Simultaneous confidence intervals incorporating historical control data

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Rationale

Objective: Analysis of bioassays with binary response variable

Typical design: Model organisms are randomly assigned to several dose and control groups under standardized conditions

Issue: Incorporation of historical data from previous control groups

Usual approach: Using the beta distribution taking the extra binomial variation among historical studies into account; modified Cochran-Armitage test based on a weighted linear regression on proportions

Proposed approach: Incorporation the historical control data using the beta distribution and usage of multiple contrast tests for multiple comparisons

Example

Study from the National Toxicology Program (NTP) on long-term carcinogenicity of Anthraquinone. Focus is on incidence of Hepatocellular Carcinoma in liver in male $B6C3F_1$ mice.

Dose (mg/kg)	0	90	265	825
Total number of animals	50	50	50	50
Tumor bearing animals	8	13	17	21

Table shows mortality unadjusted tumor data. Interest is in determining the carcinogenetic effect.
Historical studies (198) were available from the NTP database with the following selection criteria: Organism: $B6C3F_1$ mice, Gender: male, Exposure Route:: Dosed-Feed, Study Length: 2 years, Lesion: Hepatocellular Carcinoma, Organ: Liver.

Methods

Consider $y_i \sim Bin(n_i, \pi_i)$, i=1,. . . ,I binomial random variables with point estimator for $\pi_i : \hat{\pi}_i = y_i/n_i$ and variance estimator $\hat{V}(\hat{\pi}_i) = \hat{\pi}_i(1-\hat{\pi}_i)/n_i$. If the primary interest is in proof of demonstrating harmfulness (proof of hazard) the global hypotheses can be expressed as:

$$H_0 : \bigcap_{i=1}^{I} \pi_i - \pi_0 \leq 0 \qquad H_1 : \bigcup_{i=1}^{I} \pi_i - \pi_0 > 0.$$

The global null hypothesis is rejected, if any elementary null hypotheses is rejected.

Adjustment for moderate sample sizes

The estimators are crude, especially when the binomial proportion is close to zero. A common adjustment adds two successes and two failures to the 2×2 contingency table [1]. Thus the point estimator $\widetilde{\pi}_i = (y_i + 1)/(n_i + 2)$ and the adjusted number of successes $\widetilde{n}_i = n_i + 2$ are used. The variance of the estimated proportion is given by $\widetilde{V}_i = \widetilde{\pi}_i(1-\widetilde{\pi}_i)/(n_i+2)$.

Incorporation historical information

Suppose a number of j previous experiments, $j = 1, \ldots, J$ where the binomial proportions are beta distributed $\pi_j \sim beta(a, b)$, that takes the variability over the studies into account [5]. The joint control proportion is beta-binomial distributed ($\pi_0 \sim betabin(n, a, b)$) with point estimator $\hat{\pi}_0 = (\hat{a}+y)/(\hat{a}+\hat{b}+n)$ and variance estimator $\hat{V}(\hat{\pi}_0) = (E(\pi|y)(1-E(\pi|y)))/(\hat{a}+\hat{b}+n)$.

Simultaneous confidence intervals

The hypotheses can be decomposed to tests of M linear combinations $L_m = \sum_{i=0}^{I} c_{mi}\hat{\pi}_i$ [4]. The lower confidence boundary can be estimated via:

$$\hat{L}_m^l = \sum_{i=0}^{I} c_{im}\hat{\pi}_i - z\sqrt{\sum_{i=0}^{I} c_{im}^2 \hat{V}(\hat{\pi}_i)}$$

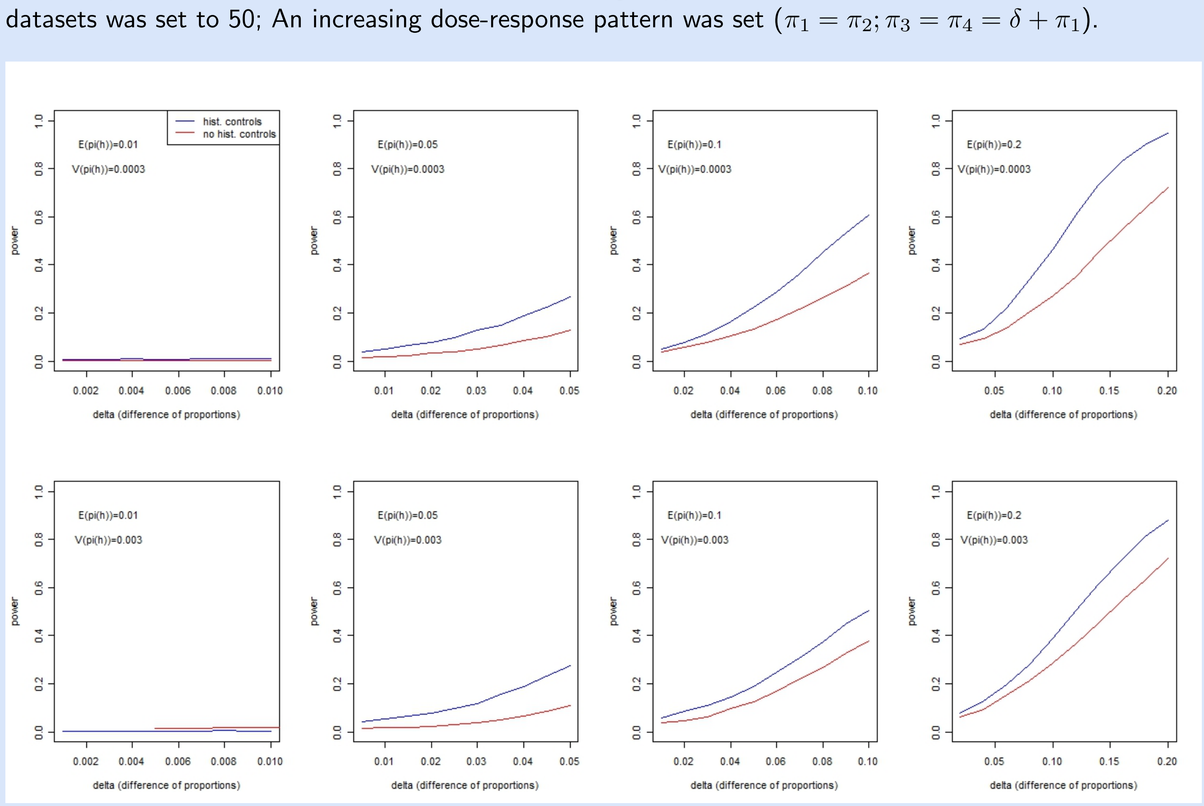
where z is an critical value $z = z_{M,R,1-\alpha}^{one-sided}$ of an M-variate standard normal distribution with the M×M correlation matrix R. [2] specified the correlation between two contrasts m and m' ($m \neq m'$) as:

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

For the control group the estimators $\hat{\pi}_0$, $\hat{V}(\hat{\pi}_0)$ and for the treatment groups the Add2 estimators are used.

Simulation studies

Power of one-sided upper 95% confidence intervals for many to one comparisons of binary proportions for different point and variance estimators of the control group. The number of available historical control datasets was set to 50; An increasing dose-response pattern was set ($\pi_1 = \pi_2; \pi_3 = \pi_4 = \delta + \pi_1$).

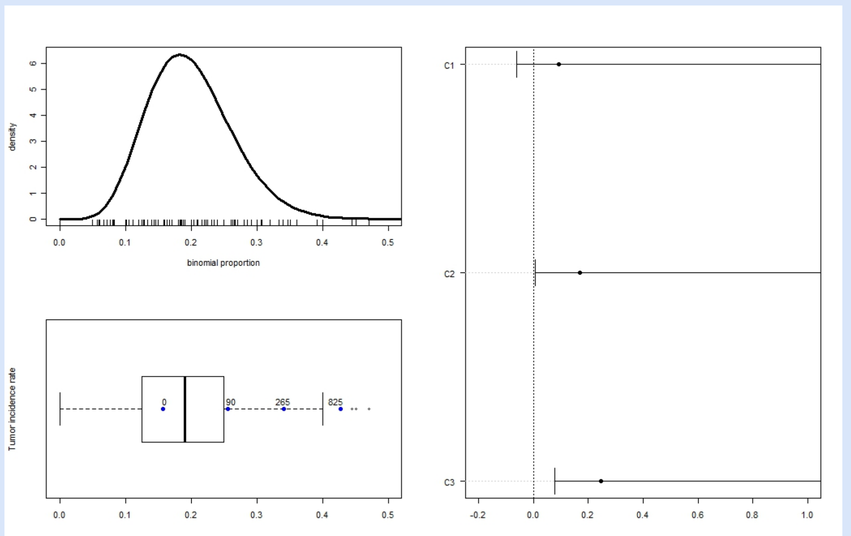


Comparison of the Add2-method (red line) with the method of incorporation historical control information (blue line).

Example evaluated

Assuming an increasing effect one-sided 95% upper confidence intervals for comparison each dose group to the control group were calculated.

					Estimate		Lower 95% limit	
Contrast	0 mg/kg	90 mg/kg	265 mg/kg	825 mg/kg	hist. controls	Add2	hist. controls	Add2
C_1	-1	1	0	0	0.092	0.096	-0.062	-0.072
C_2	-1	0	1	0	0.169	0.173	-0.007	-0.003
C_3	-1	0	0	1	0.246	0.250	0.078	0.070



Conclusions

- Incorporation of historical control information using the beta-binomial distribution is possible
- Approximate simultaneous confidence intervals for multiple contrasts can be used for inference on binomial proportions in toxicological studies
- Simulation studies show an increasing power when historical control information is used in comparison to the Add2 method
- Software available in R [3]
  - For fitting the beta-binomial distribution the gamlls-package was used
  - MCPAN-package for calculating simultaneous confidence intervals

References

[1] A. Agresti and B. Caffo. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. *American Statistician*, 55(2):172–173, 2000.

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[3] R Development Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2010. ISBN 3-900051-07-0.

[4] F. Schaarschmidt, M. Sill, and L. A. Hothorn. Approximate Simultaneous Confidence Intervals for Multiple Contrasts of Binomial Proportions. *Biometrical Journal*, 50(5, Sp. Iss. SI):782–792, 2008.

[5] R. E. Tarone. The Use of Historical Control Information in Testing for a Trend in Proportions. *Biometrics*, 38(1):215–220, 1982.