Imperial College London

MRC Centre for Outbreak Analysis and Modelling

Multivariate analysis of genetic data: an introduction

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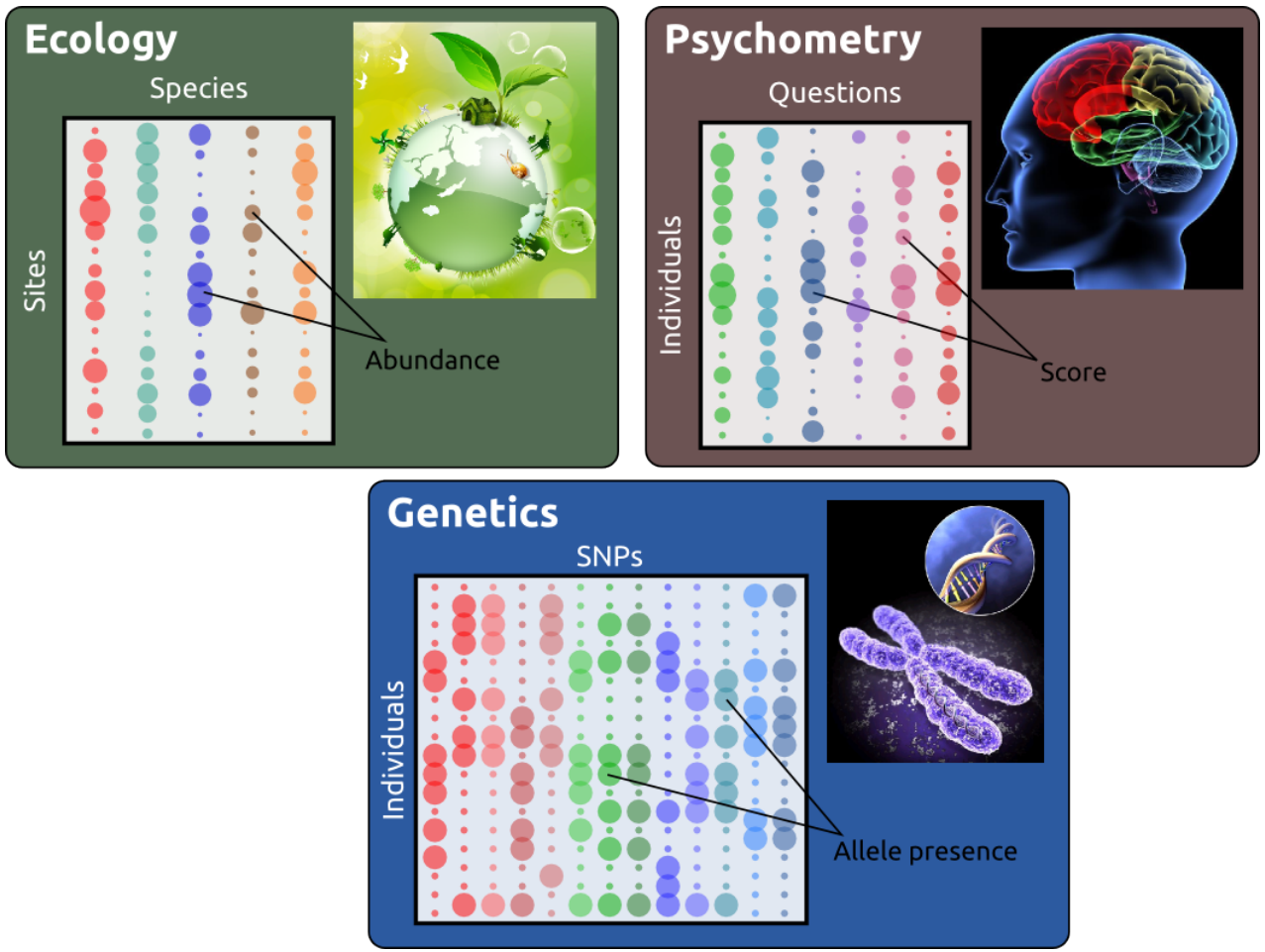
Outline

Outline

Multivariate data: some examples



Association between individuals? Correlations between variables?

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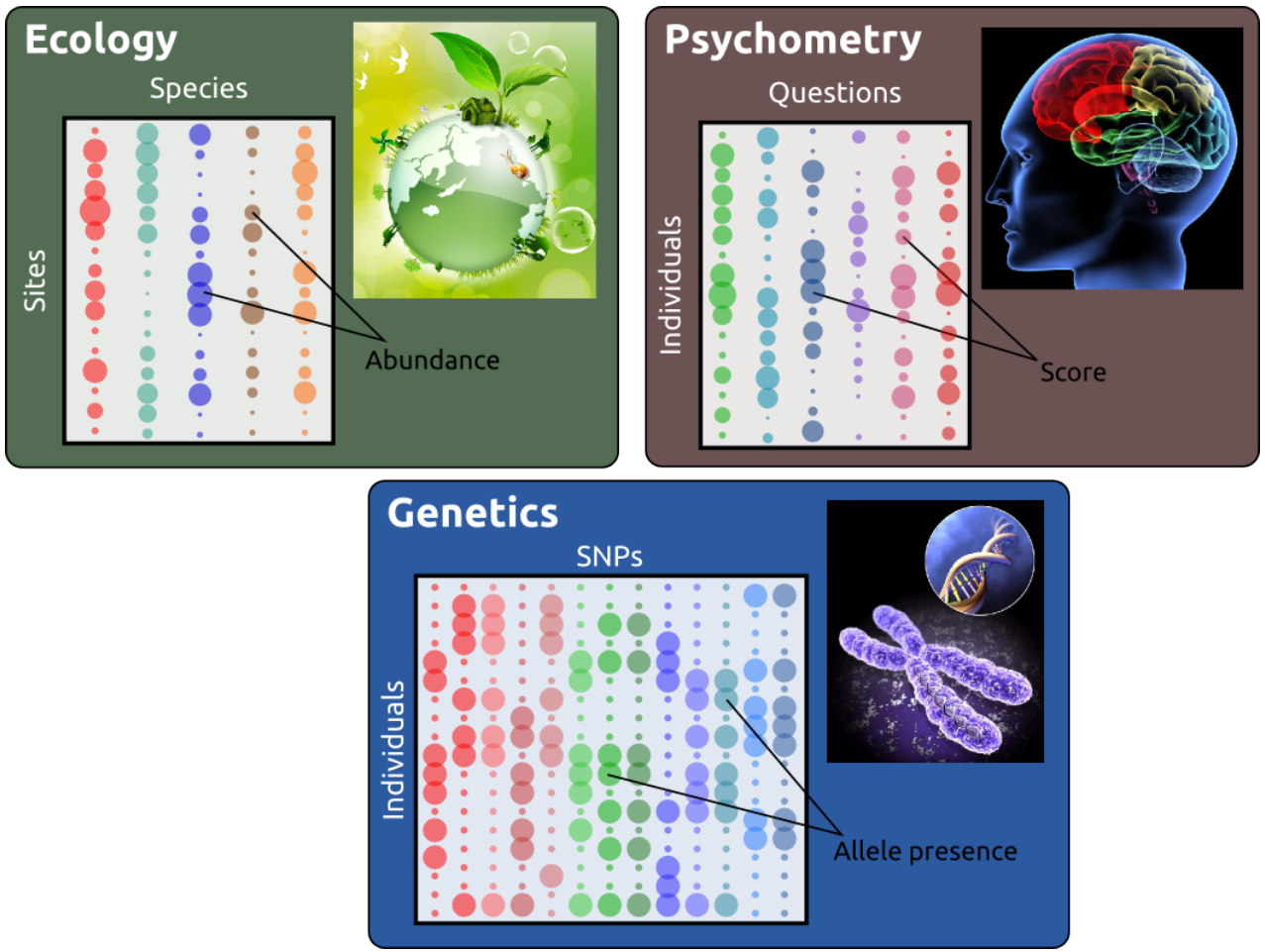

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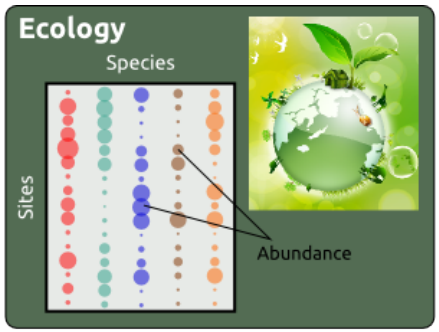
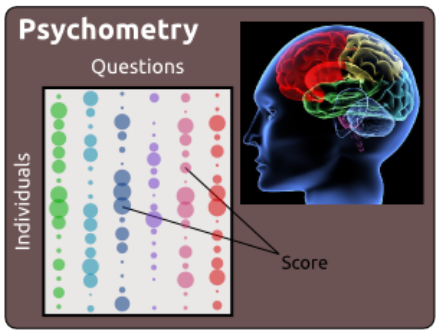
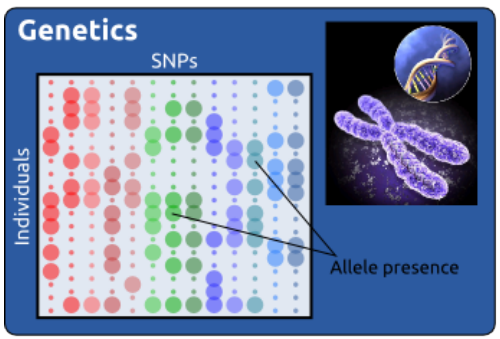
Multivariate analysis to summarize diversity







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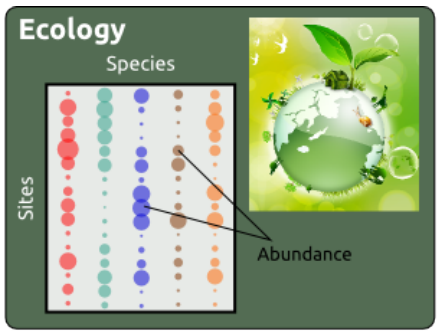
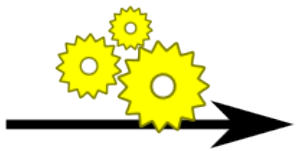
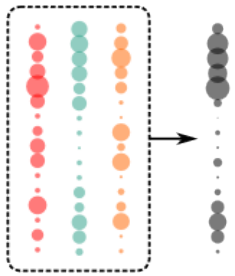
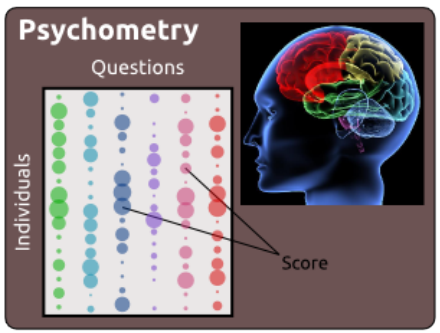


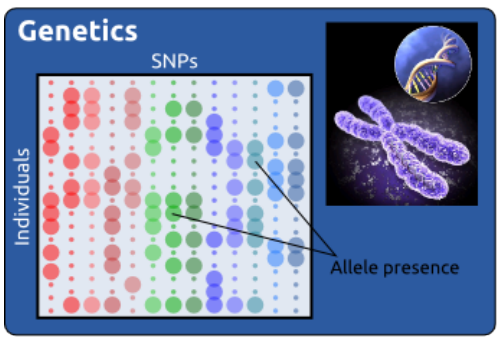




Species assemblage #1

Species assemblage #2





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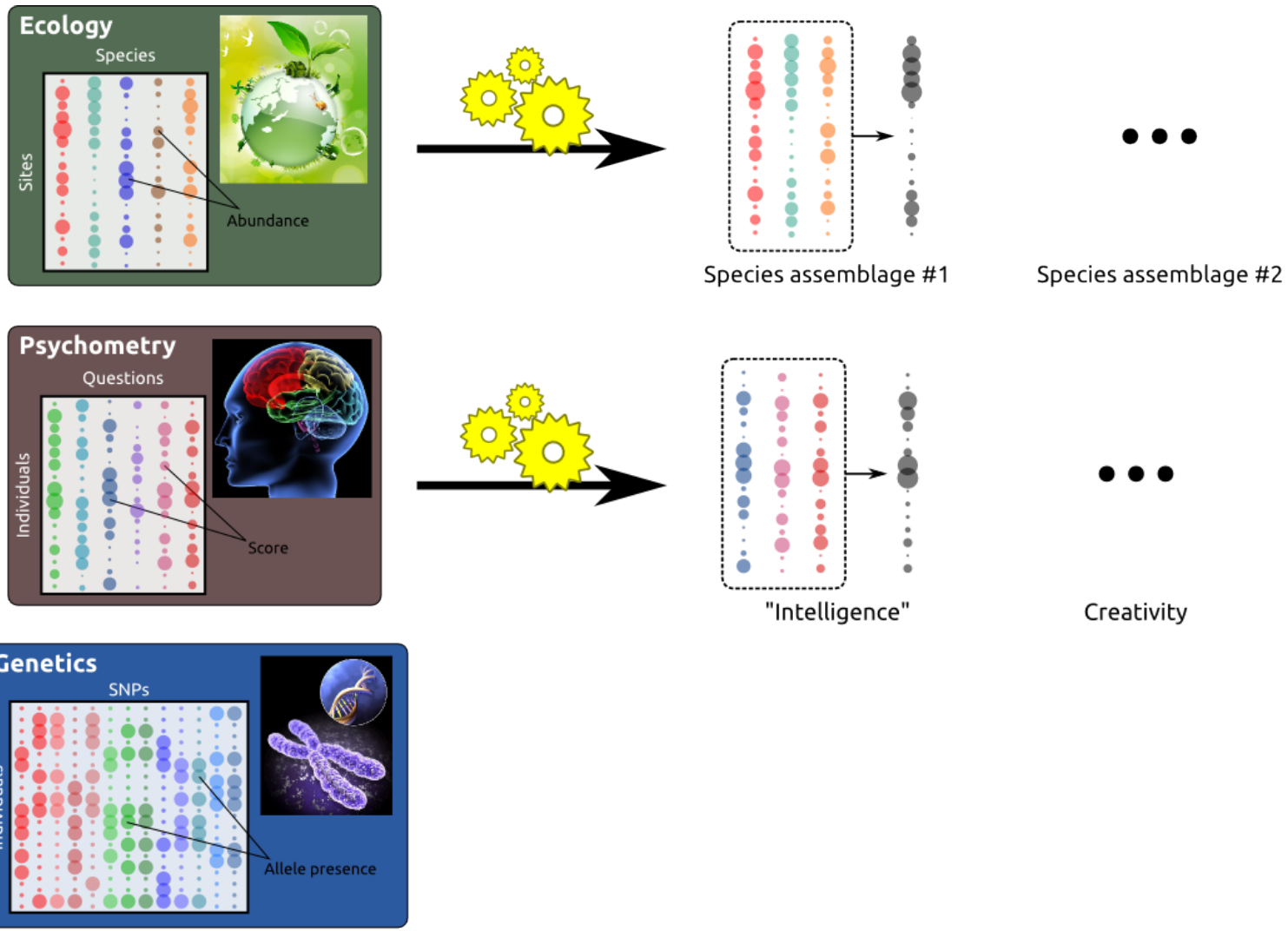

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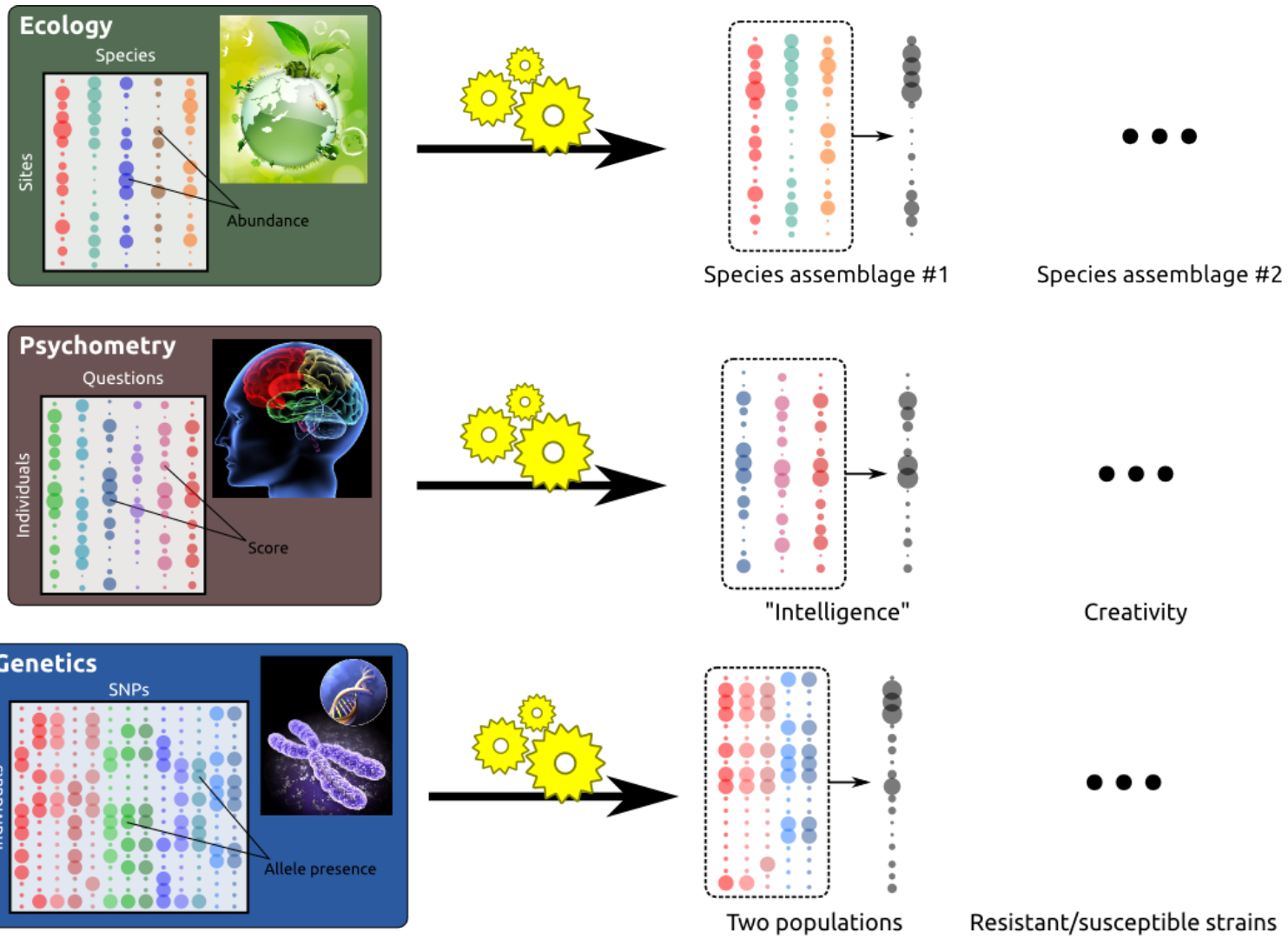

Multivariate analysis: an overview

Multivariate analysis, a.k.a:

- "*dimension reduction techniques*"
- "*ordinations in reduced space*"
- "*factorial methods*"

Purposes:

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Differences lie in input data:

- quantitative/binary variables: *Principal Component Analysis* (PCA)
- 2 categorical variables: *Correspondance Analysis* (CA)
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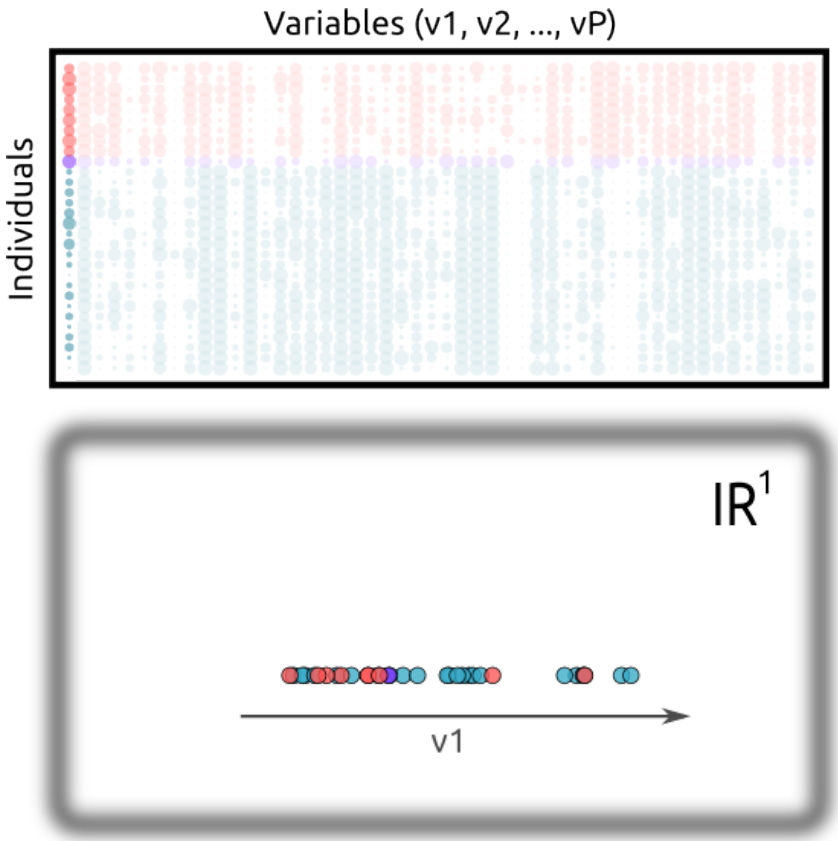
1 dimension, 2 dimensions, P dimensions



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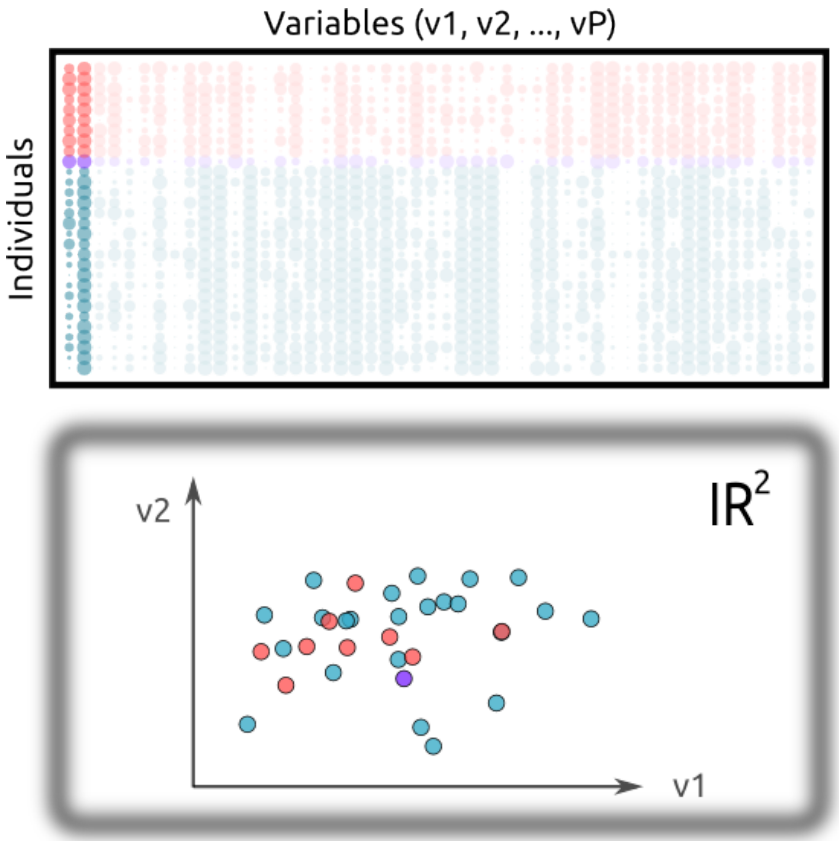

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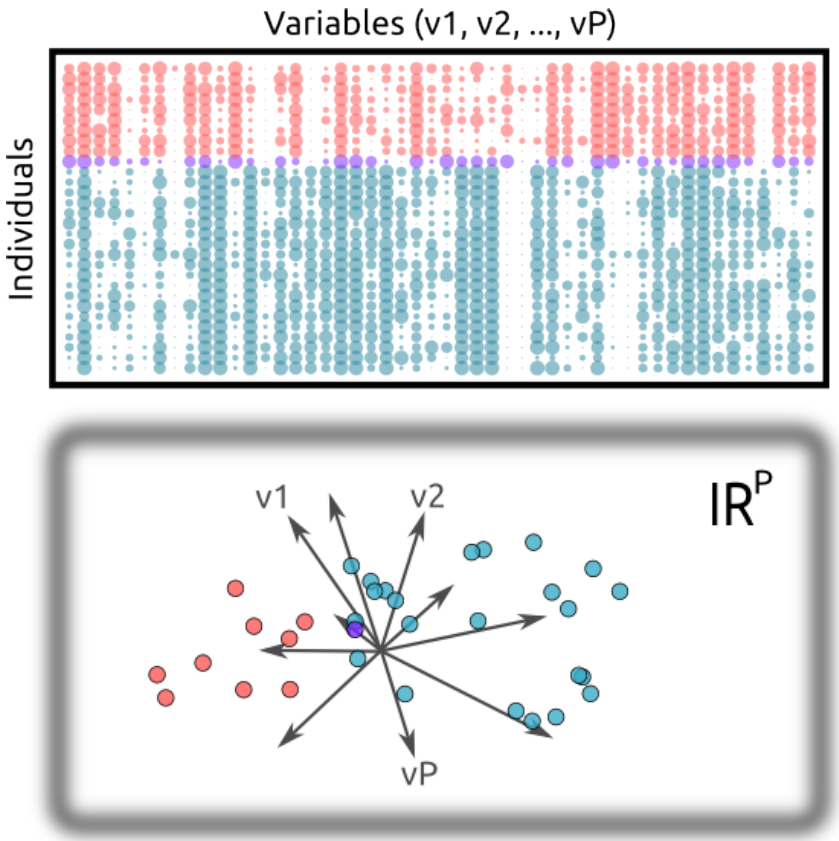

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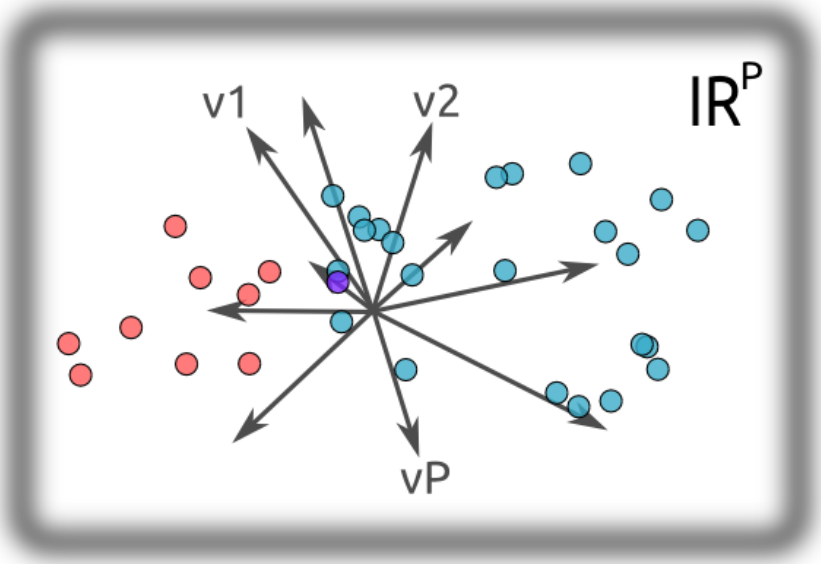
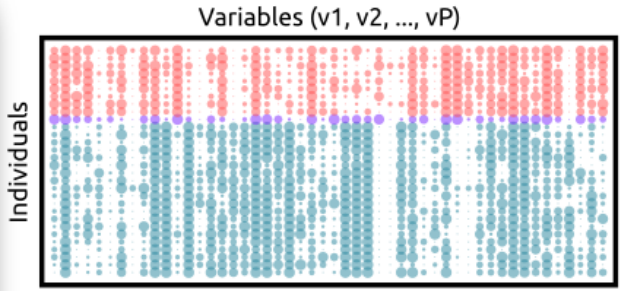
Reducing P dimensions into 1





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- $\mathbf{Q} \in \mathbb{R}^{P \times P}$ metric in $\mathbb{R}^P$; $\mathbf{D} \in \mathbb{R}^{N \times N}$ metric in $\mathbb{R}^N$
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- $\mathbf{v} \in \mathbb{R}^N$; $\mathbf{v} = \mathbf{XQu}$: **principal component**

$\rightarrow$ find $\mathbf{u}$ so that $\|\mathbf{v}\|^2_{\mathbf{D}}$ is maximum.

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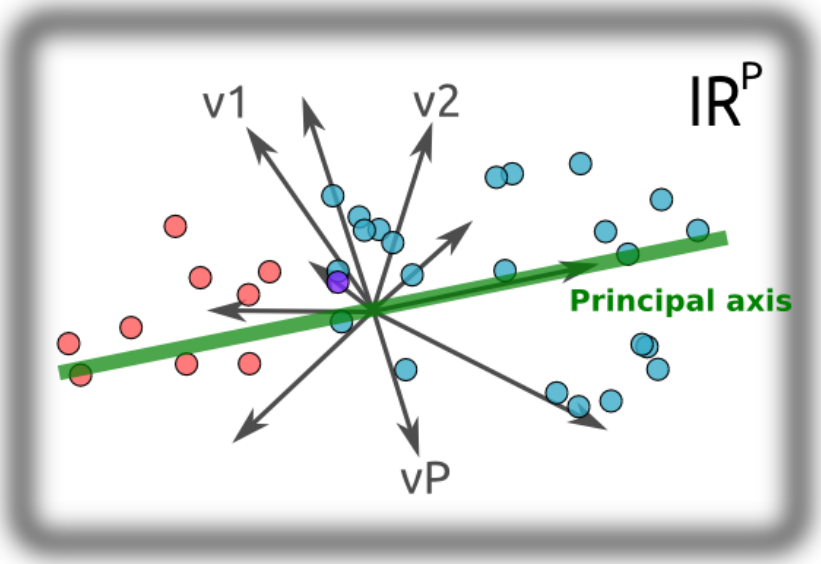

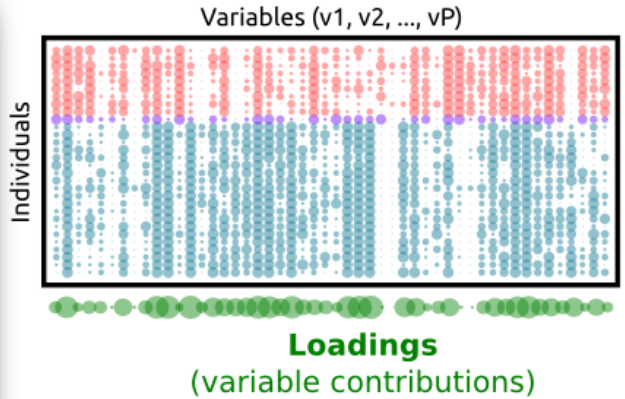

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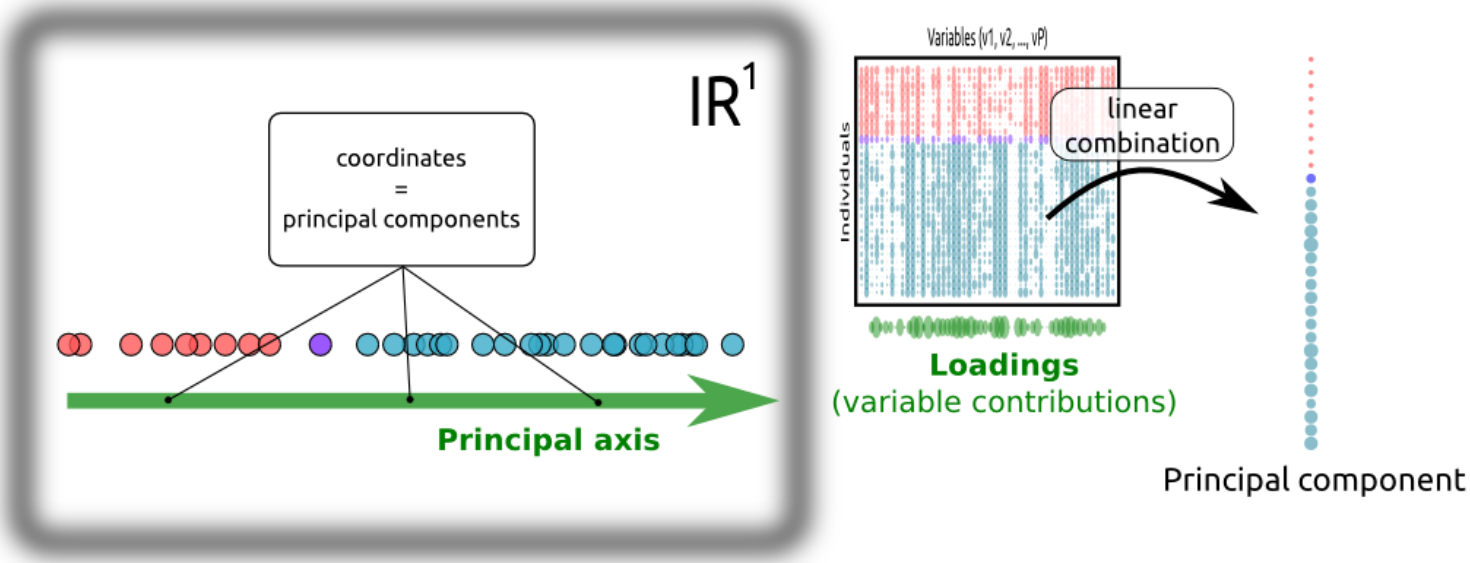

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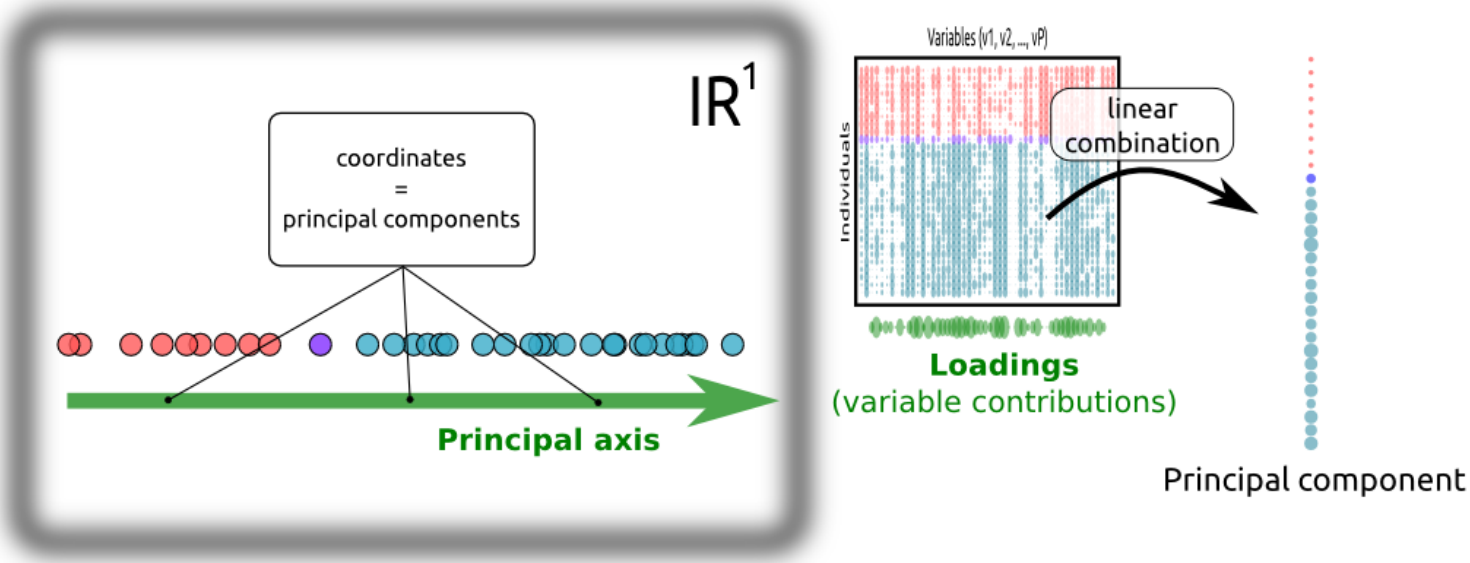

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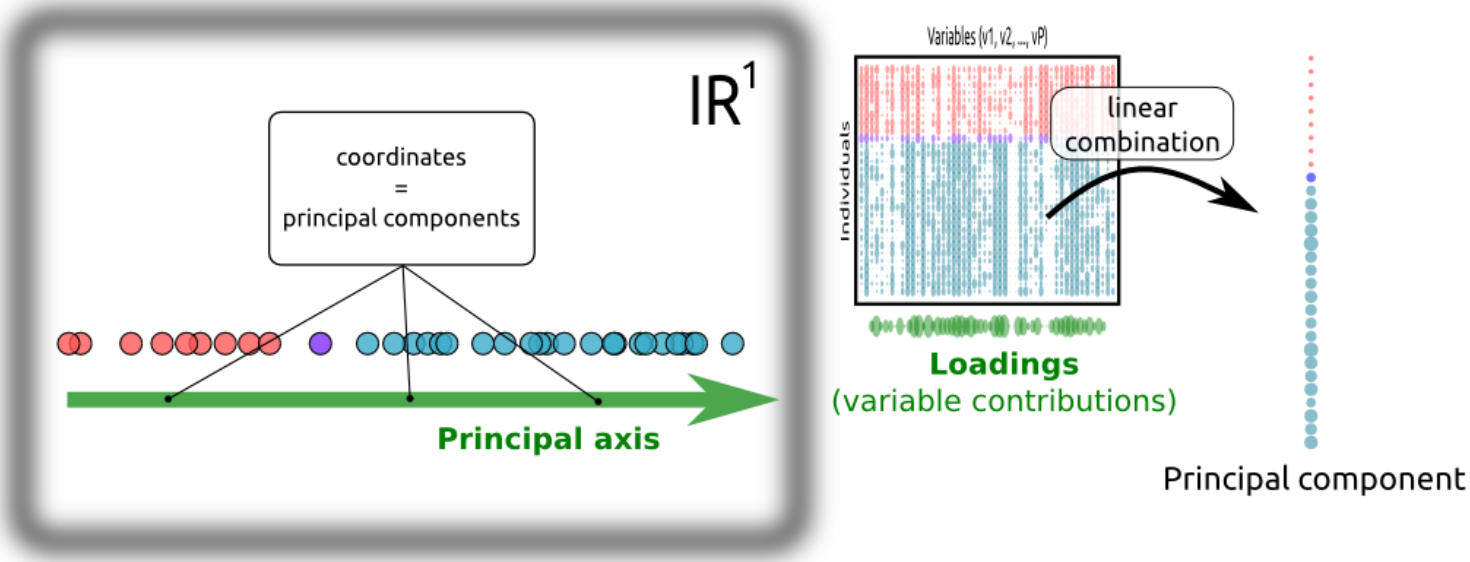

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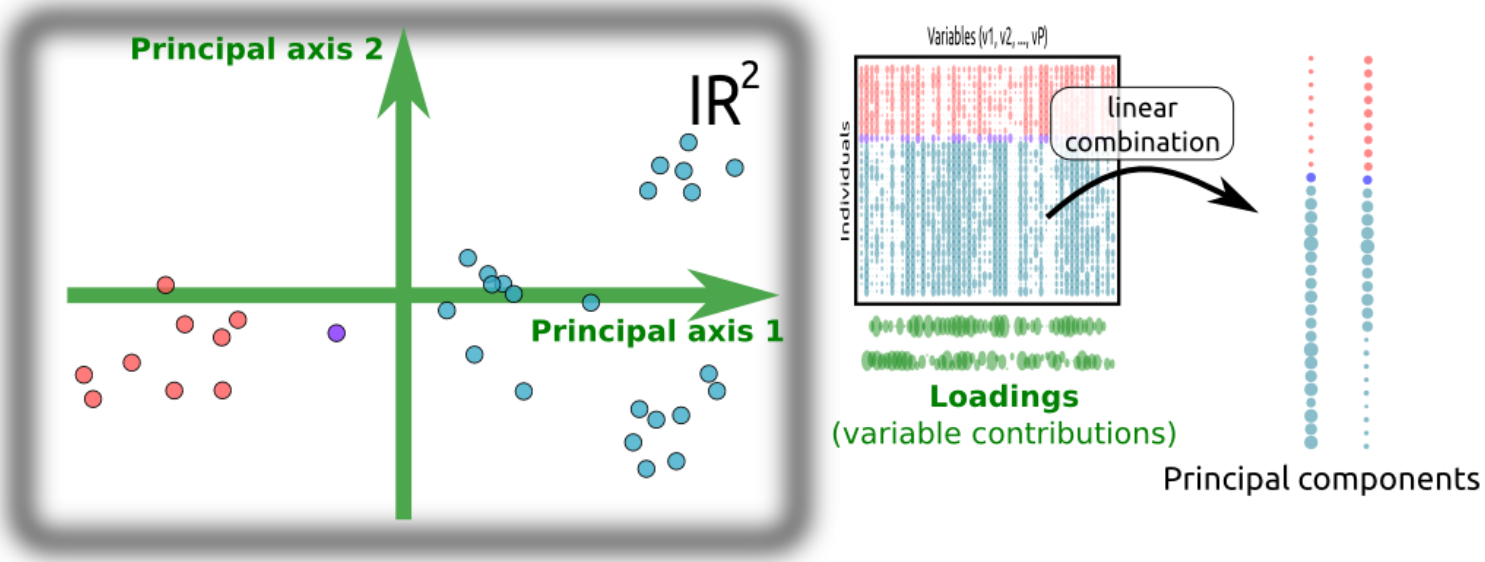

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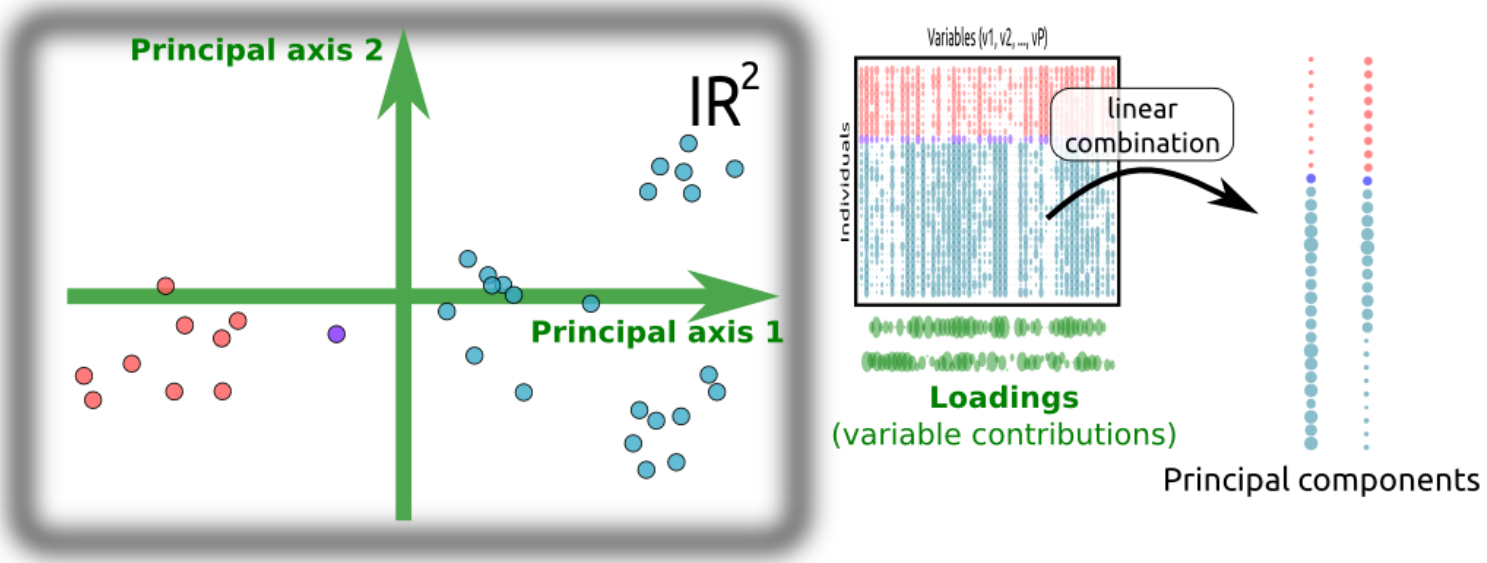

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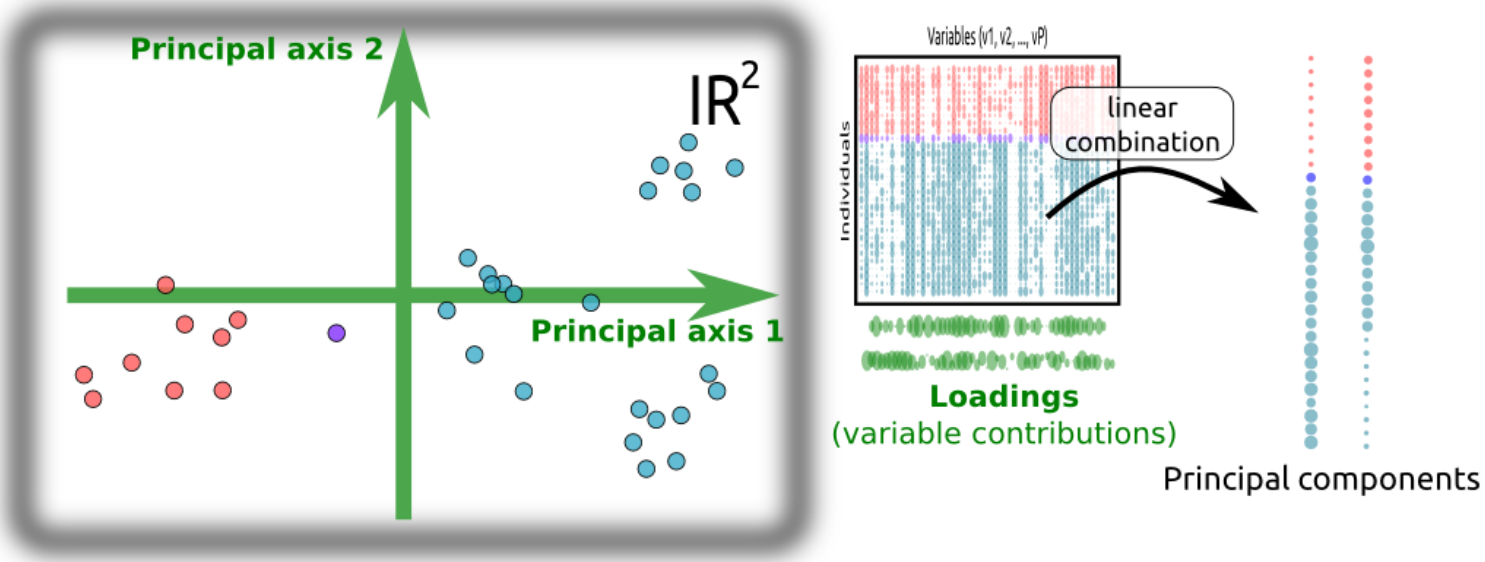

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How do we do this?

Things that don't change:

- take $\mathbf{u}_i$ the i-th eigenvector of the $\mathbf{Q}$-symmetric matrix $\mathbf{X}^T\mathbf{D}\mathbf{X}\mathbf{Q}$
- (alternatively) take $\mathbf{v}_i$ the i-th eigenvector of the $\mathbf{D}$-symmetric matrix $\mathbf{X}\mathbf{Q}\mathbf{X}^T\mathbf{D}$

Things that change:

- pre-transformations of $\mathbf{X}$ (recoding, standardisation, etc.)
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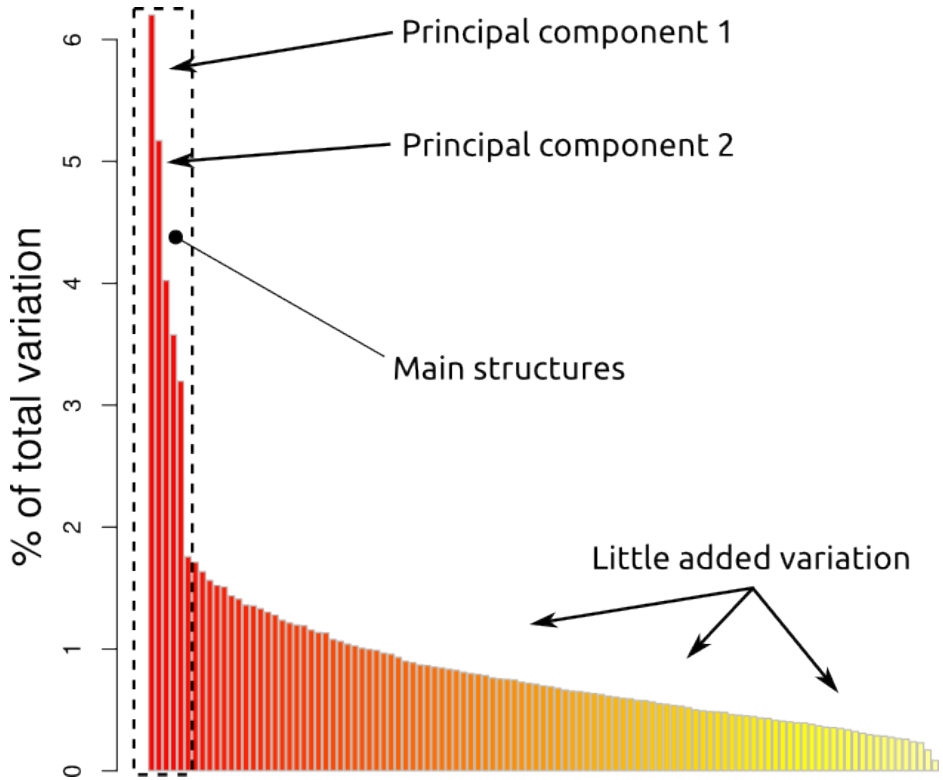
packages: *ade4*, *vegan*

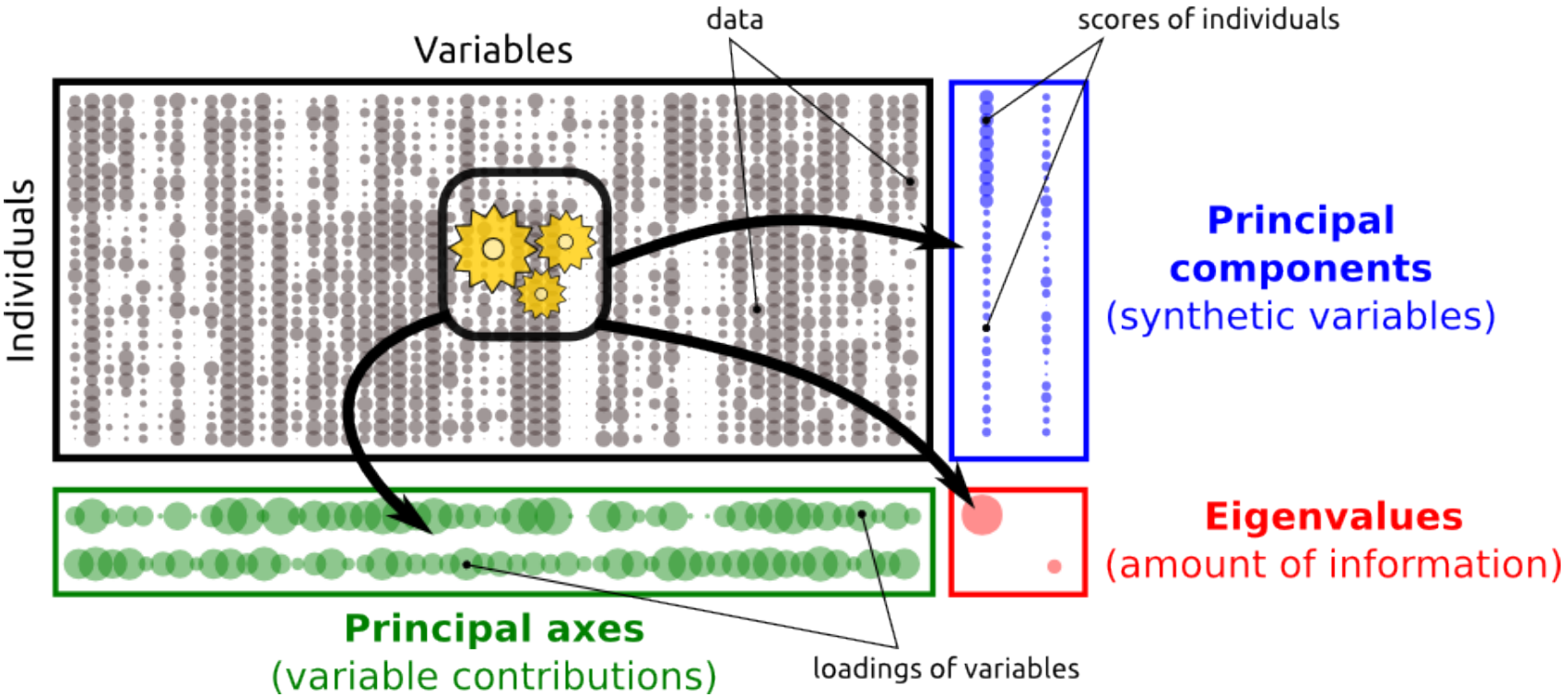
How many principal components to retain?

Choice based on "**screeplot**": barplot of eigenvalues



Retain only "significant" structures... but not trivial ones.

Outputs of multivariate analyses: an overview



Main outputs:

- **principal components**: diversity amongst individuals
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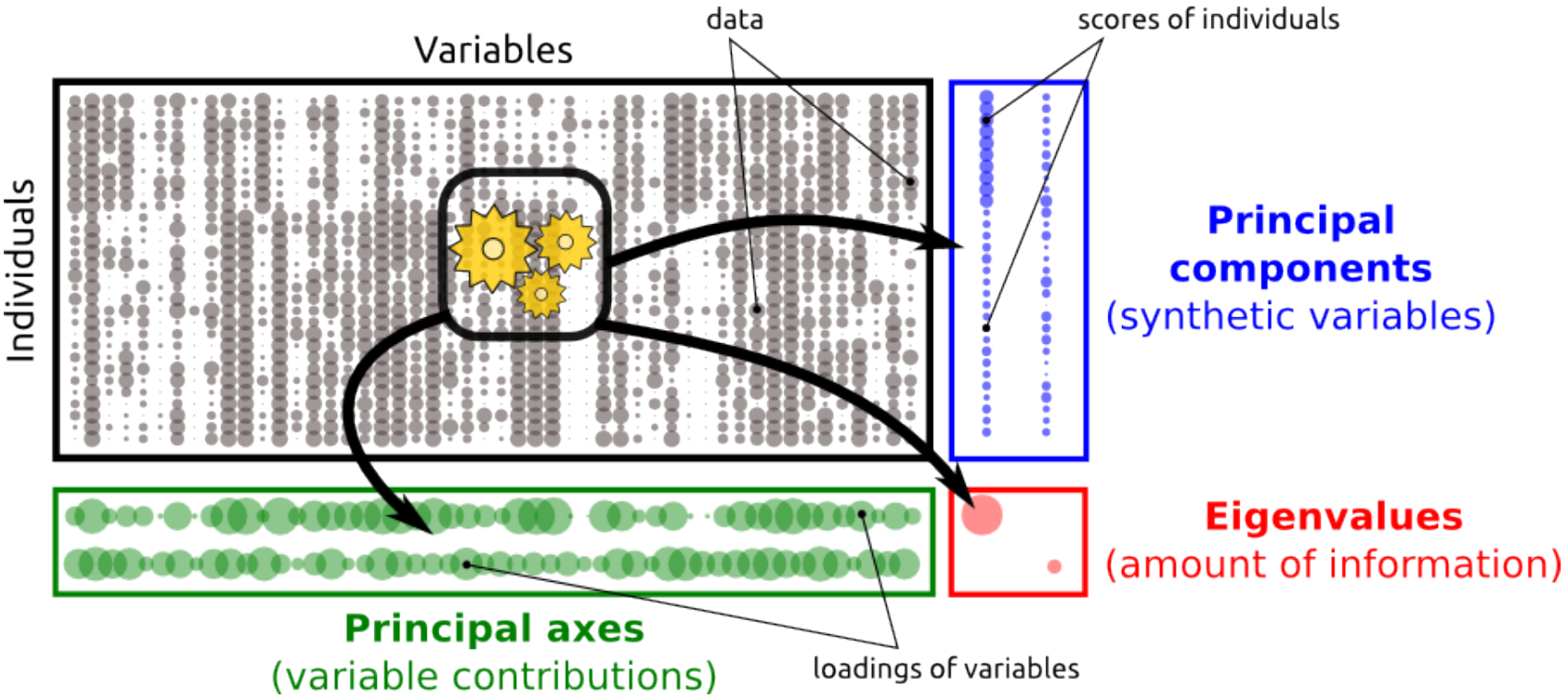

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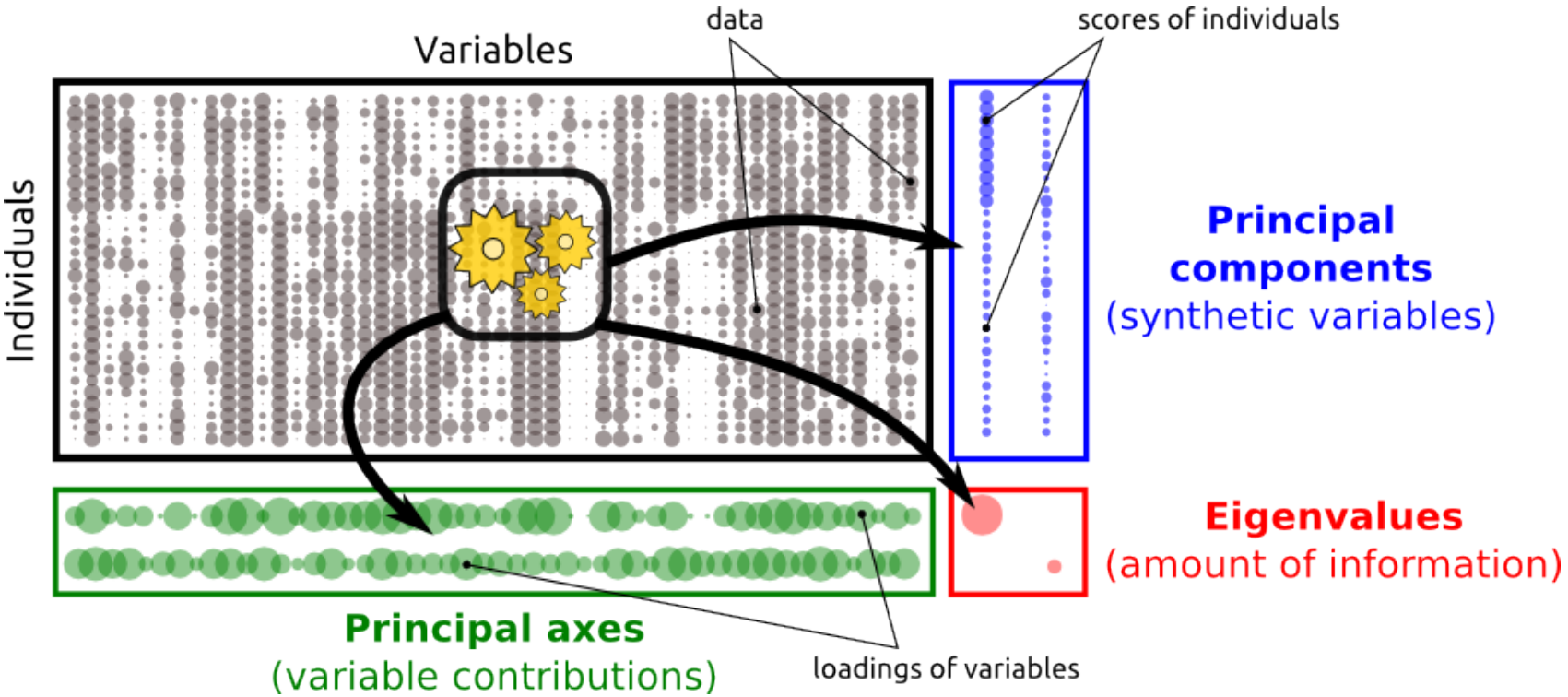

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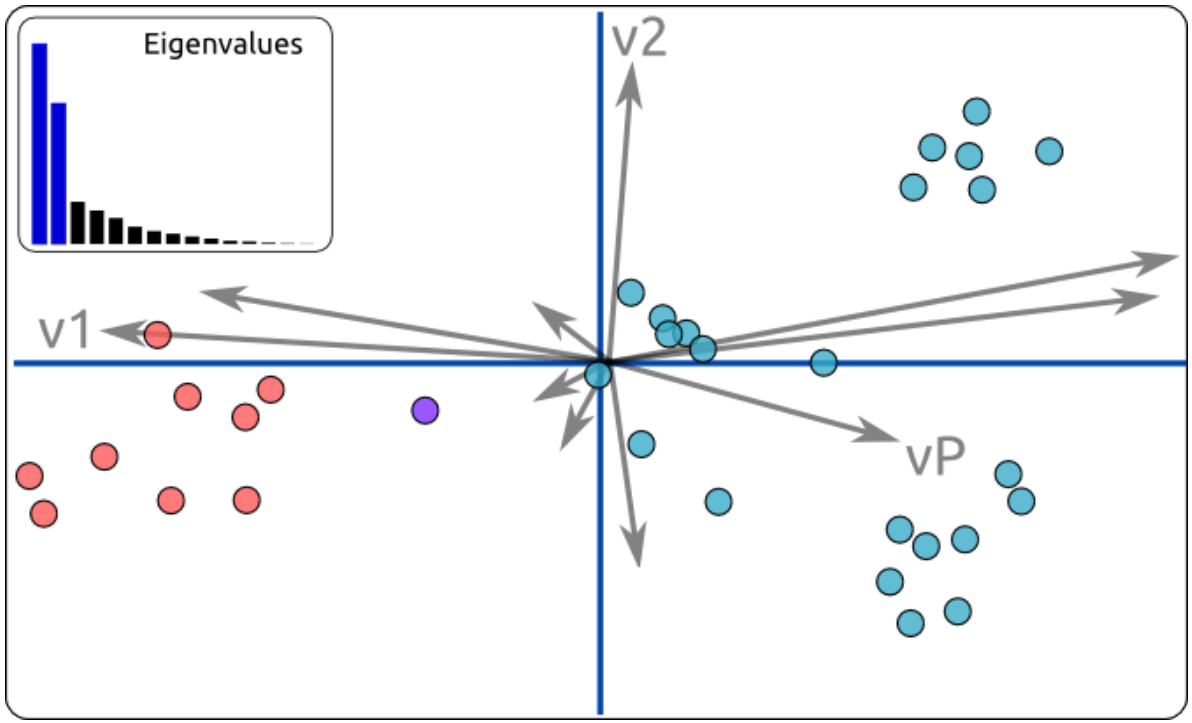
Usual summary of an analysis: the biplot



Biplot: principal components (points) + loadings (arrows)

- groups of individuals
- structuring variables (longest arrows)
- magnitude of the structures

Multivariate analysis in a nutshell

- **variety of methods** for different types of variables
- **principal components** (PCs) summarize diversity
- **variable loadings** identify discriminating variables
- other uses of PCs: **maps** (spatial structures), **models** (response variables or predictors), ...

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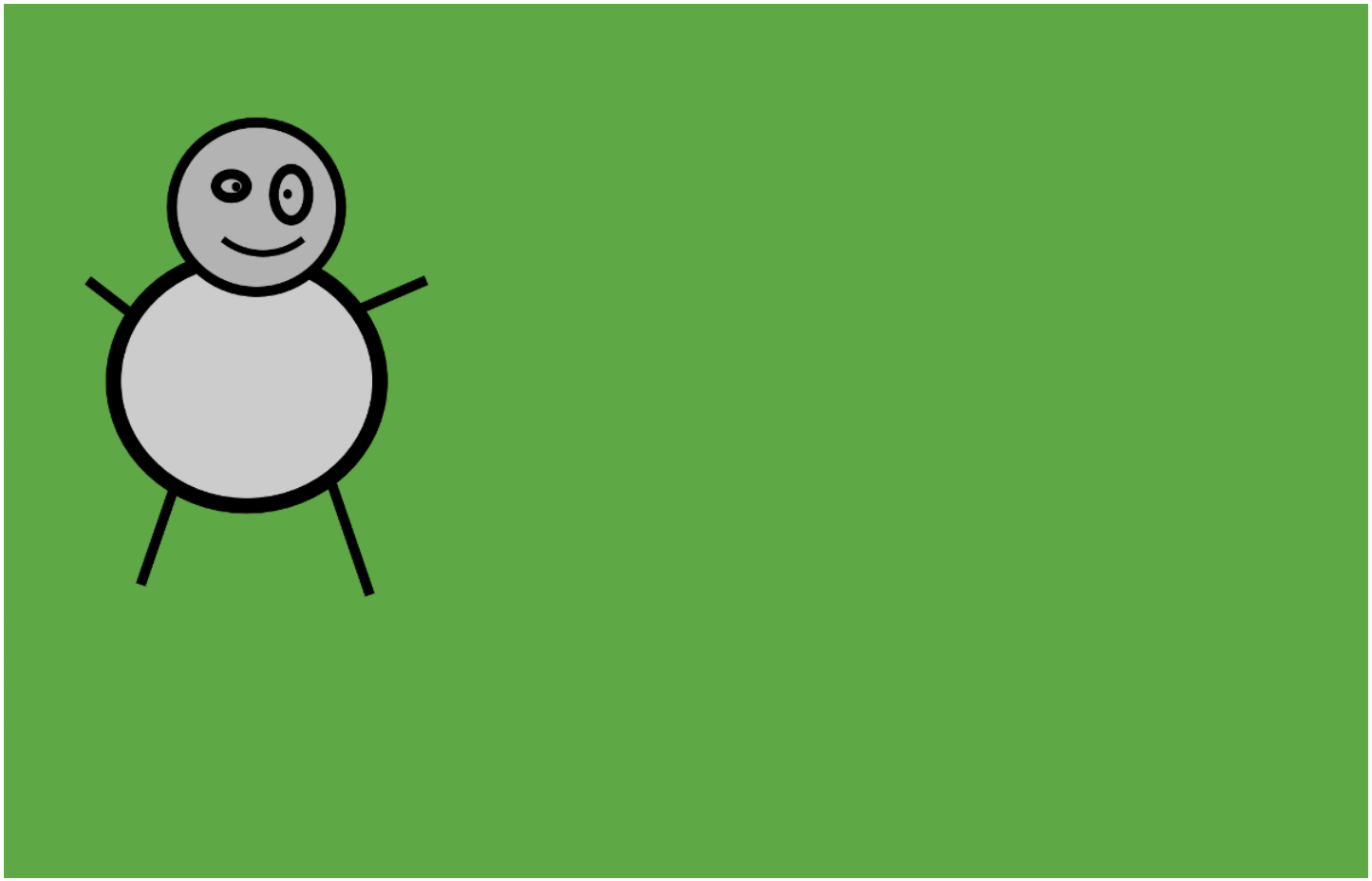

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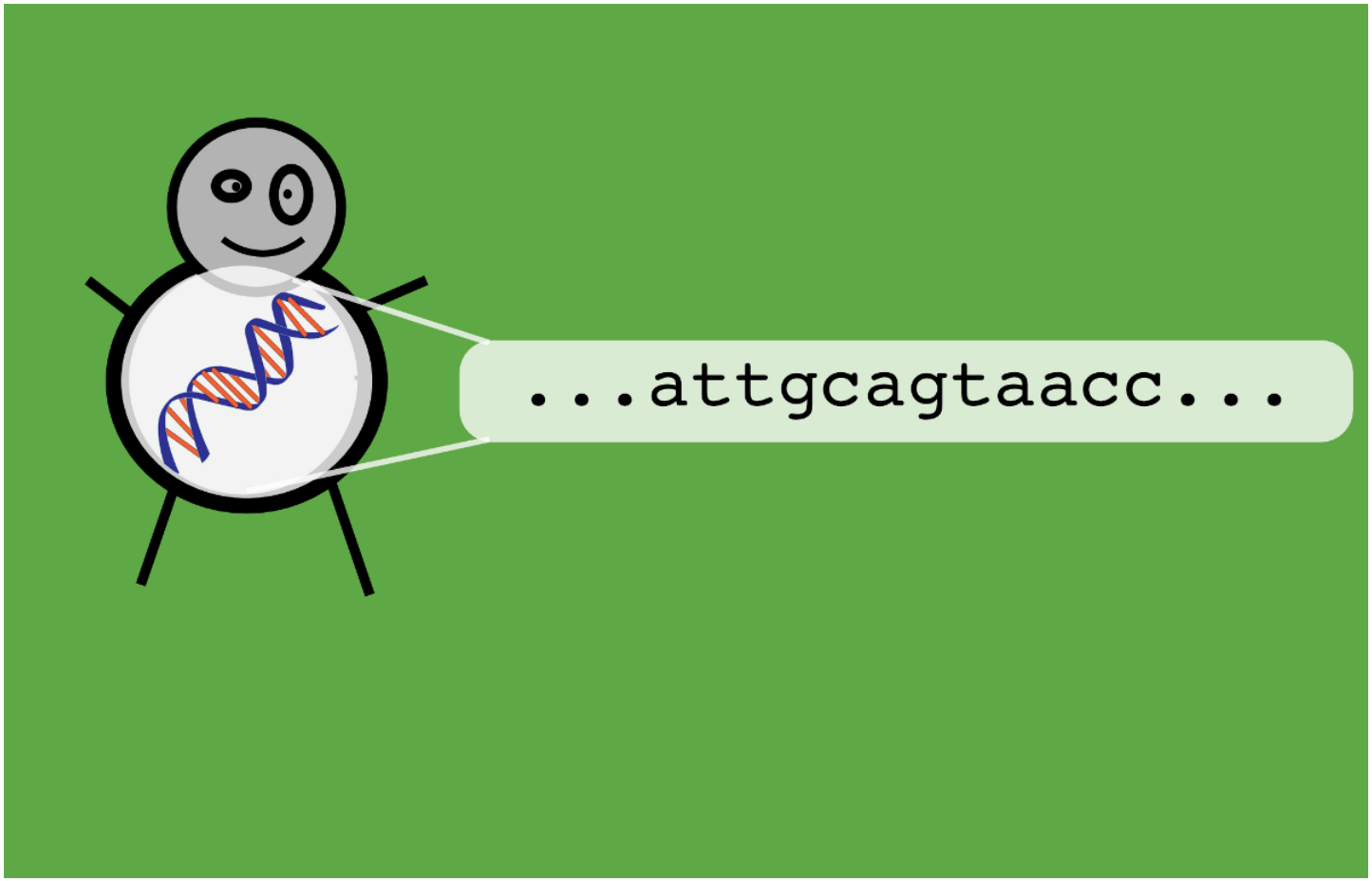

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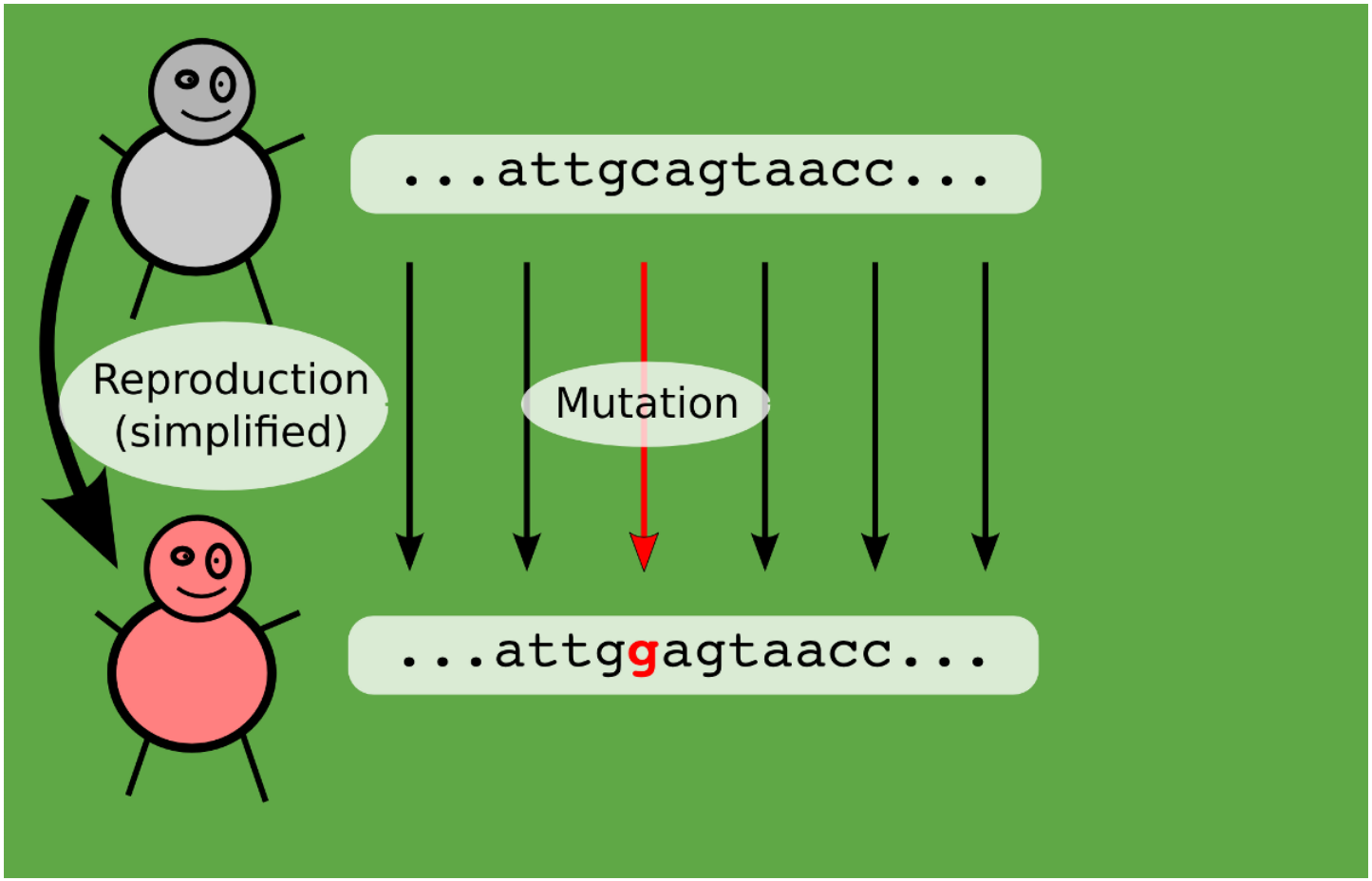

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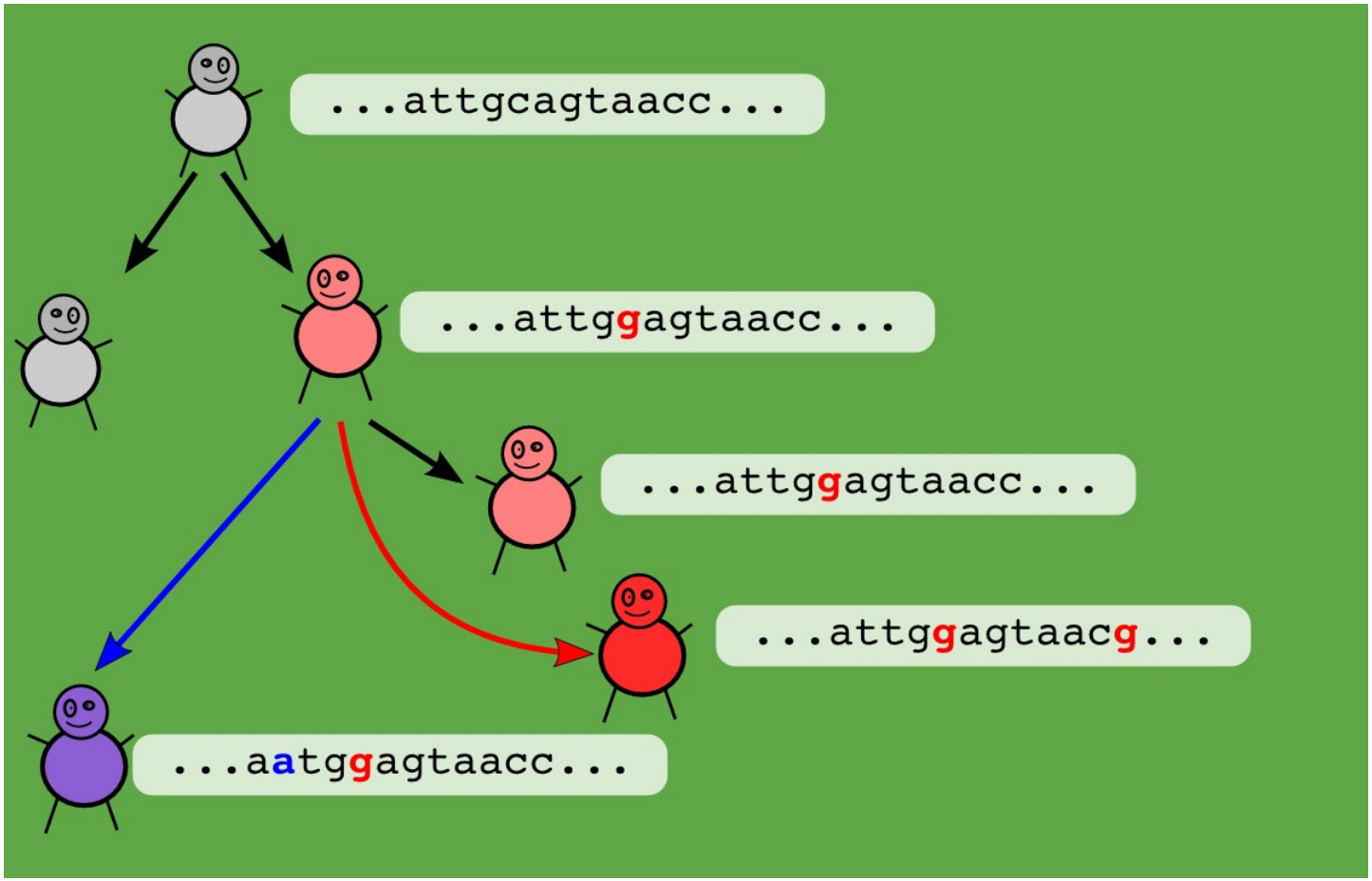

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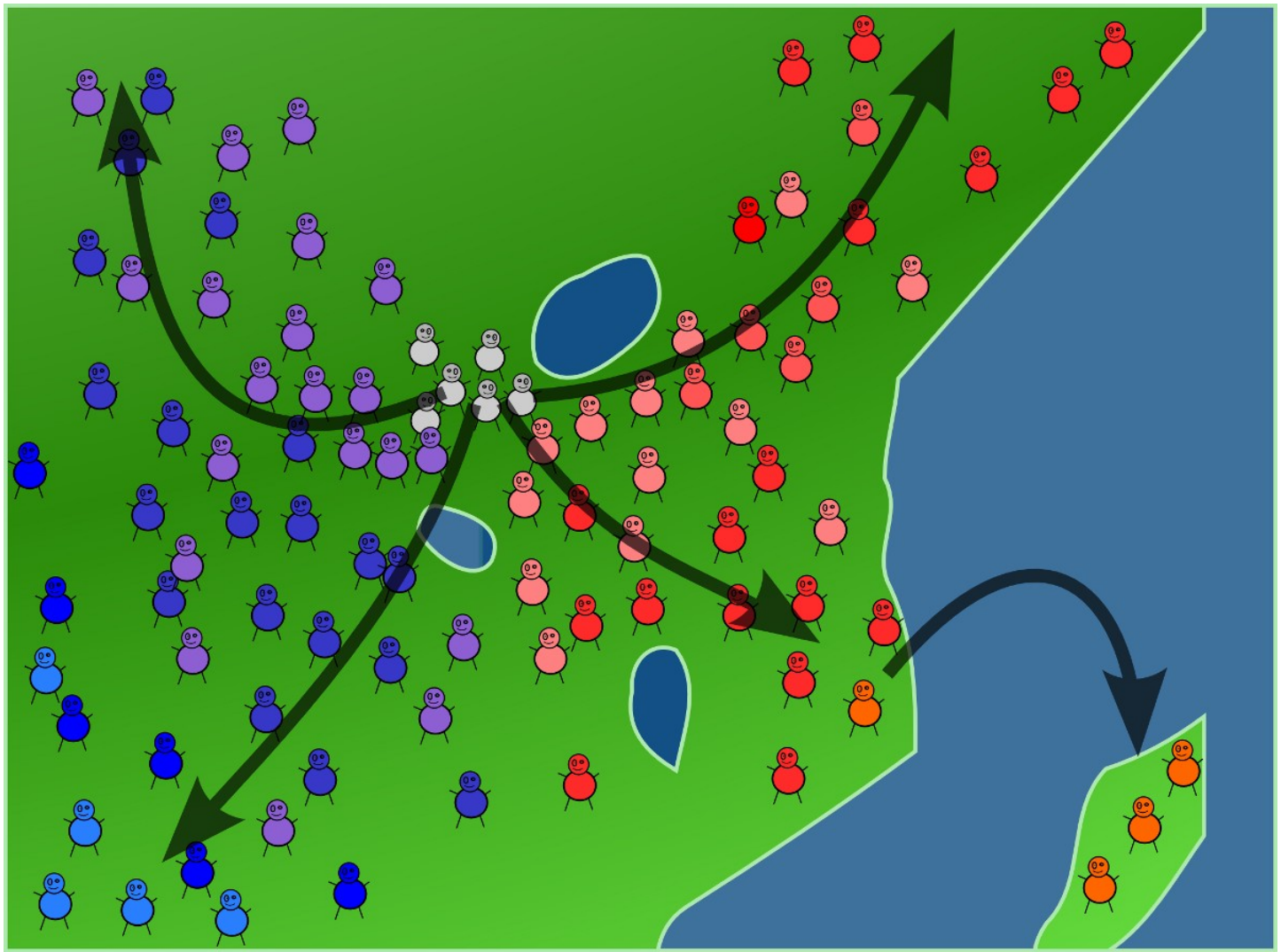

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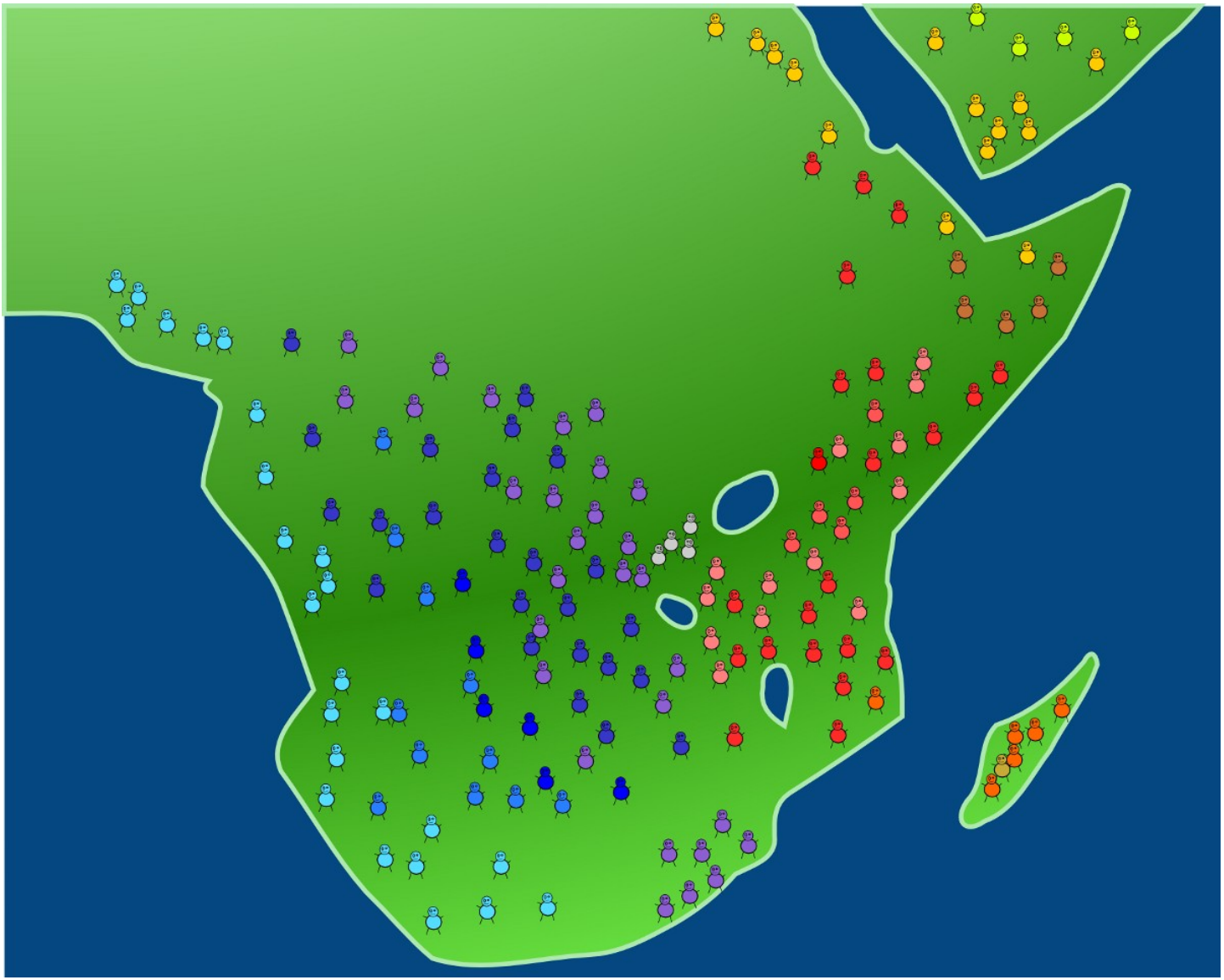

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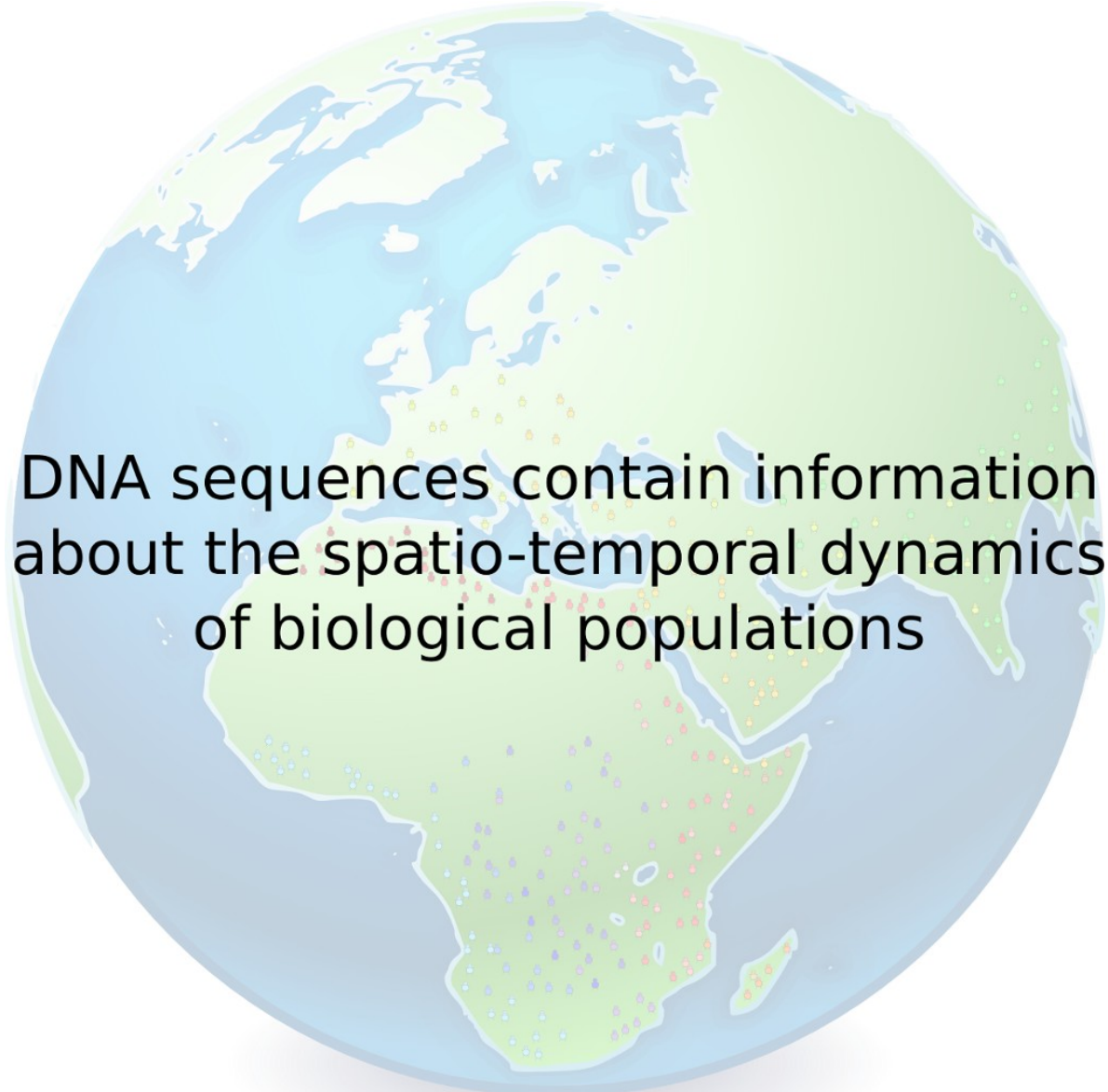

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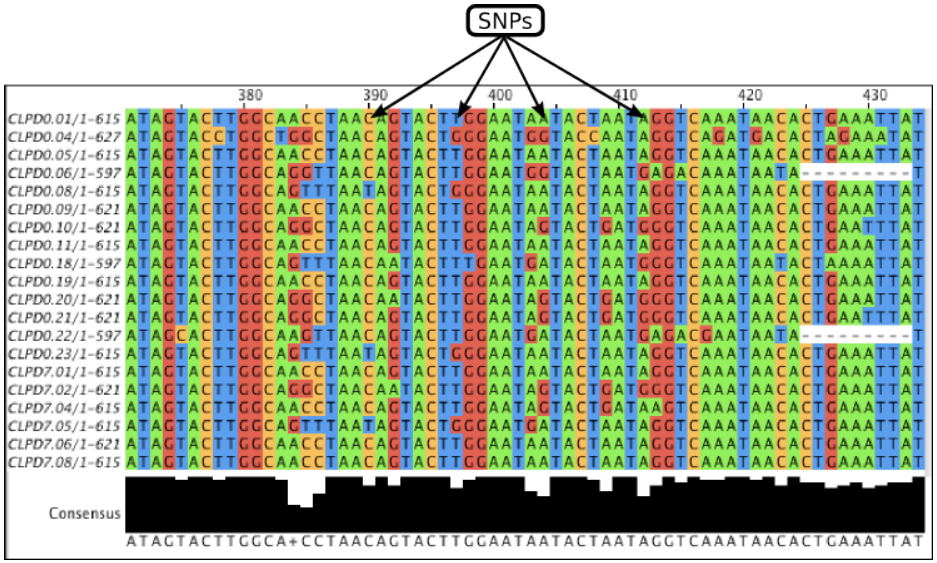

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- more generally, most genetic data can be treated as frequencies

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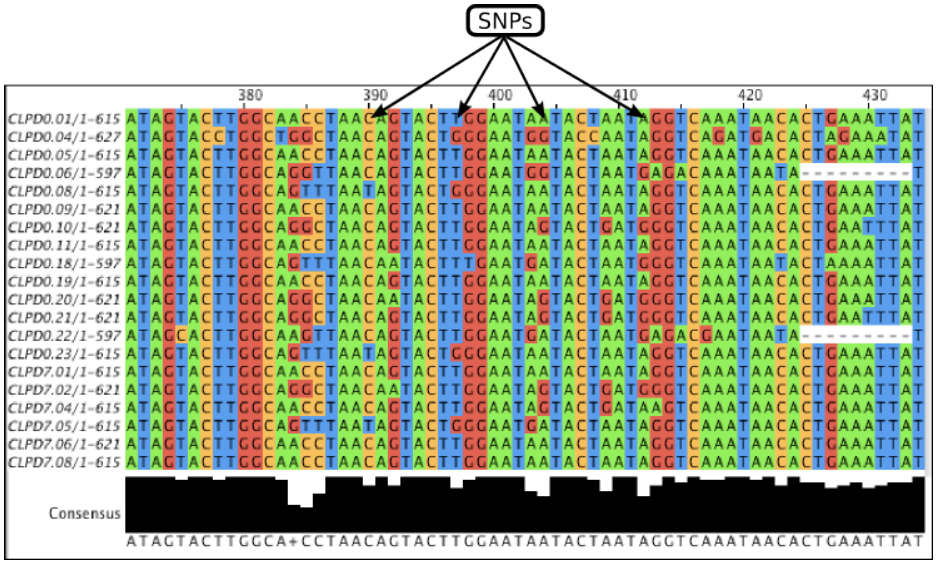

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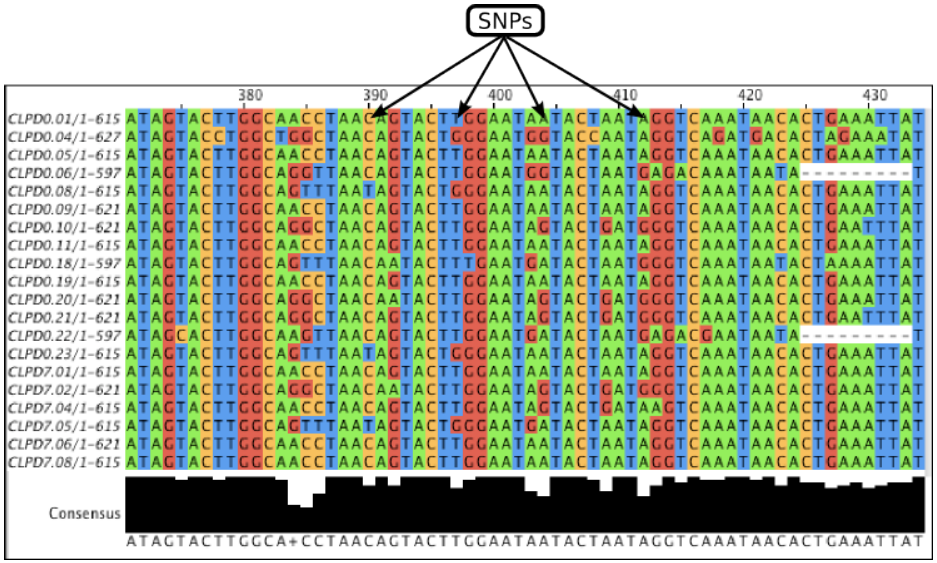

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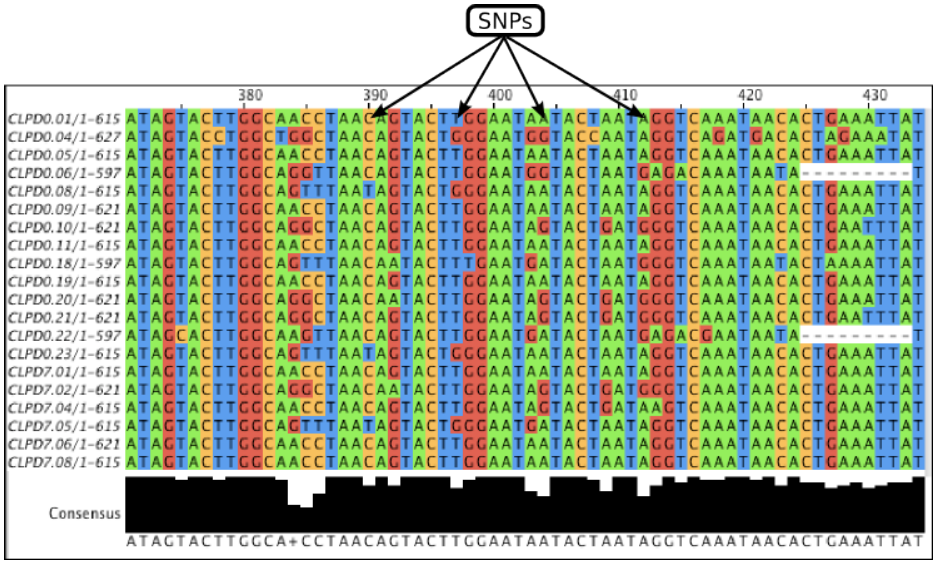

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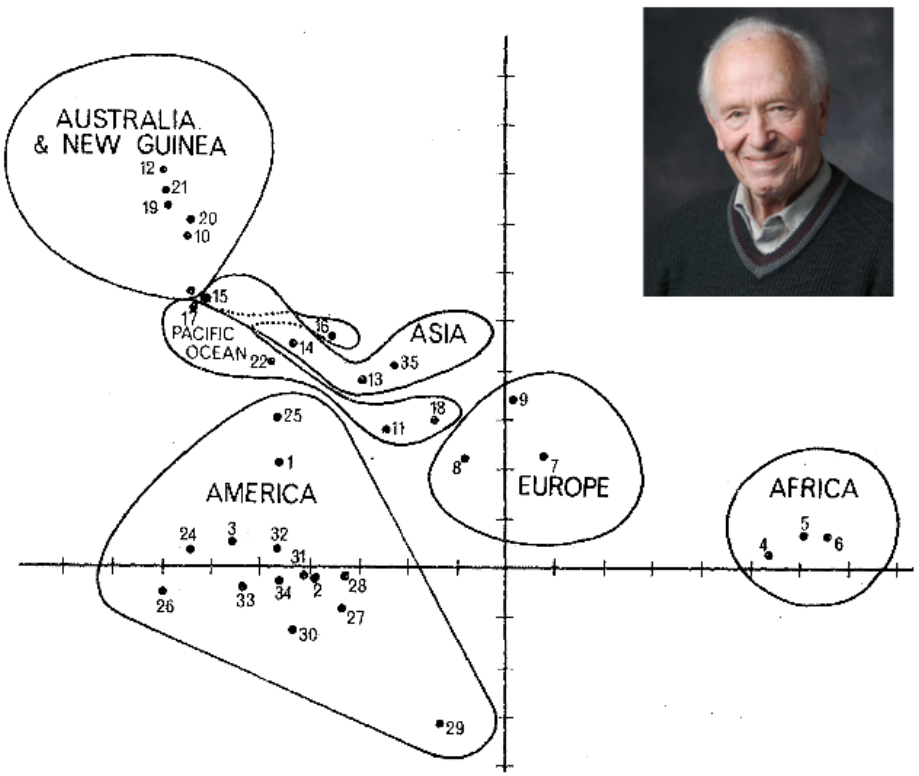
PCA of genetic data, native human populations (Cavalli-Sforza 1966, *Proc B*)



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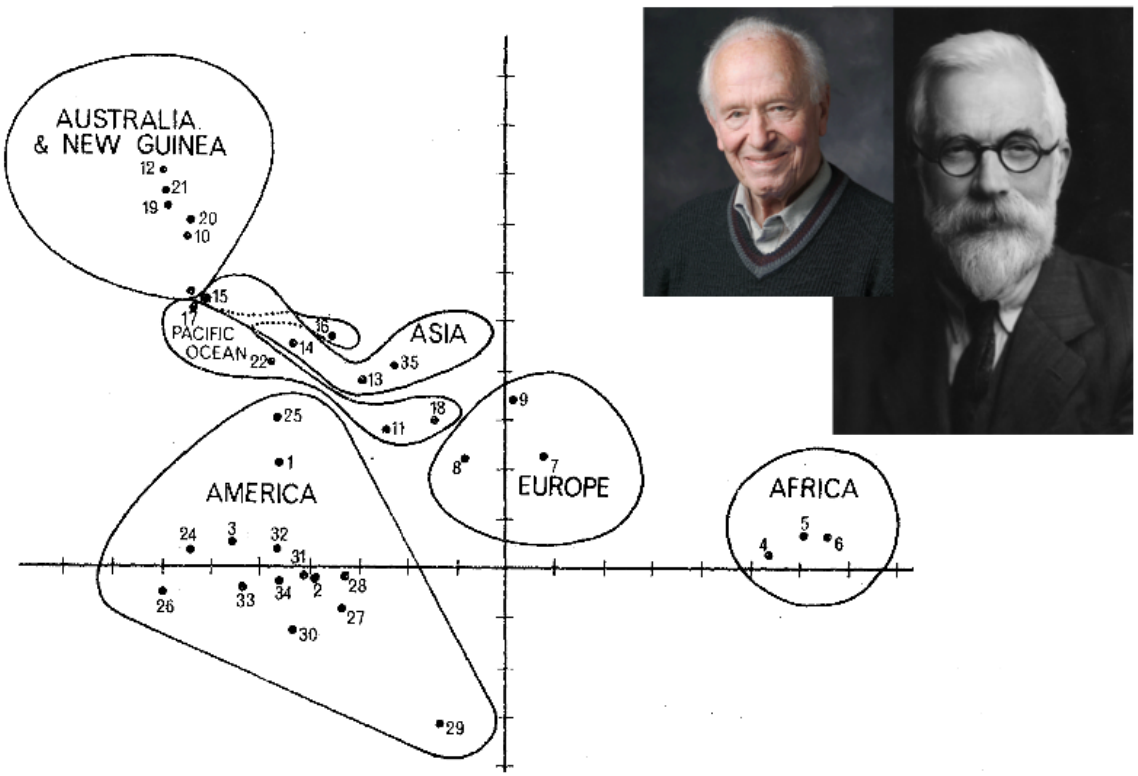

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Applications: some examples

PCA of genetic data + colored maps of principal components

(Cavalli-Sforza et al. 1993, *Science*)

Signatures of Human expansion out-of-Africa.

Since then...

Multivariate methods used in genetics

- Principal Component Analysis (PCA)
- Principal Coordinates Analysis (PCoA) / Metric Multidimensional Scaling (MDS)
- Correspondance Analysis (CA)
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 packages: *adegenet*, *ade4*, *pegas*

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Applications

- reveal spatial structures (historical spread)
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Outline

Why investigate the diversity of pathogen populations?

Genetic data: increasingly important in infectious disease epidemiology

Purposes

- classify pathogens, describe their relationships
- assess the spatio-temporal dynamics of infectious diseases
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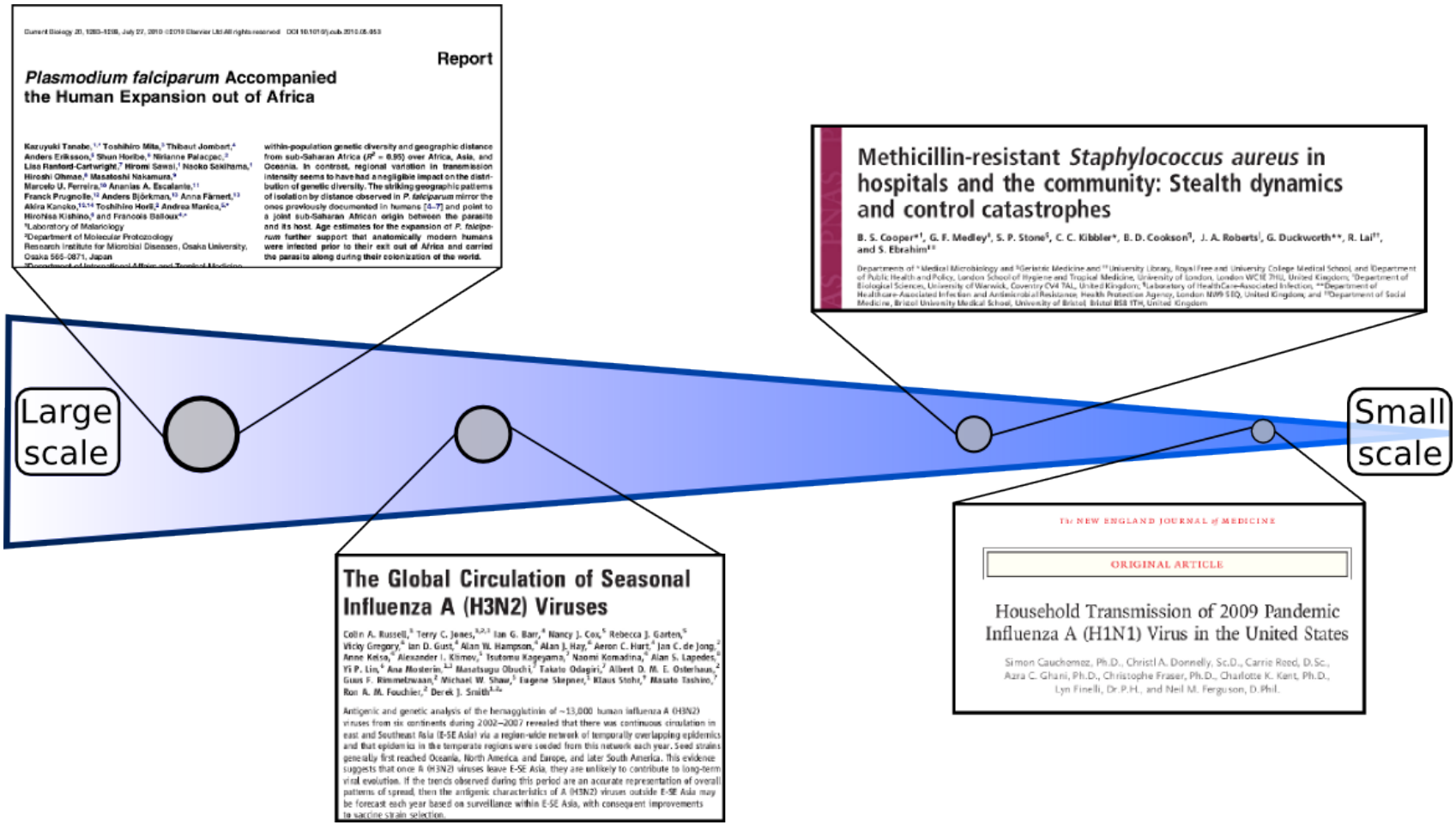

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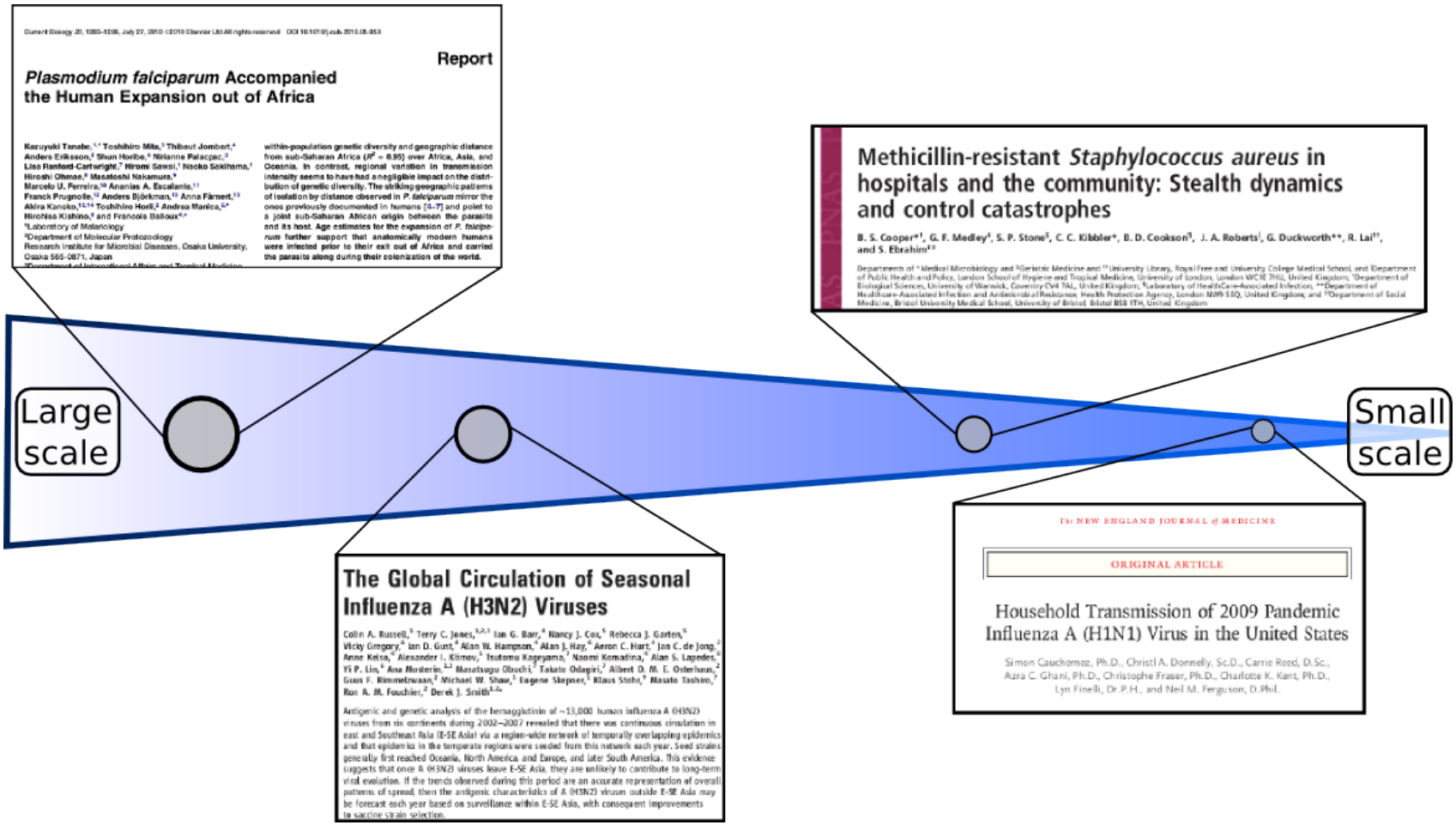

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Population genetics: identify populations of organisms and describe their relationships

What is a population?

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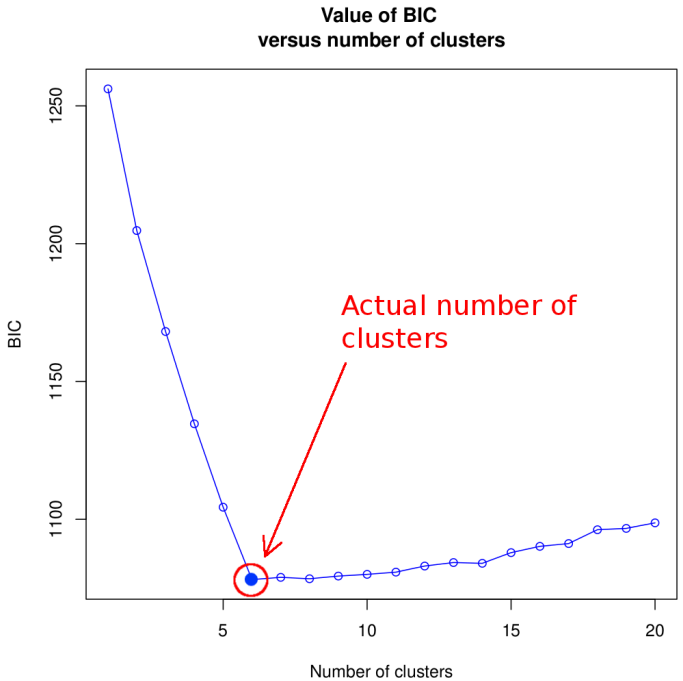
Genetic clustering using K-means & BIC

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

Variance partitioning model (ANOVA):

$$tot.\ variance = (bet.\ groups) + (wit.\ groups)$$



Performances:

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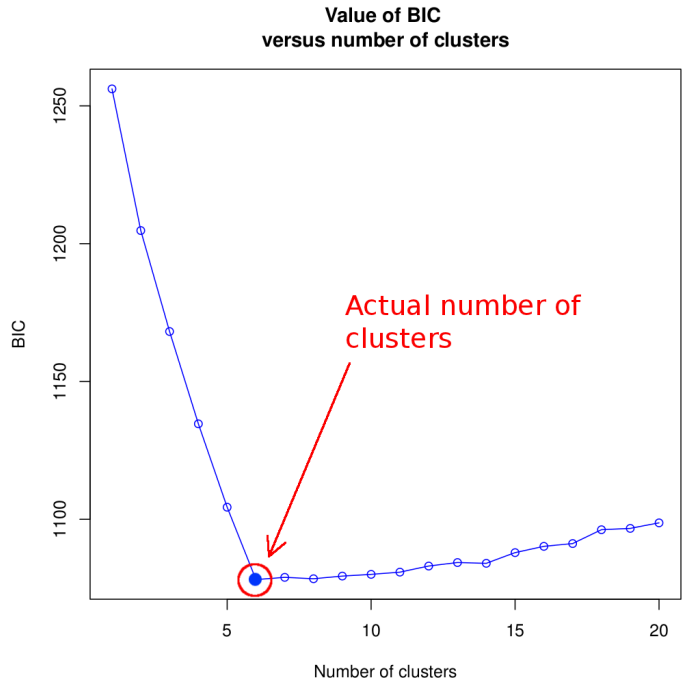

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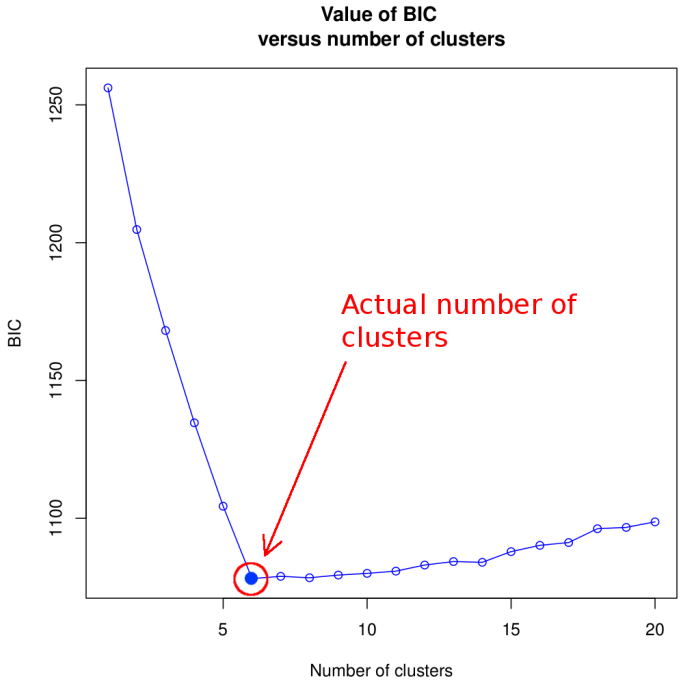

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package: *adegenet*, function `find.clusters`

PCA of seasonal influenza (A/H3N2) data

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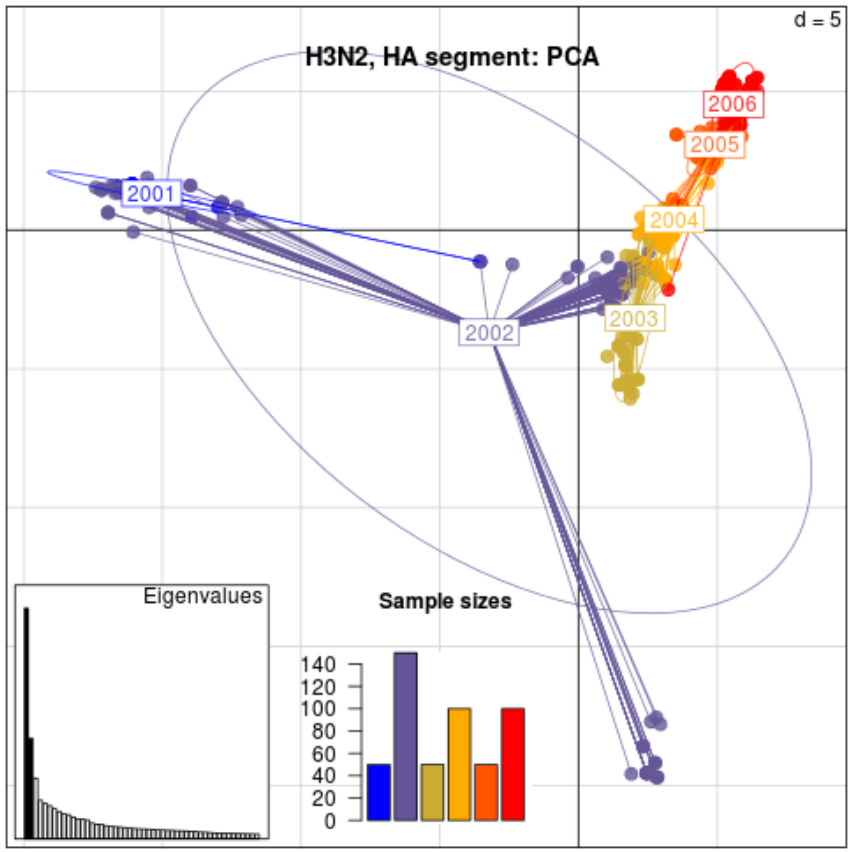

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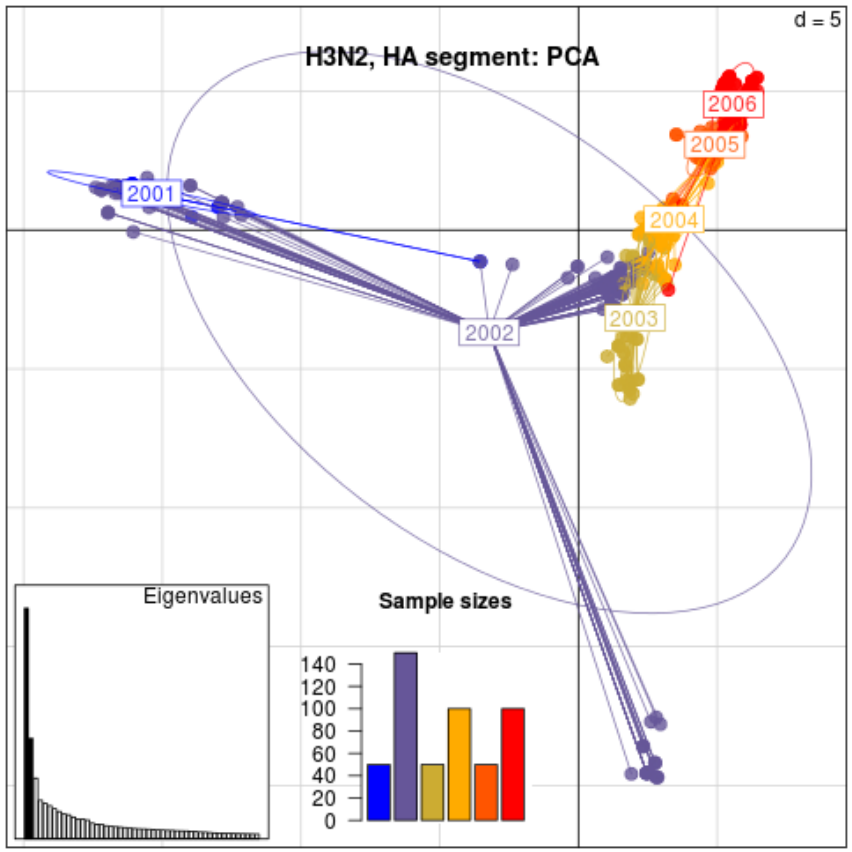

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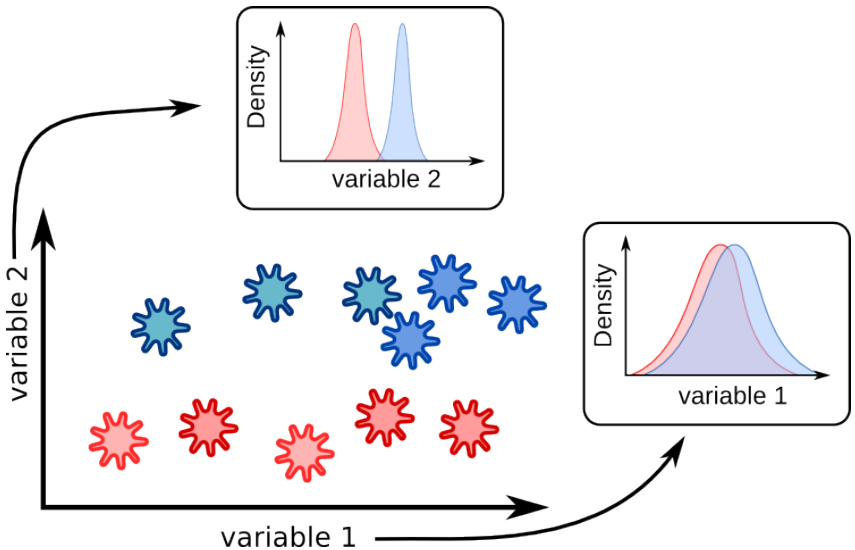

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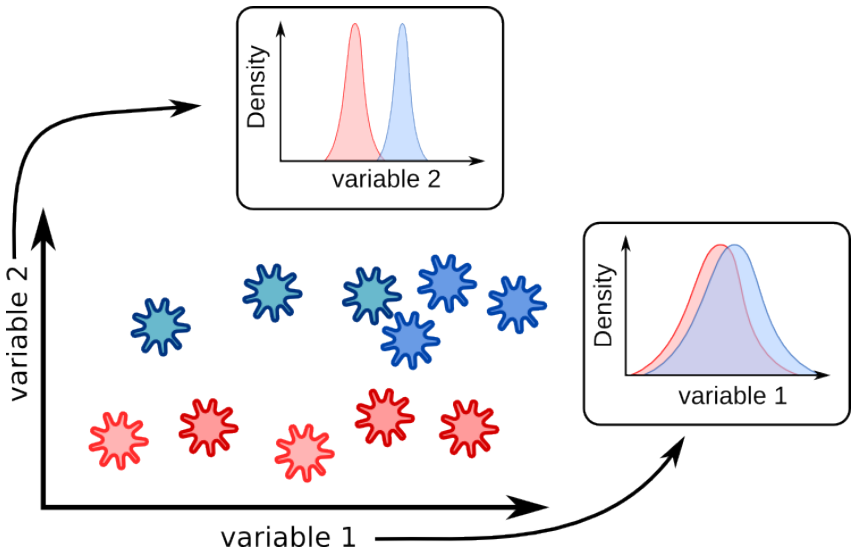

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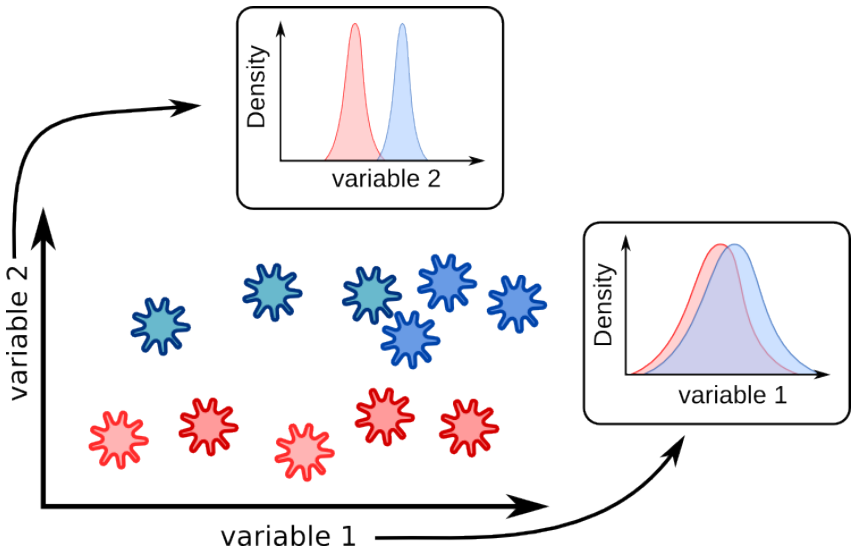

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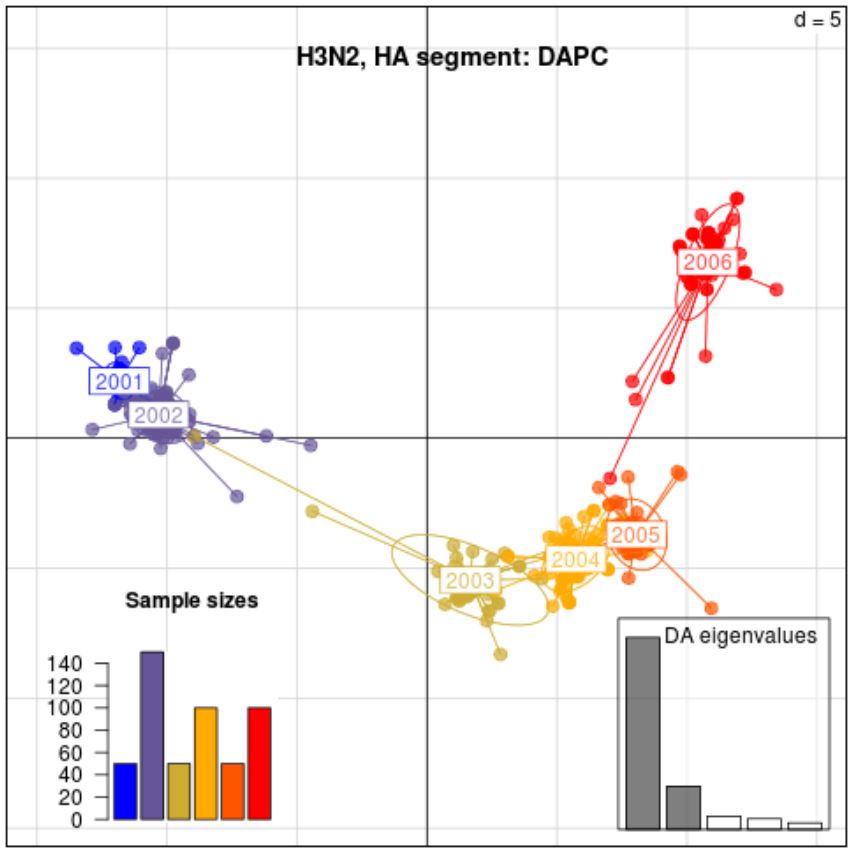

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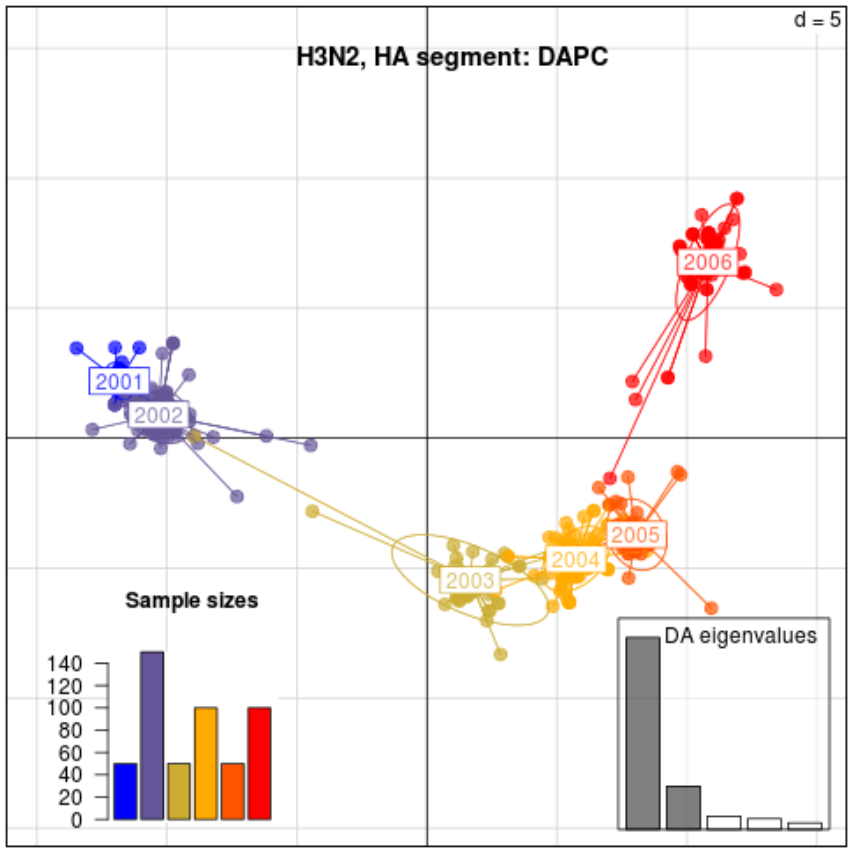

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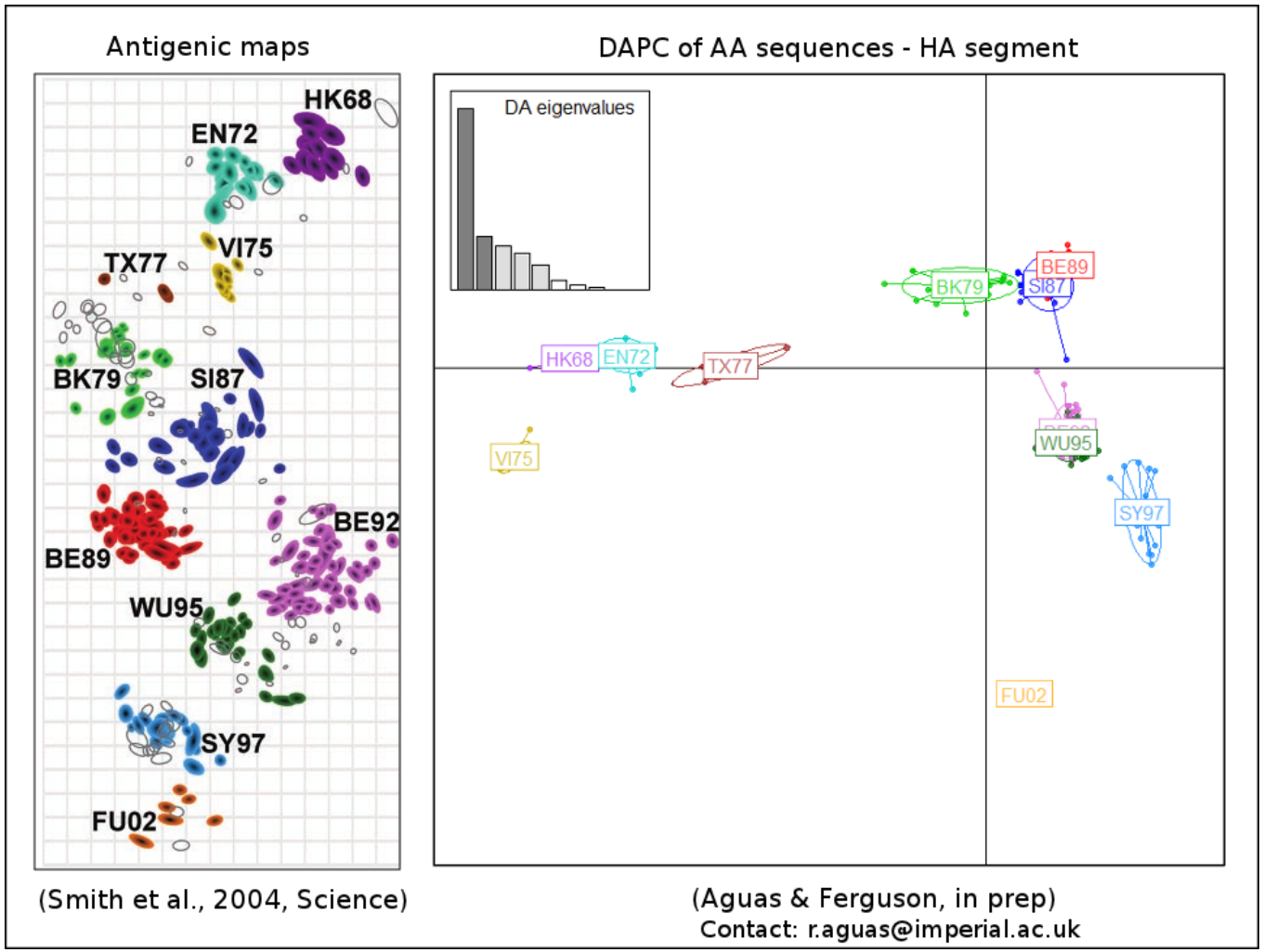

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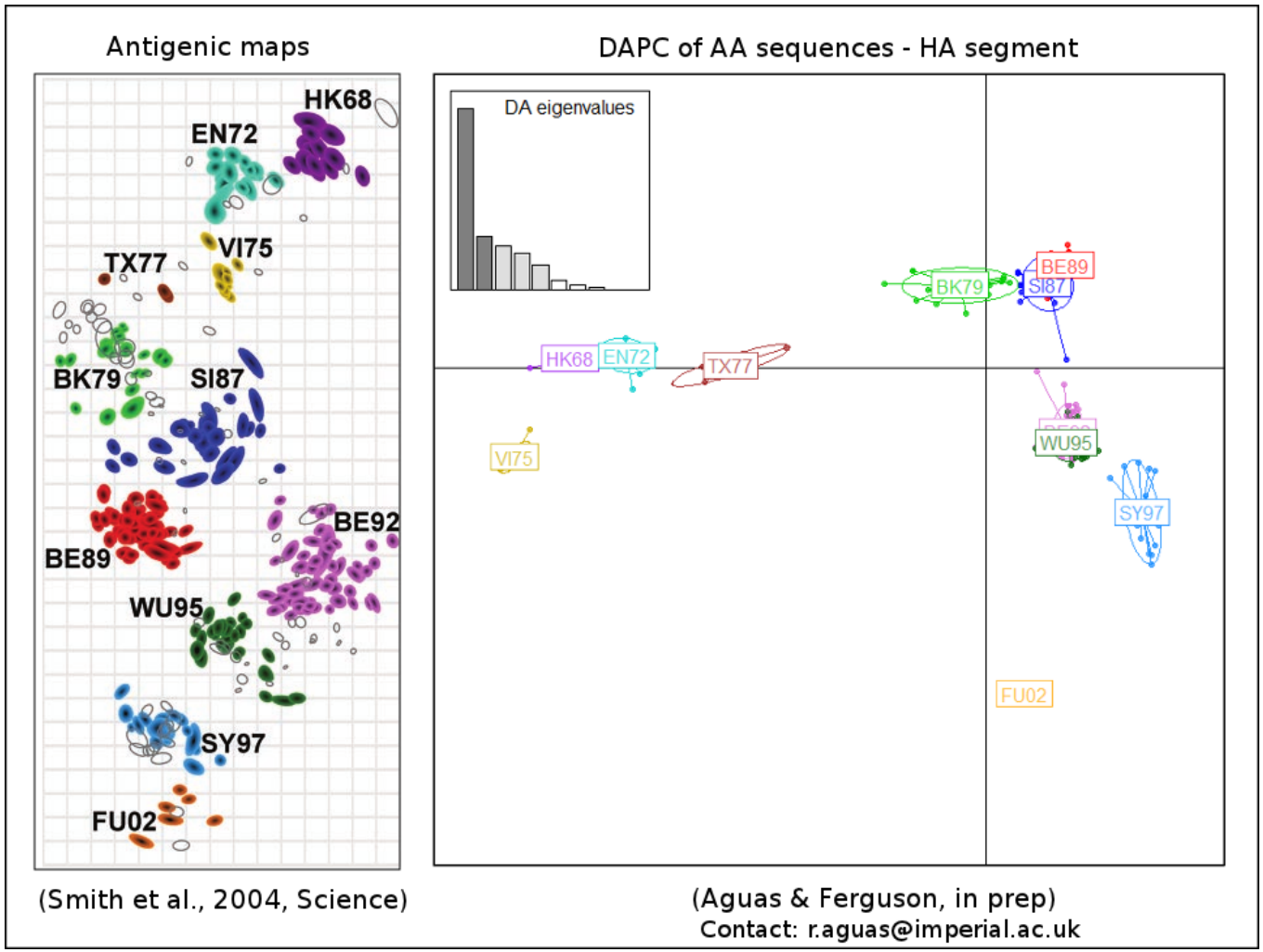

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DAPC to identify structuring alleles

DAPC finds combinations of alleles most differing between groups.

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(Jombart & Ahmed 2011, *Bioinformatics*)

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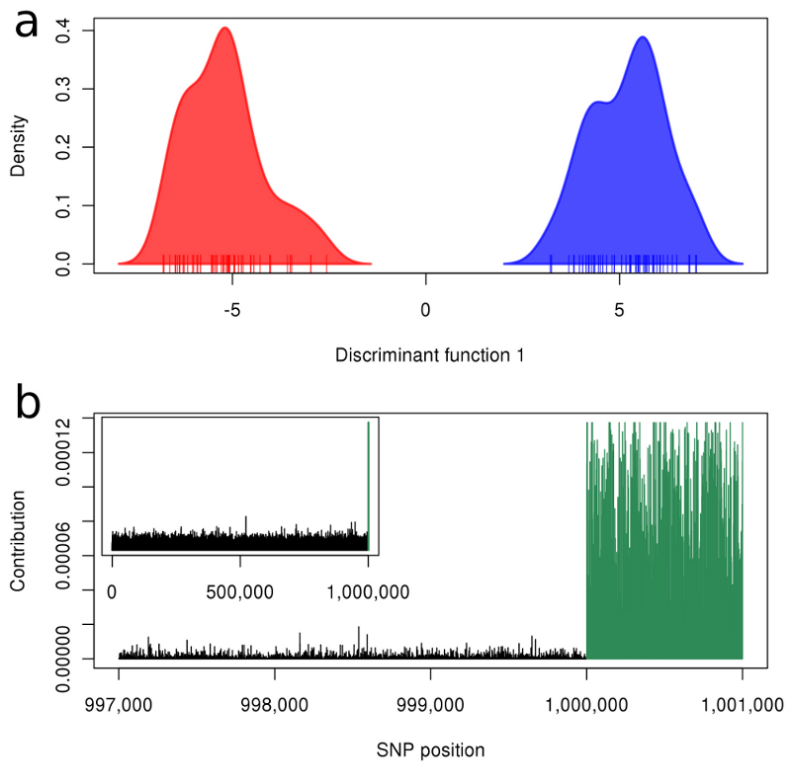

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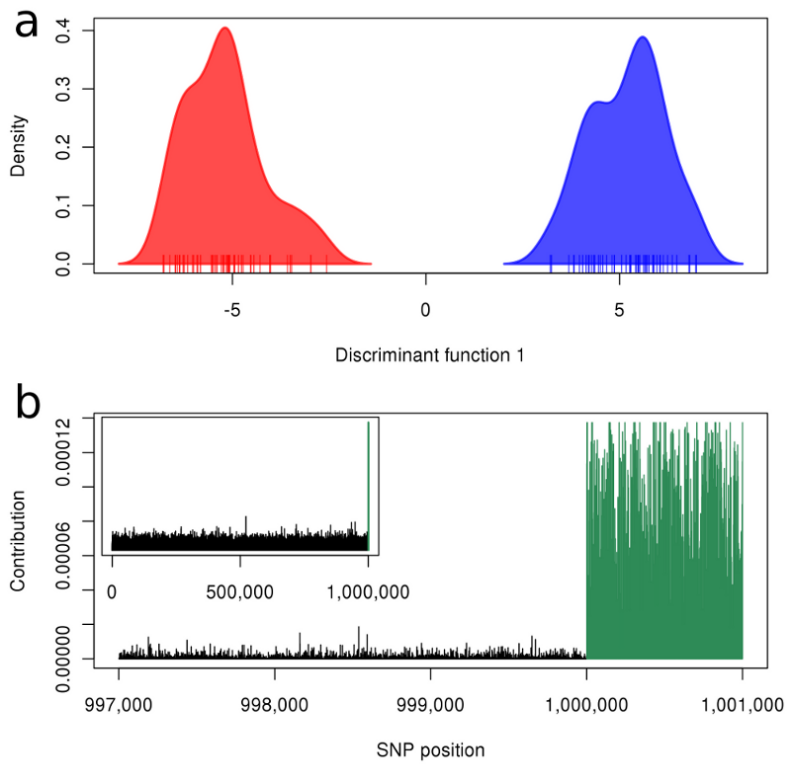

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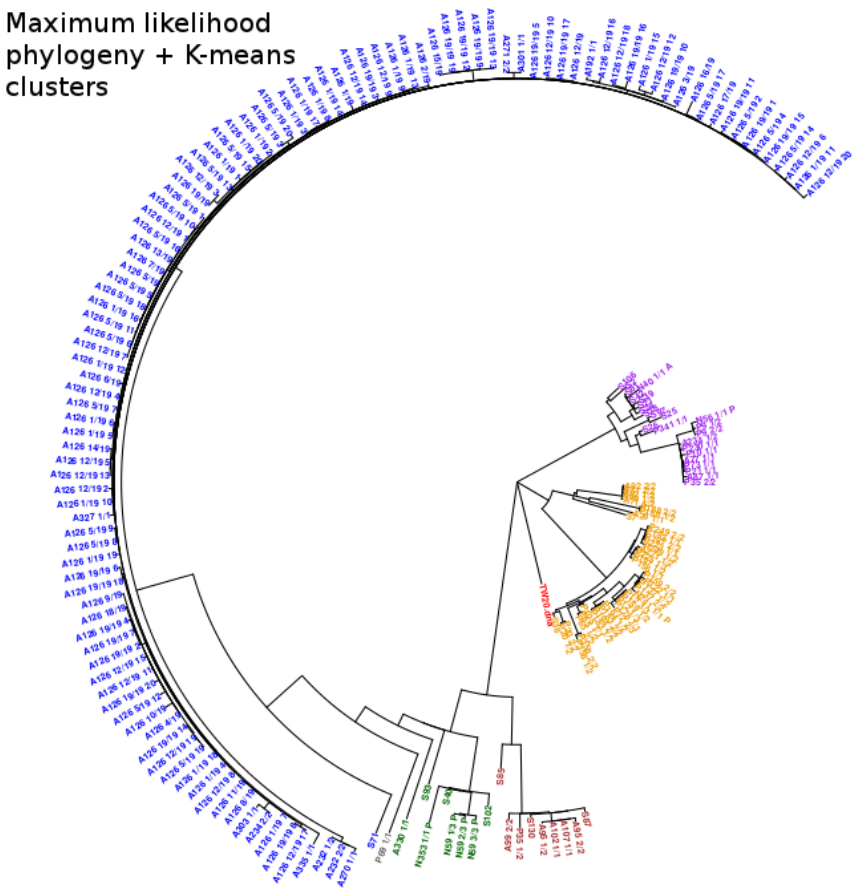

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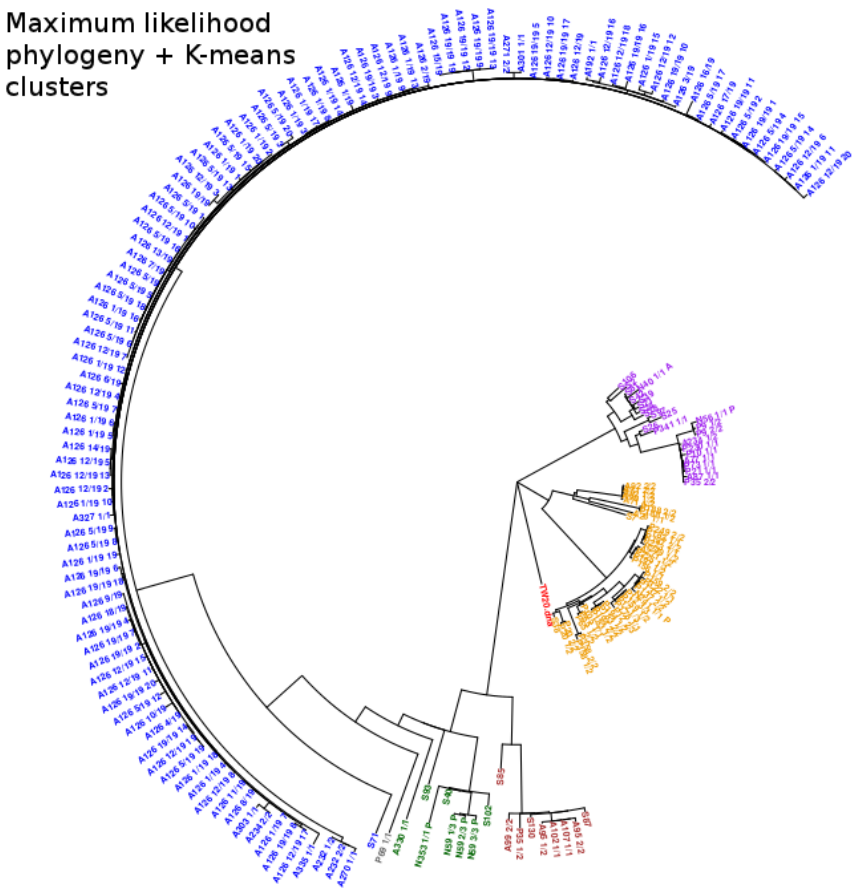

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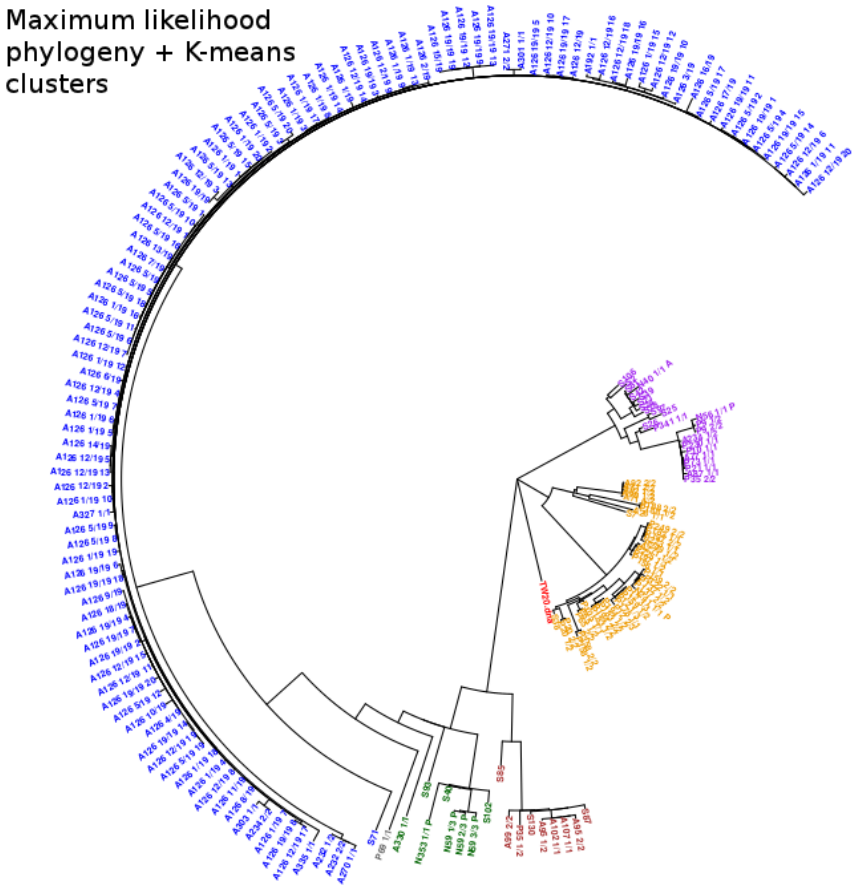

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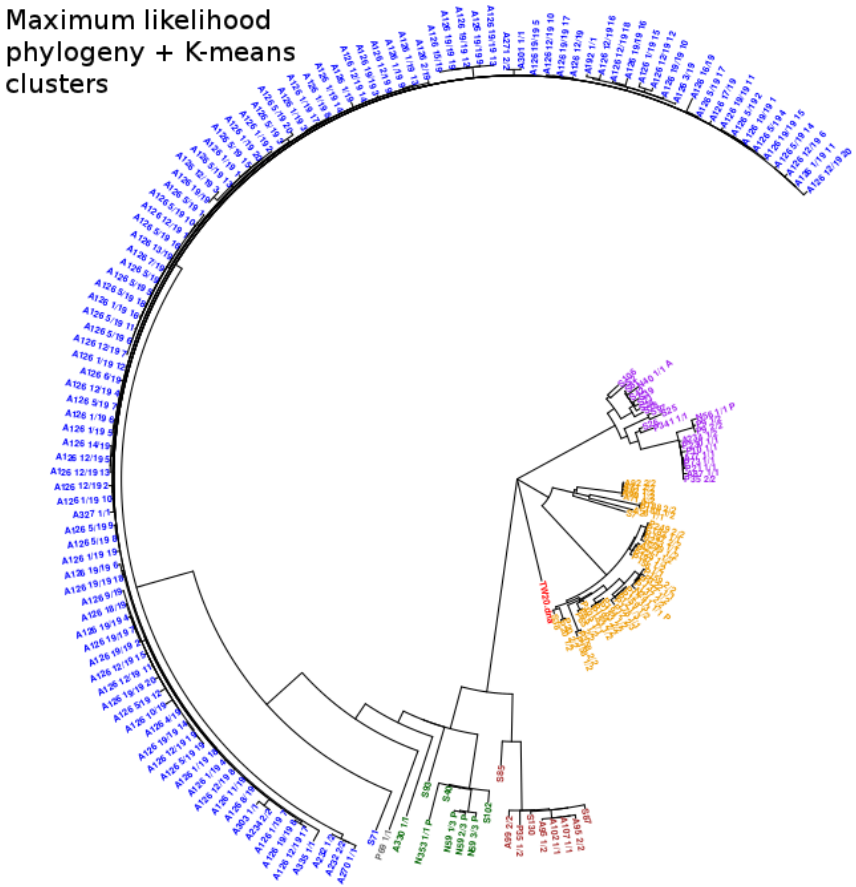

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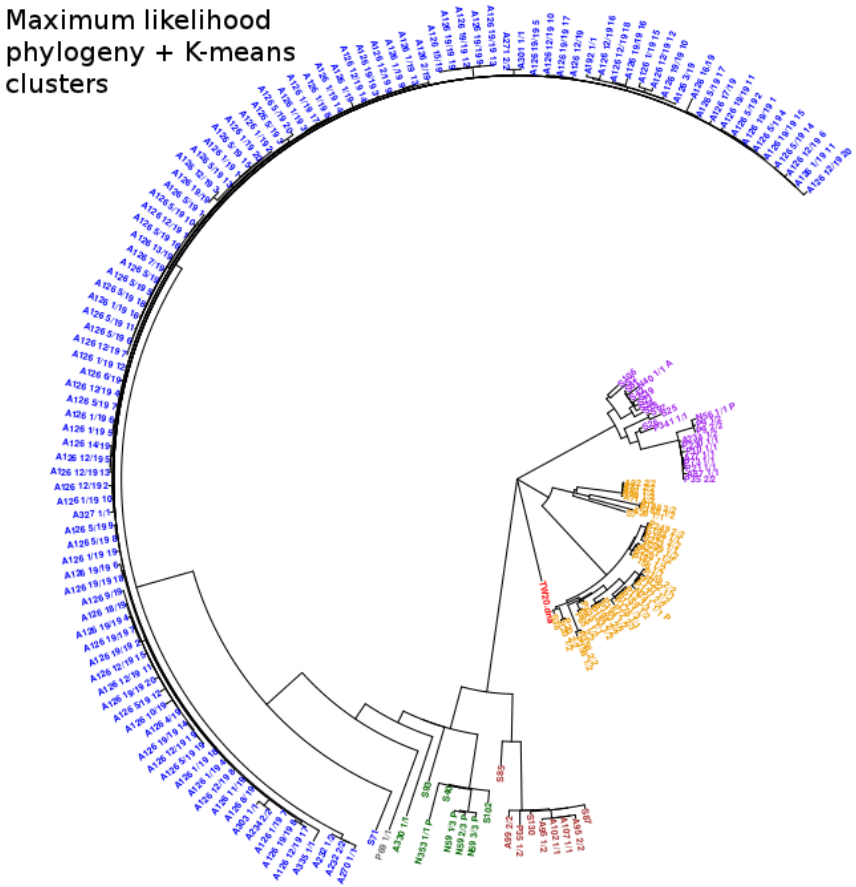

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Multivariate analysis usually not informative on small-scale processes.

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- specific applications to pathogen genetic data
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