Pre-selection bias and validation in single-step GBLUP for production traits in US Holstein

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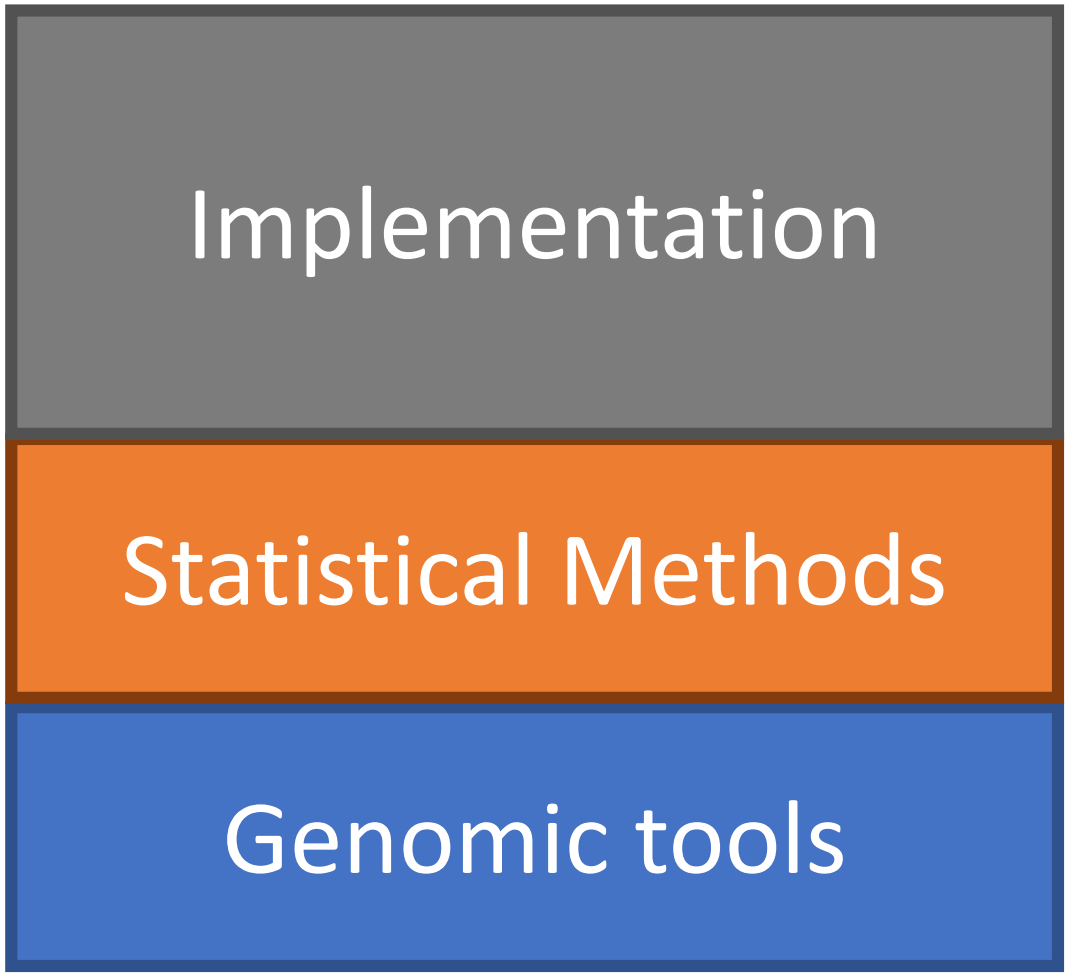
Genomic selection in practice



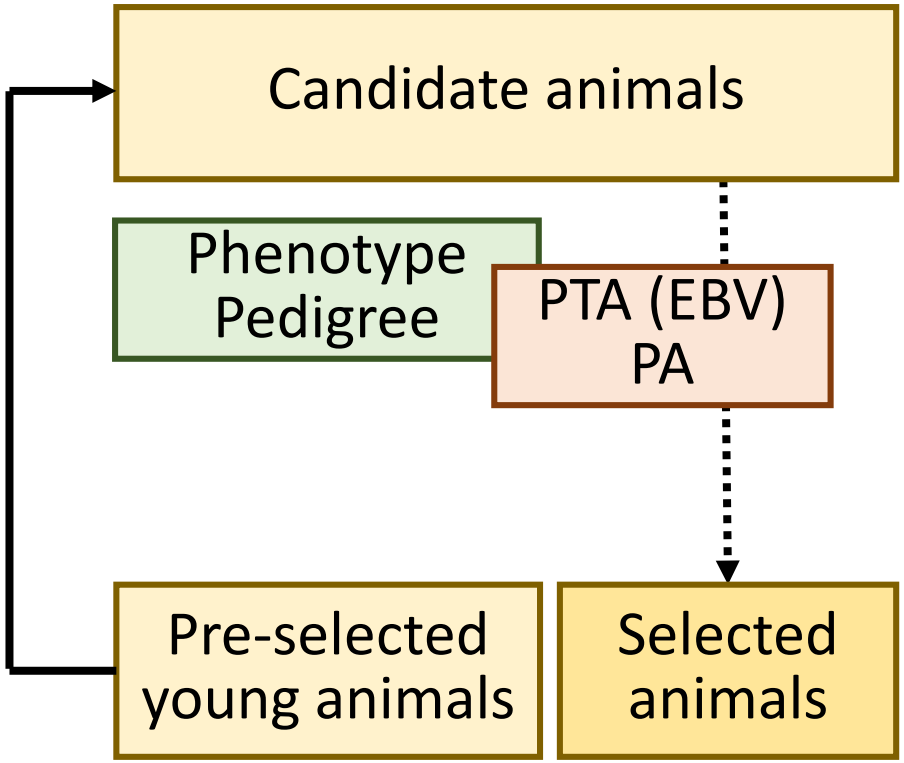
- **Use of existing data-collection systems (phenotypes & pedigrees)**
- **Integration of genomic data**
- **Stabilization of genomic predictions**

- **Breeding value prediction**
- **Adjustments for bias-reduction**
- **Computing algorithms**

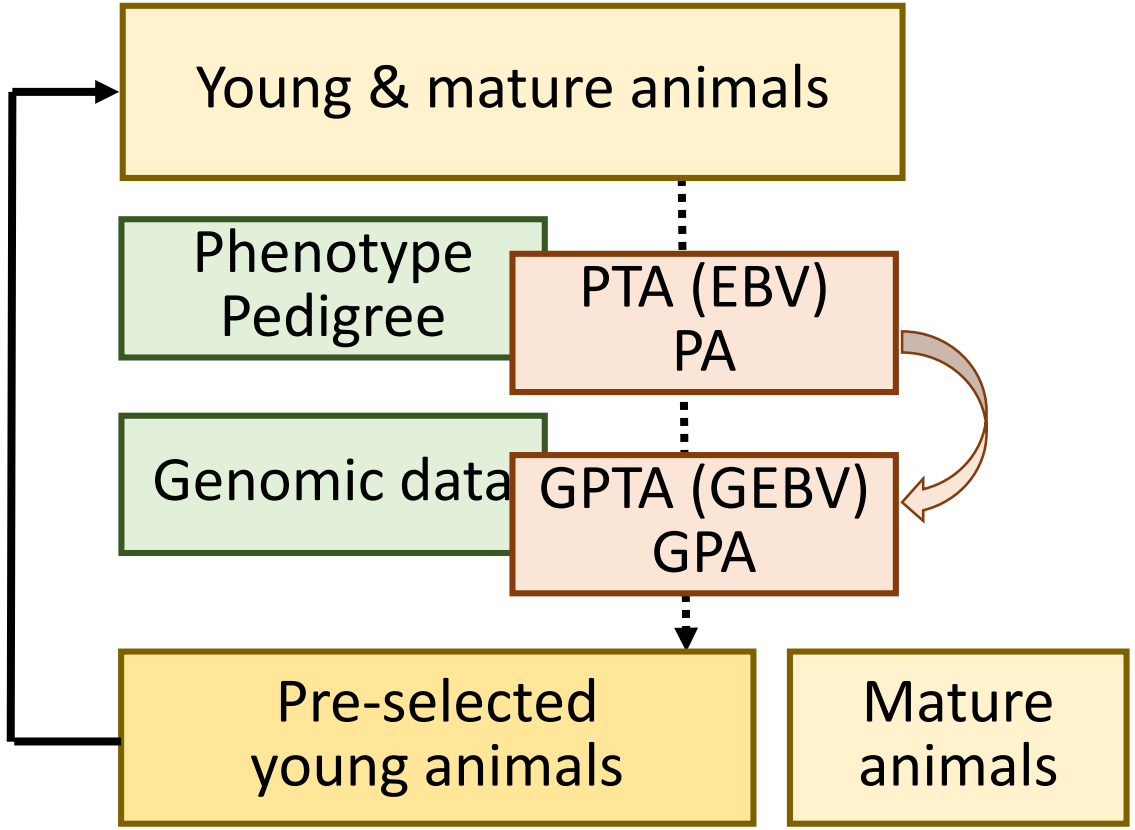
- **Efficient genotyping technique**
- **Affordable SNP chips**

Dairy cattle evaluation

Conventional animal-model BLUP

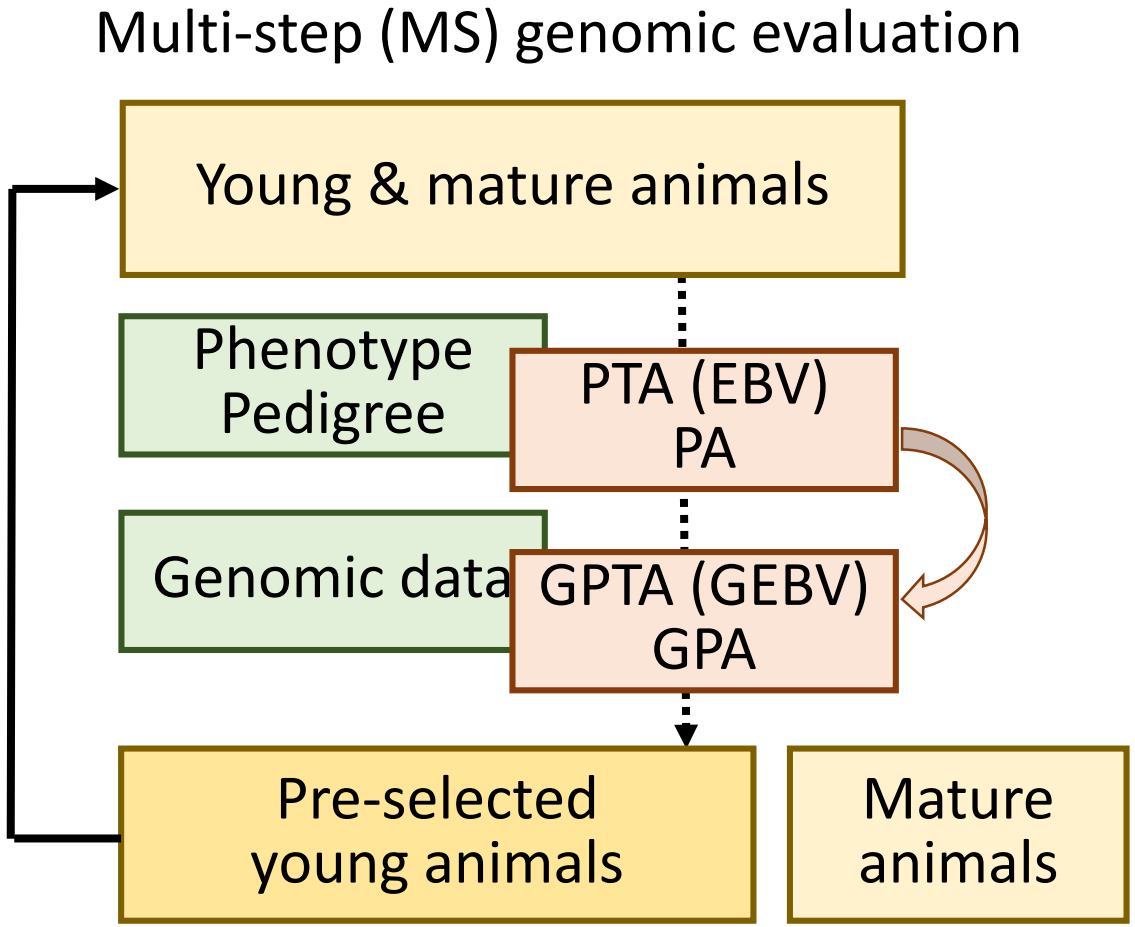


Multi-step (MS) genomic evaluation

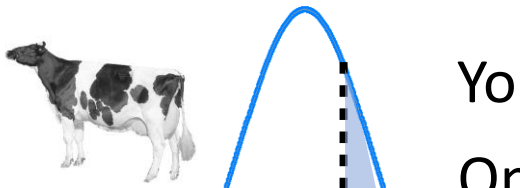


Multi-step evaluation

- Advantages
  - Keeping the traditional systems
  - Flexibly adjustable for GPTA (GEBV) in terms of bias
  - Accumulated experience
- Concerns
  - Only for genotyped animals
  - Too many options for the second step (input values & methods)
  - **“Pre-selection bias” in the traditional PTA**



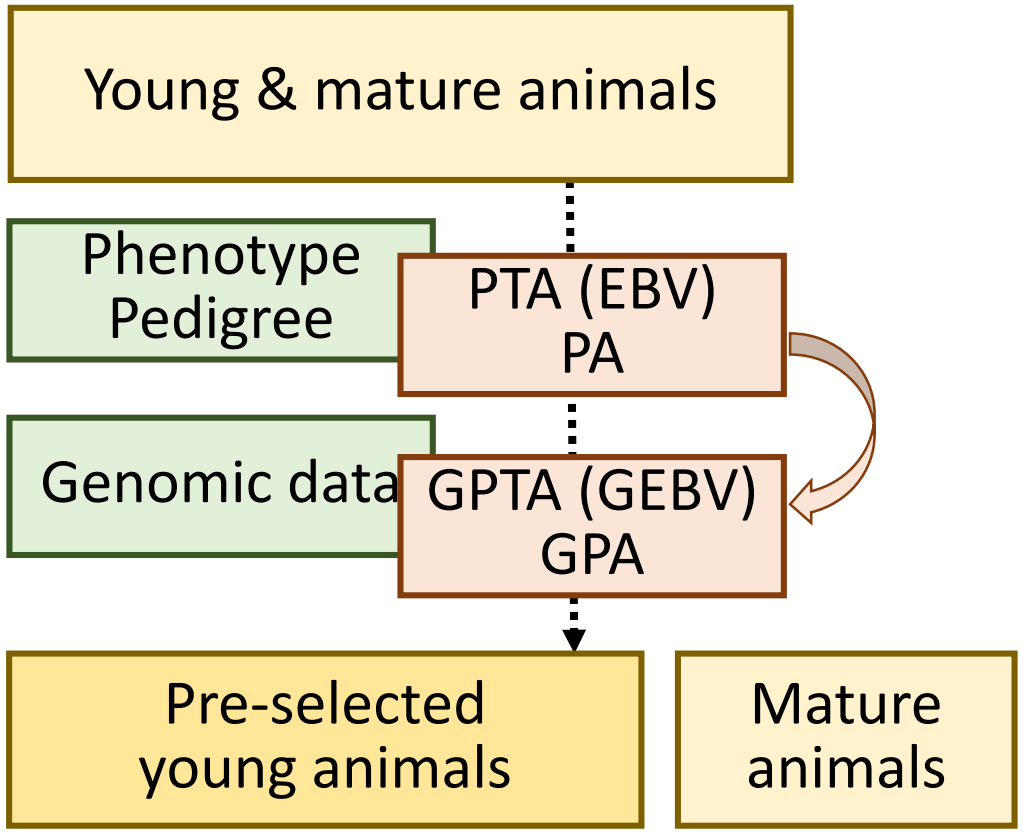
Pre-selection bias



Young genotyped animals:

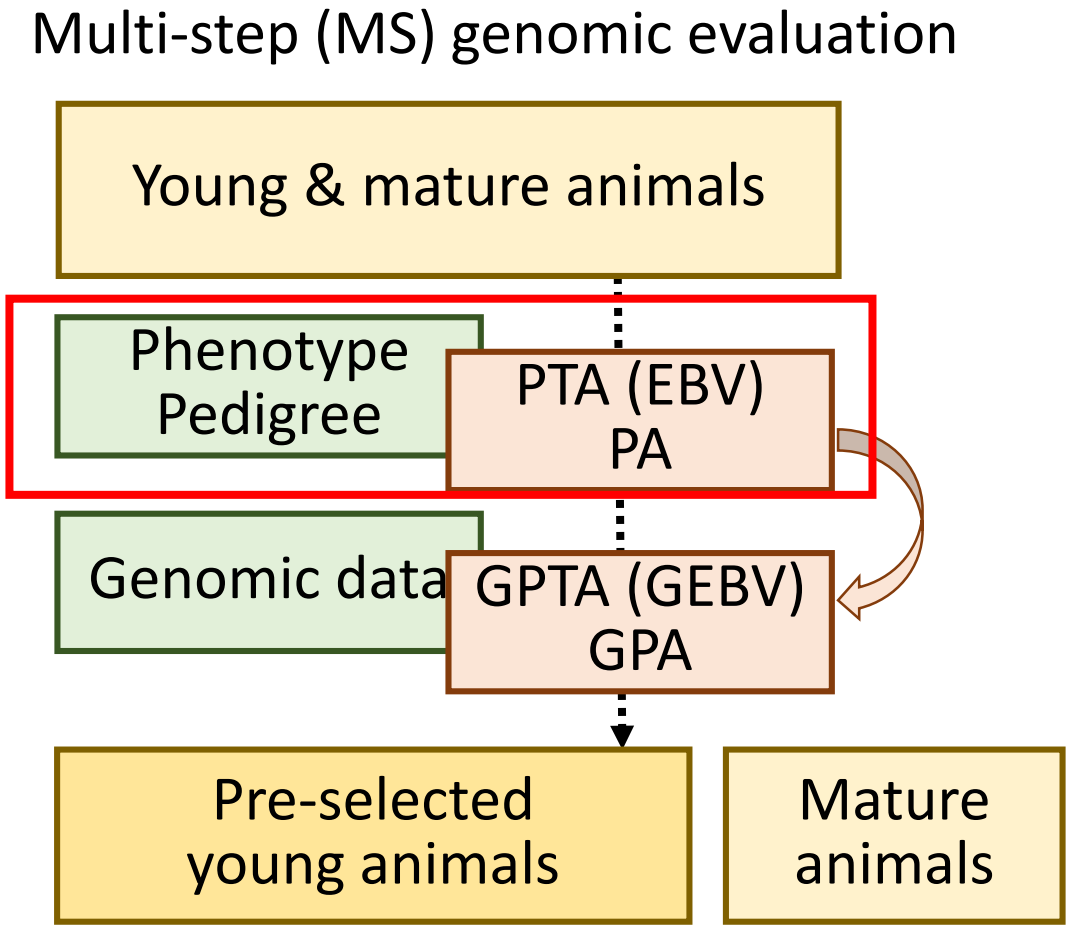
Only selected data
included in animal model BLUP

Multi-step (MS) genomic evaluation



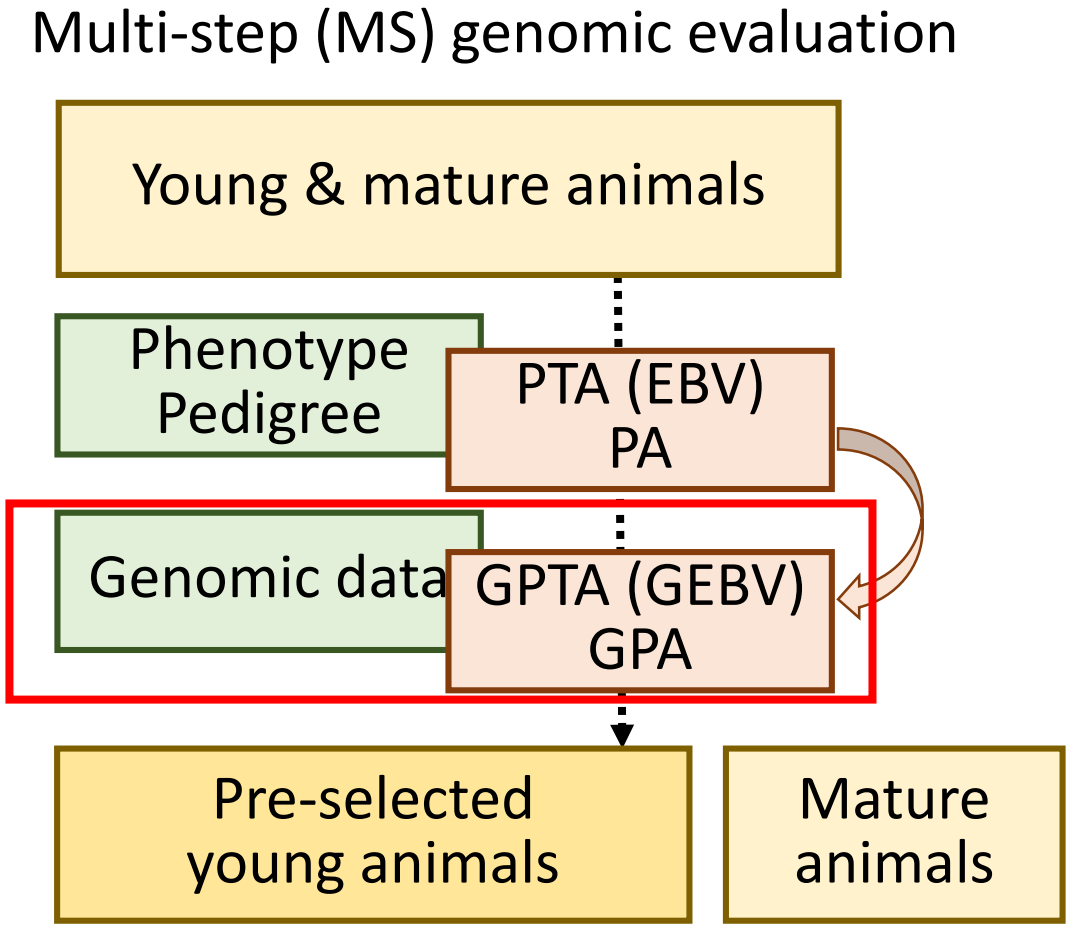
Pre-selection bias

- Selection criteria not included in MME of animal model BLUP
- Bias down in the prediction



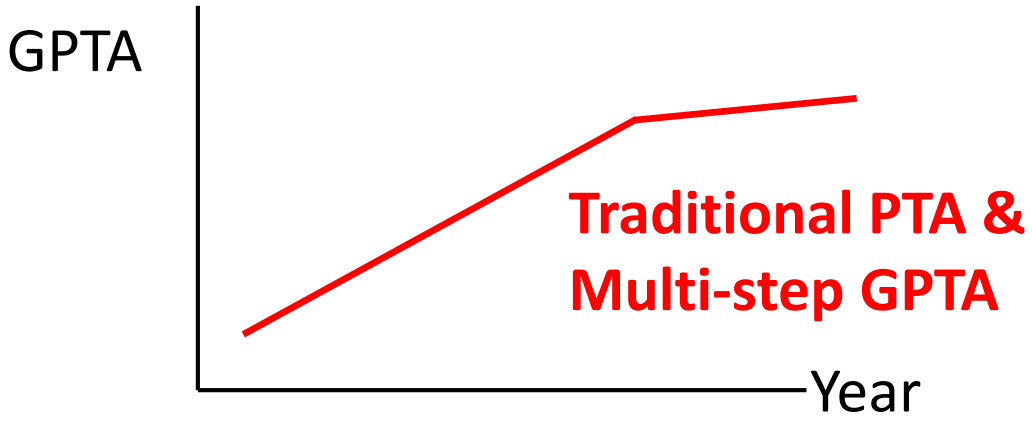
Pre-selection bias

- Biased PTA (EBV) to GPTA
- GPTA biased down

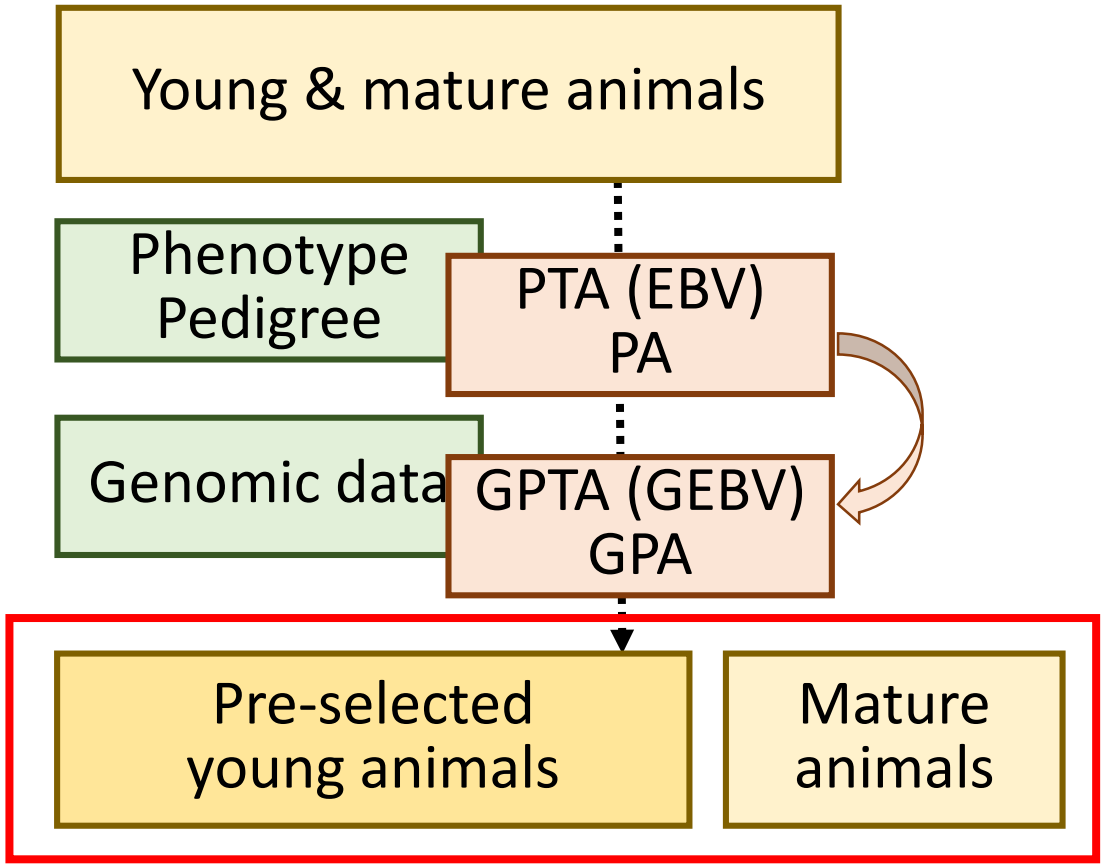


Pre-selection bias

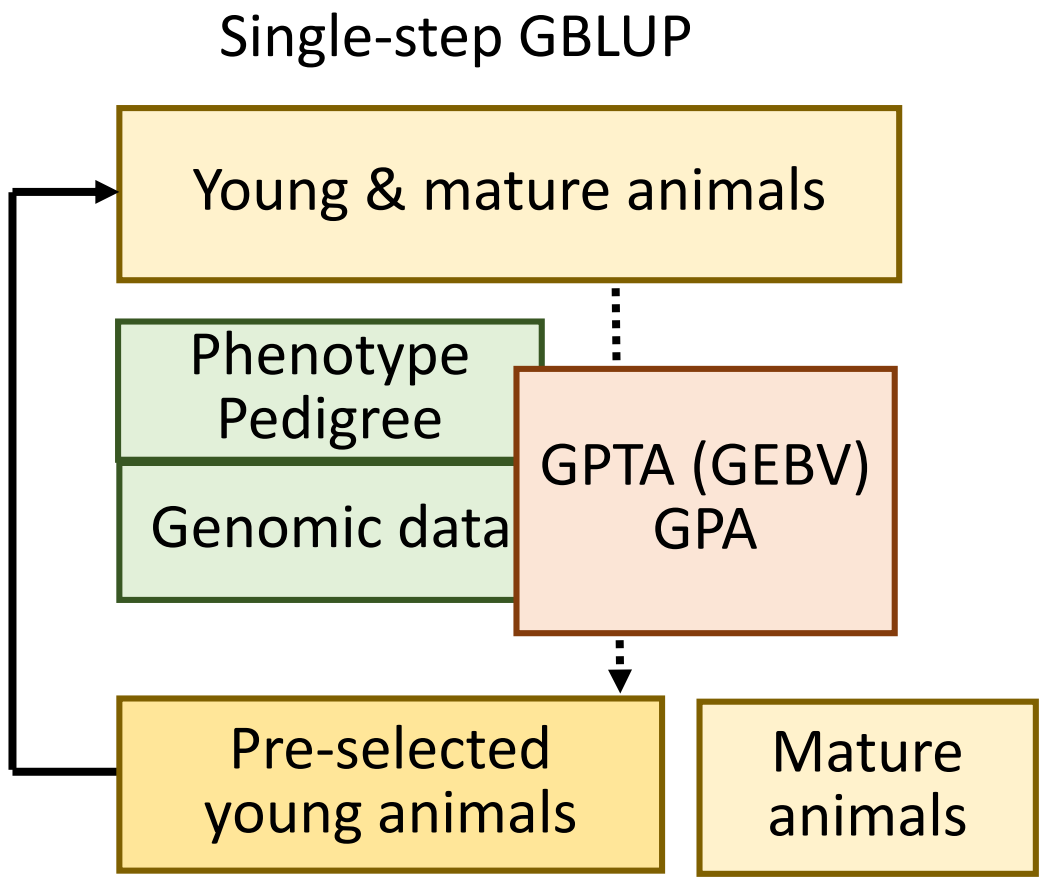
- Possible result: underestimated genetic trend for genomically selected animals



Multi-step (MS) genomic evaluation



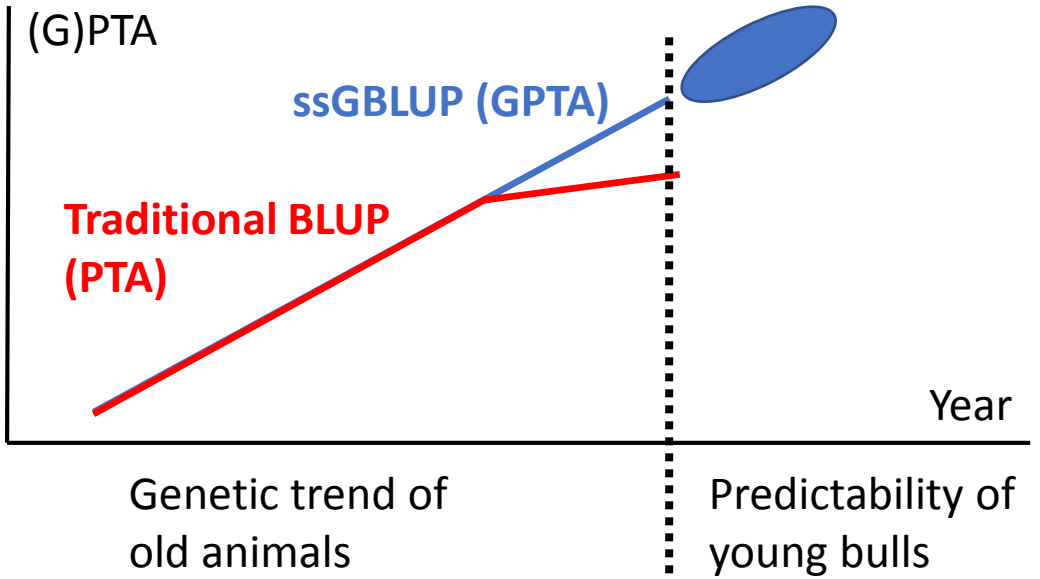
Single-step GBLUP



- Advantages
  - Expected accountability for genomic pre-selection √
  - Use of genotyped & non-genotyped in the same equations
  - Simplicity
- Concerns
  - Computational costs (solved) √
  - **Is it reliable for genomic prediction in dairy cattle?** √

Production traits of US Holsteins

- Comparison of genetic trends
  - Single-step GBLUP GPTA vs the traditional PTA (Data up to 2015)
  - Multi-step official GPTA vs the corresponding PTA (Published in 2016)
- Validation reliability for young bulls
  - 4-year truncated data
  - DYD in 2015 vs GPTA in 2011
- Computational feasibility
  - APY: Algorithm for Proven and Young for $\mathbf{G}^{-1}$



Full data

Data	Description	Number of records
Phenotypes	305-d Milk, fat, and protein yield from US Holsteins; from 1990 to 2015	50,970,954
Pedigree	3 generations back from phenotyped cows or genotyped animals; 215 unknown-parent groups (UPG)	29,651,623
Genotypes	Both male and female; including young bulls and heifers (#SNPs = 60671)	764,029

Three-trait repeatability model; same as in the official evaluation.

$\mathbf{H}^{-1}$ and GPTA

- Mixed model equations

$$\begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}'\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}'\mathbf{R}^{-1}\mathbf{Z} + \mathbf{H}^{-1} \otimes \boldsymbol{\Sigma}_{\mathrm{g}}^{-1} \end{bmatrix} \begin{bmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{u}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\mathbf{y} \\ \mathbf{Z}'\mathbf{R}^{-1}\mathbf{y} \end{bmatrix}$$

- Inverse relationship matrix

$$\mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & \mathbf{G}^{-1} - \omega\mathbf{A}_{22}^{-1} \end{bmatrix}$$

  - GPTA of a young animal

$$GPTA = w_1 PA + w_2 DGV - w_3 PI$$

  - ω: Constant to compensate for missing pedigrees ($\omega = 1$ for the full data).

Aguilar et al. (2010)

APY: Algorithm for Proven and Young

- Genotyped animals into two groups: “core” and “non-core”
  - Assumption:

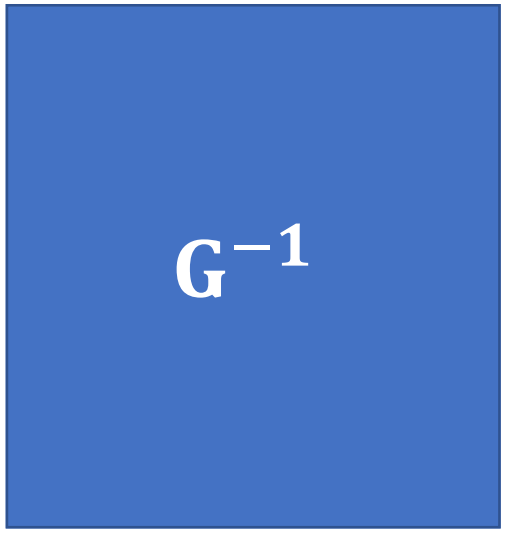
$$\mathbf{u}_n = \mathbf{P}\mathbf{u}_c + \mathbf{\Phi}$$

  - BV for non-core ($\mathbf{u}_n$) is a linear function of BV for core ($\mathbf{u}_c$).
- APY G-inverse (Misztal et al. 2016)

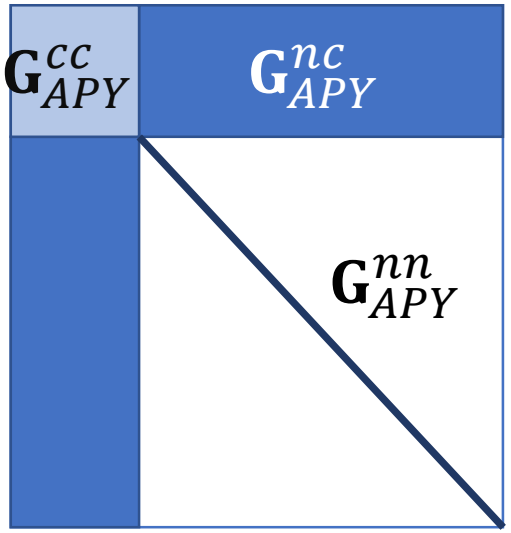
$$\mathbf{G}_{APY}^{-1} = \begin{bmatrix} \mathbf{G}_{cc}^{-1} + \mathbf{G}_{cc}^{-1}\mathbf{G}_{cn}\mathbf{M}^{-1}\mathbf{G}_{cn}'\mathbf{G}_{cc}^{-1} & \mathbf{G}_{cc}^{-1}\mathbf{G}_{cn}\mathbf{M}^{-1} \\ -\mathbf{M}^{-1}\mathbf{G}_{cn}'\mathbf{G}_{cc}^{-1} & \mathbf{M}^{-1} \end{bmatrix}$$

  - $\mathbf{M}^{-1}$: Diagonal matrix

APY $\mathbf{G}^{-1}$



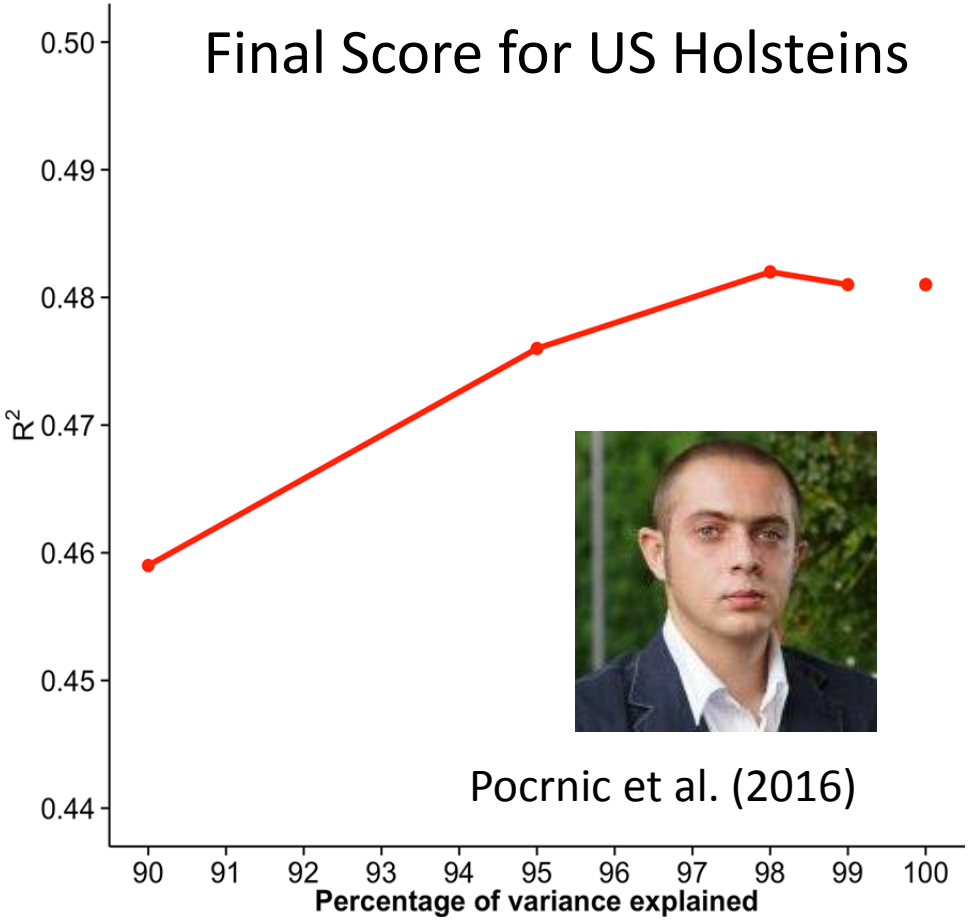
Regular $\mathbf{G}^{-1}$



APY $\mathbf{G}^{-1}$

- Sparse
- Easy computations
- Gives the same GPTA as the regular $\mathbf{G}^{-1}$ using a few core animals (Fragomeni et al., 2015)
- How to choose core animals?
  - How many? – dimensionality of G
  - Which animals? – random choice

Dimensionality of **G**

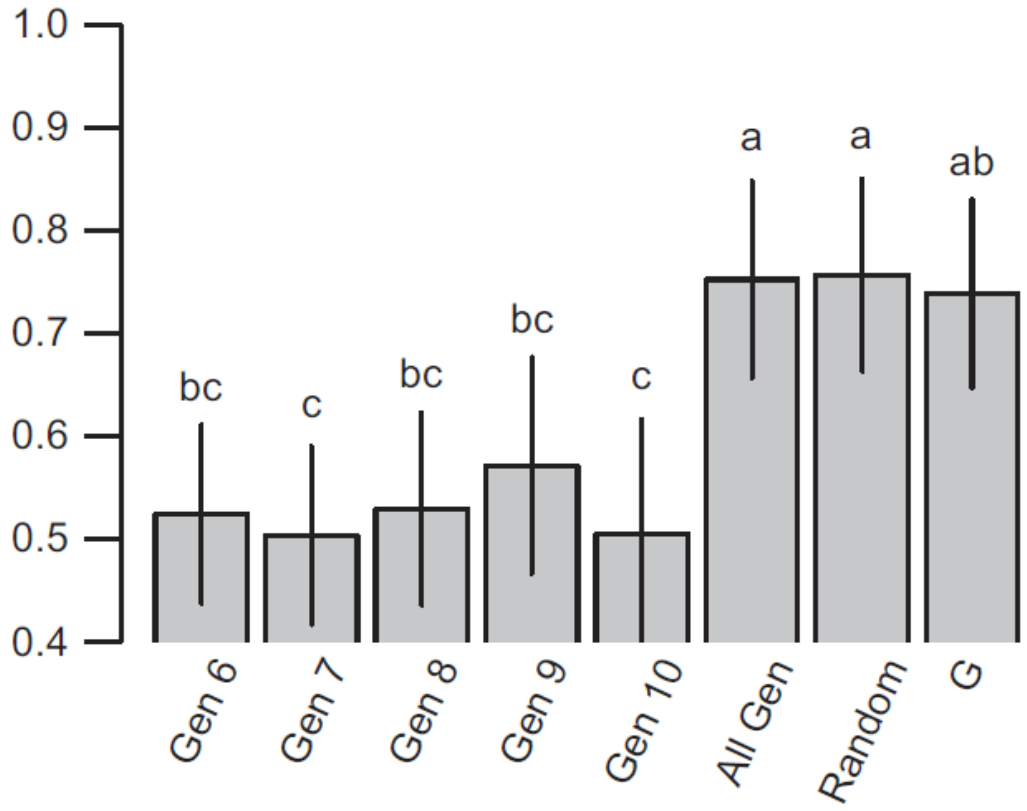


- Dim. of G ≈ M_e
  - M_e: the number of independent chromosome segments = **the optimal number of core animals**
- Estimate of dim. of G
  - M_e ≈ the # of largest eigenvalues explaining the most (98%) of variation in G
  - 18,359 cores for 760K US Holsteins

Which core animals?

Bradford et al. (2017)

Accuracy



- The best practice:
  - Core animals covering all generations.
  - Or, just randomly choose the core.
- Core animals represent independent chromosome segments in the populations.
- In this study:
  - 18,359 random core animals

Inbreeding and UPG

- QP-transformation for $\mathbf{A^{-1}}$ (Westell et al., 1988; Quaas 1988)

$$\mathbf{A}^* = \begin{bmatrix} \mathbf{A^{-1}} & \mathbf{-A^{-1}Q} \\ \mathbf{-Q'A^{-1}} & \mathbf{Q'A^{-1}Q} \end{bmatrix}$$: Henderson's rule with inbreeding

- QP-transformation for $\mathbf{H^{-1}}$ (Misztal et al., 2013)

$$\mathbf{H}^* = \mathbf{A}^* + \begin{bmatrix} 0 & 0 & 0 \\ 0 & \mathbf{G^{-1}} - \mathbf{A_{22}^{-1}} & -(\mathbf{G^{-1}} - \mathbf{A_{22}^{-1}})\mathbf{Q}_2 \\ 0 & -\mathbf{Q}_2'(\mathbf{G^{-1}} - \mathbf{A_{22}^{-1}}) & \mathbf{Q}_2'(\mathbf{G^{-1}} - \mathbf{A_{22}^{-1}})\mathbf{Q}_2 \end{bmatrix}$$

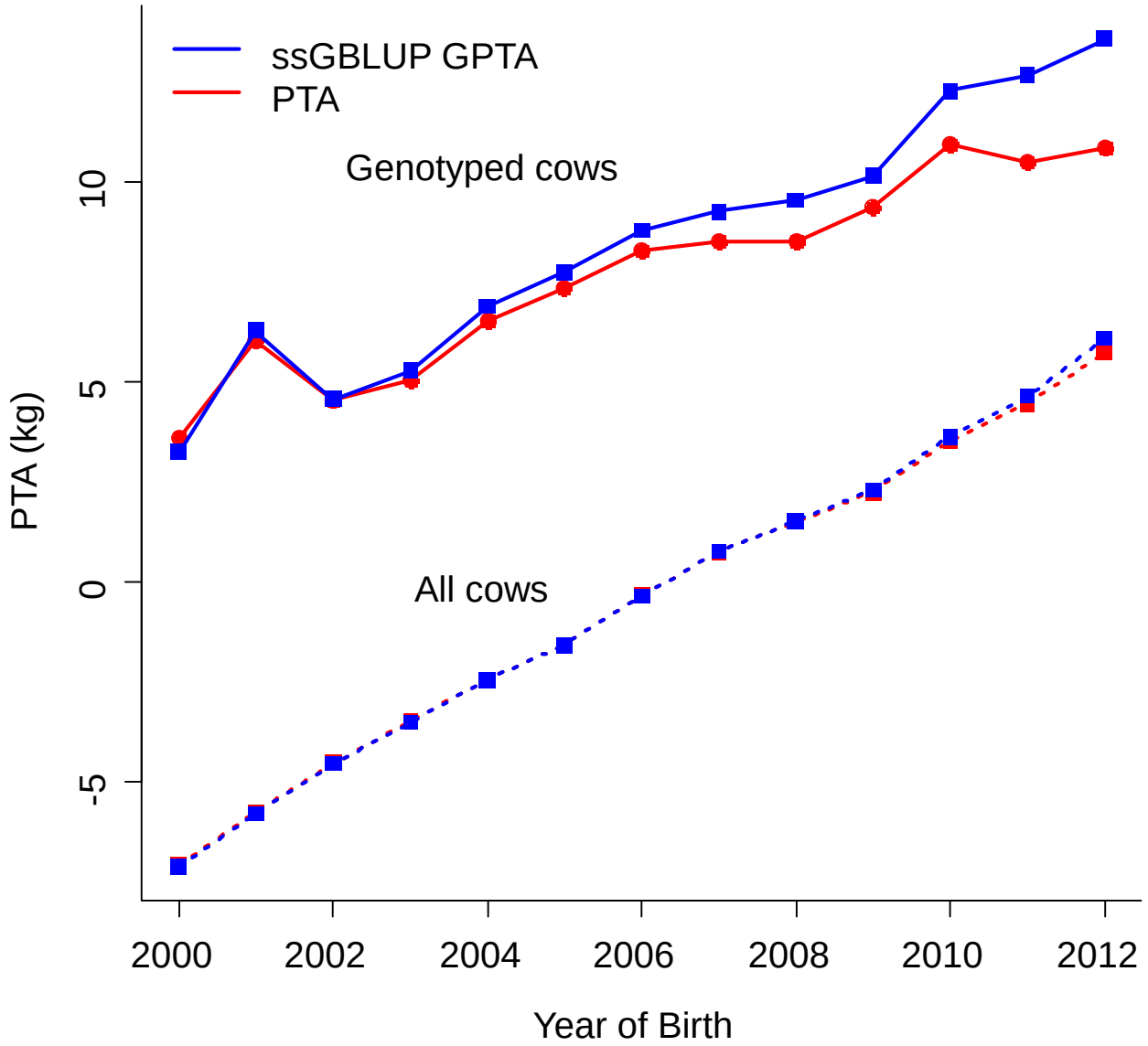
Computing time

Preparation	Traditional BLUP	Single-step GBLUP
$\mathbf{G}_{APY}^{-1}$	N/A	6 h 53 min
Other	9 min	48 min
Subtotal in preparation	9 min	**7 h 41 min**
Iteration	**Traditional BLUP**	**Single-step GBLUP**
Number of iterations	402	464
Time per PCG iteration	51 sec	83 sec
Post-processing	12 min	13 min
Subtotal in iterations	5 h 53 min	**10 h 54 min**

Intel Xeon X7650 (2.26 GHz; 20 cores for preparation and 6 cores for iterations)

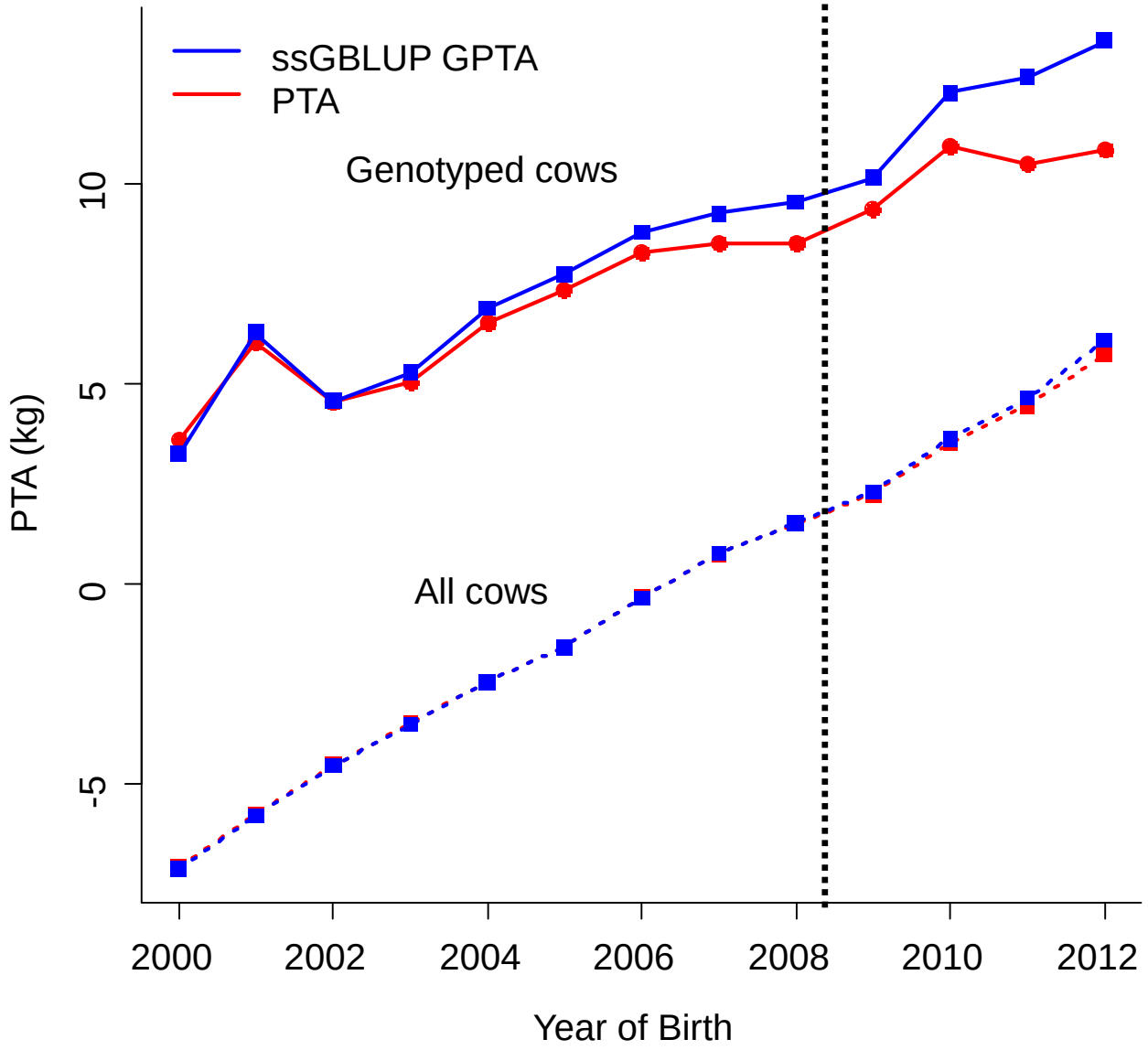
Computationally feasible

Cows : ssGBLUP vs traditional PTA (protein)



*Cows with record(s)

Cows : ssGBLUP vs traditional PTA (protein)



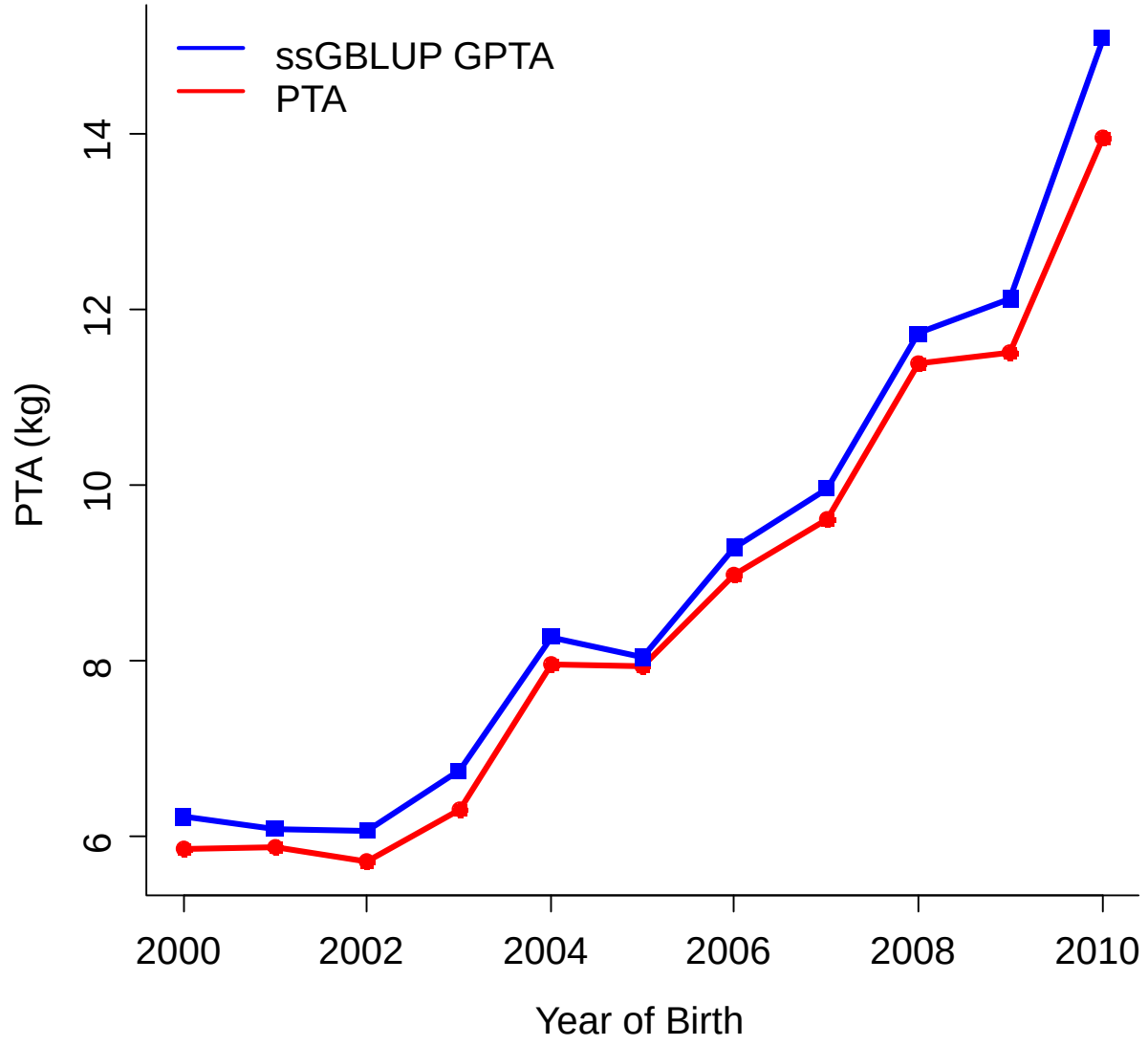
1.1 kg/yr : Reasonable

0.4 kg/yr : Biased

1.2 kg/yr

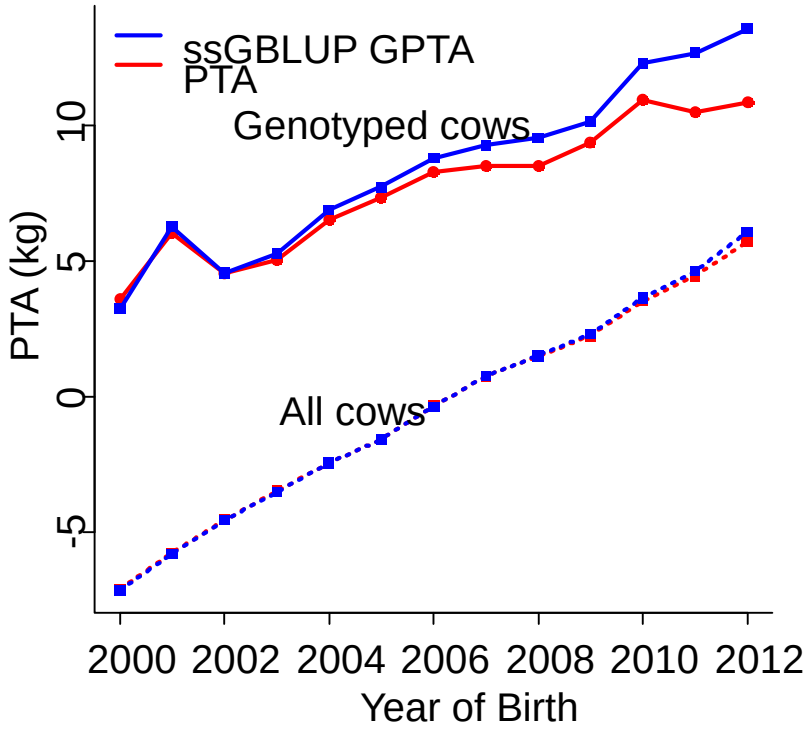
*Cows with record(s)

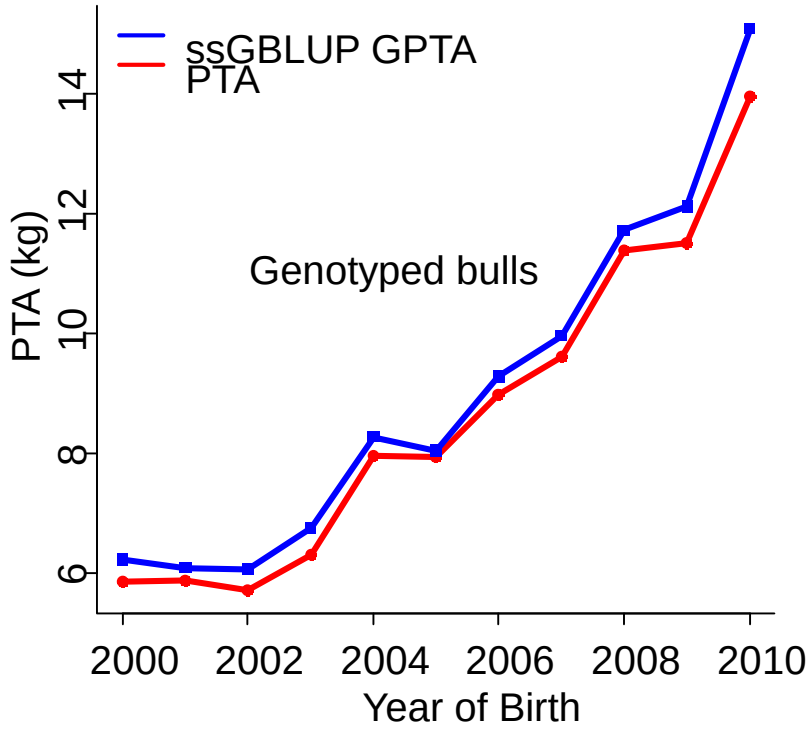
Bulls: ssGBLUP vs traditional PTA (protein)



*Genotyped bulls with at least 10 daughters with record(s)

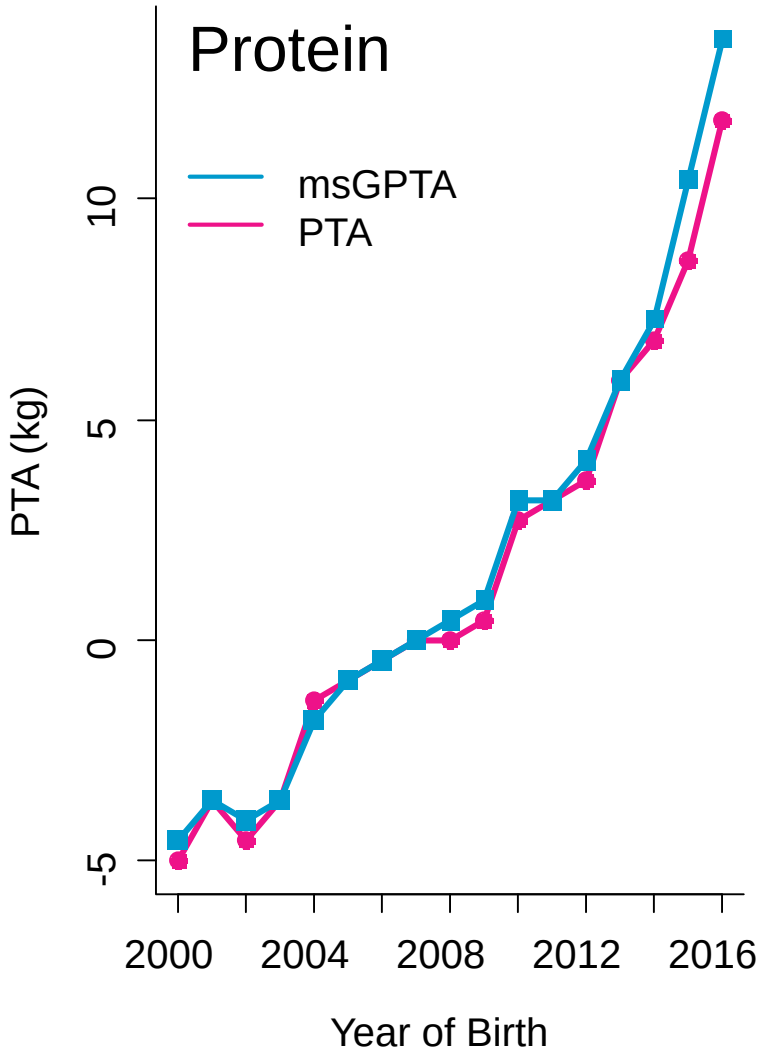
Bias in genotyped cows and bulls



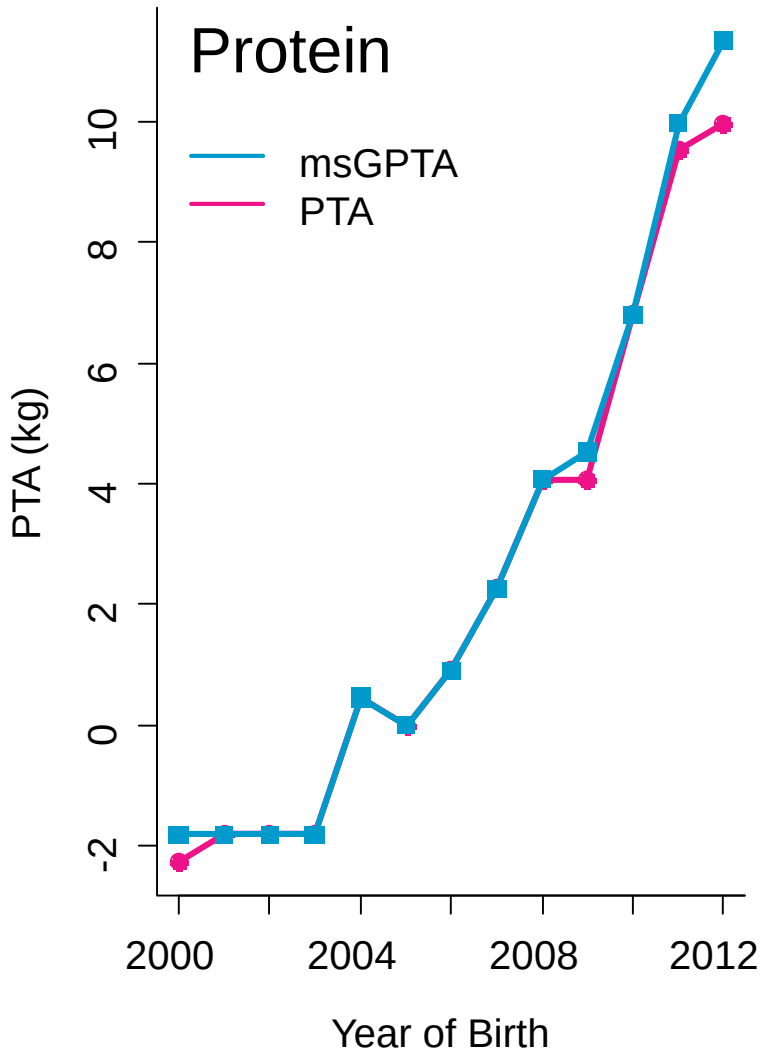


Larger bias in cows: shorter generation interval & lower reliability of GPTA

Official (G)PTA: Cows

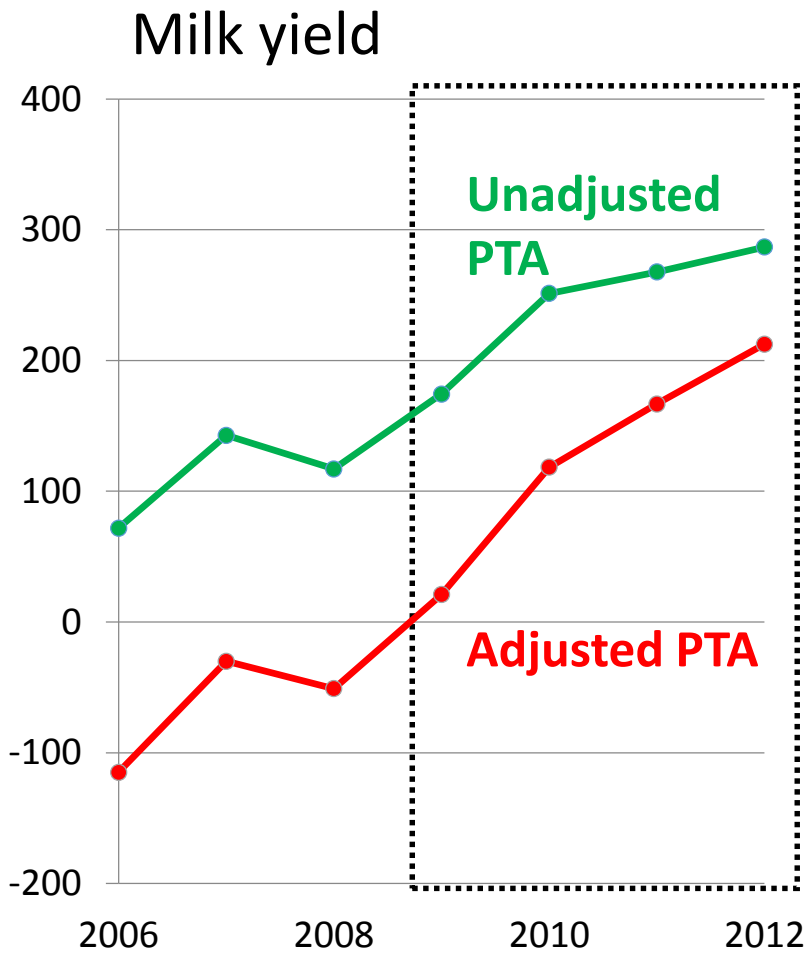


Official (G)PTA: Bulls

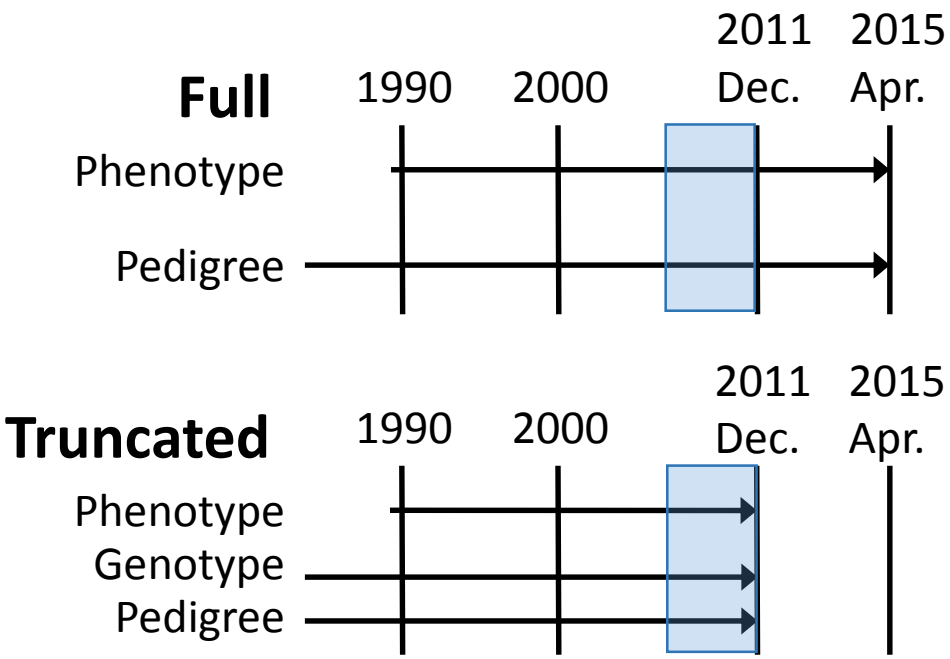


Adjustments on the official PTA

- Official PTA adjusted by Wiggans et al. (2012)
  - Cow trend aligned to bull trend (Reduction in bias for cows)
  - Same trend in PTA and GPTA
- Additional adjustments in the official evaluation
  - Breed difference
  - Inbreeding



Validation study



For Daughter Yield Deviation (DYD2015)

For GPTA using ssGBLUP (GPTA2011)

Validation Bulls: Genotyped young bulls with no tested daughters in 2011 but with at least 50 tested daughters in 2015 (N=3,797)

$$DYD2015 = b_1 \times GPTA2011 + b_0$$

- R^2 value: validation reliability
- Slope (b_1): Bias of prediction

Configurations in $\mathbf{H}^{-1}$

1. Weight (ω) on $\mathbf{A}_{22}^{-1}$: **0.9** or **1.0**
2. UPG: **pedigree only**, **pedigree + genomic UPG**, **or no UPG**

$$\mathbf{H}^* = \mathbf{A}^* + \begin{bmatrix} 0 & 0 & 0 \\ 0 & \mathbf{G}^{-1} - \omega\mathbf{A}_{22}^{-1} & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & -(\mathbf{G}^{-1} - \omega\mathbf{A}_{22}^{-1})\mathbf{Q}_2 \\ 0 & -\mathbf{Q}_2'(\mathbf{G}^{-1} - \omega\mathbf{A}_{22}^{-1}) & \mathbf{Q}_2'(\mathbf{G}^{-1} - \omega\mathbf{A}_{22}^{-1})\mathbf{Q}_2 \end{bmatrix}$$

DYD2015 vs GPTA2011 (Protein)

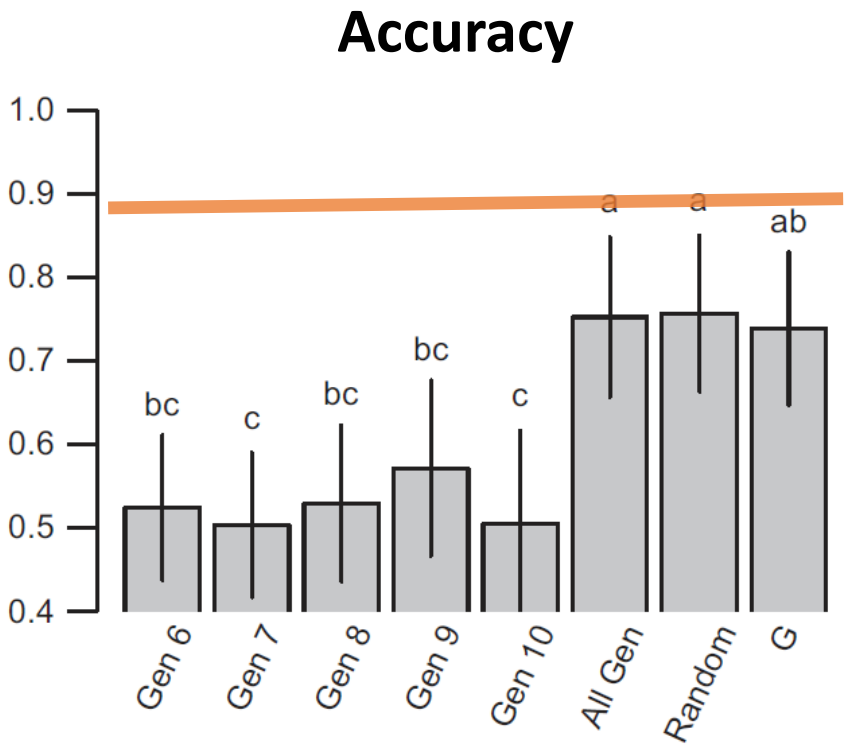
Data				R2	b1
Official GPTA 2011				0.51	0.81
Data	**UPG**	**ω=0.9 R2**	**b1**	**ω=1.0 R2**	**b1**
Truncated 2011	Pedigree	0.50	0.96	0.52	0.78
	Ped. + Genomic	0.39	0.74	0.32	0.51
	No UPGs			0.50	0.78

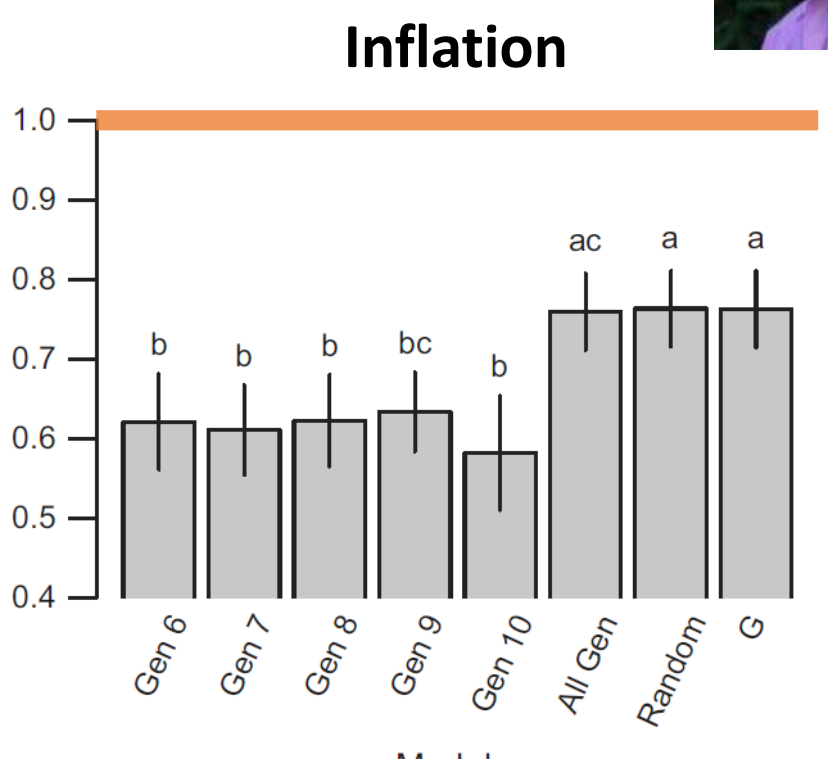
Different predictions by UPG

Incomplete pedigree on accuracy & inflation

Complete pedigree

Incomplete pedigree





* Simulated data (Bradford et al., 2017)

Low accuracy with genomic UPG

- GPTA for young genotypes
  - No UPG: $GPTA = w_1 PA + w_2 DGV - w_3 PI \approx DGV$
  - With UPG: $GPTA = w_1 PA + w_2 DGV - w_3 PI + w_4 UPG \approx DGV + UPG$

Larger weights with many genotypes

Not needed for young animals

- Specific pattern of missing pedigree
  - Production traits: many grade animals
  - No problem in Finland (Koivula et al. 2017) or for US type traits (Tsuruta 2017)
- Solutions: research in progress
  - Option: only DGV for young genotypes
  - Metafounders

Indirect prediction

- Optional step to ssGBLUP
  1. Compute DGV $\hat{\mathbf{u}}$ from ssGBLUP without young animals
  2. Compute SNP effects as $\hat{\mathbf{a}} = k\mathbf{Z}'\mathbf{G}\hat{\mathbf{u}}$.
  3. Compute DGV for young animals as $\hat{\mathbf{u}}_{young} = \mathbf{Z}\hat{\mathbf{a}}$.
- Successfully applied to Angus & simulated data

Lourenco et al. (2015)

Bradford et al. (2017)

Metafounders

- Regular ssGBLUP: scaling $\mathbf{G}$ to $\mathbf{A}$; reasonable in complete pedigree
- Metafounders: scaling $\mathbf{A}$ to $\mathbf{G}$
  - Treat UPG as metafounders
  - Estimate genomic relationships among metafounders ($\boldsymbol{\Gamma}$) using $\mathbf{G}$
  - Construct $\mathbf{A}^{-1}$ and $\mathbf{A}_{22}^{-1}$ with $\boldsymbol{\Gamma}$ using the Henderson's and Collau's methods
- Final form:

$$\mathbf{H}^{\Gamma-1} = \mathbf{A}^{\Gamma-1} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}^{-1} - \mathbf{A}_{\mathbf{22}}^{\Gamma-1} \end{bmatrix}$$

Legarra et al. (2015)

Summary

- The traditional PTA for genotyped animals are likely underestimated; Needs adjustments in multi-step methods.
- Single-step GBLUP can account for the pre-selection bias.
- Single-step GBLUP may give a reasonable genetic trend without adjustments.
- Missing pedigree may reduce predictability of genomic predictions.
- We can recover the predictability for young animals; research in progress.

Acknowledgement

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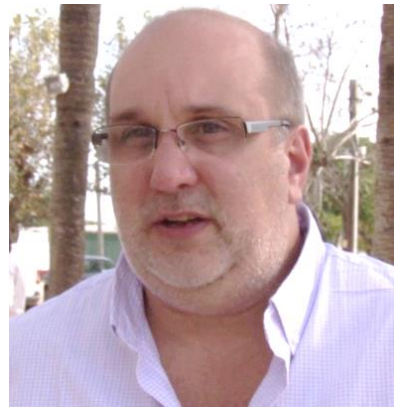

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