Estimation of the effective number of genes underlying quantitative traits based on chromosomal partitioning of the genomic variance

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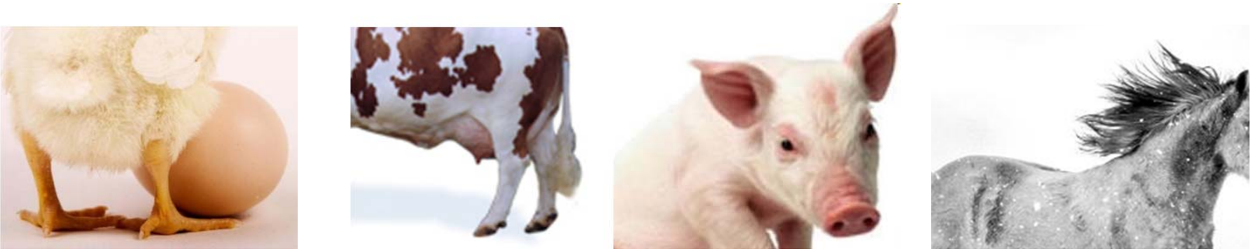


Old question: how many genes are involved in the inheritance of a quantitative trait?

Results are highly variable:

- Chamberlain *et al.* (2007): ~ 30 QTL underlying milk yield in Holsteins
- Daetwyler *et al.* (2010) applied to data of Luan *et al.* (2009): ~ 750 genes underlying milk yield in Norwegian Red Cattle
- Reed *et al.* (2008): ~ 6000 genes underlying growth in mice

When does a gene count as ‚involved'?

Data

- SNP genotypes (Illumina BovineSNP50 BeadChip) of 2294 progeny-tested bulls (born 1981 – 2003)

- Pedigree with 21‘646 animals, back to 1906.

- After filtering w.r.t.
  - ⇨ call rate > 97%
  - ⇨ MAF > 0.05
  - ⇨ known autosomal position

  39’557 SNPs on 29 autosomes (2562 on BTA1 ⇲ 742 on BTA28)

- Haplotype reconstruction with fastPHASE (Scheet & Stephens, 2001) incl. Imputation of missing genotypes

- Phenotypes = EBVs for milk yield (Mkg), fat percentage (F%), protein percentage (P%) and somatic cell score (SCS)

Data processing

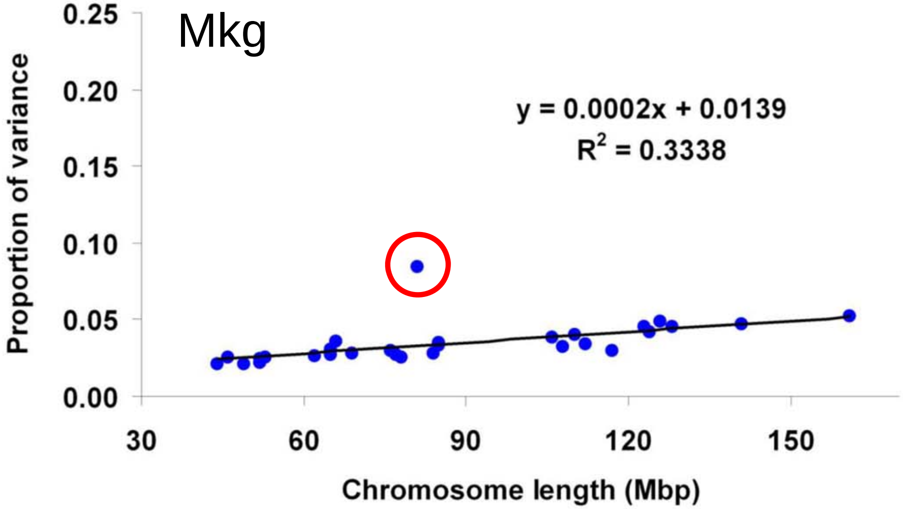
- Genomic SNP effects estimated using random regression BLUP (Meuwissen et al. 2001), variance components estimated from the data using REML → $\hat{\alpha}_i$
- Allele frequency at SNP i in the founder generation estimated by the approach of Gengler et al. (2007) → $\hat{p}_i$
- Variance for chromosome *j* with n_j SNPs calculated as

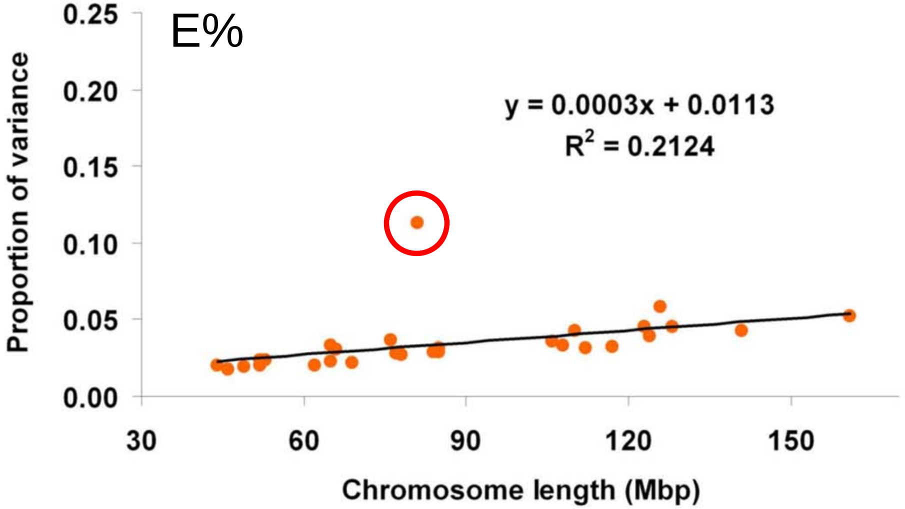
$$V_j = \sum_{i=1}^{n_j} 2\hat{p}_i(1-\hat{p}_i)\hat{\alpha}_i^2$$

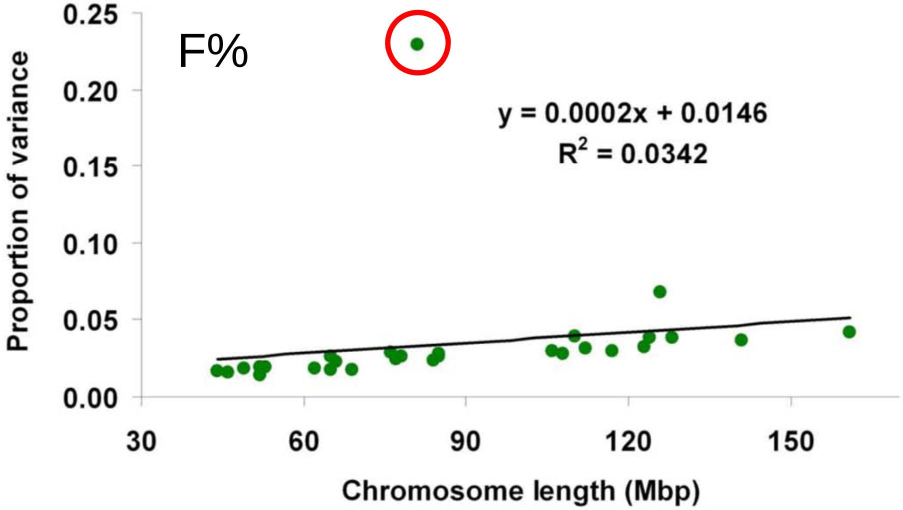
- Proportion of variance of chromosome *j* calculated as

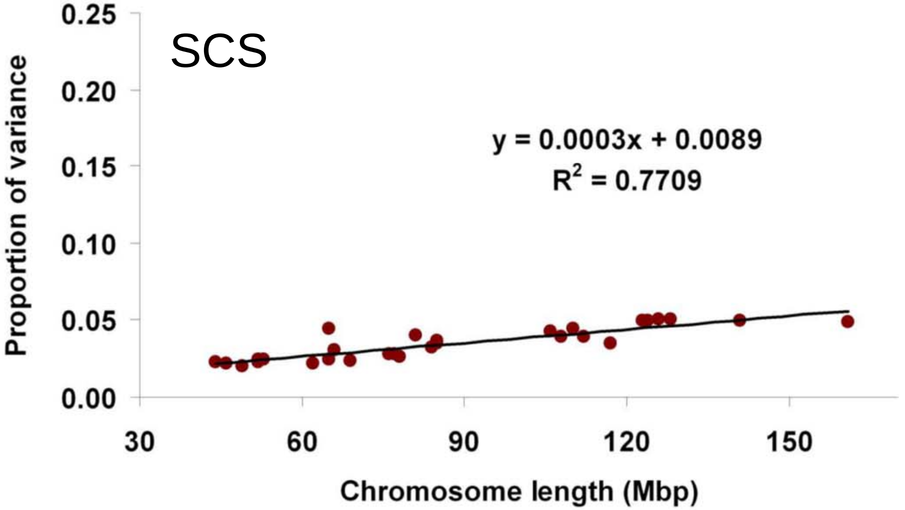
$$Q_j = V_j / \textstyle\sum_{k=1}^{29} V_k$$

Regression of the proportion of variance on the physical chromosome length

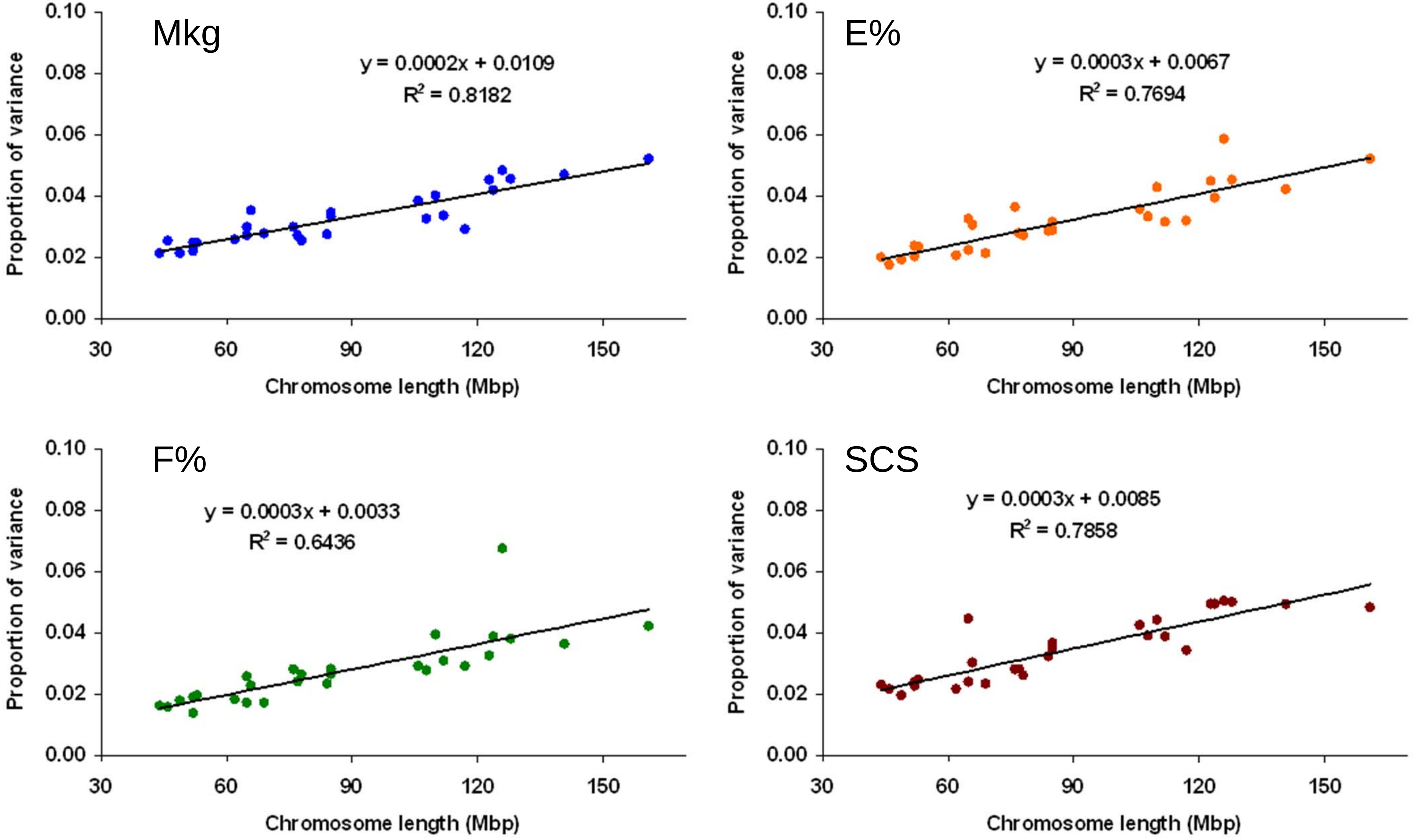








Regression of the proportion of variance on the physical chromosome length – BTA 14 excluded

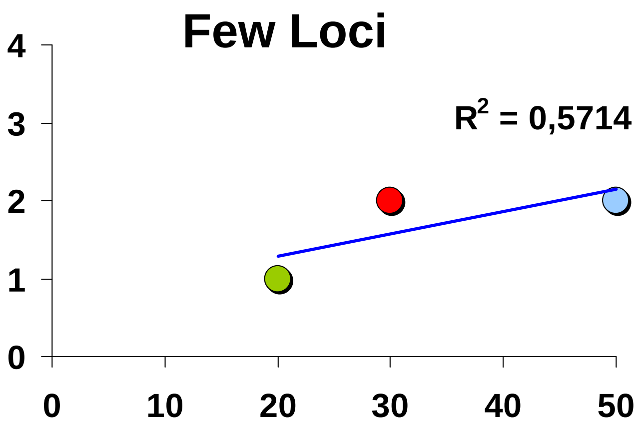


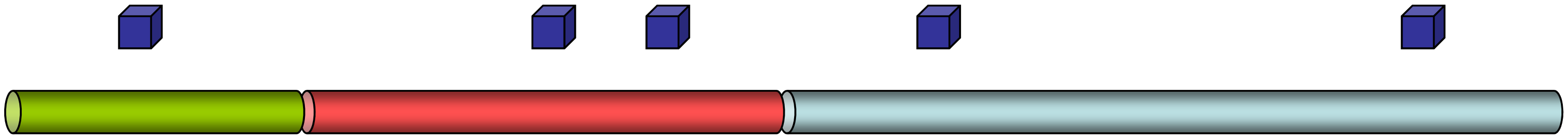
The concept of the effective number of genes

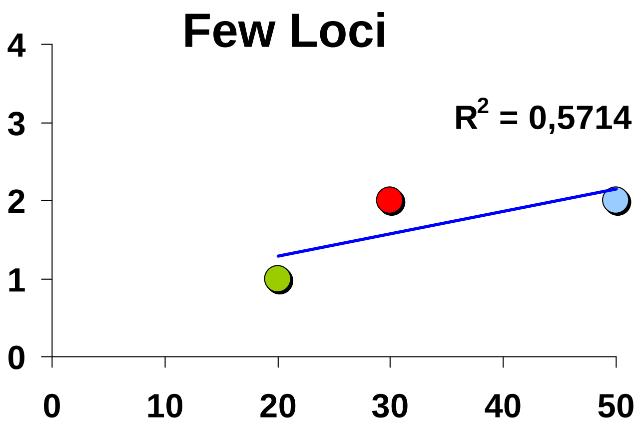
Effective number of genes *N_g* is the number of hypothetical genes which

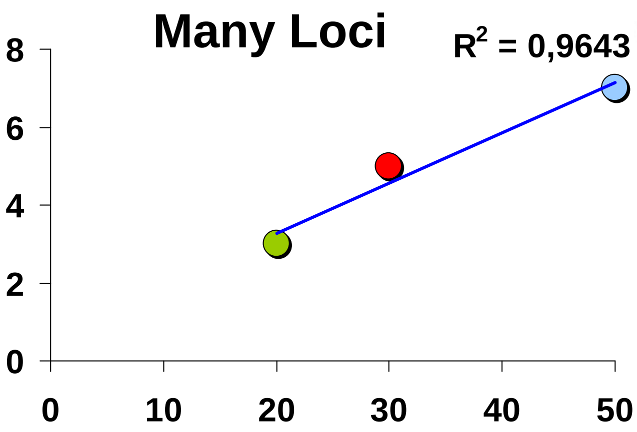
- have the same genetic variance
- are in linkage equilibrium
- are randomly (Poisson) distributed across the genome

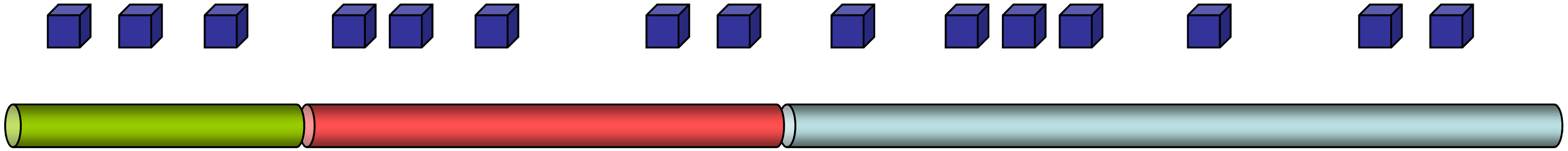
that leads to the same coefficient of determination R^2 in variance partitioning as obtained in the empirical analysis


Few Loci
R² = 0,5714
4
3
2
1
0
0
10
20
30
40
50



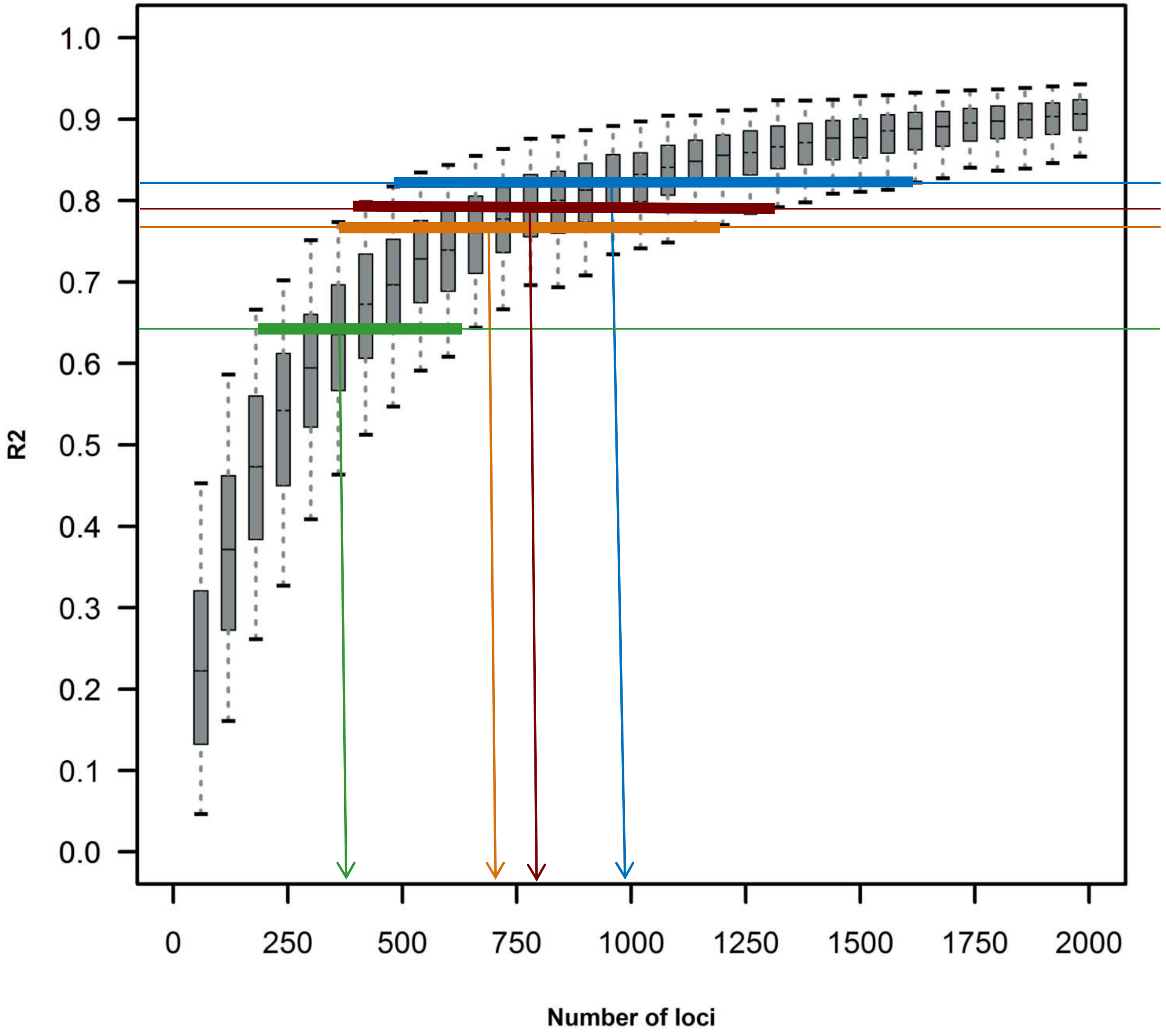

Few Loci
$R^2 = 0,5714$
4
3
2
1
0
0
10
20
30
40
50


Many Loci
$R^2 = 0,9643$
8
6
4
2
0
0
10
20
30
40
50



Simulation results

1000 replicates per number of loci, without BTA 14



Mkg: N_g = 949 [462;1593]

SCS: N_g = 779 [366;1337]

P%: N_g = 710 [337;1213]

F%: N_g = 378 [157;696]

Final remarks

- The concept provides a sensible and consistent definition of the number of genes underlying quantitative traits
- The approach is conservative, i.e. N_g is a lower bound estimate.
- Unequal variance of genes and non-random distribution of genes increase the true number of genes relative to N_g
- The resulting values are in the expected range, substantial variation between traits is observed (F%: 378 → Mkg: 949)
- The link of N_g with the accuracy of genomic prediction and the relative performance of different estimation procedures is subject to further studies

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Genome partitioning of genetic variation for milk production and composition traits in Holstein cattle

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Thank you!