ON SENSITIVITY VALUE OF PAIR-MATCHED OBSERVATIONAL STUDIES

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Abstract. An observational study may be biased for estimating causal effects by failing to control for unmeasured confounders. This paper proposes a new quantity called the “sensitivity value”, which is defined as the minimum strength of unmeasured confounders needed to change the qualitative conclusions of a naive analysis assuming no unmeasured confounder. We establish the asymptotic normality of the sensitivity value in pair-matched observational studies. The theoretical results are then used to approximate the power of a sensitivity analysis and select the design of a study. We explore the potential to use sensitivity values to screen multiple hypotheses in presence of unmeasured confounding using a microarray dataset.

1. Introduction

In a pair-matched observational study, subjects are matched by their observed covariates, but the difference within a matched pair could still be due to unmeasured confounders instead of a genuine treatment effect. To study how sensitive the qualitative conclusions (in this paper significance of the treatment effect) are to unmeasured confounders, a commonly used model of Rosenbaum (2002, Chapter 4) uses a single parameter $\Gamma$ to represent the magnitude of departure from random assignment; $\Gamma = 1$ means random assignment and larger $\Gamma$ means a larger departure from random assignment. In such sensitivity analyses, the user typically computes the range of $p$-values $[p_\Gamma, \Gamma]$ under different levels of $\Gamma$. When $\Gamma = 1$, $p_\Gamma = p$, and they are equal to the usual $p$-value under the null hypothesis.

We illustrate the typical process of sensitivity analysis using a microarray dataset. This microarray experiment investigates where genes are differentially expressed in human brain with respect to gender (Vawter et al, 2004). By assuming a linear structural model between gene expressions, gender and unmeasured confounders, Gagnon-Bartsch and Speed (2012) and Wang et al. (2016) studied the dataset and found evidence of serious unmeasured confounding. The 84 observations in this dataset were obtained from three different laboratories on two different microarray platforms. To form a pair-matched observational study, we match the observations exactly by the lab and platform and obtain 41 pairs of males and females.

To assess which genes are differentially expressed in males and females, we can use Wilcoxon’s signed rank test to compute a $p$-value for each of the 12,600 genes in the dataset. A sensitivity analysis augments the significance test by considering possible departures from random assignment. Table 1 shows the sensitivity analysis of 9 probe sets in the dataset. The $\Gamma = 1$
Table 1. Illustration of a two-sided sensitivity analysis table and the corresponding sensitivity values.

<table>
<thead>
<tr>
<th>probe set</th>
<th>sensitivity analysis</th>
<th>sensitivity value</th>
</tr>
</thead>
<tbody>
<tr>
<td>41214_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>4.69 8.10</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.00 0.00 0.01 0.03 0.08</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>38355_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>4.69 8.10</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.00 0.00 0.01 0.03 0.08</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>37583_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.84 2.44</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.02 0.13 0.60 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>35885_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.79 2.36</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.02 0.15 0.66 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>32052_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.68 2.20</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.03 0.20 0.80 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>34477_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.50 1.93</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.06 0.33 1.00 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>38446_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.43 1.84</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.08 0.40 1.00 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>31687_f_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.24 1.57</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.17 0.67 1.00 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>31525_s_at</td>
<td>$\Gamma$ 1 2 3 5 7 10</td>
<td>1.23 1.57</td>
</tr>
<tr>
<td></td>
<td>$p_\Gamma$ 0.00 0.17 0.68 1.00 1.00 1.00</td>
<td>0.01 0.05</td>
</tr>
</tbody>
</table>

Column corresponds to the usual Wilcoxon’s signed rank test. All the 5 probe sets shown in Table 1 have very small two-sided p-values (< 0.01). As we increase the sensitivity parameter $\Gamma$, the p-value upper bounds $p_\Gamma$ become larger and will eventually converge to 1 as $\Gamma \to \infty$.

When there are many hypotheses tested at the same time, the full sensitivity analysis produces a lengthy table (the middle columns of Table 1 under “sensitivity analysis”) and is a rather inefficient way of presenting information. In this paper we propose a new quantity—sensitivity value—to summarize the sensitivity analyses. The sensitivity value is simply the critical $\Gamma$ where the p-value upper bound $p_\Gamma$ crosses a pre-specified significance level $\alpha$; for the formal definition, see Section 3. This concept is illustrated in the last two columns of Table 1 where the bolded numbers are the corresponding sensitivity values of the probe sets.

Although the term “sensitivity value” is new, it has already been routinely reported in observational studies to strengthen their qualitative conclusions. The sensitivity value speaks to the assertion “it might be bias” in an observational study in much the same way as the p-value speaks to the assertion “it might be bad luck” in a randomized trial (Rosenbaum, 2015b, Section 1.2). A large sensitivity value means that it would take a large bias (departure from random assignment) for an association between treatment and outcome to be non-causal in an observational study, just as a small p-value in a randomized trial means it would take a large amount of bad luck for the association to be due to chance alone. See Section 8 for more discussion on the different roles of p-value and sensitivity value.

The main goal of this paper is to investigate how to design an observational study to maximize its sensitivity value (in a stochastic sense). Previously, this objective is indirectly pursued by maximizing the probability that the p-value upper bound is less than $\alpha$ at a fixed sensitivity level $\Gamma$ (Heller et al., 2009; Rosenbaum, 2010a, 2015a). This paper takes the first step towards directly achieving this goal by establishing the asymptotic distribution of
the sensitivity value in pair-matched studies. Additionally, we explore the potential to use sensitivity values in genomics screening when unobserved confounding is a major concern.

In Section 2 we review sensitivity analysis for pair-matched observational study. We formally define sensitivity value in Section 3 and derive its asymptotic distribution in Section 4. Then in Sections 5 to 7 we discuss the implications of our theoretical results in designing observational studies. We conclude the paper with some brief discussion in Section 8. Technical proofs can be found in the supplementary file.

2. Review: Sensitivity Analysis

Consider a typical setting of an observational study with \( I \) independent matched pairs, \( i = 1, \ldots, I \). Each pair has two subjects, \( j = 1, 2 \), one treated, denoted by \( Z_{ij} = 1 \), and one control, denoted by \( Z_{ij} = 0 \). Pairs are matched for observed covariates so \( x_{i1} = x_{i2} \), but the investigator may be concerned that matching failed to control for an unmeasured confounder \( u_{ij} \), so possibly \( u_{i1} \neq u_{i2} \) for some or all \( i \). Let \( r_{Tij} \) be the potential outcome of the \( j \)-th subject in the \( i \)-th pair if subject \( j \) in matched pair \( i \) receives treatment. Similarly, \( r_{Cij} \) is the potential outcome if the subject receives control. The observed outcome is \( R_{ij} = Z_{ij}r_{Tij} + (1 - Z_{ij})r_{Cij} \) and the individual treatment effect \( r_{Tij} - r_{Cij} \) cannot be observed for any subject \( \text{[Rubin 1974]} \). Let \( Y_i \) be the treatment-minus-control difference \( Y_i = (Z_{i1} - Z_{i2})(R_{i1} - R_{i2}) \) for the \( i \)-th pair. Let \( \mathcal{F} = \{ (r_{Tij}, r_{Cij}, x_{ij}, u_{ij}) : i = 1, \ldots, I, j = 1, 2 \} \) and \( \mathcal{Z} \) be the event that \( \{ Z_{i1} + Z_{i2} = 1, i = 1, \ldots, I \} \). The sharp null hypothesis of no treatment effect assumes that \( H_0 : r_{Tij} = r_{Cij}, \forall i, j \). If \( H_0 \) is true and the treatments are randomly assigned (i.e., \( P(Z_{i1} = 1|\mathcal{F}, \mathcal{Z}) = 1/2 \) for all \( i \)), then conditioning on \( \mathcal{F} \) and \( \mathcal{Z}, Y_i = (Z_{i1} - Z_{i2})(r_{C1i} - r_{C2i}) \) attaches equal probabilities to \( \pm |r_{C1i} - r_{C2i}| \).

To test for \( H_0 \), a commonly used family of statistics are the signed score statistics

\[
(2.1) \quad T(Z, R) = \frac{\sum_{i=1}^{I} \text{sgn}(Y_i)q_i}{\sum_{i=1}^{I} q_i},
\]

where \( \text{sgn}(y) = 1_{y > 0} \) and \( q_i \geq 0 \) is a function of \( |Y_i| \) such that \( q_i = 0 \) if \( Y_i = 0 \). A special case is Wilcoxon’s signed rank statistic for which \( q_i = \text{rank}(|Y_i|) \). The statistic \( T \) in (2.1) is normalized by \( \sum_{i=1}^{I} q_i \) so it is always between 0 and 1. Under \( H_0 \) and random treatment assignment, conditioning on \( \mathcal{F} \) and \( \mathcal{Z} \), \( q_i \) are fixed constants and \( \text{sgn}(Y_i) \) are i.i.d. Bernoulli variables with \( P(\text{sgn}(Y_i) = 1) = P(\text{sgn}(Y_i) = 0) = 1/2 \). This yields the null distribution of signed score statistics. The exact distribution is usually difficult to compute for large \( I \). In this case, Monte-Carlo simulations or central limit theorems can be used to approximate the distribution of \( T \).

In an observational study, matching may fail to control a relevant unobserved covariate \( u_{ij} \), so \( P(Z_{i1} = 1|\mathcal{F}) \neq 1/2 \). A simple model for sensitivity analysis in an observational study asserts that the odds of treatment deviates from 1 by at most a factor of \( \Gamma \geq 1 \),

\[
(2.2) \quad \frac{1}{\Gamma} \leq \frac{P(Z_{i1} = 1|\mathcal{F}, \mathcal{Z})}{P(Z_{i1} = 0|\mathcal{F}, \mathcal{Z})} \leq \Gamma, \quad i = 1, \ldots, I,
\]

with independent assignments in distinct pairs. \( \Gamma = 1 \) yields random assignment and each fixed \( \Gamma > 1 \) indicates an unknown but limited departure from random assignment.

A typical sensitivity analysis computes the range of plausible \( p \)-values using the test statistic (2.1) under the sensitivity model (2.2). Let \( T_{\Gamma} \) be the sum of \( I \) independent random variables, \( i = 1, \ldots, I \), taking the value \( q_i \) with probability \( \Gamma/(1 + \Gamma) \) and 0 with probability \( 1/(1 + \Gamma) \). Note that this is also well-defined for \( 0 < \Gamma < 1 \). Similarly, let \( T_{\Gamma} \) be the random
variable created by replacing $\Gamma$ with $1/\Gamma$ in the definition of $\overline{T}_\Gamma$. In other words, $\overline{T}_\Gamma \overset{d}{=} \overline{T}_{1/\Gamma}$.

This fact will be useful when we define the untruncated sensitivity value in the next Section.

In Rosenbaum (2002, Section 4.4), it is shown that, under the sensitivity model (2.2),

$$P_{\overline{T}} = P(T \geq t|F, Z) \leq P\left(T \geq t|F, Z \right) \leq P\left(\overline{T}_{\Gamma} \geq t|F, Z \right) = \overline{p}_{\Gamma}, \quad \forall t, \quad \Gamma \geq 1.$$  

The bounds are sharp in the sense that they can be attained for a particular $P(z_{i1} = 1|F, Z)$ satisfying (2.2). When $\Gamma = 1$ (no unmeasured confounder), both bounding distributions are equal to the null distribution of $T$. Therefore $\overline{p}_1 = p_1$ are equal to the conventional $p$-value.

When the sample size $I$ is large, the distribution of the bounding variable $\overline{T}_\Gamma$ can be approximated by a central limit theorem (Hájek et al., 1999, Section 6.1). Conditioning on $F$ and $Z$, we have

$$\sqrt{I} \cdot \frac{T_{\Gamma} - \Gamma/(1 + \Gamma)}{\sqrt{\Gamma/(1 + \Gamma)^2} \sigma_{q,I}^2} \overset{d}{\rightarrow} N(0, 1),$$

where

$$\sigma_{q,I}^2 = \frac{I^{-1} \sum_{i=1}^I q_i^2}{(I^{-1} \sum_{i=1}^I q_i^2) T},$$

providing $(\sum_{i=1}^I q_i^2)/(\max_i q_i^2) \rightarrow \infty$. In this paper we further assume $\lim_{I \rightarrow \infty} \sigma_{q,I}^2 = \sigma_q^2$ exists. This holds for Wilcoxon’s signed rank test and all other test statistics considered in this paper. The $p$-value upper bound $\overline{p}_T$ can be subsequently approximated by the tail probability of the normal distribution.

3. Definition of sensitivity value

We are ready to give the formal definition of sensitivity value:

**Definition 1.** Given the data $(Z, R)$ and significance level $\alpha$, the truncated sensitivity value is the smallest $\Gamma \geq 1$ such that the upper bound $\overline{p}_T(Z, R)$ is not significant. Formally,

$$\Gamma_{\alpha}^{\ast*}(Z, R) = \inf \left\{ \Gamma \geq 1 | \overline{p}_T(Z, R) > \alpha \right\}.$$  

Note that the $p$-value upper bound $\overline{p}_T$ is always increasing in $\Gamma$, so the set in (3.1) is an interval $[\Gamma_{\alpha}^{\ast*}, \infty)$ and its infimum is well defined. Note that, similar to Fisher’s $p$-value, the sensitivity value is a deterministic function of the data.

By definition, $\Gamma_{\alpha}^{\ast} = 1$ if $\overline{p}_1 \geq \alpha$ (the naive $p$-value is not significant). Therefore, when analyzing the distribution of $\Gamma_{\alpha}^{\ast*}$ with randomly generated data $(Z, R)$, $\Gamma_{\alpha}^{\ast*}$ usually has a point mass at 1. We find it more convenient to consider the untruncated version of $\Gamma_{\alpha}^{\ast*},$

$$\Gamma_{\alpha}^{\ast}(Z, R) = \inf \left\{ \Gamma > 0 | \overline{p}_T(Z, R) \geq \alpha \right\}.$$  

Although a typical sensitivity analysis is only performed for $\Gamma \geq 1$, the bounding variable $\overline{p}_T$ can still be defined for $0 < \Gamma < 1$ and it is obvious that $\Gamma_{\alpha}^{\ast*} = \max(\Gamma_{\alpha}^{\ast}, 1)$. By allowing the sensitivity value to be less than 1, $\Gamma_{\alpha}^{\ast}$ becomes a continuous variable and provides extra information. To see this, if the $p$-value is not significant under $\Gamma = 1$, the untruncated sensitivity value $\Gamma_{\alpha}^{\ast} < 1$ and its reciprocal $1/\Gamma_{\alpha}^{\ast}$ is where the $p$-value lower bound $\overline{p}_T$ first becomes significant, since $\overline{p}_1/\Gamma = \overline{p}_T$ (see the paragraph before equation (2.3)). In other words, when $\Gamma_{\alpha}^{\ast} < 1$, $1/\Gamma_{\alpha}^{\ast}$ is the smallest magnitude of bias needed to make the test significant. In the development below we will always work with $\Gamma_{\alpha}^{\ast}$ and refer to it as sensitivity value.

To compute the sensitivity value, we can use the normal approximation of the bounding variable $\overline{T}_\Gamma$ in (2.4). In what follows, we will suppress $\alpha$ in the subscript of $\Gamma_{\alpha}^{\ast}$ if it causes no confusion. Let $\kappa^{\ast} = \Gamma^{\ast}/(1 + \Gamma^{\ast})$ so $\Gamma^{\ast} = 1$ corresponds to $\kappa^{\ast} = 1/2$. The value $\kappa^{\ast}$, referred to
Table 2. Accuracy of formula (3.3) for computing sensitivity value. In each scenario, we compute two approximations of the sensitivity value: the transformed sensitivity value \( \kappa^* \) computed by formula (3.3), and a finite-sample value computed by grid-searching a Monte-Carlo sensitivity analysis table (at each \( \Gamma \) we compute the \( p \)-value upper bound \( p_{\Gamma} \) by 100,000 realizations of \( T_{\Gamma} \)). This table reports the mean and 10% and 90% quantiles in 100 simulations of the differences between the two approximations of \( \kappa^* \).

<table>
<thead>
<tr>
<th>( I )</th>
<th>dist. of ( Y )</th>
<th>( \alpha = 0.05 )</th>
<th>( \alpha = 0.005 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( 10% )</td>
<td>( 90% )</td>
<td>( 10% )</td>
</tr>
<tr>
<td>30</td>
<td>( N(1,1) )</td>
<td>0.006 0.010 0.015</td>
<td>0.018 0.031 0.047</td>
</tr>
<tr>
<td></td>
<td>( t_2 + 1.5 )</td>
<td>0.003 0.009 0.015</td>
<td>0.011 0.030 0.050</td>
</tr>
<tr>
<td>100</td>
<td>( N(1,1) )</td>
<td>0.004 0.004 0.005</td>
<td>0.012 0.014 0.016</td>
</tr>
<tr>
<td></td>
<td>( t_2 + 1.5 )</td>
<td>0.003 0.004 0.005</td>
<td>0.008 0.012 0.014</td>
</tr>
</tbody>
</table>

as transformed sensitivity value hereafter, should solve \( \sqrt{I} \cdot (T - \kappa) = \sqrt{\kappa(1 - \kappa)} \sigma_q \cdot (\Phi^{-1}(\alpha) + o_p(1)) \) where \( \Phi^{-1}(\alpha) \) is the upper-\( \alpha \) quantile of the standard normal distribution. Taking the square of this equation and then solving a quadratic equation of \( \kappa^* \), we obtain

\[
(3.3) \quad \kappa^* = \frac{2IT + c^2 - \sqrt{4c^2IT(1 - T) + c^4}}{2(I + c^2)} + o_p\left(\frac{1}{\sqrt{I}}\right),
\]

where \( c = \sigma_q \cdot \Phi^{-1}(\alpha) \). The larger root is discarded because \( T - \kappa^* \) must be non-negative.

The sensitivity value \( \Gamma^* \) can be subsequently obtained by \( \Gamma^* = \kappa^*/(1 - \kappa^*) \). As a remark, the additional \( o_p(1/\sqrt{I}) \) term in (3.3) comes purely from the normal approximation of the bounding variable \( T_{\Gamma} \) in (2.4). The normal approximation is known to be very accurate for Wilcoxon’s signed rank test for as small as 30 matched pairs.

Alternatively, the exact sensitivity value may be computed by binary-searching a full sensitivity analysis as demonstrated in Table 1. This method is free of asymptotic error but more computationally intensive. Table 2 reports the difference between the transformed sensitivity values \( \kappa^* \) computed by the approximation (3.3) and by grid-searching a full sensitivity analysis table. Since the exact distribution of \( T_{\Gamma} \) is too complicated even for moderate sample size, we approximate it using \( 10^5 \) Monte-Carlo samples. In most cases, the asymptotic approximation (3.3) is quite accurate, especially if the sample size \( I \) or the significance level \( \alpha \) is not too small.

So far we have only discussed sensitivity analysis for one-sided test. Following the suggestion by Cox (1977, Section 4.2), a simple way to obtain a two-sided \( p \)-value in sensitivity analysis (e.g. in Table 1) is to double the smaller of the two one-sided \( p \)-value upper bounds. Consequently, to compute the two-sided sensitivity value, one can simply take the maximum of the two one-sided sensitivity values with significance level \( \alpha/2 \).

4. Distribution of sensitivity value

4.1. Asymptotic normality. Next we derive the asymptotic distribution of the sensitivity value \( \Gamma^* \) when the data \( (Z_i, R_i) \) are generated i.i.d. from \( F \). We should emphasize that all our theoretical analysis is made in the favorable situation that \( F \) satisfies the random treatment assignment mechanism \( \text{P}(Z_{i1} = 1|F, Z) = 1/2 \) but possibly has a non-zero treatment effect (Rosenbaum 2010a).
Under weak regularity conditions, the test statistic $T$ has a normal limiting distribution [Hettmansperger (1984) Section 2.8]:

\[ \sqrt{I} \cdot \frac{T - \mu_F}{\sigma_F} \xrightarrow{d} N(0, 1). \]  

The mean and variance parameters usually depend on the distribution $F$. When $F$ satisfies the null hypothesis of no treatment effect, then $\mu_F = 1/2$ and $\sigma_F^2 = \sigma_q^2/4$.

Combining the approximation (4.1) and formula (3.3), after some algebra we get

**Theorem 1.** Assume the central limit theorem (2.4) holds for the bounding variable $T_I$, and $\lim_{I \to \infty} \sigma^2_{q,I} = \sigma_q^2$ exists. For test statistic $T$ satisfying (4.1), the transformed sensitivity value $\kappa^*_\alpha$ for fixed $0 < \alpha < 1$ has an asymptotic normal distribution:

\[ \sqrt{I} \left[ \kappa^*_\alpha - \mu_F \right] \xrightarrow{d} N\left( -\sigma_q \bar{\Phi}^{-1}(\alpha) \sqrt{\mu_F(1 - \mu_F)}, \sigma_F^2 \right), \]

where $N$ is the standard normal distribution and $\bar{\Phi}(y) = 1 - \Phi(y)$ is its complementary CDF.

The value $\mu_F$, or more precisely the corresponding sensitivity value $\tilde{\Gamma} = \mu_F/(1 - \mu_F)$, is called “design sensitivity” by Rosenbaum (2004). This value describes how sensitive a test statistic $T$ is to unobserved bias when the sample size $I \to \infty$. In other words, the design sensitivity $\tilde{\Gamma}$ is the (stochastic) upper bound of the sensitivity value $\Gamma^*$. When the distribution $F$ satisfies Fisher’s sharp null, the design sensitivity $\tilde{\Gamma}$ is 1.

In Theorem 1 we assume the significance level $\alpha$ is fixed. This is useful to eliminate several terms in (3.3). In finite samples, the ratio $c^2/I$ can be nonnegligible when $I$ is moderate. For example, when $\alpha = 0.05$ and Wilcoxon’s signed rank test is used, $c^2 \approx 3.6$ and $c^2/I$ is nonnegligible for $I = 50$. If we assume $\sigma_q^2 \bar{\Phi}^{-1}(\alpha)^2/I \approx \eta > 0$, then using an asymptotic analysis similar to Theorem 1, we have

\[ \sqrt{I} \left[ \kappa^*_\alpha - \left( \mu_F - \frac{2\mu_F^2 - 1}{2(1 + \eta)} \eta + \sqrt{\frac{4\eta\mu_F(1 - \mu_F) + \eta^2}{2(1 + \eta)}} \right) \right] \approx N\left( 0, \frac{\sigma_F^2}{(1 + \eta)^2} \left( 1 + \frac{\eta(2\mu_F - 1)}{\sqrt{4\eta\mu_F(1 - \mu_F) + \eta^2}} \right)^2 \right). \]  

The relationship in (4.3) is not convergence in distribution, because to make $c^2/I$ converging to a constant, the significance level $\alpha$ has to decrease to 0 and the normal approximation (2.4) of $T_I$ becomes less and less accurate. Nonetheless, we find (4.3) provides a more accurate approximation of $\kappa^*_\alpha$ than (4.2) when sample size is moderate and $\alpha$ is not too small.

In a related work, Rosenbaum (2015a) derived the limit of log $p_T$ using large deviations theory. The asymptotic results in Theorem 1, the finite sample approximation (4.3), and the approximation in Rosenbaum (2015a) should be used for different purposes. Theorem 1 describes the asymptotic behavior of the transformed sensitivity value and in particular how $\Gamma^*$ converges to the design sensitivity $\tilde{\Gamma}$. Equation (4.3) is more accurate in computing the power of sensitivity analysis when sample size $I$ is moderate. The large deviations approximation in Rosenbaum (2015a) can be inverted to approximate the sensitivity value, but it is applicable only if the significance level $\alpha$ is very small and is more difficult to compute as it uses the moment generating function of $F$ rather just the first two moments.
function

Hettmansperger (1984, Section 2.5) showed that 

\[ \mu \psi \text{design sensitivity } \tilde{\Gamma} \text{ (the asymptotic limit of power of sensitivity analysis).} \]

\[ \mu \]

\[ \mu \psi \text{sensitivity value } \Gamma \text{ (the asymptotic limit of } \psi \text{).} \]

\[ \mu \]

\[ \mu \psi \text{term } (4.3) \text{ is } 33. \]

\[ \mu \]

\[ \mu \psi \text{Wilcoxon’s test has mean } Y \approx 0.76 \text{ (corresponds to design sensitivity } \Gamma = \mu F/(1 - \mu F) \approx 3.17) \text{ and the variance } \sigma^2_{\mu F} \text{ is about } 0.26 \text{. Suppose we are interested the power at } \Gamma = 2.5 \text{ and } \alpha = 0.05 \text{. Using } 10,000 \text{ simulations, we find that the actual power is about } 33.6\% \text{. The approximate power using (4.2) is } 37.1\%, \text{ the approximate power using (4.3) is } 33.5\%, \text{ and the power calculated ignoring the constant term in (4.2) is } 90.8\%. \]

5. Selecting test statistics

In the next three Sections, we discuss the implications of the results obtained in Section 4 in selecting the design of an observational study. First, we consider how to maximize the sensitivity value \( \Gamma^* \) by picking a test statistic.

Consider the general signed score statistic (2.1) with \( q_i = \psi(\text{rank}(|Y_i|)/(I + 1)) \), where the function \( \psi(u) \geq 0 \), \( 0 < u < 1 \) satisfies \( \int_0^1 \psi(u) \, du < \infty \), and \( \int_0^1 \psi^2(u) \, du < \infty \). Then

\[ \sigma^2_{q,I} = \left( \frac{(1/I) \sum_{i=1}^I q_i^2}{(1/I) \sum_{i=1}^I q_i} \right)^2 \rightarrow \frac{\int_0^1 \psi^2(u) \, du \, \nu^2}{\left( \int_0^1 \psi(u) \, du \right)^2} = \frac{\|\psi\|_2^2}{\|\psi\|_1^2} \]

Under the alternative model that \( Y_i \overset{i.i.d.}{\sim} F \), the asymptotic distribution of \( T(Z, R) \) is given by the normal approximation (4.1) with mean (Hettmansperger, 1984, page 104)

\[ \mu_F = \mu_F[\psi] = \int_0^\infty \psi(P(|Y| \leq y)) \, dF(y) \right. \]

\[ \int_0^\infty \psi^2(u) \, du \left. \right) \]

\[ \int_0^\infty \psi(u) \, du \]

\[ \langle \psi, g \rangle = \int_0^1 \psi(u) g(u) \, du \text{ and} \]

\[ g(u) = \frac{f((F^+)^{-1}(u))}{f((F^+)^{-1}(u)) + f(-(F^+)^{-1}(u))}, \]

\[ F^+(y) = P(|Y| \leq y) = F(y) - F(-y), \quad y > 0. \]

The variance parameter \( \sigma^2_{\mu F} \) is more complicated and in our theoretical analysis we will only compare the means of \( \kappa^* \) for different statistics.
(A) Function $g(u)$ for design sensitivity. The location shift is 0, 0.5, 1 or 2 and the noise distribution is normal or $t$-distribution with 2 degrees of freedom.

(B) Score functions $\psi/\|\psi\|_1$ for several $U$-statistics.

**Figure 1.** Design sensitivity is determined by the inner product of $g$ (left plot) and $\psi/\|\psi\|_1$ (right plot).

By Theorem 1, $\mu_F$ is the limit of the transformed sensitivity value $\kappa^*$ when the sample size $I \to \infty$. Formula (5.1) suggests that $\mu_F$ is just a weighted average of $g(u)$. Notice that $g(0) = 1/2$, $g(u) \leq 1$, and $\lim_{u \to 1} g(u)$ depends on the tail of $F$. To see this, suppose $F$ is symmetric and unimodal with mean $d$. Furthermore assume the density $f(y) = f_0(y - d)$ is positive on the real line, so $(F^+)^{-1}(u) \to \infty$ as $u \to 1$. Then

$$
\lim_{u \to 1} g(u) = \lim_{y \to \infty} \frac{1}{1 + f_0(y - d)/f_0(-y - d)}.
$$

Therefore, if the tail is a power law, $f_0(y) \propto |y|^{-\lambda}$, then $\lim_{u \to 1} g(u) = 1/2$ and hence $g(u)$ cannot be monotonically increasing. If the tail decay is exponential, $f_0(y) \propto e^{-\lambda |y|}$, then $\lim_{u \to 1} g(u) \in (1/2, 1)$. If the tail decay is faster than exponential, for example $f_0(y) \propto e^{-\lambda y^2}$, then $\lim_{u \to 1} g(u) = 1$. Figure 1a plots the function $g(u)$ for some familiar distributions.

Rosenbaum (2004) proposed to select the test statistics to maximize the design sensitivity $\Gamma$ or equivalently $\mu_F$ in the transformed scale; see also Rosenbaum (2011, 2010b). With this objective in mind, the optimal choice of the score function $\psi$ should converge to $\delta_{u^*}$, where $\delta_u$ is the Dirac-$\delta$ function and $u^* = \arg\max_u g(u)$.

However, in finite samples $I < \infty$, Theorem 1 suggests that the mean of $\kappa^*$ is approximately

$$
\mu_{F,I}[\psi] = \langle \psi, g \rangle - \frac{\Phi^{-1}(\alpha)}{\sqrt{I}} \| \psi \|_2 \sqrt{\langle \psi, g \rangle (1 - \langle \psi, g \rangle)}
$$
Table 3. Distributions of \( \kappa_{0.05}^* \) for different U-statistics when \( Y \sim N(0.3, 1) \). Three sample sizes are considered: \( I = 100 \), \( I = 500 \) and \( I = \infty \). In the first two sample sizes, we report the median and standard deviation in the normal approximation [3.3], as well as the median and standard deviation from 1000 simulations which compute \( \kappa^* \) using [3.3]. The largest median in each column is bolded.

<table>
<thead>
<tr>
<th>((m, \overline{m}, \overline{m}))</th>
<th>( I = 100 )</th>
<th>( I = 500 )</th>
<th>( I = \infty )</th>
</tr>
</thead>
<tbody>
<tr>
<td>approximation</td>
<td>simulation</td>
<td>approximation</td>
<td>simulation</td>
</tr>
<tr>
<td>((2, 2, 2))</td>
<td>0.57 (0.0584)</td>
<td>0.57 (0.056)</td>
<td>0.623 (0.026)</td>
</tr>
<tr>
<td>((8, 8, 8))</td>
<td>0.581 (0.0943)</td>
<td>0.585 (0.0956)</td>
<td>0.677 (0.0423)</td>
</tr>
<tr>
<td>((8, 7, 8))</td>
<td><strong>0.587</strong> (0.0814)</td>
<td><strong>0.595</strong> (0.0715)</td>
<td>0.663 (0.0362)</td>
</tr>
<tr>
<td>((8, 6, 8))</td>
<td>0.582 (0.0708)</td>
<td>0.587 (0.0688)</td>
<td>0.648 (0.0314)</td>
</tr>
<tr>
<td>((8, 5, 8))</td>
<td>0.575 (0.0618)</td>
<td>0.58 (0.0625)</td>
<td>0.633 (0.0275)</td>
</tr>
<tr>
<td>((20, 20, 20))</td>
<td>0.528 (0.138)</td>
<td>0.543 (0.131)</td>
<td><strong>0.681</strong> (0.0657)</td>
</tr>
<tr>
<td>((20, 18, 20))</td>
<td>0.576 (0.0962)</td>
<td>0.579 (0.0987)</td>
<td>0.678 (0.0433)</td>
</tr>
<tr>
<td>((20, 16, 20))</td>
<td>0.584 (0.0724)</td>
<td>0.584 (0.0855)</td>
<td>0.666 (0.0323)</td>
</tr>
<tr>
<td>((8, 7, 7))</td>
<td>0.568 (0.0761)</td>
<td>0.569 (0.0729)</td>
<td>0.638 (0.0334)</td>
</tr>
<tr>
<td>((8, 6, 7))</td>
<td>0.559 (0.0666)</td>
<td>0.554 (0.068)</td>
<td>0.623 (0.0297)</td>
</tr>
</tbody>
</table>

provided that \( \psi \) is normalized so that \( \| \psi \|_1 = 1 \). Therefore, it is not a good idea to choose a spiky score function \( \psi \) since the \( L_2 \) norm of \( \psi \) can blow up to infinity.

As an example, consider the following class of U-statistics proposed by [Rosenbaum 2011] that are indexed by three parameters \((m, \overline{m}, \overline{m})\). Let \( h(y) \) be a function of \( m \) variables that count the number of positive differences among the order statistics between \( |y|_{(m)} \) and \( |y|_{(\overline{m})} \). The corresponding U-statistic is defined as \( T = \left( \frac{m}{n} \right)^{-1} \sum_{|Y|_{(m)}} h(Y_{(m)}) \), which can be written as the signed score form [2.1]. Let \( a_i \) be the rank of \( |Y_i| \). In absence of ties, the score of \( Y_i \) is given by [Rosenbaum 2011, Section 3.1]

\[
q_i = \left( \frac{1}{m} \right)^{-1} \sum_{l=|\overline{m}|}^{m} \left( a_{i-1} - 1 \right) \left( I - a_i \right) \frac{I}{l-1} \left( m - l \right) \approx I^{-1} \sum_{l=|\overline{m}|}^{m} \left( \frac{m}{l} \right)^{l-1} (1 - p)^{m-l} \text{ for } p = \text{rank}(|Y_i|)/I.
\]

Note that the choice \((m, \overline{m}, \overline{m}) = (2, 2, 2)\) closely approximates Wilcoxon’s statistic [Rosenbaum 2011]. Figure 1b plots the approximate score function \( \psi \) for several choices of \((m, \overline{m}, \overline{m})\).

Tables 3 and 4 show the median and standard deviation of \( \kappa^* \) using various U-statistics. Our theoretical approximations are very close to the values obtained by simulations. When \( Y \sim N(0.3, 1) \), the design sensitivity is maximized by \((20, 20, 20)\). This statistic still has the largest mean when \( I = 500 \), but its performance quickly deteriorates in smaller sample size because its 2-norm is quite large. When \( I = 100 \), the best performer is \((8, 7, 8)\), which is still monotone but less steep than \((20, 20, 20)\) as shown in Figure 1b.

When \( F \) has a heavy tail such as \( t_2 \), it is reasonable to expect that a redescending score function (such as \((8, 7, 7)\) and \((8, 6, 7)\) as shown in Figure 1b) yields a large sensitivity value. This is confirmed by Table 3 in which \((8, 6, 7)\) is the clear winner in all three sample sizes.

In the supplementary file, we consider another class of test statistics whose score functions are binary and obtained similar conclusions to the U-statistics.

Based on the observations above, a reasonable strategy in practice is to choose a statistic with large design sensitivity when the sample size is large (e.g. \( I \geq 500 \)). This can be done if
prior knowledge of the tail behavior is available, or a small planning sample can be used to estimate $\mu_F$. In the latter case, a even better strategy is to estimate the parameters $\mu_F$ and $\sigma_F^2$ from the planning sample (for example by the Jackknife). Then one can choose a statistic that maximizes the mean or some quantile of the transformed sensitivity value $\kappa^*$ computed from the theory-predicted distribution in Theorem 4.

### 6. Selecting subpopulations

In presence of effect modification (interaction between treatment and covariates), Hsu et al. (2013) discovered an interesting phenomenon that the investigator might prefer to test on subgroups with larger effects because they are less sensitive to hidden bias. However, when the sample size is small, Hsu et al. (2013) found it more advantageous to use all the subgroups.

This phenomenon can be easily explained by the theoretical results in Section 4 as the mean sensitivity value depends on both the design sensitivity $\tilde{\Gamma} = \mu_F/(1 - \mu_F)$ and the sample size $I$. Suppose we have two subgroups whose tests statistics $T$ have mean $\mu_{F_1} > \mu_{F_2}$ and the proportions of the two subgroups are $\pi_1$ and $(1 - \pi_1)$, $0 < \pi_1 < 1$. When the sample size is sufficiently large, Theorem 4 implies that the transformed sensitivity value obtained by using the first subgroup only converges to $\mu_{F_1}$, and the transformed sensitivity value obtained by using both subgroups converges to $\mu_F = \pi_1 \mu_{F_1} + (1 - \pi_1) \mu_{F_2} < \mu_{F_1}$. Therefore it is preferable to use the first subgroup only. However, when the sample size $I$ is small, using only $\pi_1$ proportion of the data is less efficient and may produce smaller sensitivity value.

Next we compute the sample size threshold where the above transition happens. Given $(\mu_{F_1}, \mu_{F_2}, \pi_1)$, our goal is to determine the critical sample size $I^*$ such that if $I > I^*$, using the subgroup with larger effect gives larger transformed sensitivity value $\kappa^*$ on average, and if $I < I^*$, using both groups gives larger transformed sensitivity value $\kappa^*$ on average. Using

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**Table 4.** Distributions of $\kappa^*_{0.05}$ for different U-statistics when $Y \sim t_2 + 0.8$. Three sample sizes are considered: $I = 100$, $I = 500$ and $I = \infty$. In the first two sample sizes, we report the mean and standard deviation in the normal approximation $\{\text{3.3}\}$, as well as the mean and standard deviation from 1000 simulations which compute $\kappa^*$ using the first expression in $\{\text{3.3}\}$. The largest mean/median in each column is bolded.

<table>
<thead>
<tr>
<th>$(m, \underline{m}, \overline{m})$</th>
<th>$I = 100$</th>
<th>$I = 500$</th>
<th>$I = \infty$</th>
</tr>
</thead>
<tbody>
<tr>
<td>approximation</td>
<td>simulation</td>
<td>approximation</td>
<td>simulation</td>
</tr>
<tr>
<td>(2, 2, 2)</td>
<td>0.693 (0.0531)</td>
<td>0.693 (0.0499)</td>
<td>0.744 (0.023)</td>
</tr>
<tr>
<td>(8, 8, 8)</td>
<td>0.579 (0.0827)</td>
<td>0.587 (0.105)</td>
<td>0.676 (0.0371)</td>
</tr>
<tr>
<td>(8, 7, 8)</td>
<td>0.646 (0.0747)</td>
<td>0.649 (0.0826)</td>
<td>0.721 (0.0326)</td>
</tr>
<tr>
<td>(8, 6, 8)</td>
<td>0.681 (0.066)</td>
<td>0.686 (0.0618)</td>
<td>0.744 (0.0285)</td>
</tr>
<tr>
<td>(8, 5, 8)</td>
<td>0.698 (0.0615)</td>
<td>0.697 (0.0526)</td>
<td>0.754 (0.0265)</td>
</tr>
<tr>
<td>(20, 20, 20)</td>
<td>0.5 (0.147)</td>
<td>0.5 (0.154)</td>
<td>0.575 (0.0731)</td>
</tr>
<tr>
<td>(20, 18, 20)</td>
<td>0.568 (0.118)</td>
<td>0.578 (0.103)</td>
<td>0.671 (0.053)</td>
</tr>
<tr>
<td>(20, 16, 20)</td>
<td>0.633 (0.0746)</td>
<td>0.641 (0.0851)</td>
<td>0.715 (0.0327)</td>
</tr>
<tr>
<td>(8, 7, 7)</td>
<td>0.689 (0.075)</td>
<td>0.694 (0.0638)</td>
<td>0.756 (0.0323)</td>
</tr>
<tr>
<td>(8, 6, 7)</td>
<td>0.707 (0.0588)</td>
<td>0.711 (0.0643)</td>
<td>0.768 (0.0252)</td>
</tr>
</tbody>
</table>
the approximation (4.3), the value \( I^* \) can be determined by solving

\[
\mu_F = \frac{(2\mu_F - 1)\eta^* + \sqrt{4\eta^*\mu_F(1 - \mu_F) + (\eta^*)^2}}{2(1 + \eta^*)}
\]

\[
\mu_F = \frac{(2\mu_{F1} - 1)(\eta^*/\pi_1) + \sqrt{4(\eta^*/\pi_1)\mu_{F1}(1 - \mu_{F1}) + (\eta^*/\pi_1)^2}}{2(1 + \eta^*/\pi_1)},
\]

where the root \( \eta^* = \sigma_q^2\Phi^{-1}(\alpha)^2/I^* \). We numerically solve the equation for 50 equally spaced \( \mu_{F1} \) and \( \mu_{F2} \) from 0.5 to 10/11 and \( \pi_1 = 0.5 \) and 0.75. The critical sample sizes \( I^* \) are plotted in Figure 2 for the Wilcoxon’s test. For other statistics, \( I^* \) can be obtained by multiplying a factor that depends on their \( \sigma_q^2 \). Surprisingly, Figure 2 shows \( I^* \) primarily depend on the difference \( \mu_{F1} - \mu_{F2} \). The curves in Figure 2 define three regions where we would prefer the first group, the second group, or both groups to minimize sensitivity to unobserved bias. In practice, if effect modification is expected to be substantial, one can estimate \( \mu_{F1} - \mu_{F2} \) from a pilot sample and use Figure 2 to determine if just one or both subgroups should be used.

7. Selecting outcomes

Lastly we consider observational studies with many outcomes of interest. Our goal is to find the outcomes whose apparent effects are least sensitive to unmeasured confounding. In these problems, it is often helpful to reduce the number of outcomes, for possibly two reasons:

(1) In many problems, most of the outcomes have no or minuscule treatment effect. In this case, the \( p \)-value upper bound \( p_{1p} \) is conservative if \( \Gamma > 1 \), and an unnecessary price of multiplicity is paid in multiple comparisons. Based on this observation, Heller et al. (2009) proposed a sample splitting procedure to screen out uninteresting outcomes and gain power; see also Zhao et al. (2017).
Figure 3. Illustration of unmeasured confounding in the gender study. The investigator analyze the samples in different batches, laboratories, or microarray platforms which may affect the gene expression. This introduces unmeasured confounding bias to the treatment effect.

(2) The observational study may simply be a preliminary study. In microarray studies, it is common to select some biomarkers (for example by a procedure controlling the false discovery rate) and see if they can be replicated in follow-up studies (Heller et al., 2014).

Sensitivity value is a natural way to screen the outcomes when we are concerned about unmeasured confounding. Next we return to the genomics example in Section 1 and use the sensitivity value as an exploratory tool. In many microarray experiments, the target effects are confounded by technical or non-biological experimental variation when samples are processed in multiple batches. Figure 3 illustrates this source of unmeasured confounding. When some samples are processed differently than others, for example, in different laboratories or by different technicians, significant batch effects may arise and confound the treatment effect we are interested in (Leek et al., 2010). In the gender example in Section 1, even after the observations are matched by laboratory label and microarray platform, our results below suggest that the study is still likely biased by other unmeasured confounders.

Many statistical methods have been proposed to adjust for the unmeasured confounding (e.g. Gagnon-Bartsch and Speed, 2012; Sun et al., 2012), but most of them need to assume a linear model for the data (see Wang et al. (2016) for an exposition). Sensitivity values provide a nonparametric and computationally efficient way to screen thousands of hypotheses. When unobserved confounding (e.g. batch effect) is a major concern, we can compute a sensitivity value for each hypothesis. Genes with extraordinarily large sensitivity values are more likely to have genuine effects since their associations are less sensitive to unobserved confounders.

This new proposal is demonstrated in Figure 4 using the gender example. We compute one-sided transformed sensitivity values $\kappa_{0.05}^*$ with respect to the alternative that gene expressions in males are higher. The left three panels of Figure 4 show the quantile-quantile (Q-Q) plot of the transformed sensitivity values $\kappa^*$ versus the standard normal distribution for three different test statistics. The rightmost panel shows the histogram of the sensitivity values.

The empirical distribution of sensitivity values provides useful information about genomics dataset, as it is usually safe to presume that most genes have no or little genuine effects. In
Theorem 1, the main assumption is that the data are in the favorable situation, i.e. the random treatment assignment is satisfied after matching. If that is true and the genes are independent, then by equation (4.3), the empirical distribution of the sensitivity values should be close to the normal distribution with mean 0.36 for Wilcoxon, 0.31 for $(8, 7, 8)$, or 0.33 for $(8, 6, 7)$. The Q-Q plots in Figure 4 show clear deviation from this theoretical prediction: the empirical distribution have heavier tails and the medians are different. This indicates unmeasured confounding bias or very strong dependence between the genes (not very likely as genetic dependence is usually local) or possibly both.

![Figure 4. Using sensitivity values to screen genes in the microarray example (significance level $\alpha = 0.05$). The one-sided sensitivity values are computed with respect to the alternative hypothesis that male gene expressions are higher than female.](image)

Among all the sensitivity values, a few of them are clearly outliers. They correspond to the genes that are least sensitive to unobserved bias and are more likely genuine effects. The 9 genes listed in Table 1 have two-sided $\kappa^*_0$ greater than 0.6 using Wilcoxon’s test (5 of them can be seen in Figure 4). Among them, 6 are on the X/Y chromosome which are more likely to be related to the gender as argued by Gagnon-Bartsch and Speed (2012). Using the method in Wang et al. (2016) that estimates unmeasured confounders by factor analysis and assumes genetic effects are sparse, all these 9 genes have two-sided $p$-values less than $10^{-5}$.

8. Discussion

Both sensitivity value and $p$-value are deterministic functions of the data and indicate the level of confidence to reject the null hypothesis. They are closely related: both of them are increasing functions of the signed score statistic $T$ if $T \geq 1/2$. In other words, they give essentially the same ordering if we use them to screen outcomes as in Section 4.

However, $p$-value and sensitivity value are different transforms of $T$ and should be used in different study designs: $p$-value is only meaningful when there is no unmeasured confounding,
which is exactly what sensitivity value speaks to. The distinction between sensitivity value and \( p \)-value is most clear if we consider different test statistics. For example, Wilcoxon’s test has very good Pitman’s efficiency for normal error \(^{[1]}\text{Hettmansperger 1984}\), Section 2.6 but has poor efficiency in sensitivity analysis as shown in Table 3 (the first row). From the theoretical perspective, the distribution of the \( p \)-value is commonly studied under local alternatives (e.g. location shift of the order \( 1/\sqrt{T} \)). For fixed alternative distributions, the \( p \)-value in general converges to 0 and does not carry much information. On the contrary, the sensitivity value \( \Gamma^* \) is not very meaningful under local alternatives but behaves interestingly under fixed alternatives as illustrated in this paper.

Throughout this paper, we have been working on pair-matched observational studies and obtained some clean theoretical results. When there are multiple controls for each treated observation, the theoretical analysis becomes more difficult as there is no closed form solution of the bounding variable \( T^* \) though it is possible to find the asymptotic normal distribution of \( T^* \) \(^{[1]}\text{Gastwirth et al. 2000}\). Of course one can still compute the sensitivity value by binary-searching a sensitivity analysis table, but it remains an open problem if there exists a simple formula like (3.3) for the sensitivity value. A preliminary simulation study shows that \( \kappa^* \) is still asymptotically normal. We leave the theoretical analysis for future research. More broadly, it would be interesting to see if the concept of sensitivity value can extend to other sensitivity analysis frameworks that do not assume homogeneous treatment effect.

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REFERENCES


Jeffrey T Leek, Robert B Scharpf, Héctor Corrada Bravo, David Simcha, Benjamin Langmead, W Evan Johnson, Donald Geman, Keith Baggerly, and Rafael A Irizarry. Tackling


**APPENDIX A. PROOFS**

**A.1.Proof of Theorem 1.** Let $V_I = \sqrt{I}(T - \mu_F)$. By assumption, $V_I \overset{d}{\rightarrow} N(0, \sigma^2_q)$. Since the limit of $\sigma^2_{q,I}$ exists and $\alpha$ is fixed, the value $c$ converges to a constant $\sigma_q \Phi^{-1}(\alpha)$. Hence (3.3) implies

$$
\kappa^* = \frac{2IT - \sqrt{4c^2IT(1-T)}}{2I} + o_p\left(\frac{1}{\sqrt{I}}\right) \\
= T - \frac{\sigma_q \Phi^{-1}(\alpha) \sqrt{T(1-T)}}{\sqrt{I}} + o_p\left(\frac{1}{\sqrt{I}}\right) \\
= \mu_F + \frac{V_I}{\sqrt{I}} - \frac{\sigma_q \Phi^{-1}(\alpha) \sqrt{(\mu_F + \frac{V_I}{\sqrt{I}})(1 - \mu_F - \frac{V_I}{\sqrt{I}})}}{\sqrt{I}} + o_p\left(\frac{1}{\sqrt{I}}\right) \\
= \mu_F + \frac{V_I}{\sqrt{I}} - \frac{\sigma_q \Phi^{-1}(\alpha) \sqrt{\mu_F(1 - \mu_F)}}{\sqrt{I}} + o_p\left(\frac{1}{\sqrt{I}}\right).
$$
Therefore

$$\sqrt{I}(\kappa^* - \mu_F) = -\sigma_q \Phi^{-1}(\alpha) \sqrt{\mu_F(1 - \mu_F)} + V_I + o_p(1) \rightarrow N(-\sigma_q \Phi^{-1}(\alpha) \sqrt{\mu_F(1 - \mu_F)}, \sigma^2_F).$$

A.2. Derivation of Equation (4.3). In (4.3), we assume \( c^2 \approx \eta I \) instead of a constant. By (3.3), we have

$$\kappa^* = \frac{2IT + \eta I - \sqrt{4\eta I^2 T(1 - T) + \eta^2 I^2}}{2(I + \eta I)} + o_p\left(\frac{1}{\sqrt{I}}\right)$$

$$= \frac{2(\mu_F + \frac{V_I}{\sqrt{I}}) + \eta - \sqrt{4\eta(\mu_F + \frac{V_I}{\sqrt{I}})(1 - \mu_F - \frac{V_I}{\sqrt{I}}) + \eta^2}}{2(1 + \eta)} + o_p\left(\frac{1}{\sqrt{I}}\right).$$

Now use the Taylor expansion \( \sqrt{a + x} = \sqrt{a} + x/(2\sqrt{a}) + o(x) \), we get

$$\kappa^* = \mu_F - \frac{(2\mu_F - 1)\eta}{2(1 + \eta)} + \frac{V_I}{\sqrt{I}} \frac{1}{1 + \eta} - \frac{\sqrt{4\eta \mu_F(1 - \mu_F) + \eta^2}}{2(1 + \eta)} + o_p\left(\frac{1}{\sqrt{I}}\right).$$

Rearranging the terms, we get

$$\sqrt{I}\left\{\kappa^* - \left[\mu_F - \frac{(2\mu_F - 1)\eta}{2(1 + \eta)} + \frac{\sqrt{4\eta \mu_F(1 - \mu_F) + \eta^2}}{2(1 + \eta)}\right]\right\} = \frac{V_I}{\sqrt{I}} \frac{1}{1 + \eta} + o_p(1)$$

$$\approx N\left(0, \frac{\sigma^2_F}{(1 + \eta)^2} \left(1 + \frac{\eta(2\mu_F - 1)}{\sqrt{4\eta \mu_F(1 - \mu_F) + \eta^2}}\right)^2\right).$$

APPENDIX B. Binary score functions

To illustrate that larger design sensitivity does not always imply larger sensitivity value in finite samples, consider the simple case that \( \psi \) is a binary function: for \( 0 \leq \tau_u < \tau_l \leq 1 \),

$$\psi(u) = \begin{cases} 
1/(\tau_u - \tau_l), & \tau_l \leq u \leq \tau_u, \\
0, & \text{otherwise}. 
\end{cases}$$

This class of statistics generalize the sign test (corresponding to \( \tau_l = 0, \tau_u = 1 \)) and were considered by Noether (1973). The score function is already normalized such that \( \|\psi\|_1 = 1 \) and note that \( \|\psi\|_2 = 1/(\tau_u - \tau_l) \).

As an illustration, suppose the data is generated by \( Y_i \overset{i.i.d.}{\sim} N(0.3, 1) \). Since \( g(u) \) is increasing in this case, the optimal \( \tau_u \) is 1. We vary the value \( \tau_l \) over \( (0, 1) \) and plot in Figure 5a the theoretical means of \( \kappa^* \) (computed by (4.3)) for sample sizes \( I = 50, 100, 500, \infty \). When the sample size is finite, the mean of \( \kappa^* \) starts to decrease as \( \tau_l \) becomes close to 1. This is expected because \( \|\psi\|_2 \to \infty \) as \( \tau_l \to 1 \).

When the tail of \( F \) is heavy (such as \( t_2 \)), it is sensible to choose \( \tau_u \) away from 1. Figure 5b shows the contour plot of the mean of \( \kappa^* \) when \( Y_i \overset{i.i.d.}{\sim} t_2 + 0.8, I = 500, \) and \( (\tau_l, \tau_u) \) vary from 0 to 1. The optimal binary score function is \( \tau_l = 0.45 \) and \( \tau_u = 0.87 \), and the maximum mean of \( \kappa^* \) is about 0.776.
\( Y \sim N(0.3, 1) \) and \( \tau_u = 1 \).

(b) \( Y \sim t_2 + 0.8 \) and \( I = 500 \).

Figure 5. The mean of sensitivity value versus different sample sizes and choices of \( \tau_l \) and \( \tau_u \).