Accuracy of Genomic Prediction

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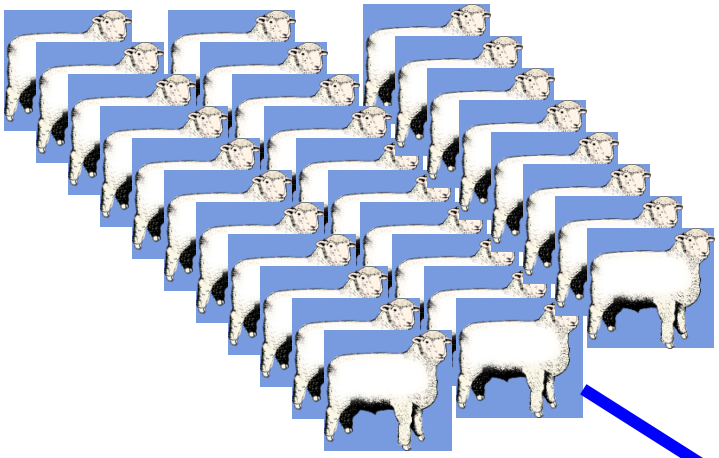
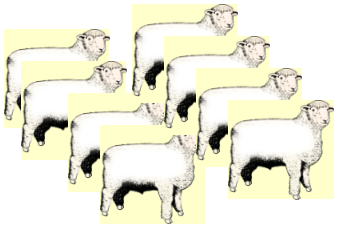
An Australian Government Initiative

CRC AUSTRALIA

Genomic Prediction: basic idea



Reference population
measured and DNA tested

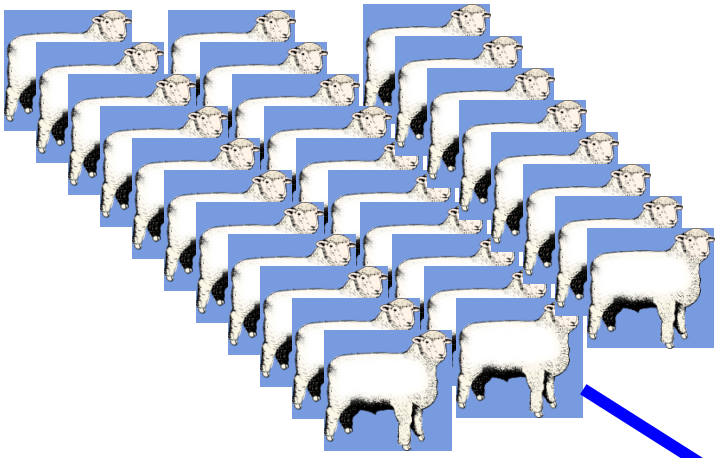


Young sires
Only DNA tested

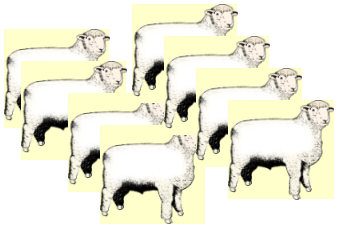
To predict a trait EBV at a young age,

good for for: late traits
hard to measure traits

Genomic Prediction: basic idea



Reference population
measured and DNA tested



Young sires
Only DNA tested

What if reference population is

- Another breed
- Multi-breed
- Crossbreds
- Small
- Less related
- Sire Ebvs
- EBVs

?

How does genomic prediction work?

- Markers in LD with QTL?
- Genomic Relationships?
- We know that GBLUP is equivalent to SNP-BLUP
- We observe that SNP BLUP and Bayesian methods are pretty similar → "infinitesimal model"

Genomic Prediction: GBLUP

Example:
Data on sire 1, his sons (2 and 3) and an unrelated individual (4)

want to predict 5 (also a son of 1) ← no data

A-matrix (pedigree-based)

1	0.5	0.5	0	0.5
0.5	1	0.25	0	0.25
0.5	0.25	1	0	0.25
0	0	0	1	0
0.5	0.25	0.25	0	1

G-matrix (DNA-based)

1	0.5	0.5	0.02	0.5
0.5	1	0.20	0.015	0.20
0.5	0.20	1	0.025	0.30
0.02	0.015	0.025	1	0.025
0.5	0.20	0.30	0.025	1

Variation in relationship (animal 5 with 2 and 3

Also a small relationship with 'unrelated'

Genomic Prediction: GBLUP

Example:
Data on sire 1, sons 2 and 3, 4 unrelated, want to predict 5

A-matrix (pedigree-based)

1	0.5	0.5	0	0.5
0.5	1	0.25	0	0.25
0.5	0.25	1	0	0.25
0	0	0	1	0
0.5	0.25	0.25	0	1

G-matrix (DNA-based)

1	0.5	0.5	0.02	0.5
0.5	1	0.20	0.015	0.20
0.5	0.20	1	0.025	0.30
0.02	0.015	0.025	1	0.025
0.5	0.20	0.30	0.025	1

BLUP

$\hat{u}_5 = 0.1136.y_1 + 0.0455.y_2 + 0.0455.y_3$

GBLUP

$\hat{g}_5 = 0.1135.y_1 + 0.0328.y_2 + 0.0591.y_3 + 0.00519.y_4$

Genomic Prediction: GBLUP

Example:
Data on sire 1, sons 2 and 3, 4 unrelated, want to predict 5

A-matrix (pedigree-based)

1	0.5	0.5	0	0.5
0.5	1	0.25	0	0.25
0.5	0.25	1	0	0.25
0	0	0	1	0
0.5	0.25	0.25	0	1

BLUP uses: Family Info

G-matrix (DNA-based)

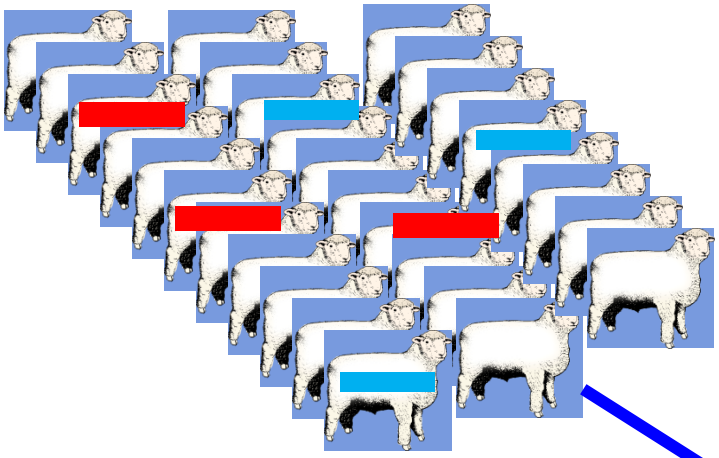
1	0.5	0.5	0.02	0.5
0.5	1	0.20	0.015	0.20
0.5	0.20	1	0.025	0.30
0.02	0.015	0.025	1	0.025
0.5	0.20	0.30	0.025	1

GBLUP uses: Family Info
Segregation within family
Info on 'unrelated'

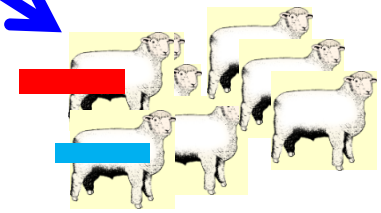
Genomic prediction accuracy

- Derive from the model, e.g. PEV from GBLUP mixed model equations
- Validate with other EBVs or phenotypes
  - Validation population
  - Cross-validation
- Predict in advance based on theory and assumptions about population

Genomic Prediction: basic idea



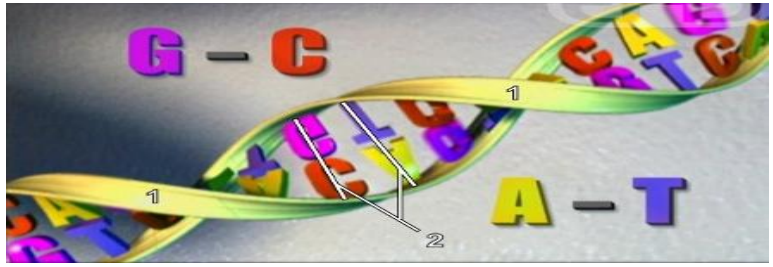
1) Somebody (else) measures lots of sheep, and their DNA
→ Reference population



2) A breeder tests DNA on young rams

Illustrating (dis-)similarity of chromosome segments

Genotype information



Father

```
10100 1 110111 0 01110 0 1110011
01010 0 111000 1 10001 1 0011010
```

Mother

```
00010 0 111100 1 0101100 110011
10101 1 101011 1 111111 1 111110
```

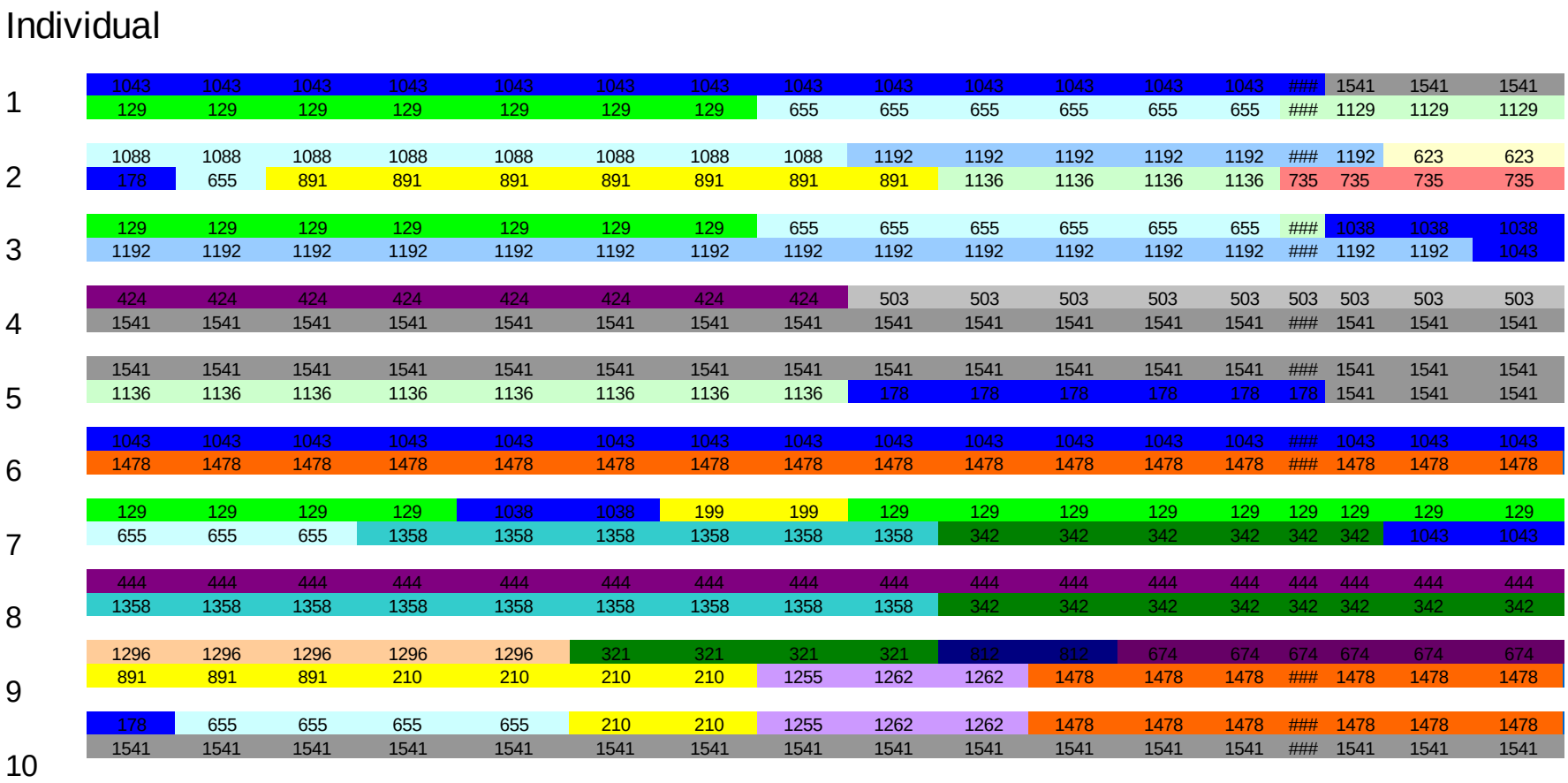
Chromosome segments are passed on

Progeny

```
10100 1 110111 0 01110 0 1110011
00010 0 111100 1 01011 0 0110011
```

genotypes

A whole population of haplotypes



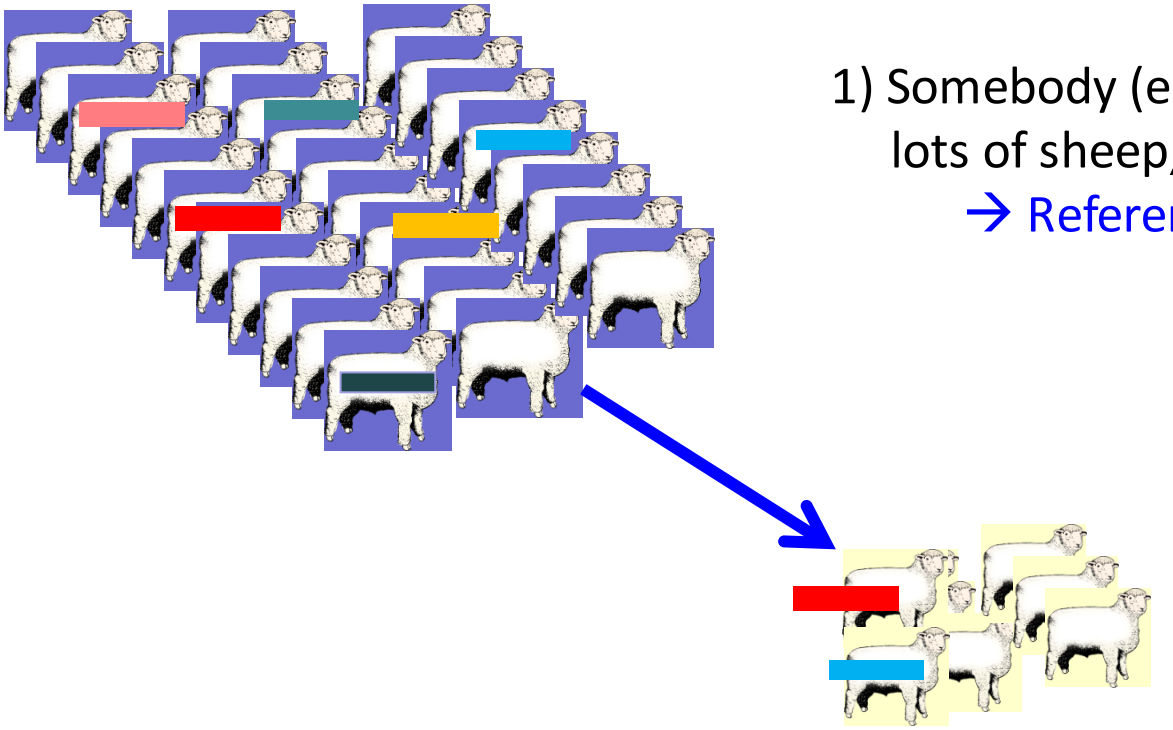
Within a population, members will share chromosome segments

We can follow inheritance via SNPs

Degree of sharing can be represented in a genomic relationship (= observed based on SNPs)

(similar to genetic relationship = expected based on pedigree)

Genomic Prediction: basic idea

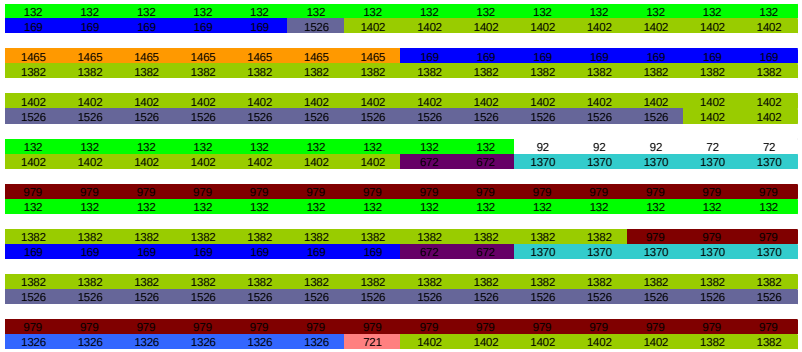


1) Somebody (else) measures lots of sheep, and their DNA
→ Reference population

2) A breeder tests DNA on young rams

Large diversity of segments → less accuracy

populations of haplotypes



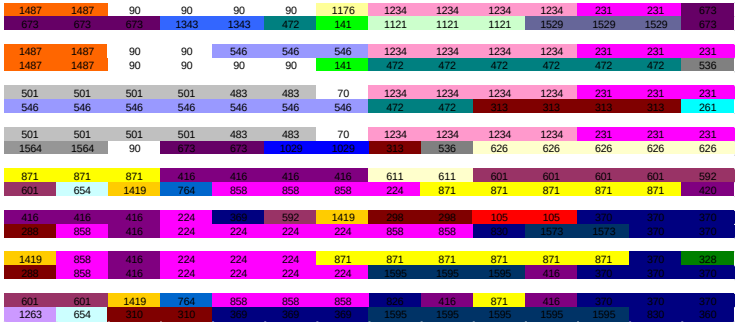
Holstein Friesian, a pig/poultry nucleus

Limited diversity
Long segment sharing

Smaller N_e, longer segment sharing, fewer “effective loci”

Merino sheep, humans

More diversity
Short segment sharing
Sub populations



Not only recent N_e but also historic N_e is relevant

Genomic prediction accuracy

Design parameters

- Effective population size (N_e)
- Effective # chromosome segments (M_e)
- Sample size in reference data (N)
- Heritability (h^2)

Genomic prediction accuracy *Using Daetwyler et al, 2008*

Accuracy^2 of estimating a random effect = $n / (n+\lambda)$ $\lambda = V_e / V_a$

If genome exists of M_e independently segregating 'effective chromosome segments'

And each segment has variance VA/ M_e, then accuracy^2 of estimating each segment

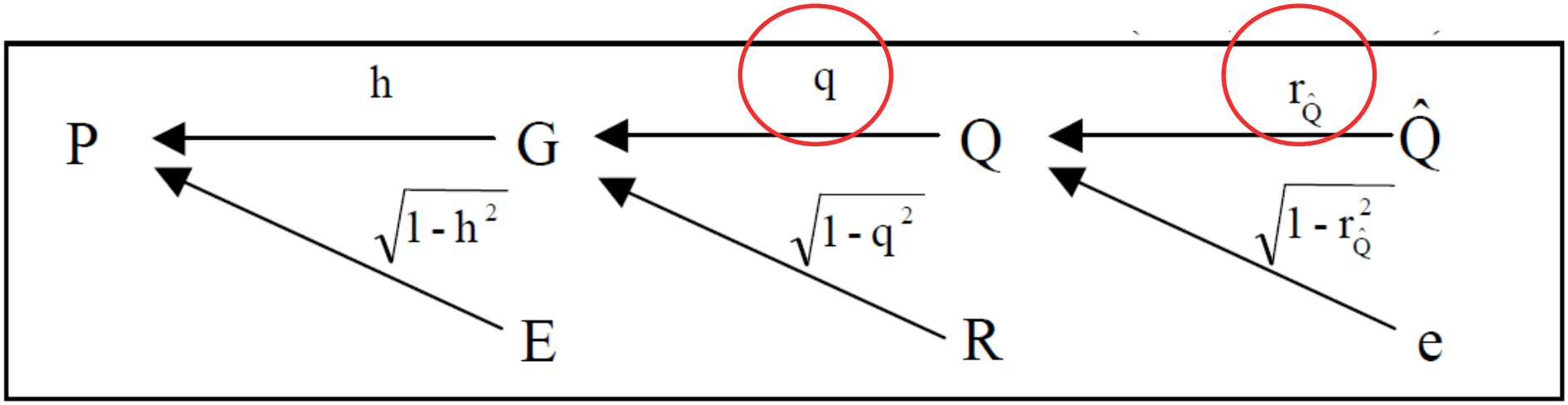
$$\frac{N}{N+V_e / (V_a/M_e)} = \frac{NV_a}{NV_a + V_e M_e} = \frac{h^2}{h^2 + M_e/N}$$

$$r_{g,\hat{g}} = \sqrt{\frac{h^2}{h^2 + M_e / N}}$$

N = nr observations
M_e = effective nr loci

Valid if "all genetic variance is captured by markers"

See also Dekkers 2007 (Path coefficient method)



Trait heritability = h^2

G = total BV

Q = genetic effects captured by marker(s)

R = residual polygenic effects

Model for phenotype: P = G + E

Model for BV: G = Q + R

Genomic prediction accuracy *Using Goddard et al, 2011*

Depends on

i) Proportion of genetic variance at QTL captured by markers q^2

i) Reliability of estimating marker effects r^2_{Qhat}

Accuracy = $\sqrt{(q^2 . r^2_{Qhat})}$

= $q . r_{Qhat}$

Genomic prediction accuracy *Using Goddard et al, 2011*

Depends on

i) Proportion of genetic variance at QTL captured by markers

$q^2 = M/(M_e + M)$

↳ Depends on marker-QTL LD

↳ Depends on

M = # markers

M_e = 'effective number of chromosome segments'

i) Accuracy of estimating marker effects

Genomic prediction accuracy *Using Goddard et al, 2011*

Depends on

i) Proportion of genetic variance at QTL captured by markers $q^2 = M/(M_e + M)$

↳ Depends on marker-QTL LD

↳ Depends on M = # markers

M_e = 'effective number of chromosome segments'

i) Accuracy of estimating marker effects

$$r^2_{Qhat} = V_{qhat}/V_q = N/(N+ \lambda)$$

$$\lambda = M_e/(q^2 .h^2)$$

$$\text{Accuracy} = \sqrt{(q^2 . r^2_{Qhat})}$$

$$= q . r_{Qhat}$$

Comparing

Daetwyler et al, 2008 Goddard et al, 2011

With very many markers

i) Proportion of genetic variance at QTL captured by markers $q^2 = M/(M_e + M)$

$$q^2 = 1$$

i) Accuracy of estimating marker effects

$$r^2_{Qhat} = V_{qhat}/V_q = N/(N+ \lambda) = h^2 / (h^2 + M_e/N)$$

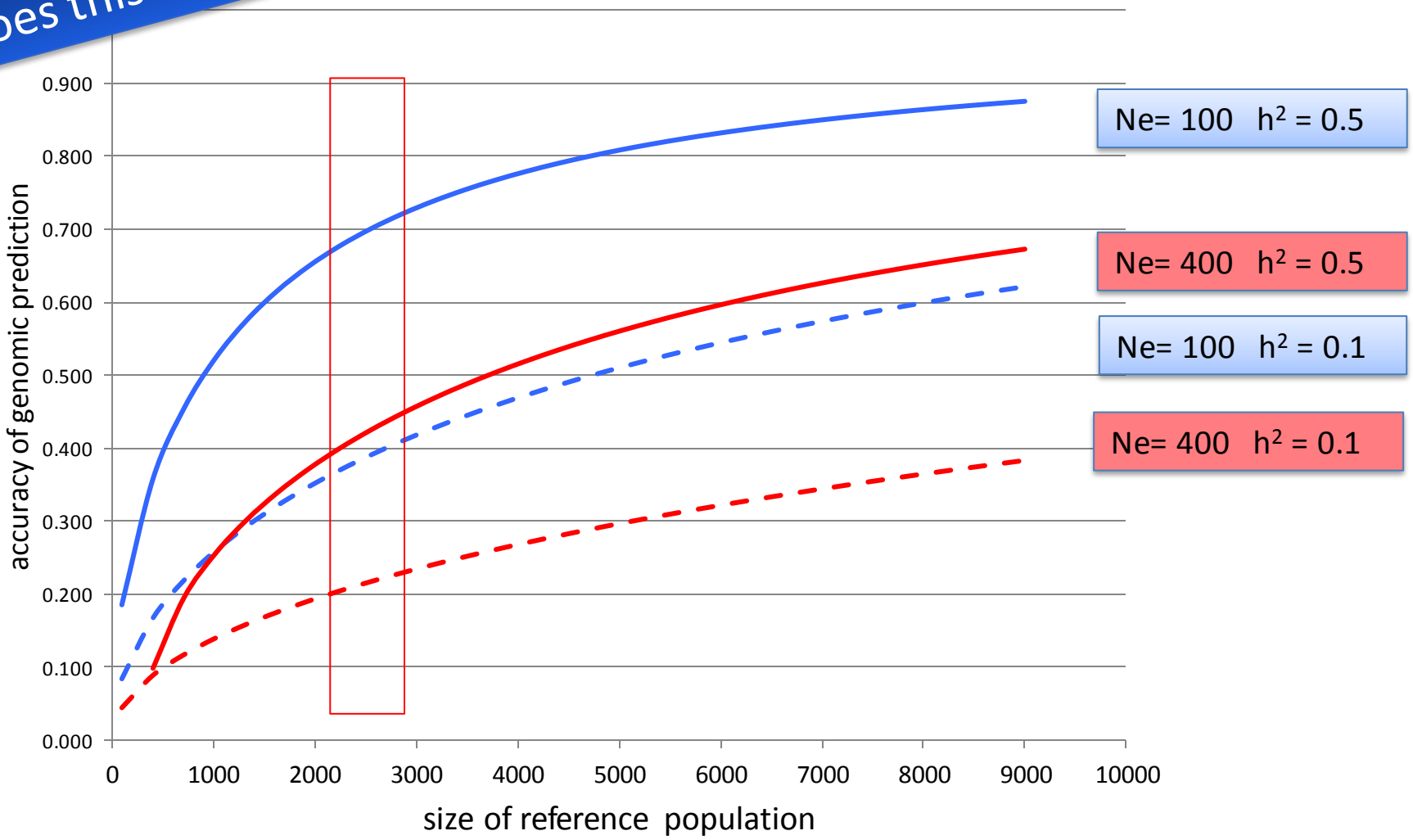
$$\lambda = M_e/h^2$$ same as Daetwyler

$$\text{Accuracy} = \sqrt{(\ r^2_{Qhat})}$$

$$= r_{Qhat}$$

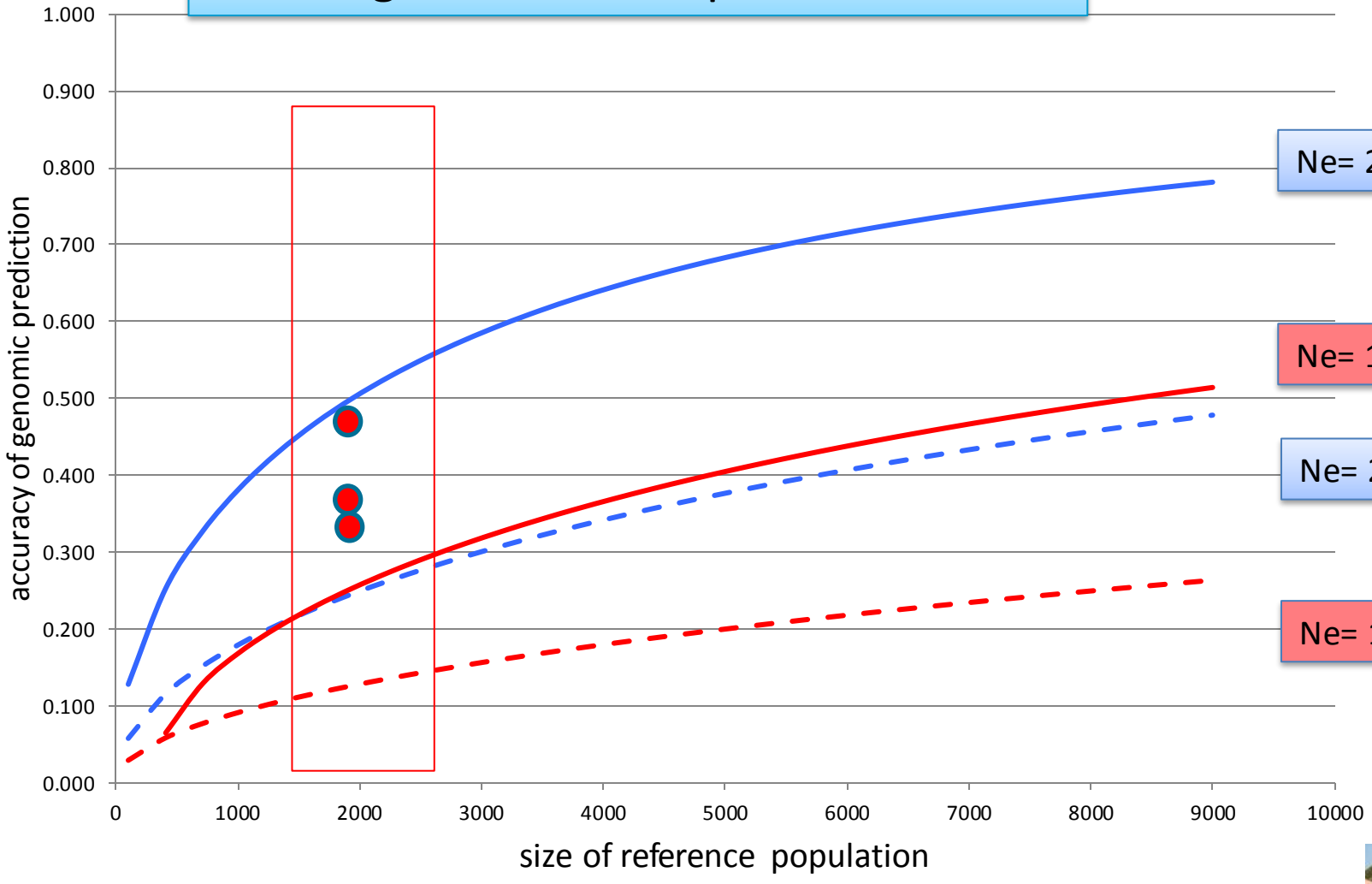
Genomic prediction accuracy *Using Goddard et al, 2011*

Does this work?



Genomic prediction accuracy *Using Goddard et al, 2011*

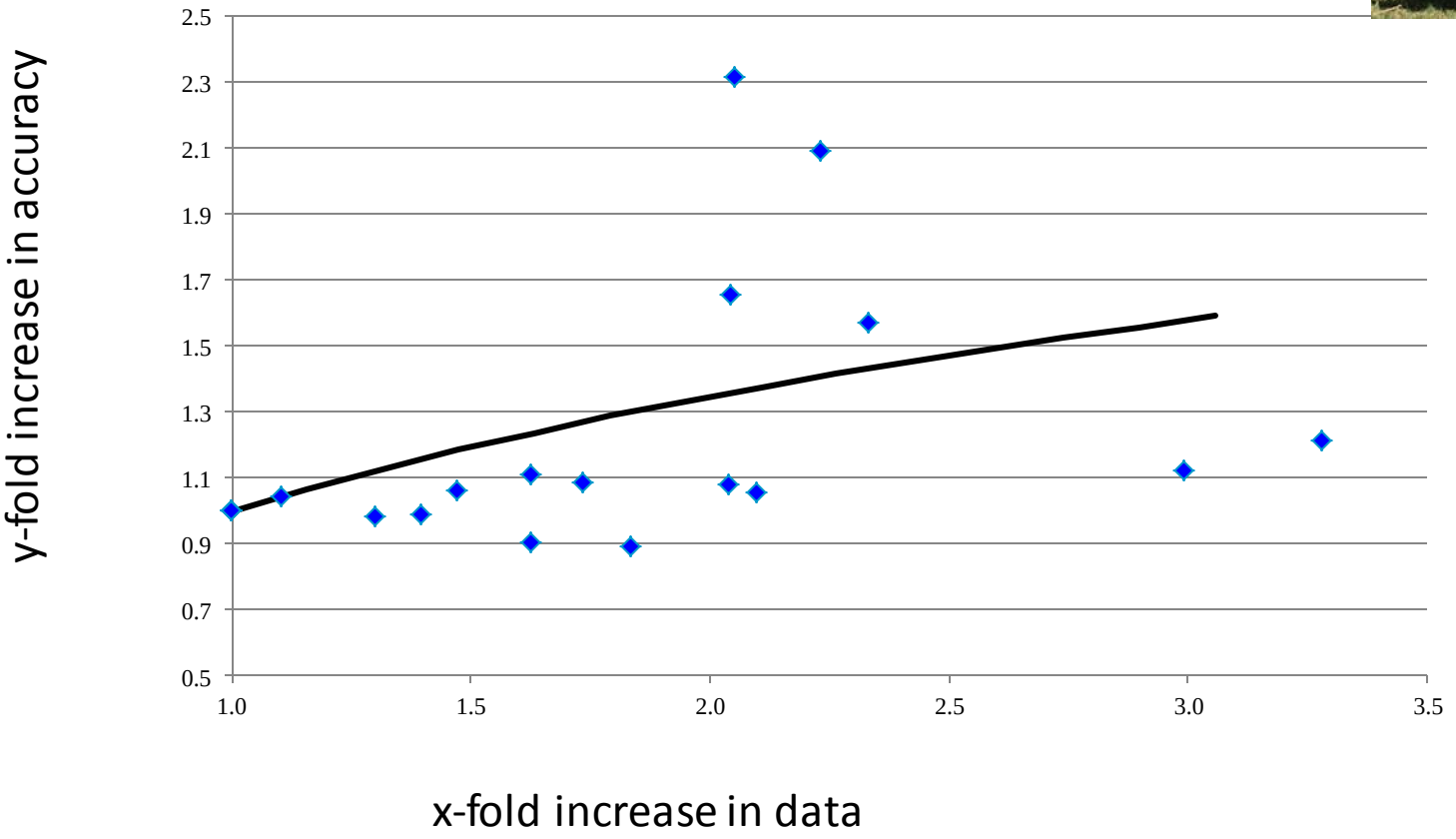
Did we get what we expected?



Validating ‘Genomic Prediction Accuracy’

More data is always good

But does it increase accuracy as expected?



What effective population size?

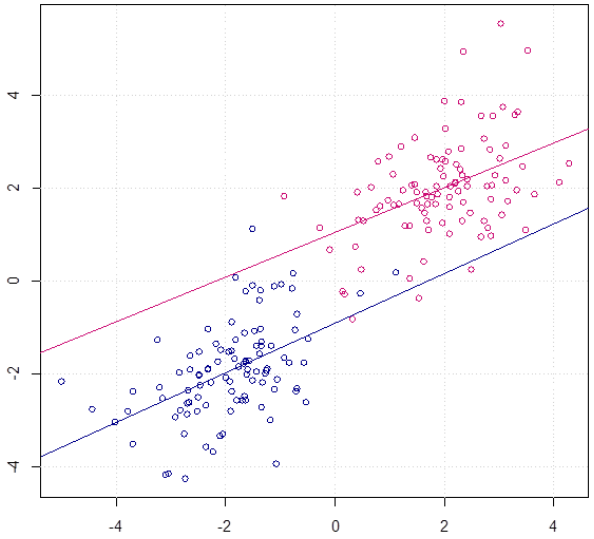
Kijas et al 2012

- Sampling?

Populations not homogeneous.

Within and between breed/line accuracies

Some accuracy due to population structure



Summary so far

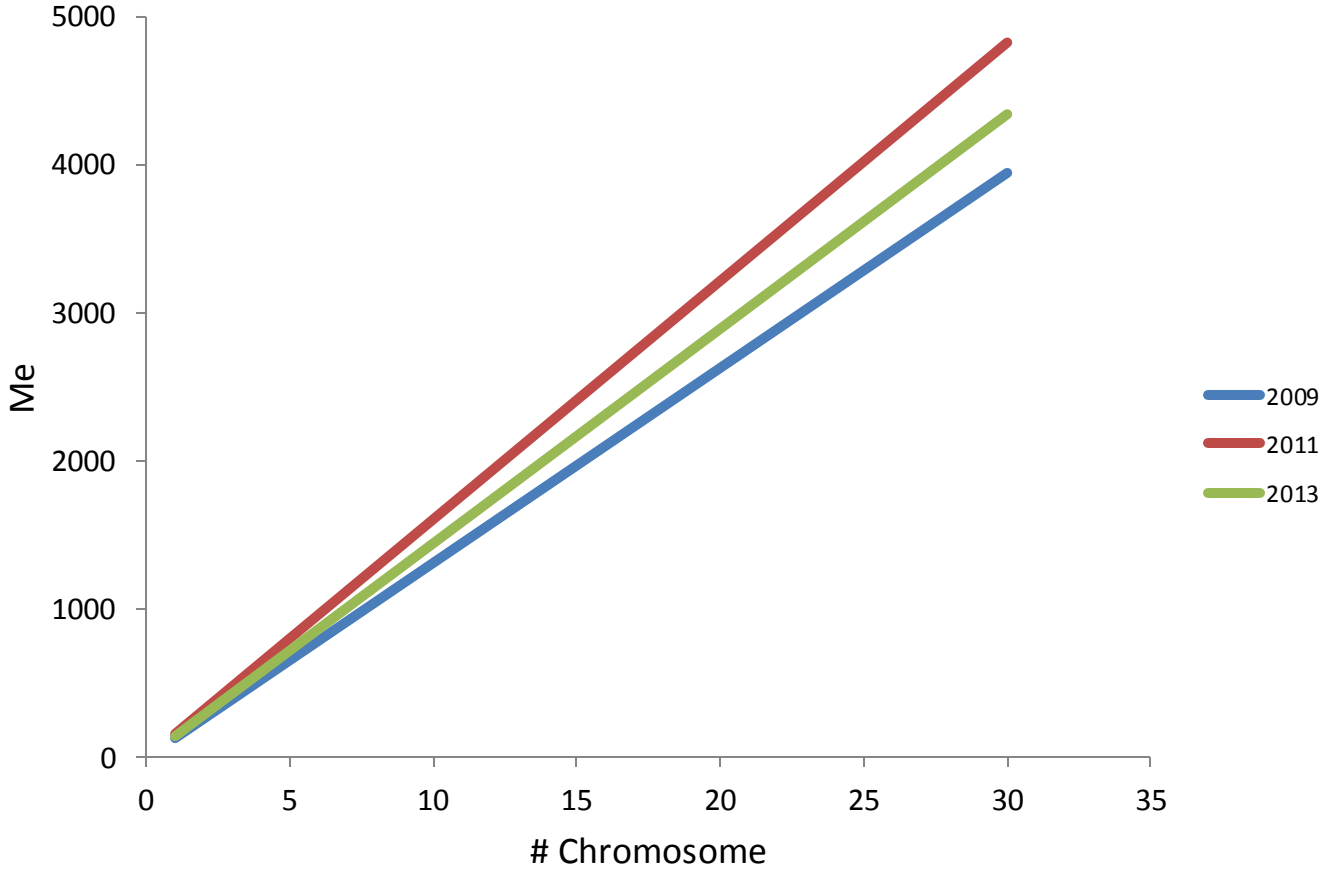
- Theory exists to predict genomic prediction accuracy in advance: depends on nr. effective segments, nr records
- Relies on assumptions regarding effective population size
- And some (unclear) theory about effective nr of loci
- Ignores heterogeneity of populations and relationships
- *We observe more inital acc and less increase with more data*

How to derive the effective number of loci?

M_e is a function of N_e

- $M_e = 2N_eLN_{chr} / \ln(4N_eL)$ (Goddard 2009)
- $M_e = 2N_eLN_{chr} / \ln(N_eL)$ (Goddard et al. 2011)
- $M_e = 2N_eLN_{chr} / \ln(2N_e)$ (Meuwissen et al. 2013)

Difference among the formulas



Example: N_e = 500, L=1M h^2 = 0.5 and N = 5000,

→ accuracy = 0.62, 0.58, 0.60

Validating 'Effective number of segments'

Can use actual data on A and G to test this

Compare G and A matrices G - A = D + E

D =deviation in relationship at QTL

Var(D) = $1/M_e$

$$M_e = 1/\mathrm{var}\left(A_{ij}\right)$$

E = error

Var(E) = 1/nr Markers

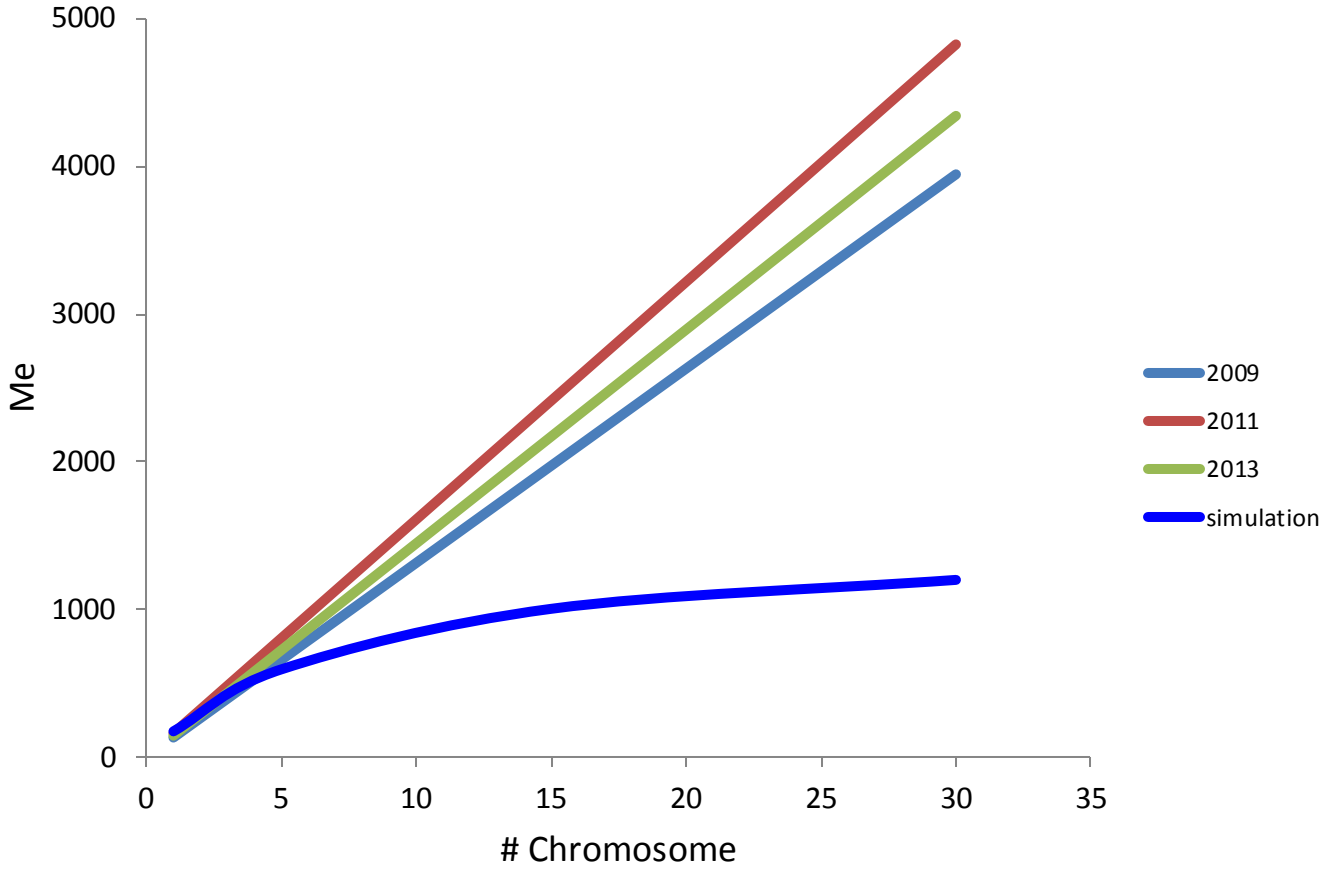
Given genomic relationships (after collecting data), it is possible to empirically get M_e from the data

Simulation

- Coalescence gene dropping
  - N_e = 500 for 500 generations
  - L = 1 Morgan
  - N_{chr} = 30
  - Recombination according to *L*
  - Mutation rate = 10E-08
  - N = 3000 in the last generation

- Estimate A_{ij} and obtain empirical M_e

Difference from empirical M_e



h^2 = 0.5 and N = 5000,

accuracy = 0.62, 0.58, 0.60 vs. 0.82 (simulation)

Revisit the theory

$$M_e = \frac{N_{chr}}{[\ln(4N_eL+1)+4N_eL(\ln(4N_eL+1)-1)]/(8N_e^2L^2)+(1/3N_e)\times(N_{chr}-1)}$$

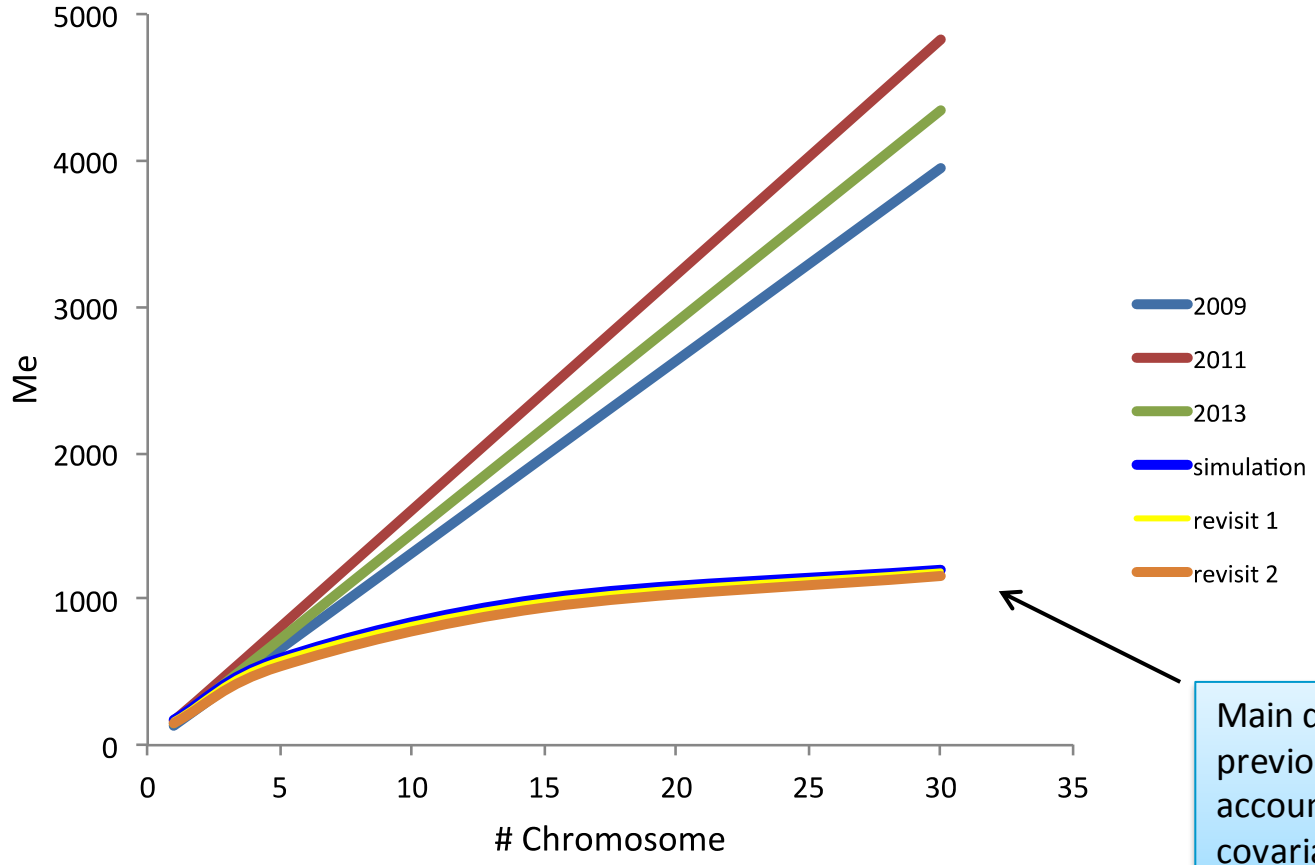
Assuming LD $r^2 = 1 / (1 + 4N_e \times c)$

$$M_e = \frac{N_{chr}}{[\ln(2N_eL+1)+2N_eL(\ln(2N_eL+1)-1)]/(4N_e^2L^2)+(1/3N_e)\times(N_{chr}-1)}$$

Assuming LD $r^2 = 1 / (2 + 4N_e \times c)$

For more detail, see a bioRxiv paper Lee *et al*, 2016
doi: http://dx.doi.org/10.1101/054494

Empirical M_e and new formula

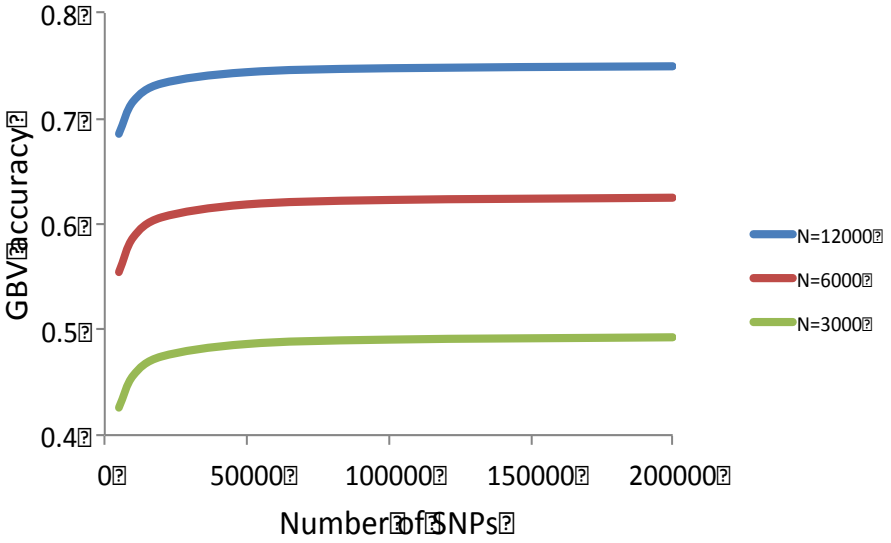


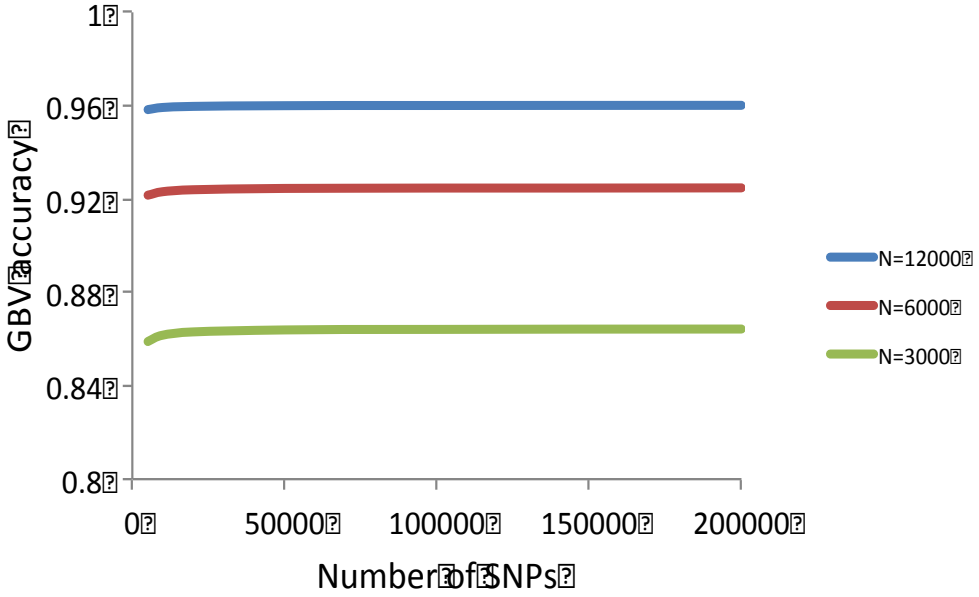
Main difference with previous work is due to accounting for covariance between chromosomes

- Agreed well

Genomic prediction accuracy

Effect of marker density





Ne = 1,000

Ne = 100

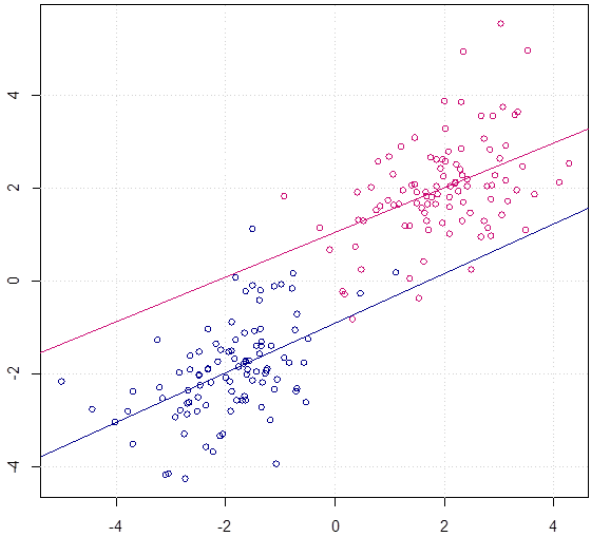
Expect very little improvement with denser markers

What effective population size?

Holstein Friesian	*< 100*
Merino Sheep	*~1000*

Populations not homogeneous.

- Within and between breed/line accuracies
- Some accuracy due to population structure



How do we validate accuray?

- Validation population
  - EBV (based on progeny test)
  - Phenotype
  - Is it a homogeneous group?
- Cross-validation
  - Across families
  - Random(also within families)

Main questions

- How many records are needed in the reference population to achieve a certain accuracy?

But some important sub questions:

- What if you are more related to the reference?
- the value of own herd/flock versus the '*general*' reference population

Relationship with reference population

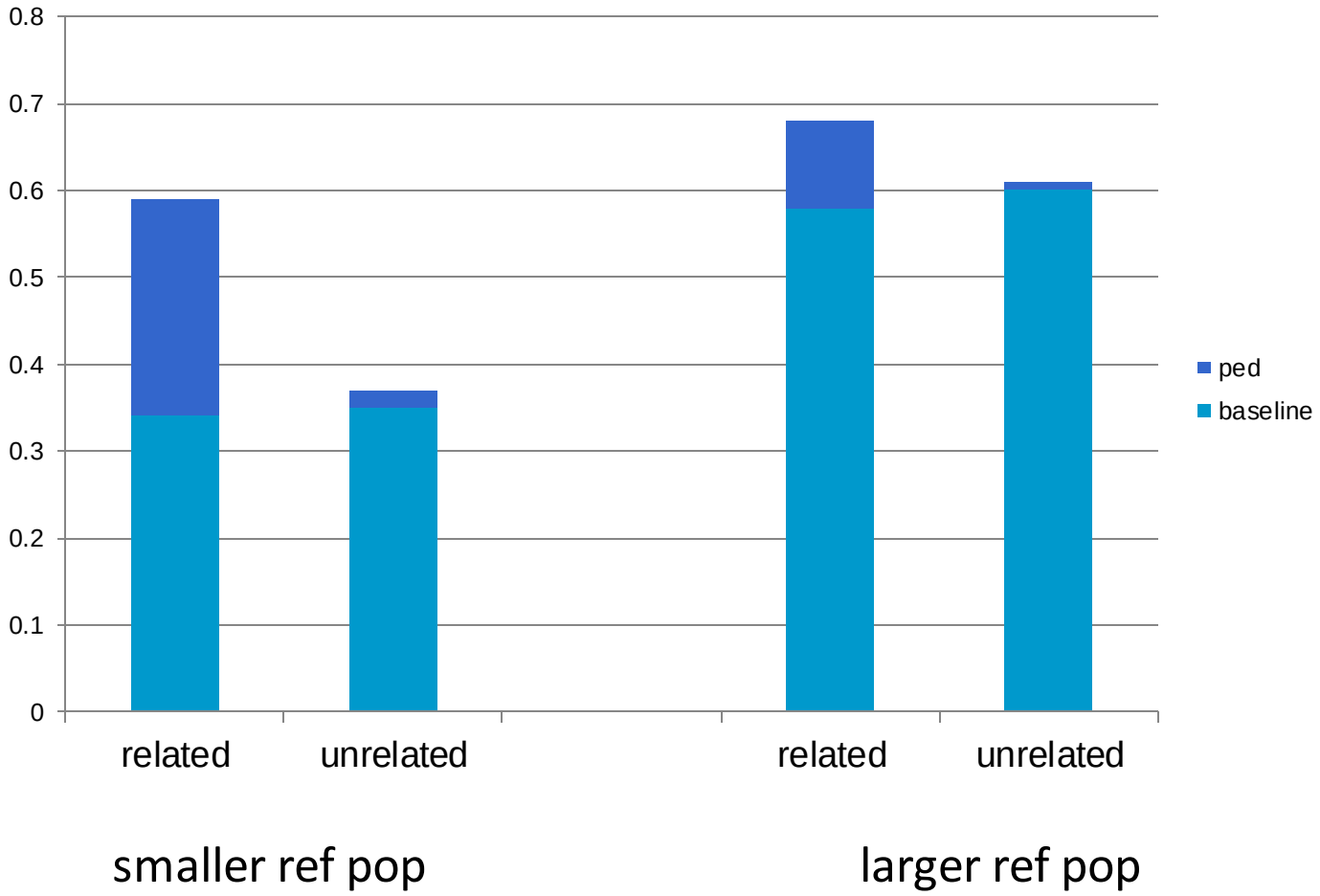
Clark et al 2011

Method	**Close** Ped 0 - 0.25 Genom 0.08 – 0.35	**Distant** 0 - 0.125 0.08 – 0.26	**Unrelated** 0 - 0.05 0.08 – 0.16
BLUP- Shallow pedigree	0.39	0.00	0.00
BLUP- Deep Pedigree	0.42	0.21	0.04
gBLUP	**0.57**	0.41	0.34

Additional accuracy from family info

'baseline accuracy': graphs predict 0.36 for Ne=100, N=1750, h^2=0.3

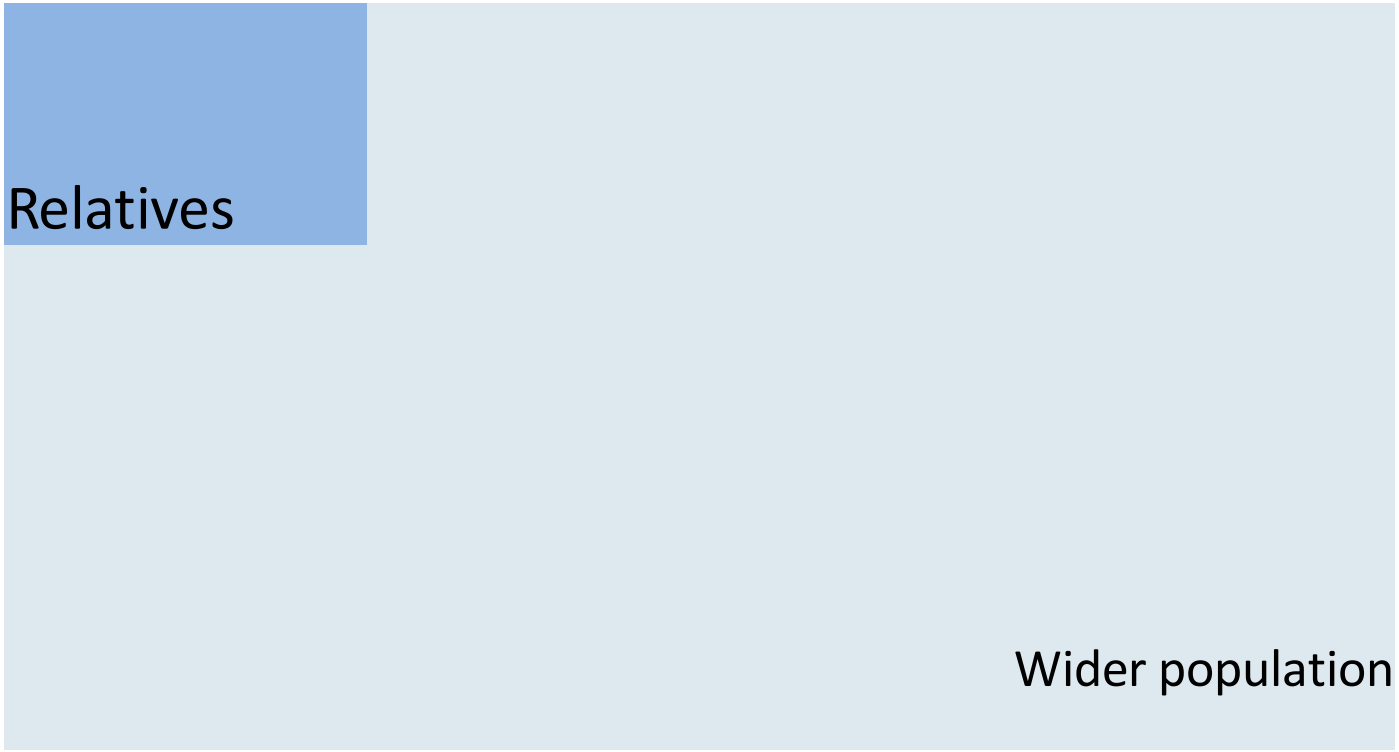
Relatedness matters more if the reference population is smaller



(hypothesis)

Van der Werf AAABG 2011

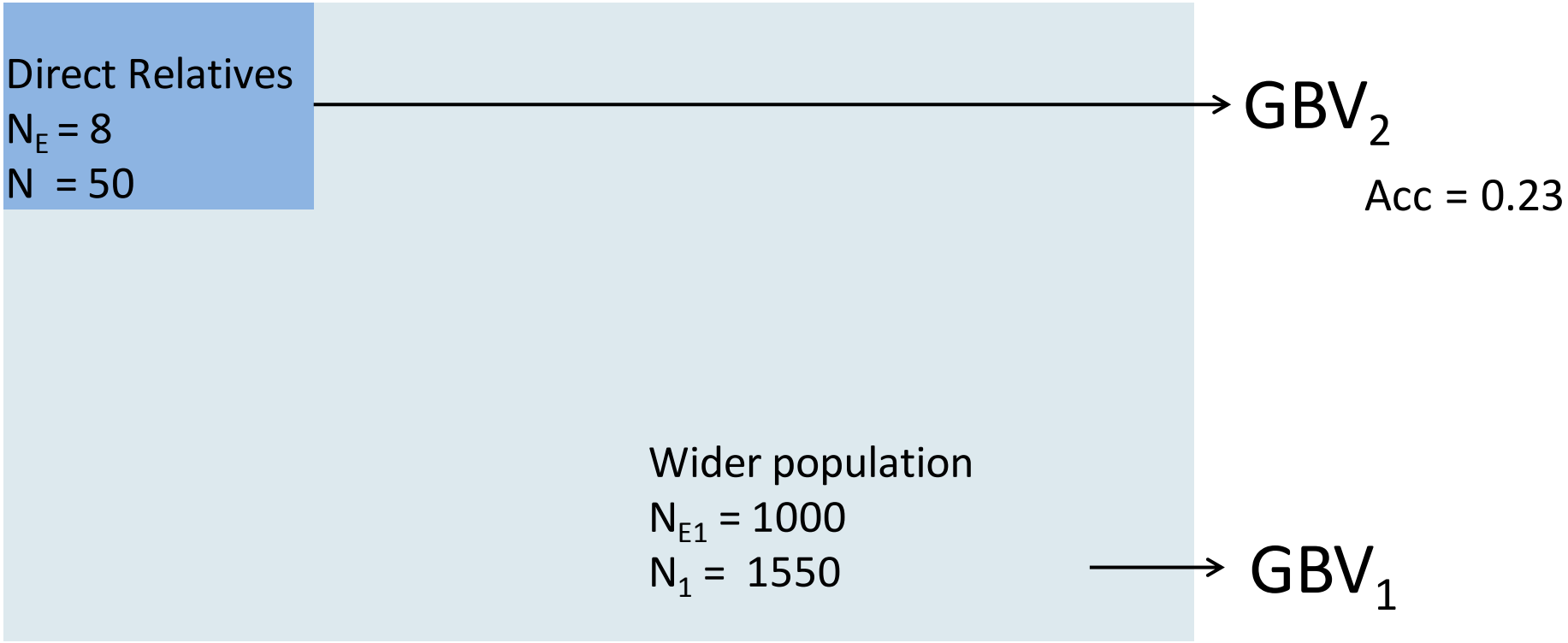
A reference population may have relatives



‘Relatedness’ can be represented by effective size

Hayes et al 2009

Information from different subsets can be combined

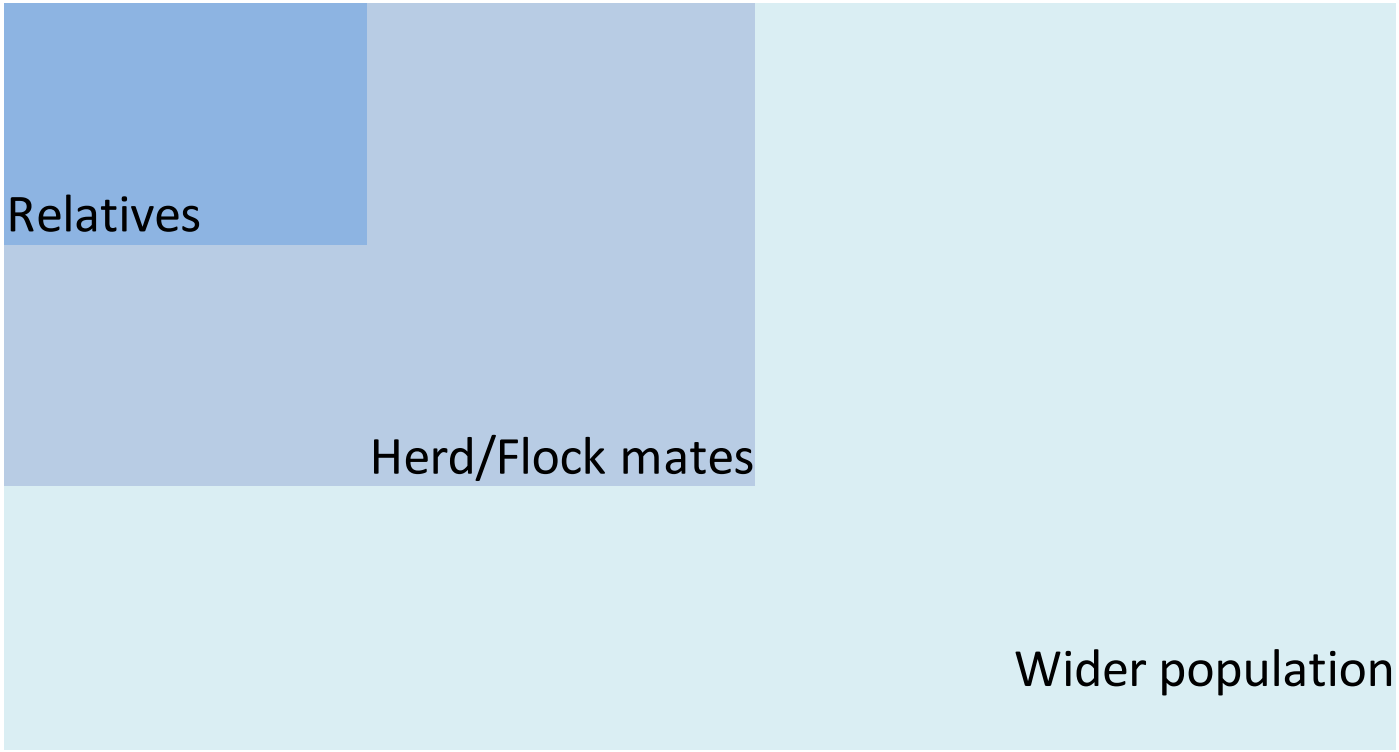


Calculate overall accuracy using selection index

$$GBV = \sum b_i GBV_i$$

Acc = 0.31

Using a stratified reference population -populations are not homogeneous



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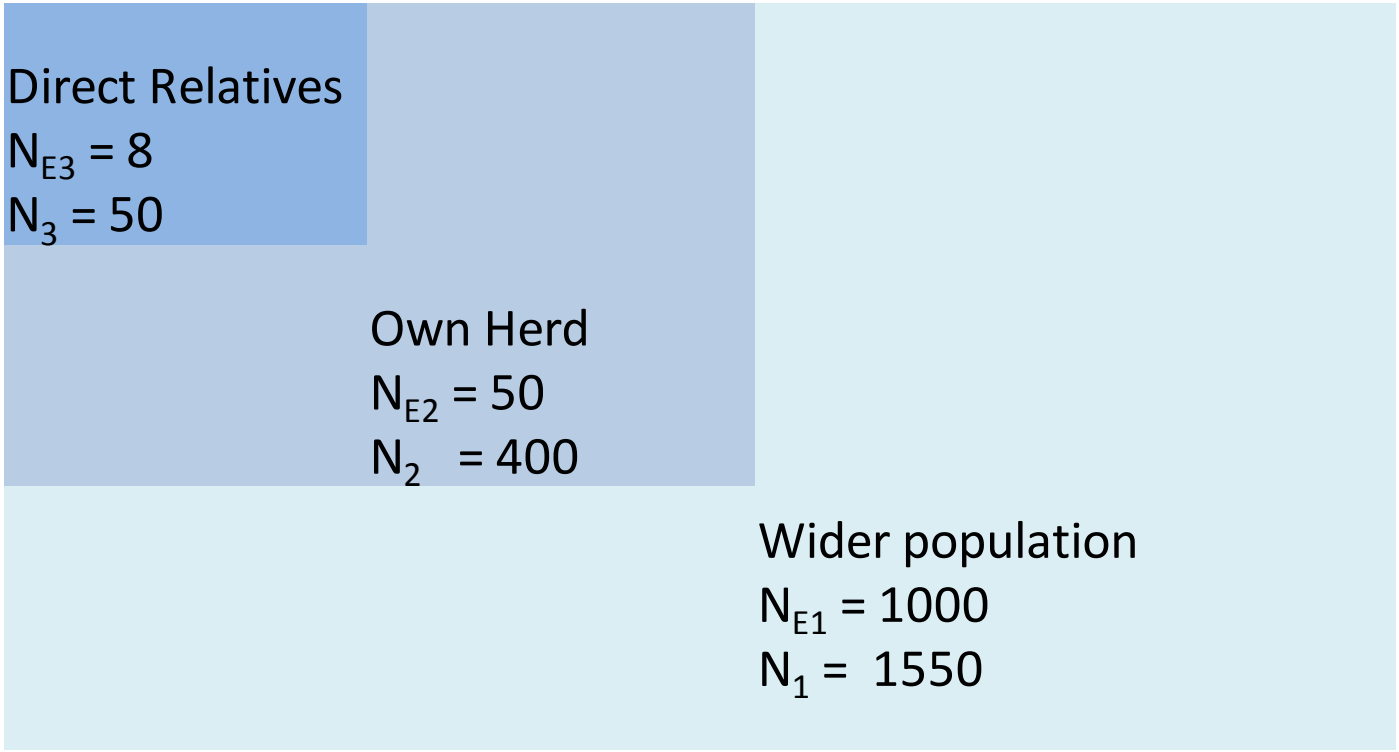

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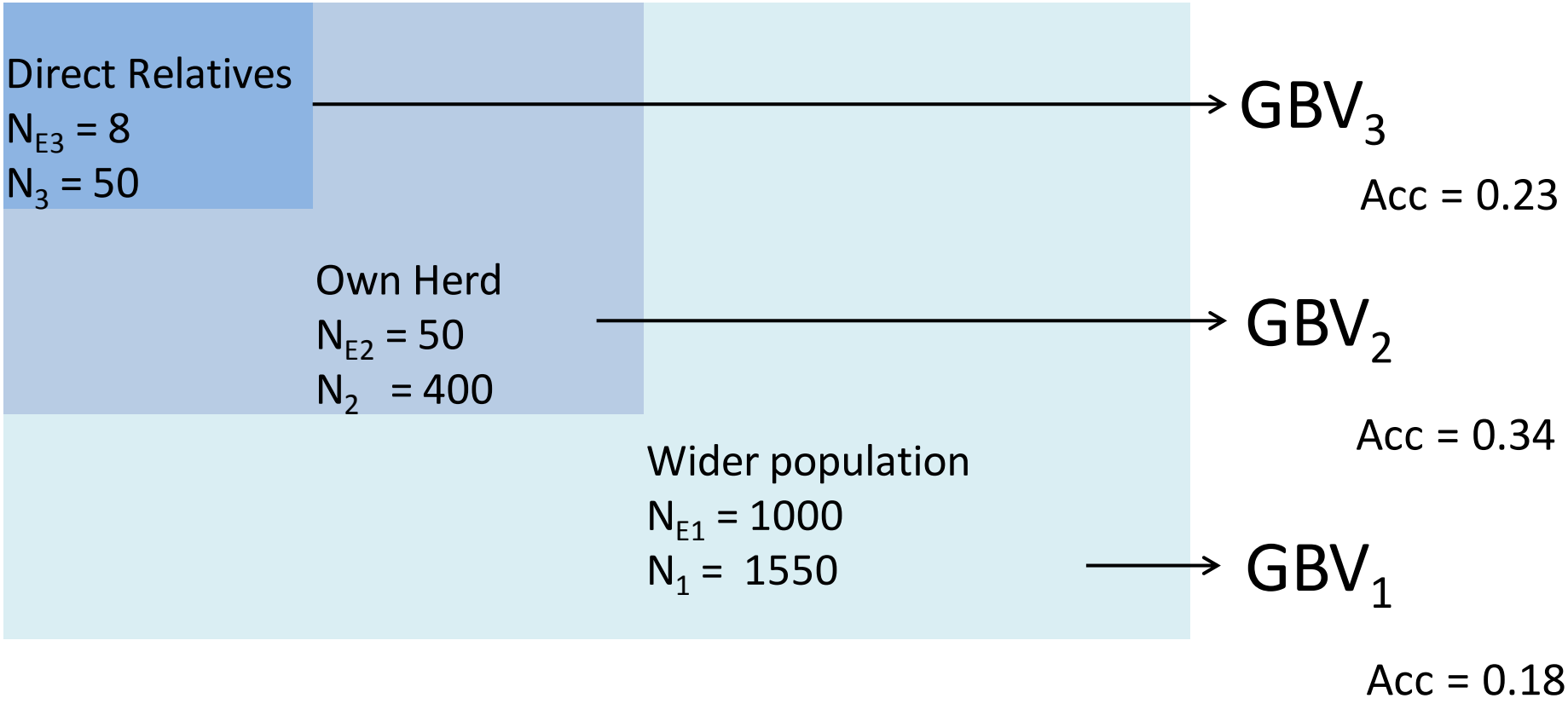


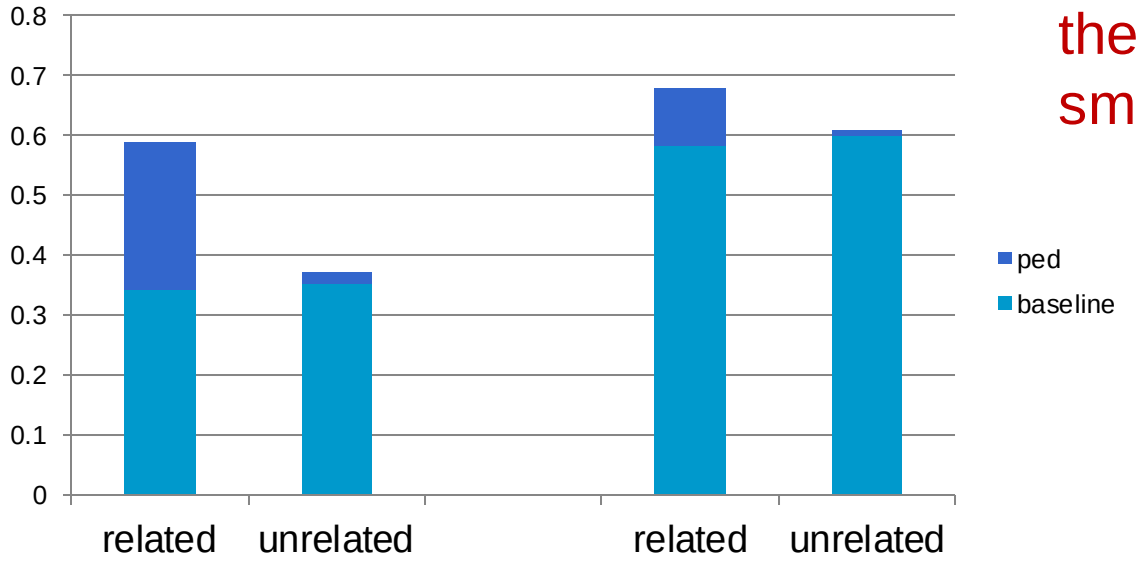
Calculate overall accuracy using selection index

$$GBV = \Sigma b_i GBV_i$$

Acc = 0.42

NE_1 = 1000

	Value of information source			GBV accuracy		
N_1	breed (N1)	flock **(400)**	relatives **(50)**	all info	breed only	diff
2,000	16%	52%	21%	0.43	0.22	95%
5,000	31%	39%	15%	0.47	0.32	48%
10,000	45%	26%	10%	0.53	0.42	26%



Relatedness matters more if the reference population is smaller

hypothesis confirmed

Van der Werf AAABG 2011

NE_1 = 1000

	Value of information source			GBV accuracy		
N_1	breed (N1)	flock 400	relatives 50	all info	breed only	diff
2,000	16%	52%	21%	0.43	0.22	95%
5,000	31%	39%	15%	0.47	0.32	48%
10,000	45%	26%	10%	0.53	0.42	26%
N_1	breed (N1)	flock 100	relatives 10	all info	breed only	diff
2,000	48%	36%	48%	0.28	0.21	36%
5,000	68%	19%	68%	0.36	0.31	15%
10,000	79%	11%	79%	0.45	0.41	7 %

With fewer relatives the reliance on the reference population increases

$NE_1 = 1000$

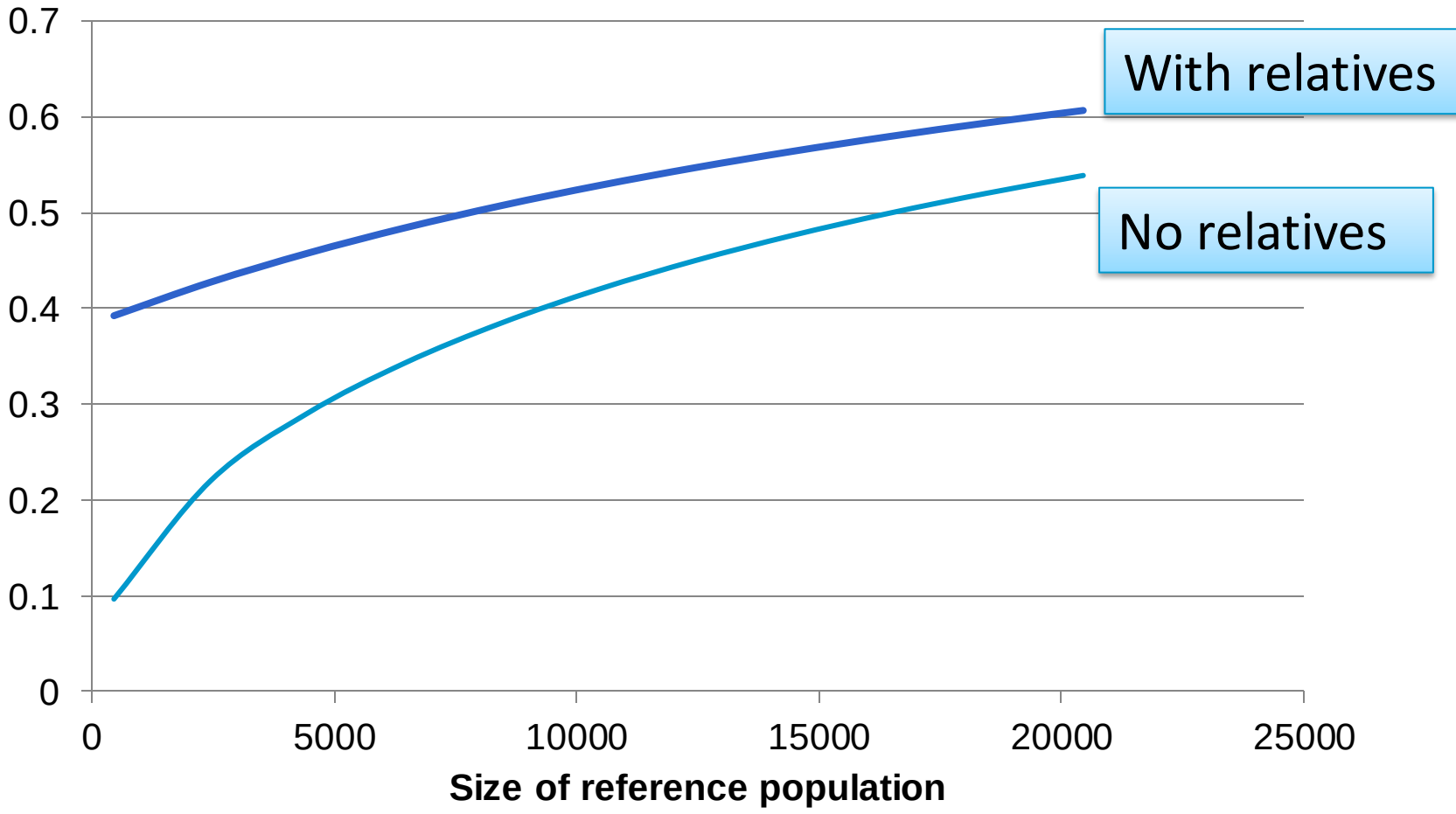
	Value of information source			GBV accuracy		
N_1	breed (N1)	flock **(400)**	relatives **(50)**	all info	breed only	diff
2,000	16%	52%	21%	0.43	0.22	95%
5,000	31%	39%	15%	0.47	0.32	48%
10,000	45%	26%	10%	0.53	0.42	26%

$NE_1 = 200$

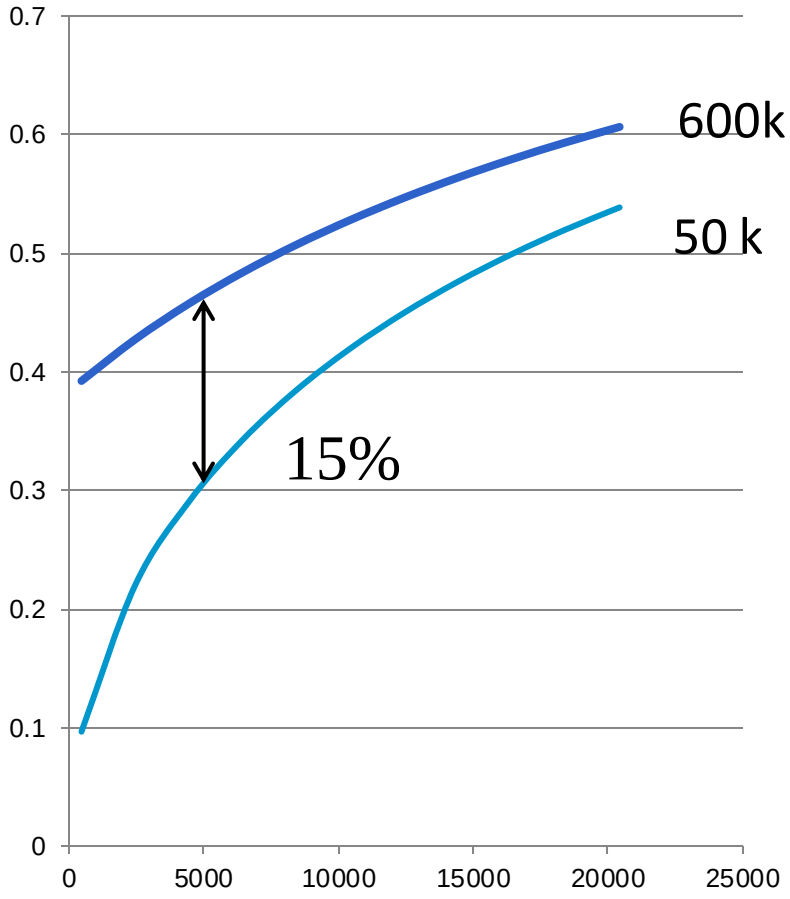
N_1	breed (N1)	flock **(400)**	relatives **(50)**	all info	breed only	diff
2,000	45%	26%	10%	0.53	0.45	18%
5,000	62%	12%	5%	0.64	0.60	7%
10,000	72%	5%	2%	0.74	0.72	3%

With less diverse populations the relatives matter a lot less

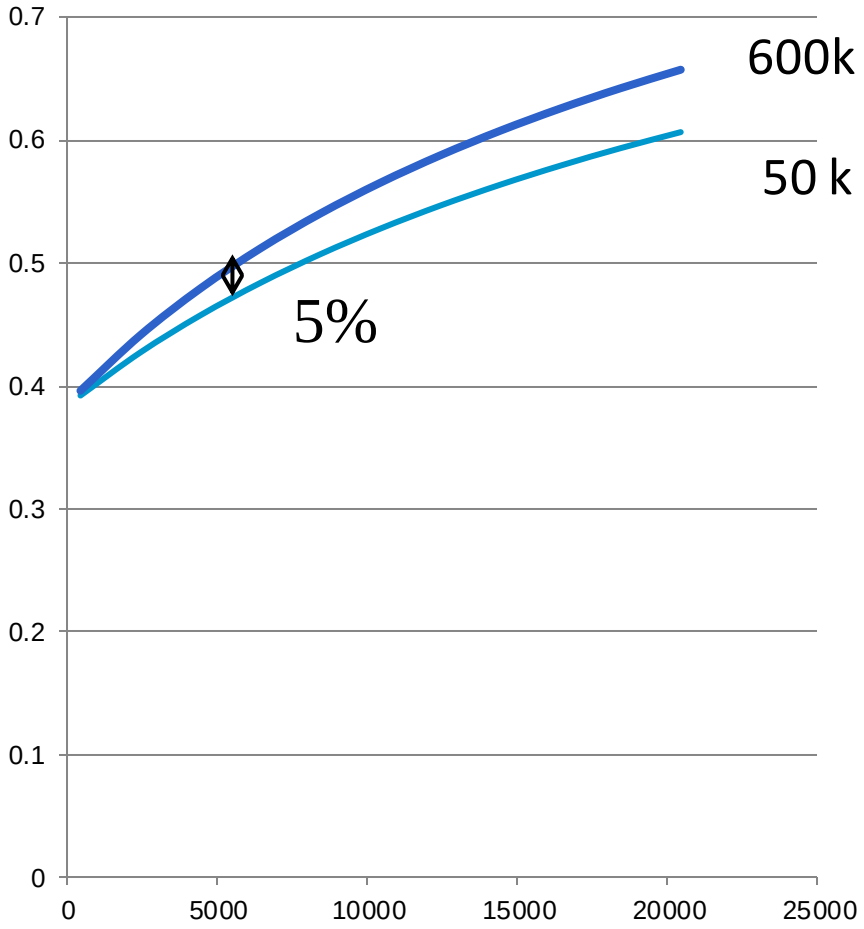
The effect of a larger reference population.



The effect of denser marker panels



No relatives

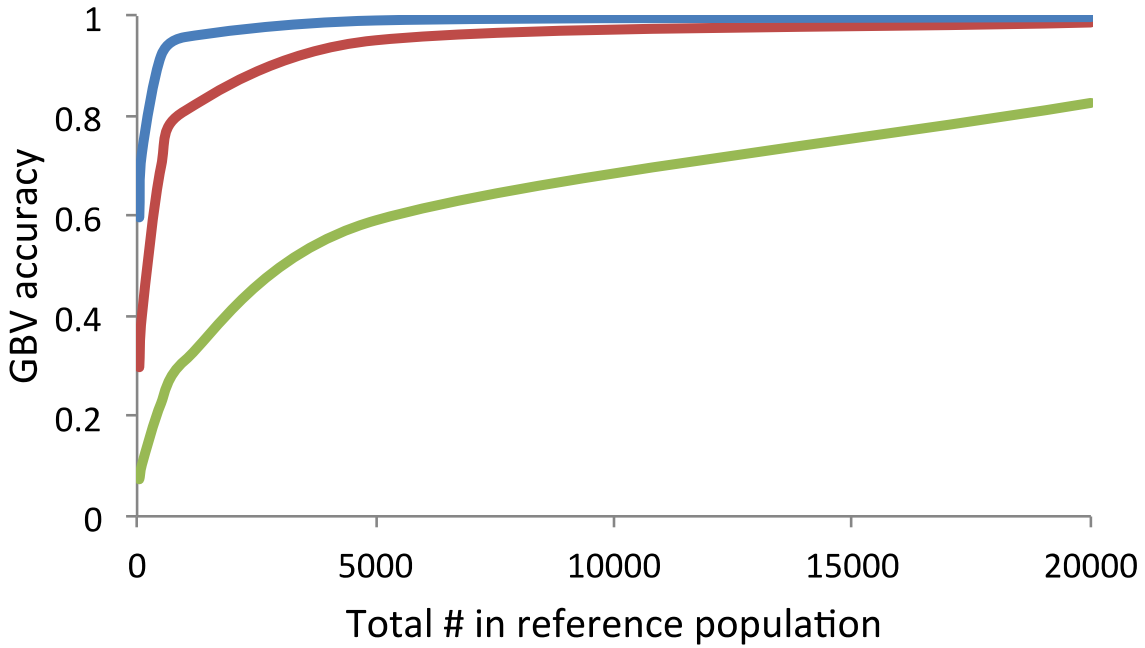


With relatives

Conclusion

- Theory exists to predict genomic prediction accuracy in advance: depends on population diversity, nr records
- Reference populations are heterogeneous, with closer as well as distant relatives
- Relatives and flock/herd mates will increase accuracy and decrease reliance on wider reference population (and denser marker panels)

Sample availability



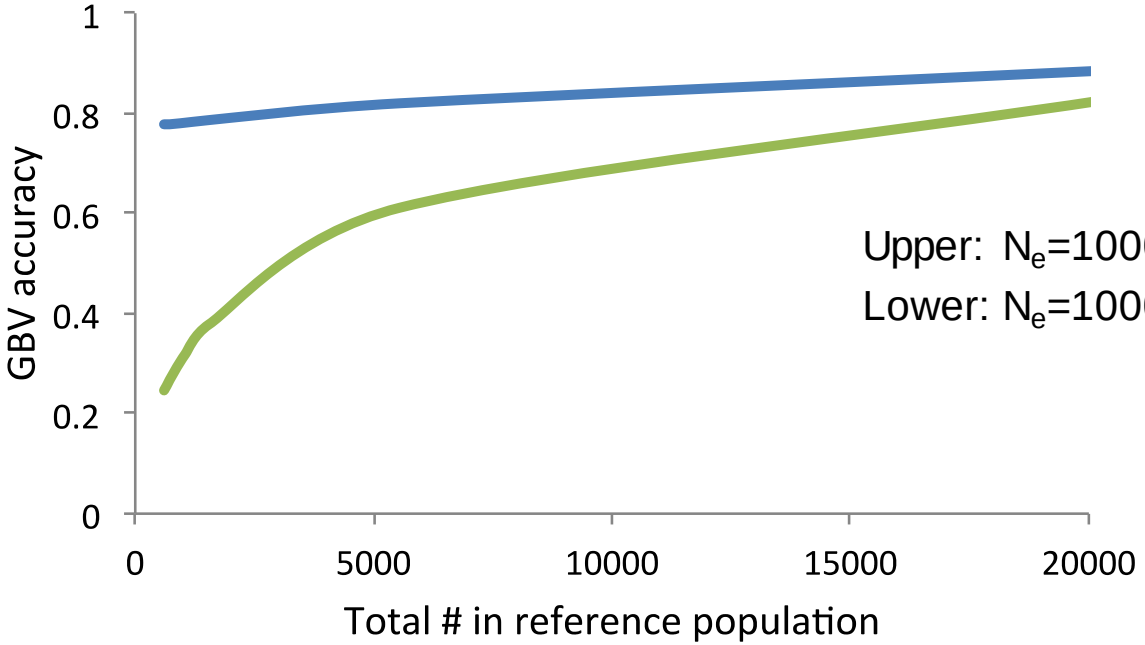
Upper: N_e=10 only

Middle: N_e=100 only

Lower: N_e=1000 only

- h^2=0.25
- N_e=10 would have < N = 100 (maximum acc. = 0.73)
- N_e=100 would have < N = 1,000 (maximum acc. = 0.81)
- N_e=1,000 can have N = 20,000 (acc. = 0.83)

Composite design



Upper: N_e=1000 + N_e=100 (N=500) + N_e=10 (N=50)

Lower: N_e=1000 only

Implication

- Marker density
  - For beef cattle or sheep, very dense markers (e.g. 600K) may not be cost-effective, compared to 50K
  - For N_e = 1000, accuracy is similar between 50K and 600K

- Marker density is not a critical design parameter
  - > 50K with N_e = 1000 (livestock)
  - > 200K with N_e = 10,000 (human)

- But, it may matter with very large N_e
  - Multi-breeds or multi-ethnicities

Implication

- To maximise prediction accuracy
  - give a priority to genotype reference sample of smaller N_e,
  - e.g. close relatives > flocks (local, village) > states > country > …
  - When h^2 is lower, reference sample of smaller N_e is more important

Note that N_e can be changed, depending on the target sample

Implication

- MTG2

https://sites.google.com/site/honglee0707/mtg2

Given design parameters, MTG2 can provide the expected accuracy and power

See section 7 and 9 in the manual