Inference after human genetic clustering

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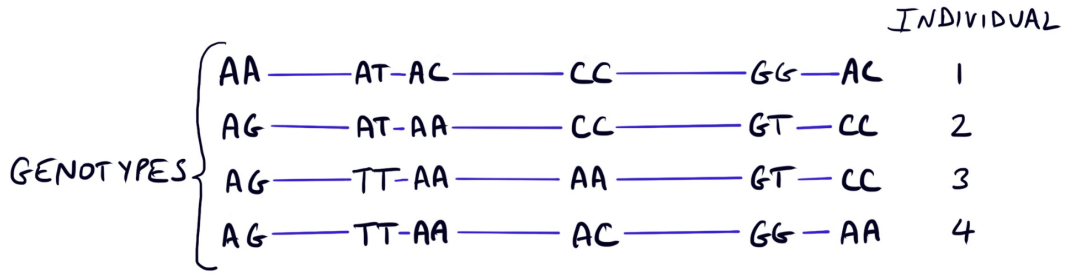
Genetic diversity and population structure

SNP data describing genotypes in a population



Figures : *An introduction to human population genetics, variation, and disease*, Jonathan K Pritchard.

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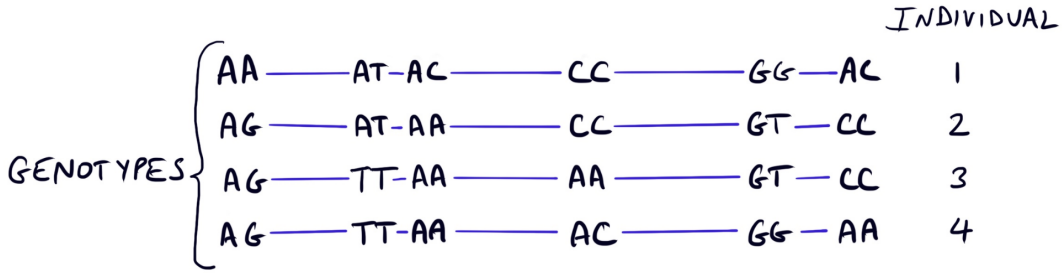

Allele configurations $\rightarrow$ SNP code

AA $\rightarrow$ 0, Aa $\rightarrow$ 1, aa $\rightarrow$ 2,
with A (resp. a) being the reference (resp. alternate) allele.

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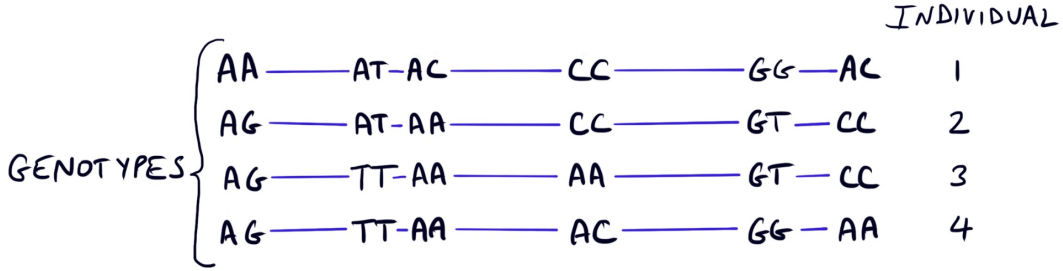

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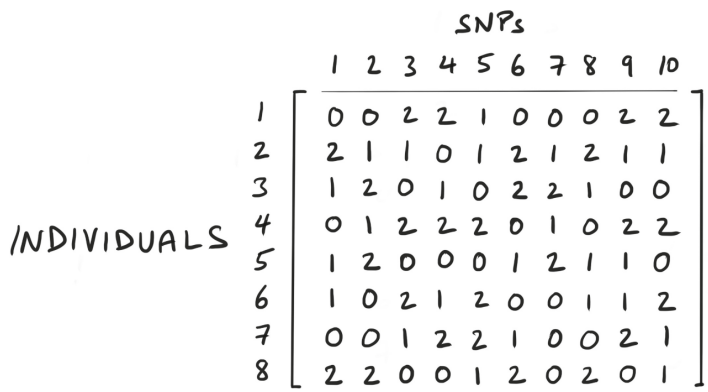

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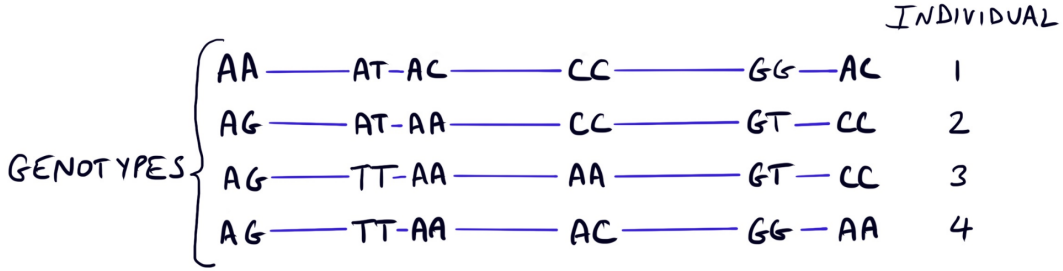

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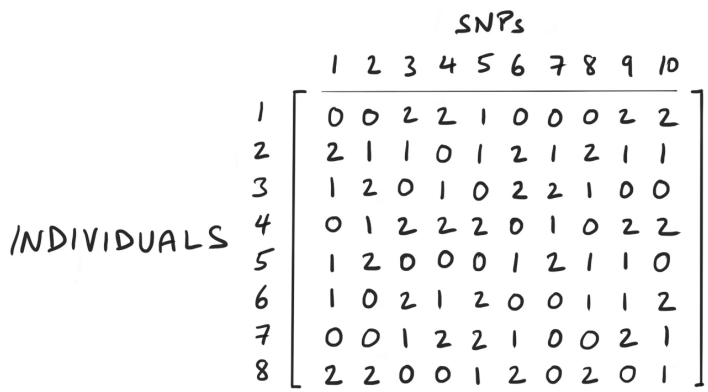

→ Is it possible to **find structure in that genotype matrix** ?

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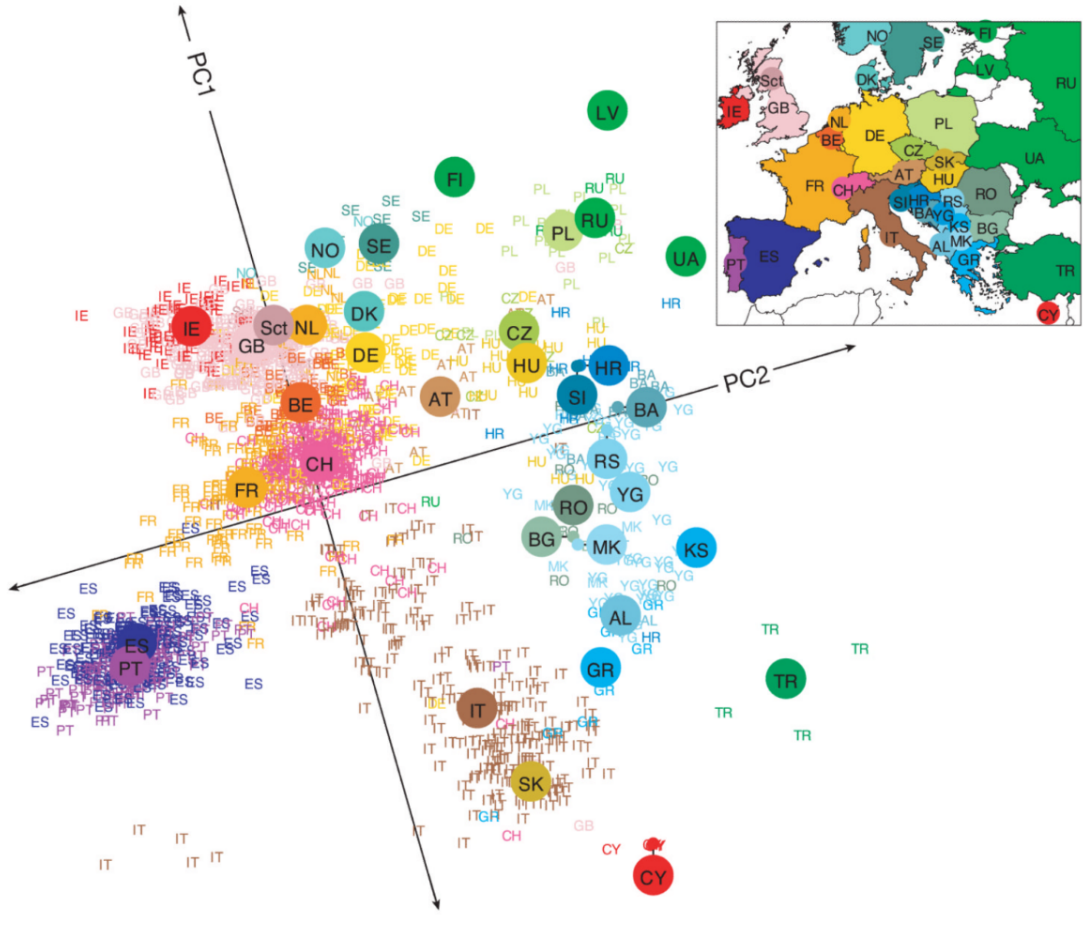
Genotype data unveils population structure



PCA on genome-wide SNP data for 1387 European individuals (Novembre *et al.*, Nature, 2008).

Population structure and genotype data

Fundamental question in Population Genetics

Can we infer/observe population structure and/or ancestry from genetic data ?

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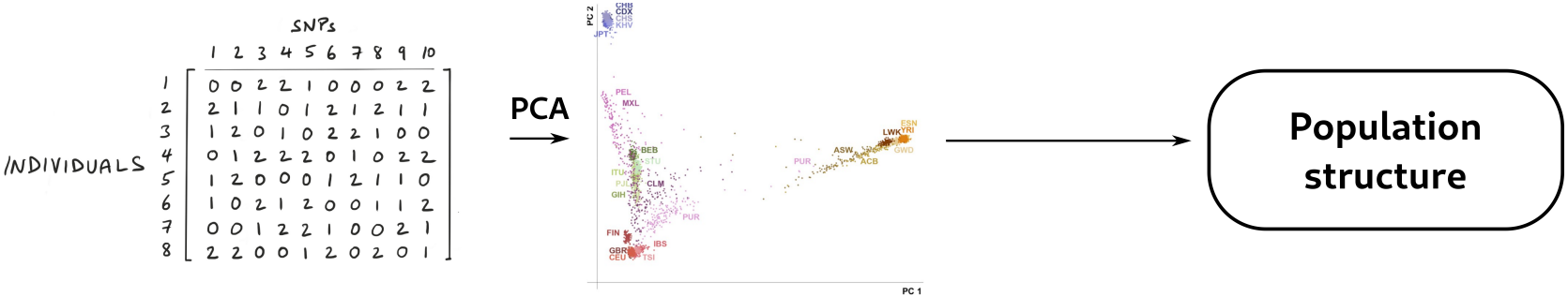

Population structure and genotype data

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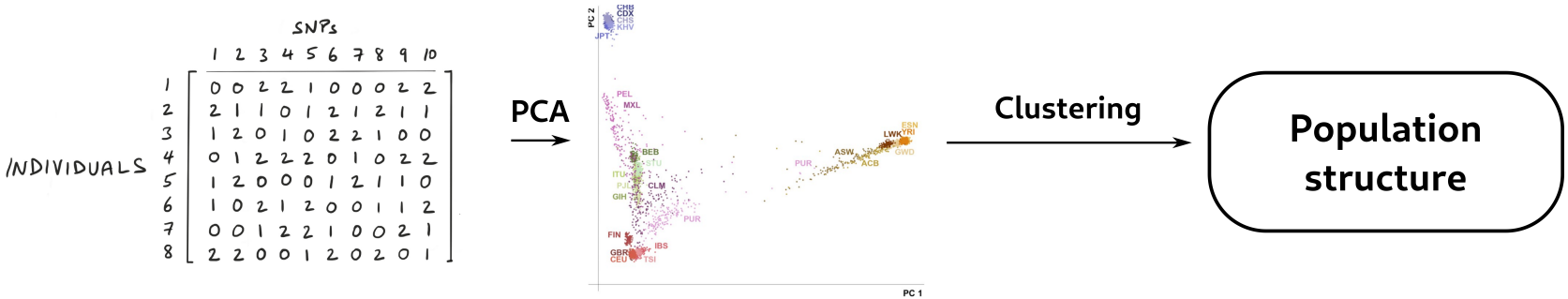


Population structure and genotype data

Fundamental question in Population Genetics

Can we infer/observe population structure and/or ancestry from genetic data ?

- Simple clustering algorithms like hierarchical clustering reveal broad (continental) structure[1].

1. Mountain and Cavalli-Sforza (1997).

Population structure and genotype data

Fundamental question in Population Genetics

Can we infer/observe population structure and/or ancestry from genetic data ?

- Simple clustering algorithms like hierarchical clustering reveal broad (continental) structure[1].
- More complex algorithms can reveal population structure at finer levels[2] (e.g. the UMAP+HDBSCAN($\hat{\epsilon}$) pipeline[3]).

1. Mountain and Cavalli-Sforza (1997), 2. Rosenberg *et al.* (2002), Hollfelder *et al.* (2017), 3. Diaz-Papkovich *et al.* (2025).

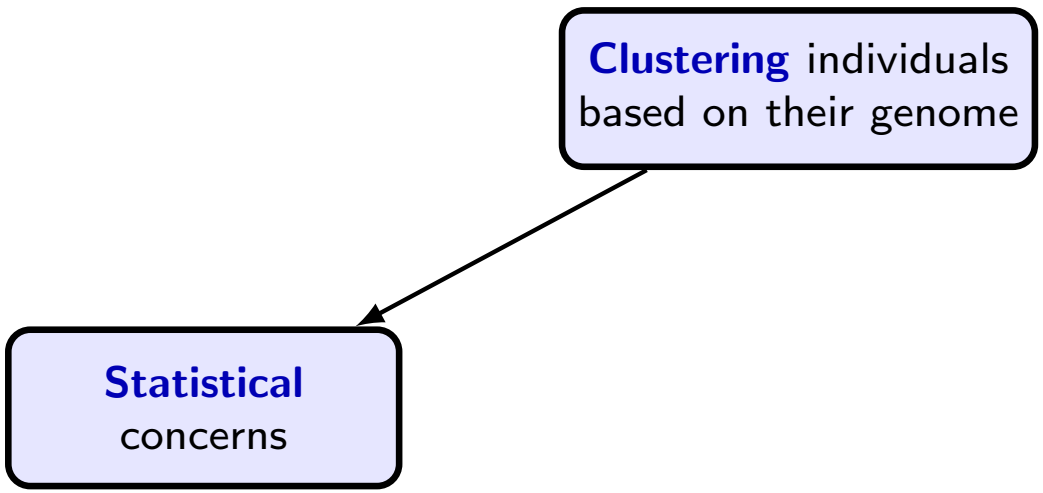
Clustering genetic data

Main challenges

Clustering individuals based on their genome

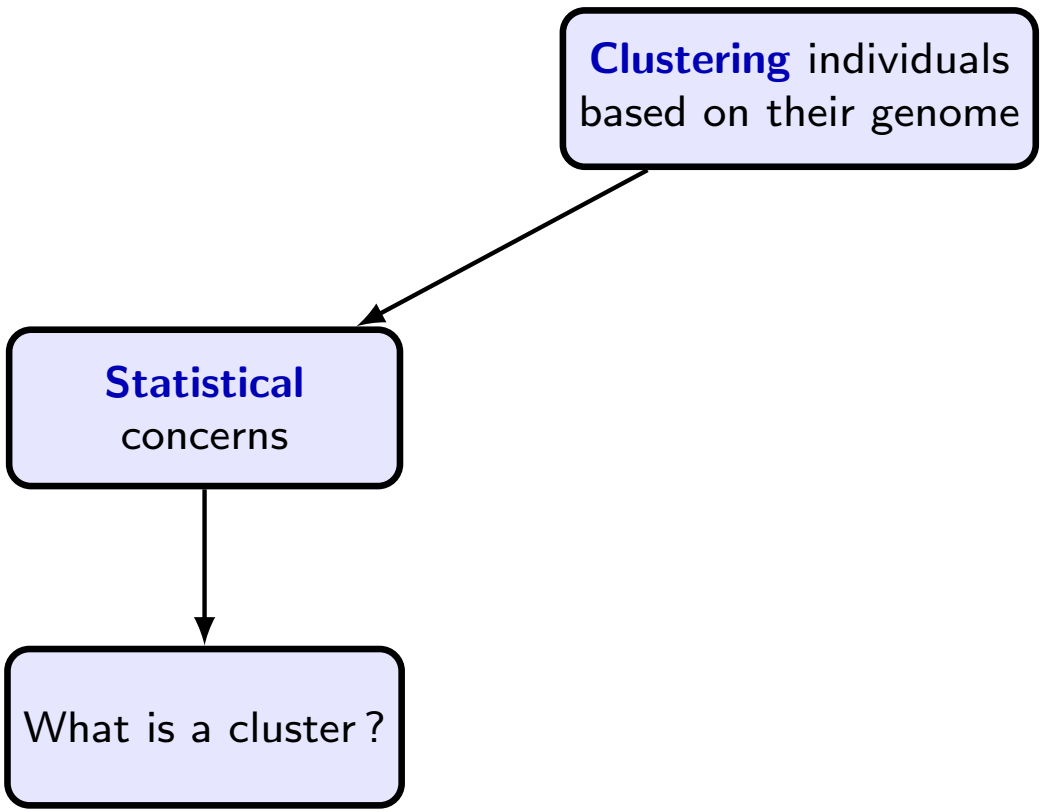
Clustering genetic data

Main challenges



Clustering genetic data

Main challenges



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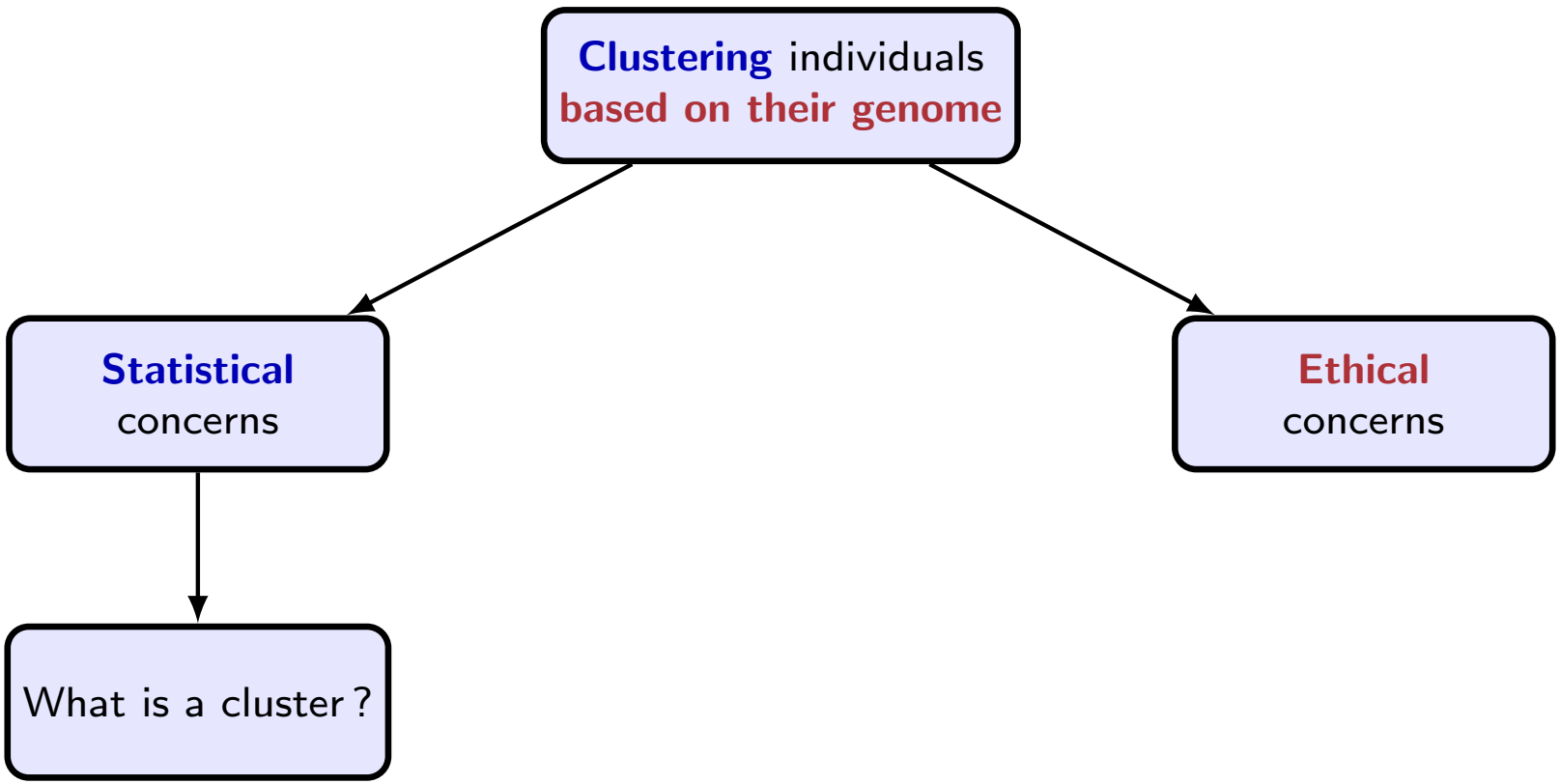

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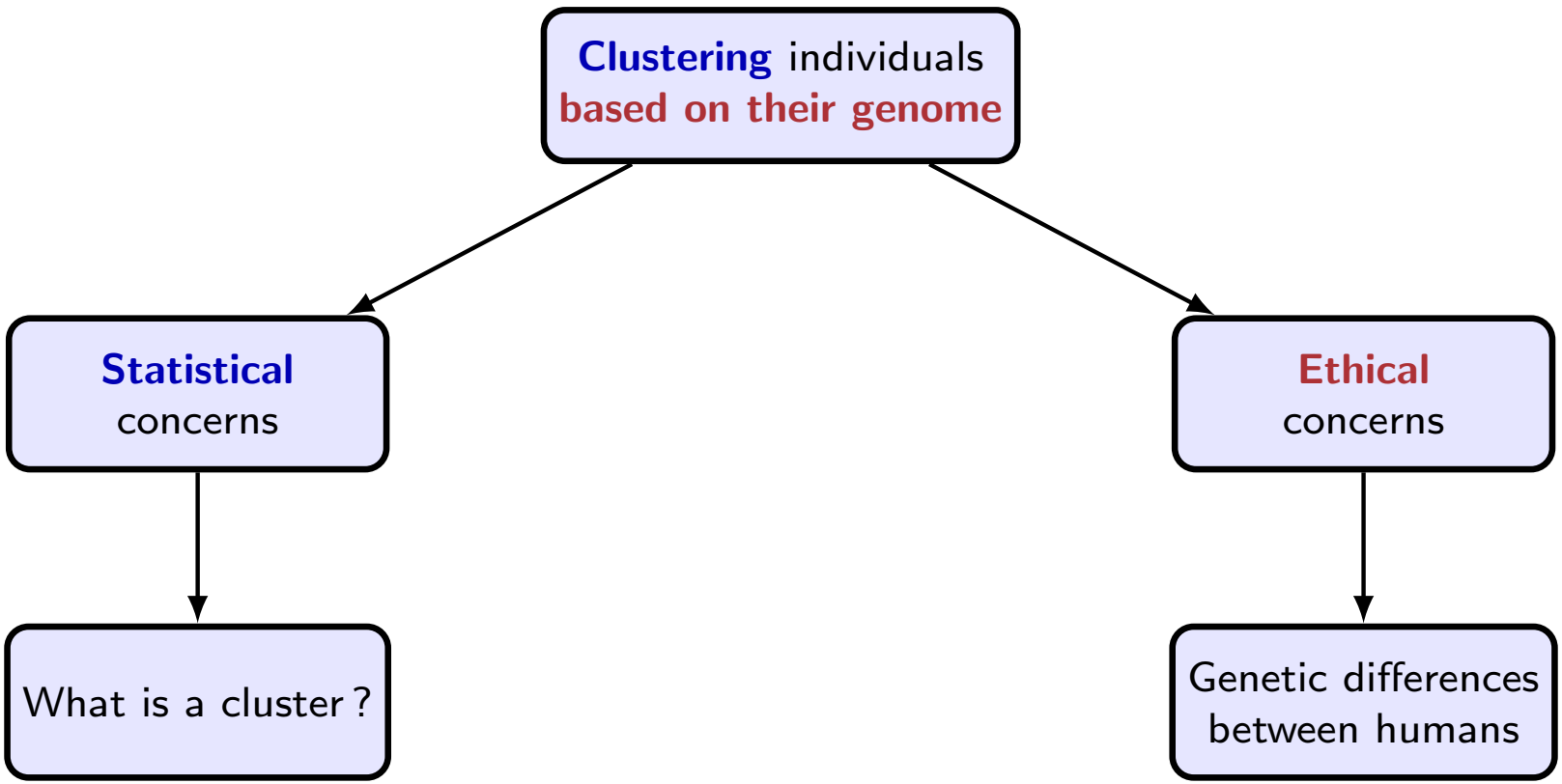

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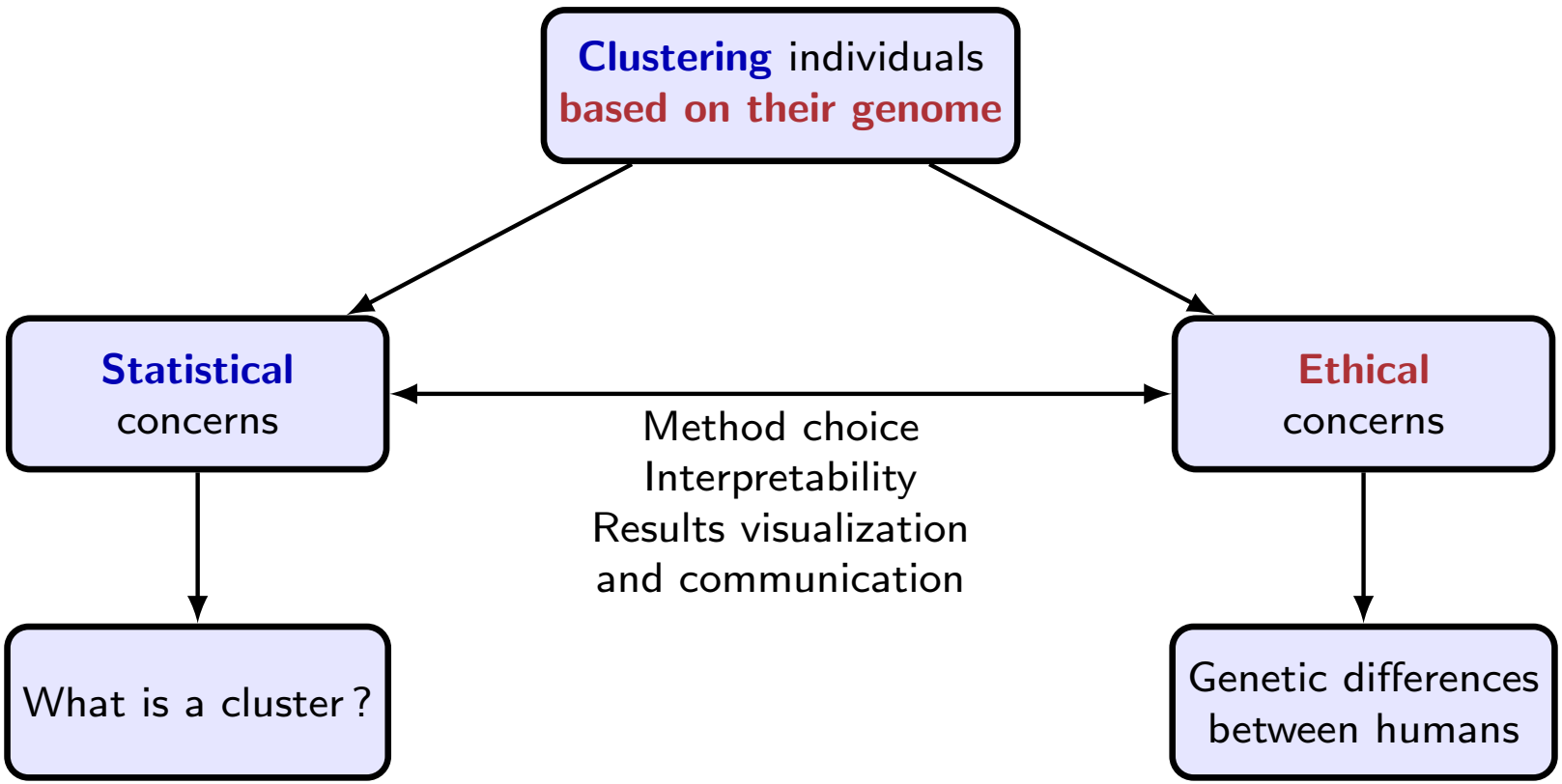

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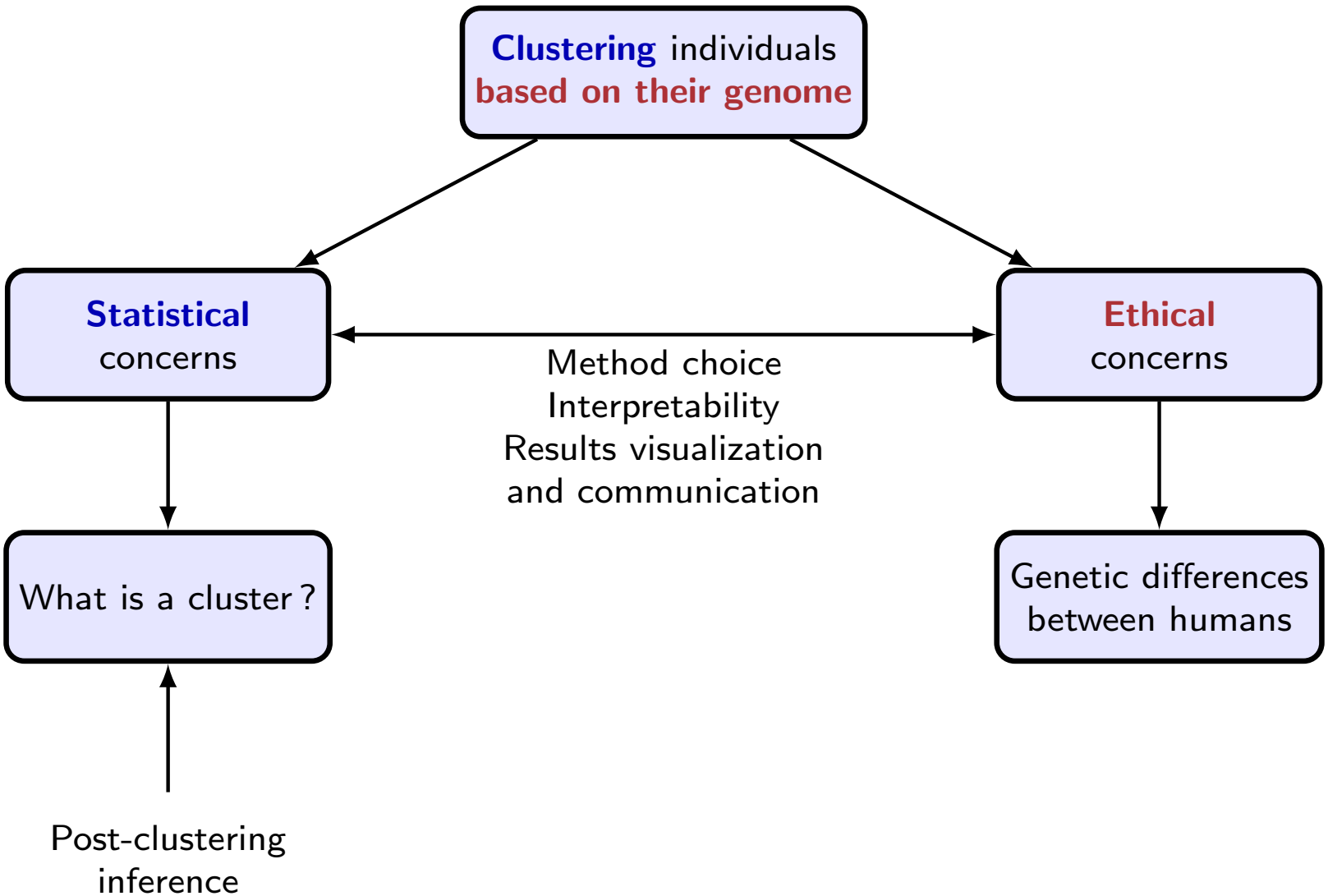
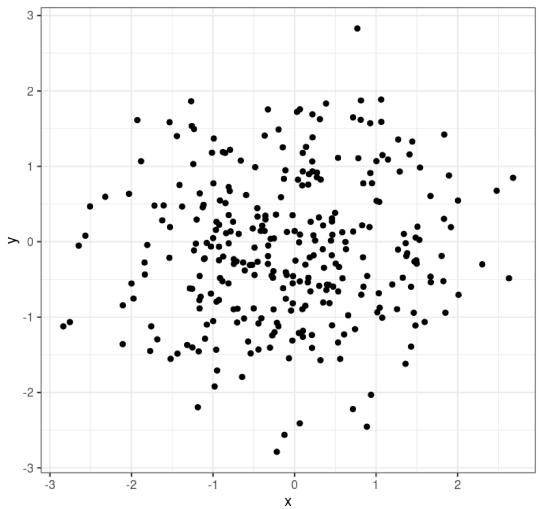


Post-clustering inference

The problem of *double-dipping*



Data

Inspired from Boris Hejblum's SMPGD 2026 slides.

Post-clustering inference

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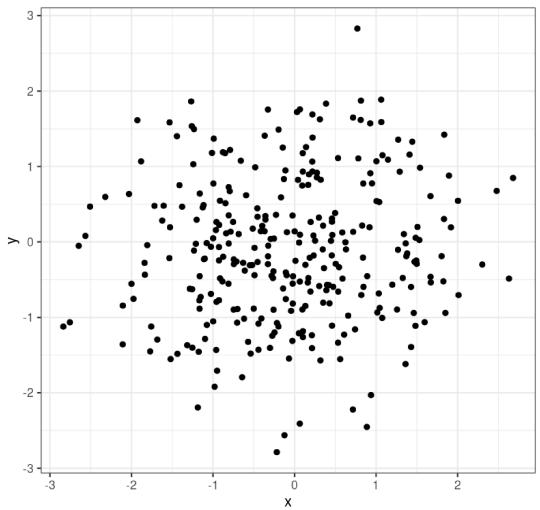

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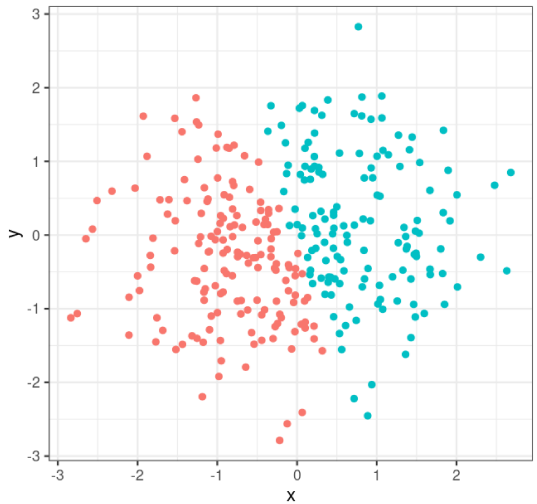

Clustering

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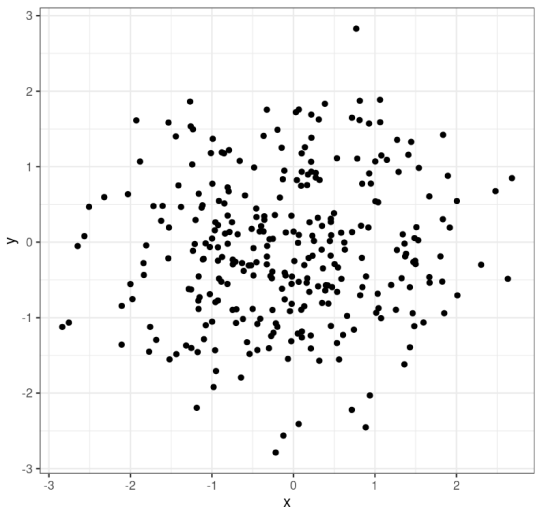
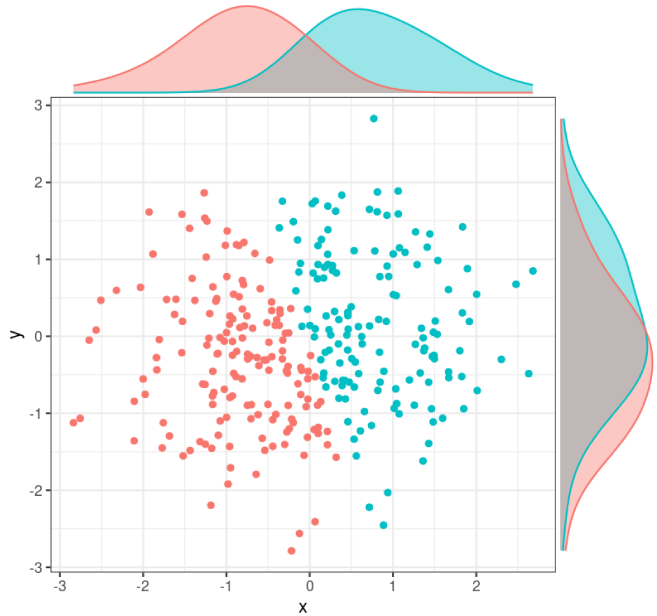


Data



Cluster● = Cluster●?

Inspired from Boris Hejblum's SMPGD 2026 slides.

Post-clustering inference

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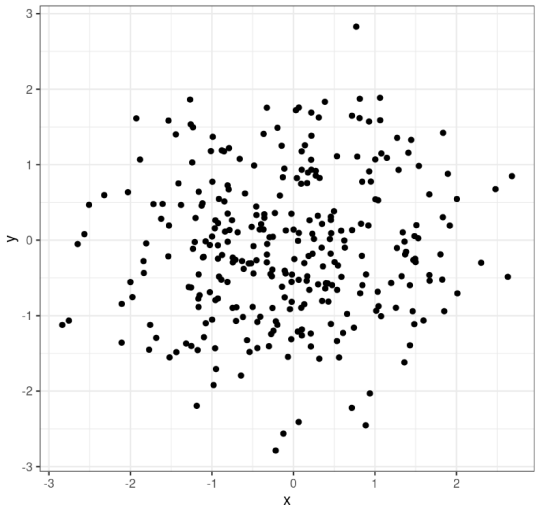

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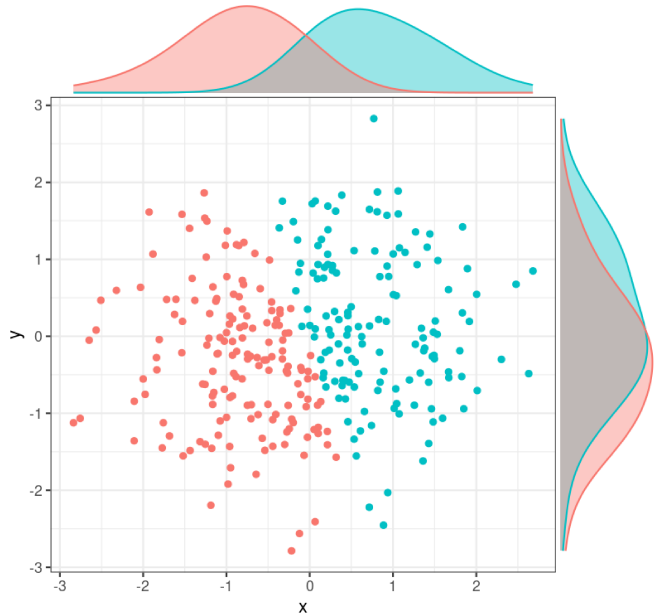


Cluster● = Cluster●?

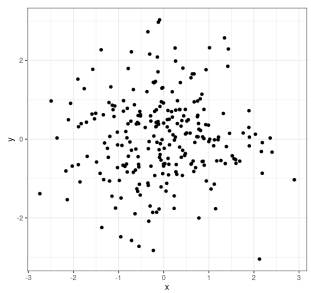
Double dipping

Same data used for both clustering and testing ⇒ Lost of type I error control.

Inspired from Boris Hejblum's SMPGD 2026 slides.

Post-clustering inference approaches

Sample splitting is not a solution



X

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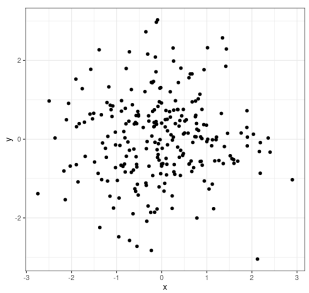

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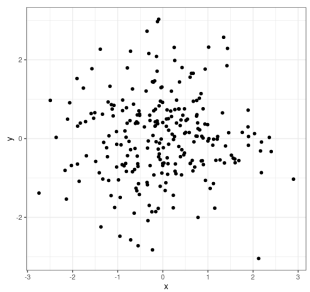
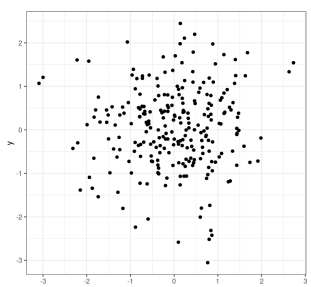


X_{train}



X_{test}

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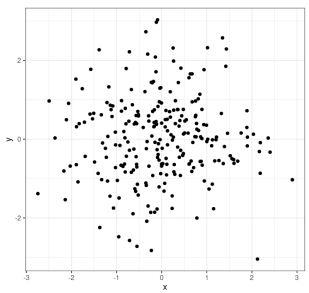

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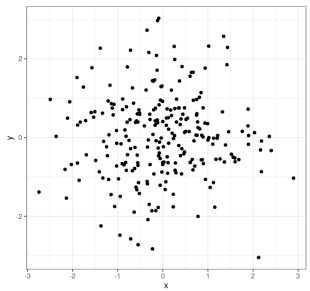

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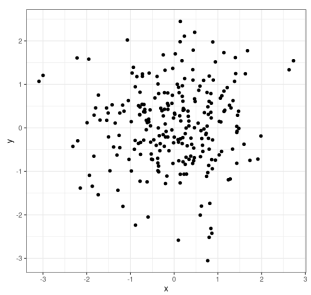

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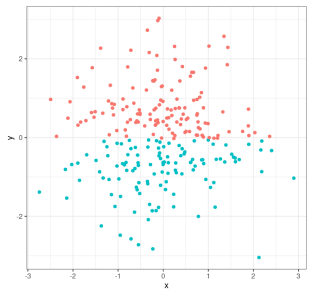

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1. Learn a clustering on X_{train}

Inspired from Boris Hejblum's SMPGD 2026 slides.

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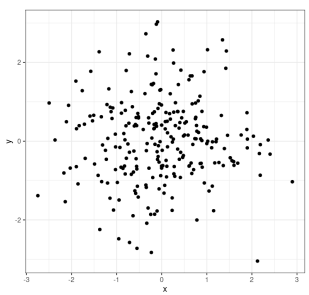

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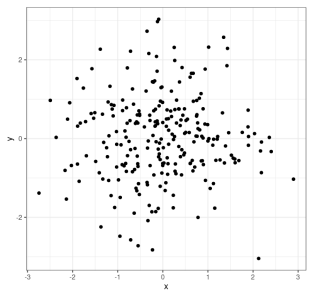

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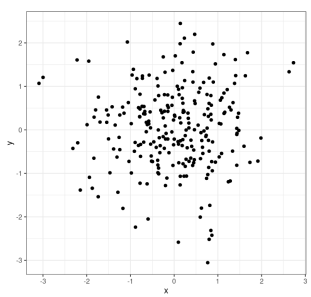
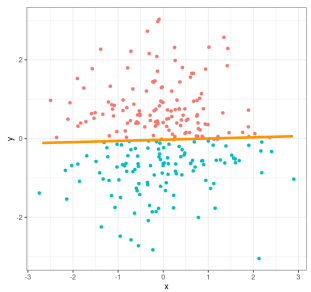


X_{test}



X_{train}

1. Learn a clustering on X_{train}
2. Train a classifier on X_{train}

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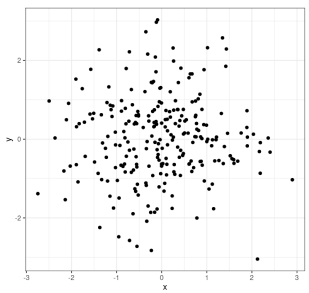

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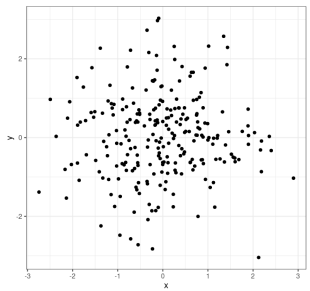

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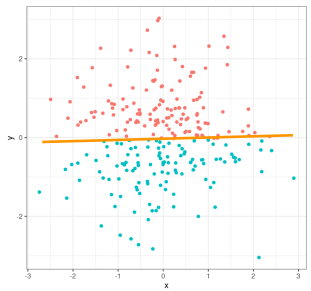

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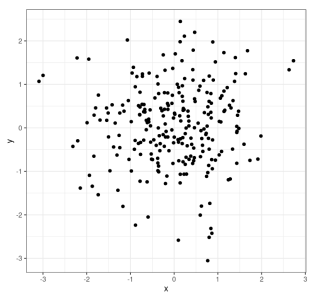
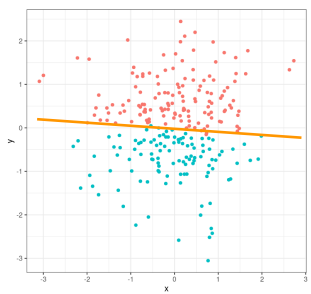


X_{test}

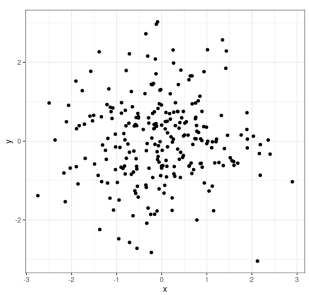


X_{test}

1. Learn a clustering on X_{train}
2. Train a classifier on X_{train}
3. Predict a clustering on X_{test}

Inspired from Boris Hejblum's SMPGD 2026 slides.

Sample splitting is not a solution



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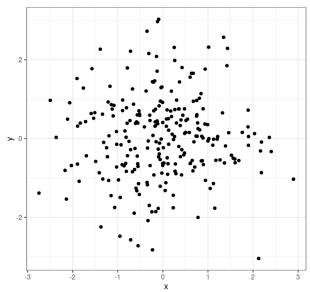

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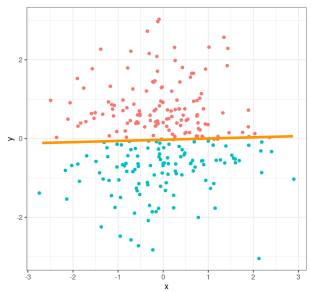

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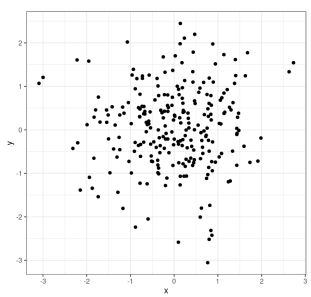
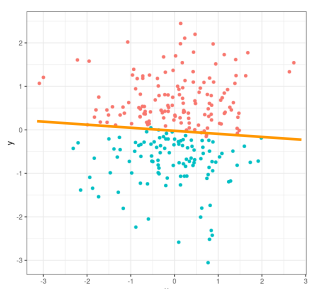


X_{test}

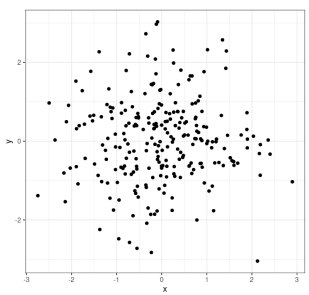


X_{test}

3. Predict a clustering on X_{test}
4. Test cluster differences on X_{test}

Inspired from Boris Hejblum's SMPGD 2026 slides.

Sample splitting is not a solution



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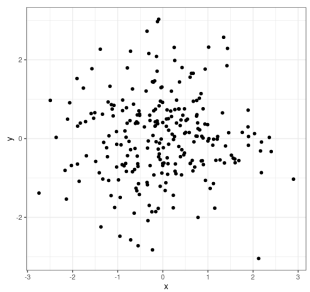
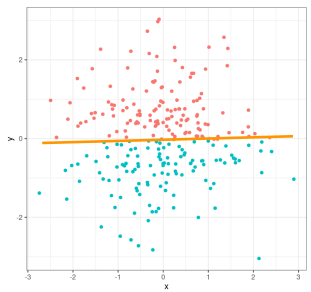


X_{train}



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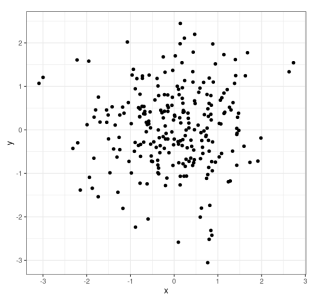

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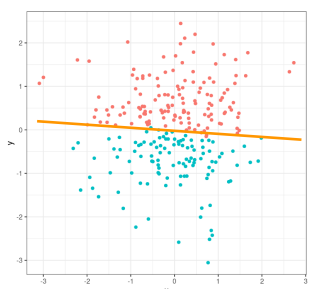

X_{test}

1. Learn a clustering on X_{train}
2. Train a classifier on X_{train}

3. Predict a clustering on X_{test}
4. Test cluster differences on X_{test}

3 and 4 both use the same data:

still double dipping!

Inspired from Boris Hejblum's SMPGD 2026 slides.

Information partitioning approaches

Data fission / data thinning

Information partitioning approaches

Data fission / data thinning

Idea

Decompose the dataset $\mathbf{X}$ into two independent datasets $\mathbf{X}^{(1)}$, $\mathbf{X}^{(2)}$ and :

- Use $\mathbf{X}^{(1)}$ for clustering,
- Use $\mathbf{X}^{(2)}$ for testing.

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Data fission / data thinning

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Known decompositions for Gaussian data $X_1, \overset{\text{i.i.d.}}{\ldots}, X_n \sim \mathcal{N}(\mu, \mathbf{\Sigma})$

Data fission (Leiner *et al.*, 2023)

$$X_i^{(1)} = X_i + \tau W_i$$

$$X_i^{(2)} = X_i + W_i/\tau$$

with $W \sim \mathcal{N}(0, \mathbf{\Sigma})$ and $\tau > 0$.

Data thinning (Neufeld *et al.*, 2024)

$$X_i^{(1)} \mid X_i = x_i \sim \mathcal{N}(\tau x_i, \tau(1-\tau)\mathbf{\Sigma})$$

$$X_i^{(2)} = X_i - X_i^{(1)}$$

with $\tau \in (0, 1)$.

Inspired from Boris Hejblum's SMPGD 2026 slides.

Information partitioning approaches

Data fission / data thinning

Idea

Decompose the dataset $\mathbf{X}$ into two independent datasets $\mathbf{X}^{(1)}$, $\mathbf{X}^{(2)}$ and :

- Use $\mathbf{X}^{(1)}$ for clustering,
- Use $\mathbf{X}^{(2)}$ for testing.

Known decompositions for Gaussian data $X_1, \overset{\text{i.i.d.}}{\ldots}, X_n \sim \mathcal{N}(\mu, \mathbf{\Sigma})$

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with $\tau \in (0, 1)$.

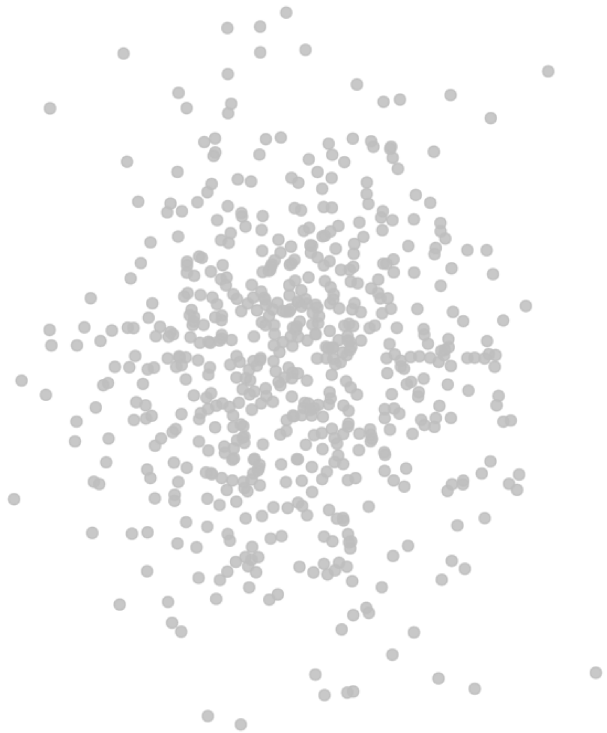
$$\mathbb{P}_{H_0}\left(\text{Reject } H_0 \text{ based on } \mathbf{X}^{(2)} \,\middle|\, \text{Select } H_0 \text{ based on } \mathbf{X}^{(1)}\right) = \mathbf{P}_{H_0}\left(\text{Reject } H_0 \text{ based on } \mathbf{X}^{(2)}\right)$$

$\rightarrow$ Thanks to independence.

Inspired from Boris Hejblum's SMPGD 2026 slides.

Information partitioning approaches

Data fission / data thinning



X

Inspired from Boris Hejblum's SMPGD 2026 slides.

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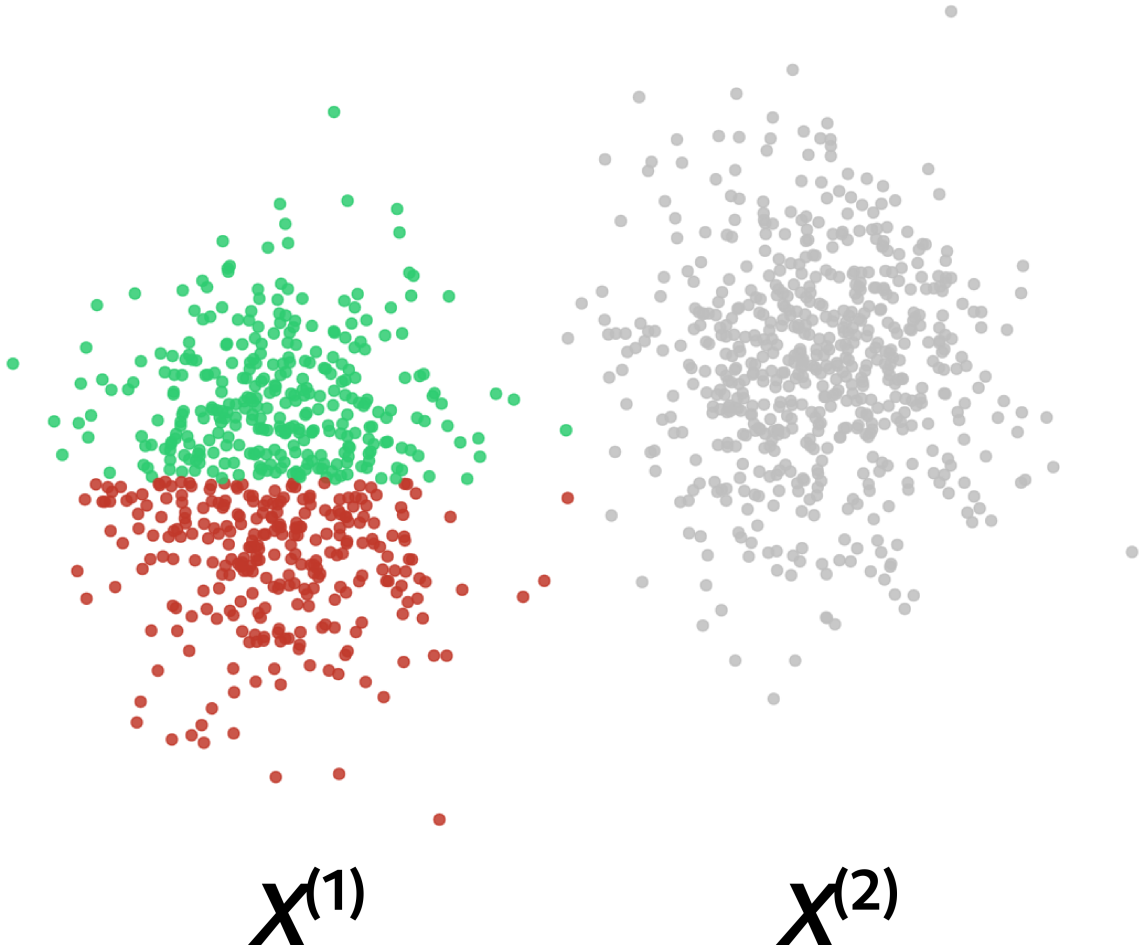

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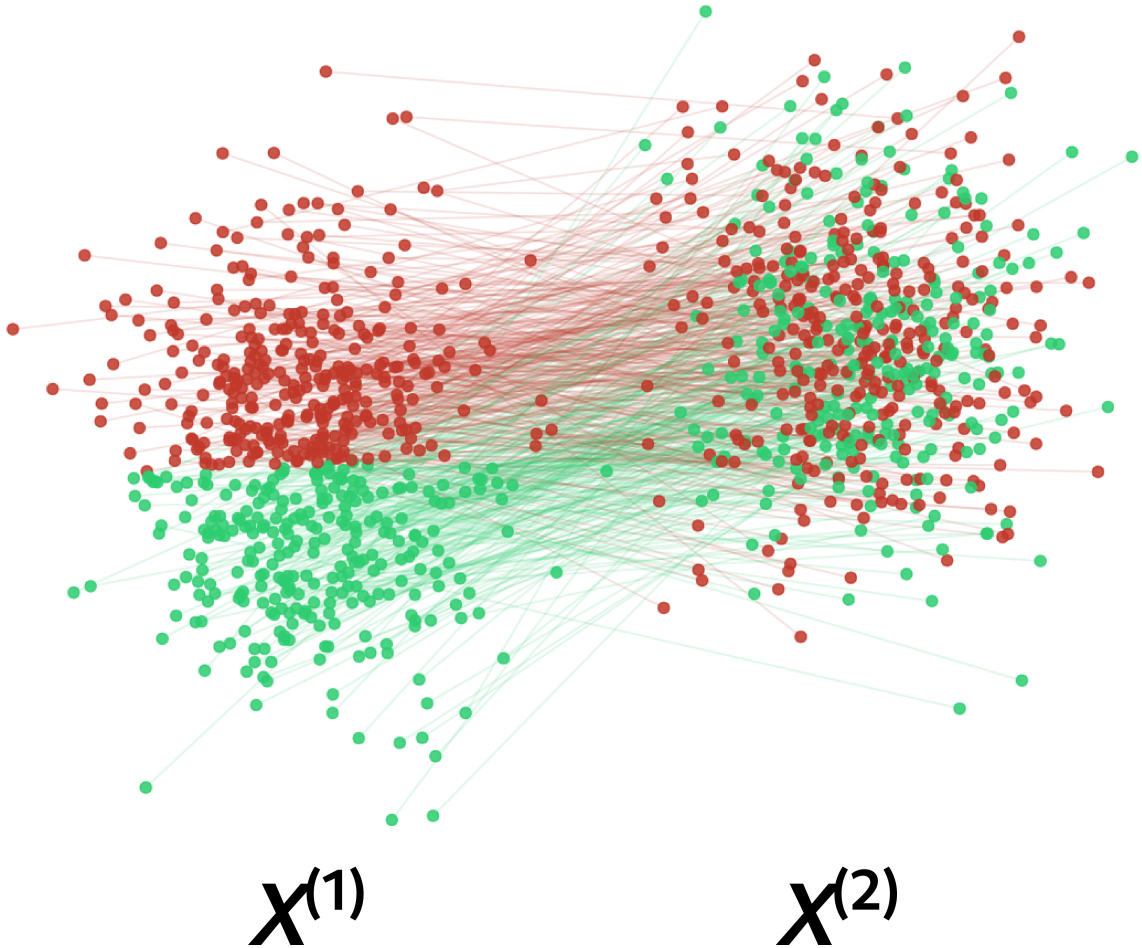
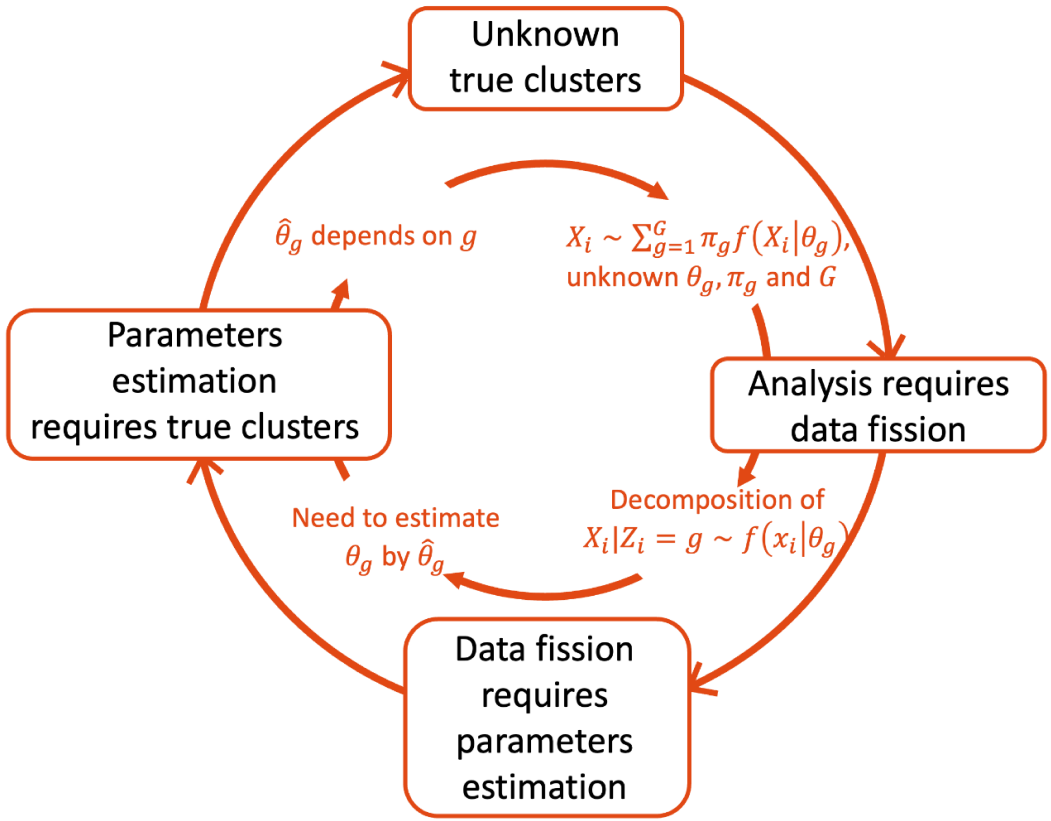


Inspired from Boris Hejblum's SMPGD 2026 slides.

Information partitioning approaches

Unsuitable for clustering



Extracted from Supplementary Figure 1 in Hivert *et al.* 2025, arXiv :2405.13591v3.

Conditional inference

Type I error control

$$\mathbb{P}_{H_0}\left(\text{Reject } H_0 \text{ based on } \mathbf{X}\right) \leq \alpha \quad \forall\, \alpha \in (0,1).$$

Conditional inference

Selective type I error control (Fithian *et al.* 2014)

$$\mathbb{P}_{H_0}\left(\text{Reject } H_0 \text{ based on } \mathbf{X} \,|\, H_0 \text{ selected using } \mathbf{X}\right) \leq \alpha \quad \forall\, \alpha \in (0,1).$$

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Selective type I error control for clustering

$$\mathbb{P}_{H_0}\left(\text{Reject } H_0 \text{ based on } \mathbf{X} \,|\, \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}(\mathbf{X})\right) \leq \alpha \quad \forall\, \alpha \in (0,1),$$

$\rightarrow \mathcal{G}_1, \mathcal{G}_2$ are two non-overlapping groups of observations,

$\rightarrow \mathcal{C}$ is a clustering algorithm.

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To date, **conditional approaches** are the only methods that have been demonstrated to be suitable for post-clustering inference.

State-of-the-art and goal

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(Main) state-of-the-art and its model assumptions

- Independent observations $X_i \sim \mathcal{N}_p(\mu_i, \sigma^2 \mathbb{I}_p)$ + estimation of σ.

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  For $\mathbf{U} \in \mathbb{R}^{n\times n}$ and $\boldsymbol{\Sigma} \in \mathbb{R}^{p\times p}$ positive definite, that means :

  - $\text{vec}(\mathbf{X}) \sim \mathcal{N}_{n\times p}\left(\text{vec}(\boldsymbol{\mu}), \boldsymbol{\Sigma} \otimes \mathbf{U}\right)$,
  - $X_i \sim \mathcal{N}_p(\mu_i, U_{ii}\boldsymbol{\Sigma})$ ($\boldsymbol{\Sigma} \leftrightarrow$ dependence between features),
  - $X^j \sim \mathcal{N}_n(\mu^j, \Sigma_{jj}\mathbf{U})$ ($\mathbf{U} \leftrightarrow$ dependence between observations).

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Simplistic model

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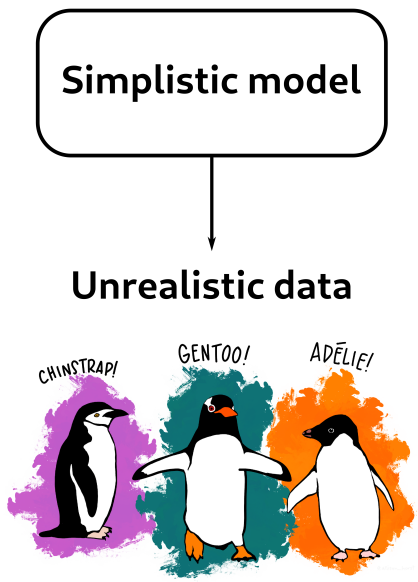

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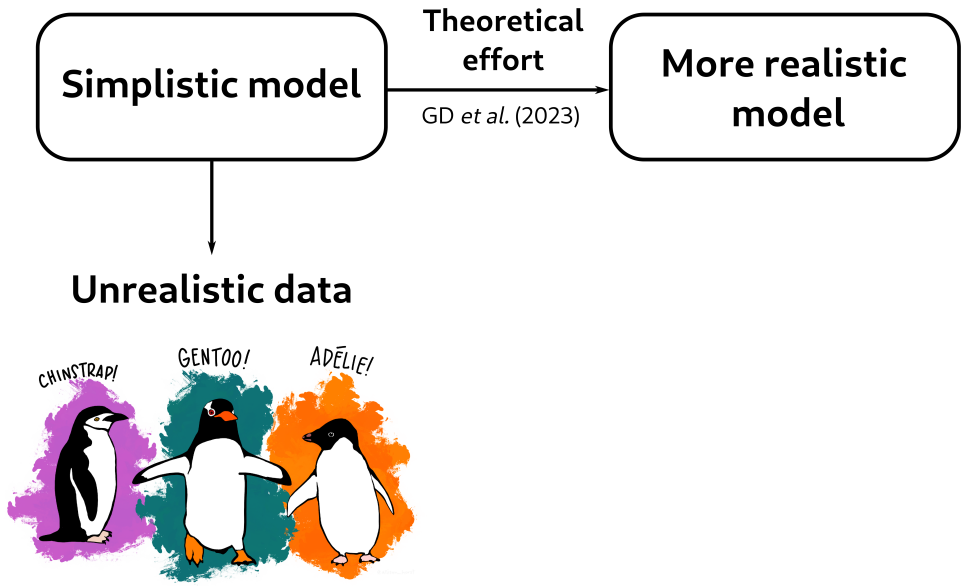

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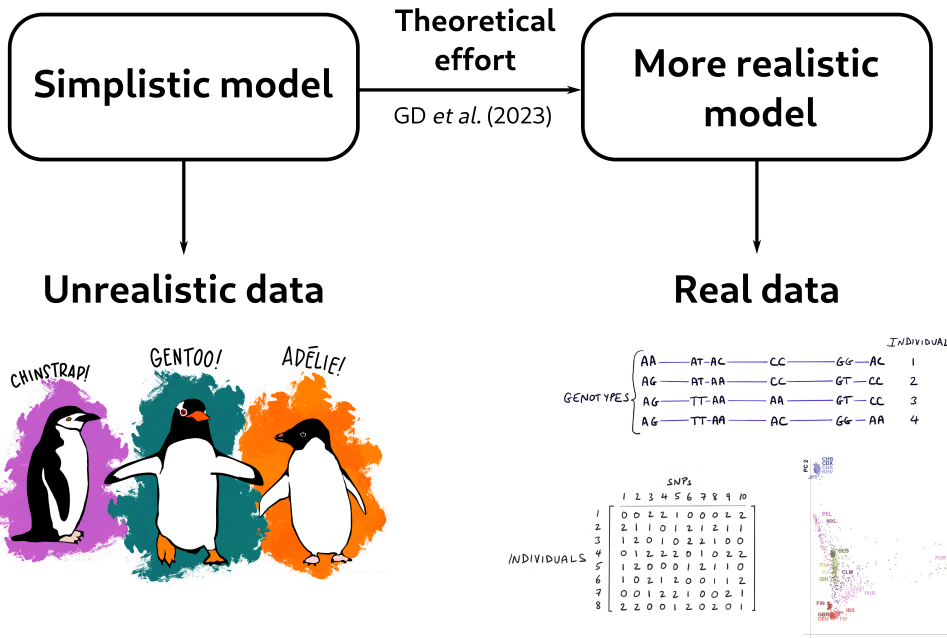

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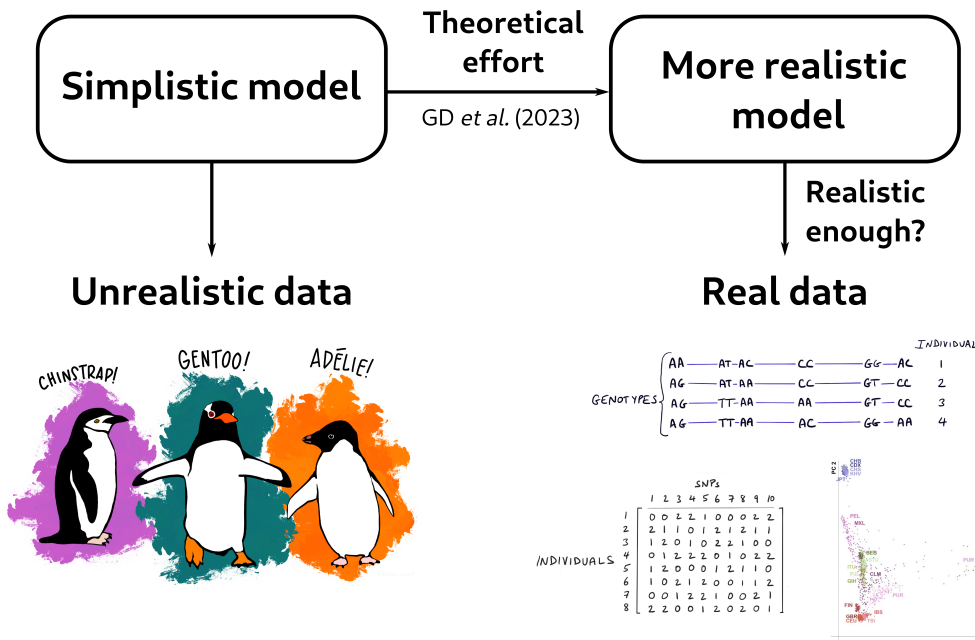

Conditional approaches on real data

Framework setting

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- Let $C(\cdot)$ be a clustering algorithm, $\mathbf{X}$ a $n \times p$ random matrix with $\mathbb{E}(\mathbf{X}) = \boldsymbol{\mu}$.

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- Let X_i (resp. μ_i) denote the i-th row of $\mathbf{X}$ (resp. $\boldsymbol{\mu}$) for $i \in [n] = \{1, \ldots, n\}$.

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- For any $\mathcal{G} \subset \{1, \ldots, n\}$, let $\bar{X}_{\mathcal{G}} = \frac{1}{|\mathcal{G}|} \sum_{i \in \mathcal{G}} X_i$ and $\bar{\mu}_{\mathcal{G}} = \frac{1}{|\mathcal{G}|} \sum_{i \in \mathcal{G}} \mu_i$.

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- Let $\mathcal{G}_1, \mathcal{G}_2 \subset \{1, \ldots, n\}$ be two non-overlapping groups of observations. Considering the column vector $\nu_{\mathcal{G}_1, \mathcal{G}_2} = \nu$ having as components

$$\nu_i = \mathbb{1}\{i \in \mathcal{G}_1\}/|\mathcal{G}_1| - \mathbb{1}\{i \in \mathcal{G}_2\}/|\mathcal{G}_2|,$$

for $i \in [n]$,

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for $i \in [n]$, we can write the difference between the (empirical) group means as

$$\bar{\mu}_{\mathcal{G}_1} - \bar{\mu}_{\mathcal{G}_2} = \boldsymbol{\mu}^T \nu \quad \text{and} \quad \bar{X}_{\mathcal{G}_1} - \bar{X}_{\mathcal{G}_2} = \mathbf{X}^T \nu.$$

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We are interested in the following null hypothesis :

$$H_0^{\{\mathcal{G}_1, \mathcal{G}_2\}} : \boldsymbol{\mu}^T \nu = 0. \qquad \text{(H0)}$$

Standard strategy

1. Choose a model

$$\mathbf{X} \sim \mathcal{MN}_{n\times p}(\boldsymbol{\mu}, \mathbf{U}, \boldsymbol{\Sigma}),$$

where $\boldsymbol{\Sigma}$ can be (over-)estimated and $\mathbf{U}$ is known.

González-Delgado *et al.*, 2025.

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2. Consider a p-value of the form

$$p(\mathbf{x}; \{\mathcal{G}_1, \mathcal{G}_2\}) = \mathbb{P}_{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}}\left(\|\mathbf{X}^T\nu\|_{\mathbf{V}} \geq \|\mathbf{x}^T\nu\|_{\mathbf{V}} \;\middle|\; \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}(\mathbf{X}),\right.$$

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where $\boldsymbol{\pi}_\nu^\perp = \mathbb{I}_n - \frac{\nu\nu^T}{\|\nu\|_2^2}$ and $\mathrm{dir}_{\mathbf{V}}(u) = u/\|u\|_{\mathbf{V}}$ for all $u \in \mathbb{R}^p$.

González-Delgado *et al.*, 2025.

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- The p-value controls the selective type I error for clustering.

González-Delgado *et al.*, 2025.

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where $\boldsymbol{\pi}^{\perp}_{\nu} = \mathbb{I}_n - \frac{\nu\nu^T}{\|\nu\|_2^2}$ and $\mathrm{dir}_{\mathbf{V}}(u) = u/\|u\|_{\mathbf{V}}$ for all $u \in \mathbb{R}^p$.

- The p-value controls the selective type I error for clustering.
- Main challenge : derive an analitically tractable form.

González-Delgado *et al.*, 2025.

Towards a more interpretable p-value

Rewriting the conditioning set

$$\mathbf{X} = \boldsymbol{\pi}_{\nu}^{\perp}\mathbf{X} + (\mathbb{I}_n - \boldsymbol{\pi}_{\nu}^{\perp})\mathbf{X}$$
$$= $$

González-Delgado *et al.*, 2025.

Towards a more interpretable p-value

Rewriting the conditioning set

$$\begin{aligned}\mathbf{X} &= \boldsymbol{\pi}_{\nu}^{\perp}\mathbf{X} + (\mathbb{I}_n - \boldsymbol{\pi}_{\nu}^{\perp})\mathbf{X} \\ &= \boldsymbol{\pi}_{\nu}^{\perp}\mathbf{X} + \frac{\nu\nu^T}{\|\nu\|_2^2}\mathbf{X}\end{aligned}$$

González-Delgado *et al.*, 2025.

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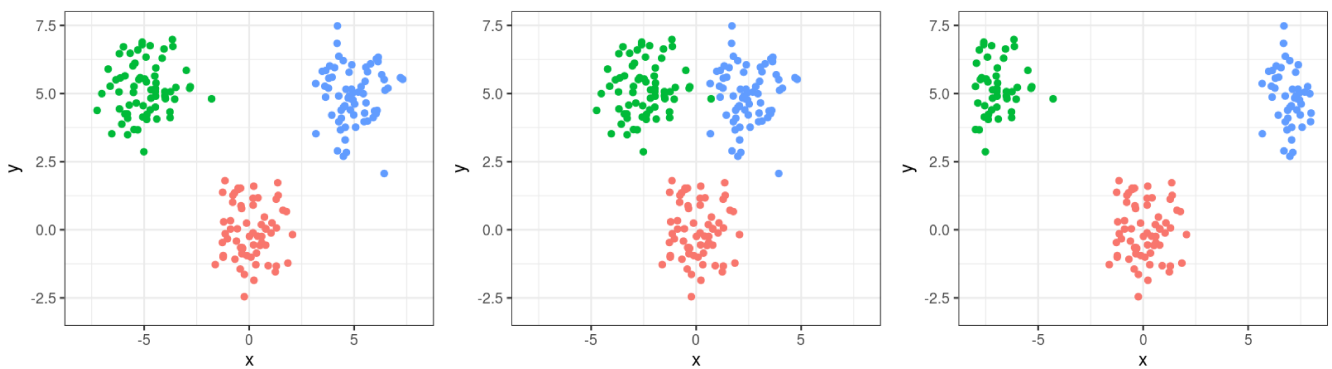
$\mathbf{x}'(\phi)$ is a perturbation of $\mathbf{x}$ such that

- If $\phi \geq \|\mathbf{x}^T\nu\|_{\mathbf{V}}$, $\mathcal{G}_1$ and $\mathcal{G}_2$ are pulled appart,
- If $\phi \leq \|\mathbf{x}^T\nu\|_{\mathbf{V}}$, $\mathcal{G}_1$ and $\mathcal{G}_2$ are pushed together.

$\phi = \|\bar{x}_{\mathcal{G}_1} - \bar{x}_{\mathcal{G}_2}\|$ $\phi \leq \|\bar{x}_{\mathcal{G}_1} - \bar{x}_{\mathcal{G}_2}\|$ $\phi \geq \|\bar{x}_{\mathcal{G}_1} - \bar{x}_{\mathcal{G}_2}\|$



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Interpretation of p-value

A consequence of conditioning

$$p(x) = \mathbb{P}_{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}}\left(\phi \geq \|\mathbf{x}^T\nu\|_{\mathbf{V}} \,\middle|\, \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}\left(\mathbf{x}'(\phi)\right)\right)$$
$$= \frac{\mathbb{E}\left[\mathbb{1}\{\phi \geq \|\mathbf{x}^T\nu\|_{\mathbf{V}}, \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}\left(\mathbf{x}'(\phi)\right)\}\right]}{\mathbb{E}[\mathbb{1}\{\mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}\left(\mathbf{x}'(\phi)\right)\}]}$$

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Informally

Do I have room to push the clusters together while preserving the clustering ?

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- Yes $\rightarrow$ reject (H0) $\rightarrow$ different clusters.
- No $\rightarrow$ accept (H0) $\rightarrow$ same cluster.

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- We need $\{\phi : \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}(\mathbf{x}'(\phi))\} \neq \emptyset$.

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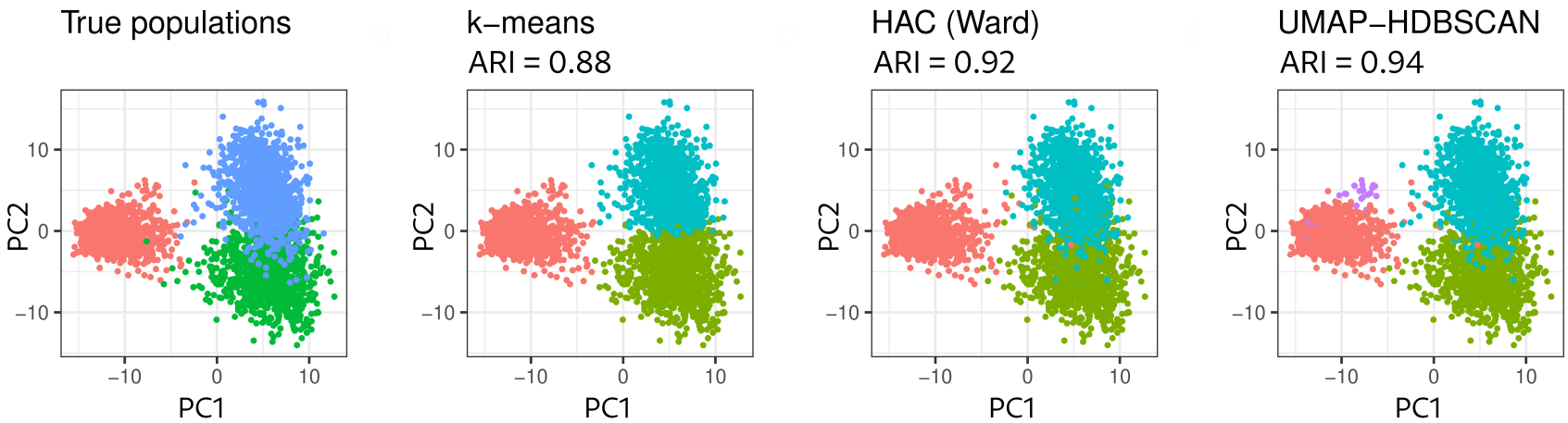
- We need $\{\phi : \mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}(\mathbf{x}'(\phi))\} \neq \emptyset$.
- If $\{\mathcal{G}_1, \mathcal{G}_2 \in \mathcal{C}(\mathbf{x}'(\phi))\}$ is unlikely, p-values will be very close to 0 or 1.

Consequences of conditioning (I)

Clustering need to be robust to small perturbations

Simulation setting

SNPs for $n = 3000$ individuals equally sampled from three populations[1] + Clustering performed on the first 100 PCs.



1. Data : Diaz-Papkovich, *unpublished*.

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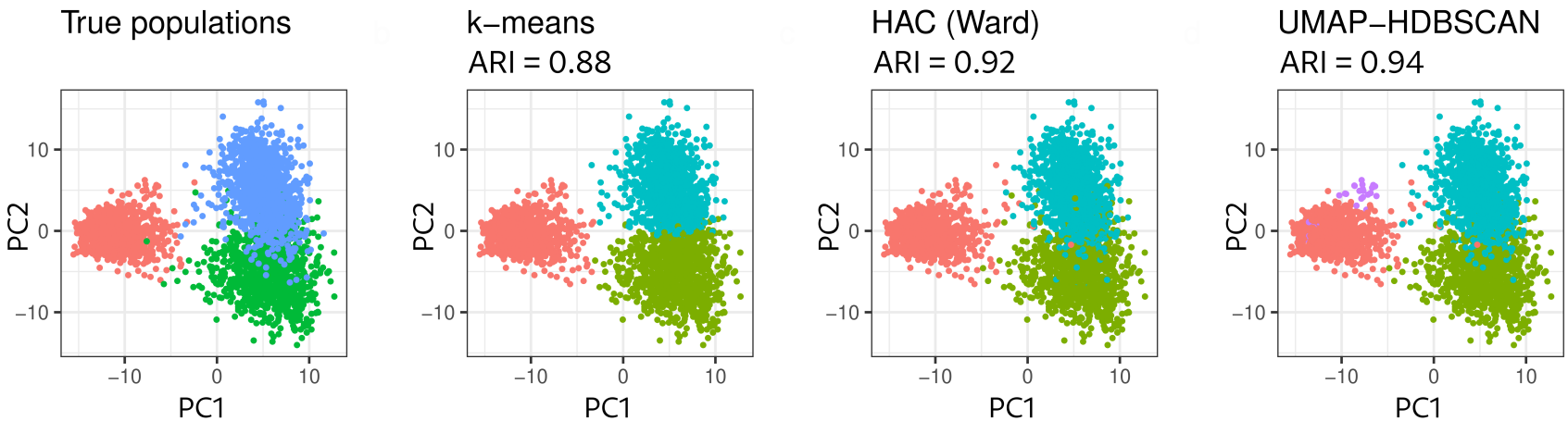

$\{\mathcal{G}_1, \mathcal{G}_2\}$	{●, ●}	{●, ●}	{●, ●}
k-means	0.279	0.554	0.178
HAC (Ward)	$< 10^{-16}$	$< 10^{-16}$	$< 10^{-16}$
UMAP+HDBSCAN	1	0.002	0.002

p-values obtained using `PCIdep` (González-Delgado *et al.* 2025).

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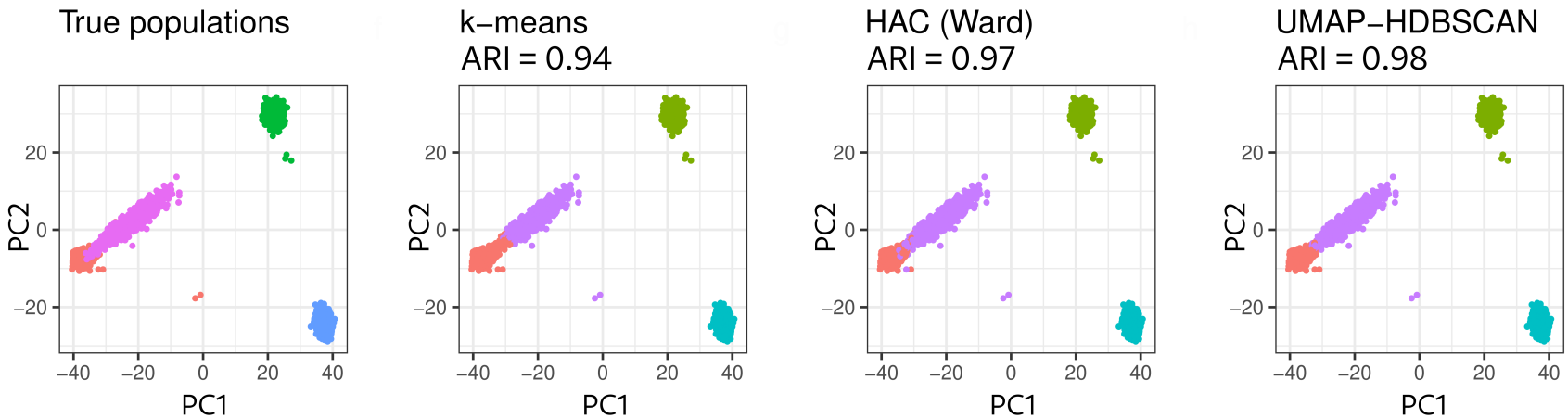
Consequences of conditioning (II)

Shapes and relative positions of clusters may hinder inference

Simulation setting

SNPs for $n = 4000$ individuals equally sampled from four populations : two sources, one unrelated population, and an admixed population derived from the sources[1] + Clustering performed on the first 100 PCs.



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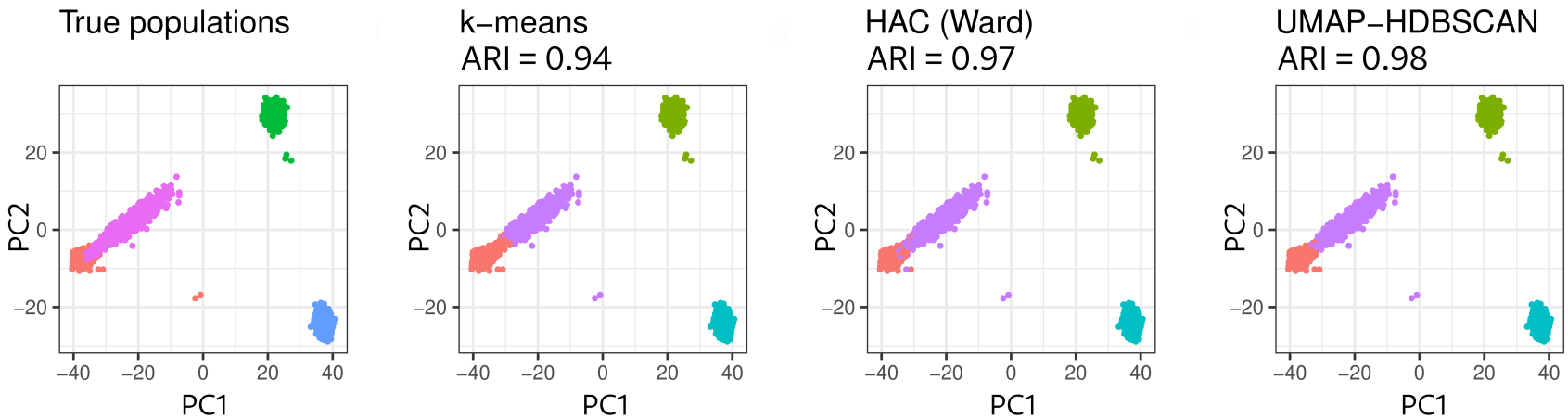

$\{\mathcal{G}_1, \mathcal{G}_2\}$	{●, ●}	{●, ●}	{●, ●}	{●, ●}	{●, ●}	{●, ●}
k-means	0.118	0.113	0.005	0.189	0.767	0.667
HAC	0.084	0.011	$< 10^{-16}$	0.343	$< 10^{-16}$	$< 10^{-16}$
UMAP+HDBSCAN	1	1	0.002	0.002	0.002	0.002

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Conclusion and perspectives

Main message

Conditional inference inherently limits post-clustering inference.

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The theory appears unsuitable in multiple practical applications

- Clustering algorithms sensitive to smooth boundaries,
- Realistic cluster placements.

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- Clustering algorithms sensitive to smooth boundaries,
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Limitations come from conditioning

Advances in this theory should proceed through a new selective inference framework, such as simultaneous inference :

$$\mathbb{P}_{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}}\left(\forall\,\{\mathcal{G}_1,\mathcal{G}_2\}\ :\ \text{Reject } H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}} \text{ based on } \mathbf{X} \text{ at level } \alpha\right) \leq \alpha.$$

Ongoing exploration...

(Some) references

Conditional inference methods

- Independence setting : L. L. Gao, J. Bien, and D. Witten. Selective inference for hierarchical clustering. *Journal of the American Statistical Association*, 119(545), 332–342, 2024.
- Extension to feature-level test : B. Hivert, D. Agniel, R. Thiébaut, and B. P. Hejblum. Post-clustering difference testing : Valid inference and practical considerations with applications to ecological and biological data. *Comput. Statist. Data Anal.*, 193 :107916, May 2024.
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- Limitations in post-clustering inference : B. Hivert, D. Agniel, R. Thiébaut and B. P. Hejblum. Practical limitations for real-life application of data fission and data thinning in post-clustering differential analysis, 2025. https://arxiv.org/abs/2405.13591.

Thank you for your attention !

https://gonzalez-delgado.github.io/