Multivariate analysis of genetic data — exploring group diversity —

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Imperial College London

Genetic data analysis using  , University of Leuven
29-10-2014

Outline

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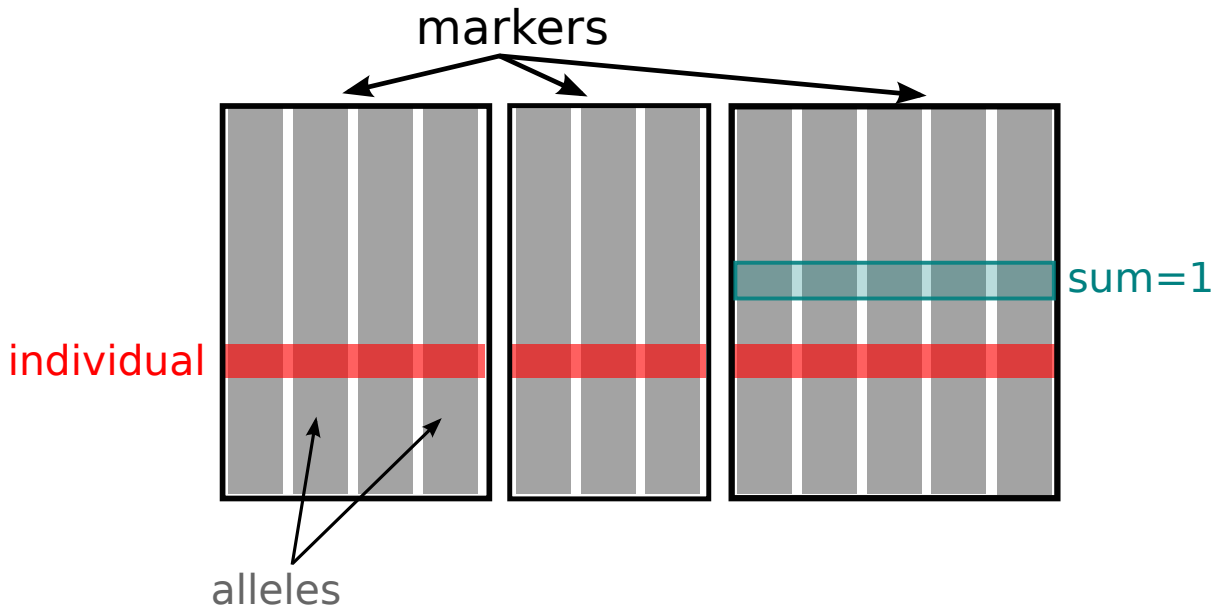
Genetic data: introducing group data



- How to identify groups?
- How to explore group diversity?

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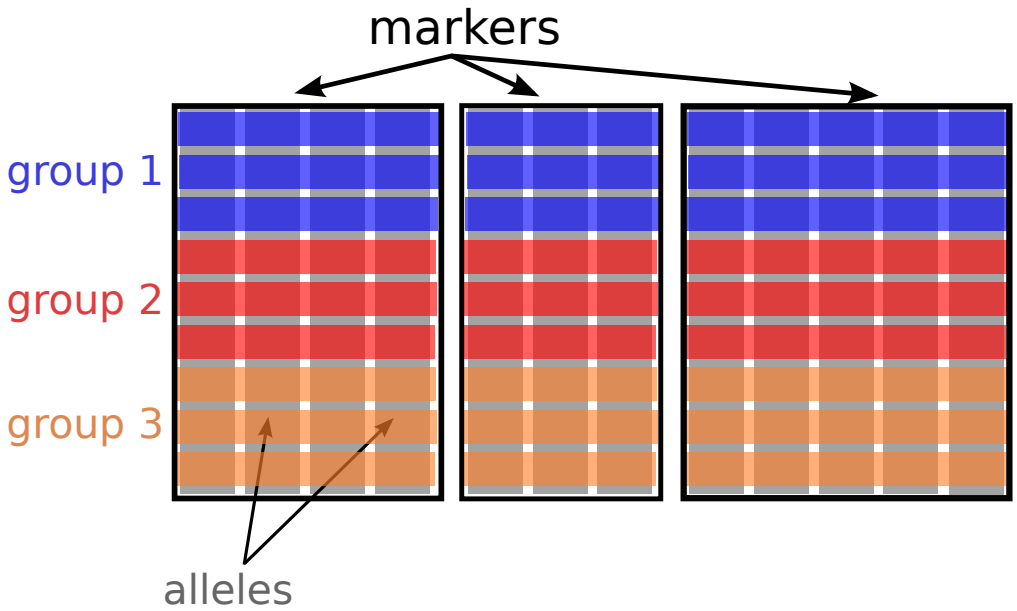

- How to identify groups?
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Hierarchical clustering: a variety of algorithms

- single linkage
- complete linkage
- UPGMA
- Ward
- ...

Rationale

1. compute pairwise genetic distances $\mathbf{D}$ (or similarities)
2. group the closest pair(s) together
3. (optional) update $\mathbf{D}$
4. return to 2) until no new group can be made

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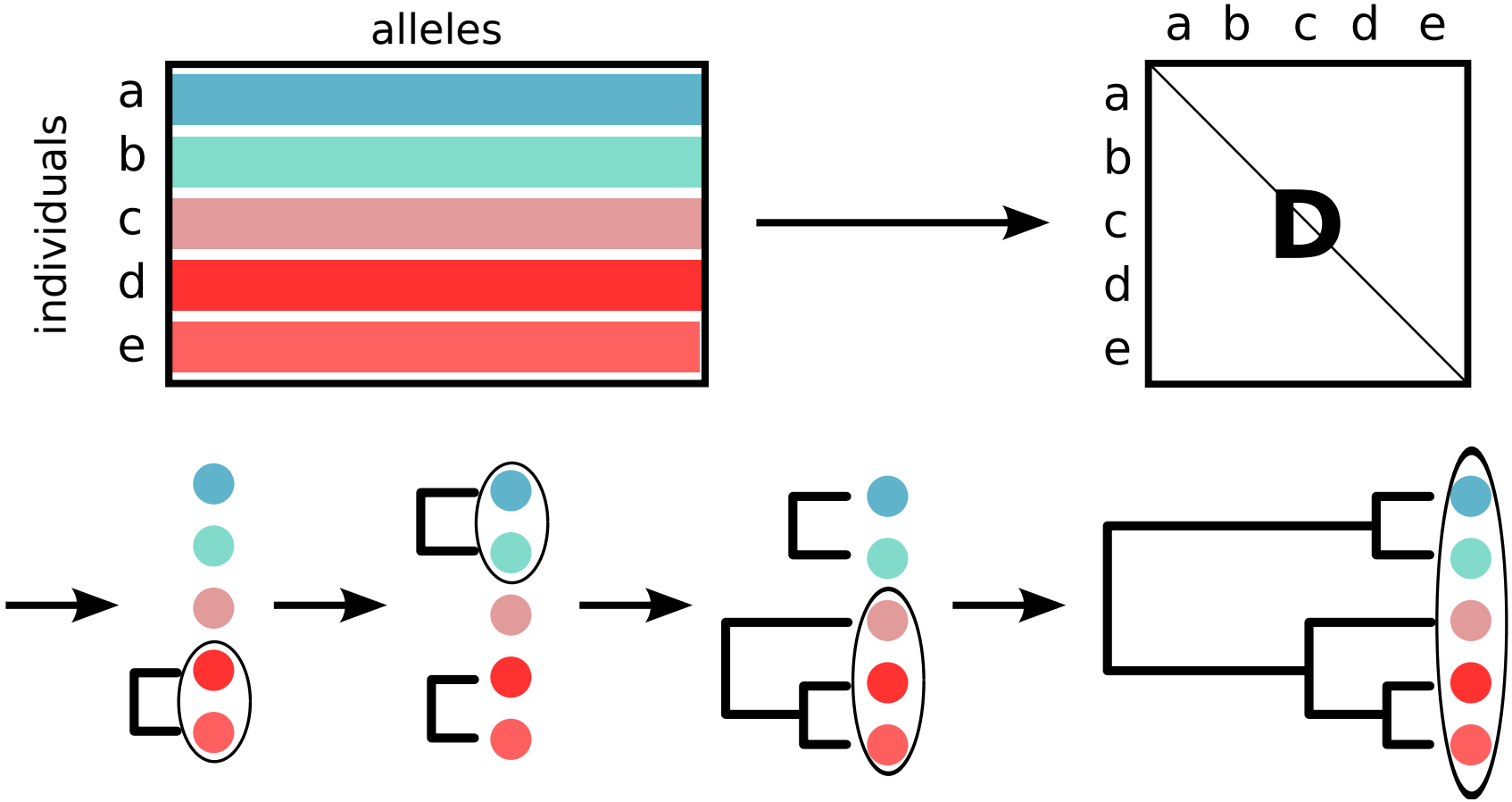
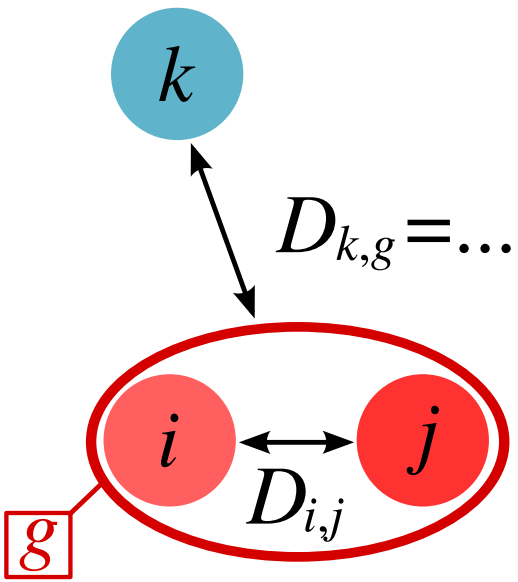


Differences between algorithms



- single linkage: $D_{k,g} = \min(D_{k,i}, D_{k,j})$
- complete linkage: $D_{k,g} = \max(D_{k,i}, D_{k,j})$
- UPGMA: $D_{k,g} = \frac{D_{k,i}+D_{k,j}}{2}$

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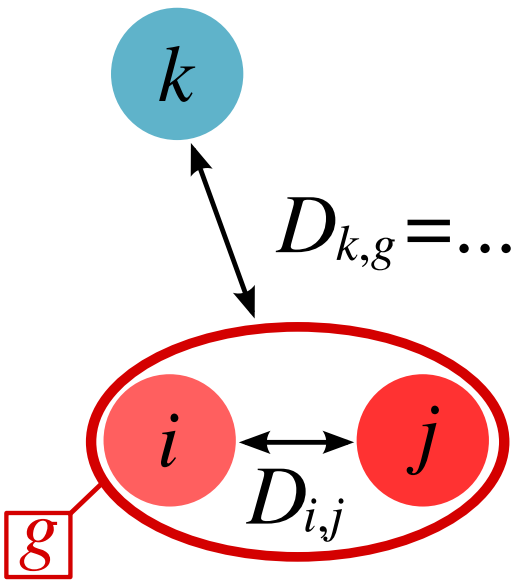

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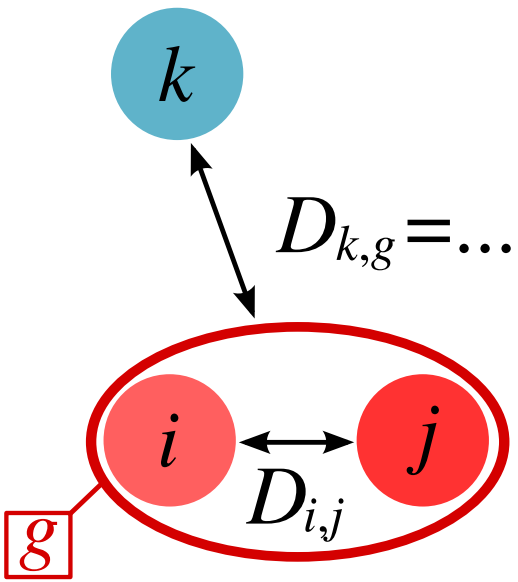

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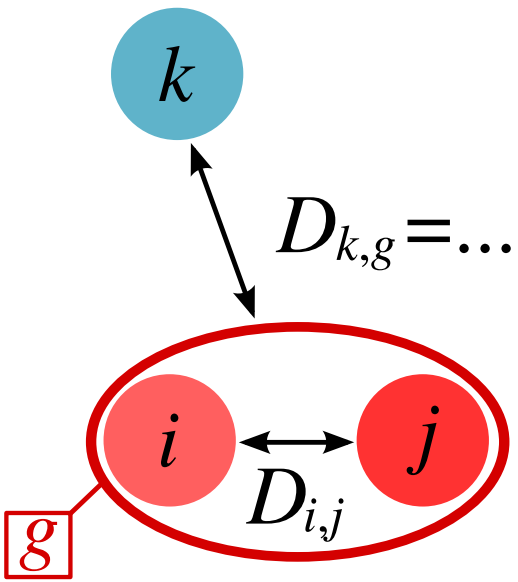

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Differences between algorithms

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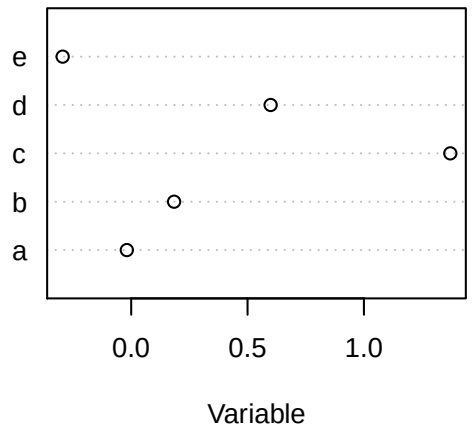
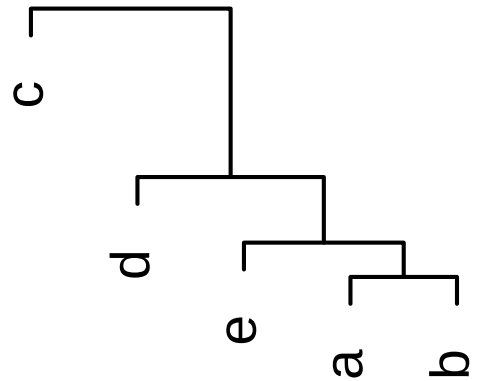
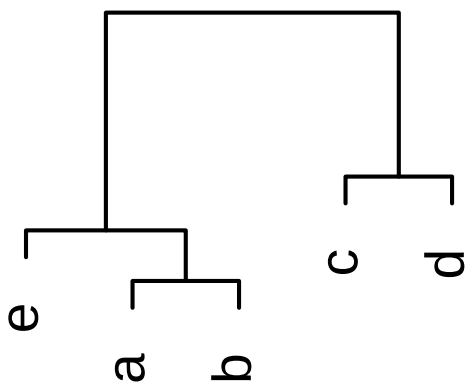


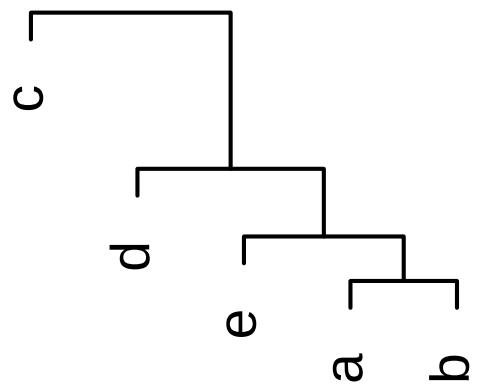
Single linkage



Complete linkage



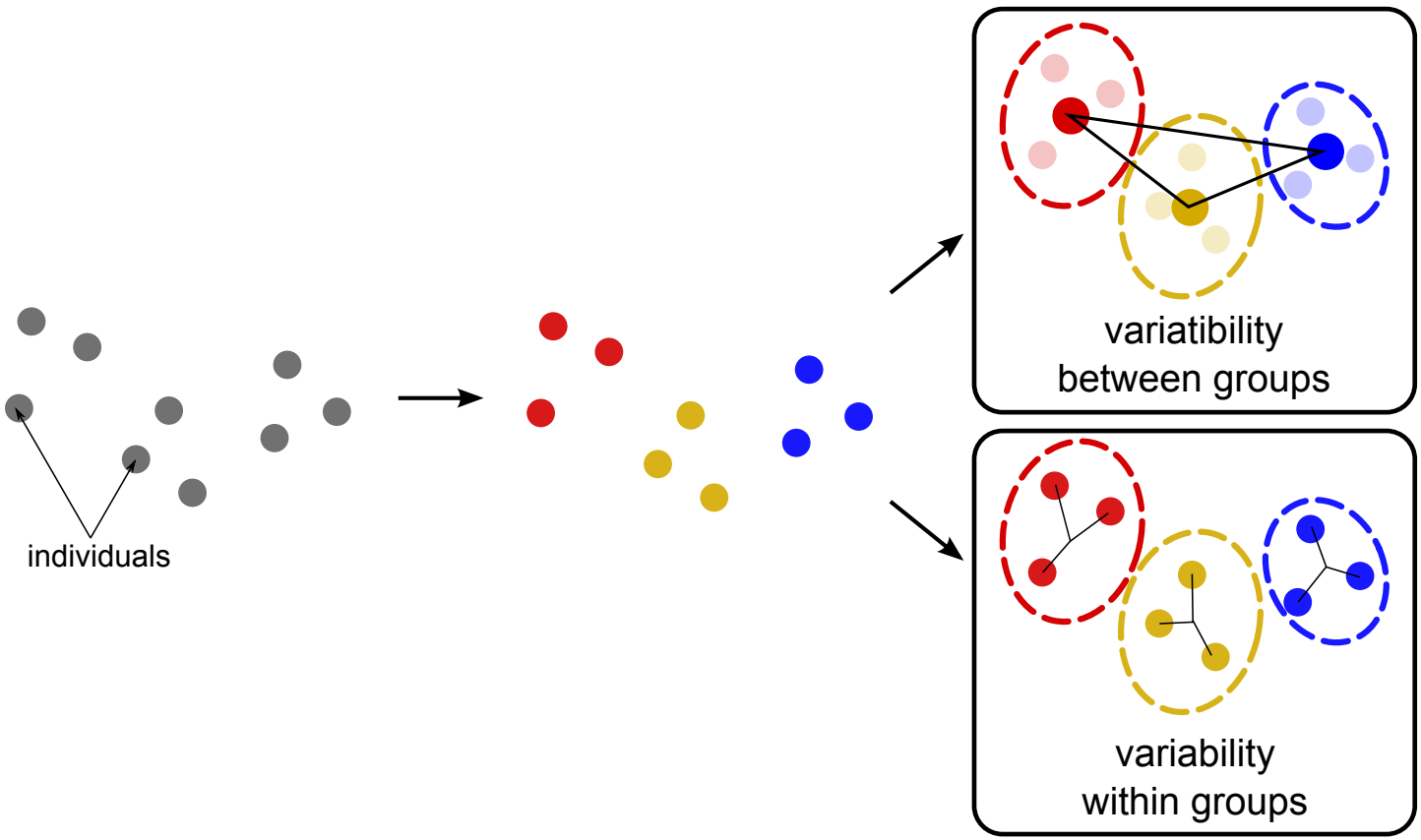
UPGMA (average linkage)



K-means underlying model

ANOVA model:

$$\text{total var.} = (\text{var. between groups}) + (\text{var. within groups})$$



K-means rationale

Find groups which minimize *within group var.* (equally: maximize *between group var.*).

In other words:
Identify a partition $\mathcal{G} = \{g_1, \ldots, g_k\}$ solving:

$$\arg \min_{\mathcal{G}=\{g_1,\ldots,g_k\}} \sum_k \sum_{i \in g_k} \|\mathbf{x}_i - \boldsymbol{\mu}_k\|^2$$

with:

- $\mathbf{x}_i \in \mathbb{R}^p$: vector of allele frequencies of individual i
- $\boldsymbol{\mu}_k \in \mathbb{R}^p$: vector of means allele frequencies of group k

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K-means algorithm

The K-mean problem is solved by the following algorithm:

1. select random group means ($\boldsymbol{\mu}_k$, $k = 1, \ldots, K$)
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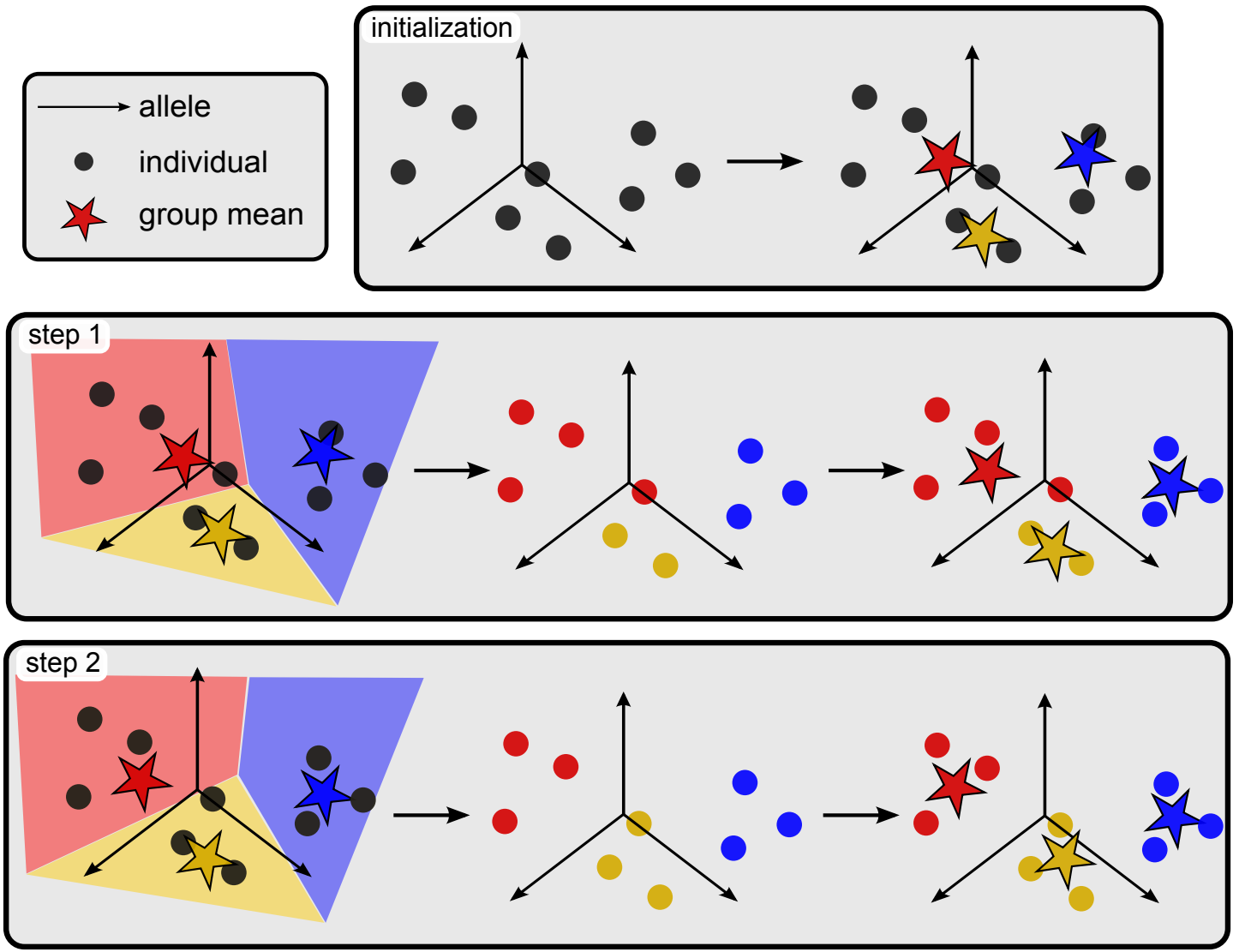

K-means: limitations and extensions

Limitations

- slower for large numbers of alleles (e.g. 100,000)
- K-means does not identify the number of clusters (K)

Extension

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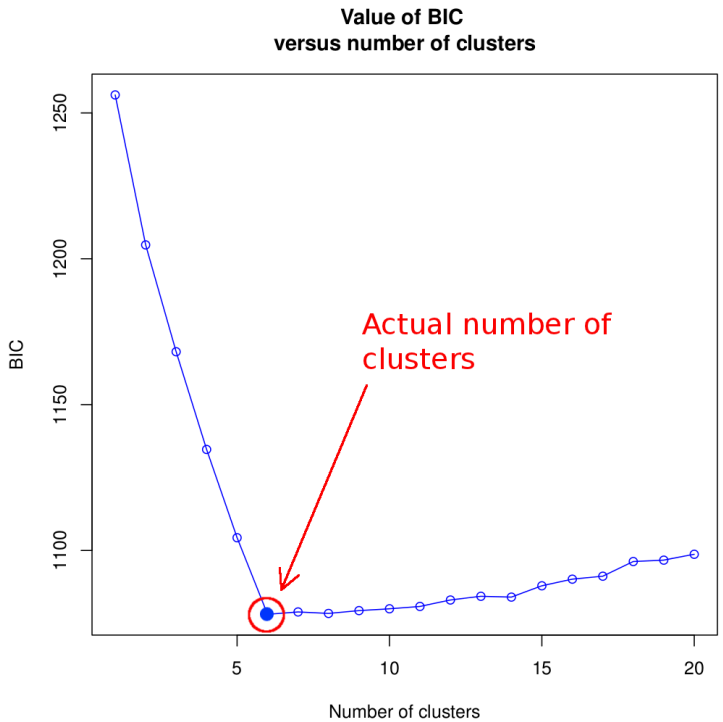
Genetic clustering using K-means & BIC

(Jombart *et al.* 2010, *BMC Genetics*)

Simulated data: island model with 6 populations



Performances:

- K-means $\geq$ STRUCTURE on simulated data (various island and stepping stone models)
- orders of magnitude faster (seconds vs hours/days)

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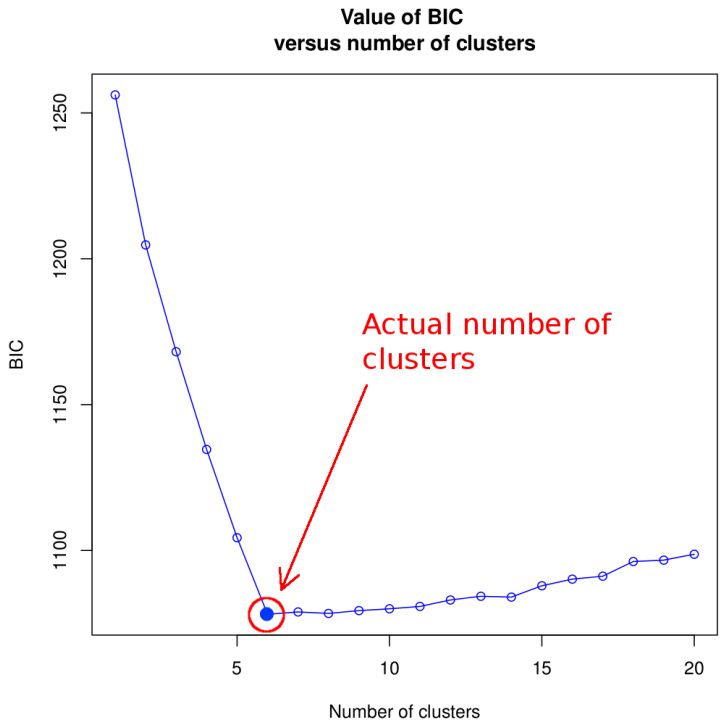

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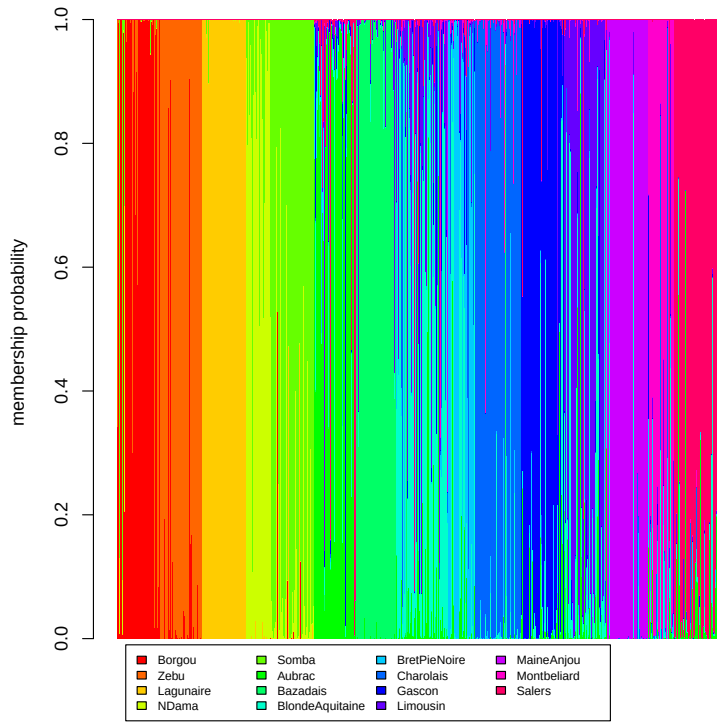
Why identifying clusters is not the whole story

Example of cattle breeds diversity (30 microsatellites, 704 individuals).

Group membership probabilities:



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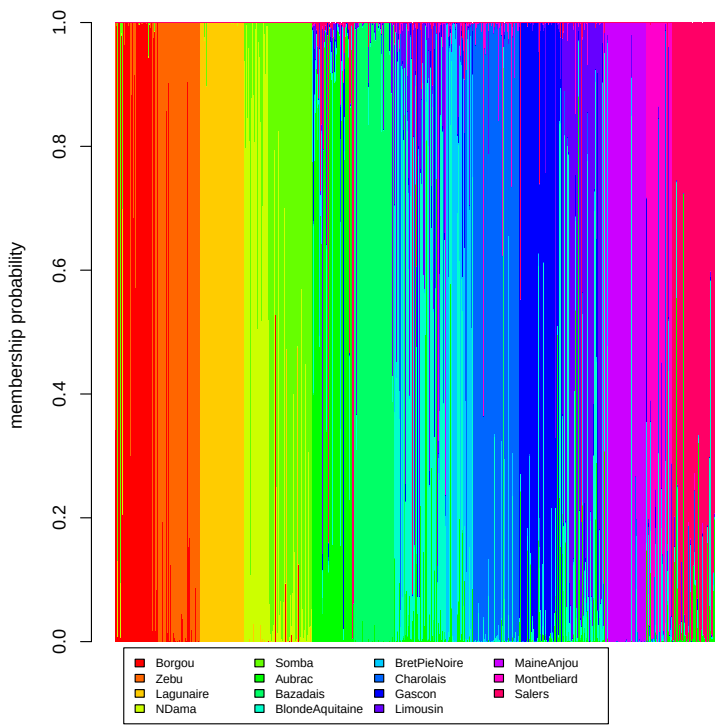

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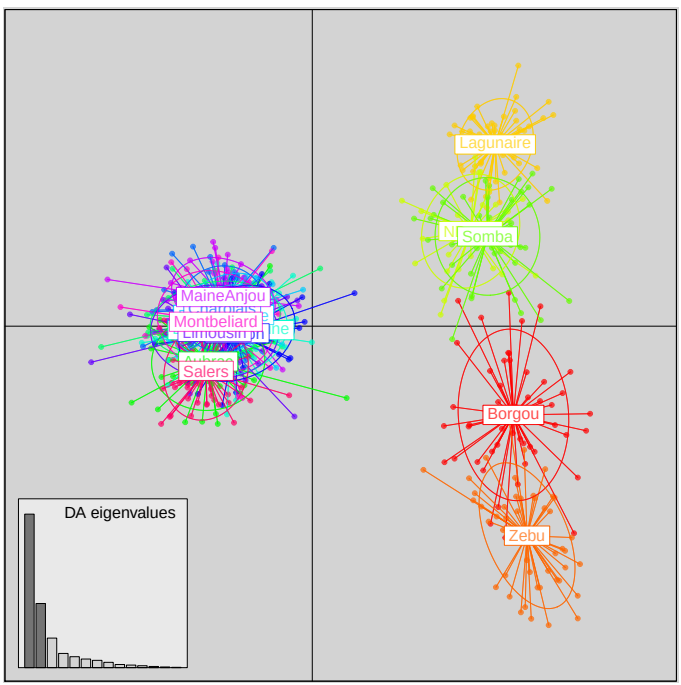

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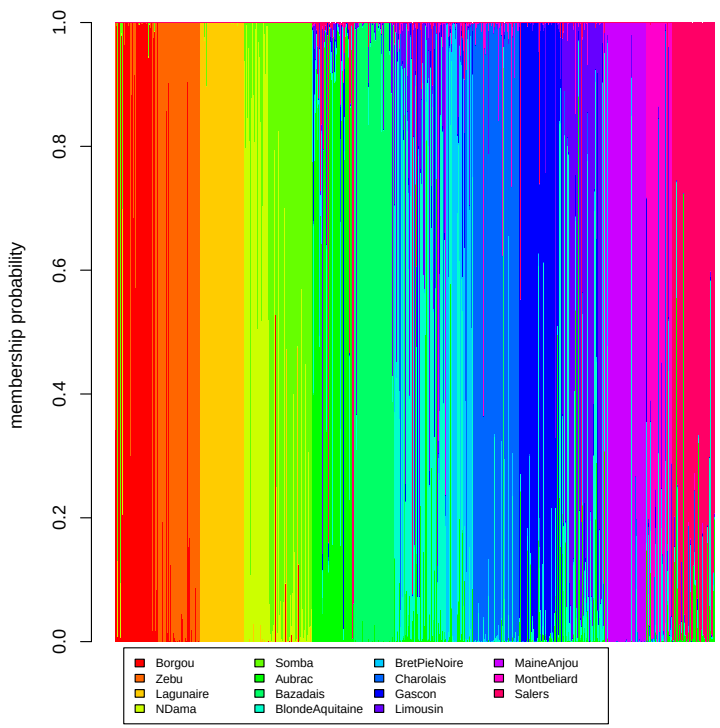

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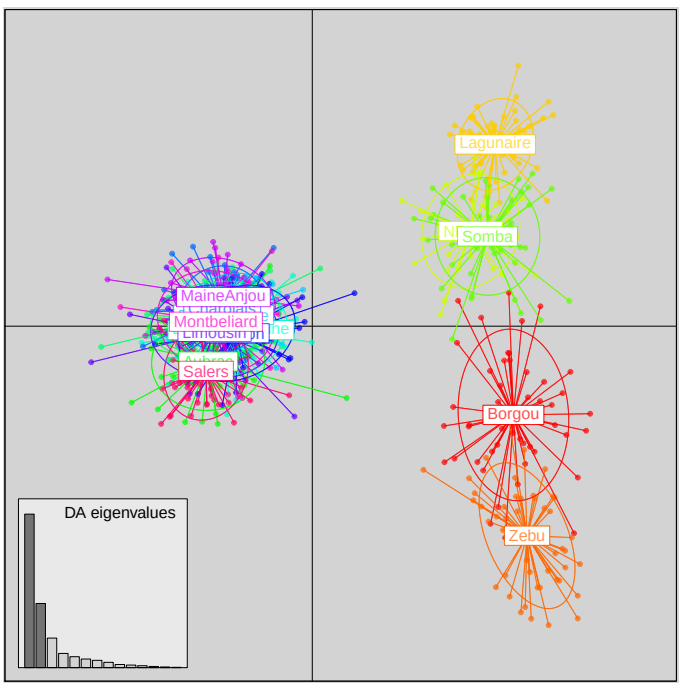

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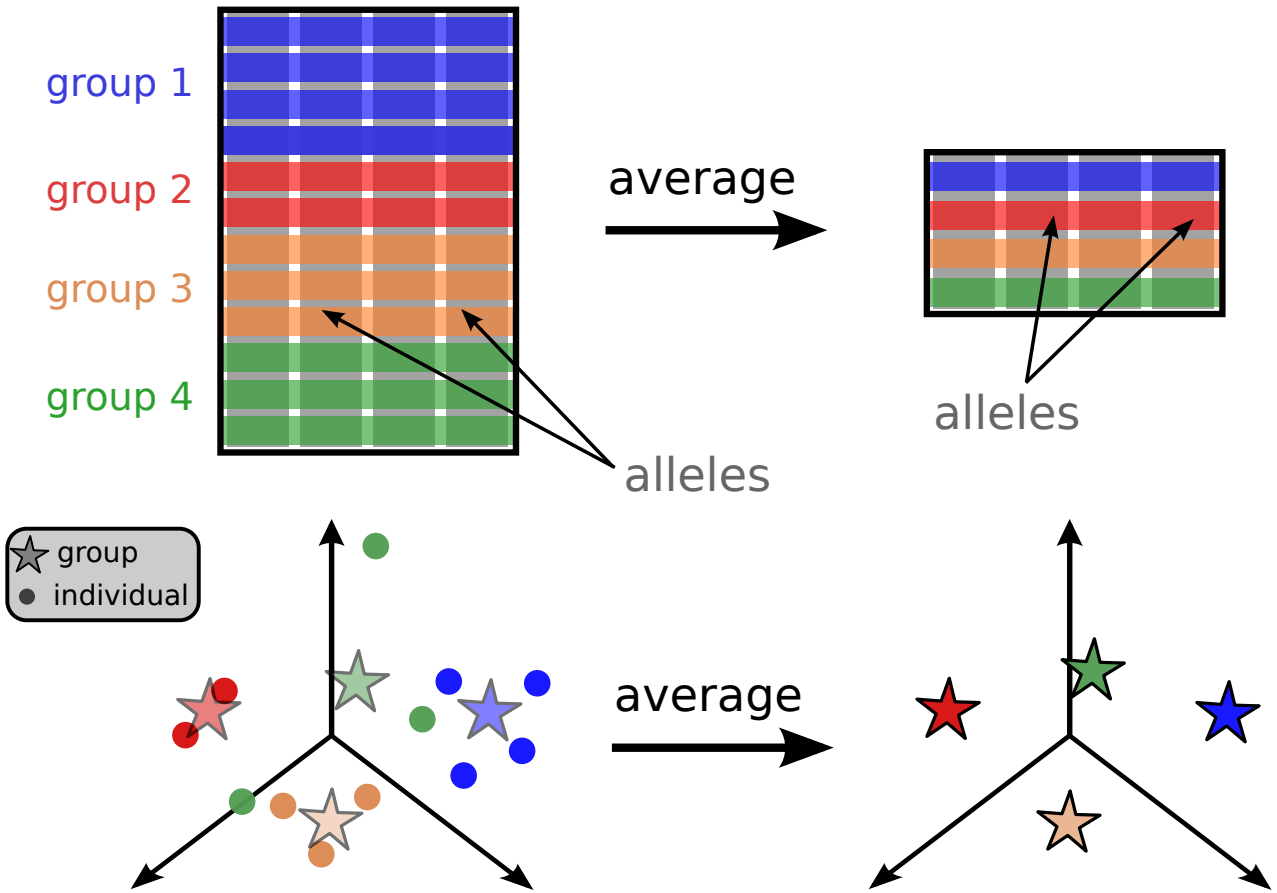
Aggregating data by groups



$\longrightarrow$ multivariate analysis of group allele frequencies.

Analysing group data

Available methods:

- Principal Component Analysis (PCA) of allele frequency table
- Genetic distance between populations $\longrightarrow$ Principal Coordinates Analysis (PCoA)
- Correspondance Analysis (CA) of allele counts

Criticism:

- Loose individual information
- Neglect within-group diversity
- CA: possible artefactual outliers

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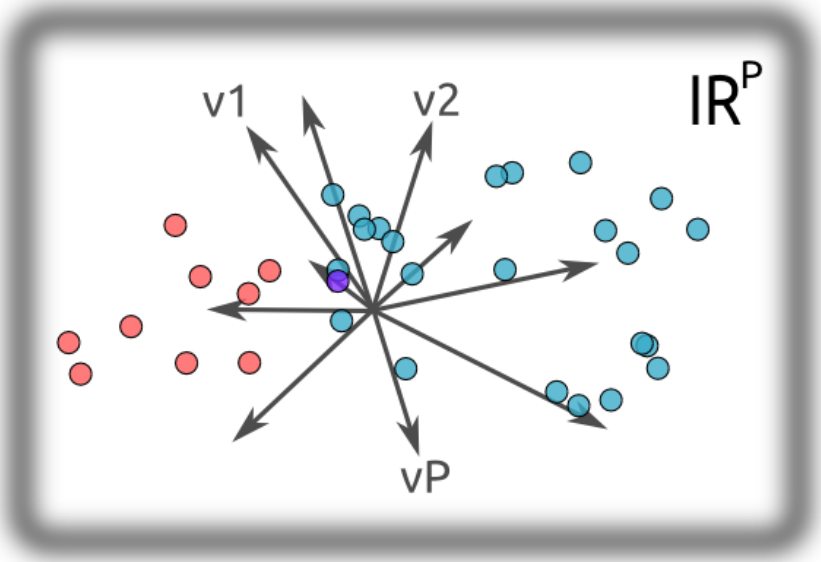

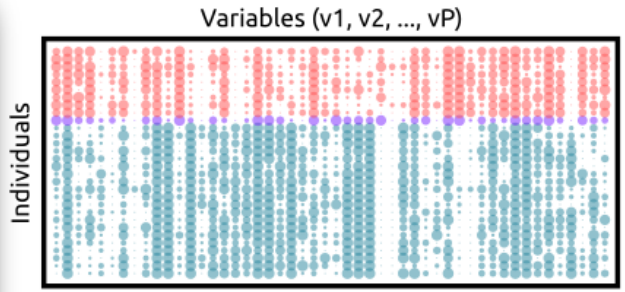

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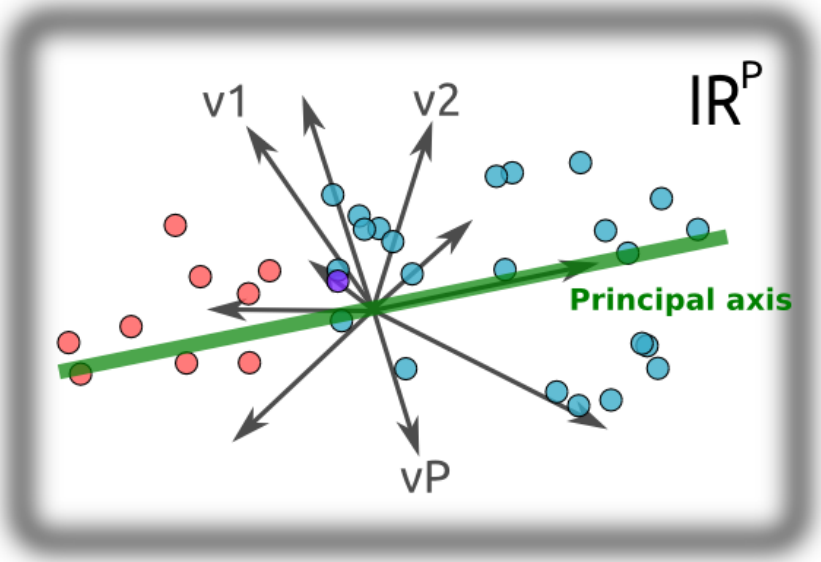

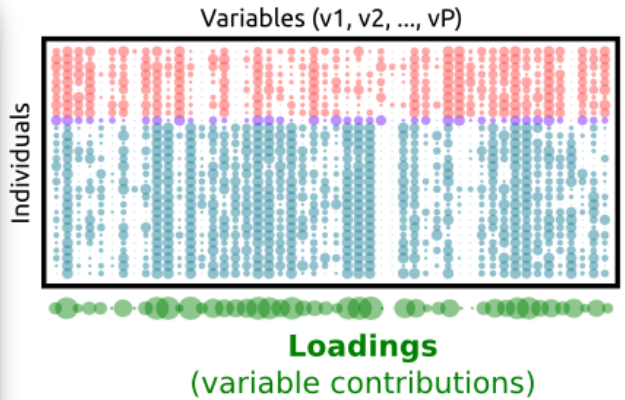

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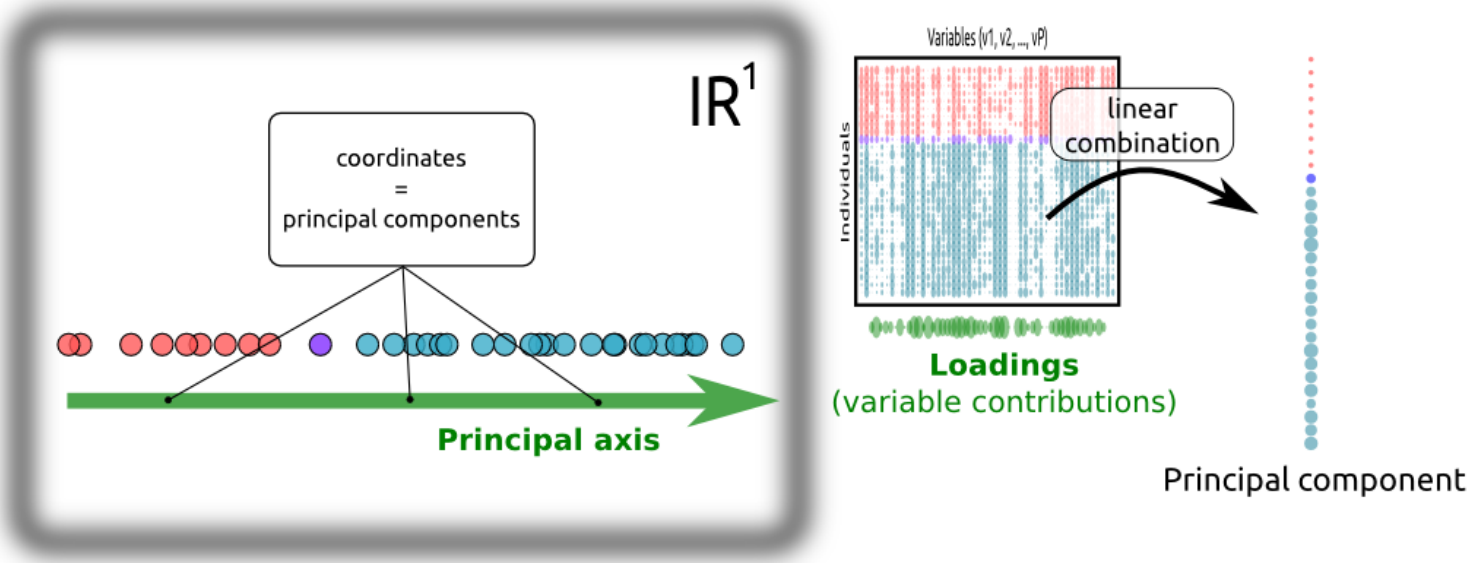

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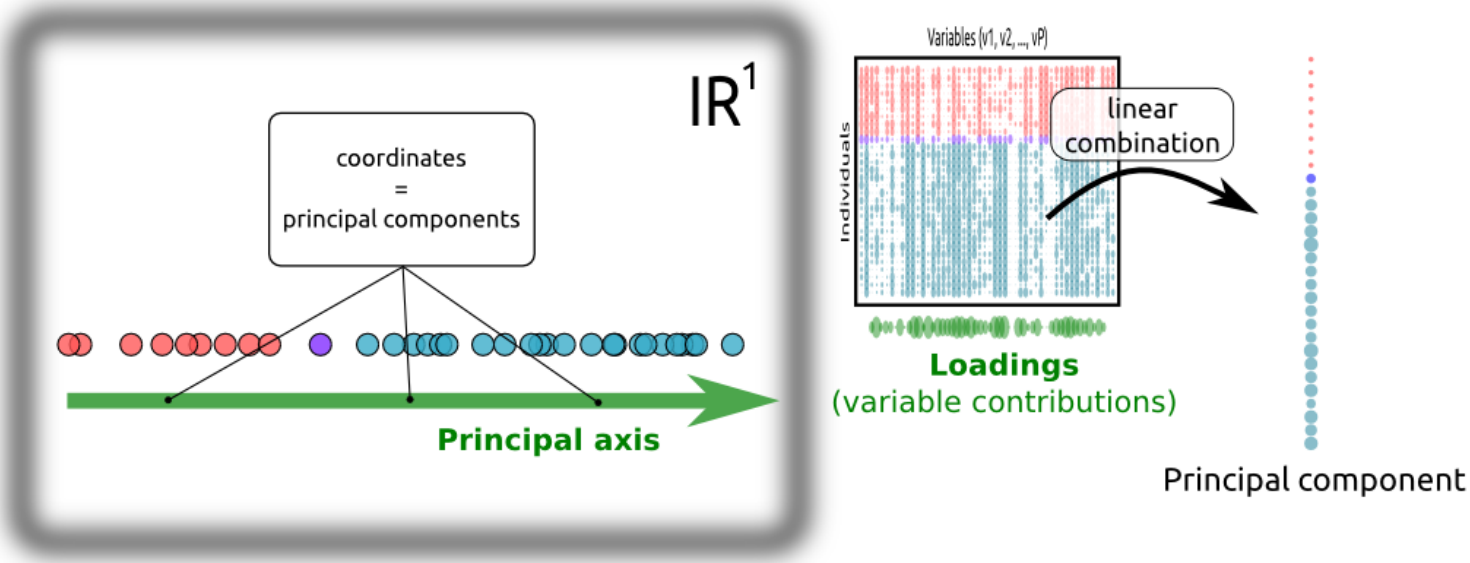

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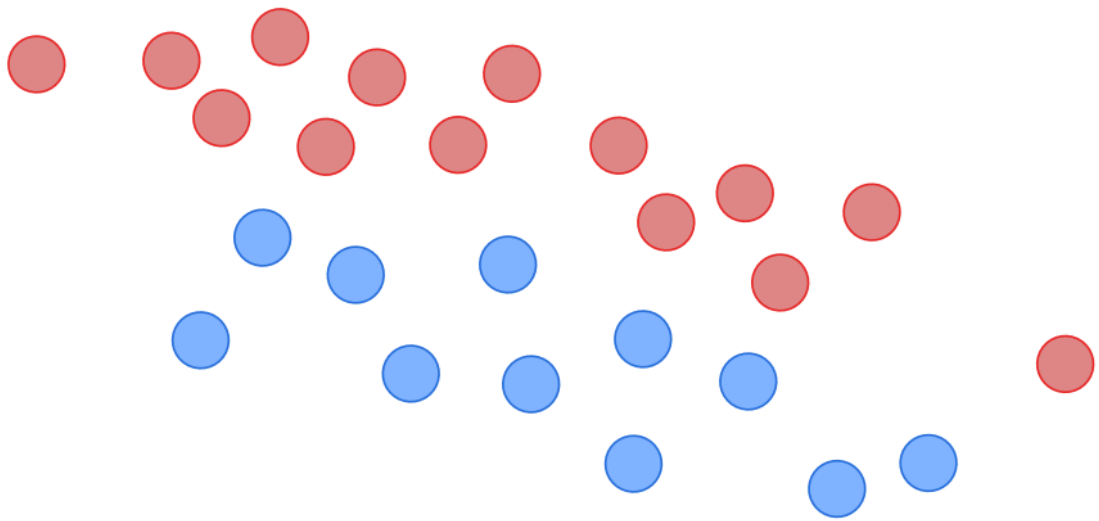

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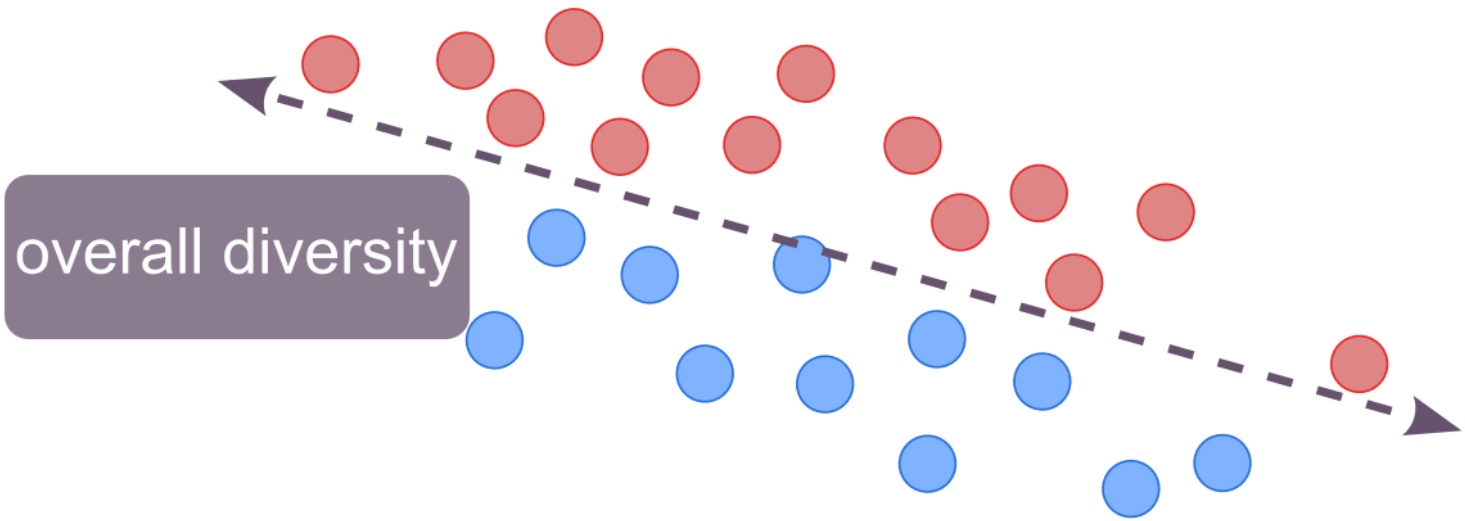

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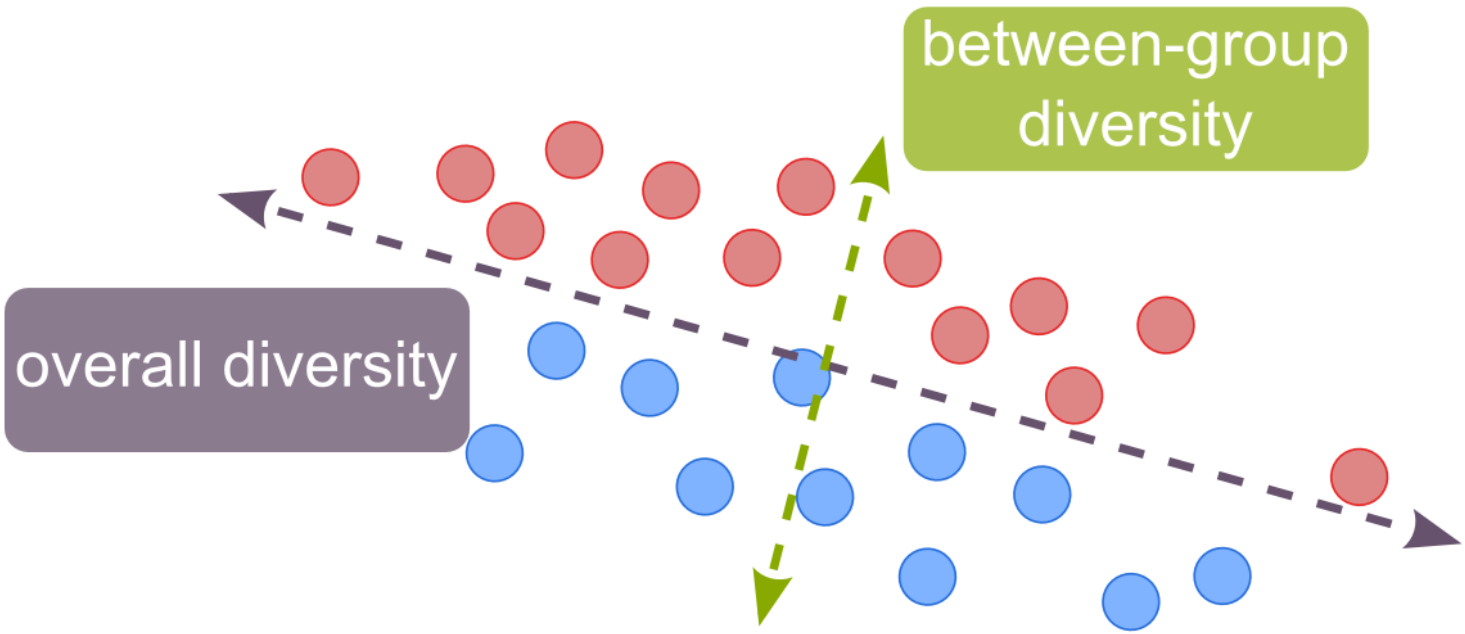

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Optimizing different criteria

Similar approaches to PCA can be used to optimize different quantities:

- **PCA**: *total* variance
- **Between-group PCA**: variance *between* groups
- **Within-group PCA**: variance *within* groups
- **Discriminant Analysis**: variance *between* groups / variance *within* groups

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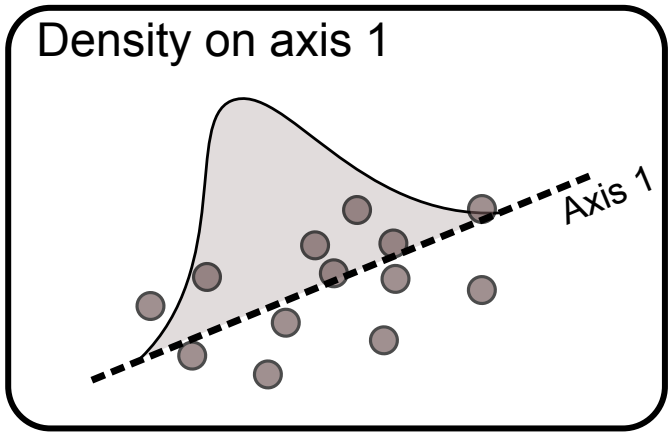
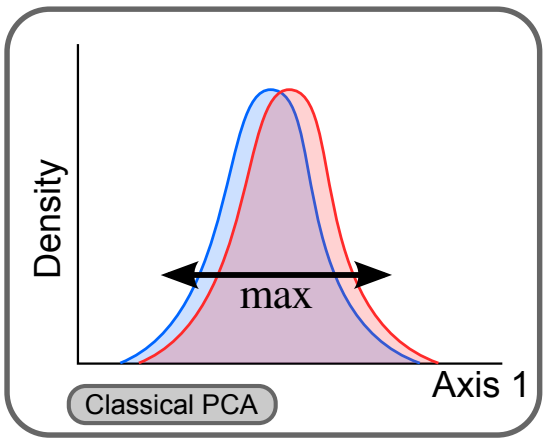
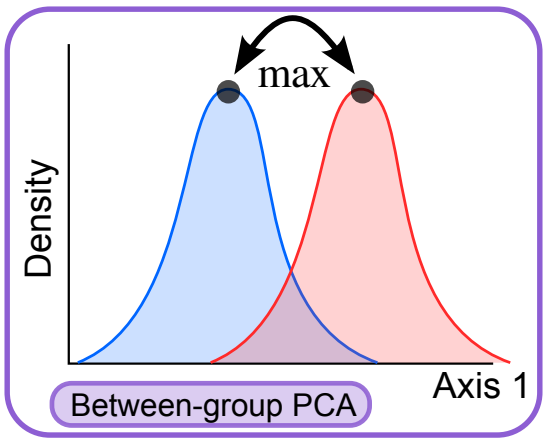
From PCA to DA: increasing group differentiation

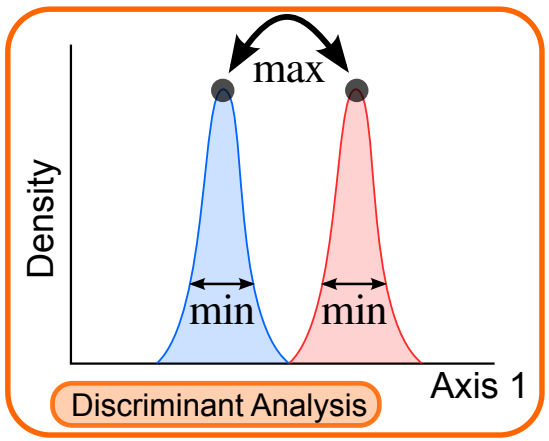




Max. total diversity



Max. diversity between groups



Max. separation of groups

Discriminant Analysis: limitations and extensions

Limitations:

- DA requires less variables (alleles) than observations (individuals)
- DA requires uncorrelated variables (no frequencies, no linkage disequilibrium)

Discriminant Analysis of Principal Components (DAPC)[1]:

- data orthogonalisation/reduction using PCA before DA
- overcomes limitations of DA
- group membership probabilities, group prediction

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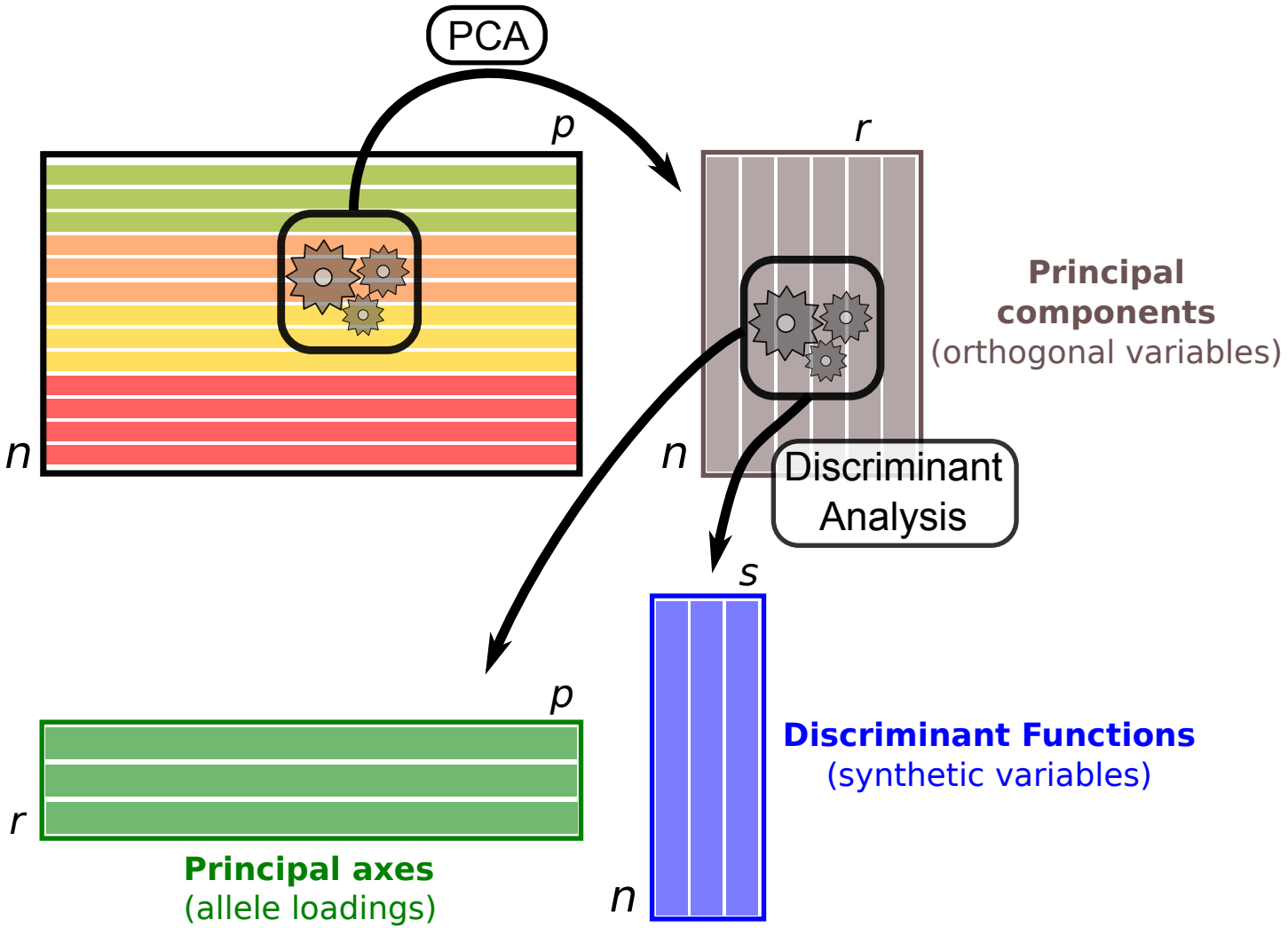
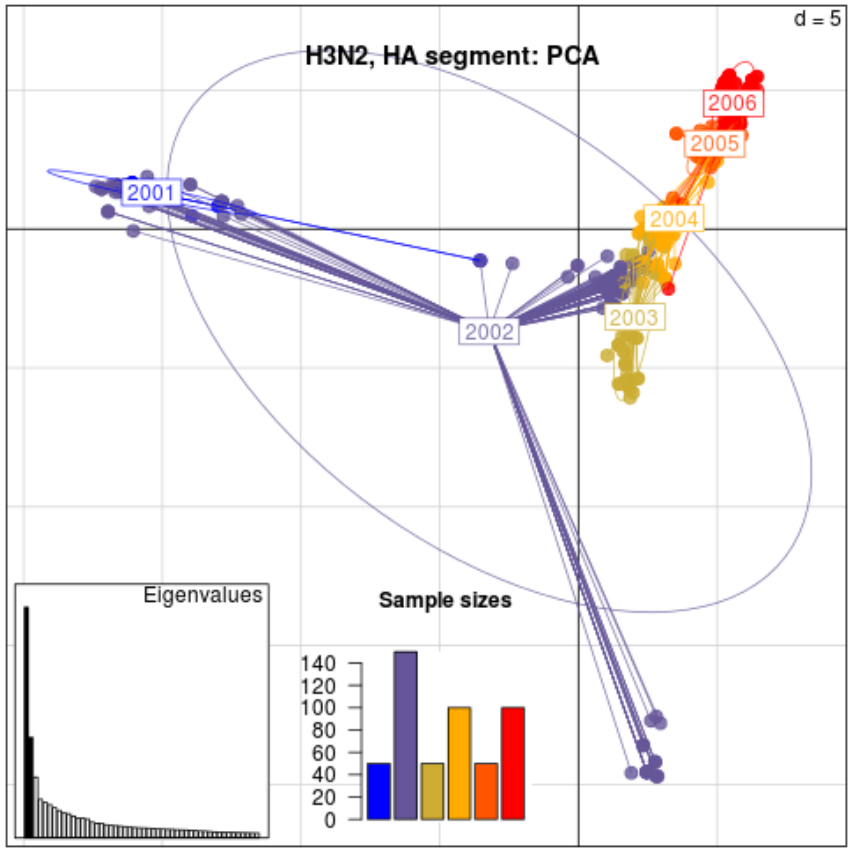
Rationale of DAPC



PCA of seasonal influenza (A/H3N2) data

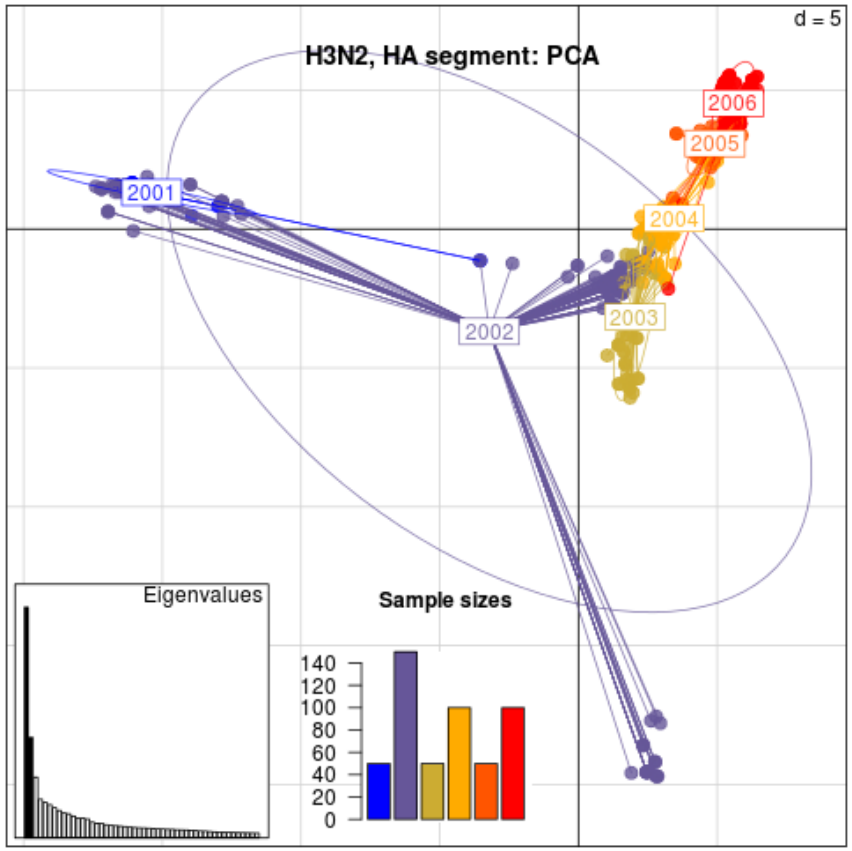
Data: seasonal influenza (A/H3N2), 500 HA segments.



Little temporal evolution, burst of diversity in 2002??

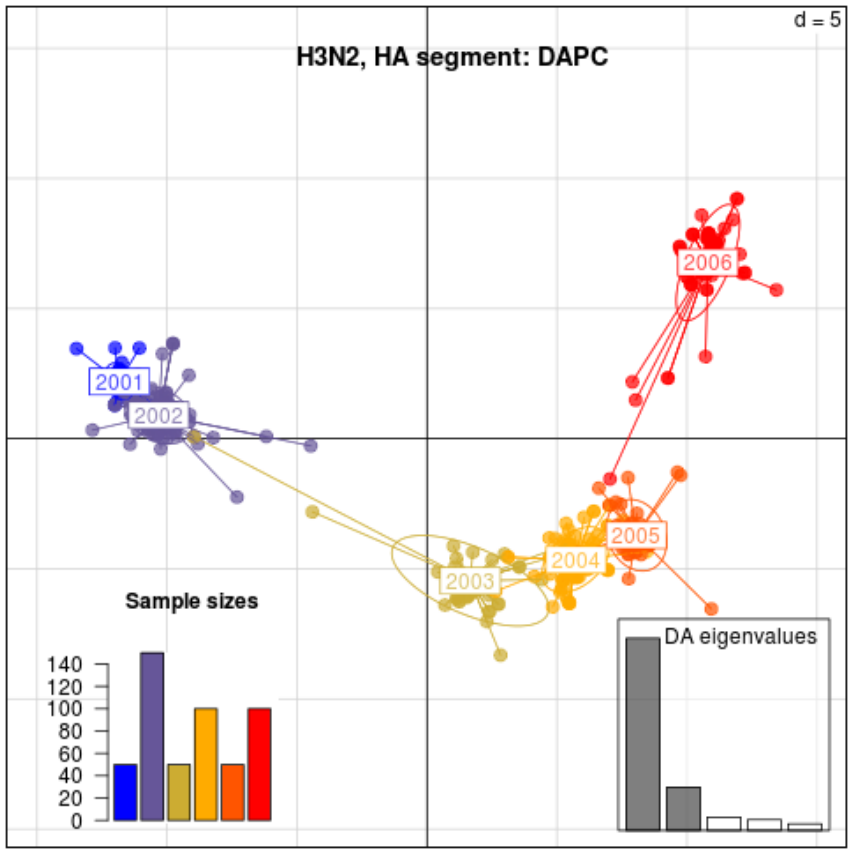
PCA of seasonal influenza (A/H3N2) data

Data: seasonal influenza (A/H3N2), 500 HA segments.



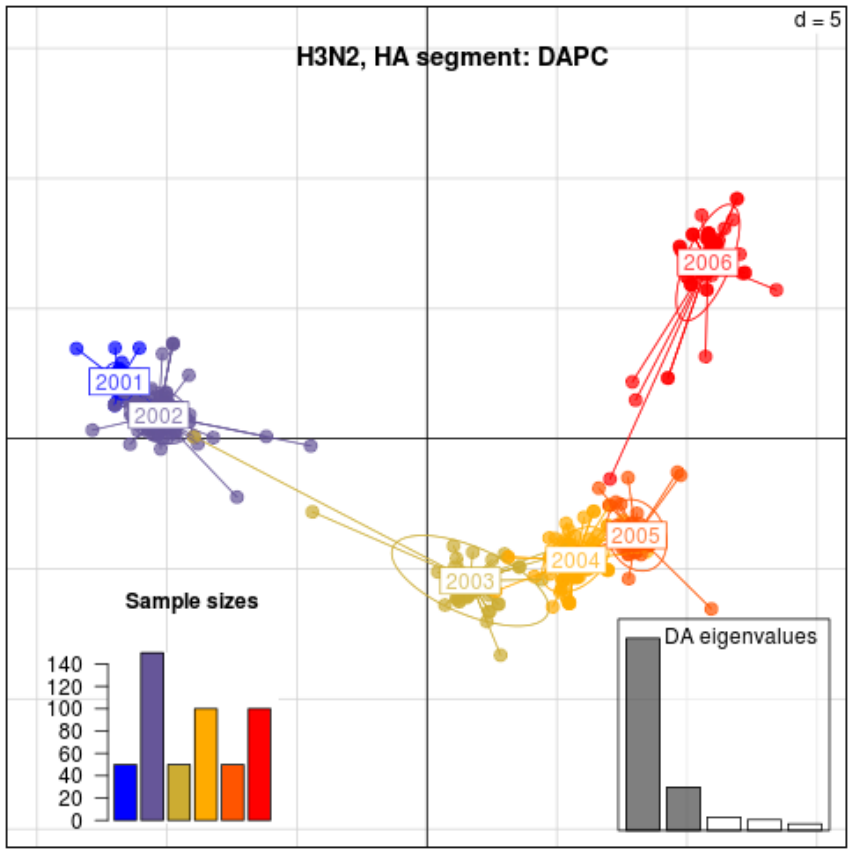
Little temporal evolution, burst of diversity in 2002??

DAPC of seasonal influenza (A/H3N2) data



Strong temporal signal, originality of 2006 isolates (new alleles).

DAPC of seasonal influenza (A/H3N2) data



Strong temporal signal, originality of 2006 isolates (new alleles).

Other features

DAPC can be used to:

- provides group assignment probabilities
- can use supplementary individuals
- can predict group membership of new data
- can be used for variable selection

Time to get your hands dirty (again)!

The pdf of the practical is online:

`http://adegenet.r-forge.r-project.org/`

or

Google → adegenet → documents → "Workshop Leuven, October 2014"