Efficient inversion of genomic relationship matrix by APY algorithm

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Advantages of single-step GBLUP

- Simplicity
  - No DYD or DP
  - No index
  - No complexity
- Accuracy
  - Avoids double counting
  - Avoids fixed index
  - Accounts for preselection bias

Current implementation of SS

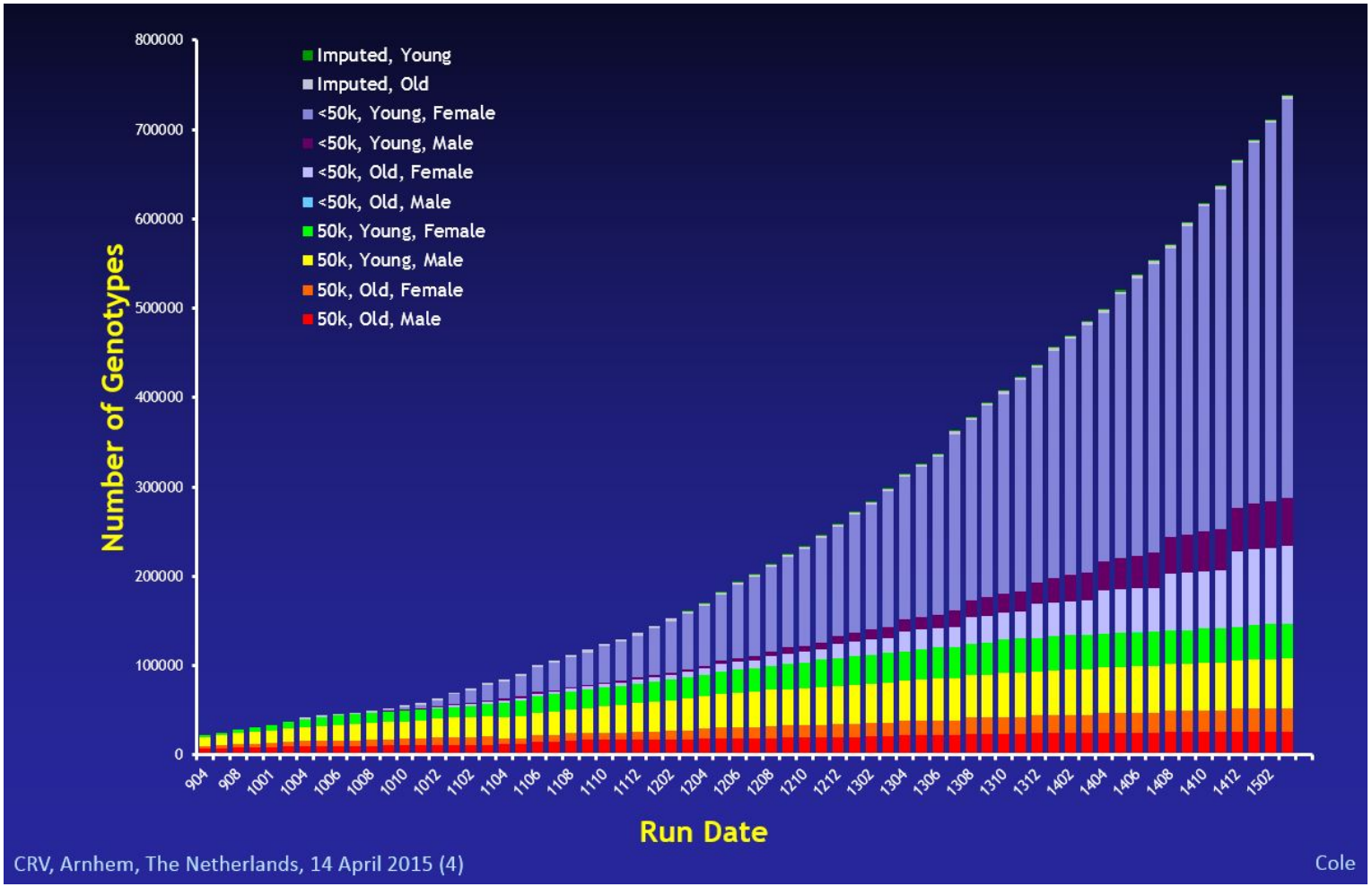
$$\mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{G}^{-1} - \mathbf{A}_{22}^{-1} \end{bmatrix}$$

- G and A_{22} created explicitly and inverted
- Cubic cost

- Cost per 100k genotypes - 1.5 hr (Aguilar et al.,2014)

Number of genotypes for US Holsteins

- Total ~ 800k in 2015



Options

- Unsymmetric Single-Step (Legarra and Ducrocq, 2011)
  - Does not converge
- SS SNP model with imputation for ungenotyped animals (Fernando et al., 2014)
  - Very expensive and new unproven machinery
- SS with SNP effects for genotyped animals only (Legarra and Ducrocq, 2011; Liu et al., 2014)
  - Does not converge

Recursions, Inversion, A^{-1}

$$u_i \mid u_1, u_2, .., u_{i-1} = \mathbf{p}_i{}' \mathbf{u} + \varphi_i$$ Generic recursion based on Cholesky decomposition

$$\mathbf{u} = \mathbf{P}\mathbf{u} + \Phi, \quad \mathrm{var}(\Phi) = \mathbf{M}\sigma_a^2$$ M diagonal

$$\mathrm{var}(\mathbf{u}) = \mathbf{A}\sigma_a^2 \qquad \mathbf{A}^{-1} = (\mathbf{I} - \mathbf{P})'\mathbf{M}^{-1}(\mathbf{I} - \mathbf{P})$$

Inverse by recursion
High cost if P dense

Henderson (1976): $u_i \mid u_1, u_2, .., u_{i-1} = u_i \mid u_{si}, u_{di}$

$$u_i = \frac{u_{si} + u_{di}}{2} + \varphi_i$$

P - 2 nonzero elements per row
Cost of computing $\mathbf{A}^{-1}$ by inversion of **A** huge
Cost of computing $\mathbf{A}^{-1}$ indirectly by recursion trivial

Genomic recursions

$$u_i = \sum_{i=1}^{i-1} p_{ij} u_j + \varepsilon_i$$

$$\mathbf{p}_{i,1:i-1} = \mathbf{g}_{i,1:i-1}' \left(\mathbf{G}_{1:i-1,1:i-1} \right)^{-1}, \quad \text{var}(\varepsilon_i) = g_{i,i} - \mathbf{p}' \mathbf{g}_{i,1:i-1} = e_i^g$$

$$E(\mathbf{a} \mid \mathbf{b}) = \text{cov}(\mathbf{a}, \mathbf{b}) \, \text{var}(\mathbf{b})^{-1}$$

$$\text{Var}(\mathbf{a} \mid \mathbf{b}) = \text{cov}(\mathbf{a}, \mathbf{b})' E(\mathbf{a} \mid \mathbf{b})$$

$$\mathbf{G}^{-1} = (\mathbf{I} - \mathbf{P})' \mathbf{M}^{-1} (\mathbf{I} - \mathbf{P}) = \mathbf{T}' \mathbf{M}^{-1} \mathbf{T}$$

Cost low only if P sparse

Recursion on relatives (Faux et al., 2011)

Number of genotyped US Holsteins in 2015

- Total ~ 800k
  - 25k proven bulls
  - 30k eligible cows
  - remaining cows and bulls not eligible for regular evaluation

Algorithm for proven and young animals (APY)

For young animals

=0 in GBLUP

$$u_i \mid u_1, u_2, \ldots, u_{i-1} = \sum_{j=\text{"proven"}} p_{ij} u_j + \sum_{j=\text{"young"}} p_{ij} u_j + \varepsilon_i$$

Misztal et al., 2014

p=proven y=young; G=ZZ'

$$\mathbf{G}^{-1} = \begin{bmatrix} \mathbf{G}_{pp}^{-1} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{bmatrix} + \begin{bmatrix} -\mathbf{G}_{pp}^{-1}\mathbf{G}_{py} \\ \mathbf{I} \end{bmatrix} \mathbf{M}^{-1} \begin{bmatrix} \mathbf{G}_{yp}\mathbf{G}_{pp}^{-1} & \mathbf{I} \end{bmatrix}$$

$\mathbf{Z_p}$ – genotypes for proven animals

$\mathbf{Z_y}$ – genotypes for young animals

$m_i = g_{ii} - \mathbf{z_i}'\mathbf{Z_p}'\mathbf{G}_{pp}^{-1}\mathbf{Z_p}\mathbf{z_i}$

Inversion for $\mathbf{G}_{pp}$ only!

Linear cost for young animals

Tests with US Holsteins

(Fragomeni et al., 2015)

- US Holstein final score (h^2=0.31)
- 10.3M animals
- 11.6M records from 7.1M cows

All Genotyped	100k out of 569k
Bulls	23k
Cows	27k
Young Animals	50k

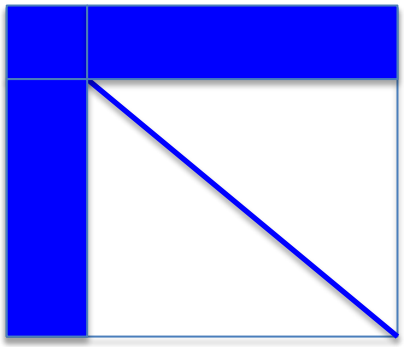
Correlations between GEBV with regular and APY G^{-1}

Treated as proven	Correlations	Rounds to conv
23k bulls	>0.99	432
23k bulls + 27k cows	>0.99	466
27k cows	>0.99	797
Random 20k animals	>0.99	~420
Random 10k animals	>0.98	~395
Random 5k animals	>0.97	~360

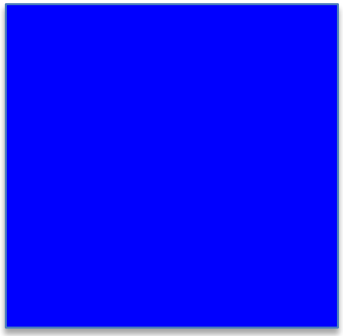
Random 5 samples

Results of APY

- High accuracy when > 10k animals in recursion



As accurate or more than



- Choice of animals not very important
- Best convergence with random samples

- "Proven" → Base "Young" → Nonbase

Everything should be made as simple as possible, but not simpler

Einstein

Theory for APY

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

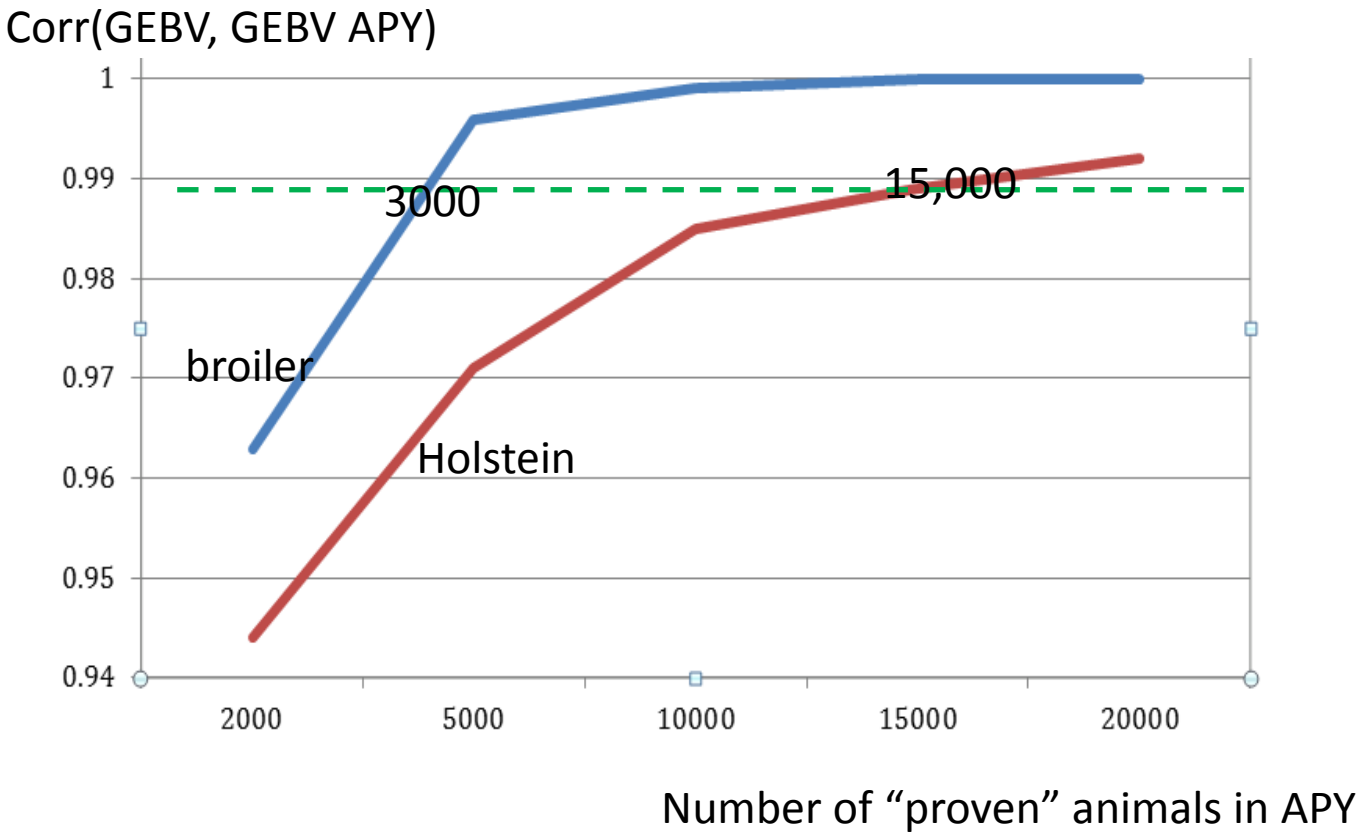
- Me=4 Ne L (Stam, 1980)

  Ne –effective population size

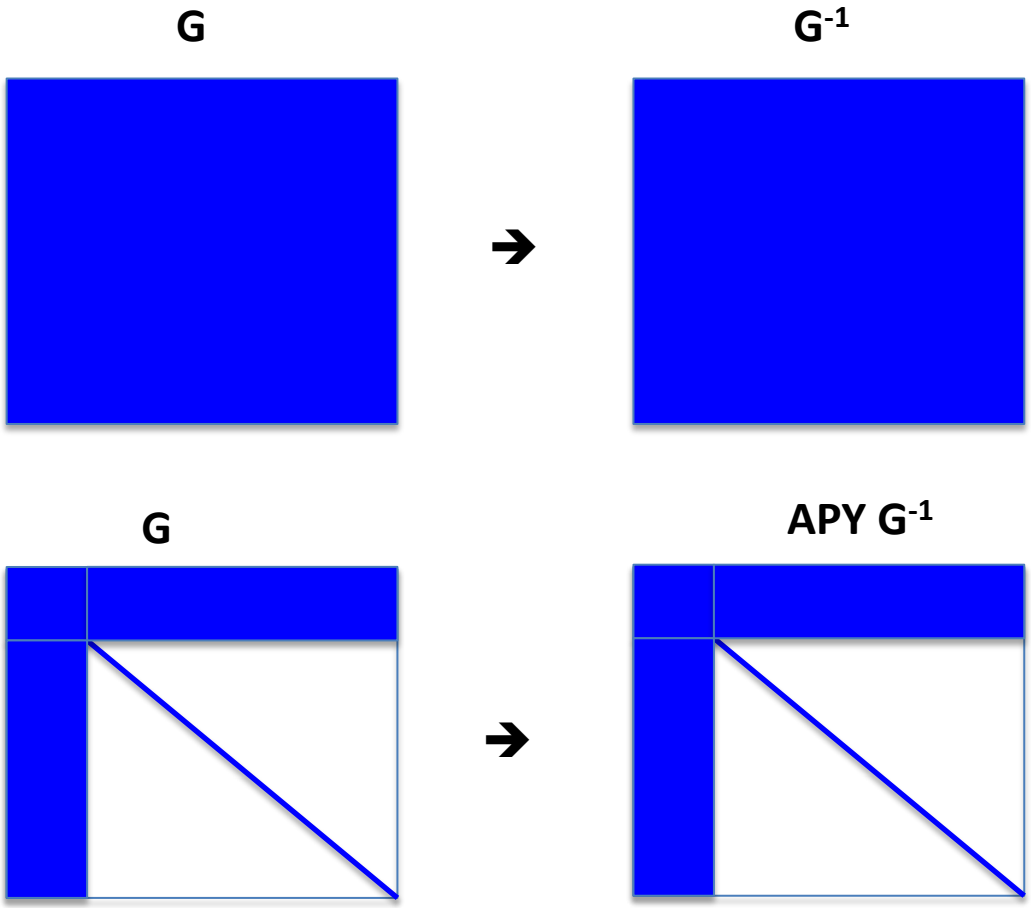
  L – length of genome in Morgans

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

Me in Holsteins and chicken



Why efficiency and accuracy of APY



Less **G** needed – less work and smaller noise from sampling variance

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

Henderson's (1976) algorithm for the genomic age

Questions and issues

- APY and major SNP or QTL
- Use of sequence data
  - Causative SNP with possible priors
- Number of independent chromosome segments, SNP density and GWAS resolution
- APY with Multibreed data
- MACE and External (G)EBV (Vanderplas et al., 2015)
- Use all genotypes in G^{-1} or indirect prediction for lower quality genotypes?

Conclusions

- Size limitations from single-step removed
- APY inverse applicable to SNP weights and causative SNP
- Potential to better address:
  - Multibreed evaluation
  - Comprehensive MACE

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