Improving Efficiency of Tests for Composite Null Hypotheses

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Abstract: The goal of mediation analysis is to study the effect of exposure on an outcome interceded by a mediator. Two simple hypotheses are tested: the effect of the exposure on the mediator, and the effect of the mediator on the outcome. When either of these hypotheses is true, a predetermined significance level can be assured. When both nulls are true, the same test becomes conservative. Adaptively finding the correct scenario enables customizing the tests and consequently enlarges their efficiency, which is most important in a multiple testing framework. In this work, we link between adaptive two-stage procedures and shrinkage estimators. We first study the properties of shrinkage estimators, and characterize their behavior at different parameter points using local asymptotics. We formulate theoretical results regarding shrinkage estimators, compared to regular estimators. We then discuss the multiple-testing framework and state results about using shrinkage estimator in two-stage procedures for controlling the FWER. Taking advantage of these theoretical results, we suggest a number of estimators and test statistics for the two-stage mediation procedures. We then investigate their empirical FWER and power, compared to regular estimators and tests, through simulations.

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1. Introduction

Mediation analysis, a research area within the field of causal inference, is a collection of methods employed for studying the causal effect of an exposure on an outcome, interceded by a mediator.

For instance, obesity has already been found to be correlated to poor socioeconomic level in childhood (Senese et al., 2009), as well as to changes in DNA methylation process (Borghol et al., 2012, Agha et al., 2015). Huang (2019) hypothesized that socioeconomic disadvantages in childhood alter DNA methylation, which in turn affects obesity in adulthood, and used mediation methods for testing this hypothesis. This is a typical example of the mediation process: the hypothesis tested whether the outcome (obesity) is affected by the exposure (socioeconomic level) through a mediator (DNA methylation).

In mediation analysis, two hypotheses are tested: the effect of the exposure on the mediator, and the effect of the mediator on the outcome. Finding both of them as true is accepting the hypothesis that the influence of the exposure on the
outcome is mediated, and that the mediator is essential for understanding the connection between them. Hence, we are interested in a composite hypothesis which contains both of the preceding hypotheses. Some statistical literature refers to this setting of composite hypotheses, as the intersection-union test (Berger and Hsu, 1996, Liu and Berger, 1995, Berger, 1982).

The null hypothesis of mediation can be divided into three cases: The first is when the mediator is not significantly influenced by the exposure but significantly influence the outcome; the second is when the mediator is significantly influenced by the exposure but it does not significantly influences the outcome; and the third case is when both influences are insignificant. Standard tests for the hypothesis, such as the joint significance test, which rejects the hypothesis if both influences were found as significant (MacKinnon et al., 2002), may be optimal under the first two cases, but become much more conservative under the third, as their significance level decreases. In genome-wide epidemiological research, when the number of hypotheses can be extremely large, the third case emerges more often. Consequently, employing more adaptive methods of analyzing mediation data is crucial for efficient research (Barfield et al., 2017).

One way to handle the power loss in the third case, is to use two-stage testing procedures (Ignatiadis et al., 2016, Djordjilović et al., 2020). Consider a multiple testing problem over a common parameter space. Assume that the first and the second cases of the null are composite hypotheses while the third case is a simple hypothesis consisting of a single parameter point. Assume also that for each hypothesis there is a test which is efficient for the first two cases, but not for the third case. We refer to this test as the base test.

The two-stage procedure is defined as follows. In the first stage, for every hypothesis, a stricter test called the filtration test is performed. Its aim is to filter, or retain, null hypotheses that are easy to identify, specifically the third case hypotheses. In the second stage, the original (base) test, up to an adjustment, is performed for the unfiltered hypotheses. This adjustment depends not only on the filtration test itself, but also on the size of the unfiltered hypotheses set.

The asymptotic behavior of this two-stage procedure needs to be considered cautiously. In practice, depending on the parameter values under the null, one may not be able to distinguish between, say, the first and the third cases. Thus, one has to take into account the local asymptotic behavior, which can vary across different parameter points and different kinds of filtration tests. In fact, the commonly used terminology to describe the parameter points' characterization is discrete and composed of the three aforementioned cases of the null and the alternative case. We use a continuous terminology to describe the parameter points. Specifically, we consider sequences of null hypotheses which belong, for instance, to the first case but converge to the third. We also consider sequences of filtration tests, which, depending on the convergence rate, may or may not be able to distinguish between the first and the third case. This approach is more appropriate for this context, in which there are infinite null parameter points, which are distinct from each other by their local geometry and asymptotic behavior, as well as alternatives that can approach different null points with various rates.
In order to get insights about this two-stage procedure, we first present the connection between filtration tests and shrinkage estimators. Indeed, the filtration test retains the null if it is likely that the value of the test statistic is a function of observations which are distributed according to the single parameter point of the third case. This in fact means that the null is retained for all parameter points which are closed, in some sense, to the third case. However, when the observations are drawn from parameter points that are not closed to the third case, the hypothesis is not filtered, and thus the base test, up to adjustment, is performed. This is related to shrinkage estimators, where the estimator is either shrinked to a specific point, when it is likely that the observations were distributed according to this parameter point, but otherwise it remains as is.

The canonical example of shrinkage estimator is the well-known Hodges’ estimator (Le Cam, 1953). For a location parameter model (e.g., normal distribution with unknown mean), Hodges’ estimator aims to identify more efficiently whether the true parameter point is 0 or not. Asymptotically, the variance of the Hodges’ estimator is lower than the Cramér-Rao bound at 0, which was considered to be the optimal that can be achieved. Such estimators are called super-efficient. Le Cam (1953) then showed that the Hodges’ estimator has various undesirable properties in a neighborhood of the parameter where the super-efficiency was obtained.

In this work we study the properties of shrinkage estimators, and characterize their behavior in different parameter points. We formulate theoretical results about filtration estimators, compared to regular estimators, in different scenarios of convergence rates and filtration probabilities, under some regularity conditions. We return to the multiple-testing framework in order to state results about the two-stage tests and controlling the FWER. We suggest a number of estimators and test statistics for the two-stage mediation procedures. We then investigate their empirical FWER and power, compared to regular estimators and tests, through simulations.

This work is organized as follows. In Section 2, we describe the mediation test setting and discuss the power loss challenge. In Section 3, the filtration tests framework is formulated, and linked to shrinkage estimators. In Section 4, we define efficiency in this setting and investigate convergence rates of estimators depending on the convergence of the parameter points. In Section 5, we present theoretical results about these estimators and the two-stage testing procedure. In Section 6, we perform simulation study of the two-stage procedure on the multiple-testing framework with various estimators. Proofs that were omitted from the main paper are provided in the Appendix.

2. Testing for Mediation

2.1. Definitions and Assumptions

Being one of the main tools in causal analysis, mediation analysis has become a statistical subject of major interest. In the basic setting, one considers a causal
system, which includes (see Figure 2.1): (a) an exposure \(A\); (b) an outcome \(Y\) affected by the exposure; (c) a mediator, i.e., a variable \(M\) added to the system, which is examined for how significantly it is influenced by \(A\) and influences \(Y\); and (d) a vector of baseline covariates \(X\), which includes every other variable that may possibly have an influence on some of the variables above. Having been revealed as a significant part of the system, the mediator might give a better perspective for statistical inference.

Formally, consider the following linear model for the connection between the variables:

\[
M = \gamma_0 + \gamma_X^T X + \gamma_A A + \varepsilon^M,
\]
\[
Y = \beta_0 + \beta_X^T X + \beta_A A + \beta_M M + \varepsilon^Y. \tag{2.1}
\]

The mediation hypothesis concerns whether or not the mediator \(M\) explains significantly the causal connection between the exposure \(A\) and the outcome \(Y\). The extent to which the mediator effects this connection is formulated by the natural indirect effect, NIE, whose definition requires an additional notation.

For two random variables, \(B\) and \(C\), where \(C\) is affected by \(B\), the potential outcome \(C_b\) is used for the random variable that its possible values correspond to the possible values \(C\) would attain had a variable \(B\) had been set to a value \(b\) (Pearl, 2001, 2009). The NIE is defined as

\[
\text{NIE}_{a,a^*}(Y) = E[Y_{a,M_a^*} - Y_{a^*,M_a^*}],
\]

which is the expected change in the value of \(Y\), when the value of the exposure \(A\) is fixed to \(a^*\), and the value of the mediator \(M\) changes its value from \(M_a\) to \(M_{a^*}\) (Robins and Greenland, 1992, Pearl, 2001, Vanderweele and Vansteelandt, 2009). Defined that way, the NIE is nonzero exactly when a change in the exposure would make such change in the mediator that in turn would change the effect, therefore it formally conveys our notion of mediation (VanderWeele, 2013).

The mediation hypothesis can now be phrased formally as

\[
H_0 : \text{NIE}_{a,a^*}(Y) = 0 \quad \text{vs.} \quad H_1 : \text{NIE}_{a,a^*}(Y) \neq 0.
\]
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Fig 2.2: Assumptions (i)-(iv) in Section 2.1 mean that connections through variables I, II, III and IV, respectively, do not exist.

Note that $Y_{aM_a^*}$ and $Y_{a^*M_a^*}$ are counterfactual quantities, i.e., they are not observed directly, thus in many cases the NIE cannot be evaluated from data with no additional assumptions. Consider the following four assumptions about the model, illustrated in Figure 2.2, for all possible values $a$, $a^*$ and $m$ of $A$ and $M$, respectively. Here, the independence of $B$ and $C$ conditional on $D$ is denoted by $B \perp \perp C \mid D$.

(i) $Y_a \perp \perp A \mid X$: No unknown confounders for the exposure-outcome relationship.
(ii) $Y_{am} \perp \perp M \mid A, X$: No unknown confounders for the mediator-outcome relationship, conditional on the exposure.
(iii) $M_a \perp \perp A \mid X$: No unknown confounders for the exposure-mediator relationship.
(iv) $Y_{am} \perp \perp M_a^* \mid X$: No unknown confounders for the mediator-outcome relationship, that itself is affected by exposure.

Under those assumptions, the NIE can be evaluated using the coefficients in the regression equations from the mediation model in (2.1). As mentioned, a test for the mediation effect, formulated as NIE nonzero, is equivalent to a test for the hypothesis in (2.2). Put in statistical terms, for the parameter of interest $\theta = (\gamma, \beta)$, the full parameter space is $\Theta = \mathbb{R}^2$, whereas the null space of this hypothesis is $\Theta_0 = \{\theta \mid \gamma A \beta M = 0 \}$.

2.2. Conservativity in Composite Hypotheses

Let $\gamma = \gamma_A$ and $\beta = \beta_M$ be the coefficients in the regression equations from the mediation model in (2.1). As mentioned, a test for the mediation effect, formulated as NIE nonzero, is equivalent to a test for the hypothesis in (2.2). Put in statistical terms, for the parameter of interest $\theta = (\gamma, \beta)$, the full parameter space is $\Theta = \mathbb{R}^2$, whereas the null space of this hypothesis is $\Theta_0 =$
\{ (\gamma, \beta) \in \mathbb{R}^2 \mid \gamma \beta = 0 \}. The null space \( \Theta_0 \) can be naturally divided into three complementary sub-spaces, \( \Theta_0 = \Theta_{00} \cup \Theta_{01} \cup \Theta_{10} \) (where \( \cup \) stands for disjoint union),

\begin{align*}
\Theta_{00} &= \{ (\gamma, \beta) \in \Theta_0 \mid \gamma = 0 \text{ and } \beta = 0 \}, \\
\Theta_{01} &= \{ (\gamma, \beta) \in \Theta_0 \mid \gamma = 0 \text{ and } \beta \neq 0 \}, \\
\Theta_{10} &= \{ (\gamma, \beta) \in \Theta_0 \mid \gamma \neq 0 \text{ and } \beta = 0 \}.
\end{align*}

We refer to the case that the true parameter \( \theta \in \Theta_{ij} \) as Case \((ij)\), for \( i,j = 0, 1 \). Cases \((01)\) and \((10)\) were mentioned in the introduction as the first and the second cases, whereas Case \((00)\) was mentioned as the third case.

Let \( \hat{\gamma} \) be a linear-regression estimator for the parameter \( \gamma \) and let \( \hat{\beta} \) be an estimator for \( \beta \). From the above four assumptions, one can show that the errors \( \varepsilon_M \) and \( \varepsilon_Y \) are independent (Huang, 2019). A natural point estimator for the function of the parameter which appears in (2.2),

\[ \psi = \psi(\gamma, \beta) = \gamma \beta, \]

would be \( T = \hat{\gamma} \hat{\beta} \). Similarly, the same \( T \) can be used as a test statistic for the hypothesis (2.2). This product estimator’s asymptotic behavior depends on which of the sub-spaces of the null contains the true parameter. As explained below, when \( \psi = 0 \), the rate of convergence of \( T \) is root-\( n \) for Cases \((01)\) and \((10)\), but is \( n \) for Case \((00)\).

Treating each of the parameters \( \gamma \) and \( \beta \) separately and considering the two simple hypotheses,

\begin{align*}
H_0^{(\gamma)} : \gamma &= 0 \quad \text{vs.} \quad H_1^{(\gamma)} : \gamma \neq 0, \quad (2.4) \\
H_0^{(\beta)} : \beta &= 0 \quad \text{vs.} \quad H_1^{(\beta)} : \beta \neq 0, \quad (2.5)
\end{align*}

yields to another approach. Rephrased as

\[ H_0 : \gamma = 0 \text{ or } \beta = 0 \quad \text{vs.} \quad H_1 : \gamma \neq 0 \text{ and } \beta \neq 0, \]

hypothesis (2.2) becomes a special case of intersection-union hypotheses:

\[ H_0 = H_0^{(\gamma)} \cup H_0^{(\beta)}. \quad (2.6) \]

Here, the null hypothesis \( H_0 \) is true if and only if at least one of the two simple hypotheses is true.

It is possible to test the hypothesis (2.2), decomposed as union hypothesis in (2.6), using the joint significance test. Let \( p^{(\gamma)} \) and \( p^{(\beta)} \) denote the \( p \)-values for the hypotheses in (2.4) and (2.5), respectively, based on the estimators \( \hat{\gamma} \) and \( \hat{\beta} \). When \( \gamma = 0 \), then \( p^{(\gamma)} \sim U(0, 1) \), while when \( \gamma \neq 0 \), we have \( p^{(\gamma)} \rightarrow 0 \), assuming consistency of \( \hat{\gamma} \), as the sample size increases. A natural statistic for the union test is \( p_{\text{joint}} = \max\{p^{(\gamma)}, p^{(\beta)}\} \). Under Case \((01)\), and by symmetry also under Case \((10)\), \( p_{\text{joint}} \) is distributed approximately \( U(0, 1) \). Indeed, for \( \alpha \in (0, 1) \),

\[ P(p_{\text{joint}} \leq \alpha) = P(p^{(\gamma)} \leq \alpha)P(p^{(\beta)} \leq \alpha) \rightarrow 1 \cdot \alpha = \alpha, \]
where we used the independence of $p^{(\gamma)}$ and $p^{(\beta)}$. However, under Case (00),
\[ P(p_{\text{joint}} \leq \alpha) = P(p^{(\gamma)} \leq \alpha)P(p^{(\beta)} \leq \alpha) \rightarrow \alpha \cdot \alpha = \alpha^2. \]

In our framework, maintaining a significance level of $\alpha$ would force rejection of the joint-significance test only for $p$-values that are less than the threshold $\alpha$, for Cases (01) and (10). However, if we knew in advance that we are under Case (00) is the only possible option in the null, we could adjust the threshold to a larger value, $\sqrt{\alpha}$, and as a result amplify the power in that case. An oracle revealing the current case would allow us to optimally customize our test and maximize the power, at least asymptotically.

3. Filtration

So far we discussed a single mediation problem, which yields a single hypothesis testing. In this section, we consider the mediation problem in a multiple-testing framework.

3.1. The Filtration Algorithm

In general, given a set of hypotheses, filtration is a preliminary test (the filtration test) performed on every hypothesis ahead of the main test (the base test), in order to determine which hypotheses are likely to belong to the null. The idea behind the filtration is that some null hypotheses may behave in a way that will ease identifying them, thus adjusting the criteria for them to be rejected, and hopefully increase power. Filtration is a popular method of increasing power in multiple hypotheses testing (McClintick and Edenberg, 2006, Talloen et al., 2007, Hackstadt and Hess, 2009).

A filtration procedure is a two-stage process, which might have the form detailed in Algorithm 1 (Bourgon et al., 2010, Ignatiadis et al., 2016). The algorithm is described for $\mathcal{H}$, a collection of $m$ hypotheses, with $T^i$ and $R^i$ as test statistic and rejection region, respectively, for the base test of the $i$-th hypothesis, and $S^i$ and $Q^i$ as test statistic and rejection region for the filtration test.

3.2. Shrinkage Estimators

In Algorithm 1, fix a specific hypothesis of index $i$, and omit the index for convenience. Consider a base test statistic $T$ which is an estimator for $\psi(\theta)$, and a filtration test statistic $S$ with rejection region $Q$, which, depending on filtering or un-filtering event, indicates the distance from the true parameter $\psi(\theta)$ to the predefined point $\psi(\theta_0)$ (in the mediation hypothesis, $\theta_0 = (0, 0)$). A point-estimation equivalent of this two-stage process can be phrased as
\[ T^{(S)} = (T - \psi(\theta_0))\mathbb{1}_{[S \in Q]} + \psi(\theta_0). \]
The estimator \( (3.1) \) encodes inside itself the two-stage process of Algorithm 1. Indeed, if the filtration test was not rejected (i.e., a filtration event occurred), the estimator’s value becomes \( \psi(\theta_0) \) for \( \theta_0 \in \Theta_0 \), and when the filtration test was rejected, \( (3.1) \) remains the same as the original \( T \). Thus, \( T(S) \) can be used as a test statistic to the test with an adjusted rejection region \( R_{\text{adj}} \). Note that the obtained estimator is a so-called shrinkage estimator. As an example, consider the base-test statistic \( T = \gamma \beta \) and the filtration test \( S \notin Q \) as \( |\gamma \beta| < cn^{-\delta} \), for a constant \( \delta > 0 \). The estimator obtained is \( \gamma \beta 1[|\gamma \beta| > cn^{-\delta}] \).

Shrinkage estimators were originally produced in order to improve performance over standard estimators, usually in a specific parameter point, obtained by “stretching” the values of estimator towards a fixed parameter point. In many cases, the obtained improvement depends on the performance measurement (e.g., the loss function used) and might be problematic at a closer look.

A possible form of a shrinkage estimator, based on an existing estimator \( T \) for \( \psi(\theta) \), and some shrinkage function \( A_{\theta_0} \), can be written as

\[
S_{\theta_0}(T) = (T - \psi(\theta_0))A_{\theta_0}(T) + \psi(\theta_0),
\]

which generalizes the form in \( (3.1) \). Two well-known examples of shrinkage estimators which fit into this form are James-Stein estimator (James and Stein, 1992) and Hodges’ estimator (Le Cam, 1953, van der Vaart, 1998).

One of the versions of Hodges’ estimator is defined as follows. Consider a location model, specifically normal distribution \( N(\mu, 1) \) with unknown mean and a fixed variance. Let \( X_1, \ldots, X_n \) be a sequence of i.i.d. observations from the distribution, and define, for estimating the expectation \( \mu \),

\[
\tilde{\mu} = \overline{X}1[|\overline{X}| > n^{-1/4}].
\]

It can be shown (van der Vaart, 1998) that while at every parameter point \( \mu \neq 0 \) the estimator \( \tilde{\mu} \) behaves asymptotically similar to the regular \( \overline{X} \) with root-\( n \) rate of convergence, when \( \mu = 0 \), \( \tilde{\mu} \) converges to \( \mu = 0 \) with an “arbitrarily fast” rate. The case \( \mu = 0 \) is now distinguished from all the others.

The idea behind the shrinkage estimators we discussed and showed in \( (3.1) \) is inspired from the idea behind Hodges’ estimator, and shrinkage estimators...
generally. In both situations, a regular estimator is manipulated in order to use inference about the current case of the parameter, and by that improve estimation. Unfortunately, the superiority of Hodges’ estimator at $\mu = 0$ comes with shortcomings at parameter points in its neighborhood. For the sake of formulating this idea, we shall use the local asymptotic framework of statistical experiments and their limits.

3.3. Shrinkage Estimators for Testing Mediation

Consider the multiple mediation problem, with a collection of hypotheses $H^*_0: \gamma^i \beta^i = 0$ vs. $H^*_1: \gamma^i \beta^i \neq 0$, for $i = 1, \ldots, m$. (3.4)

For each of the hypotheses, the null space contains parameter points with at least one coordinate equals to 0, and similarly composed to three sub-spaces as in (2.3). In our setting, the aim of the filtration step is to identify null hypotheses of Case (00), based on the different properties that these null hypotheses have. The filtration test thus, has a simple null hypothesis form

$$\tilde{H}^*_0: \theta^i = \theta_0 \text{ vs. } \tilde{H}^*_1: \theta^i \neq \theta_0,$$

where $\theta^i = (\gamma^i, \beta^i)$ and $\theta_0 = (0,0)$.

One approach for finding test statistic is using the likelihood-ratio test,

$$\Lambda = \sup_{\theta \in \Theta} \frac{L(\theta | X)}{L(\theta_0 | X)}.$$

Direct calculation shows that the likelihood-ratio test statistic is $\| (\tau, \bar{\theta}) \|^2$, so it can be considered as a natural test statistic $T^*$ for the filtration test.

The likelihood-ratio approach can be applied also to the base test statistic $T$. Here, the separation is between the null $\Theta_0 = (\{0\} \times \mathbb{R}) \cup (\mathbb{R} \times \{0\})$ and $\Theta = \mathbb{R}^2$. Given the estimator $\tau$ and $\bar{\theta}$, the numerator always equals to a constant, i.e. the value the likelihood function returns for $\theta = (\tau, \bar{\theta})$. The denominator is the likelihood function’s value when $\theta = (\gamma, 0)$ if $\gamma \leq \beta$ and $\theta = (0, \beta)$ otherwise. Therefore, the test statistic is $\min \{ |\gamma|, |\beta| \}$, which is equivalent to $\max \{ p^{(\gamma)}, p^{(\beta)} \}$. This supplies a justification for choosing this statistic for the base test hypothesis.

Phrasing the abstract separation idea can be as follows. We would like to find a function $\phi$ which maximizes $P_\theta(\phi(\tau, \bar{\theta}) > t)$ under an arbitrary parameter $\theta$, which is not in Case (00), while maintaining the same probability $P_\theta(\phi(\tau, \bar{\theta}) > t) \leq \alpha$ for $\theta$ in Case (00). Not always there is a perfect test which has the uniformly best power among those with the same level.

Let us restrict ourselves only to filtration tests $S \in Q$ of the form $\phi(\tau, \bar{\theta}) \leq t$. Thus, we should consider and compare various functions $\phi$, when the purpose of each of them is to separate or distinguish between the point $(0,0)$ and other points in $\Theta$. Later on we will study the function $\phi : (x, y) \mapsto xy$ in depth. We
will also discuss other functions, such as \((x, y) \mapsto \|(x, y)\|, (x, y) \mapsto \|(x, y)\|^2, (x, y) \mapsto \max \{|x|, |y|\}, (x, y) \mapsto |x| + |y|,\) and in general \((x, y) \mapsto \|(x, y)\|_p,\) for the \(L^p\)-norm \(\|\cdot\|_p, p \in [1, \infty].\) The induced shrinkage estimators for the product estimator would have the form \(\gamma \beta \in R^*, \) and the shrinkage estimator for the screen-min procedure (Djordjilović et al., 2020), which filters according to the minimal \(p\)-value, will be \(\min \{|\gamma|, |\beta|\} 1_{\max \{|\gamma|, |\beta|\} \in Q}.\) Shrinkage estimators for other statistics can be constructed similarly.

In order to draw useful insights about these estimators as well as others, we need to study and compare their local asymptotic behavior in neighborhoods of parameter points.

### 4. Convergence Rates

#### 4.1. Convergence Rates

Let \(\gamma = \gamma^A\) and \(\beta = \beta^M\) be the coefficients from the regression equation (2.1), and let \(\gamma, \beta\) their respective estimators. Under standard regularity conditions, \(\sqrt{n}(\hat{\gamma} - \gamma) \rightarrow N(0, \sigma_\gamma^2)\) and \(\sqrt{n}(\hat{\beta} - \beta) \rightarrow N(0, \sigma_\beta^2).\) Thus, \(\hat{\gamma} = \gamma + o_p(1), \) \(\hat{\tau} \sim N(\gamma, \frac{1}{n} \sigma_\gamma^2)\) and \(\hat{\beta} = \beta + o_p(1), \) \(\hat{\beta} \sim N(\beta, \frac{1}{n} \sigma_\beta^2),\) where \(\gamma\) and \(\beta\) can be thought of as sample means approximations. In this section we will analyze the estimators \(\hat{\gamma}, \hat{\beta}\) based on their normal approximation \(\gamma, \beta\) (see also discussion in Huang, 2019). As we show below, the estimator \(\hat{\gamma} \hat{\beta},\) similarly to the original estimator \(\gamma \beta,\) behaves differently in the parameter point \((0, 0)\) compared to the other parameter points in the null.

Consider the estimator \(\theta = \gamma \beta.\) In order to calculate the exact convergence rate, write

\[ \gamma \beta - \gamma \beta = (\gamma - \gamma)(\beta - \beta) + \beta(\gamma - \gamma) + \gamma (\beta - \beta). \quad (4.1) \]

When \(\gamma = \beta = 0,\) the last two summands vanish, and we are left with one summand of \(n\)-rate.

Another way of showing that is using the delta method. Sobel (1982) showed that,

\[ \sqrt{n}(\hat{\gamma} \hat{\beta} - (\gamma, \beta)) \rightarrow N(0, \Sigma) \]

for \(\Sigma = \text{diag} \left(\sigma_\gamma^2, \sigma_\beta^2\right).\) Then, for \(\phi(x, y) = xy,\)

\[ \sqrt{n}(\hat{\gamma} \hat{\beta} - (\gamma, \beta)) = \sqrt{n}(f(\gamma, \beta) - f(\gamma, \beta)) \rightarrow N\left(0, \sigma_\gamma^2 f'(\gamma, \beta) + \sigma_\beta^2 f'(\gamma, \beta)\right). \quad (4.2) \]

Note that for parameter points in Cases (01) and (10), the convergence rate is root-\(n.\) As already proved in exact terms in (4.1), Case (00) yields a higher rate.
The delta method argument can be generalized to show that the estimator \( \gamma \beta \) is not the only example for estimator with higher rate of convergence in \((0, 0)\).

Consider the shrinkage estimator in (3.1) where the filtration test statistic \( S \) has the form \( \phi(\gamma, \beta) \). Interestingly, under some conditions on \( \phi \), the convergence rate of \( \phi(\gamma, \beta) \) might depend on the parameter point.

**Lemma 4.1.** Let \( \phi : \mathbb{R}^p \to \mathbb{R} \) be a function which is differentiable and attains its minimum at \( \theta_0 \). Let \( T_n = (T_{n1}, \ldots, T_{np}) \) be a consistent estimator for \( \theta \) with convergence rate \( r_n \). Then, the convergence rate of \( \phi(T_n) \) at \( \theta_0 \) that is faster than \( r_n \).

**Proof.** Since \( \phi \) is convex and symmetric, it attains a global minimum at \( \theta_0 \). Let \( r_n(X_n - \theta) \sim L \), for some distribution law \( L \). By the delta method (van der Vaart, 1998, Theorem 3.1), \( r_n(\phi(X_n) - \phi(\theta)) \sim \phi'(\theta_0) \cdot L \). At the minimum point \( \theta_0 \) the derivative vanishes, so the latter limit equals 0, and thus the rate is higher than \( r_n \).

Consider for instance the separation function \( \phi(x, y) = x^2 + y^2 \). This function can be used for creating a test statistic for the filtration test. Using Lemma 4.1, it can shown that \( \gamma^2 + \beta^2 \) is another example for an estimator with higher rate of convergence at \((0, 0)\).

### 4.2. Irregularity of Estimators

One way of coping with the problem of different convergence rates is using normalization. Consider the following two examples: the squared-norm estimator \( \gamma^2 + \beta^2 \), and the product estimator \( \gamma \beta \). As mentioned in the previous section, for both of them, the convergence rate at 0 is different from other parameter point, which can be thought of as a singularity point of the standard deviation in 0. Dividing these estimators by (an estimator for) their limit standard deviation, as it appears in the limit distribution in the delta method, can be used in order to remedy the difference in rates. The obtained normalized estimators, up to an asymptotically negligible terms in the standard deviation are, respectively,

\[
\frac{\gamma^2 + \beta^2}{\sqrt{\sigma_\gamma^2 \gamma^2 + \sigma_\beta^2 \beta^2}}
\]

and the so-called Sobel’s test statistic (Sobel, 1982, MacKinnon et al., 2002, MacKinnon, 2012, Huang, 2019),

\[
\frac{\gamma \beta}{\sqrt{\sigma_\gamma^2 \gamma^2 + \sigma_\beta^2 \beta^2}} \tag{4.3}
\]

Sobel’s test is usually performed as a \( t \)-test or \( z \)-test based on the normal approximation in (4.2).
It can be shown that the convergence rate of both estimators is indeed root-\(n\), even at Case (00). However, the asymptotic behavior of these estimators is still problematic for Case (00), and for the sake of formulating this idea, we will first need the following definition of regular estimators.

**Definition 4.2** (van der Vaart, 1998, Chapter 8.5). An estimator \(T\) for \(\psi(\theta)\) is regular at a parameter point \(\theta\) if

\[
\sqrt{n} \left( T - \psi \left( \theta + \frac{h}{\sqrt{n}} \right) \right) = L_\theta
\]

\(L_\theta\) is the same limit distribution for every \(h \in \mathbb{R}\).

The following lemma, whose its proof is given in the Appendix, sheds light on the behavior of the normalized estimators in (0, 0).

**Lemma 4.3.** Both of the estimators

\[
\frac{\pi \beta}{\sqrt{\sigma_\beta^2 \gamma^2 + \sigma_\gamma^2 \beta^2}}
\]

and

\[
\sqrt{\sigma_\beta^2 \gamma^2 + \sigma_\gamma^2 \beta^2}
\]

are irregular at (0, 0).

Note that the original, unnormalized estimators, \(\pi \beta\) and \(\sigma_\beta^2 \gamma^2 + \sigma_\gamma^2 \beta^2\), are regular at (0, 0) as the limit distribution is always 0. As it turns out, by performing the normalization, the problem of different rates of convergence is only replaced with the irregularity at the point (0, 0), which makes the estimator’s limit behavior depend on small neighborhood of the parameter and the convergence direction of the parameter sequence.

As a conclusion of the previous discussion, we see that different estimators, have various strengths and weaknesses. Therefore, choosing the base and filtration test statistics for the shrinkage estimator in (3.1) becomes complicated. There is not necessarily one optimal way to do so, and there is a trade-off to be considered between the different options.

### 5. Local Asymptotic Analysis

In order to examine efficiency of estimators in the neighborhood of a parameter point, we use the local asymptotics framework, which basically lets the parameter space depend on \(n\). In this section, we follow van der Vaart (1998, Chapters 7, 9, and 15). Formally, the probability measure is of the form \(P_{n,\theta} = P_\theta^n\), which means that as the number of observations increases, the true parameter also changes. Usually \(\theta_n = \theta + r_n^{-1}h\), i.e., \(\theta_n\) converges to a constant parameter \(\theta\) with rate \(r_n\).
Back to the Hodges example presented in (3.3), the Hodges’ estimator should also be examined in the local asymptotic framework, for a sequence of parameters $\mu_n$ that approaches 0. When $\mu_n = o(n^{-1/4})$ and also $\mu_n = \omega(n^{-1/2})$, for instance when $\mu_n = n^{-1/3}$, then $n^{1/2}(\mu n - \mu) \to -\infty$ (van der Vaart, 1998, Example 8.1). This means that although the estimator looks more efficient than the regular one at 0, there are sequences of parameters $\mu_n$ which their normalized distance from the estimator and diverges. The exact rate of convergence depends on the problem in question.

5.1. Characterization of Shrinkage Estimators

Filtration estimators, in general, have properties similar to the Hodges’ estimator. Asymptotic improvement in the rate of convergence in some points exists only with corresponding low performance in others. We aim to identify the regions in which a filtration estimator is better as well as weaker than the original one.

The common measure for comparing efficiency of two estimators $T_1$ and $T_2$ of a parameter $\psi(\theta)$ in a parameter point $\theta$ is the asymptotic relative efficiency (ARE). The ARE is equivalent to the limit ratio of the corresponding variances,

$$\text{ARE}(T_1, T_2; \theta) = \lim \frac{\sigma_2^2(\theta)}{\sigma_1^2(\theta)}.$$  

The interpretation for the ARE is the rate it takes to $T_2$ to estimate $\psi(\theta)$ with variance 1, relative to $T_1$. Thus, ARE less than 1 indicates that $T_2$ is more efficient than $T_1$, and vice versa.

The ARE, as formulated explicitly above, takes into account only the variance of the estimators, and not the asymptotic bias rate of convergence. In Hodges-like filtration estimators, the asymptotic bias is usually the cost for the super-efficiency in some points. In order to consider both these quantities, the asymptotic variance and the asymptotic bias, into the comparison, we shall compare their mean squared error (MSE). Indeed, the MSE weighs the variance and the square of the bias with equal weights: $\text{MSE}(T, \theta) = E[(T - \theta)^2] = \text{var}(T) + E[T - \theta]^2$. Generalizing the definition of ARE, we treat MSE-ratio less than 1 as indicating that $T_2$ is more efficient than $T_1$ and vice versa.

Let $M$ be the limit MSE-ratio of $T_2$ relatively to $T_1$. We say that $T_2$ is much more efficient than $T_1$ when $M = 0$; more efficient when $0 < M < 1$, equivalent when $M = 1$; less efficient when $1 < M < \infty$; and much less efficient when $M = \infty$.

Assumption 5.1. The original estimator $T_n$ is $r_n$-consistent for some rate $r_n$, such that the sequence $r_n(T - \psi(\theta))$ has limit distribution with mean 0 and finite variance.

This assumption holds true, for example, for all asymptotically linear estimators, with $r_n = \sqrt{n}$. Under this assumption, the following theorem holds.
Theorem 5.2. Let $T_n$ be the regular estimator, and $T_n^{(S)} = (T_n - \psi(\theta_0))1_{|S| \leq Q} + \psi(\theta_0)$ be the filtration estimator based on it. Let $L = \lim P_{\theta_0}(S_n \notin Q_n)$ and $K = \lim \frac{1}{\sigma_n^2}(\psi(\theta_n) - \psi(\theta_0))$.

1. When $L = 1$, then $T_n^{(S)}$ is much more efficient than $T_n$ when $K = 0$; more efficient when $0 < K < 1$; equivalent when $K = 1$; less efficient when $1 < K < \infty$; and much less efficient when $K = \infty$.
2. When $0 < L < 1$, then when $K = 0$, $T_n^{(S)}$ is more efficient than $T_n$, and when $K = \infty$, the estimator is much less efficient, and for $0 < K < \infty$, the relative MSE of the estimators can be either more efficient, equivalent or less efficient.
3. When $L = 0$, then $T_n^{(S)}$ equivalent to the original $T_n$.

Note that the existence of the cases discussed above is affected by the chosen test statistics and the rejection regions for the base and filtration tests.

5.2. Case Study: The Product Statistic

Recall that $\gamma$ and $\beta$ are the estimators for the regression coefficients $\gamma$ and $\beta$ in the regression Model (2.1), respectively. In this section we use Theorem 5.2 to study the properties of the shrinkage estimator $T_n^{(S)} = \overline{\gamma}\overline{\beta}1_{n^t[|\overline{\gamma}| > \epsilon]}$ based on the base and filter test statistic $\overline{\gamma}\overline{\beta} = \psi(\overline{\gamma}, \overline{\beta})$, for $\psi(x, y) = xy$. Its aim, as detailed in Section 3, is to filter hypotheses which are likely to belong to the null parameter point $(0, 0)$.

We now consider sequences of parameters $\theta_n = \gamma_n\beta_n$ approaching the constant true parameter $\theta_0 = \gamma_0\beta_0$. The rate of convergence, $K = \lim \frac{1}{\sigma_n^2}(\psi(\theta_n) - \psi(\theta_0))$, is in this case

$$K = \lim \frac{\gamma_n\beta_n}{\sqrt{n^{-1}(n^{-1} + \gamma_n^2 + \beta_n^2)}}.$$

The value of $K$ can be partially characterized as a function of $\gamma_n$ and $\beta_n$. Without loss of generality, we assume that both $\gamma_n$ and $\beta_n$ are non-negative. Since $2\gamma_n\beta_n \leq \gamma_n^2 + \beta_n^2$, we have

$$K \leq \lim \frac{\gamma_n^2 + \beta_n^2}{2\sqrt{n^{-1}(n^{-1} + \gamma_n^2 + \beta_n^2)}} = \lim \frac{n(\gamma_n^2 + \beta_n^2)}{2\sqrt{1 + n(\gamma_n^2 + \beta_n^2)}}.$$ (5.1)

When $n(\gamma_n^2 + \beta_n^2) \to 0$, then $K = 0$. When $n(\gamma_n^2 + \beta_n^2) \to c$ then $K \leq \frac{c}{\sqrt{1+c}}$, so for $c$ smaller than the golden ratio $\phi = \frac{1+\sqrt{5}}{2}$, then, by (5.1), we have $K < 1$. Similarly, it can be bounded below: When $n(\gamma_n^2 + \beta_n^2) \to \infty$, then $K \geq \alpha$, and when $n(\gamma_n^2 + \beta_n^2) \to c$ then $K \geq \frac{c}{\sqrt{1+c}}$.

The limit probability $L = \lim P_{\theta_0}(S \notin Q)$ can be characterized into regions according to Table 5.1, where $A = \max \{\lim n^\delta \gamma_n \beta_n, \lim n^{\delta-1/2} \sqrt{n^{-1} + \gamma_n^2 + \beta_n^2}\}$.
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The classification in Table 5.1 comes from approximating the statistic by its mean and standard deviation,
\[
γ \beta = E[γ \beta] + O_{P(\cdot)} \left( \frac{\text{var}(γ \beta)}{n} \right)^{1/2} = γ_n β_n + O_{P(\cdot)} \left( \sqrt{n^{-1}(n^{-1} + γ_n^2 + β_n^2)} \right).
\]

\[\text{(5.2)}\]

Explanation to the classification in the table may be provided as follows. When \(δ < 1\), the statistic \(n^δ γ \beta\) might be bounded in high probability by the constant \(c\). When both \(\lim n^δ γ_n β_n = 0\) and \(\lim n^{δ-1/2} \sqrt{γ_n^2 + β_n^2} = 0\), then \(γ \beta \to 0\), which means \(L = 1\). The rate of convergence \(K\) directly influences the MSE-ratio.

When \(δ > 1\), we have that \(L = 0\), for every rate of convergence to the parameters. Indeed, the estimator \(n^δ γ \beta\) will have to have standard deviation which converges to \(∞\), so it is not possible for the estimator to be bounded in positive probability. When \(A = ∞\), for any value of \(δ\), the same reasoning holds, since by definition either the mean or the standard deviation converges to \(∞\) and cannot be bounded in positive probability, which means that the estimators are equivalent for every rate of convergence of the parameters.

When \(0 < A < ∞\), then \(0 < L < 1\). It may happen for \(δ = 1\), and then there is no possibility of the extreme cases \(K = 0\) and \(K = ∞\); When \(n^{δ/2} γ_n / n^{1/2} β_n → h\), \(0 < h < ∞\), \(K\) also gets values in \((0, ∞)\), and so as the MSE-ratio. When \(h = 0\), the MSE-ratio is also in \((0, ∞)\), and \(h = ∞\) is not possible since it belongs to the case \(L = 0\).

Simulations of different MSE-ratios, as functions of \(L\) and \(K\), are shown in Figure 5.1. The filtration test in Figure (a) is \(|γ \beta| < 4n^{-0.7}\), in Figure (b) is \(|γ \beta| < 2.5n^{-1}\), and in Figure (c) is \(|γ \beta| < 2.5n^{-1.5}\). The true means \((γ_n, β_n)\) for Figure (a) are (from the least value of \(K\) to the greatest) \((n^{-0.5}, n^{-0.6})\), \((n^{-0.5}, n^{-0.5})\), \((2n^{-0.5}, n^{-0.5})\), \((2n^{-0.5}, 2n^{-0.5})\), and \((2n^{-0.4}, n^{-0.4})\). The true means for Figure (b) are (from the least value of \(K\) to the greatest) \((0.7n^{-0.5}, 0.7n^{-0.5})\), \((1.075n^{-0.5}, 1.075n^{-0.5})\), and \((2n^{-0.5}, 2n^{-0.5})\). The true means for Figure (c) are \((n^{-1}, n^{-1})\).

The intermediate case can be bounded theoretically, as shown in the Appendix.

5.3. Multiple Mediation Hypotheses

So far, we discussed the asymptotic behavior of shrinkage estimators under different parameter points. Now, we would like to return to the multiple-hypotheses framework.
Considering alternatives as parameter points approaching to the null with the usual rate of root-n, i.e., the alternative has the form $\theta = \theta_0 + \frac{h}{\sqrt{n}}$, where $\theta_0$ is in the null. Hence, the parameter of interest is a re-scaled version of the original parameter, which can be rephrased as $h = \sqrt{n}(\theta - \theta_0)$.

Furthermore, the parameter space as a whole is re-scaled and gets the form $H = \sqrt{n}(\Theta - \Theta_0)$. The notion of local parameter space, enables studying the asymptotic properties by capturing the local behavior around parameter points. When the parameter point $\theta_0$ is in the interior of the space $\Theta \subseteq \mathbb{R}^k$, the local space converges to whole $\mathbb{R}^k$. Otherwise, the local space structure depends on the geometry of the parameter space at a vicinity of $\theta_0$.

When the null hypothesis consists of a unique interior point, the geometry of the local null space is trivial, yet the situation is still complicated. As discussed in van der Vaart (1998, p. 217), “if $\theta$ is of dimension $k > 1$, then there exists no uniformly most powerful test, not even among the unbiased tests. A variety of tests are reasonable, and whether a test is ‘good’ depends on the alternatives at which we desire high power”.

For composite hypotheses, it can be even more challenging. There is need to consider the local null parameter spaces as well, namely $H_0 = \sqrt{n}(\Theta_0 - \Theta_0)$ for points $\theta_0 \in \Theta_0$. These local spaces can have different properties such as geometry and rates of convergence. When $\theta_0$ is an inner point of $\Theta_0$ in the usual Euclidean topology, then the local null space converges to $\mathbb{R}^k$. Otherwise, the geometry can be non-trivial and may affect the properties of the test in the limit, such as the distribution under the null.

When testing for mediation, the null hypothesis is composite, so the local parameter depends on the true point in the null. More formally, for the null point $(0, 0)$, the local space of null parameter points is composed of $\{(h, 0) \mid h \in \mathbb{R}\} \cup \{(0, h) \mid h \in \mathbb{R}\}$, while the alternative consists $\{(h_1, h_2) \mid h_1h_2 \neq 0\}$. However, the local null space of $(c, 0)$, $c \neq 0$, is $\{(c + h, 0) \mid h \in \mathbb{R}\}$, while the local alternative space is $\{(c + h_1, h_2) \mid h_2 \neq 0\}$. These spaces are illustrated in Figure 5.2. As a result, these different spaces shed light on the difficulty in estimation and testing for mediation.
5.4. Controlling the FWER

As a conclusion from the above discussion, considering null points as divided into the discrete cases does not take into account the local behavior of the points. Using this understanding, we provide two ways to bound the finite-sample FWER which take this understanding into account.

In the following we provide an upper bound on the FWER for the two-stage procedure presented in Section 3.1. For set of $m$ hypotheses, we denote by $f \in \{0, 1\}^m$ the vector whose $i$-th coordinate is $1_{[S \in Q]}$. Let $F = \sum_{i=1}^m f_i$.

**Theorem 5.3.** Assume that all $m$ mediation hypotheses are independent. Assume that $\theta_0 = \arg \min_\theta P_\theta(S \in Q)$ (the parameter point with the lowest filtration probability is $\theta_0$). Assume also we use an adaptive adjusting method (after filtration step, and after computing $F$, number of unfiltered hypotheses), such that under the null $P_\theta(T \in R^{adj} \mid F) = \frac{P_{\theta_0}(S \in Q)}{F} \alpha$. For the special case that $T$ is a p-value, it can be achieved for example by multiplying the rejection threshold by $\frac{P_{\theta_0}(S \in Q)}{F}$ (similarly to Bonferroni). Let $V$ be the number of true null rejected. Then $P(V \geq 1) \leq \alpha$.

The following result generalizes the FWER bound given by Proposition 1 of Djordjilović et al. (2020) for the two-stage screen-min procedure, in which Djordjilović et al. (2020) assumed discrete separation of the null into cases (Denoted here as Cases (00), (01) and (10)).

**Theorem 5.4.** Assume that all $m$ mediation hypotheses are independent. Assume we use an adaptive adjusting method (after filtration step, and after computing $F$, number of unfiltered hypotheses), such that under the null $P_\theta(T \in R^{adj}) = \frac{\alpha}{F}$. For the special case that $T$ is a p-value, it can be achieved for example by multiplying the rejection threshold by $1/F$ (similarly to Bonferroni). Let $V$ be the number of true null rejected. Then

$$P(V \geq 1) \leq E\left[\left(1 - \max_{\theta \in \Theta} P_\theta(T^i \in R^i \mid S^i \in Q^i)\right)^F \right] 1_{[F > 0]}.$$

As stated, hypotheses with filtration probability 0 are not altered by the filtration stage, thus remain with the same (wanted) behavior of the original, base test. Other hypotheses may be filtered, depending on the filtration stage.

The advantage of the first theorem is that it is possible, at least numerically, to calculate $P_{\theta_0}(S \in Q)$, thus the bound can easily be used. While the bound in the second theorem may be less conservative, it is more difficult to explicitly calculate it, as the bound involves both calculating $\max_{\theta \in \Theta} P_\theta(T^i \in R^i \mid S^i \in Q^i)$ and taking expectation. Relative to a fixed alternative, both bounds can be used to optimize the power while controlling the FWER. As discussed in Section 5.3, the challenge is more complicated since the alternatives are unknown. Given a prior over both null and alternative parameter points, one can optimize the tests to achieve better bounds, see, for example, discussion in Djordjilović et al. (2020), Section 4. Specifically, while the stated theorems concern controlling the
finite-sample FWER, $L$ and $K$ in Theorem 5.2 with the local asymptotic framework can be used to achieve better bounds for the asymptotic FWER. These are important questions, which deserve future research.

In some settings, one can explicitly show that the two-stage procedure controls the FWER. Assume that we use an adaptive adjusting method (after filtration step, and after computing $F$, number of unfiltered hypotheses), such that under the null $P_{θ}(T ∈ R^{adj}) = α/F$. For the special case that $T$ is a p-value, it can be achieved for example by multiplying the rejection threshold by $1/F$ (similarly to Bonferroni). The following example, inspired by Huang (2019), is such an example.

**Example 5.5.** Assume that statistics follow the normal distribution with $γ_0 \sim N(γ_n, n^{-1/2}σ)$ and $β_0 \sim N(β_n, n^{-1/2}σ)$, for some constant $σ$, and the means are distributed as follows:

- With probability $π_0$ (Case (00)), $γ_n = β_n = 0$.
- With probability $π_1$ (Case (10)), $γ_n \sim N(1 + n^{-1/2}, n^{-1/2})$ and $β_n = 0$.
- With probability $π_2$ (the alternative), $γ_n \sim N(1 + n^{-1/2}, n^{-1/2})$ and $β_n \sim N(n^{-1/2}, n^{-1/2})$.

Here $π_0 + π_1 + π_2 = 1$ are unknown. Let us have $m$ true null hypotheses, tested with the two-stage procedure, where an hypothesis is filtered (at the first stage) if $|γβ| < cn^{-δ}$, for some predefined $c > 0$, $\frac{1}{2} < δ < 1$. In this scenario, with
adjusting as proposed in Theorem 5.4,

\[ P(V \geq 1) \leq \sum_{i=1}^{m} P(T^i \in R_{i,\text{adj}} \text{ and } S^i \in Q^i) \]

\[ = \sum_{i=1}^{m} \left( \frac{\pi_0}{\pi_0 + \pi_1} P(T^i \in R_{i,\text{adj}} \text{ and } S^i \in Q^i \mid \text{Case (00)}) \right. \]

\[ + \left. \frac{\pi_1}{\pi_0 + \pi_1} P(T^i \in R_{i,\text{adj}} \text{ and } S^i \in Q^i \mid \text{Case (10)}) \right) \]

\[ = \sum_{i=1}^{m} \frac{\pi_1}{\pi_0 + \pi_1} P(T^i \in R_{i,\text{adj}} \mid \text{Case (10)}). \]

Now, since \( F \to \frac{\pi_1}{\pi_0 + \pi_1}, \) and \( P(T^i \in R_{i,\text{adj}}) = \frac{1}{\pi} P(T^i \in R^i), \) we have FWER no more than the predefined level \( P(T^i \in R^i) = \alpha. \)

6. Applications to Multiple Comparison

Consider the multiple tests framework discussed in Sections 3.1 and 5.3. In this section we aim to compare the proposed two-stage procedure through simulations. We present three settings. The first is similar to the setting of Djordjilović et al. (2020). We simulate the estimators \( \gamma \) and \( \beta \) for the regression coefficients in Section 4.1, from normal distribution with means \( \gamma_n \) and \( \beta_n \) and standard deviations \( \frac{1}{\sqrt{n}} \sigma. \) The true means \( \gamma_n \) and \( \beta_n \) are distributed as detailed in the configurations columns in Table 6.1.

| \( \gamma_n \) | \( \beta_n \) | Configuration 1 | Configuration 2 | Configuration 3 |
|---|---|---|---|---|
| 1 | 0 | 65% | 25% | 25% |
| 2 | 3n^{-3/4} | 0 | 0% | 15% | 0% |
| 3 | 3n^{-1/2} | 0 | 30% | 25% | 35% |
| 4 | 3n^{-1/3} | 0 | 0% | 10% | 0% |
| 5 | 1 + 3n^{-1/2} | 0 | 0% | 15% | 15% |
| 6 | 3n^{-1/2} | 3n^{-1/2} | 5% | 4% | 0% |
| 7 | 3n^{-1/3} | 3n^{-1/2} | 0% | 3% | 0% |
| 8 | 1 + 3n^{-1/2} | 3n^{-1/2} | 0% | 3% | 10% |

**Table 6.1**

Parameters

Following Algorithm 1, we first use filtration tests. We compare numerous filtration methods, where the filtering event \( A \) is each of the following:

- \( A = \left[ \min \{ p^{(\gamma)}, p^{(\beta)} \} \geq 0.0004 \right] \)
- \( A = \left[ F^{-1}_{\chi^2_2} (\gamma^2 + \beta^2) \geq 0.001 \right] \), where \( F^{-1}_{\chi^2_2} \) is the \( \chi^2_2 \)-distribution CDF.
- \( A = \left[ \gamma \beta < cn^{-\delta} \right], \) for \( \delta = 0.8, 0.9 \) and \( 1 \) and \( c = 1, 2, 3 \) respectively, similar to the filtration used in the Case Study in Section 5.2.

We retain each of the hypotheses that its filtration event \( A \) is true. We are then left with \( F \) hypotheses that were not filtered. In all methods, we then
compute for every remaining hypothesis another \( p \)-value, \( \max \{ p^{(\gamma)}, p^{(\beta)} \} \) for the original mediation hypotheses, as in (3.4). We adjust the remaining \( p \)-values with Bonferroni method, and then reject hypotheses whose \( p \)-values are below a certain threshold. In each test there are 200 hypotheses, and we repeated the simulation 500 times. The FWER bounds in Theorems 5.3 and 5.4 are conservative, and following Djordjilović et al. (2020), we conducted the base test with Bonferroni correction, without considering the filtration probability.

In all configurations, the only change is the filtration \( p \)-value, and the base test \( p \)-values and adjusting method are the same (beside the exact adjustment performed, which depend on the set of remaining hypotheses, after the filtration). In Figure 6.1 are shown the FWER and the power of the different two-stage methods. An R package that implements the different testing procedures and the examples presented above can be found at https://github.com/yotamleibovici/twostageshrink.

In all methods the simulated FWER was approximately under 0.05. In both configurations, there was a significant improvement of the filtration procedures compared to the procedure without filtering at all. In Configuration 2, there is an improvement of the product methods with limit probability 1 (i.e., \( \delta = 1 \)).
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0.8 and 0.9) above the rest of the filtration procedures, that are all have similar results in terms of power.

7. Concluding Remarks

In this work, we considered the mediation problem arises often and in large numbers in genome-wide research, and the power-loss challenge involves it. We examined the two-stage approach for testing the mediation problem, which includes a filtration test prior to some base test. We linked the two-stage procedure to shrinkage estimators, and studied their properties in the local asymptotics framework, which is essential in this context of composite hypotheses with filtration. We also stated result concerning FWER control for the multiple hypotheses framework, using similar terminology from the point-estimation framework. We then demonstrated the theoretical results about estimators through a case study, and performed simulation study for the multiple hypotheses framework, which shows superiority of the filtration methods, and for some scenarios, of some of them on the others.

Proofs

Proof of Lemma 4.3. For Sobel’s test statistic \( \frac{\pi \beta}{\sigma_\beta^2 + \sigma_\gamma^2} \), let \( \gamma = \frac{h_\gamma}{\sqrt{n}} \) and \( \beta = \frac{h_\beta}{\sqrt{n}} \), and consider it as an estimator for \( \frac{h_\gamma h_\beta}{\sqrt{\sigma_\beta^2 \gamma + \sigma_\gamma^2 \beta}} \). Now,

\[
\sqrt{n} \left( \frac{\gamma \beta}{\sqrt{\sigma_\beta^2 \gamma + \sigma_\gamma^2 \beta}} - \frac{\gamma \beta}{\sqrt{\sigma_\beta^2 \gamma^2 + \sigma_\gamma^2 \beta^2}} \right) = \frac{h_\gamma h_\beta}{\sqrt{\sigma_\beta^2 \gamma + \sigma_\gamma^2 \beta}} - \frac{h_\gamma h_\beta}{\sqrt{\sigma_\beta^2 \gamma + \sigma_\gamma^2 \beta}} \rightarrow \frac{(h_\gamma + Z_\gamma)(h_\beta + Z_\beta)}{\sqrt{\sigma_\beta^2 (h_\gamma + Z_\gamma)^2 + \sigma_\gamma^2 (h_\gamma + Z_\gamma)^2}} - \frac{h_\gamma h_\beta}{\sqrt{\sigma_\beta^2 h_\gamma^2 + \sigma_\gamma^2 h_\beta^2}}.
\]

For \( Z_\gamma \) and \( Z_\beta \) independent standard normal random variables. Clearly, for different values of \((h_\gamma, h_\beta)\), for instance for \((0, 0)\) (which represent a constant series at the origin) and \((1, 0)\) (which represent converging from the positive side of the \(x\)-axis to the origin), the distributions obtained are different. Similar arguments can be applied also for \( \sqrt{\gamma^2 + \beta^2} \). \( \square \)

Lemma A.1. Let \( X_n \geq 0 \) be a sequence of non-negative uniformly integrable random variables, and \( A_n \) sets such that \( P(A_n) \rightarrow L \), \( 0 \leq L < 1 \). Then

\[
0 < \lim \inf E[X_n 1_{A_n}] < \lim \sup E[X_n 1_{A_n}] < 1
\]

Proof. The sets \( A_n \) are eventually (for \( n > N \) and some \( N \)) of probability \( P(A_n) > L - \varepsilon \) for some (any) \( 0 < \varepsilon < L \). Let \( B_n \subset A_n \) such that \( P(B_n) = L - \varepsilon \), for \( n > N \). It holds that for \( n > N \)

\[
E[X_n 1_{A_n}] > E[X_n 1_{B_n}]. \tag{A.1}
\]
Assume by contradiction that the right hand side had partial limit 0. Then there was an indices series \( m_n \) such that for any \( \delta > 0 \), \( P(X_{m_n} < \varepsilon \mid B_n) \to 1 \) (otherwise, ) Thus, for every \( \delta > 0 \), \( \lim P(X_{m_n} < \varepsilon) > L - \varepsilon \), in contradiction to the convergence to normal distribution.

**Proof of Theorem 5.2.** Consider the ratio

\[
\frac{\text{MSE}(T_n^{(S)}; \theta)}{\text{MSE}(T_n; \theta)} = \frac{\text{var}(T_n^{(S)}) + E\left[\frac{T_n^{(S)} - \theta}{\text{var}(T_n)}\right]^2}{\text{var}(T_n) + E[T_n - \theta_n]^2}
\]

where the last equality holds since, by Assumption 5.1,

\[
\frac{\text{var}(T_n)}{\text{var}(T_n) + E[T_n - \theta_n]^2} = \frac{\text{var}(r_nT_n)}{\text{var}(r_nT_n) + E[r_n(T_n - \theta_n)]^2} = 1 - o(1).
\]

When \( L = 1 \),

\[
E\left[\frac{(T_n^{(S)} - \theta_n)^2}{\text{var}(T_n)}\right] = E\left[\frac{1}{\sigma^2_{T_n}}(T_n - \theta_n)^21_{[S_n \in Q_n]}\right] = E\left[\frac{1}{\sigma^2_{T_n}}(\theta_0 - \theta_n)^21_{[S_n \notin Q_n]}\right]
\]

(A.2)

The first summand converges to 0 since the sequence \( \frac{1}{\sigma^2_{T_n}}(T_n - \psi(\theta_n))^2 \) is uniformly integrable by Assumption 5.1. The second summand converges to \( K \) by assumption. Thus,

\[
\frac{\text{MSE}(T_n^{(S)}; \theta)}{\text{MSE}(T_n; \theta)} \to (0 + K)^2 \cdot (1 - o(1)) = K^2
\]

(A.3)

Consequently, every one of the relative efficiency possibilities may occur, depending directly on the value of \( K \).

When \( 0 < L < 1 \), the MSE-ratio can be decomposed as in (A.2). This time, the second summand is

\[
E\left[\frac{1}{\sigma^2_{T_n}}(\theta_0 - \theta_n)^21_{[S_n \in Q_n]}\right] \to K^2L,
\]

For the first summand, with no further assumption, it can be bounded in the limit by 0 and 1, but not strictly. Sharp inequalities can be achieved with Lemma A.1, assuming all the following limits exist:

\[
\lim E\left[\frac{1}{\sigma^2_{T_n}}(T_n - \psi(\theta_n))^21_{[S_n \in Q_n]}\right] = \lim E\left[\frac{1}{\sigma^2_{T_n}}(T_n - \psi(\theta_n))^21_{[S_n \notin Q_n]}\right] = 1
\]

\[
\lim E\left[\frac{1}{\sigma^2_{T_n}}(T_n - \psi(\theta_n))^2\right] - E\left[\frac{1}{\sigma^2_{T_n}}(T_n - \psi(\theta_n))^21_{[S_n \notin Q_n]}\right] < 1,
\]

(A.1)
Improving efficiency of tests for composite null hypotheses

and symmetrically have sharp lower bound of 0. When the variance ratio is
indeed approaches to a constant $0 < c < 1$, then the whole expression goes to
$K^2 L + c$, which means that the relative efficiency can be any of the options,
besides much more efficient. Otherwise, there are case of which it is possible to
gain much more efficiency, or alternatively, that even (just) more efficiency is
not possible.

When $L = 0$, the MSE ratio is 1 since $P\left(T_n = T_n^{(S_j)}\right) \to 1$. □

Proof of Theorem 5.3. Formally, the assumption for the adjusting method is
that

$$P_\theta \left( T \in R^{adj} \mid \sum_{j \neq i} f_i \right) = \frac{P_0(S \in Q)}{\sum_{j \neq i} f_i + 1}$$

i.e., the adjusting of the reject region is independent of the $i$-th filtration event.

Let $f$ be the vector with value 1 or 0 in its $i$-th element with correspondence
to whether $S_i \in Q_i$ or not. We have

$$P(V \geq 1 \mid f) = P\left( \bigcup_{i=1} \{ T_i \in R^{i,adj} \} \mid f \right)$$

$$\leq \sum_{f_i=1} P\left( T_i \in R^{i,adj} \mid f_i = 1, \sum_{j \neq i} f_i \right)$$

$$\leq \sum_{f_i=1} P\left( T_i \in R^{i,adj} \text{ and } S_i \in Q_i \mid \sum_{j \neq i} f_i \right)$$

$$\leq \sum_{f_i=1} P\left( T_i \in R^{i,adj} \mid \sum_{j \neq i} f_i \right)$$

$$\leq F \frac{P_0(S_i \in Q_i)}{\alpha} \frac{1}{P_\theta(S_i \in Q_i)}$$

$$\leq \alpha,$$

where (A.4) follows from the independence of the hypotheses. The un-conditional
bound can be achieved by taking an expectation over $f$ values. (It will be still
bounded by $\alpha$).

Proof of Theorem 5.4. Let $f$ be the vector with value 1 or 0 in its $i$-th element
with correspondence to whether $S_i \in Q_i$ or not.
\[ P(V \geq 1 \mid f) = 1 - P(V = 0 \mid f) \]
\[ = 1 - P \left( \bigcap_{i=1}^{n} \{ T^i \notin R^i,\text{adj} \} \mid f \right) \]
\[ = 1 - \prod_{i=1}^{n} P(T^i \notin R^i,\text{adj} \mid f_i = 1, F) \]
\[ = 1 - \prod_{i=1}^{n} (1 - P_{\theta}(T^i \notin R^i,\text{adj} \mid S^i \in Q^i, F)) \]
\[ \leq 1 - \left( 1 - \max_{\theta \in \Theta} P_{\theta}(T^i \in R^i,\text{adj} \mid S^i \in Q^i, F) \right)^F \]

When the final bound is achieved by taking expectation over \( f \) values. \( \square \)

**MSE-ratio for \( 0 < L < 1 \) in the Case Study 5.2.**

\[
\text{MSE}(\hat{\theta}_n) = E \left[ (\hat{\theta}_n - \theta_n)^2 \right]
\]
\[ = E \left[ (\bar{X}_n \bar{Y}_n - \mu_X^2 \mu_Y^2)^2 \right]
\]
\[ = E \left[ (\bar{X}(\bar{Y}_n - \mu_Y^2) + (\bar{X} - \mu_X^2)\mu_Y^2)^2 \right]
\]
\[ = E \left[ (\bar{X}(\bar{Y}_n - \mu_Y^2))^2 \right] + E \left[ ((\bar{X} - \mu_X^2)\mu_Y^2)^2 \right]
\]
\[ + 2E \left[ \bar{X}(\bar{Y}_n - \mu_Y^2)(\bar{X} - \mu_X^2)\mu_Y^2 \right]
\]
\[ = 2E \left[ \bar{X}(X - \mu_X^2) \bar{Y}_n - \mu_Y^2 \right] E \left[ \bar{Y}_n - \mu_Y^2 \right] \mu_Y^2
\]
\[ + E \left[ \bar{X}^2 \right] E \left[ (\bar{Y} - \mu_Y^2)^2 \right] + E \left[ (\bar{X} - \mu_X^2)^2 \right] \mu_Y^2
\]
\[ = \left( n^{-1} + \mu_X^2 \right) n^{-1} + n^{-1} \mu_Y^2
\]
\[ = n^{-1} \left( n^{-1} + \mu_X^2 + \mu_Y^2 \right). \]

Hence,

\[
\text{MSE}(\hat{\theta}_n) - \text{MSE}(\hat{\theta}_n) = E \left[ (\hat{\theta}_n - \theta_n)^2 \right] - E \left[ (\hat{\theta}_n - \theta_n)^2 \right]
\]
\[ = E \left[ \hat{\theta}_n^2 - \hat{\theta}_n^2 - 2\theta_n E \left[ \hat{\theta}_n - \theta_n \right] + \theta_n^2 - \theta_n^2 \right]
\]
\[ = E \left[ \bar{X}^2 \bar{Y}_n^2 \mathbf{1}_{||\bar{X}|| \leq cn^{-1}} \right] + 2\theta_n E \left[ \bar{X}\bar{Y} \mathbf{1}_{||\bar{X}|| \leq cn^{-1}} \right]
\]
\[ = E \left[ (2\theta_n\bar{X}\bar{Y} - \bar{X}^2 \bar{Y}^2) \mathbf{1}_{||\bar{X}|| \leq cn^{-1}} \right]
\]
\[ \leq E \left[ (2\theta_n\bar{X}\bar{Y}) \mathbf{1}_{||\bar{X}|| \leq cn^{-1}} \right]
\]
\[ \leq 2\theta_n \cdot cn^{-1} P(||\bar{X}|| \leq cn^{-1})
\]
\[ = 2c n^{-1} \mu_X \mu_Y \cdot n^{-1} P(||\bar{X}|| \leq cn^{-1}). \]
Therefore,
\[
\frac{\text{MSE}(\hat{\theta}_n) - \text{MSE}(\tilde{\theta}_n)}{\text{MSE}(\tilde{\theta}_n)} \leq \frac{2c \mu_X^n \mu_Y^n n^{-\gamma} P(|XY| \leq cn^{-\gamma})}{n^{-1} (n^{-1} + \mu_X^n + \mu_Y^n)} \\
\leq \frac{2c \mu_X^n \mu_Y^n}{n^{-1} + \mu_X^n + \mu_Y^n} h^{1-\gamma} \\
\leq \frac{c (\mu_X^n \mu_Y^n)}{n^{-1} + \mu_X^n + \mu_Y^n} h^{1-\gamma}.
\]
When \( \gamma = 1 \) and \( \mu_X^n + \mu_Y^n \sim n^{-1} \), for instance when \( n^{0,5}(\gamma^n, \beta^n) \to h \), \( 0 < h < \infty \), the expression tends to \( 1 + c \).

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