Extension of single-step ssGBLUP to many genotyped individuals

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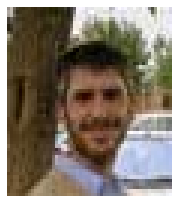
Genomic selection and single-step

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

Aguilar et al., 2010
Christensen and Lund, 2010


- Simplicity
  - No DYD or DP
  - No index
  - No complexity

- Accuracy
  - Avoids double counting
  - Avoids fixed index
  - Accounts for preselection bias

Current implementation of SS

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

- G and A_{22} created explicitly
- Quadratic memory and cubic computations
- Cost per 100k genotypes - 1.5 hr (Aguilar et al.,2014)

Number of genotypes and impending problem

> 2 M for Holsteins

> 400k for Angus

Genomic pre-selection issue (Patry and Ducrocq, 2011; VanRaden et al., 2013)

- BLUP increasingly biased
- Need all data on preselection included

Unsymmetric equations

$$\begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\mathbf{Z} \\ \mathbf{H}\mathbf{Z}'\mathbf{X} & \mathbf{H}\mathbf{Z}'\mathbf{Z} + \alpha\mathbf{I} \end{bmatrix} \begin{bmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{u}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \mathbf{H}\mathbf{Z}'\mathbf{y} \end{bmatrix}$$

Misztal et al., 2009

No convergence without good preconditioner
No convergence with large H or A

No G or A_{22} inverse model

$$\begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}_1'\mathbf{W}_1 & \mathbf{X}_2'\mathbf{W}_2 & \mathbf{0} & \mathbf{0} \\ \mathbf{W}_1'\mathbf{X}_1 & \mathbf{W}_1'\mathbf{W}_1 + \alpha_u \mathbf{A}^{11} & \alpha_u \mathbf{A}^{12} & \mathbf{0} & \mathbf{0} \\ \mathbf{W}_1'\mathbf{X}_2 & \alpha_u \mathbf{A}^{12} & \mathbf{W}_2'\mathbf{W}_2 + \alpha_u \mathbf{A}^{22} & \alpha_u \mathbf{I} & -\alpha_u \mathbf{I} \\ \mathbf{0} & \mathbf{0} & \alpha_u \mathbf{I} & \alpha_u \mathbf{A}_{22} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \alpha_u \mathbf{I} & \mathbf{0} & \alpha_u \mathbf{G} \end{bmatrix} \begin{bmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{u}}_1 \\ \hat{\mathbf{u}}_2 \\ -\hat{\boldsymbol{\varphi}} \\ -\hat{\boldsymbol{\gamma}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \mathbf{W}_1'\mathbf{y}_1 \\ \mathbf{W}_2'\mathbf{y}_2 \\ \mathbf{0} \\ \mathbf{0} \end{bmatrix},$$

Legarra and Ducrocq (2011)

Slow convergence with few genotypes

Divergence with many genotypes

SNP model for genotyped animals

$$\begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}_1'\mathbf{W}_1 & \mathbf{X}_2'\mathbf{W}_2\mathbf{Z} & \mathbf{0} \\ \mathbf{W}_1'\mathbf{X}_1 & \mathbf{W}_1'\mathbf{W}_1 + \alpha_u\mathbf{A}^{11} & \alpha_u\mathbf{A}^{12}\mathbf{Z} & \mathbf{0} \\ \mathbf{Z}'\mathbf{W}_2'\mathbf{X}_2 & \alpha_u\mathbf{Z}'\mathbf{A}^{12} & \mathbf{Z}'\mathbf{W}_2'\mathbf{W}_2\mathbf{Z} + \alpha_u\mathbf{Z}'\mathbf{A}^{22}\mathbf{Z} + \mathbf{D}^{-1}\sigma_e^2 & \alpha_u\mathbf{Z}' \\ \mathbf{0} & \mathbf{0} & \alpha_u\mathbf{Z} & \alpha_u\mathbf{A}_{22} \end{bmatrix} \begin{bmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{u}}_1 \\ \hat{\mathbf{g}} \\ -\hat{\boldsymbol{\varphi}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \mathbf{W}_1'\mathbf{y}_1 \\ \mathbf{Z}'\mathbf{W}_2'\mathbf{y}_2 \\ \mathbf{0} \end{bmatrix}.$$

Legarra and Ducrocq, 2011

No successful programming

SNP model for genotyped animals

$$\begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\mathbf{Z}_p & \mathbf{X}'\mathbf{W}_1 & \mathbf{X}'\mathbf{W}_2 & \mathbf{0} \\ \mathbf{Z}_p'\mathbf{X} & \mathbf{Z}_p'\mathbf{Z}_p + \mathbf{I}\delta & \mathbf{Z}_p'\mathbf{W}_1 & \mathbf{Z}_p'\mathbf{W}_2 & \mathbf{0} \\ \mathbf{W}_1'\mathbf{X} & \mathbf{W}_1'\mathbf{Z}_p & \mathbf{W}_1'\mathbf{W}_1 + \lambda\mathbf{A}^{11} & \lambda\mathbf{A}^{12} & \mathbf{0} \\ \mathbf{W}_2'\mathbf{X} & \mathbf{W}_2'\mathbf{Z}_p & \lambda\mathbf{A}^{21} & \mathbf{W}_2'\mathbf{W}_2 + \lambda\left(\mathbf{A}^{22} + \left(\frac{1}{k} - 1\right)\mathbf{A}_{22}^{-1}\right) & -\frac{1}{k}\lambda\mathbf{A}_{22}^{-1}\mathbf{Z} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & -\frac{1}{k}\lambda\mathbf{Z}'\mathbf{A}_{22}^{-1} & \lambda\left(\mathbf{B}^{-1} + \frac{1}{k}\mathbf{Z}'\mathbf{A}_{22}^{-1}\mathbf{Z}\right) \end{bmatrix} \begin{bmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{p}} \\ \hat{\mathbf{u}}_1 \\ \hat{\mathbf{u}}_2 \\ \hat{\mathbf{g}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{y} \\ \mathbf{Z}_p'\mathbf{y} \\ \mathbf{W}_1'\mathbf{y} \\ \mathbf{W}_2'\mathbf{y} \\ \mathbf{0} \end{bmatrix}$$

Liu et al, 2014

SNP effects for all animals (Fernando et al., 2014)

imputed genotypes

centered genotypes

$$\hat{\mathbf{M}}_1 = \mathbf{A}_{12}\mathbf{A}_{22}^{-1}\mathbf{M}_2$$

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1^* \\ \mathbf{X}_2^* \end{bmatrix} \boldsymbol{\beta}^* + \begin{bmatrix} \mathbf{Z}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_2 \end{bmatrix} \begin{bmatrix} \hat{\mathbf{M}}_1\boldsymbol{\alpha} + \boldsymbol{\epsilon} \\ \mathbf{M}_2\boldsymbol{\alpha} \end{bmatrix} + \mathbf{e}$$

Cost of imputation

Requires new type of programming

Extension to complex models unclear

Can regular ssGBLUP be made more efficient?

Scaling up A_{22}^{-1}

$$\mathbf{A}_{\mathbf{22}}^{-\mathbf{1}} = \mathbf{A}^{\mathbf{22}} - \mathbf{A}^{\mathbf{21}}\left(\mathbf{A}^{\mathbf{22}}\right)^{-\mathbf{1}}\mathbf{A}^{\mathbf{12}}$$

- $\mathbf{A}_{\mathbf{22}}^{-\mathbf{1}}$ dense (Faux et al., 2014)
- For PCG iteration (Stranden et al., 2014)

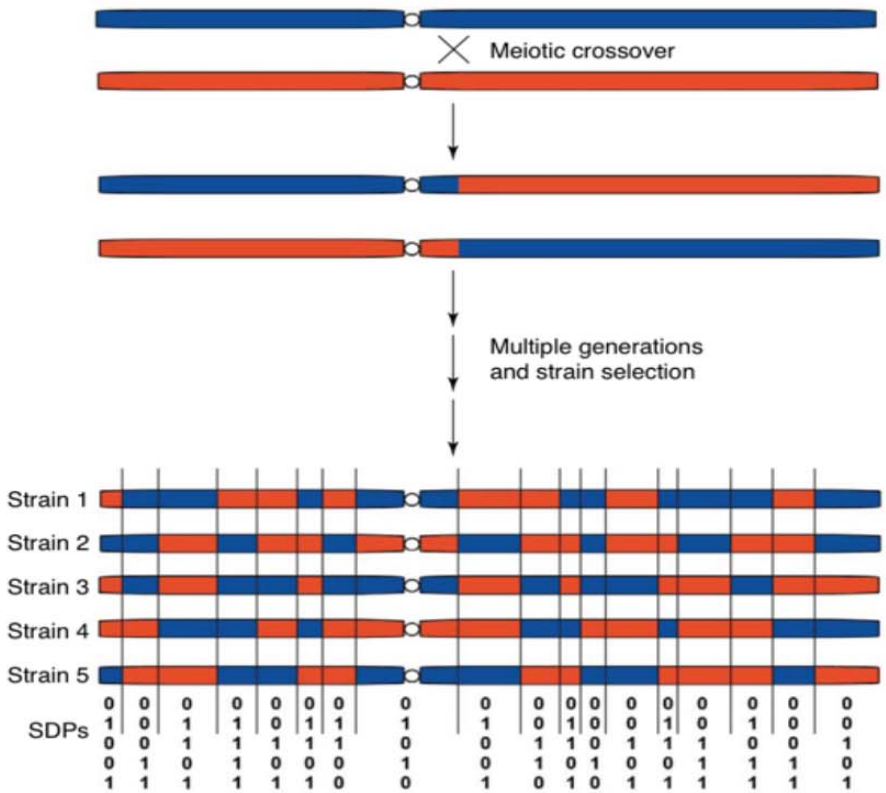
$$\mathbf{A}_{\mathbf{22}}^{-\mathbf{1}}\mathbf{q} = \mathbf{A}^{\mathbf{22}}\mathbf{q} - \left\{\mathbf{A}^{\mathbf{21}}\left[\left(\mathbf{A}^{\mathbf{22}}\right)^{-\mathbf{1}}\left(\mathbf{A}^{\mathbf{12}}\mathbf{q}\right)\right]\right\}$$

- Seconds for 500k animals with good programming (Masuda et al., 2017)

Is dimensionality of genomic information limited?

- Regular G not positive definite past ~5k
  - Blending with A (VanRaden, 2008)
- Dimensionality of SNP BLUP small (Maciotta et al., 2013)
- Success of imputation
- Manhattan plots noisy until averaged by 300k-10Mb (depending on species)

Origin of Haplotype blocks



Cuppen, 2005

Heterogenetic and homogenic tracts in genome (Stam, 1980)

E(#tracts)=4NeL (Stam, 1980)

Ne – effective population size

L –length of genome in Morgans

Holsteins: Ne ≈100 L=30

Me=12,000

Inversion via SVD/eigenvalue decomposition

Assume 1 million animals genotyped with 60k chip

$\mathbf{G} = \mathbf{ZZ}' = \mathbf{UDU}'$ Eigenvalue decomposition (1M x 1M)

$\mathbf{G}^{-} = \mathbf{UD}^{-}\mathbf{U}'$ Generalized inverse (1M x 1M)

$\mathbf{Z} = \mathbf{USV} = \mathbf{UD}^{0.5}\mathbf{V}$ - SVD decomposition (1M x 60k)

10h for 720k animals (Masuda, 2017)

t - index for non-negligible eigenvalues, say 10k

$\mathbf{G}^{-} = \mathbf{U}_t\ \mathbf{D}_t^{-1}\mathbf{U}_t' = \mathbf{U}_t\ \mathbf{S}_t^{-1}\mathbf{S}_t^{-1}\mathbf{U}_t' = \mathbf{U}_*\ \mathbf{U}_*$

For PCG iteration

$\mathbf{G}^{-1}\mathbf{q} = \mathbf{U}_*\ (\mathbf{U}_*\ \mathbf{q})$ - only 1 M x 10k elements

Inverse by Woodbury formula

$\mathbf{G} = \mathbf{Z}\mathbf{Z}' + \mathbf{I}\boldsymbol{\varepsilon}$, Woodbury formula

$\mathbf{G}^{-1} = \frac{1}{\boldsymbol{\varepsilon}}\mathbf{I} - \frac{1}{\boldsymbol{\varepsilon}}\mathbf{Z}(\frac{1}{\boldsymbol{\varepsilon}}\mathbf{Z}'\mathbf{Z} + \mathbf{I})^{-1}\mathbf{Z}'\frac{1}{\boldsymbol{\varepsilon}}$ **Z'Z** 60k x 60k

For PCG iteration:

Mantysaari et al., 2017

$$\mathbf{G}^{-1}\mathbf{q} = \frac{\mathbf{1}}{\boldsymbol{\varepsilon}}\{\mathbf{I} - \mathbf{Z}(\mathbf{U}\mathbf{D}\mathbf{U}')^{-1}\mathbf{Z}'\}q = \frac{\mathbf{1}}{\boldsymbol{\varepsilon}}\{\mathbf{I} - \mathbf{S}\mathbf{S}'\}q$$

$$\mathbf{S} = \mathbf{Z}\mathbf{U}'\mathbf{D}^{-1/2}$$

With reduced rank $\mathbf{S} = \mathbf{Z}\mathbf{U}_t{}'(\mathbf{D}_t)^{-\frac{1}{2}}$ (1M x 10k)

Ostersen et al., 2017

If G has limited dimensionality, can G^{-1} be sparse like A^{-1}?

Use of a la Henderson's rules?

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A recursive algorithm for decomposition and creation of the inverse of the genomic relationship matrix

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Use of relatives for $\mathbf{G}^{-1}$
Accuracies not good enough
Theory not clear

Assumption of limited dimensionality

s – n x 1 vector containing additive information of population (haplotypes, chromosome segments, LD blocks)?

Breeding value

Very small error

$$\mathbf{u} = \mathbf{T}\mathbf{s} + \mathbf{e}$$

If $\mathbf{u}_c$ contains n animals:

$$\mathbf{s} \approx \mathbf{T}_c^{-1}\mathbf{u}_c$$

Breeding values of any n animals contains all additive information

Choose core "**c**" and noncore "**n**" animals

$$\mathbf{u}_n = \mathbf{P}_{nc}\mathbf{u}_c + \varepsilon_n$$

$$\mathbf{u}_c = \mathbf{u}_c$$

$$\begin{bmatrix} \mathbf{u}_c \\ \mathbf{u}_n \end{bmatrix} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{P}_{nc} & \mathbf{I} \end{bmatrix} \begin{bmatrix} \mathbf{u}_c \\ \boldsymbol{\varepsilon}_n \end{bmatrix}$$

$$\text{var}(\boldsymbol{\varepsilon}_n) = \mathbf{M}_{\mathbf{nn}}$$

$$\mathbf{G} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{P}_{nc} & \mathbf{I} \end{bmatrix} \begin{bmatrix} \mathbf{G}_{cc} & \mathbf{0} \\ 0 & \mathbf{M}_{nn} \end{bmatrix} \begin{bmatrix} \mathbf{I} & \mathbf{P}_{cn} \\ \mathbf{0} & \mathbf{I} \end{bmatrix}$$

$$\mathbf{G}^{-1} = \begin{bmatrix} \mathbf{I} & -\mathbf{P}_{cn} \\ \mathbf{0} & \mathbf{I} \end{bmatrix} \begin{bmatrix} \mathbf{G}_{cc}^{-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{M}_{nn}^{-1} \end{bmatrix} \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ -\mathbf{P}_{nc} & \mathbf{I} \end{bmatrix}$$

How to estimate **P** and inv(**G**)?

$$\text{var}\left(\begin{bmatrix}\mathbf{u}_c\\ \mathbf{u}_n\end{bmatrix}\right)=\begin{bmatrix}\mathbf{G}_{cc} & \mathbf{G}_{cn}\\ \mathbf{G}_{nc} & \mathbf{G}_{nn}\end{bmatrix}\sigma_u^2$$

G is “true” relationship matrix

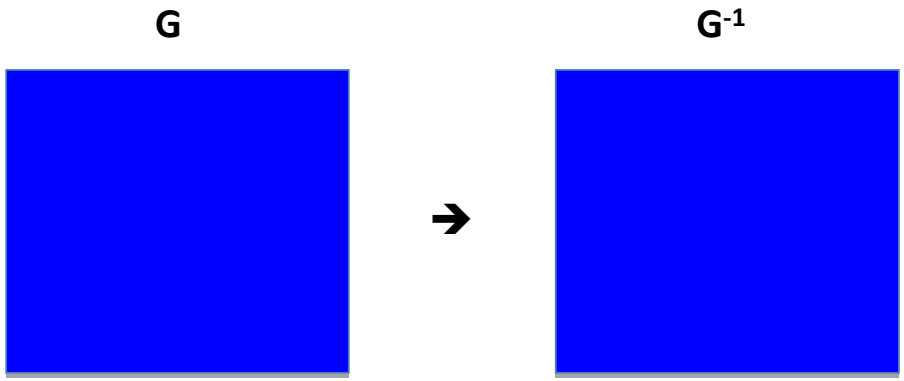
$$\mathbf{u}_n \mid \mathbf{u}_c = \mathbf{G}_{nc}\mathbf{G}_{cc}^{-1}\mathbf{u}_c, \quad \mathbf{P}=\mathbf{G}_{nc}\mathbf{G}_{cc}^{-1}$$

$$\mathbf{G}^{-1} = \begin{bmatrix}\mathbf{G}_{cc}^{-1} & \mathbf{0}\\ \mathbf{0} & \mathbf{0}\end{bmatrix} + \begin{bmatrix}\mathbf{G}_{cc}^{-1}\mathbf{G}_{cn}\\ \mathbf{I}\end{bmatrix}\mathbf{M}^{-1}\begin{bmatrix}\mathbf{G}_{nc}'\mathbf{G}_{cc}^{-1} & \mathbf{I}\end{bmatrix}$$

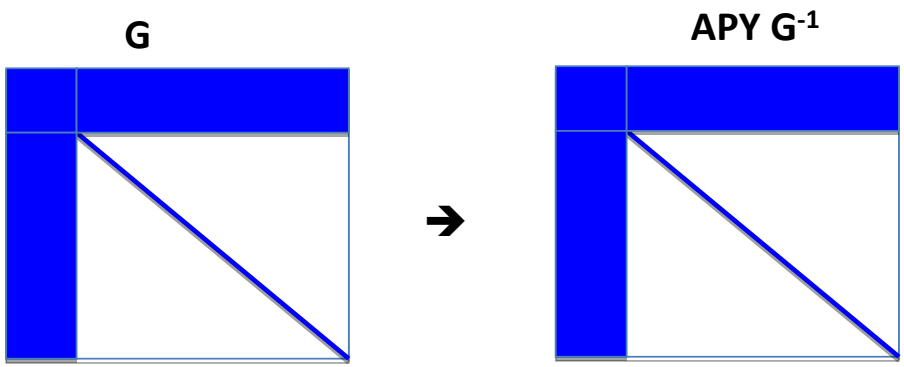
APY algorithm

(Algorithm for Proven and Young)

Properties of APY algorithm



Cost:
Quadratic memory and cubic computations



Cost:
Almost linear memory and computations

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http://dx.doi.org/10.3168/jds.2013-7752

Using recursion to compute the inverse of the genomic relationship matrix

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http://dx.doi.org/10.3168/jds.2014-9125

Hot topic: Use of genomic recursions in single-step genomic best linear unbiased predictor (BLUP) with a large number of genotypes

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GENETICS | **INVESTIGATION**

Inexpensive Computation of the Inverse of the Genomic Relationship Matrix in Populations with Small Effective Population Size

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GENETICS | **INVESTIGATION**

The Dimensionality of Genomic Information and Its Effect on Genomic Prediction

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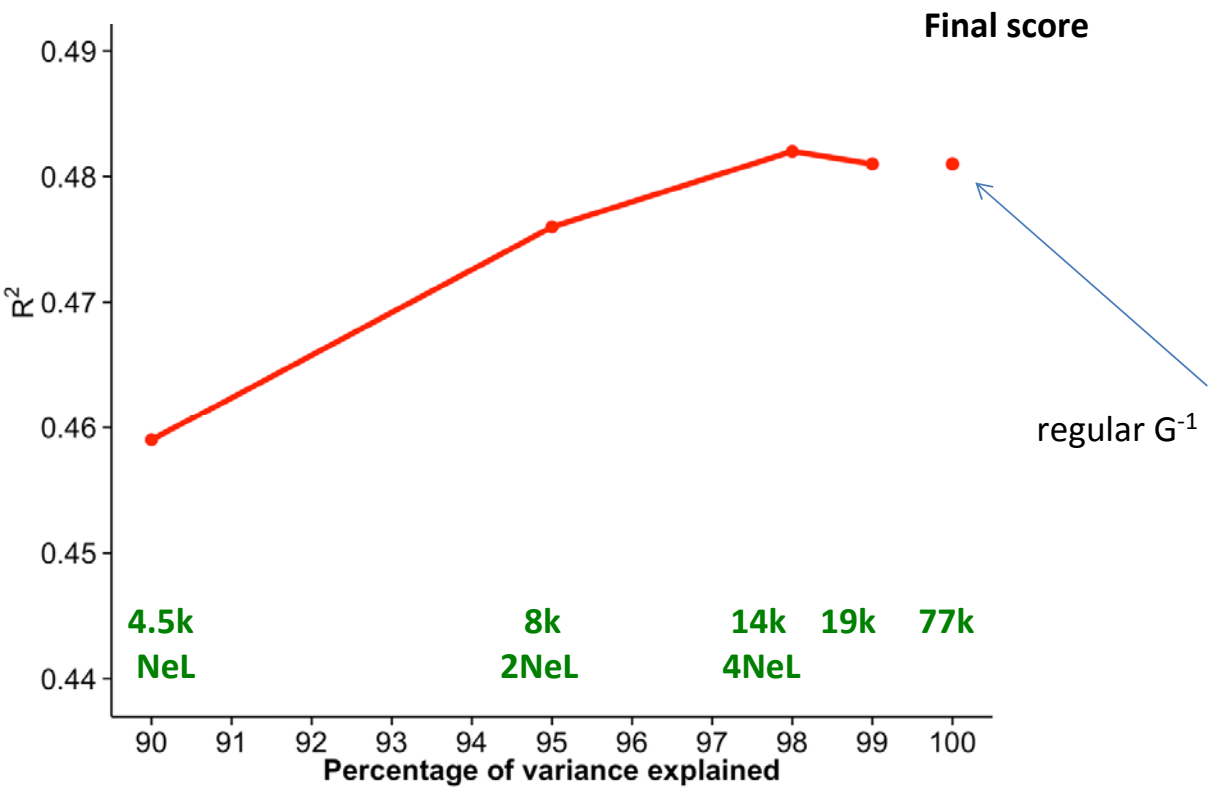
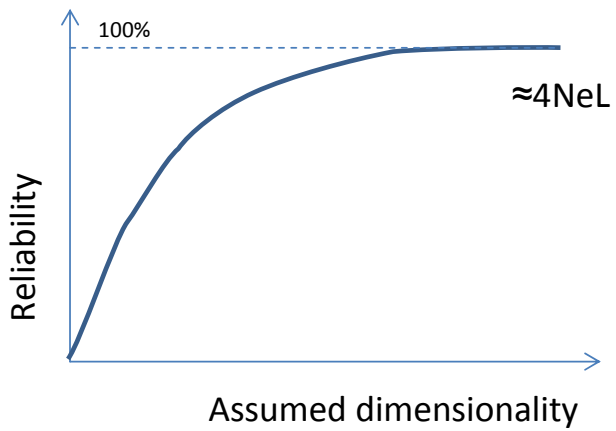
Reliabilities – Holsteins (77k)



Pocrnic et al., 2016b

Distribution of segments/haplotypes/..



Costs with 720k genotyped animals

- 30 M Holsteins
- 50 M records
- 764k 60k genotypes

Item	BLUP	ssGBLUP
APY G	-	7 h
A22-1	-	10 min
rounds	402	464
Time/round	51 s	83 s
Total time	**6 h**	**17 h**

Masuda et al., 2017

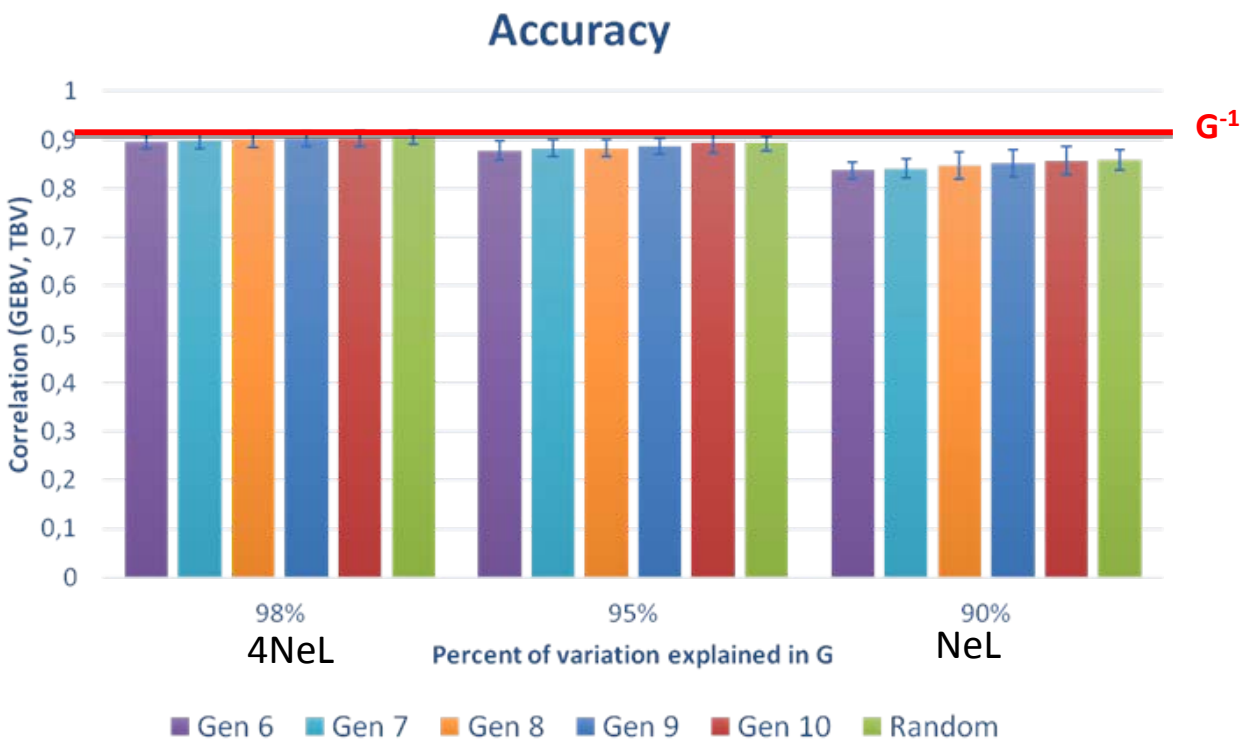
Which core animals in APY?

Bradford et al. (2017)

- Simulated populations (QMSim; Sargolzaei and Schenkel, 2009)
- Ne = 40
- #genotyped animals = 50,000

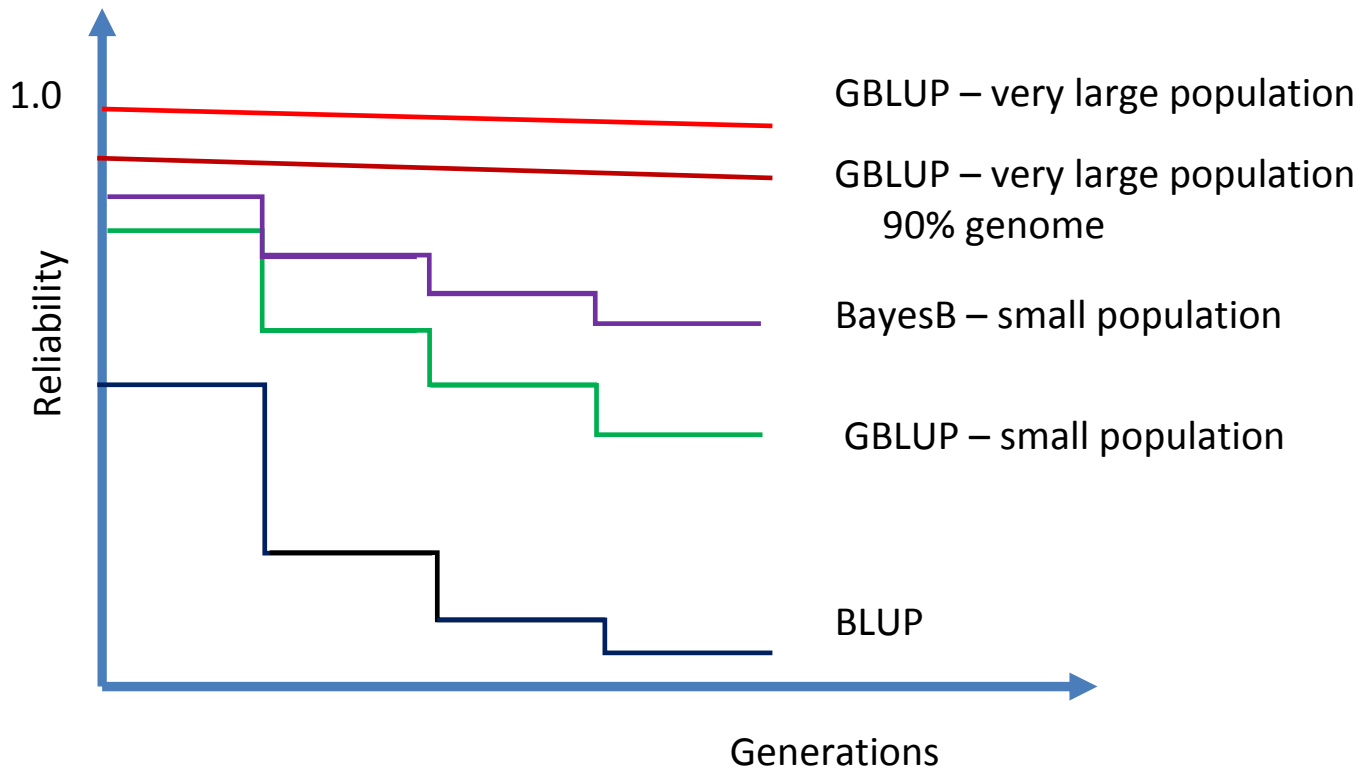
- Core animals:
  - Random gen 6 || gen 7 || gen8 || gen9 || gen 10 (y)
  - Random all generations

Which core animals in APY?



Bradford et al. (2016)

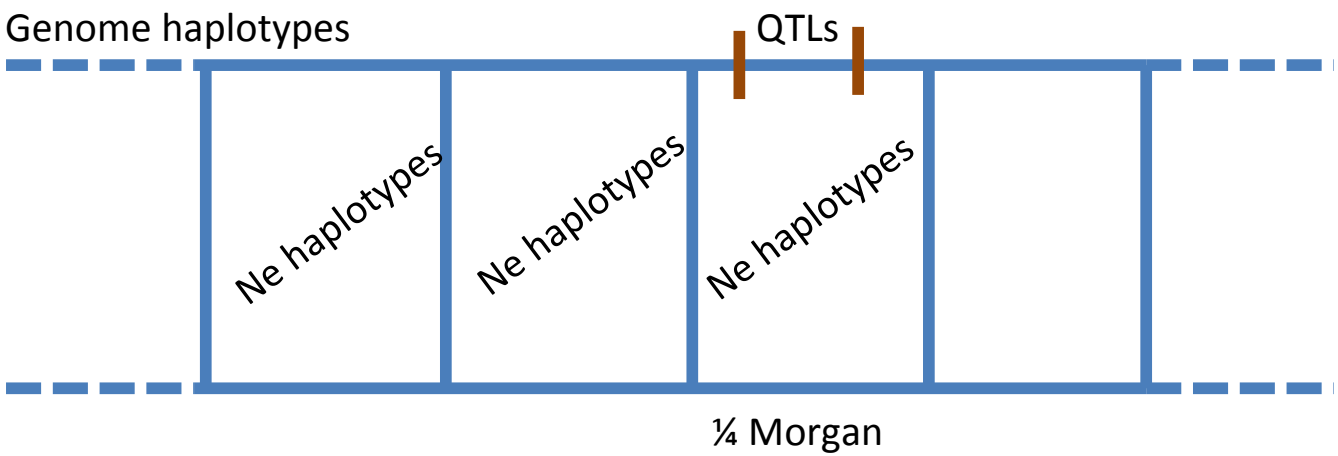
Persistence over generations



Very large – equivalent to 4NeL animals with 99% accuracy
Are SNP effects from Holstein national populations converging

Theory of limited dimensionality

Number of haplotypes: 4 Ne L
Ne within each ¼ Morgan segment



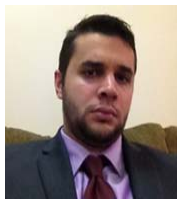
Dimensionality of ¼ Morgan case: Ne

or number of identified QTLs

➔Reduced dimensionality with weighted GRM

Fragomeni et al., 2018

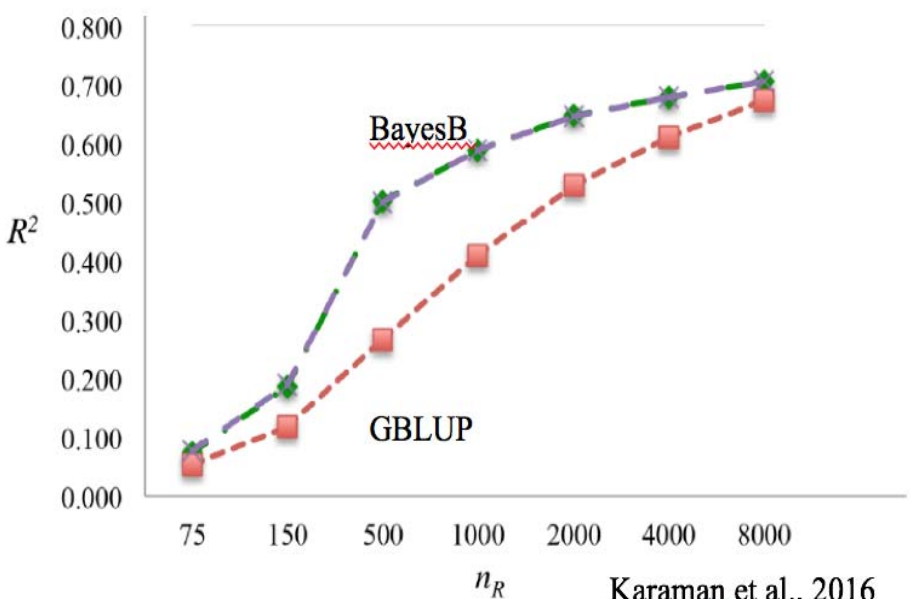
ssGBLUP accuracies using SNP60K and 100 QTNs – simulation study



Fragomeni et al. (2017)

Multitrait ssGBLUP or SNP selection?

- SNP selection/weighting (BayesB, etc.)
  - Large impact with few genotypes
  - Little or no impact with many



Karaman et al., 2016

Variance components

- Based on SNP
  - limitations
- REML based on relationships
  - Equations no longer sparse
  - YAMS sparse matrix package –up to 100 times speedup (Masuda et al., 2017)
  - APY for REML
- Method R (Legarra and Reverter, 2017)

Extra topics

- Matching pedigrees and genomic relationships
- Missing pedigrees
- Crossbreeding
- Causative SNP

- Haplotypes for crossbreds (Christensen et al., 2016)
- Metafounders (Legarra et al., 2016)
- Approximation of reliabilities

Conclusions

- Limited dimensionality of genomic information due to limited effective population size
- ssGBLUP suitable for any data set and model
- With large data sets for Holsteins:
  - Good persistence of predictions
  - Convergence of predictions from different countries

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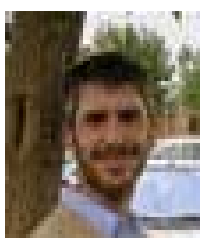

Andres Legarra

Heather Bradford

Theory for APY

- Breeding values of core animals linear functions of:
  - Independent chromosome segments (Me)
  - Independent effective SNP

- E(Me)=4 Ne L (Stam, 1980; VanRaden, 2008)

  Ne –effective population size

  L – length of genome in Morgans

  Me = 4 (Ne=100) (L=30) =12,000

Accuracy and distance from markers to QTL

Fragomeni et al. (2017)