Multiple Comparisons Between Two Groups on Multiple Bernoulli Outcomes While Accounting for Covariates

James F. Troendle, Ph.D.
Biometry and Mathematical Statistics Branch
DESPR, NICHD, NIH, DHHS
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I. Motivation

- DIEP study of pregnancy outcome
- 467 diabetic and 277 non-diabetic mothers
- 55 minor malformations
- One-sided Fisher's exact tests applied to each
- Step-down p-value adjustment using Bootstrap (Westfall and Young, 1993; Troendle, 1995)

Unadjusted and Adjusted p-Values for DIEP Data Without Correction for Birthweight

		Adjusted p-Value
Malformation Number	Unadjusted p-Value	Step-down Bootstrap
32	.00033	.0026
30	.00097	.0088
18	.00916	.1090
4	.02424	.2885
27	.03290	.3604
16	.04228	.4436

II. Model

$$\mathbf{Y_i} = \begin{pmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \\ Y_{ik} \end{pmatrix} \sim MVB\left[\theta_{\mathbf{i}} = \begin{pmatrix} \theta_{i1} \\ \theta_{i2} \\ \vdots \\ \theta_{ik} \end{pmatrix}, \ \mathbf{\Sigma}\right], \ i = 1, \ldots, n$$

$$T_i = \begin{cases} 0 & \text{if } i^{th} \text{ patient is in group 0} \\ 1 & \text{if } i^{th} \text{ patient is in group 1} \end{cases}, \ i = 1, \ldots, n$$

$$\mathbf{X_i} = \begin{pmatrix} X_{i1} \\ \vdots \\ X_{ip} \end{pmatrix}, \ i = 1, \ldots, n$$

II. Model (Continued)

$$\log\left(\frac{\theta_{ij}}{1-\theta_{ij}}\right) = a + \gamma_j T_i + \beta'_{\mathbf{j}}\ , \quad \begin{array}{l} i = 1, \ldots, n \\ j = 1, \ldots, k \end{array}$$

$$\beta_{\mathbf{j}} = \begin{pmatrix} \beta_{j1} \\ \vdots \\ \beta_{jp} \end{pmatrix}, \quad j = 1, \ldots, k$$

$$H_0 : \gamma_j = 0$$

$$P_j = 2\left[1 - \Phi\left(\left|\frac{\hat{\gamma}_j}{\sqrt{\widehat{var(\hat{\gamma}_j)}}}\right|\right)\right] \qquad j = 1, \ldots, k,$$

III. Methods - Vector Bootstrap

- $\mathbf{Z_i} = \begin{pmatrix} \mathbf{Y_i} \\ T_i \\ \mathbf{X_i} \end{pmatrix}$, $i = 1, \ldots, n$

- Bootstrapping within group not recommended (Troendle et al. 2004)

- Bootstrapping regardless of group

$$P_j^* = 2\left[1 - \Phi\left(\left|\frac{\hat{\gamma}_j^* - \hat{\gamma}_j}{\sqrt{\widehat{var(\hat{\gamma}_j^*)}}}\right|\right)\right] \qquad j = 1, \ldots, k,$$

- Step-down testing

III. Methods - Permute Within Strata

- C Strata defined by $\{\mathbf{X_i}, \ldots, \mathbf{X_n}\}$

- Permute $\{T_1, T_2, \ldots, T_{n_h}\}$ within h^{th} stratum, $h = 1, \ldots, C$

$$P_j^* = 2\left[1 - \Phi\left(\left|\frac{\hat{\gamma}_j^*}{\sqrt{\widehat{var(\hat{\gamma}_j^*)}}}\right|\right)\right] \qquad j = 1, \ldots, k,$$

- Step-down testing

- Method strongly controls the FWE if logistic model holds

IV. Properties

- CBRAND used to generate exchangeable (corr=ρ) MVB

- $B = 199$ random permutations
- $a = -1.5, \qquad \beta_{jl} = 1, \qquad j = 1, \ldots, k,\ \ l = 1, 2$
- 10000 replications yields Sim. SE $\approx$ 0.22%

Simulated FWE(%) with nominal level 5%

				Multiple Comparison Procedure		
k	n	p	ρ	Holm	Vector Bootstrap	Within Strata Permutation
50	100	1	0.0	1.30	5.14	4.73
			0.5	1.01	**5.62**	5.13
			0.8	0.41	**5.81**	5.05
		2	0.0	1.57	5.17	4.88
			0.5	1.33	5.16	4.90
			0.8	0.60	**5.89**	5.19
	500	1	0.0	3.75	4.70	4.71
			0.5	2.89	5.29	5.33
			0.8	1.11	5.18	5.04
		2	0.0	3.46	4.76	4.83
			0.5	2.18	4.72	4.59
			0.8	1.01	5.00	4.84

Simulated average power(%) with nominal level 5%

				Multiple Comparison Procedure		
					Vector	Within Strata
k	n	p	ρ	Holm	Bootstrap	Permutation
50	100	1	0.0	.615	.593	**.703**
			0.5	.629	.661	**.745**
			0.8	.607	.755	**.807**
		2	0.0	.540	.512	**.629**
			0.5	.566	.575	**.689**
			0.8	.554	.706	**.771**

$$\gamma_j = 1.5, \quad j = 1, \ldots, k$$

V. DIEP Analysis

- Birth Weight assigned score 1-5 based on quintiles
- B=99999 random permutations

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Adjusted p-Values for DIEP Data With Correction for Birthweight

Malformation Number	Unadjusted p-Value	Adjusted p-Value Holm		
		Holm	Vector Bootstrap	Within Strata Permutation
32	.00028	.0152	.0009	.0007
30	.00243	.1312	.0151	.0141
4	.02839	1.0000	.3119	.3022
36	.04043	1.0000	.4499	.4068
27	.04501	1.0000	.5010	.4383
13	.06332	1.0000	.6815	.6050