

Sensitivity Analysis for the Cross-Match Test, With Applications in Genomics

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The cross-match test is an exact, distribution-free test of no treatment effect on a high-dimensional outcome in a randomized experiment. The test uses optimal nonbipartite matching to pair $2I$ subjects into I pairs based on similar outcomes, and the cross-match statistic A is the number of times that a treated subject was paired with a control, rejecting for small values of A . If the test is applied in an observational study in which treatments are not randomly assigned, then it may be comparing treated and control subjects who are not comparable, and thus may falsely reject a true null hypothesis of no treatment effect. We develop a sensitivity analysis for the cross-match test and apply it in an observational study of the effects of smoking on gene expression levels. In addition, we develop a sensitivity analysis for several multiple testing procedures using the cross-match test and apply it to 1627 molecular function categories in Gene Ontology.

KEY WORDS: Cross-match test; Multiple testing; Nonbipartite matching; Observational study; Sensitivity analysis.

1. THE CROSS-MATCH TEST FOR A RANDOMLY ASSIGNED TREATMENT

1.1 An Observational Study of the Effects of Smoking on Gene Expression Levels

Does smoking cause changes in gene expression? If so, what specific changes does it cause? Spira et al. (2004) compared expression levels in human airway epithelial cells of 9968 genes in 34 current smokers and 23 never-smokers. Analyses of data of this sort typically emphasize the dimensionality of the response and the associated problems of multiple testing. These are two important problems, but there are others. The treatment (here smoking) is not assigned at random to some individuals and denied to others, so smokers and nonsmokers may differ systematically in unmeasured ways that affect gene expression, and thus differing expression levels may not be effects caused by smoking. To what extent are conclusions sensitive to small or moderate departures from random treatment assignment? Would a high-dimensional test or multiple-comparison procedure reach very different conclusions if the analysis allowed for moderate departures from random assignment? We investigate these questions by developing a sensitivity analysis for a multivariate permutation test—the cross-match test—and for associated multiple-test procedures. In the study by Spira et al. (2004), some of the changes in expression levels turn out to be quite insensitive to bias from nonrandom assignment to smoking or control, but other changes are fairly sensitive.

In a randomized experiment, the cross-match test is a randomization test, and Section 1 applies the test to the data from Spira et al. (2004) to test the null hypothesis that smoking does not affect the 9968 gene expression levels, ignoring for a moment the fact that people were not randomly assigned to smoke or not smoke. In Section 2, issues of multiple testing are addressed and the cross-match test is applied to 1627 hypotheses about subsets of genes defined by Gene Ontology (GO),

continuing to ignore the absence of random assignment. Then Section 3 introduces a sensitivity analysis for the cross-match tests, asking about the magnitude of bias from nonrandom assignment that would need to be present to alter the conclusions reached by the randomization test. The sensitivity analysis is combined with corrections for testing many hypotheses in Section 4. Uses, limitations and practicalities of the cross-match test are discussed in Section 5.

1.2 Definition of the Cross-Match Statistic

There are $2I$ subjects, $\ell = 1, 2, \dots, 2I$, where subject ℓ is treated if $Z_\ell = 1$ and is a control if $Z_\ell = 0$, and there are $n = \sum_{\ell=1}^{2I} Z_\ell$ treated subjects and $2I - n$ controls in total. If subject ℓ receives the treatment, then this subject exhibits an M -dimensional response $\mathbf{y}_{T\ell}$, whereas if subject ℓ receives the control, then response $\mathbf{y}_{C\ell}$ is observed instead. Thus the response actually observed from subject ℓ is $\mathbf{Y}_\ell = Z_\ell \mathbf{y}_{T\ell} + (1 - Z_\ell) \mathbf{y}_{C\ell}$, and the effect of the treatment on ℓ , namely $\mathbf{y}_{T\ell} - \mathbf{y}_{C\ell}$, is not observed for any subject ℓ (see Neyman 1923; Rubin 1974). Write $\mathcal{F} = \{(\mathbf{y}_{T\ell}, \mathbf{y}_{C\ell}), \ell = 1, 2, \dots, 2I\}$. Fisher's (1935) sharp null hypothesis H_0 of no treatment effect says $H_0: \mathbf{y}_{T\ell} = \mathbf{y}_{C\ell}$ for $\ell = 1, 2, \dots, 2I$.

The cross-match test (Rosenbaum 2005) is performed as follows. A $2I \times 2I$ symmetric distance matrix is defined, with row k and column ℓ giving a "distance" between \mathbf{Y}_k and \mathbf{Y}_ℓ . The $2I$ subjects are then paired into I nonoverlapping pairs to minimize the total of the I distances within pairs. For notational convenience, the subjects are renumbered, $j = 1, \dots, 2I$ so that subjects $2i - 1$ and $2i$ are paired for $i = 1, \dots, I$. The cross-match statistic, A , is the number of pairs containing a treated subject and a control, that is,

$$A = \sum_{i=1}^I Z_{2i-1}(1 - Z_{2i}) + (1 - Z_{2i-1})Z_{2i}. \quad (1)$$

A small value of A suggests that the distribution of \mathbf{Y}_ℓ is different for treated subjects and control subjects (Rosenbaum 2005).

The optimal pairing of $2I$ subjects into I pairs to minimize the total distance inside pairs is an "optimal nonbipartite matching."

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See Papadimitriou and Steiglitz (1982), Cook et al. (1988) for a textbook discussion, Derigs (1988) for an algorithm with Fortran code, Cook and Rohe (1999) for a literature review and C code, and Lu et al. (2001), Greevy et al. (2004), Lu and Rosenbaum (2004), Lu (2005) for several applications of non-bipartite matching in statistics. In particular, Lu (2005), Lu et al. (2010) have made Derigs' (1988) Fortran code available from inside R.

If there is an odd number, $2I + 1$, of subjects, then a pseudo-subject is added to the distance matrix at zero distance from everyone else, $I + 1$ pairs are formed as before, and the pair containing the pseudosubject is discarded. In this way, the least matchable subject is the discarded subject.

1.3 Example of Computing the Cross-Match Statistic

In the study by Spira et al. (2004), \mathbf{Y}_ℓ is the 9968-dimensional vector of logarithms of expression levels. The distance matrix is the 57×57 matrix of Euclidean distances among the \mathbf{Y}_ℓ . Because $34 + 23 = 57$ is odd, a pseudosubject is added at zero distance from all 57 subjects (as discussed in Section 1.2), making a 58×58 matrix. The 58 subjects are paired to minimize the total distance within the 58 pairs, and the pair containing a pseudosubject is discarded; in this case, the discarded subject is a smoker. Then there are $2I = 56$ subjects, $n = 33$ of whom are smokers, in $I = 28$ pairs.

Figure 1 depicts the calculations with the aid of a multidimensional scaling that plays no role in the test itself but is helpful in illustrating what is happening. For the $2I = 56$ paired individuals, the 56×56 distance matrix was used in Kruskal's nonmetric multidimensional scaling algorithm (isoMDS in the

MASS package in R, with two dimensions and the default settings). Paired points are connected by a line. The leftmost pair is a cross-match, pairing a smoker with a nonsmoker. There are $A = 5$ cross-matches and $I - A = 28 - 5 = 23$ matches that are not cross-matches.

With expression levels, \mathbf{Y}_ℓ has numeric coordinates, but this is not an essential feature of the cross-match test. Instead, \mathbf{Y}_ℓ might be a "word" consisting of a sequence of "letters," such as a DNA base sequence, with a suitable distance defined between different "words." Alternatively, \mathbf{Y}_ℓ might record both numeric intensities and geometric locations of those intensities, as in fMRI brain imaging, where two individuals, i and ℓ , are close if they have similar intensities at neighboring locations. Instead, \mathbf{Y}_ℓ might record the dates and locations of the international travel of person ℓ , where two people, i and ℓ , are close if they were often in the same locations on the same dates.

1.4 Null Distribution of the Cross-Match Statistic

Write $\mathbf{Z} = (Z_1, \dots, Z_{2I})^T$, where subject $2i - 1$ is paired with subject $2i$, $i = 1, \dots, I$. Write $|S|$ for the number of elements in a finite set S . In a randomized experiment, n of the $2I$ subjects would be picked at random for treatment, so there are $\binom{2I}{n}$ possible values, \mathbf{z} , of \mathbf{Z} , namely the values in the set \mathcal{Z} ,

$$\mathcal{Z} = \left\{ \mathbf{z} = (z_1, \dots, z_{2I})^T : \sum_{j=1}^{2I} z_j = n, z_j \in \{0, 1\}, j = 1, \dots, 2I \right\},$$

so $|\mathcal{Z}| = \binom{2I}{n}$. To say that \mathbf{Z} is picked at random from \mathcal{Z} is to say that

$$\Pr\left(\mathbf{Z} = \mathbf{z} \mid \sum_{j=1}^{2I} Z_j = n, \mathcal{F}\right) = \frac{1}{|\mathcal{Z}|} = \frac{1}{\binom{2I}{n}} \quad \text{for each } \mathbf{z} \in \mathcal{Z}. \tag{2}$$

If Fisher's sharp null hypothesis of no treatment effect, $H_0: \mathbf{y}_{T\ell} = \mathbf{y}_{C\ell}$ for $\ell = 1, 2, \dots, 2I$, is true, then $\mathbf{Y}_\ell = Z_\ell \mathbf{y}_{T\ell} + (1 - Z_\ell) \mathbf{y}_{C\ell} = \mathbf{y}_{C\ell}$ is a function of \mathcal{F} , so the matching is a function of \mathcal{F} , and the randomization (2) determines the exact null distribution of the cross-match statistic, A , in (1). Alternatively, the same null distribution of A may be obtained from the null hypothesis that the \mathbf{Y}_ℓ 's are independent and identically distributed independent of \mathbf{Z} (see Rosenbaum 2005).

The null distribution $\Pr(A = a | \mathcal{F})$ has a simple form. We must first determine the support of this distribution. Write $\mathcal{A}_{n,I}$ for the possible values of A with n treated subjects and $2I - n$ controls. Clearly, $A \leq \min(n, 2I - n)$, and $A = \min(n, 2I - n)$ is possible. If there are $a < \min(n, 2I - n)$ cross-matches, then there must be a pair i with $Z_{2i-1} + Z_{2i} = 2$ and a pair i' with $Z_{2i'-1} + Z_{2i'} = 0$; swapping Z_{2i} and $Z_{2i'}$ increases the number of cross-matches by 2. If n is odd, then there must be at least one cross-match, but if n is even, then there can be 0 cross-matches. If n is even and $n \leq I$, then $\mathcal{A}_{n,I} = \{0, 2, 4, \dots, n\}$, whereas if n is odd and $n \leq I$, then $\mathcal{A}_{n,I} = \{1, 3, 5, \dots, n\}$. If $n > I$ and n is even, then $\mathcal{A}_{n,I} = \{0, 2, 4, \dots, 2I - n\}$, whereas if $n > I$ and n is odd, then $\mathcal{A}_{n,I} = \{1, 3, 5, \dots, 2I - n\}$.

If there are $a \in \mathcal{A}_{n,I}$ cross-matched pairs with $Z_{2i-1} + Z_{2i} = 1$, then there are $(n - a)/2$ pairs with $Z_{2i-1} + Z_{2i} = 2$ and $I - a - (n - a)/2 = I - (n + a)/2$ pairs with $Z_{2i-1} + Z_{2i} = 0$,

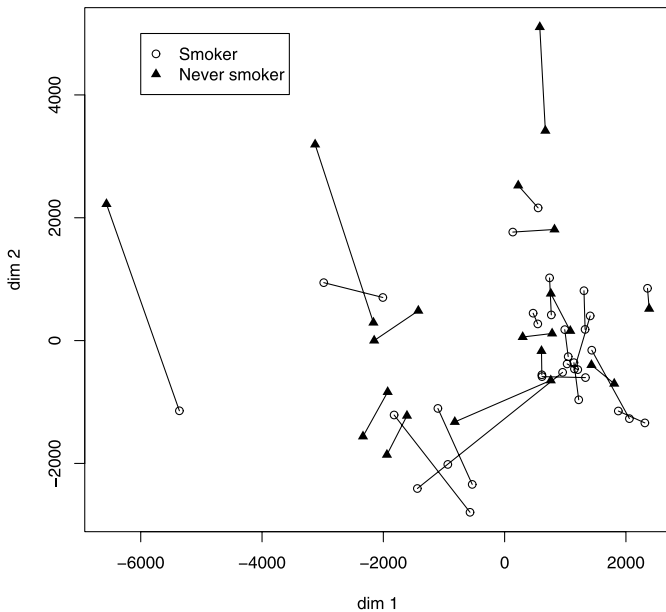


Figure 1. A two-dimensional representation of the 9968-dimensional cross-match test. Paired subjects are connected by a line. The two dimensions are from a multidimensional scaling of the 56×56 distance matrix for the 56 subjects who were paired. The multidimensional scaling is for graphical purposes only; it plays no role in the test. Because there are five instances in which a circle is connected to a triangle, the cross-match statistic is $A = 5$.

Table 1. Exact null randomization distribution of the cross-match statistic, A , for $2I = 56$ subjects in $I = 28$ pairs with $n = 33$ treated subjects

a	$\Pr(A = a)$	$\Pr(A \leq a)$
1	0.00000023	0.00000023
3	0.00002705	0.00002728
5	0.00081143	0.00083871
7	0.00973713	0.01057583
9	0.05625895	0.06683478
11	0.17184552	0.23868030
13	0.29081550	0.52949580
15	0.27696714	0.80646294
17	0.14662966	0.95309261
19	0.04115920	0.99425181
21	0.00548789	0.99973970
23	0.00026030	1.00000000

making a total of $a + (n - a)/2 + I - (n + a)/2 = I$ pairs with $\sum_{j=1}^{2I} Z_j = a + 2(n - a)/2 = n$ treated subjects. Under the null hypothesis, the $\binom{2I}{n}$ values of $\mathbf{z} \in \mathcal{Z}$ are equally probable, so

$$\begin{aligned} \Pr(A = a | \mathcal{F}) &= \kappa(a, n, I) \\ &= \begin{cases} \frac{2^a I!}{\binom{2I}{n} a! ((n - a)/2)! (I - (n + a)/2)!} & \text{for } a \in \mathcal{A}_{n,I} \\ 0 & \text{for } a \notin \mathcal{A}_{n,I}. \end{cases} \quad (3) \end{aligned}$$

Table 1 gives the randomization distribution of A for $2I = 56$ subjects in $I = 28$ pairs with $n = 33$ treated subjects and $2I - n = 23$ controls. If the study by Spria et al. (2004) had been a randomized experiment, with individuals randomly assigned to their roles as smokers or never-smokers, and if smoking had not affected expression levels, then the chance of $A = 5$ or fewer cross-matches would have been 0.000839, and thus the null hypothesis would be rejected at the conventional 0.05 level.

2. TESTING MULTIPLE HYPOTHESES OF NO TREATMENT EFFECT

When Fisher's sharp null hypothesis of no treatment effect, $H_0: \mathbf{y}_{T\ell} = \mathbf{y}_{C\ell}$ for $\ell = 1, 2, \dots, 2I$, is rejected, we often will want to determine which coordinates of \mathbf{Y}_ℓ are affected. Let \mathbf{s} be an M -dimensional vector of 0's and 1's with at least one 1, and let $\mathbf{Y}_\ell(\mathbf{s})$, $\mathbf{y}_{T\ell}(\mathbf{s})$, and $\mathbf{y}_{C\ell}(\mathbf{s})$ be the subvectors of \mathbf{Y}_ℓ , $\mathbf{y}_{T\ell}$, and $\mathbf{y}_{C\ell}$ of dimension $s_+ = \sum_{m=1}^M s_m$ containing the coordinates for which $s_m = 1$. The hypothesis H_s asserts that the treatment does not affect these s_+ coordinates, $H_s: \mathbf{y}_{T\ell}(\mathbf{s}) = \mathbf{y}_{C\ell}(\mathbf{s})$, for $\ell = 1, 2, \dots, 2I$. Apply the cross-match test to $\mathbf{Y}_\ell(\mathbf{s})$, count the number of cross-matches, $a(\mathbf{s})$, and let $p(\mathbf{s})$ be the resulting p -value computed as done in Section 1.4. In a randomized experiment, each such p -value is a valid test of its null hypothesis, so $\Pr\{p(\mathbf{s}) \leq \alpha\} \leq \alpha$ if H_s is true.

There are $2^M - 1$ hypotheses H_s , and one cannot test them all and reject whenever $p(\mathbf{s}) \leq 0.05$, because this would lead to a large number of false rejections. There are many possible strategies (see, e.g., Dudoit and van der Laan 2007).

Bonferroni inequality. A simple, familiar strategy is to test all $2^M - 1$ hypotheses and reject all hypotheses H_s with $p(\mathbf{s}) \leq$

$\alpha/(2^M - 1)$. Under this strategy, the probability of falsely rejecting at least one true hypothesis [i.e., the familywise error rate (FWER)] is at most α , and the expected number of false rejections is α . In many contexts, this strategy will be quite conservative.

Holm's procedure. Holm's (1979) procedure involves a few more steps, but it also falsely rejects at least one true hypothesis with probability at most α , thereby controlling the FWER. It is less conservative than the Bonferroni procedure.

Closed testing. In closed testing (Marcus, Peritz, and Gabriel 1976), one would follow the approach of Lehman, Wassmer, and Reitmeir (1991), rejecting H_s at level α if $p(\mathbf{s}') \leq \alpha$ for all \mathbf{s}' such that $s_m = 1$ implies that $s'_m = 1$ for all m . An advantage of this procedure is that all tests are done at level α , and yet the probability of falsely rejecting at least one true hypothesis is at most α . The procedure tends to be impractical for large M , but it is practical when M is small or when M itself is large but a suitably restricted subset of hypotheses H_s is tested.

Benjamini-Hochberg procedure. The method of Benjamini and Hochberg (1995) has been shown to control the false discovery rate (FDR, the proportion of rejections that are false rejections) when the $p(\mathbf{s})$'s are independent and under certain other conditions. In these circumstances, the Benjamini-Hochberg procedure's more lenient standard typically rejects many more hypotheses than the Holm procedure. The Benjamini-Hochberg procedure appears to control the FDR in most circumstances that are not highly artificial (Romano, Shaikh, and Wolf 2008; Yekutieli 2008), but artificial exceptions are known to exist (Guo and Rao 2008; see also Samuel-Cahn 1996). The $p(\mathbf{s})$'s produced by the cross-match test are not independent, so the use of the Benjamini-Hochberg procedure might be reasonable, but it is not formally known to control the FDR.

Complementary partitions. Suppose that the M coordinates of \mathbf{Y}_ℓ can be partitioned into $\tilde{M} \leq M$ mutually exclusive sets of coordinates, ordered by priority, where hypothesis $\tilde{H}^{(1)}$ asserts that set 1 is unaffected; $\bar{H}^{(1)}$ asserts that the union of the remaining $\tilde{M} - 1$ sets, $2, 3, \dots, \tilde{M}$ is unaffected; $\tilde{H}^{(2)}$ asserts that set 2 is unaffected; $\bar{H}^{(2)}$ asserts that the union of the remaining $\tilde{M} - 2$ sets, $3, 4, \dots, \tilde{M}$ is unaffected; and so on. Note that for the last hypothesis, $\bar{H}^{(\tilde{M}-1)} = \tilde{H}^{(\tilde{M})}$; for instance, with $\tilde{M} = 2$, $\tilde{H}^{(1)}$ might refer to the expression levels of all known oncogenes, and $\tilde{H}^{(2)}$ might refer to all other genes. Let $p^{(0)}$ be the p -value from the test of no effect on \mathbf{Y}_ℓ (from Section 1.4), and let $\tilde{p}^{(k)}$ and $\bar{p}^{(k)}$ be the p -values when the cross-match test is used to test $\tilde{H}^{(k)}$ and $\bar{H}^{(k)}$, respectively. Test the hypothesis of no effect, H_0 , as was done in Section 1.4, rejecting if $p^{(0)} \leq \alpha$. If H_0 is rejected, then test both $\tilde{H}^{(1)}$ and $\bar{H}^{(1)}$, rejecting $\tilde{H}^{(1)}$ if $\tilde{p}^{(1)} \leq \alpha$, rejecting $\bar{H}^{(1)}$ if $\bar{p}^{(1)} \leq \alpha$; ... if both $\tilde{p}^{(k)} \leq \alpha$ and $\bar{p}^{(k)} \leq \alpha$, then test both $\tilde{H}^{(k+1)}$ and $\bar{H}^{(k+1)}$, rejecting $\tilde{H}^{(k+1)}$ if $\tilde{p}^{(k+1)} \leq \alpha$, rejecting $\bar{H}^{(k+1)}$ if $\bar{p}^{(k+1)} \leq \alpha$; ... As discussed by Rosenbaum (2008, prop. 3), the chance that this procedure tests and rejects at least one true hypothesis is at most α , because the hypotheses

$$\{H_0, \{\tilde{H}^{(1)}, \bar{H}^{(1)}\}, \{\tilde{H}^{(2)}, \bar{H}^{(2)}\}, \dots, \{\tilde{H}^{(\tilde{M}-1)}, \bar{H}^{(\tilde{M}-1)}\}\}$$

form a sequentially exclusive sequence of hypotheses.

As this incomplete list of multiple testing procedures suggests, there is often an advantage in lending some priority or structure to the $2^M - 1$ possible hypotheses. For instance, in genomics the molecular function categories within GO (Gene Ontology Consortium 2000) provide one possible approach to either limiting the number of hypotheses or organizing the hypotheses.

2.1 Application to the Genomics Study of the Effects of Smoking

We used the 1627 GO molecular function categories (Gene Ontology Consortium 2000) that contain at least two probe sets to identify the functional categories in which smoking has an effect on the expression profile. We did not use all $2^{9968} - 1$ hypotheses, but rather used the 1627 hypotheses H_s in which the binary vector \mathbf{s} picked out the genes in a function category.

We applied the Holm and Benjamini–Hochberg procedures with $\alpha = 0.05$ to the 1627 p -values, $p(\mathbf{s})$, from the cross-match test. Using the Holm procedure, 30 hypotheses were rejected, corresponding to the functional categories in which at most 3 cross-matches were observed. Using the Benjamini–Hochberg procedure, 83 hypotheses were rejected, corresponding to the functional categories in which at most 5 cross-matches were observed. Figure 2 displays the sorted p -values and the adjusted p -values from the Holm and the Benjamini–Hochberg procedures. The appearance of Figure 2 reflects the discrete nature of the statistic A in (1). Here the adjusted p -values for a hypothesis H_i is the smallest nominal level of the multiple testing procedure at which H_i would be rejected, given the value of all test statistics involved (see Westfall and Young 1993).

The foregoing analyses were done under the assumption that the study of Spira et al. (2004) was a randomized experiment, with individuals randomly assigned to their roles as smokers

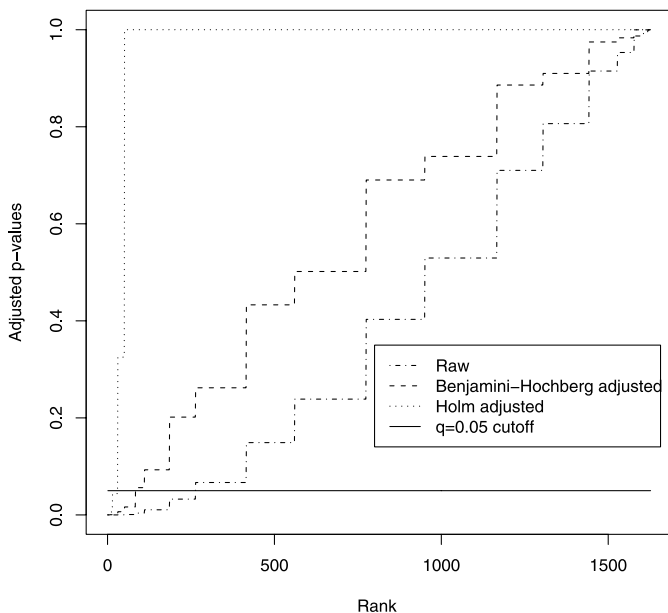


Figure 2. The raw p -values and the adjusted p -values from the Holm and Benjamini–Hochberg procedures. At the 0.05 level, 30 hypotheses are rejected using the Holm procedure, and 83 hypotheses are rejected using the Benjamini–Hochberg procedure.

or never smokers. Of course, individuals are not randomly assigned to smoke or not; indeed, smokers and nonsmokers differ in various ways. Could the significant differences in gene expression have been due to small biases from nonrandom treatment assignment, or are very large departures from random assignment required to produce these differences?

3. SENSITIVITY ANALYSIS FOR THE CROSS-MATCH TEST

3.1 Sensitivity to Nonrandom Treatment Assignment

In point of fact, subjects were not randomly assigned to their roles as smokers and never-smokers, so the randomization distribution of (2) that would be applicable in a randomized experiment is not applicable in the study of Spira et al. (2004). What magnitude of departure from random assignment in (2) would need to be present to alter the conclusion that smoking causes changes in expression levels in human airway epithelial cells?

The sensitivity model (Rosenbaum and Krieger 1990; Rosenbaum 1995, 2002) builds a family of distributions on \mathcal{Z} in two steps. First, the treatment assignments, Z_j , given \mathcal{F} are independent with unknown probabilities,

$$\Pr(Z_j = 1|\mathcal{F}) = \pi_j.$$

Second, the distribution of \mathbf{Z} is returned to \mathcal{Z} by conditioning on $\sum_{j=1}^{2I} Z_j = n$,

$$\Pr\left(\mathbf{Z} = \mathbf{z} \mid \mathcal{F}, \sum_{j=1}^{2I} Z_j = n\right) = \frac{\prod_{j=1}^{2I} \pi_j^{z_j} (1 - \pi_j)^{1-z_j}}{\sum_{\mathbf{b} \in \mathcal{Z}} \prod_{j=1}^{2I} \pi_j^{b_j} (1 - \pi_j)^{1-b_j}} \quad \text{for } \mathbf{z} \in \mathcal{Z}. \quad (4)$$

Following in the spirit of Cornfield et al. (1959), the magnitude of the departure from random assignment is measured by a parameter, $\Gamma \geq 1$, such that two subjects may differ in their odds of treatment by at most a factor of Γ ,

$$\frac{1}{\Gamma} \leq \frac{\pi_j(1 - \pi_k)}{\pi_k(1 - \pi_j)} \leq \Gamma \quad \forall j, k. \quad (5)$$

If $\Gamma = 1$, then $\pi_j = \pi_k \forall j, k$, and (4) equals the randomization distribution (2). For fixed $\Gamma > 1$, the distribution (4) is unknown but deviates from random assignment by a bounded magnitude. A sensitivity analysis considers, for several values of $\Gamma \geq 1$, the range of possible inferences, say the interval of possible significance levels.

The model (4) could be rewritten in terms of a logit model involving an unmeasured covariate u_j , with $u_j \in [0, 1] \forall j$. Specifically, set $\gamma = \log(\Gamma) \geq 0$,

$$\pi_j = \frac{\exp(\alpha + \gamma u_j)}{1 + \exp(\alpha + \gamma u_j)},$$

so that

$$\Pr\left(\mathbf{Z} = \mathbf{z} \mid \mathcal{F}, \sum_{j=1}^{2I} Z_j = n\right) = \frac{\exp(\gamma \mathbf{z}^T \mathbf{u})}{\sum_{\mathbf{b} \in \mathcal{Z}} \exp(\gamma \mathbf{b}^T \mathbf{u})}, \quad \mathbf{u} \in [0, 1]^{2I}. \quad (6)$$

To see that this representation is always possible, set $\alpha = \min_j \log\{\pi_j/(1 - \pi_j)\}$ and $u_j = [\log\{\pi_j/(1 - \pi_j)\} - \alpha]/\gamma$ for $\gamma > 0$ or $u_j = 0$ for $\gamma = 0$. Then the odds ratio of (5), namely $\pi_j(1 - \pi_k)/\{\pi_k(1 - \pi_j)\}$, becomes $e^{-\gamma} \leq \exp\{\gamma(u_j - u_k)\} \leq e^\gamma$ for $\forall j, k$, implying that $u_j \in [0, 1]$.

3.2 Bounds on the Significance Level for Fixed Γ

For fixed $\mathbf{u} \in [0, 1]^{2I}$, the distribution of the cross-match statistic under model (6) and the null hypothesis H_0 of no effect is

$$\Pr\left(h(\mathbf{Z}) \leq a \mid \mathcal{F}, \sum_{j=1}^{2I} Z_j = n\right) = \frac{\sum_{\mathbf{z} \in \mathcal{Z}} \chi\{h(\mathbf{z}) \leq a\} \exp(\gamma \mathbf{z}^T \mathbf{u})}{\sum_{\mathbf{b} \in \mathcal{Z}} \exp(\gamma \mathbf{b}^T \mathbf{u})}, \quad (7)$$

where

$$h(\mathbf{z}) = \sum_{i=1}^I z_{2i-1}(1 - z_{2i}) + (1 - z_{2i-1})z_{2i} \quad (8)$$

and $\chi(E) = 1$ if event E occurs and $\chi(E) = 0$ otherwise. Of course, (7) is unknown because \mathbf{u} is unknown. For each fixed $\Gamma \geq 1$, the following proposition places an upper bound on (7) and hence an upper bound on the p -value from the cross-match statistic. Proposition 1 is proved in the Appendix.

Proposition 1. For fixed $\gamma = \log(\Gamma) \geq 0$, the probability (7) is maximized for $\mathbf{u} \in [0, 1]^{2I}$ by a vector \mathbf{u} with $u_j = 0$ or $u_j = 1$ for every j , and with $u_{2i-1} = u_{2i}$ for at least $I - 1$ pairs.

In Proposition 1, the fewest cross-matches occur for a \mathbf{u} , such that at least $I - 1$ pairs have $u_{2i-1} = u_{2i}$; that is, paired subjects have the same u_j . Because $h(\mathbf{z})$ in (8) is symmetrical in the I pairs, the bound on (7) may be obtained at a \mathbf{u} with $u_j = 0$ or $u_j = 1$ for all j and $u_1 \leq u_2 \leq \dots \leq u_{2I}$, so the number of candidate \mathbf{u} 's is of order $O(I)$. Proposition 2 in the next section gives a practical method for computing the probability (7).

3.3 Sensitivity Distribution of the Cross-Match Statistic

In light of Proposition 1, we evaluate (7) with $u_{2i-1} = u_{2i}$ for all I pairs. A single pair has a negligible effect on (7) for moderate I . The following proposition gives an explicit form for the bounding distribution.

Proposition 2. Suppose that

$$\pi_j = \frac{e^{\alpha+\gamma}}{1 + e^{\alpha+\gamma}}, \quad j = 1, \dots, 2m,$$

$$\pi_j = \frac{e^\alpha}{1 + e^\alpha} \quad \text{for } j = 2m + 1, \dots, 2I.$$

Then, for $a \in \mathcal{A}_{n,I}$,

$$\Pr\left(h(\mathbf{Z}) = a \mid \mathcal{F}, \sum_{j=1}^{2I} Z_j = n\right) = \sum_{k=\max(0, n+2m-2I)}^{\min(2m, n)} \binom{2m}{k} \binom{2I-2m}{n-k} \exp(\gamma k)$$

$$\begin{aligned} & / \left(\sum_{\ell=\max(0, n+2m-2I)}^{\min(2m, n)} \binom{2m}{\ell} \binom{2I-2m}{n-\ell} \exp(\gamma \ell) \right) \\ & \times \sum_{b \in \mathcal{A}_{k,m}} \kappa(b, k, m) \kappa(a - b, n - k, I - m), \end{aligned}$$

where $\kappa(\cdot, \cdot, \cdot)$ is as defined in (3).

Proof. Before conditioning on $\sum_{j=1}^{2I} Z_j = n$, the quantity $\sum_{j=1}^{2m} Z_j$ is the number of treated subjects among the m pairs with $\pi_j = e^{\alpha+\gamma}/(1 + e^{\alpha+\gamma})$, so $\sum_{j=1}^{2m} Z_j$ is binomial with $2m$ trials and probability of success $e^{\alpha+\gamma}/(1 + e^{\alpha+\gamma})$. Similarly, $\sum_{j=2m+1}^{2I} Z_j$ is an independent binomial with $2I - 2m$ trials and probability of success $e^\alpha/(1 + e^\alpha)$. Then the conditional probability is given by the extended hypergeometric distribution,

$$\Pr\left(\sum_{j=1}^{2m} Z_j = k \mid \sum_{j=1}^{2I} Z_j = n\right) = \frac{\binom{2m}{k} \binom{2I-2m}{n-k} \exp(\gamma k)}{\sum_{\ell=\max(0, n+2m-2I)}^{\min(2m, n)} \binom{2m}{\ell} \binom{2I-2m}{n-\ell} \exp(\gamma \ell)}.$$

Conditionally, given $(\sum_{j=1}^{2m} Z_j = k, \sum_{j=1}^{2I} Z_j = n)$, the $\binom{2m}{k}$ possible values of (Z_1, \dots, Z_{2m}) are equally probable, so the conditional probability of b cross-matches in the first m pairs is $\kappa(b, k, m)$ for $b \in \mathcal{A}_{k,m}$. In parallel, conditional on $(\sum_{j=1}^{2m} Z_j = k, \sum_{j=1}^{2I} Z_j = n)$, the $\binom{2I-2m}{n-k}$ possible values of $(Z_{2m+1}, \dots, Z_{2I})$ are equally probable, so the chance of $a - b$ cross-matches is $\kappa(a - b, n - k, I - m)$. Moreover, these two events are conditionally independent. Therefore, conditional on $(\sum_{j=1}^{2m} Z_j = k, \sum_{j=1}^{2I} Z_j = n)$, the chance of $a \in \mathcal{A}_{n,I}$ cross-matches is

$$\sum_{b \in \mathcal{A}_{k,m}} \kappa(b, k, m) \kappa(a - b, n - k, I - m),$$

proving the proposition.

3.4 Application to the Genomics Study of the Effects of Smoking

Table 2 presents the sensitivity analysis. The table gives the upper bound on the p -value for a bias of size Γ when, as in Section 1.3, there are $A = 5$ cross-matches in a study of this size. Again, the parameter Γ measures the magnitude of the departure from random assignment. A bias of magnitude $\Gamma = 10$ is enormous. Two subjects might differ in their odds of smoking by a factor of 10—that is, one subject might be 10 times more likely to smoke than the other—because of an unmeasured co-

Table 2. Sensitivity analysis for the cross-match test when applied to all 9968 expression levels. The table shows the maximum possible p -value from the cross-match test for departures from random assignment of various magnitudes, Γ

	Γ				
	1	2	5	8	10
$\max_{\mathbf{u}} \Pr(A_1 \leq 5)$	0.00084	0.00142	0.00931	0.02877	0.04799

variate with very strong association with gene expression levels. At the conventional 0.05 level, the null hypothesis would be rejected even if the bias Γ was of size 10.

For comparison, one of the least sensitive conclusions from an observational study is that heavy cigarette smoking is a cause of lung cancer. Hammond's (1964) study of smoking and lung cancer, for instance, becomes sensitive at about $\Gamma = 6$ (see Rosenbaum 2002, section 4). This is true despite the smaller sample size and numerous outcomes in the study of Spira et al. (2004). Table 2 exhibits far less sensitivity to unmeasured bias; much more bias would be needed to explain the results of Spira et al. (2004) than to explain the results of Hammond (1964), even though Hammond's study was insensitive to large unmeasured biases. In pondering this, one should keep in mind that Hammond (1964) matched for many covariates, whereas Table 2 compares unmatched groups, so larger biases may be plausible in Table 2. (See Heller et al. 2009 for a discussion of matching in genomics.)

In a nonrandomized study of treatment effects, a conclusion that is sensitive to small departures from random assignment (e.g., $\Gamma = 1.1$) should not be dismissed, but should be viewed with greater caution. See Rosenbaum (2002, 2010) for discussion with numerous examples.

4. SENSITIVITY ANALYSIS FOR TESTING MULTIPLE HYPOTHESES

The method illustrated in Section 3.4 suffices to examine sensitivity to bias in testing one hypothesis. We now turn to the issues that arise when, as in Section 2, multiple hypotheses are tested. Many of these issues are discussed in Rosenbaum and Silber (2009) and so are only sketched here.

For each hypotheses H_s in Section 2, for each specific value of $\Gamma \geq 1$, and for each value of the unobserved covariate $\mathbf{u} \in [0, 1]^{2I}$, there is a p -value, say $p_{\Gamma, \mathbf{u}}(\mathbf{s})$, from the cross-match test. The computations in Section 3 provide a sharp upper bound, say $\bar{p}_{\Gamma}(\mathbf{s})$, on $p_{\Gamma, \mathbf{u}}(\mathbf{s})$, so $p_{\Gamma, \mathbf{u}}(\mathbf{s}) \leq \bar{p}_{\Gamma}(\mathbf{s})$ for all $\mathbf{u} \in [0, 1]^{2I}$.

In principle, there is one true value of the unobserved covariate, \mathbf{u} , and we would like to use the corresponding $p_{\Gamma, \mathbf{u}}(\mathbf{s})$ in a multiple-testing procedure, perhaps one of the procedures described in Section 2. But we cannot do this, because we do not know \mathbf{u} .

All of the procedures in Section 2 are monotone in the $2^M - 1$ possible p -values. If H_s is not rejected by a given set of p -values, then making some of the p -values larger while making none of them smaller will not lead to rejection of H_s . It follows that if H_s were rejected by using $\bar{p}_{\Gamma}(\mathbf{s})$ in place of $p_{\Gamma, \mathbf{u}}(\mathbf{s})$, then it would be rejected by the correct but unknown $p_{\Gamma, \mathbf{u}}(\mathbf{s})$'s as well.

In other words, it is safe to assume that the multiple-testing procedure would reject H_s at the true \mathbf{u} if it rejected H_s with the upper bounds, with $\bar{p}_{\Gamma}(\mathbf{s})$, used in place of the unknown $p_{\Gamma, \mathbf{u}}(\mathbf{s})$. Is the converse true as well? Is it safe to assume that the multiple-testing procedure would accept H_s for some $\mathbf{u} \in [0, 1]^{2I}$ if it accepted H_s with the upper bounds, $\bar{p}_{\Gamma}(\mathbf{s})$, used in place of the unknown $p_{\Gamma, \mathbf{u}}(\mathbf{s})$? The answer depends on the multiple-testing procedure used. The issue has been developed precisely and in detail in Rosenbaum and Silber (2009), and we only sketch it briefly here.

Although each bound $p_{\Gamma, \mathbf{u}}(\mathbf{s}) \leq \bar{p}_{\Gamma}(\mathbf{s})$ is sharp, being attained for some $\mathbf{u} \in [0, 1]^{2I}$, there may be no one $\mathbf{u} \in [0, 1]^{2I}$

such that $p_{\Gamma, \mathbf{u}}(\mathbf{s}) = \bar{p}_{\Gamma}(\mathbf{s})$ for all \mathbf{s} . The unobserved covariate \mathbf{u} that most disrupts the inference about H_s is unlikely to be the same as the unobserved covariate \mathbf{u}' that most disrupts the inference about $H_{s'}$. For instance, with just two hypotheses, \mathbf{s} and \mathbf{s}' , one might have $p_{\Gamma, \mathbf{u}}(\mathbf{s}) = 0.025$ and $p_{\Gamma, \mathbf{u}}(\mathbf{s}') = 0.05$, so Holm's procedure would reject both hypotheses at this \mathbf{u} , and one might have $p_{\Gamma, \mathbf{u}'}(\mathbf{s}) = 0.05$ and $p_{\Gamma, \mathbf{u}'}(\mathbf{s}') = 0.025$, so Holm's procedure also would reject both hypotheses at this \mathbf{u}' . But $\bar{p}_{\Gamma}(\mathbf{s}) \geq 0.05 = p_{\Gamma, \mathbf{u}'}(\mathbf{s})$ and $\bar{p}_{\Gamma}(\mathbf{s}') \geq 0.05 = p_{\Gamma, \mathbf{u}}(\mathbf{s}')$, so Holm's procedure rejects neither hypothesis with the upper bounds, $\bar{p}_{\Gamma}(\mathbf{s})$, used in place of the unknown $p_{\Gamma, \mathbf{u}}(\mathbf{s})$. In other words, Holm's procedure might reject H_s for a given Γ for all $\mathbf{u} \in [0, 1]^{2I}$, but when applying it to the upper bounds, $\bar{p}_{\Gamma}(\mathbf{s})$, it might accept H_s . Applying Holm's procedure to the bounds $\bar{p}_{\Gamma}(\mathbf{s})$ is valid but conservative; the FWER is controlled, but some hypotheses that would be rejected by checking the \mathbf{u} 's one at a time might not be rejected by the bounds, $\bar{p}_{\Gamma}(\mathbf{s})$.

In Rosenbaum and Silber (2009), it is shown that the situation is different for the method of complementary partitions in Section 2. That procedure and other instances of testing in order (Rosenbaum 2008) are not conservative; that is, if H_s is rejected by the upper bounds [the $\bar{p}_{\Gamma}(\mathbf{s}')$'s], then it is rejected for every $\mathbf{u} \in [0, 1]^{2I}$, and if H_s is not rejected by the upper bounds [the $\bar{p}_{\Gamma}(\mathbf{s}')$'s], then there exists a $\mathbf{u} \in [0, 1]^{2I}$ for which H_s is not rejected. Certain procedures, including those mentioned in this paragraph, are stopped by one large p -value, and these are the procedures for which the sensitivity analysis is not conservative (see Rosenbaum and Silber 2009 for specifics).

4.1 Example of Sensitivity Analysis for Multiple Testing

Continuing the analysis of the data of Spira et al. (2004) in Section 3.4, we performed a sensitivity analysis for multiple testing with $\Gamma = 5$ and $\Gamma = 10$. Table 3 gives the results, including results considered previously using the randomization test for which $\Gamma = 1$. As in Section 3.4, the results for several molecular function categories are remarkably insensitive to unmeasured biases, comparable to the studies linking heavy smoking with lung cancer.

Table 4 displays the six least-sensitive molecular function categories, with rejected null hypotheses by the Holm procedure at $\Gamma = 5$ and by the Benjamini-Hochberg procedure at $\Gamma = 10$. As shown in the table, the six rejected sets are those in which the observed number of cross-matches is 1, its smallest possible value in a data set with n odd. Figure 3 parallels Figure 1, but refers only to the 92-dimensional cross-match test for molecular function category GO:0016616; here there is $A = 1$ cross-match.

How does this analysis compare to that of Spira et al. (2004)? Those authors found 97 genes to be differentially expressed between never-smokers and current smokers. A significant molecular function category in the GO ontology was then determined by overrepresentation in that category of the 97 significant genes, with the judgment of overrepresentation depending on an assumption that the genes are independent. There are several differences between the analyses. Of course, our work has emphasized a sensitivity analysis, addressing the possibility that the division of people into smokers and nonsmokers is not random, but rather is related to unmeasured attributes of these individuals. Moreover, when performing a cross-match test in a

Table 3. Sensitivity analysis with $\Gamma = 1$, $\Gamma = 5$, or $\Gamma = 10$. The case where $\Gamma = 1$ is the usual randomization inference. The left side of the table indicates the number of hypotheses that were rejected at the 0.05 level by the three methods of multiple testing. The right side of the table gives the value of the cross-match statistic, A , required for rejection

Γ	Number of rejected null hypotheses			Value of A required for rejection		
	Bonferroni	Holm	Benjamini–Hochberg	Bonferroni	Holm	Benjamini–Hochberg
1	30	30	83	3	3	5
5	6	6	30	1	1	3
10	0	0	6	Not possible	Not possible	1

GO category, we do not assume that these genes are independent. Assuming independent expression levels for genes that share a GO category is perhaps not the most comfortable of assumptions.

Three of the six least-sensitive functional categories found by our analysis (GO:0004033, GO:0004601, and GO:0016616) also were judged to be significantly overrepresented in the analysis of Spira et al. Our analysis strengthens that group’s conclusions about these three categories by adding the observation that only large biases from nonrandom treatment assignment could explain this pattern of expression level. In agreement with Spira et al., we found that an additional category, “glucuronosyltransferase activity” category (GO:0015020), was overexpressed when judged as if from a randomized experiment ($\Gamma = 1$), but with $A = 5$ cross-matches, this finding was sensitive to biases of moderate size from nonrandom treatment assignments. Another category, “transferase activity, transferring hexosyl groups” (GO:00016758), was found to be significantly overrepresented by Spira et al. (they quote a p -value of 0), but was not significant by our analysis, even in a randomization test ($\Gamma = 1$), because the number of cross-matches was 7. Obviously, the discrepancy here is not due to the sensitivity analysis, because it is present even in the randomization test ($\Gamma = 1$). Rather, it reflects some difference in the judgments of the two testing procedures, possibly the reliance on independent genes in their analysis.

5. DISCUSSION

The cross-match test judges whether treated and control groups differ on a high-dimensional response \mathbf{Y}_ℓ by pairing individuals with similar values of \mathbf{Y}_ℓ and counting the number of times, A , that treated individuals are paired with controls. If A is small, then the hypothesis of no effect of the treatment

on \mathbf{Y}_ℓ is rejected. Previous work (Rosenbaum 2005) considered the behavior of the cross-match statistic A in a randomized experiment, but many applications (in, e.g., genomics), are not experiments, so the behavior of A might be affected by some unmeasured way in which treated and control subjects are not comparable. Spira et al.’s (2004) study of gene expression levels in smokers and nonsmokers was not an experiment; people were not randomly assigned to smoke or not, and they might have differ in ways that were not recorded. Here we have proposed a sensitivity analysis for the cross-match test that investigates the magnitude of bias from unmeasured covariates that would be needed to alter the rejection of the null hypothesis. In Spira et al.’s (2004) study, the magnitude Γ of the departure from randomized assignment required to alter certain conclusions is quite large, greater even than the magnitude required to alter the conclusion in Hammond (1964) that heavy smoking causes lung cancer, one of the least-sensitive conclusions found in an observational study. We also showed how the statistic can be used in conjunction with multiple-testing procedures to isolate affected parts of \mathbf{Y}_ℓ .

The cross-match test is an omnibus test. It is an appropriate test when the investigator does not know the nature of the effect of the treatment on the coordinates of \mathbf{Y}_ℓ . As far as we know,

Table 4. The six molecular function categories identified in Table 3 with $\Gamma = 10$

Gene Set ID	Description
GO:0004033	Aldo-keto reductase activity
GO:0004601	Peroxidase activity
GO:0016614	Oxidoreductase activity, acting on CH-OH group of donors
GO:0016616	Oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor
GO:0016903	Oxidoreductase activity, acting on the aldehyde or oxo group of donors
GO:0016684	Oxidoreductase activity, acting on peroxide as acceptor

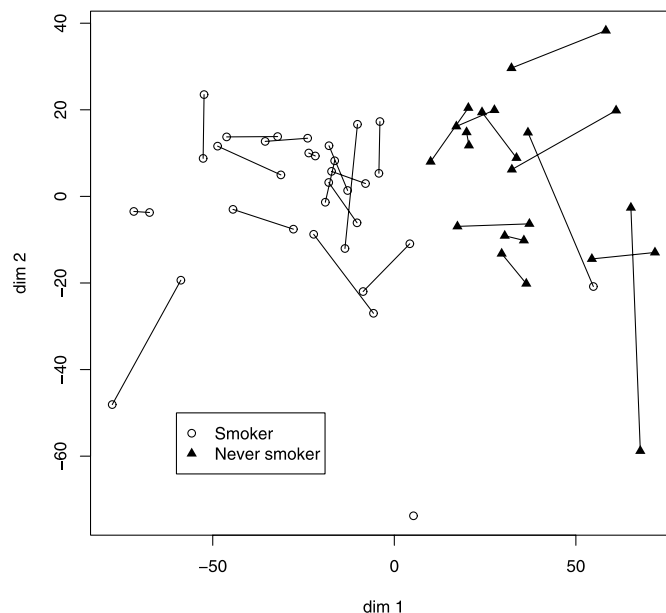


Figure 3. A two-dimensional representation of the 92-dimensional cross-match test of the molecular function GO:0016616. Because there is only one instance in which a circle is connected to a triangle, the cross-match statistic is $A = 1$.

it is currently the only omnibus nonparametric test for which a sensitivity analysis is available. An omnibus test should not be used if one is interested only in focused alternatives to the hypothesis of no effect, such as shifts in location. For instance, if the investigator knew the direction of the effect for every coordinate of \mathbf{Y}_ℓ , then multivariate tests that exploit this knowledge would have much greater power. One such test would orient the M coordinates of \mathbf{Y}_ℓ in the anticipated direction, calculate the M separate Wilcoxon rank-sum statistics, and take the sum of these M statistics as the test statistic (Rosenbaum 1991). This is actually a univariate rank test with scores summed over the M coordinates of \mathbf{Y}_ℓ , so the method of sensitivity analysis for univariate rank tests in Rosenbaum and Krieger (1990) could be used. This test also could be applied to test each subhypothesis H_s involving a subset of the coordinates of \mathbf{Y}_ℓ , and so it could be combined with multiple-testing procedures along the lines illustrated here for the cross-match test.

The behavior of the cross-match test is affected by the choice of distance function used to judge whether \mathbf{Y}_i is close \mathbf{Y}_ℓ . We used the Euclidean distance applied to the log of expression levels. An advantage of the Euclidean distance is that it is not estimated from the data, so the distance between \mathbf{Y}_i and \mathbf{Y}_j is not affected if \mathbf{Y}_ℓ is an outlier. Other properties of the Euclidean distance are as follows: (a) The distance between \mathbf{Y}_i and \mathbf{Y}_j might be strongly affected by a single coordinate of \mathbf{Y}_i or \mathbf{Y}_j ; (b) the coordinates of \mathbf{Y}_ℓ must be in commensurate units, because they are combined without further standardization; and (c) covariances among the coordinates of \mathbf{Y}_ℓ are not taken into account. These properties could be viewed as advantages or disadvantages, depending on the context. The Mahalanobis distance addresses (b) and (c) but can be strongly distorted by a single outlier and, at the least, it requires care when $2I \leq M$.

APPENDIX: PROOF OF PROPOSITION 1

In Proposition 1, the proof that (7) is maximized with $u_j = 0$ or $u_j = 1$ for every j is exactly parallel to the proof of proposition 2 of Rosenbaum and Krieger (1990, p. 495) and thus is omitted here. Thus, for the remainder of the proof, we assume that $u_j \in \{0, 1\}$. To complete the proof, we also must show that (7) is maximized with $u_{2i-1} = u_{2i}$ for at least $I - 1$ pairs. If $\gamma = 0$, then there is nothing to prove; thus, because $\Gamma \geq 1$ and $\gamma = \log(\Gamma)$, we can restrict our attention to $\gamma > 0$.

For $i = 1, \dots, I$, let $V_i = Z_{2i-1} + Z_{2i}$, so that $V_i \in \{0, 1, 2\}$, the V_i 's are independent, $V_i = 1$ for a cross-match, A is the number of 1's among the V_i 's, and $\sum_{i=1}^I V_i = \sum_{j=1}^{2I} Z_j$. Thus $\Pr(A \leq a | \sum_{j=1}^{2I} Z_j = n)$ in (7) equals the probability of a or fewer 1's among the V_i 's given that $\sum_{i=1}^I V_i = n$.

Because conditioning on $\sum_{j=1}^{2I} Z_j = n$ eliminates α in (6), we can set α to any arbitrary number without changing the distribution on \mathcal{Z} . Write $\lambda = \gamma/2$. It is tidy to set $\alpha = -\gamma/2 = -\lambda$, because the interval of π_j 's is then symmetric about $\frac{1}{2}$,

$$\pi_j \in \left[\frac{e^{-\gamma/2}}{1 + e^{-\gamma/2}}, \frac{e^{\gamma/2}}{1 + e^{\gamma/2}} \right] = \left[\frac{e^{-\lambda}}{1 + e^{-\lambda}}, \frac{e^{\lambda}}{1 + e^{\lambda}} \right] = \left[\frac{1}{1 + e^{\lambda}}, \frac{e^{\lambda}}{1 + e^{\lambda}} \right].$$

In light of this and using $u_j \in \{0, 1\}$, we have

$$\pi_j \in \left\{ \frac{e^{\lambda}}{1 + e^{\lambda}}, \frac{1}{1 + e^{\lambda}} \right\} \text{ for every } j, \tag{A.1}$$

with the consequence that

$$\begin{aligned} \Pr(V_i = 1) &= \pi_{2i-1}(1 - \pi_{2i}) + \pi_{2i}(1 - \pi_{2i-1}) \\ &= \frac{2e^{\lambda}}{(1 + e^{\lambda})^2} \text{ if } \pi_{2i} = \pi_{2i-1} \\ &= \frac{e^{2\lambda} + 1}{(1 + e^{\lambda})^2} \text{ if } \pi_{2i} \neq \pi_{2i-1}. \end{aligned}$$

Thus the unconditional probability of a cross-match, $\Pr(V_i = 1)$, is larger for $\pi_{2i} \neq \pi_{2i-1}$ than for $\pi_{2i} = \pi_{2i-1}$.

Now every π_j satisfies (A.1). Suppose that there are two pairs, say i and k , such that $\pi_{2i} \neq \pi_{2i-1}$ and $\pi_{2k} \neq \pi_{2k-1}$. To simplify notation without loss of generality, suppose that the pairs are $i = 1$ and $k = 2$ and that

$$\pi_1 = \pi_3 = \frac{e^{\lambda}}{1 + e^{\lambda}}, \quad \pi_2 = \pi_4 = \frac{1}{1 + e^{\lambda}}. \tag{A.2}$$

We show that swapping π_2 and π_3 does not decrease $\Pr(A \leq a | \sum_{j=1}^{2I} Z_j = n)$. If such swaps are pursued for as many pairs, i and k , as possible, then we obtain the bounding \mathbf{u} described in the statement of Proposition 1, thereby proving the result. Thus, to complete the proof, it suffices to show that swapping π_2 and π_3 does not decrease $\Pr(A \leq a | \sum_{j=1}^{2I} Z_j = n)$.

Because $(V_1, V_2) \perp\!\!\!\perp (V_3, \dots, V_I)$, it follows that

$$(V_1, V_2) \perp\!\!\!\perp (V_3, \dots, V_I) \left| \left(V_1 + V_2, \sum_{i=3}^I V_i \right) \right.$$

(see Dawid 1979). In particular, if $A_{g,h} = \sum_{i=g}^h Z_{2i-1}(1 - Z_{2i}) + (1 - Z_{2i-1})Z_{2i}$, then $A = A_{1,2} + A_{3,I}$ and

$$A_{1,2} \perp\!\!\!\perp A_{3,I} \left| \left(V_1 + V_2, \sum_{i=3}^I V_i \right) \right., \tag{A.3}$$

so that, continuing to use $\sum_{i=1}^I V_i = \sum_{j=1}^{2I} Z_j$,

$$\begin{aligned} \Pr\left(A \leq a \mid \sum_{j=1}^{2I} Z_j = n \right) &= \Pr\left(A_{1,2} + A_{3,I} \leq a \mid \sum_{i=1}^I V_i = n \right) \\ &= E \left\{ \Pr\left(A_{1,2} + A_{3,I} \leq a \mid \sum_{i=1}^2 V_i, \sum_{i=3}^I V_i \right) \mid \sum_{i=1}^I V_i = n \right\}. \end{aligned} \tag{A.4}$$

Combining $(V_1, V_2) \perp\!\!\!\perp (V_3, \dots, V_I)$, (A.3), and (A.4), $\Pr(A \leq a | \sum_{j=1}^{2I} Z_j = n)$ would be made larger (i.e., not smaller) for all a if $\Pr(A_{1,2} \leq c | \sum_{i=1}^2 V_i = m)$ were made larger (i.e., not smaller) for all (c, m) .

Now, given $V_1 + V_2 = m$,

$$\begin{aligned} A_{1,2} &= Z_1(1 - Z_2) + (1 - Z_1)Z_2 + Z_3(1 - Z_4) + (1 - Z_3)Z_4 \\ &= \begin{cases} 0 & \text{if } m = 0 \\ 1 & \text{if } m = 1 \\ 1 & \text{if } m = 3 \\ 0 & \text{if } m = 4, \end{cases} \end{aligned}$$

whereas if $m = 2$, then $\Pr(A_{1,2} = 0 | V_1 + V_2 = 2) = \Psi / (\psi + \Psi)$ and

$$\begin{aligned} \Pr(A_{1,2} = 2 | V_1 + V_2 = 2) &= 1 - \Pr(A_{1,2} = 0 | V_1 + V_2 = 2) \\ &= \psi / (\psi + \Psi), \end{aligned}$$

where

$$\begin{aligned}\Psi &= \Pr\{(V_1, V_2) = (2, 0) \text{ or } (V_1, V_2) = (0, 2)\} \\ &= \pi_1\pi_2(1 - \pi_3)(1 - \pi_4) + \pi_3\pi_4(1 - \pi_1)(1 - \pi_2)\end{aligned}$$

and

$$\begin{aligned}\psi &= \Pr\{(V_1, V_2) = (1, 1)\} \\ &= \{\pi_1(1 - \pi_2) + \pi_2(1 - \pi_1)\}\{\pi_3(1 - \pi_4) + \pi_4(1 - \pi_3)\}.\end{aligned}$$

If (A.2) is true, then

$$\Pr(A_{1,2} = 0 | V_1 + V_2 = 2) = \frac{2e^{2\lambda}}{\{e^{2\lambda} + 1\}\{e^{2\lambda} + 1\} + 2e^{2\lambda}},$$

but if π_2 and π_3 are interchanged, then this probability increases to

$$\Pr(A_{1,2} = 0 | V_1 + V_2 = 2) = \frac{e^{4\lambda} + 1}{\{e^{2\lambda} + 1\}\{e^{2\lambda} + 1\} + 2e^{2\lambda}}.$$

It follows that the swap of π_2 and π_3 (or of Z_2 and Z_3) does not decrease $\Pr(A \leq a | \sum_{j=1}^{2I} Z_j = n)$, proving Proposition 1.

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