Possible implications of limited dimensionality of genomic information

Ignacy Misztal, Ivan Pocrnic and Daniela Lourenco

University of Georgia

Dimensionality of genomic information

BV — genotypes — SNP effects

$$\mathbf{u} = \mathbf{Za}$$

$$\mathbf{Z} = \mathbf{U}\ \boldsymbol{\Delta}\ \mathbf{V}$$

Singular value decomposition
U'U=I, V'V=I, **Δ**

$$\mathbf{G} = \mathbf{U\Delta\Delta U'} = \mathbf{UDU'}$$

Genomic relationship matrix
Rank(G) ≤ min(#SNP,#anim)

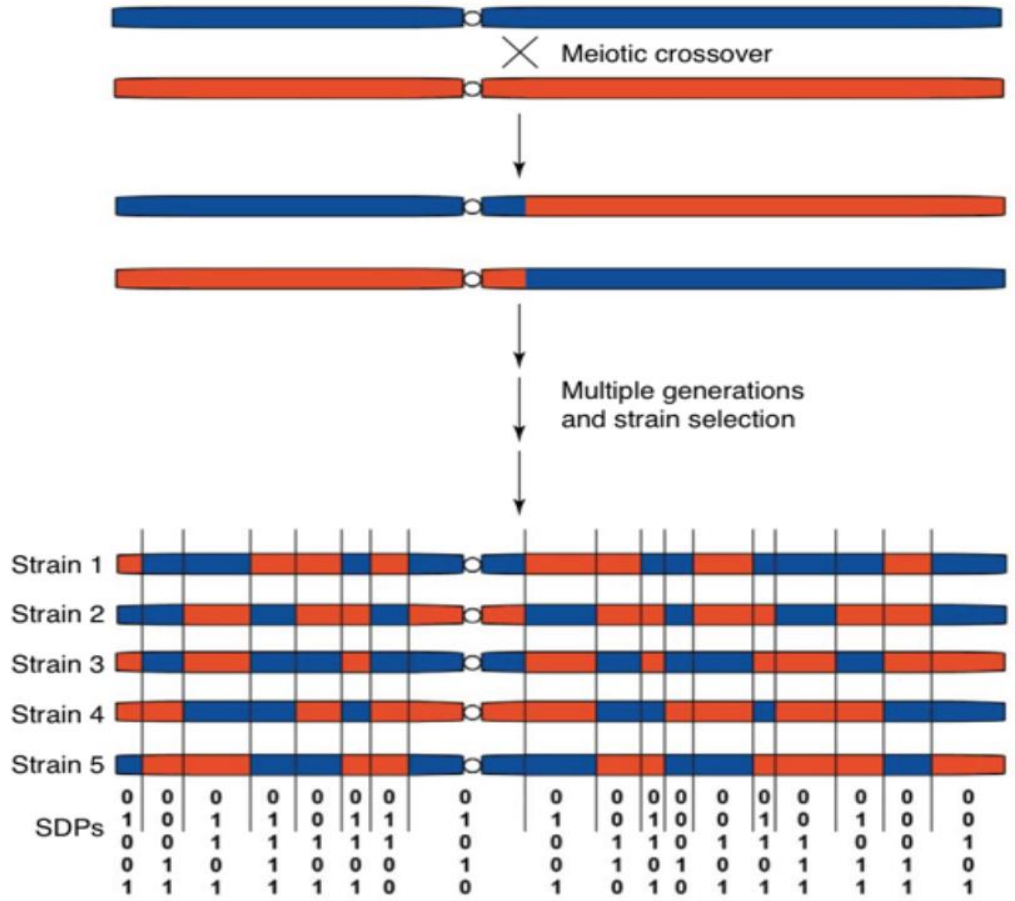
$$\mathbf{Z'Z} = \mathbf{V'\Delta\Delta V}$$

SNP BLUP design matrix
Rank(Z'Z) ≤ min(#SNP,#anim)

Same dimensionality for genotypes, GRM and SNP BLUP

Dimensionality around 5-15k (VanRaden, 2008; Maciotta et al., 2013)

Origin of Haplotype blocks



Cuppen, 2005

Chromosome segments

- Theory of junctions (Fisher, 1949):
  - Heterogenetic and homogenic tracts in genome
- For randomly mating population of constant size the number of tracts:

E(Me)=**4 Effective population size (Ne) * Genomic size (L)** (Stam, 1980)

- Independent chromosome segments Me (Goddard, 2009; Daetwyler et al., 2010)
- Need 12 Me SNPs to detect 90% of junctions (MacLeod et al., 2005)

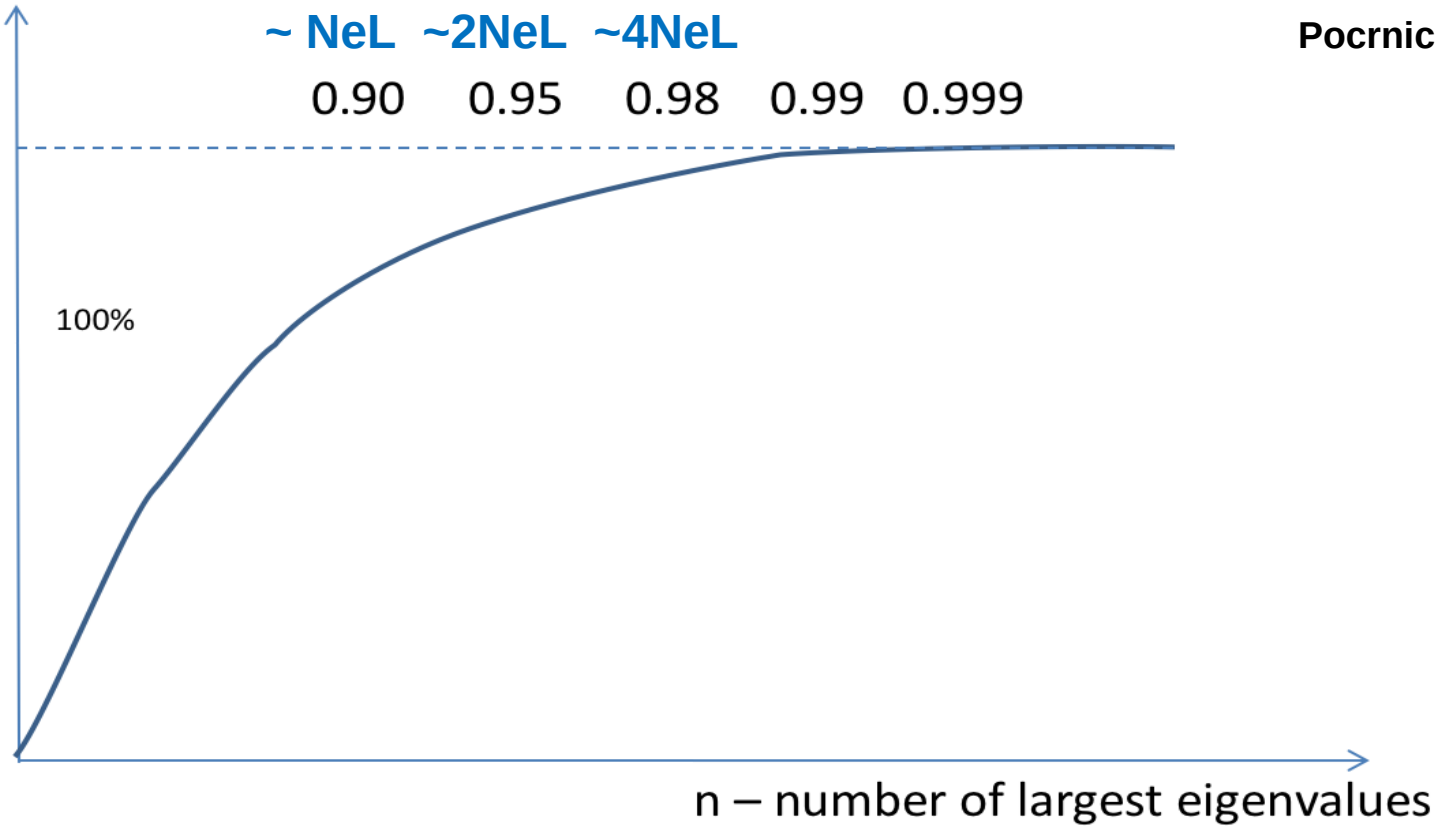
Number of junctions/chromosome segments/haplotype blocks

• $\sim 4N_eL$	Stam (1980)	12,000 for Holsteins
• $2N_eL$	Hayes et al. (2009)	6,000
• $2N_eL/[\log(N_eL)]$	Goddard et al. (2011)	~500

Fraction of **G** variance explained

$$\mathbf{G} = \mathbf{UDU}'$$

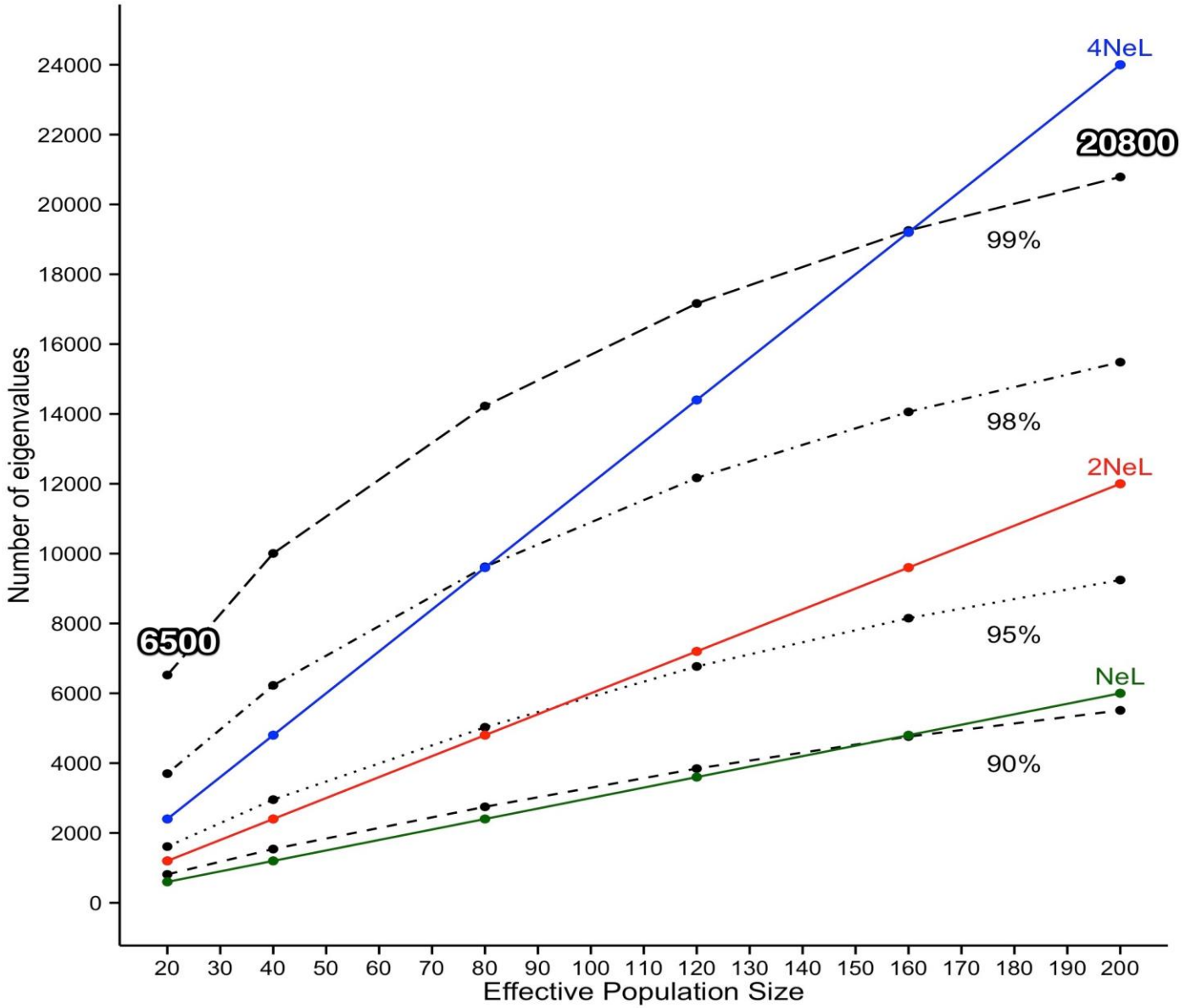
$$\frac{sum(d_{1:n})}{sum(\mathbf{D})}$$



Pocrnic et al., 2016a

What fraction of variance in G is information and what is noise?

Number of largest eigenvalues to account for a given variance



Pocrnic et al., 2016a

How to determine dimensionality in practice - APY inversion of GRM

Breeding values N chromosome segments

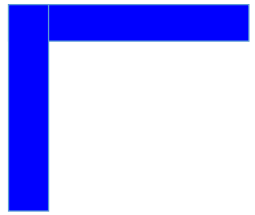
$$\mathbf{u} = \mathbf{T}\mathbf{s}$$

Choose any N animals called "core": $\mathbf{u}_c$

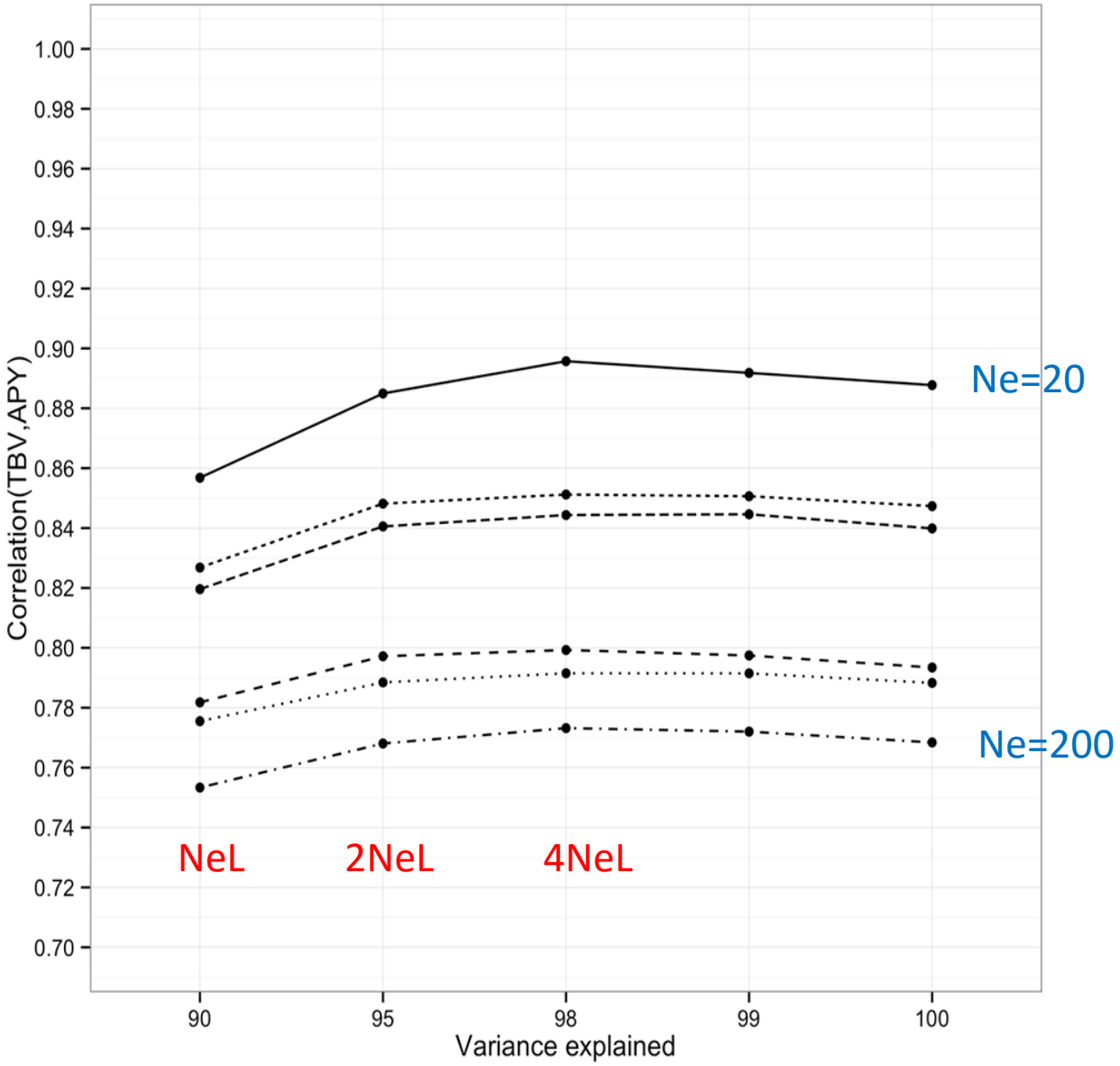
$$\mathbf{s} = \mathbf{Q}\mathbf{u}_c + \boldsymbol{\varepsilon}_c$$ Segments linear function of core N animals

$$\mathbf{u}_n = \mathbf{T}_\mathbf{n}\mathbf{s} = \mathbf{P}_{nc}\mathbf{u}_c + \boldsymbol{\varepsilon}_n$$ Noncore animals linear functions of core animals

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

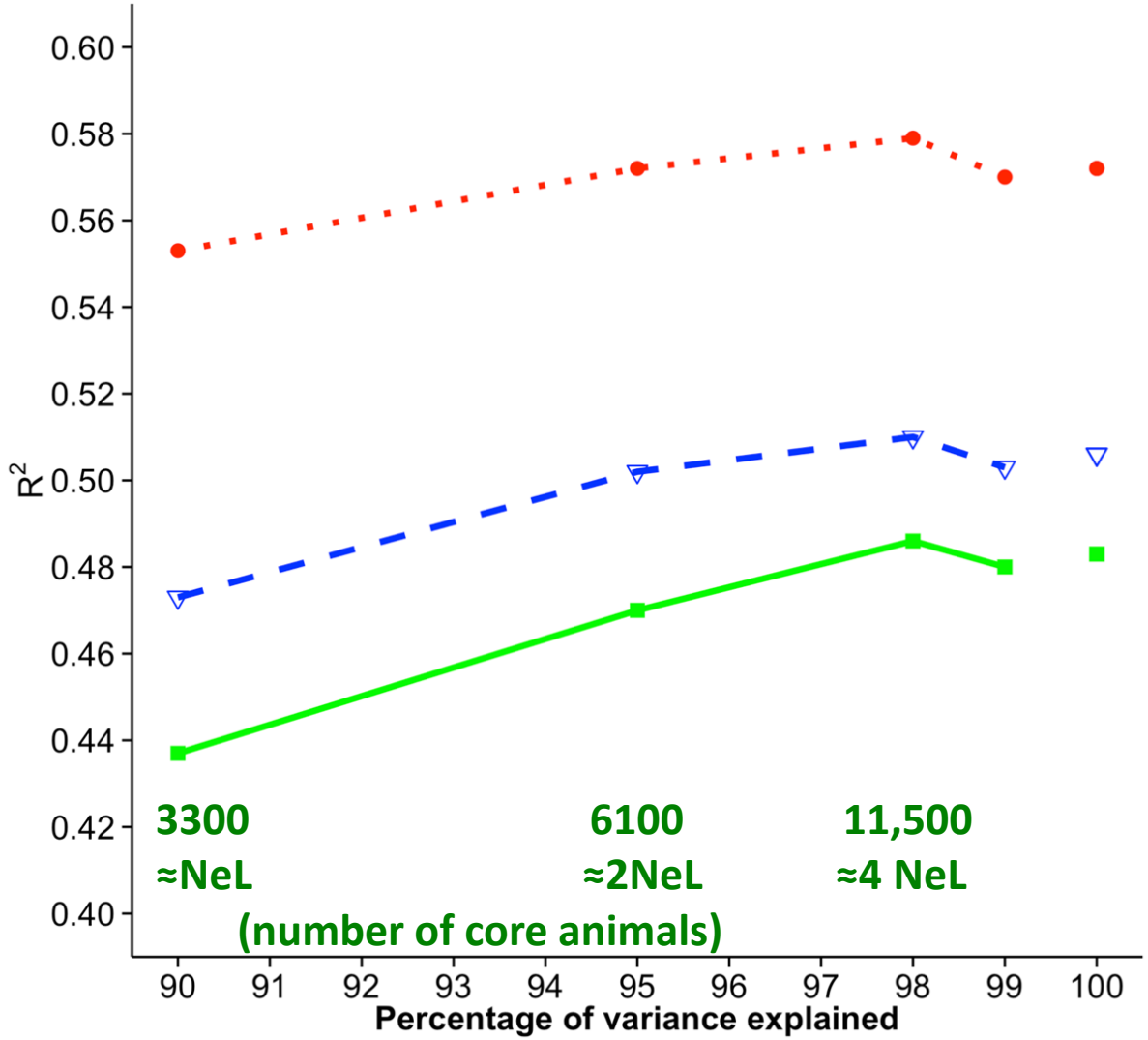


True accuracies as function of number of eigenvalues



Pocrnic et al., 2016a

Reliabilities – Jerseys (75k animals)



Pocrnic et al., 2016b

100% = full inverse ➔ lower accuracy

Estimated effective population size and the number of segments

Specie	Effective population size	Me
Holsteins	149	18k
Jerseys	101	12k
Angus	113	13k
Pigs	43	4k
Chicken	44	4k

Pocrnic et al. (2016b)

Impact of reduced dimensionality

- Accuracy with SNP selection
- Theoretical accuracies
- Persistency of GEBV
- GWAS

Understanding of limited dimensionality (I)

Genome

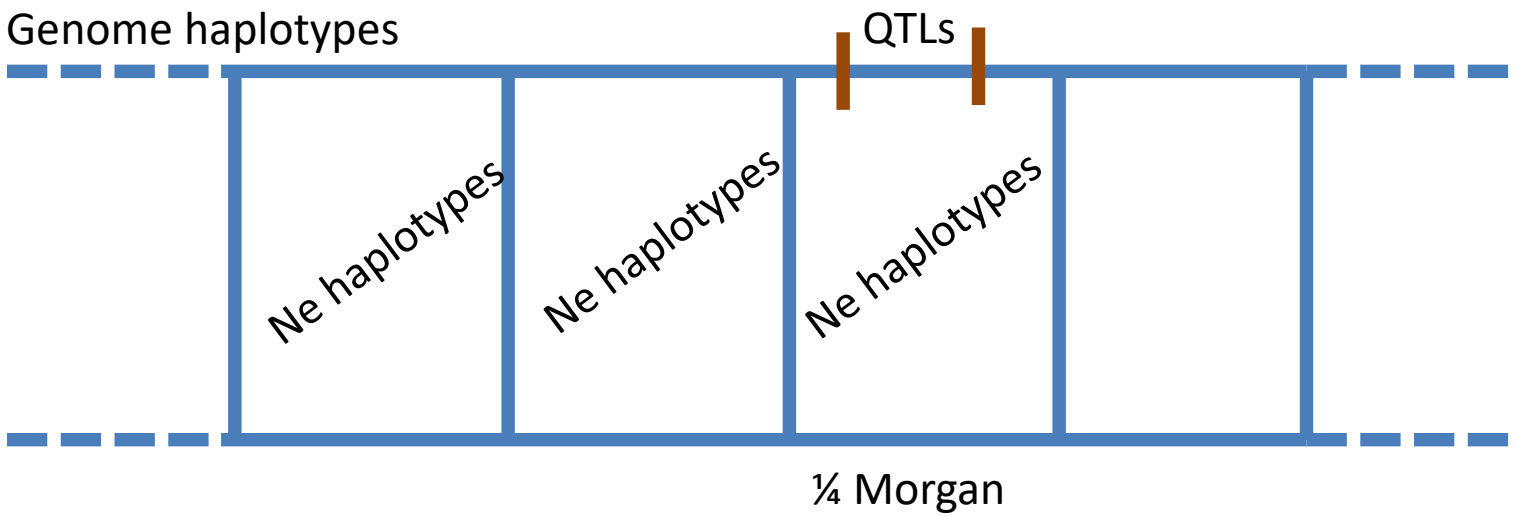
≈ 4 Ne L segments

Average size L/(4NeL)

With Ne=100, L=30, Genome size 3 Gb => 1 segment ≈ 250 kb

Understanding of limited dimensionality (II)

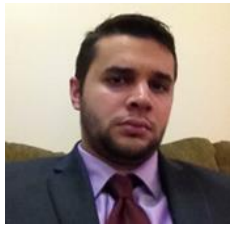
Number of haplotypes: 4 Ne L
Ne within each ¼ Morgan segment



Dimensionality of ¼ Morgan case: Ne

➔ Reduced dimensionality with weighted GRM

ssGBLUP accuracies using SNP60K and 100 QTNs – simulation study

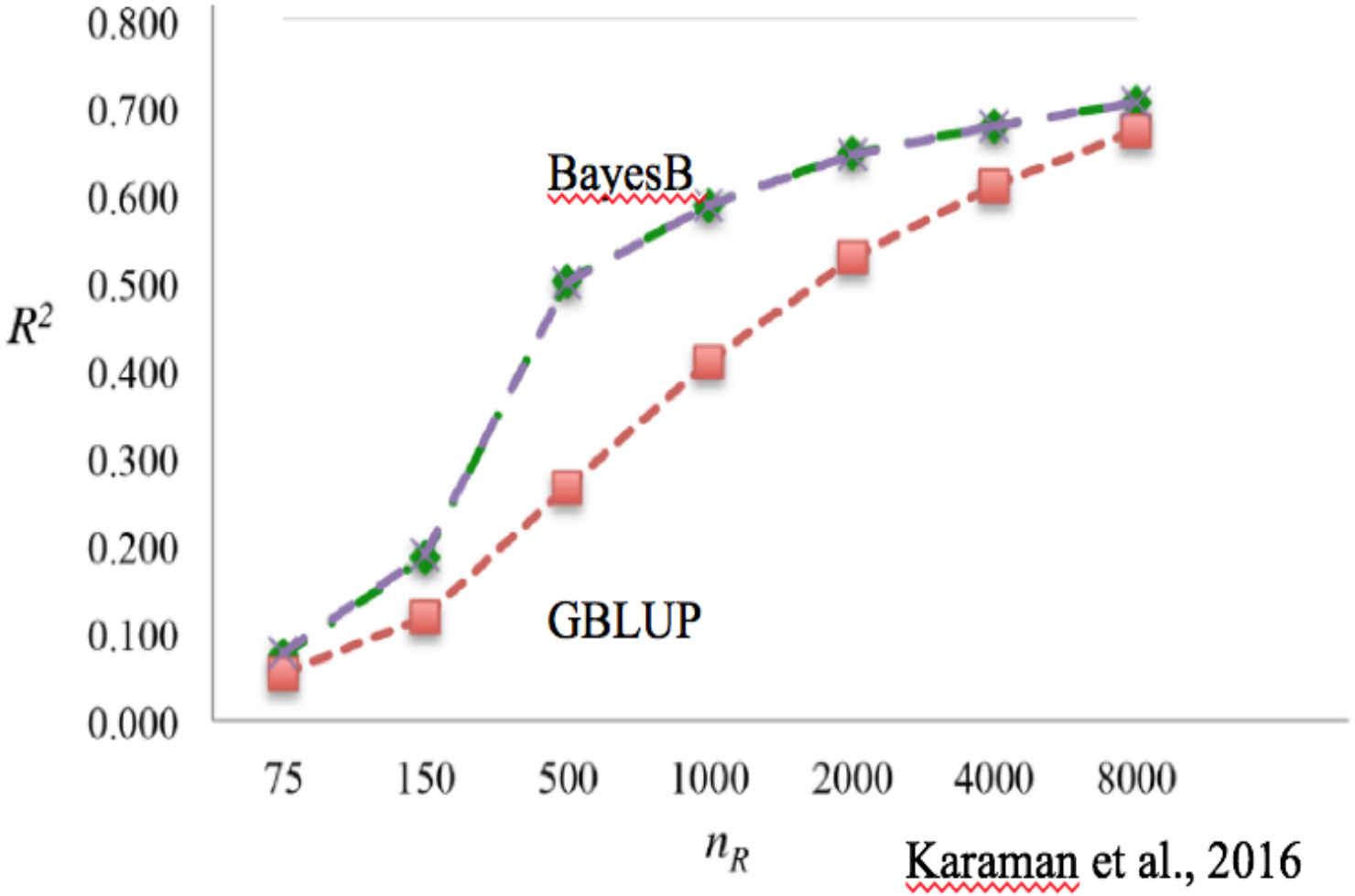


Fragomeni et al. (2017)

Data: 60k genotyped animals
60k SNP + 100 QTN

98% Dimensionality:
19k – unweighted G
5k - weighted G
98 - only QTN

Advantage of SNP selection and size of data



Karaman et al., 2016

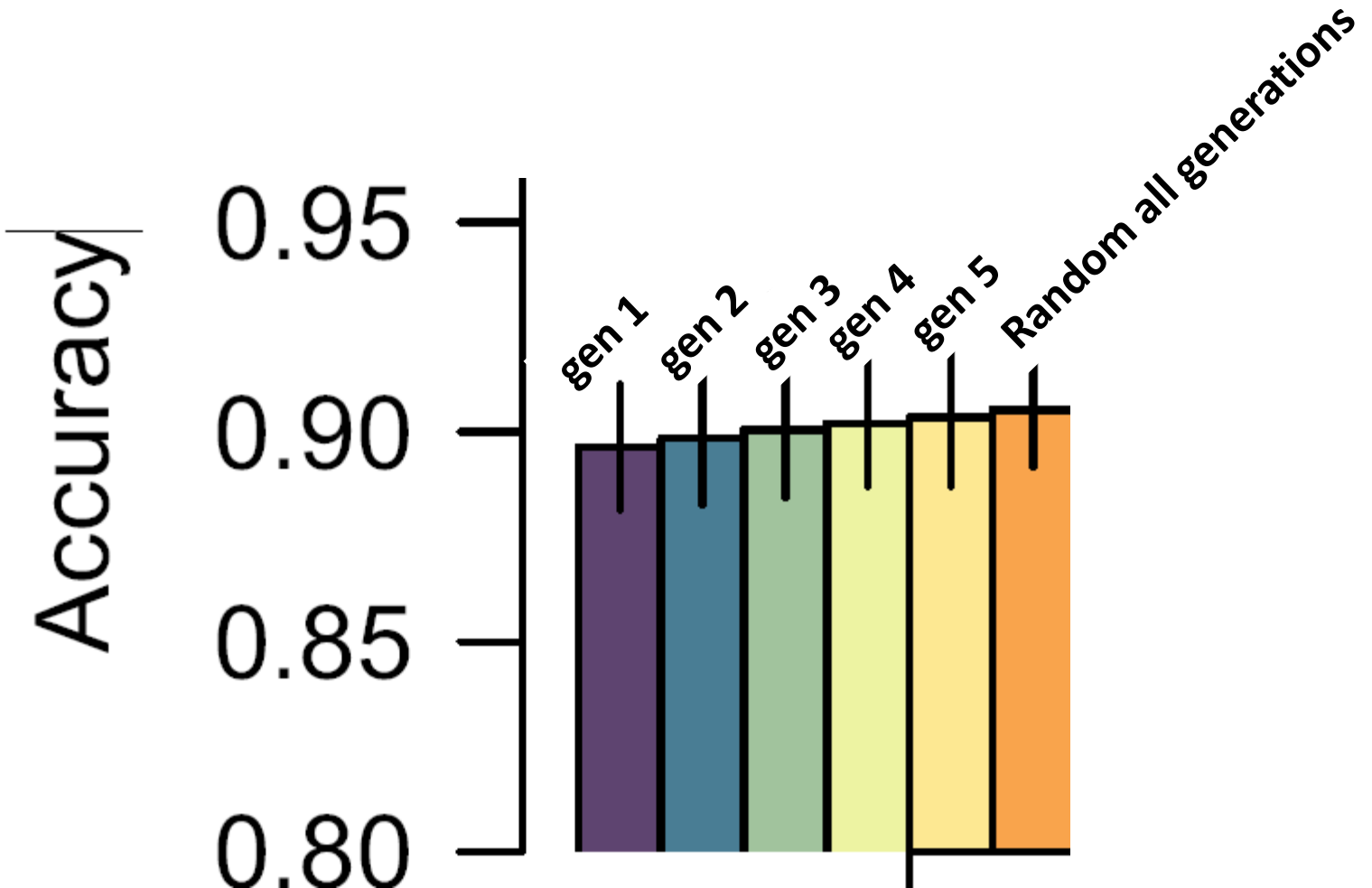
Accuracy as generation of core animals

Bradford et al. (2017)

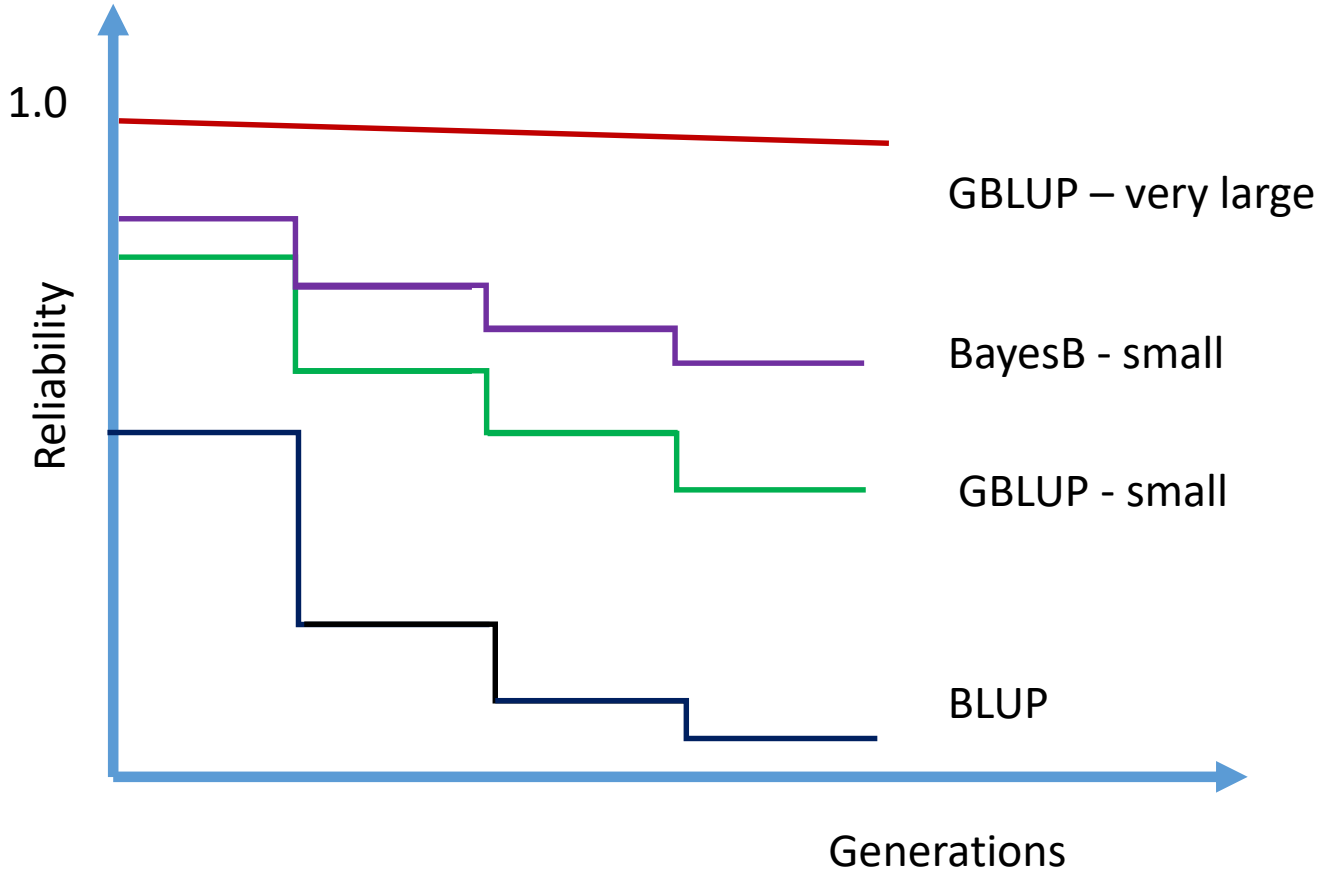
Noncore animals linear functions of core animals

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

Selection does not change segments (additive model only)



Persistence over generations with different sizes of reference populations



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

Accuracy approximations

- Based on equal sized segments (Daetwyler et al., 2008)

$$r = \sqrt{\frac{Nh^2}{Nh^2 + M_e}}$$

N – number of animals

Me – number of segments

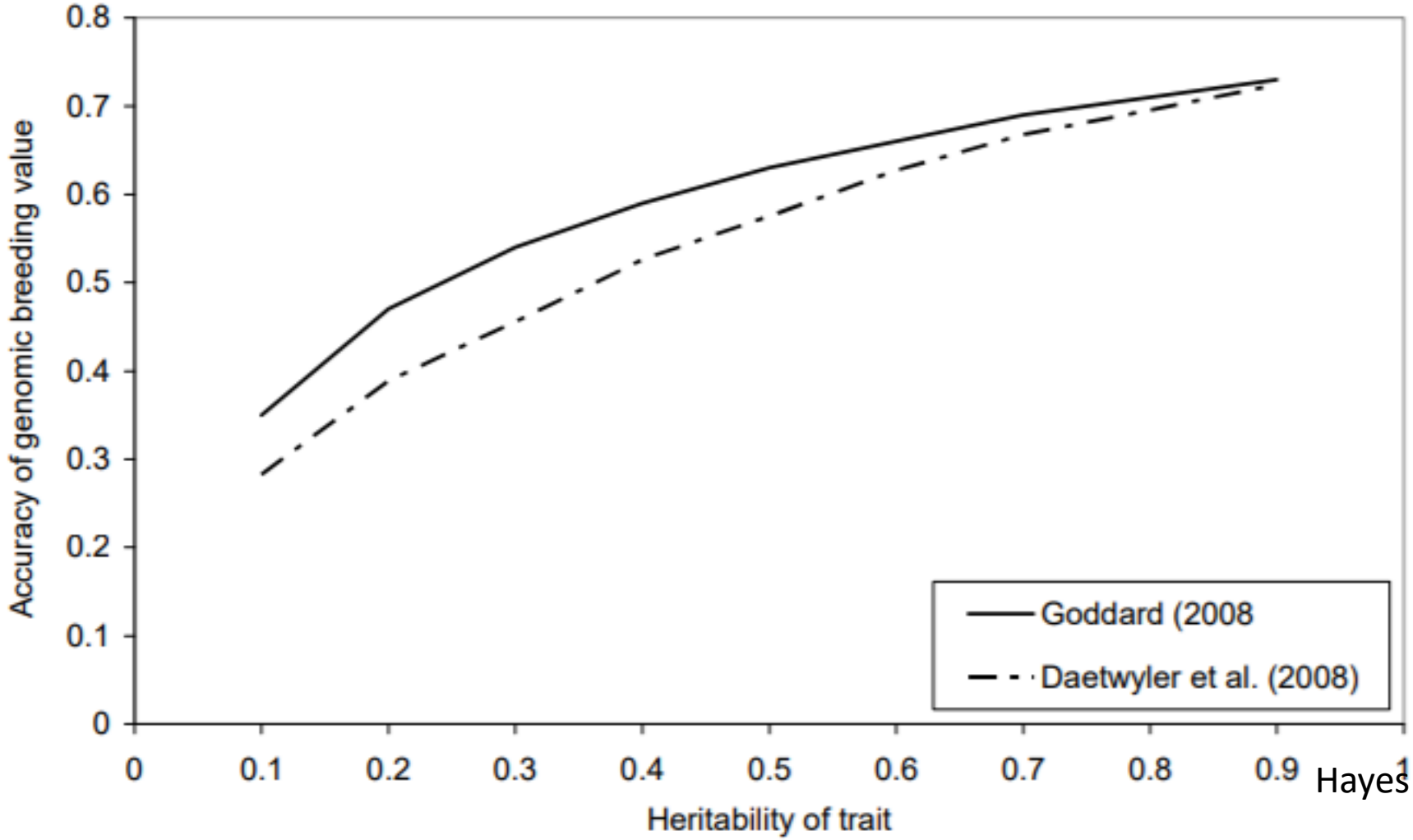
- Based on segments modified by QTL frequencies (Goddard, 2009)

$$r = \sqrt{1 - \frac{\lambda}{2N\sqrt{\alpha}} \ln\left(\frac{1 + \alpha + 2\sqrt{\alpha}}{1 + \alpha - 2\sqrt{\alpha}}\right)}$$

$$M_e/(h^2 \ln(2N_e))$$

$$1 + 2(M_e/Nh^2 \ln(2N_e))$$

Figure 1. Accuracy of genomic breeding values with 5000 phenotypic records, effective population size of 100 and increasing heritability, predicted by the deterministic formula of Goddard (2008) or Daetwyler et al. (2008).

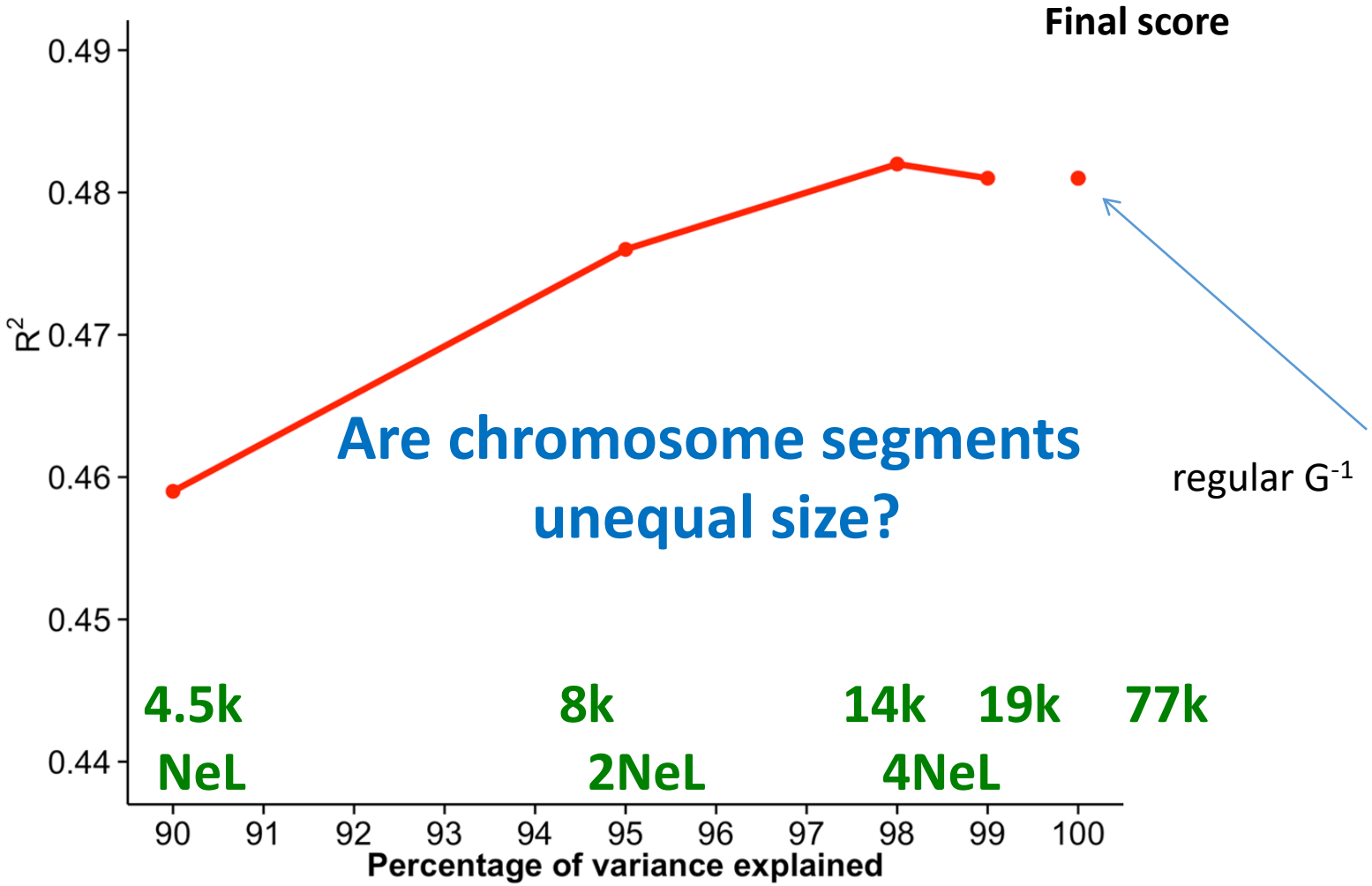


Hayes et al., 2009

Theory and practice

- Theoretical formulas not useful (Brard and Ricard, 2015)
  - Effect of selection?
  - Wrong numbers?
  - Segments not equal?

Reliabilities assuming different dimensionality with APY inverse – Holsteins

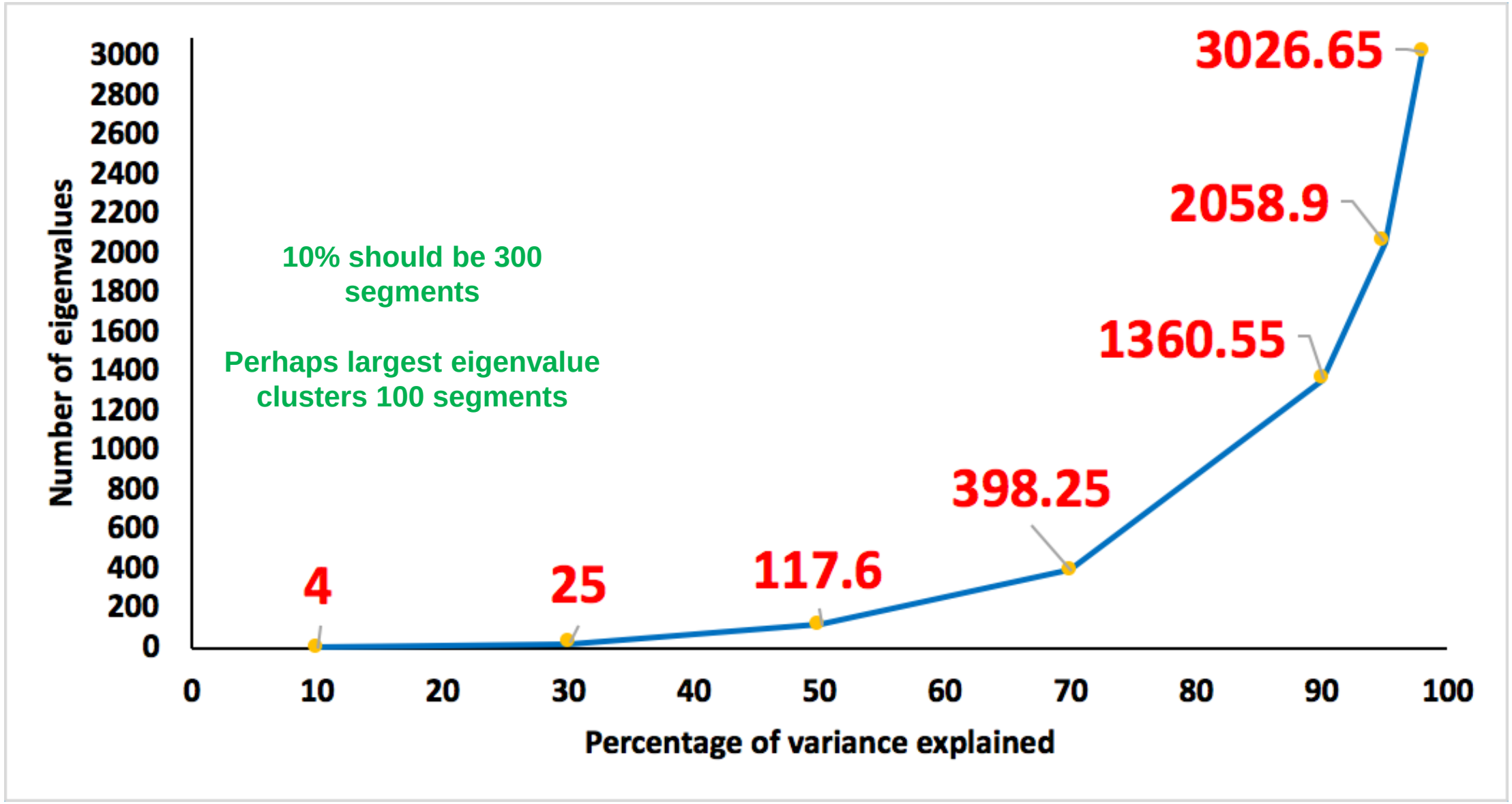


Pocrnic et al., 2016b

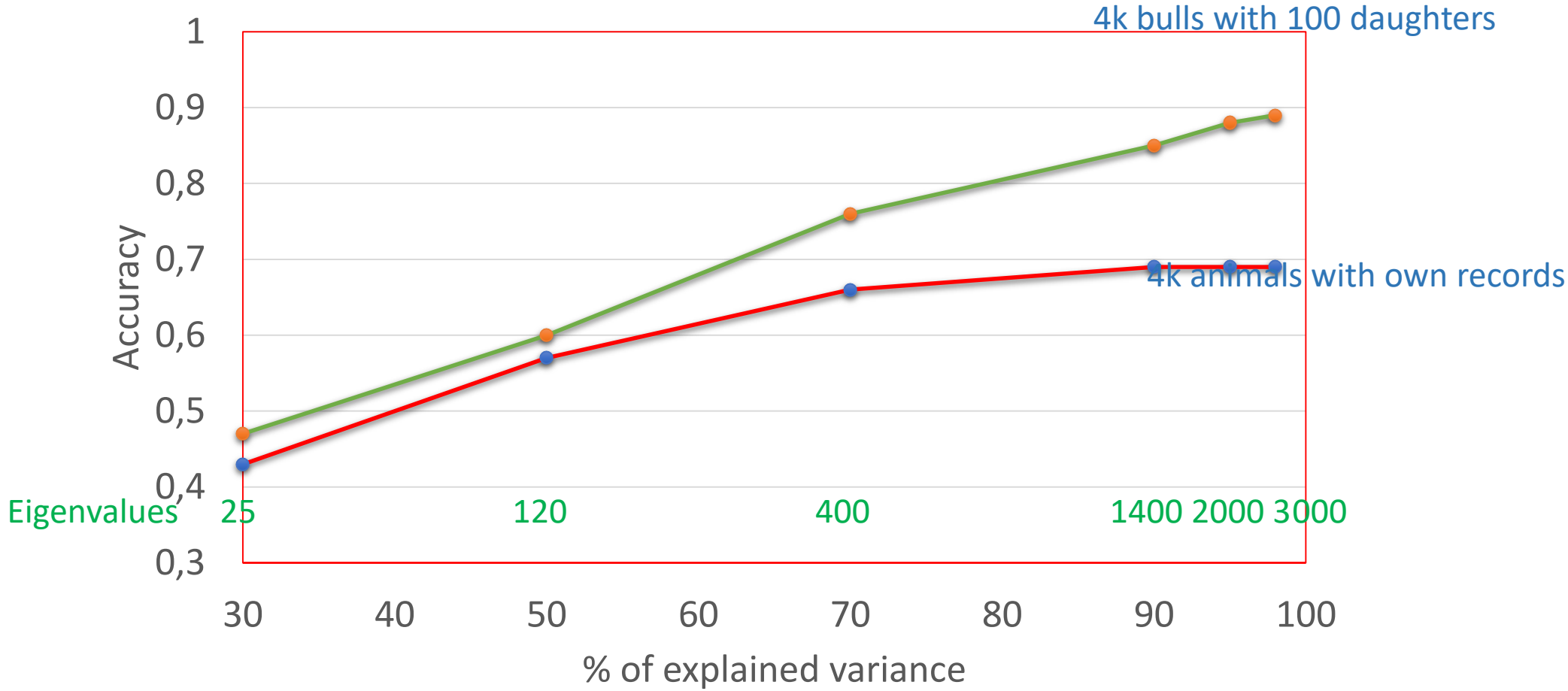
Is genomic selection on chromosome segments or chromosome clusters ?

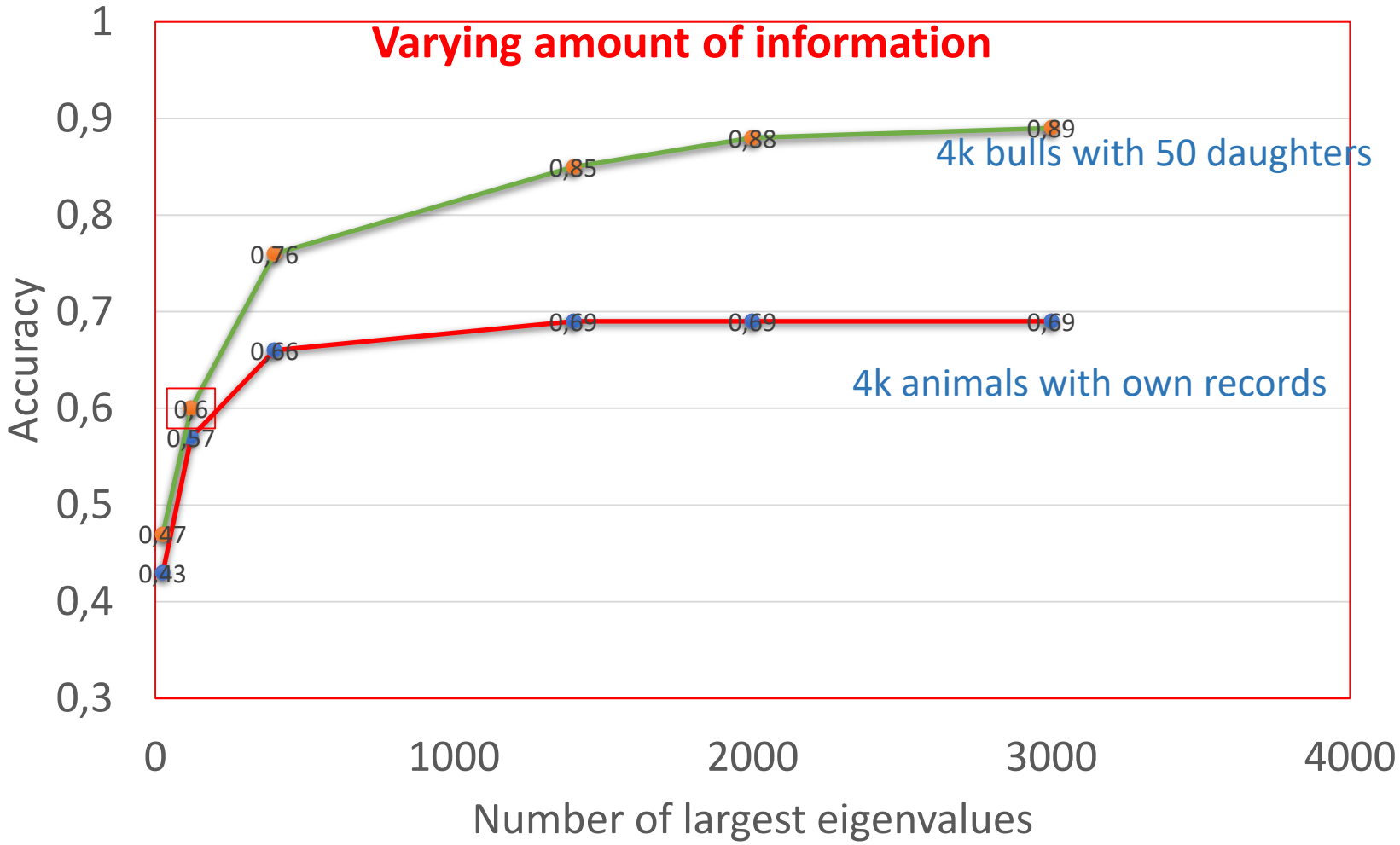
- Simulation
  - 6k animals with 50 k SNP
  - $N_e \approx 50$, L = 10M
- GBLUP
  - Use GRM with limited number of eigenvalues (corresponding to 10 to 99% variation)
  - 4k animals in reference population, 2k in validation

Eigenvalue profile of GRM

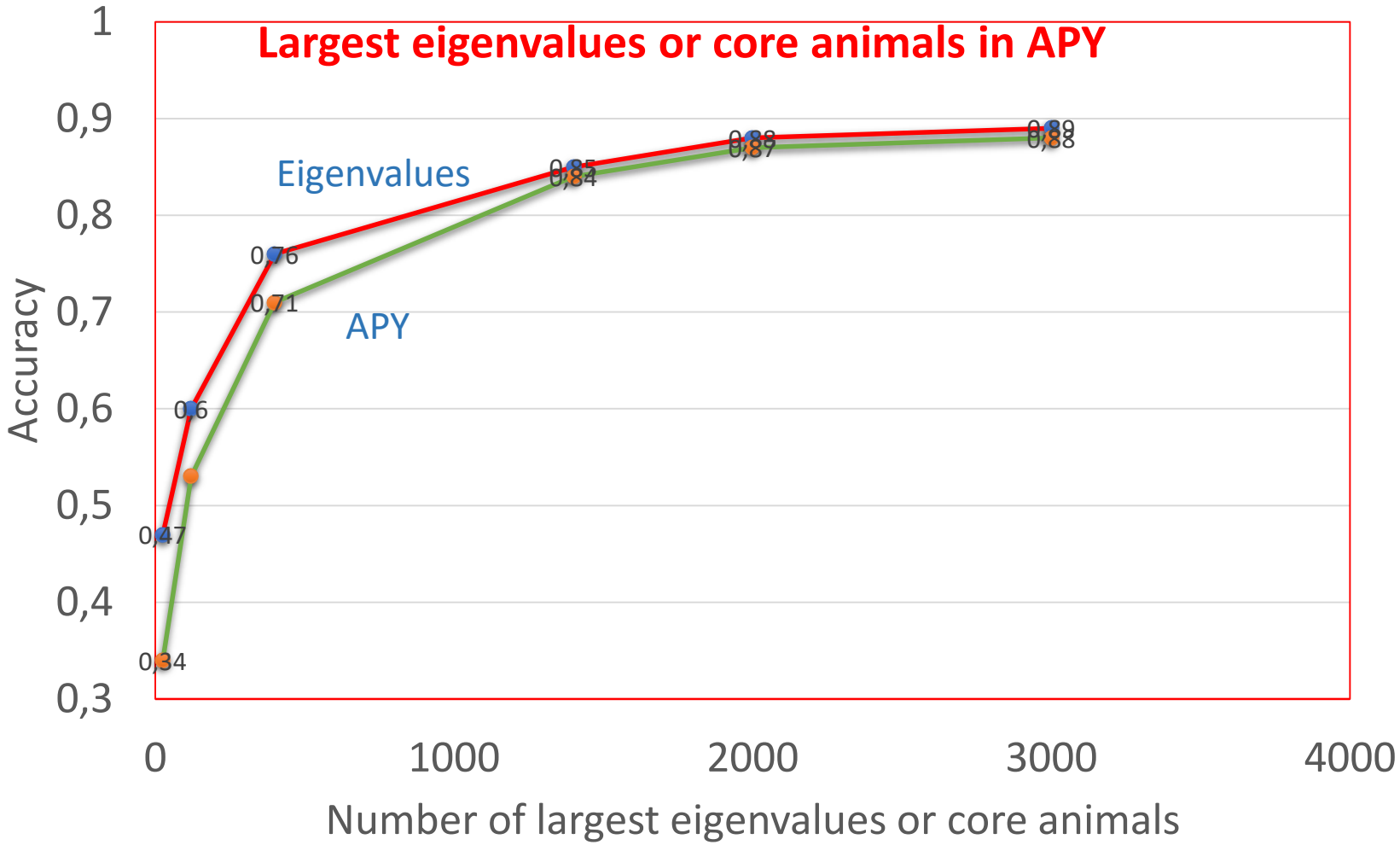


Accuracies of GBLUP using GRM with largest eigenvalues only




Varying amount of information
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
Accuracy
0
1000
2000
3000
4000
Number of largest eigenvalues
4k bulls with 50 daughters
4k animals with own records
0,47
0,76
0,85
0,88
0,89
0,43
0,57
0,66
0,69
0,69
0,69

Does APY algorithm for inversion of GRM work on segments or eigenvalues

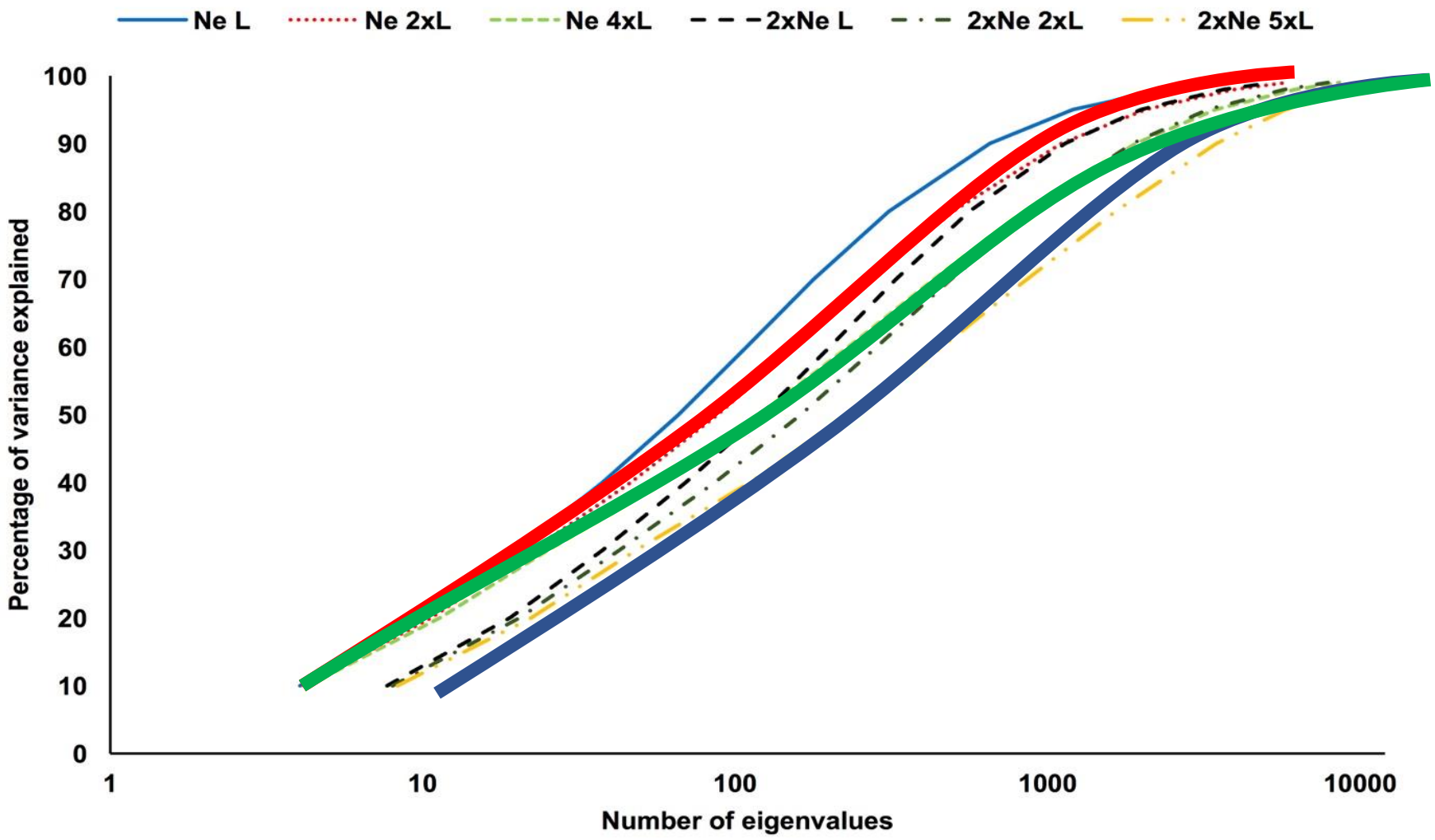


Selection on largest eigenvalues – important ancestors – reduced Ne

If largest eigenvalues excluded- increased diversity?

How are eigenvalues influenced by effective population size and genome length?

Graph of dimensionality as % for different Ne and L



Ne L

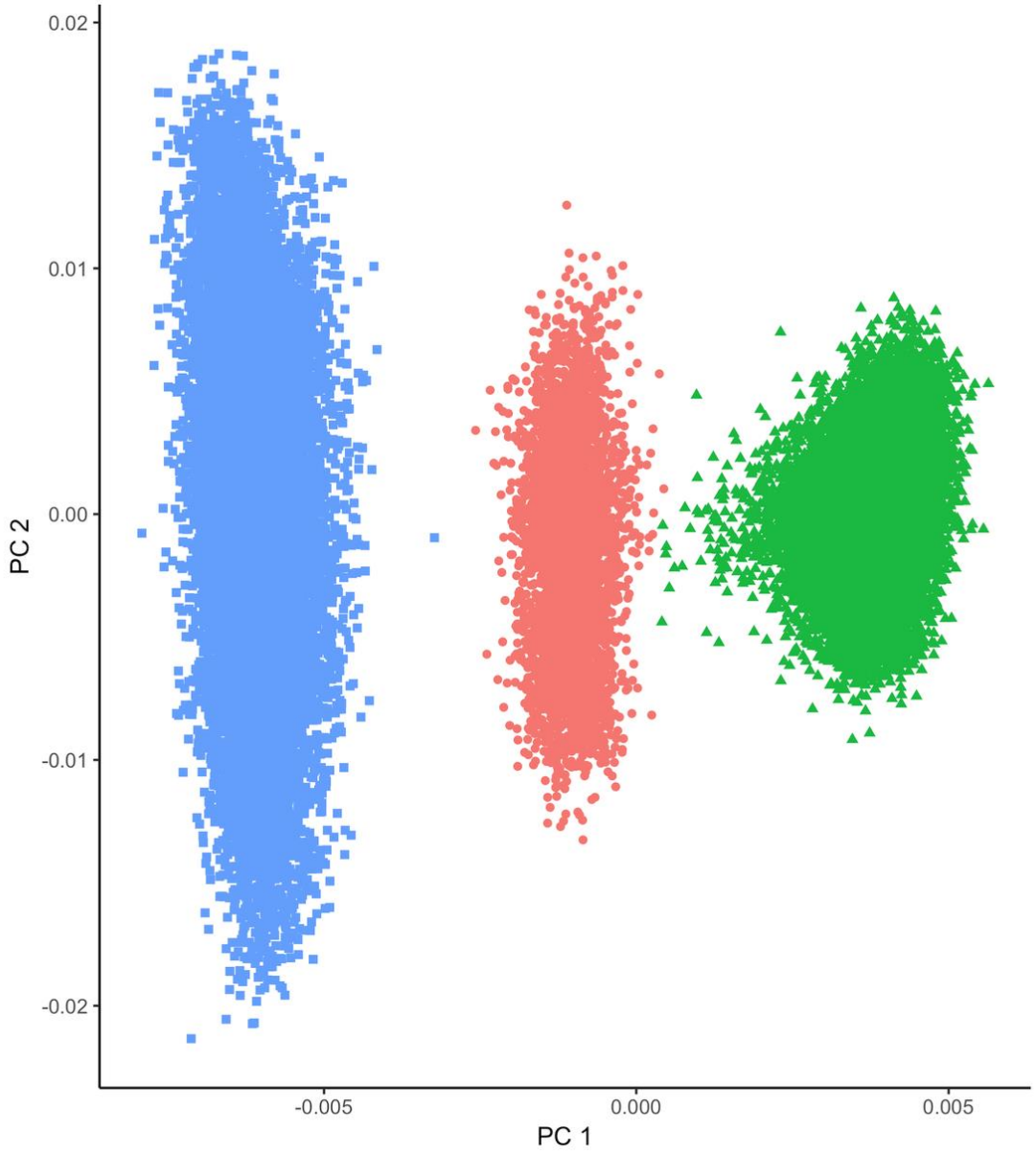
2Ne L

Ne 2L

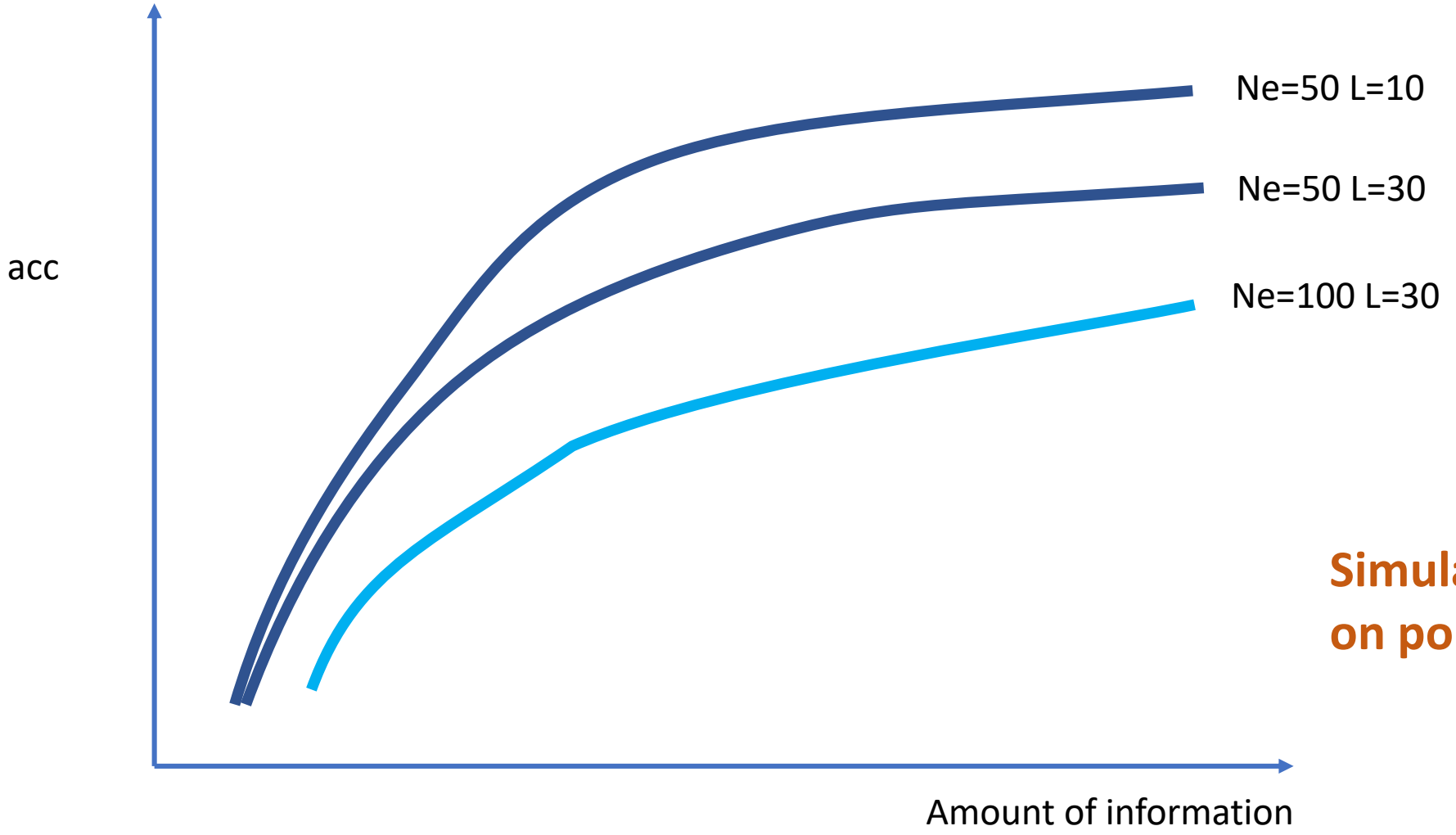
Largest eigenvalues do not depend on genome size - cluster haplotypes across all genome

PCA Plot

PC1 and PC2 pool segments across genome



Hypothetical accuracies as function of Ne and genome length

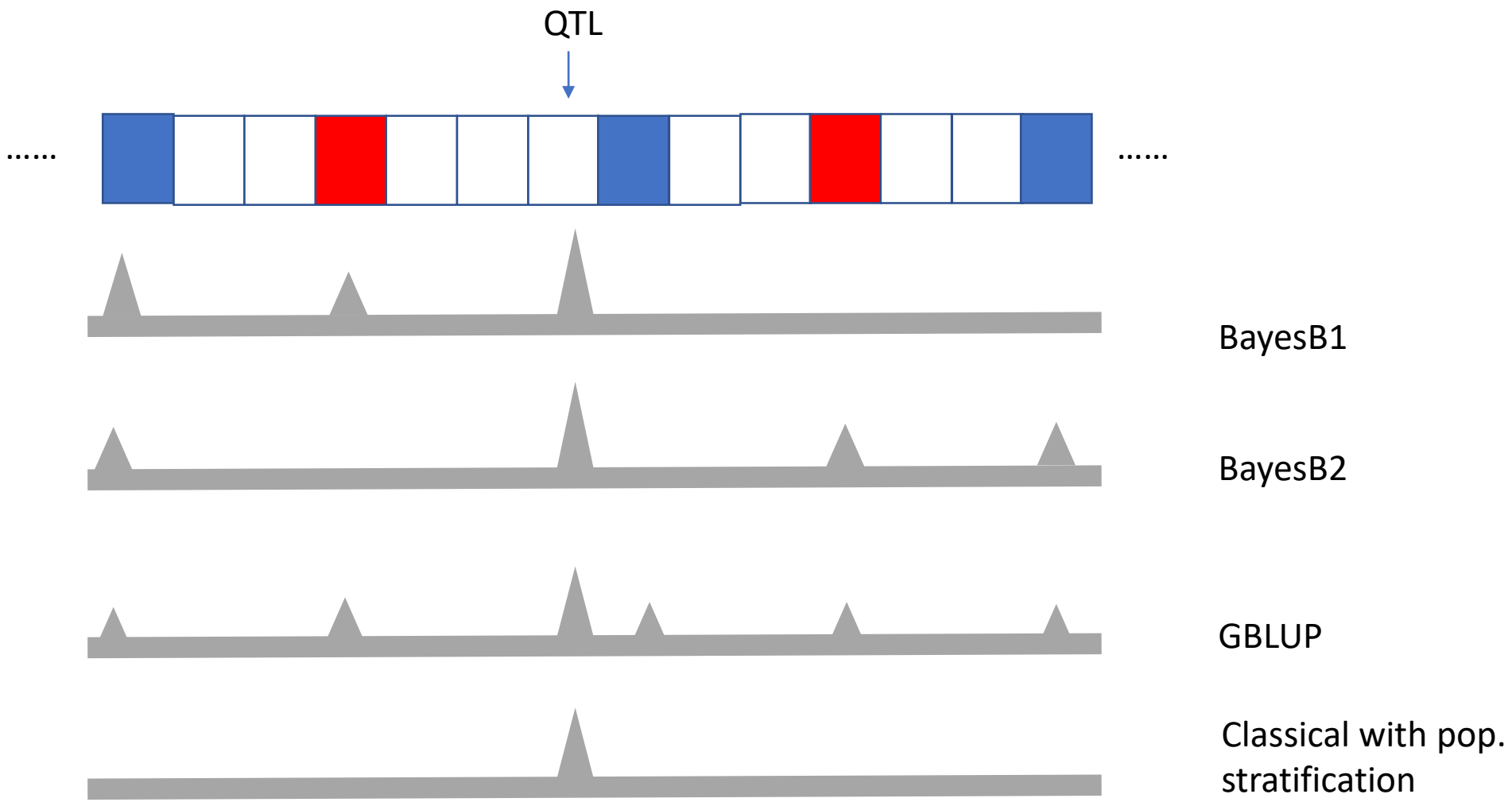


Simulation results depend on population parameters

Some hypothesis on GWAS

First cluster

Second cluster

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Conclusions

- Large impact of limited dimensionality of genomic info
  - Accuracies
  - Persistence
  - GWAS
  - …
- Little data required for medium accuracy, large data for high accuracy
- Many hypotheses - potential studies with real data sets
- Collaborators welcome, funding available

Group and sponsors

United States Department of Agriculture

National Institute of Food and Agriculture


Shogo Tsuruta


Ignacio Aguilar


Breno Fragomeni


Ivan Pocrnic


Daniela Lourenco

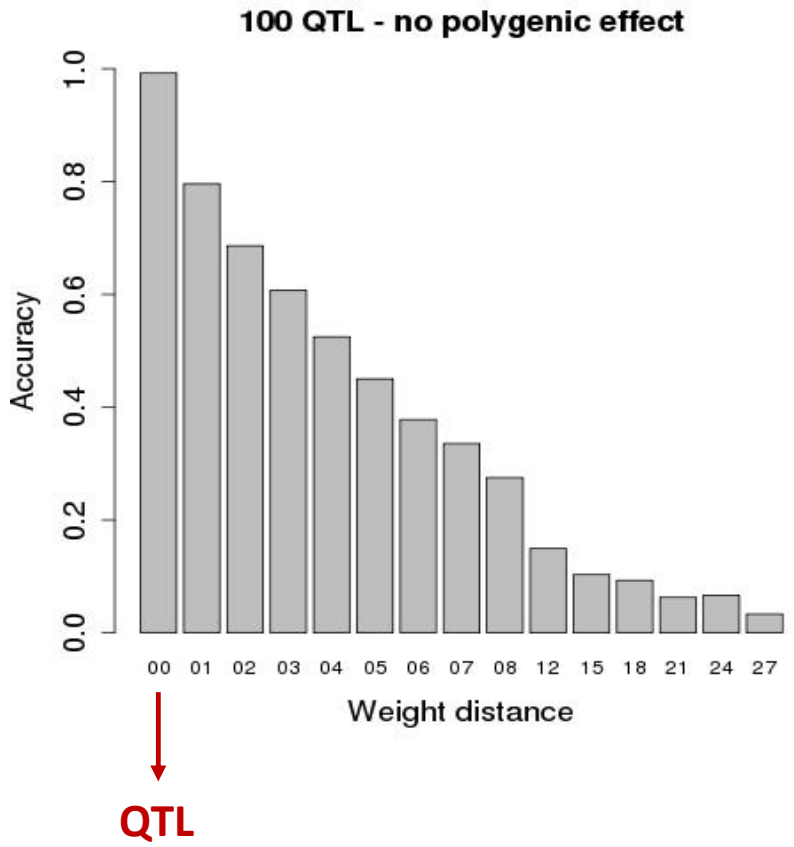

Yutaka Masuda


Andres Legarra


Heather Bradford

Accuracy and distance from markers to QTL

Fragomeni et al. (2017)



Questions - summary

- Is accuracy of GBLUP proportional to explained variance in **G**?
- Can accuracy of GBLUP be expressed in the terms of variance explained by N largest segments, i.e. eigenvalues of **G**
  - e.g. 10% variance = 10% accuracy; 50%=50%; … ?
- Is dimensionality of **G** related to number of core animals?
- What accuracies with n core animals that have perfect BV?
- Do accuracies of GBLUP reach 0.99 with many animals?
- Are APY and SVD/EIGEN methods related?