Multivariate analysis of genetic data: an introduction

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Outline

Multivariate analysis in a nutshell

Applications to genetic data

Genetic diversity of pathogen populations
Multivariate data: some examples

Association between individuals? Correlations between variables?
Multivariate data: some examples

- Ecology: Species, Sites, Abundance
- Psychometry: Questions, Individuals, Score
- Genetics: SNPs, Individuals, Allele presence

Association between individuals? Correlations between variables?
Multivariate analysis to summarize diversity

- **Ecology**
  - Species
  - Sites
  - Abundance

- **Psychometry**
  - Questions
  - Individuals
  - Score

- **Genetics**
  - SNPs
  - Individuals
  - Allele presence
Multivariate analysis to summarize diversity

Species assemblage #1

Species assemblage #2
Multivariate analysis to summarize diversity
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- Ecology
  - Species
  - Abundance

- Psychometry
  - Questions
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- Genetics
  - SNPs
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Species assemblage #1
Species assemblage #2
"Intelligence"
Creativity
Two populations
Resistant/susceptible strains

Multivariate analysis in a nutshell
Applications to genetic data
Genetic diversity of pathogen populations
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Applications to genetic data

Genetic diversity of pathogen populations

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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Reducing $P$ dimensions into 1

- $X \in \mathbb{R}^{N \times P}$; $X = [x_1 | \ldots | x_P]$: data matrix
- $Q \in \mathbb{R}^{P \times P}$ metric in $\mathbb{R}^P$; $D \in \mathbb{R}^{N \times N}$ metric in $\mathbb{R}^N$
- $u \in \mathbb{R}^P$; $u = [u_1, \ldots, u_P]$: principal axis ($\|u\|_Q^2 = 1$)
- $v \in \mathbb{R}^N$; $v = XQu$: principal component

$\rightarrow$ find $u$ so that $\|v\|_D^2$ is maximum.
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Keeping more than one principal component

- $\mathbf{u}_1$ and $\mathbf{v}_1$: 1st principal axis and component
- $\mathbf{u}_2$ and $\mathbf{v}_2$: 2nd principal axis and component

→ constraint: $\mathbf{u}_1 \perp \mathbf{u}_2$ (i.e., $\langle \mathbf{u}_1, \mathbf{u}_2 \rangle_Q = 0$)
→ find $\mathbf{u}_2$ so that $\|\mathbf{v}_2\|_D^2$ is maximum
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\[ \langle u_1, u_2 \rangle_Q = 0 \]

\[ \| v_2 \|_D^2 \text{ is maximum} \]
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→ find $\mathbf{u}_2$ so that $\|\mathbf{v}_2\|_D^2$ is maximum
How do we do this?

Things that don’t change:

- take $u_i$ the $i$-th eigenvector of the $Q$-symmetric matrix $X^TDXQ$
- (alternatively) take $v_i$ the $i$-th eigenvector of the $D$-symmetric matrix $XQX^TD$

Things that change:

- pre-transformations of $X$ (recoding, standardisation, etc.)
- metrics $Q$ and $D$ (implicitly distances in $\mathbb{R}^P$ and $\mathbb{R}^N$)
- most usual analyses are defined by $(X, Q, D)$
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\texttt{R} 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
- **principal axes**: nature of the structures
- **eigenvalues**: magnitude of structures
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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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Applications to genetic data

Genetic diversity of pathogen populations
From DNA sequences to patterns of biological diversity
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...attgcagtaacc...

Reproduction (simplified)
From DNA sequences to patterns of biological diversity

Reproduction (simplified)

Mutation

...attgcagtaacc...

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From DNA sequences to patterns of biological diversity
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DNA sequences contain information about the spatio-temporal dynamics of biological populations
DNA sequences: a rich source of information

- hundreds/thousands individuals
- up to millions of single nucleotide polymorphism (SNPs)
- more generally, most genetic data can be treated as frequencies

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\[ \Rightarrow \text{Multivariate analysis use to summarize genetic diversity.} \]
First application of multivariate analysis in genetics

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

First 2 principal components separate populations into continents.
First application of multivariate analysis in genetics

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

First 2 principal components separate populations into continents.
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...

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Multivariate methods used in genetics

- Principal Component Analysis (PCA)
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- Correspondance Analysis (CA)
- Discriminant Analysis (DA)
- Canonical Correlation Analysis (CCA)
- ...

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packages: adegenet, ade4, pegas
Since then...

Applications

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


Applications in genetics of pathogen populations.
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Genetic diversity of pathogen populations
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
- reconstruct epidemiological processes (transmission)
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Different questions at different scales

Where and how can multivariate analysis of pathogen genetic data be useful?
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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
- *Problem:* no “mating” in most pathogens (e.g. viruses, bacteria)
- *Genetic clusters:* set of genetically related pathogens (e.g. same outbreak, same epidemic).

⇒ aim: identify and describe genetic clusters
Describing pathogen populations

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Genetic clustering using K-means & BIC

(Jombart et al. 2010, BMC Genetics)

Variance partitioning model (ANOVA):

\[ \text{tot. variance} = (\text{bet. groups}) + (\text{wit. groups}) \]

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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\( \text{R} \) package: adegenet, function find.clusters
PCA of seasonal influenza (A/H3N2) data

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

Little temporal evolution, burst of diversity in 2002??
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Total diversity not relevant to analyse clusters.

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- maximizes group discrimination ("between/within" ratio)
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**R** package: *adegenet*, function `dapc`
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Strong temporal signal, originality of 2006 isolates (new alleles).
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Identifying antigenic clusters in influenza (A/H3N2)

Antigenic clusters identified directly from AA sequences.

(Smith et al., 2004, Science)

(Aguas & Ferguson, in prep)
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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).
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Methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak within hospital, Thailand. \(\sim 200\) full-genome sequences. \(\sim 1,000\) SNPs.

Observations:

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- genetic clusters can be defined
- transmissions at within-cluster level
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Multivariate analysis usually not informative on small-scale processes.
Summary

• multivariate analysis used for \(\sim 50\) years in genetics, still an active field for methodological development

• increasingly useful as datasets grow

• specific applications to pathogen genetic data

• limits reached when reconstructing fine-scale processes

• more at: http://adegenet.r-forge.r-project.org/
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