Overview

These notes give details on how the mid-p adjustment is done. Section 1 describes the mid-p adjustment as it is done for the `exact2x2` and `uncondExact2x2` functions. Section 2 describes the mid-p adjustment as implemented in the `binomMeld.test` function.

1 Usual Mid-p Adjustment for Two Binomial Distributions

The following is how the usual mid-p adjustment is done (for example in the `exact2x2` and `uncondExact2x2` functions). The mid-p value has a long history (see e.g., Lancaster, 1961 or the list of references in Hirji 2006, p. 50).

Let \( X = [X_1, X_2] \) 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, \( \beta_{or} = \{\theta_2(1 - \theta_1)\} / \{\theta_1(1 - \theta_2)\} \).

Let \( T(X) \) be some test statistic, where larger values are most extreme with respect to the null hypothesis. Let \( \Theta_0 \) be the set of all possible values of \([\theta_1, \theta_2]\) under the null hypothesis. Then a valid (i.e., exact) p-value is

\[
p(x, \Theta_0) = \sup_{\theta \in \Theta_0} \Pr[ T(X) \geq T(x) ].
\]

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

\[
Pr[ p(X, \Theta_0) \leq \alpha ] < \alpha.
\]

A less conservative approach, but one that is no longer valid (i.e., no longer exact), is to use a mid-p value. The mid-p value is

\[
p_{\text{mid}}(x, \Theta_0) = \sup_{\theta \in \Theta_0} \left\{ \Pr[ T(X) > T(x) ] + \frac{1}{2} \Pr[ T(X) = T(x) ] \right\}.
\]

It is convenient to write \( \Theta_0 \) 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,

\[
H_0 : \quad \beta = \beta_0 \\
H_1 : \quad \beta \neq \beta_0
\]
or one of the one-sided hypotheses,

<table>
<thead>
<tr>
<th>Alternative is Less</th>
<th>Alternative is Greater</th>
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<tbody>
<tr>
<td>$H_0 : \beta \geq \beta_0$</td>
<td>$H_0 : \beta \leq \beta_0$</td>
</tr>
<tr>
<td>$H_1 : \beta &lt; \beta_0$</td>
<td>$H_1 : \beta &gt; \beta_0$</td>
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Let $p_{ts}(x, \beta_0)$ be the p-value for testing the two-sided hypotheses, let $p_U(x, \beta_0)$ be the p-value for testing $H_0 : \beta \geq \beta_0$, and $p_L(x, \beta_0)$ be the p-value for testing $H_0 : \beta \leq \beta_0$.

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,

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

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,

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

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

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

and

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

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

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

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

### 2 Mid-p Modifications with Binomial Melding

For a single binomial response, the mid p-value and associated central confidence interval can be represented using confidence distribution random variables. Suppose that the exact central $100(1-\alpha)$ percent binomial confidence interval for a single binomial random variable (i.e., the default in `binom.test`) is $(L(1 - \alpha/2), U(1 - \alpha/2))$. Then the lower and upper confidence distribution random variables are respectively, $W_L = L(A_1)$ and $W_U = U(A_2)$, where $A_1$ and $A_2$ and independent uniform random variables. Let $B$ be an independent Bernoulli random variable with parameter 1/2. Then the 95 percent central mid-p confidence interval for the binomial parameter is the middle 95 percent of the distribution of $W = B*W_L + (1-B)*W_U$. This is shown in the appendix of Fay and Brittain (2016).
The way the midp=TRUE option is done in binomMeld.test is to replace the upper and lower confidence distribution random variables in the usual melding equations, with the “mid-p” confidence distribution random variable (CD-RV) analogous to $W$ for each group. For example if the lower and upper CD-RVs for group 1 are $W_{1L}$ and $W_{1U}$, then the mid-p CD-RV is $W_1 = B_1 \cdot W_{1L} + (1 - B_1) \cdot W_{1U}$, where $B_1$ is a Bernoulli random variable with parameter 1/2. The mid-p CD-RV $W_2$ is defined analogously. It is fairly simple to program a Monte Carlo estimate of the “mid” p-value and associated confidence interval. Let $g(\theta_1, \theta_2)$ be the parameter of interest (e.g., $g(\theta_1, \theta_2) = \theta_2 - \theta_1$ for parmtype="difference"). The one-sided p-values are the proportion of times that $g(W_{1L}, W_{2L}) \leq \text{nullparm}$ (for alternative="greater") or $\geq \text{nullparm}$ (for alternative="less"). The confidence intervals just use the appropriate quantiles of the Monte Carlo values of $g(W_1, W_2)$.

When nmc=0, we estimate the one-sided p-values with numeric integration. Conceptually, the usual melded p-value might be, for example when alternative="greater" and nullparm=$\beta_0$:

$$Pr[g(W_{1L}, W_{2L}) \leq \beta_0] = \int Pr[g(W_1, w_2) \leq \beta_0 | W_2 = w_2] Pr[W_2 = w_2]$$

where $W_{1U}$ is the upper confidence distribution random variable (CD-RV) for group 1 and $W_{2L}$ is the lower CD-RV for group 2. These CD-RVs are beta distributions (see Fay, Proschan, and Brittain, 2015). For the mid-p version, we use

$$Pr[g(W_1, W_2) \leq \beta_0] = \frac{1}{4} \int Pr[g(W_{1L}, w_2) \leq \beta_0 | W_{2L} = w] Pr[W_{2L} = w] + \frac{1}{4} \int Pr[g(W_{1L}, w_2) \leq \beta_0 | W_{2U} = w] Pr[W_{2U} = w] + \frac{1}{4} \int Pr[g(W_{1U}, w_2) \leq \beta_0 | W_{2L} = w] Pr[W_{2L} = w] + \frac{1}{4} \int Pr[g(W_{1U}, w_2) \leq \beta_0 | W_{2U} = w] Pr[W_{2U} = w].$$

The integration simplifies for special cases (e.g., when $x_1 = 0$), and in other case we just use the integrate function. For the confidence intervals we solve for the $\beta_0$ values such that the p-values equal either $\alpha$ (for one-sided alternatives) or $\alpha/2$ (for two-sided alternatives), where alpha=1-conf.level. If there is no $\beta_0$ value that solves that, we set the confidence limit to the appropriate extreme.

It is known that the p-values that match the melded confidence intervals for two independent binomial observations exactly equal the one-sided Fisher’s exact p-values (see Fay, et al, 2015). For example,

```r
> x1<-6
> n1<-12
> x2<-15
> n2<- 17
> exact2x2(matrix(c(x2,n2-x2,x1,n1-x1),2,2), tsmethod="central", midp=FALSE)

Central Fisher's Exact Test
data:  matrix(c(x2, n2 - x2, x1, n1 - x1), 2, 2)
p-value = 0.06506
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.9119249  89.4167455
sample estimates:
odds ratio
  6.924704

> binomMeld.test(x1,n1,x2,n2, parmtype="oddsratio", midp=FALSE)

melded binomial test for oddsratio

data: sample 1:(6/12), sample 2:(15/17)
proportion 1 = 0.5, proportion 2 = 0.88235, p-value = 0.06506
alternative hypothesis: true oddsratio is not equal to 1
95 percent confidence interval:
  0.909023 106.265540
sample estimates:
odds ratio \( \frac{p_2(1-p_1)}{p_1(1-p_2)} \)
  7.5

Note, the confidence intervals for the two methods are not equal.
This does not necessarily mean that the midp versions give equivalent p-values:

> x1<-6  
> n1<-12  
> x2<-15  
> n2<-17  
> exact2x2(matrix(c(x2,n2-x2,x1,n1-x1),2,2), tsmethod="central", midp=TRUE)

Central Fisher's Exact Test (mid-p version)

data:  matrix(c(x2, n2 - x2, x1, n1 - x1), 2, 2)
p-value = 0.03578
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  1.12685 62.05021
sample estimates:
odds ratio
  6.924704

> binomMeld.test(x1,n1,x2,n2, parmtype="oddsratio", midp=TRUE)

melded binomial test for oddsratio, mid-p version
data: sample 1:(6/12), sample 2:(15/17)
proportion 1 = 0.5, proportion 2 = 0.88235, p-value = 0.02899
alternative hypothesis: true oddsratio is not equal to 1
95 percent confidence interval:
1.214721 66.148301
sample estimates:
odds ratio \{p2(1-p1)\}/\{p1(1-p2)\}
7.5

References


