Prevented Fraction Methods: PF Package Vignette

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1 Introduction

The `PF` package is a collection of functions related to estimating prevented fraction, $PF = 1 - RR$, where $RR = \pi_2/\pi_1$.

Technical note

Optimization. Unless otherwise stated, optimization is by the DUD algorithm (Ralston and Jennrich 1978).

2 Score based methods

2.1 The score statistic

Confidence intervals for the risk ratio may be based on the score statistic (Koopman 1984; Miettinen and Nurminen 1985),

$$\frac{\hat{\pi}_2 - \rho_0 \hat{\pi}_1}{\sqrt{(\tilde{\pi}_2(1-\tilde{\pi}_2)/n_2\ ) + \rho_0^2\,(\tilde{\pi}_1(1-\tilde{\pi}_1)/n_1\ )}}$$

where hat indicates the MLE and tilde indicates the MLE under the restriction that $\rho = \rho_0$.

2.2 Asymptotic intervals

`RRsc()` estimates asymptotic confidence intervals for the risk ratio or prevented fraction based on the score statistic. Interval estimates are returned for three estimators. The score method was originally introduced by Koopman (1984). Gart and Nam's modification includes a skewness correction (Gart and Nam 1988). The method of Miettinen and Nurminen (1985) is a version made slightly more conservative than Koopman's by including a factor of $(N-1)/N$.

```
> require(PF)
> RRsc(c(4,24,12,28))

PF
95% interval estimates

                 PF     LL    UL
MN method    0.611 0.0251 0.857
score method 0.611 0.0328 0.855
skew corr    0.611 0.0380 0.876
```

Starting estimates for the algorithm are obtained by the modified Katz method (log method with 0.5 added to each cell). Both forms of the Katz estimate may be retrieved from the returned object using `RRsc()$estimate`.

2.3 Exact intervals

These methods give intervals that are 'exact' in the sense that they are based on the actual sampling distribution rather than an approximation to it. The score statistic is used to select the 2×2 tables that would fall in the tail area, and the binomial probability is estimated over the tail area by taking the maximum over the nuisance parameter. The search over the tail area is made more efficient by the Berger-Boos correction (Berger and Boos 1994).

`RRtosst()` gives intervals obtained by inverting two one-sided score tests; `RRotsst()` gives intervals obtained by inverting one two-sided score test. `RRtosst()` is thus more conservative, preserving at least $\alpha/2$ in each tail. Agresti and Min (2001) discuss the properties and relative benefits of the two approaches. The price of exactnesss is conservatism, due to the discreteness of the binomial distribution (Agresti 2001). This means that the actual coverage of the confidence interval does not exactly conform to the nominal coverage, but it will not be less than it. (See also Agresti (2003).) Both functions use a simple step search algorithm.

```
> RRotsst(c(4,24,12,28))

PF
95% interval estimates

    PF     LL     UL
0.6111 0.0148 0.8519

> RRtosst(c(4,24,12,28))

PF
95% interval estimates
```

```
   PF    LL    UL
0.611 0.012 0.902
```

3 Stratified designs

Methods for estimating a common *RR* from stratified or clustered designs depend on homogeneity with respect to the common parameter.

3.1 Gart-Nam score method

Gart (1985) and Gart and Nam (1988) derived a score statistic for a common estimate of *RR* from designs with multiple independent strata, and they showed that it is identical to one proposed by Radhakrishnan (1965) from a different perspective.

`RRstr()` provides confidence intervals and a homogeneity test based on Gart's statistic.

Data may be input two ways, either using a formula and data frame, or as a matrix.

```
> RRstr(cbind(y,n) ~ tx + cluster(clus), Table6 , pf = F)

[1] "ok"
[1] "end"

Test of homogeneity across clusters

stat         0.954
df         3
p         0.812

RR
95% interval estimates

            RR   LL   UL
starting  2.66 1.37 5.18
mle       2.65 1.39 5.03
skew corr 2.65 1.31 5.08

> # Data matrix input:
> # RRstr(Y = table6, pf = F)
```

3.2 Mantel-Haenszel estimator

A widely-used heuristic method for sparse frequency tables is the weighted average approach of Mantel and Haenszel (1959).[1] MH interval estimates are based on the asymptotic normality of the log of the risk ratio. `RRmh()` utilizes the variance estimator given by Greenland and Robins (1985) for sparse strata. The resulting asymptotic estimator is consistent for both the case of sparse strata where the number of strata is assumed increasing, and the case of limited number of strata where the stratum size is assumed increasing. In the latter case, however, it is less efficient than maximum likelihood (Agresti and Hartzel 2000; Greenland and Robins 1985). Additional discussion may be found in Lachin (2000, Section 4.3.1), Landis et al. (2005), and Somes and O'Brien (2006). [2]

```
> RRmh(cbind(y,n) ~ tx + cluster(clus), Table6 , pf = F)

[1] "ok"
[1] "end"

RR
95% interval estimates

  RR   LL   UL
2.67 1.37 5.23

> # Data matrix input:
> # RRmh(Y = table6, pf = F)
```

3.3 Examples

A fuller set of examples is being prepared for the vignette *Examples for Stratified Designs*.

4 Model based intervals

4.1 Logistic regression estimates

Intervals may be estimated from logistic regression models with `RRor()`. It takes the fit of a `glm()` object and estimates the intervals by the delta method.

[1] Kuritz et al. (1988) review the Mantel-Haenzel approach and point out its relationship to a method proposed by Cochran (1954), which was the basis of Rhadakrishnan's method (Radhakrishnan 1965), alluded to in section 3.1.

[2] SAS Proc FREQ provides MH interval estimates of *RR*. The other estimator calculated by Proc FREQ, which it calls "logit," is actually a weighted least squares estimator (Lachin 2000) that has a demonstrable and severe bias for sparse data (Greenland and Robins 1985). It should be avoided.

```
> bird.fit <- glm(cbind(y,n-y) ~ tx - 1, binomial, bird)
> RRor(bird.fit)
```

```
95% t intervals on 4 df

PF
     PF      LL      UL
 0.5000 -0.0406  0.7598

      mu.hat    LL    UL
txcon  0.733 0.896 0.466
txvac  0.367 0.624 0.168
```

4.2 Estimating the dispersion parameter

The binomial GLM weights are

$$\frac{\hat{\pi}(1-\hat{\pi})}{a(\hat{\varphi})/n}$$

where $a(\hat{\varphi})$ is a function of the dispersion parameter.

4.2.1 Dispersion parameter φ

A simple estimator of the dispersion parameter, φ, may be estimated by the method of moments (Wedderburn 1974). It is given by `phiWt()`. This form of the dispersion parameter has $a(\varphi) = \varphi$, and φ is estimated by X^2/df , the Pearson statistic divided by the degrees of freedom.

Note that φ is the same estimator as may be obtained by the `quasibinomial` family in `glm()` which is, in fact, what is used by `phiWt()` to reweight the original fit:

```
> phiWt(bird.fit, fit.only = F)$phi
```

```
     all
2.471592
```

```
> summary(update(bird.fit, family = quasibinomial))$disp
```

```
[1] 2.471592
```

`phiWt()` makes it easy to estimate PF intervals with a single command.

```
> # model weighted by phi hat
> RRor(phiWt(bird.fit))
```

```
95% t intervals on 4 df

PF
    PF     LL     UL
 0.500 -0.583  0.842

      mu.hat    LL     UL
txcon  0.733 0.943 0.3121
txvac  0.367 0.752 0.0997
```

It also allows different estimates of $\hat{\varphi}$ for specified subsets of the data.

```
> # model with separate phi for vaccinates and controls
> RRor(phiWt(bird.fit, subset.factor = bird$tx))

95% t intervals on 4 df

PF
    PF     LL     UL
 0.500 -0.645  0.848

      mu.hat    LL     UL
txcon  0.733 0.938 0.3330
txvac  0.367 0.767 0.0925
```

If you want to subtract a degree of freedom for each additional parameter, you can do that by entering the degrees of freedom as an argument to `RRor()`.

```
> # subtract 2 degrees of freedom
> RRor(phiWt(bird.fit, subset.factor = bird$tx), degf = 2)

95% t intervals on 2 df

PF
    PF     LL     UL
 0.500 -2.164  0.921

      mu.hat    LL     UL
txcon  0.733 0.975 0.1635
txvac  0.367 0.895 0.0377
```

4.2.2 Dispersion parameter τ

When overdispersion is due to intra-cluster correlation, it may make sense to estimate the dispersion as a function of the intra-cluster correlation parameter τ. In other words, $a(\varphi_{ij}) = 1 + \tau_j(n_{ij} - 1)$. `tauWt()` does this using the Williams procedure (Williams 1982).

```
> # model weighted using tau hat
> RRor(tauWt(bird.fit, subset.factor = bird$tx))

95% t intervals on 4 df

PF
    PF      LL      UL
 0.500 -0.645  0.848

      mu.hat     LL      UL
txcon  0.733 0.938 0.3330
txvac  0.367 0.767 0.0925
```

In this example the `tauWt()` estimates are the same as the `phiWt()` estimates. That is because the cluster sizes are all the same. Let's see what happens if we modify the `bird` data set. The `birdm` data set has the same cluster fractions but differing cluster sizes.

```
> # different cluster sizes, same cluster fractions
> birdm.fit <- glm(cbind(y,n-y) ~ tx - 1, binomial, birdm)
> RRor(tauWt(birdm.fit, subset.factor = birdm$tx))

95% t intervals on 4 df

PF
    PF      LL      UL
 0.490 -0.605  0.838

      mu.hat     LL     UL
txcon  0.737 0.942 0.328
txvac  0.376 0.764 0.101
```

Note that increasing cluster size can make things worse when there is intra-cluster correlation.

Now let's compare the weights from `phiWt()` and `tauWt()` with unequal cluster sizes. In the output below, w represents $1/a(\hat{\varphi})$ and nw is $n/a(\hat{\varphi})$

```
> # Compare phi and tau weights
> #
> phi.wts <-phiWt(birdm.fit,fit.only = F, subset.factor = birdm$tx)$weights
> tau.wts <- tauWt(birdm.fit,fit.only = F, subset.factor = birdm$tx)$weights
> w <- cbind(w.phi=phi.wts,w.tau=tau.wts,nw.phi=phi.wts*birdm$n,
+                   nw.tau=tau.wts*birdm$n)
> print(cbind(birdm[,c(3,1,2)],round(w, 2)), row.names=F)
```

```
  tx  y  n w.phi w.tau nw.phi nw.tau
 vac  1 10  0.32  0.35   3.20   3.55
 vac  8 20  0.32  0.21   6.40   4.13
 vac  9 15  0.32  0.26   4.80   3.92
 con  8 16  0.21  0.27   3.39   4.33
 con  8 10  0.21  0.38   2.12   3.82
 con 27 30  0.21  0.16   6.36   4.84
```

Look at the last two rows. Note that the `nw.phi` are directly proportional to n within treatment group, while the `nw.tau` are not. With intra-cluster correlation, increasing cluster size does not give a corresponding increase in information.

4.3 Rao-Scott weights

Rao and Scott (1992) give a method of weighting clustered binomial observations based on the variance inflation due to clustering. They relate their approach to the concepts of design effect and effective sample size familiar in survey sampling, and they illustrate its use in a variety of contexts. `rsbWt()` implements it in the same manner as `phiWt()` and `tauWt()`. For more general use, the function `rsb()` just returns the design effect estimates and the weights.

```
> # model weighted with Rao-Scott weights
> RRor(rsbWt(birdm.fit, subset.factor = birdm$tx))
```

```
95% t intervals on 4 df


PF
    PF     LL     UL
 0.479 -0.314  0.793

      mu.hat    LL    UL
txcon  0.768 0.960 0.311
txvac  0.400 0.717 0.149
```

```
> # just the design effect estimates
> rsb(birdm$y, birdm$n, birdm$tx)$d

     con      vac
5.137107 2.500000
```

5 Likelihood based intervals

The `RRlsi()` function estimates likelihood support intervals for RR by the profile likelihood (Royall 1997, Section 7.6).

Likelihood support intervals are usually formed based on the desired likelihood ratio, $1/k$, often $1/8$ or $1/32$. Under some conditions the log likelihood ratio may follow the chi-square distribution. If so, then $\alpha = 1 - F_{\chi^2}(2\log(k), 1)$. `RRsc()` will make the conversion from α to k with the argument `use.alpha = T`.

```
> RRlsi(c(4,24,12,28))

1/8 likelihood support interval for PF

corresponds to 95.858% confidence
  (under certain assumptions)

PF
    PF     LL     UL
0.6111 0.0168 0.8859

> RRlsi(c(4,24,12,28), use.alpha = T)

1/6.826 likelihood support interval for PF

corresponds to 95% confidence
  (under certain assumptions)

PF
    PF     LL     UL
0.6111 0.0495 0.8792
```

6 Incidence ratio

The incidence is the number of cases per subject-time. Its distribution is assumed Poisson. Under certain designs, the incidence ratio (IR) is used as a measure of treatment effect.

Correspondingly, $PF_{IR} = 1 - IR$ would be used as a measure of effect for an intervention that is preventive, such as vaccination. *IR* is also called incidence density ratio (*IDR*), and that is the term used in the following functions.

6.1 Score method

`IDRsc()` estimates a confidence interval for the incidence density ratio using Siev's formula (Siev 1994, Appendix 1) based on the Poisson score statistic.[3]

$$IDR = \widehat{IDR}\left\{1 + \left(\frac{1}{y_1} + \frac{1}{y_2}\right)\frac{z^2_{\alpha/2}}{2} \quad \pm \quad \frac{z^2_{\alpha/2}}{2y_1y_2}\sqrt{y_\bullet\left(y_\bullet z^2_{\alpha/2} + 4y_1y_2\right)}\right\}$$

```
> IDRsc(c(26,204,10,205), pf = F)

IDR
95% interval estimates

 IDR   LL   UL
2.61 1.28 5.34
```

6.2 Likelihood method

A likelihood support interval for *IDR* may be estimated based on orthogonal factoring of the reparameterized likelihood. (Royall 1997, Section 7.2) `IDRlsi()` implements this method.

Likelihood support intervals are usually formed based on the desired likelihood ratio, $1/k$, often $1/8$ or $1/32$. Under some conditions the log likelihood ratio may follow the chi square distribution. If so, then $\alpha = 1 - F_{\chi^2}(2\log(k), 1)$. `IDRlsi()` will make the conversion from α tp k with the argument `use.alpha = T`.

```
> IDRlsi(c(26,204,10,205), pf = F)

1/8 likelihood support interval for IDR

corresponds to 95.858% confidence
  (under certain assumptions)

IDR
```

[3] This formula was published in a Japanese journal (Sato 1988) several years before Siev. See also Graham et al. (2003) and Siev (2004).

```
 IDR   LL   UL
2.61 1.26 5.88
```

```
> IDRlsi(c(26,204,10,205), pf = F, use.alpha = T)
```

```
1/6.826 likelihood support interval for IDR

corresponds to 95% confidence
  (under certain assumptions)

IDR
 IDR   LL   UL
2.61 1.30 5.69
```

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