Metafounders

MiX99 course on genomic prediction

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March 9, 2026

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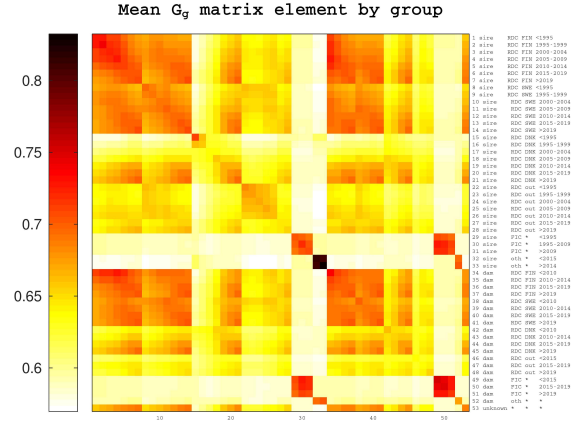
Contents

- Why metafounders are needed.
- What metafounders are.
- How to estimate metafounder relations.
- With dairy and beef population examples.

Why: Pedigree relations vs. Genomic relations

- Mean **genomic relations**.
- Nordic Red Dairy Cattle (RDC).
- Grouped in:
  - Sex.
  - Breed.
  - Country of origin.
  - Year classes.



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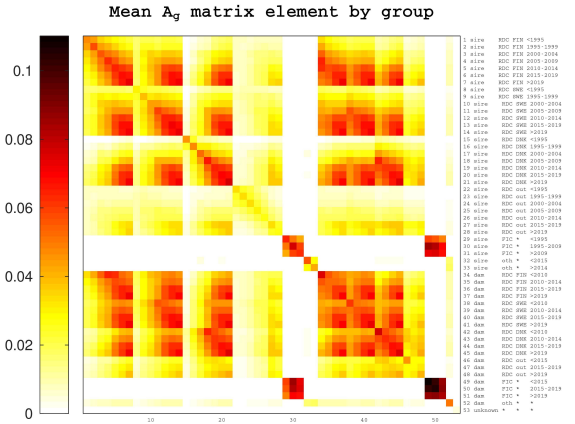
Why: Pedigree relations vs. Genomic relations



- Mean **pedigree relations**.
- Pedigree relations seem to have similar structures as the genomic relations.

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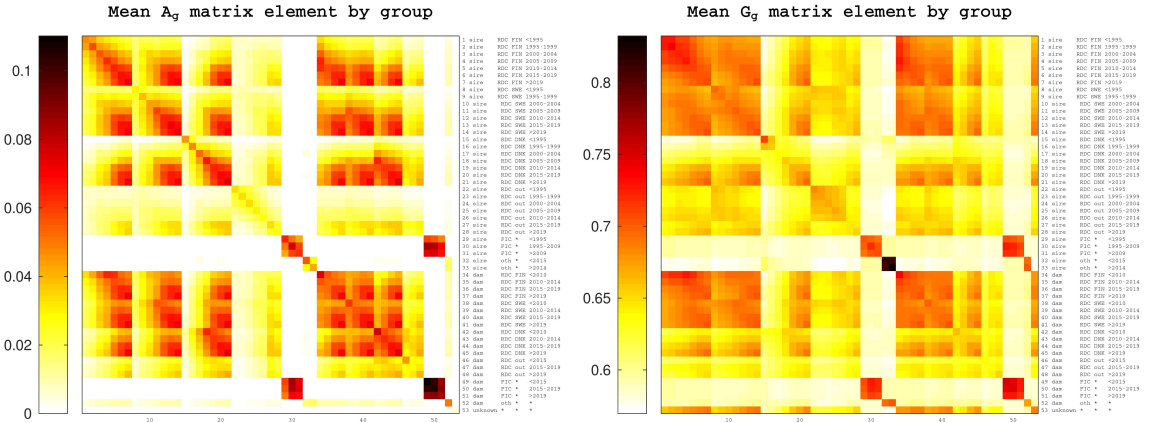
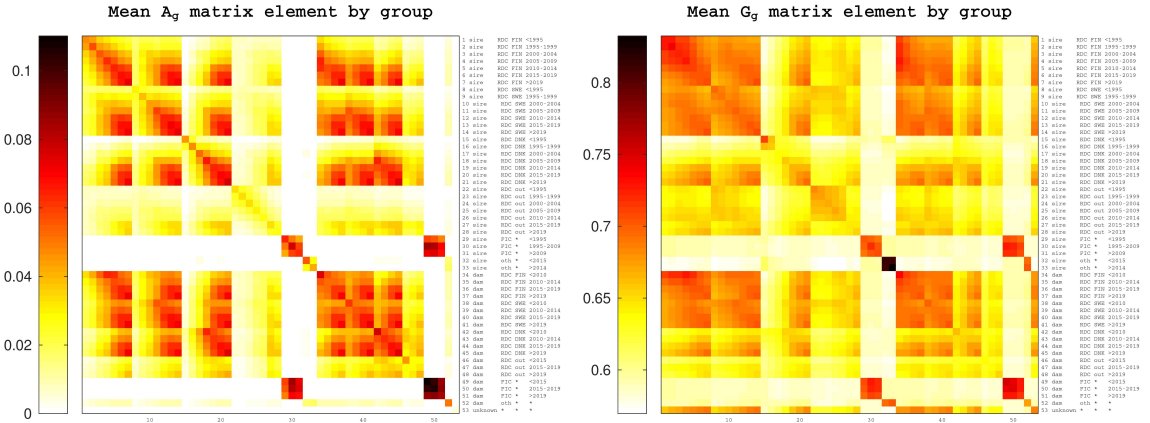
Why: Pedigree relations vs. Genomic relations



- Pedigree relations (left) are much smaller than genomic relations (right).

Why: Pedigree relations vs. Genomic relations

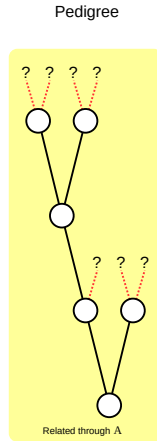


- Pedigree relations (left) are much smaller than genomic relations (right).
- Goal for metafounders: make this difference smaller.

Why: Incomplete pedigree relations

- In traditional breeding value models individuals are related through **pedigree relationship matrix** $\mathbf{A}$.

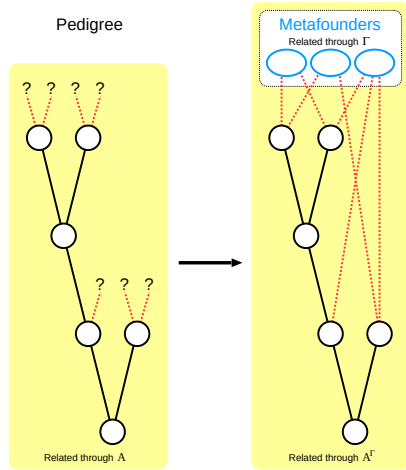
- Pedigree relationships are incomplete:
  - Some parents are unknown.
  - Oldest are assumed to be unrelated.



Why: Supplementing pedigree with genomic data

Metafounders concept:

- Unknown parents replaced with "metafounder" **ancestor groups**.
- Metafounders are assumed to be related through so called **Gamma matrix Γ**.
- Γ matrix needs to be estimated from the genomic information.



Why: Γ "corrected" pedigree relations ($\mathbf{A}^{\Gamma}$ matrix)

- Pedigree relations can be efficiently expressed using very **sparse matrices**.

Pedigree relations:

$$\mathbf{A}^{-1} = \mathbf{L}\mathbf{D}\mathbf{L}', \quad \mathbf{L} = \mathbf{I} - \frac{1}{2}\mathbf{P}$$

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- Metafounder "corrected" pedigree relations, $\mathbf{A}^{\mathbf{\Gamma}}$ matrix, has similar very efficient form.

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$\mathbf{\Gamma}$ "corrected" pedigree relations:

$$(\mathbf{A}^{\mathbf{\Gamma}})^{-1} = \mathbf{L}_{\mathbf{\Gamma}} \begin{bmatrix} \mathbf{\Gamma}^{-1} & 0 \\ 0 & \mathbf{D}_{\mathbf{\Gamma}} \end{bmatrix} \mathbf{L}'_{\mathbf{\Gamma}}$$

Why: $\mathbf{\Gamma}$ "corrected" pedigree relations ($\mathbf{A}^{\mathbf{\Gamma}}$ matrix)

- Pedigree relations can be efficiently expressed using very **sparse matrices**.
- Metafounder "corrected" pedigree relations, $\mathbf{A}^{\mathbf{\Gamma}}$ matrix, has similar very efficient form.
- $\mathbf{\Gamma}$ matrix needs to be invertible.

Pedigree relations:

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How many metafounder groups?

- Unknown parents in pedigree are **classified** to metafounder groups.
- Number of metafounder groups depends on:
  - Variation in population.
  - Amount of genomic contributions.
  - Old unknown parent groups.

Grouping examples:

- Country of origin.
- Breed.
- Sex.
- Year classes.
- . . .

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- Enough metafounders to separate subpopulations.

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How many metafounder groups?

- Unknown parents in pedigree are **classified** to metafounder groups.
- Number of metafounder groups depends on:
  - Variation in population.
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- Enough metafounders to separate subpopulations.
- But metafounders may need to be distinguishable.

Grouping examples:

- Country of origin.
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- Year classes.
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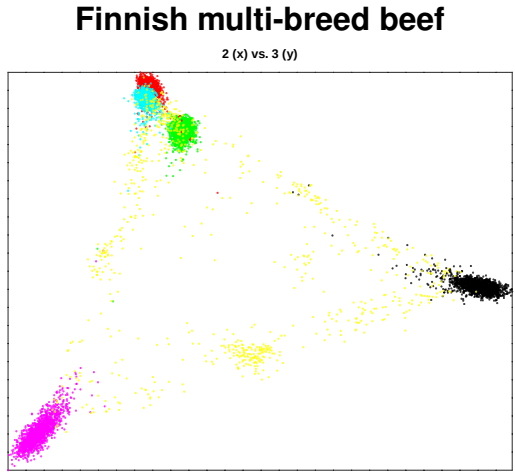
Principal Component Analysis of genomic data

Princical Component Analysis of genomic data can be used to check that:

- Breeds can be separated.



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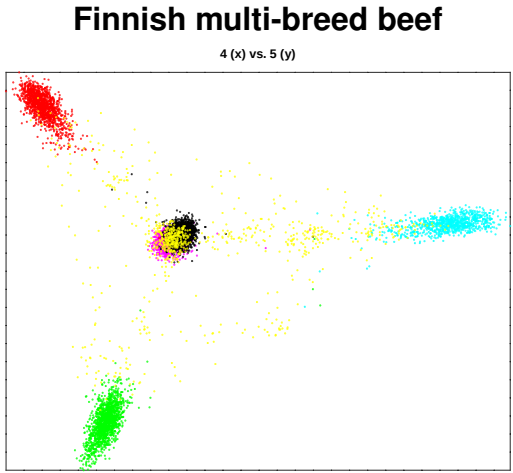

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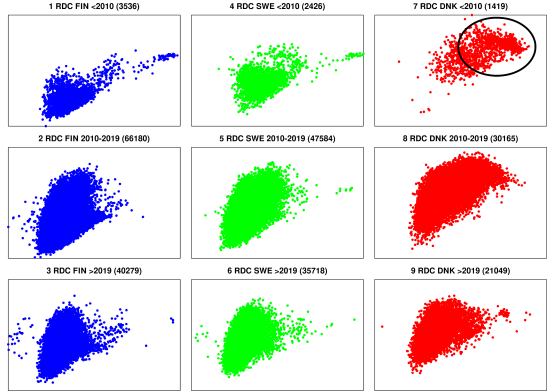
- Breeds can be separated.
- There are differences between countries and year classes.

Nordic Red Dairy Cattle (RDC)



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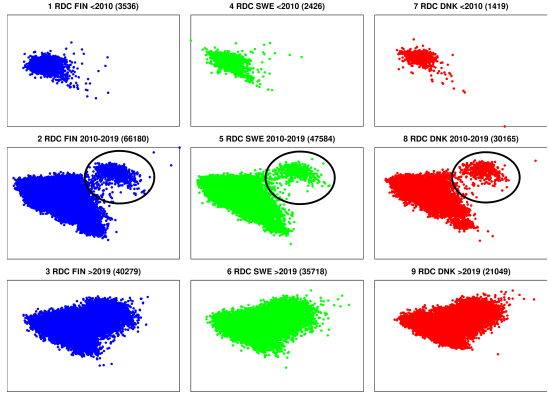
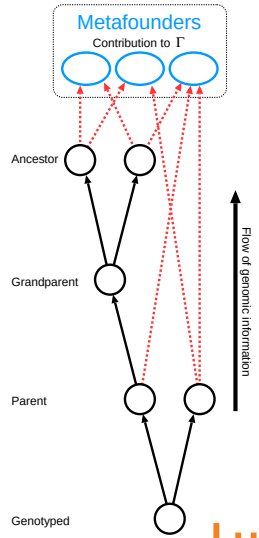


Flow of genomic information to metafounders

Metafounder relations estimated from pedigree using **base population allele frequencies**:



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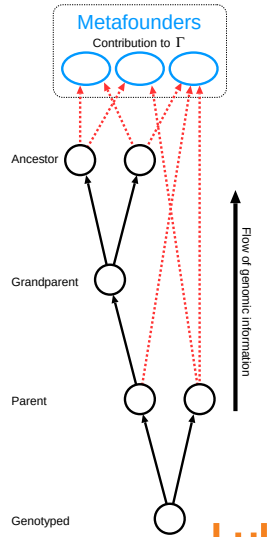

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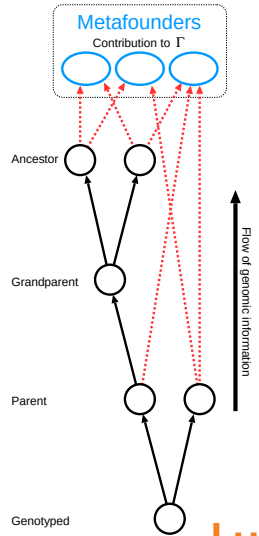

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Metafounder relations estimated from pedigree using **base population allele frequencies**:

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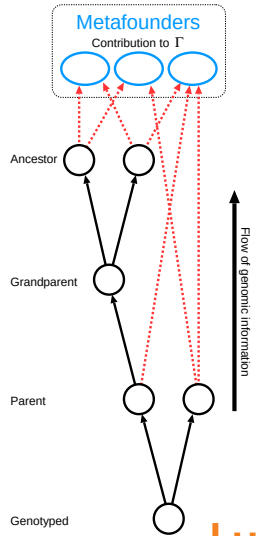
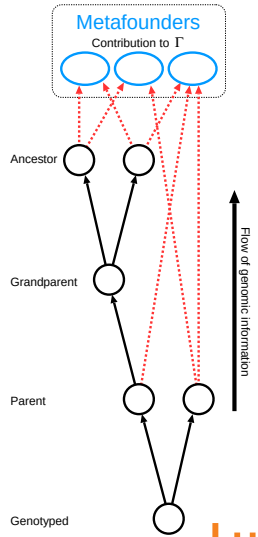
- Then from parents to grandparents and other ancestors.
- Genomic contributions are channeled to metafounders through missing parents in the pedigree.



Flow of genomic information to metafounders

- Metafounder relations can be estimated from smaller pedigree of genotyped and their ancestors.



Flow of genomic information to metafounders

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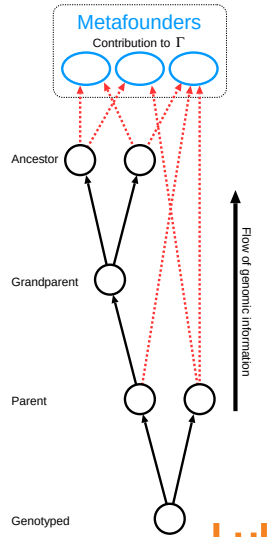
- Enough missing parents and genomic contributions for each metafounder:



Flow of genomic information to metafounders

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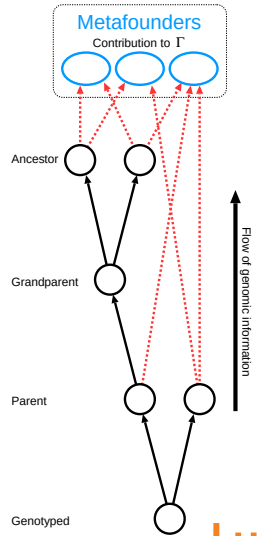
  - ► No missing parents $\Rightarrow$ no contributions.



Flow of genomic information to metafounders

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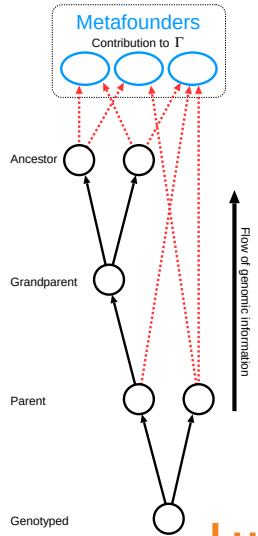
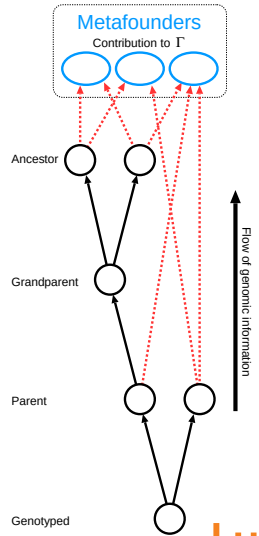


Flow of genomic information to metafounders

- Metafounder relations can be estimated from smaller pedigree of genotyped and their ancestors.
- Enough missing parents and genomic contributions for each metafounder:
  - No missing parents $\Rightarrow$ no contributions.
  - Evaluation pedigree may have missing parents even if none in $\mathbf{\Gamma}$ estimation pedigree!
- Metafounders get genomic contributions also from other group's genotypes:
  - Important for older metafounder groups.



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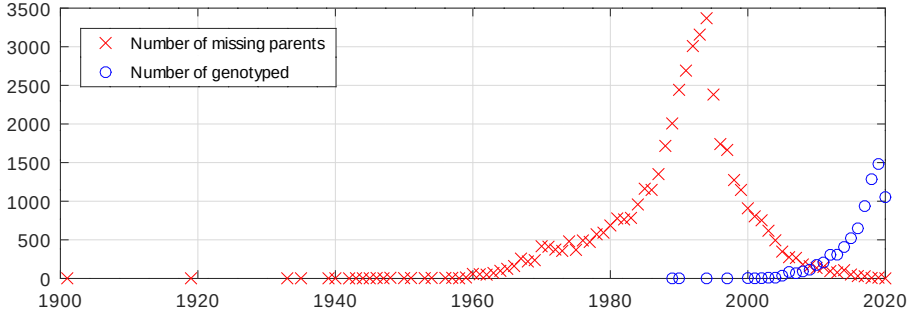
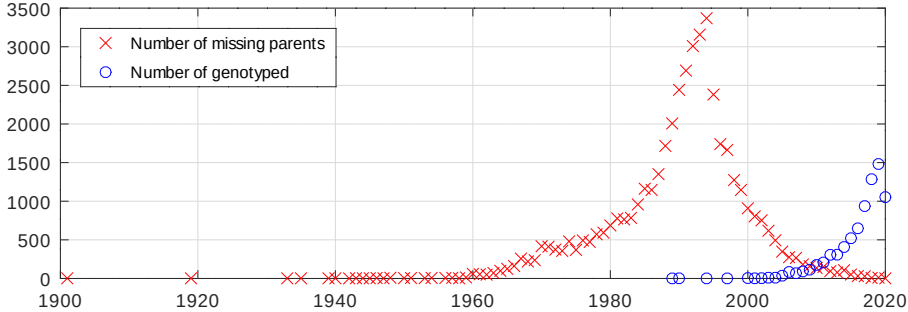


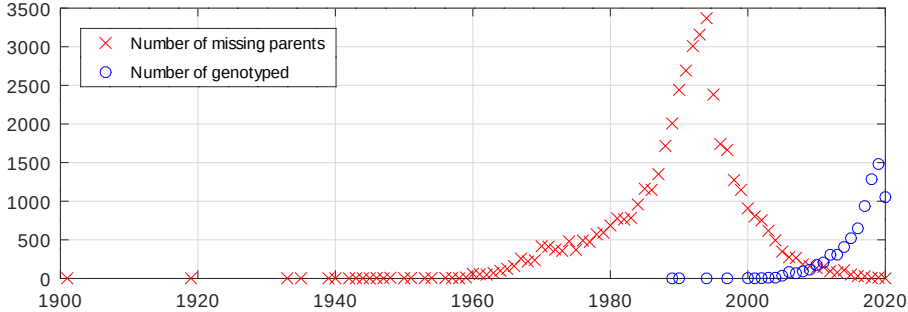
- Genotyped animals (blue) are mostly from last few years.

Flow of genomic information to metafounders



- Genotyped animals (blue) are mostly from last few years.
- Missing parents (red) in pedigree can be quite far in past.

Flow of genomic information to metafounders



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- Metafounder relations need to be estimated 30 years ago.

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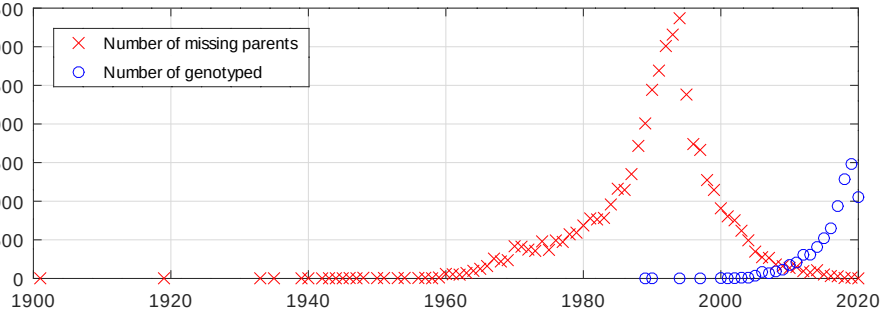

- Genotyped animals (blue) are mostly from last few years.
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- Metafounder relations need to be estimated 30 years ago.
- Note: Avoid **pruning** pedigree to certain depth.

Estimating metafounder relations from genotypes

Estimating metafounder relations:

- MiX99 companion utility: `Bpop`

```
# Calculate base population allele frequencies:
LOG="$(OUTPUTFILE).log"
echo                                                                    >&2
echo "Base polulation allele frequencies (Bpop):"                       >&2
echo " - Pedigree   file: $(basename $PEDIGREE)"                        >&2
echo " - Inbreeding file: $(basename $INBREEDING)"                      >&2
echo " - Genotype   file: $(basename $GENOFILE)"                        >&2
echo " - Output     file: $(basename $OUTPUTFILE)"                      >&2
echo " - Log        file: $(basename $LOG)"                             >&2
$(SCRIPT)/Bpop -CHM -nthr 4 -nospace 12 -F "$INBREEDING" -groups "$NGROUPS" \
       -a "$OUTPUTFILE" "$PEDIGREE" "$GENOFILE" >&2 > "$LOG"
```

Estimating metafounder relations from genotypes

Estimating metafounder relations:

- MiX99 companion utility: `Bpop`
- Pedigree: missing parents replaced with negative metafounder groups.

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- $\mathbf{\Gamma}$ matrix (or inverse): option `-gamma` (`-igamma`).

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- MiX99 companion utility: `Bpop`
- Pedigree: missing parents replaced with negative metafounder groups.
- $\mathbf{\Gamma}$ matrix (or inverse): option `-gamma` (`-igamma`).
- Or from base population allele frequencies: option `-a`.

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```

Allele frequencies $\mathbf{F}$:

$$\mathbf{F} = \begin{bmatrix} \mathbf{F}_1 & \mathbf{F}_2 & \cdots & \mathbf{F}_n \end{bmatrix}$$

Calculating $\mathbf{\Gamma}$ matrix from $\mathbf{F}$:

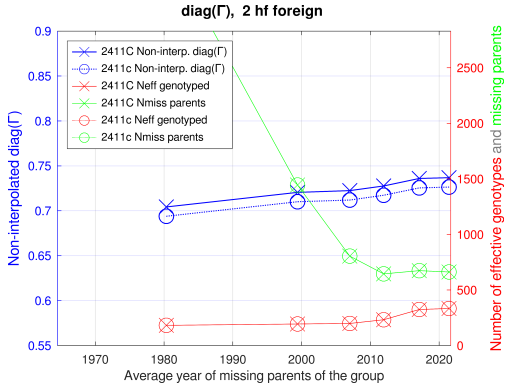
$$\mathbf{\Gamma} = 8 * \mathrm{cov}(\mathbf{F})$$

or

$$\mathbf{\Gamma} = \frac{8}{m} * (\mathbf{F} - \tfrac{1}{2})'(\mathbf{F} - \tfrac{1}{2})$$

Estimating metafounder relations from genotypes

Ensuring good coverage of genomic contributions:



Estimating metafounder relations from genotypes

Ensuring good coverage of genomic contributions:

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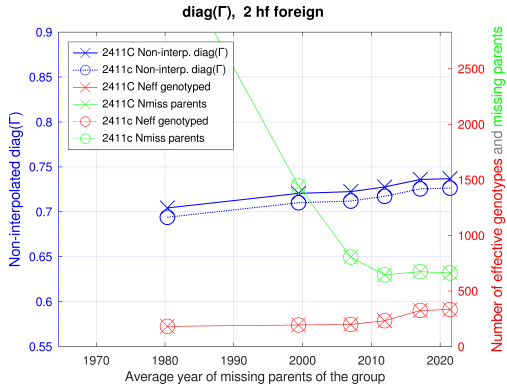
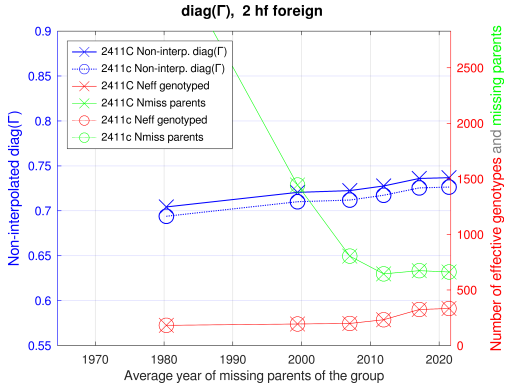


Estimating metafounder relations from genotypes

Ensuring good coverage of genomic contributions:

- Number of missing parents (green).
- Effective genomic contributions (red).

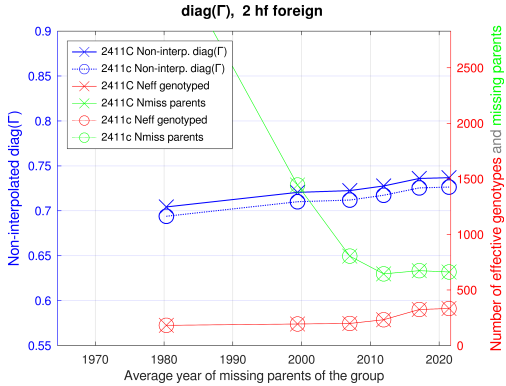



```
Number of genotyped animals,                    n : 15744
Effective number of genotyped animals,      n_m :  9524 9458
Effective number of genotyped contributions, f:  831.7358 175.9585
Proportion of effective N genotyped,      n_m/n :    60.49%   60.07%
Measure of direct genotyped,              f/n_m :     8.73%    1.86%
```

Estimating metafounder relations from genotypes

Ensuring good coverage of genomic contributions:

- Number of missing parents (green).
- Effective genomic contributions (red).
- Stability of Γ matrix values (blue).

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Measure of direct genotyped,             f/n_m :     8.73%    1.86%
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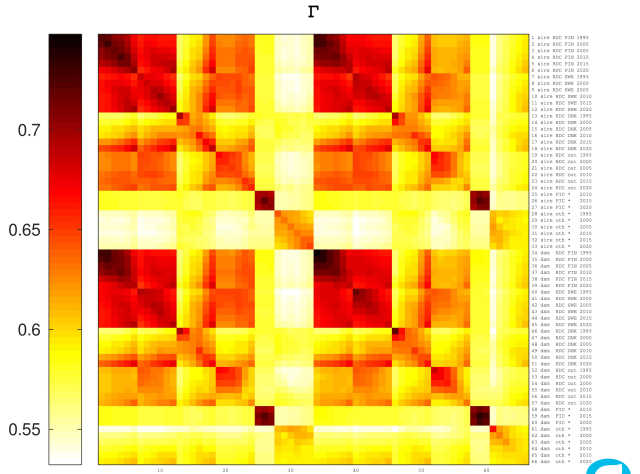
Estimated Γ matrix visualized using colors

- Nordic RDC.
- Metafounders needed to match old unknown parent groups.
- 66 metafounders:
  - Sires and dams.
  - RDC, Finncattle, and other breeds.
  - 3 Nordic countries and outside.
  - Year classes.



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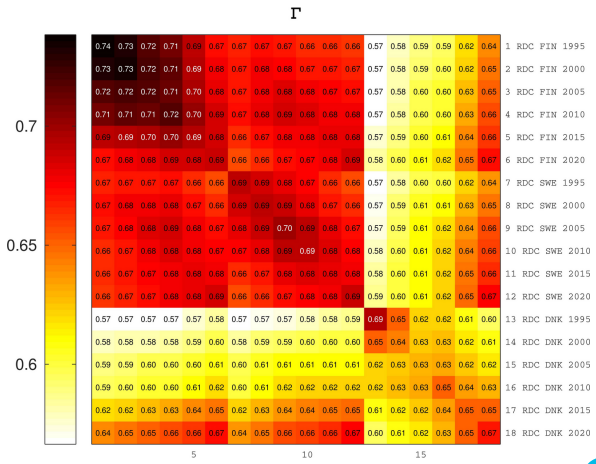
Estimated Γ matrix shows population dynamics

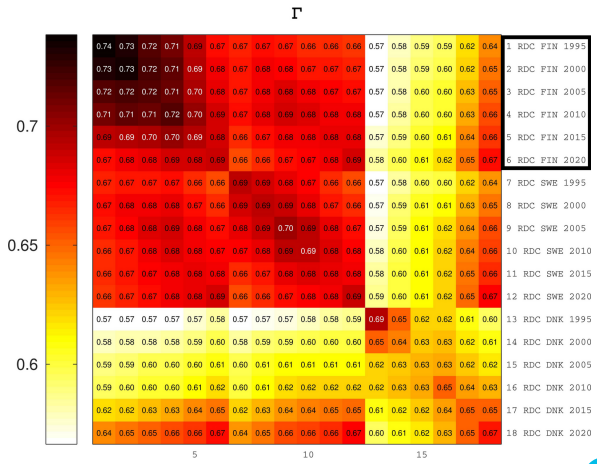
Estimated Γ matrix (partial):



Estimated Γ matrix shows population dynamics

Estimated $\mathbf{\Gamma}$ matrix (partial):

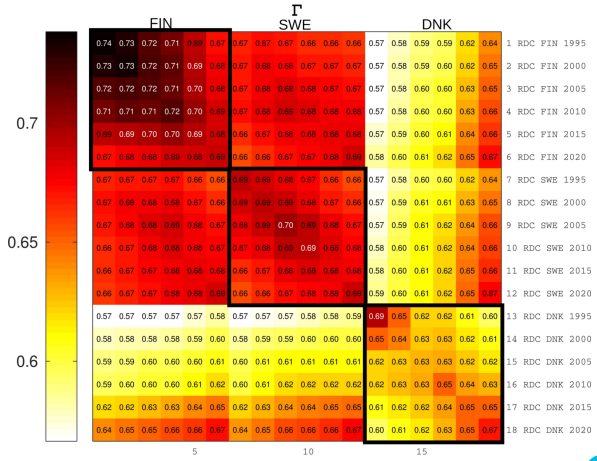
- 6 year classes.



Estimated Γ matrix shows population dynamics

Estimated Γ matrix (partial):

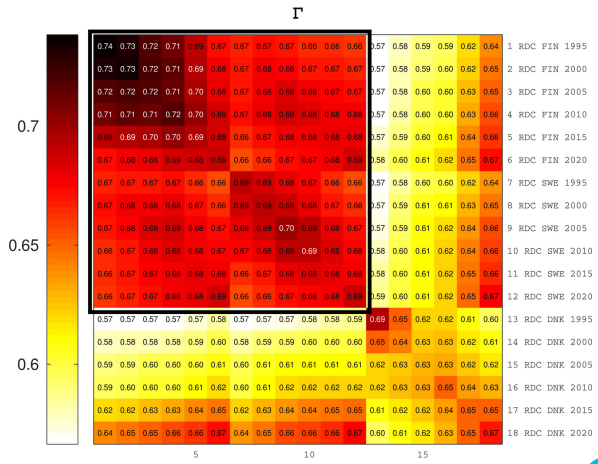
- 6 year classes.
- FIN, SWE, and DNK:



Estimated Γ matrix shows population dynamics

Estimated Γ matrix (partial):

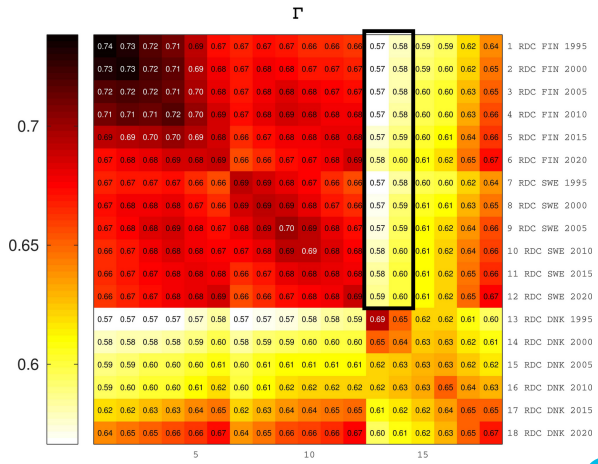
- 6 year classes.
- FIN, SWE, and DNK:
  - FIN and SWE more closely related.



Estimated Γ matrix shows population dynamics

Estimated Γ matrix (partial):

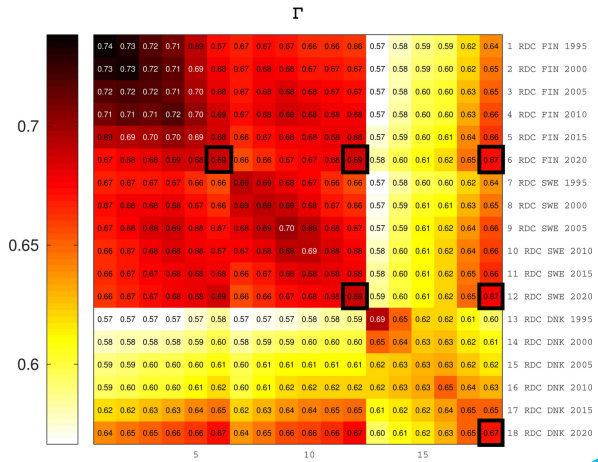
- 6 year classes.
- FIN, SWE, and DNK:
  - ► FIN and SWE more closely related.
- Older DNK less related to FIN/SWE.



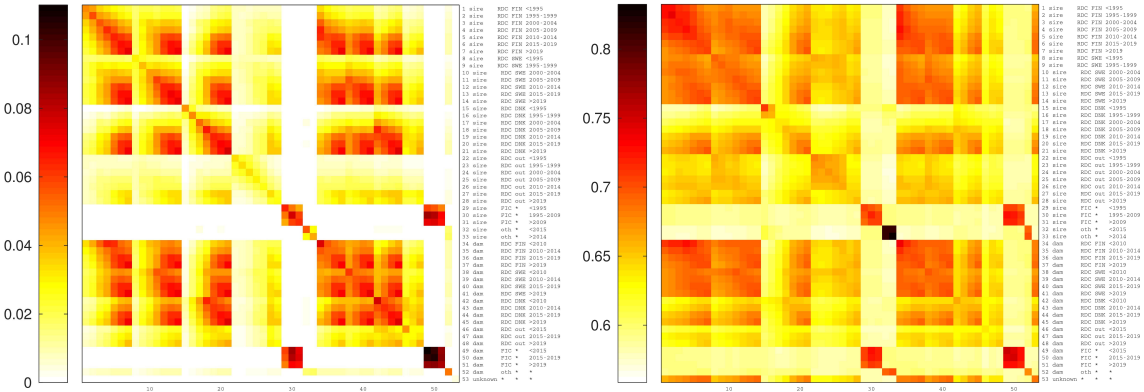
Estimated Γ matrix shows population dynamics

Estimated Γ matrix (partial):

- 6 year classes.
- FIN, SWE, and DNK:
  - ► FIN and SWE more closely related.
- Older DNK less related to FIN/SWE.
- Newest year classes more closely related in all 3e countries.

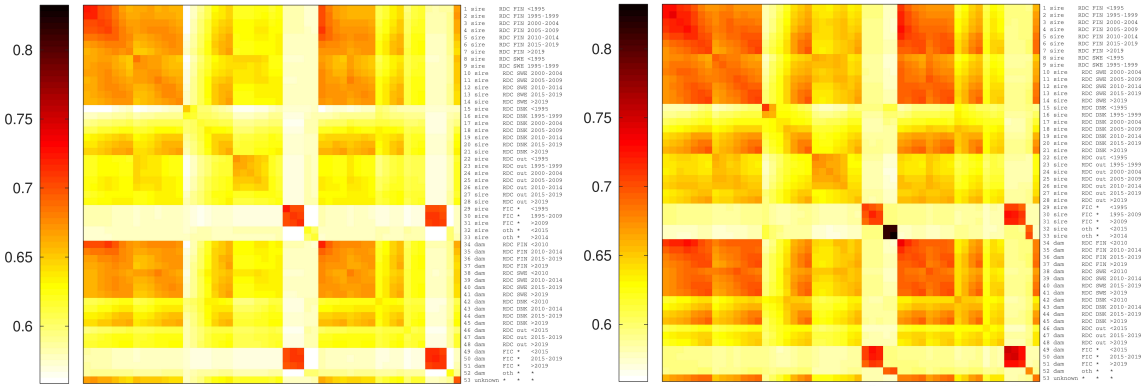


Γ "corrected" pedigree vs. genomic relations



- Average pedigree relations ($\mathbf{A}$, left) were much smaller than average genomic relations (right).

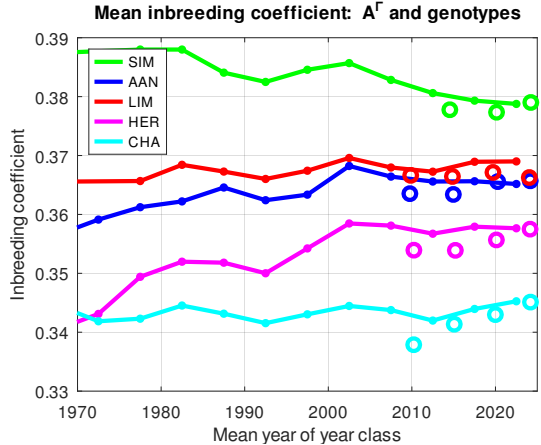
Γ "corrected" pedigree vs. genomic relations



- With metafounders average pedigree relations ($\mathbf{A}^{\mathbf{\Gamma}}$, left) are much closer to average genomic relations (right).

Γ "corrected" pedigree vs. genomic inbreeding

- Finnish multi-breed beef.
- Comparing average **inbreeding coefficients**:
  - Metafounder "corrected" pedigree inbreeding (lines).
  - Genomic inbreeding (circles).
- With metafounders average inbreeding coefficients are close to genomic coefficients.



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