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Testing for equal correlation matrices with application to paired gene expression data

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Abstract

We present a novel method for testing the hypothesis of equality of two correlation matrices using paired high-dimensional datasets. We consider test statistics based on the average of squares, maximum and sum of exceedances of Fisher transform sample correlations and we derive approximate null distributions using asymptotic and non-parametric distributions. Theoretical results on the power of the tests are presented and backed up by a range of simulation experiments. We apply the methodology to a case study of colorectal tumor gene expression data with the aim of discovering biological pathway lists of genes that present significantly different correlation matrices on healthy and tumor samples. We find strong evidence for a large part of the pathway lists correlation matrices to change among the two medical conditions.

keywords correlation matrix, Fisher transform, hypothesis testing, high-dimensional data, extreme values, dependent data, gene expression

1 Introduction

In recent years, the improvements in technology have made it possible to collect and store reliable information for a large number of genes, metabolomics or proteins, among others, on an organism in a single sample. This typically generates datasets where the number of variables p is much larger than the number of observations n . Statistical techniques that deal with this type of data, commonly known as high-dimensional data, with the purpose of answering biological questions, are well studied in the literature (Buhlmann and van de Geer, 2011; Sánchez and Villa, 2008). One of the main challenges relates to understanding how the genes function in a biological process and how they interact between each others in a cell. In this regard, measuring and assessing variations of gene interactions on the presence of an illness process such as cancer is important to biologists as part of discerning the gene regulatory mechanisms that control the disease.

A statistical technique that is widely used to measure interaction between pairs of genes from data is given by the Pearson correlation, which quantifies the strength of the linear dependence between two random variables. The main hypothesis testing (HT) problem we study in this chapter assesses the evidence of equality of two correlation matrices $R_1 = [r_{ij}^{(1)}]$ and $R_2 = [r_{ij}^{(2)}]$ that correspond to genomic data $Y^{(1)}$ and $Y^{(2)}$ measured in two different conditions (e.g, healthy and tumor tissues),

$$H_0 : R_1 = R_2 \quad \text{vs} \quad H_1 : R_1 \neq R_2$$

The likelihood ratio test statistic for testing equality of correlation matrices (Kullback, 1967), when the vectors $Y^{(1)}$ and $Y^{(2)}$ are Gaussian, depends on the determinant of the two sample matrices and is not well defined when the sample size n is less than the dimension p . However, datasets that arise from biological experiments are frequently high-dimensional, with $p \gg n$. There are two main directions that address this hypothesis testing problem for high-dimensional data in the literature. The first is based on sum of squares statistics, see Schott (2007) and Li and Chen (2012), who use the Frobenius norm as a distance measure to compare the two sample correlation matrices. The second is based on extreme value statistics, see Cai et al. (2013), who derive the asymptotic null distribution of the maximum of the square of sample correlation coefficient differences.

To the best of our knowledge, the tests considered so far in the literature are applicable when the random vectors $Y^{(1)}$ and $Y^{(2)}$ are independent. Here we study the implications of using the sample correlation matrices when the two datasets are dependent, particularly when they come from paired observations, in which case the cross-correlation is not zero. We propose three different tests which apply to paired data, and that are based on the average, maximum and threshold exceedances of the elementwise correlation differences.

The proposed methodology is motivated by a genomic data set (Hinoue et al., 2012) that contains the gene expression information of approximately $p \approx 25 \times 10^3$ genes in two different samples, from the same $n = 25$ patients, corresponding to two different medical conditions. These are the gene expression of a tumor cell and its adjacent normal tissue. The gene pairwise correlation is a reasonable measure to understand the relationship between genes in a biological process, so our purpose in the analysis of these data is to assess whether the correlation matrix varies or not when going from a healthy to a tumor state. Even though the complete $p \times p$ correlation matrix is expected to change considerably, testing the equality of linear dependence structures for subgroups of the 25×10^3 genes that are known to have functions in a biological process is highly important. We test if the genes interact

similarly in the two conditions for 1320 pathway lists of sizes going from 20 to 900 which contain groups of genes with known biochemical connections.

The article is structured as follows. In Section 2 we present the hypothesis testing problem and we propose several test statistics which are motivated by the type of statistics mentioned in the literature. In Section 3 we determine approximate distributions of these test statistics under the null hypothesis and we give lower bounds for their asymptotic powers. In Section 4 we use simulated data in order to assess the accuracy of the tests under the null hypothesis and to compare the power of the tests for several types of alternative hypothesis. Finally, in Section 5 we consider a case study on genomic data where the proposed methodology is used to answer questions that arise from a biological process. We have implemented the methodology presented in this paper within the R package **ldstatsHD** (Caballe, 2016).

2 Hypothesis testing problem

2.1 Problem setting and Fisher transformation

Consider n independent and identically distributed (i.i.d.) $2p$ -dimensional random vectors $Y_k = (Y_k^{(1)}, Y_k^{(2)})$, $k = 1, \dots, n$, where $Y^{(1)}$ and $Y^{(2)}$ are associated with population I and population II, respectively, and that follow a standard multivariate normal distribution with correlation R , i.e.,

$$(Y_k^{(1)}, Y_k^{(2)}) \stackrel{iid}{\sim} N_{2p}(0, R), \quad R = [r_{ij}] = \begin{bmatrix} R_1 & R_{12} \\ R_{12}^\top & R_2 \end{bmatrix}, \quad (1)$$

where R_1 and R_2 are the category-specific correlation matrices and the cross-correlation R_{12} is non-zero if the two random vectors $Y^{(1)}$ and $Y^{(2)}$ are linearly dependent. We assume, without loss of generality, unit variances and zero mean vector. The main goal of this section is to test whether the correlation matrix R_1 is equal to the correlation matrix R_2 with hypothesis $H_0 : R_1 = R_2$ vs $H_1 : R_1 \neq R_2$. We denote the sample correlation matrix by \hat{R} , which is determined by $\hat{R}_1 = [\hat{r}_{ij}^{(1)}] = Y^{(1)\top} Y^{(1)} / n$, $\hat{R}_2 = [\hat{r}_{ij}^{(2)}] = Y^{(2)\top} Y^{(2)} / n$ and $\hat{R}_{12} = [\hat{r}_{ij}^{(12)}] = Y^{(1)\top} Y^{(2)} / n$. Given the symmetry in the correlation matrices, we consider their lower triangular matrices instead using the same notation with

$$M = \{(i, j) \in \{1, \dots, p\} : i < j\}, \quad m = \text{Card}(M) = p(p-1)/2. \quad (2)$$

An approximate pivot for the correlation coefficient is given by the Fisher transformation (Fisher, 1921), which is defined by $g : (-1, 1) \mapsto \mathbb{R}$, $g(z) =$

$\log\{(1+z)/(1-z)\}/2$, such that the elementwise Fisher transformation of \hat{R}_K , $K \in \{1, 2\}$, weakly converges to a multivariate normal distribution

$$\hat{U}_K = g(\hat{R}_K)\sqrt{n-3} \sim N(g(R_K)\sqrt{n-3}, \Psi_K), \quad K \in \{1, 2\}, \quad (3)$$

where $\Psi_K = [\psi_{th}^{(k)}]$ is the $m \times m$ correlation matrix between elements in \hat{U}_K as $\psi_{tt}^{(k)} = 1$ for any $t \in M$ and $K \in \{1, 2\}$.

2.2 Correlation of sample correlation coefficients

We assume here and throughout that $r_t < 1$ for any $t \in M$. The non-zero dependence structure between the two random vectors $Y^{(1)}$ and $Y^{(2)}$ leads to correlation between elements in the estimator $\hat{U} = [\hat{U}_1, \hat{U}_2]$ (Elston, 1975; Steiger, 1980), which is found as in eq. (3). Take $s = (h, i)$ and $t = (j, l)$, $s, t \in M$, as defined in eq. (2), following derivations from Dunn and Clark (1969), the asymptotic correlation of \hat{u}_s and \hat{u}_t , $\psi_{st} = \psi_{hi,jl} = \text{cor}(\hat{u}_s, \hat{u}_t)$, as $n \rightarrow \infty$, is expressed by

$$\psi_{st} = \psi_{hi,jl} = (\omega_{hh|l} \omega_{jj|l})^{-1} [(\omega_{hj|i} \omega_{il|j} + \omega_{hj|l} \omega_{il|h}) + (\omega_{hl|i} \omega_{ij|l} + \omega_{hl|j} \omega_{ij|h})] / 2, \quad (4)$$

where $\omega_{hi|j} = r_{hi} - r_{hj}r_{ij}$ and $\omega_{hh|l} = 1 - r_{hl}^2$.

The difference of Fisher transformed coefficients also approximately follows a normal distribution $\Delta\hat{U} := (\hat{U}_2 - \hat{U}_1) \sim N(U_2 - U_1, \Psi_1 + \Psi_2 - 2\Psi_{12})$ where Ψ_{12} describes the correlation between coefficients in \hat{U}_1 and \hat{U}_2 . The diagonal elements $(\psi_{tt}^{(12)})$, $t \in M$, are estimated by plugging-in the sample correlation coefficients in eq. (4). This yields a consistent estimator of $(\psi_{tt}^{(12)})$ for large n but produces non-negligible bias in the estimation for small n . Let \hat{d}_t be the standardized expression of $\Delta\hat{u}_t$, such that

$$\hat{d}_t = \Delta\hat{u}_t \{2(1 - \hat{\psi}_{tt}^{(12)})\}^{-1/2}, \quad t \in M, \quad \hat{D} = (\hat{d}_t). \quad (5)$$

Under the null hypothesis of equality in the correlation matrices, \hat{d}_t has zero expected value and variance $(\sigma_t^2)_n$ with $(\sigma_t^2)_n \rightarrow 1$, $n \rightarrow \infty$ for any $t \in M$. Moreover, if $\psi_{tt}^{(12)}$ is known, then $\text{cov}(\hat{d}_t, \hat{d}_k)$ is proportional to $\psi_{tk}^{(1)} + \psi_{tk}^{(2)} - 2\psi_{tk}^{(12)}$, which is non-zero for some $k \neq t$, unless $R = I$.

2.3 Test statistics

The three test statistics considered here are based on the elementwise standardized differences between transformed sample correlation coefficients in

eq. (5). These are average of squares (T_S), extreme value (T_M) and sum of exceedances (T_E) test statistics

$$T_S = m^{-1} \sum_{t \in M} \hat{d}_t^2, \quad T_M = \max_{t \in M} |\hat{d}_t|, \quad T_E^w(u) = \sum_{t \in M} (|\hat{d}_t| - uw)^2 I(|\hat{d}_t| > u). \quad (6)$$

In the sum of exceedances test, w is either 0 or 1 and it is incorporated to weight the importance of high values over the threshold u .

3 Null distributions and asymptotic power

3.1 Average of squares test

The next lemma provides expressions for the expected value and variance of the average of squares test statistic T_S , which is defined in eq. (6).

Lemma 1 (*Expected value and variance of T_S*) Let $\mu_2 = \mathbf{E}(\hat{d}_t^2)$ and $\mu_4 = \mathbf{E}(\hat{d}_t^4)$. Define $\bar{\gamma}_2 = 2(m^2 - m)^{-1} \sum_{t < h} \text{cov}(\hat{d}_t^2, \hat{d}_h^2)$. The expected value and variance of T_S are expressed by

$$\mathbf{E}[T_S] = \mu_2; \quad \text{var}(T_S) = (\mu_4 - \mu_2^2)/m + (1 - 1/m)\bar{\gamma}_2. \quad (7)$$

Proof The proof of lemma 7 can be found in Section 7.1 of the appendix.

Under H_0 , asymptotically with $n \rightarrow \infty$, $\hat{d}_t^2 \sim \chi_1^2$, for any $t \in M$. Besides, for sufficiently large n , it follows from the properties of χ_1^2 that $\mu_2 \doteq 1$ and $\mu_4 \doteq 3$. Let $\nu = \sum_{t < h} I[\text{cov}(\hat{d}_t^2, \hat{d}_h^2) \neq 0]$ be an integer ranging in $[0, m(m-1)/2]$. If $\text{cov}(\hat{d}_t^2, \hat{d}_h^2) \leq k$, for any $t < h$, for a finite constant k , and $\nu/m \rightarrow 0$ as $m \rightarrow \infty$, then it follows that $\text{var}(T_S) = (2/m)(1 + O(\nu/m))$.

However, for a finite dimension, if the correlation matrices are not highly sparse, ν/m is not negligible and the dependence parameter $\bar{\gamma}_2$ must be incorporated to assure uniformity in the p-values of the test under H_0 . Moreover, since an estimator for the covariance between Fisher transform sample correlations $\psi_{tt}^{(12)}$ (defined in eq. (3)) is used, parameters μ_2 and μ_4 can differ slightly from their limiting values (1 and 3) and should be estimated. For sufficiently large m and n , T_S is well approximated by a normal distribution with parameters $\mu = \mu_2$ and $\sigma^2 = (\mu_4 - \mu_2^2)/m + (1 - 1/m)\bar{\gamma}_2$ with $\Pr(T_S \leq x | H_0) \doteq \Phi(x; \mu, \sigma^2)$ where $\Phi(\cdot; \mu, \sigma^2)$ is the CDF of normal distribution with parameters μ and σ^2 . Following the central limit theorem, the Gaussian approximation can be appropriate even when n if parameters μ_2 and μ_4 are well specified (not approximated by their limiting values).

Hence, the null hypothesis is rejected at significance level α if the observed value of T_S is greater than

$$t_{S,\alpha} \doteq \mu_2 + z_\alpha \sqrt{(\mu_4 - \mu_2^2)/m + (1 - 1/m)\bar{\gamma}_2}. \quad (8)$$

The following theorem shows a lower bound for the power of the average of squares test.

Theorem 1 (*Power of the average of squares test*) *Let $t_{S,\alpha}$ be asymptotic α -quantile of the distribution for T_S under H_0 defined by (8) with $0 < \alpha < 1/2$. Under the alternative hypothesis, let $\bar{\gamma}'_2 = 2(m^2 - m)^{-1} \sum_{t < h} \text{cov}(\hat{d}_t^2, \hat{d}_h^2 | H_1)$ and $\delta_t = |g(r_{Y_t}) - g(r_{X_t})|$ with $\mathcal{S}_d = \{t \in M : \delta_t \neq 0\}$. Denote $\delta_0^2 = \sum_{t \in \mathcal{S}_d} \delta_t^2$. If condition*

$$\delta_0^2 > z_\alpha \sqrt{2m} \{1 + (m-1)\bar{\gamma}_2/2\}^{1/2} / (n-3) \quad (9)$$

holds, then, as $n, m \rightarrow \infty$,

$$\Pr(T_S \geq t_{S,\alpha} | H_1) \geq 1 - \exp(-A^2/2)(1 + o(1)).$$

with

$$A = \frac{\frac{(n-3)}{m} \delta_0^2 - z_\alpha \sqrt{\frac{2}{m} \{1 + (m-1)\bar{\gamma}_2/2\}}}{(m^{-1/2} \{2 + \frac{4s(n-3)}{m} \delta_0^2 + (m-1)\bar{\gamma}'_2\})^{1/2}}$$

Corollary 1 *For $\bar{\gamma}_2 < \nu k$ and $\nu/m = o(1)$, condition (9) becomes $\delta_0^2 \gtrsim \frac{m^{1/2}}{n}$ as $(n, m) \rightarrow \infty$. Under condition (9), when $(n/\sqrt{m})\delta_0^2 \rightarrow \infty$, $\Pr(T_S \geq t_{S,\alpha} | H_1) \rightarrow 1$.*

3.2 Extreme value test

In this section we provide a heuristic approach to approximating the limiting distribution of T_M , defined in eq. (6), based on two key assumptions: (i) we suppose that the sample size n is sufficiently large so that $(\hat{d}_t : t \in M)$ has a Gaussian distribution with standard $N(0, 1)$ margins and (ii) we assume

$$\max_{t < s \in M} |\text{cov}(\hat{d}_t, \hat{d}_s)| < 1 \quad \text{and} \quad \nu_t = \sum_{s \in M \setminus t} I\{\text{cov}(\hat{d}_t, \hat{d}_s) \neq 0\} = O(m^{\eta_t}), \quad (10)$$

for some $\eta_t \in (0, 1)$, $t \in M$. Condition (10) implies that no two elements of (\hat{d}_t) are perfectly dependent and that there is sufficiently weak dependence structure in the process. If condition (10) holds, then adapted versions of extreme value limits for non-stationary Gaussian processes apply (Leadbetter

et al., 1983), i.e., there exist location and scale functions $\mu(m) \in \mathbb{R}$ and $\sigma(m) > 0$, such that

$$\lim_{m \rightarrow \infty} \Pr \left(\frac{T_M - \mu(m)}{\sigma(m)} < x \mid H_0 \right) = \exp \{ - \exp(-x) \}, \quad (11)$$

describes a Gumbel distribution with $\mu(m) + \sigma(m)x \rightarrow \infty$, as $m \rightarrow \infty$, for all x . We note that a similar type of extreme value limits are obtained in Cai et al. (2013) for the less general setting where $(Y_k^{(1)}, Y_k^{(2)})$ in expression (1) are independent. Additionally, our empirical findings from simulations confirm that this is a reasonable approximation for the distribution of T_M provided n and m are sufficiently large. To back up this result, we illustrate in Appendix 7.3 how condition (10) links with Leadbetter et al. (1983) conditions for convergence of the maximum of non-stationary Gaussian processes.

In real applications, where m is finite, limit expression (11) may fail to approximate the distribution of T_M in two respects. Firstly, it is known that the rate of convergence to the limit distribution is very slow. Secondly, its form is independent of the dependence structure of the process $(\hat{d}_t : t \in M)$, a result that stems from the joint tail properties of the multivariate Gaussian distribution (Sibuya, 1959; Tiago de Oliveira, 1962).

An improved approximation that does take into account the dependence characteristics can be obtained from a sub-asymptotic correction (Eastoe and Tawn, 2012),

$$\Pr \left(\frac{T_M - \mu(m)}{\sigma(m)} < x \mid H_0 \right) \doteq \exp \left\{ - \left(\frac{m_E}{m} \right) \exp(-x) \right\}, \quad \text{for large } m, \quad (12)$$

where $m_E = m_E(m, x)$ satisfies $m_E/m \rightarrow 1$, as $m \rightarrow \infty$, for all $x \in \mathbb{R}$, and describes the effective sample size of independent and identically distributed $N(0, 1)$ random variables whose maximum has the same distribution with T_M . Note that the distribution of T_M in eq. (12) is a Gumbel distribution as in eq. (11) but with an updated location parameter, say $\mu_{m_E}(m)$, which depends on m_E .

Hence, the null hypothesis is rejected at significance level α if the observed value of T_M is greater than

$$\begin{aligned} t_{M,\alpha} &\doteq \mu_{m_E}(m) - \sigma(m) \log(-\log(\alpha)) \\ &\sim \sqrt{2 \log(2m)} - [\log \theta_m + \log \{-\log(\alpha)\}] / \sqrt{2 \log(2m)}. \end{aligned} \quad (13)$$

The following theorem shows a lower bound for the power of the extreme value test

Theorem 2 (Power of the extreme value test) Assume (10) holds. Let $t_{M,\alpha}$ be the asymptotic α -quantile of the distribution for T_M under H_0 defined by (13) with $0 < \alpha < 1/2$. Under the alternative hypothesis, let $\delta_t = |g(r_{Y_t}) - g(r_{X_t})|$ with $\mathcal{S}_d = \{t \in M : \delta_t \neq 0\}$. If the following condition holds

$$\max_{t \in \mathcal{S}_d} \delta_t > \frac{1}{\sqrt{n-3}} \left[\sqrt{2 \log(2m)} - \frac{\log\{-\log(\alpha)\}}{\sqrt{2 \log(2m)}} \right], \quad (14)$$

then, as $n, m \rightarrow \infty$,

$$\Pr(T_M \geq t_{M,\alpha} \mid H_1) \geq 1 - \exp \left[-\frac{(n-3)}{2} \left\{ \max_{t \in \mathcal{S}_d} \delta_t - \sqrt{\frac{2 \log(2m)}{(n-3)}} \right\}^2 \right] (1 + o(1)).$$

If $s = |\mathcal{S}_d| \rightarrow \infty$ and

$$\min_{t \in \mathcal{S}_d} \delta_t > \frac{1}{\sqrt{n-3}} \left[\sqrt{2 \log(2m)} - \frac{\log\{-\log(\alpha)\}}{\sqrt{2 \log(2m)}} \right], \quad (15)$$

then, as $n, m \rightarrow \infty$,

$$\Pr(T_M \geq t_{M,\alpha} \mid H_1) \geq 1 - \exp \left\{ -e^{-\sqrt{2(n-3) \log(2s)} \left[\min_{t \in \mathcal{S}_d} \delta_t - \sqrt{\frac{2 \log(2m)}{(n-3)}} \right]} \right\} (1 + o(1)).$$

Corollary 2 As $n, m \rightarrow \infty$, condition (14) becomes $\max_{t \in \mathcal{S}_d} \delta_t^2 \gtrsim (2 \log 2m)/(n-3)$. Under this condition, if $\sqrt{n}(\max_{t \in \mathcal{S}_d} \delta_t - \sqrt{2 \log(2m)/n}) \rightarrow \infty$, $\Pr(T_M \geq t_{M,\alpha} \mid H_1) \rightarrow 1$.

Similarly, as $n, m \rightarrow \infty$ and $s = |\mathcal{S}_d| \rightarrow \infty$, condition (15) becomes $\min_{t \in \mathcal{S}_d} \delta_t^2 \gtrsim (2 \log 2m)/(n-3)$. Under this condition, if $\sqrt{n \log s}(\min_{t \in \mathcal{S}_d} \delta_t - \sqrt{2 \log(2m)/n}) \rightarrow \infty$, $\Pr(T_M \geq t_{M,\alpha} \mid H_1) \rightarrow 1$.

3.3 Sum of exceedances test

Let $\mathcal{S}_u = \{t \in M : |\hat{d}_t| \geq u\}$ be the set of exceedances above some threshold $u \geq 0$, let $N_u = \text{Card}(\mathcal{S}_u)$ be the number of elements in \mathcal{S}_u and recall that $m = p(p-1)/2$. The cumulative distribution function of the test statistic T_E under H_0 is

$$\Pr(T_E^w(u) < x \mid H_0) = \sum_{k=1}^m [\Pr(N_u = k \mid H_0) \Pr(T_E^w(u) < x \mid H_0, N_u = k)]. \quad (16)$$

We define several parameters that are used to determine the limiting distribution of T_E :

$$\begin{aligned}\gamma_{utj}^{(w)} &= \text{cov}((|\hat{d}_t| - uw)^2, (|\hat{d}_j| - uw)^2 \mid \hat{d}_t^2 > u, \hat{d}_j^2 > u, d_t = d_j = 0), \\ \eta_0 &= \Pr(|\hat{d}_t| > u \mid d_t = 0), \\ \phi_{tj} &= \Pr(\hat{d}_t^2 > u^2, \hat{d}_j^2 > u^2 \mid d_t = d_j = 0), \quad \bar{\phi} = [m(m-1)]^{-1} \sum_{t \neq j} \phi_{tj}.\end{aligned}\tag{17}$$

Let φ and Φ be the density and cumulative distribution function of the standard normal distribution, respectively. For sufficiently large expected number of exceedances, the central limit theorem yields $\Pr(T_E^w(u) < x \mid H_0) \doteq \Phi\{x, \mu(m, w), \sigma^2(m, w)\}$ for any $w = \{0, 1\}$, with

$$\begin{cases} \mu(m, w) = m \eta_0 \mu_w \\ \sigma^2(m, w) = m \{\eta_0 \sigma_w^2 + \mu_w^2 (\eta_0 - \bar{\phi})\} + m^2 \mu_w^2 (\bar{\phi} - \eta_0^2) + \sum_{t \neq j} \gamma_{utj}^{(w)} \phi_{tj}, \end{cases}\tag{18}$$

where μ_w and σ_w^2 are defined for $w = 0$ by

$$\begin{cases} \mu_0 = 1 + u \varphi(u) / \{1 - \Phi(u)\} \\ \sigma_0^2 = 3 + (u^3 + 3u) \varphi(u) / \{1 - \Phi(u)\} - \mu_0^2, \end{cases}\tag{19}$$

whereas for $w = 1$ these are

$$\begin{cases} \mu_1 = u^2 + 1 - u \varphi(u) / \{1 - \Phi(u)\} \\ \sigma_1^2 = 3 + u^4 + 6u^2 - (5u + u^3) \varphi(u) / \{1 - \Phi(u)\} - \mu_1^2. \end{cases}\tag{20}$$

[The derivation of equations (18), (19) and (20) can be found in Section 7.2 of the Appendix]. Note that if the elements in \hat{D} are near independence, then $\bar{\phi} \approx \eta_0^2$, making the third term in the expression for the variance in eq. (18) approximately zero, and the whole expression simplifies to $\sigma^2(m, w) \doteq m \eta_0 \{ (1 - \eta_0) \mu_w^2 + \sigma_w^2 \}$.

The null hypothesis is rejected at significance level α if the observed value of $T_E^{(w)}$ is greater than

$$t_{E,\alpha}^{(w)} \doteq \mu(m, w) + z_\alpha \sigma(m, w).\tag{21}$$

The following theorem shows a lower bound for the power of the sum of exceedances test.

Theorem 3 (Power of the sum of exceedances test) *Let $t_{E,\alpha}^{(w)}$ be the asymptotic α -quantile of the distribution for $T_E^{(w)}$ under H_0 defined by (21) with*

$0 < \alpha < 1/2$ and w being either 0 or 1. Consider μ_0 and μ_1 defined by eq. (19) and eq. (20), η_0 defined by eq. (17) and $\sigma^2(m, w)$ defined by eq. (18). Under the alternative hypothesis, let $\delta_t = |g(r_{Y_t}) - g(r_{X_t})|$ with $\mathcal{S}_d = \{t \in M : \delta_t \neq 0\}$, $s = |\mathcal{S}_d|$, $\eta_t = \Pr(|\hat{d}_t| > u \mid d_t \neq 0)$ and $\mu_{t_w} = \mathbf{E}((|\hat{d}_t| - wu)^2 \mid |\hat{d}_t| > u, d_t \neq 0)$. If the following condition holds

$$\sum_{t \in \mathcal{S}_d} \mu_{t_w} \eta_t > s \eta_0 \mu_w - z_\alpha \sigma(m, w), \quad (22)$$

then the lower bound for the asymptotic power of sum of exceedances test, with $w = \{0, 1\}$, as $n, m \eta_0 \rightarrow \infty$, is

$$\Pr(T_E^{(w)} \geq t_{E, \alpha}^{(w)} \mid H_1) \geq 1 - \exp(-B(\delta_t, s, u, n, m, w)^2/2)(1 + o(1)),$$

with

$$B(\delta_t, s, u, n, m, w) = \frac{\sum_{t \in \mathcal{S}_d} \mu_{t_w} \eta_t - s \eta_0 \mu_w - z_\alpha \sigma(m, w)}{\sigma_{H_1}(m, w)}, \quad (23)$$

where $\sigma_{H_1}^2(m, w)$ is defined in Section 7.5.3 of the appendix.

Note: Gaussian approximation represents well the asymptotic power if and only if $m \eta_0$ is sufficiently large, with $u < \sqrt{2 \log 2m}$ being a necessary condition.

Corollary 3 Assume $\sigma^2(m, w) \doteq m \eta_0 \{(1 - \eta_0) \mu_w^2 + \sigma_w^2\}$. Let $u = u(\beta)$ with $\beta = 2(1 - \Phi(u))$, and let $\mathcal{S}_{du} = \{t \in M, |d_t| \gg u\}$ with $s_u = |\mathcal{S}_{du}|$. When $(m, n, u) \rightarrow \infty$, under condition (22), if $s_u = k \max(1, s \eta_0, (2m \eta_0)^{1/2})$ for some integer $k > 0$, and $\delta_t^2(n/u^2) \rightarrow \infty$ for some $t \in \mathcal{S}_{du}$, $\Pr(T_E^{(w)} \geq t_{E, \alpha}^{(w)} \mid H_1) \rightarrow 1$.

1. $u = 0$: recovery conditions coincide with the average of squares test (Section 3.1).
2. $u = \sqrt{2 \log 2m} - o(1)$: recovery conditions are similar to extreme value test (Section 3.2).

3.4 Threshold selection for sum of exceedances test

The threshold u is key to find the test statistic that maximizes the power and its selection is the focus of attention of this section. Under notation in Theorem 3, $B(\delta_t, s, u, n, m, w)$ depends on parameters n, m, w, u (known), and s, δ_t (unknown). Let $\rho_s = s/m$ be the proportion of non-zero elements in $R_2 - R_1$. To show the influence that ρ_s has in the asymptotic power, the function f , defined in eq. (23), is evaluated for several values of ρ_s ,

u , with fixed sizes $n = 100$, $m = 10000$ and generating values of δ_t from a Gamma(a, b) distribution with parameters $a = 3$ and $b = 10$. In Figure 1, the optimal threshold, defined by the value of u that maximizes B , is decreasing with ρ_s for both $w = 0$ and $w = 1$.

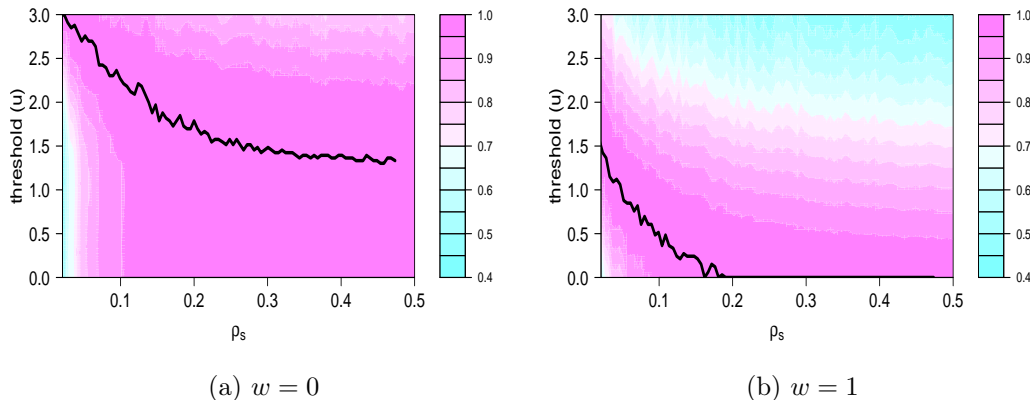


Figure 1: Relative power of sum of exceedances test with respect to threshold (u) and proportion of non-zero correlation differences (ρ_s) for (a) $w = 0$ and (b) $w = 1$. The black line corresponds to the threshold with highest power.

Moreover, in panels (a) and (b) of Figure 2, the optimal values for u using a range of sample sizes and three different values for $\rho_s \in \{0.01, 0.1, 0.3\}$ are obtained. We also considered several dimension sizes, but their impact on the threshold selection was very low and for simplicity we only show the cases for $m = 1000$, which corresponds to $p \approx 43 - 44$. For $w = 0$, the optimal threshold increases with the sample size, whereas for $w = 1$, the optimal threshold decreases with the sample size. In panel (c) of Figure 2, we show the lower bound of the power differences between $w = 0$ and $w = 1$. We consider the best power for both $w = 0$ and $w = 1$ and then we take the difference between the two. In the figure we present the average sign of such power differences over 1000 simulations for the set of parameters $(\delta_t : t \in \mathcal{S}_d)$. Only for small sample sizes ($n < 100$) and low ρ_s , $w = 1$ reaches better rates than $w = 0$. Otherwise, $w = 0$ dominates the asymptotic power.

As Figure 1 and Figure 2 show, the fraction of zero elements in $R_2 - R_1$ denoted by ρ_s is essential to find the best threshold. We propose to find an estimator for ρ_s using the q-values approach of Storey (2015) where the input are approximated p-values $2(1 - \Phi(|\hat{d}_t|))$ for all $t \in M$. Even though testing if $\rho_s = 0$ is the same as our hypothesis testing of $R_1 = R_2$, here we only use

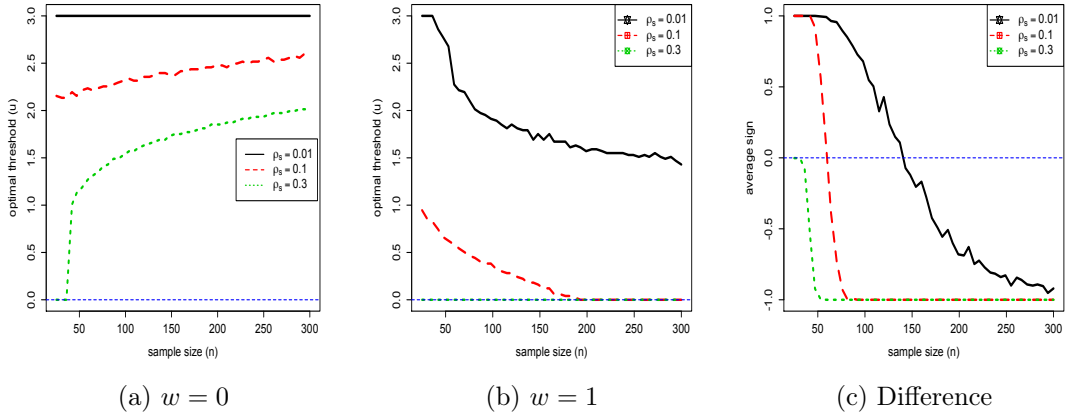


Figure 2: Optimal threshold in sum of exceedances test with respect to several values of the sample size for (a) $w = 0$ and (b) $w = 1$. In (c) is shown the average sign for the difference between best power using $w = 1$ and best power using $w = 0$ over 1000 simulated sets of differential correlation coefficients.

this testing procedure to find a first crude estimation of ρ_s . This estimator is shown to be asymptotically unbiased with $n \rightarrow \infty$ but biased downwards when $\delta_t \sqrt{n-3}$ is small for all $t \in \mathcal{S}_d$ under mild dependence assumptions. However, in the application to biological data we generally have a relatively small n and we have seen that the dependence process in $(\hat{d}_t : t \in M)$ can bias quite heavily the testing procedures in simulated data.

The other unknown parameters are the Fisher transform correlation differences δ_t , for all $t \in \mathcal{S}_d$. Below we propose a prior specification for δ_t to control the amount of elements that might be masked by the coefficients \hat{d}_k , $k \notin \mathcal{S}_d$, when $\delta_k = 0$. However, other distributions or other specifications for the hyper-parameters could be employed instead. We assume that (δ_t) are i.i.d. random variables with a known distribution, for instance we explore $\delta_t \sim \text{gamma}(a, b)$, with hyper-parameters satisfying $\text{mode} = (a-1)/b = Z_\alpha (n-3)^{-1/2}$, so the mode is assumed to be at the $1-\alpha$ quantile of the marginal distribution of $\hat{d}_t (n-3)^{-1/2}$ under H_0 . Moreover, we set the variance of the prior, $\text{var} = a/b^2$, so a and b are fully defined.

We numerically integrate out δ_t from the function $B(\delta_t, s, u, n, m, w)$ defined in eq. (23) for threshold selection, i.e.,

$$\hat{u}^w = \arg \max_u \int_{\Omega_{\delta_t}} B(\delta_t, m\hat{\rho}_s, u, n, m, w) p(\delta_t) d\delta_t.$$

As final estimate we use the minimum between the optimal threshold and the $1 - \alpha$ quantile of a standard normal distribution with default value $\alpha = 0.05$ in order to prevent cases with infinite thresholds.

3.5 Estimation of dependence parameters and permutations based distributions

Under H_0 , $X_1, \dots, X_n \sim N(0, R_X)$ and $Y_1, \dots, Y_n \sim N(0, R_Y)$ with $R_X = R_Y$. In case X_k and Y_k were independent for all $k \in \{1, \dots, n\}$, the elements in $[X_1, \dots, X_n, Y_1, \dots, Y_n]$ would be exchangeable (i.e., permutation invariant). For paired datasets, $R_{XY} \neq 0$ and standard permutation methods are not suitable. Alternatively, we consider a resampling method which keeps paired observations together: find $[(Z_1^{\pi_1}, \dots, Z_n^{\pi_n}), (Z_1^{\bar{\pi}_1}, \dots, Z_n^{\bar{\pi}_n})]$ where $\bar{\pi}_k = 1 - \pi_k$, and $Z_k^{\pi_k} = X_i$ if $\pi_k = 0$ or $Z_k^{\pi_k} = Y_k$ if $\pi_k = 1$, with $\pi_k \sim \text{Bern}(1/2)$. The permutation process is repeated B times and for each replicate ($i = 1, \dots, B$) the difference of Fisher transform correlation matrices, defined in eq. (5), is calculated and denoted by $\hat{D}^{(i)}$. Finally, a $B \times m$ matrix \tilde{D} is considered where row i contains the lower triangular matrix of $\hat{D}^{(i)}$.

We denote \tilde{D}^2 by the elementwise product of the matrix \tilde{D} and \tilde{D}^4 by the elementwise product of the matrix \tilde{D}^2 . The parameters μ_2 , μ_4 and $\bar{\gamma}_2$ for the average of squares test defined in eq. (7) are estimated using permuted samples such that

$$\hat{\mu}_2 = \frac{1}{mB} \sum_{i=1}^B \sum_{t=1}^m \tilde{D}_{it}^2, \quad \hat{\mu}_4 = \frac{1}{mB} \sum_{i=1}^B \sum_{t=1}^m \tilde{D}_{it}^4,$$

$$\hat{\gamma}_2 = \frac{2}{Bm(m-1)} \sum_{i=1}^B \sum_{t < h} \text{cov}(\tilde{D}_{it}^2, \tilde{D}_{ih}^2).$$

Regarding the extreme value test, for each replicate of the permutation process, $i = 1, \dots, B$, the maximum $\hat{T}_M^{(i)} = \max_{t \in M} |\tilde{D}_{it}|$ is computed so that for sufficiently large sample size n , $\hat{T}_M^{(i)}$ for all $i = 1, \dots, B$ can be considered as an independent replicate of a Gumbel distributed random variable with parameters $\mu_{m_E}(m)$ and $\sigma(m)$. The location parameter $\mu_{m_E}(m)$ of the Gumbel distribution is estimated by maximum likelihood. Besides, for the sum of exceedances test, the parameter $\sigma^2(m, w)$ defined in eq. (18) is estimated by maximum likelihood using permuted samples such that $\Pr(T_E^w(u) < x \mid H_0) \doteq \Phi\{x, \mu(m, w), \hat{\sigma}^2(m, w)\}$ where the parameter $\mu(m, w)$ is also expressed in eq. (18).

A non-parametric null distribution for T_Q , $Q \in S, M, E$, based on permuted samples is also considered by recording the value of B test statistics

computed by $\hat{T}_S^{(i)} = m^{-1} \sum_{t=1}^m \tilde{D}_{it}^2$, $T_M^{(i)} = \max_{t \in M} |\tilde{D}_{it}|$ or $\hat{T}_E^{(i)} = \sum_{t \in \mathcal{S}_u} (\tilde{D}_{it} - uw)^2$, for $i = 1, \dots, B$, with $\Pr(T_Q \leq x \mid H_0) \doteq B^{-1} \sum_{i=1}^B I(\hat{T}_Q^{(i)} \leq x)$.

3.6 Comparison of the tests

Extreme value test is more powerful when it comes to sparse alternatives whereas sum of squares test is useful when the differential correlation matrix is non-sparse and the magnitude of the coefficients is small. The sum of exceedances test lies in between the other two tests. For threshold u near zero, the test statistic is similar to the average of squares test and for $u \approx \sqrt{2 \log m}$ it finds similar powers to the extreme value test. The weight w is added to the expression of the sum of exceedances since the underlying test powers are complementary regarding sample sizes and number of non-zero correlation differences. For instance, for $w = 1$ the test is powerful for highly sparse differential correlation matrix and small sample sizes (or small magnitude for the difference coefficients). Otherwise, $w = 0$ achieves the most powerful test of the two. We consider a default value of $w = 0$. The theoretical results obtained in this section are completed empirically using simulated data in Section 4.

4 Comparison of the tests for simulated data

We analyze the accuracy of the proposed methods in simulated data sets. We study different structures for the correlation matrix R directly (Section 4.1) or indirectly by setting different graph structures for the precision matrix $\Omega = R^{-1}$ (Section 4.2).

4.1 Independent datasets, dense correlation matrices

We can observe in real data, some groups of highly dependent genes whose underlying correlation matrix is non-sparse. In such a case, we argue that asymptotic independence tests are not reliable under H_0 even when the datasets are independent. We show this in simulated data by considering a dense correlation matrix denoted by \tilde{R} . This matrix is obtained by the sample correlation matrix of a subset of 50 variables from the real dataset described in Section 5. In order to obtain a positive definite matrix, we regularize \tilde{R} by

$$\Sigma = \tilde{R} + I\lambda, \quad (24)$$

where $\lambda > 0$. Note that as we increase λ , off-diagonal elements of the correlation matrix decrease.

Data $Y_k^{(1)} \sim N(0, \Sigma_1)$ and $Y_k^{(2)} \sim N(0, \Sigma_2)$, i.i.d. for all $k = 1, \dots, n$ are generated using the following specifications for the covariance matrices: (i) under H_0 , we consider $\Sigma_1 = \Sigma_2 = \Sigma$; (ii) under H_1 , we consider $\Sigma_1 = \Sigma$ and for Σ_2 , we create a two-block diagonal matrix of sizes 40 and 10 by setting to zero the between-block covariance elements of the matrix Σ . We refer to this model in the results presented in Sections 4.3 as model 1, which is applied for $n = 50, 100$ and $\lambda = 1/2, 1, 2, 3$.

4.2 Dependent datasets, sparse correlation matrices

Sparse correlation matrices are obtained by setting almost-block diagonal precision matrices, where each block has a power-law underlying graph structure (Peng et al., 2009) and some extra random connections between blocks. Let A be the adjacency matrix with the non-zeros of the precision matrix, the coefficients of the precision matrix are simulated by

$$\Omega^{(0)} = [\omega_{ij}^{(0)}], \quad \omega_{ij}^{(0)} = \begin{cases} \text{Unif}(0.5, 0.9) & \text{if } A_{ij} = 1 \text{ with probability } 0.5 ; \\ \text{Unif}(-0.5, -0.9) & \text{if } A_{ij} = 1 \text{ with probability } 0.5 ; \\ 0 & \text{if } A_{ij} = 0. \end{cases} \quad (25)$$

Data $(Y_k^{(1)}, Y_k^{(2)}) \sim N(0, \Omega^{-1})$, i.i.d. for all $k = 1, \dots, n$ are generated using a direct effect model (Wit and Abbruzzo, 2015) with the following specifications for the joint precision matrix Ω : (i) under H_0 , Ω is determined by $\Omega_1 = \Omega^{(0)}$, $\Omega_2 = \Omega^{(0)}$ and Ω_{12} being a diagonal matrix with $(\Omega_{12})_{ii} = 0.6$ for $\lfloor p/2 \rfloor$ diagonal elements and $(\Omega_{12})_{ii} = 0$ for the other $\lceil p/2 \rceil$; under H_1 , let D_1 and D_2 be two different precision matrices which are generated with the same model as for $\Omega^{(0)}$. We consider $\Omega_1 = \text{diag}(\Omega^{(0)}, D_1, I)$, $\Omega_2 = \text{diag}(\Omega^{(0)}, I, D_2)$ and the same specification for Ω_{12} given under H_0 . In both setting, to obtain a positive definite matrix, we regularize Ω by $\Omega = \Omega + \lambda I$, with λ such that the condition number of Ω is less than the number of nodes (Cai and Liu, 2011). We use $p = 70, 120, 210$ and sample sizes $n = 25, 50, 100, 200$. We refer to this model in the results presented in Section 4.3 as model 2.

4.3 Power and size of the tests

We use the average of squares test -S-, the extreme value test -M- and the sum of exceedances test -E- for both $w = 0$ and $w = 1$ (see definition in eq. (6)) with threshold selected as defined in Section 3.3. We compute the empirical power of the tests defined as $\Pr(\text{Reject } H_0 \mid H_1 \text{ true})$ as well as the test size described by $\Pr(\text{Reject } H_0 \mid H_0 \text{ true})$ using significance level of $\alpha = 0.05$. We approximate the null distributions by assuming linear independence

Table 1: Size, uniformity and power of the test using model 1 -dense correlation matrices- ($\times 10^3$). Test statistics S (average of squares), M (extreme values) and E (exceedances with $w = 0$ or $w = 1$), and null distributions AI (asymptotic independence), AD (asymptotic dependence) and NP (non-parametric) are compared at $\alpha = 0.05$ level.

λ	n=50				n=100			
	0.5	1	2	3	0.5	1	2	3
	Empirical size							
S(AD)	62	50	58	53	52	59	60	52
S(NP)	61	47	54	52	53	54	57	50
S(AI)	306	238	192	133	304	254	192	126
M(AD)	45	43	49	61	42	48	54	50
M(NP)	51	44	47	59	50	50	51	48
M(AI)	68	58	59	66	62	54	59	61
E(AD) ⁽⁰⁾	49	54	59	48	52	50	48	54
E(NP) ⁽⁰⁾	54	50	60	55	46	60	46	58
E(AI) ⁽⁰⁾	103	126	92	86	200	158	121	88
	ks.test p-value to test for uniformity in the correlation test p-values							
S(AD)	247	23	716	317	72	400	151	79
S(NP)	432	15	134	181	62	432	500	148
S(AI)	0	0	0	0	0	0	0	0
M(AD)	865	121	835	426	147	52	245	646
M(NP)	936	69	400	969	181	48	288	181
M(AI)	0	0	24	27	0	0	193	150
E(AD) ⁽⁰⁾	51	416	779	211	231	123	532	883
E(NP) ⁽⁰⁾	288	618	241	500	400	723	648	785
E(AI) ⁽⁰⁾	0	0	0	0	0	0	0	0
	Empirical power							
S(AD)	890	690	342	240	998	992	802	542
S(NP)	897	684	380	250	998	992	806	574
M(AD)	667	270	110	109	996	758	250	122
M(NP)	652	280	106	105	996	766	254	118
E(AI) ⁽⁰⁾	950	735	374	202	998	992	790	447
E(NP) ⁽⁰⁾	943	723	380	223	998	992	787	442
E(NP) ⁽¹⁾	940	692	304	143	998	992	687	413
	Estimated θ							
$\hat{\theta}_m$.593	.843	.915	.955	.574	.828	.912	.953

between elements in \hat{D} (denoted by AI) since it is computationally very fast. Moreover, we approximate the distributions estimating the dependence parameters using permuted samples (AD) and also using a non-parametric distribution (NP) as described in Section 3.5. For $w = 1$ we only show the power of the non-parametric null distribution which is labeled by E(NP)⁽¹⁾. Nevertheless, test sizes when $w = 1$ are seen to be similar to the ones provided when $w = 0$.

In Table 1 we present the empirical approximations of power and size for the dense correlation matrices scenario (model 1). Generally, tests show a good trade off between false rejection and true rejection rates. For low regularization λ , as defined in (24), asymptotic linear independence tests are not suitable with empirical sizes being larger than the expected 0.05. The average of squares test is the one that dominates the powers in this model for $\lambda \geq 2$ and gives similar results to the sum of exceedances test (with $w = 0$) for $\lambda < 2$. Sum of exceedances test with $w = 1$ achieves worse powers than the test with $w = 0$ for large λ .

In Table 2 we show a similar analysis for dependent datasets with sparse

Table 2: Size, uniformity and power of the test using model 2 -sparse correlation matrices- ($\times 10^3$). Test statistics S (average of squares), M (extreme value) and E (sum of exceedances with $w = 0$ or $w = 1$), and null distributions AI (asymptotic independence), AD (asymptotic dependence) and NP (non-parametric) are compared at $\alpha = 0.05$ level.

n	p=70				p=120				p=210			
	50	100	200	500	50	100	200	500	50	100	200	500
	Empirical size											
S(AD)	50	50	50	52	49	42	56	52	38	46	48	54
S(NP)	58	54	50	52	55	48	58	50	52	50	50	53
S(AI)	32	58	78	78	22	40	62	69	4	26	44	62
M(AD)	55	46	51	58	48	54	46	48	48	50	56	44
M(NP)	55	44	51	57	48	54	46	47	47	51	54	44
M(AI)	60	41	47	54	56	57	47	47	62	54	58	42
E(AD) ⁽⁰⁾	50	50	52	51	56	54	56	44	50	43	46	53
E(NP) ⁽⁰⁾	47	48	49	49	52	53	54	44	48	46	47	52
E(AI) ⁽⁰⁾	56	42	38	66	66	47	46	52	64	52	54	46
	ks.test p-value to test for uniformity in the correlation test p-values											
S(AD)	1	376	37	895	0	929	351	31	0	0	886	286
S(NP)	5	536	29	794	0	648	370	48	0	0	500	164
S(AI)	0	0	0	0	0	0	0	1	0	0	0	0
M(AD)	58	662	528	266	701	836	917	423	5	837	50	498
M(NP)	87	500	466	341	648	859	936	241	3	723	33	341
M(AI)	173	255	19	798	513	241	298	78	435	701	19	267
E(AD) ⁽⁰⁾	888	58	914	374	155	819	725	349	598	191	85	42
E(NP) ⁽⁰⁾	43	536	913	263	43	648	794	466	610	988	241	466
E(AI) ⁽⁰⁾	138	360	10	135	28	207	856	39	0	5	100	42
	Empirical power											
S(AD)	60	144	437	730	78	88	178	398	4	78	152	439
S(NP)	62	150	430	720	96	106	182	404	86	94	160	440
M(AD)	76	220	715	944	68	76	176	722	42	72	180	651
M(NP)	82	228	706	950	60	58	174	710	44	72	174	649
E(AD) ⁽⁰⁾	101	200	631	910	80	82	170	520	70	74	180	550
E(AI) ⁽⁰⁾	102	204	615	960	82	80	180	544	72	76	182	534
E(NP) ⁽¹⁾	94	316	800	984	102	94	272	816	70	84	232	836
	Estimated θ											
$\hat{\theta}_m$.790	.871	.908	.943	.788	.848	.913	.945	.770	.841	.903	.937

correlation matrices. Null distributions accounting for dependence (AD and NP) achieve better estimates of the size than asymptotic linear independence tests. Particularly, in the average of squares and sum of exceedances tests adjusting for dependence is desired to obtain a good representation of the null distribution. The asymptotic linear independence extreme value test finds good estimates for the size. It is slightly conservative for large p-values but these do not affect the evidence interpretation. Hence, for sparse dependence structures, the asymptotic extreme value test could be used to speed up the process. The sum of exceedances test with $w = 1$ (i.e., see NP) produces consistently the highest powers among the three tests. Contrarily of what we observe in Table 1, the test with $w = 1$ gives better results than the one with $w = 0$. Moreover, the extreme value test provides higher powers than the average of squares for large sample sizes.

We also analyze the behavior of the tests with respect to the proportion of non-zero correlation differences ρ_s . In a global analysis, we compute the average power for small proportions ($\rho_s \leq 0.3$) and large proportions ($\rho_s > 0.3$) using the three test statistics. The sum of exceedances test has average

powers 0.426 and 0.543 respectively, the extreme value test obtains 0.373 and 0.465, and the average of squares produces 0.312 and 0.477. It is T_S that benefits the most from the increase of difference coefficients.

For model 1 (dense difference correlations matrix), the correlation between p-values for the same test statistic using both non-parametric and asymptotic null distributions is very high (around 0.994 in average) whereas the average correlation between extreme value and average of squares p-values is [0.61, 0.48, 0.36, 0.30] in the four regularization parameters used. The p-values for the sum of exceedances test (for both w), seem to be more correlated to the p-values for the other two tests with [0.91, 0.88, 0.82, 0.75] against the average of squares and [0.75, 0.63, 0.55, 0.52] against the extreme value. For model 2 (sparse difference correlation matrix), the correlations are smaller with an average of [0.19, 0.12, 0.07] between average of squares and extreme value p-values for the three dimensions used, [0.55, 0.39, 0.27] between average of squares and exceedances and [0.49, 0.49, 0.48] between extreme value and exceedances.

We estimate the extremal index θ_m , which quantifies the dependence structure over high exceedances, and it is defined in Section 3.2. In the sparse model 2, the average estimated θ_m gets close to 1 as the sample size increases. For large n , we could assume that θ_m is equal to 1 and use the asymptotic approximation which would speed up the results. However, for dense correlations as in model 1, θ_m can be quite small (≈ 0.6 for small regularization λ) and permutations-based tests should be used instead.

5 Application to colon cancer gene expression data

We apply the methods to a case study of gene expression data which can be downloaded at <http://www.ebi.ac.uk/arrayexpress/> and that it is presented in Hinoue et al. (2012). A total of 25 patients are examined, the gene expression profiling is obtained in each one of them for a colorectal tumor sample and its healthy adjacent colonic tissue: in total 50 samples and 24,526 genes.

We use the equality between correlation matrices tests for multiples subgroup of genes (of the 25×10^3). We are particularly interested in knowing how standard gene pathways change in different medical conditions. To assess which biological processes might be linked to changes in the gene connections we download 1,320 gene sets from the MSig database (Subramanian et al., 2005), which represent canonical pathways compiled from two sources:

KeGG (Kanehisa et al., 2016) and Reactome (Milacic et al., 2012). Then we compare correlations in the two medical conditions by only considering genes in each of the pathways. Hence, we test 1,320 different correlation matrices. Note that in the original data some genes are represented by more than one probe/sequence (these are not identical, so they are not merely technical replicates), in order to compare correlation matrices, we take the average of these probe/sequence for the same gene.

In Figure 3(a) we present the approximated p-values using the three dependence-correction tests. In the sum of exceedances test we give the results for $w = 0$, although they are quite similar to the p-values found for $w = 1$. The 18% of the average of squares test p-values, the 9% of the extreme value test p-values and the 19% of the sum of exceedances test p-values are smaller than 0.01 and under H_0 we were expecting only 1%. About 4% of the lists have the three tests with p-values smaller than 0.01. Moreover, about 35% of the lists have the three p-values larger than 0.10, indicating some similarity in the correlation matrices even with conditions as different as cancer and healthy. We further adjust the p-values for multiple testing by controlling the false discovery rate, and in Figure 3(b) we present a Venn's diagram of the adjusted p-values smaller than 0.05. Moreover, in Table 3 we highlight some of the pathways lists that had significant adjusted p-values in the three tests.

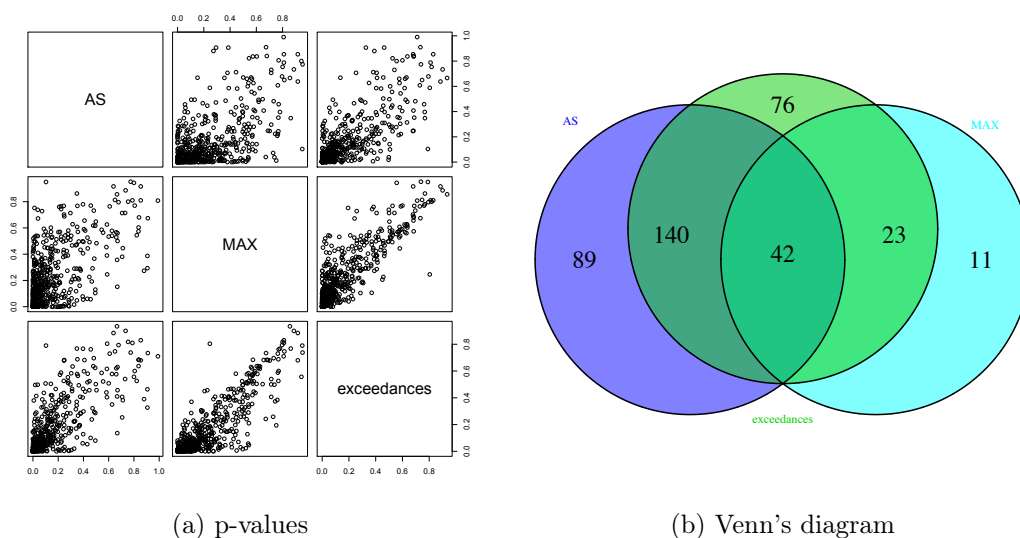


Figure 3: P-values for equality of correlations on 1,320 pathway lists of genes. Venn's diagram shows the number of rejected lists with an adjusted p-value smaller than 0.05.

Table 3: Lists with p-values smaller than 0.0003 for all the tests. Highly overlap label corresponds to pathways lists that contain more than 50% of their genes common to another list.

1-	"KEGG_SPLICEOSOME"	
2-	"KEGG_JAK_STAT_SIGNALING_PATHWAY"	
3-	"BIOCARTA_INFLAM_PATHWAY"	(highly overlaps with [2])
4-	"BIOCARTA_ERYTH_PATHWAY"	(highly overlaps with [3])
5-	"BIOCARTA_STEM_PATHWAY"	(highly overlaps with [2] and [3])
6-	"REACTOME_SIGNALING_BY_GPCR"	
7-	"REACTOME_GPCR_DOWNSTREAM_SIGNALING"	
8-	"REACTOME_SIGNALING_BY_ILS"	
9-	"REACTOME_CYTOKINE_SIGNALING_IMMUNE_SYSTEM"	
10-	"REACTOME_TELOMERE_MAINTENANCE"	

We preferred to use the dependence-correction tests rather than the asymptotic independence ones since the dependence in the sample correlation matrices for each of the lists resulted to be quite strong. Besides, the obtained results assuming non-parametric distributions were very similar to dependence-correction, and for simplicity we only show the p-values for the latter.

The sample correlations between test p-values are also remarkably large, 0.59 between average of squares and extreme value, 0.87 between extreme value and exceedance and 0.75 between average of squares and exceedance (these are more similar to the values obtained in the simulation study from the dense scenario described in Section 4.1 than to the sparse one in Section 4.2).

6 Discussion

In this article we propose three tests for equality of two correlation matrices: average of squares, extreme value and sum of exceedances tests. These are especially useful for high-dimensional dependent datasets. We further suggest considering dependence-correction or non-parametric tests instead of asymptotic linear independence tests when the correlation matrices are known to be dense. Asymptotic tests, which assume independence among sample correlation coefficients, are much faster than the other two tests and could be used for highly sparse correlation matrices to speed up the process. For dense correlation matrices though, asymptotic tests can produce a non-negligible bias in the approximated p-values when the null hypothesis is true.

The idea of dependence-correction tests diverges with the methods seen so far in the literature. For instance, the extreme value test proposed in this

paper contrasts with the results by Cai et al. (2014) who test the equality of mean vectors by employing the maximum of the square value of element-wise differences. The authors, as we have also done in Section 7.3 of the appendix, prove that the limiting distribution of the maximum of dependent samples converges to the extreme value distribution of type I under very mild conditions and they examine this limiting distribution to assess the evidence of the test. We estimate the parameters given permuted samples since it is known that the convergence of the parameters to the asymptotic ones is slow and we account for bias that arise in dependent datasets due to estimating correlation of sample correlation coefficients (Olkin and Finn, 1990).

In terms of test power, for a sensible selection of the exceedance threshold, sum of exceedances test is shown to be the most powerful test for sparse alternatives. If the sparsity levels are high, the extreme value also provides competitive results. In contrast, for dense alternatives and small sample size, the average of squares dominates the asymptotic power.

We use 1,320 pathway lists to test equality of gene dependence's structures between normal and cancer human samples in groups of genes that are known to interact together in a cell. A large part of the total number of lists has significantly small p-values. Especially, this happens in the average of squares and sum of exceedances tests. The extreme value test also gives smaller p-values than expected under the null hypothesis but it is more inclined to not reject H_0 than the other two tests. This could be an indication, if H_1 is true, that dependence structures are closer to the dense alternative scenario rather than the sparse scenario.

As future work, we intend to use the sum of exceedances test statistic for higher criticism testing (Donoho and Jin, 2004) as a way to avoid the threshold selection problem and maximize the power of the test.

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7 Appendix

7.1 Variance of mean of squares for dependent samples

Here we proof the result in Lemma 1 that gives the expression of the variance of the average of squares for dependent random variables. Consider n dependent random variables $Z = (z_1, \dots, z_n)$ which marginally follow a standard normal distribution. Take $\mathbf{E}[z_i^2] = \mu_2 = 1$ and $\mathbf{E}[z_i^4] = \mu_4 = 3$ for any $z_i \in Z$ and $\bar{\gamma}_2 = 2(n(n-1))^{-1} \sum_{i < j} \text{cov}(z_i^2, z_j^2)$ which is function of the dependence structure between variables.

The mean square of elements in Z is found by $S^2 = n^{-1} \sum_{i=1}^n z_i^2$ and has variance $\text{var}[S^2] = \mathbf{E}[S^4] - \mathbf{E}[S^2]^2$. The second term is determined by μ_2 such that $\mathbf{E}[S^2]^2 = \mu_2^2$. Moreover, the first term is expressed as

$$\mathbf{E}[S^4] = \mathbf{E}\left[n^{-2} \left(\sum_{i=1}^n z_i^2\right)^2\right] = \mu_4/n + (\bar{\gamma}_2 + \mu_2)(n-1)/n.$$

Hence, $\text{var}[S^2] = (\mu_4 - \mu_2^2)/n + \bar{\gamma}_2(n-1)/n$.

7.2 First and second order statistics for estimated exceedances

We show the expected value and variance of $(|\hat{d}_t| - w_u u)^2 | \hat{d}_t^2 > u^2$ for a general case of d_t being any value. This is used in the paper to obtain the lower bound of the power of the sum of exceedances test, and also to select the threshold u .

7.2.1 Scenario $w_u = 0$

Take $x_t = \hat{d}_t \sim N(d_t, 1)$. Expected value is determined by

$$\begin{aligned} E[x_t^2 | x_t^2 > u^2] &= \frac{\int_u^\infty x_t^2 (2\pi)^{-1/2} e^{-\frac{(x_t-d_t)^2}{2}} dx_t + \int_{-\infty}^{-u} x_t^2 (2\pi)^{-1/2} e^{-\frac{(x_t-d_t)^2}{2}} dx_t}{\Phi(d_t - u) + \Phi(-d_t - u)} \\ &= 1 + d_t^2 + \frac{(u - d_t)\varphi(u - d_t)}{\Phi(d_t - u) + \Phi(-d_t - u)} + \frac{(u + d_t)\varphi(-u - d_t)}{\Phi(d_t - u) + \Phi(-d_t - u)} \\ &\quad + 2d_t \frac{\varphi(u - d_t) - \varphi(-u - d_t)}{\Phi(d_t - u) + \Phi(-d_t - u)} \\ &= 1 + d_t^2 + A + B, \end{aligned} \tag{26}$$

where $A = u\{\varphi(u - d_t) + \varphi(u + d_t)\}/\{\Phi(d_t - u) + \Phi(-d_t - u)\}$ and $B = d_t\{\varphi(u - d_t) - \varphi(u + d_t)\}/\{\Phi(d_t - u) + \Phi(-d_t - u)\}$. If $|d_t| > u$, then $E[x_t^2 | x_t^2 > u^2] \geq d_t^2 + 1$. Under H_0 , where $d_t = 0$, $\mu_0 = 1 + u\frac{\varphi(u)}{1-\Phi(u)}$.

The expression for the variance is

$$\begin{aligned} \text{var}[x_t^2 | x_t^2 > u^2] &= \frac{(2\pi)^{-1/2}[\int_u^\infty x_t^4 e^{-\frac{(x_t-d_t)^2}{2}} dx_t + \int_{-\infty}^{-u} x_t^4 e^{-\frac{(x_t-d_t)^2}{2}} dx_t]}{\Phi(d_t - u) + \Phi(-d_t - u)} - E[x_t^2 | x_t^2 > u^2]^2 \\ &= d_t^4 + d_t^3 D + d_t^2(6 + uC) + d_t(u^2 + 5)D + (u^3 + 3u)C + 3 \\ &\quad - E[x_t^2 | x_t^2 > u^2]^2, \end{aligned} \tag{27}$$

where $C = \{\varphi(u + d_t) + \varphi(u - d_t)\}/\{\Phi(d_t - u) + \Phi(-d_t - u)\}$ and $D = \{\varphi(u + d_t) - \varphi(u - d_t)\}/\{\Phi(d_t - u) + \Phi(-d_t - u)\}$. Under H_0 , $\sigma_0^2 = 3 + (u^3 + 3u)\frac{\varphi(u)}{1-\Phi(u)} - \mu_0^2$.

7.2.2 Scenario $w_u = 1$

Take $x_t = \hat{d}_t \sim N(d_t, 1)$. Expected value is determined by

$$\begin{aligned} E[(|x| - u)_t^2 | x_t^2 > u^2] &= \frac{1}{\sqrt{2\pi}} \left[\frac{\int_u^\infty (x_t - u)^2 e^{-\frac{(x_t-d_t)^2}{2}} dx_t + \int_{-\infty}^{-u} (-x_t - u)^2 e^{-\frac{(x_t-d_t)^2}{2}} dx_t}{\Phi(d_t - u) + \Phi(-d_t - u)} \right] \\ &= E[x_t^2 | x_t^2 > u^2] + u^2 - 2u \frac{\varphi(d_t - u) + \varphi(-d_t - u)}{\Phi(d_t - u) + \Phi(-d_t - u)} \\ &\quad - 2d_t u \frac{\Phi(d_t - u) - \Phi(-d_t - u)}{\Phi(d_t - u) + \Phi(-d_t - u)} \\ &= 1 + d_t^2 + u^2 + A + B - E, \end{aligned} \tag{28}$$

where A and B are defined above, and

$$E = 2u \frac{\varphi(d_t - u) + \varphi(-d_t - u)}{\Phi(d_t - u) + \Phi(-d_t - u)} - 2d_t u \frac{\Phi(d_t - u) - \Phi(-d_t - u)}{\Phi(d_t - u) + \Phi(-d_t - u)}.$$

Note that if $|d_t| > u$, then $E[(|x| - u)_t^2 | x_t^2 > u^2] \geq (|d_t| - u)^2 + 1$ can be used as a lower bound. Under H_0 , $\mu_1 = (u^2 + 1) - u\frac{\varphi(u)}{1-\Phi(u)}$.

The expression for the variance is

$$\begin{aligned} \text{var}[(|x| - u)_t^2 | x_t^2 > u^2] &= \frac{1}{\sqrt{2\pi}} \left[\frac{\int_u^\infty (x_t - u)^4 e^{-\frac{(x_t-d_t)^2}{2}} dx_t + \int_{-\infty}^{-u} (-x_t - u)^4 e^{-\frac{(x_t-d_t)^2}{2}} dx_t}{\Phi(d_t - u) + \Phi(-d_t - u)} \right] \\ &\quad - E[(|x| - u)_t^2 | x_t^2 > u^2]^2 \\ &= E[x_t^4 | x_t^2 > u^2] + 6uE[x_t^2 | x_t^2 > u^2] + u^4 + 4u^3(d_t C - D) - F, \end{aligned} \tag{29}$$

where

$$F = 8uC + 12ud_t^2C + (4ud_t^3 + 12d_tu)(\Phi(d_t - u) - \Phi(-d_t - u))/\{\Phi(d_t - u) + \Phi(-d_t - u)\} \\ + \frac{4u\{(u - d_t)^2\varphi(u - d_t) + (u + d_t)\varphi(u + d_t)\} + 12d_tu\{(u - d_t)\varphi(u - d_t) - (u + d_t)\varphi(u + d_t)\}}{\Phi(d_t - u) + \Phi(-d_t - u)}.$$

$$\text{Under } H_0, \sigma_0^2 = 3 + u^4 + 6u^2 - (5u + u^3)\frac{\varphi(u)}{1 - \Phi(u)} - \mu_1^2.$$

7.3 Gumbel approximation of extreme value test statistic

Let $V_{tj} = \text{cov}(\hat{d}_t, \hat{d}_j)$ be the covariance between two elements in the matrix \hat{D} . For $\text{op} \in \{=, \neq\}$, we define

$$\nu_t^{\text{op}} = \sum_{j \in A} I(V_{tj} \text{ op } 0), \quad A = M \setminus \{t\},$$

so $\nu_t^- + \nu_t^{\neq} = m - 1$. Following sparsity constrains in Meinshausen and Bühlmann (2006), the sparsity level ν_t^{\neq} is assumed to be

$$\nu_t^{\neq} = O(m_t^\eta) = L(m) m^{\eta t},$$

where $0 \leq \eta_t < 1$ and $L(m)$ is a slowly varying function, i.e., $\lim_{m \rightarrow \infty} L(mx)/L(m) \rightarrow 1$. Moreover,

$$\nu_t^- = m - 1 - O(m_t^\eta) = m(1 - m^{-1} - L(m) m^{\eta t - 1}) = m(1 + o(1)) = L(m) m.$$

Assume that $\max_{i < j} |V_{tj}| < 1$ and that there exists a permutation \hat{D}^* of elements in \hat{D} such that $V^* = [\text{cov}(\hat{d}_t^*, \hat{d}_j^*)]$ is block diagonal. Then for all rows in V^* there exists h such that for all $j > h$: $V_{tj}^* = 0$. Let $\epsilon_n \in o(1/\log n)$ and take ϵ any positive number such that $\max_{i < j} |V_{ij}^*| + \epsilon < 1$. Define

$$\rho_n = \begin{cases} \max_{t < j} |V_{tj}| + \epsilon, & n < |j - t| \\ \epsilon_n, & n \geq |k - t|. \end{cases}$$

It then follows that $|V_{tj}^*| < \rho_{|j-t|}$, and $\rho_n \log n \rightarrow 0$ as $n \rightarrow \infty$. This is a sufficient condition (Leadbetter et al., 1983) for the distribution of $T_{MAX} = \max_{t \in M} |\hat{d}_t|$ to converge weakly to a Gumbel distribution.

7.4 Sub-asymptotic model for structured non-stationary processes

The heuristic approach proposed in this section follows results and notation from Aldous (1989). Let $\mathcal{S}_x = \{t \in M : |\hat{d}_t| \geq x\}$ be a random set that, for large x , defines a sparse mosaic on the sub-integer lattice \mathbb{Z}^2 corresponding to the lower triangular matrix M (defined in eq.(2)). We assume a structured dependence structure on the process $(\hat{d}_t : t \in M)$ such that \mathcal{S}_x contains several (near) independent clusters defined by a compound Bernoulli process with cluster intensity $\lambda_x(t)$. Let $C_x(t)$ denote the cluster area (or cardinality) at point t , and assume that as the number of variables increase, $C_x(t)$, in any position $t \in M$, is finite and does not exceed a given constant κ . Besides, assume that $\lambda_x(t)$ and $C_x(t)$ do not vary much as t moves around the same cluster. For $x(m) = \mu(m) + \sigma(m)x$, $x \in \mathbb{R}$, the distribution of $T_M = \max_{t \in M} |\hat{d}_t|$ can be approximated by

$$\begin{aligned} \Pr(T_M < x(m)) &= \Pr(\mathcal{S}_{x(m)} \cap M \text{ empty}) \\ &\doteq \exp\left(-\int_M \lambda_{x(m)}(t) dt\right) \\ &\doteq \exp\left\{-\int_M \frac{\Pr(|\hat{d}| > x(m))}{\mathbb{E}(C_t^{x(m)})} dt\right\} \\ &= \exp\left\{-\Pr(|\hat{d}| > x(m)) \int_M \frac{1}{\mathbb{E}(C_t^{x(m)})} dt\right\} \\ &= \exp\left\{-\Pr(|\hat{d}| > x(m)) \sum_{t \in M} \frac{1}{\mathbb{E}(C_t^{x(m)})}\right\}, \end{aligned}$$

where $\hat{d} \sim N(0, 1)$, $\mathbb{E}(C_t^x)$ is the expected cluster area at cell t and threshold level x . The result obtained above is equivalent to the cumulative distribution function of the cluster maxima for sub-asymptotic models ($u < \sup\{|\hat{d}_t| : \Phi(|\hat{d}_t|) < 1\}$) in a stationary process (Eastoe and Tawn, 2012),

$$\begin{aligned} \Pr(T_M < x) &= \exp\left\{-m\theta_x \Pr(|\hat{d}_t| > x)\right\} \\ &\doteq \exp[-mp_u\theta_x \exp\{-(x-u)/\sigma_u\}], \quad (x \geq u) \end{aligned}$$

when $m\theta_x = \sum_{t=1}^m \frac{1}{\mathbb{E}(C_t^x)}$ and with $p_u = \Pr(|\hat{d}_t| > u)$.

7.5 Asymptotic power

Let's first acknowledge the Mill's ratio which approximates $\Phi(-x) \doteq \frac{\varphi(x)}{x}$, where $\varphi(x) = e^{-\frac{1}{2}x^2}$, when x is large. We recall that we use the set of variables

($\hat{d}_t : t \in M$), with $m = \text{card}(M)$ such that $\mathcal{S}_d = \{t \in M : d_t \neq 0\}$ and $s = \text{Card}(\mathcal{S}_d)$ is the sparsity level. We assume that $|g(r_{Y_t}) - g(r_{X_t})| = \delta_t$ for all $t \in \mathcal{S}_d$ with $d_t = \sqrt{n-3}\delta_t$. Moreover, we consider normality for the Fisher transform correlation differences such that for all $t \in \mathcal{S}_d$, $\hat{d}_t \sim N(\delta_t, (n-3)^{-1})$ and for all $t \notin \mathcal{S}_d$, $\hat{d}_t \sim N(0, (n-3)^{-1})$.

The power of the test is given by the probability of rejecting the null hypothesis when the H_1 is true. Hence, the objective is to find the test that provides the maximum power. For all tests ($q = s, m, e$), we define a rejecting level $t_{q,\alpha}$ such that we reject the null hypothesis when the observed test statistic is larger than $t_{q,\alpha}$ at significance level α .

7.5.1 Asymptotic power for average of squares test

Here we assume that the test statistic T_S defined in eq. 6 of the main paper is well approximated by a normal distribution under both H_0 and H_1 . We define μ_{H_0} and $\sigma_{H_0}^2$ as the expected value and variance of T_S when H_0 holds. Moreover, μ_{H_1} and $\sigma_{H_1}^2$ are the correspondent expected value and variance of T_S when H_1 holds. The power of the average of squares test is

$$\Pr(T_S \geq t_{S,\alpha} | H_1) \doteq \Pr\left(Z \geq \frac{\mu_{H_1} - t_{S,\alpha}}{\sqrt{\sigma_{H_1}^2}}\right), \quad (30)$$

approximated using the Mill's ratio, with rejecting level given by $t_{S,\alpha} = \mu_{H_0} + z_\alpha \sqrt{\sigma_{H_0}^2}$.

Denote $\delta_0^2 = \sum_{t \in \mathcal{S}_d} \delta_t^2$ and recall that $\bar{\gamma}_2 = 2(m^2 - m)^{-1} \sum_{t < h} \text{cov}(\hat{d}_t^2, \hat{d}_h^2 | H_0)$. Under H_0 , the parameters $\mu_{H_0} \doteq 1$ and $\sigma_{H_0}^2 \doteq \frac{2}{m} \{1 + (m-1)\bar{\gamma}_2/2\}$. The expected value of T_S under H_1 is found by a weighted average $\mu_{H_1} = (m-s)\mu_0/m + s\mu_1/m$ with $\mu_0 = \mathbf{E}[\hat{d}_t^2 | t \notin \mathcal{S}_d] \doteq 1$ and $\mu_1 = \text{var}[\hat{d}_t | t \in \mathcal{S}_d] + \mathbf{E}[\hat{d}_t | t \in \mathcal{S}_d]^2 \doteq 1 + d_t^2$. Similarly, the parameter $\sigma_{H_1}^2$ can be found by the variance of a weighted average, so $\sigma_{H_1}^2 = 2/m(1 + 2s(n-3)\delta_0^2/m + (m-1)\bar{\gamma}'_2/2)$ where $\bar{\gamma}'_2 = 2(m^2 - m)^{-1} \sum_{t < h} \text{cov}(\hat{d}_t^2, \hat{d}_h^2 | H_1)$. Note that $\bar{\gamma}'_2$ is different to $\bar{\gamma}_2$ as it depends on the values ($d_t, t \in \mathcal{S}_d$). Plugging in the expressions for $t_{S,\alpha}$, μ_{H_1} and $\sigma_{H_1}^2$ in (30), we obtain the stated expression for the power.

7.5.2 Asymptotic power of the extreme value test

We assume $(\hat{d}_t) \sim MVN$, $t \in M$ under both H_0 and H_1 . Hence, the maximum $T_M = \max_{t \in M} |\hat{d}_t|$, in the limit, is well represented by a Gumbel distribution. We further define the parameters $\mu_t = \mathbf{E}[\hat{d}_t | t \in \mathcal{S}_d]$,

$\sigma_t^2 = \text{var}[\hat{d}_t \mid t \in \mathcal{S}_d]$ with $|\mu_t|$ being sufficiently large. Assume independence on the sequence (\hat{d}_t) , the power of the extreme value test is defined by

$$\begin{aligned} \Pr(T_M \geq t_{M,\alpha} \mid H_1) &= 1 - \Pr(|d_t| < t_{M,\alpha}, \forall t) \geq 1 - \Pr(|d_t| < t_{M,\alpha} : t \in \mathcal{S}_d) \\ &= 1 - \Pr\left(\frac{-t_{M,\alpha} - \mu_t}{\sigma_t} < Z_t < \frac{t_{M,\alpha} - \mu_t}{\sigma_t}, t \in \mathcal{S}_d\right) \\ &\geq 1 - \Pr\left(Z_t < \frac{t_{M,\alpha} - |\mu_t|}{\sigma_t}, t \in \mathcal{S}_d\right), \end{aligned}$$

where $Z_t = (|d_t| - \mu_t)/\sigma_t$. The rejecting level $t_{M,\alpha}$ is found using the quantile function of the Gumbel distribution that in the limit ascertains that

$$Q_G(\alpha) \doteq (2 \log 2m)^{1/2} - \frac{\log \log 2m + \log(4\pi \log_2 2)}{2(2 \log 2m)^{1/2}} - \frac{\log(-\log(\alpha))}{(2 \log 2m)^{1/2}}.$$

We use the main term of the expression to find $Q_G(\alpha)$ such that

$$t_{M,\alpha} = (2 \log 2m)^{1/2} - \frac{\log(-\log(\alpha))}{(2 \log 2m)^{1/2}} > Q_G(\alpha).$$

For the expected value of the test statistic under H_1 we use $|\mu_t| \doteq \delta_t \sqrt{n-3}$, and for the variance we approximate $\sigma_t^2 \doteq \text{var}(\hat{d}_t) \doteq 1$, for all $t \in \mathcal{S}_d$.

If $s = |\mathcal{S}_d| \rightarrow \infty$ and the conditions of the Gumbel approximation described in Section 7.3 hold (namely that the maximum correlation between pairs of d_t , $t \in \mathcal{S}_d$, is bounded above by a constant strictly less than 1), we have

$$\begin{aligned} \Pr(T_M \geq t_{M,\alpha} \mid H_1) &\geq 1 - \Pr\left(Z_t < \frac{t_{M,\alpha} - \min_{t \in \mathcal{S}_d} |\mu_t|}{\sigma_t}, t \in \mathcal{S}_d\right) \\ &\geq 1 - \exp\{-\exp\{-(2 \log 2s)^{1/2}[(n-3)^{1/2} \min_{t \in \mathcal{S}_d} \delta_t - (2 \log 2m)^{1/2} + (2 \log 2s)^{1/2}]\}\} \\ &\approx 1 - \exp\{-\exp\{-(2 \log 2s)^{1/2}[(n-3)^{1/2} \min_{t \in \mathcal{S}_d} \delta_t - (2 \log 2m)^{1/2}]\}\}. \end{aligned}$$

If $s = |\mathcal{S}_d|$ is a constant, then, using the Mill's ratio to approximate the normal probabilities,

$$\begin{aligned} \Pr(T_M \geq t_{M,\alpha} \mid H_1) &\geq 1 - \Pr\left(Z_t < \frac{t_{M,\alpha} - |\mu_t|}{\sigma_t}, t \in \mathcal{S}_d\right) \geq 1 - \min_{t \in \mathcal{S}_d} \Pr\left(Z_t < \frac{t_{M,\alpha} - |\mu_t|}{\sigma_t}\right) \\ &\geq 1 - \min_{t \in \mathcal{S}_d} \exp\left[-\frac{1}{2} \left\{ (n-3)^{1/2} \delta_t - \left((2 \log 2m)^{1/2} - \frac{\log(-\log(\alpha))}{(2 \log 2m)^{1/2}} \right) \right\}^2\right] \\ &\approx 1 - \min_{t \in \mathcal{S}_d} \exp\left[-\frac{1}{2} \left\{ (n-3)^{1/2} \delta_t - (2 \log 2m)^{1/2} \right\}^2\right]. \end{aligned}$$

7.5.3 Asymptotic power of the exceedances test

We set an arbitrary large threshold u , such that we define set $\mathcal{S}_u = \{t \in M : |\hat{d}_t| > u\}$. We define the probabilities $\eta_0 = \Pr(t \in \mathcal{S}_u \mid t \notin \mathcal{S}_d)$ and $\eta_t = \Pr(t \in \mathcal{S}_u \mid t \in \mathcal{S}_d)$ as well as the standard normal distribution density function at quantile u which we denote by $\varphi(u)$. Under both H_0 and H_1 , we approximate the test statistic $T_E^{(w)}$ described in eq. (6) by a normal distribution. We define $\mu_{H_0}(m, w)$ and $\sigma_{H_0}^2(m, w)$ as the expected value and variance of $T_E^{(w)}$ when H_0 holds. Moreover, $\mu_{H_1}(m, w)$ and $\sigma_{H_1}^2(m, w)$ are the correspondent expected value and variance of $T_E^{(w)}$ when H_1 holds. To find both $\mu_{H_1}(m, w)$ and $\sigma_{H_1}^2(m, w)$, we redefine the measures in eq.(17) by assuming that the expected value of \hat{d}_t can be different from zero for some $t \in M$:

$$\begin{aligned}\gamma_{utj}^{(H1,w)} &= \text{cov}((|\hat{d}_t| - uw)^2, (|\hat{d}_j| - uw)^2 \mid \hat{d}_t^2 > u, \hat{d}_j^2 > u), \\ \eta_t &= \Pr(|\hat{d}_t| > u), \\ \phi_{tj}^{H1} &= \Pr(\hat{d}_t^2 > u^2, \hat{d}_j^2 > u^2),\end{aligned}$$

The power is described by

$$\Pr(T_E^{(w)} \geq t_{E,\alpha}^{(w)} \mid H_1) \doteq \Pr\left(Z \geq \frac{\mu_{H_1}(m, w) - t_{E,\alpha}^{(w)}}{\sqrt{\sigma_{H_1}^2(m, w)}}\right),$$

where $\mu_{H_1}^{(w)} = (m - s)\eta_0\mu_w + \sum_{t \in \mathcal{S}_d} \eta_t \mu_{t_w}$, rejecting level $t_{E,\alpha}^{(w)} = \mu_{H_0}^{(w)} + z_\alpha \sqrt{\sigma_{H_0}^2(m, w)}$, and

$$\sigma_{H_1}^2(m, w) = \sum_{t \in \mathcal{S}_d} \eta_t \{(1 - \eta_t) \mu_{t_w}^2 + \sigma_{t_w}^2\} + (m - s)\eta_0 \{(1 - \eta_0) \mu_w^2 + \sigma_w^2\} + C_w,$$

where $C_w = \sum_{t,h \in M, t \neq h} (\gamma_{ut_h}^{(H1,w)} + \mu_{t_w} \mu_{h_w}) \phi_{th}^{H1} - \eta_t \mu_{t_w} \eta_{h_w} \mu_{h_w}$ is different from zero if elements in \hat{D}^2 are dependent. Let $\mu_{H_0}(m, w) = \mu(m, w)$ and $\sigma_{H_0}^2(m, w) = \sigma^2(m, w)$ defined by eq. (18). The lower bound for the asymptotic power of sum of exceedances test, with $w = \{0, 1\}$, is

$$\Pr(T_E^{(w)} \geq t_{E,\alpha}^{(w)} \mid H_1) \geq 1 - \exp\left\{-\frac{1}{2} \left(\frac{\sum_{t \in \mathcal{S}_d} \mu_{t_w} \eta_t - s \eta_0 \mu_w - z_\alpha \sigma_{H_0}(m, w)}{\sigma_{H_1}(m, w)}\right)^2\right\}.$$

Let $\mathcal{S}_{du} = \{t \in M, |d_t| \gg u\}$ with $s_u = |\mathcal{S}_{du}|$. For $w = 0$, when $(n, m, u) \rightarrow \infty$, under weak independence, i.e., $C_w \ll \sigma_{H_1}^2(m, w)$, the asymptotic power leading terms are

$$\frac{\sum_{t \in \mathcal{S}_{du}} d_t^2 - B_0(s\eta_0^{1/2} + z_\alpha(2m)^{1/2})}{\sqrt{\sum_{t \in \mathcal{S}_{du}} d_t^2 + mB_0^2}},$$

where $B_0 = u^2 \eta_0^{1/2}$. Let $\delta_{00}^2 = s_u^{-1} \sum_{t \in \mathcal{S}_{du}} d_t^2$, asymptotic recovery condition is

$$\delta_{00}^2 \gg \frac{u^2 \max(1, s\eta_0, (2m\eta_0)^{1/2})}{n s_u},$$

If $s_u = k \max(1, s\eta_0, (2m\eta_0)^{1/2})$, for any positive integer k , and $d_t^2/u^2 \rightarrow \infty$, for any $t \in \mathcal{S}_{du}$, $\Pr(T_E^{(0)} \geq t_{E,\alpha}^{(0)} | H_1) \rightarrow 1$.

Similarly for $w = 1$, when $(n, m, u) \rightarrow \infty$, $\mu_1 \approx 2/(u^2 - 1)$ and $\sigma_1^2 \approx 4/(u^2 - 1)^2$ (these rates can be found using L'Hospital rule), and similar weak independence conditions, the asymptotic power leading terms are

$$\frac{\sum_{t \in \mathcal{S}_{du}} |d_t| - u^2 - B_1(s_u \eta_0^{1/2} + z_\alpha(2m)^{1/2})}{\sqrt{\sum_{t \in \mathcal{S}_{du}} |d_t| - u^2 + 2mB_1^2}},$$

where $B_1 = 2\eta_0/(u^2 - 1)$. Let $\delta_{01}^2 = s_u^{-1} \sum_{t \in \mathcal{S}_{du}} (|d_t| - u)^2$, asymptotic recovery condition is

$$\delta_{01}^2 \gg 2/(u^2 + 1) \frac{\max(1, s\eta_0, (2m\eta_0)^{1/2})}{s_{du}},$$

If $s_u = k \max(1, s\eta_0, (2m\eta_0)^{1/2})$, for any positive integer k , and $d_t^2/u^2 \rightarrow \infty$, for any $t \in \mathcal{S}_{du}$, $\Pr(T_E^{(1)} \geq t_{E,\alpha}^{(1)} | H_1) \rightarrow 1$.

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