Farrington-Manning in the Extreme Case

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Abstract

The Farrington-Manning method is a common method for evaluating equivalence and non-inferiority of independent proportions. It is implemented in various software, in particular SAS® PROC FREQ, and the R® function farrington.manning(), which is part of the DescrTab2 package. The equations for the estimated proportions can create numerical issues in case both sample proportions equal 1, and neither of these packages will yield an acceptable solution in this special case. In this note we demonstrate a closed form solution for the situation in this and other extreme cases.

We assume that the reader has available the original paper of Farrington and Manning [1], and we repeat only a minimal amount from the paper. Some text is quoted verbatim from the paper.

1 The setting

We consider a comparative binomial trial involving two groups of sizes \(N_1, N_2\) in the predetermined ratio \(\theta = N_2/N_1\), and independent response variables \(r_1 \sim \text{Bi}(N_1, p_1)\) and \(r_2 \sim \text{Bi}(N_2, p_2)\). The binomial probabilities \(p_1\) and \(p_2\) are estimated by \(\hat{p}_1 = r_1/N_1, \hat{p}_2 = r_2/N_2\). The true difference is \(s_T = p_1 - p_2\), estimated by \(s = \hat{p}_1 - \hat{p}_2\). In the equivalence or non-inferiority setting the null hypothesis is \(p_1 - p_2 = s_0\), where \(s_0\) is a predetermined value, often called the non-inferiority margin.
The Farrington-Manning method is to compute maximum likelihood estimates $\hat{p}_1D$ and $\hat{p}_2D$ for $p_1$ and $p_2$, under the constraint that $\hat{p}_1D - \hat{p}_2D = s_0$. These estimates will typically be different from $\hat{p}_1$ and $\hat{p}_2$. The method is described in the original paper \[1\], and in many other places, including section 11.2.3 of Rothmann et al. \[6\]. This method is implemented in many statistical software packages, including SAS\textsuperscript{®} PROC FREQ, and the R\textsuperscript{®} function farrington.manning(), which is part of the DescrTab2 package. \[2\]

There is no restriction on the sign of $s_0$, but, of course, $s_0$ must have a value suitable for the difference of proportions. Reading between the lines, it appears that Farrington and Manning had in mind positive $s_0$. In practice, one can arrange this choice by choosing the groups appropriately. The farrington.manning() function allows for negative $s_0$; SAS PROC FREQ does not.

Then the test statistic is

$$z_D = \hat{p}_1 - \hat{p}_2 - s_0$$  \hspace{1cm} (1)

For large $N$, $z_D$ is approximately Normally distributed. Under the null hypothesis, the variance of $z_D$ is estimated by:

$$\hat{v}_0 = \frac{\hat{p}_1D\hat{q}_1D}{N_1} + \frac{\hat{p}_2D\hat{q}_2D}{N_2} = \frac{[\hat{p}_1D\hat{q}_1D + \hat{p}_2D\hat{q}_2D]}{N_1}$$  \hspace{1cm} (2)

where $\hat{p}_1D$ and $\hat{p}_2D$ are maximum likelihood estimators for $p_1$ and $p_2$ under the null hypothesis and $\hat{q}_1D = 1 - \hat{p}_1D$, $\hat{q}_2D = 1 - \hat{p}_2D$. The null hypothesis may then be tested by referring the statistic:

$$z = (\hat{p}_1 - \hat{p}_2 - s_0)/\sqrt{\hat{v}_0}$$  \hspace{1cm} (3)

to the standard normal distribution.

In the general case, the estimates $\hat{p}_1D$ and $\hat{p}_2D$ are obtained by solving a cubic equation, as will be seen below.

However, this procedure has potential numerical issues when both $\hat{p}_1 = 1$ and $\hat{p}_2 = 1$. This situation may seem unlikely in an actual trial, but it can

\[1\] The farrington.manning() function was written by Kevin Kunzmann, and the DescrTab2 package is maintained by Jan Meis. As of the date of this note, Version 2.1.9 of the package, dated January 20, 2022, is the most current.

\[2\] Thanks to Jan Meis for many helpful comments relating to the package, and to the issues described here.
occur when one is doing a simulation with assumed probabilities \( p_1 \) and \( p_2 \) both close to 1. In this situation the SAS PROC FREQ simply refuses to compute the risk difference, and the R function farrington.manning() may cause an error condition.

## 2 Computing the maximum likelihood estimators

The estimate \( \hat{p}_{1D} \) is obtained by solving the maximum likelihood equation

\[
ax^3 + bx^2 + cx + d = 0
\]

with

\[
a = 1 + \theta \\
b = -[1 + \theta + \hat{p}_1 + \theta \hat{p}_2 + s_0(\theta + 2)] \\
c = s_0^2 + s_0(2\hat{p}_1 + \theta + 1) + \hat{p}_1 + \theta \hat{p}_2 \\
d = -\hat{p}_1 s_0(1 + s_0)
\]

Any method for solving a cubic equation could in principle be used to compute \( \hat{p}_{1D} \), but one must be careful to choose the root that maximizes the underlying likelihood function. Some considerations on this point are given in section 5 below.

In the special case of interest here, both \( \hat{p}_1 = 1 \) and \( \hat{p}_2 = 1 \). The coefficients of the cubic equation (4) take a simpler form, and the equation can be factored.

\[
a x^3 + b x^2 + c x + d = (1 + \theta)x^3 \\
- [2 + 2\theta + s_0(\theta + 2)]x^2 \\
+ [s_0^2 + s_0(3 + \theta) + 1 + \theta]x \\
- s_0(1 + s_0) \\
= (x - 1)(x - (1 + s_0))(1 + \theta)x - s_0).
\]

The cubic has three real roots, and the choices for \( \hat{p}_{1D} \) and \( \hat{p}_{2D} \) are given in table 9 below.
\[
\begin{bmatrix}
\tilde{p}_{1D} \\
\tilde{p}_{2D}
\end{bmatrix} = \begin{bmatrix}
1 & 1 + s_0 & s_0/(1 + \theta) \\
1 - s_0 & 1 & -s_0\theta/(1 + \theta)
\end{bmatrix}
\]  \tag{6}

- If \(s_0 > 0\), only \(\tilde{p}_{1D} = 1\) and \(\tilde{p}_{2D} = 1 - s_0\) give valid proportions for \(\tilde{p}_{1D}\) and \(\tilde{p}_{2D}\).

- If \(s_0 < 0\), only \(\tilde{p}_{1D} = 1 + s_0\) and \(\tilde{p}_{2D} = 1\) give valid proportions for \(\tilde{p}_{1D}\) and \(\tilde{p}_{2D}\).

An alternative method for finding the estimates is to note that the likelihood function is monotonic increasing in \(\tilde{p}_{1D}\) and \(\tilde{p}_{2D}\). Accordingly the maximum likelihood will be obtained when these two are as large as possible. That is when one of the \(\tilde{p}_{iD}\) is 1, and the other is \(1 - |s_0|\).

### 3 Hypothesis tests and confidence intervals

Using the general variance equation (2), the variance then becomes

\[
\hat{v}_0 = \begin{cases}
    s_0(1 - s_0)/N_2 & s_0 > 0 \\
    -s_0(1 + s_0)/N_1 & s_0 < 0
\end{cases}
\]  \tag{7}

Using this variance and the test statistic of (3) we have for \(s_0 > 0\)

\[
z = (\hat{p}_1 - \hat{p}_2 - s_0)/\sqrt{\hat{v}_0} = -s_0/\sqrt{s_0(1 - s_0)/N_2} = -\sqrt{N_2 s_0/(1 - s_0)}.
\]

Similarly, for \(s_0 < 0\)

\[
z = (\hat{p}_1 - \hat{p}_2 - s_0)/\sqrt{\hat{v}_0} = -s_0/\sqrt{-s_0(1 + s_0)/N_1} = \sqrt{-N_1 s_0/(1 + s_0)}.
\]

The two-sided confidence limits for the difference are obtained by inversion of the two-sided hypothesis test For the general Farrington-Manning
case the computations require an iterative solution, because there is no simple formula relating the $z$-statistic to $s_0$. For the special case here limits are simply obtained by setting $z$ to the critical values, and solving for $s_0$.

The confidence interval is

$$
\left( \frac{-z_{\alpha}^2}{N_1 + z_{\alpha}^2}, \frac{z_{\alpha}^2}{N_2 + z_{\alpha}^2} \right)
$$

As a practical matter, if one really had data this extreme, exact methods would likely be used for evaluating hypothesis tests and computing confidence limits. The intention here is simply to give reasonable limits that can be used to let a simulation proceed.

### 4 Other extreme cases

A number of other extreme cases can be considered in the same manner. Here we give only minimal details, leaving the rest to the reader.

*Suppose $\hat{p}_1 = 0$ and $\hat{p}_2 = 0$.*

The maximum likelihood equation (4) factors

$$
ax^3 + bx^2 + cx + d = (1 + \theta)x^3 - [1 + \theta + s_0(\theta + 2)]x^2 + [s_0^2 + s_0(\theta + 1)]x - 0 = x(x-s_0)((1+\theta)x-(1+\theta+s_0)).
$$

(8)

The possibilities for $\tilde{p}_{1D}$ and $\tilde{p}_{2D}$ are given in table (9) below. The appropriate choice depends on the sign of $s_0$.

$$
\begin{bmatrix}
\tilde{p}_{1D} \\
\tilde{p}_{2D}
\end{bmatrix} =
\begin{bmatrix}
0 & (1 + \theta + s_0)/(1 + \theta) & s_0 \\
-s_0 & (1 + \theta - s_0 \theta)/(1 + \theta) & 0
\end{bmatrix}
$$

(9)

- If $s_0 > 0$, only $\tilde{p}_{1D} = s_0$ and $\tilde{p}_{2D} = 0$ give valid proportions for $\tilde{p}_{1D}$ and $\tilde{p}_{2D}$.
- If $s_0 < 0$, only $\tilde{p}_{1D} = 0$ and $\tilde{p}_{2D} = -s_0$ give valid proportions for $\tilde{p}_{1D}$ and $\tilde{p}_{2D}$.
The remaining computations are highly similar to those above. Suppose \( \hat{p}_1 = 0 \) and \( \hat{p}_2 = 1 \). The maximum likelihood equation (4) factors

\[
ax^3 + bx^2 + cx + d = (1 + \theta)x^3 - [1 + 2\theta + s_0(\theta + 2)]x^2 + [s_0^2 + s_0(\theta + 1) + \theta]x - 0 = x(x - (1 + s_0))(1 + \theta)x - (\theta + s_0)). \tag{10}
\]

The possibilities for \( \tilde{p}_{1D} \) and \( \tilde{p}_{2D} \) are given in table (11) below. The appropriate choice depends on the sign of \( \theta + s_0 \).

\[
\begin{bmatrix} \tilde{p}_{1D} \\ \tilde{p}_{2D} \end{bmatrix} = \begin{bmatrix} 0 & (\theta + s_0)/(1 + \theta) & 1 + s_0 \\ -s_0 & (\theta - s_0\theta)/(1 + \theta) & 1 \end{bmatrix} \tag{11}
\]

- If \( \theta + s_0 > 0 \), the choice \( \tilde{p}_{1D} = (\theta + s_0)/(1 + \theta) \) and \( \tilde{p}_{2D} = (\theta - s_0\theta)/(1 + \theta) \) gives the maximum likelihood estimator. (If additionally \( s_0 < 0 \), all three choices give valid proportions, but the other two choices give minima).

- If \( \theta + s_0 = 0 \), the choice \( \tilde{p}_{1D} = 0 \) and \( \tilde{p}_{2D} = -s_0 \) is a double root, and gives the maximum.

- If \( \theta + s_0 < 0 \), the choice \( \tilde{p}_{1D} = 0 \) and \( \tilde{p}_{2D} = -s_0 \) gives the maximum. (The choice \( \tilde{p}_{1D} = 1 + s_0 \) and \( \tilde{p}_{2D} = 1 \) also gives valid proportions, but this is a minimum.)

The remaining computations proceed as above. The upper confidence limit for the difference will be 1; we have not found a simple form for the lower confidence limit.

Suppose \( \hat{p}_1 = 1 \) and \( \hat{p}_2 = 0 \). The maximum likelihood equation (4) factors

\[
ax^3 + bx^2 + cx + d = (1 + \theta)x^3 - [2 + \theta + s_0(\theta + 2)]x^2 + [s_0^2 + s_0(\theta + 3) + 1]x - s_0(1 + s_0) = (x - 1)(x - s_0)((1 + \theta)x - (1 + s_0)).
\]
The possibilities for $\tilde{p}_{1D}$ and $\tilde{p}_{2D}$ are given in table (12) below. The appropriate choice depends on the sign of $1 - s_0 \theta$.

$$
\begin{bmatrix}
\tilde{p}_{1D} \\
\tilde{p}_{2D}
\end{bmatrix} =
\begin{bmatrix}
 s_0 & (1 + s_0)/(1 + \theta) & 1 \\
 0 & (1 - s_0 \theta)/(1 + \theta) & 1 - s_0 
\end{bmatrix}
$$

(12)

- If $1 - s_0 \theta > 0$, the choice $\tilde{p}_{1D} = (1 + s_0)/(1 + \theta)$ and $\tilde{p}_{2D} = (1 - s_0 \theta)/(1 + \theta)$ gives the maximum likelihood estimator. (If additionally $s_0 > 0$, all three choices give valid proportions, but the other two choices give minima).

- If $1 - s_0 \theta = 0$, the choice $\tilde{p}_{1D} = s_0$ and $\tilde{p}_{2D} = 0$ is a double root, and gives the maximum.

- If $1 - s_0 \theta < 0$, the choice $\tilde{p}_{1D} = 0$ and $\tilde{p}_{2D} = -s_0$ gives the maximum. (The choice $\tilde{p}_{1D} = 1$ and $\tilde{p}_{2D} = 1 - s_0$ also gives valid proportions, but this is a minimum.)

The remaining computations proceed as above. The lower confidence limit for the difference will be -1; we have not found a simple form for the upper confidence limit.

Suppose $s_0 = 0$. This is in effect a standard superiority test, but there seems to be no mathematical reason not to compute using the methods above. In this case the special form of the equation becomes.

$$ax^3 + bx^2 + cx + d = (1 + \theta)x^3 - [1 + \theta + \hat{p}_1 + \theta \hat{p}_2]x^2 + [\hat{p}_1 + \theta \hat{p}_2]x - 0 = x(x - 1)((1 + \theta)x - (\hat{p}_1 + \theta \hat{p}_2)).$$

The desired solution is $x = (\hat{p}_1 + \theta \hat{p}_2)/(1 + \theta) = (r_1 + r_2)/(N_1 + N_2)$. The resulting statistical test is algebraically identical to the chi-squared test without the continuity correction.
5 Solution Considerations

The confidence intervals above are computed by inverting the two-sided hypothesis test. We note that the intervals using the farrington.manning() function are obtained in this manner, while those in SAS PROC FREQ are not. Various other methods of computing confidence intervals are discussed in the textbooks of Newcombe [4] and Rothmann et al [6]. In reading any of the references it is vital to check on the definition of $s_0$; in some cases the sign is reversed from the original paper.

The Farrington-Manning paper [1] states without proof that the cubic equation (4) has a unique solution in ($s_0$, 1).

- For $s_0 > 0$, the interval ($s_0$, 1) makes sense, since $\tilde{p}_{2D} = \tilde{p}_{1D} - s_0$ must be a proportion.

- But if $s_0 < 0$, the appropriate interval is (0, 1 + $s_0$), because $\tilde{p}_{2D} > \tilde{p}_{1D}$.

This situation is why it seems that the authors had in mind $s_0 > 0$.

The paper [1] uses the cubic formula to solve (4). The particular form of the cubic formula is the trigonometric form, which is appropriate for the case when the cubic has three real roots. Only one of the three roots is given by the formula used in the paper. It appears that the this form of the cubic formula is appropriate, and that the chosen root is the correct one, even in the extreme cases. However, the paper [1] does not give any proofs in this regard. In this note we simply accept the situation, and have made no attempt to present proofs. This use of the cubic formula is implemented in both SAS PROC FREQ, and the R function farrington.manning(). It is straightforward to program the formula in Excel.

Numerical problems with the formulas occur in two different situations:

- The cubic formula involves computing an arc cosine. If there is a double root, the numeric argument for the arc cosine function may be exactly 1. But roundoff can cause the computed argument to be slightly greater than 1. One can fix the problem using the formulas for $\tilde{p}_{1D}$ and $\tilde{p}_{1D}$ above. Alternatively one could check the argument of the arc cosine function, and set arguments microscopically greater than 1 to exactly 1.

An example would be when $\hat{p}_1 = 0$, $\hat{p}_2 = 1$, $\theta = 2$, and $s_0 = 0.5$. In computation for the farrington.manning() function roundoff causes
the argument of the acos() function to be microscopically greater than 1, which produces an error condition. One could fix the situation by checking the argument before the acos() function is used. Excel does not generate an error for this example, nor does SAS.

- Inverting the computation to find the confidence limits involves solving a non-linear equation over a defined range. Too small a range can result in missing the root. This situation can arise in the case \( \hat{p}_1 = 0 \) and \( \hat{p}_2 = 1 \), or vice versa. In these cases one confidence limit is obvious, and it may be reasonable to write special code to compute the other limit. As mentioned above, if real data produced this situation one would likely use exact methods, and the formulas here would be irrelevant.

- Jan Meis \[3\] has modified the farrington.manning() function to incorporate both suggestions in this paragraph. Those suggestions might appear in a later version of the DescrTab2 package.

In the examples above the closed form values for \( \tilde{p}_{1D} \) and \( \tilde{p}_{2D} \) were obtained by factoring the cubic equation (4). One could speculate as to whether such factoring can always be done. For an example to the contrary, suppose that \( \hat{p}_1 = 1/3 \), \( \hat{p}_2 = 1/2 \), \( s_0 = 1/2 \), and \( \theta = 2/3 \). Then the equation becomes

\[
\begin{align*}
(5/3)x^3 - (11/3)x^2 + (25/12)x - (3/12) &= 0 \\
20x^3 - 44x^2 + 25x - 3 &= 0
\end{align*}
\]

Any rational root of the form \( m/n \) must have \( m | 3 \) and \( n | 20 \). There are only a finite number of cases to check, and none yield a rational root. Since (13) is a cubic, it must therefore be irreducible over the rationals, and the full complications of cubic fields enter into the solution.

References

[1] CP Farrington and G. Manning. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Statistics in Medicine*, 9:1447–54, 1990.
[2] Jan Meis, Lukas Baumann, Maximilian Pilz, and Lukas Sauer. DescrTab2: Publication Quality Descriptive Statistics Tables, 2022. R package version 2.1.9.

[3] Jan Mies. Personal Communication, 2022.

[4] Robert Newcombe. Confidence Intervals for Proportions and Related Measures of Effect Size. CRC Press, Boca Raton, 2013.

[5] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2021.

[6] Mark Rothmann, Brian Wiens, and Ivan Chan. Design and Analysis of Non-Inferiority Trials. CRC Press, Boca Raton, 2012.

[7] SAS Institute Inc., Cary, NC. SAS/STAT® 15.1 User’s Guide, 2018.