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Approximate Simultaneous Confidence Intervals for Multiple Contrasts of Binomial Proportions and Poly-3-adjusted Tumour Rates

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1. Introduction

Situation: Toxicological or Long-term carcinogenicity studies
Completely randomized design, moderate sample sizes
Comparison of different dose groups to an untreated control
Response variable: Proportions
Tumour rates: Confounded by treatment dependent mortality rates
Proportions with Poly-3-adjustment (Bailer & Portier, 1988), if time of death and tumour status, but no cause-of-death information available
Objective: Difference of proportions
Many-to-one comparisons, inference for order restricted alternatives, e.g. Williams contrasts, Umbrella-protected Williams contrasts
Simultaneous confidence intervals close to nominal level

2. Example

NTP study on long-term carcinogenicity of methyleugenol (Peddada, 2005)

Dose	0 mg/kg	37mg/kg	75 mg/kg	150 mg/kg
# animals treated	50	50	50	50
# tumours	1	9	8	5
Raw tumour proportion	0.02	0.18	0.16	0.1
# died before study end	30	34	35	50
Poly-3-adjusted proportion	0.024	0.223	0.207	0.153

Interest might be in comparison of raw tumour proportions, total survival rates, or in comparison of Poly-3-adjusted tumour rates.

3. Methods

i) Binomial proportions

$Y_i \sim Bin(n_i, \pi_i), i = 1,...,I$, point estimators $\hat{\pi}_i = y_i / n_i$, and $\hat{V}(\hat{\pi}_i) = \hat{\pi}_i(1-\hat{\pi}_i)/n_i$. Interest is in simultaneous inference for M contrasts: $L_m = \sum_{i=1} c_{im}\pi_i,\ m = 1,...,M$

Simultaneous ($1-\alpha$)-confidence intervals (Wald):

$$\left[\sum_{i=1}^{I} c_{im}\hat{\pi}_i \pm z^{twosided}_{M,R,1-\alpha}\sqrt{\sum_{i=1}^{I} c_{im}^2 \hat{V}(\hat{\pi}_i)}\right]$$

The quantile $z^{twosided}_{M,R,1-\alpha}$ is the two-sided equi-coordinate $(1-\alpha)$-quantile of an M-variate normal distribution with correlation matrix R (Bretz and Hothorn, 2002), with elements $\rho_{mm'}$ depending on the sample estimates (Piegorsch, 1991):

$$\rho_{mm'} = \sum_{i=1}^{I} c_{im}c_{im'}\hat{V}(\hat{\pi}_i) \Big/ \sqrt{\sum_{i=1}^{I} c_{im}^2 \hat{V}(\hat{\pi}_i) \sum_{i=1}^{I} c_{im'}^2 \hat{V}(\hat{\pi}_i)}$$

ii) Tumour rates in long-term carcinogenicity studies

Final tumour rates p_i depend on unknown hazard rates λ_i for tumour development and β_i for death (time of death t_{ij} for jth individual in ith group recorded):

$$p_i = \int_{t=0}^{t=t_s} \lambda_i(t) \exp\left[-\int_{s=0}^{s=t} (\lambda_i(s) + \beta_i(s))ds\right] dt$$

$$\lambda_i(t) = \lim_{\varepsilon \to 0}\left\{P(t \le T < t+\varepsilon, Y(t) = 1 \mid T \ge t)/\varepsilon\right\}, \text{and } \beta_i(t) \text{accordingly}$$

Bailer and Portier (1988) yield point estimators for λ_i: $p_i^* = y_i / n_i^*$ where $n_i^* = \sum_{j=1}^{n_i} (t_{ij}/t_{\max})^3$ accounts for different individual time under risk. Variance estimators as for binomials: $\hat{V}(p_i^*) = p_i^*(1-p_i^*)/n_i^*$

Adjustment for moderate sample sizes:

Wald intervals with adjusted center and variance adapting methods of Agresti and Caffo (2000), Bonett and Price (2004).

Add-1 $\hat{\pi}_i = (y_i + 0.5)/(n_i + 1), \hat{V}(\hat{\pi}_i) = \hat{\pi}_i(1-\hat{\pi}_i)/(n_i - 1)$

Add-2 $\hat{\pi}_i = (y_i + 1)/(n_i + 2), \quad \hat{V}(\hat{\pi}_i) = \hat{\pi}_i(1-\hat{\pi}_i)/(n_i - 2)$

4. Simulation studies: Coverage probabilities

i) Binomial proportions

Simultaneous lower 95% confidence intervals for **many-to-one comparisons** of 4 groups, mean coverage probability for $\pi_i \sim U(0,1)$

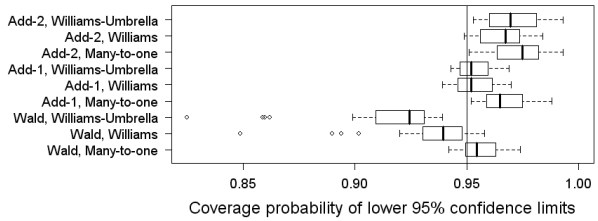
Method	n_i=10	n_i=20	n_i=40	n_i=80
Wald	0.884	0.920	0.936	0.943
Add-1	0.948	0.948	0.949	0.949
Add-2	0.960	0.956	0.953	0.951

Simultaneous lower 95% confidence intervals for **Williams contrasts** (Bretz, 2006) of 4 groups, mean coverage probability for $\pi_i \sim U(0,1)$

Method	n_i=10	n_i=20	n_i=40	n_i=60	n_i=100
Wald	0.908	0.930	0.941	0.944	0.946
Add-1	0.951	0.950	0.950	0.950	0.950
Add-2	0.959	0.956	0.953	0.952	0.951

ii) Poly-3-adjusted tumour proportions

Simultaneous lower 95% intervals for Poly-3-adjusted proportions, 4 groups, n_i=50, various contrast types (Bretz & Hothorn, 2003; Bretz, 2006), hazard rates for tumour development $\lambda_i(t_{max})$= 0.05,…,0.3, and death $\beta_i(t_{max})$= 0.3,…,0.6.



5. Example evaluated

Umbrella-protected Williams contrasts (Bretz & Hothorn, 2003) for the raw tumour proportions: Lower 95% confidence limits:

Contrast	0 mg/kg	37 mg/kg	75 mg/kg	150 mg/kg	Lower 95% limit	Estimate
c_1	-1	0	0	1	-0.030	0.08
c_2	-1	0	0.5	0.5	0.017	0.11
c_3	-1	0.33	0.33	0.33	0.042	0.13
c_4	-1	0	1	0	0.011	0.14
c_5	-1	0.5	0.5	0	0.049	0.15
c_6	-1	1	0	0	0.026	0.16

Williams contrast (Bretz, 2006) for the Poly-3-adjusted tumour proportions: Lower 95% confidence limits:

Contrast	0 mg/kg	37 mg/kg	75 mg/kg	150 mg/kg	Lower 95% limit	Estimate
c_1	-1	0	0	1	-0.009	0.13
c_2	-1	0	0.5	0.5	0.048	0.16
c_3	-1	0.33	0.33	0.33	0.075	0.17

6. Conclusions

- Approximate simultaneous confidence intervals for multiple contrasts can be used for inference on binomial proportions or Poly-3-adjusted tumour proportions in toxicolgical studies.
- Simulation studies show acceptable coverage probability of confidence limits using the add-1 adjustment following Agresti and Caffo (2000) for moderate sample sizes such as 40, or 60 per group.
- The add-2 adjustment can be conservative.
- R code is available from the first author.

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