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Testing for Inequality Constraints in Singular Models by Trimming or Winsorizing the Variance Matrix

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ABSTRACT

There are many applications in which a statistic follows, at least asymptotically, a normal distribution with a singular or nearly singular variance matrix. A classic example occurs in linear regression models under multicollinearity but there are many more such examples. There is well-developed theory for testing linear equality constraints when the alternative is two-sided and the variance matrix is either singular or nonsingular. In recent years, there is considerable, and growing, interest in developing methods for situations in which the estimated variance matrix is nearly singular. However, there is no corresponding methodology for addressing one-sided, that is, constrained or ordered alternatives. In this article, we develop a unified framework for analyzing such problems. Our approach may be viewed as the trimming or winsorizing of the eigenvalues of the corresponding variance matrix. The proposed methodology is applicable to a wide range of scientific problems and to a variety of statistical models in which inequality constraints arise. We illustrate the methodology using data from a gene expression microarray experiment obtained from the NIEHS’ Fibroid Growth Study. Supplementary materials for this article are available online.

1. Introduction

A common problem in many applications is to compare two or more ordered experimental groups in terms of one or more outcome variables. For example, a toxicologist may be interested in comparing different dose groups in terms of several outcomes such as body weight, red blood cell count, hematocrits and so forth. Often the statistical problem reduces to drawing inferences regarding a parameter \( \theta \in \mathbb{R}^p \) using a statistic \( S_n \), which, under suitable standardization and regularity conditions, is asymptotically normally distributed, that is,

\[
\sqrt{n}(S_n - \theta) \Rightarrow N_p(0, \Sigma)
\]  

(1)

as \( n \to \infty \) where \( \Rightarrow \) denotes convergence in distribution. The statistic \( S_n \) may be a vector of differences among means, a collection of rank statistics or an estimator of a regression parameter. In general, \( \Sigma \) is unknown and must be estimated from the data; furthermore \( \Sigma \) may be nonsingular, singular, or nearly singular. By nearly singular we mean that its condition number, that is, the ratio of its largest to its smallest eigenvalue, is extremely large. As an example, near singularity arises in regression models due to multicollinearity (Silvey 1969; Montgomery and Peck 2012). It is well known that common statistical methods, especially those based on matrix inversion, perform poorly when \( \Sigma \) is nearly singular and cannot be directly used when \( \Sigma \) is singular.

Unconstrained statistical inference when the underlying variance matrix is singular is well studied in the context of linear regression (Khatri 1968; Rao and Mittra 1971; Rao 1972), where \( \Sigma \) is typically known up to a constant. However, in many applications \( \Sigma \) must be estimated from the data. Moreover, \( \Sigma \) and/or its estimator denoted here by \( \Sigma_n \), may be singular and, additionally, their rank may not be known in advance. Unconstrained inference in such settings has been addressed by numerous authors in the statistical and econometric literature. Some examples include Moore (1977), Andrews (1987), Hadi and Wells (1990, Hadi and Wells 1991), Lutkepohl and Burda (1997), Dufour and Valery (2015), and Duplinskiy (2014). We note that in nonlinear regression singularity or near singularity of the variance matrix is rather common. For example, in the context of quantitative high throughput screening (qHTS) assays, where thousands of chemicals are evaluated for toxicity using cell lines, Lim, Sen, and Peddada (2013) noticed that the condition number of the information matrix may be very large; sometimes as large as \( 10^9 \) or higher. Hadi and Wells (1990) provided examples of nonlinear models for which the information matrix is singular for some values of the model parameters; in fact, these are often the values specified by the null hypothesis. Another mechanism by which singular variance matrices arise is when \( \theta = h(\eta) \), \( \eta \) is estimated by \( \hat{\eta}_n \) and the Jacobian of \( h \) is rank deficient. This leads, by the \( \delta \)-method, to a singular variance matrix.

When the experimental groups are naturally ordered researchers are often interested in performing one-sided tests in which case the parameter space under the alternative hypothesis is not a linear subspace but a convex cone, denoted by \( C \). Tests for equality against an ordering are often formalized as

\[
H_0 : \theta \in \mathcal{L} \quad \text{versus} \quad H_1 : \theta \in C \setminus \mathcal{L},
\]  

(2)

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where $\mathcal{L}$ is a linear subspace and $\mathcal{L} \subset \mathcal{C} \subset \mathbb{R}^p$. In practice, $\mathcal{L}$ is often the singleton $\{0\}$ and $\mathcal{C}$ is often defined by a finite set of linear inequalities. The theory for such testing problems is well developed, see Silvapulle and Sen (2005), when both $\mathbf{\Sigma}$ and its estimator $\hat{\mathbf{\Sigma}}$ are nonsingular. Models, both parametric and nonparametric, in which the variance matrix is known to be singular and in which testing (2) is of interest arise in a wide range of scientific problems, such as dose–response studies. A concrete example will be discussed in more detail later on. We are not aware of a general theory or methodology for ordered inference when $\mathbf{\Sigma}$ and/or $\hat{\mathbf{\Sigma}}$ are singular or nearly singular. In this article, we address this open class of problems in a principled manner. Pioneered by Dixon (1960) and Tukey (1962), trimming and winsorizing data are two well-known strategies for dealing with extreme observations, or outliers, and are widely used in robust statistics (Huber and Ronchetti 2009). Inspired by the use of trimming and winsorizing in classical data analysis, in this article we develop trimming and winsorizing-based approaches to address near singularities in multivariate data. In this setting, the role of outliers is played by eigenvalues that are associated with a large condition number, that is, the eigenvalues that are different from zero but much smaller than the largest eigenvalue. These are exactly the eigenvalues that create challenges when analyzing multivariate data. Our proposed methodology builds on and extends the existing methods developed for unconstrained singular models as referenced earlier.

The article is organized in the following way. In Section 2, we develop a modified likelihood ratio test assuming a known singular variance matrix. In Section 3, we extend the methodology to the case of unknown, possibly singular, or nearly singular variance matrices by introducing trimmed and winsorized tests. Since these two tests depend upon a threshold parameter, specified by the user, we modify them by introducing corresponding data-driven supremum type tests that do not require any input from the data analyst. The performance of the proposed tests in terms of their Type I errors and powers was evaluated using an extensive simulation study. The study design and results are summarized in Section 4. In Section 5, we describe the NIEHS Fibroid Growth Study (FGS) of Peddada et al. (2008) and illustrate our proposed methodology by reanalyzing gene expression data obtained in FGS. Although there have been studies in which single genes have been correlated with tumor size (see Grandhi, Guo, and Peddada 2016), to the best of our knowledge there are no studies in which a collection of genes, or a pathway, were correlated with tumor size; thus, as far as we know, this is the first article that performs such a multivariate analysis. Section 6 provides a brief summary and further discussion. Additional results, as well as all proofs, are provided in the online supplementary text.

2. Known Singular Variance Matrix

Since $\mathbf{\Sigma}$ is symmetric and nonnegative definite, we may write its spectral decomposition as $\mathbf{\Sigma} = \mathbf{E} \mathbf{\Lambda} \mathbf{E}^T$ where $\mathbf{E}$ is an orthogonal matrix whose columns are the eigenvectors of $\mathbf{\Sigma}$ and $\mathbf{\Lambda}$ is a diagonal matrix with nonnegative elements $\lambda_1, \ldots, \lambda_p$, which are the eigenvalues of $\mathbf{\Sigma}$. Without loss of generality assume that $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_p$. Moreover if $\mathbf{\Sigma}$ is singular then $q = \text{rank}(\mathbf{\Sigma}) < p$ and thus $\lambda_i > 0$ when $i \leq p - q$ and $\lambda_i = 0$ when $i \geq p - q + 1$. It is well known that the Moore–Penrose generalized inverse of $\mathbf{\Sigma}$ denoted by $\mathbf{\Sigma}^+$ is equal to $\mathbf{E} \mathbf{\Lambda}^+ \mathbf{E}^T$ where $\mathbf{\Lambda}^+$ is a diagonal matrix with elements $1/\lambda_i$ if $i \leq p - q$ and 0 otherwise. Let $\mathbf{M}$ be the $q \times p$ matrix obtained by dropping the last $p - q$ rows of the matrix $(\mathbf{\Lambda}^+)^{1/2} \mathbf{E}^T$, which are easily verified to be identically zero. Finally, let $\mathbf{S}(\mathbf{\Sigma})$ denote the column space of $\mathbf{\Sigma}$. We shall index by “$\leq$” the intersection of any set with $\mathbf{S}(\mathbf{\Sigma})$. Thus, we define $\mathcal{L}_s = \mathcal{L} \cap \mathbf{S}(\mathbf{\Sigma})$, $\mathcal{C}_s = \mathcal{C} \cap \mathbf{S}(\mathbf{\Sigma})$, and $\mathcal{R}_s = \mathcal{R} \cap \mathbf{S}(\mathbf{\Sigma})$, where $\mathcal{R}_s = \mathcal{C} \cap \mathcal{L}_s^*$ and $\mathcal{L}_s^*$ is the orthogonal complement of $\mathcal{L}_s$. Clearly, $\mathcal{L}_s$ is a linear space, and $\mathcal{C}_s$ and $\mathcal{R}_s$ are convex cones.

The following theorem defines, and then describes, the distribution of the modified likelihood ratio test (mLRT) assuming a normal model with a known singular variance matrix. We use the qualification modified for the LRT because the singular normal distribution does not have a density and therefore the LRT does not exist.

**Theorem 1.** Consider testing (2) when $\mathbf{Y} \sim \mathcal{N}_q(\mathbf{\Theta}, \mathbf{\Sigma})$ and $\mathbf{\Sigma}$ is known and singular. Assume that $\mathbf{0} \in \text{support}(\mathbf{Y})$. Then, if $\mathcal{C}_s \neq \{\mathbf{0}\}$ the mLRT exists and is given by

$$
T = \mathbf{Y}^T \mathbf{\Sigma}^+ \mathbf{Y} - \min \{ (\mathbf{Y} - \mathbf{\Theta})^T \mathbf{\Sigma}^+ (\mathbf{Y} - \mathbf{\Theta}) : \mathbf{\Theta} \in \mathcal{R}_s \}. 
$$

(3)

Furthermore in the notation of Silvapulle and Sen (2005), under the null the statistic (3) is distributed as $\chi^2(I_q, \mathbf{M}\mathcal{R}_s)$, which is defined by

$$
\chi^2 = \mathbf{X}^T \mathbf{X} - \min \{ (\mathbf{X} - \mathbf{\eta})^T (\mathbf{X} - \mathbf{\eta}) : \mathbf{\eta} \in \mathbf{M}\mathcal{R}_s \},
$$

(4)

where $\mathbf{X} \in \mathcal{N}_q(\mathbf{Y}_q, \mathbf{I}_q)$ random variable (RV) and $\mathbf{I}_q$ is the $q \times q$ identity matrix.

Theorem 1 generalizes several results published in the literature. First, it generalizes Theorem 3.7.1 in Silvapulle and Sen (2005) to the case where $\mathbf{\Sigma}$ is not a full rank matrix. Next it generalizes Lemmas 1 and 2 in Moore (1977), originally discovered by Khatri (1968) and Rao and Mitra (1971), from two-sided to one-sided hypotheses. In the proof of Theorem 1, it is shown that there are two equivalent forms for the mLRT, (3) and (4); the distribution of the mLRT is an immediate consequence of this equivalence. In other words, it is shown that testing (2) with a singular $\mathbf{\Sigma}$ is equivalent to testing $H_0 : \mathbf{\Theta} = \mathbf{0}$ versus $H_1 : \mathbf{\Theta} \in \mathbf{M}\mathcal{R}_s$ based on a random variable (RV) $\mathbf{X}$ distributed as $\mathcal{N}_q(\mathbf{Y}_q, \mathbf{I})$ where $\mathbf{M}\mathcal{R}_s = \{ \mathbf{M}\mathbf{\Theta} : \mathbf{\Theta} \in \mathcal{R}_s \}$ is a cone. Thus, the original problem is solved by the usual procedure but in a lower dimensional space. Effectively the test is carried out as if $\mathcal{L} \subset \mathcal{C} \subset \mathbf{S}(\mathbf{\Sigma})$ but we need not specify that in advance. This feature is of practical importance when $\mathbf{\Sigma}$ is unknown as in Section 3. It is also important to note that Theorem 1 remains valid if we replace the Moore–Penrose inverse $\mathbf{\Sigma}^+$ with any other generalized inverse $\mathbf{\Sigma}^*$ and choose instead of $\mathbf{M}$, as defined above, any $q \times p$ matrix $\mathbf{N}$ that satisfies $\mathbf{\Sigma}^* = \mathbf{N}^T \mathbf{N}$.

The statistic (3) may be computed using low-rank quadratic programming (see Boyd and Vandenberghe 2004) where the cone $\mathcal{R}_s$ is given in Proposition 1. In some applications, there may be an interest in computing (4) directly, which requires expressing the cone $\mathbf{M}\mathcal{R}_s$ in standard form, that is, as $\{ \mathbf{\eta} \in \mathbb{R}^q : \mathbf{D}\mathbf{\eta} \geq \mathbf{0} \}$ for some matrix $\mathbf{D}$. In some cases, the cone $\mathbf{M}\mathcal{R}_s$ may be found by simple and direct analysis. In general, though, this is not the case. Fortunately, a broadly applicable scheme
for explicitly finding the inequalities defining $MR_\ast$ is available and known as the double description method (Avis and Fukuda 1992). Explaining the underlying key ideas requires some additional notation. Assume for now that $C$ is a polyhedral pointed convex cone, that is, $C = \{\theta \in \mathbb{R}^p : C\theta \geq 0\}$ for some restriction matrix $C$ with a finite number of rows. This form is referred to as the $H$-representation of $C$ ($H$ for half-planes). Alternatively, by the Minkowski–Weyl Theorem (see Proposition 3.12.10 in Silvapulle and Sen 2005), $C$ can be also expressed as

$$C = \text{cone}(\theta_1, \ldots, \theta_m) = \{\lambda_1\theta_1 + \cdots + \lambda_m\theta_m : \lambda_1, \ldots, \lambda_m \geq 0\},$$

where the set $\{\theta_1, \ldots, \theta_m\}$ contains the extreme rays of $C$. This form is referred to as the $V$-representation of $C$ ($V$ for vertices). Recall that an extreme ray in a convex cone $C$ is an element $\theta \in C$, such that if $\theta = \theta_1 + \theta_2$ with $\theta_1, \theta_2 \in C$ then $\theta = \lambda_1\theta_1$, or $\theta = \lambda_2\theta_2$ for some $\lambda \geq 0$. The set of extreme rays of $C$ is denoted by $\text{extr}(C)$. Clearly, if $\theta$ is an extreme ray so is $\lambda\theta$ for all $\lambda \geq 0$, thus for convenience we will pick only one element from this equivalence class. Since $C = \text{cone}(\text{extr}(C))$, the extreme rays are those elements that are necessary for generating the cone. Both the $H$-representation and the $V$-representation may be redundant, that is, the matrix $C$ may include unnecessary rows and the set $\{\theta_1, \ldots, \theta_m\}$ may contain unnecessary rays. Such redundancies can always be removed. The conversion from the $H$-representation to the $V$-representation is known as the vertex enumeration problem and the reverse as the facet enumeration problem, see Lauritzen (2011) for a beautiful account of the theory that involves polyhedral geometry and computational linear algebra. Both conversions are used for computing the standard form of the cone $MR_\ast$.

**Proposition 1.** Let $C = \{\theta \in \mathbb{R}^p : C\theta \geq 0\}$ and let $L$ and $S$ be matrices, the rows of which are bases for $L$ and $S(\Sigma)^\perp$, respectively. Then

$$MR_\ast = \text{cone}(\text{extr}(M\theta) : \theta \in \text{extr}(R_\ast)),$$

where $R_\ast = \{\theta \in \mathbb{R}^p : R\theta \geq 0\}$ and $R_\ast^T = (C^T, L^T, -L^T, S^T, -S^T)$.

By Proposition 1, $MR_\ast$ is the conic combination of the finite set $\text{extr}(M\theta)$ where $\theta \in \text{extr}(R_\ast)$. The $H$-representation for $R_\ast$ is given in Proposition 1, hence finding $\text{extr}(R_\ast)$ requires the solution of a vertex enumeration problem. Proposition 1 provides a $V$-representation of $MR_\ast$ from which an $H$-representation is found via a facet enumeration problem. In some settings, intermediate, redundancy removal steps, may be applied. Although Proposition 1 discusses only convex polyhedral cones, with suitable modifications, it can be generalized to arbitrary convex cones.

Finally, it is well known that if $T \sim \mathcal{N}(I_q, MR_\ast)$ then

$$\mathbb{P}(T \geq c) = \sum_{j=1}^{q} w_j \mathbb{P}\left(\chi_j^2 \geq c\right),$$

where $w_j = \omega_j(I_q, MR_\ast)$, $j = 0, \ldots, q$ are nonnegative weights that sum to unity and are functions of the constraints specified in the alternative hypothesis. The weights can be computed in closed form, when $q \leq 4$ and $MR_\ast$ is the orthant, or some other simple cone. Otherwise the weights or the entire distribution may be estimated by simulation as discussed in detail by Silvapulle and Sen (2005).

### 3. Unknown and Possibly Singular Variance Matrix

Theorem 1 shows how to test (2) when (1) holds and $\Sigma$ is a fixed known singular matrix. However, in most situations $\Sigma$ is unknown and thus needs to be estimated along with $\theta$. Let $\hat{\Sigma}_n$ denote an estimator of $\Sigma$, which is assumed to be symmetric and nonnegative definite. We will further assume that $\hat{\Sigma}_n$ is consistent and that

$$b_n(\hat{\Sigma}_n - \Sigma) \Rightarrow Q,$$  \hspace{1cm} (5)

where $Q$ is a matrix valued RV and $b_n \to \infty$ is a sequence of constants; usually $b_n = \sqrt{n}$. Note that $\hat{\Sigma}_n$ need not be singular for some, or even all finite $n$, even if $\Sigma$ is singular. Conversely, $\hat{\Sigma}_n$ may be singular even if $\Sigma$ is not. As noted in Andrews (1987), if $\text{rank}(\Sigma) = \text{rank}(\hat{\Sigma}_n)$ then quadratic forms associated with $\hat{\Sigma}_n$ may not converge to those associated with $\Sigma$ due to the discontinuity of generalized inverses, that is, $X_n^T\hat{\Sigma}_nX_n$ may not converge to $X^T\Sigma^+X$ even if $X_n \to X$ and $X_n \to \Sigma$. Hence, quadratic form-based statistics, such as projected tests common in order restricted inference, may not converge to their assumed limits.

#### 3.1. Trimmed Tests

To overcome the above noted problem, we trim the variance matrix by dropping all eigenvalues smaller than some prespecified $\varepsilon$. Formally,

**Definition 1.** Let $\varepsilon > 0$. We refer to the matrix $\Sigma_T(\varepsilon) = E_\varepsilon^T\Lambda_T(\varepsilon)E_\varepsilon^T$, where $\Lambda_T(\varepsilon)$, which is the diagonal matrix obtained from $\Lambda$ by replacing any element of $\Lambda$, which is smaller than $\varepsilon$ by 0, as the $\varepsilon$-trimmed variance matrix. Its Moore–Penrose inverse, that is, $E_\varepsilon^T\Lambda_T(\varepsilon)^+E_\varepsilon$ is referred to as the $\varepsilon$-trimmed inverse of $\Sigma$ and denoted by $\Sigma_T^+(\varepsilon)$.

For convenience, we now drop the subscript $T$ whenever possible. Let $\hat{\Sigma}_n(\varepsilon)$ denote the trimmed variance, then its Moore–Penrose inverse, that is, the matrix $\Sigma_n(\varepsilon)$ equals $E_n^T\Lambda_n^+(\varepsilon)E_n$, where $\Lambda_n^+(\varepsilon)$ is a diagonal matrix whose elements are $1/\lambda_{i,n}$ if $\lambda_{i,n} \geq \varepsilon$ and 0 otherwise. Dufour and Valery (2015) referred to $\Sigma_n^+(\varepsilon)$ as the spectral cut-off Moore–Penrose inverse. We now introduce a database-based test for (2), which is motivated by the mLRT for normal means given in (3) and the above definition, that is, for each $n$ we define the trimmed constrained test statistic as

$$T_n(\varepsilon_n) = \min \left\{ \frac{1}{n}(S_n - \theta)^T\Sigma_n^+(\varepsilon_n)(S_n - \theta) : \theta \in \mathcal{L}_n^\ast \right\} - \min \left\{ \frac{1}{n}(S_n - \theta)^T\Sigma_n^+(\varepsilon_n)(S_n - \theta) : \theta \in \mathcal{C}_n^\ast \right\},$$  \hspace{1cm} (6)

where $\mathcal{L}_n^\ast = \mathcal{L}_n(\varepsilon_n) = \mathcal{L} \cap S(\Sigma_n(\varepsilon_n))$, $\mathcal{C}_n^\ast = \mathcal{C}_n(\varepsilon_n) = \mathcal{C} \cap S(\Sigma_n(\varepsilon_n))$, and $S(\Sigma_n(\varepsilon_n))$ is the column space of $\Sigma_n(\varepsilon_n)$. Note that by definition $T_n(\varepsilon_n)$ is a function of the threshold $\varepsilon_n$. Since in general the value of the smallest eigenvalue may not be known in advance, it is appropriate to allow $\varepsilon_n$ to vary with $n$. If
\(\varepsilon_n \to 0\) we denote \(T_n(\varepsilon_n)\) by \(T_n\). The limiting distribution of \(T_n\) is given below; a discussion of the statistic \(T_n(\varepsilon)\) for a fixed \(\varepsilon\) is deferred to Section 3.2.

**Theorem 2.** Consider testing (2). Suppose that (1) holds and the limit distribution satisfies the conditions of Theorem 1. In addition suppose that \(\Sigma_n\) satisfies (5). Then under \(H_0\) and for any sequence of cut-off values \{\(\varepsilon_n\)\} satisfying \(\varepsilon_n \to 0\) and \(b_n\varepsilon_n \to \infty\), we have

\[
T_n \Rightarrow \chi^2(I_d, M R_+),
\]

where \(d, M, \text{ and } R_+\) were defined in the context of Theorem 1.

Theorem 2 shows that Theorem 1 can be extended to the case where \(\Sigma\) is unknown. Note that if \(\lambda_q\), the value of the smallest nonzero eigenvalue of \(\Sigma\), were known, then Theorem 2 would hold with any fixed \(\varepsilon < \lambda_q\). Similarly, if \(\lambda_q\) were known then simply set the smallest \(p - q\) eigenvalues to be zero. However, in practice \(q\) and \(\lambda_q\) are not known. Hence, we truncate the estimated eigenvalues by a small number \(\varepsilon_n\). The stated conditions guarantee that with probability one rank \((\Sigma_n(\varepsilon_n)) = \text{rank}(\Sigma)\) for large enough \(n\). This rank condition ensures the convergence of the Moore–Penrose inverse and consequently the convergence of the associated quadratic forms (Andrews 1987). An important feature of the proposed test is that it is well defined whether \(\Sigma\) is, or is not, singular, that is, it adapts to the rank of \(\Sigma\).

Note that if \(\Sigma_n(\varepsilon_n) \to \Sigma^+\) then the conclusion of Theorem 2 holds with \(\varepsilon_n = 0\). However, there are many situations (see, Craig and Donald 1996) in which rank \((\Sigma_n) = p\) for all \(n\) even though \(\text{rank}(\Sigma) < p\). Obviously the proposed method will be useful in such a setting. We note that in most applications \(b_n = \sqrt{n}\) so Theorem 1 is valid for any sequence \(\varepsilon_n = n^{\delta}\) with \(\delta < -1/2\). For example, we may choose \(\varepsilon_n \propto 1/n^{1/3}\). By choosing \(\varepsilon_n \to 0\) and \(b_n\varepsilon_n \to \infty\), we are ensuring that in large samples we are not setting a nonzero eigenvalue to zero which means that with very high probability the rank of \(\Sigma\) will not be overestimated. A discussion of how to choose \(\varepsilon_n\) in practice is deferred to Section 3.3.

### 3.2. Winsorized Tests

One may consider other forms of regularization of nearly singular variance matrices. One potential alternative to trimming is winsorizing as defined below.

**Definition 2.** Let \(\varepsilon > 0\). We refer to the matrix \(\Sigma_W(\varepsilon) = E A_W(\varepsilon) E^T\), where \(A_W(\varepsilon)\), which is the diagonal matrix obtained from \(A\) by replacing any element of \(A\) which is smaller than \(\varepsilon\) by \(\varepsilon\), as the \(\varepsilon\)-winsorized variance matrix. Its inverse \(E^T A_W^{-1}(\varepsilon) E\) is referred to as the \(\varepsilon\)-winsorized inverse of \(\Sigma\) and denoted by \(\Sigma_W(\varepsilon)\).

We note that winsorizing is closely related to ridging. However, in contrast with ridging only the small eigenvalues are modified. In fact, the winsorized inverse shrinks \(1/\lambda_i\) to a fixed constant \(1/\varepsilon\) and is therefore of full rank. Both trimming and winsorizing can be obtained as special cases of \(\varepsilon\)-regularized inverses (Dufour and Valery 2015).

**Definition 3.** Fix \(\varepsilon \geq 0\), the \(\varepsilon\)-regularized inverse of \(\Sigma\) is \(\Sigma_\varepsilon(\varepsilon) = E^T A_\varepsilon(\varepsilon) E\), where \(A_\varepsilon(\varepsilon) = \text{diag}(v(\lambda_1, \varepsilon), \ldots, v(\lambda_p, \varepsilon))\) and \(v(\lambda, \varepsilon)\) is a nonnegative bounded function satisfying \(v(\lambda, \varepsilon) = 1/\lambda\) when \(\lambda \geq \varepsilon\). The value of \(v(\lambda, \varepsilon)\) when \(\lambda < \varepsilon\) is determined by the analyst. The function \(v\) is referred to as a variance regularizing function.

For example, if \(v(\lambda, \varepsilon) = \delta\) when \(\lambda < \varepsilon\) and \(\lambda_1 < \varepsilon\) when \(j \geq q + 1\) then \(A_\varepsilon(\varepsilon) = \text{diag}(1/\lambda_1, \ldots, 1/\lambda_q, 0_{p-q})\) where \(0_{p-q}\) is a vector of 0’s with length \(p-q\). It is clear that with this choice \(A_\varepsilon(\varepsilon)\), the regularized inverse, coincides with the trimmed inverse. Another natural choice is \(v(\lambda, \varepsilon) = 1/\lambda\) when \(\lambda \geq \varepsilon\) and \(v(\lambda, \varepsilon) = 1/\varepsilon\) when \(\lambda < \varepsilon\), which leads to \(A_\varepsilon(\varepsilon) = \text{diag}(1/\lambda_1, \ldots, 1/\lambda_q, \varepsilon^{-1} 0_{p-q})\) in which case the regularized inverse coincides with the winsorized inverse. Since for \(\lambda < \varepsilon\) we have \(\lambda < \varepsilon\), it follows that all variance regularization functions interpolate between trimming and winsorizing, the two possibilities addressed in this article.

Before presenting our next result, we require the following notation. Let \(Y\) be \(N_p(0, \Sigma)\), define \(\overline{T}^2(\Sigma_R)\) to be

\[
\overline{T}^2(\Sigma, R) = Y^T Y - \min \{ (Y - \theta)^T (Y - \theta) : \theta \in R \}.
\]

Note that the quadratic forms appearing in \(\overline{T}^2(\Sigma, R)\) are the unweighted versions of those in \(\chi^2(I_q, M R_+)\). We can now modify the statistic \(T_n(\varepsilon)\) by replacing \(\Sigma_n(\varepsilon)\) with \(\Sigma_\varepsilon(\varepsilon)\) to obtain the winsorized constrained test statistic:

\[
W_n(\varepsilon_n) = \min \left\{ n (S_n - \theta)^T \Sigma_\varepsilon^{-1}(\varepsilon_n) (S_n - \theta) : \theta \in C^*_n \right\}
\]

where, as before, \(W_n = W_n(\varepsilon_n)\) when \(\varepsilon_n \to 0\). The limiting distribution of \(W_n(\varepsilon_n)\) is given in the following Theorem, which applies to general variance regularizing functions.

**Theorem 3.** Suppose that the assumptions given in Theorem 2 hold. Then

\[
W_n \Rightarrow \chi^2(I_q, M_1 R_+) + \chi^2(V_{q-r}, M_2 R_+),
\]

with \(M\) as defined earlier. Furthermore, let \(r\) be the number of eigenvalues of \(\Sigma\), which are larger than \(\varepsilon\). Then as \(n \to \infty\)

\[
W_n(\varepsilon) \Rightarrow \chi^2(I_q, M_1 R_+) \oplus \chi^2(V_{q-r}, M_2 R_+),
\]

where the matrices \(M_1 \in \mathbb{R}^{q \times p}\), \(M_2 \in \mathbb{R}^{(q-r) \times p}\), and \(V_{q-r} \in \mathbb{R}^{(q-r) \times (q-r)}\) are defined in the body of the proof and \(\oplus\) denotes the sum of independent RVs.

Theorem 3 is a generalization of Theorems 1 and 2. First, it shows that \(W_n\) and \(T_n\) have the same limiting distribution. This result may seem a bit surprising since \(\Sigma_\varepsilon(n) \to \chi^2(0)\) and \(\Sigma_n(\varepsilon_n) \to \Sigma^+\) but \(\Sigma^+ \neq \Sigma^0(0)\) whenever \(n(0, 0)\) is nonzero. We also note that if \(\varepsilon\) is “sufficiently small,” that is, if with high probability \(\varepsilon\) is smaller than \(\lambda_{q,n}\), the \(q\)th eigenvalue of \(\Sigma_n\), then \(T_n(\varepsilon)\) and \(W_n(\varepsilon)\) coincide. If, however, \(\varepsilon\) is “too large” then instead of the limit (7) we obtain the limit (9). It is also clear that in this case \(T_n(\varepsilon) \Rightarrow \chi^2(I_q, M_1 R_+)\) as \(n \to \infty\). The relative merits of these statistic are investigated below.

**Proposition 2.** Under the stated conditions, the tests \(T_n, W_n\), and \(W_n(\varepsilon)\) are consistent. The test \(T_n(\varepsilon)\) is consistent if and only if \(M_1 \theta \in M_1 R_+ \setminus \{0\}\) where the matrix \(M_1\) is defined in the proof of Theorem 3.
Proposition 2 shows that a test based on $T_n(\varepsilon)$ may not be consistent for some configurations in the alternative. Nevertheless, for other configurations it may be more powerful than $W_n(\varepsilon)$, $W_m$, or $T_n$. Hence, no test dominates the others as demonstrated in the simple example below.

Example 1. Assume that $Y_1, Y_2, \ldots$ are $N(\theta, \Sigma)$ with $\Sigma = \text{diag}(\sigma_1^2, \sigma_2^2, \sigma_3^2)$ where $\sigma_1^2 > \sigma_2^2 > \sigma_3^2 = 0$. It is further assumed that $\Sigma$ is not known in advance. Consider testing $H_0: \theta = 0$ versus $H_1: \theta \in \mathbb{R}^3 \backslash \{0\}$. Let $Y = n^{-1/2} \sum_{i=1}^n Y_i$, and $\Sigma_n = n^{-1} \sum_{i=1}^n (Y_i - \bar{Y}_n)(Y_i - \bar{Y}_n)^T$. Choose $\varepsilon$ such that $\sigma_1^2 > \varepsilon > \sigma_2^2$. It can be verified that for large $n$

\[
T_n = \max \left\{ 0, Z_1 + \sqrt{n} \frac{\sigma_1^2}{\sigma_1^2} + \max \left\{ 0, Z_2 + \sqrt{n} \frac{\sigma_1^2}{\sigma_2^2} \right\} \right\} + o_p(1),
\]

\[
W_n = \max \left\{ 0, Z_1 + \sqrt{n} \frac{\sigma_1^2}{\sigma_1^2} + \max \left\{ 0, Z_2 + \sqrt{n} \frac{\sigma_1^2}{\sigma_2^2} \right\} \right\} + o_p(1),
\]

\[
T_n(\varepsilon) = \max \left\{ 0, Z_1 + \sqrt{n} \frac{\sigma_1^2}{\sigma_1^2} + \varepsilon \max \left\{ 0, Z_2 + \sqrt{n} \frac{\sigma_1^2}{\sigma_2^2} \right\} \right\} + o_p(1),
\]

\[
W_n(\varepsilon) = \max \left\{ 0, Z_1 + \sqrt{n} \frac{\sigma_1^2}{\sigma_1^2} + \varepsilon \max \left\{ 0, Z_2 + \sqrt{n} \frac{\sigma_1^2}{\sigma_2^2} \right\} \right\} + o_p(1),
\]

where $Z_1, Z_2$ are independent $\mathcal{N}(0, 1)$ RVs. It is clear that the distribution of $T_n(\varepsilon)$ is the same for all $(\theta_1, \theta_2) \in \{(c, 0), (c, \theta_2)\}$, and $\varepsilon > 0$. It follows that $T_n(\varepsilon)$ cannot detect if $\theta_2 > 0$. However, if $(\theta_1, \theta_2) = (c, 0)$ and $\varepsilon > 0$, then $T_n(\varepsilon)$ will be more powerful than the other tests. This will also often be the case when $\theta_1$ is large and $\theta_2$ is small. The relative merit of $W_n(\varepsilon)$ compared to $W_n$ depends on the value of $\varepsilon$ and $\theta_1, \theta_2$ and is more difficult to assess. Note that $T_n(\varepsilon)$ and $W_n(\varepsilon)$ are actually the test one would use if it were known in advance that $\Sigma$ is diagonal with $\sigma_1^2 > \varepsilon > \sigma_2^2 > 0$, and $\sigma_3^2 = 0$.

### 3.3. Choosing $\varepsilon$ and Two Supremum Statistics

The statistics (6) and (8) are functions of $\varepsilon$. We now describe a few approaches for choosing $\varepsilon$ when using (6) or (8). First, in some settings there may be prior knowledge regarding the rank of $\Sigma$ or the size of its smallest eigenvalue. Such information, when available, should of course guide our choice. In general, $\Sigma$ is not known and therefore it seems that an automated data-driven procedure should be developed. A natural approach, motivated by numerical stability considerations, is to truncate or winsorize the small eigenvalues until the modified condition number of $\Sigma_n$, that is, the ratio of the largest to the smallest nonzero eigenvalue, is bounded by some constant. More concretely let $\lambda_{1,n} \geq \cdots \geq \lambda_{p,n}$ denote the eigenvalues of the $\Sigma_n$. Let

\[
\kappa = \max \left\{ \lambda_i: \frac{\lambda_{1,n}}{\lambda_{1,n}} \leq \Delta \right\},
\]

where $\Delta$ is a prespecified constant (typically between 50 and 200), then choose $\varepsilon_n = \lambda_{\kappa,n}$. This type of approach is well known and extensively discussed in the literature on numerical linear algebra where systems of linear equations with large condition numbers are solved (El Ghaoui 2002; Montgomery and Peck 2012; Golub and Van Loan 2012). We remark that this method is a variation on the choice provided by Fan, Han, and Gu (2012).

However, their choice was inspired by multiple testing problems for correlated data where the objective was to approximate the population covariance by a matrix derived from a factor analytic model. Although numerical experiments show that this approach is flexible, easy to implement and results in a good power for the test statistic under consideration, we have developed a more general approach discussed below.

Recall that by Theorems 2 and 3 if $\varepsilon_n \to 0$ and $b_n \varepsilon_n \to \infty$, then $T_n$ and $W_n$ converge to the same limit. Usually $b_n = \sqrt{n}$, therefore the Theorems will be satisfied if $\varepsilon = C/n^{1/k}$ for some constant $C$ and $k > 2$. A reasonable choice is $k = 3$ and $C = \lambda_{1,n}$, that is, each eigenvalue is compared to largest estimated eigenvalue scaled by $1/n^{1/3}$. Obviously the aforementioned choice of the constant $C$ is arbitrary and one can compare to any other function of the eigenvalues such as the trace, the product of the eigenvalues, the sum/product of the top $r$ eigenvalues and so forth. Although, in large samples, all such choices are equivalent, there may be differences in small to moderate samples. Moreover, it is important to note that any scaling, $1/n^{1/k}$, with $k > 2$ will result in the same limit. This is very different from many other statistical problems in which the order of the regularizing parameter is very important, see Cule, Vineis, and De Iorio (2011), Buhlmann (2013), and Van de Geer et al. (2014) for ridge regression and lasso examples and Wand and Jones (1995) for kernel smoothing. Moreover, note that in all of the above-mentioned articles the constant factor is also chosen in an ad hoc manner.

**Conclusion 3.1.** Choosing $\varepsilon$ in (6) and (8) is fundamentally different from the problem of choosing the value of a regularizing parameter in settings such as ridge regression or nonparametric regression. First, regardless of the value chosen for $\varepsilon$, the resulting test always has the prescribed level, at least asymptotically. Consequently, the choice of $\varepsilon$ may only affect power. Our numerical experiments indicate that usually the power is only marginally influenced by the choice of $\varepsilon$. Moreover, and as indicated by Proposition 2 and Example 1, the power of $W_n(\varepsilon)$ is much less influenced by the choice of $\varepsilon$ compared with $T_n(\varepsilon)$. It is also important to realize that there does not exist an optimal choice of $\varepsilon$ as the best $\varepsilon$ is a function of the unknown value of $\theta$.

In contrast, the choice of the ridging parameter affects the performance of both estimators and tests see, for example, Vinod and Ullah (1981) as well as the above-mentioned references. The same holds for nonparametric regression where the regularizing parameter is chosen to balance the bias and variance. Such a balancing act is not required here.

Nevertheless, some users may be uncomfortable choosing a single value for $\varepsilon$. To accommodate such a preference, we introduce two supremum statistics, based on (6) and (8), which depend on a range of $\varepsilon$ values. Let $0 < \varepsilon_1 \leq \varepsilon_2$ and set $I = [\varepsilon_1, \varepsilon_2]$. Define

\[
T_\varepsilon(I) = \sup_{\varepsilon \in I} T_n(\varepsilon) \quad \text{and} \quad W_\varepsilon(I) = \sup_{\varepsilon \in I} W_n(\varepsilon). \tag{10}
\]

The statistics (10) are motivated by Davies (1987) and Andrews and Ploberger (1994) where tests are developed for the case where a nuisance parameter is present only under the alternative. Here, $\varepsilon$ varies over the interval $I$ and plays the role of the nuisance parameter.

In the following, we derive the limiting distributions of the statistics (10). First fix $\varepsilon > 0$. Then by Eq. (6) and from the proof...
of Theorem 2, it follows that

\[ T_n(\epsilon) \Rightarrow T(\epsilon) = X^T I_{\eta(\epsilon)} X - \min_{\eta \in M' \mathcal{R}_+^k} \{(X - \eta)^T I_{\eta(\epsilon)} (X - \eta) : \eta \in M' \mathcal{R}_+^k\}, \]

where \( X \) is an \( N_q(0, I) \) RV, \( r(\epsilon) = \sum_{i=1}^{p-1} I_{\lambda_i(\epsilon) \geq 1} \) is the number of eigenvalues larger than \( \epsilon \), \( I_{\eta(\epsilon)} = \text{diag}(1_{\eta(\epsilon)}, 0_{q-\eta(\epsilon)}) \), \( M' \) is the \( r(\epsilon) \times p \) matrix obtained by dropping the last \( p - r(\epsilon) \) rows of the matrix \((A^+ \epsilon)^{1/2} E\), and \( \mathcal{R}_+^k = C \cap L^+ \cap \mathcal{S}(\Sigma(\epsilon)) \). Conditioning on \( X \) we note that \( T(\epsilon) \) is a function of \( \epsilon \) only through \( r(\epsilon) \), which is a step function. This implies that

\[ \{ T(\epsilon) : \epsilon \in I \} \subset \{ T(\lambda_j) : i = j, \ldots, k \}, \quad (11) \]

where \( j = \min\{i : \lambda_i \geq \epsilon_2\} \) and \( k = \min\{i : \lambda_i \geq \epsilon_1\} \), that is, \( T(\epsilon) \) assumes only a finite number of values. Finally, we note that conditionally \( T(\epsilon) \) is a decreasing function of \( \epsilon \). Therefore, it follows by Theorem 1.A.6 in Shaked and Shanthikumar (2007) that unconditionally we have \( T(\epsilon'_2) \leq_T T(\epsilon'_1) \) whenever \( \epsilon'_1 \leq \epsilon'_2 \) where \( \leq_T \) denotes the usual stochastic order.

Similarly, by Theorem 3

\[ W_n(\epsilon) \Rightarrow W(\epsilon) = W_1(\epsilon) + W_2(\epsilon), \]

where

\[ W_1(\epsilon) = X_1^T I_{\eta(\epsilon)} X_1 - \min_{\eta \in M_1' \mathcal{R}_+^k} \{(X_1 - \eta)^T I_{\eta(\epsilon)} (X_1 - \eta) : \eta \in M_1' \mathcal{R}_+^k\}, \]

\[ W_2(\epsilon) = X_2^T I_{\eta(\epsilon)} X_2 - \min_{\eta \in M_2' \mathcal{R}_+^k} \{(X_2 - \eta)^T I_{\eta(\epsilon)} (X_2 - \eta) : \eta \in M_2' \mathcal{R}_+^k\}, \]

\( X_1 \) and \( X_2 \) are independent \( N\{0, I\} \) and \( N\{0, V'\} \) and \( V' = \text{diag}(\lambda_{\eta(\epsilon)}, \ldots, \lambda_{q/\epsilon}) \) where \( \Sigma = \text{diag}(\sigma_1^2, \sigma_2^2, \sigma_3^2) \) with \( \sigma_1^2 > \sigma_2^2 > \sigma_3^2 \). For which a direct calculation shows that

\[ W(\epsilon) = \psi(\epsilon, \sigma_2^2) \max(0, X_1^2) + \psi(\epsilon, \sigma_3^2) \max(0, X_2^2), \]

where \( X = (X_1, X_2)^T \) is an \( N\{0, I\} \) RV and \( \psi(\epsilon, \sigma^2) = 1 \) if \( \sigma^2 \geq \epsilon \) and \( \psi(\epsilon, \epsilon^2) = 1 \) if \( \epsilon^2 < \epsilon \). Thus, conditional on \( X \), \( W(\epsilon) \) is a decreasing, continuous function of \( \epsilon \). Furthermore, arguing as before, it can be shown that unconditionally \( W(\epsilon'_2) \leq_T W(\epsilon'_1) \). To summarize:

**Theorem 4.** Suppose that the assumptions given in Theorems 2 and 3 hold. Then as \( n \to \infty \) we have

\[ T_n(I) \Rightarrow T(\epsilon_1) \quad \text{and} \quad W_n(I) \Rightarrow W(\epsilon_1). \]

**Theorem 4** shows that the theoretical critical values of the statistics \( T_n(I) \) and \( W_n(I) \) should be computed at \( \epsilon_1 \). However, in finite samples \( T_n(I) \) and \( W_n(I) \) may not be maximized at \( \epsilon_1 \) even under the null. In practice, the interval \( I \) can be chosen using the estimated eigenvalues of \( \Sigma_n \). We propose choosing \( I = [\lambda_{\rho_n}, \lambda_{1, n}] \), that is, maximizing (6) and (8) over the full spectrum of \( \Sigma_n \). Note that choosing values of \( \epsilon_1 \) smaller than \( \lambda_{\rho_n} \) will not yield numerically different results, whereas choosing \( \epsilon_2 \) larger than \( \lambda_{1, n} \) will result in a loss of power. Our numerical studies, as well Theorem 4, indicate that the Type I error is always maintained. Moreover as indicated by our simulations, the power of the resulting tests is comparable to the power obtained by choosing the best value for \( \epsilon \) when its value is known in advance. Thus, our approach completely eliminates the need to choose a value for \( \epsilon \) while hardly compromising the power of the test.

Finally, we emphasize that the statistics (6) and (8) as well as (10) converge to the same limit if the conditions in Theorem 2 are satisfied. The consistency of tests based on \( T_n(I) \) and \( W_n(I) \) follows immediately from Proposition 2.

### 3.4. Implementation

Finally, a few remarks regarding implementation. Suppose first, that the statistic \( S_n \) satisfies (1) and that \( \Sigma \) is known. If \( \epsilon \) is found \( \Sigma^+ \) the spectral cut-off Moore–Penrose inverse of \( \Sigma \), as described in Section 2, and compute the statistic \( T_n \) given by (3) using rank reduced quadratic programming. Denote its observed value by \( t_n \). To calculate the significance level:

**Step 1:** Simulate a sample of size \( n \) from a multivariate normal distribution with mean vector \( \theta \) and variance matrix \( \Sigma \).

**Step 2:** Compute \( \hat{\theta} \), the sample mean for the 4th sample.

**Step 3:** Compute the test statistic \( T_{n,i} \) in the same manner, using \( \hat{\theta} \) in place of \( \theta \).

Repeat Steps 1–3 \( B \) times, where \( B \) is large enough to ensure that the null distribution is estimated sufficiently well. In our examples, we used \( B = 10^5 \). Then we approximate the \( p \)-value by

\[ \frac{1}{B} \sum_{i=1}^B I_{(T_{n,i},_n) < (t_n)}. \quad (12) \]

Modifications of the procedure above are necessary when the variance matrix \( \Sigma \) is unknown. We will describe the procedure for the supremum statistic \( W_n(I) \); analogous procedures are used for (6), (8), and \( T_n(I) \). The first step is to calculate \( \Sigma_n \), a consistent estimator of \( \Sigma \). Given \( \Sigma_n \) an interval \( I \) of values for \( \epsilon \) is set forth as described in Section 3.3. The observed value of the statistic is calculated using (8) and (10) and denoted \( W_n(I) \). The significance level is calculated by repeating steps 1–3 above, where: in Step 1 we simulate from a multivariate normal distribution with mean vector \( \theta \) and variance matrix \( \Sigma_n \). Step 2 is exactly as described above and in Step 3 we compute \( W_n(\epsilon) \), where at each iteration we reestimate \( \Sigma \). Finally, the \( p \)-value is calculated as in (12) with \( T_n(\epsilon) \) replaced by \( W_n(\epsilon) \) and \( t_n \) replaced by \( W_n(I) \). Our approach is quite standard and falls within the framework of Monte Carlo tests (see Dufour 2006; MacKinnon 2009), where a plug-in estimator for the nuisance parameter is used when constructing the test statistic. Of course this approach relies on large sample theory. It is clear from our simulations that it works well in this application. The procedures described above were programmed in MATLAB.

### 4. Simulations

We conducted a wide range of simulation studies to compare the proposed test statistics. More specifically, we provide two different simulation settings in which the Type I errors and powers of the proposed statistics are compared. We focus on the statistics \( T_n = T_n(0), T_n(\epsilon) \) and \( W_n(I) \), although results for \( T_n(\epsilon) \) and \( W_n(\epsilon) \) for various values of \( \epsilon \) are also reported but presented
Table 1. Patterns of the mean vector under the alternative hypothesis for the case of $p = 3$.

<table>
<thead>
<tr>
<th>$i$</th>
<th>Value of $\theta_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design A</td>
<td>Simple: 0.00 0.25 0.00; Orthant: 0.50 0.50 0.00; Tree: 0.00 0.50 0.00</td>
</tr>
<tr>
<td>Design B</td>
<td>Simple: 0.00 0.25 0.50; Orthant: 0.50 0.50 0.50; Tree: 0.00 0.50 0.50</td>
</tr>
</tbody>
</table>

This variance matrix has eigenvalues 1.25, 0.75, and 0.00. Under the null hypothesis, the mean vector $\theta$ was taken to be the null vector. We considered three different patterns of alternative hypotheses, namely, the simple order, the orthant order, and the tree order. The values of $\theta$ under the corresponding alternatives are given in Table 1. For the case of $p = 8$, we chose

$$
\Sigma_{8 \times 8} = \begin{pmatrix}
1.00 & 0.25 & 0 \\
0.25 & 1.00 & 0 \\
0 & 0 & 0
\end{pmatrix}.
$$

This variance matrix has eigenvalues 1.25, 0.75, and 0.00. Under the null hypothesis, the mean vector $\theta$ was taken to be the null vector. We considered three different patterns of alternative hypotheses, namely, the simple order, the orthant order, and the tree order. The values of $\theta$ under the corresponding alternatives are given in Table 1. For the case of $p = 8$, we chose

$$
\Sigma_{8 \times 8} = \begin{pmatrix}
\Omega & 0_{4 \times 4} \\
0_{4 \times 4} & \Psi
\end{pmatrix},
$$

where $\Omega = (1 - \rho)I_4 + \rho J_4$, $I_4$ is the identify matrix, $J_4$ is the $4 \times 4$ matrix of all 1's, and $\text{diag}(\Psi) = \{10^{-3}, 10^{-5}, 0, 0\}$. For this simulation, we set $\rho = 0.25$. The resulting variance matrix has eigenvalues 1.75, 0.75, 0.75, 0.75, 10^{-3}, 10^{-5}, 0, and 0. Thus in this example, two eigenvalues are identically zero and at least one is nearly zero. Once again we considered patterns of mean vectors satisfying either the simple order, the orthant order, or the tree order alternative. The values of $\theta$ under the corresponding alternatives is given in Table 1. For both $p = 3$ and $p = 8$, the values of $I$ for $\epsilon$ were taken to be all nonzero eigenvalues of $\Sigma$. For the case $\Sigma$ known, we used 10,000 replications to simulate the sampling distribution of all three test statistics under the null hypothesis and the Type I error rates and powers were estimated using 5000 replications. In the case of $\Sigma$ unknown, which is more realistic, the test statistic was calculated using the sample covariance matrix.

### 5. Illustration: Changes in Gene Expression by the Tumor Size in the NIEHS Fibroid Growth Study

Uterine leiomyoma (also called uterine fibroids) are benign hormonally mediated smooth muscle tumors commonly found in premenopausal women. According to some estimates at least 70% of white women in the U.S. have fibroids and the estimates are even higher for black women. Furthermore, the total annual cost associated with these tumors in the US is over 30 billion dollars. Despite such high prevalence rates and associated costs, these tumors are not very well characterized. The NIEHS Fibroid Growth Study (FGS) is one of the largest studies, involving 72 premenopausal women, where the growth patterns of fibroids were investigated (Peddada et al. 2008). Tissue samples obtained from women in the FGS who underwent either myomectomy or hysterectomy provide a great opportunity for researchers to investigate the molecular characteristics of these benign tumors. In this section, we compare the mean expression of two sets of important genes using the proposed methodology. Specifically, we consider a subset of genes belonging to the Interleukin-1 (IL-1) signaling pathway, which are known to be involved in the initial stages of tumor formation (Dunne et al. 2003) and a subset of genes called collagen, which are well-known to be associated with tumor development and growth.
Figure 1. Powers for $W_n(I)$ (triangle, dotted lines), $T_n(I)$ (diamonds, dashed lines), and $T_n(0)$ (circles, solid lines) for simulation 1, Design A, the case where $p = 3$.

Figure 2. Powers for $W_n(I)$ (triangle, dotted lines), $T_n(I)$ (diamonds, dashed lines), and $T_n(0)$ (circles, solid lines) for simulation 1, Design A, the case where $p = 8$. 
Following Grandhi, Guo, and Peddada (2016), we shall consider four groups: (1) normal myometrium; (2) small tumors (between 0.08 and 5.70 cm$^3$); (3) medium tumors (between 9.0 and 132.0 cm$^3$); and large tumors (between 240 and 2016 cm$^3$). The respective sample sizes were, $n_1 = 8$, $n_2 = 14$, $n_3 = 25$, and $n_4 = 13$.

Let $Y_{ij}$ denote the $m$-dimensional gene expression vector of the $j$th individual in the $i$th group. Let $\bar{Y}_i = n_i^{-1} \sum_j Y_{ij}$, $i = 1, \ldots, 4$ denote the group means. Let $\theta_i = \mathbb{E}(Y_{ij})$ be the mean gene expression level in group $i$. We also assume that $\text{Var}(Y_{ij}) = \Psi$ for all $i$ and $j$, that is, the variance are homogenous across groups. Define,

$$Z_n^T = (\sqrt{n_1}(\bar{Y}_1 - \theta_1), \sqrt{n_2}(\bar{Y}_2 - \theta_2), \sqrt{n_3}(\bar{Y}_3 - \theta_3), \sqrt{n_4}(\bar{Y}_4 - \theta_4)).$$

Clearly, $\mathbb{E}(Z_n) = 0$ and $\Psi = \text{Var}(Z_n) = I \otimes \Psi$, where $\Psi$ is $m \times m$ and $I$ is the $4 \times 4$ identity matrix. Hence, $\Sigma$ is a $p \times p$
(\(p = 4m\)) block diagonal matrix with blocks \(\Psi\) repeated four times. We shall assume that \(Z_n \sim \mathcal{N}_p(0, \Sigma)\).

An important component of growth and development of fibroids is angiogenesis or vascularization, the formation of blood vessels. According to Grandhi, Guo, and Peddada (2016), the Interleukin-1 (IL-1) signaling pathway is involved in a cascade of events including inflammatory response and production of prostaglandins that trigger the expression of growth factors involved in angiogenesis. Therefore, in this article, we investigated the relationship between tumor size and gene expression patterns of \(m = 25\) genes belonging to the IL-1 signaling pathway. The names of the 25 genes along with the log-transformed (to base 2) mean gene expression data, and pooled variance matrix, are provided in supplementary Tables S12 and S13, respectively. A priori we do not know if the 25 genes considered in this analysis are positively or negatively correlated. For illustration purposes, we conducted the tests \(H_0: \theta_1 = \theta_2 = \theta_3 = \theta_4\) against the alternative \(H_1: \theta_1 \leq \theta_2 \leq \theta_3 \leq \theta_4\). Stacking \(\theta = (\theta_1, \theta_2, \theta_3, \theta_4)^T\) and choosing a suitable contrast matrix \(C\), we restate the above hypotheses as \(H_0: C\theta = 0\), versus \(H_1: \{C\theta \geq 0\} \cup \{C\theta \leq 0\}\). As often done (Peddada et al. 2003), we tested this union-intersection hypotheses by testing for each alternative hypothesis separately and then applying Bonferroni corrections to the resulting \(p\)-values. Thus, suppose \(p_1\) is the \(p\)-value associated with testing \(H_0\) versus \(H_{a1}\) and \(p_2\) is the \(p\)-value associated with testing \(H_3\) versus \(H_{a3}\), then the Bonferroni corrected \(p\)-values are \(\min(1, 2p_i)\) \(i = 1, 2\).

### 5.1. Data-Driven Simulation Study

A simulation study motivated by the data obtained from the FGS was carried out. Data from four \(p\)-variate normal distributions was generated. A test for \(H_0: \theta_1 = \theta_2 = \theta_3 = \theta_4\) against the alternative \(H_1: \theta_1 \leq \theta_2 \leq \theta_3 \leq \theta_4\) was conducted as described above. By stacking the random vectors from the four groups, the data can be represented by a single \(4m \times 1\) normal vector with a \(4m \times 4m\) variance matrix of the form \(\Sigma = I \otimes \Psi\), where \(I\) is a \(4 \times 4\) identity matrix, \(\Psi\) is a \(m \times m\) matrix, and \(\otimes\) denotes the usual Kronecker product of matrices. Thus, in terms of the previous notations \(p = 4m\) and \(m = 25\). Our choice of parameters for the multivariate normal distribution were inspired by the real data in the IL-1 signaling pathway in FGS. Let \(\theta\) denote the pooled sample mean vector and let \(\Psi\) denote the pooled sample covariance matrix of the 25 genes in the IL-1 signaling pathway from four groups. Out of the 25 genes, we arbitrarily chose five of the genes (i.e., components 4, 8, 12, 16, and 20 of the mean vector) to satisfy the alternative hypothesis and the remaining genes (or components) satisfy the null hypothesis. For these five nonnull genes, the elements of \(\theta\) were set to increase by 1% from group to group. For example, the means of the 4th gene were \(\theta_{41} = 1.0101, 1.0202, 1.0303\), \(1.0404\), for groups 1, 2, 3, and 4, respectively. See supplementary Tables S12 and S13 for the values of the mean vectors, and \(\Psi\).

Our goal was to investigate the effect of the degree of singularity, as measured by the condition number of the matrix \(\Psi\), on the performance of the proposed tests. Recall that we may write the spectral decomposition of \(\Psi = \Psi = \Lambda E^T\) where \(\Lambda\) is a diagonal matrix of the eigenvalues. Denote by \(\Lambda_2\) the eigenvalues observed in the FGS. In addition, we constructed the matrices \(\Lambda_1\) and \(\Lambda_3\) defined by \(\Lambda_1 = s \times W_1\) and \(\Lambda_3 = s \times W_3\) where \(s\) is the sum of the eigenvalues of \(\Lambda_2\) and \(W_j = \text{diag}(w_j), j = 1, 2\) are diagonal weight matrices with decreasing weights (i.e., \(w_j \geq w_{j+1}\) when \(i \leq j\)), which preserve the sum of the eigenvalues while modifying the condition number, see Table S17 in the supplementary text. Specifically, \(\Lambda_1\) has a condition number of \(\Delta = 24\) and \(\Lambda_3\) has a condition number of \(\Delta = 1301\).

The performance of the proposed tests was evaluated assuming the variance was unknown. The results are displayed in Figure 5, and in the supplementary materials, Section S3. As can be seen, \(W_n(I)\), generally achieves as high or higher power compared to \(T_n(I)\) and \(T_n(0)\).

### 5.2. Data Analysis

The variance matrix \(\Psi\) has 25 eigenvalues with a condition number of 557. For illustration purposes, we conducted the tests \(T_n(I), W_n(I),\) and \(T_n(0)\). The interval \(I\), for computing \(W_n(I)\) and \(T_n(I)\), was selected to cover the full range of eigenvalues of \(\Psi\). Thus, the set \(I\) included the 1st, 5th, 10th, 15th, 20th, and 25th eigenvalues. All tests were carried out assuming that \(\Sigma\) was unknown. According to our analysis, after performing Bonferroni corrections, \(T_n(0)\) rejected the null hypothesis in favor of an increasing trend, but neither \(W_n(I)\) nor \(T_n(0)\) did so. The respective \(p\)-values were 0.007, 1, and 1. Similarly, \(T_n(I)\) declared a significant decreasing trend, while \(W_n(I)\) and \(T_n(0)\) did not, with

![Figure 5](https://example.com/image5.png)  
**Figure 5.** Powers for \(W_n(I)\) (triangle, dotted lines), \(T_n(I)\) (diamonds, dashed lines), and \(T_n(0)\) (circles, solid lines) for simulation design 2.
Bonferroni corrected p-values of 0.007, 0.36, and 0.64. However, it should be noted that the null distribution of $T_n$ was highly skewed. Of the 10,000 replications used to simulate the null distribution of $T_n$ for the increasing trend, 9965 of them resulted in a test statistic of exactly 0. The degree of singularity in the IL-1 signaling pathway data may render $T_n$ an untrustworthy test.

We emphasize that this is the first article to assess the association between tumor size and gene expression in this context. There are two possible explanations for not detecting a significant increasing or a significant decreasing trend in the gene expression of the vector of 25 IL-1 pathway genes considered here. The first is that failing to reject a null hypothesis does not imply the null is true but may just be an indication that the study may be underpowered for discovering the multivariate trends considered in this article. The second is that some genes are positively associated while others are negatively associated (and some may not be associated at all). To discern if the latter is the case, we performed a univariate trend analyses for each gene separately using ORIOGEN (Peddada et al. 2003, 2005), a bootstrap-based univariate order restricted inference method to detect patterns in an ordered gene expression data. After controlling the false discovery rate at 5%, we discovered that 4 out of 25 genes had a highly significant increasing trend whereas all remaining 21 genes had a highly significant decreasing trend. Results of these ORIOGEN-based analyses are provided in the supplementary text (Table S16). Due to these conflicting trends, it is not surprising that the multivariate trend test did not find all 25 genes to have significant increasing trend or all to have a significant decreasing trend. Moreover, Grandhi, Guo, and Peddada (2016) discovered that the genes in the IL-1 pathway were enriched only in the small tumors and hence are potentially involved in tumor genesis and initiation. Therefore, we performed an additional post hoc analysis using ORIOGEN to investigate if there were significant differences in the gene expression between small and medium tumors and between small and large tumors. Consistent with Grandhi, Guo, and Peddada (2016), we discovered that none of these 25 genes were differentially expressed in these pairwise comparisons (at FDR = 0.05) although we found all of them to be differentially expressed between the normal myometrium and the small tumors.

6. Summary and Discussion

In this article, we introduced a general framework and concrete tools for testing hypotheses under linear inequality constraints when the variance matrix is potentially singular. The new methodology extends the existing literature in several directions and since it adapts to the true rank of $\Sigma$ it can handle singularity as well as nearly singularity of variance matrices in a unified way. Adding to the novelty, the ideas of trimming and winsorizing are extended to the present context of singular and nearly singular variance matrices. It is well-known that these techniques were originally developed to deal with extreme observations in the data.

Specifically, we propose trimmed and winsorized tests (6) and (8) and two supremum tests (10), which are based on them. Although all tests are asymptotically equivalent there are substantial differences in power in finite sample. Interestingly, when comparing (6) and (8), we discovered that in most cases the test statistic based on the winsorized variance matrix has larger power than the test based on the trimmed variance matrix. The gain in power was often substantial. Recall that, under normality, Winsorizing leads to asymptotically efficient estimators and is therefore preferred to trimming. Similarly, we found that the statistic $W_n$ results in more powerful tests than $T_n$. Further, we observe that the supremum tests (10), which do not require choosing $\varepsilon$ are only minimally less powerful than the tests (6) and (8) assuming that the best value for $\varepsilon$ is known. For these reasons, we recommend using $W_n$.

The proposed methodology can be extended in several directions. As an example, we discuss the regression setting. First, note that to estimate a regression parameter it is often necessary to first invert the variance matrix $\Sigma$. This is not possible if $\Sigma$ is singular. Hence, additional assumptions on the data-generating mechanism, beyond those given by (1), are required. Of course, if the matrix $X^T X$ has very large but finite condition number, then the ordinary least-square estimator exists and is unbiased and a trimming or winsorizing test can be applied as discussed above. This holds true whenever the matrix $n^{-1}\sum x_i x_i^T$ converges to a nonsingular matrix. However, if $n^{-1}\sum x_i x_i^T$ converges to a singular matrix, as in Knight (2008), then a different analysis is required. To fix ideas consider the linear regression $Y_i = \beta^T x_i + \varepsilon_i$ where $i = 1, \ldots, n$. The least-square estimator is given by

$$\hat{\beta}_n = \beta + (X_n^T X_n)^{-1} X_n^T \varepsilon_n.$$  

Note that if $\varepsilon_i$ are independent $N(0, \sigma^2)$ RVs, then the $\varepsilon_i$ are independent $N(0, \sigma^2)$ RVs, then

$$c_n (\bar{\beta}_n - \beta) \sim \mathcal{N}_p(0, \sigma^2 c_n^2 (X_n^T X_n)^{-1})$$

for $n \to \infty$, where $x_i x_i^T \to 0$ if $S \subset \mathbb{R}^p$ is a subspace, such that, is a sequence of constants where the observations are increasingly concentrated on a subspace.

It follows that $n^{-1}\sum x_i x_i^T \to S$ where $S$ is a singular matrix. We first exclude the possibility that $\lim inf n^{-1}\sum x_i x_i^T < \infty$ in which case $\hat{\beta}_n$ is not consistent. It is further evident that a limit in (13) will exist if and only if $c_n^2 (X_n^T X_n)$ converges to some positive definite matrix and $c_n$ is a sequence of constants increasing to infinity. By letting $\|x_n - S\| \to 0$ at various rates, we can obtain different normalizing constants $c_n$. It follows that our methodology will apply here if we replace $\sqrt{n}$ with $c_n$ in (1) and proceeding as before.

In this article, the focus had been on the case where $\Sigma$ is not a function of the unknown mean parameter $\theta$. However, in many applications $\Sigma = \Sigma(\theta)$ is a function of $\theta$ and is estimated by a plug-in procedure, that is, $\hat{\Sigma} = \hat{\Sigma}(\hat{\theta})$. Such situations arise in nonlinear regression models, where $Y_i = f(X_i; \theta) + \varepsilon_i$, and in generalized linear models. In all such cases, although the theoretical asymptotic variance of the $\hat{\theta}$ may be nonsingular matrix, its estimated variance $\hat{\Sigma}(\hat{\theta})$ may be nearly singular. As seen in
Lim, Sen, and Peddada (2013) and in Lim (2015), the condition number (in log scale) of the estimated variance matrix can be as high as 10^5 or more. Thus, the theory and methodology discussed in this article are relevant to nonlinear as well as generalized linear models.

Finally, as noted by a referee it is of interest to extend the current methodology within the framework of order restricted model selection (see Mulder, Hoijtink, and Klugkist 2010; Kuiper, Hoijtink, and Silvapulle 2012). An additional direction is to explore the performance of the proposed tests in high dimensions.

**Supplementary Materials**

The supplementary materials are comprised of three primary sections: Section S1 contains all of proofs of theorems presented in the main text. Section S2 contains full results from the simulation described and presented in Section 4 of the main text. Section S3 contains full results from the simulation described and presented in section 5.1 of the main text. Theorem and equation references throughout are consistent with the main text.

The supplementary materials also contain additional references used in the proofs.

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**References**


