Selected studies at UGA

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Wageningen University, Netherlands, September 18, 2024

Topics to finish

- Artifacts of GWAS and impact on analyzes with sequence data
- Potential negative effects of genomic selection
- Estimation of parameters with complete commercial data
- Does selection for heat stress make sense
  - Does selection for robustness make sense?
  - Is selection for resilience possible?

- Alternative model for social effects
- Estimation of number of effective number of chromosome segments from small data sets

Questions with GWAS and predictions in animal datasets

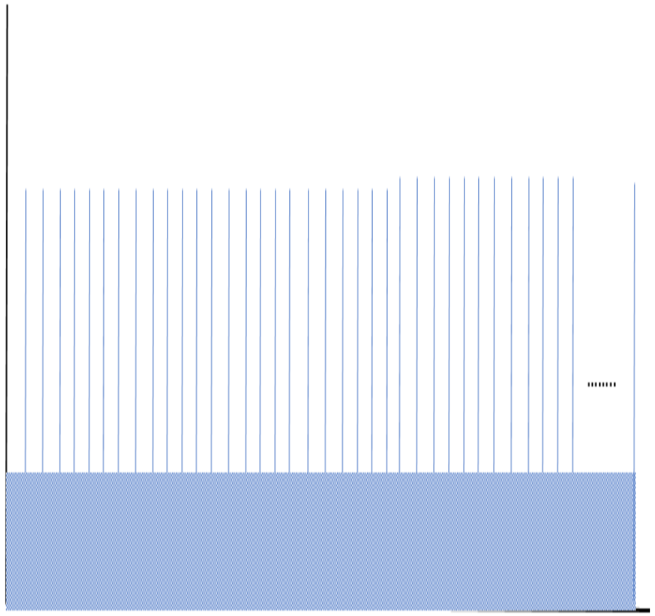
- GWAS by
  - p-values
  - % of variance explained usually per 1Mb, why 1 Mb?

- Lots of QTLs “detected” with small data sets
- Little gain of accuracy with sequence data

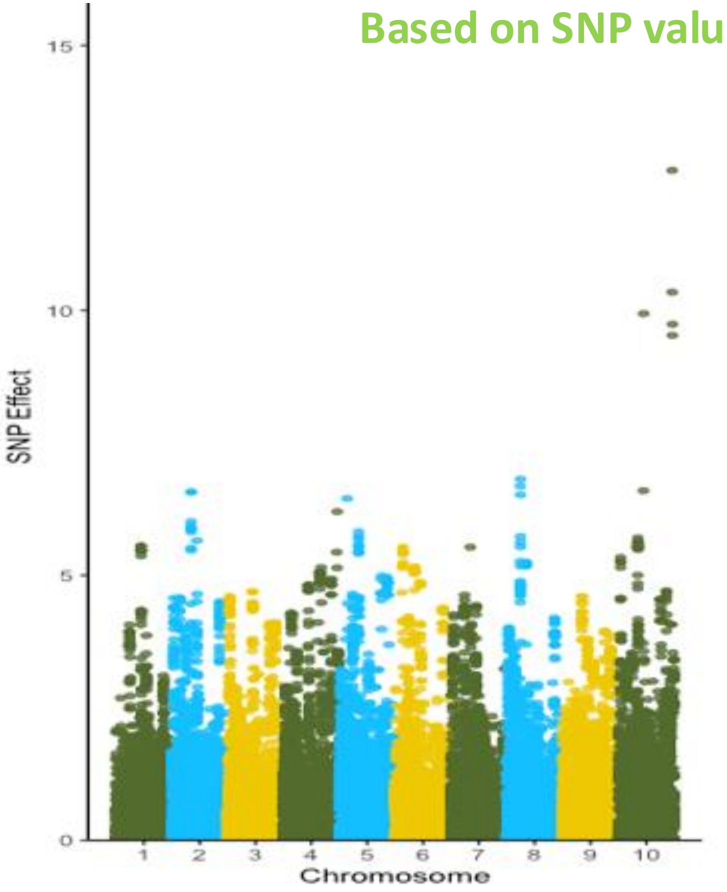
Why?

Manhattan plots for simulated population with 100 identical equidistant QTNs

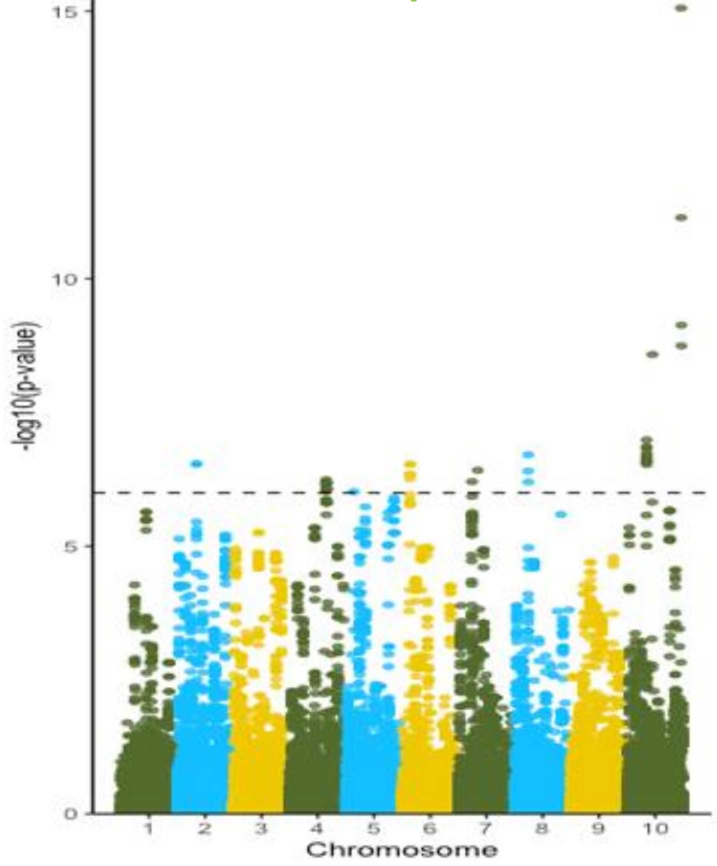
Expectation



Based on SNP values

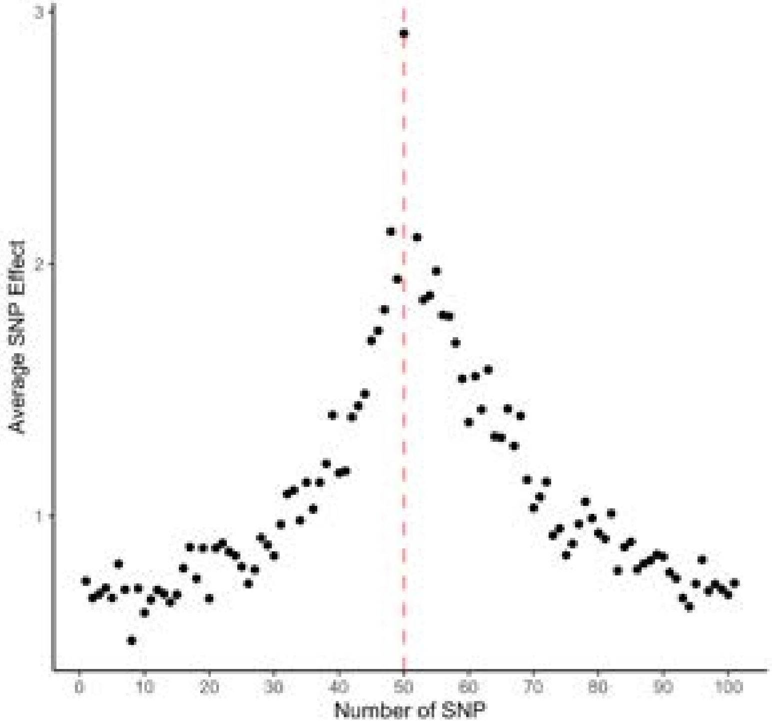


Based on p-values



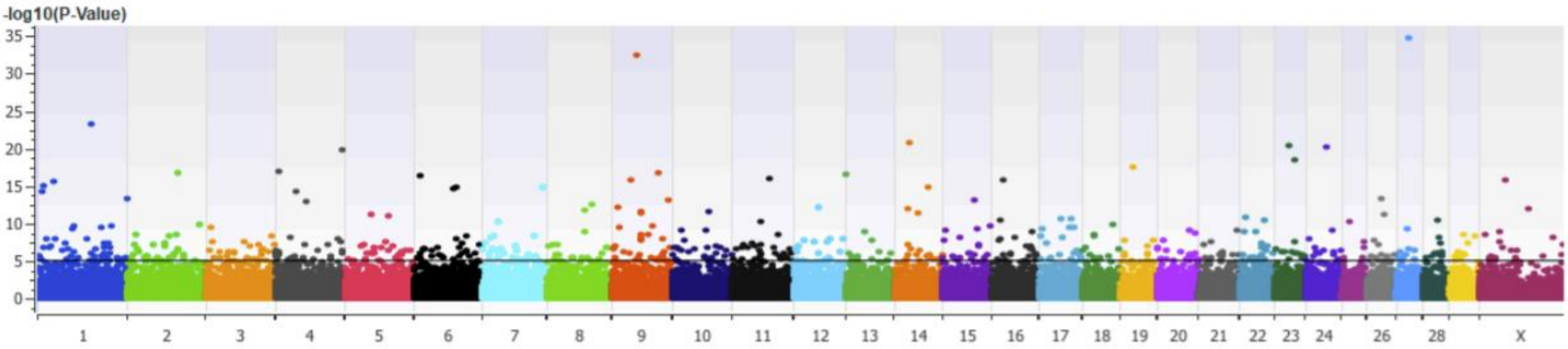
Work started by Pocrnic et al. (2018)

Plots averaged for 100 QTN



Paper submitted to Genetics in 2018 rejected

First conception rate on 2k Holstein heifers

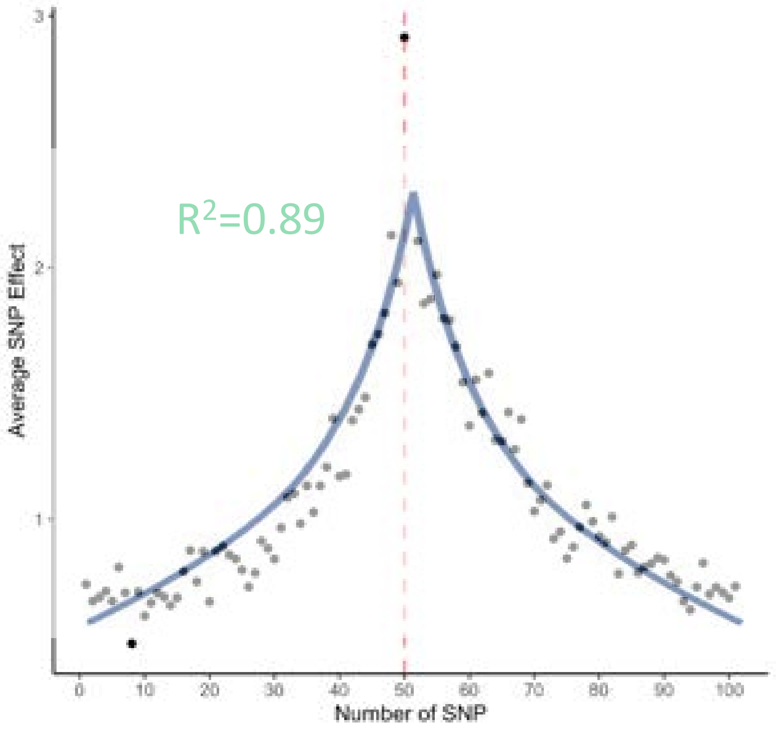


Estimated heritability 36% (normally 1%)

Identified 146 unique loci at $p < 5 \times 10^{-8}$ level

Galliou et al., 2020, https://doi.org/10.3390/genes11070767

Plots averaged for 100 QTN



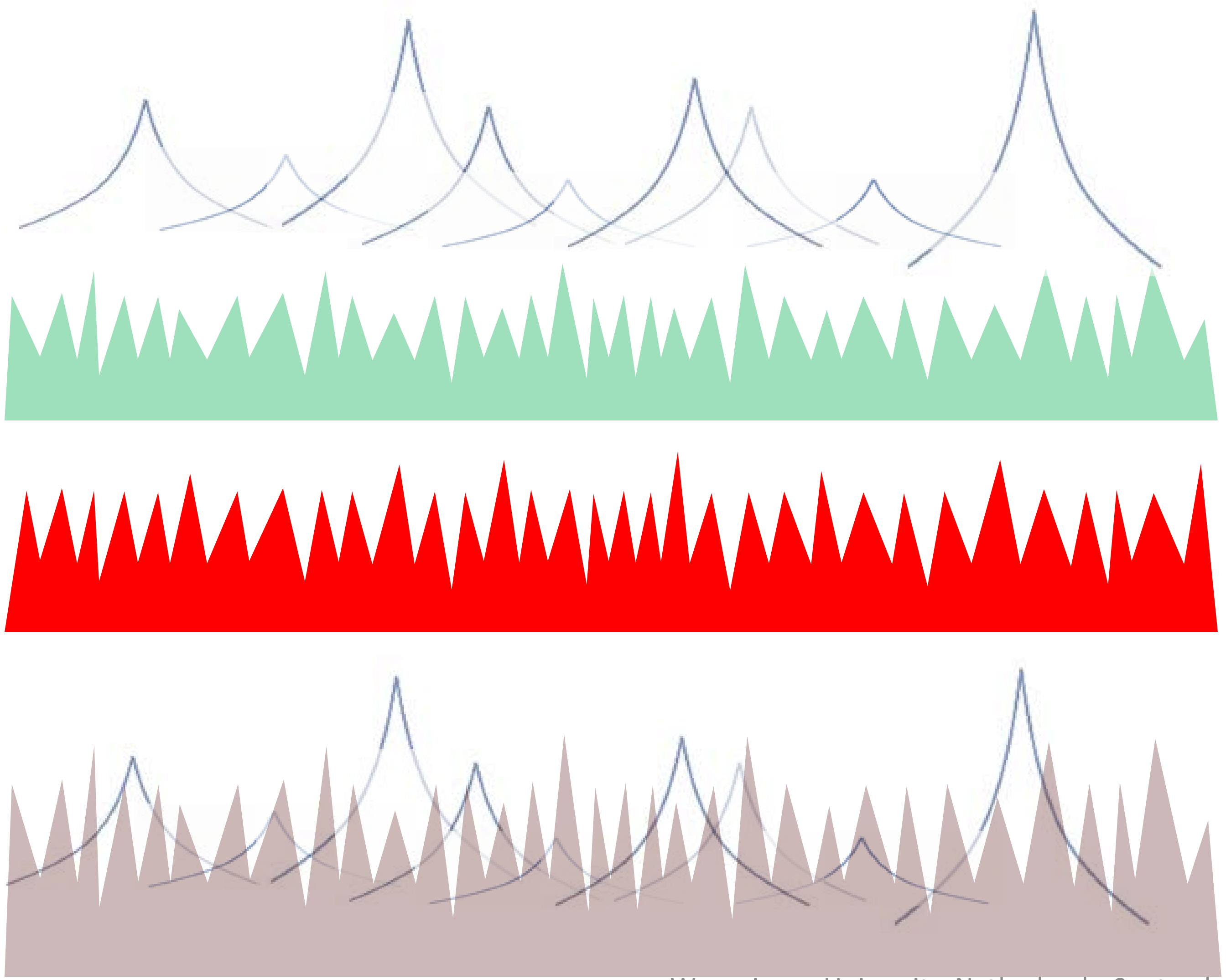
Pairwise linkage disequilibrium curve

~ 2 Mb for cattle
~ 5 Mb for pigs/chickens

~ 15 kb for humans

1/Ne Morgans for 80% QTN variance
Ne - effective population size

What is Manhattan plot composed of?



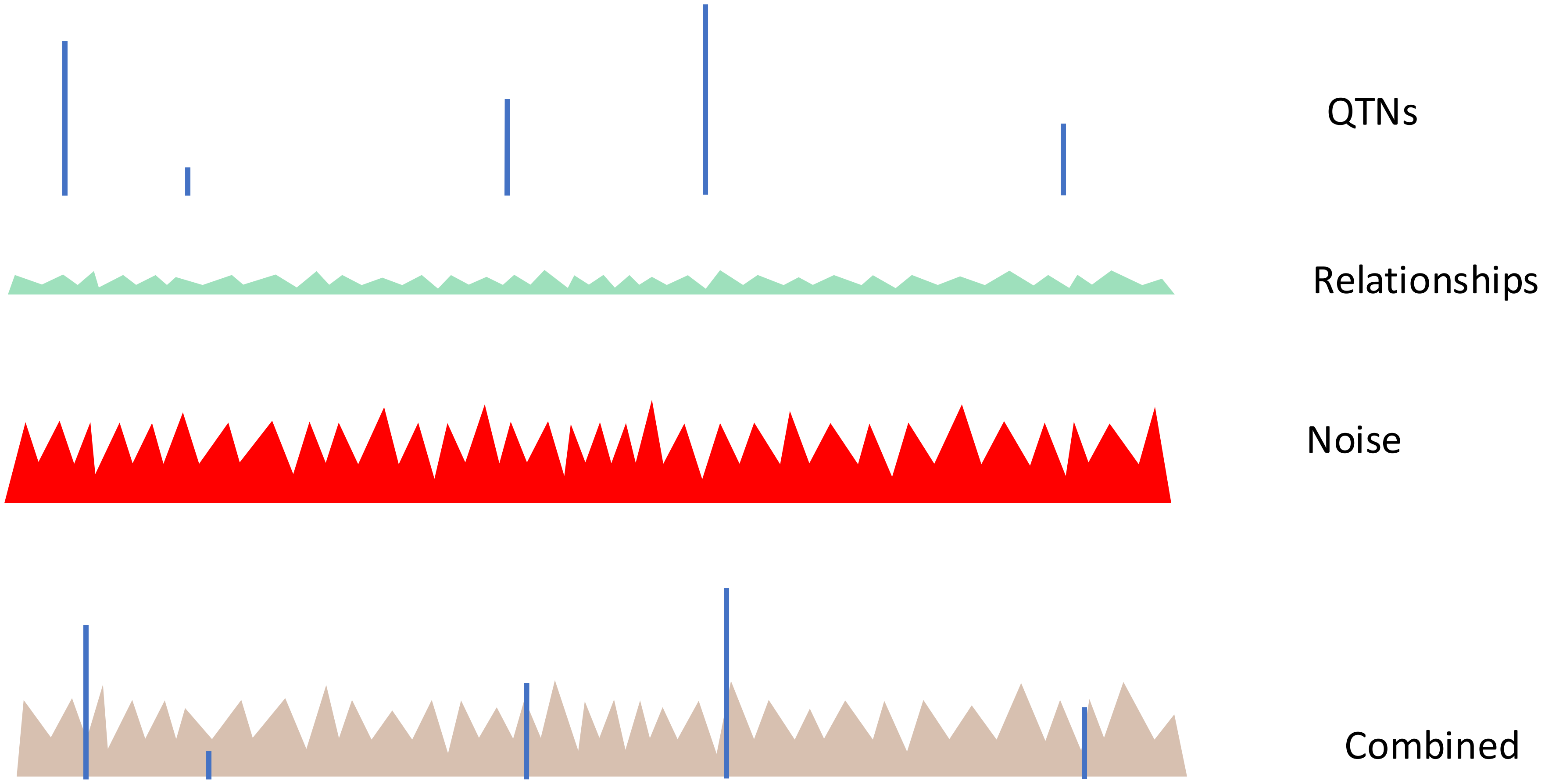
QTNs **Bigger with larger QTN and larger data**

Relationships

Noise **Smaller with more data**

Combined

Large effective population size



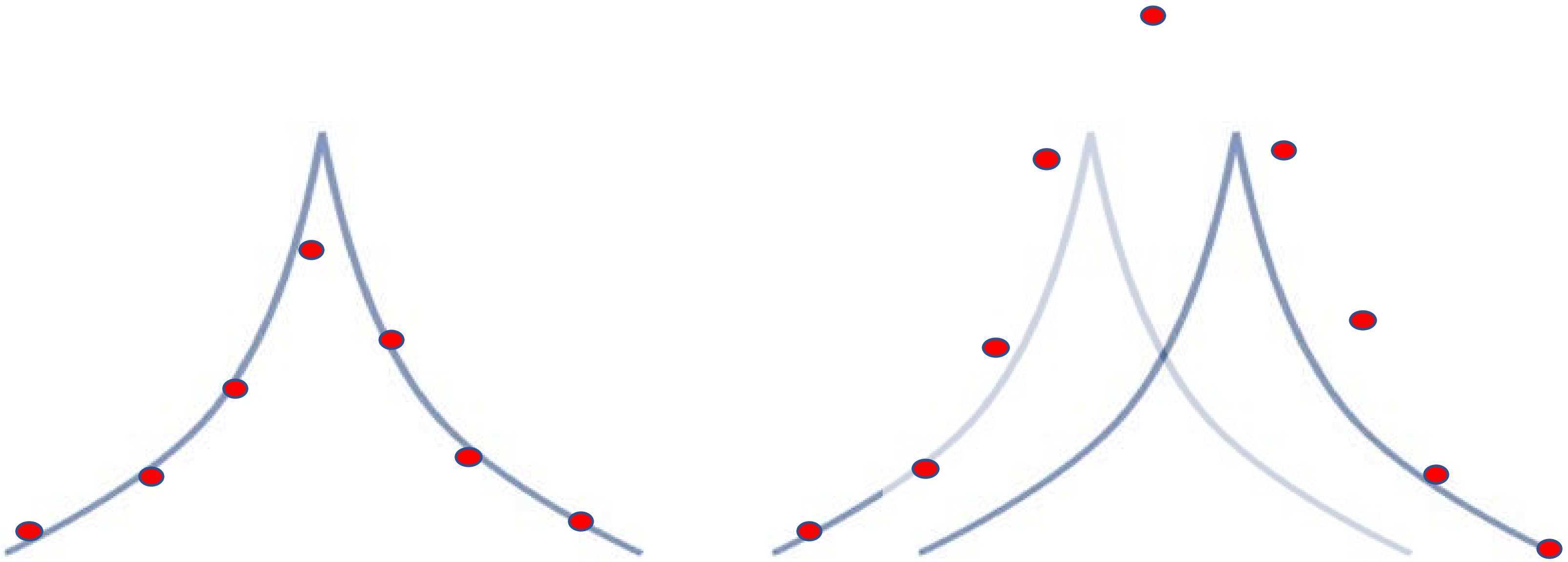
QTNs

Relationships

Noise

Combined

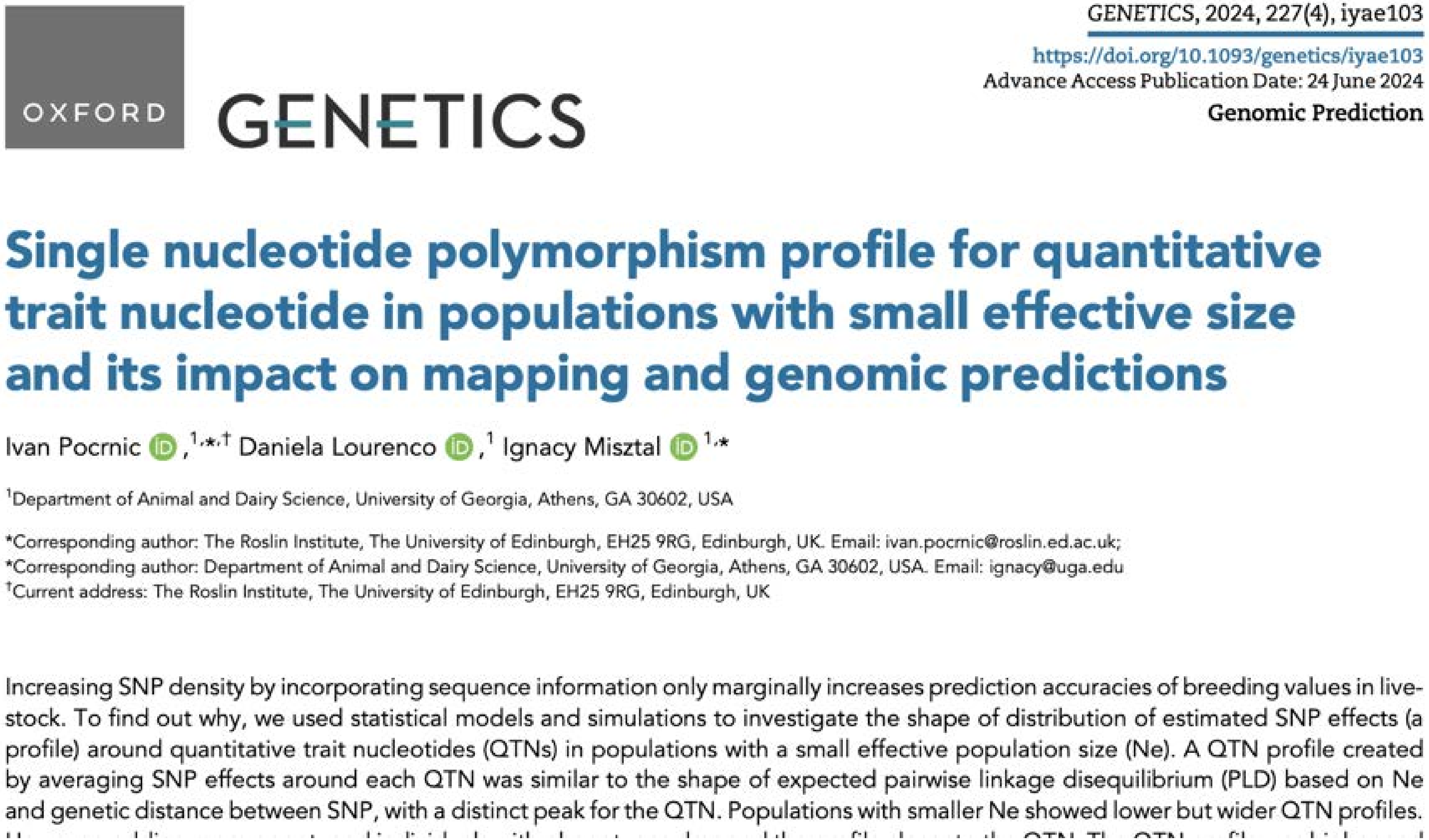
Why GBLUP accounts for QTN?



If 4 SNP per segment, 32 SNP account for 80% of QTN variance

Need chip with 16 NeL SNP to mostly account for QTN

About 20k for pigs/broilers, 60k for cattle, 5m for humans



OXFORD GENETICS

GENETICS, 2024, 227(4), iyae103
https://doi.org/10.1093/genetics/iyae103
Advance Access Publication Date: 24 June 2024
Genomic Prediction

Single nucleotide polymorphism profile for quantitative trait nucleotide in populations with small effective size and its impact on mapping and genomic predictions

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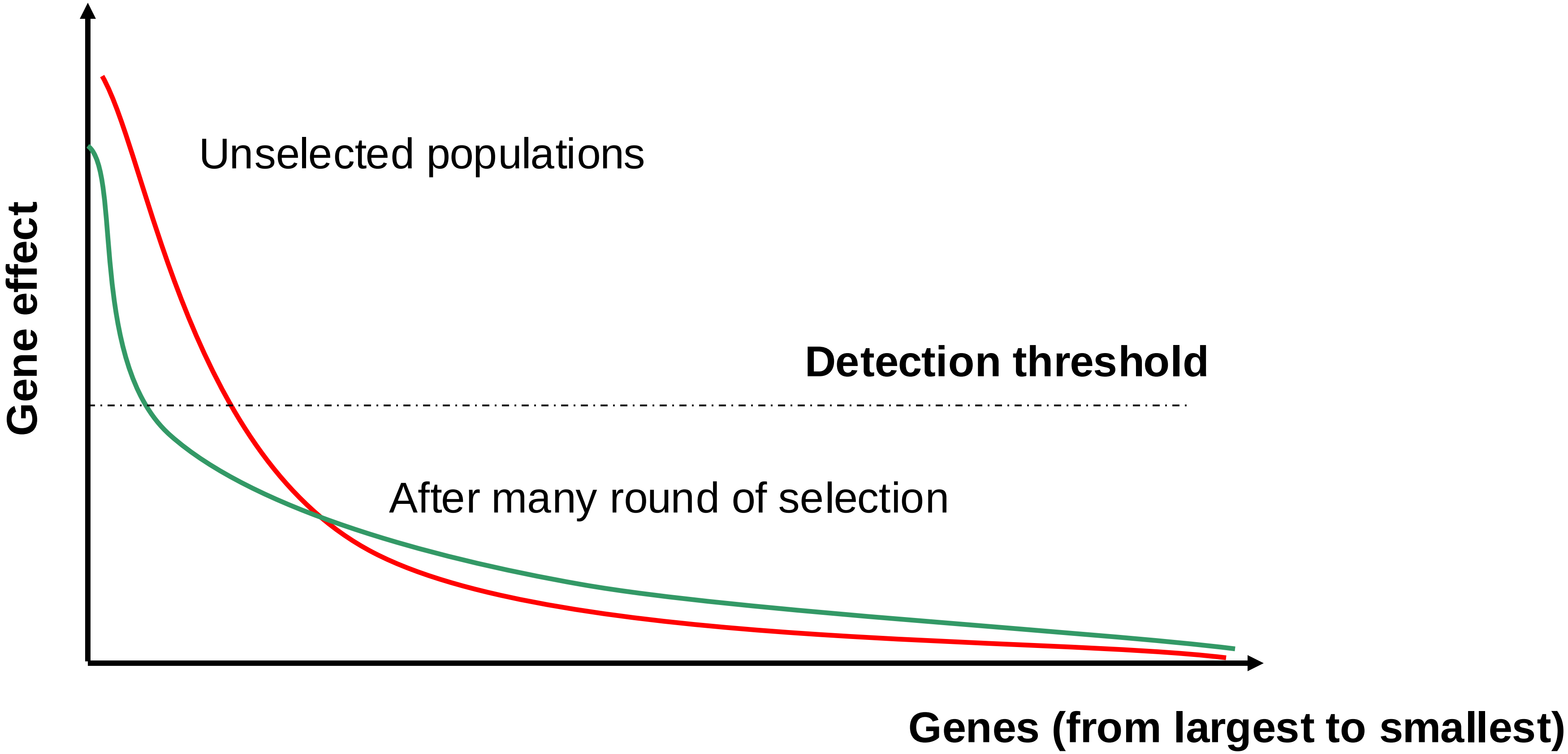
Increasing SNP density by incorporating sequence information only marginally increases prediction accuracies of breeding values in livestock. To find out why, we used statistical models and simulations to investigate the shape of distribution of estimated SNP effects (a profile) around quantitative trait nucleotides (QTNs) in populations with a small effective population size (Ne). A QTN profile created by averaging SNP effects around each QTN was similar to the shape of expected pairwise linkage disequilibrium (PLD) based on Ne and genetic distance between SNP, with a distinct peak for the QTN. Populations with smaller Ne showed lower but wider QTN profiles.

Distribution of QTL effects

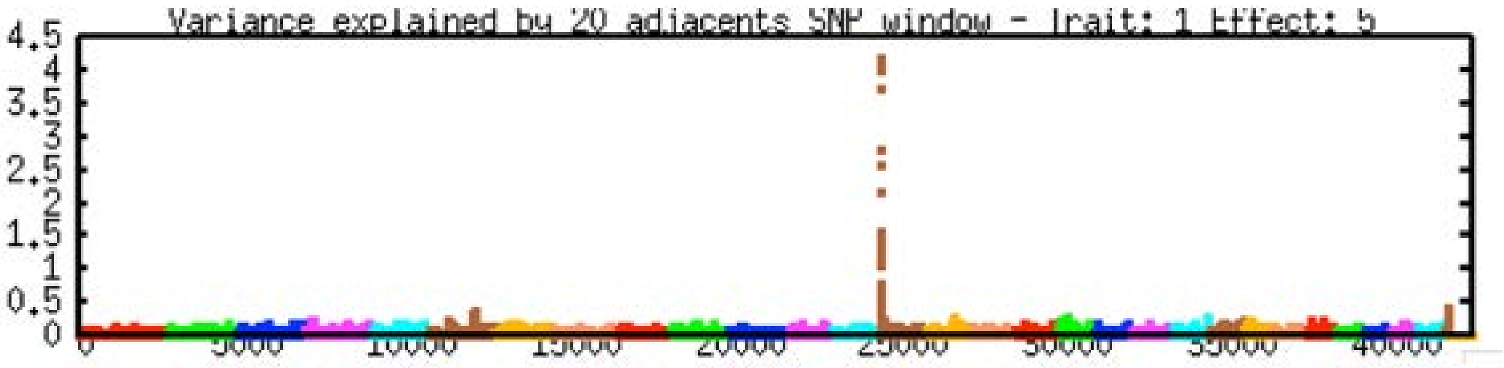


Can large QTL exist despite selection?

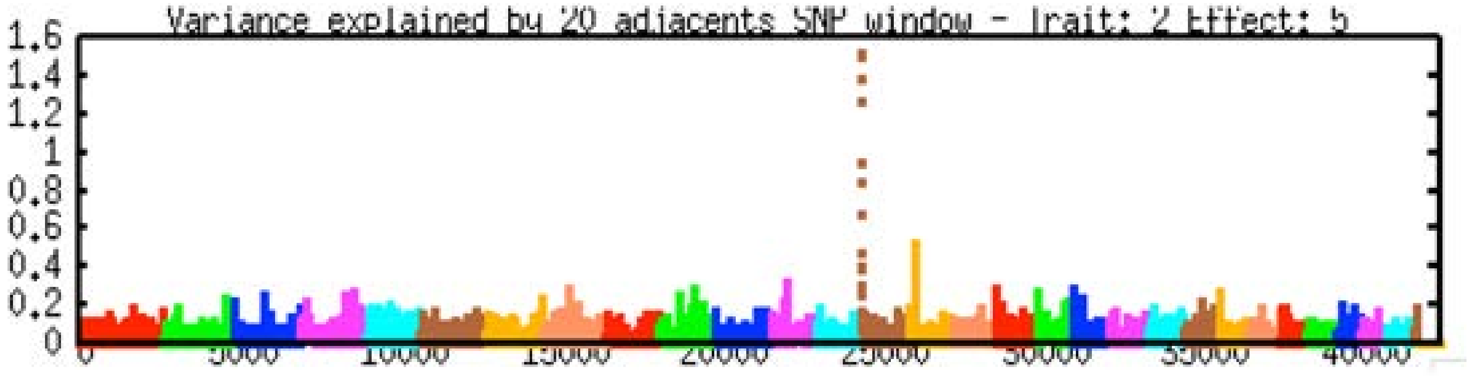
- Genetics and genomics of mortality in US Holsteins
- (Tokuhisa et al, 2014; Tsuruta et al., 2014)

- 6M records, SNP50k genotypes of 35k bulls

Milk – first parity

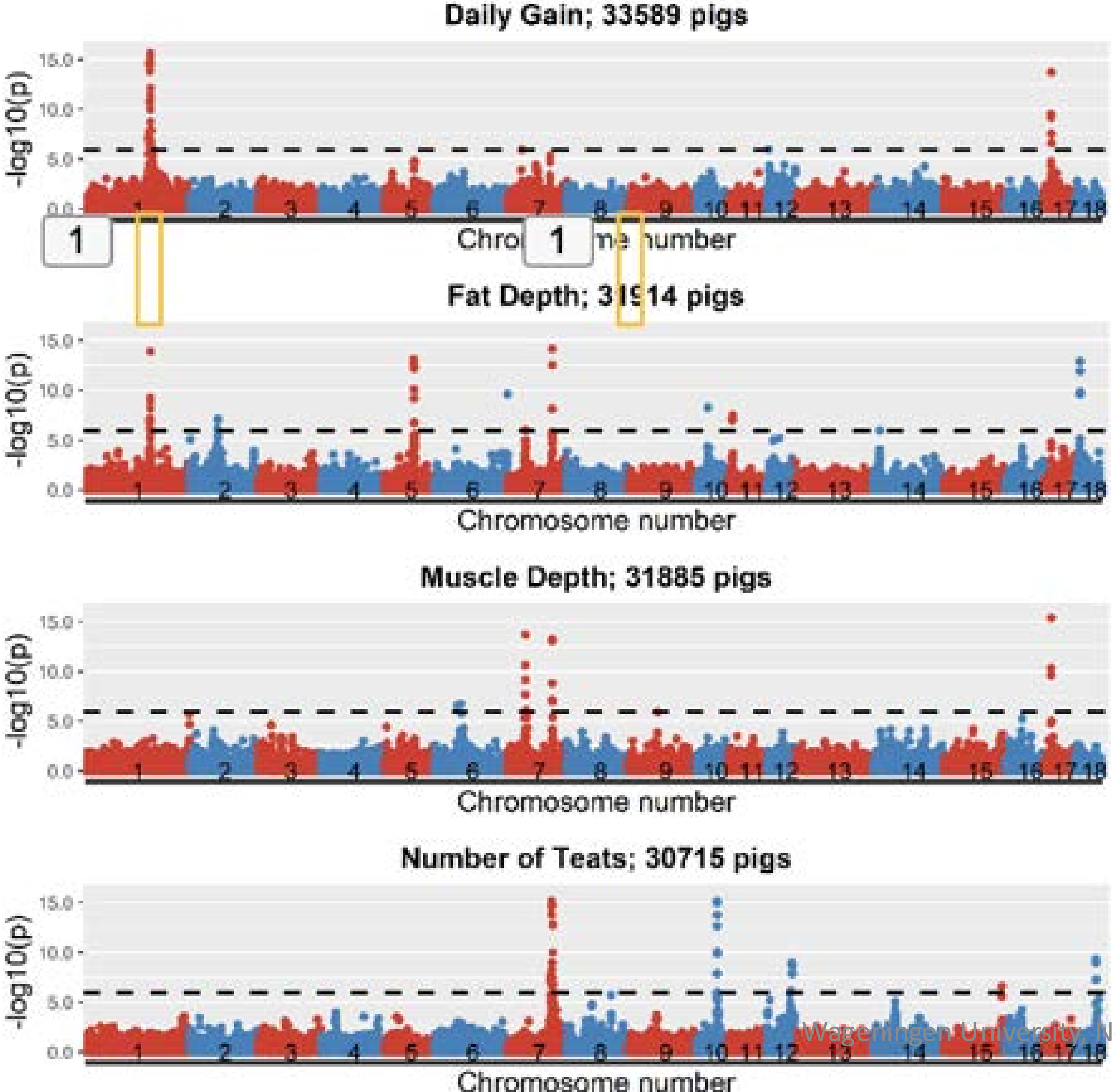


Mortality – first parity



GWAS for various traits and index in pigs

Bijma, EAAP 23



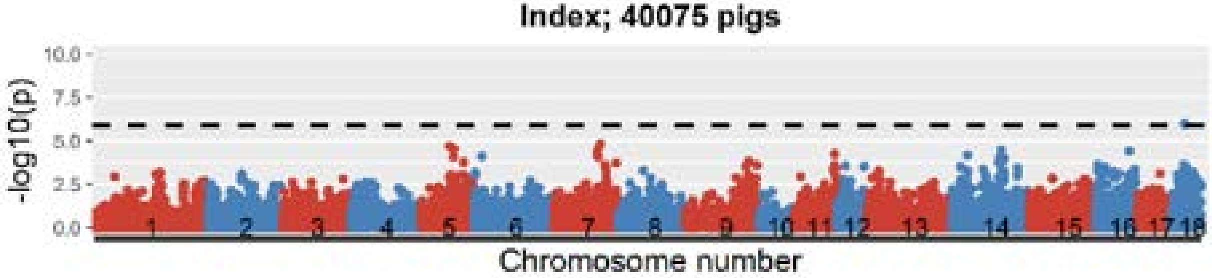
Daily Gain; 33589 pigs

Fat Depth; 31914 pigs

Muscle Depth; 31885 pigs

Number of Teats; 30715 pigs

Index



Index; 40075 pigs

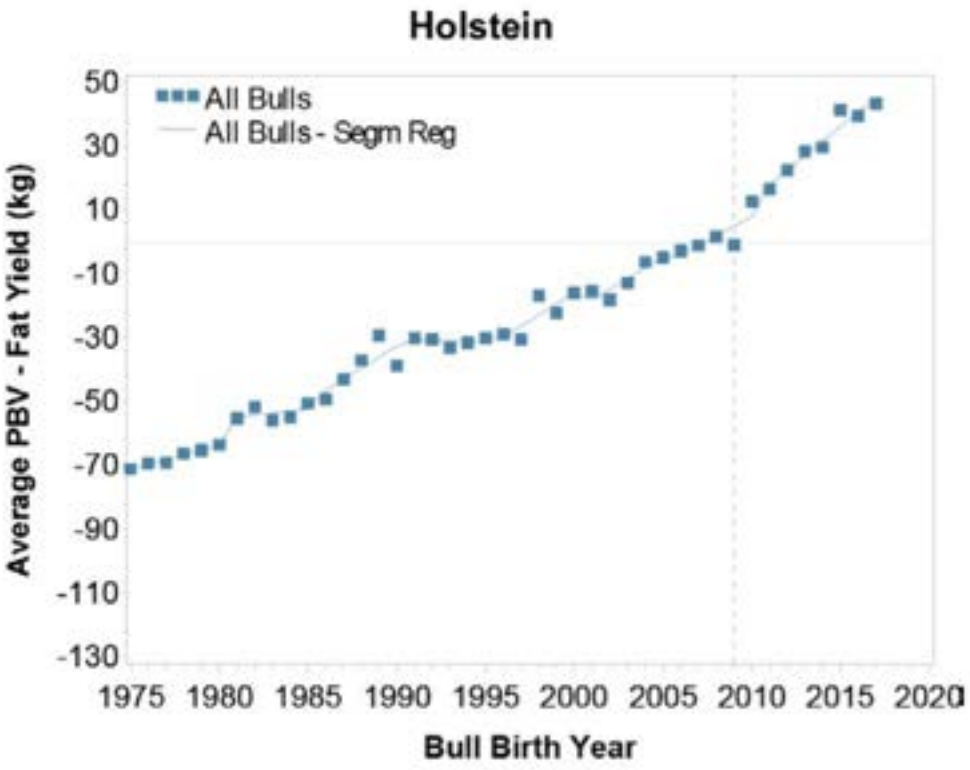
- Different peaks in different lines
- Antagonistic pleiotropy

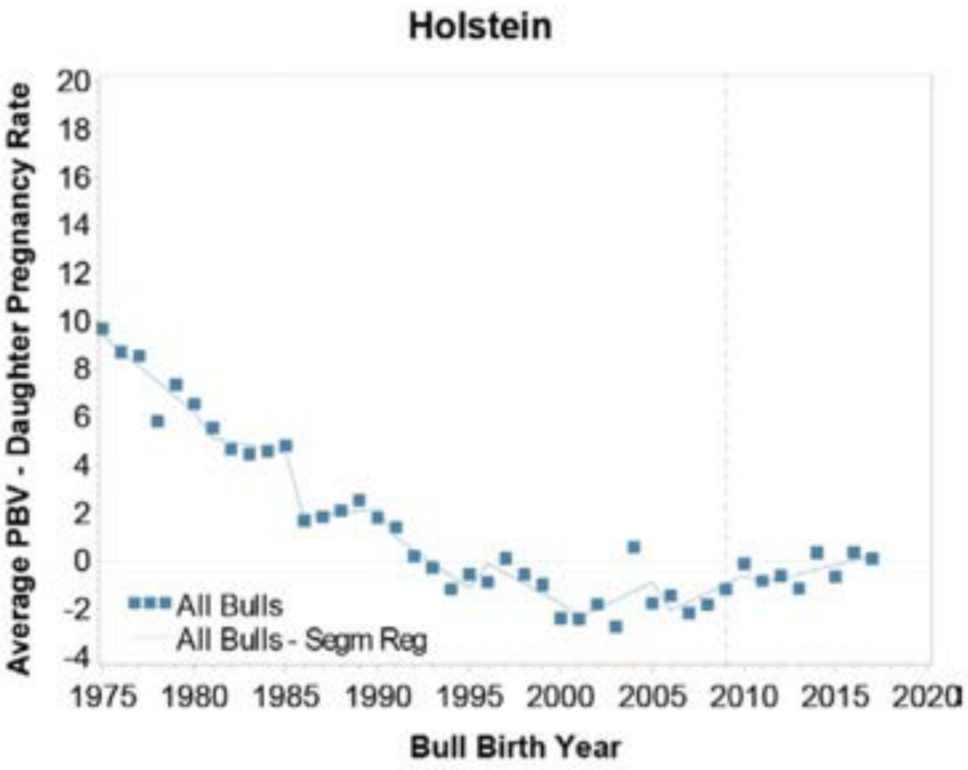
Conclusions

- GWAS affected by effective population size
- Optimal window size for GWAS 1-2 Mb for Ne=100
- Large signals in GWAS due to QTN, relationships and noise (incl. imputation)
- Large QTL in farm populations show pleiotropy – QTL not visible in index

Potential negative effects of genomic selection

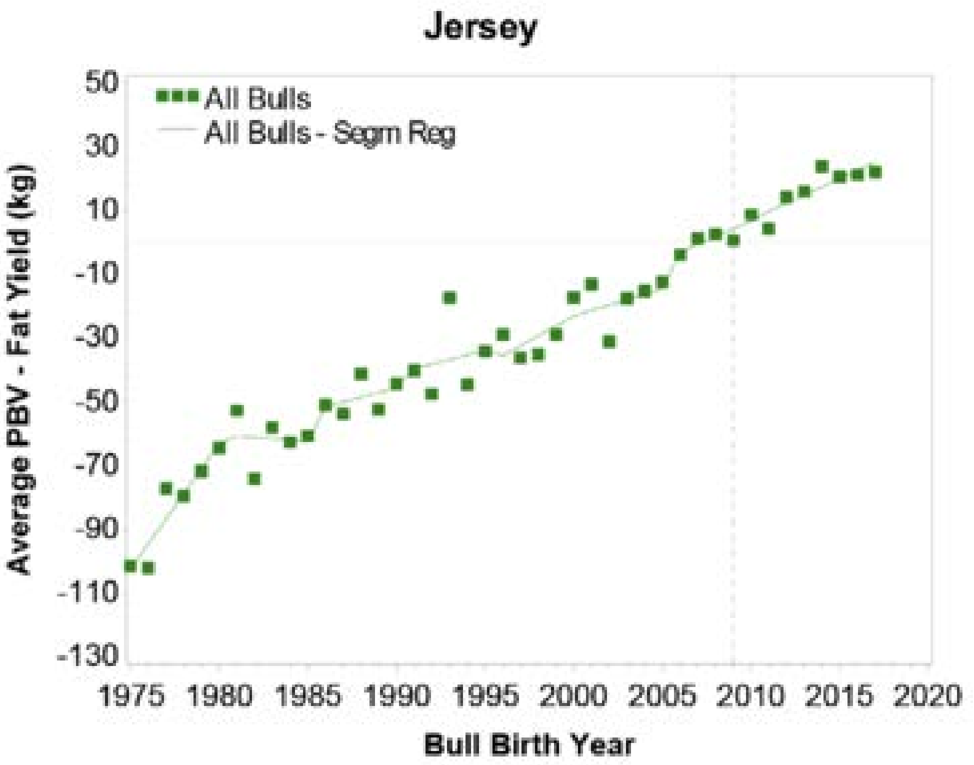
Trends for bulls for fat and fertility - Holsteins

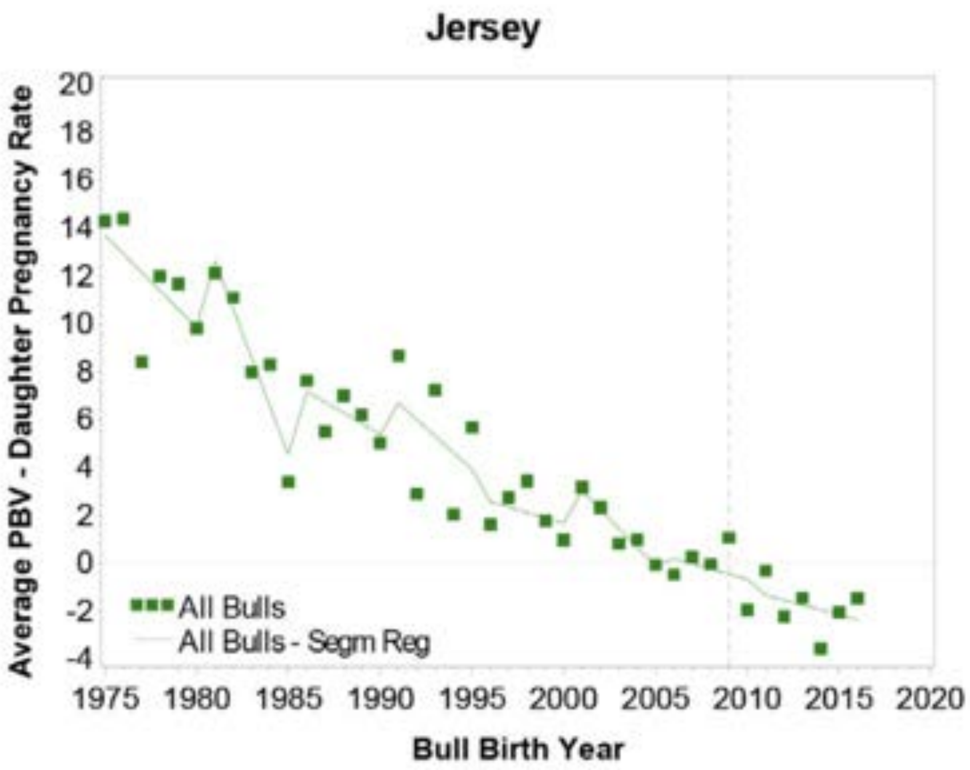




Guinan et al., 2023

Trends for bulls for fat and fertility - Jerseys





Guinan et al., 2023

Recent informal reports

- Deteriorating sow survival and pig mortality in pigs
- Deteriorating feet & legs in beef
- Short teats and increased calf mortality in dairy
- Increased sensitivity to heat stress in dairy
- Deteriorating disease resistance across species

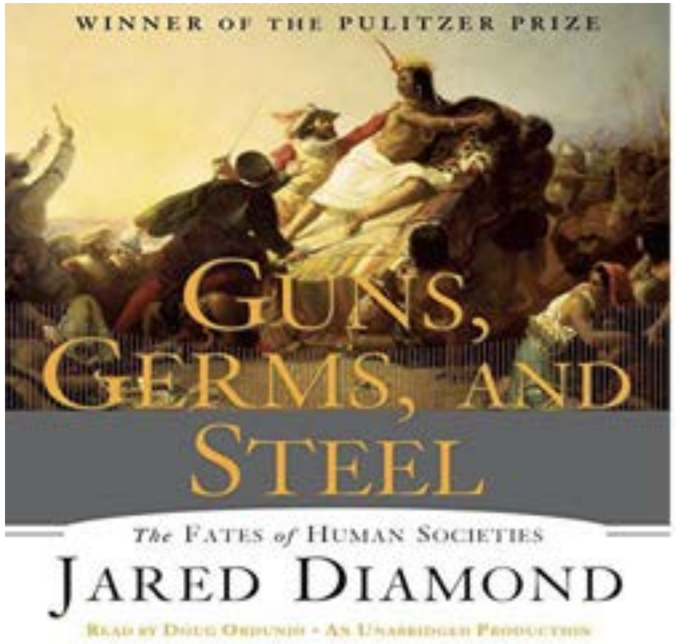
Genetic selection as optimization

- Selection for one trait or an index
- Gains on selected traits
- Losses on correlated antagonistic traits

- Losses compensated by improved environment/management

History of selection strategies

- Domestication
- Unformal
- Large-scale single-trait for production traits
- Multi-trait with fitness traits
- Genomic




Livestock Production Science

Volume 93, Issue 1, 1 April 2005, Pages 3-14

Go to Livestock Production Science on ScienceDirect

Genetics of adaptation and domestication in livestock ☆

Sandrine Mignon-Grasteau [a], Alain Boissy [b], Jacques Bouix [c], Jean-Michel Faure [a], Andrew D. Fisher [d], Geoffrey N. Hinch [e], Per Jensen [f], Pierre Le Neindre [b], Pierre Mormède [g], Patrick Prunet [h], Marc Vandeputte [i], Catherine Beaumont [a]

Domestication

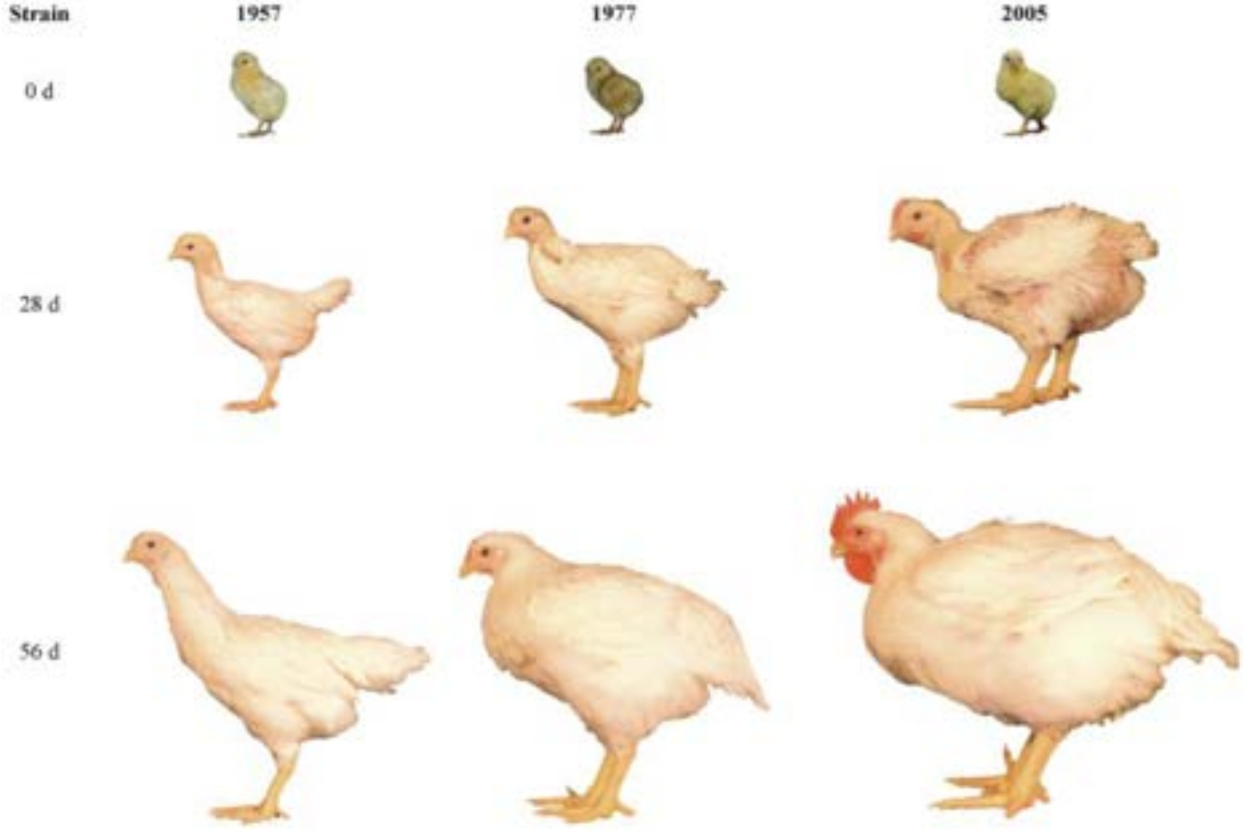
Winners

Growth
Milk
Mating procedures

Losers

Food finding
Seasonal reproduction
Predator avoidance
Brain size
…

Example of effects of mostly single-trait selection



1957 1977 2005

0 d

4 week

8 week

Zuidhof et al. (2014) http://dx.doi.org/10.3382/ps.2014-04291

Side effects of intensive selection for growth in broiler chicken

- Unlimited appetite / obesity ➔ artificial lightning
- Poor survival of males ➔ male supplementation
- Increased susceptibility to diseases ➔ antibiotics
- Low hatchability ➔ alternate heating/cooling of incubators
- …

All companies – similar problems at same time

Initially problems kept confidential

Eitan and Soller, 2014

Undesirable side effects of selection for high production efficiency in farm animals: a review

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[b] Animal Breeding and Genetics Group, Wageningen Institute of Animal Science, Wageningen Agricultural University, P.O. Box 338, 6700 AH Wageningen, The Netherlands
[c] Department of Herd Health and Reproduction and Interdepartmental Section Veterinary Medicine and Society, University of Utrecht, P.O. Box 80151, 3508 TD Utrecht, The Netherlands

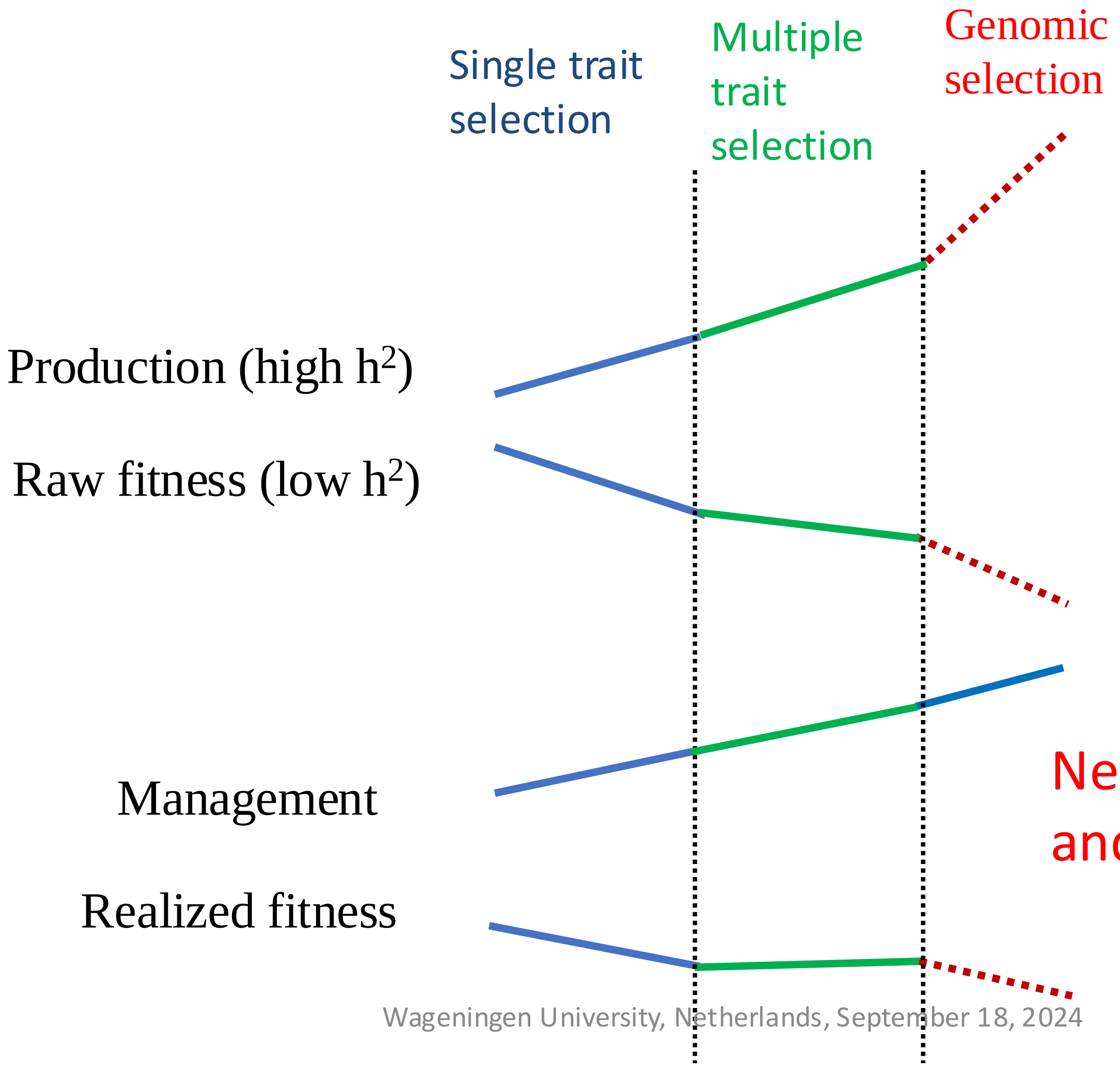
Received 4 July 1997; accepted 29 April 1998

…over 100 references on undesirable(cor)related effects of selection … in broilers, pigs and dairy cattle….

Future application … DNA-techniques .. ….more dramatic consequences….

Selection for more than production traits alone may prevent such.

Hypothetical trend changes in 3 stages of genetic selection



Single trait selection

Multiple trait selection

Genomic selection

Production (high h^2)

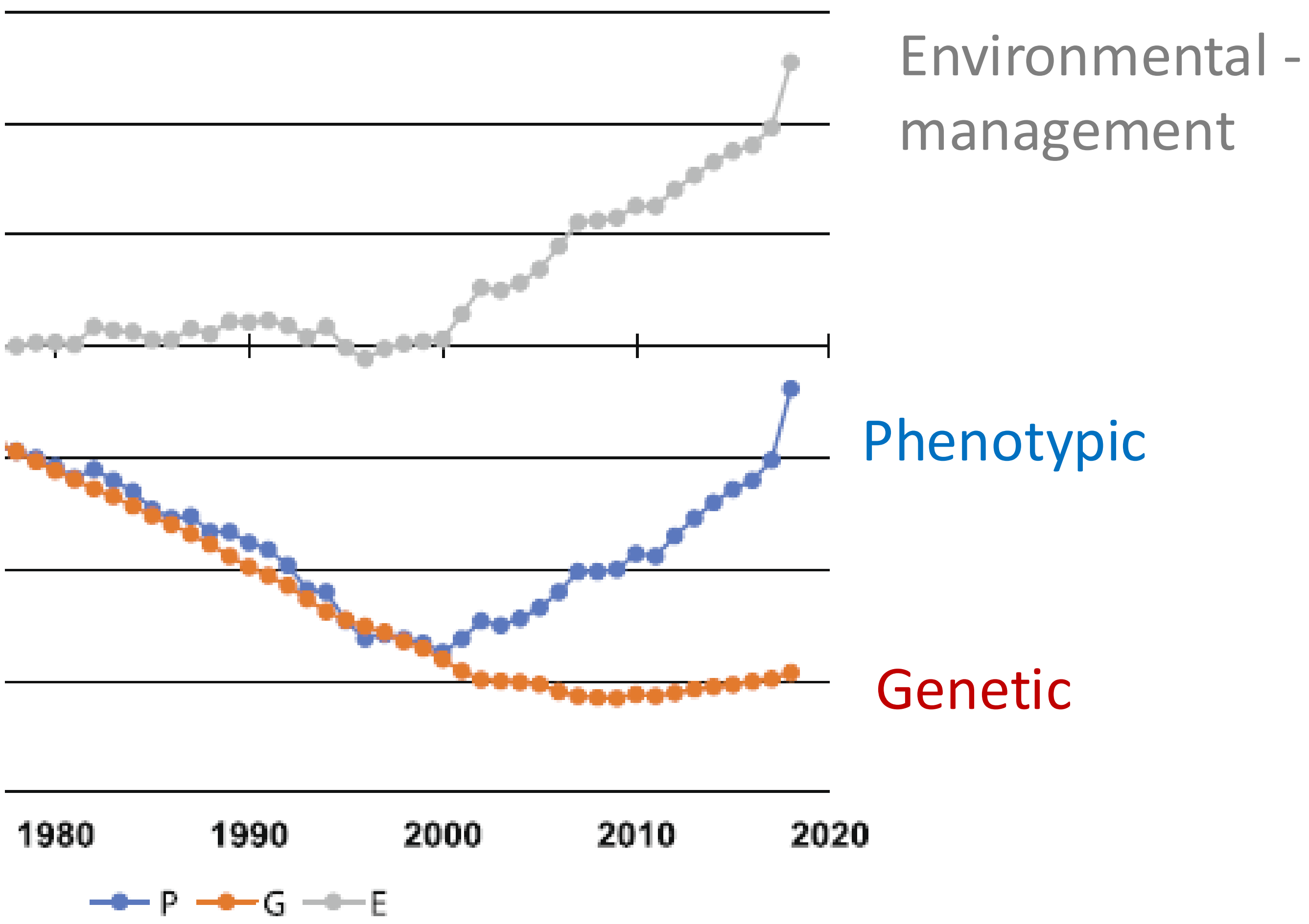
Raw fitness (low h^2)

Management

Realized fitness

Negative changes accelerate
and management cannot catch up!

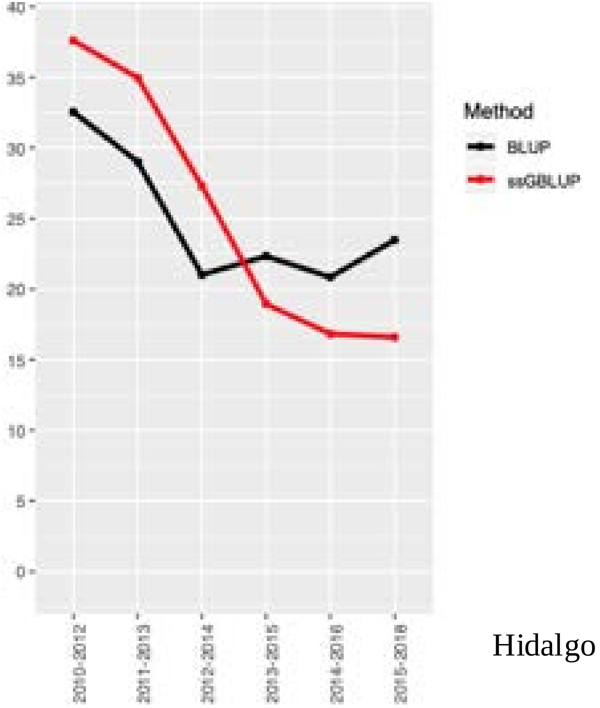
Trends for daughter pregnancy rate



Brito et al., 2021

Changes in (co)variances in pigs due to genomic selection

Heritability for growth



Hidalgo et al. (2019)

Genetic correlation with reproduction

Hidalgo et al., 2023

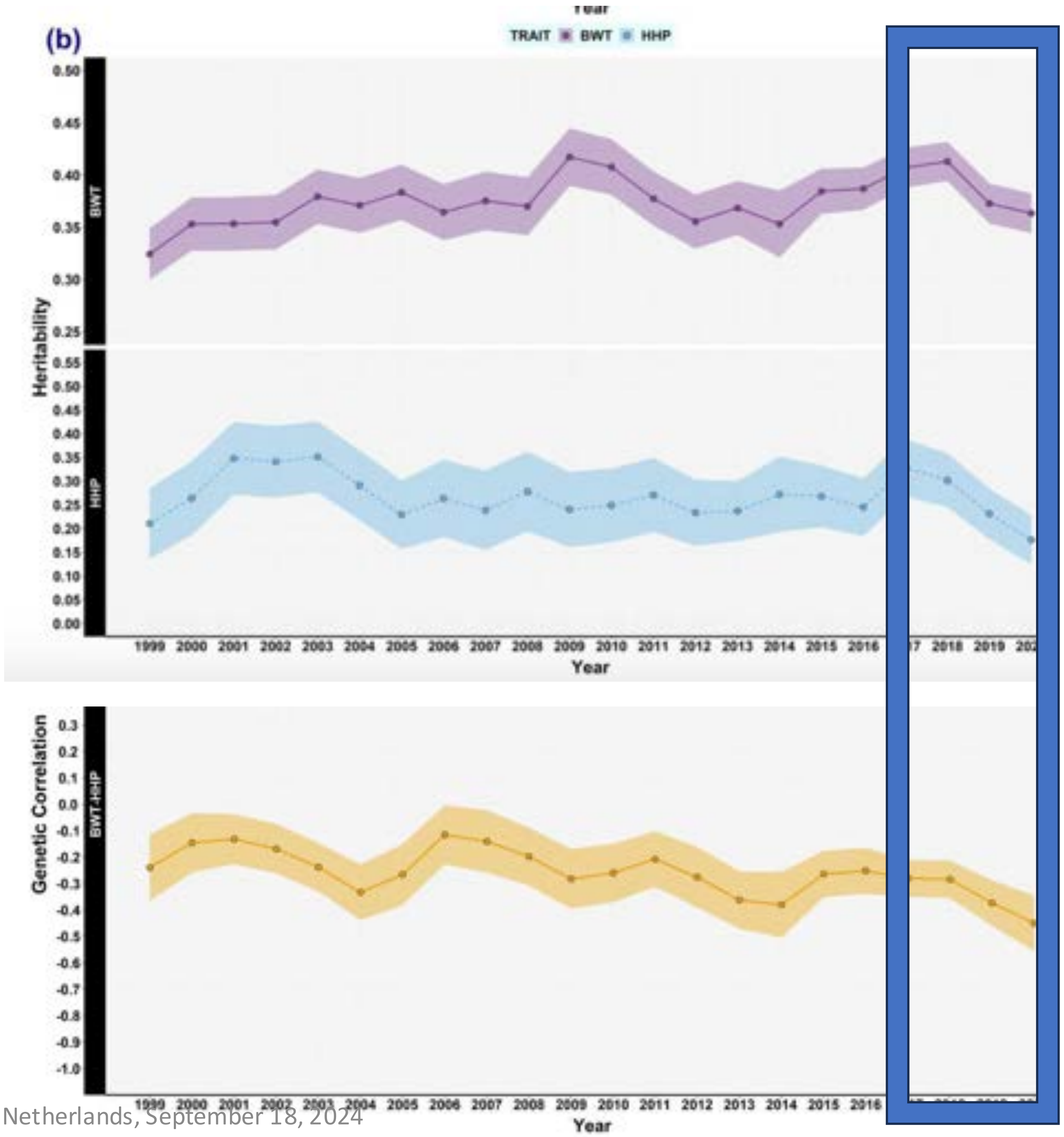
Heritability halved, antagonistic correlations -0.3 → -0.5

Parameters for body weight and egg production (Sosa-Madrid, 2023)

2M body weights
45k eggs counts

3 year windows
No genomics

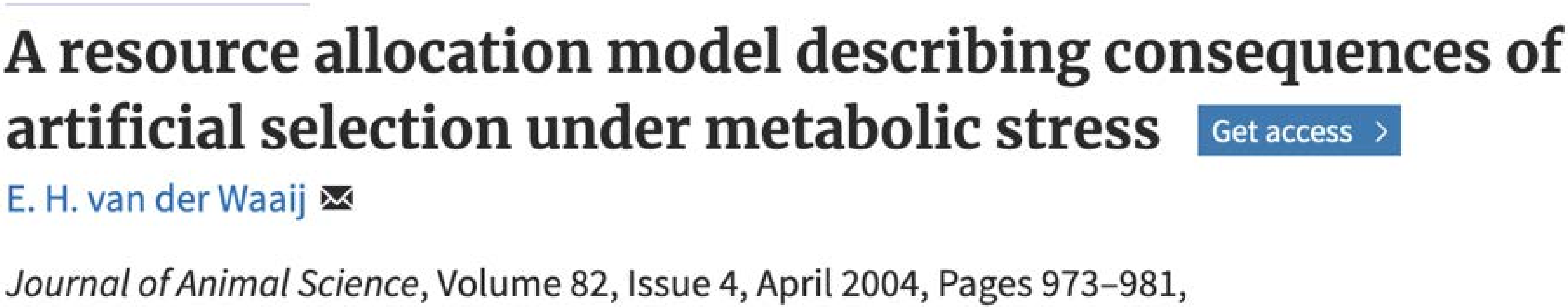
gibbsf90



Why changes in genetic parameters?

- Bulmer effect
- G x E
- Recessives
- Changes in gene frequencies
- Drift

- Changing resource allocation
- Changes in trait definitions
- …



A resource allocation model describing consequences of artificial selection under metabolic stress

E. H. van der Waaij

Journal of Animal Science, Volume 82, Issue 4, April 2004, Pages 973–981,

The Woman and Her Hen

by Aesop

Reference on dangers of overfeeding 2500 years old…

A WOMAN possessed a Hen that gave her an egg every day. She often thought with herself how she might obtain two eggs daily instead of one, and at last, to gain her purpose, determined to give the Hen a double allowance of barley. From that day the Hen became fat and sleek, and never once laid another egg.

How to circumvent negative effects?

- Start or expand recording for problematic traits
- Update selection index
  - Needs estimates for last generation
- Focus on traits where the parameters are changing rapidly
  - Needs estimates generation by generation
- *Make veterinarians and nutritionists work harder!*

Journal of Animal Science, 2024, **102**, skae155
https://doi.org/10.1093/jas/skae155
Advance access publication 7 June 2024
Special Topics

Potential negative effects of genomic selection

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Challenge of parameter estimation in genomic era

- Possibly rapidly changing parameters
- Need estimates using complete data including genomic
- Computing issues with REML and Bayesian methods
- Can we estimate parameters without size restriction, generation by generation?

Simplest estimation

$$\widehat{h^2} \approx var(GEBV)$$

$$\widehat{r_{ij}} \approx corr\left(GEBV_i, GEBV_j\right)$$

Good with many genotypes and higher h^2

Function of accuracies

Possibly pathological properties in MT models

Realized and theoretical accuracies

Realized accuracy $acc = corr(y - Xb, \hat{u})/h$

Legarra et al. (2008)

y-Xb - adjusted phenotype
$\hat{u}$ - breeding value obtained without that phenotype
h^2 - heritability

Theoretical accuracy $$acc = \sqrt{\frac{Nh^2}{Nh^2 + M_e}}$$

Daetwyler et al. (2008)

N – number of genotyped animals with phenotypes
M_e – number of independent chromosome segments

Me ≈ 5k (chickens, pigs), 10k (beef), 15k (Holsteins)
Pocrnic et al. (2017)

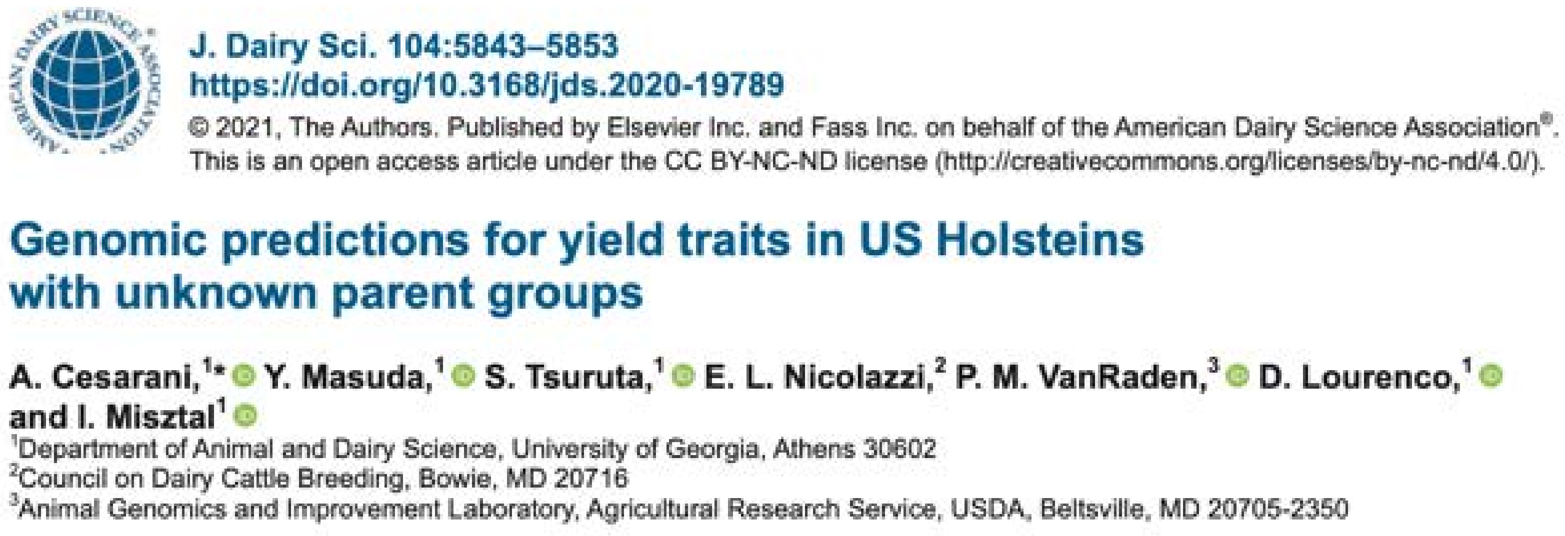
Formula for estimating heritability

$$\widehat{h^2} = \frac{c^2 + \sqrt{c^4 + 4c^2 M_e / N_{ref}}}{2} \mp \frac{3c}{\sqrt{N_{val}}}$$

$$c = corr(y - Xb, \hat{u})$$

N_{ref} – animals in reference population
Me – effective chromosome segments, ~5k in pigs and chicken, ~15k in cattle
N_{val} – number of animals in validation population

Heritability for milk in Holsteins



J. Dairy Sci. 104:5843–5853
https://doi.org/10.3168/jds.2020-19789

Genomic predictions for yield traits in US Holsteins with unknown parent groups

A. Cesarani,[1*] Y. Masuda,[1] S. Tsuruta,[1] E. L. Nicolazzi,[2] P. M. VanRaden,[3] D. Lourenco,[1] and I. Misztal[1]
[1]Department of Animal and Dairy Science, University of Georgia, Athens 30602
[2]Council on Dairy Cattle Breeding, Bowie, MD 20716
[3]Animal Genomics and Improvement Laboratory, Agricultural Research Service, USDA, Beltsville, MD 20705-2350

Reference: 580k Validation 381k

Starting $h^2 = 0.35$ Me=15k chromosome segments

Predictivity = 0.55

Calculated $h^2 = 0.33$

Formula for genetic correlations

$corr(y_i - Xb_i, \widehat{u_j})$ Predictivity of trait i by trait j

$$corr_{ij} = \frac{corr(y_i - Xb_i, \widehat{u_j})}{h_i \ acc_j} \mp \frac{1}{h_i \ acc_j \sqrt{N_{val}}}$$

Under correct model: $corr_{ij} = corr_{ji}$

Procedure

- Select reference population, number of genotyped N > 10,000
- Select validation population, number of genotyped $N_{val} > 5000$
- Estimate GEBV with phenotypes of reference population and genotypes of both populations; treat traits uncorrelated
- Calculate predictivities within and across traits
- Recalculate heritabilities $\widehat{h^2} = \frac{c^2 + \sqrt{c^4 + 4c^2 M_e / N}}{2}$
- Recalculate accuracies $acc = corr(y - Xb, \hat{u})/h$
- Calculate genetic correlations $corr_{ij} = \frac{corr(y_i - Xb_i, \widehat{u_j})}{h_i \; acc_j} \pm \frac{1}{h_i \; acc_j \sqrt{N}}$

Data simulation with changing parameters

- y_i^j, u_i^j - phenotype and breeding values of trait i in j-th generation

- Two uncorrelated traits
  - “production” with $h^2 = 0.4$
  - “base fitness” with $h^2 = 0.1$

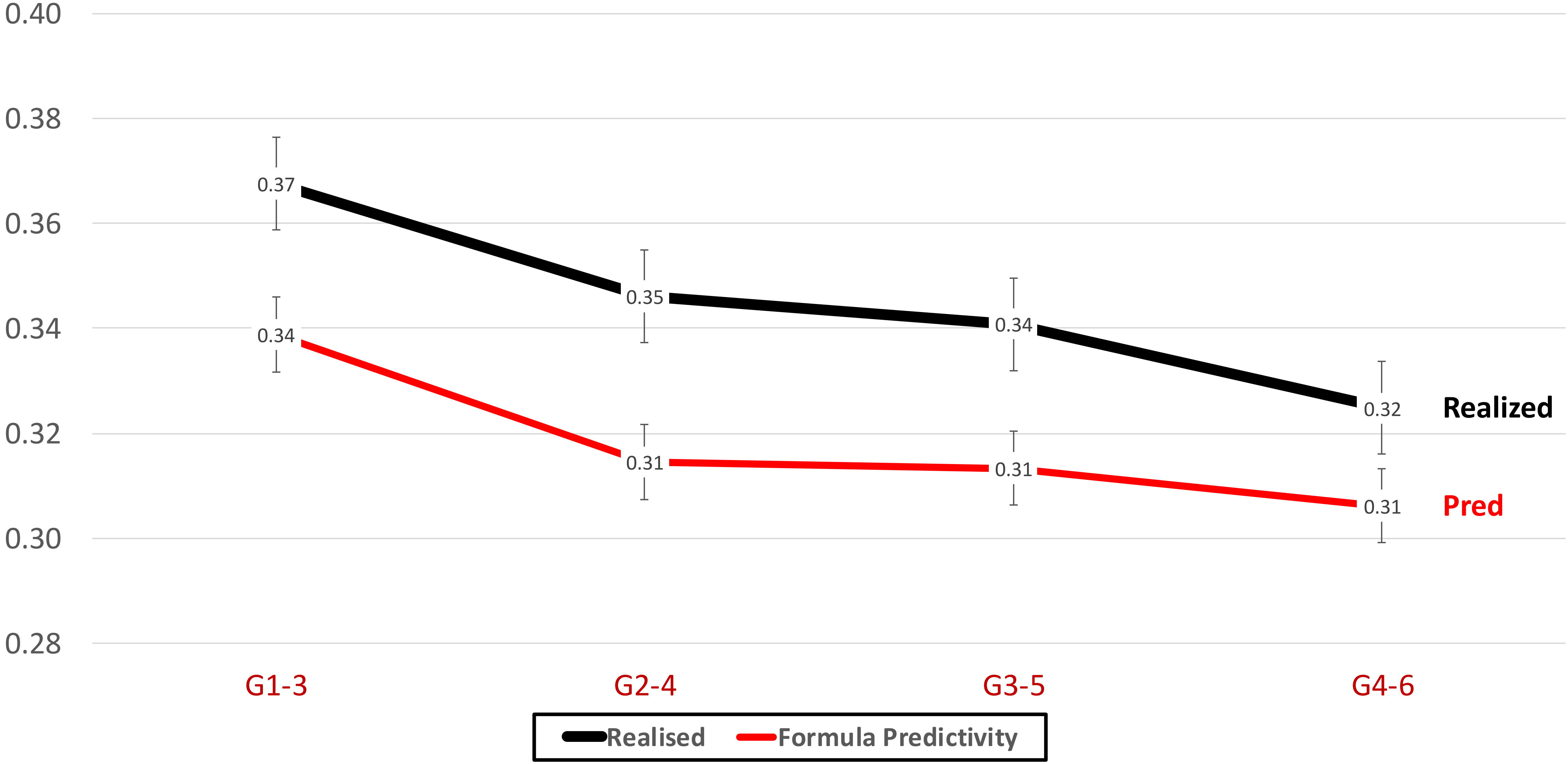
- Evolving fitness trait $u_3^j = \alpha_j\left(u_2^j - \beta u_1^j(\overline{u_1^j - u_1^0})\right)$
  - α_j - scaling factor so that $var\left(u_3^j\right) = const$
  - β - chosen to change genetic correlation between traits 1 and 3 by about -0.1 each generation.

Data simulation (2)

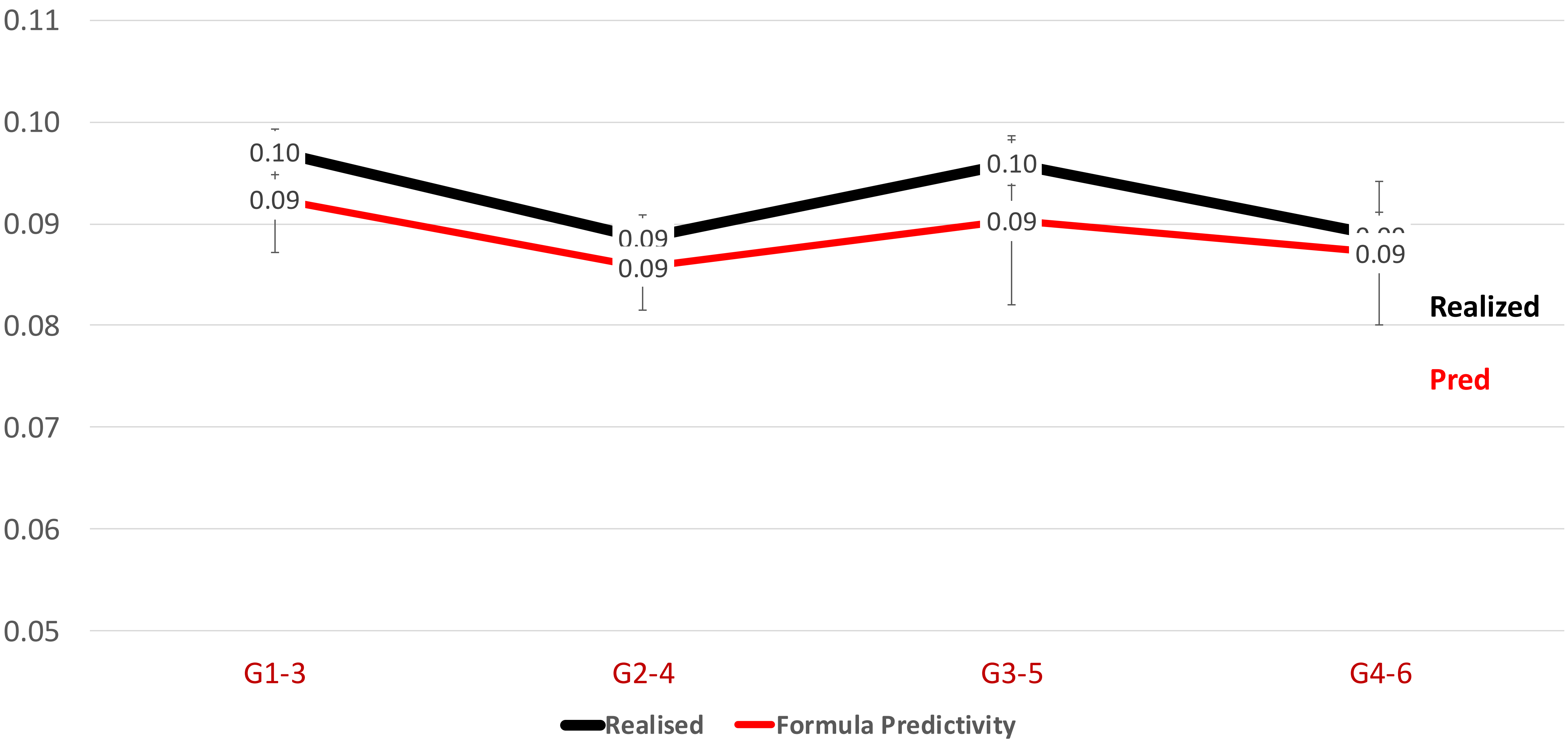
- Simulation by AlphaSim
  - 40k genotyped and phenotyped per generation
  - 6 generations
  - GBLUP selection in each generation
  - Effective population size 50

- Analyzes
  - Realized parameters for each generation
  - Parameters by predictivity, use 2 reference generations

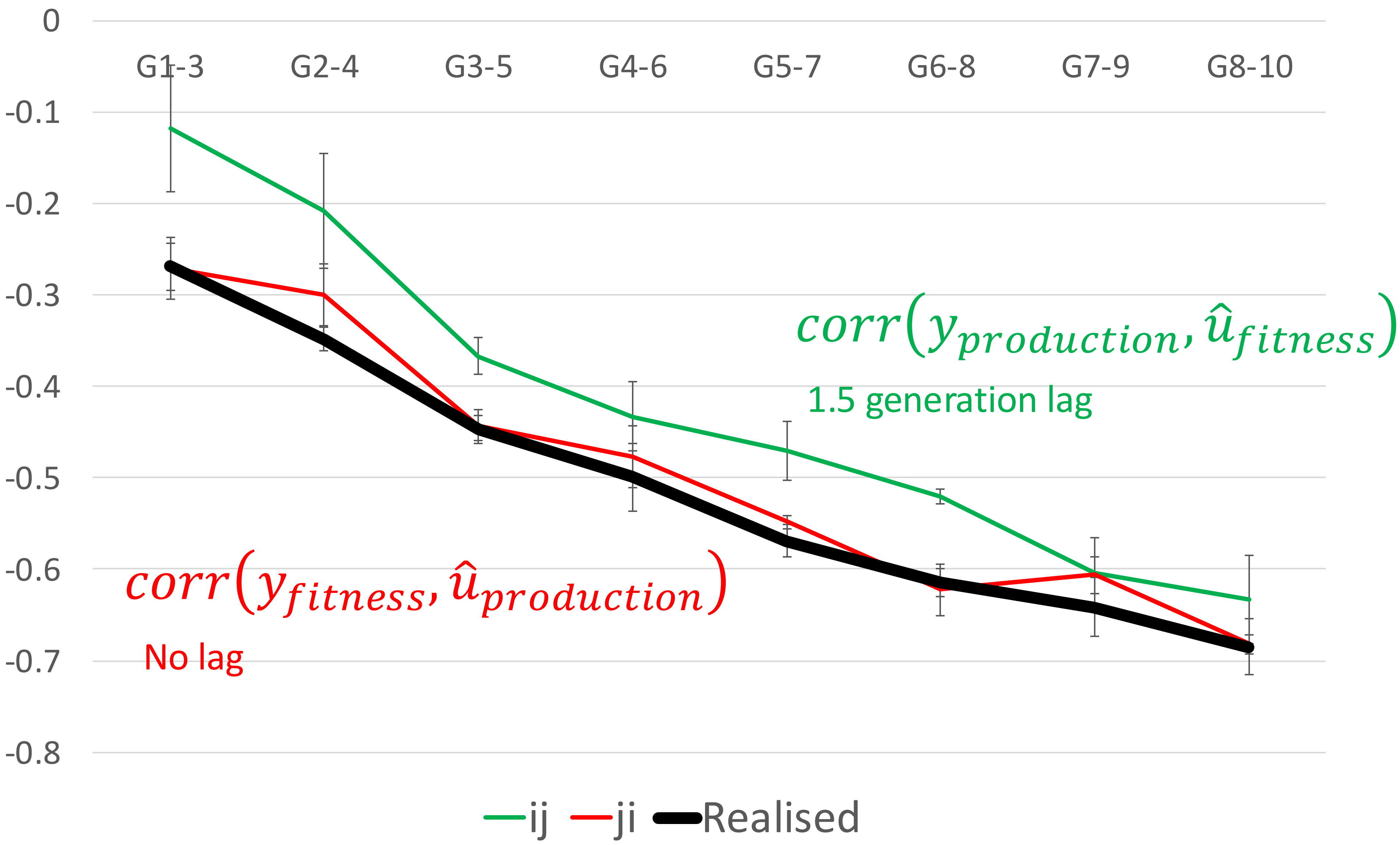
Heritability for "Production" Trait



Heritability for “Fitness” Trait



Genetic correlations: ij and ji



$corr(y_{production}, \hat{u}_{fitness})$

1.5 generation lag

$corr(y_{fitness}, \hat{u}_{production})$

No lag

Over-time genetic correlations based on accuracy in GEBV for 18 linear type traits in US Holsteins

Shogo Tsuruta, Daniela Lourenco, Ignacy Misztal, and *Tom Lawlor

UGA and *Holstein Association USA

Wageningen University, Netherlands, September 18, 2024

Model and 18 traits

- Single-step GBLUP model (covariances=0) with current(⇓) h^2 (0.22 on average) from VCE and arbitrary h^2: 0.1 and 0.5 for more comparison
- Focusing on correlations of Stature (trait 1) or Udder Depth (trait 13) with other 17 traits <= 153 correlations in total

No	Traits	h^2	No.	Traits	h^2
1	Stature	0.456	10	Rear Udder Height	0.214
2	Strength	0.270	11	Rear Udder Width	0.172
3	Body Depth	0.337	12	Udder Cleft	0.178
4	Dairy Form	0.298	13	Udder Depth	0.332
5	Rump Angle	0.341	14	Front Teat Placement	0.267
6	Rump Width	0.248	15	Teat Length	0.254
7	Rear Legs - Side View	0.173	16	Rear Legs - Rear View	0.106
8	Foot Angle	0.110	17	Feet & Legs Score	0.182
9	Fore Attachment	0.230	18	Rear Teat Placement	0.213

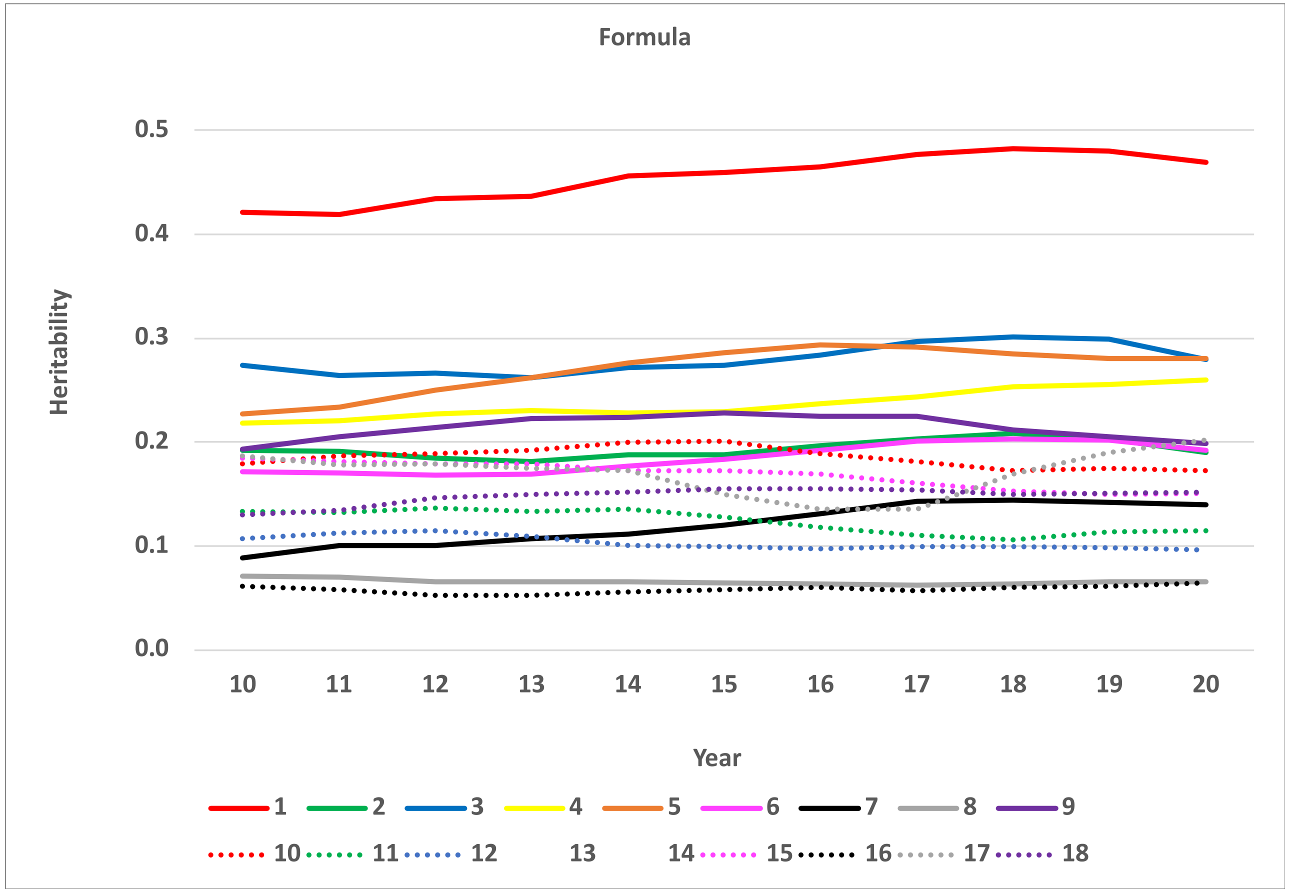
Data (in thousand, K)

Validation = VCE*				Reference		
Year of birth	# genotyped animals	# records	# animals with records	Year of birth	# records	# genotyped animals
2009-2011	33	685	515	**2001-2008**	2,725	367
2010-2012	47	674	513	**2001-2009**	2,956	375
2011-2013	65	647	499	**2001-2010**	3,188	385
2012-2014	83	609	476	**2001-2011**	3,411	400
2013-2015	96	565	445	**2001-2012**	3,630	422
2014-2016	102	522	409	**2001-2013**	3,834	450
2015-2017	105	494	388	**2001-2014**	4,019	483
2016-2018	108	466	371	**2001-2015**	4,195	518
2017-2019	112	429	360	**2001-2016**	4,356	551
2018-2020	103	348	310	**2001-2017**	4,514	589
2019-2021	67	203	191	**2001-2018**	4,661	625

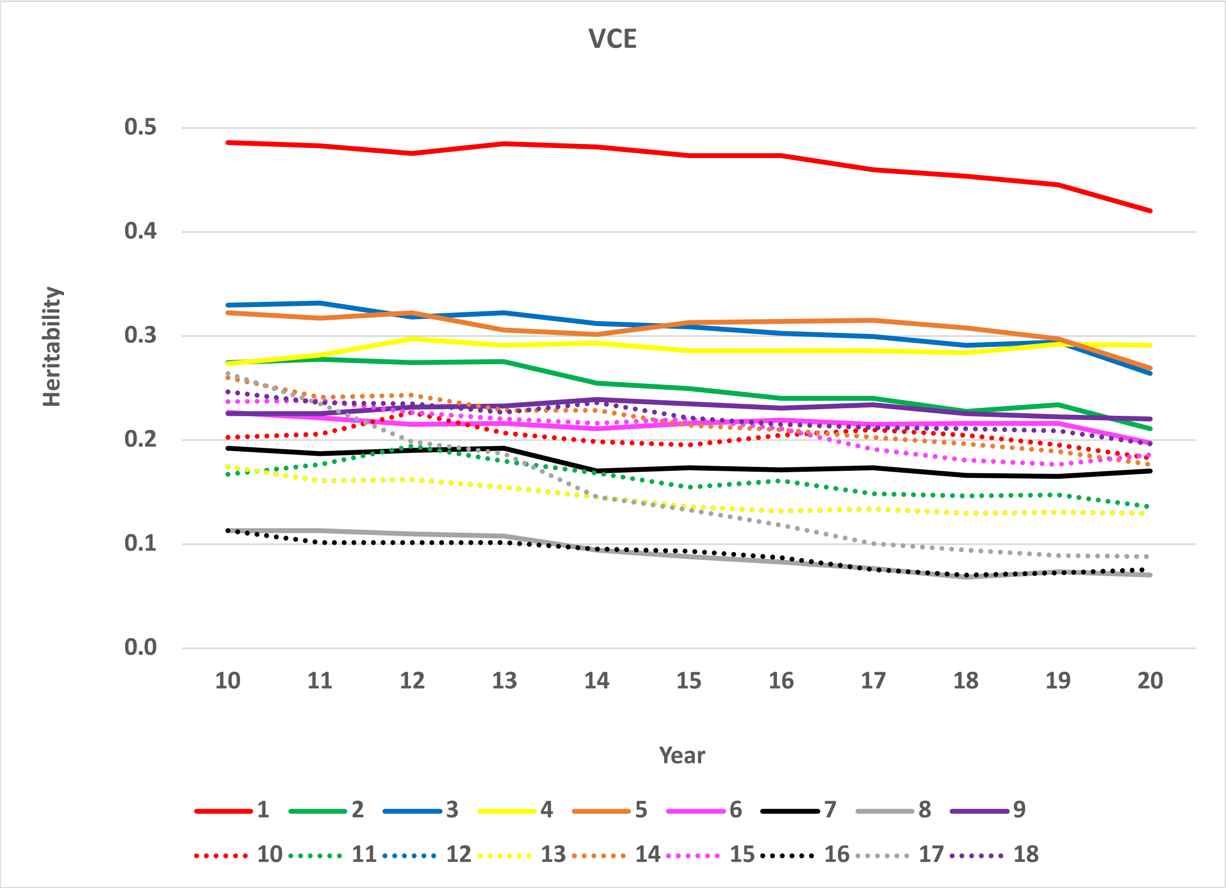
* VCE: Model ignoring genomic information

Heritability over time

Formula

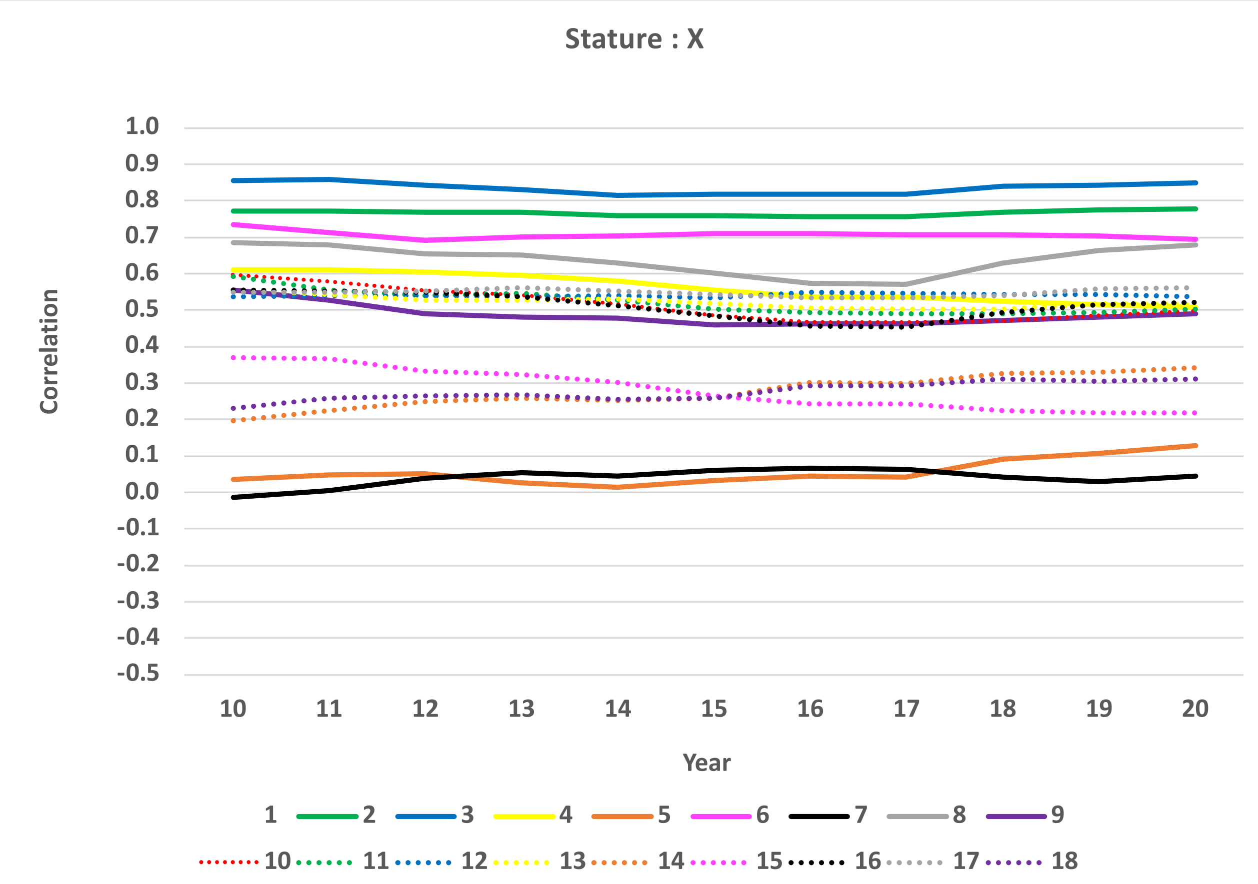


VCE –no gen

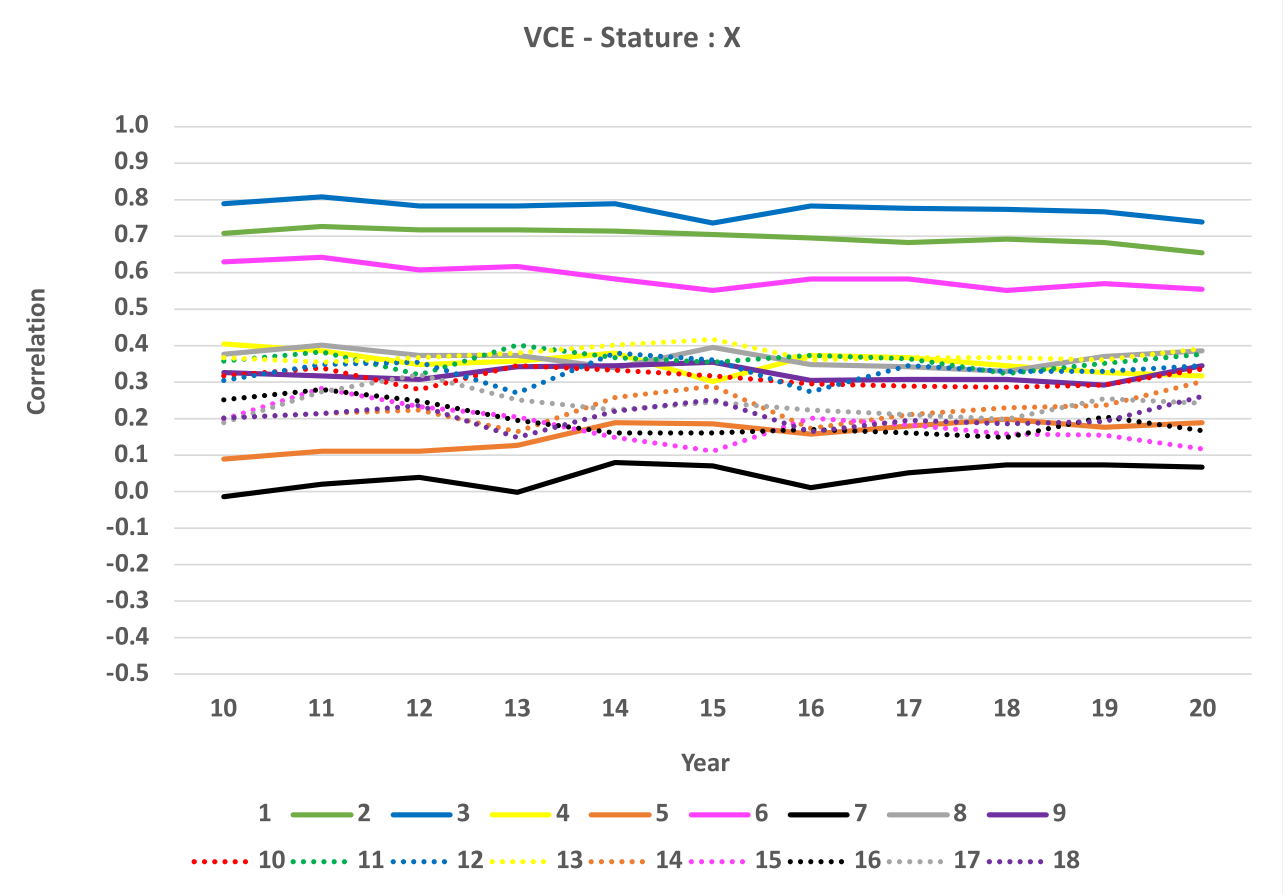


Genetic correlations over time (Stature)

Formula



VCE – no gen



Breeding for improved heat tolerance: methods, challenges, and progress

Ignacy Misztal, Daniela Lourenco
University of Georgia
Luiz Brito, Purdue University

Wageningen University, Netherlands, September 18, 2024

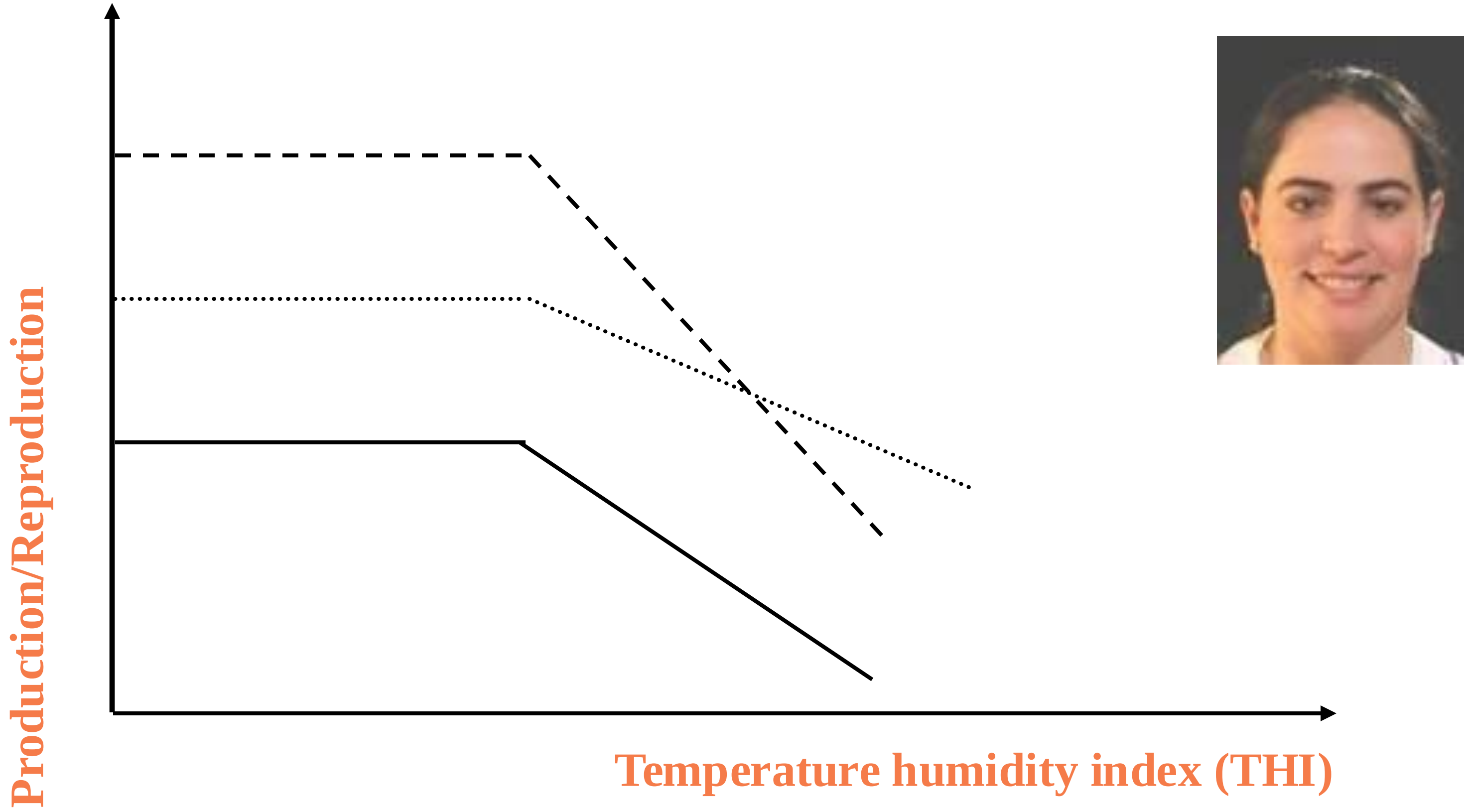
Heat tolerant cow and genetics

- Under heat stress, cow should:
  - keep milk flowing
  - reproduce
  - keep healthy
  - do not die

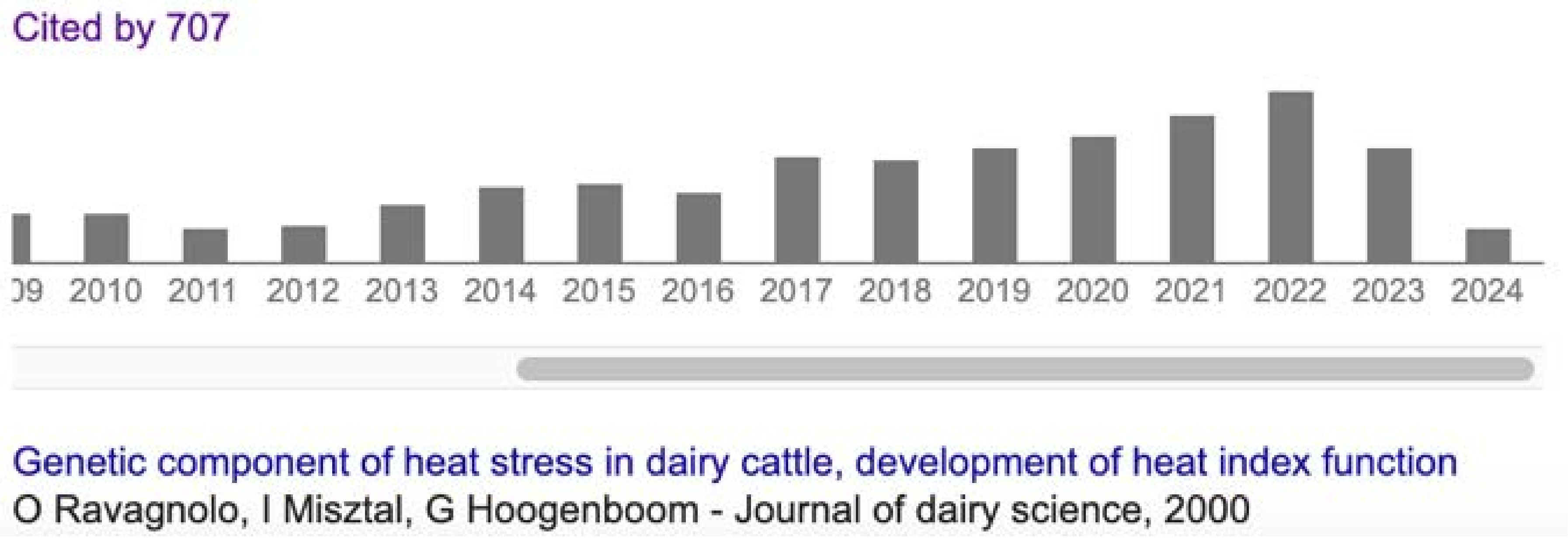
- Constantly improving management available under heat stress

- Does it make sense to select for heat stress?

Assumption for heat stress model



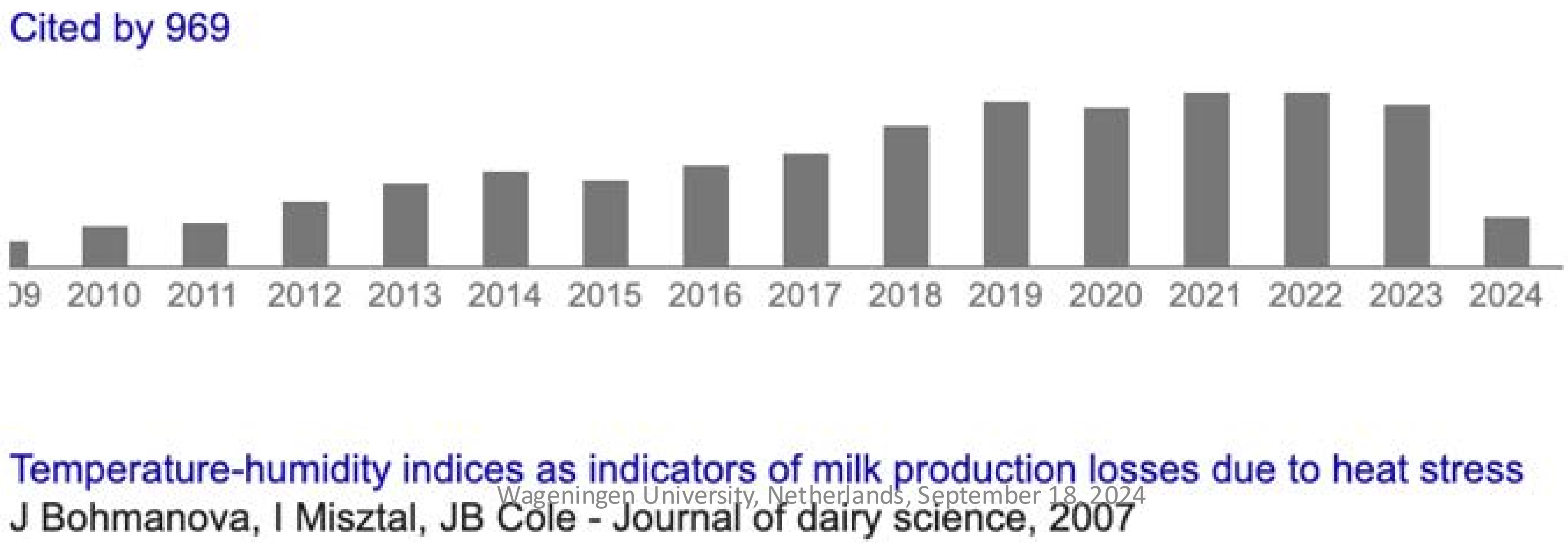
Weather data from public weather stations; matching by postal codes



Cited by 707

Genetic component of heat stress in dairy cattle, development of heat index function

O Ravagnolo, I Misztal, G Hoogenboom - Journal of dairy science, 2000

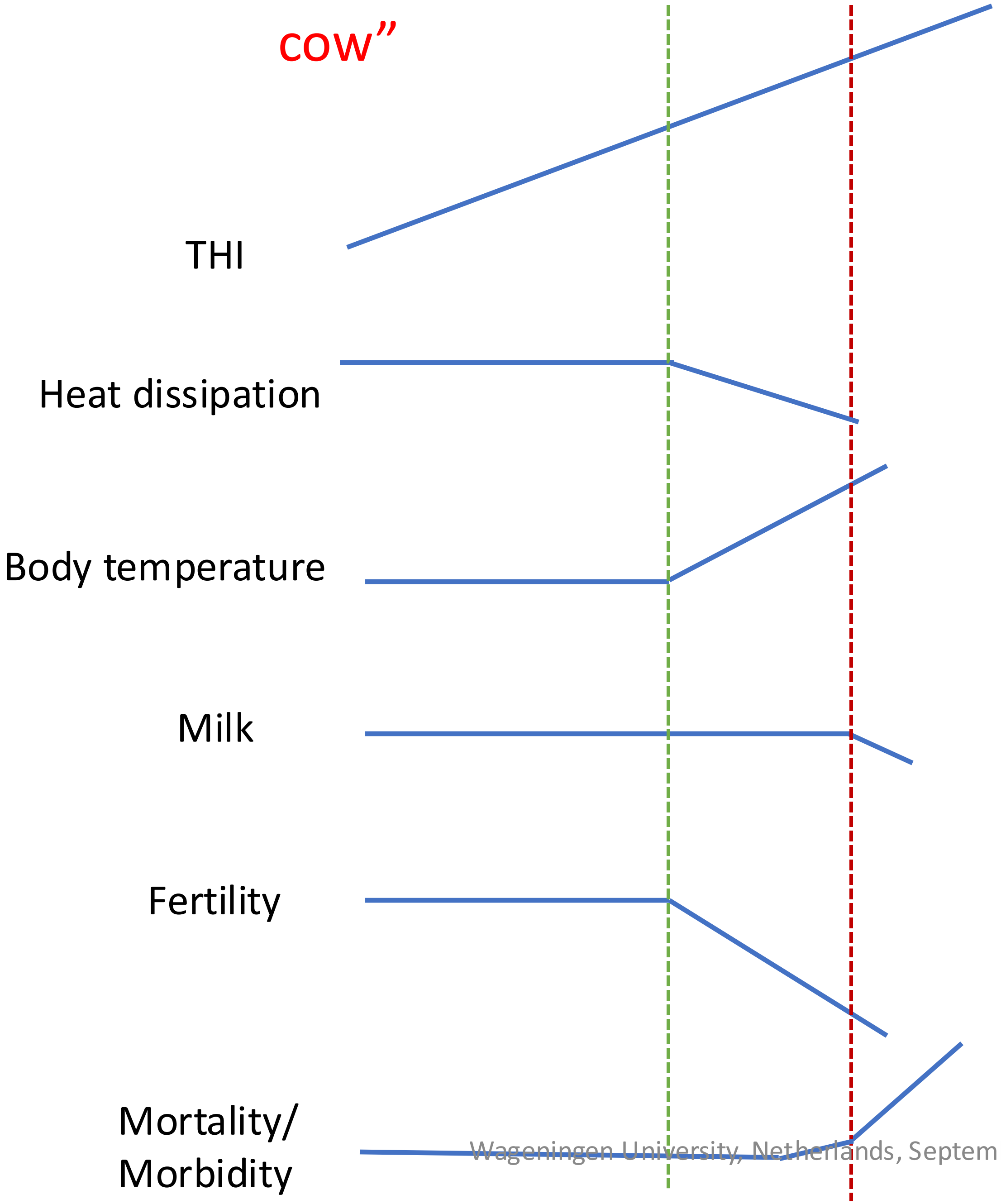


Cited by 969

Temperature-humidity indices as indicators of milk production losses due to heat stress

J Bohmanova, I Misztal, JB Cole - Journal of dairy science, 2007

Profile of a “heat-tolerant cow”



THI

Heat dissipation

Body temperature

Milk

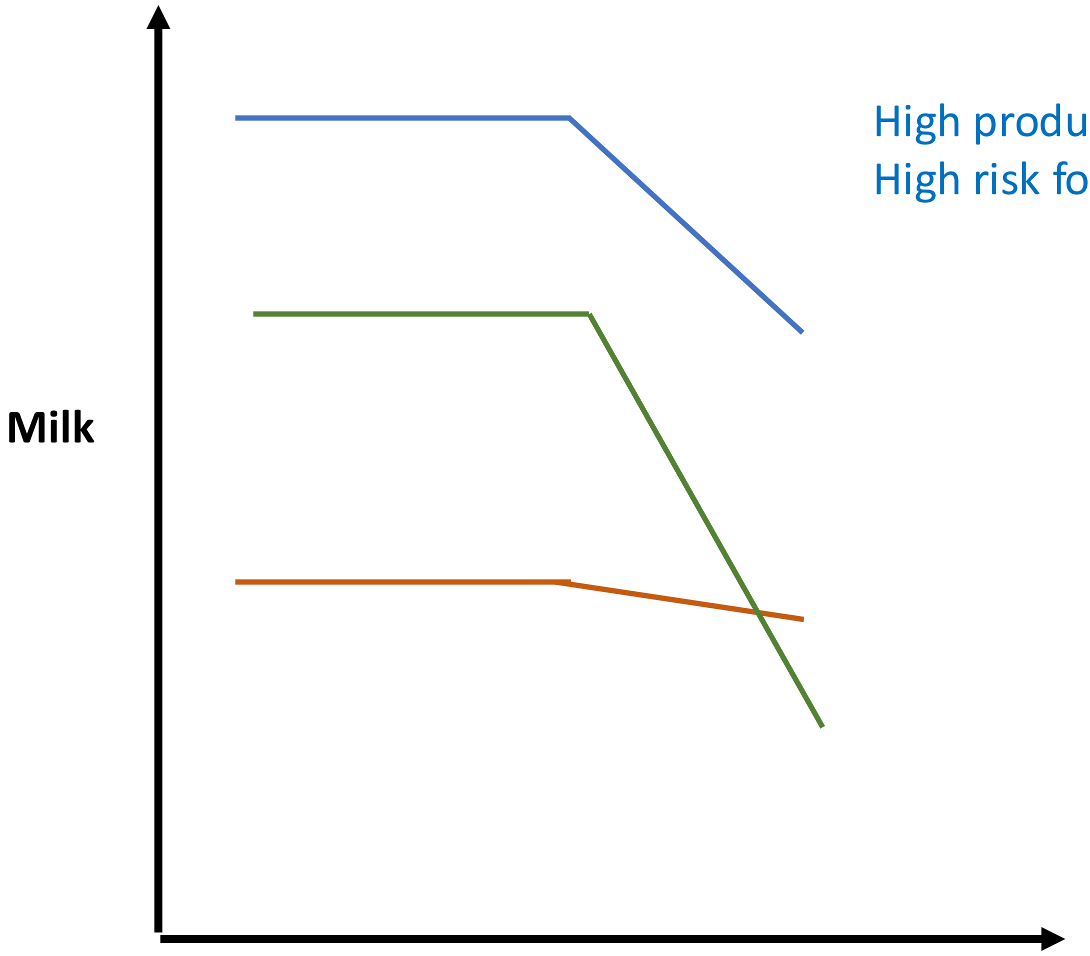
Fertility

Mortality/
Morbidity

- “Heat tolerant” cow – workaholic
- Thresholds like in resource allocation studies (Waaij, 2004; Rauw, et al. 2008))

Partially based on Dikmen et al. (2012)

Which is a desirable cow?

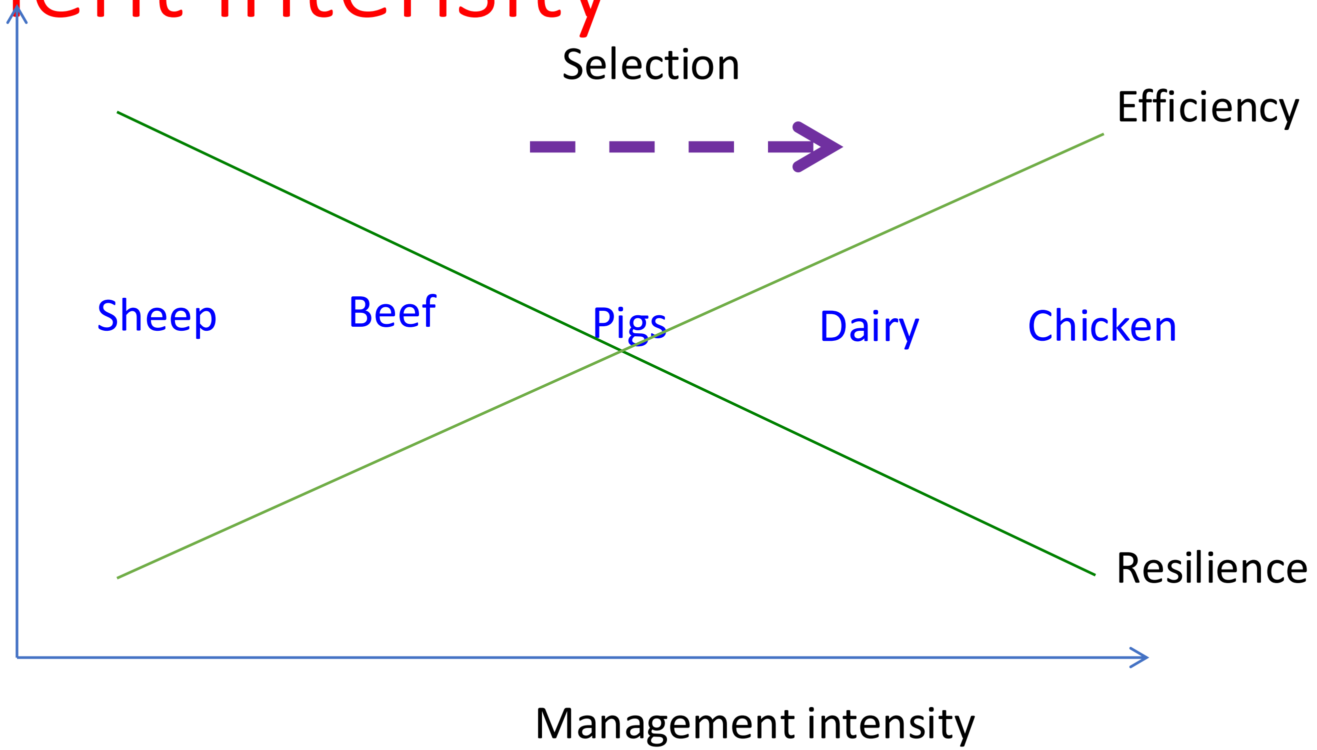


High producing
High risk for death and morbidity

Resilient
Low risk for death and morbidity

Heat tolerant & robust
Lower risk for death and morbidity

Resilience (heat tolerance)/efficiency and management intensity

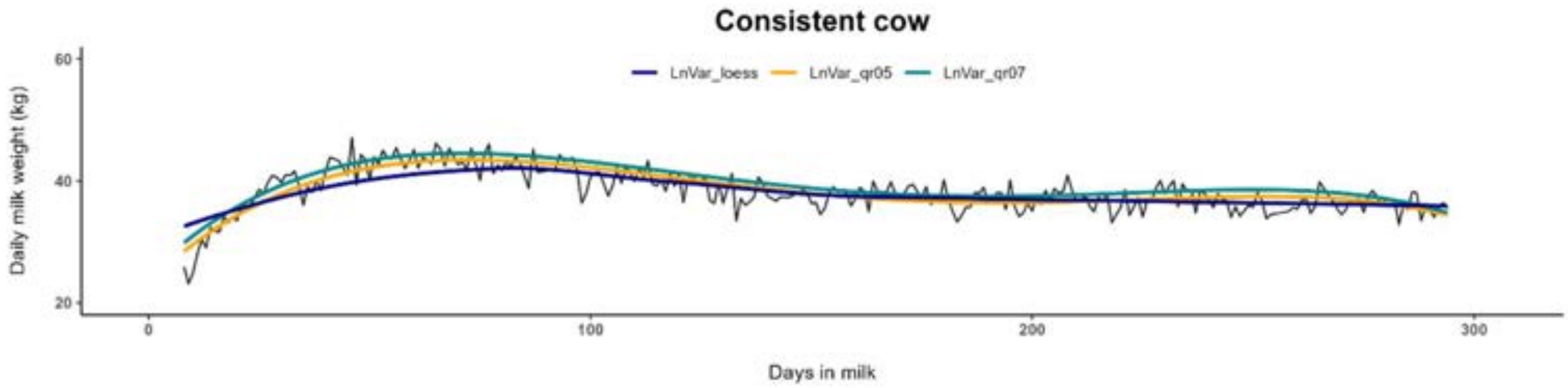


Is increasing production and resilience simultaneously possible?

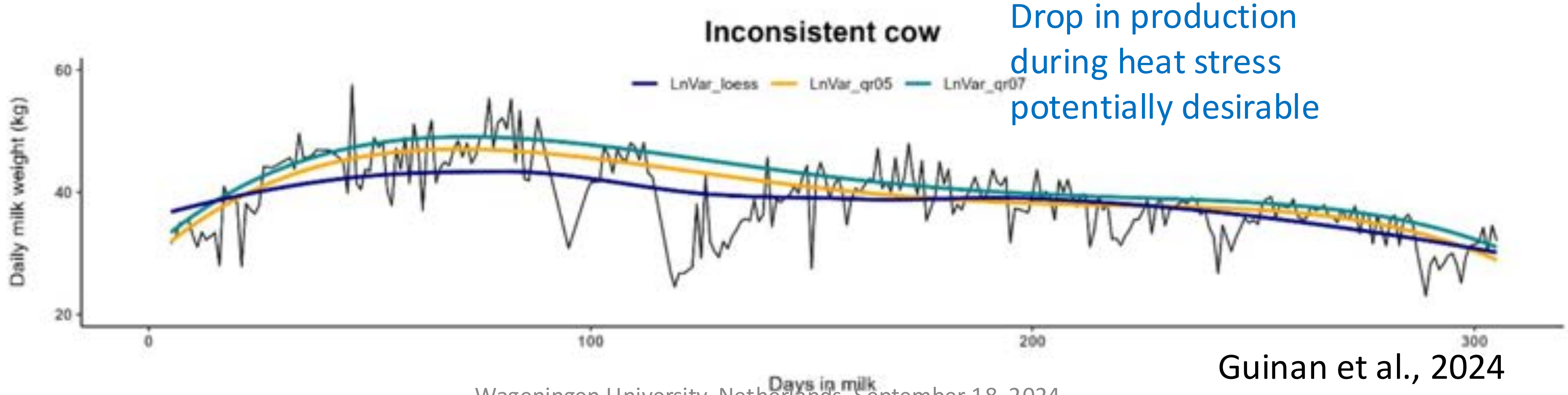
Zefeh et al, 2023 https://doi.org/10.3389/fgene.2023.1127530

Deviation from averages

Good or workaholic cow?



Drop in production during heat stress potentially desirable



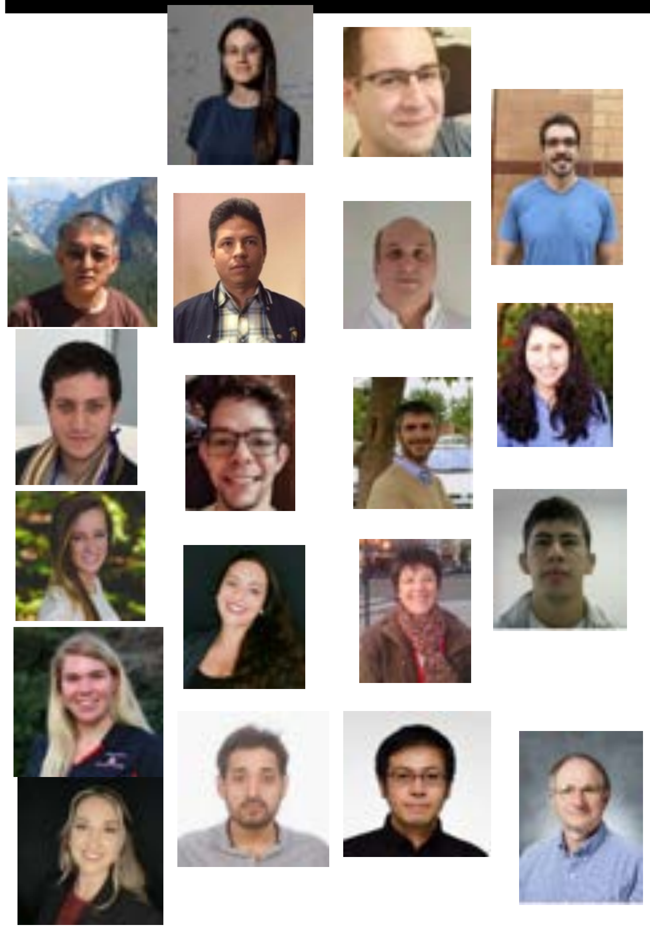
Guinan et al., 2024

Conclusions

- Heat tolerance and production antagonistic
- Current selection against heat tolerance
- Modern cow bred for sophisticated management
- Dilemma: high producing or resilient cow?

UNIVERSITY OF GEORGIA

UGA AB&G team



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Agricultural Research Service
Warmwater Aquaculture Research Unit

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