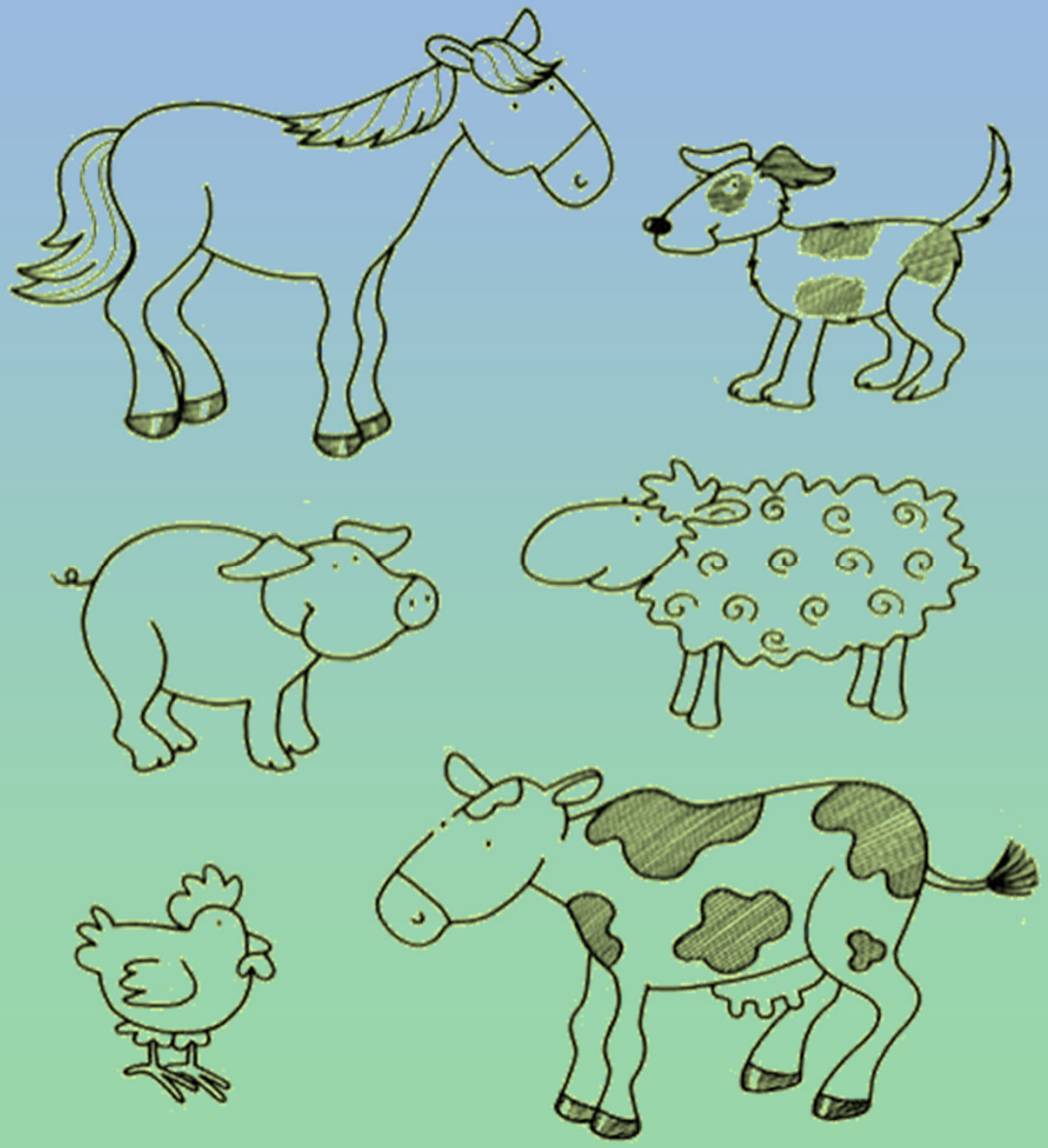
Genomic characterization of animal genetic resources

Johannes A. Lenstra, Utrecht University

FAO Webinar December 14, 2022



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New FAO guidelines: most comprehensive description of

Sample → DNA isolation → dataset (SNPs, WGS) → analysis

The FAO Guidelines will be recommended in the Authors' Guidelines of the ISAG journal Animal Genetics

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- Datasets more and more powerful
- Analysis more and more sophisticated
- Basic analysis still relies on the golden trio

1. PCA → survey, clines
2. Model Based Clustering (STRUCTURE, ADMIXTURE) → Genomic components
3. Genetic distances → Breed relationships, phylogeny

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But:

1. **What's in a breed?** Check prior to downstream analysis!

2. The basic analyses by **PCA and Model Based Clustering (STRUCTURE, ADMIXTURE)** are often distorted by uneven sampling and inbreeding and are often misinterpreted

3. NeighborNet of **F_{ST} genetic distances** + **f_3 / f_4 / BSAA** are the most informative methods for inferring genetic history

1. What's in a breed?

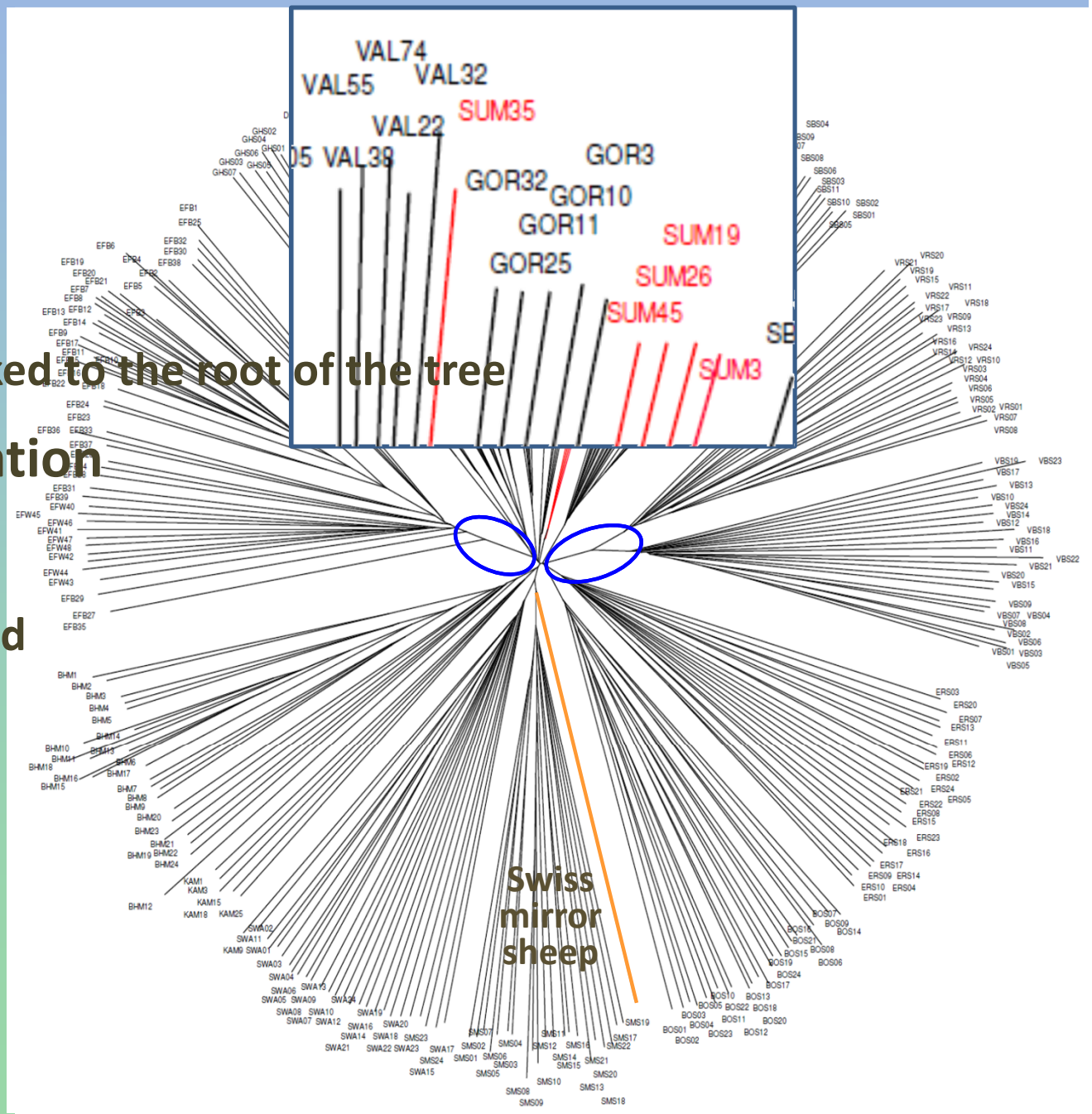
← NJ trees of allele sharing distances

Errors

- identical samples
- mislabelling
- crossbred outliers linked to the root of the tree

Pattern of differentiation

- genetic isolation →
- PCA, ADMIXTURE spoiled by inbreeding bias



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⚠ **Errors**

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- 😟 **mislabelling**
- 😟 crossbred **outliers** linked to the root of the tree

🔍 **Pattern of differentiation**

- 🙂 genetic **isolation** → 😟 PCA, ADMIXTURE spoiled by **inbreeding bias**
- 😯 degree of breed differentiation

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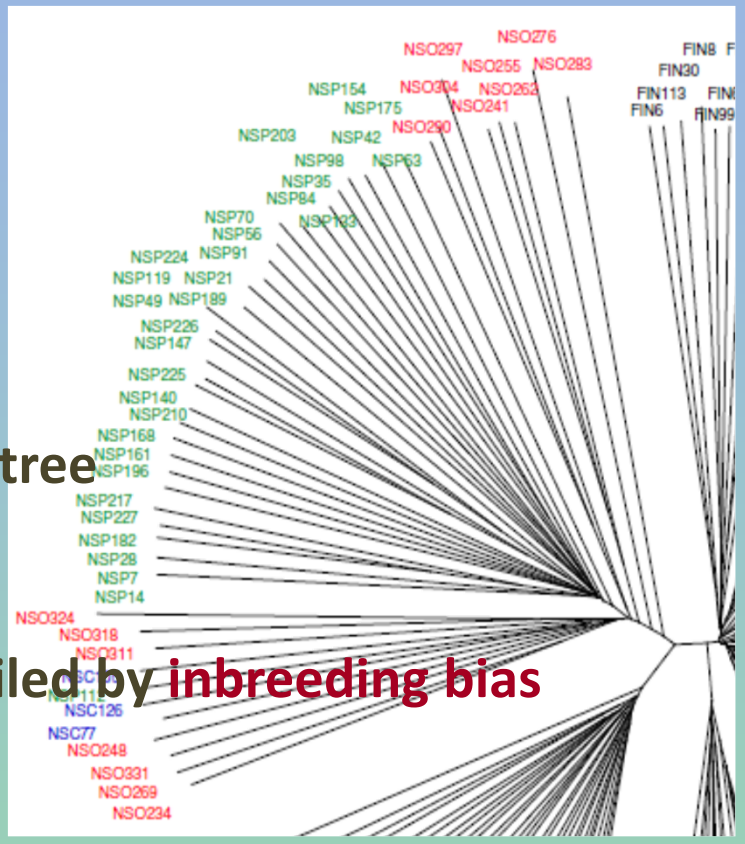

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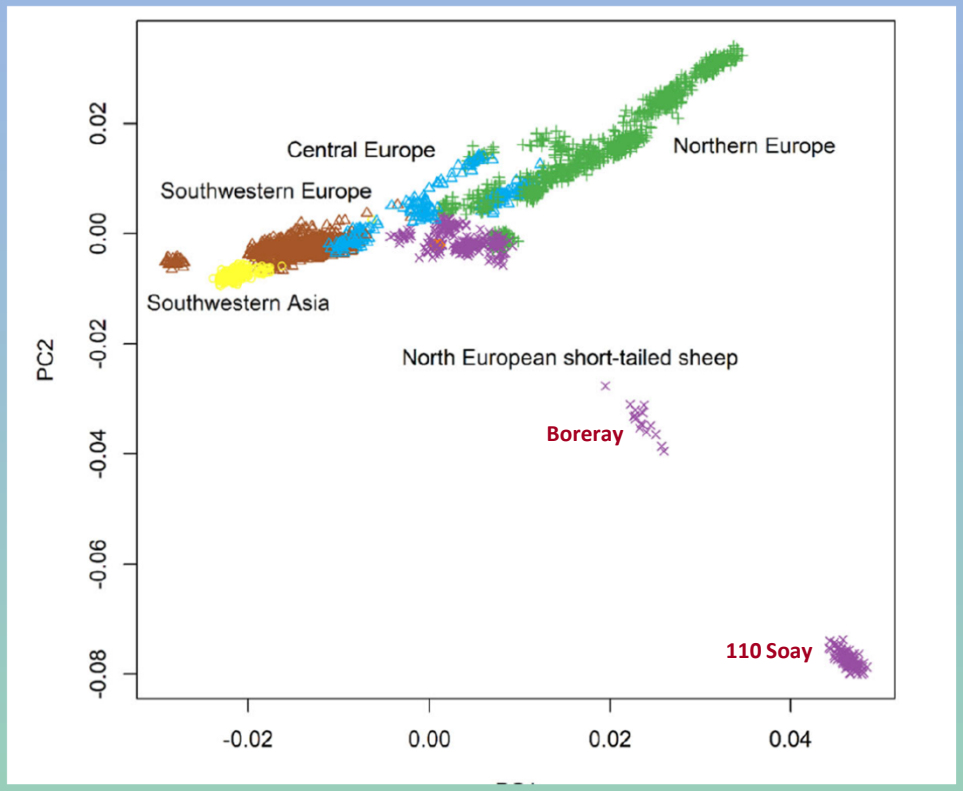
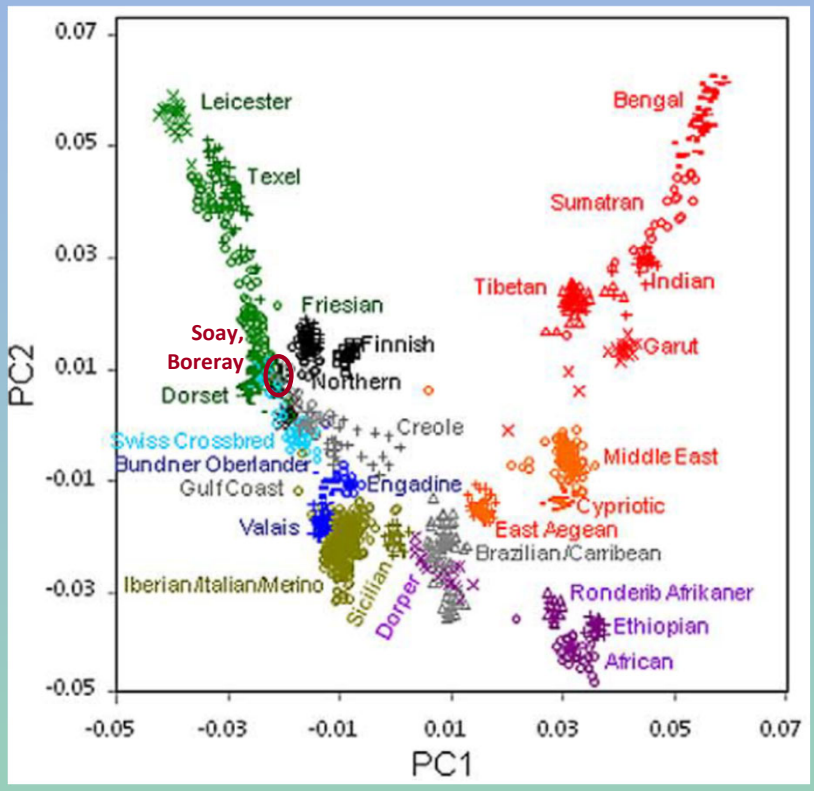
🔍 **Pattern of differentiation**

- 🙂 genetic **isolation** → 😟 PCA, ADMIXTURE spoiled by **inbreeding bias**
- 😯 degree of breed differentiation
- 😯 **subdivision** within breeds → keep separate for downstream analysis!

2. PCA often distorted by uneven sampling and inbreeding

→ Gradual clines by ancient migrations not displayed





European and Asian sheep, ~20/breed,
110 Soay, highly inbred Scottish island sheep

☹ PC2 reflects Soay ↔ others

☹ Boreray from nearby island intermediate

Overlapping samples, **20 Soay**

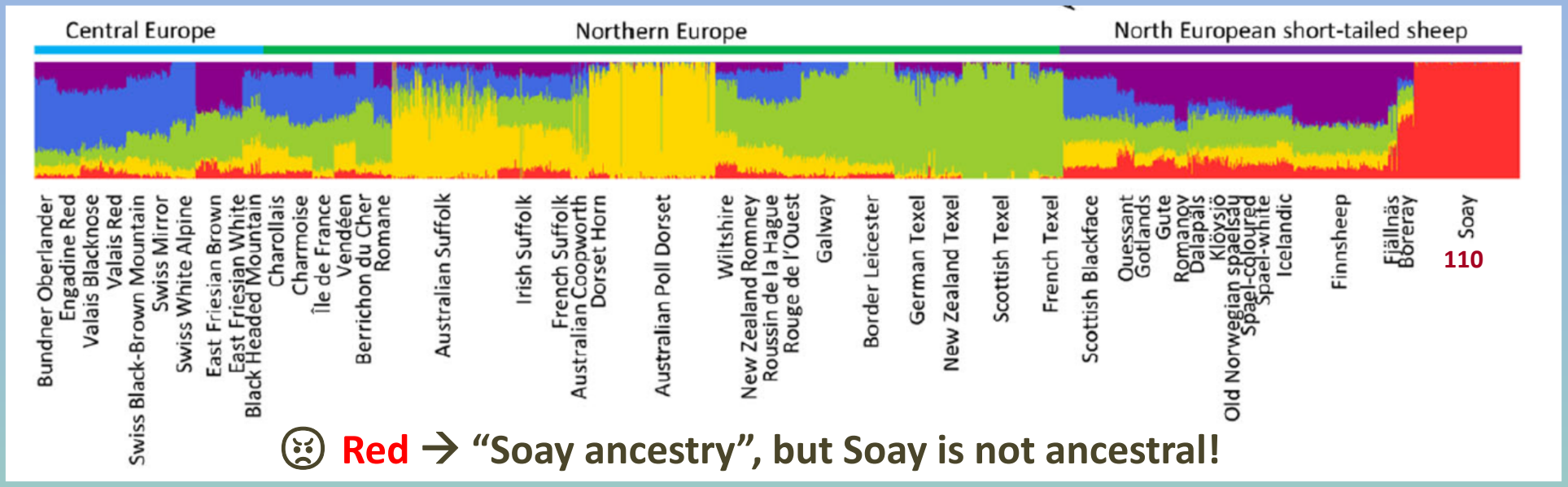
☺ Soay and Boreray plotted according to their ancestry

😊 PC1 and PC2 show several clines

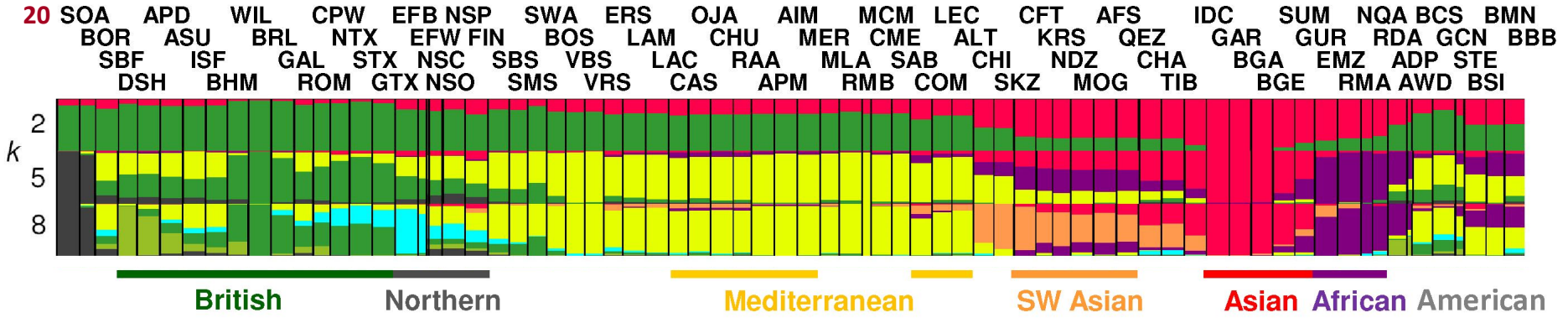
😄 Powerful alternative: **Supervised PCA**:

- PCs are set by a subset of samples
- Other samples are interpolated within this subset

2. ADMIXTURE also distorted by uneven sampling and inbreeding



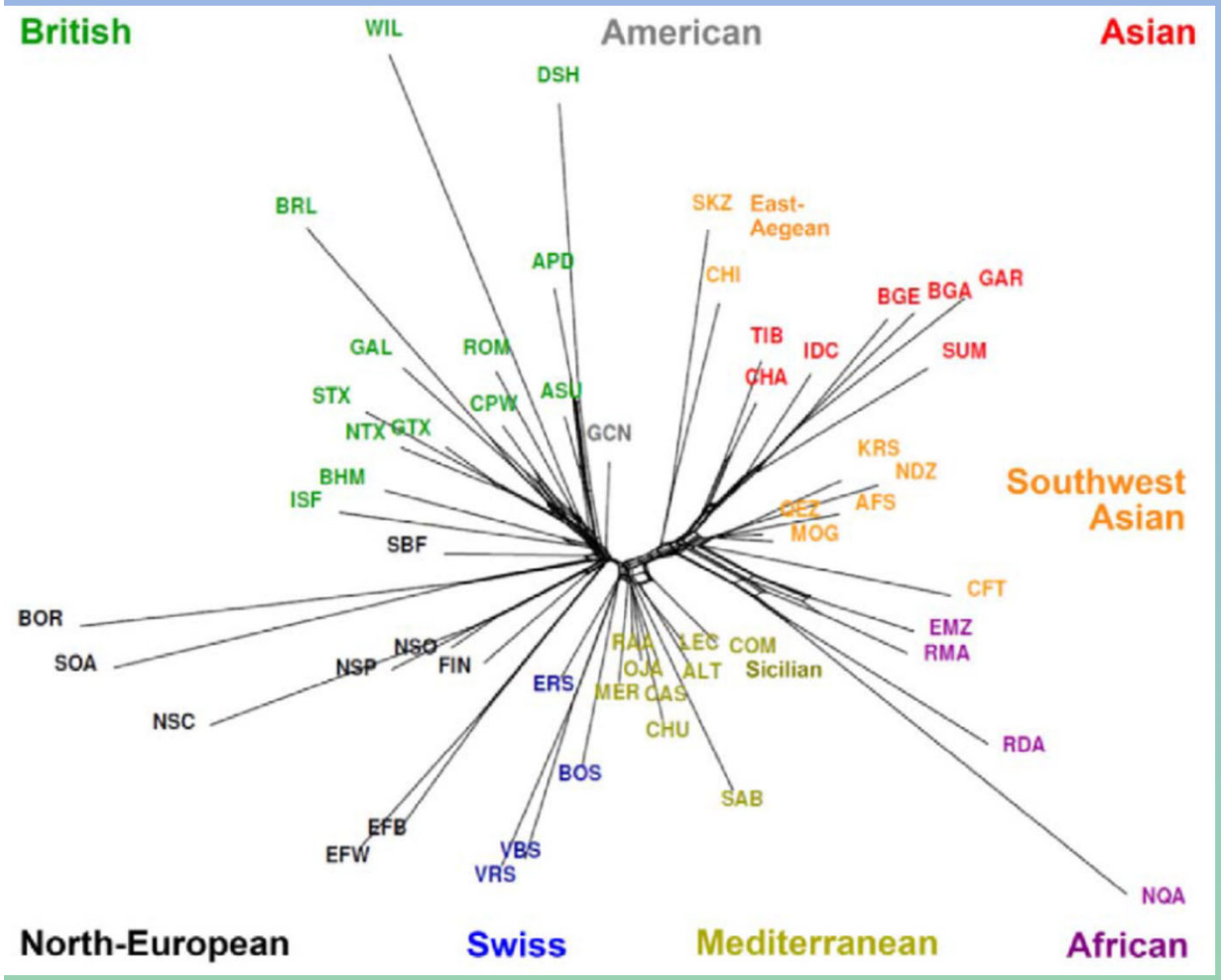
😠 **Red → "Soay ancestry", but Soay is not ancestral!**



😟 **Dark grey shows a reduced Soay+Boreray ancestry ~ Nordic ancestry**

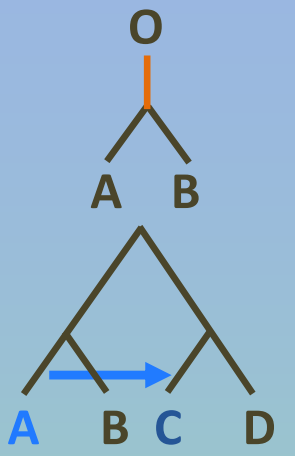
Inferred clusters are a group or related animals, but are ~~not always~~ almost never an ancestral component !!

3. NeighborNet of F_{ST} genetic distances



- ☺ Not influenced by sampling or inbreeding bias
- ☺ Shows regional clusters
- 😄 Lines reconstruct gene flows → link with history
- 😮 Reticulations by crossbreeding only partially shown

3. f_3 / f_4 / BSAA are the most informative methods for inferring crossbreeding



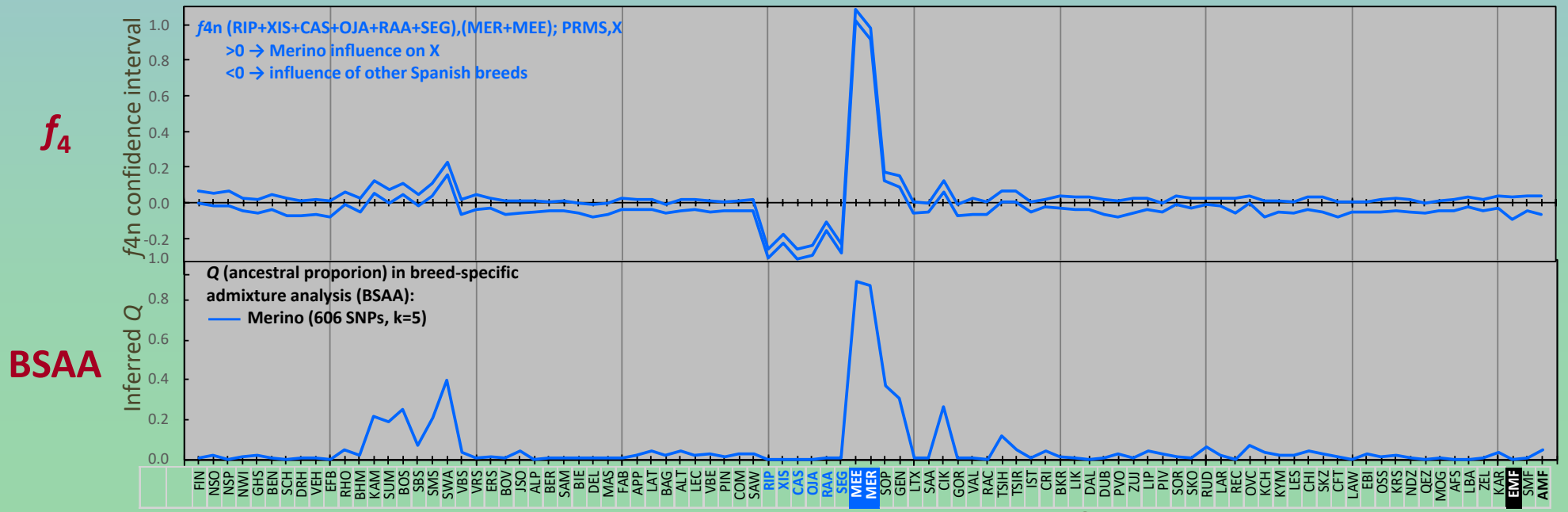
f_3, coancestry coefficient, gene flow shared by A and B
after diverging from outgroup; increases by gene flow A → B

f_4, admixture coefficient, correlation of alleles of breeds
in different part of the tree; >0 by gene flow from A → B

BSAA (breed-specific admixture analysis): model based clustering (STRUCTURE, ADMIXTURE) with Ancestry Informative Markers (AIMs): SNPs that differentiate the donor and nearby other breeds

f_4

BSAA



Swiss

Merino Hungary: forgotten Merino incrossing in 18th

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Keep in mind

- Using sophisticating programs does not imply that you are dumb and the computer is bright.
- Those software developers may lose sight of the biological reality
- “All models are wrong, but some are useful”. Many models are useless!

Do's and Don’ts

- Don’t cut-and-paste from computer output in your paper
- **Understand** the algorithm
- Do **validate** a program as in the lab: positive and negative controls, varying parameters, omitting strategic breeds, splitting the dataset, etc.
- Read about **human molecular genetics** on advanced methodology