

# Multivariate analysis of genetic data — exploring group diversity —

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# Outline

## Introduction

## Identifying groups

- Hierarchical clustering

- K-means

## Exploring group diversity

- Aggregating data

- Optimizing group differences

- Discriminant Analysis of Principal Components

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### Identifying groups

Hierarchical clustering

K-means

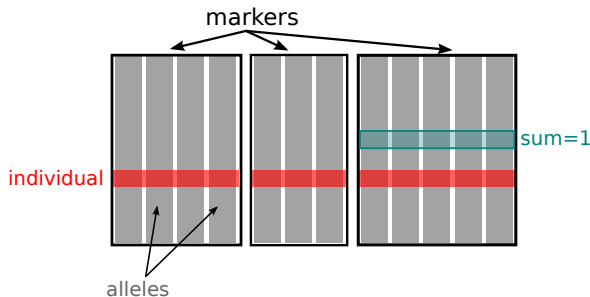
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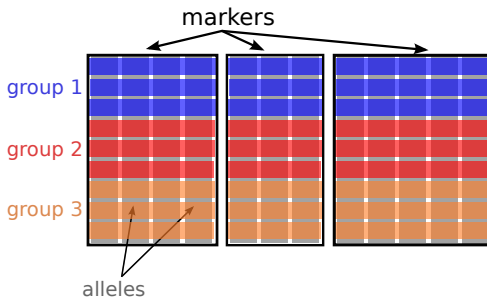
Discriminant Analysis of Principal Components

## Genetic data: introducing group data



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

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# Hierarchical clustering: a variety of algorithms

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

# Rationale

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



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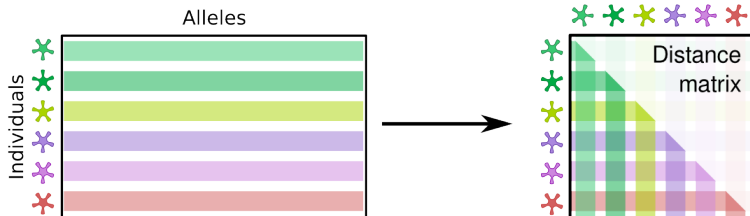
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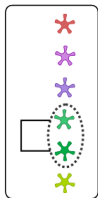
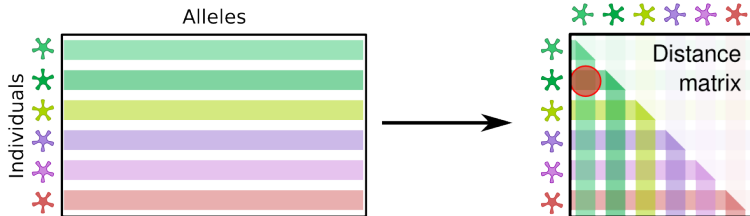
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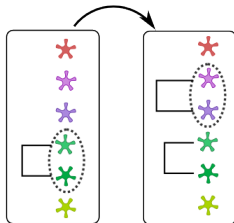
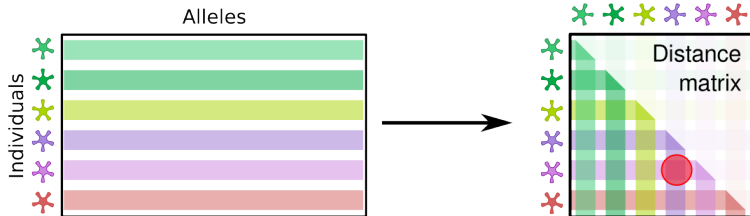
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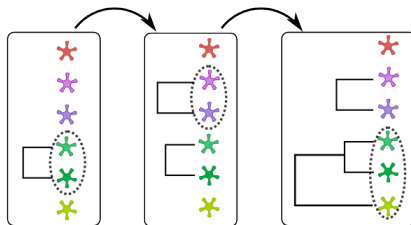
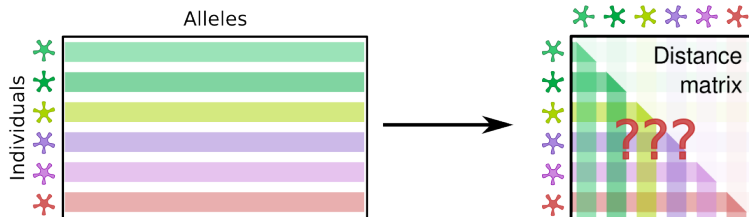
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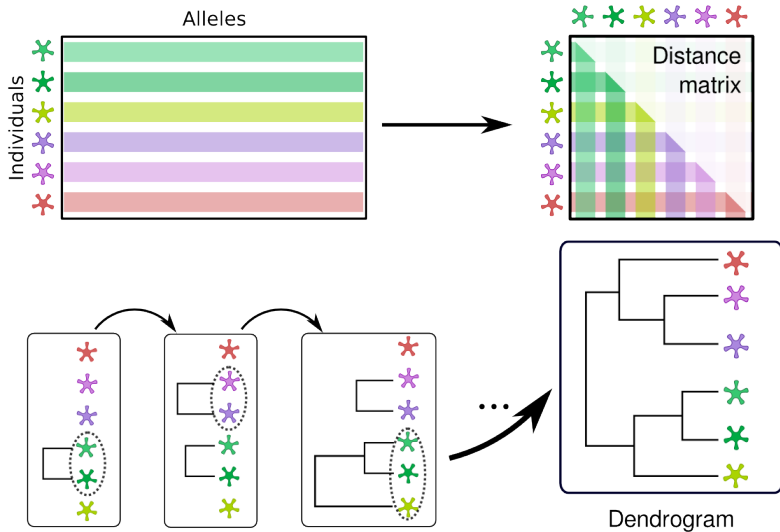
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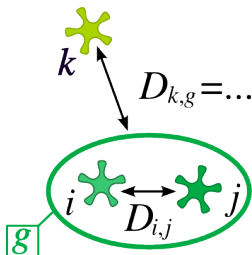


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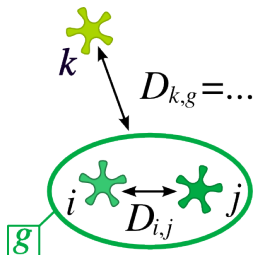


## Differences between algorithms



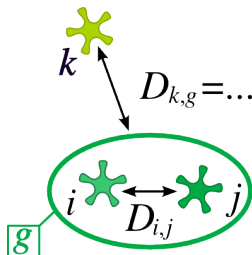
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- complete linkage:  $D_{k,g} = \max(D_{k,i}, D_{k,j})$
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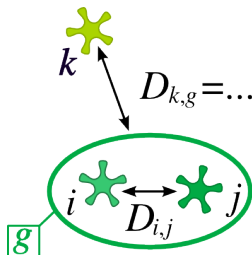
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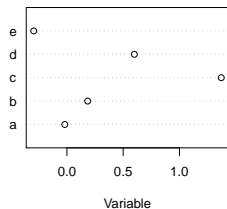
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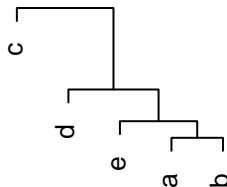
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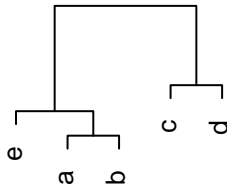
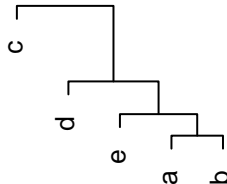
Data



Single linkage



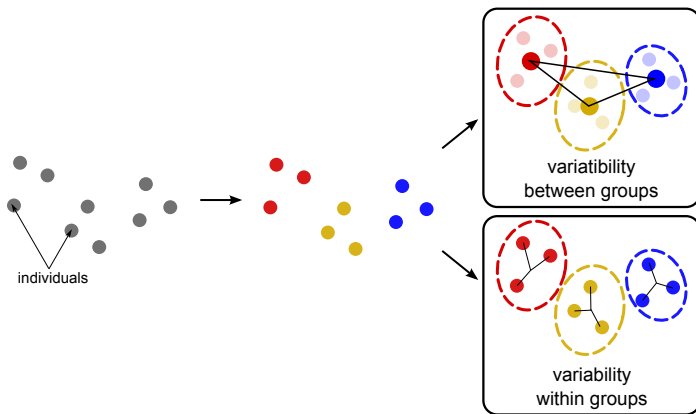
Complete linkage

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  $\mathcal{G} = \{g_1, \dots, g_k\}$  solving:

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

with:

- $\mathbf{x}_i \in \mathbb{R}^p$ : vector of allele frequencies of individual  $i$
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The K-mean problem is solved by the following algorithm:

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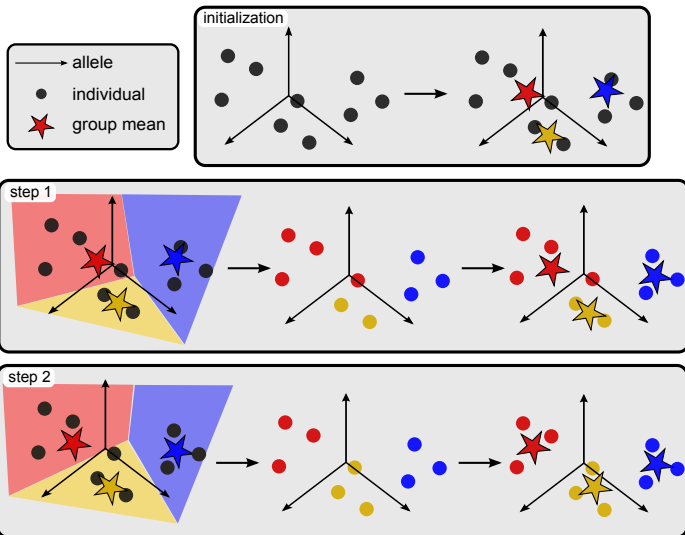
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# K-means: limitations and extensions

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

## Extension

- run K-means after dimension reduction using PCA
- try increasing values of  $K$
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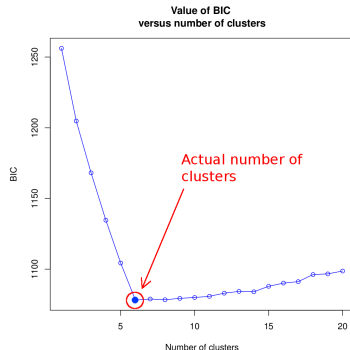
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# Genetic clustering using K-means & BIC

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

Simulated data: island model with 6 populations



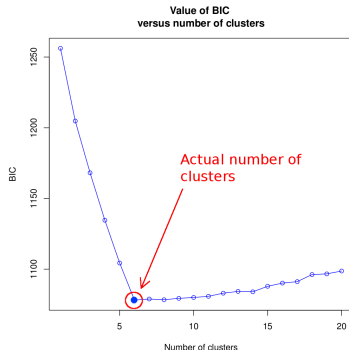
## Performances:

- 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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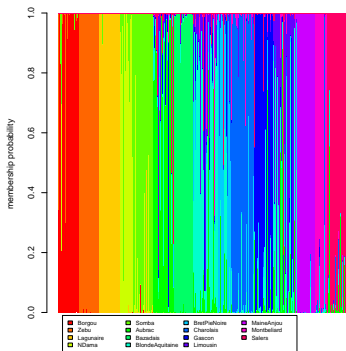
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# Why identifying clusters is not the whole story

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

Group membership probabilities:

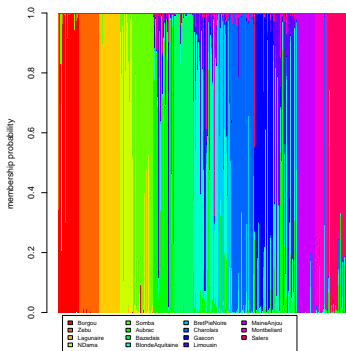


Important to assess the relationships between clusters.

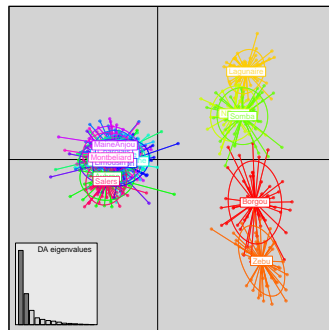
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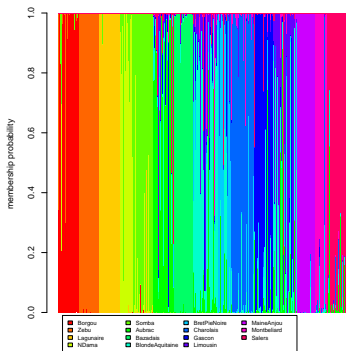


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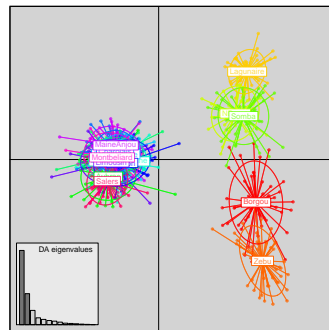
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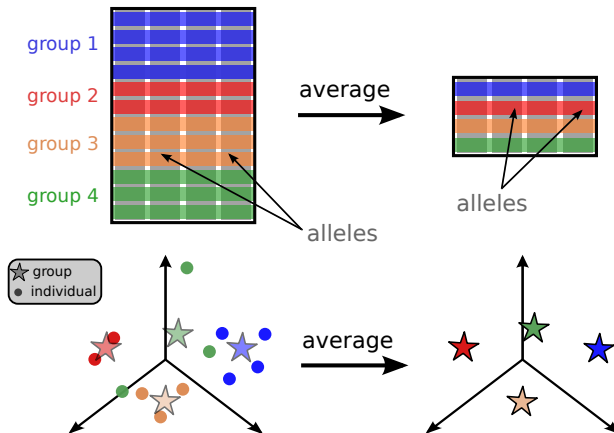


Multivariate analysis:



**Important to assess the relationships between clusters.**

## Aggregating data by groups



→ multivariate analysis of group allele frequencies.

# Analysing group data

## Available methods:

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

## Criticism:

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



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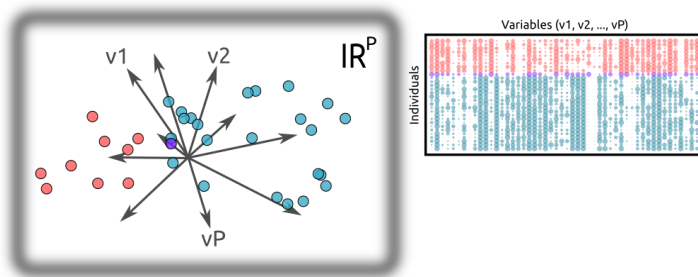
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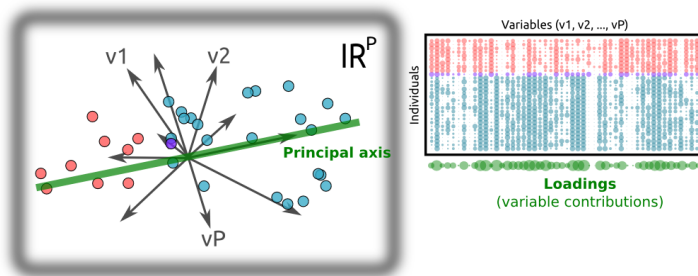
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## Multivariate analysis: reminder



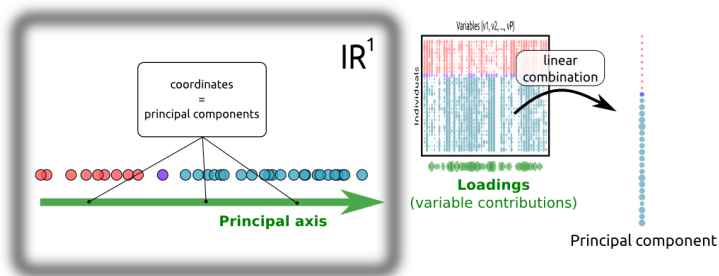
Find principal components with *maximum total variance*.

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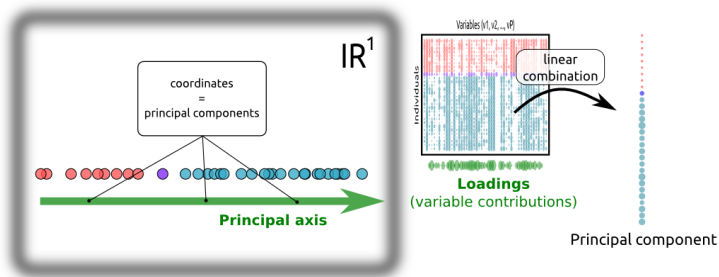
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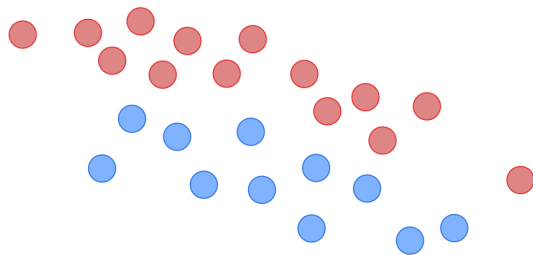
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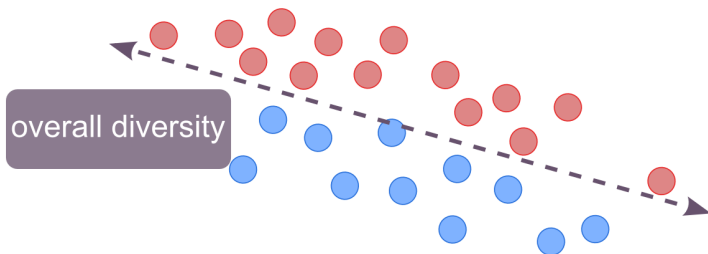
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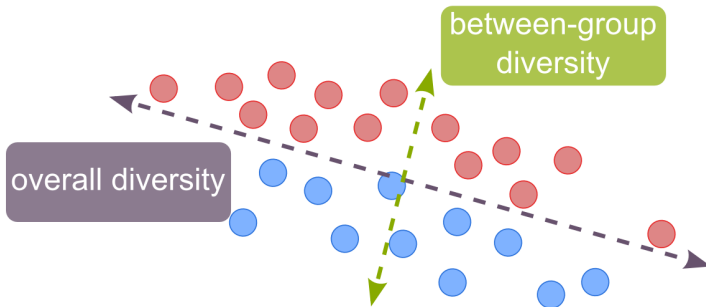
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# Optimizing different criteria

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

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

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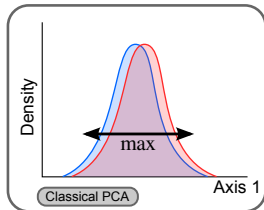
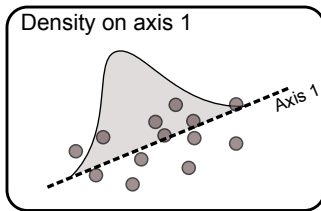
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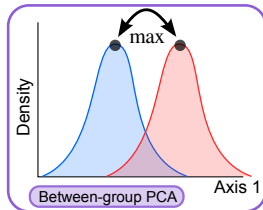
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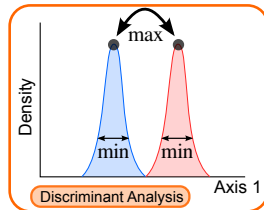
# From PCA to DA: increasing group differentiation



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)<sup>1</sup>:

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

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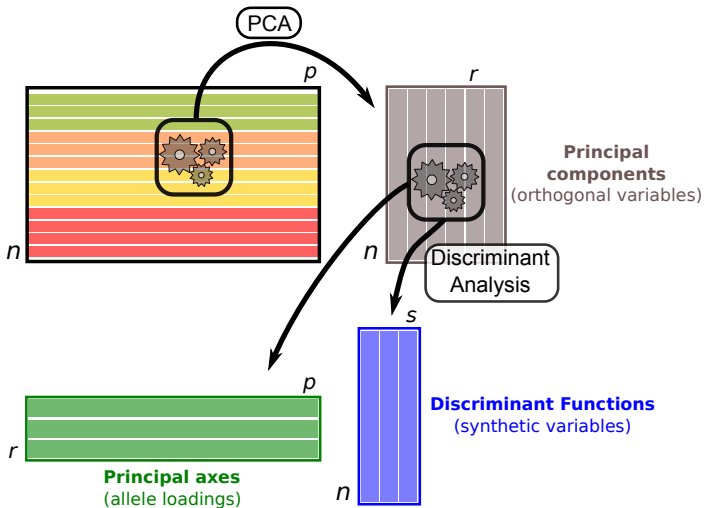
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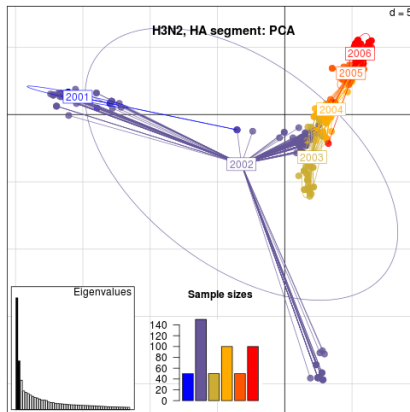
## Rationale of DAPC





## PCA of seasonal influenza (A/H3N2) data

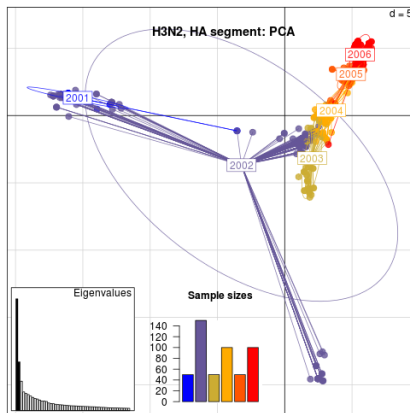
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Little temporal evolution, burst of diversity in 2002??

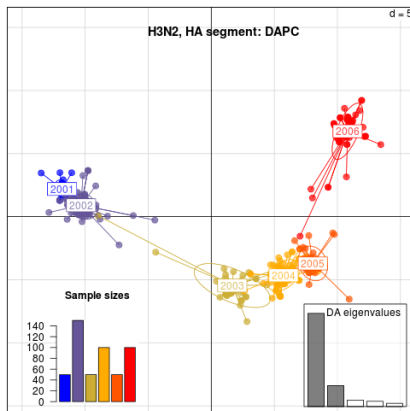
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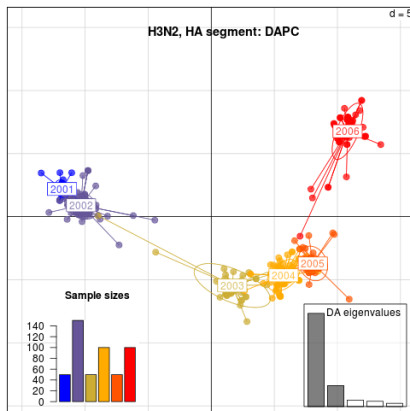
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Strong temporal signal, originality of 2006 isolates (new alleles).

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## 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 Barcelona, October 2015"