Introduction to multivariate analysis — applications in genomics —

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22-03-2013

Outline

Multivariate analysis in a nutshell

Applications to genomic data

Genetic diversity of pathogen populations

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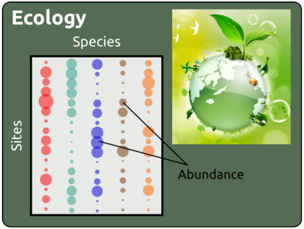
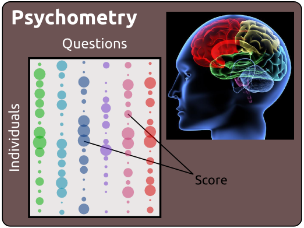
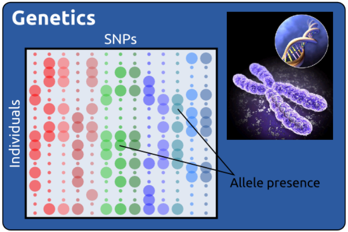
Multivariate data: some examples







Association between individuals? Correlations between variables?

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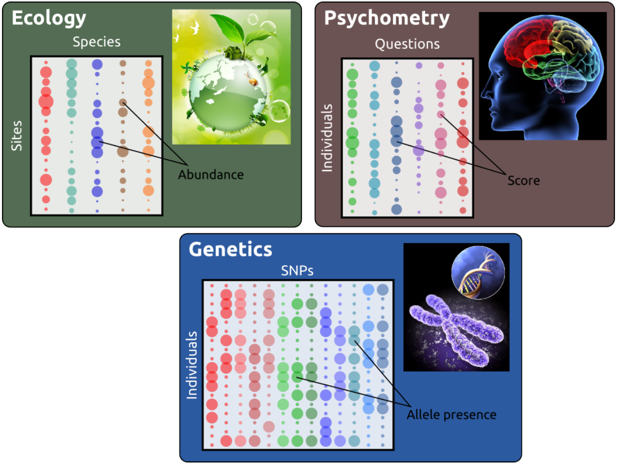
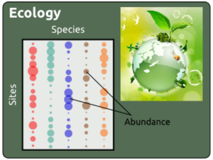
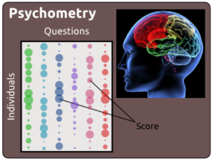
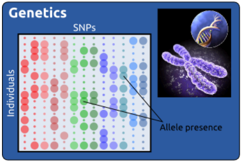


Association between individuals? Correlations between variables?

Multivariate analysis to summarize diversity







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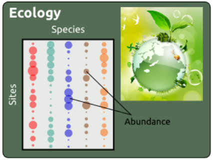
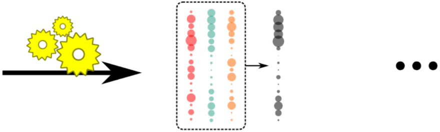
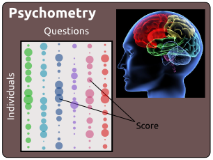
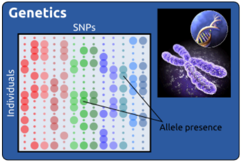




Species assemblage #1 Species assemblage #2





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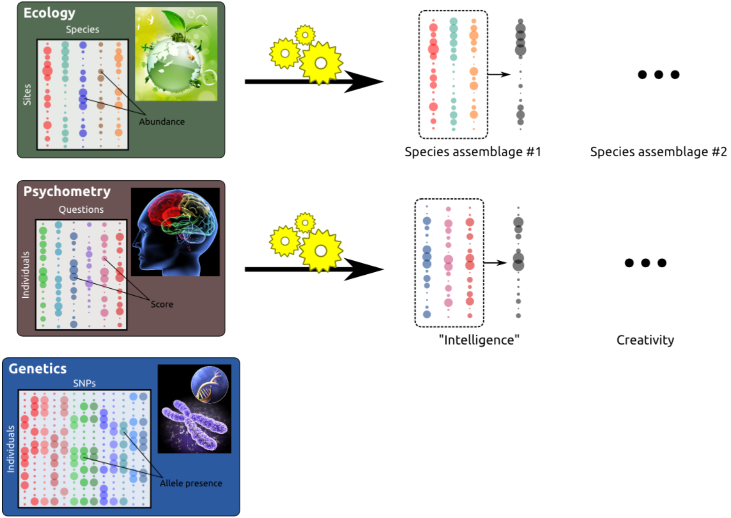

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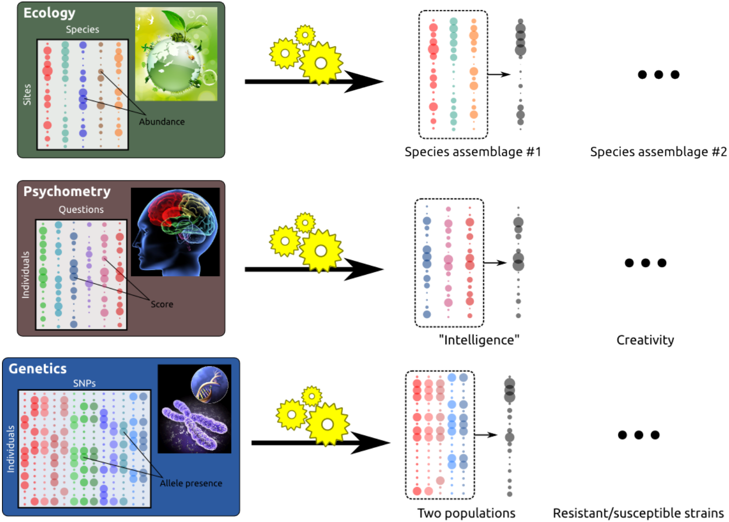

Multivariate analysis: an overview

Multivariate analysis, a.k.a:

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

Purposes:

- summarize diversity amongst observations
- summarize correlations between variables

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Most common methods

Differences lie in input data:

- quantitative/binary variables: *Principal Component Analysis* (PCA)
- 2 categorical variables: *Correspondance Analysis* (CA)
- >2 categorical variables: *Multiple Correspondance Analysis* (MCA)
- Euclidean distance matrix: *Principal Coordinates Analysis* (PCoA) / *Metric Multidimensional Scaling* (MDS)

Many other methods for ≥ 2 data tables, spatial analysis, phylogenetic analysis, etc.

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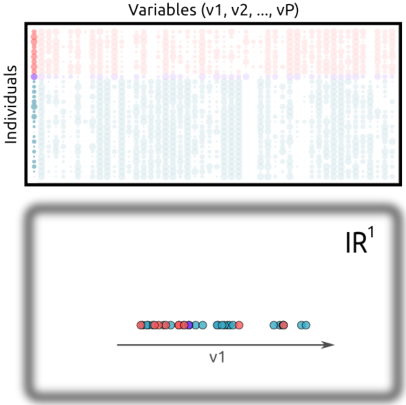
1 dimension, 2 dimensions, P dimensions



Need to find most informative directions in a P-dimensional space.

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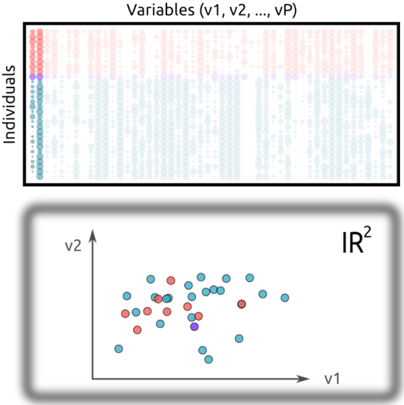

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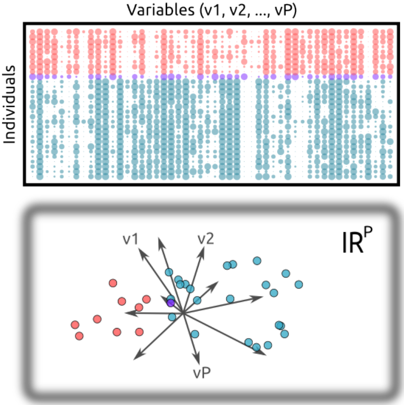

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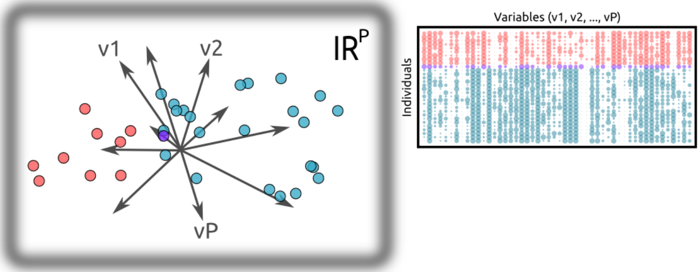
Reducing P dimensions into 1



- $\mathbf{X} \in \mathbb{R}^{N \times P}$; $\mathbf{X} = [\mathbf{x}_1 | \dots | \mathbf{x}_P]$: data matrix
- $\mathbf{u} \in \mathbb{R}^{P}$; $\mathbf{u} = [u_1, \dots, u_P]$: **principal axis** $(\|\mathbf{u}\|^2 = \sum_{j=1}^{P} u_j^2 = 1)$
- $\mathbf{v} \in \mathbb{R}^{N}$; $\mathbf{v} = \mathbf{X}\mathbf{u} = \sum_{j=1}^{P} u_j \mathbf{x}_j$: **principal component**

→ find $\mathbf{u}$ so that $\frac{1}{N}\|\mathbf{v}\|^2 = \text{var}(\mathbf{v})$ is maximum.

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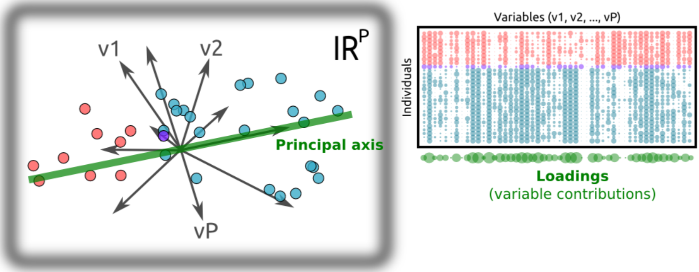

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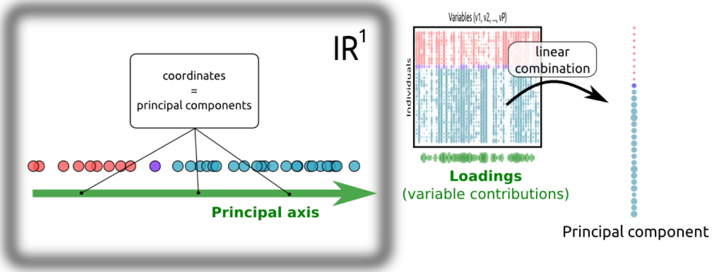

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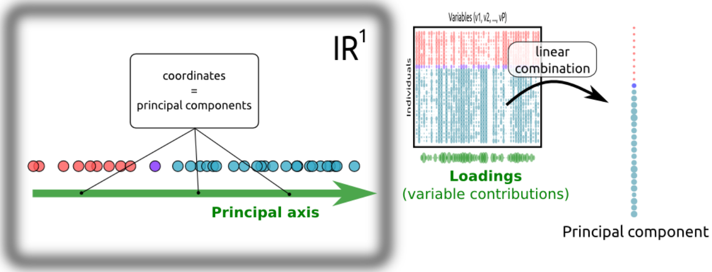

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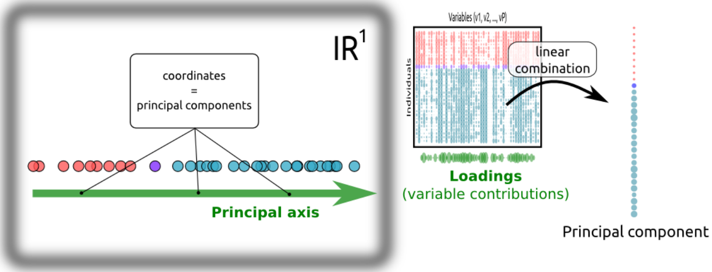
Keeping more than one principal component



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- $\mathbf{u}_2$ and $\mathbf{v}_2$: **2nd principal axis and component**

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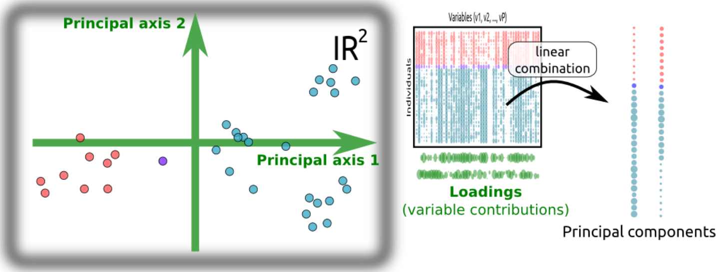

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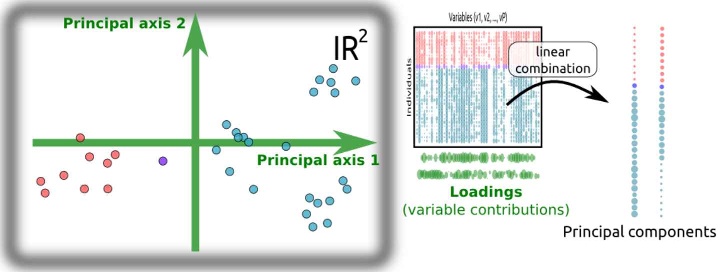

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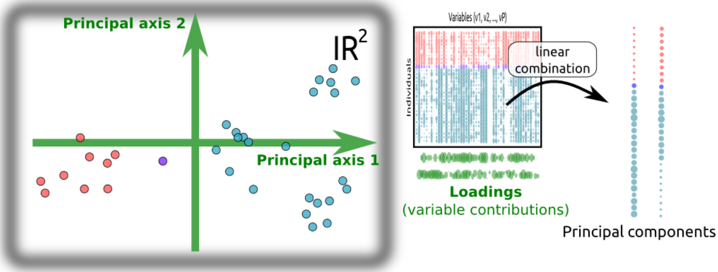

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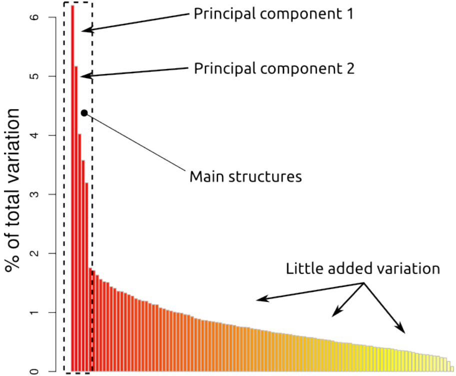
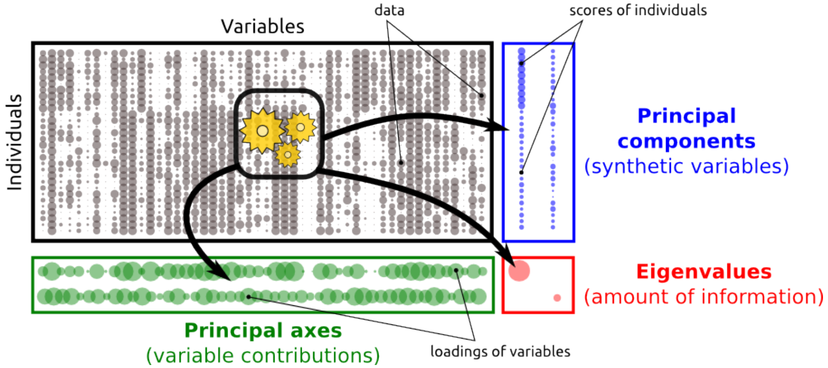
How many principal components to retain?

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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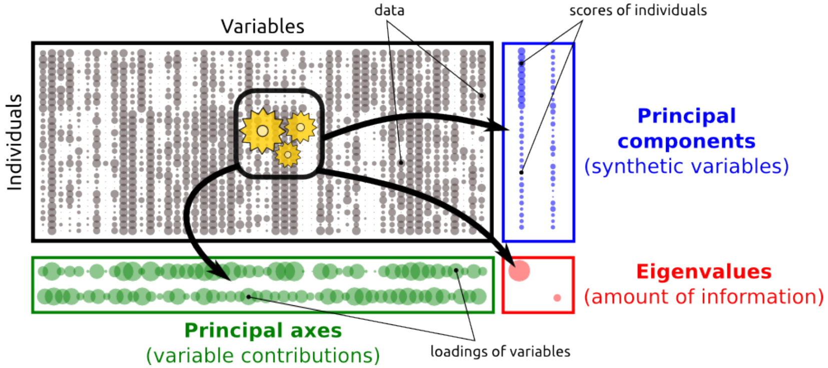

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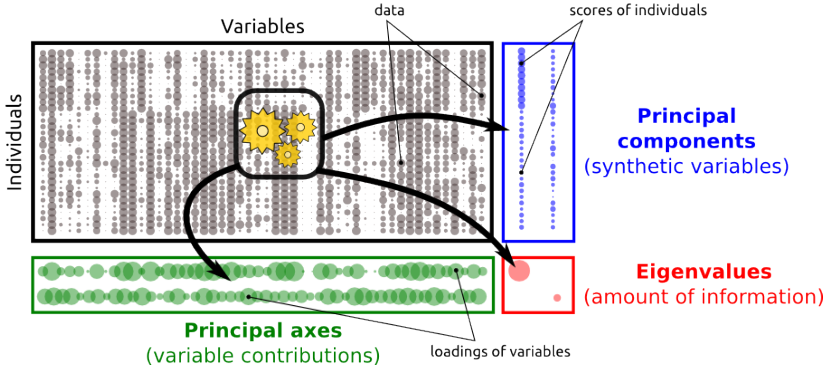

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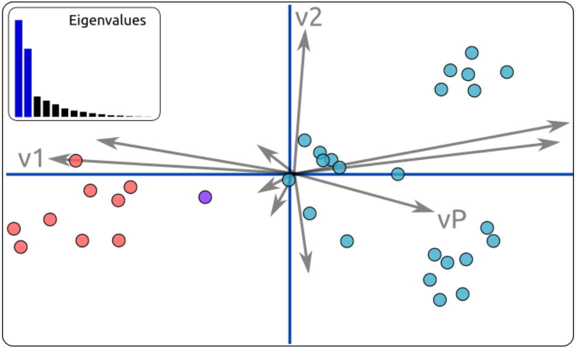
Usual summary of an analysis: the biplot



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

- groups of individuals
- discriminating 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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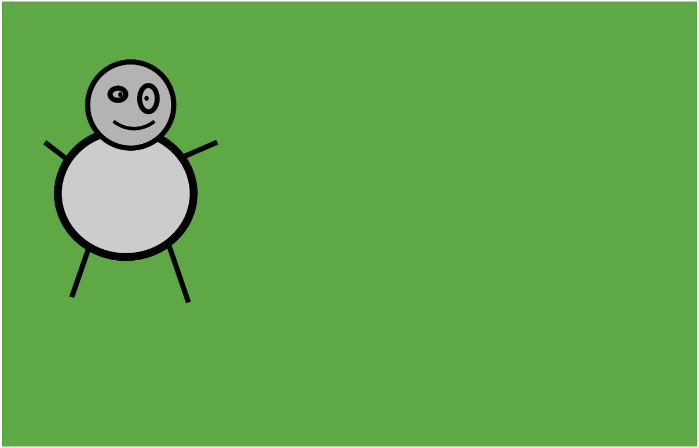
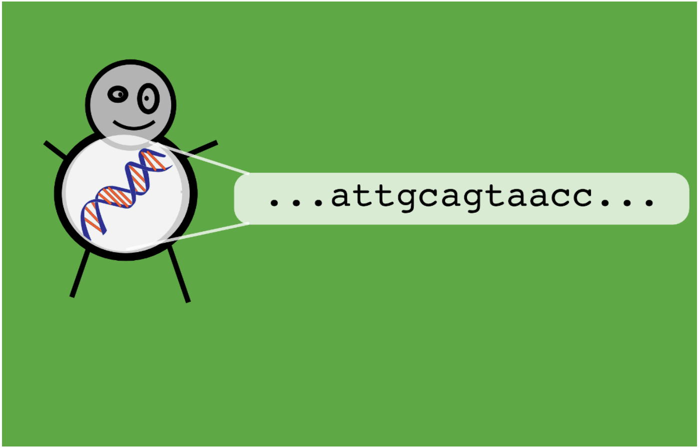
Applications to genomic data

Genetic diversity of pathogen populations

From DNA sequences to patterns of biological diversity



From DNA sequences to patterns of biological diversity



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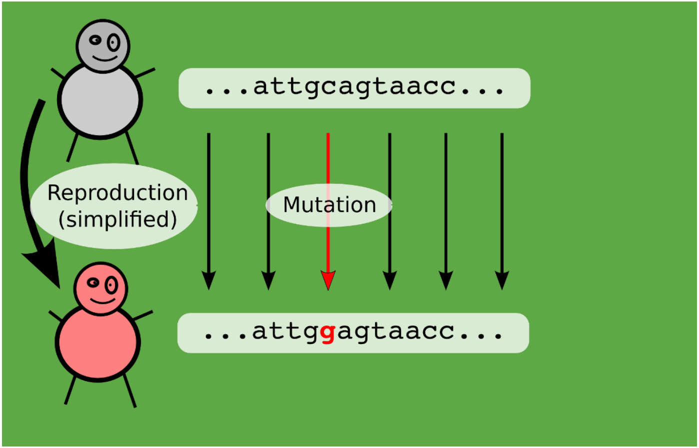

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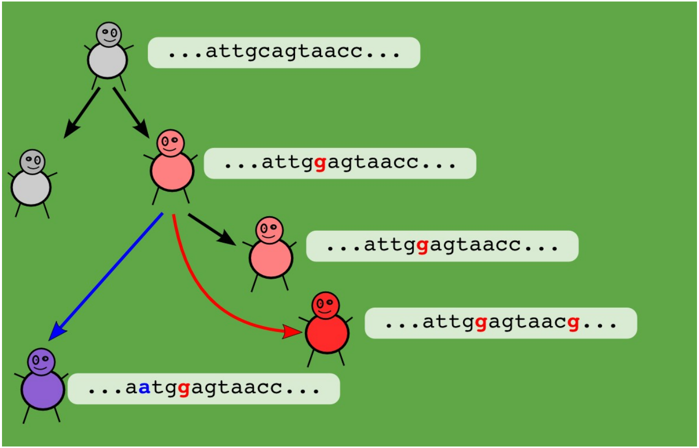

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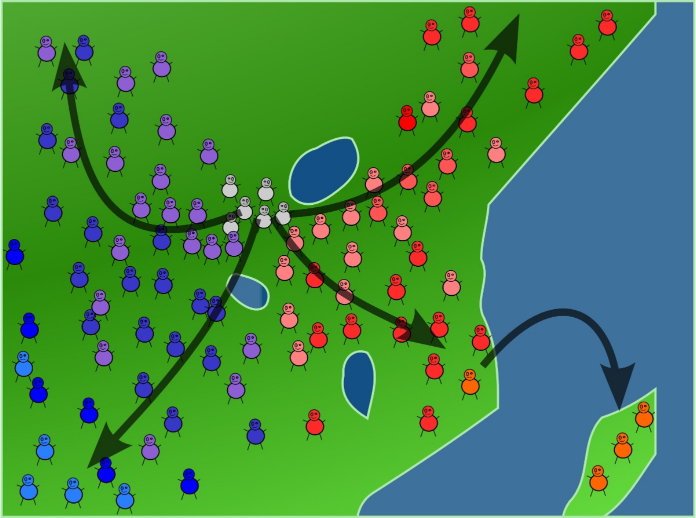

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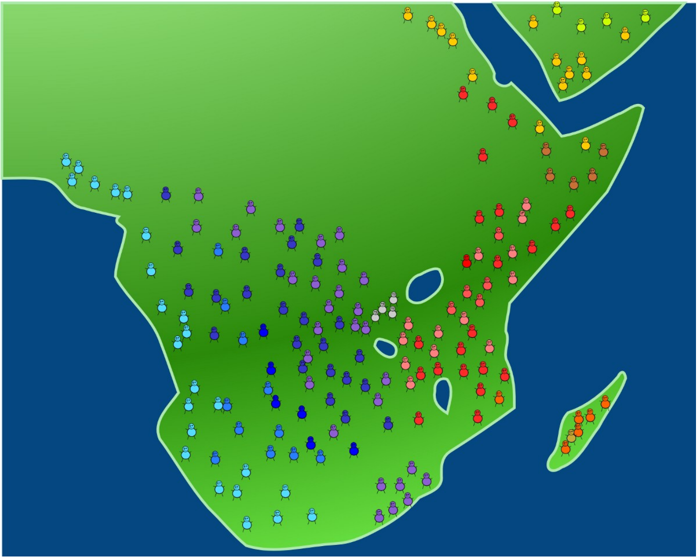

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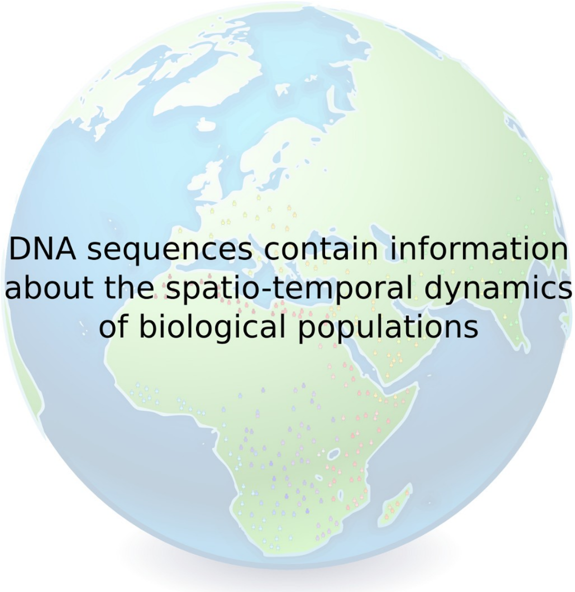
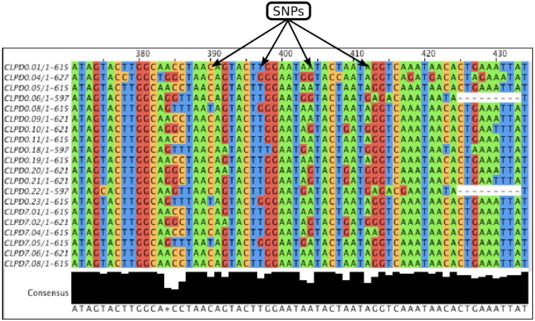


DNA sequences contain information about the spatio-temporal dynamics of biological populations

DNA sequences: a rich source of information



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CLPD7.08/1-615 ATAGTACTTGGCAACCTAACAGTACTTGGAATAATACTAATAGGTCAAATAACACTGAAATTAT

     Consensus
               ATAGTACTTGGCA+CCTAACAGTACTTGGAATAATACTAATAGGTCAAATAACACTGAAATTAT
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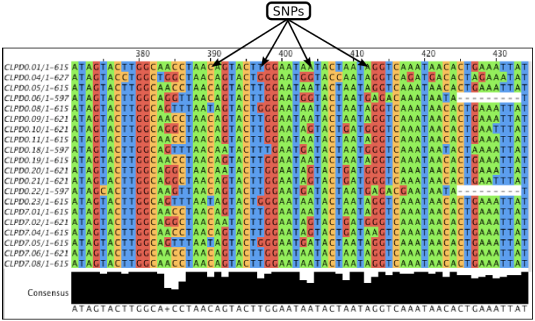
- hundreds/thousands individuals
- up to millions of single nucleotide polymorphism (SNPs)

⇒ **Multivariate analysis use to summarize genetic diversity.**

DNA sequences: a rich source of information



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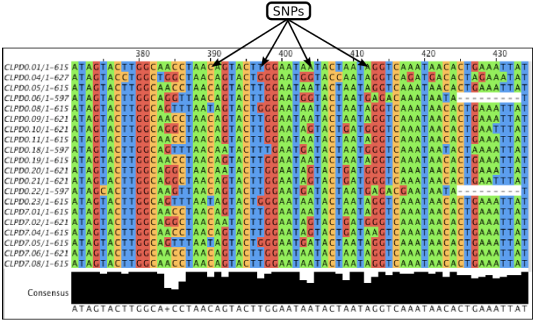

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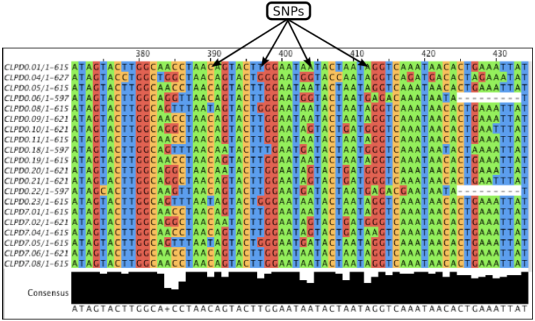

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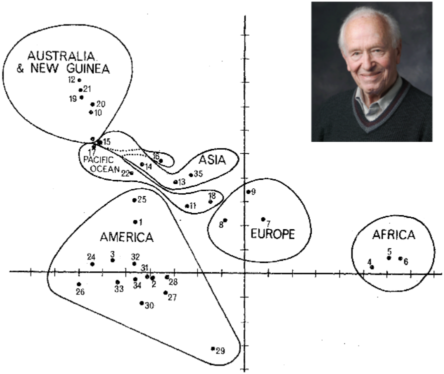

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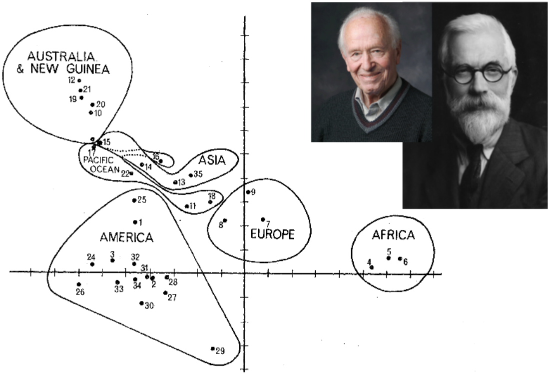

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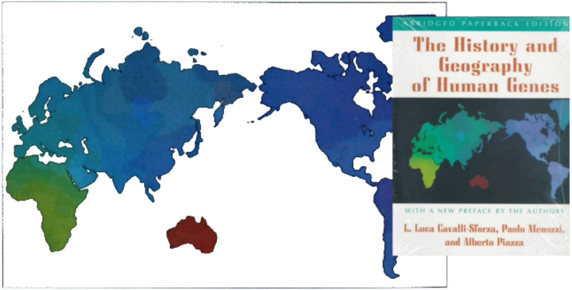
Applications: some examples

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)
- Discriminant Analysis (DA)
- Canonical Correlation Analysis (CCA)
- ...

Since then...

Applications

- reveal spatial structures (historical spread)
- explore genetic diversity
- identify cryptic species
- discover genotype-phenotype association
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Outline

Multivariate analysis in a nutshell

Applications to genomic data

Genetic diversity of pathogen populations

Why investigate the diversity of pathogen populations?

Genetic data: increasingly important in infectious disease epidemiology

Purposes

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- assess the spatio-temporal dynamics of infectious diseases
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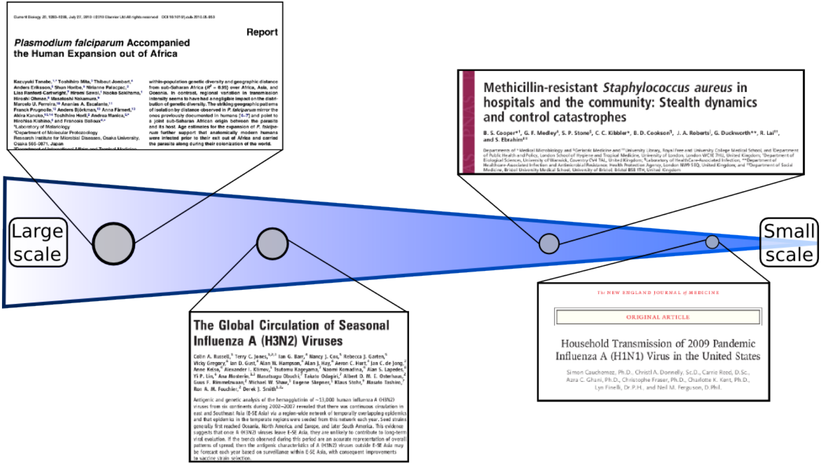

Current Biology 20, 1283–1288, July 27, 2010 ©2010 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2010.05.053

Report

***Plasmodium falciparum* Accompanied the Human Expansion out of Africa**

Kazuyuki Tanabe,[1,*] Toshihiro Mita,[3] Thibaut Jombart,[4] Anders Eriksson,[5] Shun Horibe,[6] Nirianne Palacpac,[2] Lisa Ranford-Cartwright,[7] Hiromi Sawai,[1] Naoko Sakihama,[1] Hiroshi Ohmae,[8] Masatoshi Nakamura,[9] Marcelo U. Ferreira,[10] Ananias A. Escalante,[11] Franck Prugnolle,[12] Anders Björkman,[13] Anna Färnert,[13] Akira Kaneko,[13,14] Toshihiro Horii,[2] Andrea Manica,[5,*] Hirohisa Kishino,[6] and Francois Balloux[4,*]

[1]Laboratory of Malariology
[2]Department of Molecular Protozoology
Research Institute for Microbial Diseases, Osaka University, Osaka 565-0871, Japan
[3]Department of International Affairs and Tropical Medicine

within-population genetic diversity and geographic distance from sub-Saharan Africa ($R^2 = 0.95$) over Africa, Asia, and Oceania. In contrast, regional variation in transmission intensity seems to have had a negligible impact on the distribution of genetic diversity. The striking geographic patterns of isolation by distance observed in *P. falciparum* mirror the ones previously documented in humans [4–7] and point to a joint sub-Saharan African origin between the parasite and its host. Age estimates for the expansion of *P. falciparum* further support that anatomically modern humans were infected prior to their exit out of Africa and carried the parasite along during their colonization of the world.

Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: Stealth dynamics and control catastrophes

B. S. Cooper[*,†], G. F. Medley[‡], S. P. Stone[§], C. C. Kibbler[*], B. D. Cookson[¶], J. A. Roberts[‖], G. Duckworth[**], R. Lai[††], and S. Ebrahim[‡‡]

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The Global Circulation of Seasonal Influenza A (H3N2) Viruses

Colin A. Russell,[1] Terry C. Jones,[1,2,3] Ian G. Barr,[4] Nancy J. Cox,[5] Rebecca J. Garten,[5] Vicky Gregory,[6] Ian D. Gust,[4] Alan W. Hampson,[4] Alan J. Hay,[6] Aeron C. Hurt,[4] Jan C. de Jong,[2] Anne Kelso,[4] Alexander I. Klimov,[5] Tsutomu Kageyama,[7] Naomi Komadina,[4] Alan S. Lapedes,[8] Yi P. Lin,[6] Ana Mosterin,[1,3] Masatsugu Obuchi,[7] Takato Odagiri,[7] Albert D. M. E. Osterhaus,[2] Guus F. Rimmelzwaan,[2] Michael W. Shaw,[5] Eugene Skepner,[1] Klaus Stohr,[9] Masato Tashiro,[7] Ron A. M. Fouchier,[2] Derek J. Smith[1,2,*]

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The NEW ENGLAND JOURNAL of MEDICINE

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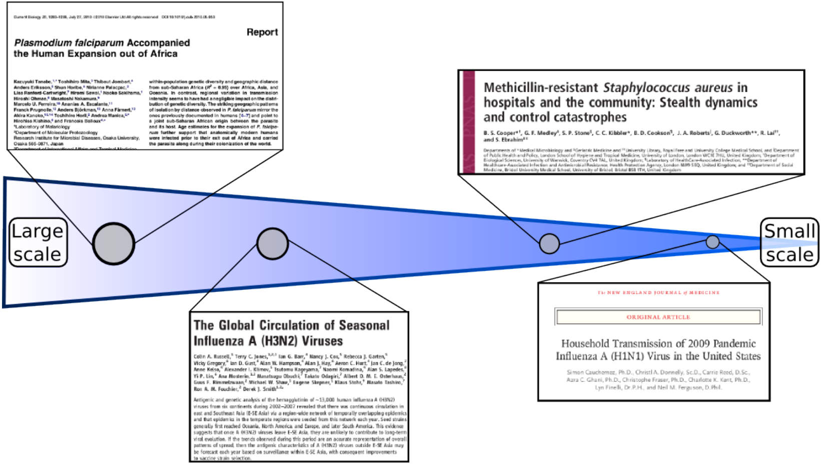

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Describing pathogen populations

Population genetics: identify populations of organisms and describe their relationships

What is a population?

- *Usual definition*: set of organisms mating at random
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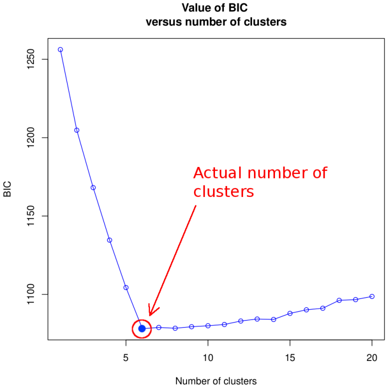
(Jombart *et al.* 2010, *BMC Genetics*)

Variance partitioning model (ANOVA):

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



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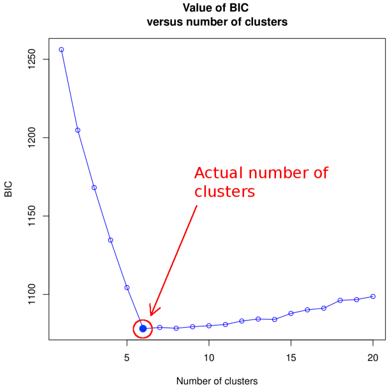

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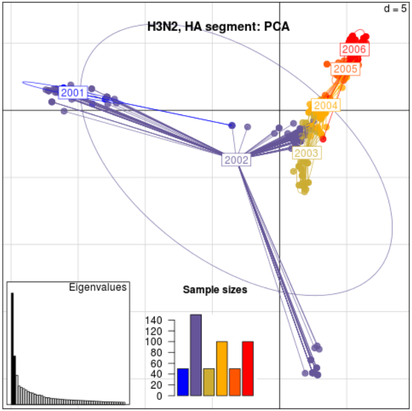

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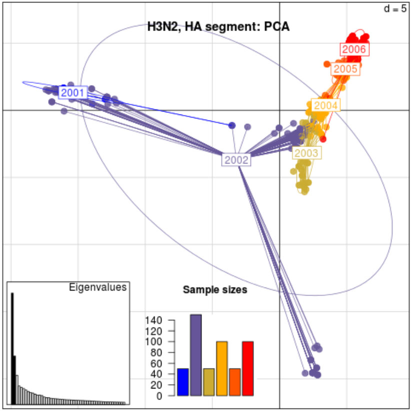

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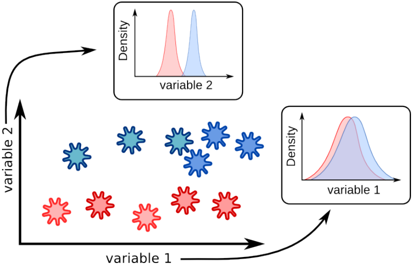

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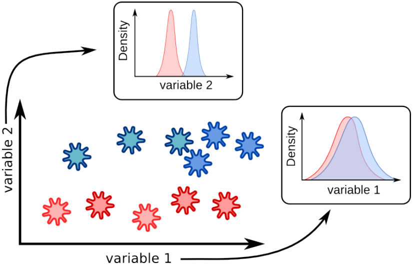

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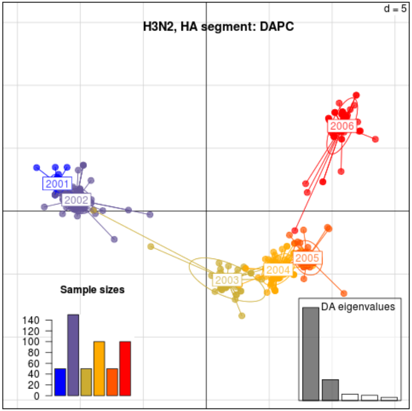

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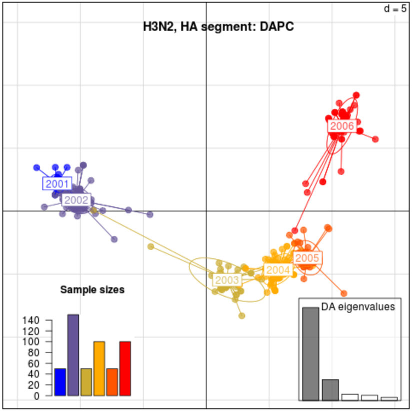

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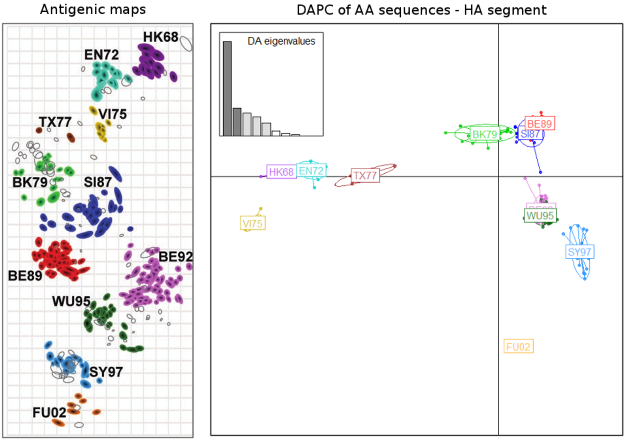
Antigenic maps

DAPC of AA sequences - HA segment

(Smith et al., 2004, Science)

(Aguas & Ferguson, in prep)
Contact: r.aguas@imperial.ac.uk

Antigenic clusters identified directly from AA sequences.

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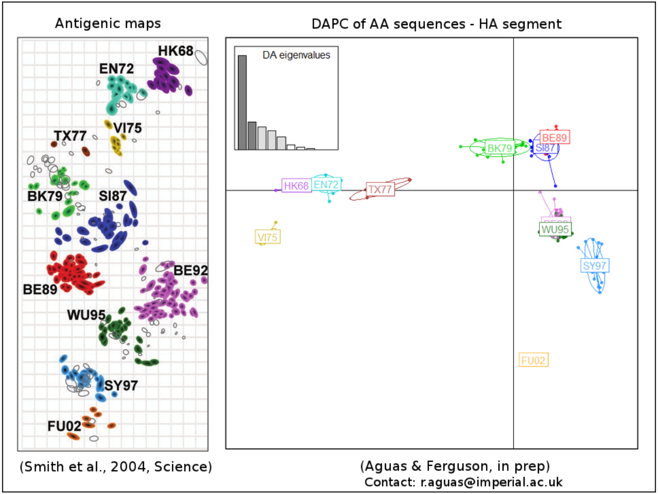

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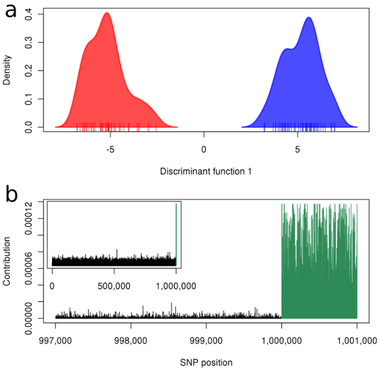
DAPC to identify structuring alleles

DAPC finds combinations of alleles most differing between groups.

Simulated data:

(Jombart & Ahmed 2011, *Bioinformatics*)

- 2 clusters, 50 isolates each
- 1,000,000 non structured SNPs
- 1,000 structured SNPs
  (i.e. different frequencies between groups)



Possible applications to pathogen GWAS (e.g. SNPs related to antibiotic resistance in bacteria).

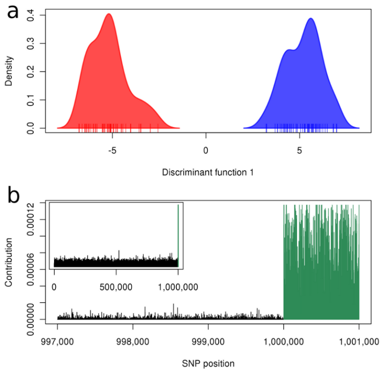
DAPC to identify structuring alleles

DAPC finds combinations of alleles most differing between groups.

Simulated data:

(Jombart & Ahmed 2011, *Bioinformatics*)

- 2 clusters, 50 isolates each
- 1,000,000 non structured SNPs
- 1,000 structured SNPs (i.e. different frequencies between groups)



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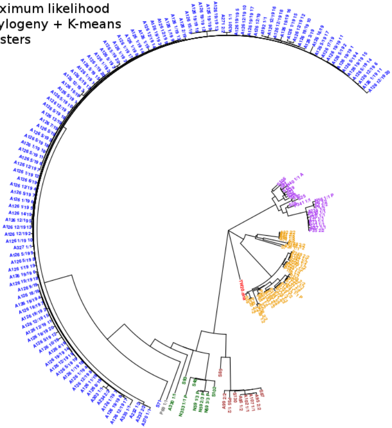
Limits of multivariate analysis

Methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak within hospital, Thailand. ~ 200 full-genome sequences. $\sim 1,000$ SNPs.



Maximum likelihood phylogeny + K-means clusters

Observations:

- greater diversity than expected
- genetic clusters can be defined
- transmissions at within-cluster level
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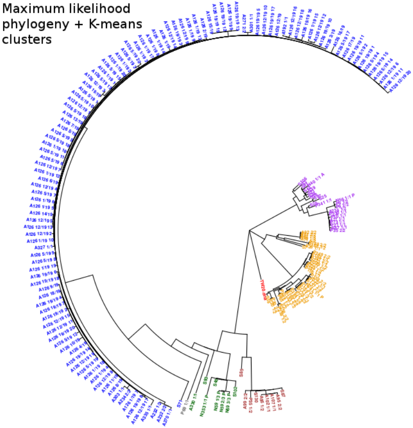

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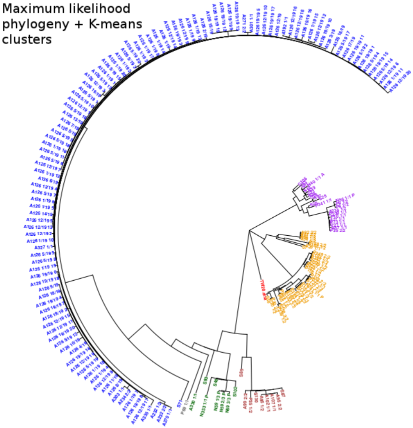

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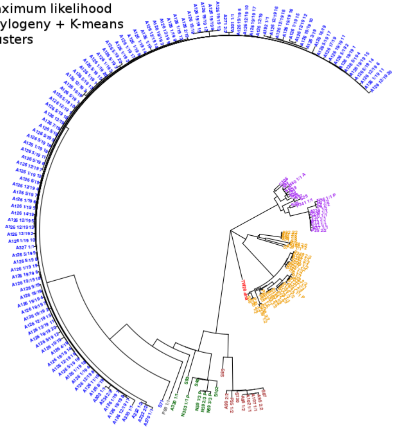

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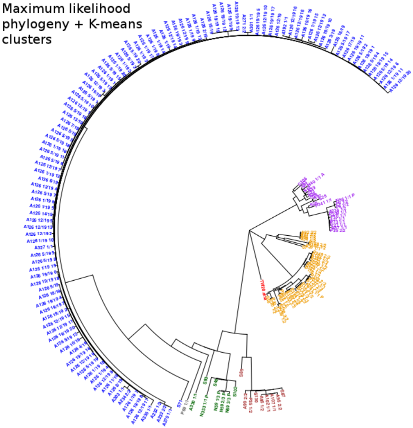

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Multivariate analysis usually not informative on small-scale processes.

Summary

- multivariate analysis used for ~ 50 years in genetics, still an active field for methodological development
- increasingly useful as datasets grow
- specific application to pathogen genetic data
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