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

Y. Masuda[1], P. M. VanRaden[2], I. Misztal[1], and T. J. Lawlor[3]

1 University of Georgia, USA
2 AGIL, USDA, USA
3 Holstein Association USA, Inc., USA

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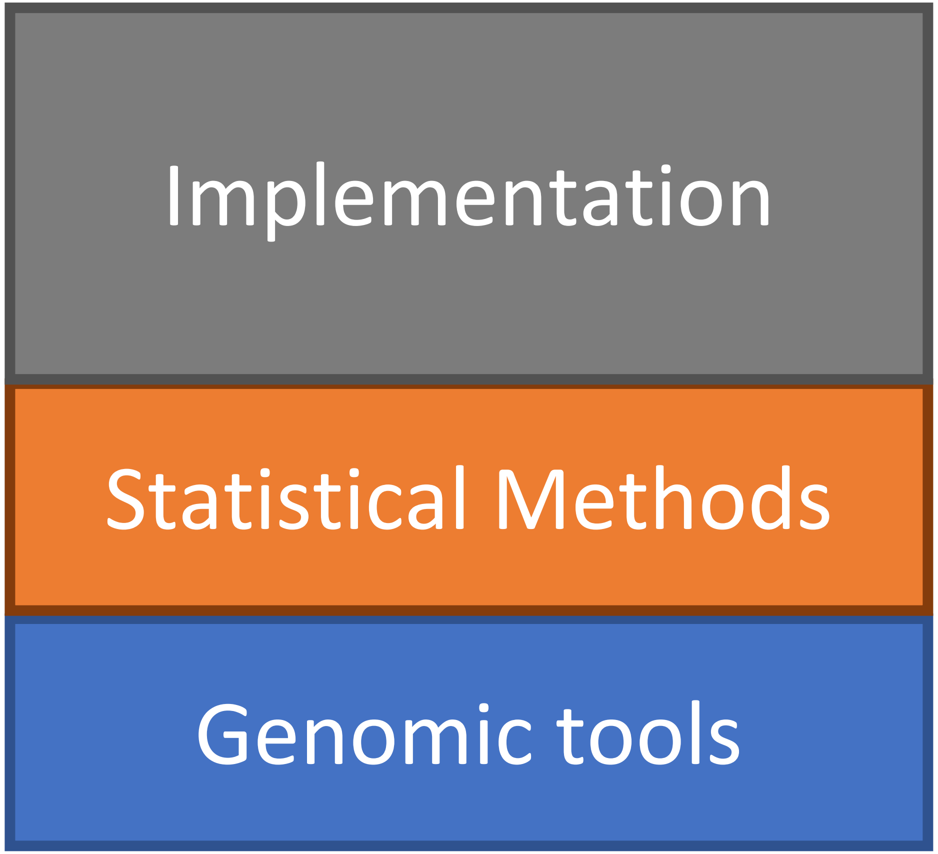
Genomic selection in practice



Implementation

Statistical Methods

Genomic tools

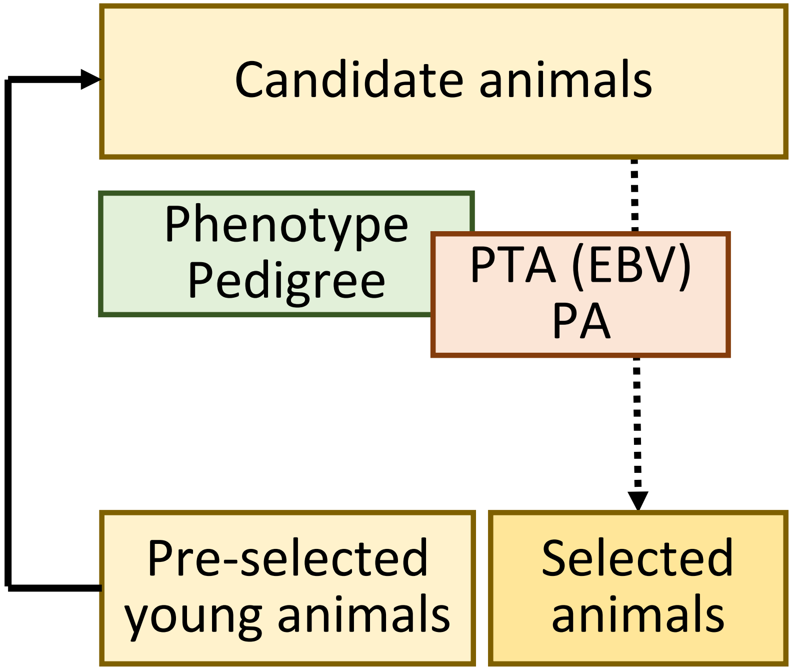
- **Use of existing data-collection systems (phenotypes & pedigrees)**
- **Integration of genomic data**
- **Stabilization of genomic predictions**

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

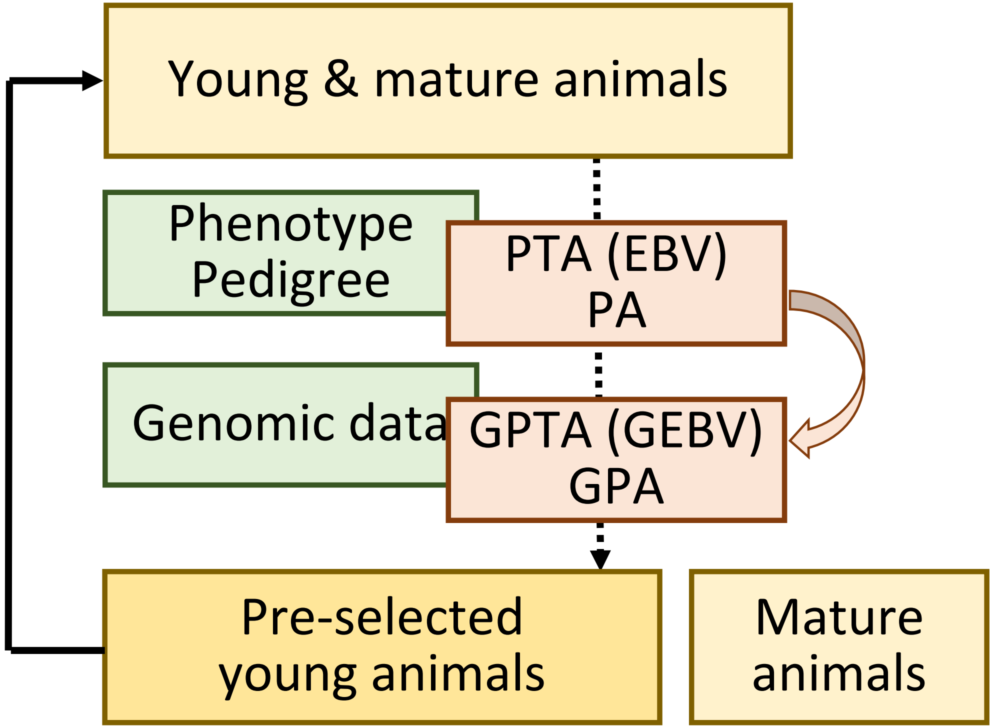
- **Efficient genotyping technique**
- **Affordable SNP chips**

Dairy cattle evaluation

Conventional animal-model BLUP



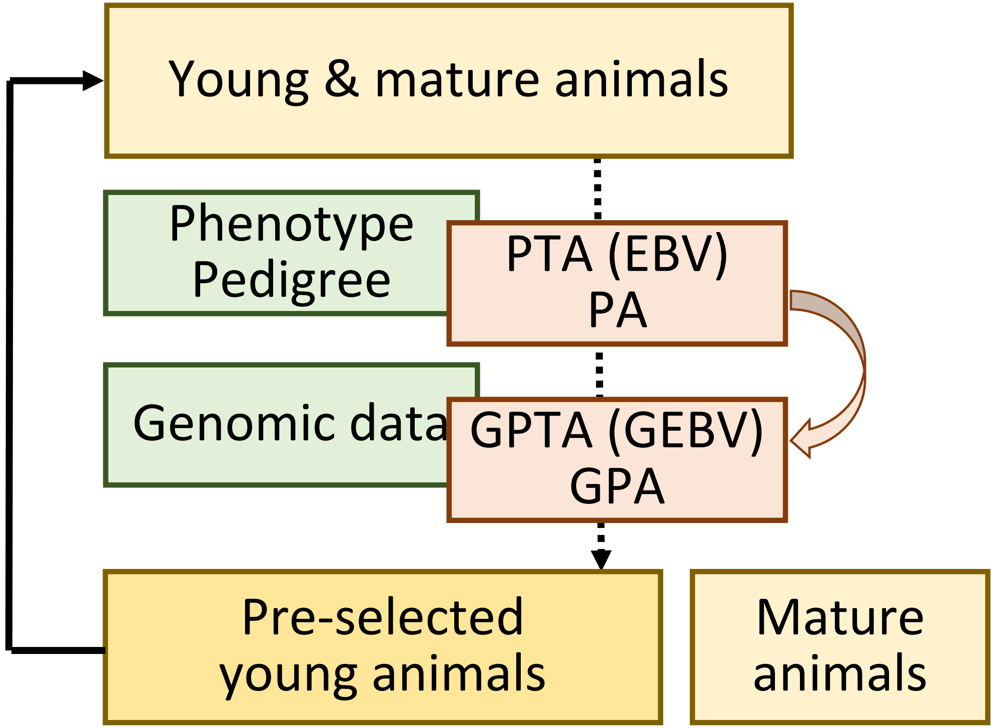
Multi-step (MS) genomic evaluation



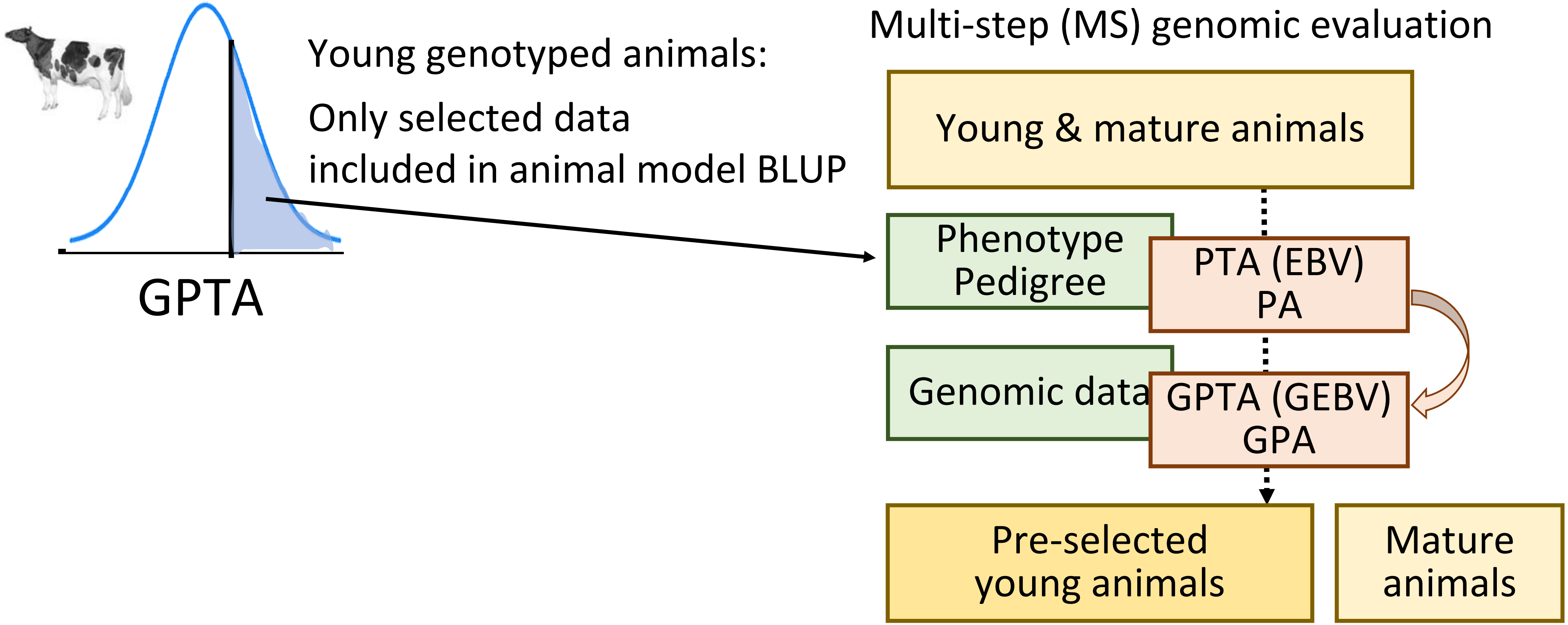
Multi-step evaluation

- 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**

Multi-step (MS) genomic evaluation



Pre-selection bias



Young genotyped animals:

Only selected data
included in animal model BLUP

Multi-step (MS) genomic evaluation

Young & mature animals

Phenotype
Pedigree

PTA (EBV)
PA

Genomic data

GPTA (GEBV)
GPA

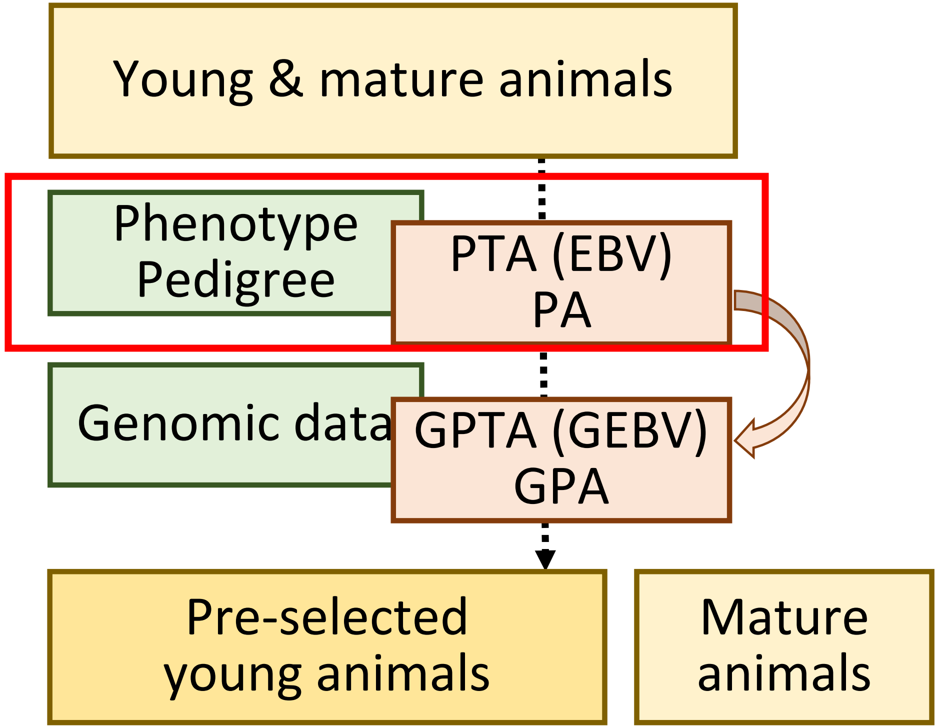
Pre-selected
young animals

Mature
animals

Pre-selection bias

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

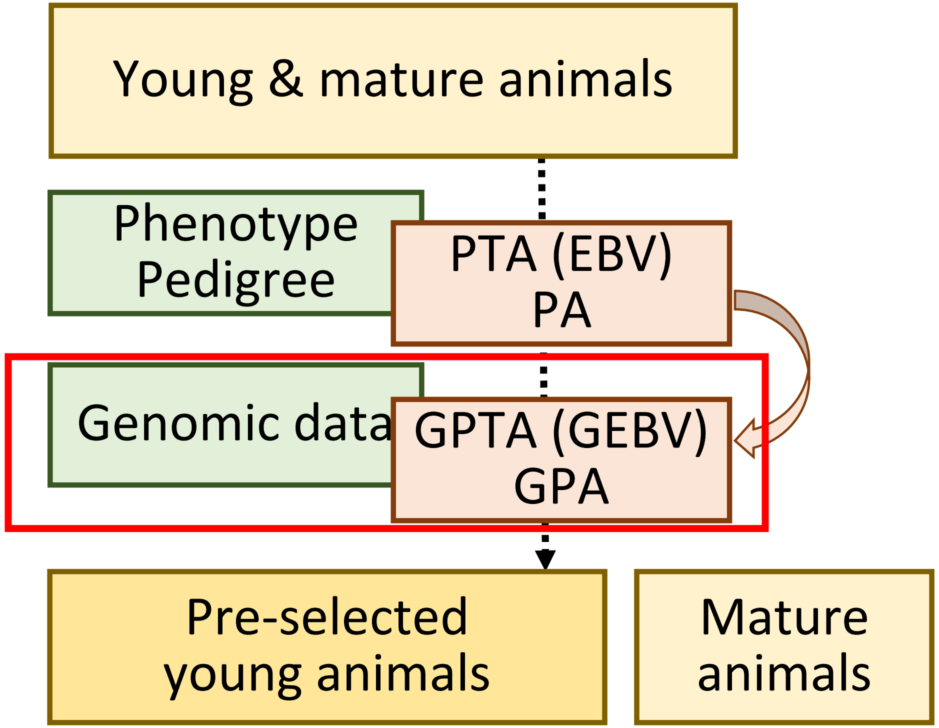
Multi-step (MS) genomic evaluation



Pre-selection bias

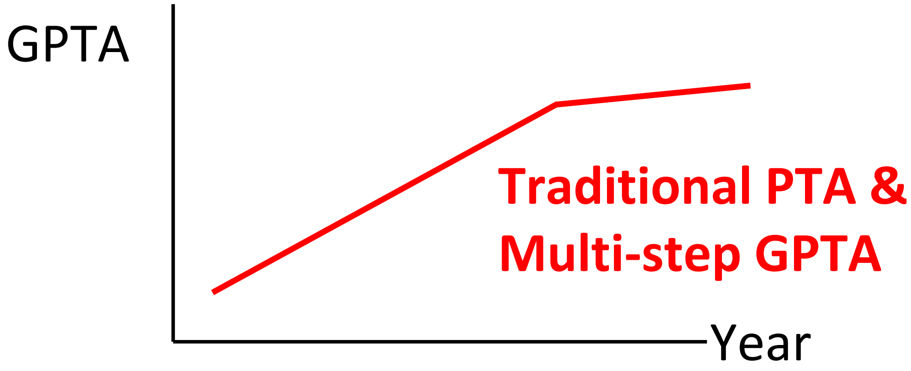
- Biased PTA (EBV) to GPTA
- GPTA biased down

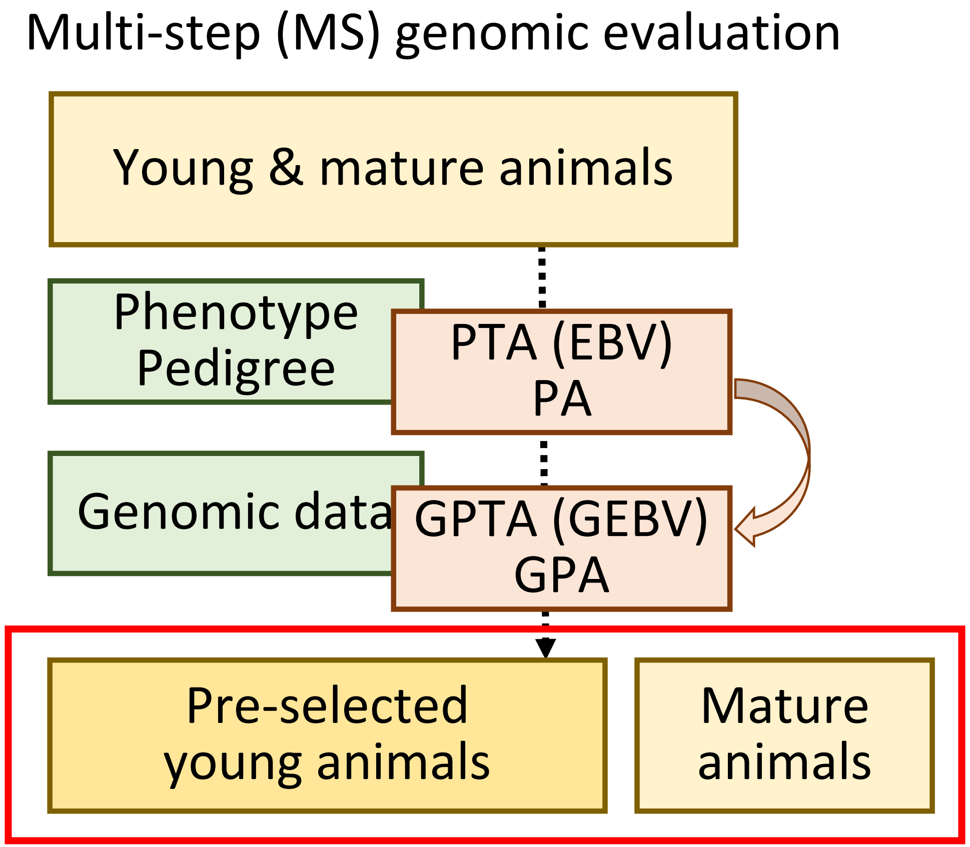
Multi-step (MS) genomic evaluation



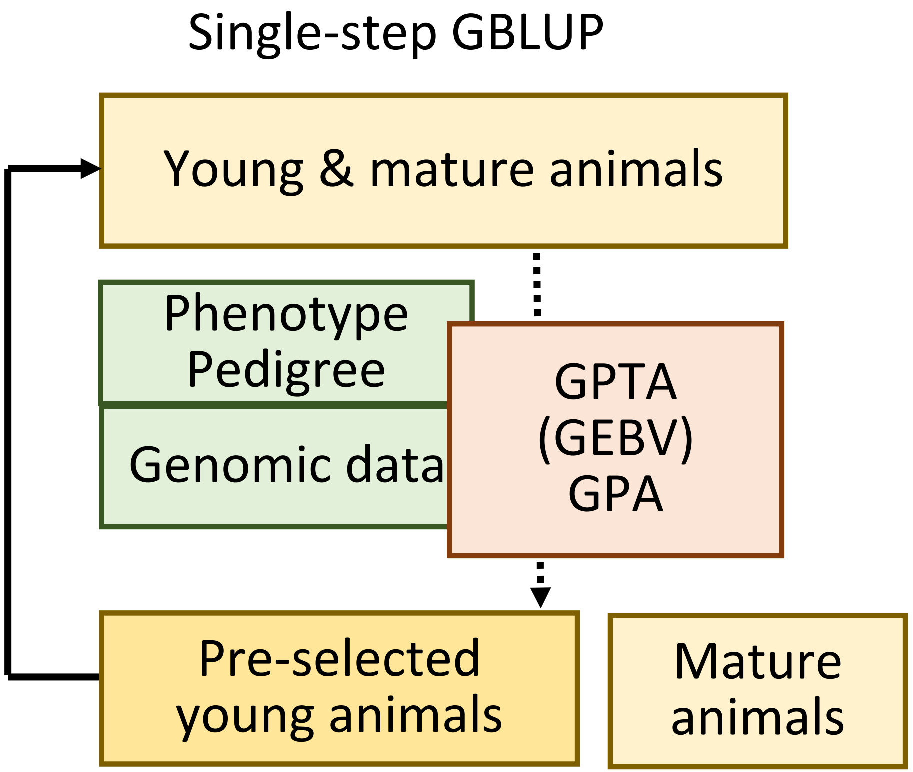
Pre-selection bias

- Possible result: underestimated genetic trend for genomically selected animals





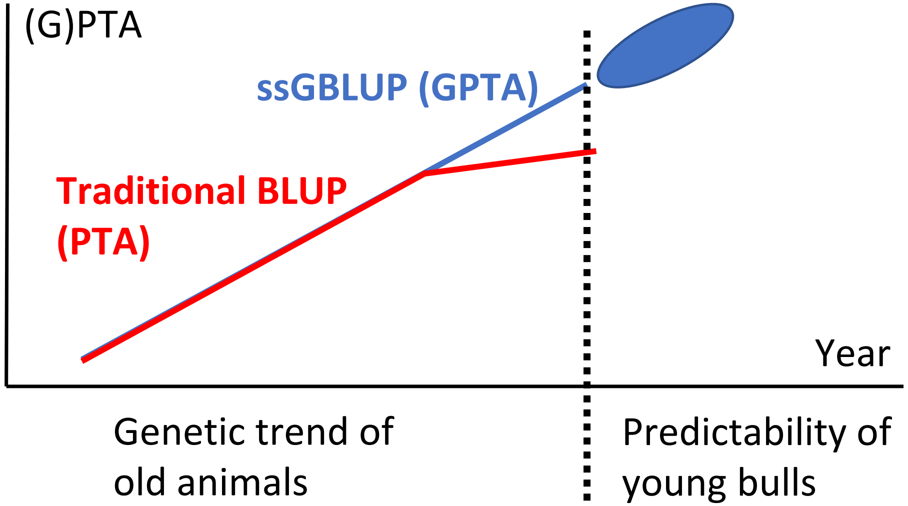
Single-step GBLUP



- 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:

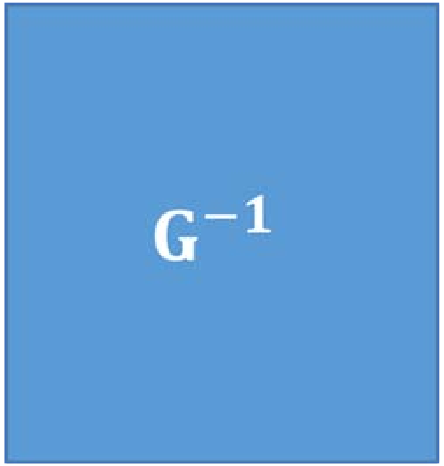
$$\mathbf{u}_n = \mathbf{P}\mathbf{u}_c + \mathbf{\Phi}$$

  - 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)

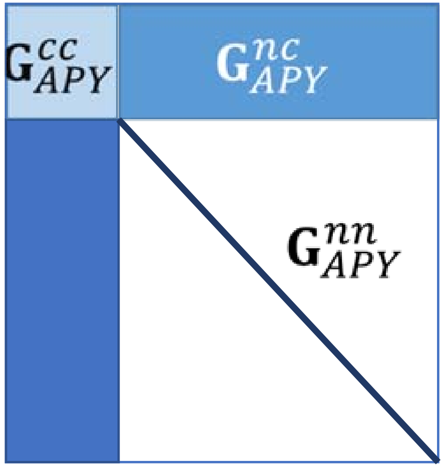
$$\mathbf{G}_{APY}^{-1} = \begin{bmatrix} \mathbf{G}_{cc}^{-1} + \mathbf{G}_{cc}^{-1}\mathbf{G}_{cn}\mathbf{M}^{-1}\mathbf{G}_{cn}'\mathbf{G}_{cc}^{-1} & \mathbf{G}_{cc}^{-1}\mathbf{G}_{cn}\mathbf{M}^{-1} \\ -\mathbf{M}^{-1}\mathbf{G}_{cn}'\mathbf{G}_{cc}^{-1} & \mathbf{M}^{-1} \end{bmatrix}$$

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

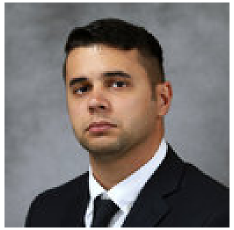
APY $\mathbf{G}^{-1}$



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

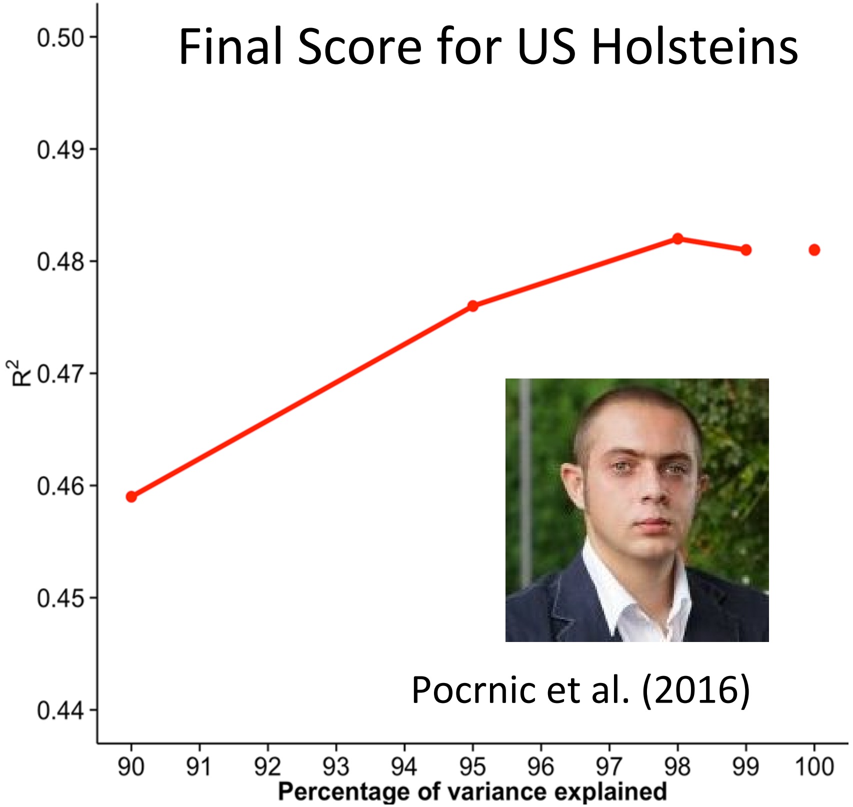


APY $\mathbf{G}^{-1}$



- 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


Final Score for US Holsteins

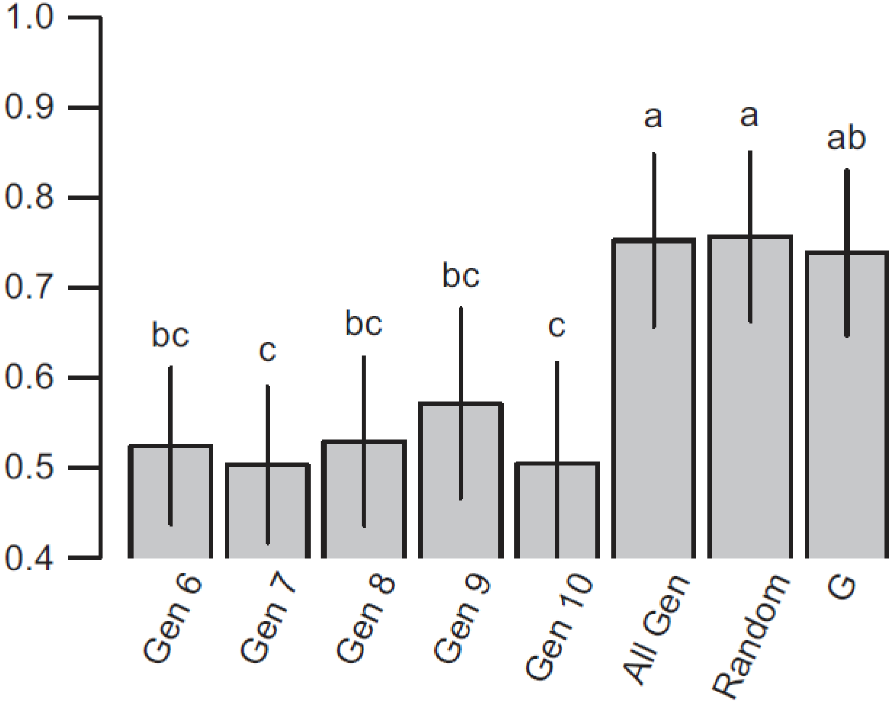
Pocrnic et al. (2016)

- 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

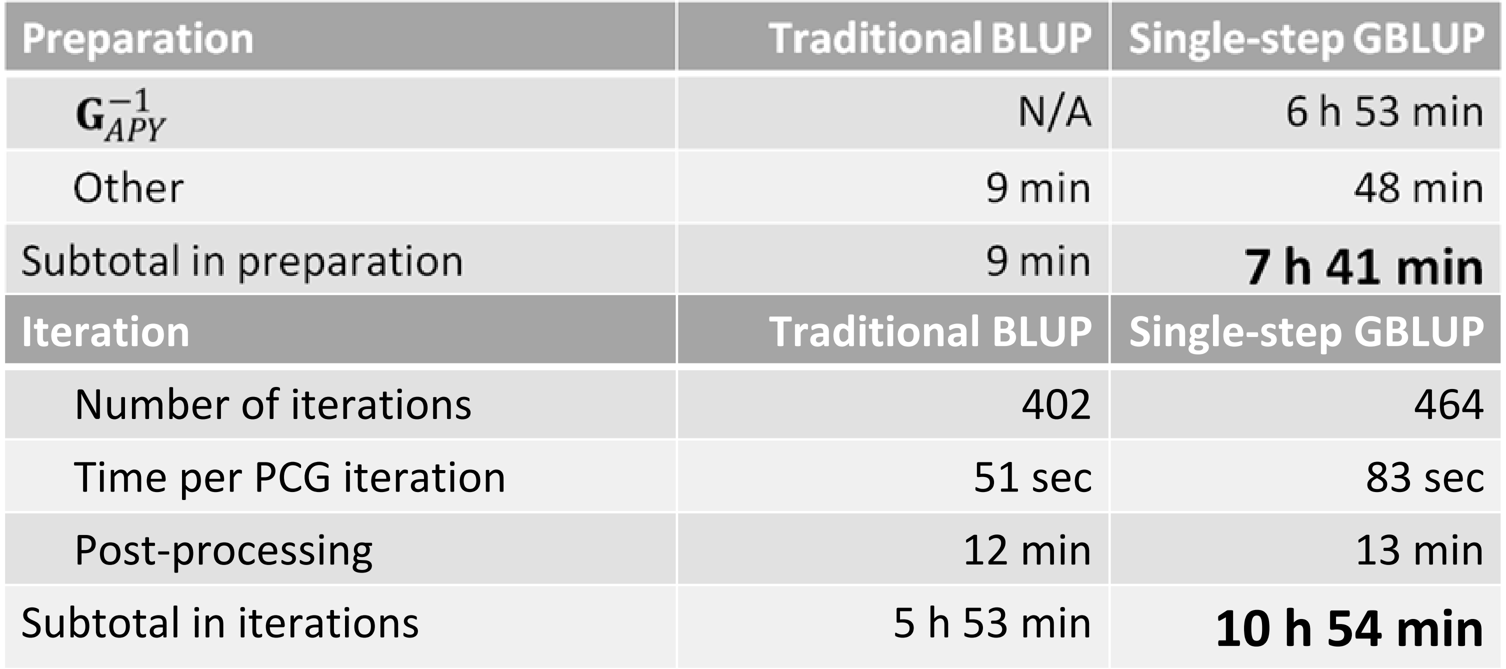
- QP-transformation for $\mathbf{A}^{-1}$ (Westell et al., 1988; Quaas 1988)

$$\mathbf{A}^{*}=\begin{bmatrix}\mathbf{A}^{-1} & -\mathbf{A}^{-1}\mathbf{Q}\\ -\mathbf{Q}'\mathbf{A}^{-1} & \mathbf{Q}'\mathbf{A}^{-1}\mathbf{Q}\end{bmatrix}$$: 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

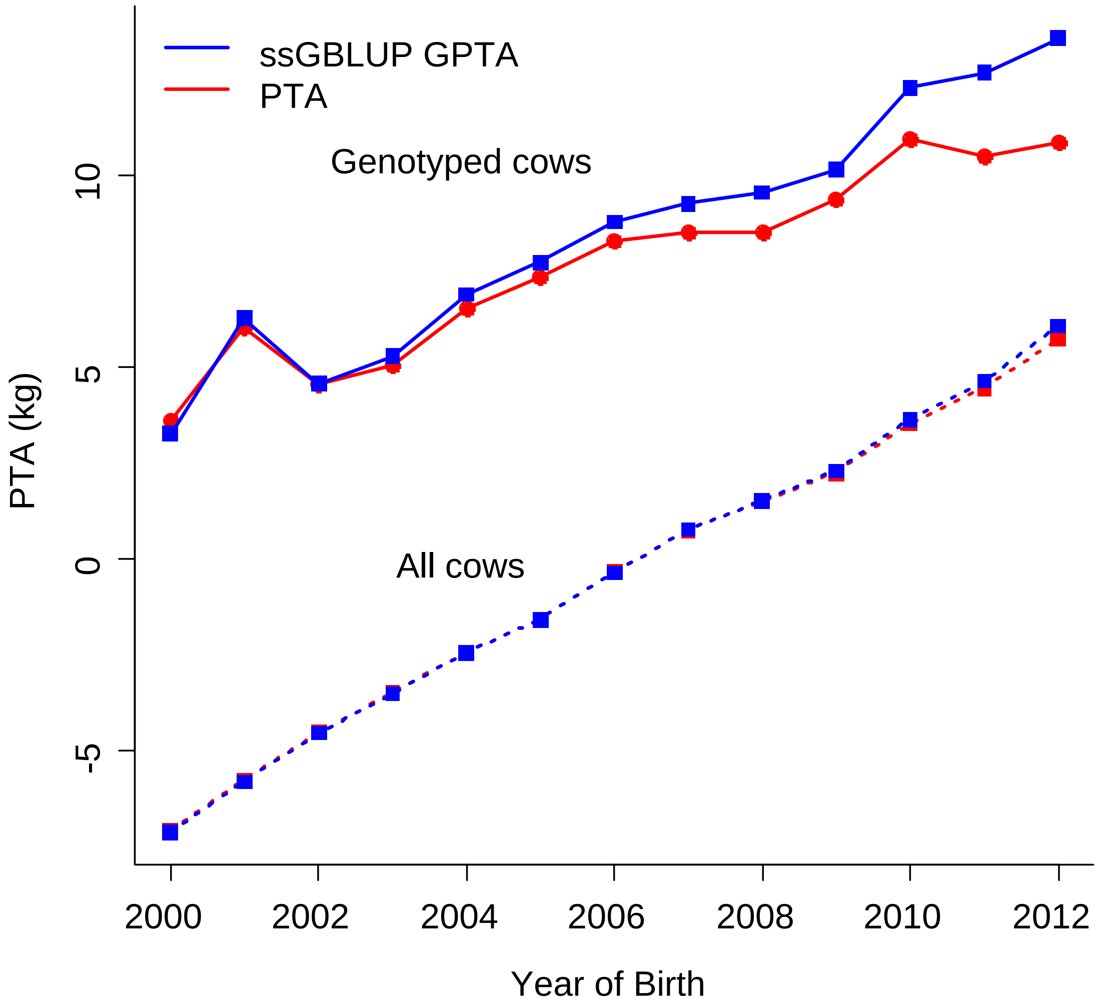


Preparation	Traditional BLUP	Single-step GBLUP
$\mathbf{G}_{APY}^{-1}$	N/A	6 h 53 min
Other	9 min	48 min
Subtotal in preparation	9 min	**7 h 41 min**
Iteration	**Traditional BLUP**	**Single-step GBLUP**
Number of iterations	402	464
Time per PCG iteration	51 sec	83 sec
Post-processing	12 min	13 min
Subtotal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

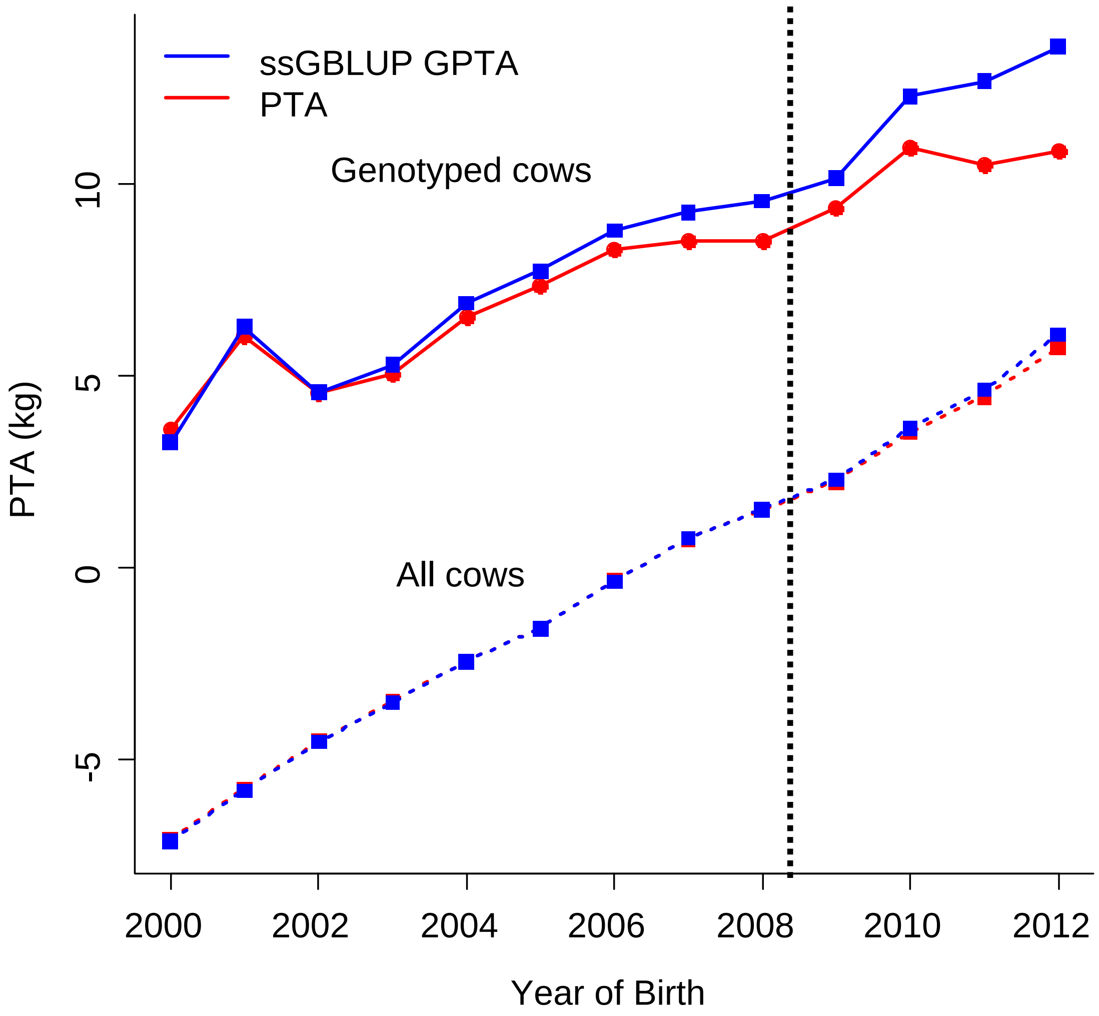
Computationally feasible

Cows : ssGBLUP vs traditional PTA (protein)



*Cows with record(s)

Cows : ssGBLUP vs traditional PTA (protein)



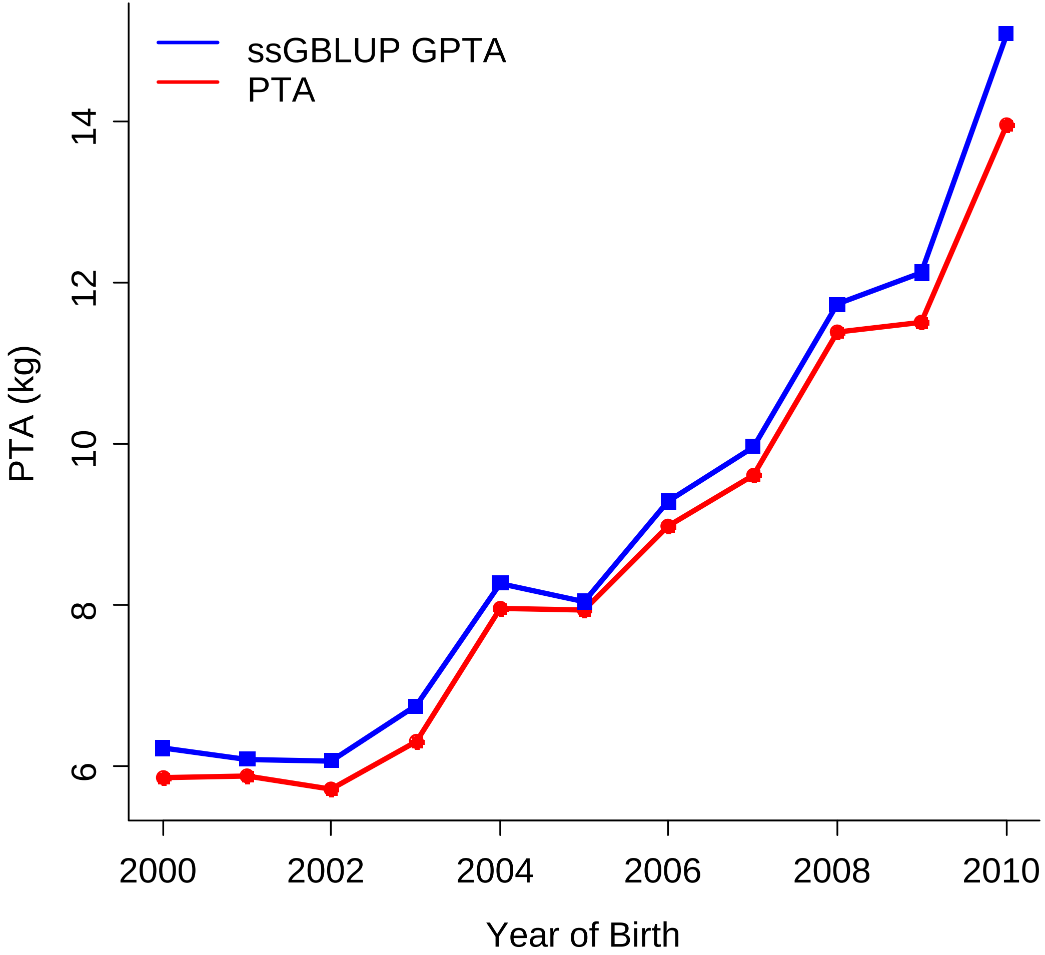
1.1 kg/yr : Reasonable

0.4 kg/yr : Biased

1.2 kg/yr

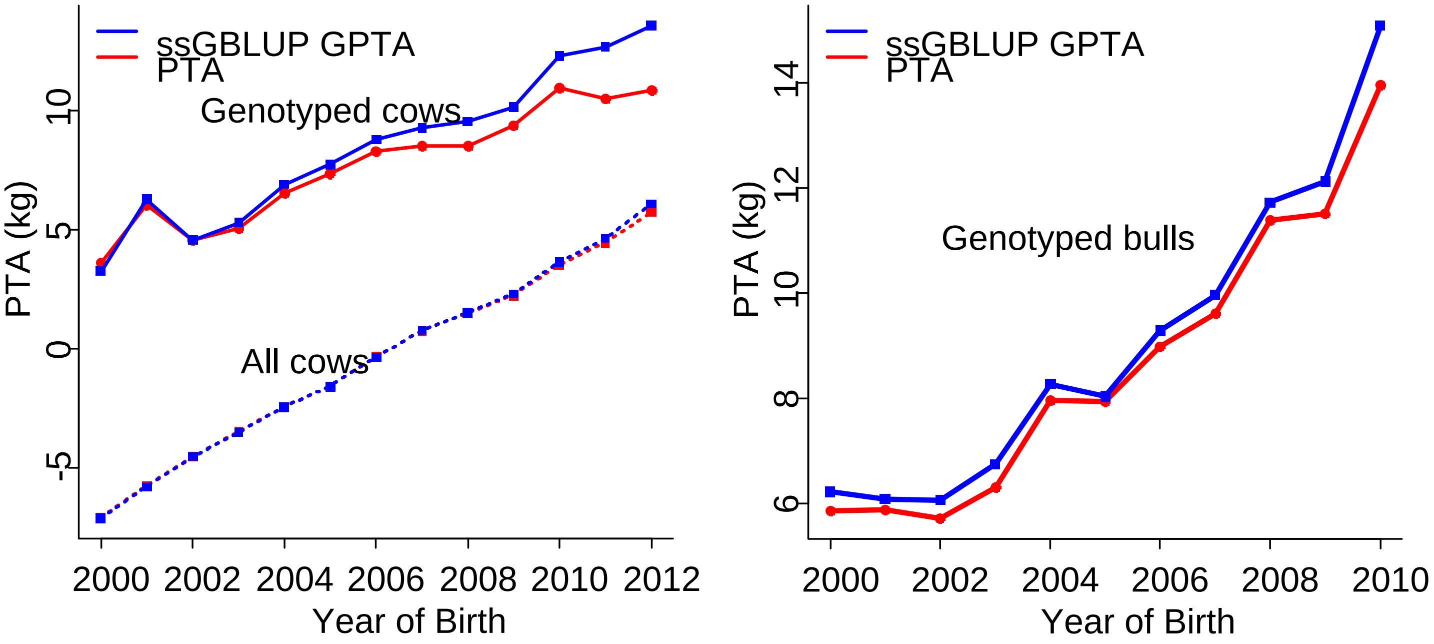
*Cows with record(s)

Bulls: ssGBLUP vs traditional PTA (protein)



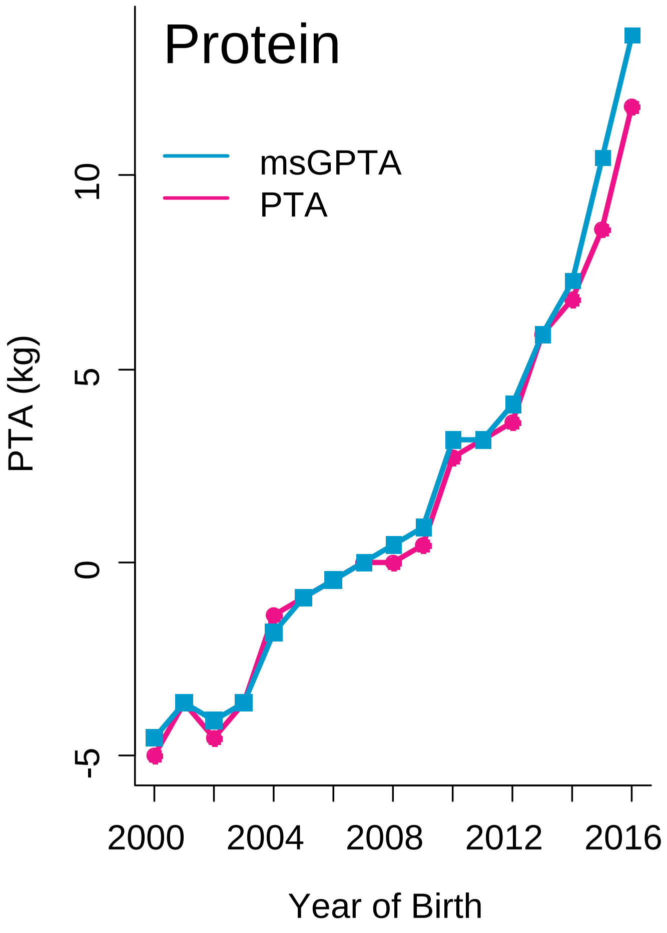
*Genotyped bulls with at least 10 daughters with record(s)

Bias in genotyped cows and bulls

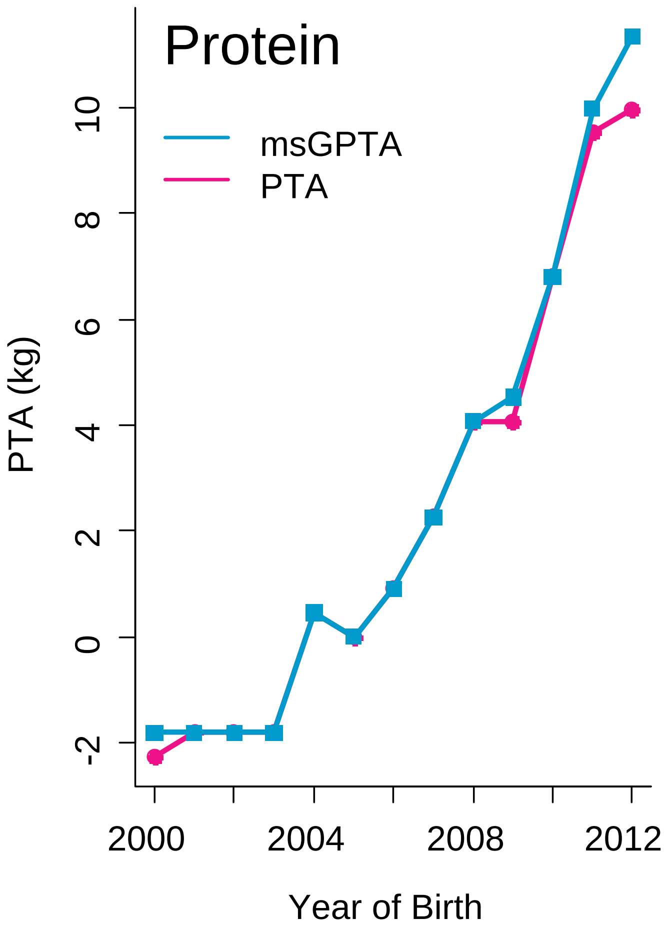


Larger bias in cows: shorter generation interval & lower reliability of GPTA

Official (G)PTA: Cows



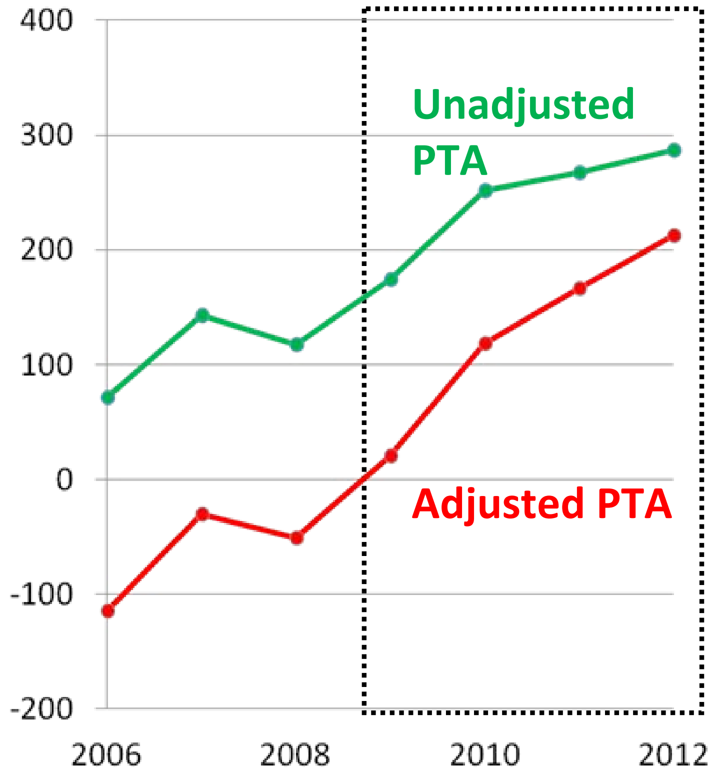
Official (G)PTA: Bulls



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

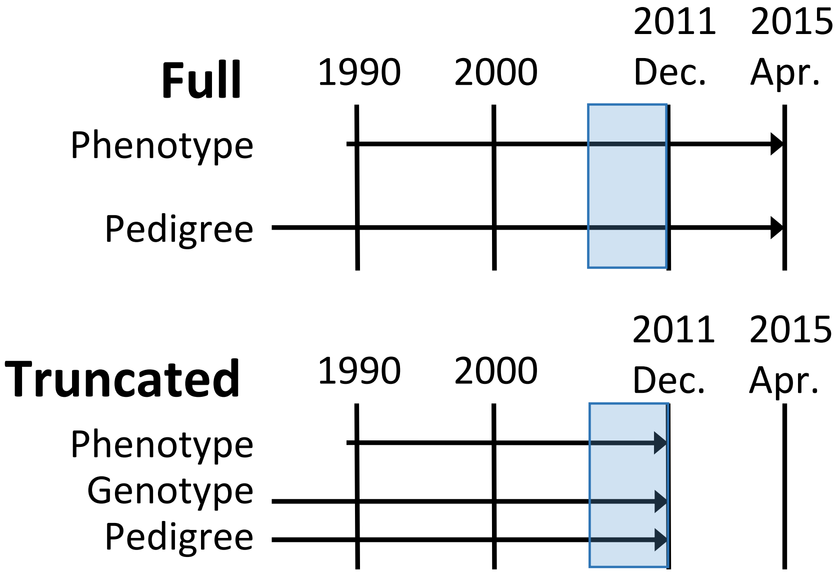
Milk yield



16kg/yr

24kg/yr
= same as GPTA

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**

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

DYD2015 vs GPTA2011 (Protein)

Data				R2	b1
Official GPTA 2011				0.51	0.81

		ω=0.9		ω=1.0	
Data	**UPG**	**R2**	**b1**	**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

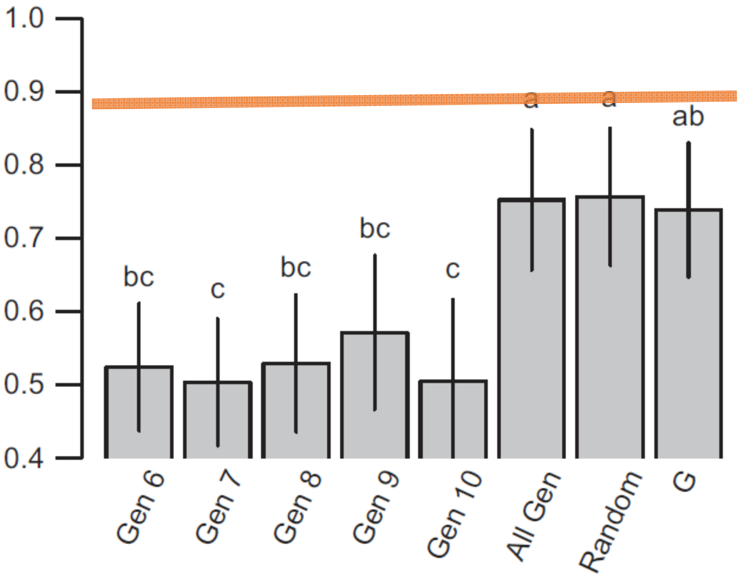
Different predictions by UPG

Incomplete pedigree on accuracy & inflation

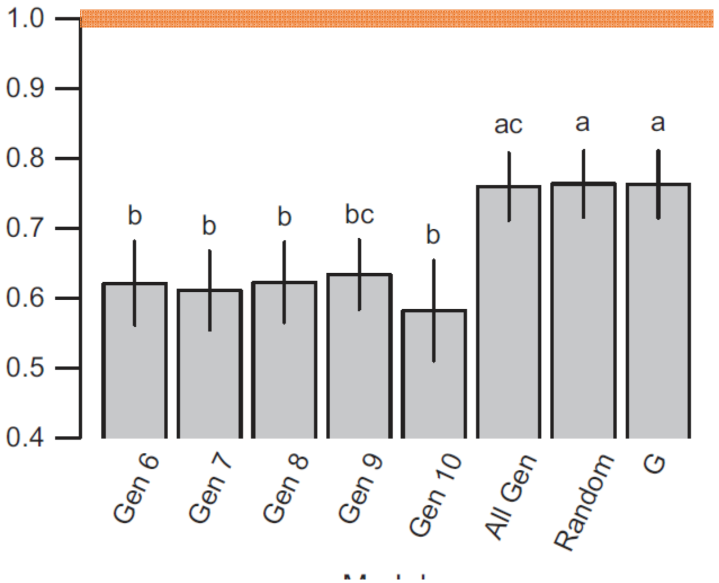
Accuracy

Complete pedigree

Incomplete pedigree



Inflation



* Simulated data (Bradford et al., 2017)

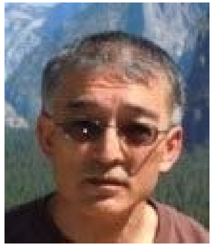
Low accuracy with genomic UPG

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

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 ($\mathbf{\Gamma}$) using $\mathbf{G}$
  - Construct $\mathbf{A}^{-1}$ and $\mathbf{A}_{22}^{-1}$ with $\mathbf{\Gamma}$ using the Henderson's and Collau's methods
- Final form:

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

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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UNIVERSITY OF GEORGIA

1785

INRA

INIA
Instituto Nacional de Investigación Agropecuaria
URUGUAY

Daniela A. L. Lourenco

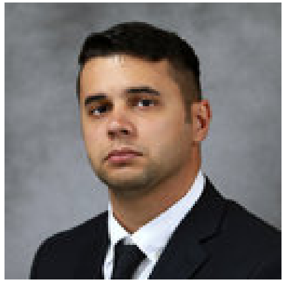
Ignacy Misztal

Yvette Steyn

Andre Garcia

Andres Legarra

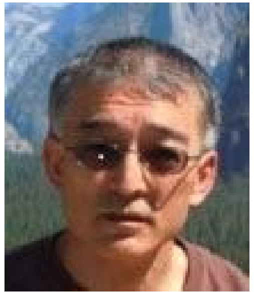
Ignacio Aguilar



Breno Fragomeni

Ivan Pocrnic

Rafael Silva



Shogo Tsuruta

USDA

Heather Bradford