Post-clustering inference under dependency

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Post-clustering inference

Toy example

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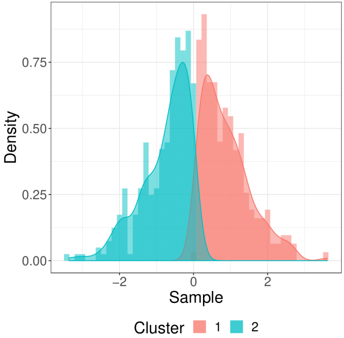
- Simulate $\mathcal{N}(0, 1) + \mathcal{U}(-0.2, 0.2)$
- Ask k-means to find 2 clusters (data-driven hypothesis selection)
- Test for the difference of cluster means (inference after selection)



Adapted from Hivert *et al.* 2024

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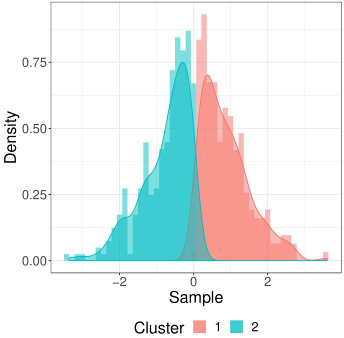

$p_Z = 10^{-67}$, $p_{SI} = 0.84$ (using Chen and Witten 2023).

Adapted from Hivert *et al.* 2024

Post-clustering inference

General strategy

Notation

- 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 $\hat{C}_1, \hat{C}_2 \subset \{1, \dots, n\}$ be two clusters estimated by $C(\cdot)$ on $\mathbf{X}$, that is, $\hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{X})$.

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Goal

Define a p-value for $H_0^{\{\hat{C}_1, \hat{C}_2\}}$ that controls the selective type I error, that is,

$$\mathbb{P}_{H_0^{\{\hat{C}_1, \hat{C}_2\}}} \left(\text{reject } H_0^{\{\hat{C}_1, \hat{C}_2\}} \text{ based on } \mathbf{X} \text{ at level } \alpha \;\middle|\; \hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{X}) \right) \leq \alpha \quad \forall \alpha \in [0, 1].$$

Independence setting

Gao *et al.* 2022

Framework

Consider the model

$$\mathbf{X} \sim \mathcal{MN}_{n\times p}(\boldsymbol{\mu}, \mathbf{I}_n, \sigma^2 \mathbf{I}_p), \tag{indep}$$

and the null hypothesis

$$H_0^{\{\hat{C}_1, \hat{C}_2\}} : \bar{\mu}_{\hat{C}_1} = \bar{\mu}_{\hat{C}_2}, \tag{null}$$

for $\hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{X})$.

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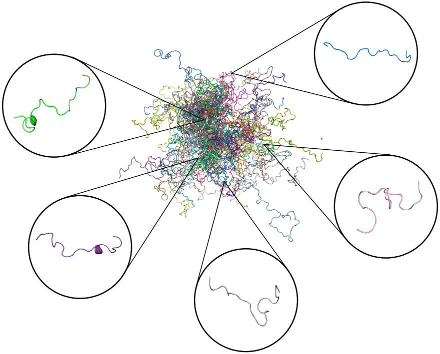
Gao *et al.* define a p-value for (null) that

- Controls the selective type I error under (indep),
- Can be be efficiently computed for hierarchical clustering (HAC) with several types of linkages and k-means (Chen and Witten 2023),
- Is asymptotically super-uniform when σ is asymptotically over-estimated. An estimator $\hat{\sigma}$ of σ is proposed [1].

1. Exact estimation of σ has been recently proposed in Yun and Foygel Barber 2023.

Independence is usually unrealistic

Example : clustering of flexible protein structures



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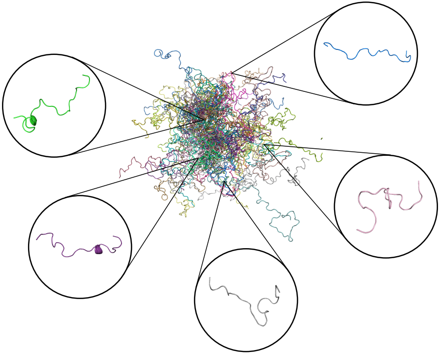

- Conformations can be featured by *p*-dimensional Gaussian descriptors (e.g. pairwise distances between amino acids),
- Features are strongly interdependent,
- Conformations may be generated by molecular dynamics simulations : temporal dependence between observations.

Arbitrary dependence setting

Adapt Gao *et al.* 2022 to realistic practical scenarios

Framework

Consider the model

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

where $\mathbf{U} \in \mathcal{M}_{n\times n}(\mathbb{R})$ and $\boldsymbol{\Sigma} \in \mathcal{M}_{p\times p}(\mathbb{R})$. We ask $\mathbf{U}$ and $\boldsymbol{\Sigma}$ to be positive definite. Let

$$H_0^{\{\hat{C}_1, \hat{C}_2\}} : \bar{\mu}_{\hat{C}_1} = \bar{\mu}_{\hat{C}_2}, \tag{null}$$

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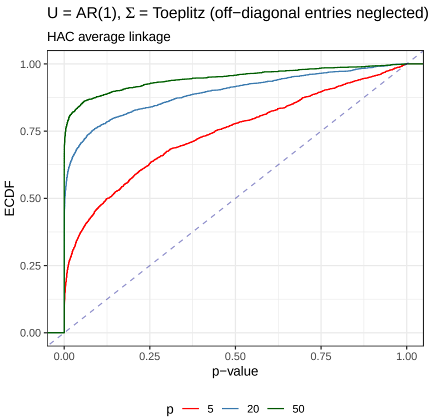
Goal

- Definition of a p-value for (null) that controls selective type I error under (dep),
- Efficient computation for HAC and k-means clustering.
- Over-estimation of either $\mathbf{U}$ or $\boldsymbol{\Sigma}$ (not both) that yields asymptoticallly super-uniform p-values.

Ignoring dependency prevents selective type I error control

- Simulate $n = 1000$ samples drawn from (dep) with $\boldsymbol{\mu} = \mathbf{O}_{n \times p}$ and set $\mathcal{C}$ to choose three clusters,
- Randomly select two groups and test for the difference of their means assuming $\mathbf{U} = \mathbf{I}_n$ and $\boldsymbol{\Sigma} = \sigma^2 \mathbf{I}_p$.



p-value definition

Independence setting

p-value for $H_0^{\{\hat{C}_1, \hat{C}_2\}}$ when $\mathbf{U} = \mathbf{I}_n$, $\boldsymbol{\Sigma} = \sigma^2 \mathbf{I}_p$ (Gao *et al.* 2022)

$$p(\mathbf{x}; \{\hat{C}_1, \hat{C}_2\}) = \mathbb{P}_{H_0^{\{\hat{C}_1, \hat{C}_2\}}}\Bigg(\|\bar{X}_{\hat{C}_1} - \bar{X}_{\hat{C}_2}\|_2 \geq \|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_2 \;\Bigg|\; \hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{X}),$$

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The p-value is computationally tractable (Gao *et al.* 2022)

$$p(\mathbf{x}; \{\hat{C}_1, \hat{C}_2\}) = 1 - \mathbb{F}_p\left(\|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_2; \sigma\sqrt{\frac{1}{|\hat{C}_1|} + \frac{1}{|\hat{C}_2|}}, \mathcal{S}_2(\mathbf{x}; \{\hat{C}_1, \hat{C}_2\}) \right)$$

where $\mathbb{F}_p(t; c, \mathcal{S})$ denotes the CDF of a $c\chi_p$ random variable truncated to the set $\mathcal{S}$.

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where $\mathbb{F}_p(t; c, \mathcal{S})$ denotes the CDF of a $c\chi_p$ random variable truncated to the set $\mathcal{S}$.

Choice of the test statistic

- Let $\mathcal{G}_1, \mathcal{G}_2 \subset \{1, \ldots, n\}$ with $\mathcal{G}_1 \cap \mathcal{G}_2 = \emptyset$
- Let
$$\mathbf{D}_{\mathcal{G}_1,\mathcal{G}_2} = \begin{pmatrix} \frac{1}{|\mathcal{G}_1|}\mathbf{I}_p & \overset{|\mathcal{G}_1|}{\cdots} & \frac{1}{|\mathcal{G}_1|}\mathbf{I}_p & -\frac{1}{|\mathcal{G}_2|}\mathbf{I}_p & \overset{|\mathcal{G}_2|}{\cdots} & -\frac{1}{|\mathcal{G}_2|}\mathbf{I}_p \end{pmatrix}.$$

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

$$\bar{X}_{\mathcal{G}_1} - \bar{X}_{\mathcal{G}_2} \overset{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}}{\sim} \mathcal{N}_p\left(0, \mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}\right),$$

where

$$\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2} = \mathbf{D}_{\mathcal{G}_1,\mathcal{G}_2}(\mathbf{U}_{\mathcal{G}_1,\mathcal{G}_2} \otimes \boldsymbol{\Sigma})\mathbf{D}^T_{\mathcal{G}_1,\mathcal{G}_2}.$$

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Consequently,

$$\|\bar{X}_{\mathcal{G}_1} - \bar{X}_{\mathcal{G}_2}\|^2_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}} \overset{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}}{\sim} \chi^2_p.$$

with $\|x\|_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}} = \sqrt{x^T \mathbf{V}^{-1}_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}} x}, \quad \forall\, x \in \mathbb{R}^p.$

p-value definition

Arbitrary dependence setting

Key idea : Replace the norm $\|\cdot\|_2$ by the *Mahalanobis distance* between the cluster means w.r.t. the null distribution of their difference.

p-value for $H_0^{\{\hat{C}_1,\hat{C}_2\}}$ for arbitrary $\mathbf{U}$ and $\boldsymbol{\Sigma}$

$$p_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\mathbf{x};\{\hat{C}_1,\hat{C}_2\}) = \mathbb{P}_{H_0^{\{\hat{C}_1,\hat{C}_2\}}}\Bigg(\|\bar{X}_{\hat{C}_1}-\bar{X}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} \geq \|\bar{x}_{\hat{C}_1}-\bar{x}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} \;\Bigg|\; \hat{C}_1,\hat{C}_2 \in \mathcal{C}(\mathbf{X}),$$

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Theorem : The p-value is computationally tractable (and controls sel. type I error)

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where $\mathbb{F}_p(t;\mathcal{S})$ denotes the CDF of a χ_p random variable truncated to the set $\mathcal{S}$.

Numerical simulations

Three dependence settings

(*a*) $\mathbf{U} = \mathbf{I}_n$ and $\boldsymbol{\Sigma}$ is the covariance matrix of an AR(1) model, i.e. $\Sigma_{ij} = \sigma^2 \rho^{|i-j|}$, with $\sigma = 1$ and $\rho = 0.5$.

(*b*) $\mathbf{U}$ is a compound symmetry covariance matrix, i.e. $\mathbf{U} = b + (a-b)\mathbf{I}_n$, with $a = 0.5$ and $b = 1$. $\boldsymbol{\Sigma}$ is a Toeplitz matrix, i.e. $\Sigma_{ij} = t(|i-j|)$, with $t(s) = 1 + 1/(1+s)$ for $s \in \mathbb{N}$.

(*c*) $\mathbf{U}$ is the covariance matrix of an AR(1) model with $\sigma = 1$ and $\rho = 0.1$. $\boldsymbol{\Sigma}$ is a diagonal matrix with diagonal entries given by $\Sigma_{ii} = 1 + 1/i$.

Numerical simulations

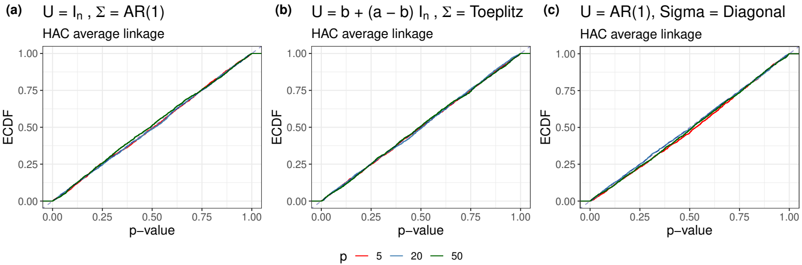
Global null hypothesis

Let $n = 100$, $\boldsymbol{\mu} = \mathbf{O}_{n \times p}$, and set $\mathcal{C}$ to choose three clusters. Then, randomly select two groups and test for the difference of their means.

Numerical simulations

Global null hypothesis

Let $n = 100$, $\boldsymbol{\mu} = \mathbf{0}_{n \times p}$, and set $\mathcal{C}$ to choose three clusters. Then, randomly select two groups and test for the difference of their means.



Numerical simulations

Conditional power

Conditional power = probability of rejecting the null for a randomly selected pair of clusters given that they are different.

Let $\boldsymbol{\mu}$ divide the $n = 50$ observations into three true clusters, for $\delta \in [4, 10.5]$:

$$\mu_{ij} = \begin{cases} -\frac{\delta}{2} & \text{if } i \leq \lfloor \frac{n}{3} \rfloor, \\ \frac{\sqrt{3}\delta}{2} & \text{if } \lfloor \frac{n}{3} \rfloor < i \leq \lfloor \frac{2n}{3} \rfloor, \\ \frac{\delta}{2} & \text{otherwise.} \end{cases} \quad \forall\, i \in \{1, \ldots, n\}, \forall\, j \in \{1, \ldots, p = 10\},$$

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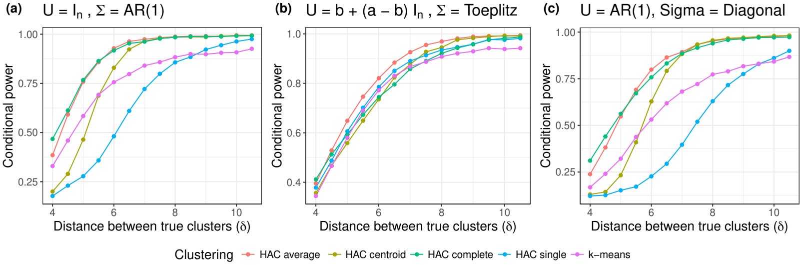
Conditional power

Conditional power = probability of rejecting the null for a randomly selected pair of clusters given that they are different.

Let $\boldsymbol{\mu}$ divide the $n = 50$ observations into three true clusters, for $\delta \in [4, 10.5]$:

$$\mu_{ij} = \begin{cases} -\frac{\delta}{2} & \text{if } i \leq \lfloor \frac{n}{3} \rfloor, \\ \frac{\sqrt{3}\delta}{2} & \text{if } \lfloor \frac{n}{3} \rfloor < i \leq \lfloor \frac{2n}{3} \rfloor, \\ \frac{\delta}{2} & \text{otherwise.} \end{cases} \quad \forall\, i \in \{1, \ldots, n\}, \forall\, j \in \{1, \ldots, p = 10\},$$



Estimation of unknown parameters

Independence setting

Let $\mathbf{X}^{(n)} \sim \mathcal{MN}_{n\times p}(\boldsymbol{\mu}^{(n)}, \mathbf{I}_n, \sigma^2\mathbf{I}_p)$ and consider

$$\hat{p}(\mathbf{x}; \{\hat{C}_1, \hat{C}_2\}) = 1 - \mathbb{F}_p\left(\|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_2; \hat{\sigma}\sqrt{\frac{1}{|\hat{C}_1|} + \frac{1}{|\hat{C}_2|}}, \mathcal{S}_2(\mathbf{x}; \{\hat{C}_1, \hat{C}_2\}) \right)$$

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Theorem 4 in Gao et al. 2022

If $\hat{\sigma}$ is an estimator of σ such that

$$\lim_{n\to\infty} \mathbb{P}_{H_0^{\{\hat{C}_1^{(n)}, \hat{C}_2^{(n)}\}}}\left(\hat{\sigma}\left(\mathbf{X}^{(n)}\right) \geq \sigma \,\middle|\, \hat{C}_1^{(n)}, \hat{C}_2^{(n)} \in \mathcal{C}\left(\mathbf{X}^{(n)}\right)\right) = 1, \qquad (\sigma \text{ over-est})$$

then, for any $\alpha \in [0,1]$, it holds

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$\rightarrow$ Gao *et al.* propose an estimator $\hat{\sigma}$ that satisfies (σ over-est) under mild assumptions on $\{\boldsymbol{\mu}^{(n)}\}_{n\in\mathbb{N}}$.

Estimation of unknown parameters

Arbitrary dependence setting

Let

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

Can we estimate both $\mathbf{U}$ and $\boldsymbol{\Sigma}$?

- Under the general model (dep), the scale matrices $\mathbf{U}$ and $\boldsymbol{\Sigma}$ are non-identifiable.
- We assume that one of the scale matrices is known, and assess the theoretical conditions that allow asymptotic control of the selective type I error when estimating the other one.
- Same reasoning for the estimation of $\mathbf{U}$ or $\boldsymbol{\Sigma}$:

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

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$\rightarrow$ How to extend the notion of over-estimation to matrices ?

How to *over*-estimate a covariance matrix

We consider the natural extension of $\geq$ to the space of Hermitian matrices.

Loewner partial order $\succeq$

Let A, B be two Hermitian matrices. $A \succeq B$ if and only if $A - B$ is positive semidefinite (PSD).

Remark : If $A = \hat{\sigma}\mathbf{I}_p$ and $B = \sigma\mathbf{I}_p$, the condition $A \succeq B$ becomes $\hat{\sigma} \geq \sigma$.

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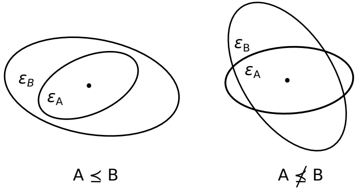
Graphical interpretation

Every PSD matrix A defines an ellipsoid $\mathcal{E}_A = \{x \in \mathbb{R}^d \;:\; x^T A x \leq 1\}$, where

- The eigenvectors of A are the principal axes of $\mathcal{E}_A$,
- The eigenvalues of A are the squared lengths of the principal axes of $\mathcal{E}_A$.

Then, it holds $\mathcal{E}_A \subset \mathcal{E}_B \Leftrightarrow A \preceq B$.



Over-estimation of $\boldsymbol{\Sigma}$ for known $\mathbf{U}$

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where $\hat{\mathbf{V}}_{\hat{C}_1,\hat{C}_2} = \mathbf{D}_{\hat{C}_1,\hat{C}_2}(\mathbf{U}_{\hat{C}_1,\hat{C}_2} \otimes \hat{\boldsymbol{\Sigma}}(\mathbf{x}))\mathbf{D}^T_{\hat{C}_1,\hat{C}_2}$.

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Theorem (extension of Theorem 4 in Gao *et al.* 2022)
If $\hat{\boldsymbol{\Sigma}}\left(\mathbf{X}^{(n)}\right)$ is a positive definite estimator of $\boldsymbol{\Sigma}$ such that

$$\lim_{n\to\infty} \mathbb{P}_{H_0^{\{\hat{C}_1^{(n)}, \hat{C}_2^{(n)}\}}} \left(\hat{\boldsymbol{\Sigma}}\left(\mathbf{X}^{(n)}\right) \succeq \boldsymbol{\Sigma} \,\middle|\, \hat{C}_1^{(n)}, \hat{C}_2^{(n)} \in \mathcal{C}\left(\mathbf{X}^{(n)}\right) \right) = 1,$$

then, for any $\alpha \in [0, 1]$, we have

$$\limsup_{n\to\infty} \mathbb{P}_{H_0^{\{\hat{C}_1^{(n)}, \hat{C}_2^{(n)}\}}} \left(p_{\hat{\mathbf{V}}_{\hat{C}_1^{(n)},\hat{C}_2^{(n)}}}\left(\mathbf{X}^{(n)}; \left\{\hat{C}_1^{(n)}, \hat{C}_2^{(n)}\right\}\right) \leq \alpha \,\middle|\, \hat{C}_1^{(n)}, \hat{C}_2^{(n)} \in \mathcal{C}\left(\mathbf{X}^{(n)}\right) \right) \leq \alpha.$$

Asymptotic over-estimator of $\boldsymbol{\Sigma}$

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

For a given estimator $\hat{\boldsymbol{\Sigma}}\left(\mathbf{X}^{(n)}\right)$ of $\boldsymbol{\Sigma}$, assessing whether $\hat{\boldsymbol{\Sigma}}\left(\mathbf{X}^{(n)}\right) \succeq \boldsymbol{\Sigma}$ asymptotically strongly depends on how the sequences $\{\boldsymbol{\mu}^{(n)}\}_{n\in\mathbb{N}}$ and $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ grow up to infinity.

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Estimator candidate

$$\hat{\boldsymbol{\Sigma}} = \hat{\boldsymbol{\Sigma}}\left(\mathbf{X}\right) = \frac{1}{n-1}\left(\mathbf{X} - \bar{\mathbf{X}}\right)^T \mathbf{U}^{-1}\left(\mathbf{X} - \bar{\mathbf{X}}\right), \tag{estimator}$$

where $\bar{\mathbf{X}}$ is a $n \times p$ matrix having as rows the mean across rows of $\mathbf{X}$.

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$\rightarrow$ Assumptions on $\{\boldsymbol{\mu}^{(n)}\}_{n\in\mathbb{N}}$ and $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ to ensure that (estimator) a.s. asymptotically overestimates $\boldsymbol{\Sigma}$?

Assumptions on $\boldsymbol{\mu}^{(n)}$

Assumptions 1 and 2 in Gao et al. 2022 *(Assumption 1)*

For all $n \in \mathbb{N}$, there are exactly K^* distinct mean vectors among the first n observations, i.e.

$$\left\{\mu_i^{(n)}\right\}_{i=1,\dots,n} = \{\theta_1, \dots, \theta_{K^*}\}.$$

Besides, the proportion of the first n observations that have mean vector θ_k converges to $\pi_k > 0$, i.e.

$$\lim_{n\to\infty} \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}\{\mu_i^{(n)} = \theta_k\} = \pi_k, \tag{as-1}$$

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⋄ If $\mathbf{U}^{(n)} = \mathbf{I}_n$, this is the only requirement to ensure asymp. over-estimation of $\boldsymbol{\Sigma}$.

⋄ For **general** $\mathbf{U}^{(n)}$, the quantities

$$\frac{1}{n} \sum_{l,s=1}^{n} \left(U^{(n)}\right)^{-1}_{ls} \mathbb{1}\{\mu_l^{(n)} = \theta_k\} \, \mathbb{1}\{\mu_s^{(n)} = \theta_{k'}\}$$

are also required to **converge with explicit limit** as n tends to infinity.

One more assumption on $\boldsymbol{\mu}^{(n)}$ for non-diagonal $\mathbf{U}^{(n)}$

Assumption on $\boldsymbol{\mu}^{(n)}$ for non-diagonal $\mathbf{U}^{(n)}$ *(Assumption 2)*

If $\mathbf{U}^{(n)}$ is non-diagonal for all $n \in \mathbb{N}$, for any $k, k' \in \{1, \dots, K^*\}$, the proportion of the first n observations at distance $r \geq 1$ in $\mathbf{X}^{(n)}$ having means θ_k and $\theta_{k'}$ converges, and its limit converges to $\pi_k \pi_{k'}$ when the lag r tends to infinity. More precisely,

$$\lim_{n\to\infty} \frac{1}{n} \sum_{i=1}^{n-r} \mathbb{1}\{\mu_i = \theta_k\} \, \mathbb{1}\{\mu_{i+r} = \theta_{k'}\} = \pi^r_{kk'} \underset{r\to\infty}{\longrightarrow} \pi_k \, \pi_{k'} . \qquad \text{(as-2)}$$

We are asking the proportion of pairs of observations having a given a pair of means to approach the product of individual proportions (as-1) when both observations are far away in $\mathbf{X}^{(n)}$.

Assumptions on the sequence $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$

Assumption on $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ *(Assumption 3)*

Every superdiagonal of $\left(\mathbf{U}^{(n)}\right)^{-1}$ defines asymptotically a convergent sequence, whose limits sum up to a real value. More precisely, for any $i \in \mathbb{N}$ and any $r \geq 0$,

$$\lim_{n\to\infty} \left(U^{(n)}\right)^{-1}_{i\,i+r} = \Lambda_{i\,i+r}, \quad \text{where} \quad \lim_{i\to\infty} \Lambda_{i\,i+r} = \lambda_r \quad \text{and} \quad \sum_{r=0}^{\infty} \lambda_r = \lambda \in \mathbb{R}.$$

Moreover, for each $r \geq 0$, the sequence $\{\left(U^{(n)}\right)^{-1}_{i\,i+r}\}_{n\in\mathbb{N}}$ satisfies any of the following conditions :

- (i) It is dominated by a summable sequence i.e. $\left|\left(U^{(n)}\right)^{-1}_{i\,i+r} - \Lambda_{i\,i+r}\right| \leq \alpha_i \ \forall\, n \in \mathbb{N}$, with $\{\alpha_i\}_{i=1}^{\infty} \in \ell_1$,
- (ii) For each $i \in \mathbb{N}$, it is non-decreasing or non-increasing.

Some admissible dependence models for $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$

Remark 1 (Diagonal)

Let $\mathbf{U}^{(n)} = \mathrm{diag}(\lambda_1, \dots, \lambda_n)$. If the sequence $\{\lambda_n\}_{n\in\mathbb{N}}$ is convergent, then the sequence $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ satisfies Assumption 3.

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Remark 2 (Compound symmetry)

Let $a, b \in \mathbb{R}$ with $b \neq a \geq 0$. If $\mathbf{U}^{(n)} = b\mathbf{1}_{n\times n} + (a-b)\,\mathbf{I}_n$, where $\mathbf{1}_{n\times n}$ is a $n \times n$ matrix of ones, then $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ satisfies Assumption 3.

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Remark 3 (AR(P))

Let $\mathbf{U}^{(n)}$ be the covariance matrix of an auto-regressive process of order $P \geq 1$ such that, if $P > 2$, $\beta_k\beta_{k'} \geq 0$ for all $k, k' \in \{1, \ldots, P\}$. Then, the sequence $\{\mathbf{U}^{(n)}\}_{n\in\mathbb{N}}$ satisfies Assumption 3.

Estimation of $\boldsymbol{\Sigma}$ for known $\mathbf{U}$

Final results

Proposition

Let $\mathbf{X}^{(n)} \sim \mathcal{MN}_{n \times p}(\boldsymbol{\mu}^{(n)}, \mathbf{U}^{(n)}, \boldsymbol{\Sigma})$, whose parameters $\boldsymbol{\mu}^{(n)}$, $\mathbf{U}^{(n)}$ satisfy Assumptions 1, 2 and 3 for some $K^* > 1$. Let $\hat{\boldsymbol{\Sigma}}$ be the estimator defined in (estimator). Then,

$$\lim_{n \to \infty} \mathbb{P}\left(\hat{\boldsymbol{\Sigma}}\left(\mathbf{X}^{(n)}\right) \succeq \boldsymbol{\Sigma}\right) = 1.$$

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$$\lim_{n\to\infty} \mathbb{P}_{H_0^{\{\hat{\mathcal{C}}_1^{(n)}, \hat{\mathcal{C}}_2^{(n)}\}}}\left(\hat{\mathbf{\Sigma}}\left(\mathbf{Y}^{(n)}\right) \succeq \mathbf{\Sigma} \,\middle|\, \hat{\mathcal{C}}_1^{(n)}, \hat{\mathcal{C}}_2^{(n)} \in \mathcal{C}\left(\mathbf{X}^{(n)}\right)\right) = 1.$$

Numerical simulations

Let

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

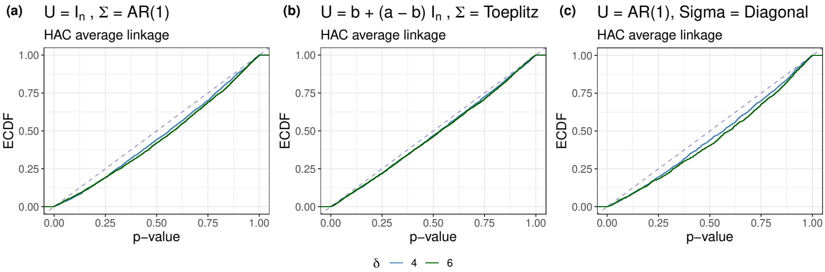
For $n = 500$ and $p = 10$, we simulated $K = 10000$ samples drawn from (dep) in settings (a), (b) and (c) with $\boldsymbol{\mu}$ being divided into two clusters :

$$\mu_{ij} = \begin{cases} \frac{\delta}{j} & \text{if } i \leq \frac{n}{2}, \\ -\frac{\delta}{j} & \text{otherwise,} \end{cases} \quad \forall\, i \in \{1, \dots, n\},\, \forall\, j \in \{1, \dots, p\},$$

with $\delta \in \{4, 6\}$.

For HAC with average linkage we set $\mathcal{C}$ to chose three clusters. Then, we kept the samples for which (null) held when comparing two randomly selected clusters.

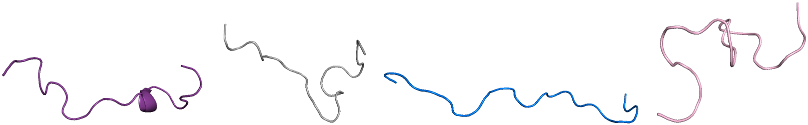
Numerical simulations



Hierarchical clustering of Hst5

Hst5 ensemble simulated with Flexible-Meccano (FM)[2] and filtered by SAXS data[3]

- $n = 2000$ conformations
- Featured by pairwise Euclidean distances of 24 amino acids $\Rightarrow p = 276$
- No temporal evolution in FM simulation : $\mathbf{U}^{(n)} = \mathbf{I}_n$
- $\boldsymbol{\Sigma}$ unknown to be estimated

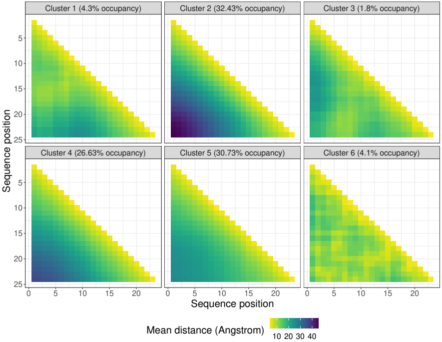


Strategy

Hierarchical clustering with average linkage, find 6 clusters.

2. Ozenne *et al. Bioinformatics* 2012, Bernadó *et al. PNAS* 2005. 3. Sagar *et al. J. Chem. Theory Comput* 2021.

Hierarchical clustering of Hst5



Pairwise p-values corrected for multiplicity (BH)

Cluster	1	2	3	4	5
2	$2.187589{\cdot}10^{-4}$				
3	$3.039844{\cdot}10^{-11}$	$1.41{\cdot}10^{-3}$			
4	$1.070993{\cdot}10^{-10}$	0.300540	$2.98464{\cdot}10^{-4}$		
5	$3.038979{\cdot}10^{-16}$	0.093018	$6.015797{\cdot}10^{-5}$	0.105446	
6	$1.729616{\cdot}10^{-6}$	0.010612	$9.290826{\cdot}10^{-9}$	$2.105{\cdot}10^{-3}$	$5.624624{\cdot}10^{-5}$

Thank you for your attention !

- Preprint : https://arxiv.org/abs/2310.11822,
- R package `PCIdep` at https://github.com/gonzalez-delgado/PCIdep/.

References

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- Extension to k-means : Y. T. Chen and D. M. Witten. Selective inference for k-means clustering. *Journal of Machine Learning Research*, 24(152) :1–41, 2023.
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- Alternative estimation of σ : Y. Yun and R. Foygel Barber. Selective inference for clustering with unknown variance. arXiv.2301.12999, 2023.

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

Truncation sets

Notation

$$\nu(\hat{C}_1, \hat{C}_2)_i = \mathbb{1}\{i \in \hat{C}_1\}/|\hat{C}_1| - \mathbb{1}\{i \in \hat{C}_2\}/|\hat{C}_2|. \tag{1}$$

$$\mathrm{dir}(u) = u/\|u\|_2 \mathbb{1}\{u \neq 0\} \tag{2}$$

$$\mathrm{dir}_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(u) = u/\|u\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} \mathbb{1}\{u \neq 0\} \tag{3}$$

Truncation sets

Independence setting

$$\hat{\mathcal{S}}_2 = \{\phi \geq 0 \, : \, \hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{x}_2'(\phi))\}, \tag{4}$$

$$\mathbf{x}_2'(\phi) = \mathbf{x} + \frac{\nu(\hat{C}_1, \hat{C}_2)}{\|\nu(\hat{C}_1, \hat{C}_2)\|_2^2} \left(\phi - \|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_2\right) \mathrm{dir}(\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}), \tag{5}$$

Arbitrary dependence setting

$$\hat{\mathcal{S}}_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} = \left\{\phi \geq 0 \, : \, \hat{C}_1, \hat{C}_2 \in \mathcal{C}\left(\mathbf{x}'_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\phi)\right)\right\}, \tag{6}$$

$$\mathbf{x}'_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\phi) = \mathbf{x} + \frac{\nu(\hat{C}_1, \hat{C}_2)}{\|\nu(\hat{C}_1, \hat{C}_2)\|_2^2} \left(\phi - \|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}\right) \mathrm{dir}_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}). \tag{7}$$

Lemma (scale transformation)

$$\hat{\mathcal{S}}_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} = \frac{\|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}}{\|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_2} \hat{\mathcal{S}}_2 \tag{8}$$

Truncation set and conditioning set

Let

$$\hat{M}_{12}(\mathbf{X}) = M_{12}(\mathbf{X}; \{\hat{C}_1, \hat{C}_2\}) = \{\hat{C}_1, \hat{C}_2 \in \mathcal{C}(\mathbf{X})\}, \tag{9}$$

and

$$\hat{T}_{12}(\mathbf{X}) = T_{12}(\mathbf{X}; \{\hat{C}_1, \hat{C}_2\}) =$$

$$\left\{ \boldsymbol{\pi}^{\perp}_{\nu(\hat{C}_1, \hat{C}_2)} \mathbf{X} = \boldsymbol{\pi}^{\perp}_{\nu(\hat{C}_1, \hat{C}_2)} \mathbf{x},\, \mathrm{dir}_{\mathbf{V}_{\hat{C}_1, \hat{C}_2}} \left(\bar{X}_{\hat{C}_1} - \bar{X}_{\hat{C}_2} \right) = \mathrm{dir}_{\mathbf{V}_{\hat{C}_1, \hat{C}_2}} \left(\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2} \right) \right\}. \tag{10}$$

The event $\hat{M}_{12}(\mathbf{X}) \cap \hat{T}_{12}(\mathbf{X})$ is the maximal event for which any analytically tractable p-value has been shown to control the sel. type I error under the general model (dep).

Truncation set and conditioning set

We have

$$p_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\mathbf{x};\{\hat{C}_1,\hat{C}_2\}) = \mathbb{P}_{H_0^{\{\hat{C}_1,\hat{C}_2\}}}\left(\|\bar{X}_{\hat{C}_1} - \bar{X}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} \geq \|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}} \;\middle|\; \hat{M}_{12}(\mathbf{X}) \cap \hat{T}_{12}(\mathbf{X})\right). \quad (11)$$

and we can write

$$\mathcal{S}_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\mathbf{x};\{\hat{C}_1,\hat{C}_2\}) = \left\{\phi \in \mathbb{R} \,:\, \hat{M}_{12}\left(\mathbf{x}'_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\phi)\right)\right\}, \quad (12)$$

so that

$$p_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\mathbf{x};\{\hat{C}_1,\hat{C}_2\}) = 1 - \mathbb{F}_p\left(\|\bar{x}_{\hat{C}_1} - \bar{x}_{\hat{C}_2}\|_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}, \left\{\phi \geq 0 \,:\, \hat{M}_{12}\left(\mathbf{x}'_{\mathbf{V}_{\hat{C}_1,\hat{C}_2}}(\phi)\right)\right\}\right). \quad (13)$$

Truncation set and conditioning set

Finer conditioning sets

Theorem

Let $\emptyset \neq E_{12}(\mathbf{X}) \subset M_{12}(\mathbf{X}) = M_{12}(\mathbf{X}; \{\mathcal{G}_1, \mathcal{G}_2\})$, $T_{12}(\mathbf{X}) = T_{12}(\mathbf{X}; \{\mathcal{G}_1, \mathcal{G}_2\})$ and

$$p_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}}(\mathbf{x}; \{\mathcal{G}_1, \mathcal{G}_2\}; E_{12}) = \mathbb{P}_{H_0^{\{\mathcal{G}_1,\mathcal{G}_2\}}} \left(\|\bar{X}_{\mathcal{G}_1} - \bar{X}_{\mathcal{G}_2}\|_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}} \geq \|\bar{x}_{\mathcal{G}_1} - \bar{x}_{\mathcal{G}_2}\|_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}} \;\middle|\; E_{12}(\mathbf{X}) \cap T_{12}(\mathbf{X}) \right).$$

Then, $p_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}}(\mathbf{x}; \{\mathcal{G}_1, \mathcal{G}_2\}; E_{12})$ is a p-value that controls the selective type I error for clustering at level α. Furthermore, it satisfies

$$p_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}}(\mathbf{x}; \{\mathcal{G}_1, \mathcal{G}_2\}; E_{12}) = 1 - \mathbb{F}_p \left(\|\bar{x}_{\mathcal{G}_1} - \bar{x}_{\mathcal{G}_2}\|_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}}, \left\{ \phi \geq 0 \,:\, E_{12}\left(\mathbf{x}'_{\mathbf{V}_{\mathcal{G}_1,\mathcal{G}_2}}(\phi) \right) \right\} \right).$$

Lemma (scale transformation)

$$E_{12}\left(\mathbf{x}'_{\mathbf{V}_{\hat{\mathcal{C}}_1,\hat{\mathcal{C}}_2}}(\phi) \right) = \frac{\|\bar{x}_{\hat{\mathcal{C}}_1} - \bar{x}_{\hat{\mathcal{C}}_2}\|_{\mathbf{V}_{\hat{\mathcal{C}}_1,\hat{\mathcal{C}}_2}}}{\|\bar{x}_{\hat{\mathcal{C}}_1} - \bar{x}_{\hat{\mathcal{C}}_2}\|_2} E_{12}\left(\mathbf{x}'(\phi) \right). \tag{14}$$