



TOWARDS IMPROVEMENT OF **RUMINANT** BREEDING
THROUGH **GENOMIC** 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
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Led to think that

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

Previous works

Compared mass selection, pedigree selection and genomic selection

Mulder et al., (2019) Genetics

Wientjes et al., (2022) GSE

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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

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Current work

- Assessment of different genomic selection strategies

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

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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

Liu et al., (2015) GSE

(2 versions: *fixed* and *moving* time horizon)

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

novel strategy

of rare favourable alleles

*plus Random selection (RS) for reference

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

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The Traits

Additive

Normally distributed additive effects, with a common variance.

Dominant

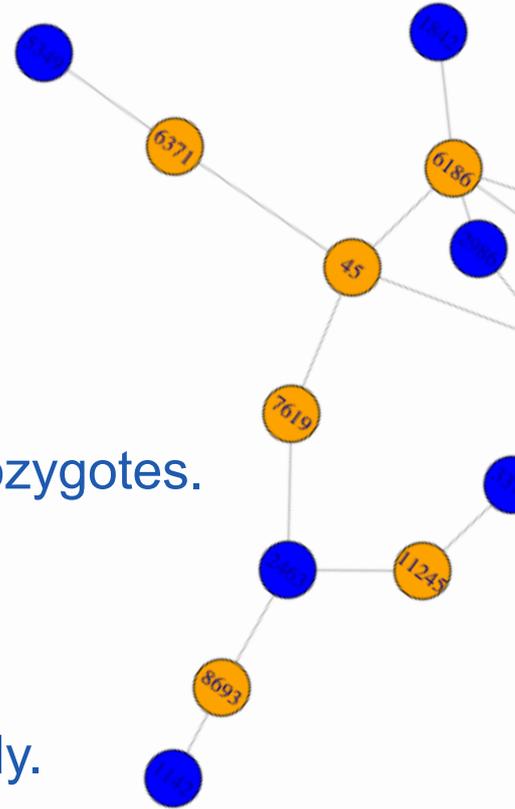
Includes dominance effects, with a small positive bias for heterozygotes.

Epistatic

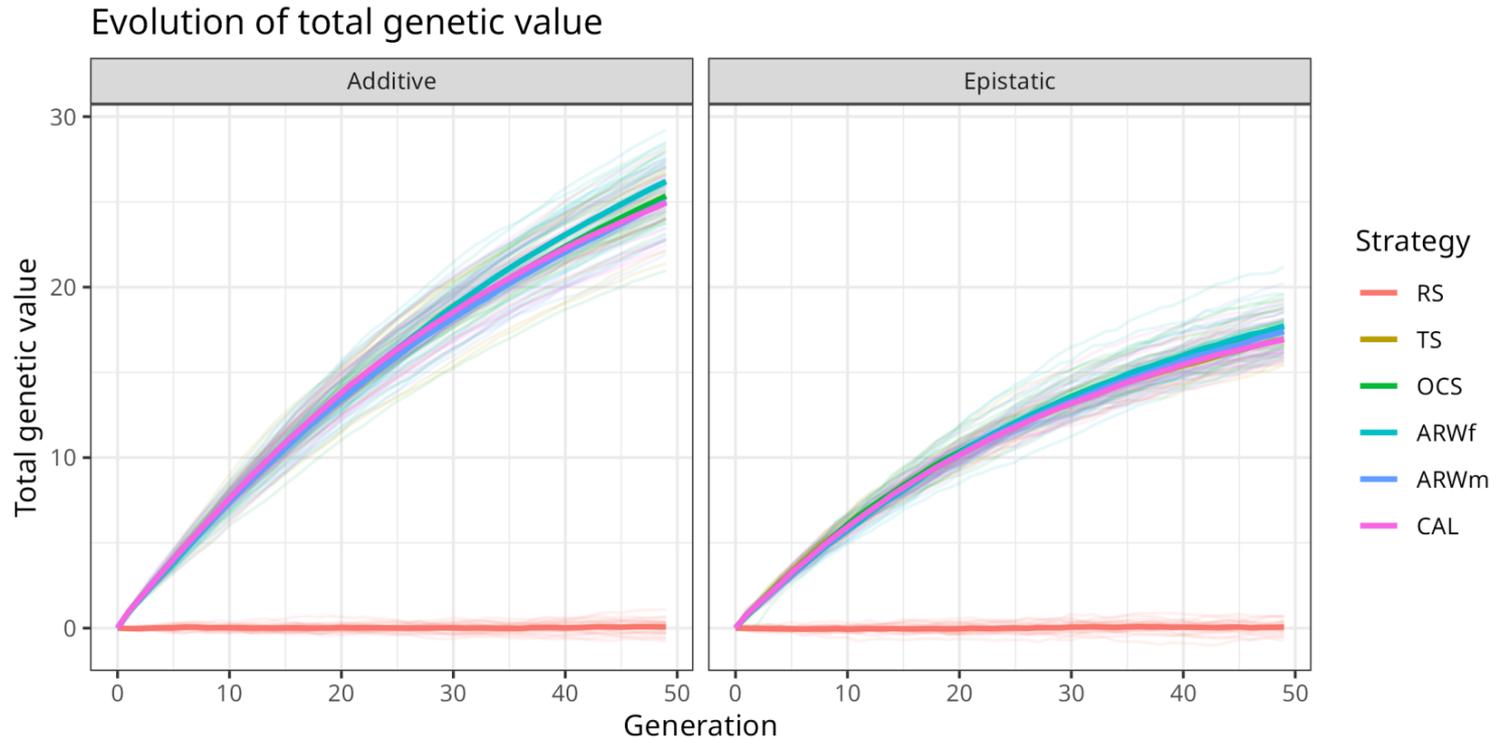
Includes pairwise interactions, with connectivity pattern taken from a yeast study.

Traits specifications taken from Wientjes, et al. 2022

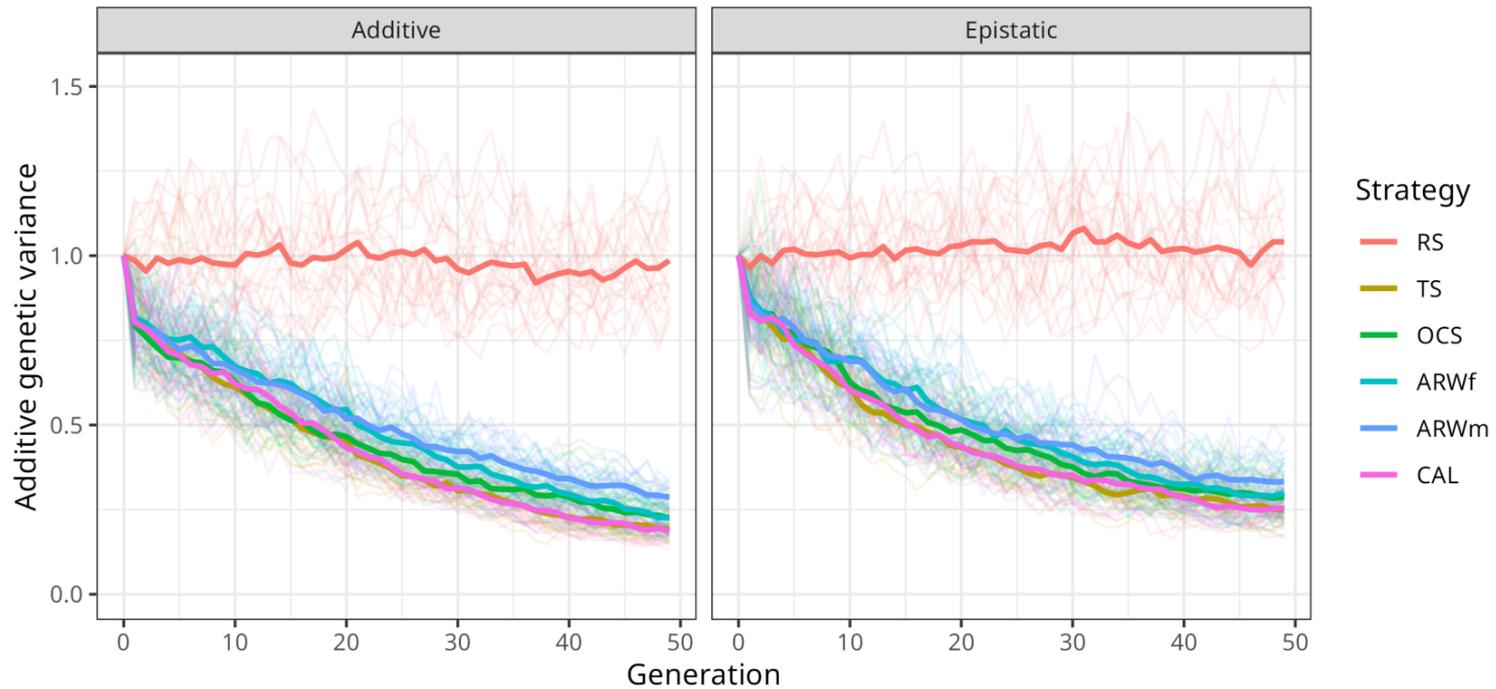
Yeast study in Costanzo et al., 2016



Results & Discussion

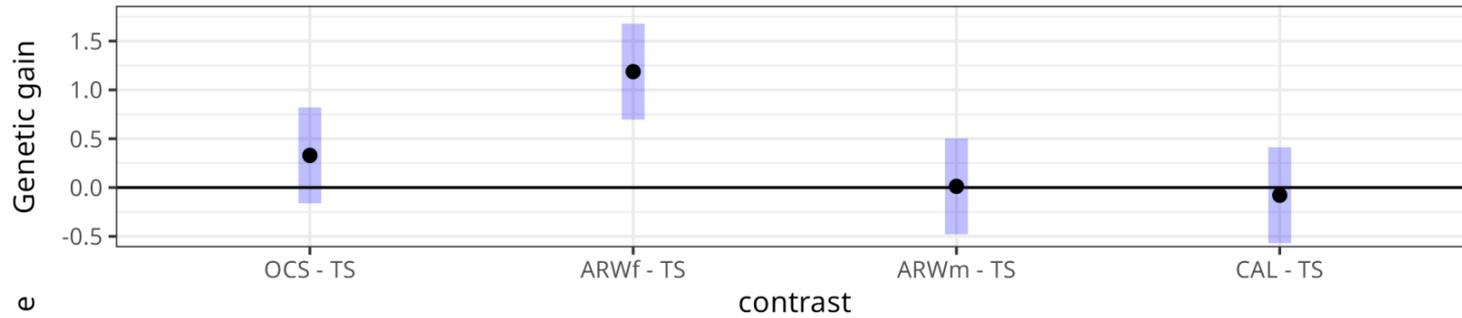


Evolution of additive genetic variance



Genetic gain vs. genetic variance

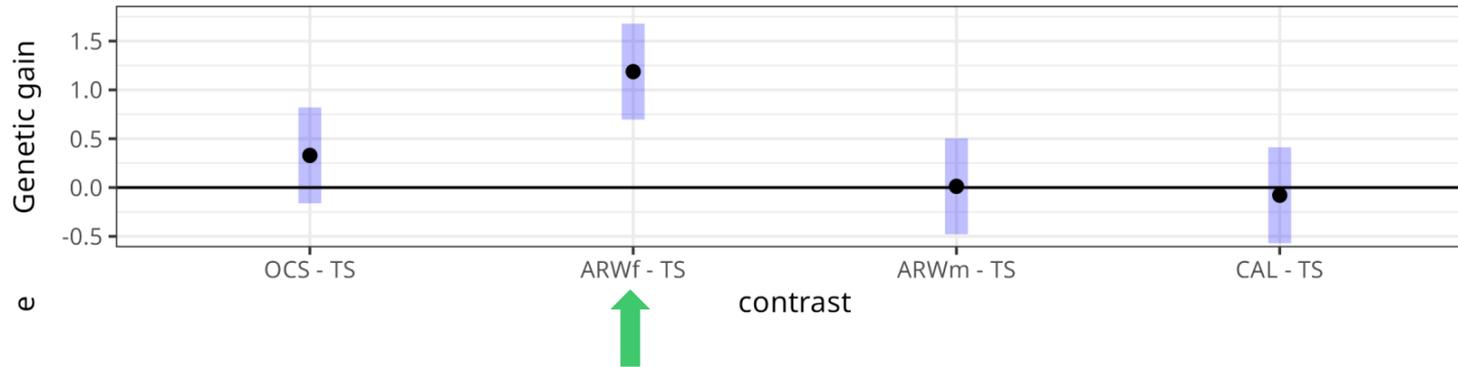
Alternative strategies compared with truncation selection (Additive)



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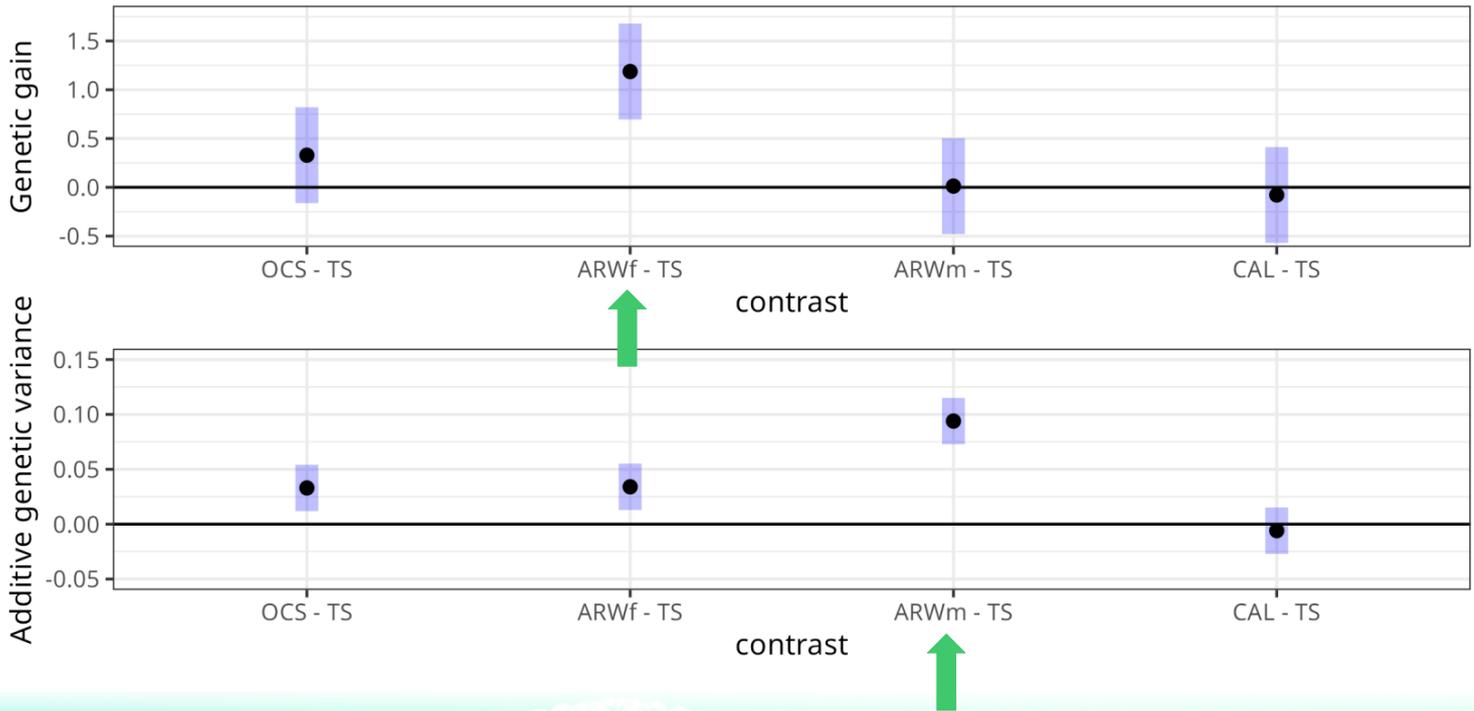
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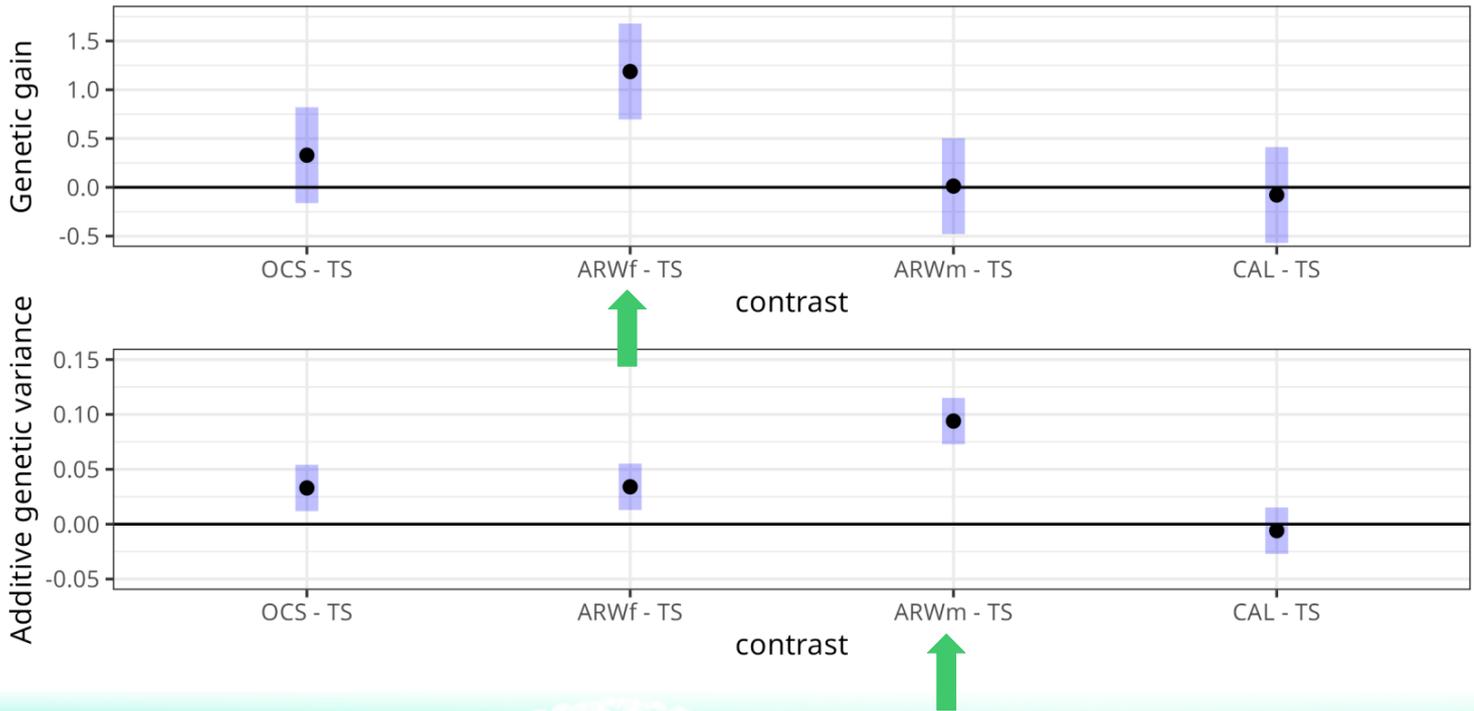
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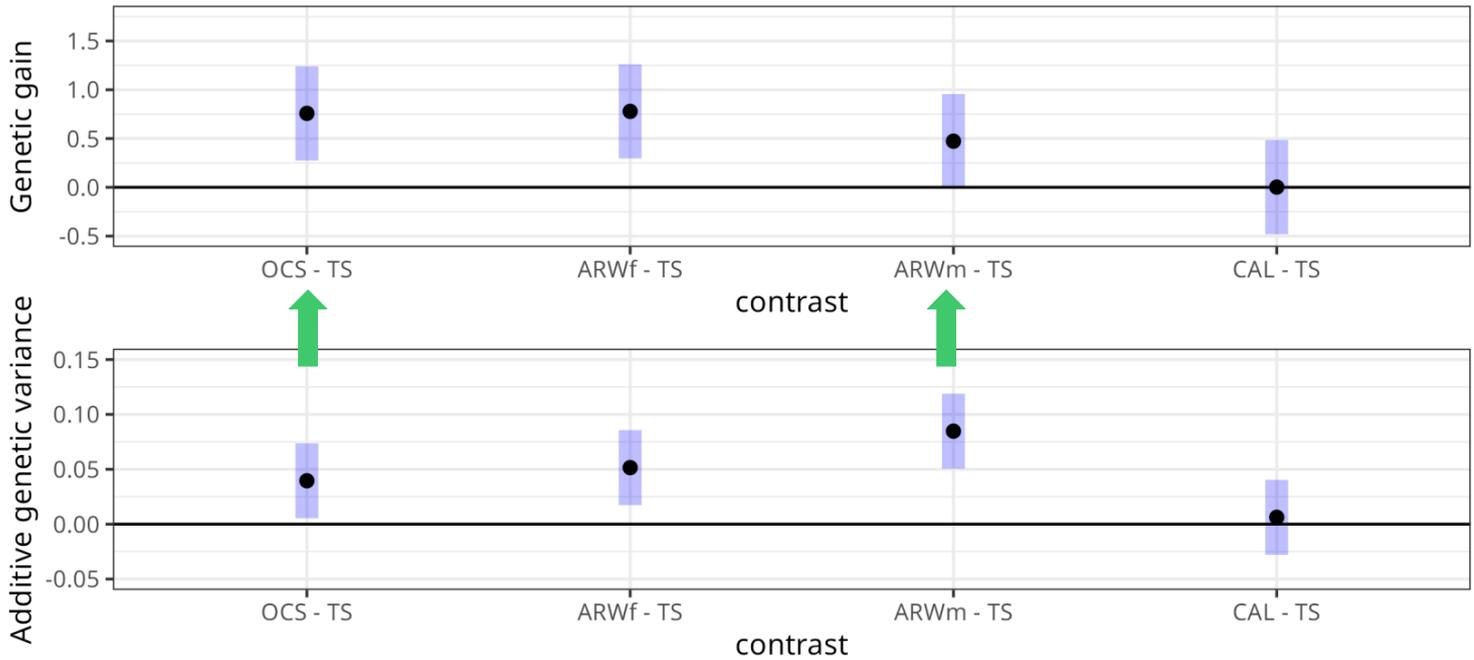
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ARW strategies allow effective trade-off between increased genetic gain and conservation of genetic variance

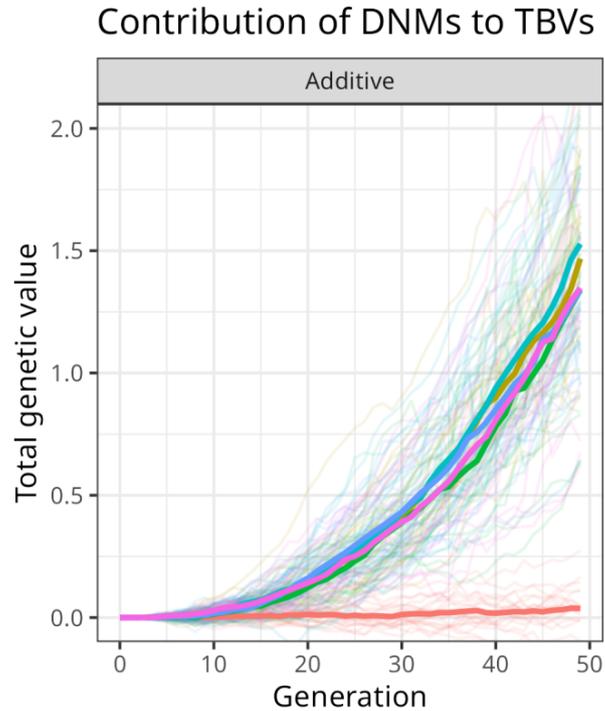
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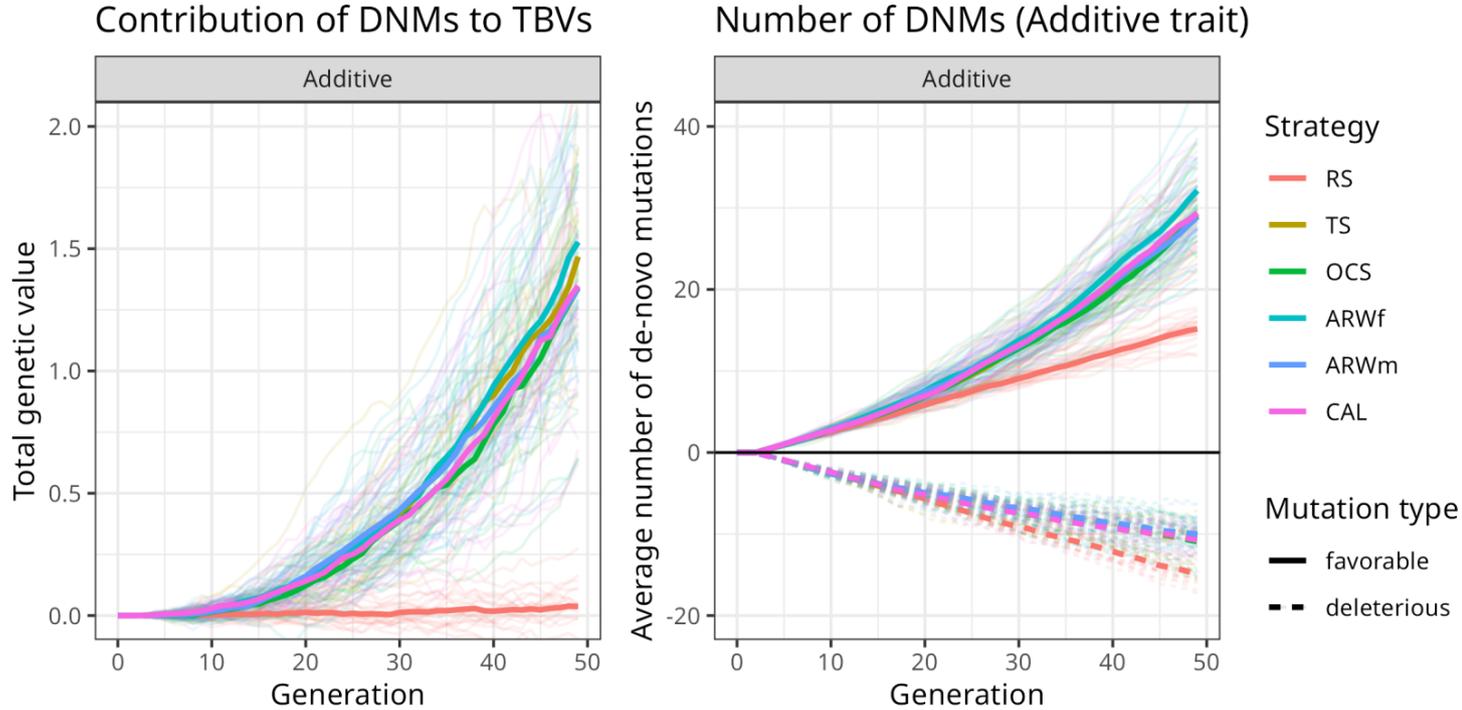


Considering traits with non-additive effects improves the assessments of OCS and ARWm for genetic gain

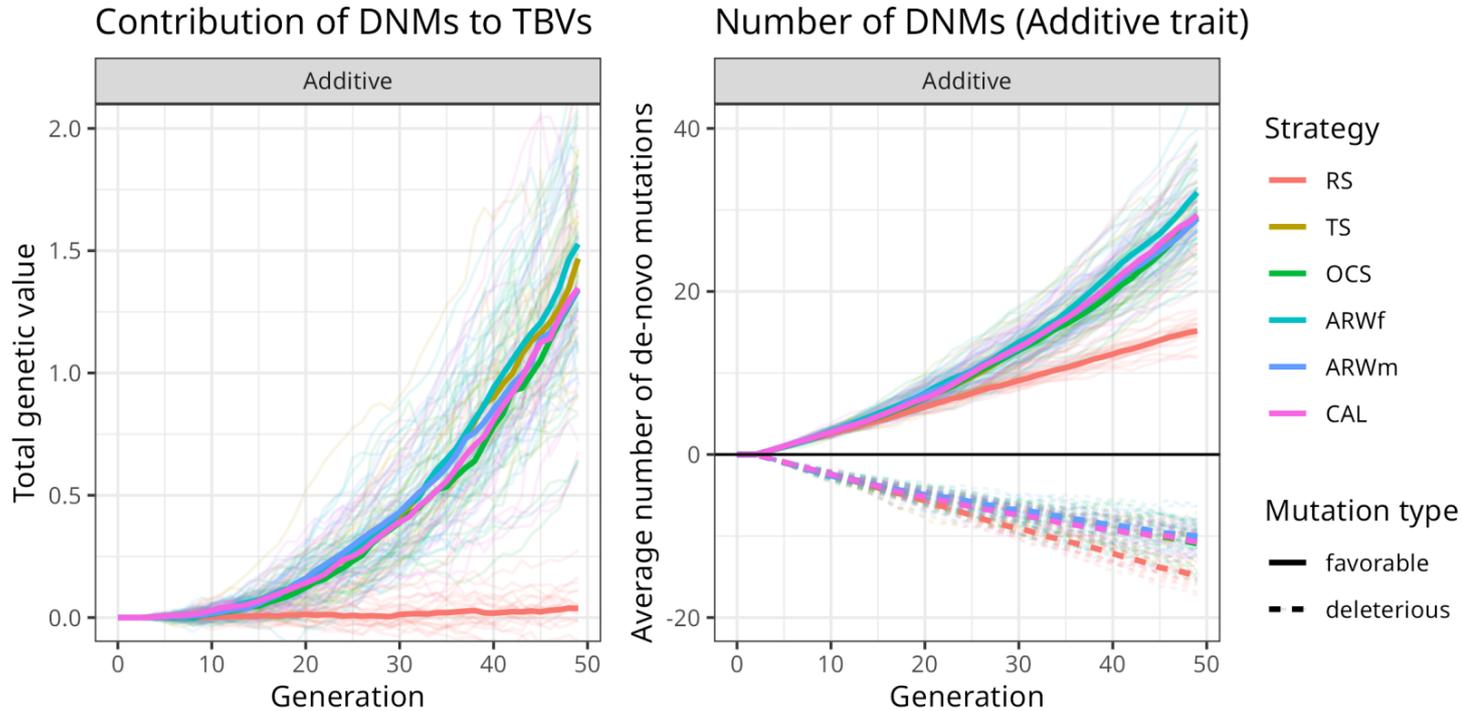
Selection of de-novo mutations



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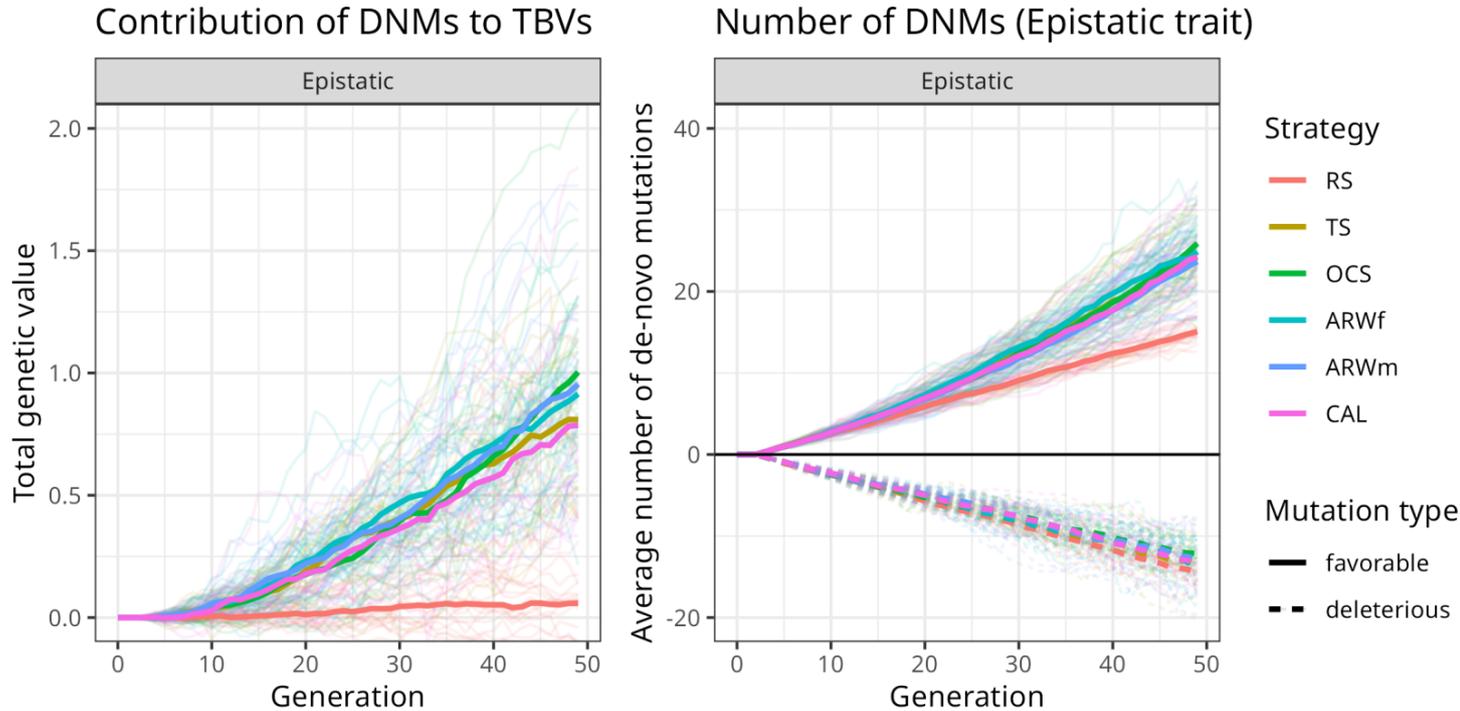
Selection of de-novo mutations



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:

$$\text{GEBVs} = \mathbf{X}\beta$$

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)

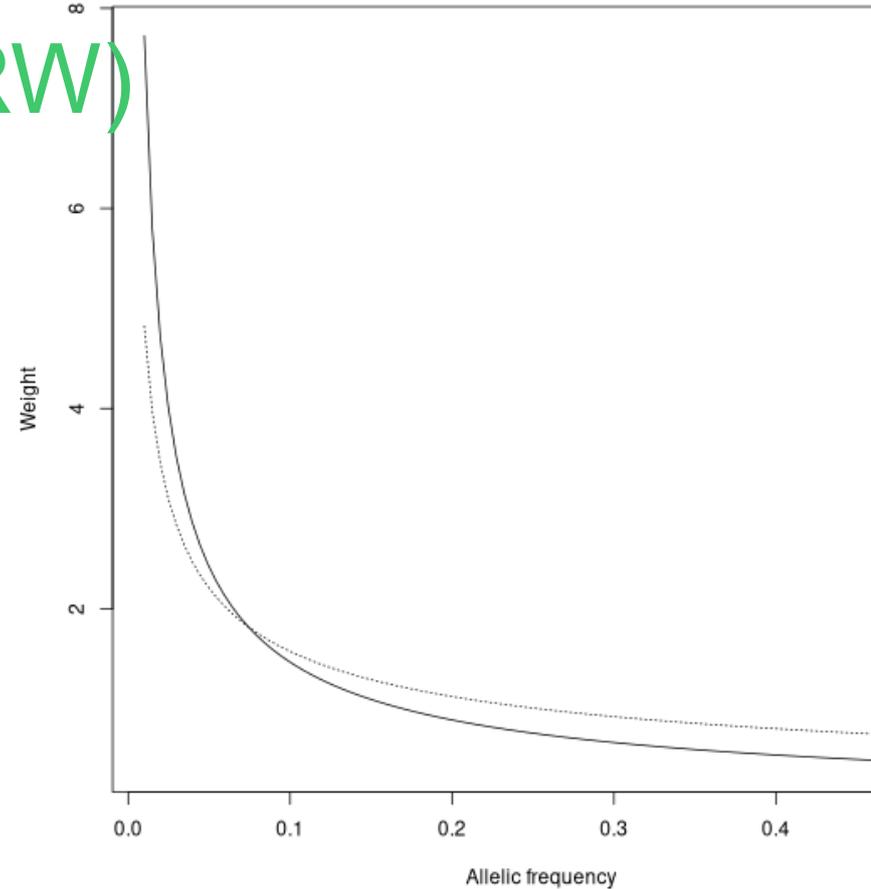
Marker effects of rare alleles re-weighted according to Liu et al., 2015

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

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

$$w\text{GEBVs} = \mathbf{xw}\boldsymbol{\beta}$$

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

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

$\mathbf{Qc} = [\frac{1}{2} \ \frac{1}{2}]'$

$\mathbf{c} \geq 0$

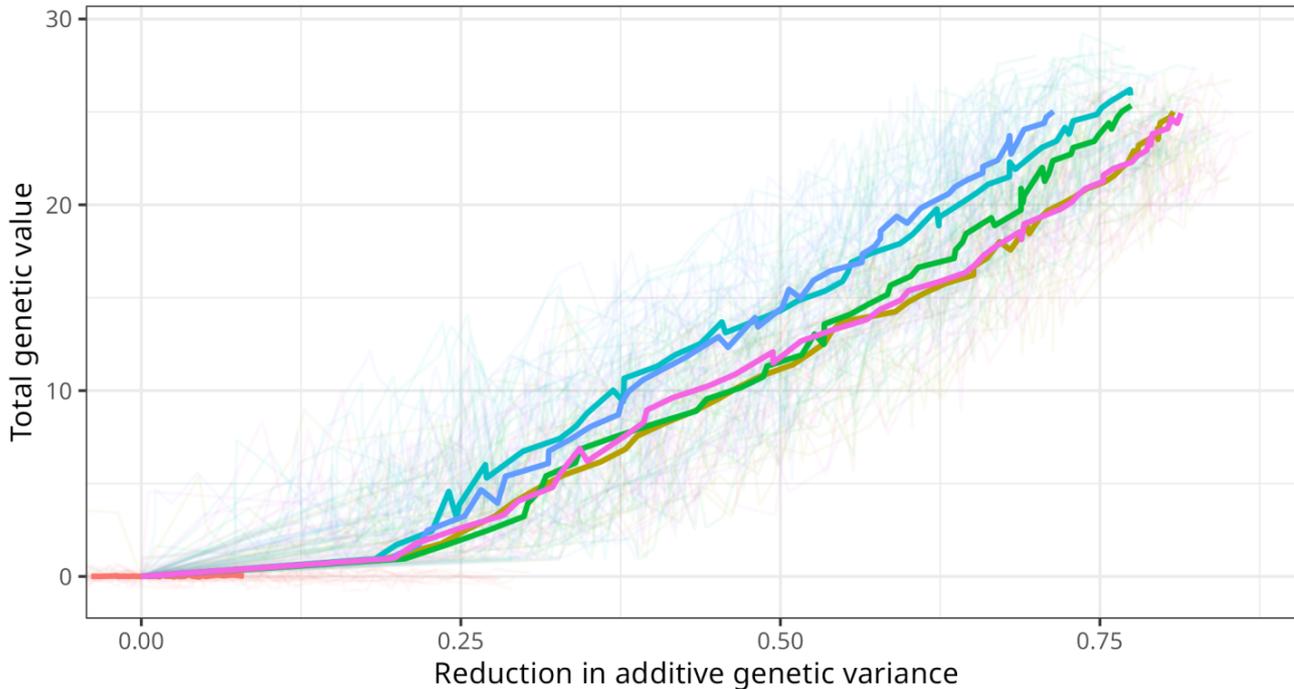
(logarithm with offset $\log(1/n + x)$)

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

Genetic improvement vs. reduction in genetic variance



- Strategy
- RS
 - TS
 - OCS
 - ARWf
 - ARWm
 - CAL

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