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多變量無母數檢定於臨床實驗之中間時期分析

Multivariate Nonparametric Tests for Interim Analysis in Clinical Trial

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中文摘要

Mann-Whitney-Wilcoxon 檢定是一種廣泛被使用在檢定有關兩個獨立樣本來自兩個母體位置不同的檢定方法。在 1984 年 Hettmansperger 曾討論有關 Mann-Whitney-Wilcoxon 的多變量檢定方法，我們將使用此多變量檢定方法發展出一個中間時期分析之多變量檢定方法，同時我們也發展出另一種分析方法，即應用標準化之 Mann-Whitney-Wilcoxon 多變量檢定統計量。對於此標準化之多變量檢定統計量的分母部分將使用 Hettmansperger 之估計值與拔靴帶估計值。

關鍵詞：中間時期分析、臨床實驗、Mann-Whitney-Wilcoxon 檢定、一致性估計量、自重抽法。

Abstract

The Mann-Whitney-Wilcoxon test is a very widely used procedure for testing the null hypothesis that two independent samples have been drawn from the population which are equal and is sensitive to different in location. A multivariate version of the Mann-Whitney-Wilcoxon test was proposed by Hettmansperger (1984). We use these multivariate methods to develop an interim analysis for this multivariate test. Also, we propose to develop an alternative analysis by employing the standardized multivariate version of Mann-Whitney-Wilcoxon test statistics. Two approaches for the unknown denominator of the standardized multivariate test statistics are employed by the Hettmasperger's estimate and bootstrap estimate.

Keywords: Interim analysis, clinical trial, multivariate version of Mann-Whitney-Wilcoxon, consistent estimate , bootstrap method.

1. Introduction

The procedure for testing the null hypothesis of equal population location parameters was proposed by Mann, Whitney and Wilcoxon. Hettmansperger (1984) considered this test in multivariate case. We would like to develop an interim analysis for this multivariate test.

Suppose that we have two independent random samples $\bar{X}'=(X_{1i},X_{2i})$ and $\bar{Y}'=(Y_{1j},Y_{2j})$ for $i=1,\cdots,n$; $j=1,\cdots,m$ from the bivariate distribution with cdfs $F(v_1,v_2)$ and $F(v_1-\Delta_1,v_2-\Delta_2)$, respectively. Let the parameter $\bar{\Delta}'=(\Delta_1,\Delta_2)$ represent the shift from the $\bar{X}$ distribution to the $\bar{Y}$ distribution for the two components. We would like to employ the multivariate version of Mann-Whitney-Wilcoxon test to conduct one interim analysis to test $H_0:\bar{\Delta}=\bar{0}$ versus $H_1:\bar{\Delta}\neq\bar{0}$ at time T_1 and continue following subjects until T_2 if H_0 is not rejected at time

T_1. We will assume that the joint distribution of $\bar{X}' = (X_{11}, X_{12}, X_{21}, X_{22})$ and $\bar{Y}' = (Y_{11}, Y_{12}, Y_{21}, Y_{22})$ have the covariance matrix $\Sigma = \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{bmatrix}$, where $\Sigma_{11} = \Sigma_{22} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{bmatrix}$, $\Sigma_{12} = \Sigma_{21} = \begin{bmatrix} \sigma_3 & \sigma_4 \\ \sigma_4 & \sigma_3 \end{bmatrix}$, $\sigma_4 < \sigma_3$ and $\sigma_4 < \sigma_{12}$. Note that (X_{p1i}, X_{p2i}) and (Y_{p1i}, Y_{p2i}) are independent bivariate samples observed at time T_p, $i = 1, \cdots, n$; $j = 1, \cdots, m$ and $p = 1, 2$. Let $\bar{U}' = (\bar{U}_1, \bar{U}_2) = (U_{11}, U_{12}, U_{21}, U_{22})$ denote the multivariate version of the Mann-Whitney-Wilcoxon test statistic, where $\bar{U}_1' = (U_{11}, U_{12})$, $\bar{U}_2' = (U_{21}, U_{22})$, $U_{1q} = \sum_{j=1}^{m} (\frac{R_{1qj}}{N+1} - \frac{1}{2})$ is computed at time T_1 and $U_{2q} = \sum_{j=1}^{m} (\frac{R_{2qj}}{N+1} - \frac{1}{2})$ is computed at time T_2 and R_{pqj} is the rank of Y_{pqj} in the combined sample of the q^{th} component at time T_p, $q = 1, 2$; $p = 1, 2$; $N = n + m$. Under H_0, it can be shown that $\bar{U}$ converges in distribution to a multivariate normal with zero means and covariance matrix, say Σ^*. Since Σ^* is unknown, Hettmansperger proposed a consistent estimate of Σ^*, $\Sigma^* = \begin{bmatrix} \hat{\Sigma}_{11}^* & \hat{\Sigma}_{12}^* \\ \hat{\Sigma}_{21}^* & \hat{\Sigma}_{22}^* \end{bmatrix}$, where $\hat{\Sigma}_{11}^* = \begin{bmatrix} \hat{\sigma}_1^{2(1)} & \hat{\sigma}_{12}^{(1)} \\ \hat{\sigma}_{12}^{(1)} & \hat{\sigma}_2^{2(1)} \end{bmatrix}$ is estimated by the ranks at time T_1 and $\hat{\Sigma}_{22}^* = \begin{bmatrix} \hat{\sigma}_1^{2(2)} & \hat{\sigma}_{12}^{(2)} \\ \hat{\sigma}_{12}^{(2)} & \hat{\sigma}_2^{2(2)} \end{bmatrix}$ is estimated by the ranks at time T_2. Define $U_1^* = \frac{1}{N} \bar{U}_1' \hat{\Sigma}_{11}^{*-1} \bar{U}_1$ and $U_2^* = \frac{1}{N} \bar{U}_2' \hat{\Sigma}_{22}^{*-1} \bar{U}_2$. To conduct the multivariate test, we have to find out the joint distribution. Unfortunately, the exact distribution is unknown, but the joint limiting distribution can be proved to follow Jensen's type bivariate distribution (1970).

A class of bivariate chi square distribution is relevant to some classical problems in statistical inference, such as the joint distribution of dependent quadratic forms which arise in connection with two stage and interim analyses. Let $\bar{V}_j' = (V_{1j}, V_{2j})$ be independent random vectors distributed as $N_2(\bar{0}, \Sigma)$, where $\Sigma = \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix}$. The distribution of $\bar{V}$ has been addressed by Hewett and Tsutakawa (1972), Hewett and Supurrier (1979). Chin and Hewett (1988). Gunst and Webser (1973) discussed some distributional properties and applications of the baivariate chi square distribution. Jensen (1970) generalized the case of the bivariate chi square distribution when $\Sigma = \begin{bmatrix} I & S' \\ S & I \end{bmatrix}$ is a nonsingular matrix. The previous bivaraite chi square distribution is a special case of the Jensen's type bivaraite chi square distribution.

2. One Interim Analysis

The testing procedure for one interim analysis is as follows : H_0 is rejected at time T_1 if $U_1^* \geq b_1$; if $U_1^* < b_1$, continue following the subjects until time T_2. At time T_2, if $U_2^* \geq b_2$, reject H_0; if $U_2^* < b_2$, do not reject H_0. We determine the α, α_1, α_2 such that $\alpha = \alpha_1 + \alpha_2$ in advance. The values of b_1 and b_2 are obtained by solving the equations: $\alpha_1 = P(U_1^* \geq b_1)$, $\alpha_2 = P\{(U_1^* < b_1) \cap (U_2^* \geq b_2)\}$, where the probabilities are computed under H_0. Thus, to solve these equations, we have to know the joint distribution of U_1^* and U_2^* under H_0. The exact joint distribution is unknown, but we will show that the joint limiting distribution of $(U_1^*, U_2^*)'$ follows the Jensen's type bivariate chi square distribution.

Theorem 1: Let $\bar{U}' = (\bar{U}_1, \bar{U}_2)$, where $\bar{U}_1' = (U_{11}, U_{12})$, $\bar{U}_2' = (U_{21}, U_{22})$, are the multivariate version of the Mann-Whitney-Wilcoxon test statistics at two time periods. Suppose that $n, m \to \infty$, $\frac{n}{N} \to \lambda$, $0 < \lambda < 1$ and under H_0, $\frac{1}{\sqrt{N}}\bar{U}' \xrightarrow{D} N_4(\vec{0}, \Sigma)$, where Σ is positive definite matrix and Σ^* is Hettmansperger's consistent estimate of Σ. Then $\frac{1}{N}(\bar{U}_1'\hat{\Sigma}_{11}^{-1}\bar{U}_1, \bar{U}_2'\hat{\Sigma}_{22}^{-1}\bar{U}_2) \xrightarrow{D}$ Jensen's type bivariate chi square distribution.

By the spectral decomposition, there exists the orthogonal matrices $P = (\bar{e}_1, \bar{e}_2)$ and $Q = (\bar{f}_1, \bar{f}_2)$, where $\bar{e}_1$ and $\bar{e}_2$ are the normalized eigenvectors of $\Sigma_{11}^{-1/2}\Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21}\Sigma_{11}^{-1/2}$ and $\bar{f}_1$ and $\bar{f}_2$ are the normalized eigenvectors of $\Sigma_{22}^{-1/2}\Sigma_{21}\Sigma_{11}^{-1}\Sigma_{12}\Sigma_{22}^{-1/2}$. Define $\bar{U}^* = \frac{1}{\sqrt{N}}A\bar{U}$, where $A = Diag(P'\Sigma_{11}^{-1/2}, Q'\Sigma_{22}^{-1/2})$. It can be shown that the $\bar{U}^* = \frac{1}{\sqrt{N}}(\bar{e}_1{}'\Sigma_{11}^{-1/2}U_{11}, \bar{e}_2{}'\Sigma_{11}^{-1/2}U_{12}, \bar{f}_1{}'\Sigma_{22}^{-1/2}U_{21}, \bar{f}_2{}'\Sigma_{22}^{-1/2}U_{22})'$. Also, $\bar{U}^* \xrightarrow{D} N_4(\vec{0}, \Sigma^*)$, where $\Sigma^* = \begin{bmatrix} I & \Sigma_{12}^* \\ \Sigma_{21}^* & I \end{bmatrix}$, $\Sigma_{12}^* = \Sigma_{21}^* = \begin{bmatrix} \rho_1 & 0 \\ 0 & \rho_2 \end{bmatrix}$. where ρ_1 and ρ_2 are the square roots of the eigenvalues of $\Sigma_{11}^{-1/2}\Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21}\Sigma_{11}^{-1/2}$ $\Sigma_{22}^{-1/2}\Sigma_{21}\Sigma_{11}^{-1}\Sigma_{12}\Sigma_{22}^{-1/2}$. Since $\frac{1}{N}(\bar{U}_1'\Sigma_{11}^{-1}\bar{U}_1, \bar{U}_2'\Sigma_{22}^{-1}\bar{U}_2) = (U_{11}^* + U_{12}^*, U_{21}^* + U_{22}^*)'$, then $\frac{1}{N}(\bar{U}_1'\hat{\Sigma}_{11}^{-1}\bar{U}_1, \bar{U}_2'\hat{\Sigma}_{22}^{-1}\bar{U}_2) \xrightarrow{D}$ Jensen's type bivariate chi square distribution. The proof is completed.

3. Alternative Analysis

Instead of using quadratic form of test statistics U_1^* and U_2^*, we propose to develop an alternative interim analysis for testing $H_0: \vec{\Delta} = \vec{0}$ versus $H_1: \vec{\Delta} \neq \vec{0}$. Let $\vec{V}' = (V_{11}, V_{12}, V_{21}, V_{22})$ be the standardized multivariate version of Mann-Whitney-Wilcoxon test statistics, where $V_{ij} = \frac{U_{ij}}{\sqrt{\hat{\sigma}_j^{2(i)}}}$ and $\sigma_j^{2(i)}$ is the Hettmansperger's estimated variance of the j^{th} variable at time T_i for $i\ j = 1, 2$. H_0 is rejected at time T_1 if $V_{11} \geq c_1$ or $V_{12} \geq c_1$. Otherwise we continue the test until time T_2. At time T_2, if $V_{21} \geq c_2$ or $V_{22} \geq c_2$, reject H_0; if $V_{21} < c_2$ and $V_{22} < c_2$, do not reject H_0.

Theorem 2: If $\vec{V}' = (V_{11}, V_{12}, V_{21}, V_{22})$ is the standardized multivariate version of Mann-Whitney-Wilcoxon test statistics for testing $H_0: \vec{\Delta} = \vec{0}$, then $\vec{V}' = (V_{11}, V_{12}, V_{21}, V_{22})$ converges in distribution to a multivariate normal with zero means and covariance matrix, say $\Sigma_{(\vec{V})}$.

The proof is quite straightforward. According to Hettmansperger's result, we can obtain that $\bar{U}' = (U_{11}, U_{12}, U_{21}, U_{22})$ is converges to the multivariate normal. Then the limiting distribution of the standardized random vector $\bar{V}$ with the consistent estimator of the variance is also a multivariate normal.

Under H_0, the probabilities of α_1, and α_2 are as follows:

$$\begin{aligned}\alpha_1 &= P(\{V_{11} \geq c_1\} \cup \{V_{12} \geq c_1\}) \\ &= P(\{V_{11} \geq c_1\}) + P(\{V_{12} \geq c_1\}) \\ &\quad - P(\{V_{11} \geq c_1\}) \cap \{V_{12} \geq c_1\})\end{aligned}$$

$$\begin{aligned}\alpha_2 &= P[(\{V_{11} < c_1\} \cap \{V_{12} < c_1\}) \cap \\ &\quad (\{V_{21} \geq c_2\} \cup \{V_{22} \geq c_2\})] \\ &= P[(\{V_{11} < c_1\} \cap \{V_{12} < c_1\} \cap (\{V_{21} \geq c_2\}) \cup\end{aligned}$$

$$(\{V_{11} < c_1\} \cap \{V_{12} < c_1\}) \cap \{V_{22} \ge c_2\})]$$
$$= P[(\{V_{11} < c_1\} \cap \{V_{12} < c_1\} \cap (\{V_{21} \ge c_2\})] +$$
$$P[(\{V_{11} < c_1\} \cap \{V_{12} < c_1\}) \cap \{V_{22} \ge c_2\})] -$$
$$P(\{V_{11} < c_1\} \cap \{V_{12} < c_1\} \cap (\{V_{21} \ge c_2\} \cap$$
$$\{V_{22} \ge c_2\})$$

Since the joint limiting distribution of V_{11} and V_{12} is bivariate normal, we may use IMSL subroutines ANORDF. BNRDF and ZBREN to solve the critical value c_1. We use the fact that the joint limiting distribution of both $(V_{11}, V_{12}, V_{21})'$ and $(V_{11}, V_{12}, V_{22})'$ are trivariate normal distributions and $(V_{11}, V_{12}, V_{21}, V_{22})'$ has a limiting multivariate normal distribution and IMSL subroutines MULNOA and ZBREN to solve the value c_2. We find that the results for the estimated variance in the denominator of the test statistics using either by the Hettmansperger consistent estimate or by the bootstrap estimate are very similar.

4. Evaluation of Project

The main parts of this project has been completed. We have derived the joint limiting distribution of the proposed test for one interim analysis. The theoretical part is done, but the application has not completed yet due to the complicated form of the density. The possible future research is to compute the probabilities of Jensen's bivariate chi square distribution. For the second method, we also obtain the joint limiting distribution and find the behavior of limiting distribution is really close to multivariate normal. The other possible future research is to show that the consistency of the bootstrap estimate.

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