

# Unconditional Exact Tests in the exact2x2 R package

Michael P. Fay, Sally A. Hunsberger

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## Summary

These notes describe the calculations for the `uncondExact2x2` function in the `exact2x2` R package. This function does unconditional exact tests for the two sample binomial problem. It has options for several different test statistics, mid p-value adjustments, and Berger and Boos adjustments.

## 1 Definition and Calculation of the Unconditional Exact Tests

### 1.1 Defining the General Method

Let  $\mathbf{X} = [X_1, X_2]$  with  $X_a \sim \text{Binom}(n_a, \theta_a)$  for  $a = 1, 2$ . Suppose we are interested in  $\beta = b(\theta)$ , where  $b(\theta)$  is some function of  $\theta_1$  and  $\theta_2$ . Common examples are the difference,  $\beta_d = \theta_2 - \theta_1$ , the ratio,  $\beta_r = \theta_2/\theta_1$ , and the odds ratio,  $\beta_{or} = \{\theta_2(1 - \theta_1)\} / \{\theta_1(1 - \theta_2)\}$ .

We want to test hypotheses of the form  $H_0 : \theta \in \Theta_0$  versus  $H_1 : \theta \in \Theta_1$ , where  $\Theta_0$  and  $\Theta_1$  are the set of all possible values of  $[\theta_1, \theta_2]$  under the null hypothesis or the alternative hypothesis, respectively. It is convenient to write  $\Theta_0$  and  $\Theta_1$  in terms of  $\beta$ . For example,

$$\Theta_0 = \{\theta : b(\theta) = \beta_0\}$$

For this example, instead of writing the null hypothesis as  $H_0 : \theta \in \Theta_0$ , we write it in terms of  $\beta = b(\theta)$  as  $H_0 : \beta = \beta_0$ . We are generally interested in three classes of hypotheses: two-sided hypotheses,

$$\begin{aligned} H_0 : & \quad \beta = \beta_0 \\ H_1 : & \quad \beta \neq \beta_0 \end{aligned}$$

or one of the one-sided hypotheses,

<u>Alternative is Less</u>	<u>Alternative is Greater</u>
$H_0 : \beta \geq \beta_0$	$H_0 : \beta \leq \beta_0$
$H_1 : \beta < \beta_0$	$H_1 : \beta > \beta_0$

First consider `parmtype="difference"`. Let  $T(\mathbf{X})$  be some test statistic, where larger values suggest that  $\theta_2$  is larger than  $\theta_1$ . Then a valid (i.e., exact) p-value for testing  $H_0 : \beta \geq \beta_0$  is

$$p_U(\mathbf{x}, \beta_0) = \sup_{\theta : b(\theta) \geq \beta_0} Pr_{\theta} [T(\mathbf{X}) \leq T(\mathbf{x})].$$

For testing  $H_0 : \beta \leq \beta_0$  the p-value is

$$p_L(\mathbf{x}, \beta_0) = \sup_{\theta : b(\theta) \leq \beta_0} Pr_{\theta} [T(\mathbf{X}) \geq T(\mathbf{x})].$$

When `parmttype='ratio'` then when  $\mathbf{x} = [0, 0]$  there is no information about the ratio and we define the p-value as 1. Similarly, when `parmttype='oddsratio'` and  $\mathbf{x} = [0, 0]$  or  $\mathbf{x} = [n_1, n_2]$  there is no information about the odds ratio and we define the p-value as 1, and we do not calculate probabilities in p-value calculations over values with no information. Specifically, let  $\mathcal{X}_I$  denote the set of  $\mathbf{X}$  values with information about  $\beta$ . Then if  $\mathbf{x} \notin \mathcal{X}_I$  set  $p_U(\mathbf{x}, \beta_0)$  and  $p_L(\mathbf{x}, \beta_0)$  to 1, otherwise let  $p_U(\mathbf{x}, \beta_0)$  be

$$\sup_{\theta: b(\theta) \geq \beta_0} P_\theta [T(\mathbf{X}) \leq T(\mathbf{x}) | \mathbf{X} \in \mathcal{X}_I] P_\theta [\mathbf{X} \in \mathcal{X}_I]$$

and analogously, let  $p_L(\mathbf{x}, \beta_0)$  be

$$\sup_{\theta: b(\theta) \leq \beta_0} P_\theta [T(\mathbf{X}) \geq T(\mathbf{x}) | \mathbf{X} \in \mathcal{X}_I] P_\theta [\mathbf{X} \in \mathcal{X}_I].$$

Since we never reject when  $\mathbf{x} \notin \mathcal{X}_I$ , these definitions give valid p-values, and additionally when  $\mathbf{x} \notin \mathcal{X}_I$  we do not need to define  $T(\mathbf{x})$ .

The `tsmethod` option gives two ways to calculate the two-sided p-value. The default option is 'central' to give a central p-value, which is

$$\begin{aligned} p_{ts}(\mathbf{x}, \beta_0) &= p_{central}(\mathbf{x}, \beta_0) \\ &= \min \{1, 2p_U(\mathbf{x}, \beta_0), 2p_L(\mathbf{x}, \beta_0)\} \end{aligned}$$

The second options is `tsmethod='square'`. For this option, we square the test statistic,  $T(\mathbf{x})$ , defined in the next section, and define the p-value as

$$\begin{aligned} p_{ts}(\mathbf{x}, \beta_0) &= p_{square}(\mathbf{x}, \beta_0) \\ &= \begin{cases} \sup_{\theta \in \Theta_0} Pr_\theta [T^2(\mathbf{X}) \geq T^2(\mathbf{x})] & \text{(for parmttype="difference")} \\ \sup_{\theta \in \Theta_0} Pr_\theta [T^2(\mathbf{X}) \geq T^2(\mathbf{x}) | \mathbf{X} \in \mathcal{X}_I] Pr_\theta [\mathbf{X} \in \mathcal{X}_I] & \text{(otherwise)}. \end{cases} \end{aligned}$$

Since the probability expression only depends on the ordering, and since the ordering of the square of  $T(\mathbf{X})$  is the same as the ordering of absolute value of  $T(\mathbf{X})$ , we can equivalently write  $p_{square}$  in terms of absolute values.

These exact p-values are necessarily conservative because for most  $\theta \in \Theta_0$  we have

$$Pr_\theta [p_U(\mathbf{X}, \beta_0) \leq \alpha] < \alpha.$$

A less conservative approach, *but one that is no longer valid (i.e., no longer exact)*, is to use a mid-p value. For example, the mid-p value associated with  $p_U$  is

$$p_{Umid}(\mathbf{x}, \Theta_0) = \sup_{\theta: b(\theta) \geq \beta_0} \left\{ Pr_\theta [T(\mathbf{X}) < T(\mathbf{x})] + \frac{1}{2} Pr_\theta [T(\mathbf{X}) = T(\mathbf{x})] \right\}.$$

Other mid p-values are defined analogously.

## 1.2 Options for $T(\mathbf{x})$

### 1.2.1 Overview

We now give the  $T(\mathbf{x})$  function that is defined by three options: **parmtype**, **nullparm**, and **method**. The option **parmtype** is one of ‘difference’, ‘ratio’ or ‘odds ratio’, and it determines the parameter associated with the confidence interval. The option **nullparm** defines  $\beta_0$ . The default for **nullparm**=NULL, which is replaced by  $\beta_0 = 0$  for **parmtype**=‘difference’ and  $\beta_0 = 1$  for **parmtype**=‘ratio’ or ‘odds ratio’. Finally, **method** defines the type of  $T$  function:

**simple:** then  $T$  is an estimate of the **parmtype** using the estimates  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$ .

**simpleTB:** simple with a tie break. Ties in  $T$  using the simple method are broken based on variability, with larger variability further away from the null.

**score:** here  $T$  is based on a score statistic.

**wald pooled:**  $T$  is a Wald statistic on the difference in sample means using the pooled variance estimate.

**wald unpooled:**  $T$  is a Wald statistic on the difference in sample means using an **unpooled** variance estimate.

**FisherAdj:**  $T$  is a one-sided mid p-value using Fisher’s exact test. Note that we create an exact unconditional test using the ordering by the mid p-value, so the test is valid (or exact), even though the mid p-values when used as p-values directly are not necessarily valid.

### 1.2.2 Simple: Difference

When **method**=‘simple’ and **parmtype**=‘difference’ we have,

$$T(\mathbf{x}) = T([x_1, x_2]) = \frac{x_2}{n_2} - \frac{x_1}{n_1} - \beta_0$$

The order does not change as  $\beta_0$  changes.

### 1.2.3 Simple with Tie Break: Difference

When **method**=‘simpleTB’ and **parmtype**=‘difference’ and **tsmethod**=‘central’ we use  $T(\mathbf{x})$  from the previous subsection, then break ties by ordering by  $T^*(\mathbf{x})$  *within* each tied value for  $T(\mathbf{x})$ , where

$$T^*(\mathbf{x}) = \frac{\hat{\theta}_2 - \hat{\theta}_1}{\sqrt{\frac{\hat{\theta}_1(1-\hat{\theta}_1)}{n_1} + \frac{\hat{\theta}_2(1-\hat{\theta}_2)}{n_2}}}$$

where  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$ . If  $T^*$  gives a ratio of 0/0 then it is set to 0.

The idea behind  $T^*$  is that with each  $\hat{\beta}_d = \hat{\theta}_2 - \hat{\theta}_1$  value, values with lower variability are more extreme (i.e., ranked higher when  $\hat{\beta}_d$  is positive and ranked lower when  $\hat{\beta}_d$  is negative). We do not subtract  $\beta_0$  from the numerator, because we do not want the order to change for different hypotheses, which makes calculations more difficult and could possibly lead to non-unified inferences (e.g., reject the null at level  $\alpha$  but the  $1 - \alpha$  CI for  $\beta_d$  includes 0).

#### 1.2.4 Score:Difference

When `method='score'` and `parmtime='difference'` we have,

$$T([x_1, x_2]) = \frac{\frac{x_2}{n_2} - \frac{x_1}{n_1} - \beta_0}{\sqrt{\tilde{\theta}_1(1 - \tilde{\theta}_1)/n_1 + \tilde{\theta}_2(1 - \tilde{\theta}_2)/n_2}},$$

where  $\tilde{\theta}_1$  and  $\tilde{\theta}_2$  are the maximum likelihood estimates of  $\theta_1$  and  $\theta_2$  under the restriction that  $b(\theta) = \beta_0$ . See the code of `constMLE.difference` for the formula, or the Appendix of Farrington and Manning (1990).

#### 1.2.5 Wald-Pooled: Difference

When `method='wald-pooled'` and `parmtime='difference'` we have,

$$T([x_1, x_2]) = \frac{\hat{\theta}_2 - \hat{\theta}_1 - \beta_0}{\sqrt{\hat{\theta}(1 - \hat{\theta}) \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}},$$

where  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$  and  $\hat{\theta} = (x_1 + x_2)/(n_1 + n_2)$ . If  $T$  gives a ratio of 0/0 then it is set to 0.

#### 1.2.6 Wald-Unpooled: Difference

When `method='wald-unpooled'` and `parmtime='difference'` we have,

$$T([x_1, x_2]) = \frac{\hat{\theta}_2 - \hat{\theta}_1 - \beta_0}{\sqrt{\hat{\theta}_1(1 - \hat{\theta}_1)/n_1 + \hat{\theta}_2(1 - \hat{\theta}_2)/n_2}},$$

where  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$ . If  $T$  gives a ratio of 0/0 then it is set to 0.

#### 1.2.7 Simple: Ratio

When `method='simple'` and `parmtime='ratio'` we have,

$$\begin{aligned} T(\mathbf{x}) = T([x_1, x_2]) &= \log \left( \frac{\hat{\theta}_2}{\beta_0 \hat{\theta}_1} \right) \\ &= \log(\hat{\theta}_2) - \log(\hat{\theta}_1) - \log(\beta_0), \end{aligned}$$

where  $\hat{\theta}_a = x_a/n_a$  for  $a = 1, 2$ . Note  $\log(0) \equiv \infty$  and  $\log(0) - \log(0) \equiv NA$ . We do not need to define  $NA$  values since  $x = [0, 0]$  has no information (see Section 1.1).

### 1.2.8 Simple with Tie Break: Ratio

When `method`='simpleTB' and `parmtpe`='ratio' we used  $T(\mathbf{x})$  from the previous subsection, then break ties by ordering by  $T^*(\mathbf{x})$  *within* each tied value for  $T(\mathbf{x})$ , where

$$T^*(\mathbf{x}) = \begin{cases} x_2 & \text{if } x_1 = 0 \text{ and } x_2 > 0 \\ 1/x_1 & \text{if } x_1 > 0 \text{ and } x_2 = 0 \\ 0 & \text{if } x_1 = n_1 \text{ and } x_2 = n_2 \\ \frac{\log(\hat{\theta}_2) - \log(\hat{\theta}_1)}{\sqrt{\frac{1}{x_1} - \frac{1}{n_1} + \frac{1}{x_2} - \frac{1}{n_2}}} & \text{if } x_1 > 0 \text{ and } x_2 > 0 \text{ and not}(x_1 = n_1 \text{ and } x_2 = n_2) \end{cases}$$

where  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$ .

In words, when  $x_1/n_1 = \hat{\theta}_1 = 0$  and  $x_2 > 0$  then  $T(\mathbf{x}) = -\infty$  and we order by  $x_2$ ; otherwise when we order  $x_2/n_2 = \hat{\theta}_2 = 0$  and  $x_1 > 0$  then  $T(\mathbf{x}) = \infty$  and we order by  $1/x_1$ ; otherwise when  $\hat{\theta}_1 = \hat{\theta}_2 = 1$  we do not break the ties (by setting  $T^*(\mathbf{x}) = 0$ ); otherwise for each  $\log(\hat{\beta}_r) = \log(\hat{\theta}_2/\hat{\theta}_1)$  value, we rank values with lower variability are more extreme (i.e., ranked higher when  $\hat{\beta}_r > 1$  and ranked lower when  $\hat{\beta}_r < 1$  is negative). The variance formula comes from the variance estimate of the  $\log(\hat{\beta}_r)$ . Fleiss, Levin, and Paik (2003, p. 132, equation 6.112, except there is a typo) give the variance expression,

$$\text{var}(\log(\hat{\beta}_r)) \approx \sqrt{\frac{n_1 - x_1}{x_1 n_1} + \frac{n_2 - x_2}{x_2 n_2}} = \sqrt{\frac{1}{x_1} - \frac{1}{n_1} + \frac{1}{x_2} - \frac{1}{n_2}}.$$

We do not subtract  $\log(\beta_0)$  from the numerator in the  $T^*(|bf x)$  function to keep it simple.

### 1.2.9 Score: Ratio

When `method`='score' and `parmtpe`='ratio' we have,

$$T([x_1, x_2]) = \frac{\hat{\theta}_2 - \hat{\theta}_1 \beta_0}{\sqrt{\beta_0 \tilde{\theta}_1 (1 - \tilde{\theta}_1)/n_1 + \tilde{\theta}_2 (1 - \tilde{\theta}_2)/n_2}},$$

where  $\tilde{\theta}_1$  and  $\tilde{\theta}_2$  are the maximum likelihood estimates of  $\theta_1$  and  $\theta_2$  under the restriction that  $\beta_r = b(\theta) = \beta_0$ ; for the formula for  $\tilde{\theta}_a$  for  $a = 1, 2$ , see either the `constrMLE.ratio`, Miettinen and Nurminen (1985).

### 1.2.10 Simple: Odds Ratio

When `method`='simple' and `parmtpe`='odds ratio' we have,

$$T(\mathbf{x}) = T([x_1, x_2]) = \log \left( \frac{\hat{\theta}_2 (1 - \hat{\theta}_1)}{\beta_0 \hat{\theta}_1 (1 - \hat{\theta}_2)} \right),$$

where  $\hat{\theta}_a = x_a/n_a$  for  $a = 1, 2$ .

### 1.2.11 Simple with Tie Break: Odds Ratio

When `method='simpleTB'` and `parmtpe='oddsratio'` we used  $T(\mathbf{x})$  from the previous subsection, then break ties by ordering by  $T^*(\mathbf{x})$  *within* each tied value for  $T(\mathbf{x})$ , where

$$T^*(\mathbf{x}) = \begin{cases} x_2 & \text{if } x_1 = 0 \text{ or } x_2 = n_2 \\ 1/x_1 & \text{if } x_1 = n_1 \text{ or } x_2 = 0 \\ \frac{\log(x_2) - \log(n_2 - x_2) - \log(x_1) + \log(n_1 - x_1)}{\sqrt{\frac{1}{x_1} + \frac{1}{n_1 - x_1} + \frac{1}{x_2} + \frac{1}{n_2 - x_2}}} & \text{otherwise} \end{cases}$$

where  $\hat{\theta}_1 = x_1/n_1$  and  $\hat{\theta}_2 = x_2/n_2$ .

In words, when  $\hat{\beta}_{or} = \infty$  then we order by  $x_2$ ; otherwise when  $\hat{\beta}_{or} = -\infty$  then we order by  $1/x_1$ ; otherwise for each  $\log(\hat{\beta}_{or})$  value, we rank values with lower variability are more extreme (i.e., ranked higher when  $\hat{\beta}_r > 1$  and ranked lower when  $\hat{\beta}_r < 1$  is negative). The variance formula comes from the variance estimate of the  $\log(\hat{\beta}_{or})$ . Fleiss, Levin, and Paik (2003, p. 102, equation 6.19) give the variance estimate for  $var(\hat{\beta}_{or})$ , and using the delta method, the estimate for  $var(\log(\hat{\beta}_{or}))$  is

$$var(\log(\hat{\beta}_{or})) \approx \sqrt{\frac{1}{x_1} + \frac{1}{n_1 - x_1} + \frac{1}{x_2} + \frac{1}{n_2 - x_2}}.$$

We do not subtract  $\log(\beta_0)$  from the numerator to keep it simple.

### 1.2.12 Score: Odds Ratio

When `method='score'` and `parmtpe='oddsratio'` we use (see Agresti and Min, 2002, p. 381, except we do not square the statistic because we want to allow one-sided inferences),

$$T([x_1, x_2]) = \left\{ n_2 \left( \frac{x_2}{n_2} - \tilde{\theta}_2 \right) \right\} \sqrt{\frac{1}{n_1 \tilde{\theta}_1 (1 - \tilde{\theta}_1)} + \frac{1}{n_2 \tilde{\theta}_2 (1 - \tilde{\theta}_2)}},$$

where  $\tilde{\theta}_1$  and  $\tilde{\theta}_2$  are the maximum likelihood estimates of  $\theta_1$  and  $\theta_2$  under the restriction that

$$\tilde{\beta}_{or} = \frac{\tilde{\theta}_2(1 - \tilde{\theta}_1)}{\tilde{\theta}_1(1 - \tilde{\theta}_2)} = \beta_0.$$

For the formula for  $\tilde{\theta}_a$  for  $a = 1, 2$ , see either the function `constrMLE.oddsratio` or Miettinen and Nurminen (1985).

### 1.2.13 FisherAdj: Difference, Ratio, or Odds Ratio

When `method='FisherAdj'` we order by the mid p-value from a one-sided Fisher's exact test. We do not change the ordering as the  $\beta_0$  changes, so it can be used with any `parmtpe`.

Using the `phyper` and `dhyper` functions for the hypergeometric distribution, this becomes:

$$T([x_1, x_2]) = \text{phyper}(x_2, n_2, n_1, x_2 + x_1) - 0.5 * \text{dhyper}(x_2, n_2, n_1, x_1 + x_2)$$

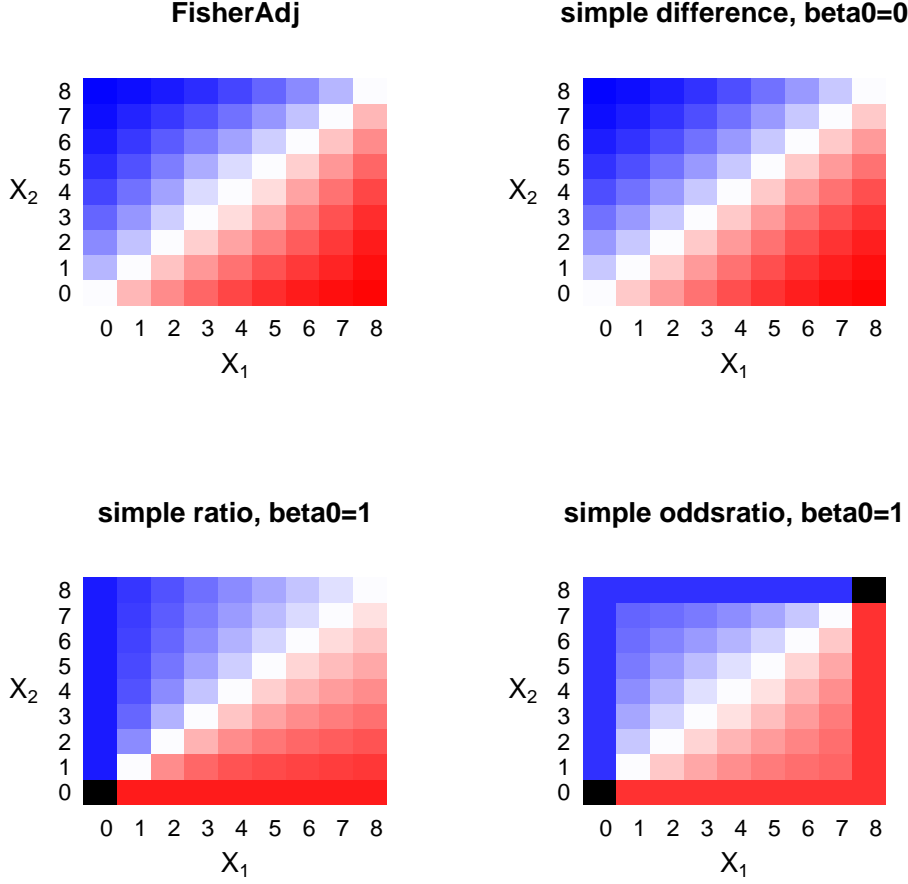


Figure 1: Plots of the orderings using `plotT`. Dark blue is highest, dark red is lowest, white is the middle, and black is no information. The default is `method="FisherAdj"` (same for all `parmtypes`), the `method="simple"` order by the plug-in estimates with sample proportions.

## 2 Comparing Orderings

In Figure 1 we show the default orderings and the `method="simple"` orderings for different values of `parmtype`.

In Figure 2 we show the similarity of several of the `parmtype="difference"` orderings.

The wald method gives a strange ordering at  $x = (0, 0)$  and  $x = (n_1, n_2)$  when  $\beta_0$  is close to zero (see Figure 3).

When `tsmethod="square"` then a small difference in  $\beta_0$  can make a big difference in the p-value (see Figure 4 for ordering difference, Figure 5 for a p-value example).

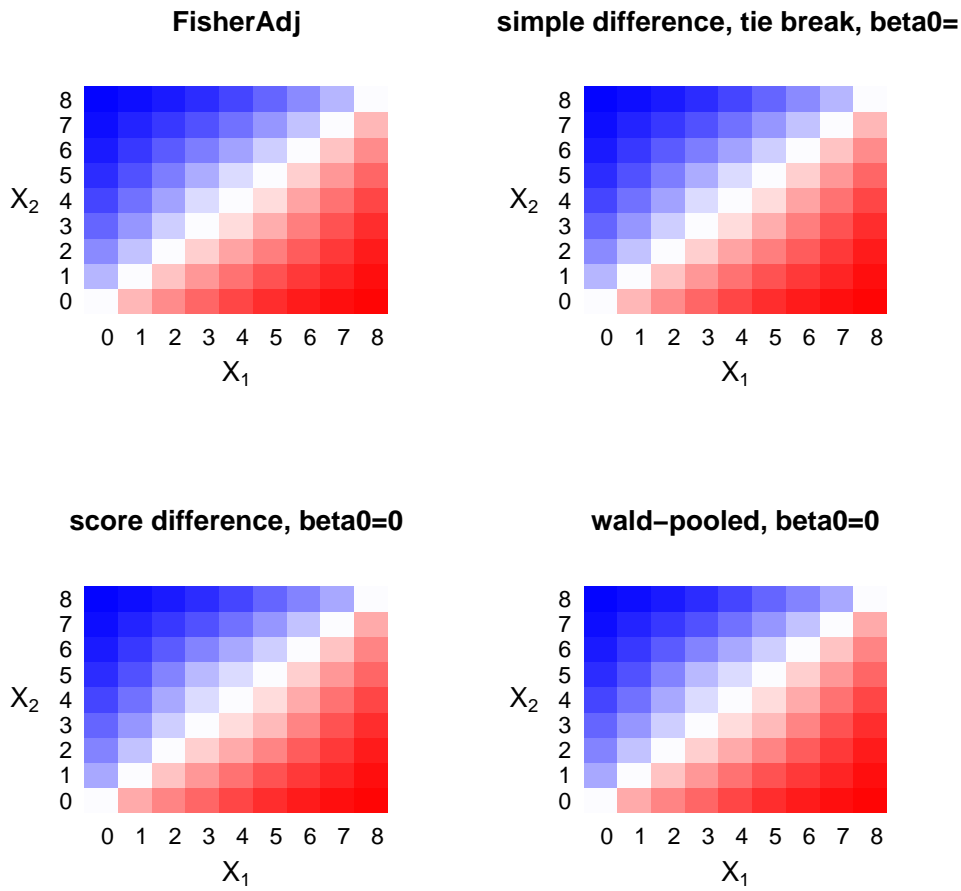


Figure 2: Plots of the orderings using `plotT`. Notice how the orderings are nearly the same for the 4 methods. The FisherAdj method has the advantage that it does not change with `parmtyp` or  $\beta_0$ .



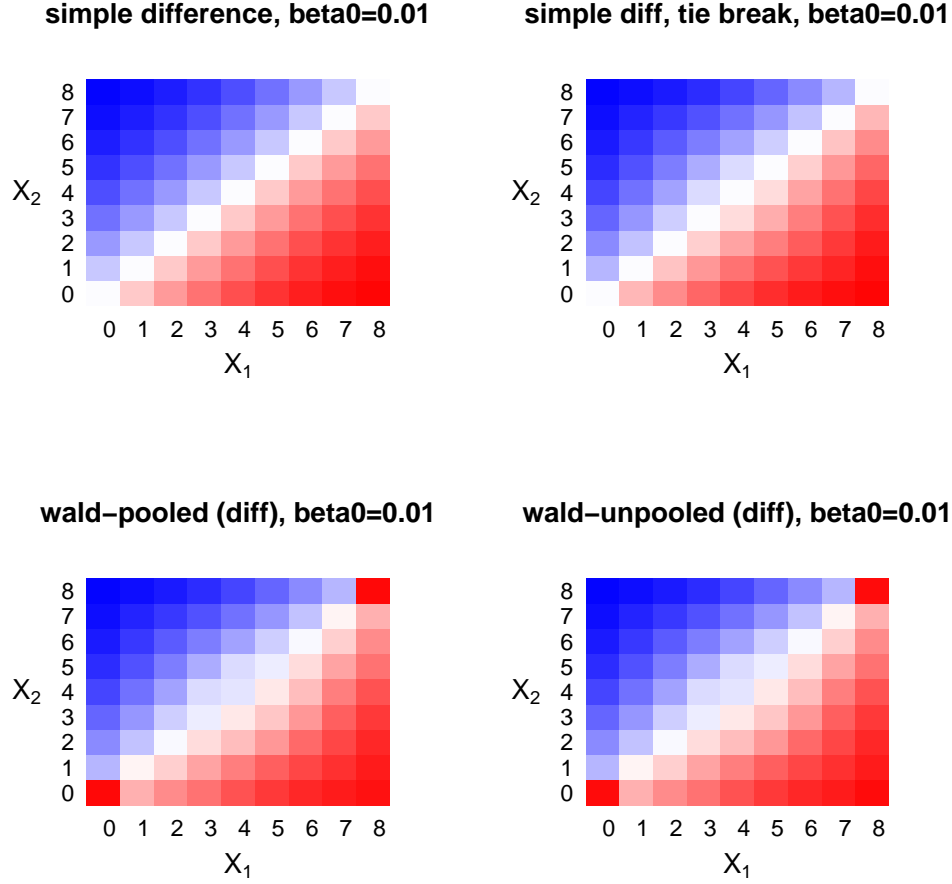


Figure 3: Plots of the orderings using `plotT`. Since we define  $0/0 = 0$ , when we have  $\hat{\theta}_1 = \hat{\theta}_2$  and  $\beta_0 = 0$  then the Wald methods give 0 (see Figure 1). But when  $\beta_0 = 0.01$  these values at  $x = (0, 0)$  and  $x = (n_1, n_2)$  go to  $-\infty$ .

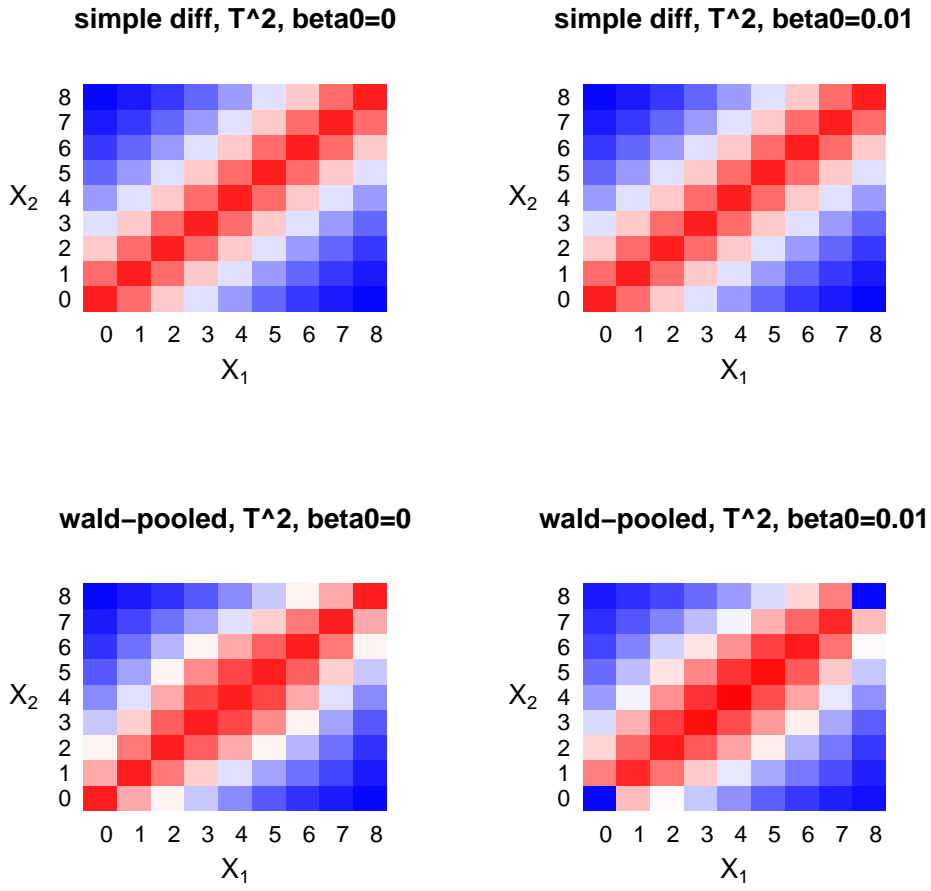


Figure 4: Plots of the orderings using `plotT`. Small changes in  $\beta_0$  can have large changes in the ordering, because of the denominators equalling 0 at  $x = (0, 0)$  and  $x = (n_1, n_2)$ .

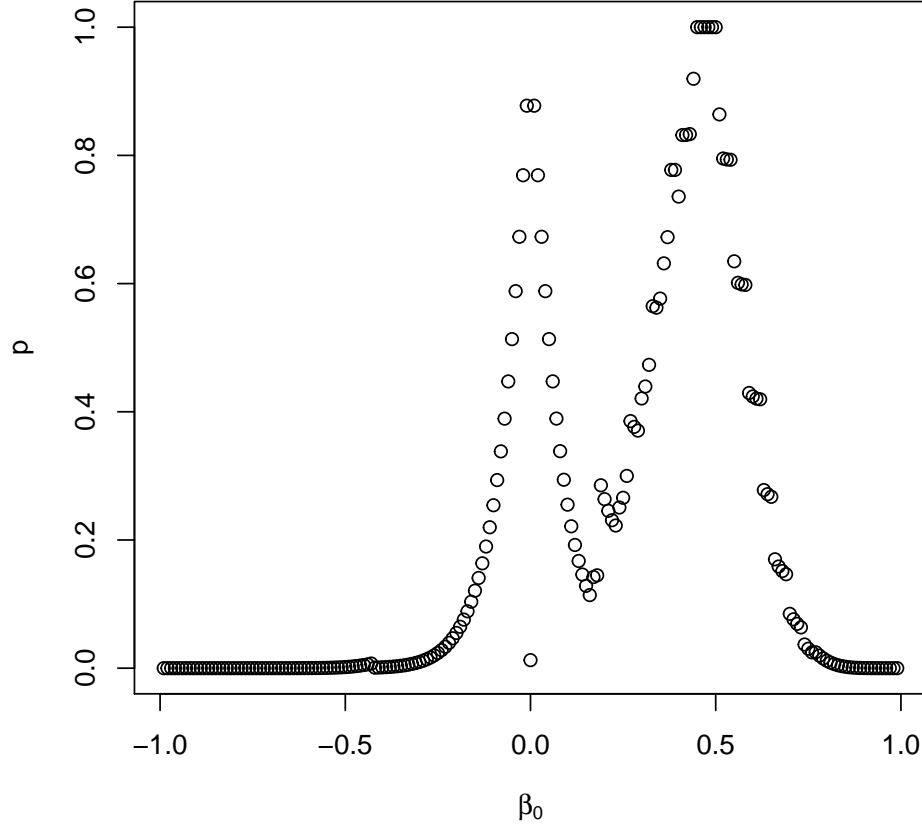


Figure 5: P-values from `method="wald-pooled"`, `tsmethod="square"`, and `parmttype="difference"` for the data  $x_1/n_1 = 5/13$  and  $x_2/n_2 = 12/14$ . Notice the strange behaviour of the p-value at  $\beta_0 = 0$ . This is because the denominator at  $x = (0, 0)$  and  $x = (n_1, n_2)$  is 0 and  $0/0$  is defined as zero, and the p-value is defined as the sup over the sample space which can give very large probability mass at  $x = (0, 0)$  or  $x = (n_1, n_2)$ .

### 3 Confidence Intervals

Then we can create  $100(1 - \alpha)\%$  confidence regions as the set of  $\beta_0$  value that fail to reject the associated null hypothesis. For example,

$$C_{ts}(\mathbf{x}, 1 - \alpha) = \{\beta : p_{ts}(\mathbf{x}, \beta) > \alpha\}$$

gives a “two-sided” confidence region. The region may not be an interval if the p-value function is not unimodal. This problem occurs with Fisher’s exact test (the Fisher-Irwin version, or ‘minlike’ version). For central confidence regions we take the union of the one-sided confidence regions, in other words,

$$C_c(\mathbf{x}, 1 - \alpha) = C_L(\mathbf{x}, 1 - \alpha/2) \cup C_U(\mathbf{x}, 1 - \alpha/2),$$

where  $C_L$  and  $C_U$  are the one-sided confidence regions,

$$C_L(\mathbf{x}, 1 - \alpha/2) = \{\beta : p_L(\mathbf{x}, \beta) > \alpha/2\}$$

and

$$C_U(\mathbf{x}, 1 - \alpha/2) = \{\beta : p_U(\mathbf{x}, \beta) > \alpha/2\}.$$

If the regions are intervals, and we let  $L(\mathbf{x}, 1 - \alpha/2) = \min C_L(\mathbf{x}, 1 - \alpha/2)$  and  $U(\mathbf{x}, 1 - \alpha/2) = \max C_U(\mathbf{x}, 1 - \alpha/2)$ , then the central interval is

$$C_c(\mathbf{x}, 1 - \alpha) = \{L(\mathbf{x}, 1 - \alpha/2), U(\mathbf{x}, 1 - \alpha/2)\}.$$

For the mid-p confidence regions, we replace the p-values with the mid-p values.

### 4 Berger and Boos Adjustment

The Berger-Boos (1994) adjustment is as follows. Do the usual unconditional exact test, but instead of taking the supremum over the entire null parameter space, we calculate a  $100(1 - \gamma)\%$  confidence region over the null space, and only search within that. The  $100(1 - \gamma)\%$  confidence region is the union of the  $100(1 - \gamma/2)$  exact central two-sided confidence interval for  $\theta_1$  and the analogous  $100(1 - \gamma/2)$  interval for  $\theta_2$ . This is the method used by StatXact. Searching over that space gives anti-conservative p-values, so we turn those anti-conservative p-values into valid p-values by adding  $\gamma$  to them. For details see Berger and Boos (1994) or the StatXact manual.

### 5 The E+M Adjustment

Lloyd (2008) proposed another adjustment called the estimated and maximized ( $E + M$ ) p-value that can be applied to any ordering and any parmtpe. In this method, we replace an ordering statistic,  $T$ , with  $T^*$ , where  $T^*$  is an estimated p-value when testing  $H_0 : \beta \leq \beta_0$  (or the negative estimated p-value when testing  $H_0 : \beta \geq \beta_0$ ). We estimate the p-value by plugging in  $\hat{\theta}_0 = [\hat{\theta}_{10}, \hat{\theta}_{20}]$  instead of taking the supremum of  $\theta$  under the null, where  $\hat{\theta}_0$  is the maximum likelihood estimator of  $\theta$  under the null hypothesis. For example, the approximation for  $p_L$  uses  $\hat{p}_L(\mathbf{x}, \beta_0) = P_{\hat{\theta}_0} [T(\mathbf{X}) \leq T(\mathbf{x})]$ . Then we “maximize” using  $T^*(\mathbf{x}) = \hat{p}_L(\mathbf{x}, \beta_0)$  instead of  $T$  as the ordering function. For details see Loyd (2008).

## References

- Agresti, A and Min, Y (2002). Biostatistics 3: 379-386.
- Berger, RL, and Boos, DD (1994). JASA 89: 1012-1016.
- Farrington and Manning (1990). Statistics in Medicine 1447-1454.
- Fay, MP, and Brittain, EH (2016). “Finite sample pointwise confidence intervals for a survival distribution with right-censored data.” *Statistics in Medicine* 35: 2726-2740.
- Fleiss, JL, Levin, B, Paik, MC (2003). *Statistical Methods for Rates and Proportions, Third edition*. Wiley: New York.
- Lloyd, CJ (2008). Exact p-values for discrete models obtained by estimation and maximization. Australian and New Zealand Journal of Statistics 50(4): 329-345.
- Miettinen and Nurminen (1985). Statistics in Medicine 213-226.