Inferences for Ratios of Normal Means

(mratios package)

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UseR! Conference

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1. Motivating Example

Multi-dose experiment including a positive control and placebo (Bauer *et al.*, 1998)

Treatment	n	mean	sd
Placebo	62	57.5	75.0
Active C.	59	67.3	90.1
Dose 50	60	76.8	75.5
100	60	109.5	87.1
150	62	105.3	85.7

Difference: $H_{0i} : \mu_i - \mu_0 \leq \delta_i$
Ratio: $H_{0i} : \mu_i / \mu_0 \leq \psi_i$

Merits of the ratio view:

- Easy to specify and interpret **thresholds**
- More **powerful** in some one-sided tests
- **Comparability** across different endpoints

Inferences regarding ratios appear in a variety of problems:

- Tests for non-inferiority (or superiority)
- Calibration
- Relative potency estimation

2. Two-Sample Ratio Problems

$Y_{1j} \sim \mathcal{N}(\mu_1, \sigma_1^2), \quad Y_{2j} \sim \mathcal{N}(\mu_2, \sigma_2^2), \quad \gamma = \mu_2/\mu_1$

- **Homogeneous** Variances
  - Test
  - Confidence Interval for γ (Fieller, 1954)
- **Heterogeneous**
  - Test (Tamhane and Logan, 2004)
  - CI (Plug-in)

3. Simultaneous Inferences: One-way Layout

$Y_{ij} \sim \mathcal{N}(\mu_i, \sigma^2), \quad i = 1, \ldots, k;\ j = 1, \ldots, n_i$

$\gamma_\ell = \frac{\boldsymbol{c}_\ell' \boldsymbol{\mu}}{\boldsymbol{d}_\ell' \boldsymbol{\mu}}, \quad \ell = 1, \ldots, r$

Distr.: Multivariate t with $df = \sum_1^k n_i - k$ and $Corr = \boldsymbol{R}(\gamma)$

- **Multiple Tests:**
  $H_{0\ell} : \gamma_\ell \leq \psi_\ell$ versus $H_{1\ell} : \gamma_\ell > \psi_\ell, \quad \ell = 1, \ldots, r$

  Contrasts: User-defined, Dunnett, Tukey, Sequence, *etc.*

- **Simultaneous CI:**
  Contrasts: User-defined, Dunnett, Tukey, Sequence, *etc.*
  Methods: Unadjusted, Bonferroni, Sidak, plug-in

4. General Linear Model

- **Calibration:** $Y = \beta_0 + \beta_1 x + \epsilon$, $\gamma = \frac{y_0 - \beta_0}{\beta_1}$
- **Multiple Assays** (Jensen, 1989)
  - Parallel line assay
    $Y_{ij} = \alpha_i + \beta X_{ij} + \epsilon_{ij}, \quad i = 0, 1, \ldots, m;\ j = 1, \ldots, n_i$
    Parameters: $\gamma_i = \alpha_i / \alpha_0, \quad i = 1, \ldots, m$
  - Slope ratio assay
    $Y_{ij} = \alpha + \beta_i X_{ij} + \epsilon_{ij}, \quad i = 0, 1, \ldots, m;\ j = 1, \ldots, n_i$
    Parameters: $\gamma_i = \beta_i / \beta_0, \quad i = 1, \ldots, m$

Simultaneous CI:

$$\gamma_\ell = \frac{\boldsymbol{c}_\ell' \boldsymbol{\eta}}{\boldsymbol{d}_\ell' \boldsymbol{\eta}} : \quad \left(\frac{-B_\ell - \sqrt{B_\ell^2 - 4A_\ell C_\ell}}{2A_\ell}, \frac{-B_\ell + \sqrt{B_\ell^2 - 4A_\ell C_\ell}}{2A_\ell} \right), \quad \ell = 1, 2, \ldots, r$$

where

$$\begin{aligned} \boldsymbol{\eta} &= \text{Vector of regression coeff. or means} \\ A_\ell &= (\boldsymbol{d}_\ell' \widehat{\boldsymbol{\eta}})^2 - q^2 S^2 \boldsymbol{d}_\ell' \boldsymbol{M} \boldsymbol{d}_\ell \\ B_\ell &= -2 \left[(\boldsymbol{c}_\ell' \widehat{\boldsymbol{\eta}})(\boldsymbol{d}_\ell' \widehat{\boldsymbol{\eta}}) - q^2 S^2 \boldsymbol{c}_\ell' \boldsymbol{M} \boldsymbol{d}_\ell) \right] \\ C_\ell &= (\boldsymbol{c}_\ell' \widehat{\boldsymbol{\eta}})^2 - q^2 S^2 \boldsymbol{c}_\ell' \boldsymbol{M} \boldsymbol{c}_\ell \\ \boldsymbol{M} &= (\boldsymbol{X}' \boldsymbol{X})^{-1} \end{aligned}$$

and

$$q = \begin{cases} t_{1-\frac{\alpha}{2}}(\nu) & \text{, unadjusted} \\ t_{1-\frac{\alpha}{2r}}(\nu) & \text{, Boole's inequality} \\ c_{1-\alpha}'(\boldsymbol{I}_r) & \text{, Šidák inequality} \\ c_{1-\alpha}'(\boldsymbol{R}(\widehat{\gamma})) & \text{, plug-in} \end{cases}$$

(Dilba *et al.*, 2006)

5. Sample size calculation: Many-to-One

- Tests for non-inferiority (or superiority)

- Sample size at LFC

The **mratios** package is available at

`http://www.bioinf.uni-hannover.de/software/`

References

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