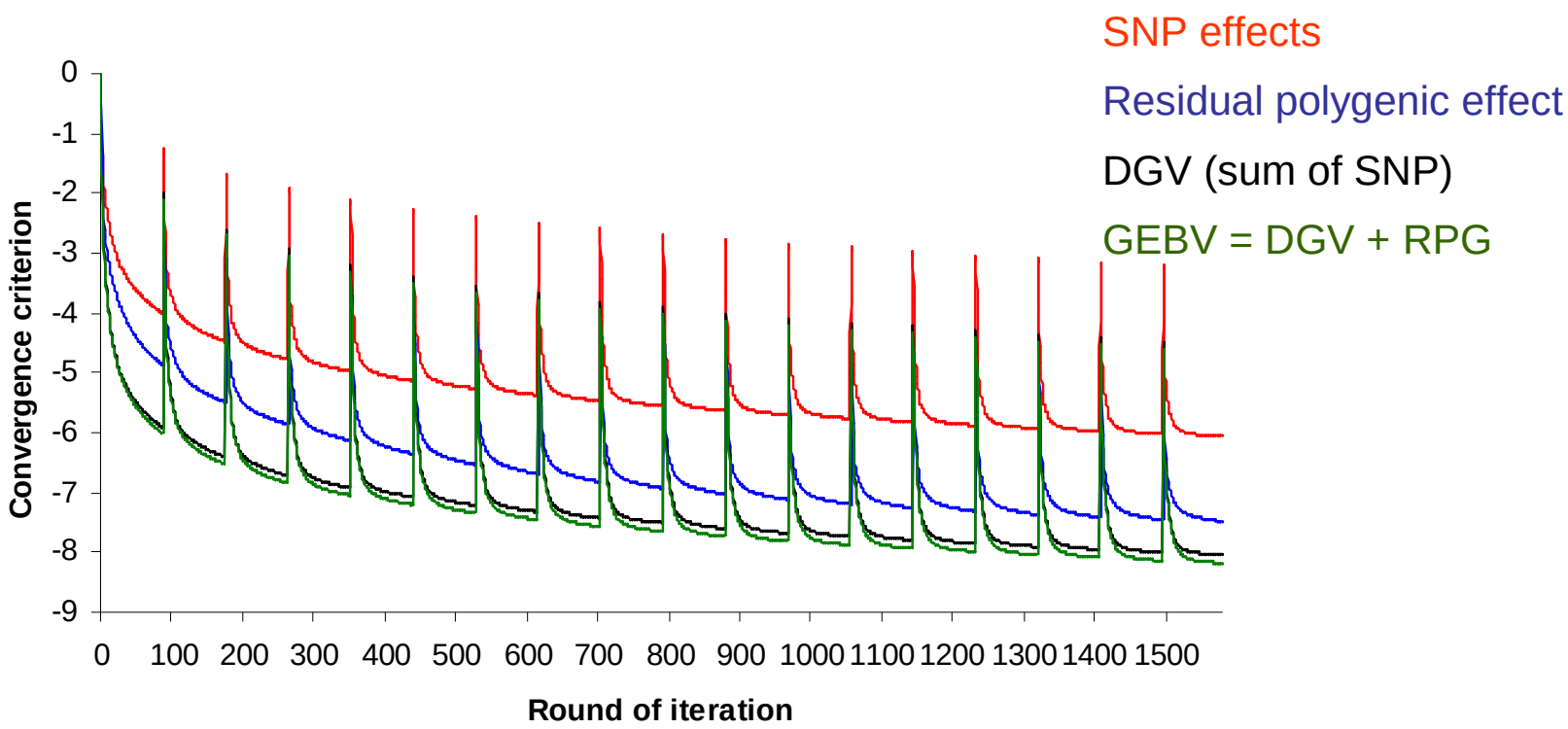
2) Convergence of genomic model estimates



Residual polygenic variance: ~0%

Milk yield

2) Convergence of genomic model estimates

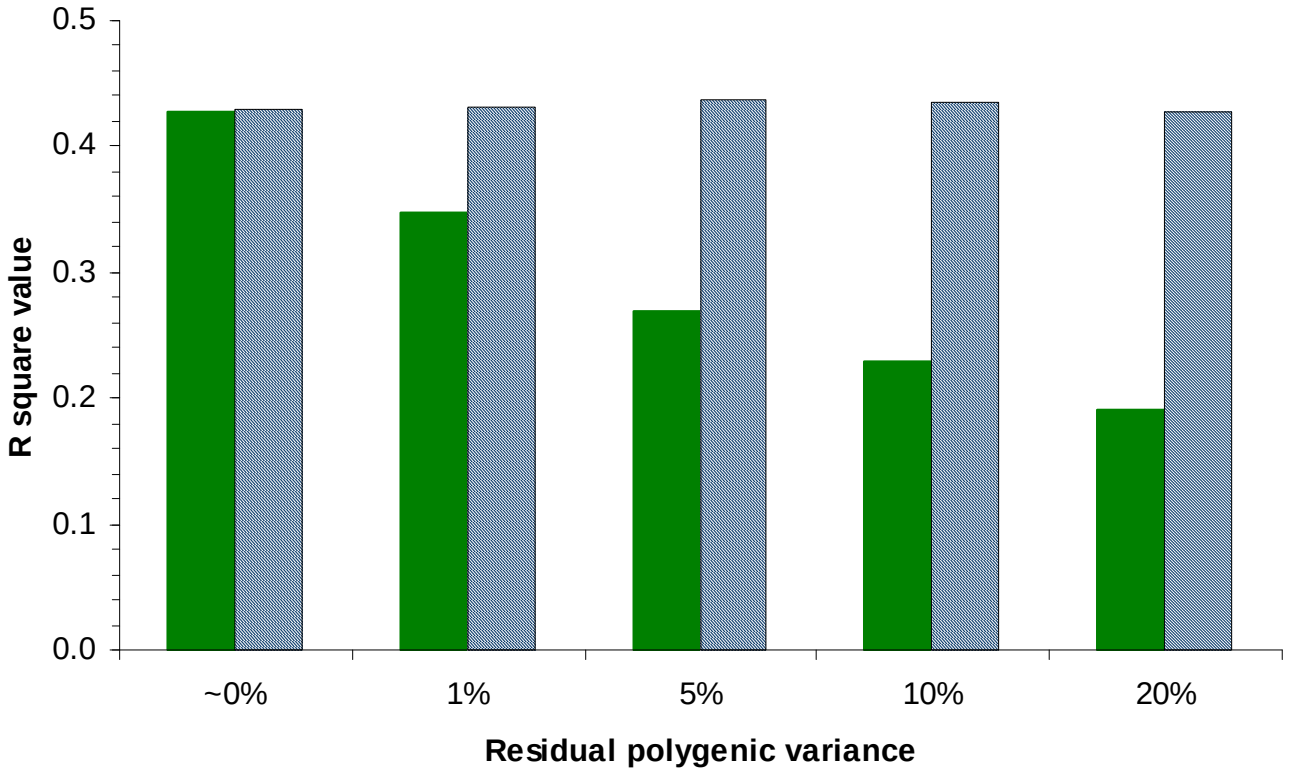


Residual polygenic variance: 1%

Milk yield

2) Reduced impact of genetic relationship on direct genomic values (training bulls)

Regression on sire EBV ($y = b_0 + b_1 * EBV_{sire}$)



GEBV= DGV + RPG

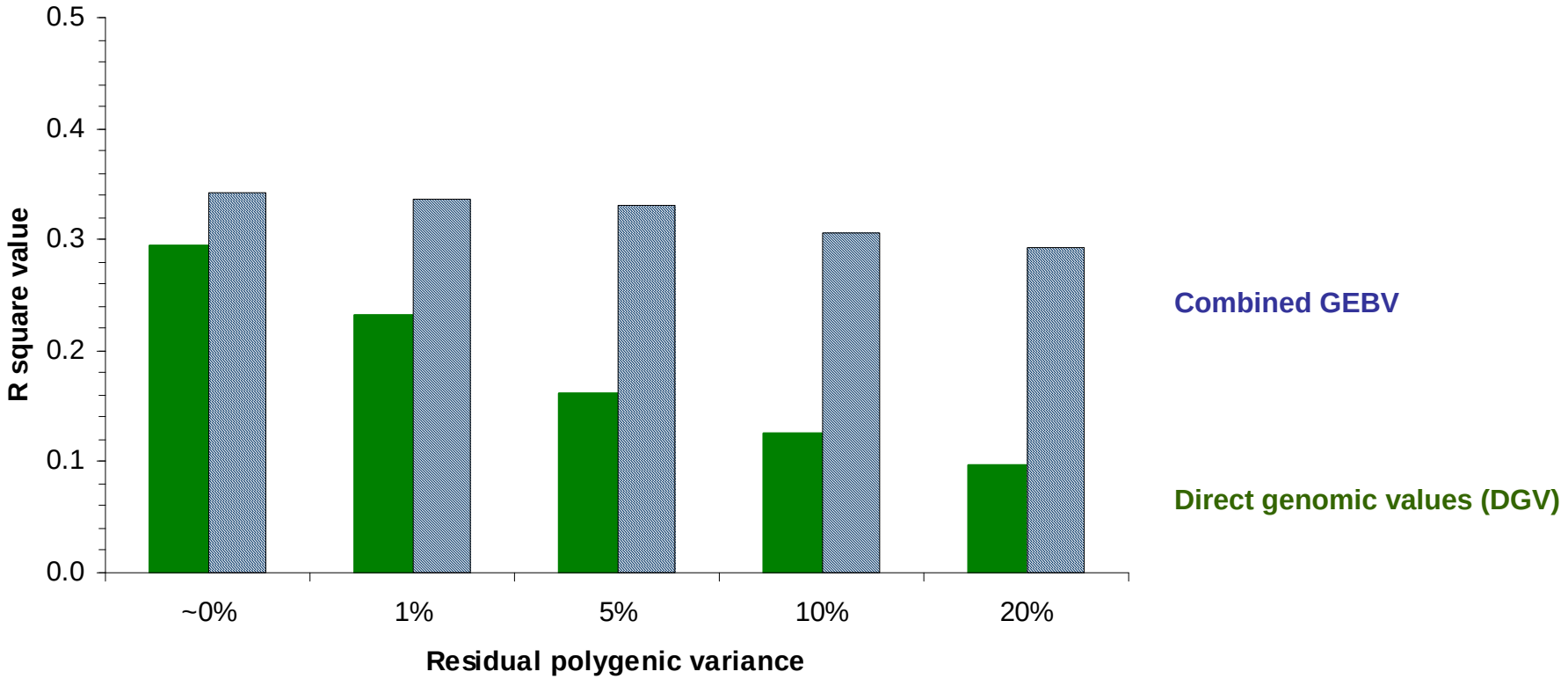
Direct genomic values (DGV)

11,987 reference bulls with 580 genotyped sires

Trait: milk yield

2) Reduced impact of genetic relationship on direct genomic values (validation bulls)

Regression on sire EBV ($y = b_0 + b_1 * EBV_{sire}$)



1211 validation bulls with 111 genotyped sires

Trait: milk yield

3) Reliability of DGV (ΣSNP): introduction

- Calculation of reliability of DGV estimates
  - Method 1: ONE single value for ALL genotyped animals
    - Realised genomic reliability obtained from validation
  - Method 2: inverting genomic relationship matrix **G**
    - animal specific reliability
    - By-product of G-matrix BLUP method

- Direct matrix inversion approach
  - Desirable properties
  - Overestimation problem mainly due to the assumption of all SNPs are in complete LD with QTLs & IBS = IBD
    - Correct level derived from validation study
  - Less feasible for large-scale genomic evaluation
    - Though special software for inverting large matrices (up to 50,000 animals)
  - Approximation needed

3) Data materials for reliability approximation

- German national genomic evaluation Jan 2010
  - 10,487 genotyped animals
    - 5025 Holstein bulls in reference population
    - 5344 genotyped Holstein animals as candidates
- Reliability values of estimated DGV for the candidates
  - Obtained by direct matrix inversion
  - Used as reference value (response variable)
- Prediction formulae for approximating the reliabilities
  - Calculating various statistics as predictor variables
  - Selecting the best subset regressions
  - Using R^2 value and MSE for model comparison

3) Reliability method: Predictor variables

- Genomic relationship of a CANDIDATE to reference animals
  - Average with all reference animals: $\bar{g}_i = (\sum_{j=1}^{n} g_{ij}) / n$
  - Squared average value: $\bar{g}_i^2$
  - Maximum relationship value: $g_i^{\max} = \max(g_{i1,} \cdots, g_{in})$
  - Sum of squared relationships: $g_i^2 = (\sum_{j=1}^{n} g_{ij}^2) / n$

- Reliability of individual reference animal
  - Daughter reliability: $pg_i^2 = (\sum_{j=1}^{n} g_{ij}^2 * \frac{g_{jj}(1 - REL_j^{DAU})}{\lambda}) / n$
  - Genomic reliability: $gg_i^2 = (\sum_{j=1}^{n} g_{ij}^2 * \frac{g_{jj}(1 - REL_j^{G})}{\lambda}) / n$
  - Genomic – daughter reliability: $dg_i^2 = (\sum_{j=1}^{n} g_{ij}^2 * \frac{g_{jj}(1 - (REL_j^{G} - REL_j^{DAU})}{\lambda}) / n$

In total, 12 predictor variables studied, 5 insignificant

3) Results: correlation with genomic reliability

Predictor variable		Correlation with candidates' genomic reliabilities
Average genomic relationship	$\overline{g}_i$	.66
Squared relationship value	$\overline{g}_i^2$	.64
Maximum relationship value	g_i^{max}	.61
Sum of squared relationship	g_i^2	.72
Daughter reliability REF	pg_i^2	.71
Genomic reliability REF	gg_i^2	.71
Genomic-daughter rel. REF	dg_i^2	.72

3) Results: Optimal subset regressions

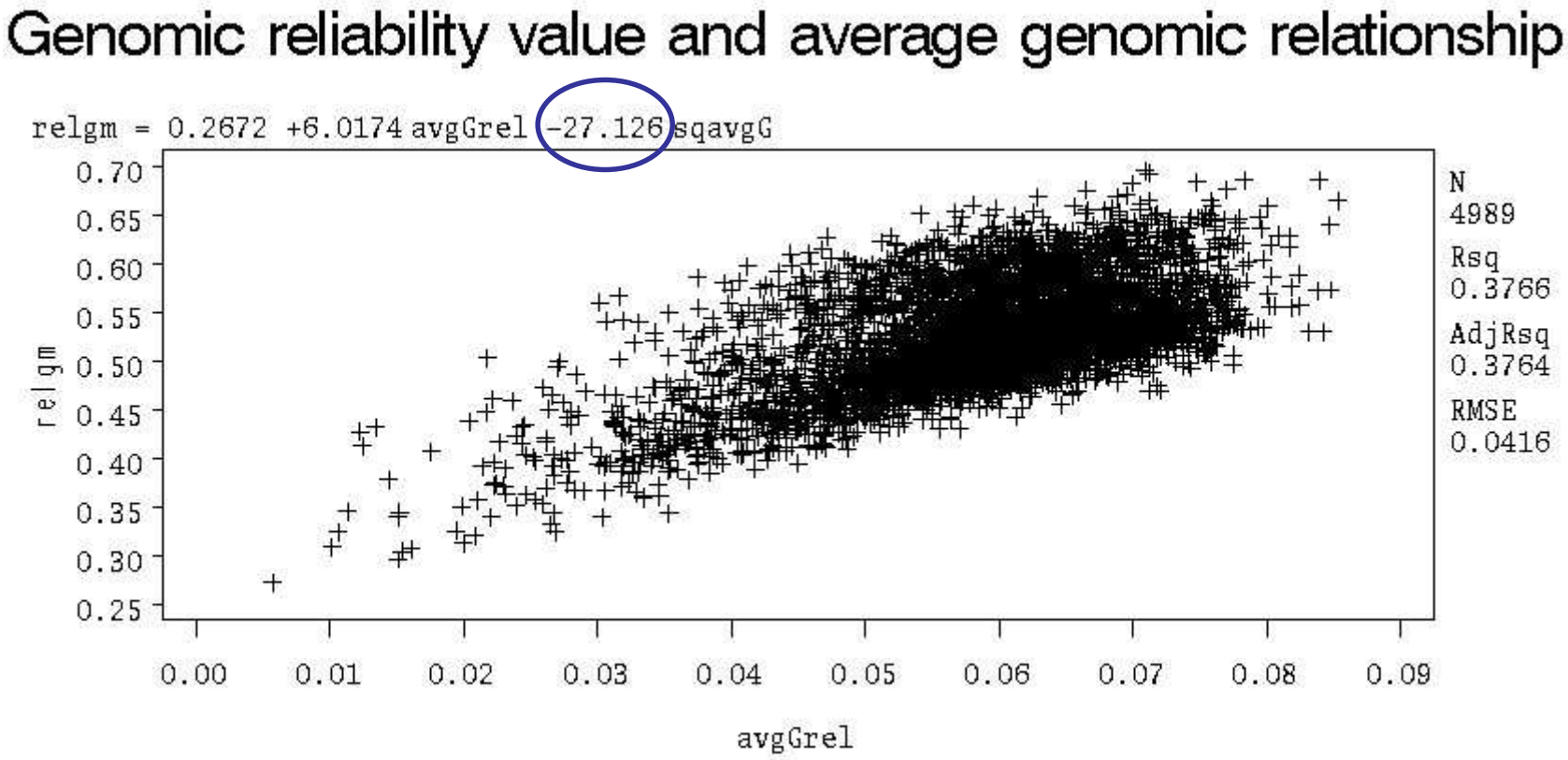
- Subset regressions
  - All combinations of 12 variables considered
    - R^2 value increased with # fitted variables
    - Balance R^2 and # variables

- Optimal subset regression for reliability prediction
  - Average genomic relationship to all training bulls $\bar{g}_i = (\sum_{j=1}^{n} g_{ij}) / n$
  - Squared average relationship $\bar{g}_i^2$
  - Maximum genomic relationship $g_i^{max} = \max(g_{i1,} \cdots, g_{in})$
  - Sum of squared relationship $g_i^2 = (\sum_{j=1}^{n} g_{ij}^2) / n$

$$REL_i = b_0 + b_1 * \bar{g}_i + b_2 * \bar{g}_i^2 + b_3 * g_i^{max} + b_4 * g_i^2$$

- Reliability of individual training bulls no longer important
- Optimal subset regressions CONSISTENT for all traits
- All 4 variables highly correlated, except g_i^{max}

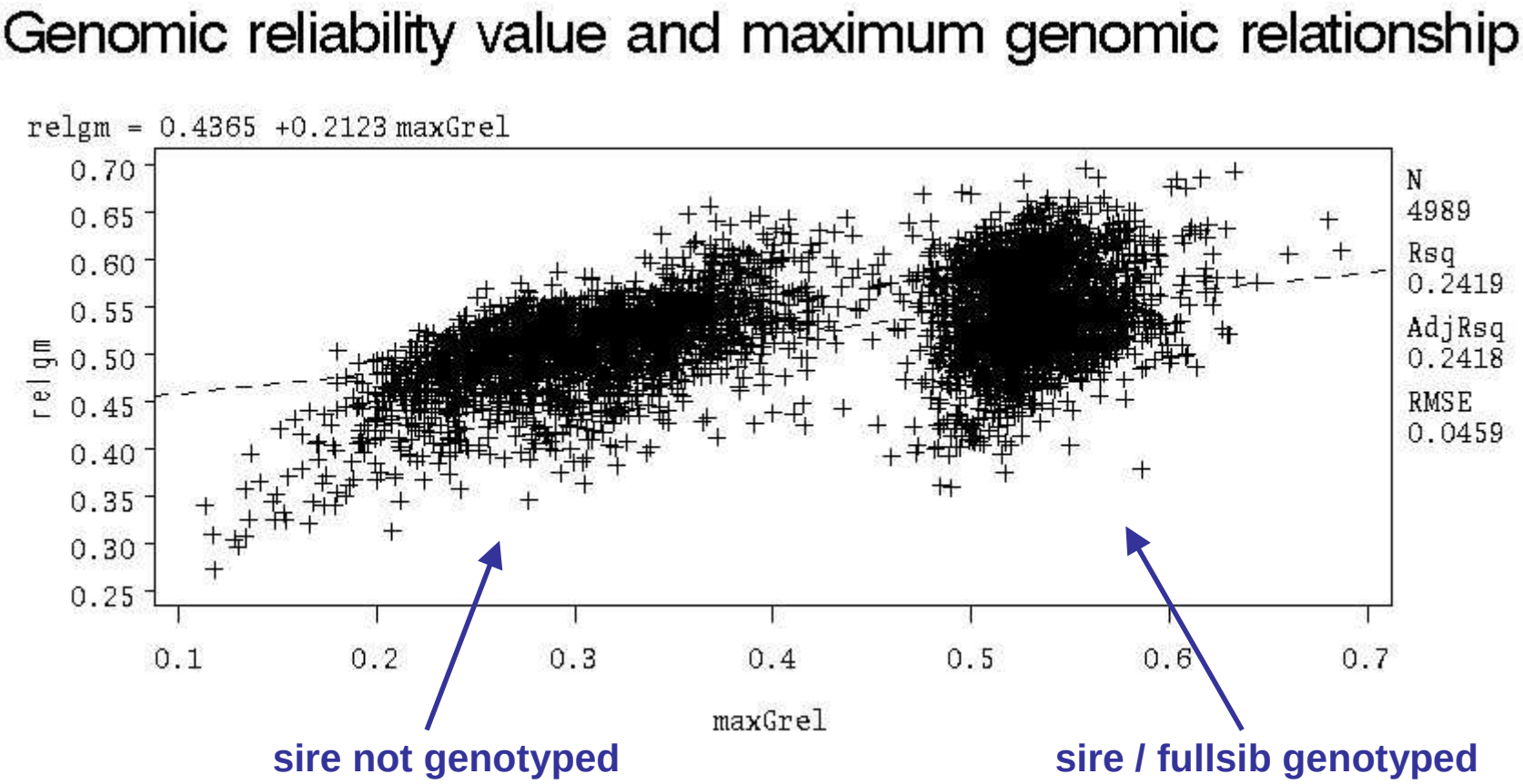
3) Results: Average genomic relationship $\bar{g}_i$



non-return rate cow

German national reference population

3) Results: Maximum genomic relationship g_i^{max}



non-return rate cow

German national reference population

3) Discussion: Approximating DGV reliability

- A method developed for approximating DGV reliabilities
  - Using genomic relationship of candidate to ALL training animals
  - 4 predictor variables selected
- Reasonably high goodness of fit achieved
- Approximated reliabilities to be adjusted to REALISED reliability level via validation study
- New derivation is needed, if reference population changes significantly in size and structure:
  - German national vs. EuroGenomics reference population
    - Size change: 5025 vs 17,054 Holstein bulls (Jan'2010)
    - Structural change in terms of genomic relationship:
      - Lower average genomic relationship for DEU candidates $\overline{g}_i$ ↓
      - Many more candidates with genotyped sire g_i^{max} ↑

Discussion: Combining genomic with conventional phenotypic information

- Turned out to be more difficult than initially assumed
  - Non-independent information sources DGV and EBV / PI
- Three alternatives for combining DGV and EBV
  1. Selection index with DGV as a new info source
     - Assume non-zero residual covariance
  2. One-Step approach (Misztal et al. 2009, Christensen & Lund 2010): the best method in theory
     - Limitation of inverting very large G matrix
     - Problem in modelling international original phenotypes in case of joint genomic reference populations
     - Reasonable simplifications:
       - Use DYD/DPRF instead of ORIGINAL phenotypic records to remove all other effects (e.g. HYS, p.e. effects)
       - Use bulls rather than cows (Germany: 25,000 bulls vs. 17 mln cows)

Combining genomic with conventional info

- Three alternatives for combining DGV and EBV
  3. BLUP 'pseudo-record' method (Ducrocq & Liu, 2009)
     - Transforming genomic info into equivalent phenotypic records
     - Takes advantage of existing efficient BLUP software
     - Correct for genomic pre-selection bias (Patry & Ducrocq, 2009; Liu et al. 2009)
     - Automatic propagation of genomic info to non-genotyped relatives
     - The genomic LHS and RHS terms may be well approximated
     - Approximation of DGV reliabilities for candidates (Liu et al. 2010)
  4. Two correlated trait approach (Mäntysaari & Stranden, 2010)
     - Correlation of DGV and EBV for validation bulls
     - Problem of properly handling training animals
- Implementations of the methods may need fine tuning via validation study

Summary

- Large-scale conventional evaluation formed solid basis for genomic selection
- The genomic model is highly efficient
- Deregressed EBV as dependent variable for (inter)national genomic evaluation in dairy cattle
- Fitting residual polygenic effect may be necessary
  - To avoid too high variance of direct genomic values
  - To reduce pedigree impact on direct genomic values
- Approximation of DGV reliability is necessary with ever increasing number of genotyped animals
- Optimal large-scale combination of genomic and conventional information is important for comparable GEBV and EBV
- More R&D is needed for fine tuning

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THANK YOU!

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