Stepwise Confidence Intervals for Monotone Dose-Response Studies

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Present at MCP 2007 Vienna

July 10, 2007

OUTLINE

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1. Introduction

Model Assumption: One-way ANOVA

A set of increasing k dose levels of a drug and a control

$Y_{ij} \sim N(\mu_i, \sigma^2)$ **independently, where** $i = 1, \ldots, k$, $j = 1, \ldots, n_i$.

Minimum Effective Dose

$$MED = min\{i : \mu_i > \mu_1 + \delta\}$$

where δ is a clinically significant difference.

Error Rate

- For the MED problem, an error is made if the inferred MED, and any of the doses higher than the inferred MED, is in fact not efficacious. That is, the probability of declaring an ineffective dose to be effective.
- Previous formulations of the MED problem, which have cast it as one of testing a family of null hypotheses of equalities against various alternatives, fail to control the aforementioned error rate (Hsu and Berger (1999)).

Prior Knowledge:

- Treatment effect of a drug usually increases with the increase of dose levels.
- Monotone Dose-Response (Simple Ordering):

$$\mu_1 \leq \cdots \leq \mu_k.$$

Hsu and Berger (1999)'s DR method does not make use of the prior knowledge.

Question: How to take the prior knowledge into account to follow the DR method?

Theorem 1 *Denote the lower confidence bound for* $\mu_i - \mu_1$ *by* $L_i(\bar{Y})$ $(2 \leq i \leq k)$. *Assume that* $P\{\mu_{\widehat{MED}} - \mu_1 > L_{\widehat{MED}}(\bar{Y})\} \geq 1 - \alpha$ *and* $L_{\widehat{MED}}(\bar{Y}) \geq \delta$. *Then under the monotonicity assumption* $\mu_1 \leq \ldots \leq \mu_k$, *the probability of inferring any ineffective dose as effective is* $\leq \alpha$.

Marcus and Peritz (1976) discussed the construction of simultaneous lower confidence bounds under certain restricted normal model when the variances are known. Their process is very lengthy.

2 A Multiple Contrast Test Statistic T_k for Testing Dose-Response.

2.1 The Likelihood Ratio Test

$H_{0k} : \mu_1 = \mu_2 = \ldots = \mu_k$ **versus** $H_{1k} : \mu_1 < \mu_k$ **under the monotonicity assumption** $\Omega_k = \{\boldsymbol{\mu} : \mu_1 \leq \ldots \leq \mu_k\}$

$$S_{01} = \sum_{i=1}^{k} n_i(\mu_i^* - \hat{\mu})^2 / \{\sum_{i=1}^{k} n_i(\bar{Y}_i - \mu_i^*)^2/\nu + S^2\},$$

The null distribution of S_{01} **under** H_{0k} **is given by**

$$P(S_{01} > s) = \sum_{j=2}^{k} P(j, k; \mathbf{w}) P\{F_{j-1,N-j} > \frac{s(N-j)}{\nu(j-1)}\} \quad (1)$$

2.2 The Multiple Contrast Test Statistic T_k

$$T_k = \max_{\mathbf{c}\in\mathbf{C_k}} \sum_{i=1}^{k} n_i c_i \bar{Y}_i / S(\sum_{i=1}^{k} n_i c_i^2)^{1/2},$$

where

$$\mathbf{C}_k = \{\mathbf{c} = (c_1, \ldots, c_k) : \sum_{i=1}^{k} n_i c_i = 0,\ c_1 \leq \ldots \leq c_k\}.$$

- $T_k^2 = \Sigma_{i=1}^{k}\, n_i(\mu_i^* - \hat{\mu})^2/S^2$.
- **The statistic T_k^2 is asymptotically equivalent tc S_{01}.**
- **The null distribution of T_k is given by**

$$P_0[T_k \geq t] = \sum_{\ell=2}^{k} P_S(\ell, k : n) P[F_{\ell-1,\nu} \geq \frac{t^2}{\ell - 1}]$$

3 Lower Confidence Bound for $\mu_k - \mu_1$

Let $t_{k,\nu,\alpha}$ be the critical value of T_k, then

$$P_{\boldsymbol{\mu}}\{\max_{\mathbf{c}\in\mathbf{C_k}}\sum_{i=1}^{k} n_i c_i(\bar{Y}_i - \mu_i)/S(\sum_{i=1}^{k} n_i c_i^2)^{1/2} \le t_{k,\nu,\alpha}\}$$

$$= P_{\mathbf{0}}\{\max_{c\in\mathbf{C_k}}\sum_{i=1}^{k} n_i c_i \bar{Y}_i/S(\sum_{i=1}^{k} n_i c_i^2)^{1/2} \le t_{k,\nu,\alpha}\}$$

It follows that

$$P_{\boldsymbol{\mu}}\Big\{\sum_{i=1}^{k} n_i c_i \mu_i \ge \sum_{i=1}^{k} n_i c_i \bar{Y}_i - t_{k,\nu,\alpha} S(\sum_{i=1}^{k} n_i c_i^2)^{1/2},\ \textbf{for all } \mathbf{c}\in\mathbf{C_k}\Big\} = 1-\alpha.$$

When the variance σ^2 is known, Marcus and Peritz (1976, Biometrika) derived the above expression.

3.1 The Lower Confidence Bound for $\mu_k - \mu_1$

Denote

$$l(\sum_{i=1}^{k} n_i c_i \mu_i) = \sum_{i=1}^{k} n_i c_i \bar{Y}_i - t_{k,\nu,\alpha} S (\sum_{i=1}^{k} n_i c_i^2)^{1/2}.$$

Let $\mathcal{K}_k = \{\mathbf{c} : \mathbf{c} \in \mathbf{C_k},\ \Sigma_{i=1}^{k} n_i c_i \mu_i \leq \mu_k - \mu_1,$ **for all** $\boldsymbol{\mu} \in \Omega_k\}$.

The largest lower confidence bound for $\mu_k - \mu_1$ **is given by**

$$L(\mu_k - \mu_1) = \max_{\mathbf{c} \in \mathcal{K}_k} l(\sum_{i=1}^{k} n_i c_i \mu_i).$$

Theorem 2 ***When*** $\boldsymbol{\mu} \in \Omega_S$, ***we have that*** $T_k > t_{k,\nu,\alpha}$ ***if and only if*** $L(\mu_k - \mu_1) > 0$.

Theorem 3 ***Suppose that*** $T_k > t_{k,\nu,\alpha}$. ***The vector*** $\mathbf{c}^o \in \mathcal{K}_k$ ***is an optimized solution if and only if there exist positive integers*** p ***and*** q, $1 \le p < q \le k$, ***such that*** $\mu_p^* < \hat{\mu} < \mu_q^*, S_{1p}^2 + S_{qk}^2 < S^2 t_{k,\nu,\alpha}^2$ ***and*** $c_1^o \le \cdots \le c_p^o < c_{p+1}^o = \cdots = c_{q-1}^o = 0 < c_q^o \le \cdots \le c_k^o$, ***where*** $c_i^o = -N_{1p}^{-1} + b^{-1}(\mu_i^* - \bar{Y}_{1p}),\ i = 1, \ldots, p,$ ***and*** $c_i^o = N_{qk}^{-1} + b^{-1}(\mu_i^* - \bar{Y}_{qk}),\ i = q, \ldots, k,$ ***with***

$$\max\left\{N_{1p}(\mu_p^* - \bar{Y}_{1p}), N_{qk}(\bar{Y}_{qk} - \mu_q^*)\right\} < b \le \min\left\{N_{1(p+1)}(\mu_{p+1}^* - \bar{Y}_{1(p+1)}), N_{(q-1)k}(\bar{Y}_{(q-1)k} - \mu_{q-1}^*)\right\} \tag{2}$$

where

$$b^2 = (t_{k,\nu,\alpha}^2 S^2 - S_{1p}^2 - S_{qk}^2)/(N_{1p}^{-1} + N_{qk}^{-1}),$$

and $N_{ab} = \Sigma_{i=a}^b n_i,\ \bar{Y}_{ab} = \Sigma_{i=a}^b n_i \mu_i^*/N_{ab},\ S_{ab}^2 = \Sigma_{i=a}^b n_i(\mu_i^* - \bar{Y}_{ab})^2$. ***When*** $q = p + 1$, ***the upper bound for*** b ***in*** (2) ***is replaced by*** $(\bar{Y}_{qk} - \bar{Y}_{1p})/(N_{1p}^{-1} + N_{qk}^{-1})$.

3.2 Iterative Algorithm

(0) Set $i = 0$, $p_0 = \max\{1 \le j < k : \mu_j^* < \hat{\mu}\}$ **and** $q_0 = \min\{2 \le j \le k : \mu_j^* > \hat{\mu}\}$.

(i) Let $\beta_{i+1} = \max\{N_{1p_i}(\mu_{p_i}^* - \bar{Y}_{1p_i}), N_{q_ik}(\bar{Y}_{q_ik} - \mu_{q_i}^*)\}$, $t_{k,\nu,\alpha_{i+1}} = [S_{1p_i}^2 + S_{q_ik}^2 + (N_{1p_i}^{-1} + N_{q_ik}^{-1})\beta_{i+1}^2]^{1/2}/S$. **If** $t_{k,\nu,\alpha_{i+1}} < t_{k,\nu,\alpha}$, **the optimization solution is c° with** $p = p_i$ **and** $q = q_i$. **Otherwise, go to (ii).**

(ii) If $N_{1p_i}(\mu_{p_i}^* - \bar{Y}_{1p_i}) > N_{q_ik}(\bar{Y}_{q_ik} - \mu_{q_i}^*)$, **then set** $p_{i+1} = \max\{j : 1 \le j < p_i, \mu_j^* < \mu_{p_i}^*\}$ **and** $q_{i+1} = q_i$. **Otherwise, set** $p_{i+1} = p_i$ **and** $q_{i+1} = \min\{j : q_i < j \le k, \mu_j^* > \mu_{q_i}^*\}$. **Set** $i = i + 1$, **go to step (i).**

4 The Stepwise Confidence Interval Procedure

Denote $L(\mu_i - \mu_1) = \max_{\mathbf{c} \in \mathbf{C_i}} \{ \Sigma_{j=1}^{i} n_j c_j \mu_j^* - t_{i,\alpha,\nu} S \sqrt{\Sigma_{j=1}^{i} n_j c_j^2} \}$ **subject to** $\Sigma_{j=l}^{i} n_j c_j \leq 1, l = 2, \cdots, i,$ **where** $\mathbf{C}_i = \{\mathbf{c} = (c_1, \ldots, c_i) : \Sigma_{j=1}^{i} n_j c_j = 0,\ c_1 \leq \ldots \leq c_i\},$

Step 1: If $L(\mu_k - \mu_1) \geq \delta$, **then claim** $\mu_k > \mu_1 + \delta$ **and go to Step 2; else claim that there is no non-zero dose level which is significantly better than the control and** $\mu_k - \mu_1 > L(\mu_k - \mu_1)$ **and stop.**

Step 2: If $L(\mu_{k-1} - \mu_1) \geq \delta$, **then claim** $\mu_{k-1} > \mu_1 + \delta$ **and go to Step 3; else claim** $\widehat{MED} = k$ **and** $\mu_{k-1} - \mu_1 > L(\mu_{k-1} - \mu_1)$, **then stop.**

Step k-1: If $L(\mu_2-\mu_1) \geq \delta$, then claim $\mu_2 > \mu_1+\delta$ and go to Step k; else claim $\widehat{MED} = 3$ and $\mu_2 - \mu_1 > L(\mu_2 - \mu_1)$ (when $\bar{Y}_2 > \bar{Y}_1$, this lower bound is the same as $\bar{Y}_2 - \bar{Y}_1 - t_{\alpha,\nu} S\sqrt{1/n_1 + 1/n_2}$, where $t_{\alpha,\nu}$ is the t critical value), then stop.

Step k: Claim every dose level is significantly better than the control, i.e., $\widehat{MED} = 2$ and stop.

5 Two Examples

Example 1: Wöhr, Borta, and Schwarting (2005).

Table 1. Immobility/min during the context phase (1-3 min) of the retest day.

Dosage	Sample size	Mean response	SEM response
0.0mA	7	8.89	3.96
0.2mA	7	5.36	1.87
0.5mA	7	32.01	6.29
0.8mA	7	42.75	4.93
1.1mA	5	48.06	3.55

Table 2. Step-down 95% Lower Confidence Bounds for $\mu_i - \mu_1$ in Example 1.

$\mu_i - \mu_1$	DUNNETT	DR	MC
$\mu_5 - \mu_1$	23.82	27.66	27.67
$\mu_4 - \mu_1$	20.55	23.35	23.74
$\mu_3 - \mu_1$	10.80	12.61	14.00

For illustration,

- If $\delta = 10.0$, $\widehat{MED} = 3$ by these three methods.
- If $\delta = 11.0$, $\widehat{MED} = 3$ by the DR method and the MC method; $\widehat{MED} = 4$ by the Dunnett method.
- If $\delta = 13.0$, $\widehat{MED} = 3$ only by the MC method; $\widehat{MED} = 4$ by the Dunnett method and the DR method.

Example 2. Williams (1971) gave an example where 6 dose levels are compared with a zero dose control under the monotonicity assumption.

Williams (1971): $\widehat{MED} = 5$ for $\delta = 0$.

Table 3. Step-down 95% Lower Confidence Bounds for $\mu_i - \mu_1$ in Example 2.

$\mu_i - \mu_1$	DUNNETT	DR	MC
$\mu_7 - \mu_1$	0.22	0.39	0.84
$\mu_6 - \mu_1$	0.26	0.59	0.78
$\mu_5 - \mu_1$	-0.20	0.09	0.28

For illustration,

- If $\delta = 0.2$, $\widehat{MED} = 6$ by the DR method and the Dunnett method; $\widehat{MED} = 5$ by the MC method.

6 Simulation Studies

We considered $\alpha = 0.05, k = 6$ with 10000 repetitions to compare multiple contrast method (MC) with methods based on linear contrasts (denoted by LC), Helmert contrasts (HC), Reverse Helmert contrasts (RH), Williams' (1971) procedure (W) and the DR method (DR).

- Helmert contrasts (HC)and Reverse Helmert contrasts (RH) procedures should not be used in the MED problems in general.
- Monotone Case: All procedures control the error rate (FWER) well. The MC procedure is best in 16/24 cases and worst in only 3/24 cases regarding the probability of identifying the true MED and best in 15/24 cases and worst in 3/24 regarding the probability of identifying at least one effective doses among LC, DR, W, and MC.

- Nonmonotone Case: If the monotone assumption is mildly violated, the MC procedure may be used with caution (may or may not control the error rate). The DR method is the only method that always controls the error rate.

- The error rate (denoted as ERROR in Table 4) is the same as Hsu and Berger (1999) but is different from Tamhane et al. (1996) and Dunnett and Tamhane (1998). To illustrate, for $\mu = (0, 1, 2, 3, 7, 1)$ and $\delta = 1.5$, a method commits an error if it infers any dose i $(2 \leq i \leq 6)$ to be the MED but Tamhane et al. (1996) and Dunnett and Tamhane (1998) define the FWER as if a method infers doses 2 and 6 to be effective.

Table 4. Estimated FWER/ERROR and Probability of Identifying True MED Under Nonmonotone Configurations

Configuration	δ	MED	HC	RH	LC	DR	W	MC
(0,1,2,3,4,3)	2.5	4	.0000	.0090	.0140	.0176	.0353	.0203
		FWER	.0000	.0056	.0029	.0042	.0083	.0071
	2.0	4	.0000	.0292	.0445	.0395	.0739	.0551
		FWER	.0000	.0162	.0143	.0157	.0244	.0173
	1.5	3	.0001	.0313	.0393	.0318	.0478	.0382
		FWER	.0000	.0139	.0045	.0057	.0078	.0078
	1	3	.0005	.0646	.0916	.0666	.0937	.0787
		FWER	.0000	.0380	.0158	.0185	.0265	.0268
(0,0,0,0,5,4)	2.5	5	.0879	.0021	.1697	.2153	.3183	.4641
		FWER	.0000	.0000	.0000	.0001	.0000	.0000
	2.0	5	.1993	.0089	.3245	.3435	.4755	.6657
		FWER	.0001	.0002	.0001	.0006	.0002	.0000
	1.5	5	.3619	.0263	.5189	.4890	.6278	.8249
		FWER	.0005	.0013	.0010	.0029	.0024	.0010
	1.0	5	.5528	.0705	.7034	.6303	.7564	.9161
		FWER	.0030	.0045	.0045	.0079	.0069	.0057
(0,1,2,3,3,1.5)	2.5	ERROR	.0000	.0199	.0047	.0086	.0209	.0119
	2.0	ERROR	.0002	.0570	.0192	.0203	.0544	.0394
	1.5	ERROR	.0005	.1328	.0628	.0464	.1192	.1026
	1.0	3	.0000	.0616	.0355	.0211	.0661	.0588
		FWER	.0000	.0372	.0067	.0101	.0240	.0233
(0,0,0,0,5,2)	2.5	ERROR	.0011	.0035	.0880	.0203	.1093	.1755
	2.0	ERROR	.0049	.0123	.2061	.0464	.2050	.3421
	1.5	5	.0158	.0237	.3303	.0909	.3390	.5605
		FWER	.0001	.0013	.0010	.0014	.0023	.0010
	1.0	5	.0499	.0657	.5389	.1601	.4944	.7541
		FWER	.0003	.0045	.0043	.0046	.0069	.0056
(0,1,2,3,7,1)	2.5	ERROR	.0000	.0809	.0708	.0034	.2117	.1771
	2.0	ERROR	.0000	.1756	.1722	.0086	.3530	.3272
	1.5	ERROR	.0000	.3170	.3401	.0203	.5171	.5295
	1.0	ERROR	.0001	.4961	.5563	.0464	.6776	.7295

7 Conclusions

- When the dose-response is monotone, the MC method is superior to the DR method. If the monotone assumption is not satisfied, one should use the DR method if the error rate control is of primary concern.
- Utilizing the Kuhn-Tucker equivalence theorem is the key to the optimization problem and the proposed algorithm, which improves the method of Marcus and Peritz (1976) significantly.

THANKS!