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Nonparametric Procedures for Simultaneous Identification of the Minimum Effective Dose in Each of Several Groups

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ABSTRACT

This paper considers the extension of the dose finding problem in a one-way layout setting to the case of several groups, in which the main goal is to identify the minimum effective dose (MED) of each group simultaneously. We propose two nonparametric procedures using the respective pairwise- and Helmert-type two-sample Mann–Whitney statistics, which are applied in a step-down testing scheme for identifying the MED simultaneously. The computation for the associated p-value of the identified MED vector is discussed. One numerical example is given to illustrate the proposed procedures.

Key Words: Dose–response study; Multi-group problem; Simultaneous inference; Step-down testing.

Mathematics Subject Classification: 62G10; 62K10.

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1. INTRODUCTION

To assess the effect of a compound in a drug development study, a dose–response experiment is often conducted in which several increasing dose levels of the compound are compared with a zero-dose control. One primary goal in this case is to identify the lowest dose level that will cause some desirable effect over that of the zero-dose control, which is commonly referred to as the minimum effective dose (MED, Ruberg, 1989).

Many nonparametric procedures have been developed for the MED identification problem. In a one-way layout setting, Shirley (1977) and Chen and Wolfe (1993) proposed multiple testing procedures using the isotonic regression estimators of the Kruskal–Wallis (1952) average ranks for a monotonic and an umbrella pattern dose–response relationships, respectively. Furthermore, Williams (1986) suggested a more powerful modification of Shirley's procedure, while Chen (1993) modified Chen–Wolfe test for peak-known umbrella setting. It is noted that the modified Chen–Wolfe test is identical to Williams' test (1986) when treatment effects are monotonically ordered. Chen (1999) further proposed a step-down closed test using the Mann–Whitney (1947) statistics for identifying the MED under any general dose–response relationship. In a randomized block design with one observation per cell, House (1986) extended Williams' test (1986) using the isotonic regression estimators of the Friedman (1937) average ranks for a monotonic dose–response relationship. Lim and Wolfe (1997) considered the isotonic regression-based multiple tests under the assumption of an umbrella pattern dose–response relationship. Chen and Jan (2002) extended Chen's test (1999) to a randomized block design with one or more observations per cell.

However, in medical and biological researches, the experimenters often encounter the multi-group situation due to different gender, age, or other factors of interest. When this multi-group situation is involved in a drug development study, the MED of interest may very well vary in different groups. Therefore, the simultaneous identification of the MED in each of the groups under study become of great importance. In this paper, we develop two nonparametric step-down closed tests using two different sets of Mann–Whitney statistics for identifying the MED in the multi-group case. We show how to compute the corresponding p-value of the estimated MED vector, which is defined as the smallest level of significance at which the dose levels would be declared as the MED vector.

In Sec. 2, we propose two nonparametric step-down closed tests for identifying the MED simultaneously. The computation and approximation for obtaining the p-value and the critical value of the proposed procedures are discussed. One numerical example is given in Sec. 3 to illustrate the proposed methods.

2. THE PROPOSED PROCEDURES

Assume the existence of r groups. Denote a set of increasing dose levels by $0, 1, \ldots, c$, where 0 corresponds to the zero-dose level (or placebo control). Consider a multi-group setting and let X_{ijk} denote the kth observation on the jth dose level of the ith group, $i = 1, \ldots, r$, $j = 0, 1, \ldots, c$, and $k = 1, \ldots, n$. We assume that all

observations X_{ijk} are mutually independent, each with a continuous distribution function $F_{ij}(x) = F(x - \mu_{ij})$, here μ_{ij} represents the effect of the jth dose level in the ith group. The MED for the ith group is defined as $\text{MED}_i = min\{j : \mu_{ij} > \mu_{i0}\}$. This problem is often formulated through a sequence hypotheses testing problems as follows:

$$\begin{aligned} &H_{0ij_i} : \mu_{i0} = \mu_{i1} = \cdots = \mu_{ij_i} \quad \text{vs.} \\ &H_{1ij_i} : \mu_{i0} = \mu_{i1} = \cdots = \mu_{i,j_i-1} < \mu_{ij_i}, \quad j_i = 1, \ldots, c. \end{aligned} \tag{2.1}$$

If j_i^* is the smallest j_i for which H_{0ij_i} is rejected, then the j_i^*th dose is identified to be the MED for the ith group, that is, $\hat{\text{MED}}_i = j_i^*$. The use of subscript i in j_i is needed for the purpose of simultaneous identification.

In this paper we wish to identify the MED_i, $i = 1, \ldots, r$, simultaneously. Therefore we consider a family of hypotheses, defined through (2.1), by $H = \{(H_{01j_1}, \ldots, H_{0rj_r}) : 1 \le j_1, \ldots, j_r \le c\}$, where $(H_{01j_1}, \ldots, H_{0rj_r})$ represents the hypotheses $H_{01j_1}, \ldots, H_{0rj_r}$ are simultaneously tested. This family of hypotheses H is closed under intersection in the sense that $(H_{01j_1}, \ldots, H_{0rj_r}) \in H$ and $(H_{01j_1'}, \ldots, H_{0rj_r'}) \in H$ imply that $(H_{01j_1} \cap H_{01j_1'}, \ldots, H_{0rj_r} \cap H_{0rj_r'}) \in H$. Therefore, a α-level closed procedure (Tamhane et al., 1996) that includes separate α-level tests of individual $(H_{01j_1}, \ldots, H_{0rj_r})$, applied in a step-down manner can be employed in finding the MED_i simultaneously. Furthermore, the closed testing scheme strongly controls the familywise error rate (FWE), which is the probability that at least one true H_{0ij_i} is rejected. Therefore, we consider using two different sets of two-sample Mann–Whitney statistics in conjunction with the step-down closed testing scheme to identify the MED in each of the r groups simultaneously.

Let U_{isj} denote the two-sample Mann–Whitney statistic comparing the jth dose level with the sth dose level in the ith group, that is,

$$U_{isj} = \sum_{u=1}^{n} \sum_{v=1}^{n} \Phi(X_{isu}, X_{ijv}), \quad i = 1, \ldots, r, \ s = 0, 1, \ldots, j-1, \ j = 1, \ldots, c,$$

where $\Phi(a, b) = 1$ if $b > a$, $1/2$ if $b = a$, and 0 otherwise. Statistics of U_{isj} can be utilized for testing H_{0ij} against H_{1ij} in (2.1), $s = 0, 1, \ldots, j-1$, $j = 1, \ldots, c$. In this paper, we consider the following two sets of statistics.

(I) Pairwise-Type Statistics. The pairwise-type Mann–Whitney statistic comparing the jth dose level with the control is defined by $P_{ij} = U_{i0j}$, $i = 1, \ldots, r$, $j = 1, \ldots, c$. Let

$$NP_{ij} = [P_{ij} - E(P_{ij})] \Big/ \sqrt{Var(P_{ij})}, \quad i = 1, \ldots, r, \ j = 1, \ldots, c, \tag{2.2}$$

where $E(P_{ij}) = n^2/2$ and $Var(P_{ij}) = n^2(N+1)/12$, with $N = 2n$, are the null (H_{0ij}) mean and variance of P_{ij}, respectively. If ties occur among the N observations, then NP_{ij} is modified by replacing the factor $(N+1)$ in $Var(P_{ij})$ with $(N+1) - \sum_{a-1}^{g}(t_a^3 - t_a)/[N(N-1)]$, where g is the number of tied groups and t_a is the size of tied group a. Moreover, because NP_{ij} has limiting standard normal distribution under H_{0ij} and

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the correlation between NP_{ij} and $NP_{ij'}$, $j \neq j'$, approaches 1/2, the results of Theorem A13 in Hettmansperger (1984) imply that, under the null hypothesis H_{0ic}, $(NP_{i1}, \ldots, NP_{ic})$ has an asymptotic c-variate normal distribution with zero mean vector and correlation matrix $A = (\rho_{jj'})$, $\rho jj' = 1$ if $j = j'$ and 1/2 otherwise. Since observations in different groups are independent, so, under H_{0ic}, $i = 1, \ldots, r$, $(NP_{11}, \ldots, NP_{1c}, \ldots, NP_{r1}, \ldots, NP_{rc})$ has an asymptotic $r \times c$-variate normal distribution with zero mean vector and correlation matrix $R = \text{diag}(A, \ldots, A)$.

(II) Helmert-Type Statistics. The Helmert-type two-sample Mann–Whitney statistic comparing the jth dose level with the combined all lower dose levels (including the control) is defined by $H_{ij} = \sum_{s=0}^{j-1} U_{isj}$, $i = 1, \ldots, r$, $j = 1, \ldots, c$. Define

$$NH_{ij} = [H_{ij} - E(H_{ij})] \Big/ \sqrt{Var(H_{ij})}, \quad i = 1, \ldots, r, \ j = 1, \ldots, c, \tag{2.3}$$

where $E(H_{ij}) = nN_{j-1}/2$ and $Var(H_{ij}) = nN_{j-1}(N_j + 1)/12$, with $N_j = n(j+1)$, are the respective null (H_{0ij}) mean and variance of statistic H_{ij}. Note that the modification of NH_{ij} for ties is the same as discussed in (I) except for N is N_j. Since NH_{ij} has limiting null standard normal distribution and NH_{ij}, $j = 1, \ldots, c$, are uncorrelated, so, under the null hypotheses H_{0ic}, $i = 1, \ldots, r$, $(NH_{11}, \ldots, NH_{1c}, \ldots, NH_{r1}, \ldots, NH_{rc})$ has an asymptotic $r \times c$-variate normal distribution with zero mean vector and identity correlation matrix.

Now we describe the extension of the step-down closed testing scheme for dose finding to a multi-group situation in terms of simultaneous hypotheses $(H_{0ij_i}$, $i = 1, \ldots, r$, $1 \leq j_1, \ldots, j_r \leq c)$ testing. Let the test statistics be Z_{ij}, $i = 1, \ldots, r$, $j = 1, \ldots, c$, which are assumed to be asymptotic normal with zero mean vector and correlation matrix R. (Here Z_{ij} refers to NP_{ij} if $R = \text{diag}(A, \ldots, A)$ and to NH_{ij} if R is identity matrix.) Denote $Z_{(r\times c)} = max\{Z_{ij} : 1 \leq i \leq r, \ 1 \leq j \leq c\}$. Let $z_{(r\times c)}$ and $Z[\alpha, r \times c, R]$ be the observed value and the upper αth percentile of $Z_{(r\times c)}$, respectively. At the first step, let c_{1i} be the number of doses to be tested in the ith group, $i = 1, \ldots, r$, and let $k_1 = \sum_{i=1}^{r} c_{1i}$ be the total number of hypotheses to be tested. Find $z_{(k_1)}$ and suppose it occurs at the $d(k_1)$th dose level of the $g(k_1)$th group. If $z_{(k_1)} \geq Z[\alpha, k_1, R]$, then reject $H_{0g(k_1)j}$ for all $j = d(k_1), \ldots, c_{1g(k_1)}$, that is, excluding the dose levels $d(k_1), \ldots, c_{1g(k_1)}$ of group $g(k_1)$ from further study, and go to the second step with redefined group sizes c_{2i} and total size k_2; otherwise, stop testing and accept all null hypotheses. In general, at the lth step with k_l total number of hypotheses remained to be tested, if $z_{(k_l)}$ is significant and occurs at the $d(k_l)$th dose level of the $g(k_l)$ group, then reject $H_{0g(k_l)j}$ for all $j = d(k_l), \ldots, c_{lg(k_l)}$; otherwise, stop testing. When the testing stops, say, at the mth step, then estimate the MED_i as $c_{mi} + 1$, that is, $\hat{\text{MED}}_i = c_{mi} + 1$, $i = 1, \ldots, r$.

Next we show how to obtain the associated p-value of the identified MED vector, which is the smallest significance level at which the dose levels would be simultaneously declared as the MED in each of the groups (Wright, 1992). In general, at the lth step for testing the k_l null hypotheses, first compute the null probabilities,

$$p'(k_l) = P(Z_{(k_l)} \geq z_{(k_l)}) = P\Big(\max_{1\leq i\leq r,\ 1\leq j\leq c_{li}} Z_{ij} \geq z_{(k_l)} \Big), \ l = 1, 2, \ldots \tag{2.4}$$

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The adjusted p-value is then defined as

$$p(k_l) = max\{p'(k_l), \ldots, p'(k_1)\}, \quad l = 1, 2, \ldots \tag{2.5}$$

Then, the MEDs can be identified at the significance level α from the adjusted p-values. That is, at the lth step, if $p(k_l) \leq \alpha$, then reject $H_{0g(k_l)j}$ for all $j = d(k_l), \ldots, c_{lg(k_l)}$. If at the mth step that $p(k_m) > \alpha$, then the testing stops, and the identified MED_i is $c_{mi} + 1$, $i = 1, \ldots, r$, and the p-value of this conclusion is $p(k_{m-1})$.

Finally, in order to implement the step-down procedures with the proposed statistics NP_{ij} and NH_{ij}, we show how to find the critical constants $Z[\alpha, k_l, R]$ and probabilities $p'(k_l)$. When statistics NH_{ij} are used, the correlation matrix R is an identity matrix, so $Z[\alpha, k_l, R] = Z[\alpha, k_l, \rho = 0]$ can be found in Table 6 of Hochberg and Tamhane (1987), and $p'(k_l)$ is approximated by $1 - [\Phi(z_{(k_l)})]^{k_l}$, where $\Phi(\cdot)$ is the distribution function of a standard normal variable. However, if statistics NP_{ij} are used, then the correlation matrix R is not of product correlation structure (Hochberg and Tamhane, 1987), thus $Z[\alpha, k_l, R]$ is difficult to compute. In this paper, we use the less conservative method of approximation suggested in Dunnett and Tamhane (1991) by replacing the off-diagonal entries in R with their arithmetic average $\bar{\rho}_l$, therefore $Z[\alpha, k_l, R] \approx Z[\alpha, k_l, \rho = \bar{\rho}_l]$. Then the critical constants $Z[\alpha, k_l, \rho = \bar{\rho}_l]$ and probabilities $p'(k_l)$ can be easily obtained, respectively, through computing the PROBMC function in SAS via $Z[\alpha, k_l, \rho = \bar{\rho}_l] = \text{PROBMC(DUNNETT1, } \cdot \text{, } 1 - \alpha, \cdot, k_l, \lambda_1, \ldots, \lambda_{k_l})$, and $p'(k_l) = \text{PROBMC(DUNNETT1, } z_{(k_l)}, \cdot, \cdot, k_l, \lambda_1, \ldots, \lambda_{k_l})$, where $\lambda_t = (\bar{\rho}_l)^{1/2}$, $t = 1, \ldots, k_l$. These values $Z[\alpha, k_l, \rho = \bar{\rho}_l]$ can also be found in Table 4 of Hochberg and Tamhane (1987) with appropriate interpolations. Moreover, because of the changing correlation matrix R at each step, $\bar{\rho}_l$ is therefore changing. For the sake of convenience and simplicity, one may use $\bar{\rho}_1$ from the first step instead of the changing $\bar{\rho}_l$ at each step.

3. AN EXAMPLE

We consider a dose–response study to compare three dose levels with a zero-dose level in a balanced three-group layout. We use the data set in Table 1, in which each group by dose cell contains five observations generated from $N(\mu_{ij}, 5)$ distribution, where the value of μ_{ij} used is given in the parenthesis of Table 1. There is no evidence that the cell variances are heterogeneous (Levene's F-test $= 1.0111$, and p-value $= 0.4512$). Moreover, the group $\times$ dose interaction is significant (p-value $= 0.0001$). We wish to identify the MED simultaneously in each of the three groups at $\alpha = 0.05$ level.

The values of the Mann–Whitney counts, their corresponding means and variances, and the proposed statistics computed using formulas (2.2) and (2.3) are reported in Table 2. The approximations of the critical constants for procedures NP and NH are presented in Table 3, which are computed by using the PROBMC function from SAS (Here $\rho = \bar{\rho}_1 = 0.125$ is used for NP test while a small value 0.00011 is used for NH test).

Table 1. Generated data.

	Dose			
Group	0	1	2	3
1	1.28	6.11	8.97	4.60
	2.96	6.21	6.36	2.68
	1.41	4.94	6.52	2.62
	2.04	−0.18	8.66	3.18
	1.61	5.67	5.28	2.33
	(1.00)	(5.00)	(7.00)	(4.00)
2	2.82	10.99	4.89	4.77
	6.40	8.58	7.23	0.82
	0.06	13.33	6.30	6.50
	1.36	7.58	3.41	6.97
	−1.34	6.27	5.04	5.02
	(2.00)	(8.00)	(5.00)	(6.00)
3	1.59	6.29	3.10	9.23
	1.22	7.06	11.42	6.42
	2.58	4.60	8.11	13.23
	5.39	4.33	6.70	12.25
	0.53	2.40	5.34	9.83
	(2.00)	(5.00)	(7.00)	(9.00)

The numbers given in parentheses are the group by dose cell means μ_{ij}, $i = 1, 2, 3$, $j = 0, 1, 2, 3$.

First we demonstrate the use of the *NP* method. At the first step, $k_1 = 9$, where $c_{11} = c_{12} = c_{13} = 3$, and $z_{(9)} = z_{12} = 2.611$ (p-value $= p(9) = p'(9) \approx 0.0388$). Since $z_{(9)} > Z[0.05, 9, \rho] = 2.519$, we go to the second step with $k_2 = 7$, where $c_{21} = 1$, $c_{22} = c_{23} = 3$. Note that $z_{(7)} = z_{33} = 2.611$ ($p'(7) \approx 0.0305$, p-value $= p(7) \approx 0.0388$) and $z_{(7)} > Z[0.05, 7, \rho] = 2.431$, so we go to the third step with $k_3 = 6$, where $c_{31} = 1$, $c_{32} = 3$, and $c_{33} = 2$. Now $z_{(6)} = z_{21} = 2.402$ ($p'(6) \approx 0.0467$, p-value $= p(6) \approx 0.0467$)

Table 2. Calculations of the proposed statistics.

Group	Dose	P	$E(P)$	$Var(P)$	NP	H	$E(H)$	$Var(H)$	NH
1	1	20	12.5	22.92	1.567	20	12.5	22.92	1.567
	2	25	12.5	22.92	2.611	47	25.0	66.67	2.694
	3	22	12.5	22.92	1.984	27	37.5	131.25	−0.917
2	1	24	12.5	22.92	2.402	24	12.5	22.92	2.402
	2	21	12.5	22.92	1.776	23	25.0	66.67	−0.245
	3	20	12.5	22.92	1.567	33	37.5	131.25	−0.393
3	1	21	12.5	22.92	1.776	21	12.5	22.92	1.776
	2	23	12.5	22.92	2.193	41	25.0	66.67	1.960
	3	25	12.5	22.92	2.611	69	37.5	131.25	1.750

Table 3. Critical constants $Z[0.05, k, \rho]$.

	k								
Procedure	1	2	3	4	5	6	7	8	9
NP	1.645	1.950	2.114	2.226	2.309	2.376	2.431	2.478	2.519
NH	1.645	1.955	2.121	2.234	2.319	2.386	2.442	2.490	2.531

and $z_{(6)} > Z[0.05, 6, \rho] = 2.376$, hence we go to the fourth step with $k_4 = 3$, where $c_{41} = 1$, $c_{42} = 0$, and $c_{43} = 2$. Since $z_{(3)} = z_{32} = 2.193$ ($p'(3) \approx 0.0412$, p-value $= p(3) \approx 0.0467$) is greater than $Z[0.05, 3, \rho] = 2.114$, therefore we continue to the next step with $k_5 = 2$, where now $c_{51} = 1$, $c_{52} = 0$, and $c_{53} = 1$. Note that $z_{(2)} = z_{31} = 1.776$ ($p'(2) \approx 0.0733$, p-value $= p(2) \approx 0.0733$) is less than $Z[0.05, 2, \rho] = 1.950$, so we stop testing and estimate the MED_i as $c_{5i} + 1$, $i = 1, 2$, and 3. Therefore, at the $\alpha = 0.05$ level, we simultaneously estimate that the MED for group 1 is the second dose level, for group 2 is the first dose level, and for group 3 is the second dose level, where the corresponding p-value of this conclusion is $p(3) \approx 0.0467$.

Following the similar arguments as above, the testing based on the *NH* procedure stops at the fourth step, where $c_{41} = 1$, $c_{42} = 0$, and $c_{43} = 2$. Hence we simultaneously estimate that the MED for groups 1, 2 and 3 are the second dose level, the first dose level, and the third dose level, respectively, where the corresponding p-value of the conclusion is $p(6) \approx 0.0479$. Table 4 summarizes the testing results of the proposed procedures *NP* and *NH*.

In this example, both *NP* and *NH* tests identify the same dose levels as the MED in both groups 1 and 2. While in group 3, *NP* test detects lower dose level as the MED than does the *NH* test.

Before concluding this example, we discuss the effect of the approximation used for critical constant in the present work. In procedure *NP*, we use $\rho = \bar{\rho}_l = 0.125$ at each step and the critical constants in the successive five steps are 2.519, 2.431, 2.376, 2.114, and 1.950, respectively. If, instead, $\bar{\rho}_l$ is recomputed at each step l, then the respective values are 0.125, 0.143, 0.133, 0.167, and 0, where the corresponding critical constants are 2.519, 2.429, 2.375, 2.111 and 1.955. In procedure *NH*,

Table 4. Testing results of the proposed procedures.

Procedure	Step (l)	k_l	$z_{(k_l)}$	$(g(k_l), d(k_l))$	$Z[0.05, k, \rho]$	$p'(k_l)$	$p(k_l)$
NP	1	9	2.611	(1, 2)	2.519	0.0388	0.0388
	2	7	2.611	(3, 3)	2.431	0.0305	0.0388
	3	6	2.402	(2, 1)	2.376	0.0467	0.0467
	4	3	2.193	(3, 2)	2.114	0.0412	0.0467
	5	2	1.776	(3, 1)	1.950	0.0733	0.0733
NH	1	9	2.750	(3, 3)	2.531	0.0265	0.0265
	2	8	2.694	(1, 2)	2.490	0.0279	0.0279
	3	6	2.402	(2, 1)	2.386	0.0479	0.0479
	4	3	1.960	(3, 2)	2.121	0.0731	0.0731

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$\rho = 0.00011$ is used and the critical constants are 2.531, 2.490, 2.386 and 2.121 in the four steps. While the actual critical values, taken from Table 6 of Hochberg and Tamhane (1987), are 2.53, 2.49, 2.39 and 2.12. In each case, we see that the approximation gives quite accurate results. Therefore, this paper suggests the use of the approximation methods, since they not only provide nice and easy results but also allow one to easily obtain the probabilities $p'(k_l)$ and the associated p-value by using the PROBMC function in SAS.

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