

# Mid-p Adjustment for exact2x2: Computational Details

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June 30, 2020

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

Let  $T(\mathbf{X})$  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

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

These exact p-values are necessarily conservative because for most  $\theta \in \Theta_0$  we have  $\Pr_{\theta} [p(\mathbf{X}, \Theta_0) \leq \alpha] < \alpha$ . A less conservative approach, *but one that is no longer valid (i.e., no longer exact)*, is to use a mid-p value.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

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

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,

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

or one of the one-sided hypotheses,

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

Let  $p_{ts}(\mathbf{x}, \beta_0)$  be the p-value for testing the two-sided hypotheses, let  $p_U(\mathbf{x}, \beta_0)$  be the p-value for testing  $H_0 : \beta \geq \beta_0$ , and  $p_L(\mathbf{x}, \beta_0)$  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,

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

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.

## 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  $A_2$  are 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  $W_1 = B_1 * W_{1L} + (1 - B_1) * W_{1U}$ , 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  $g(W_1, W_2)$  is  $\leq \text{nullparm}$  (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 =  $\beta_0$` :

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

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

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

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,

```
> 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, parmtpe="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 {p2(1-p1)}/{p1(1-p2)}
              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, parmtpe="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

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