Rumigen

TOWARDS IMPROVEMENT OF **RUMI**NANT BREEDING
THROUGH **GEN**OMIC AND EPIGENOMIC APPROACHES

Genomic selection strategies and their potential to maintain **rare alleles** and **de-novo mutations**

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Motivation

Rare alleles and de-novo mutations have...

- low correlation with phenotypes at the population level
- usually weak linkage with SNP markers

Led to think that

- genomic selection may not use favorable rare alleles effectively
- could loose rare alleles at a higher rate than pedigree selection

Previous works

Compared mass selection, pedigree selection and genomic selection

Some conclusions about genomic selection:

- inclusion of own phenotypes is a main factor in the conservation of rare alleles
- doesn’t have to be worse than pedigree selection at this
- but is much more prone, specifically, to hitch-hiking than pedigree selection

Mulder et al., (2019) Genetics Wientjes et al., (2022) GSE Wientjes et al., (2023) Genetics

Current work

- Assessment of different genomic selection strategies

  Not ***if*** genomic selection but ***how*** genomic selection may be implemented

Selection Strategies:

Truncation selection (TS) ---------→ Maximize average EBVs from selected candidates

Optimal contributions (OCS) ----→ with a constraint on the candidates' coancestry

Meuwissen et al., (2020) Frontiers

Alleles re-weighting (ARW) ------→ with favorable rare alleles up-weighted in EBVs (2 versions: *fixed* and *moving* time horizon)

Liu et al., (2015) GSE

Constrained allele loss (CAL) -----→ with a constraint on the reduction in frequency of rare favourable alleles

novel strategy

*plus Random selection (RS) for reference

The Simulation

The Population:

50 discrete generations

1000 individuals

100 sires + 100 dams selected

- selected without own phenotypes
- using marker effects learnt from the 3 prior generations

Genome:

20k SNP marker panel

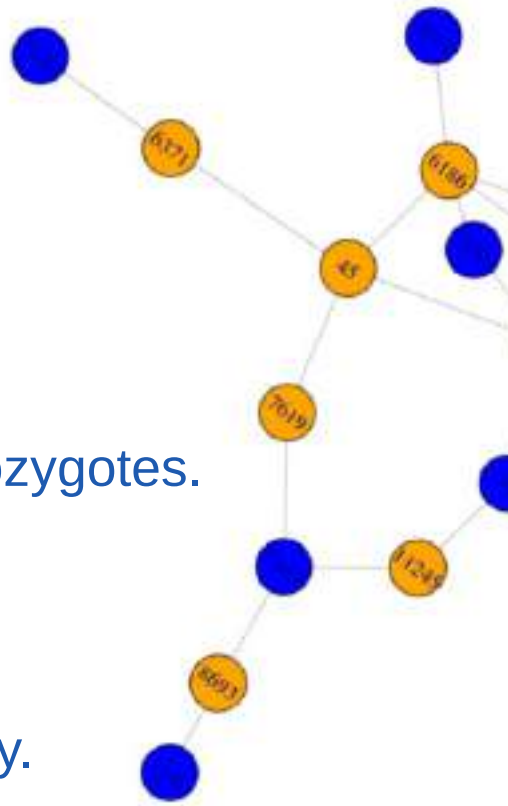
- MAFs 0.5 to 0.1
- neutral loci

2k starting causal loci

mutations rate 3.8×10^{-5} $(\text{loci.ind})^{-1}$

Simulation approach from Wientjes, et al. 2022

The Traits



Additive

Normally distributed additive effects, with a common variance.

Dominant

Includes dominance effects, with a small positive bias for heterozygotes.

Epistatic

Includes pairwise interactions, with connectivity pattern taken from a yeast study.

Traits specifications taken from Wientjes, et al. 2022

Yeast study in Costanzo et al., 2016

Results & Discussion

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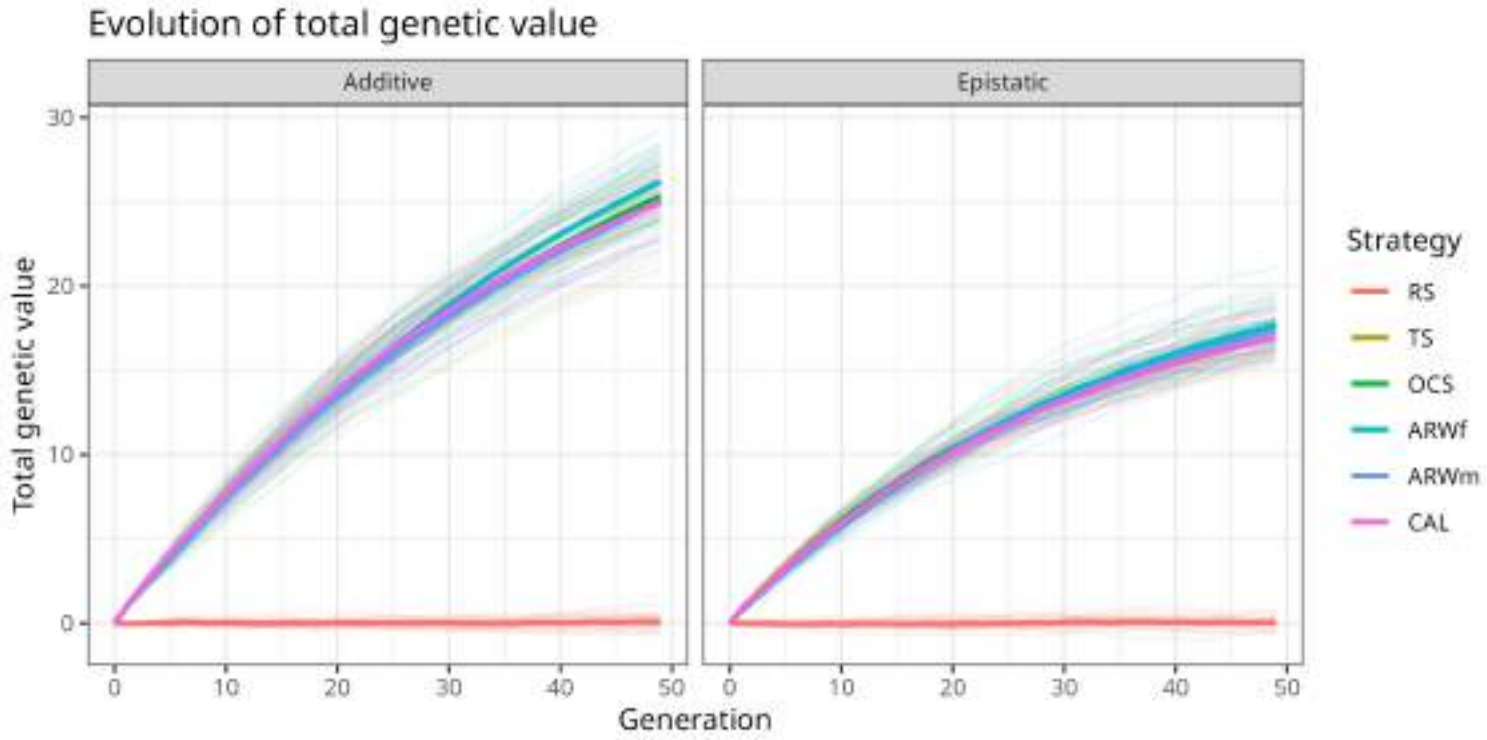
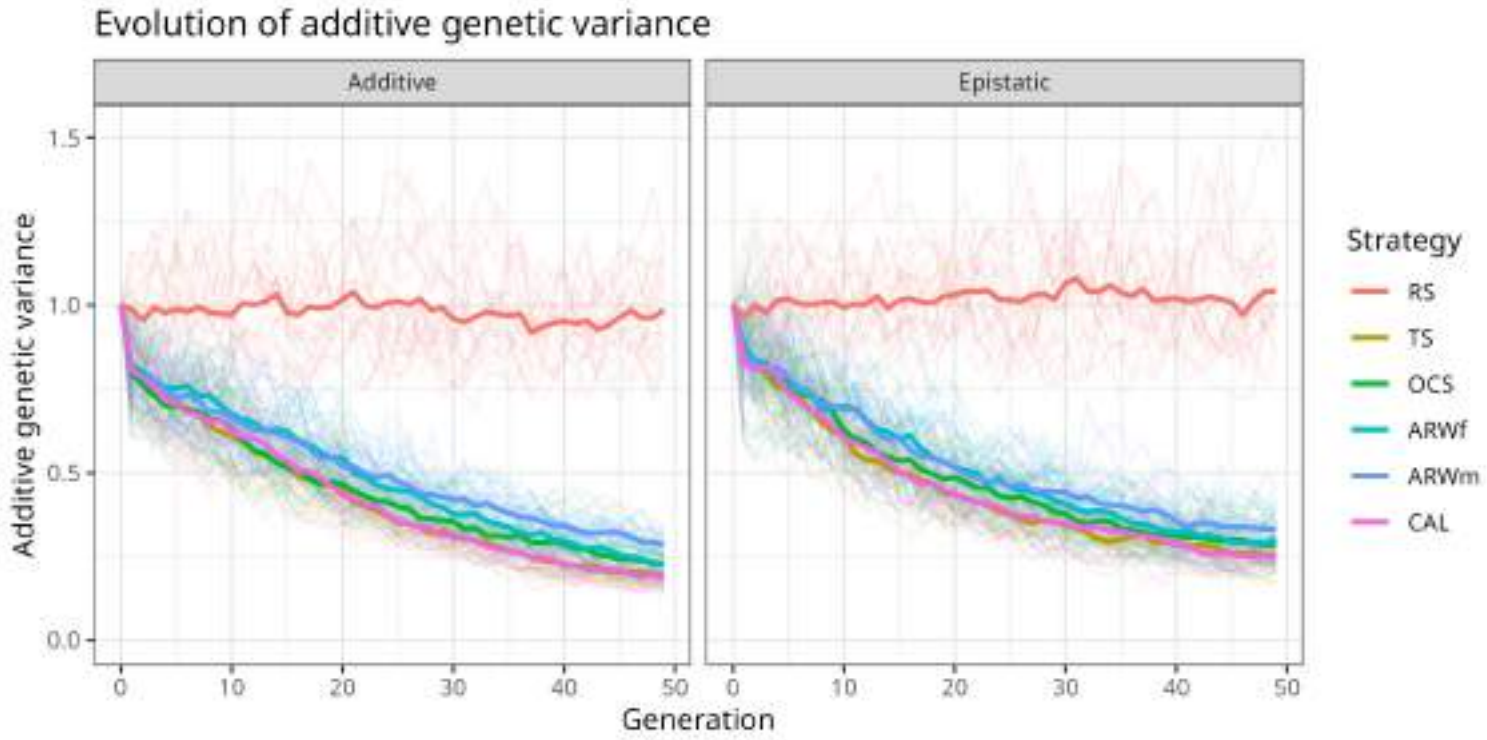
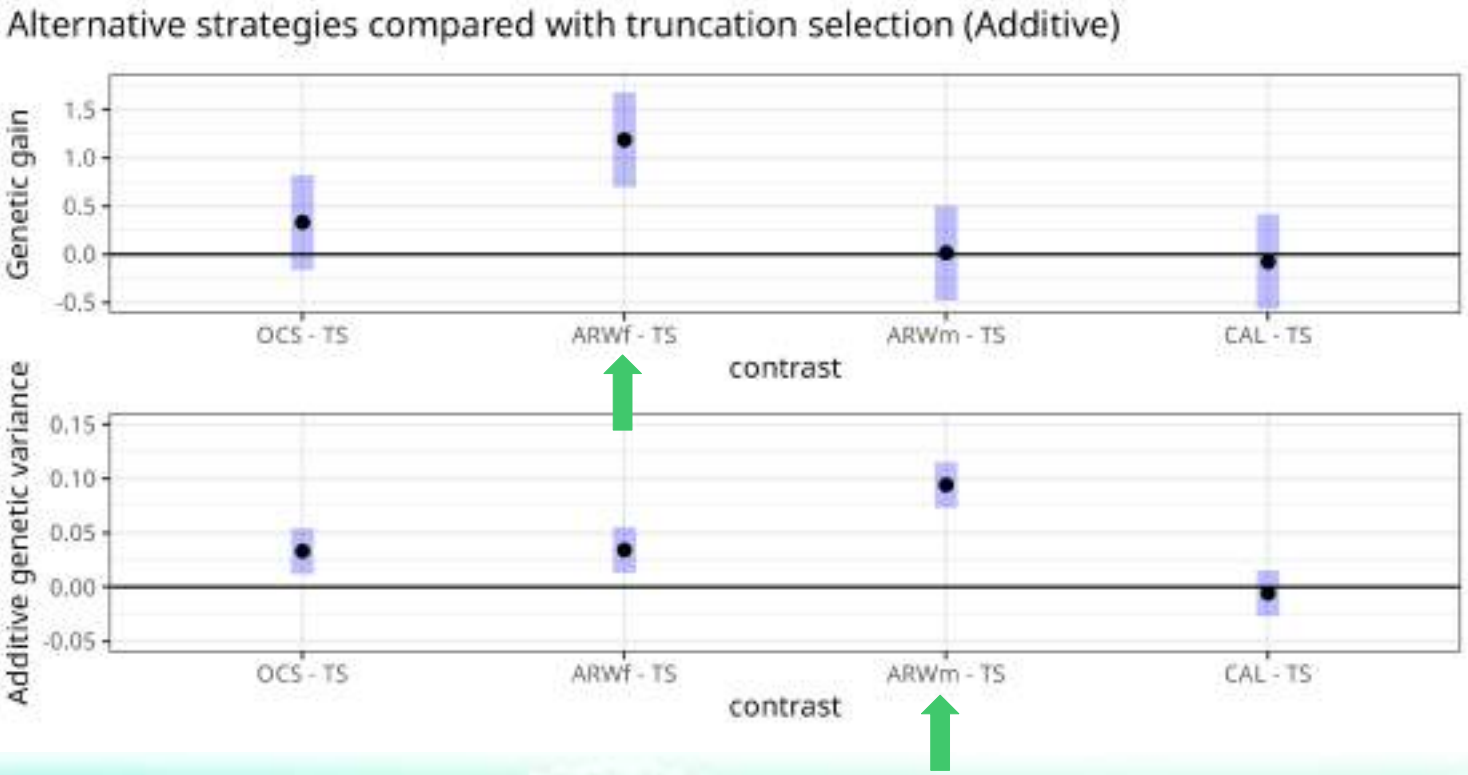


Results & Discussion

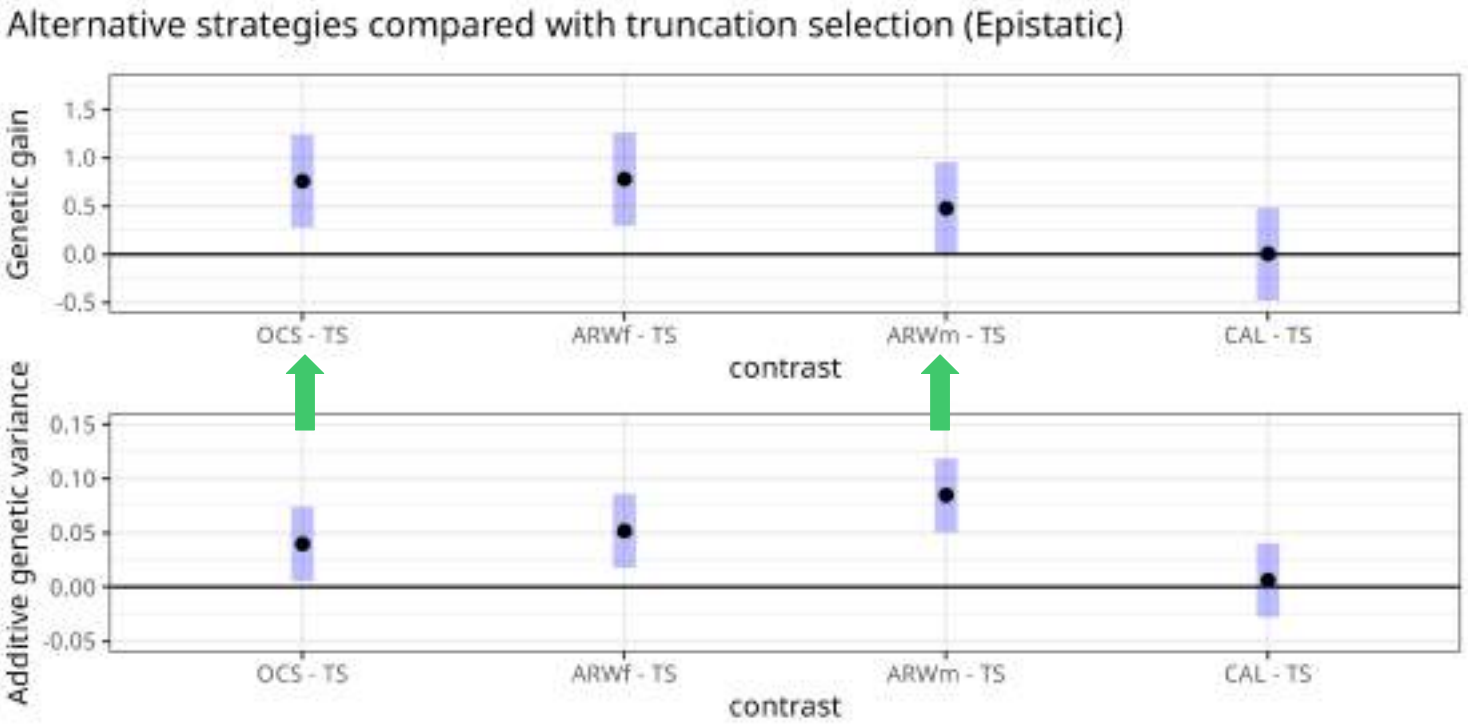


Genetic gain vs. genetic variance



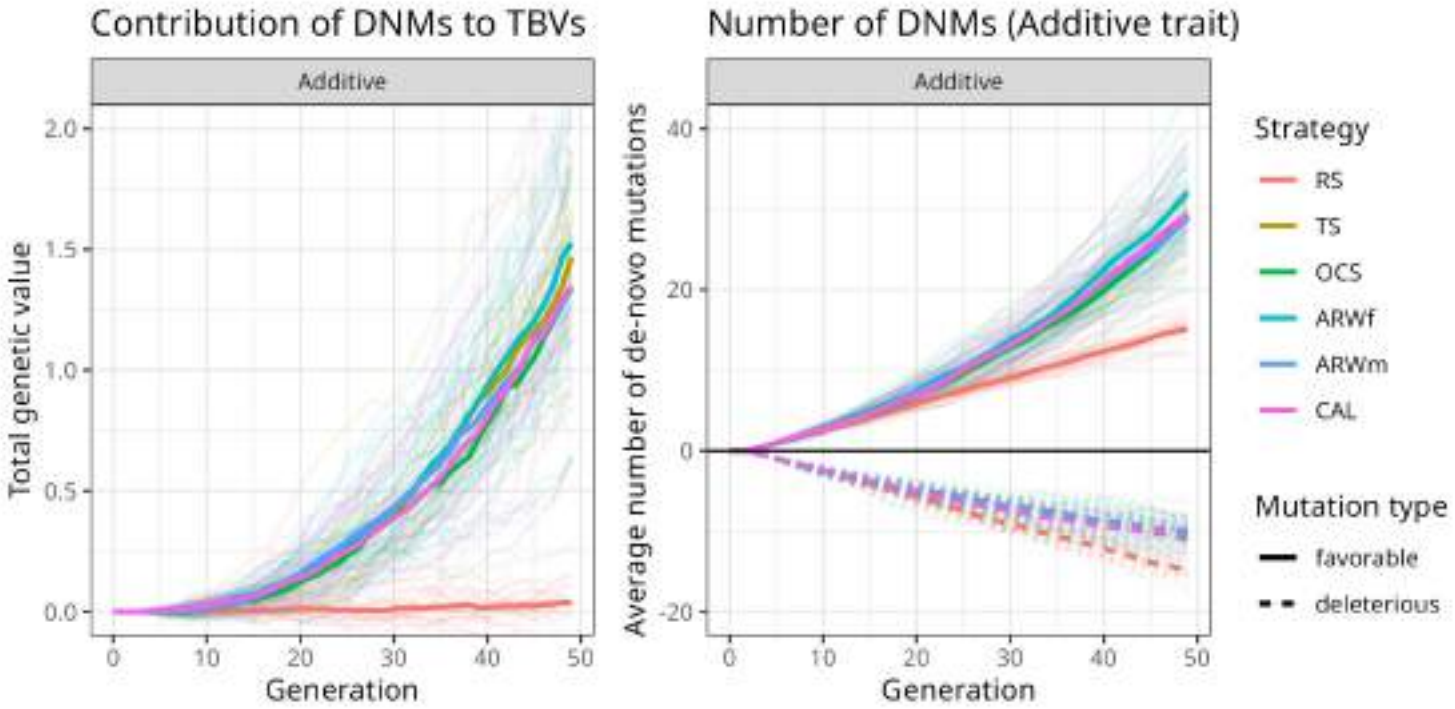
ARW strategies allow effective trade-off between increased genetic gain and conservation of genetic variance

Genetic gain vs. genetic variance



Considering traits with non-additive effects improves the assessments of OCS and ARWm for genetic gain

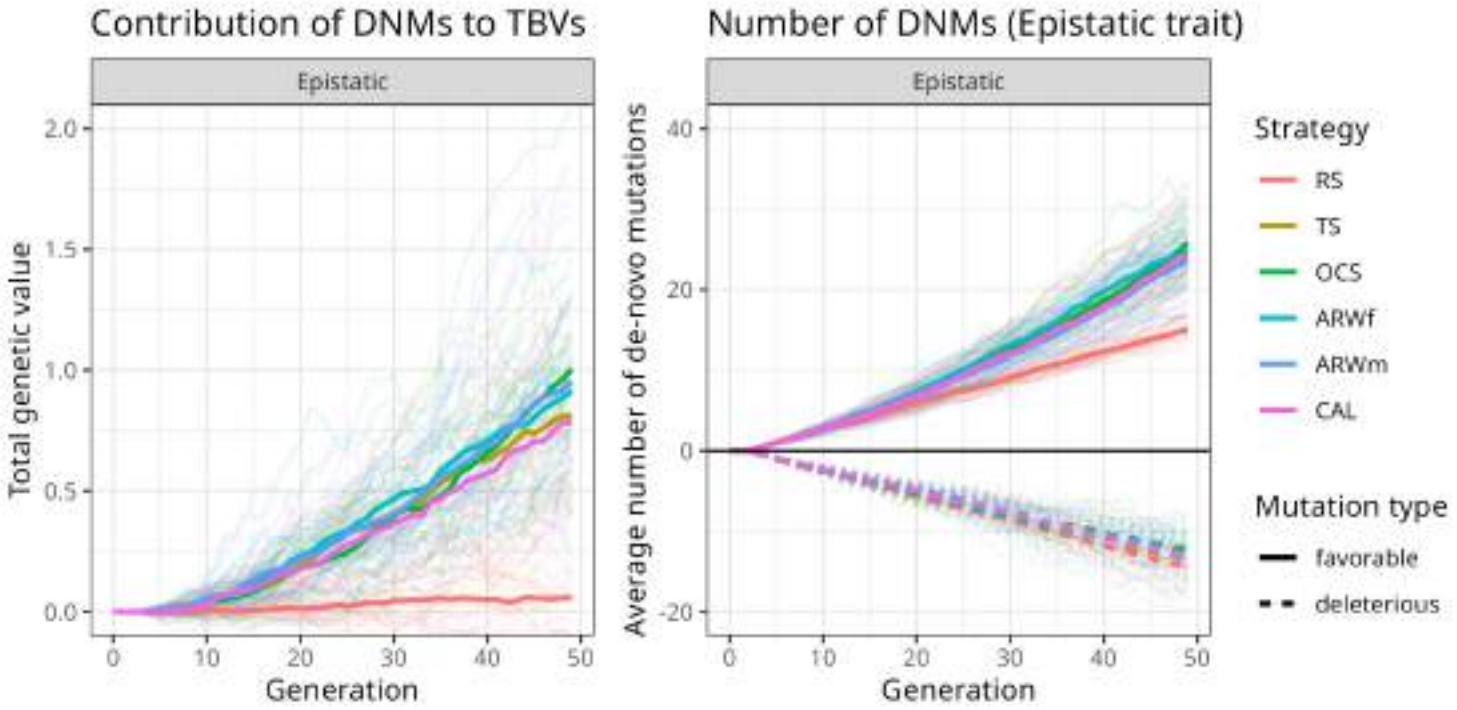
Selection of de-novo mutations



No strategy outperforms truncation selection on these metrics

All selection strategies are applying pressure on the mutations

Selection of de-novo mutations



Considering traits with non-additive effects, selection of DNMs becomes more challenging

CAL selection has the lowest and OCS the highest contribution of DNMs to TBVs

For the fully additive trait

- Truncation selection starts with higher gains,
  - Saturates earlier and gain is surpassed by a reweighting strategy.
- Allelic reweighting is an effective strategy for long term selection,
  - Even if working with markers rather than causal loci.
- No strategy is significantly more effective at keeping favourable de-novo mutations segregating,
  - Although they are all slowly purging the deleterious mutational load.

For the trait with epistasis

- Allelic reweighting remains an effective strategy for long term selection,
  - Even while favorable alleles change through generations.
- Optimal contribution outperforms truncation's long term genetic gain,
  - Which didn't happen for the fully additive trait.
- Purging deleterious mutations becomes more challenging for all the selection criteria explored,
  - Possibly due to a combination of lower narrow-sense heritability and changes in which rare alleles are estimated to be favorable.

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Thank you for your attention

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Extra Slides

Truncation selection (TS)

Maximizes average EBVs from selected candidates
without any consideration of diversity management

We estimated SNP effects (**β**) with the phenotypes
of the 3 previous generations (by means of a SNPBLUP model)

And selected the 100 top sires and 100 top dams for:

GEBVs = **Xβ**

Optimal contribution selection (OCS)

Maximize average EBVs from selected candidates
with a constraint on the candidates' coancestry

Maximize $\mathbf{g} = \mathbf{c}'\mathbf{X}\boldsymbol{\beta}$
$K_t \geq \frac{1}{2}\,\mathbf{c}'\mathbf{G}\mathbf{c}$
$\mathbf{Q}\mathbf{c} = [\frac{1}{2}\ \frac{1}{2}]'$
$\mathbf{c} \geq 0$
where $K_t = K_{t-1}+(1-K_{t-1})/(2Ne)$, using Ne=60

From Meuwissen, et al. (2020) "Management of genetic diversity in the era of genomics."

Allele re-weighting (ARW)

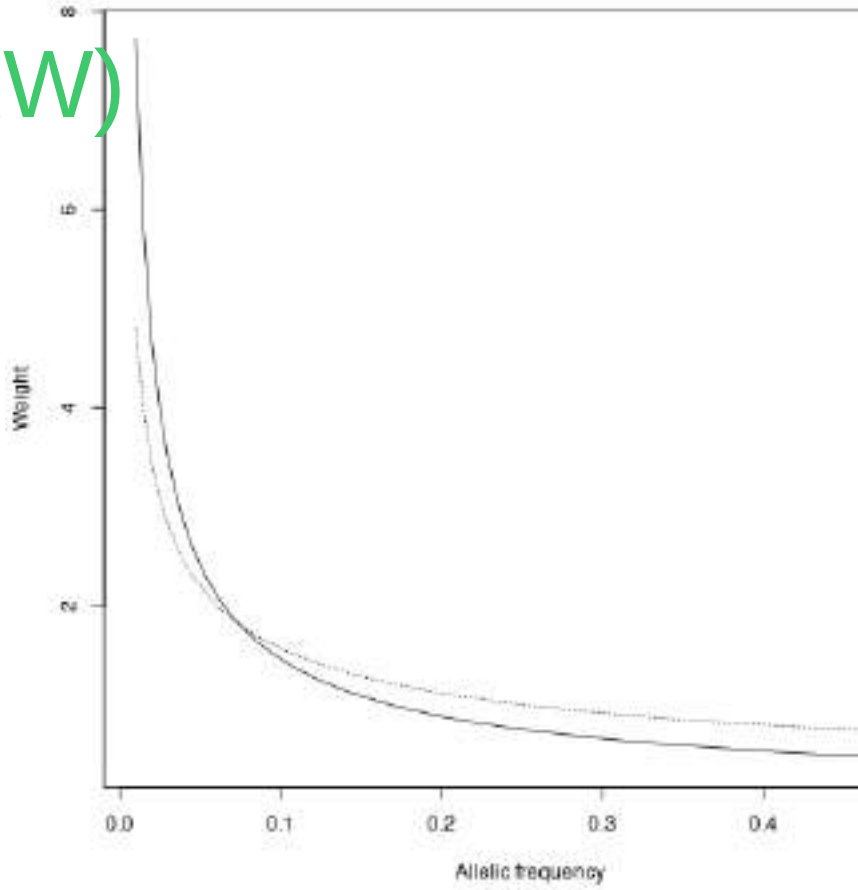
Marker effects of rare allels re-weighted according to Liu et al., 2015

$W_{jj} \propto 1/p_j^{c(t)}$

where c(0) = 0.5 and c(T) = 0.0
and p_j is the freq of the favourable allele.

wGEBVs = **XWβ**

(years to horizon; dotted line: 5 years , solid line: 20 years)



Allele re-weighting (ARW)

Included two variants of this strategy, using different definitions for the time horizons:

- ARWf (fixed): using the full length of the simulation of 50 generations, as the time horizon.
- ARWm (moving): using a moving horizon, always 5 generations ahead.

Constrained allele loss (CAL)

Maximize average EBVs from selected candidates with a constraint on the loss of rare (favourable) alleles.

Maximize $\mathbf{g} = \mathbf{c}'\mathbf{X}\boldsymbol{\beta}$

$L \geq \mathbf{c}'\mathbf{X}\boldsymbol{\alpha}$

$\mathbf{Q}\mathbf{c} = [½\ ½]'$

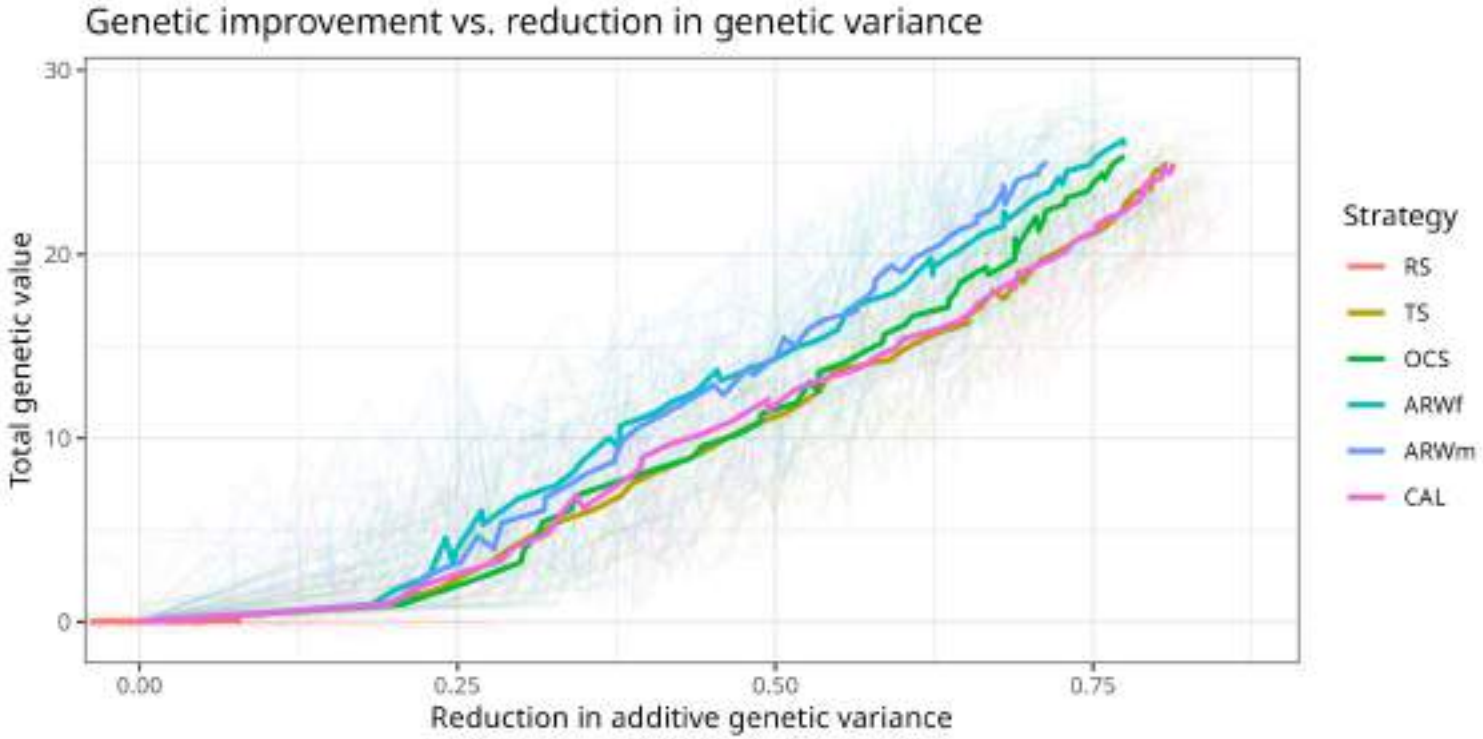
$\mathbf{c} \geq 0$

(logarithm with offset log(1/n + x))

where $\alpha_j = -\log(1/n * (1 + (\mathbf{J}'\mathbf{X})_j))$ [if $\beta_j \geq 0$],

$L = 1.10 * 1/n * (\mathbf{J}'\mathbf{X}\boldsymbol{\alpha})$, and $\mathbf{J}$ is an n-length vector of ones.

Genetic gain vs. genetic variance



ARW strategies allow effective trade-off between increased genetic gain and conservation of genetic variance