Accuracy of Genomic Prediction

Julius van der Werf

and Sang Hong Lee

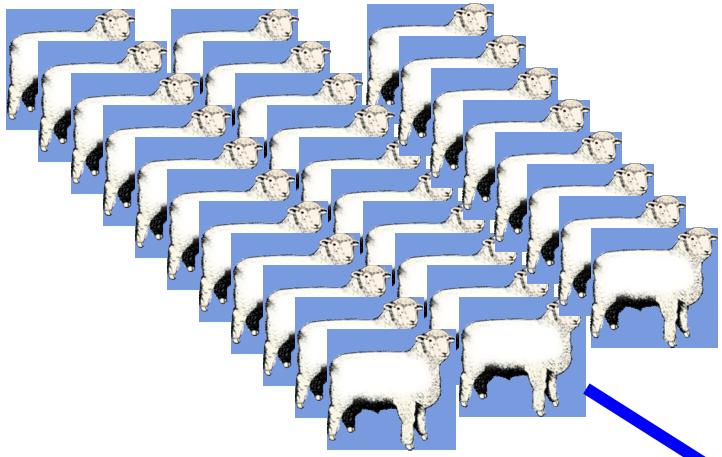
une
University of
New England

SHEEP CRC

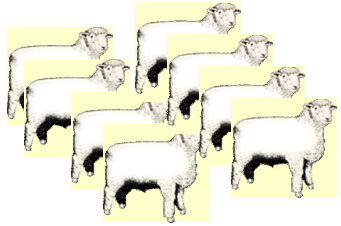
An Australian Government Initiative

CRC
AUSTRALIA

Genomic Prediction: basic idea



Reference population
measured and DNA tested

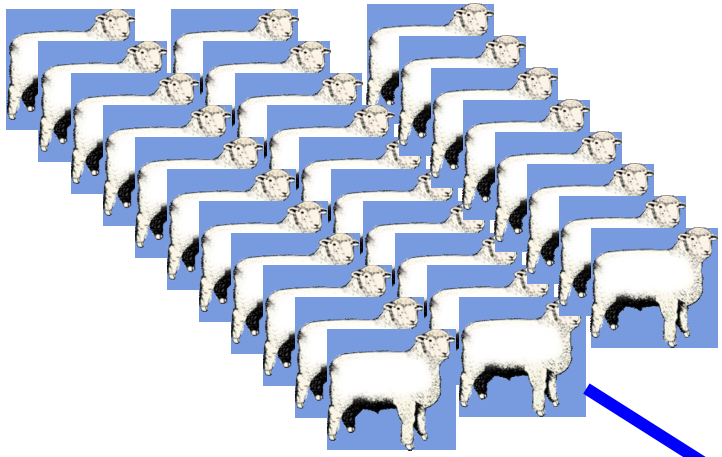


Target Set
Only DNA tested

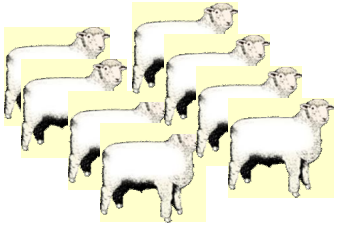
To predict a trait EBV at a young age,

good for: late traits
hard to measure traits

Genomic Prediction: basic idea



Reference population
measured and DNA tested



Target Set
Only DNA tested

What if reference population is

- Another breed
- Multi-breed
- Crossbreds
- Small
- Less related
- Heterogeneous

?

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)

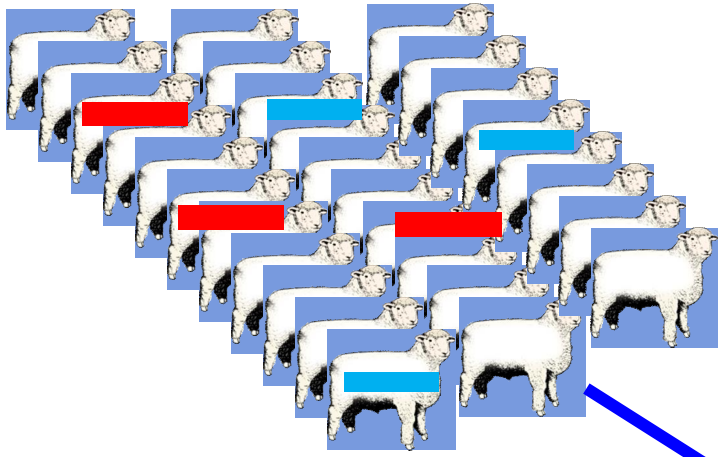
1	0.5	0.5	0.02	0.5
0.5	1	0.20	0.015	0.20
0.5	0.20	1	0.025	0.30
0.02	0.015	0.025	1	0.025
0.5	0.20	0.30	0.025	1

GBLUP uses: Family Info
Segregation within family
Info on ówunrelatedô

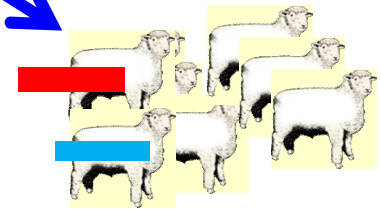
Genomic prediction accuracy

- 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



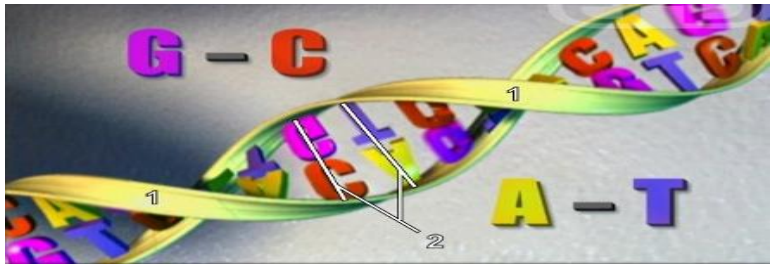
Reference population
measured and DNA tested



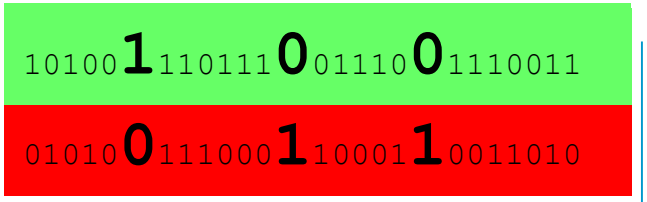
Target Set
Only DNA tested

Illustrating (dis-)similarity of chromosome segments

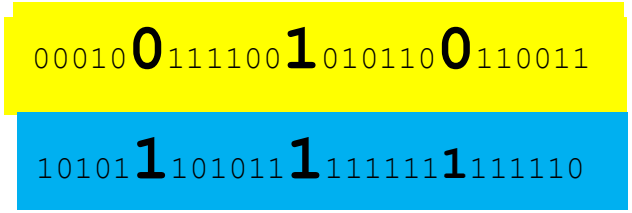
Genotype information



Father



Mother



Progeny

Chromosome segments are passed on

A whole population of haplotypes

Individual																	
1	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	###	1541	1541	1541
	129	129	129	129	129	129	129	655	655	655	655	655	655	###	1129	1129	1129
2	1088	1088	1088	1088	1088	1088	1088	1088	1192	1192	1192	1192	1192	###	1192	623	623
	178	655	891	891	891	891	891	891	891	1136	1136	1136	1136	735	735	735	735
3	129	129	129	129	129	129	129	655	655	655	655	655	655	###	1038	1038	1038
	1192	1192	1192	1192	1192	1192	1192	1192	1192	1192	1192	1192	1192	###	1192	1192	1043
4	424	424	424	424	424	424	424	424	503	503	503	503	503	503	503	503	503
	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	###	1541	1541	1541
5	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	###	1541	1541	1541
	1136	1136	1136	1136	1136	1136	1136	1136	178	178	178	178	178	178	1541	1541	1541
6	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	1043	###	1043	1043	1043
	1478	1478	1478	1478	1478	1478	1478	1478	1478	1478	1478	1478	1478	###	1478	1478	1478
7	129	129	129	129	1038	1038	199	199	129	129	129	129	129	129	129	129	129
	655	655	655	1358	1358	1358	1358	1358	1358	342	342	342	342	342	342	1043	1043
8	444	444	444	444	444	444	444	444	444	444	444	444	444	444	444	444	444
	1358	1358	1358	1358	1358	1358	1358	1358	1358	342	342	342	342	342	342	342	342
9	1296	1296	1296	1296	1296	321	321	321	321	812	812	674	674	674	674	674	674
	891	891	891	210	210	210	210	1255	1262	1262	1478	1478	1478	###	1478	1478	1478
10	178	655	655	655	655	210	210	1255	1262	1262	1478	1478	1478	###	1478	1478	1478
	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	1541	###	1541	1541	1541

Within a population, members will share chromosome segments

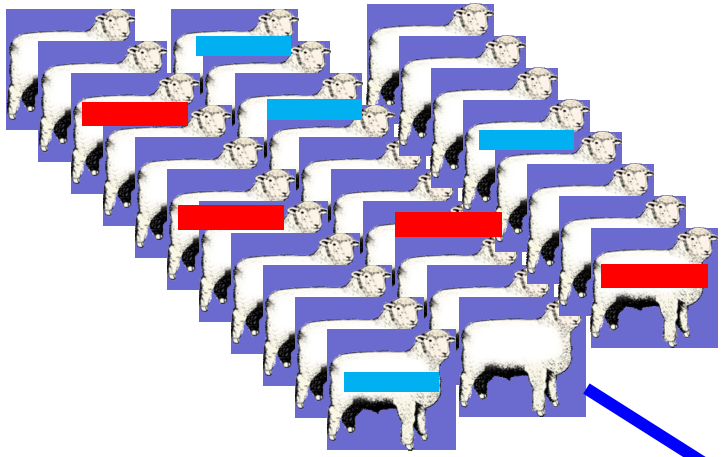
We can follow inheritance via SNPs

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

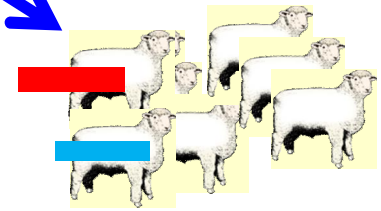
(similar to genetic relationship = expected based on pedigree)

une

Genomic Prediction: basic idea



Reference population
measured and DNA tested

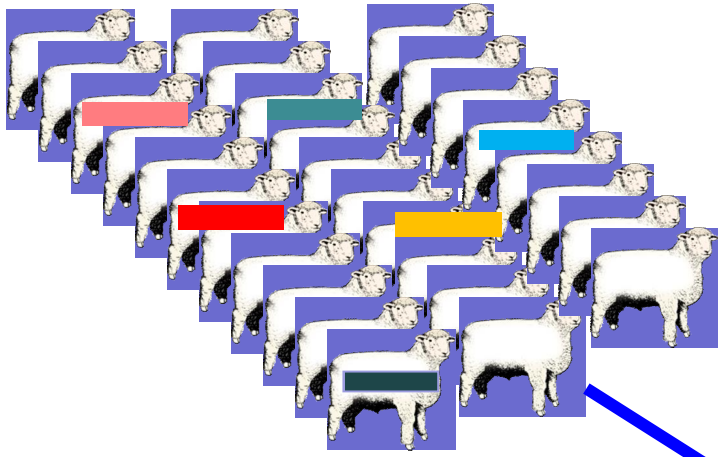


Target Set
Only DNA tested

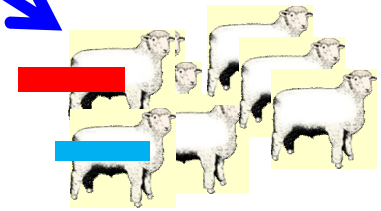
Small diversity of segments → more accuracy

une

Genomic Prediction: basic idea



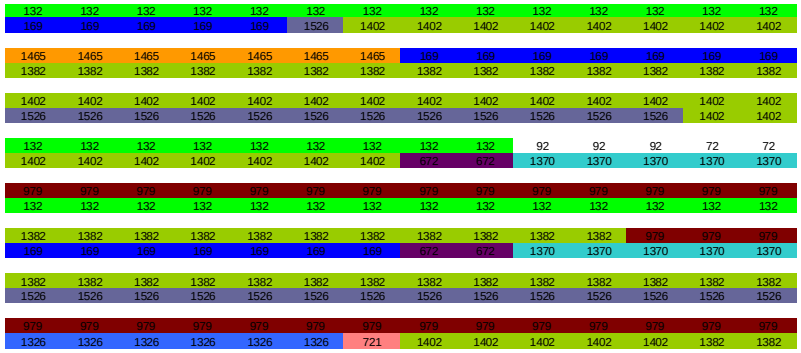
Reference population
measured and DNA tested



Target Set
Only DNA tested

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

Design parameters for predicting GP accuracy

- 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 = $n / (n+\lambda)$

$\lambda = V_e / V_a$
n = nr obs'ns per effect

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

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

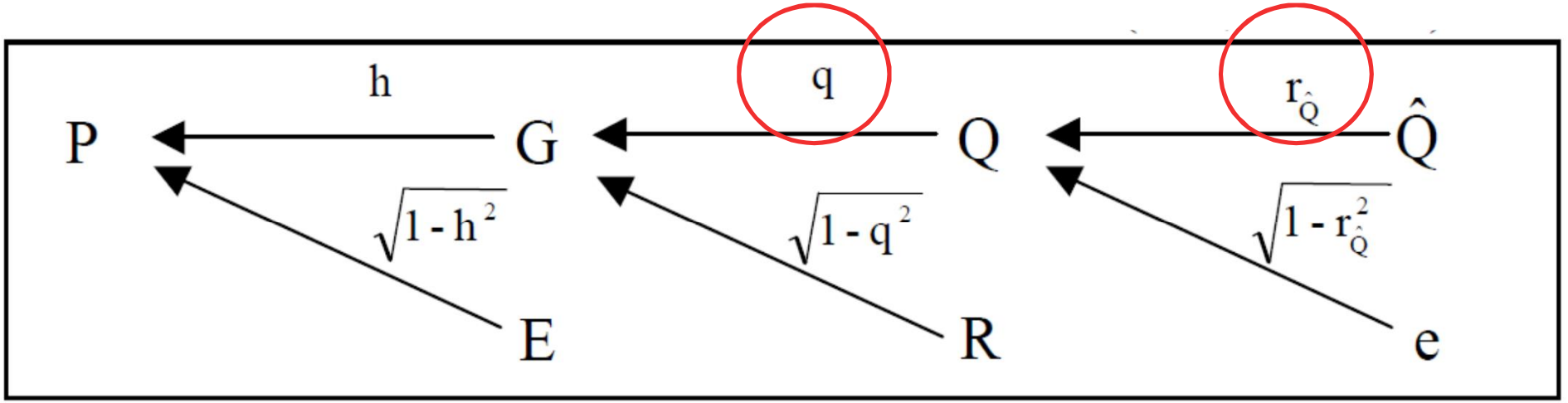
$V_e \cong V_p$

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

n = nr observations
M_e = effective nr loci

Valid if "all genetic variance is captured by markers"

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

h, q, and r_Q etc. are correlations

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'

ii) Accuracy of estimating marker effects

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

$$\text{as } \lambda = V_e / (q^2 V_a/M_e) = M_e/(q^2 h^2)$$

Accuracy of genomic prediction is

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

$= q . r_{Qhat}$

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

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

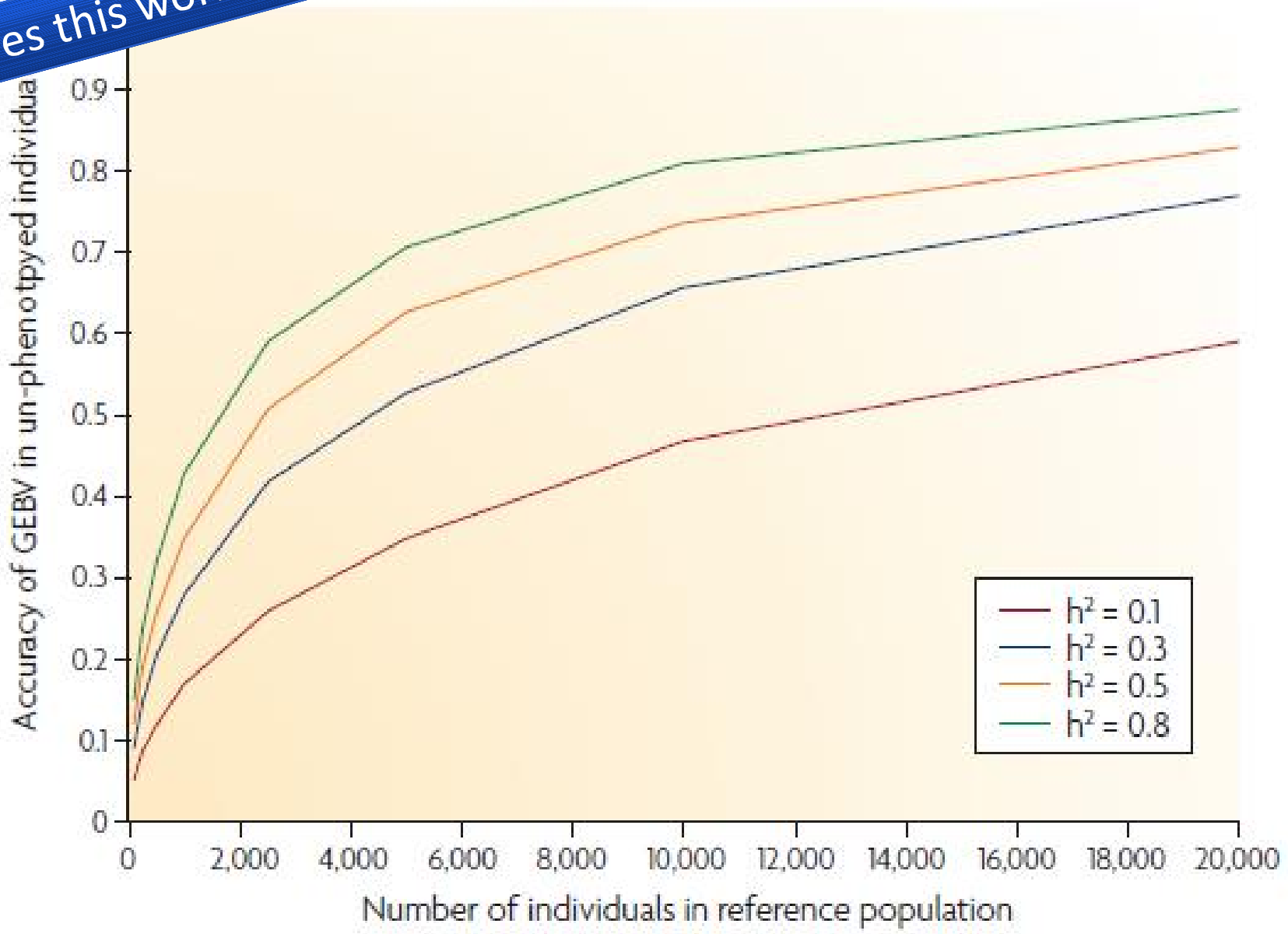
$$\lambda = M_e/h^2$$ same as Daetwyler

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

$$= r_{Qhat}$$

Deterministic prediction

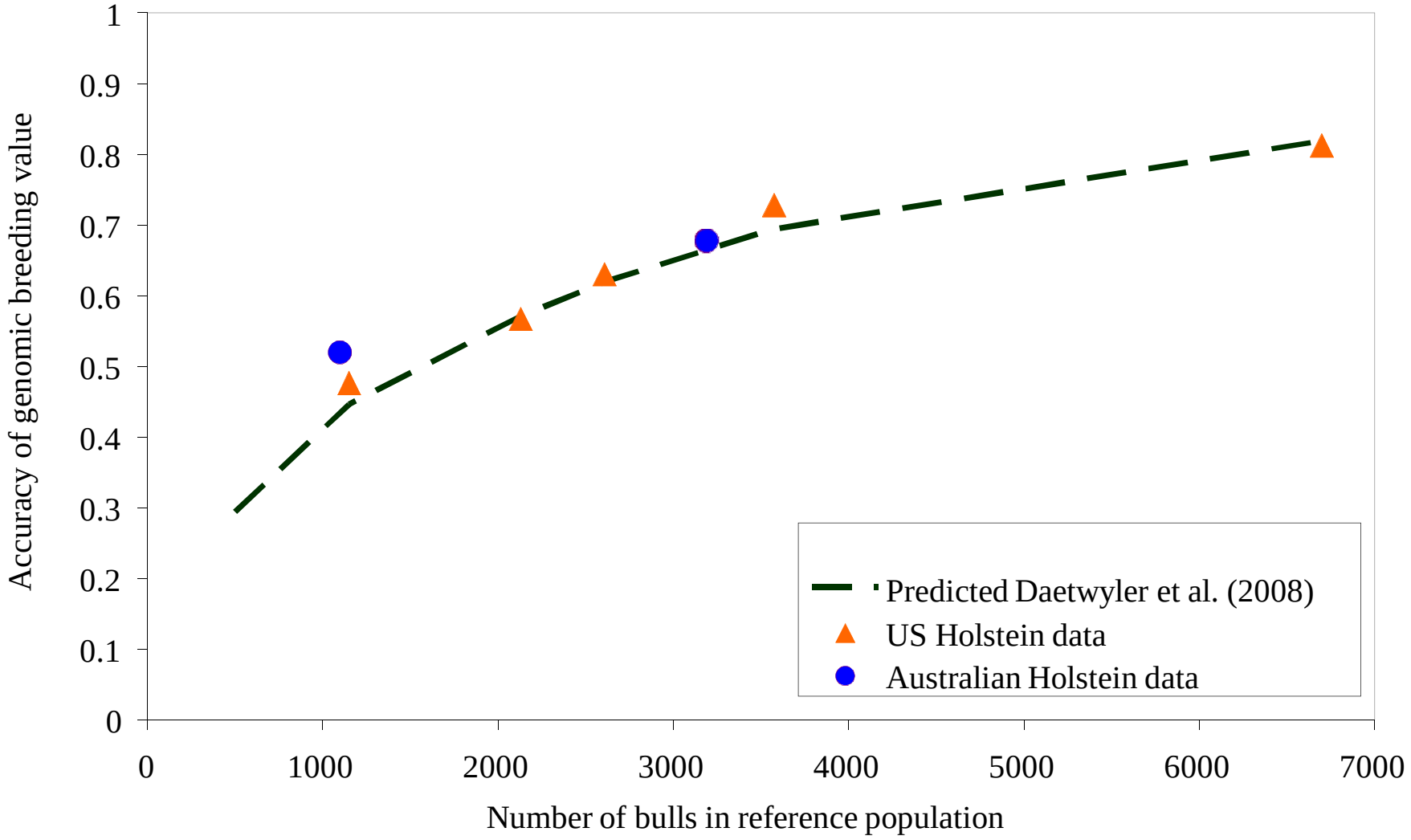
Does this work?



Real Data

- Dairy cattle (Holsteins)
  - USA results (N=1000-6700) for Net Merit Index (VanRaden et al. 2009)
  - Australian results (N=1100-3300) for Australian Profit Ranking
  - h^2=0.9 (heritability of progeny means)
  - N_e = 100
- Accuracies r(GEBV,EBV) in validation data sets

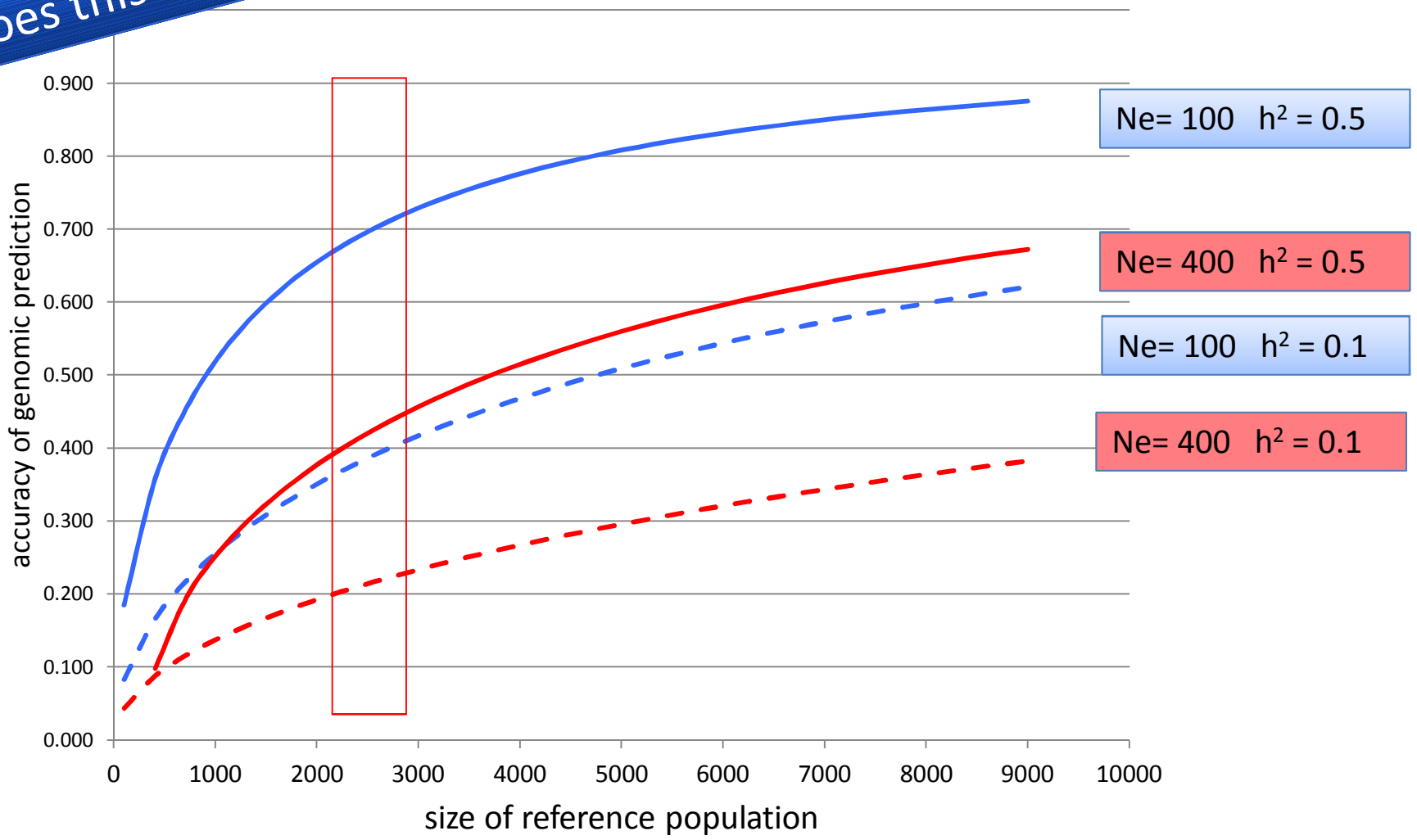
Deterministic prediction vs. Holstein data



Hayes et al., 2009, AAABG

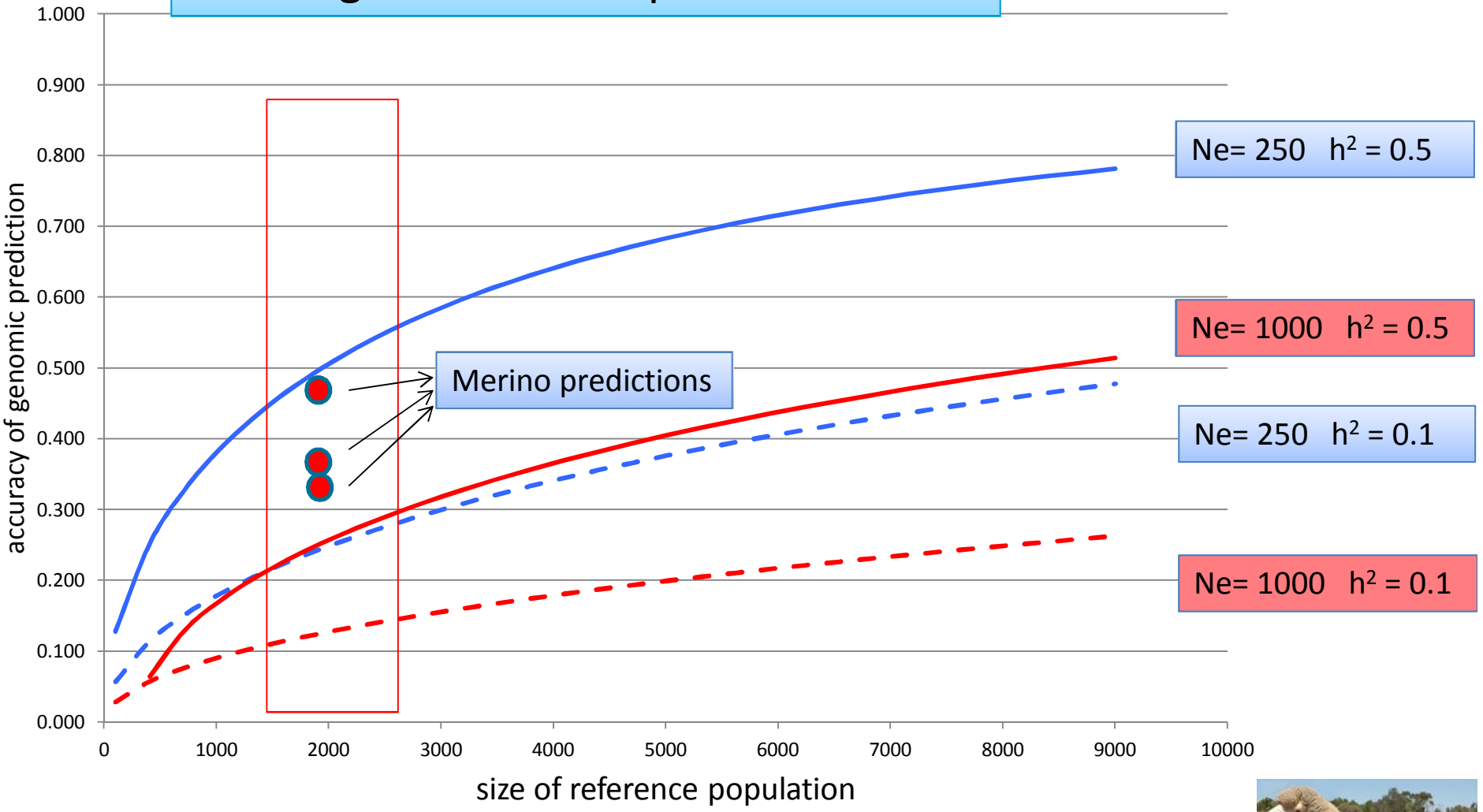
Genomic prediction accuracy *Using Goddard et al, 2011*

Does this work?



Genomic prediction accuracy *Using Goddard et al, 2011*

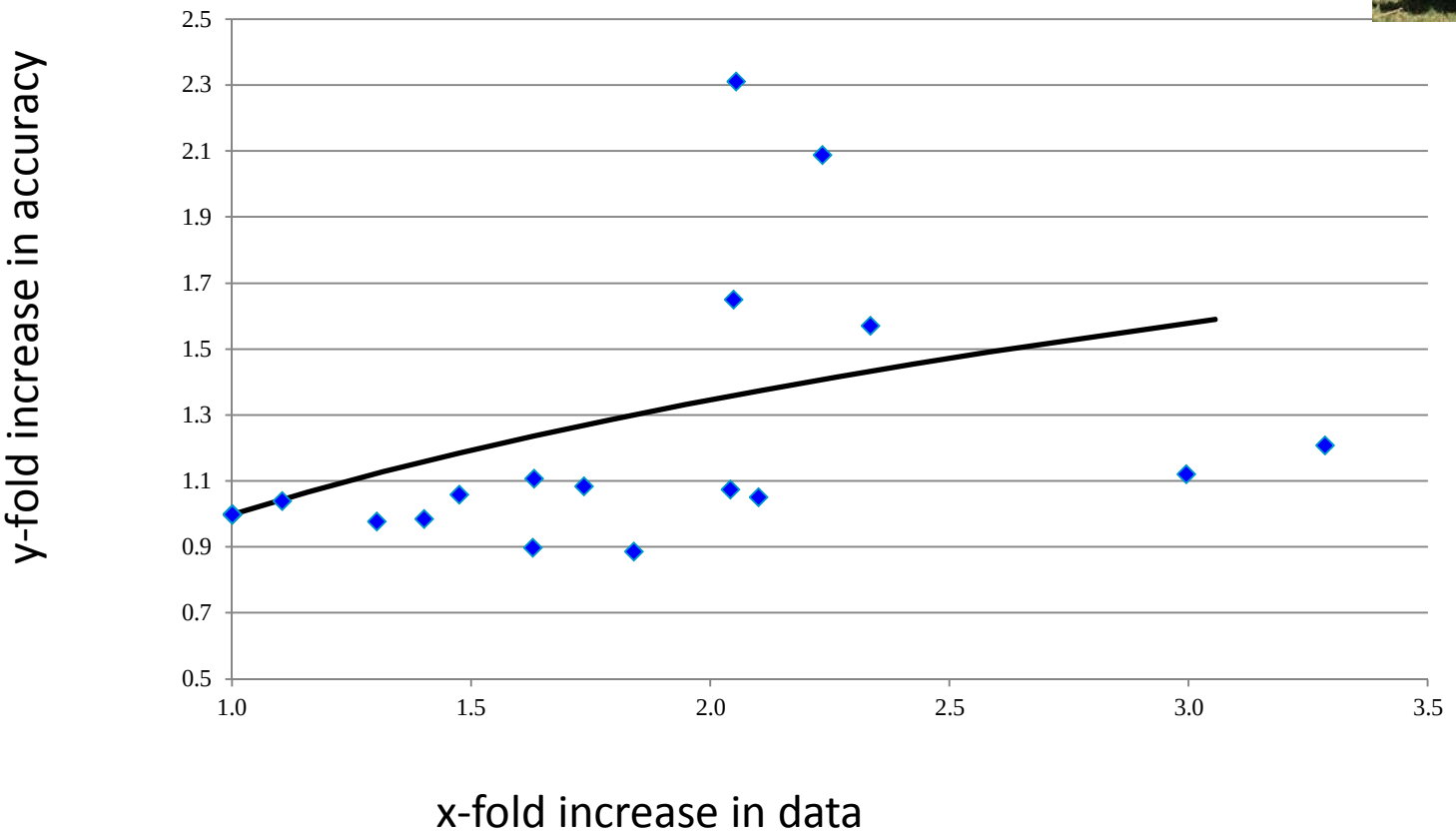
Did we get what we expected?



Validating ‘Genomic Prediction Accuracy’

More data is always good

But does it increase accuracy as expected?



What effective population size?

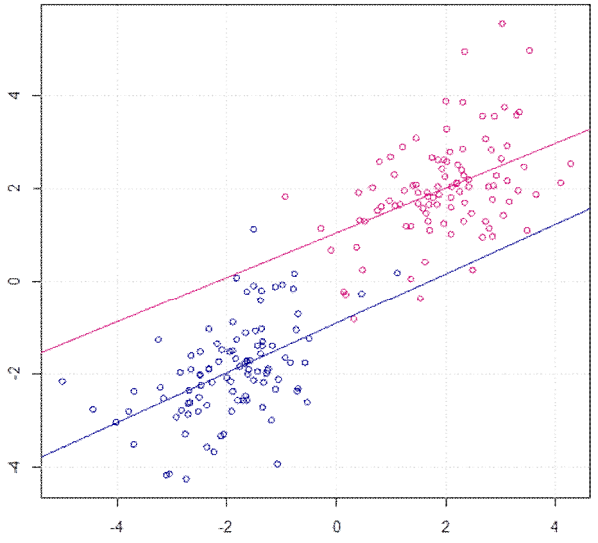
Kijas et al 2012

- 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
  - Theory assumes everyone in he population is equally unrelated
  - Some (unclear) theory about effective nr of loci
- Ignores heterogeneity of populations and relationships
- *We observe more initial acc and less increase with more data*

How to derive the effective number of loci?

M_e

y = Wu + e,

u = QTL effects,
W = genotypes
G= WW'

G= covariance matrix among marker genotypes: $r^2 = 1 / (1 + 4N_e \times c)$

$$\begin{bmatrix} 1 & r^2_{1,2} & \cdots & r^2_{1,M-1} & r^2_{1,M} \\ r^2_{2,1} & 1 & \cdots & r^2_{2,M-1} & r^2_{2,M} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ r^2_{M-1,1} & r^2_{M-1,2} & \cdots & 1 & r^2_{M-1,M} \\ r^2_{M,1} & r^2_{M,2} & \cdots & r^2_{M,M-1} & 1 \end{bmatrix}$$

Need var(G)
mean r^2 of all
these elements
→ integrate

Var(G)=1/M_e

How to derive the effective number of loci?

M_e is a (almost linear) function of *N_e and genome size*

Å $M_e = 2N_eLN_{chr} / \ln(4N_eL)$ (Goddard 2009)

Å $M_e = 2N_eLN_{chr} / \ln(N_eL)$ (Goddard et al. 2011)

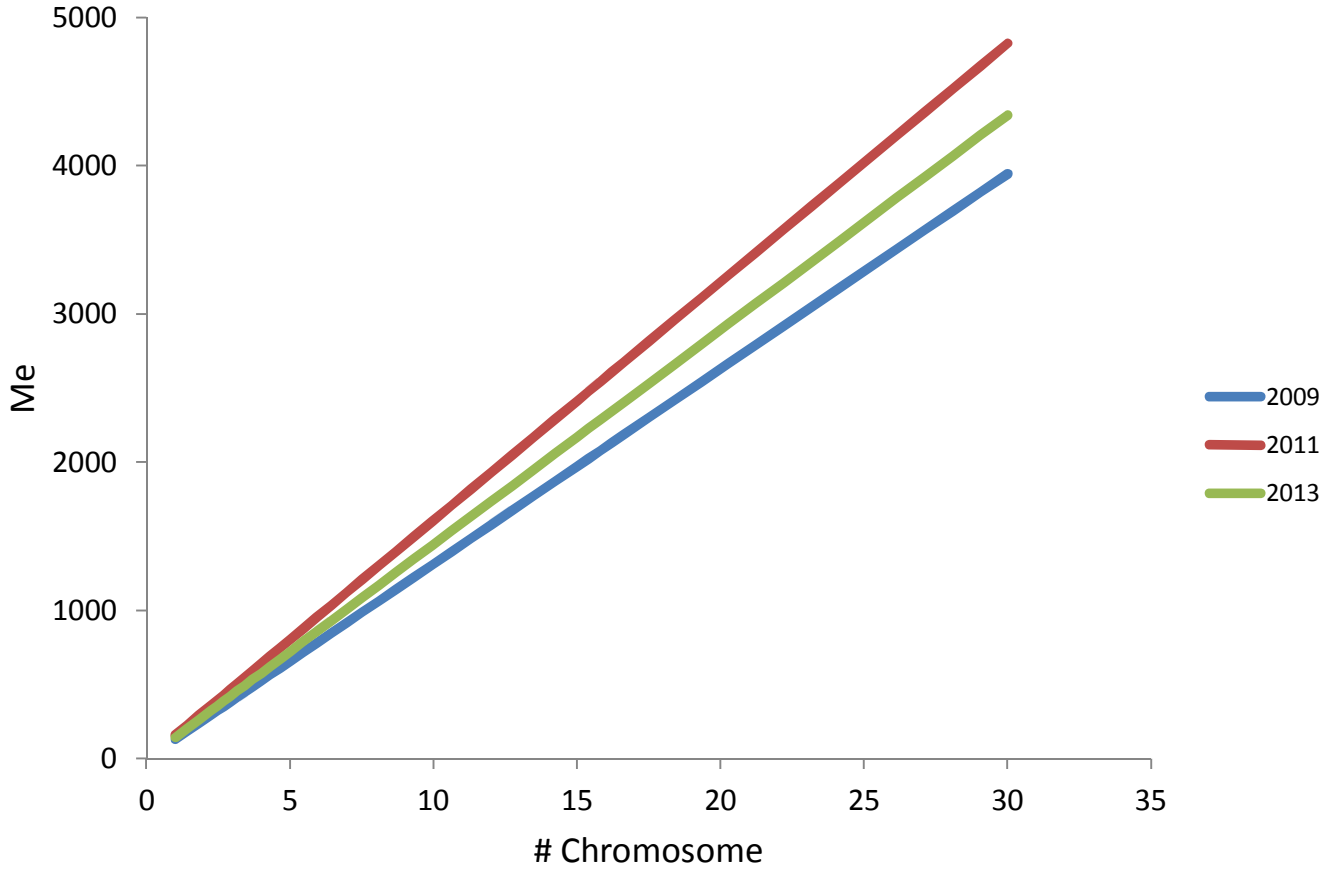
Å $M_e = 2N_eLN_{chr} / \ln(2N_e)$ (Meuwissen et al. 2013)

Different assumptions about multiple chromosomes etc.

Hard to 'know' N_e

N_e = Effective pop.size
L = Av. Length per chrom (1M)
N_{chr} = 30

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' empirically

Can use actual data on A and G to test this

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

Note, this is different from Goddard et al: var(D)=1/M_e assumed A = I

D =deviation in relationship at QTL

Var(G) = 1/M_e

$$M_e = 1/\mathrm{var}(G_{ij})$$

E = error

Var(E) = 1/nr Markers

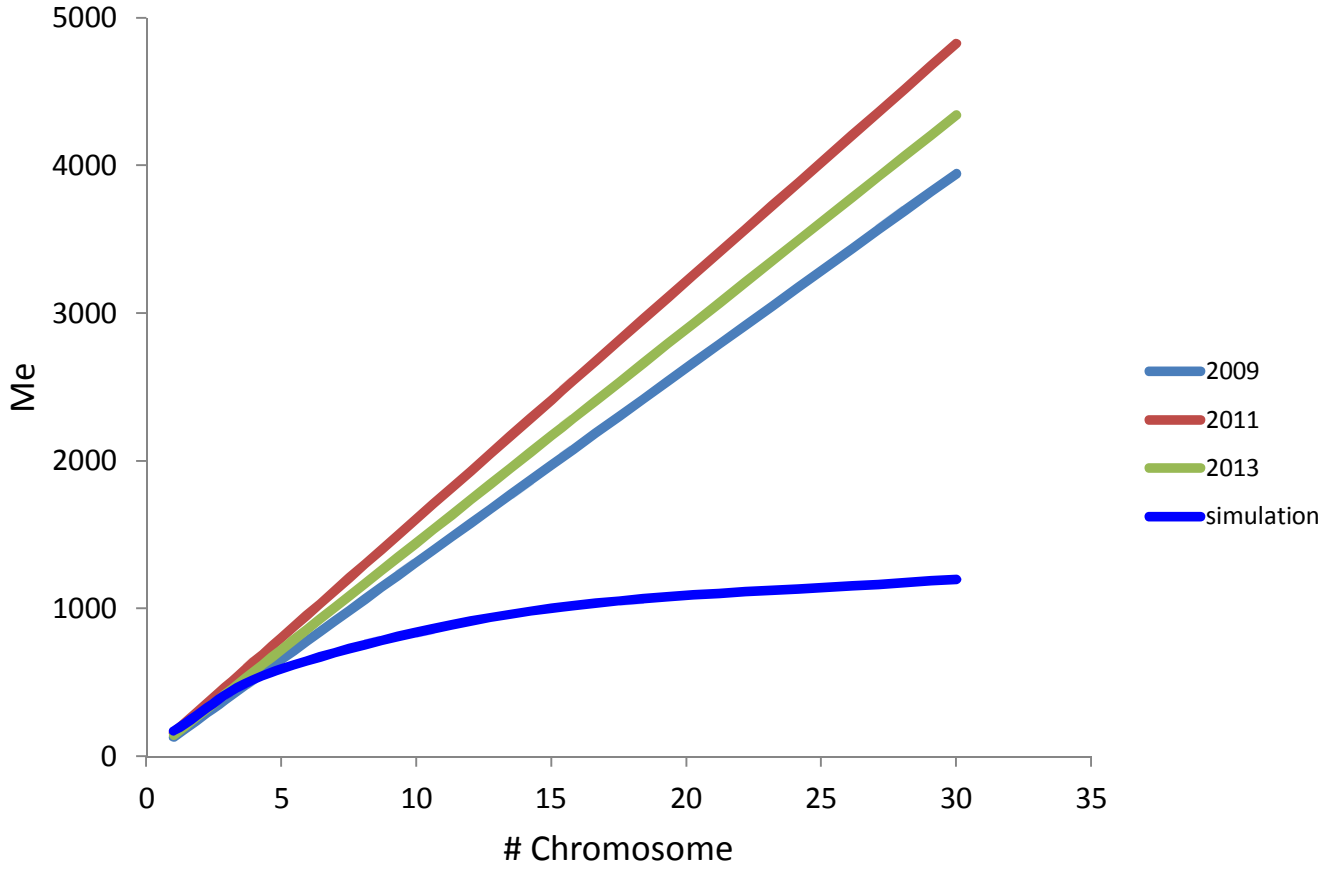
Given genomic relationships (after collecting data), it is possible to empirically get M_e from the data

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 G_{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

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

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

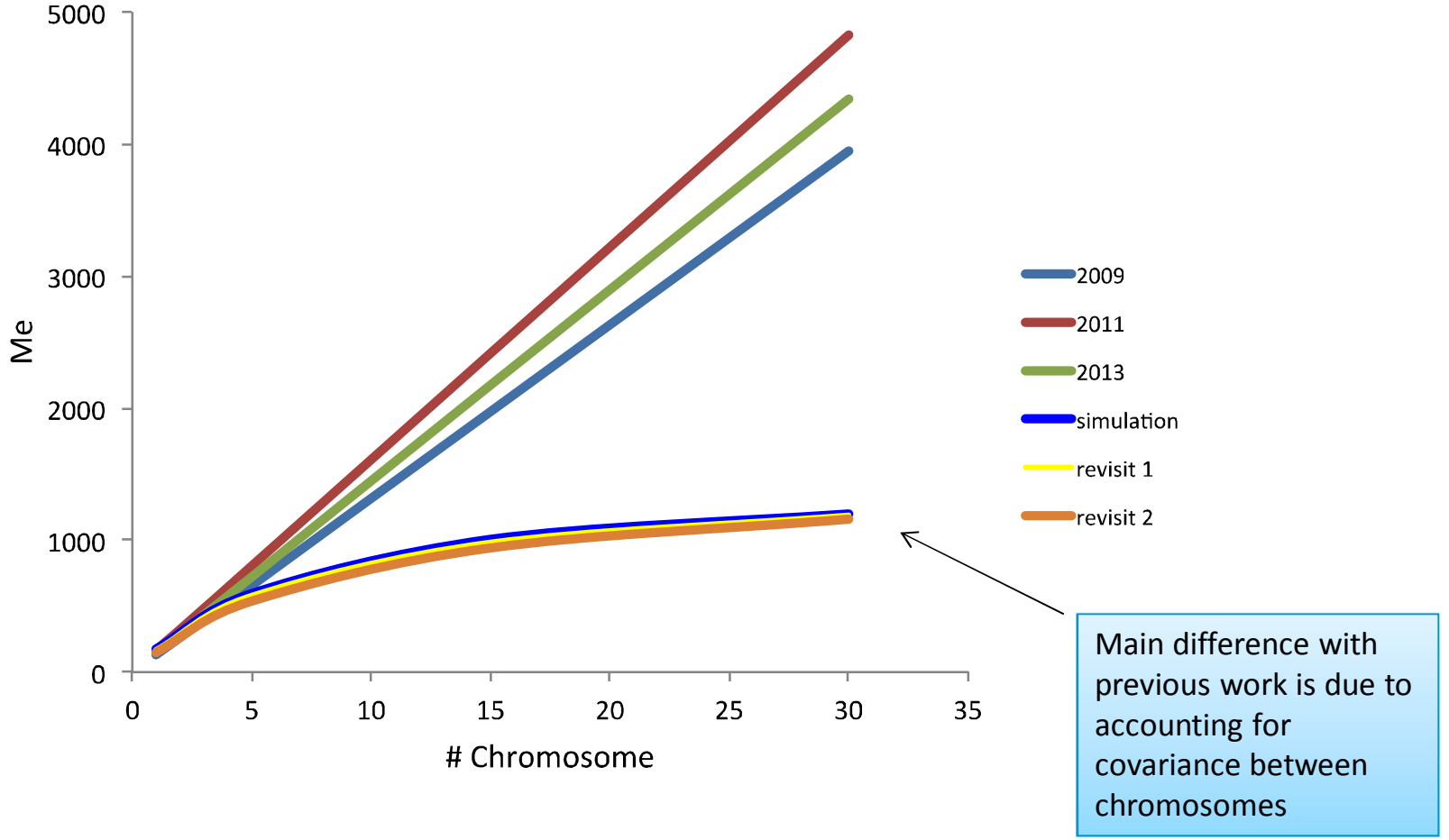
$$M_e = \frac{N_{chr}}{[\ln(2N_eL+1)+2N_eL(\ln(2N_eL+1)-1)]/(4N_e^2L^2)+(1/3N_e)\cdot(N_{chr}-1)}$$

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

For more detail,

see Lee et al, 2017 Scientific Reports

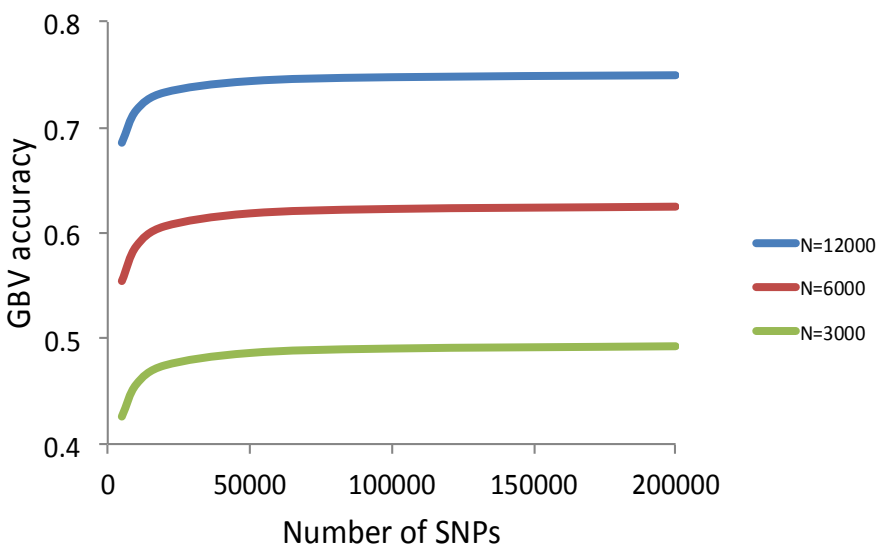
Empirical M_e and new formula

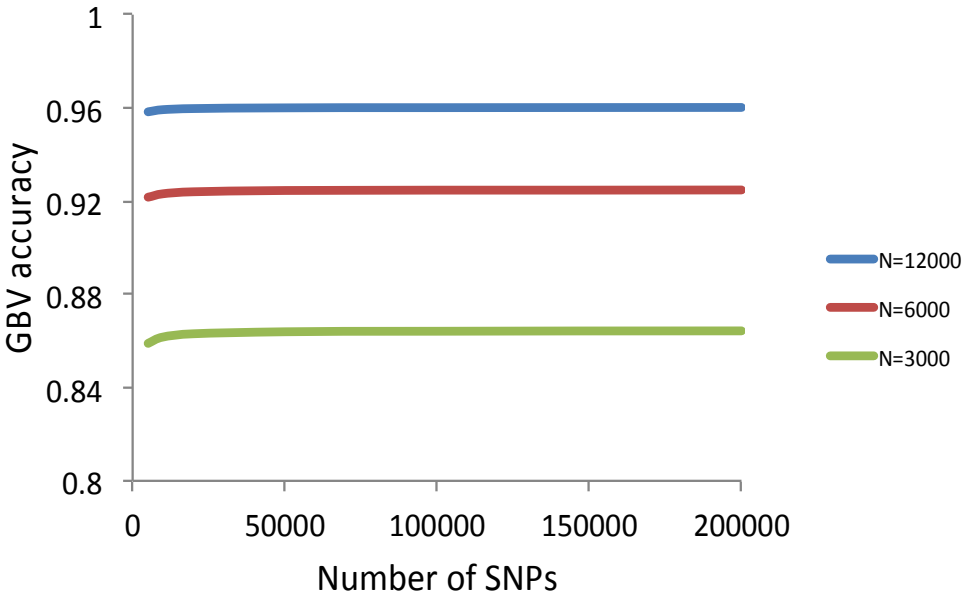


- Agreed well

Genomic prediction accuracy

Effect of marker density





Ne = 1,000

Ne = 100

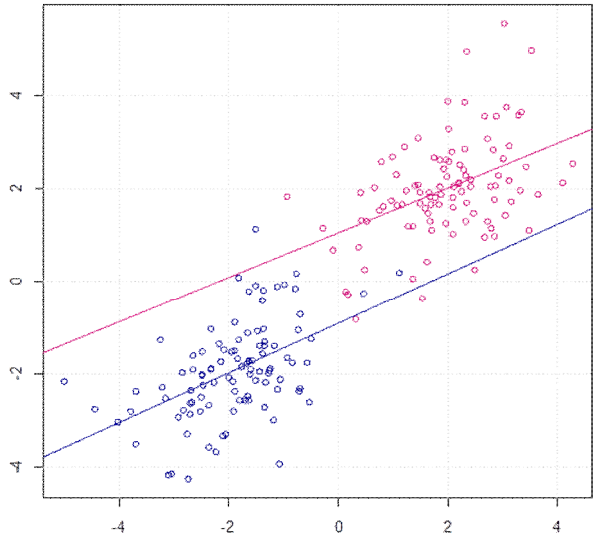
Expect very little improvement with denser markers

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?
    - Suppopulations
    - Different cohorts with genetic trend
    - Are there direct relatives between training and validation?

- Cross-validation
  - Across families
  - Random(also within families)
  - Across or within genetic groups (subpopulations)?

Main question

- 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 closer rleatives (e.g.own herd) versus the '*general*' reference population

Relationship with reference population

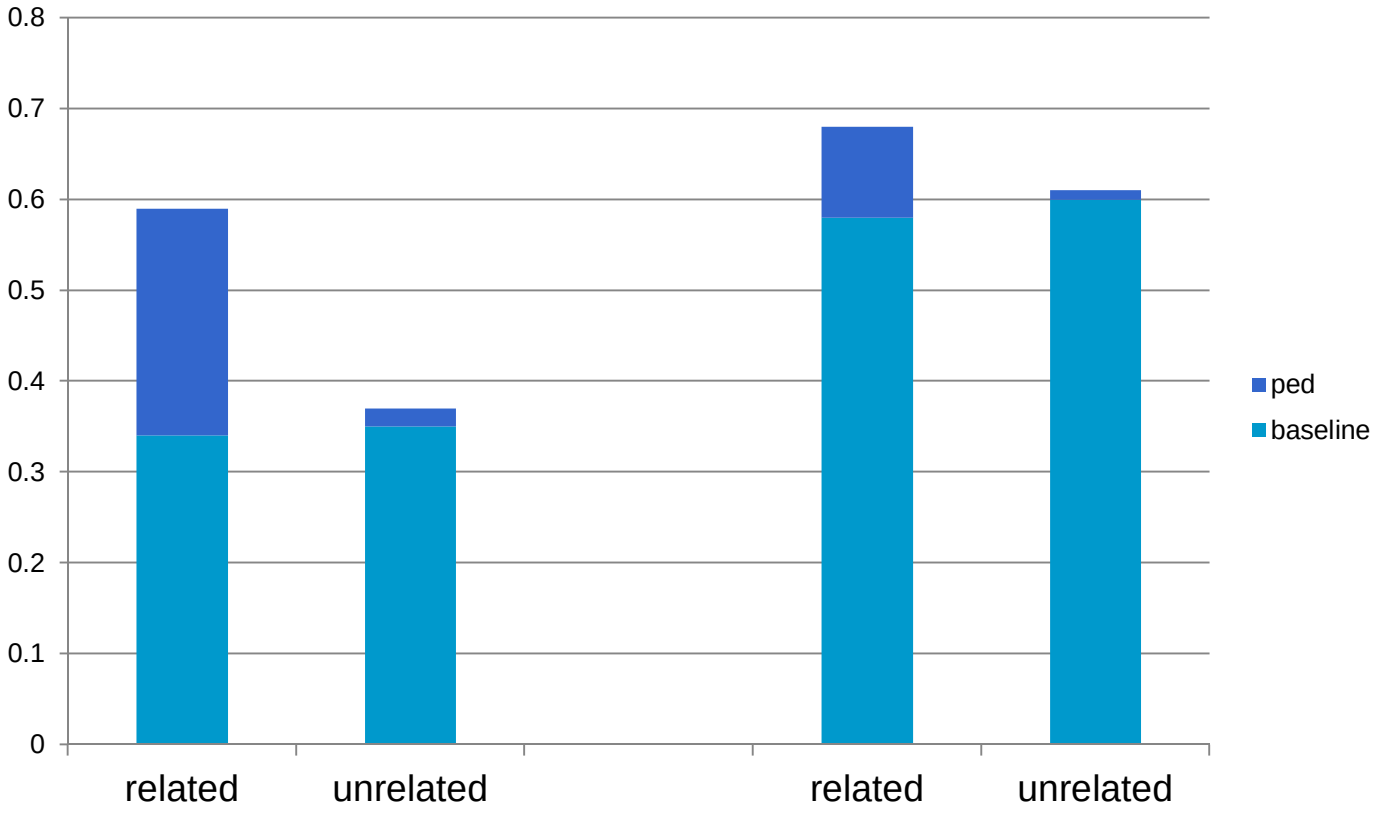
Clark et al 2011

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

ôbaseline accuracyô graphs predict 0.36 for Ne=100, N=1750, h^2=0.3

Relatedness matters more if the reference population is smaller



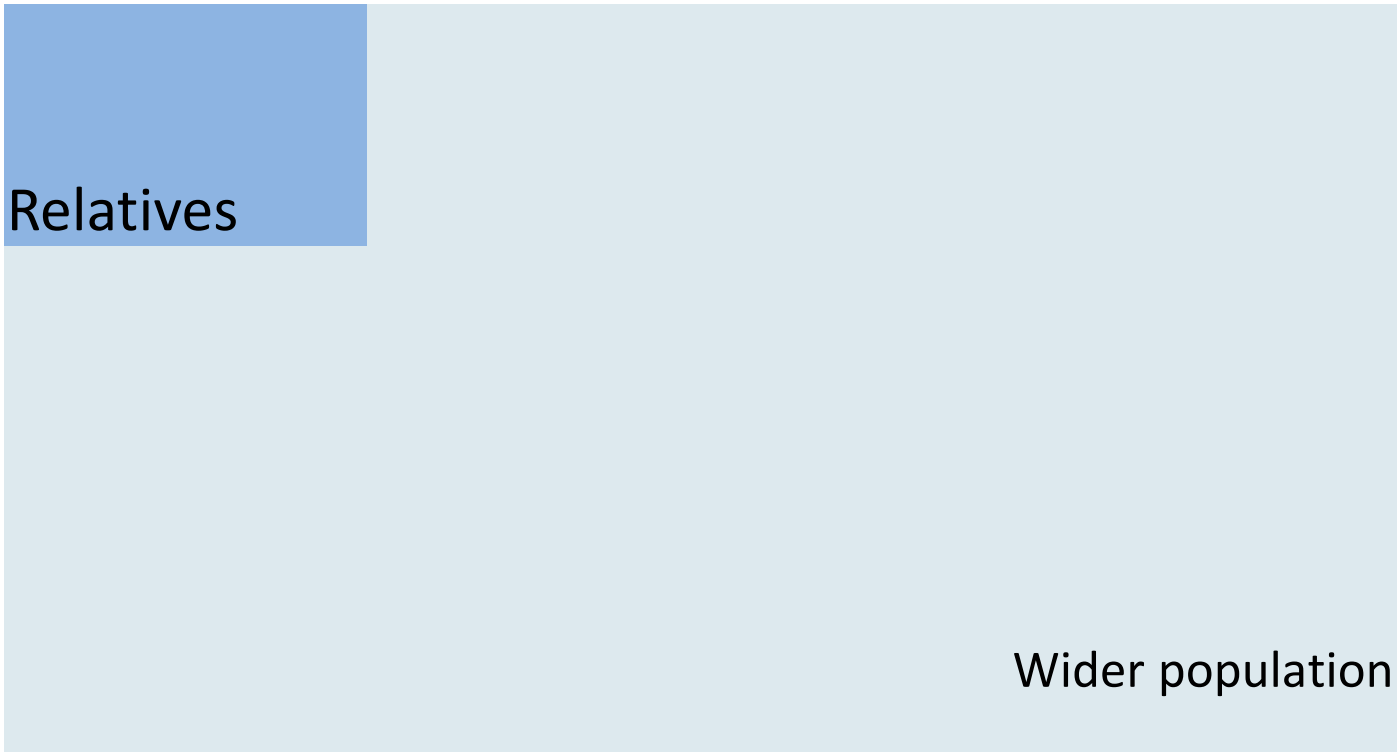
smaller ref pop

larger ref pop

(hypothesis)

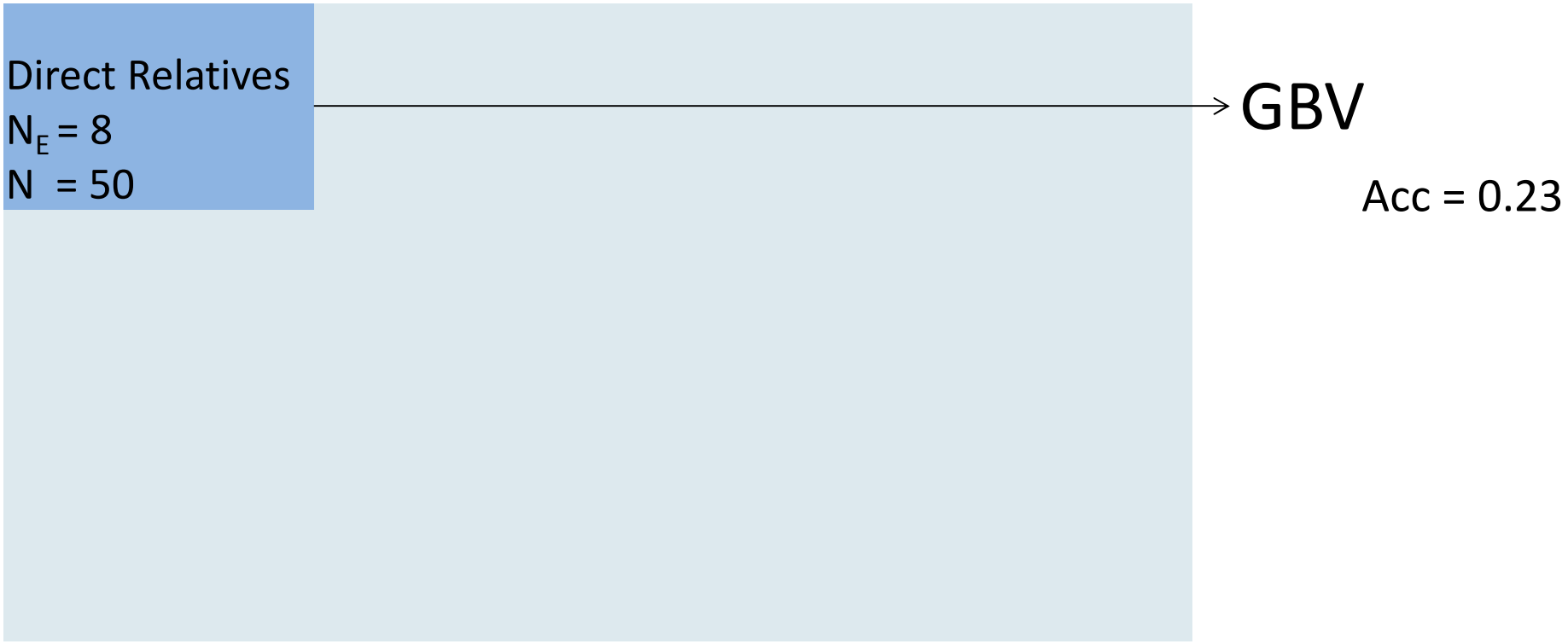
Van der Werf AAABG 2011

A reference population may have relatives

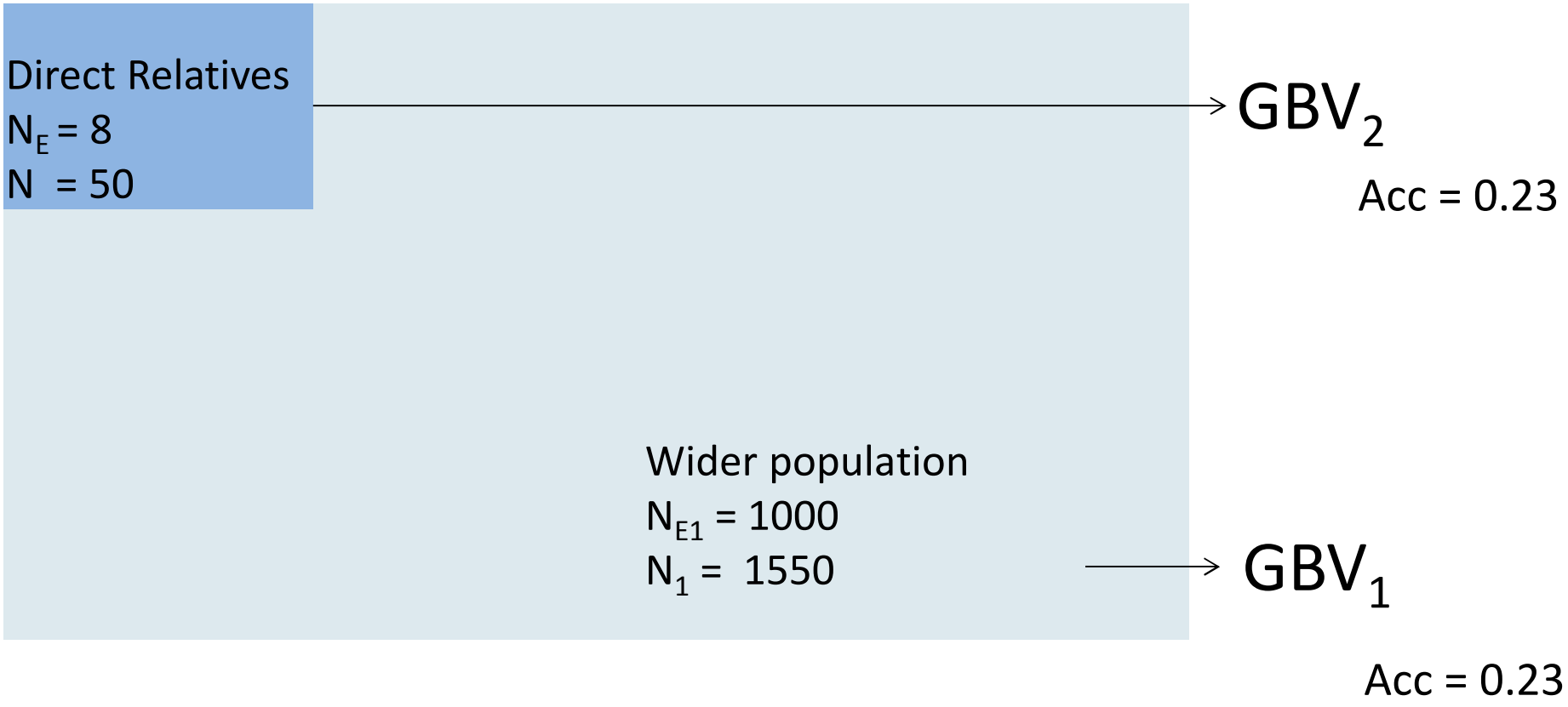


‘Relatedness’ can be represented by effective size

Hayes et al 2009



Information from different subsets can be combined



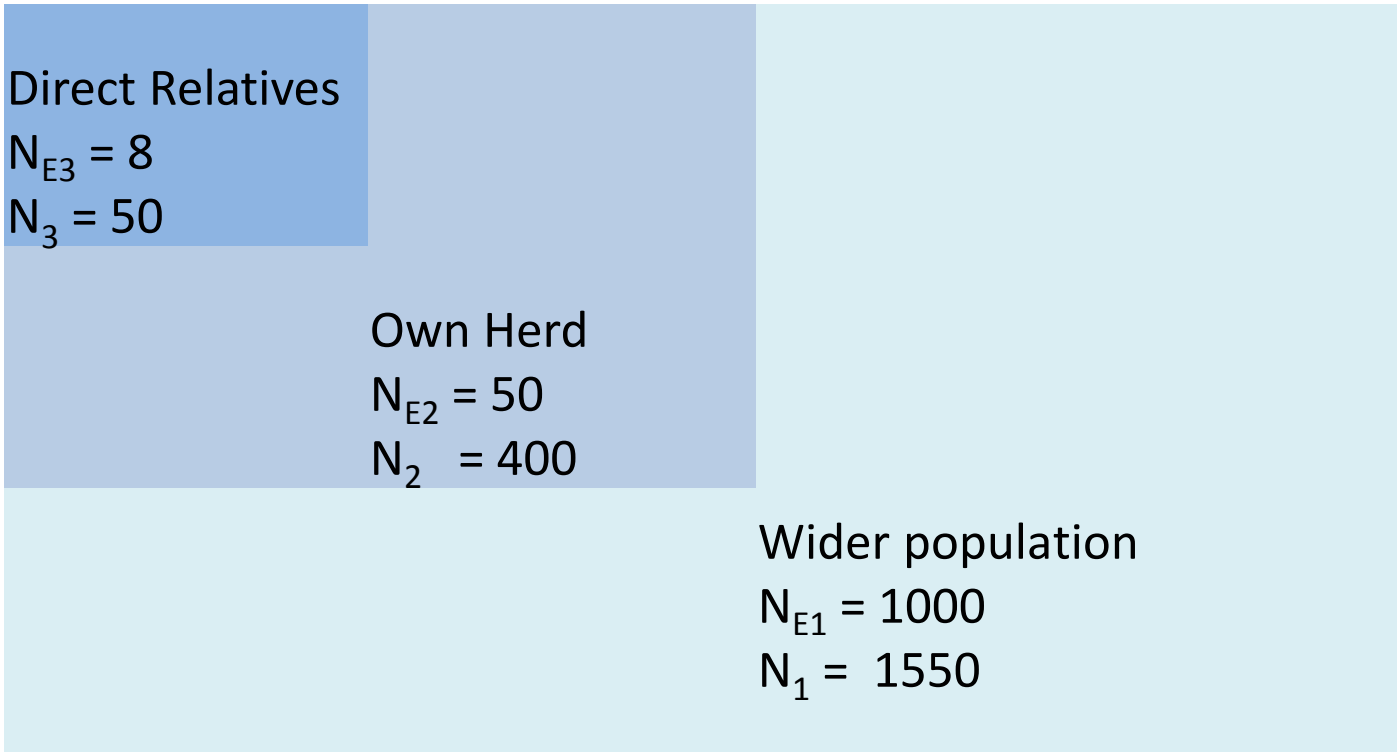
Calculate overall accuracy using selection index

$$GBV = \Sigma b_i GBV_i$$

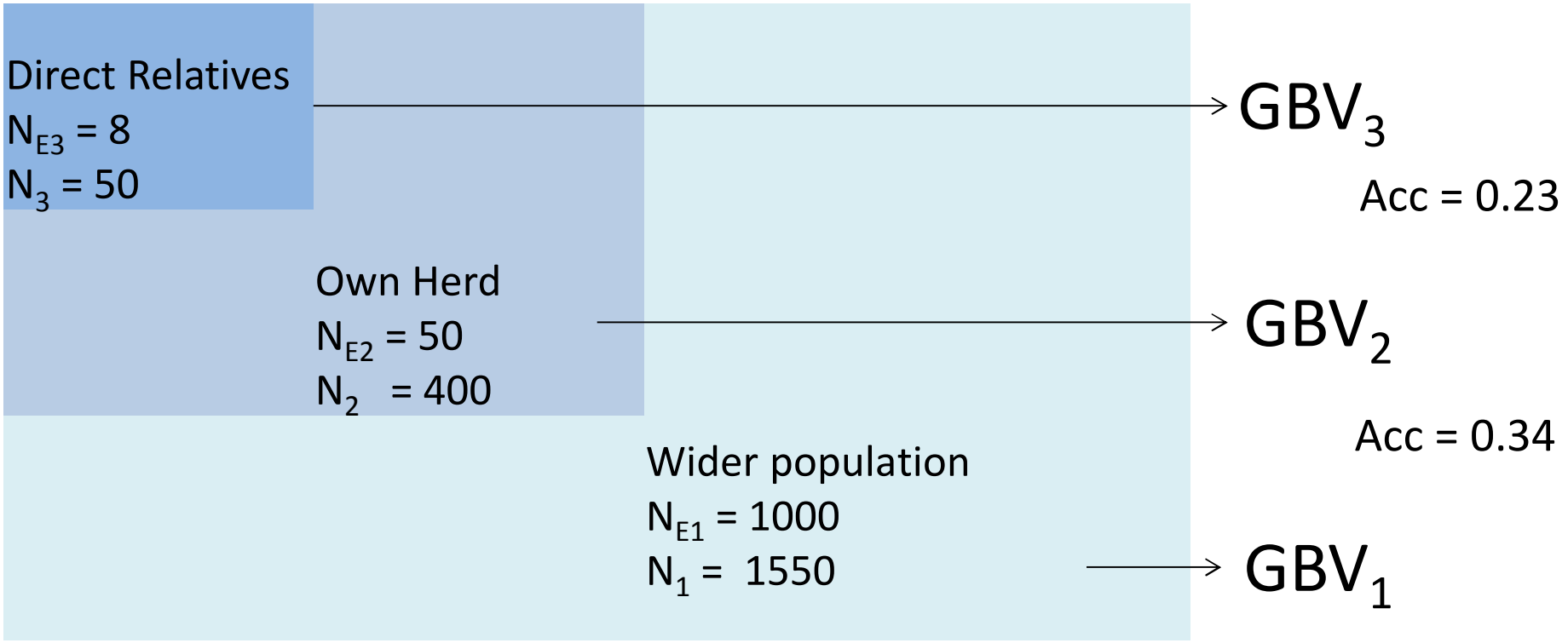
Acc = 0.31

Using a stratified reference population -populations are not homogeneous

Using a stratified reference population -populations are not homogeneous



Using a stratified reference population -populations are not homogeneous



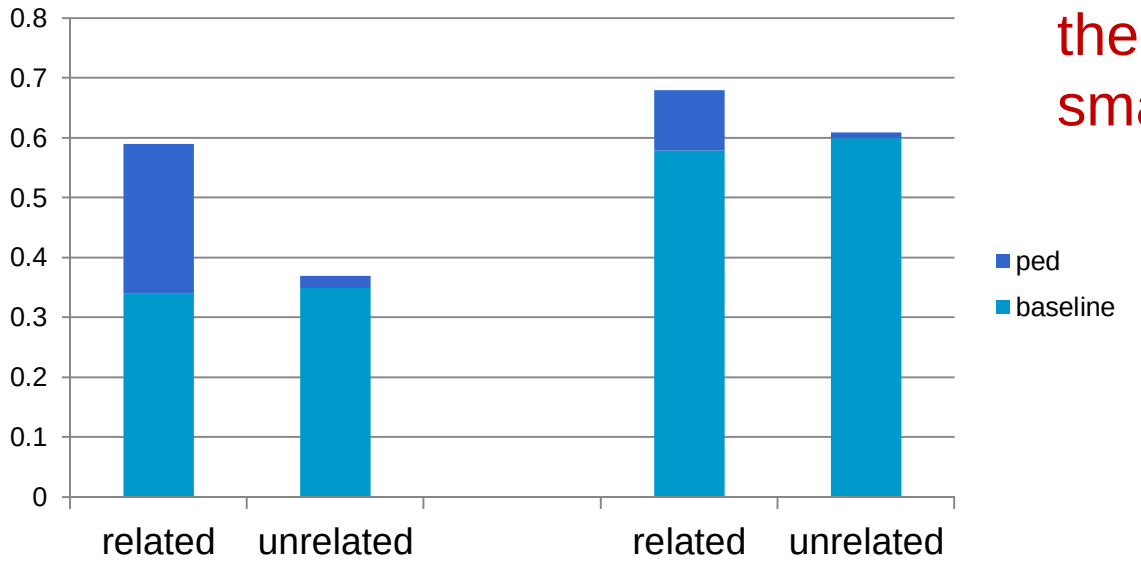
Calculate overall accuracy using selection index

$$GBV = \Sigma b_i GBV_i$$

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

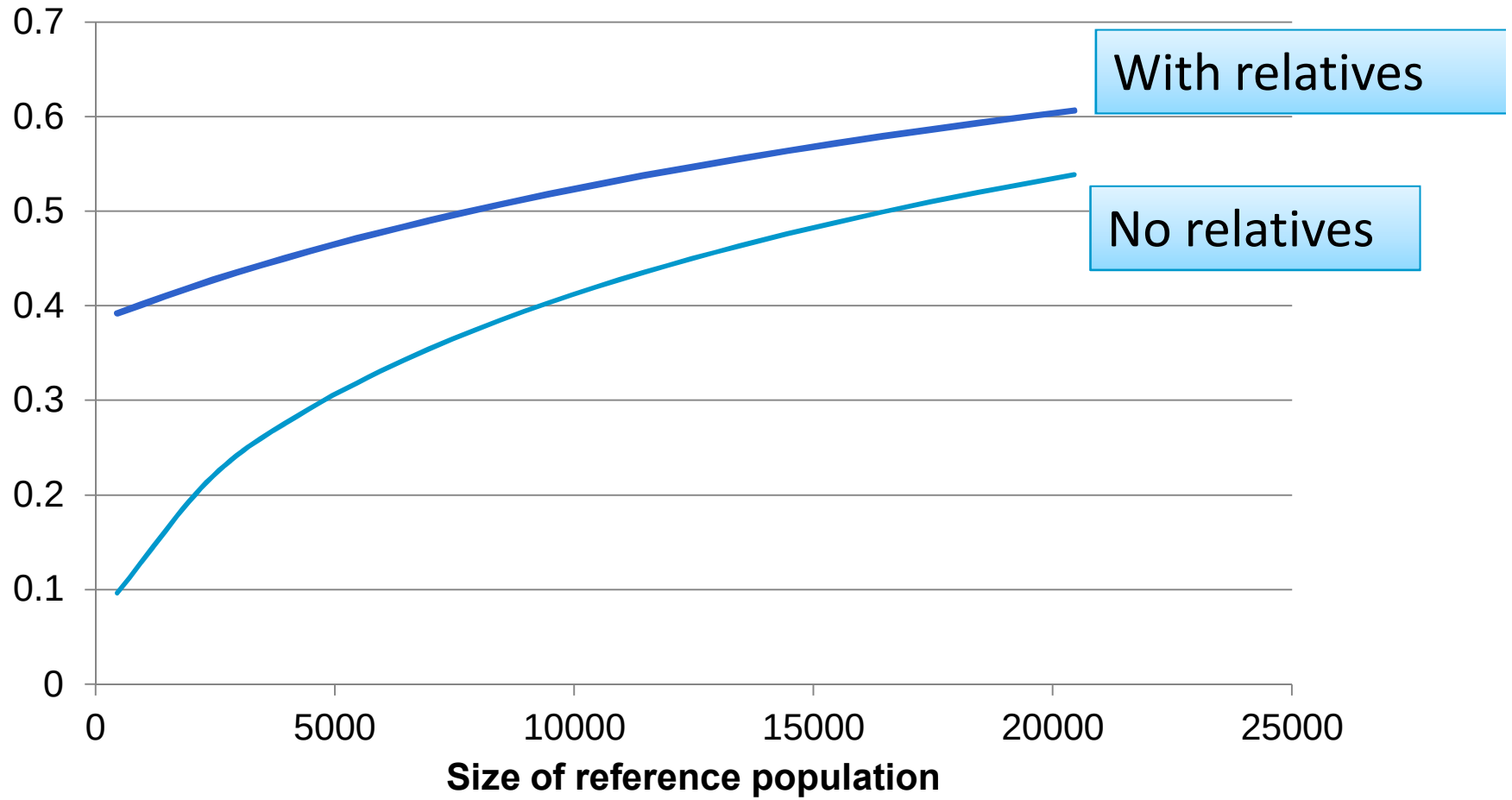
	Value of information source			GBV accuracy		
N_1	breed (N1)	flock **(400)**	relatives **(50)**	all info	breed only	diff
2,000	16%	52%	21%	0.43	0.22	95%
5,000	31%	39%	15%	0.47	0.32	48%
10,000	45%	26%	10%	0.53	0.42	26%

NE_1 = 200

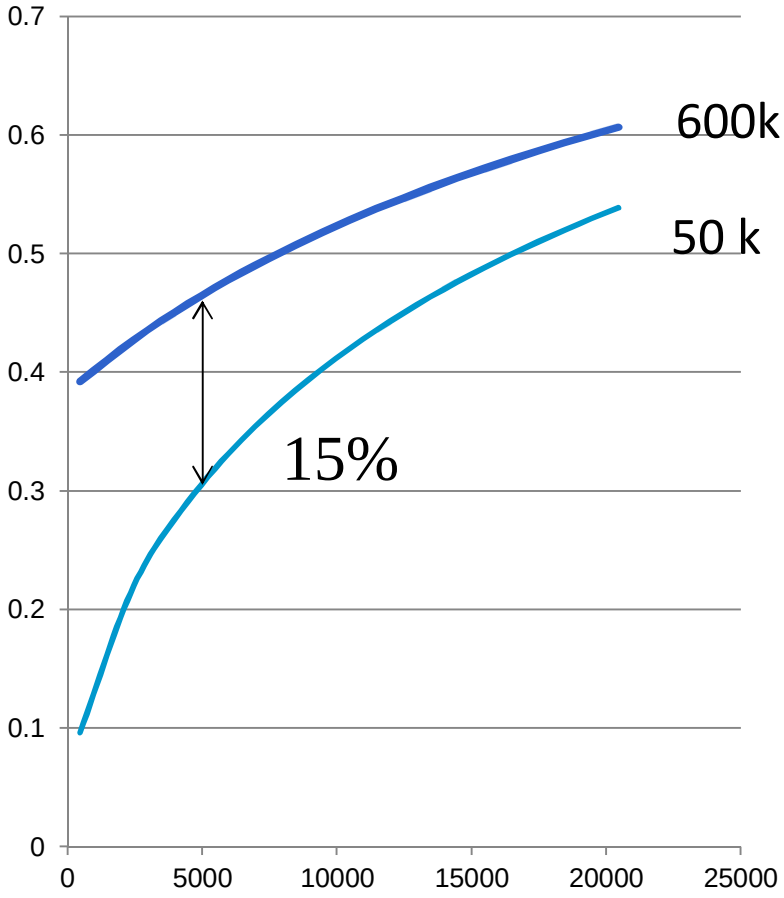
N_1	breed (N1)	flock **(400)**	relatives **(50)**	all info	breed only	diff
2,000	45%	26%	10%	0.53	0.45	18%
5,000	62%	12%	5%	0.64	0.60	7%
10,000	72%	5%	2%	0.74	0.72	3%

With less diverse populations the relatives matter a lot less

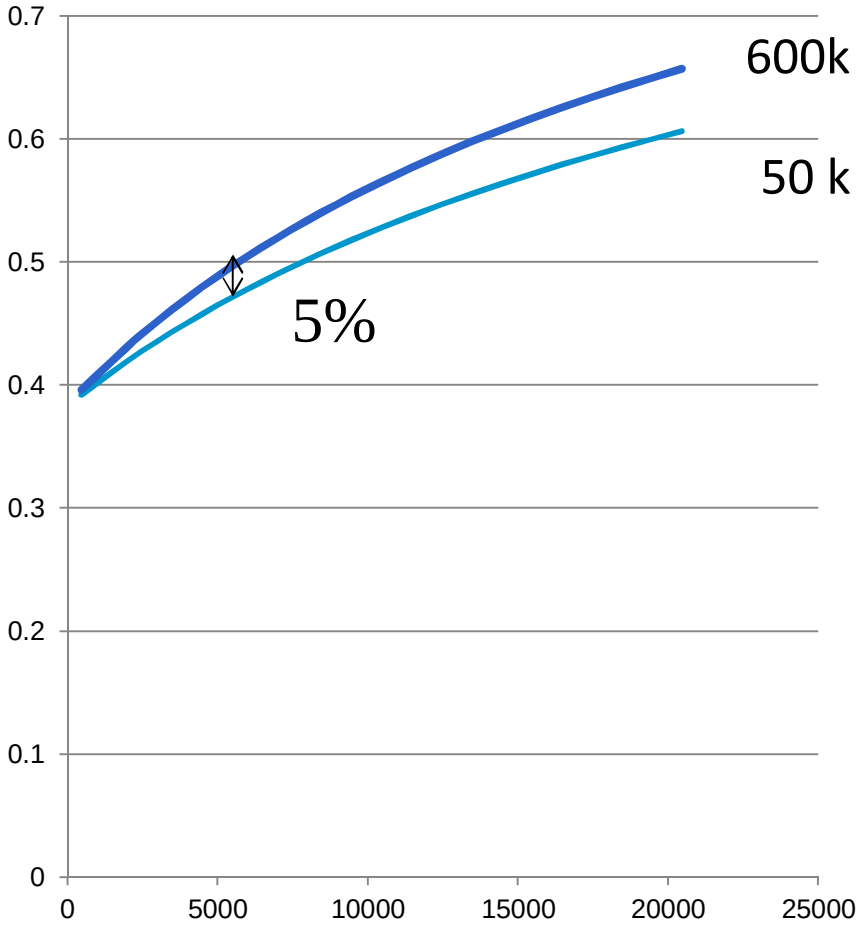
The effect of a larger reference population



The effect of denser marker panels



No relatives

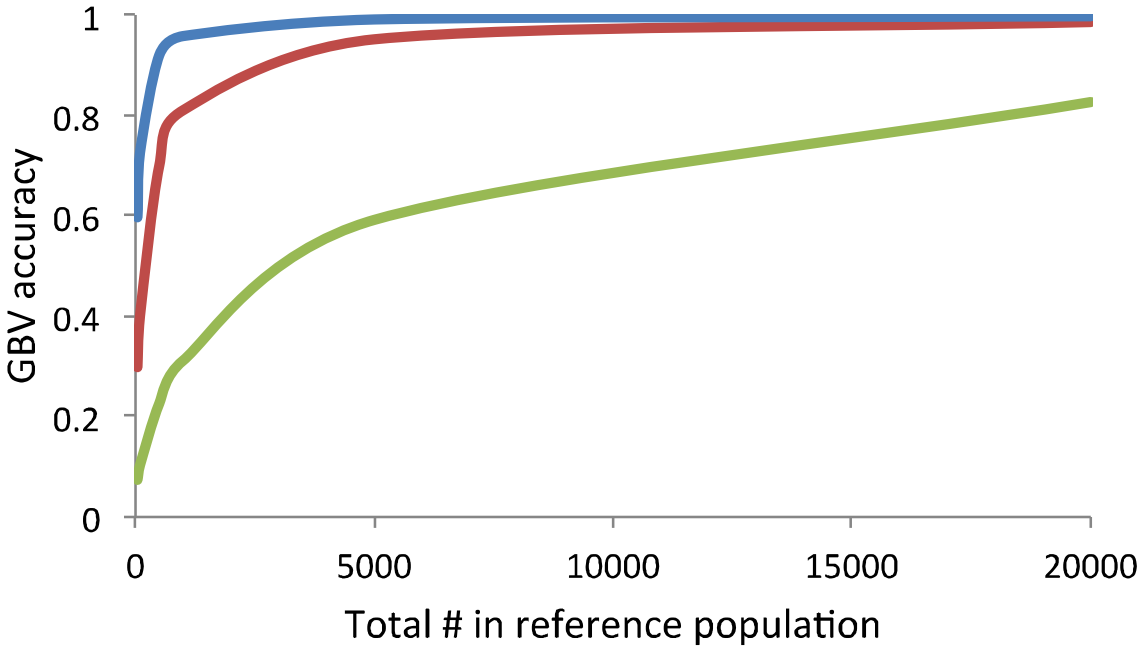


With relatives

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)

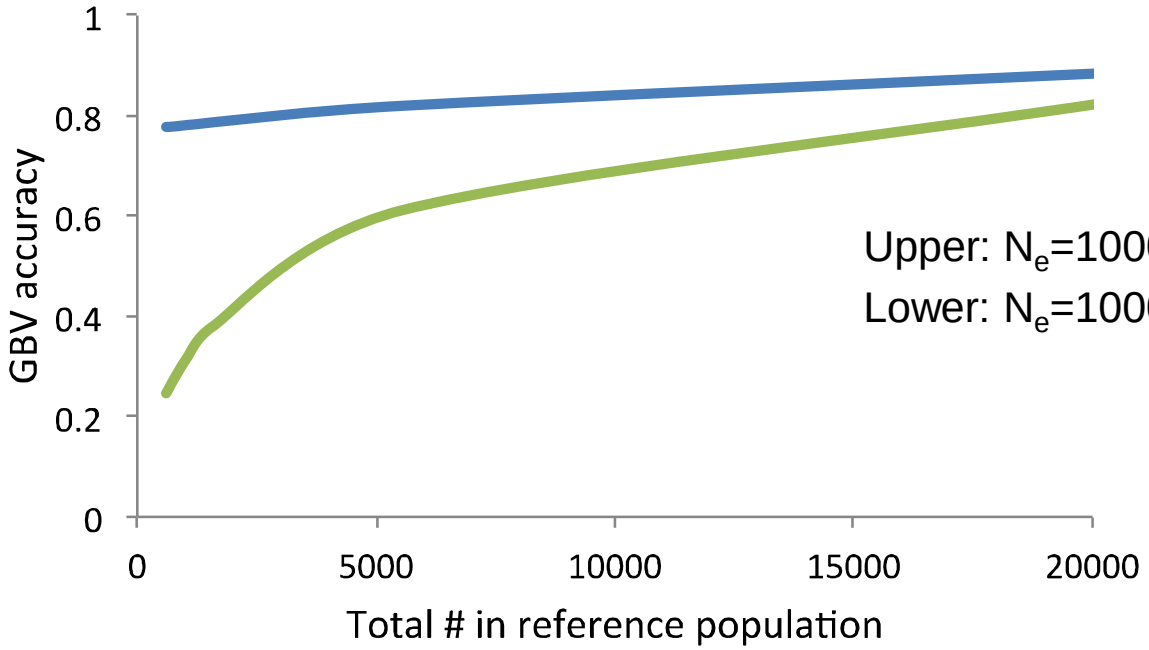
Sample availability



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
  - when > 50K with N_e = 1000 (livestock)
  - when > 200K with N_e = 10,000 (human)

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

This theory also assumes an 'infinitesimal model'

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