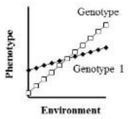
Unravelling genotype-by-environment interactions: modelling genetic variation in macro- and micro-environmental sensitivity

Dr Han Mulder



Animal Breeding and Genomics

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- Quantitative genetics and genomics of macro-environmental sensitivity
- Quantitative genetics and genomics of micro-environmental sensitivity

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Quantitative genetics and genomics of macro-environmental sensitivity

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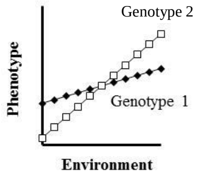
What is GxE?

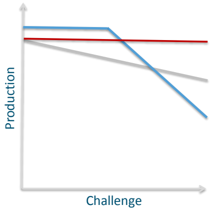


- Scaling and reranking
- Reranking may give loss of selection response due to selection of wrong animals

Mulder and Bijma, 2005. J.Anim. Sci. 83:49-6
Mulder et al. 2006. J. Dairy Sci. 89:1740-1752

GxE as a source of genetic variation in resilience/adaptation/macro-environmental sensitivity

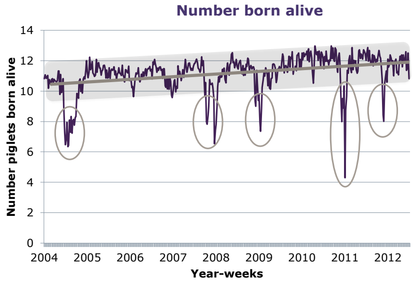
- Resilience = the ability to withstand changes in climate, feed, labor, diseases or health challenges
- Resilient ≠ invariable



Modelling macro-environmental sensitivity

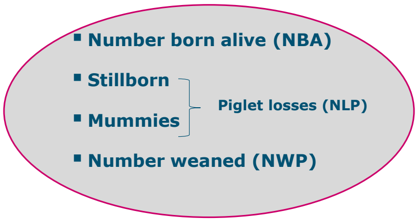
- GxE means genetic variation in slope of reaction norms = genetic variation in environmental sensitivity
- What is needed in reaction norm models?
  - Continuous environmental gradient
    - Temperature or HYS
    - Challenge load indicator for presence of diseases such as PRRS in pigs

Development of challenge load indicator



Rashidi et al. 2014. J. Anim. Sci. 92:95-105

Challenge load indicator (CL)



- **Number born alive (NBA)**
- **Stillborn**
- **Mummies**
- **Number weaned (NWP)**

Piglet losses (NLP)

$$\hat{Y}_i = w_1\, NBA_i + w_2\, NLP_i + w_3\, NWP_i$$

Mathur et al. 2014. J. Anim. Sci. 92:5374-5381.

Datasets

	Development →	**Testing** →	**Validation**
Location	Canada	Netherlands	World wide
Farms	1	15	431
Sows	10,910	65,826	831,855
Records	57,135	263,274	3,197,813
Year	2004-2012	2007-2013	2007-2013

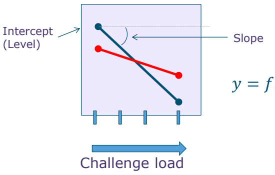
Mathur et al. 2014. J. Anim. Sci. 92:5374-5381.

Measuring challenge load and disease outbreak detection

- Method tested in 15 farms in the Netherlands
- Validated using data from over 430 farms in different regions
- The method works better than single trait
- The method detects:
  - PRRS
  - Other diseases
  - Other challenges

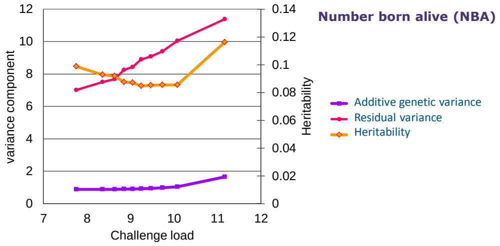
Mathur et al., 2014. J. Anim. Sci. 92:5374-5381.

Continuous environmental challenge
Reaction norm approach

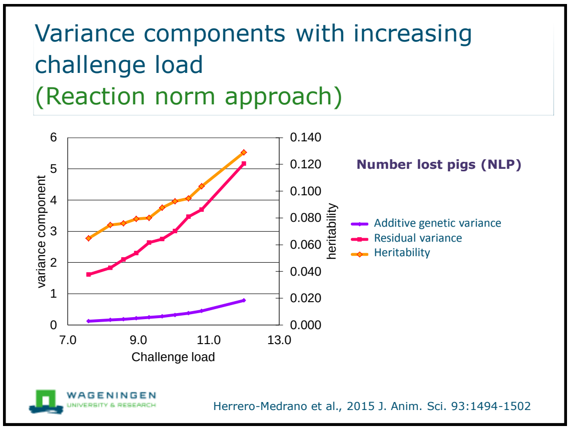


$$y = fixed + a_{int} + a_{sl}cl + ss + pe + e$$

Variance components with increasing challenge load (Reaction norm approach)



Herrero-Medrano et al., 2015. J. Anim. Sci. 93:1494-1502.



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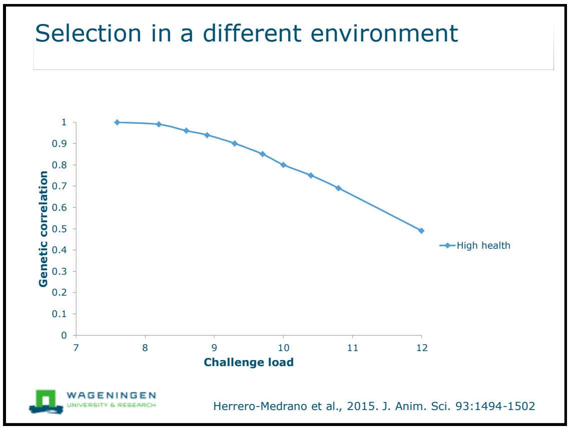
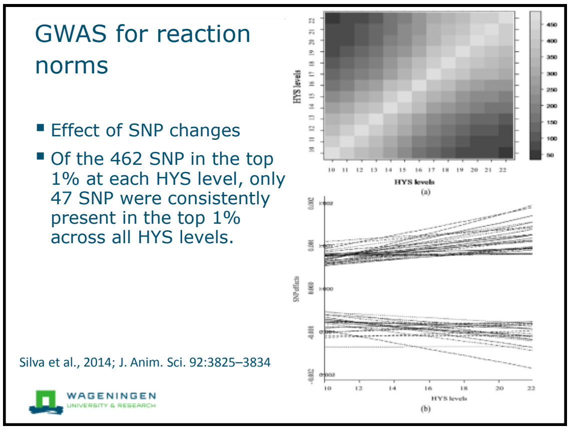


Selection in a different environment

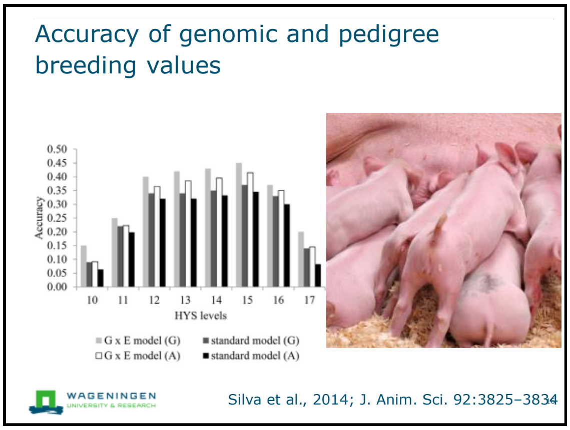
Herrero-Medrano et al., 2015. J. Anim. Sci. 93:1494-1502



GWAS for reaction norms

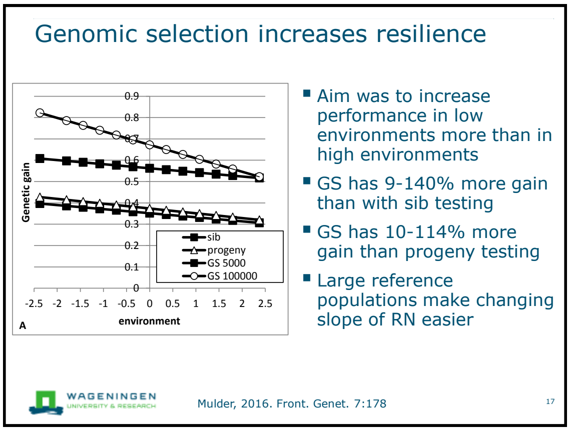
- Effect of SNP changes
- Of the 462 SNP in the top 1% at each HYS level, only 47 SNP were consistently present in the top 1% across all HYS levels.

Silva et al., 2014; J. Anim. Sci. 92:3825–3834



Accuracy of genomic and pedigree breeding values

Silva et al., 2014; J. Anim. Sci. 92:3825–3834



Genomic selection increases resilience

- Aim was to increase performance in low environments more than in high environments
- GS has 9-140% more gain than with sib testing
- GS has 10-114% more gain than progeny testing
- Large reference populations make changing slope of RN easier

Mulder, 2016. Front. Genet. 7:178

Summary

- Quite some GxE between challenged phases and no-challenged phases
- GWAS studies combined with reaction norms can help in unravelling genetic background of GxE
- Genomic selection with large reference populations can improve resilience by exploiting GxE

Quantitative genetics and genomics of micro-environmental sensitivity or uniformity

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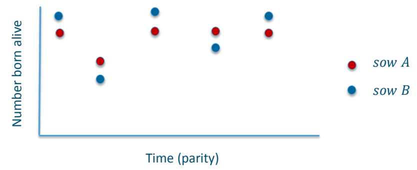
What is genetic variation in micro-environmental sensitivity or uniformity?

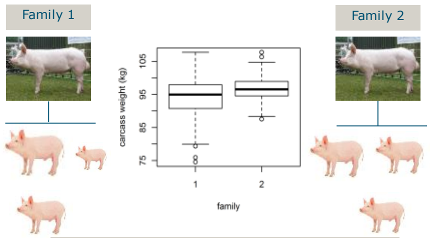
- Genetic variation in the size of the residual/environmental variance
- Observed as:
  - Differences in variances within individual with repeated observations
  - Differences in within-family variance

What is genetic variation in uniformity?

- Variation in repeated observations



What is genetic variation in uniformity?



Difference in within-family variance

Modelling the residual variance: Double hierarchical generalized linear model

- Model on the trait and on the residual variance

$$\begin{bmatrix}\mathbf{y}\\ \mathbf{y_v}\end{bmatrix} = \begin{bmatrix}\mathbf{X} & \mathbf{0}\\ \mathbf{0} & \mathbf{X_v}\end{bmatrix}\begin{bmatrix}\mathbf{b}\\ \mathbf{b_v}\end{bmatrix} + \begin{bmatrix}\mathbf{Z} & \mathbf{0}\\ \mathbf{0} & \mathbf{Z_v}\end{bmatrix}\begin{bmatrix}\mathbf{a}\\ \mathbf{a_v}\end{bmatrix} + \begin{bmatrix}\mathbf{W} & \mathbf{0}\\ \mathbf{0} & \mathbf{W_v}\end{bmatrix}\begin{bmatrix}\mathbf{pe}\\ \mathbf{pe_v}\end{bmatrix} + \begin{bmatrix}\mathbf{e}\\ \mathbf{e_v}\end{bmatrix}$$

- $\mathbf{y_v}$ uses the squared residual of $\mathbf{y}$
- $Ve = \exp(\mathbf{X_v b_v} + \mathbf{Z_v a_v} + \mathbf{W_v pe_v})$

- **Use genomic relationship matrix or H matrix is feasible**

Rönnegård et al., 2010. GSE 42:8
Felleki et al., 2012. Genet. Res. 94:307-317.

Genetic variance in uniformity in pigs

Line	Trait	varav	GCV ve	h2v
Large White	Piglet birth weight	0.04	0.19	0.01
Landrace	Piglet birth weight	0.04	0.21	0.01
Pietrain	Carcass weight	0.05	0.22	0.01
Large White	Total number born	0.03	0.17	0.01

Sell-Kubiak et al. 2015. J. Anim Sci. 93:900-911
Sell-Kubiak et al. 2015. J. Anim. Sci. 93:1471-1480
Sell-Kubiak et al. 2015. BMC Genomics 16:1049

Genetic variance in uniformity dairy cattle

Trait	varav	GCV ve	h2v
milk NL	0.03	0.19	<0.01
milk Sweden	0.05	0.22	0.01
SCS Sweden	0.05	0.21	0.01
SCS Robustmilk farms	0.08	0.28	0.01
milk Belgium	0.03	0.17	<0.01
SCS Belgium	0.03	0.16	<0.01
SFA Belgium	0.01	0.12	<0.01
UFA Belgium	0.02	0.12	<0.01
C18:1 cis-9 Belgium	0.02	0.12	<0.01

Mulder et al. 2013. J. Dairy Sci. 96:7306-7317.
Mulder et al. 2013. GSE 45:23.
Vandenplas et al., 2013. J. Dairy Sci. 96:5977-5990.

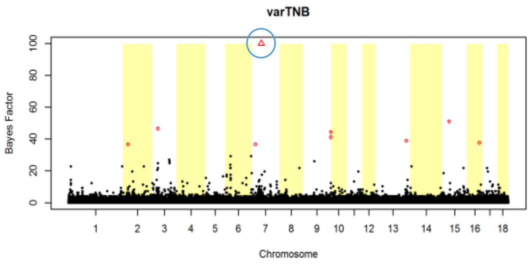
Genetic variance in uniformity laying hens

Trait	varav	GCV ve	h2v
Egg color purebreds	0.08	0.28	0.01
Egg color crossbreds	0.07	0.26	0.01

- Across species:
  - Heritability at individual record level is low, BUT heritability at litter level/repeated observations ~ 0.10
  - GCV high

Mulder et al. 2016. GSE 48:39

Genome-wide associations for uniformity litter size



Sell-Kubiak et al. 2015. BMC Genomics 16:1049

Genome-wide associations for uniformity litter size

SSC	Most sign. SNP	Position (Mbp)	BF	Gen. var. expl. by SNP (%)
7	INRA0025193	43.76	167.2	0.50
7	ASGA0031511	17.47	36.6	0.06

Uniformity of litter size seems rather polygenic

Sell-Kubiak et al., 2015. BMC Genomics 16:1049

Candidate genes uniformity litter size

- Chromosome 7:
  - Cul7: expressed in embryonic, placental, and uterus tissues
  - HSPCB: buffering under stress
  - VEGFA: angiogenesis and vasculogenesis in the fetus
- Genome-wide associations for uniformity can help in unraveling genetic architecture of response to environmental disturbances

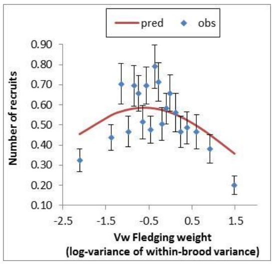
Sell-Kubiak et al. 2015. BMC Genomics 16:1049

Optimum level of residual variance?

Should we breed for no environmental variance?
Are there any trade-offs?

Relationships between Ve and fitness might be curvilinear

- Optimum variance



Mulder et al. 2016; Evolution 70:2004-2016

Summary

- Heritability of micro-environmental sensitivity/uniformity is low but GCV is high
- GWAS reveals new loci associated with total number born in pigs
- Relationship uniformity and fitness might be curvilinear

Conclusion

- Substantial genetic variation in macro- and micro-environmental sensitivity
- Genetic variation in macro- and micro-environmental sensitivity can be exploited to breed more resilient animals
- Relationships with fitness traits are important to know
- Genomics can help in unravelling genotype by environment interactions and increase biological knowledge

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