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INCORPORATING HISTORICAL INFORMATION IN TESTING FOR A TREND IN POISSON MEANS

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Abstract. An exact conditional test is developed for testing a trend in Poisson means when the historical control information is incorporated into the concurrent control data. An asymptotic conditional test is also developed as an alternative to the Tarone test. Asymptotic gains by the incorporation of the historical information is evaluated.

Key words and phrases: Poisson trend test, negative multinomial distribution, exact conditional test, asymptotic normality, asymptotic efficiency.

1. Introduction

To fix an idea consider the Ames Salmonella/microsome test (Ames *et al.* (1975)) which currently holds a preeminent position among the various tests available to genetic toxicologists for investigation of a chemical's mutagenicity. Table 1 summarizes the data from an experiment in which Poisson distributed random variables, numbers of revertants on the plates, are observed under each of several experimental dose level d_j such that $0=d_0<d_1<\cdots<d_r$. For each d_j, let n_j denote the number of observations and let x_{jk} denote the observed counts, $k=1, 2,\ldots, n_j$. The problem to be considered is to test for increases or decreases in the means, λ_j, associated with the increasing values, d_j.

Now consider the situation in which N previous experiments, similar to the experiment which gave rise to the data in Table 1, have been performed. Suppose that M_l control plates have been studied in the l-th experiment, and

Table 1. Summary of data from a microbial mutagenesis assay.

Dose level	$d_0=0$	d_1	$\ldots$	d_r
Replicate counts	$x_{01},\ldots, x_{0n_0}$	$x_{11},\ldots, x_{1n_1}$	$\ldots$	$x_{r1},\ldots, x_{rn_r}$
Total	$x_{0\cdot}$	$x_{1\cdot}$	$\ldots$	$x_{r\cdot}$

that Y_l revertants have been observed on these M_l plates, $l=1, 2, \ldots, N$. Assuming that Y_l for a given experiment follows a Poisson distribution with mean $M_l\lambda$, but that the spontaneous revertant rate varies from experiment to experiment according to a gamma distribution, Tarone (1982) developed an asymptotic test for incorporating the historical control data for the analysis of the concurrent data.

When small number of observations per group, n_j, is used and/or the mean of Poisson distribution is small, errors resulting from the use of the asymptotic test can sometimes be substantial. We develop in this paper the exact conditional test for positive dose-response, following the formulation by Tarone (1982). We also develop an asymptotic conditional test and assess the gain in incorporating historical controls.

2. Exact conditional test

We assume for $j=0, 1, \ldots, r$ that at experimental dose d_j, there are n_j random variables X_{jk}, $k=1, 2, \ldots, n_j$, which are distributed independently according to a Poisson distribution with mean λ_j. We formulate the problem of testing for a trend in the mean by assuming that

$$\lambda_j = H(a + \xi d_j) ,$$

where H is a twice differentiable and monotone function over $(-\infty, \infty)$. The statistical test of hypothesis of an increasing trend in the mean is given by

$$H_0\colon \xi = 0 \quad \text{vs.} \quad H_1\colon \xi > 0 .$$

Following the development of Tarone (1982), we assume that the spontaneous rate varies from experiment to experiment according to a gamma distribution. This enables us to assume that λ_0 (denoted by λ) is a random variable following a gamma distribution with density

$$g(\lambda) = \lambda^{\rho-1} \exp(-\rho\lambda/\mu)/\{(\mu/\rho)^{\rho}\Gamma(\rho)\} , \quad 0 < \lambda < \infty ,$$

with μ, ρ assumed known which are in fact estimated from historical control data. We defined $\lambda = H(a)$ so that a is distributed as

$$f(a) = H(a)^{\rho-1} \exp(-\rho H(a)/\mu)H'(a)/\{(\mu/\rho)^{\rho}\Gamma(\rho)\} , \quad -\infty < a < \infty .$$

Since $\{X_{jk}\}$ $k=1, 2, \ldots, n_j, j=0, 1, \ldots, r$ are conditionally independent and X_{jk} is distributed according to Poisson distribution with mean λ_j when a is given, the joint distribution of a, $\underline{X}_0$, and $\underline{\underline{X}}=(\underline{X}_1, \ldots, \underline{X}_r)$, where $\underline{X}_j=(X_{j1}, \ldots, X_{jn_j})$, is given by

$$f_\xi(a, \underline{x}_0, \underline{\underline{x}}) = \prod_{j=0}^{r} \frac{1}{\prod_{k=1}^{n_j} x_{jk}!} \exp(-n_j H(a + \xi d_j)) \{H(a + \xi d_j)\}^{x_j\cdot} f(a) ,$$

where $x_{j\cdot} = \sum_{k=1}^{n_j} x_{jk}$ $(j=0, 1,\ldots, r)$. Thus the marginal distribution of $(\underline{X}_0, \underline{\underline{X}})$ is

$$f_\xi(\underline{x}_0, \underline{\underline{x}}) = \int_{-\infty}^{\infty} f_\xi(a, \underline{x}_0, \underline{\underline{x}}) da .$$

In particular, the marginal distribution of $\underline{X}_0$ is

$$f_0(\underline{x}_0) = \frac{1}{\prod_{k=1}^{n_0} x_{0k}!} \frac{\Gamma(x_{0\cdot} + \rho)}{\Gamma(\rho)} \frac{(\rho/\mu)^\rho}{(n_0 + \rho/\mu)^{x_{0\cdot}+\rho}} ,$$

which is independent of ξ. Thus $\underline{X}_0$ is an ancillary statistic. Fisher (1956) suggests that for purpose of inference one should consider the family of conditional distributions given the observed value of the ancillary statistic in the sample. Denote by $f_\xi(\underline{\underline{x}}|\underline{x}_0)$ the conditional probability function of $\underline{\underline{X}}$ given $\underline{X}_0 = \underline{x}_0$. The conditional locally most powerful test (see for example, Rao (1973)) for H_0: $\xi=0$ vs. H_1: $\xi>0$ is given by

$$T = (d \log f_\xi(\underline{\underline{x}}|\underline{x}_0)/d\xi)|_{\xi=0} .$$

After some simple calculation we find that

$$T = \frac{(n_\cdot + \rho/\mu)^{x_{\cdot\cdot}+\rho}}{\Gamma(x_{\cdot\cdot} + \rho)} \left[\int_{-\infty}^{\infty} \left\{\sum_{j=1}^{r} x_{j\cdot} d_j - \sum_{j=1}^{r} n_j d_j H(a)\right\} H(a)^{x_{\cdot\cdot}+\rho-2} \right.$$
$$\left. \times \exp\{-(n_\cdot + \rho/\mu) H(a)\} \{H'(a)\}^2 da \right] ,$$

where $x_{\cdot\cdot} = \sum_{j=0}^{r} x_{j\cdot}$ and $n_\cdot = \sum_{j=0}^{r} n_j$. The statistic T depends on the response function H. Biological knowledge is needed to decide the functional form of H. We assume here the one-hit model in mutagenicity. The model leads to the exponential response function, i.e., $H(a) = \exp(a)$. Then we have

$$T_E = \sum_{j=1}^{r} x_{j\cdot} d_j - \tilde{x} \sum_{j=1}^{r} n_j d_j ,$$

where $\tilde{x} = (x_{\cdot\cdot} + \rho)/\tilde{n}$ and $\tilde{n} = n_\cdot + \rho/\mu$.

Denoting by t_0 the observed value of T_E, the exact p-value of the conditional test is given by

$$p\text{-value} = \Sigma' \frac{1}{\prod_{j=1}^{r} \prod_{k=1}^{n_j} x_{jk}!} \frac{\Gamma(x_{\cdot\cdot} + \rho)}{\Gamma(x_{0\cdot} + \rho)} \frac{(n_0 + \rho/\mu)^{x_{0\cdot}+\rho}}{(n_\cdot + \rho/\mu)^{x_{\cdot\cdot}+\rho}} ,$$

where the summation Σ' extends over all $(\underline{x}_1, \ldots, \underline{x}_r)$ which satisfy $T_E \geq t_0$ for given $\underline{X}_0 = \underline{x}_0$.

3. Asymptotic conditional test

Under H_0: $\xi=0$, the conditional expectation and variance of T_E given $\underline{X}_0 = \underline{x}_0$ are obtained as

$$E_0(T_E \mid \underline{X}_0 = \underline{x}_0) = 0 ,$$
$$V_0(T_E \mid \underline{X}_0 = \underline{x}_0) = \frac{x_{0\cdot} + \rho}{n_0 + \rho/\mu} \left\{ \sum_{j=1}^{r} n_j d_j^2 - \left(\sum_{j=1}^{r} n_j d_j \right)^2 \Big/ \tilde{n} \right\} .$$

We consider the statistic S defined by

$$\begin{aligned} S &= T_E / \{ V_0(T_E \mid \underline{x}_0) \}^{1/2} \\ &= T_E \Big/ \left[\frac{x_{0\cdot} + \rho}{n_0 + \rho/\mu} \left\{ \sum_{j=1}^{r} n_j d_j^2 - \left(\sum_{j=1}^{r} n_j d_j \right)^2 \Big/ \tilde{n} \right\} \right]^{1/2} . \end{aligned}$$

Note that S is equivalent to Tarone's test statistic if $x_{0\cdot}$ and n_0 in the denominator are replaced by $x_{\cdot\cdot}$ and $n_{\cdot\cdot}$. We call the test based on S the asymptotic conditional test.

We derive the asymptotic distribution of S given $\underline{X}_0 = \underline{x}_0$ under H_0 directly using the cumulants. The k-th cumulant of S, denoted by β'_k, is obtained as follows for $k=1, 2, \ldots, 6$. The calculation is given in Appendix 1. Clearly $\beta'_1 = 0$, $\beta'_2 = 1$, and

$$\beta'_3 = \frac{1}{(n_\cdot v)^{1/2}} \frac{\Sigma \eta_j d_j^3 - \theta_n^2 (\Sigma \eta_j d_j)^3}{\{\Sigma \eta_j d_j^2 - \theta_n (\Sigma \eta_j d_j)^2\}^{3/2}} ,$$

$$\beta'_4 = \frac{1}{n_\cdot v} \frac{\Sigma \eta_j d_j^4 - \theta_n^3 (\Sigma \eta_j d_j)^4}{\{\Sigma \eta_j d_j^2 - \theta_n (\Sigma \eta_j d_j)^2\}^2} + 3 \frac{1}{x_{0\cdot} + \rho} ,$$

$$\beta'_5 = \frac{1}{(n_\cdot v)^{3/2}} \frac{\Sigma \eta_j d_j^5 - \theta_n^4 (\Sigma \eta_j d_j)^5}{\{\Sigma \eta_j d_j^2 - \theta_n (\Sigma \eta_j d_j)^2\}^{5/2}} + 10 \frac{1}{x_{0\cdot} + \rho} \beta'_3 ,$$

$$\begin{aligned} \beta'_6 = {} & \frac{1}{(n_\cdot v)^2} \frac{\Sigma \eta_j d_j^6 - \theta_n^5 (\Sigma \eta_j d_j)^6}{\{\Sigma \eta_j d_j^2 - \theta_n (\Sigma \eta_j d_j)^2\}^3} \\ & + 15 \frac{1}{x_{0\cdot} + \rho} \beta'_4 + 10 \frac{1}{x_{0\cdot} + \rho} \beta'^2_3 - 15 \frac{1}{(x_{0\cdot} + \rho)^2} , \end{aligned}$$

where $\nu=(x_{0\cdot}+\rho)/(n_0+\rho/\mu)$, $\theta_n=n_\cdot/(n_\cdot+\rho/\mu)$, and $\eta_j=n_j/n_\cdot$. Therefore, when $\eta_j=n_j/n_\cdot$ is kept constant $(0<\eta_j<1)$ for $j=1, 2,\ldots, r$, we obtain the following results.

$$\begin{array}{lll} \beta_3' \to 0 & \text{as} & n_\cdot \to \infty , \\ \beta_4' \to 3/(x_{0\cdot}+\rho) & \text{as} & n_\cdot \to \infty , \\ \beta_5' \to 0 & \text{as} & n_\cdot \to \infty , \quad \text{and} \\ \beta_6' \to 30/(x_{0\cdot}+\rho)^2 & \text{as} & n_\cdot \to \infty . \end{array}$$

The limits of β_4' and β_6' depend on $x_{0\cdot}$, because the conditional asymptoticity is considered conditioned on $\underline{X}_0=\underline{x}_0$. However it would be reasonably well to expect that $x_{0\cdot}$ goes to infinity as $n_\cdot\to\infty$. Thus β_4' and β_6' go to 0 as $n_\cdot\to\infty$. Eventually we may prove that the unconditional asymptotic distribution of S under H_0 is the standard normal. The size α rejection region of the test based on S is, therefore, approximated by:

$$S \geq z_\alpha ,$$

where z_α is the upper $100\alpha\%$ point of the standard normal distribution.

4. Assessing the gain

We first consider the asymptotic power of the conditional tests under the sequence of the alternative hypotheses,

$$H_{1n}\colon \xi_n = \delta/n_\cdot^{1/2} \quad \text{for given} \quad \delta>0 .$$

Hereafter we fix $\mu=E(\lambda)$ finite and let $n_\cdot\to\infty$ by keeping $\eta_j=n_j/n_\cdot$ constant $(0<\eta_j<1)$.

THEOREM 4.1. *Under the sequence of the alternative hypothesis H_{1n} the asymptotic power of the test based on S is given by*

(a) *for ρ fixed*

$$\lim_{n_\cdot\to\infty} \Pr\{S\geq z_\alpha\} = E[\Phi\{\delta H'(H^{-1}(\lambda))\, B(1)/\lambda^{1/2} - z_\alpha\}] ,$$

where

$$B(\theta) = \{\Sigma\eta_j d_j^2 - \theta\, (\Sigma\eta_j d_j)^2\}^{1/2} ,$$

H' is the derivative of H, and the expectation is respect to the distribution of λ.

(b) *If $\rho\to\infty$ such that $\theta_n=n_\cdot/(n_\cdot+\rho/\mu)\to\theta$ $(0\leq\theta\leq1)$ as $n_\cdot\to\infty$,*

$$\lim_{n_\cdot\to\infty} \Pr\{S\geq z_\alpha\} = \Phi\{\delta H'(H^{-1}(\mu))\, B(\theta)/\mu^{1/2} - z_\alpha\} .$$

PROOF. See Appendix 2.

We next consider the asymptotic gain due to the incorporation of the historical controls. If the historical controls are not incorporated, the square root of Armitage's test (1955) for a linear trend in the Poisson mean may be applied for testing H_0: $\xi=0$ vs. H_1: $\xi>0$. This test rejects the null hypothesis if

$$Y=\left(\sum_{j=1}^{r} x_j\cdot d_j-\bar{x}\sum_{j=1}^{r} n_j d_j\right)\Bigg/\left[\bar{x}\left\{\sum_{j=1}^{r} n_j d_j^2-\left(\sum_{j=1}^{r} n_j d_j\right)^2\Big/ n\cdot\right\}\right]^{1/2}\geq z_\alpha\ ,$$

where $\bar{x}=x\cdot\cdot/n\cdot$. Through similar arguments as the above theorem, the asymptotic power of this test under H_{1n}: $\xi_n=\delta/n\cdot^{1/2}$ is obtained as follows.

$$\lim_{n\cdot\to\infty}\Pr\{Y\geq z_\alpha\}=\Phi\{\delta H'(H^{-1}(\lambda))\,B(1)/\lambda^{1/2}-z_\alpha\}\ .$$

Therefore, supposing that $\rho\to\infty$ as $n\cdot\to\infty$, Pitman's asymptotic relative efficiency of the conditional test with respect to the test which does not incorporate the historical controls is given by

$$\text{ARE}\,(S\,|\,Y)=\{B(\theta)/B(1)\}^2\ ,$$

which is equivalent to that given in the binomial case by Yanagawa and Hoel (1985).

5. Example

We shall now apply the above exact conditional test to the example given in Tarone (1982). The data is reproduced in Table 2. From his paper we get $\hat{\rho}=12.20$ and $\hat{\mu}=8.35$, which have been estimated from historical data. Since $\hat{\rho}/\hat{\mu}$ is not large compared to $n\cdot=15$, it is expected that the gain of incorporating historical controls would not be substantial. In fact, using the maximum likelihood estimates in place of ρ and μ, we have approximately

$$\text{ARE}\,(S\,|\,Y)=1.055\ .$$

Now consider the p-value of the exact conditional test. We must calculate

Table 2. Summary of microbial mutagenesis assay data for benz(a)anthracene using TA 1537.*

Dose level	0.0	0.3	1.0	3.3	10.0
Replicate counts	4,2,4	4,6,8	7,6,8	4,8,4	13,13,9
Total	10	18	21	16	35

*The data is given in Tarone (1982).

the negative multinomial probabilities on the set

$$\{(\underline{x}_1,\ldots,\underline{x}_r)\,|\,T_E \geq t_0 = 130.7 \text{ for given } \underline{X}_0 = (4,2,4)\}\ .$$

Different from the binomial case considered by Yanagawa and Hoel (1985), x_{jk} can take values from 0 to infinity. Whereas the negative multinomial probabilities vanish quickly when $x_{j\cdot}$ tends to large. We developed an efficient computer algorithm taking these points into account. The p-value obtained is 5.0402×10^{-4}. For the asymptotic conditional test we find that S=3.954, with an associated p-value of 3.8517×10^{-5}. The difference of the p-values indicates that the normal approximation in this range of probability is not so good. We suggest to use the exact conditional test. Unfortunately, however, the calculation of the exact p-values in this range of probabilities in our program takes large computation time. It would be needed to develop a more efficient computer program for the exact conditional test to be used in practice. Note that Tarone's test for incorporating the historical control data provides $\tilde{Y}^2$=11.45, with an associated one-sided p-value of 3.6×10^{-4}. The p-value is closer to the exact p-value than the conditional asymptotic test. Tarone (1982) obtained his test by considering a random variable an unknown parameter. The values of the cumulants of S, which are all equal to zero for the standard normal distribution, are calculated as follows.

$$\beta_3' = 0.38635\ , \quad \beta_4' = 0.25843\ , \quad \beta_5' = 0.21181 \quad \text{and} \quad \beta_6' = 0.22288\ .$$

Finally we note that if the dose levels are equally spaced, say Δ, then the continuity correction by means of $\Delta/2$ should be applied to the numerator of the asymptotic conditional test. This improves the approximation of the asymptotic test to the exact test at the p-values near 5% or 1%. However, the improvement is generally negligible at the range of small p-values like that in the example.

Appendix 1

Calculation of the cumulants of S

Putting

$$U = \sum_{j=1}^{r} c_j x_{j\cdot}\ ,$$

where $c_j = d_j - \sum_{k=1}^{r} n_k d_k / \tilde{n}$ (j=1, 2,..., r), we have

$$E_0(U\,|\,\underline{x}_0) = \frac{x_{0\cdot} + \rho}{n_\cdot + \rho/\mu} \sum_{j=1}^{r} n_j d_j\ ,$$

$$V_0(U\,|\,\underline{x}_0) = \frac{x_{0\cdot} + \rho}{n_0 + \rho/\mu}\left\{\sum_{j=1}^{r} n_j d_j^2 - \left(\sum_{j=1}^{r} n_j d_j\right)^2\Big/\tilde{n}\right\}$$

and

$$S = T_E/\{V_0(T_E\,|\,\underline{x}_0)\}^{1/2} = \{U - E_0(U\,|\,\underline{x}_0)\}/\{V_0(U\,|\,\underline{x}_0)\}^{1/2}\,.$$

Putting $\xi=0$ in the argument in Section 2, we obtain $f_0(\underline{x}_0, \underline{\underline{x}})$, the joint probability function of $(\underline{X}_0, \underline{\underline{X}})$ under H_0 as follows.

$$\begin{aligned} f_0(\underline{x}_0, \underline{\underline{x}}) &= \int_0^\infty \prod_{j=0}^{r} \prod_{k=1}^{n_j} \frac{\lambda^{x_{jk}}}{x_{jk}!} \exp(-n_j\lambda) g(\lambda) d\lambda \\ &= \frac{1}{\prod_{j=0}^{r} \prod_{k=1}^{n_j} x_{jk}!} \frac{(\rho/\mu)^\rho}{\Gamma(\rho)} \int_0^\infty \lambda^{x_{\cdot\cdot}+\rho-1} \exp\{-(n_\cdot + \rho/\mu)\lambda\} d\lambda \\ &= \frac{1}{\prod_{j=0}^{r} \prod_{k=1}^{n_j} x_{jk}!} \frac{\Gamma(x_{\cdot\cdot} + \rho)}{\Gamma(\rho)} \frac{(\rho/\mu)^\rho}{(n_\cdot + \rho/\mu)^{x_{\cdot\cdot}+\rho}}\,. \end{aligned}$$

When $\underline{X}_0=\underline{x}_0$ is given, the joint conditional distribution of $\underline{\underline{X}}=(\underline{X}_1,\ldots, \underline{X}_r)$ is given by

$$\begin{aligned} f_0(\underline{\underline{x}}\,|\,\underline{x}_0) &= f_0(\underline{x}_0, \underline{\underline{x}})/f_0(\underline{x}_0) \\ &= \frac{1}{\prod_{j=1}^{r} \prod_{k=1}^{n_j} x_{jk}!} \frac{\Gamma(x_{\cdot\cdot} + \rho)}{\Gamma(x_{0\cdot} + \rho)} \frac{(n_0 + \rho/\mu)^{x_{0\cdot}+\rho}}{(n_\cdot + \rho/\mu)^{x_{\cdot\cdot}+\rho}}\,, \end{aligned}$$

which is a negative multinomial distribution with parameters $x_{0\cdot}+\rho$ and $1/(n_0+\rho/\mu)$ (Johnson and Kotz (1969), p. 292). Thus the conditional characteristic function of $\underline{\underline{X}}$ given $\underline{X}_0=\underline{x}_0$ is given by

$$\begin{aligned} &\phi_{\underline{\underline{X}}}(t_{11},\ldots, t_{rn_r}) \\ &\quad = E\left\{\exp\left(i \sum_{j=1}^{r} \sum_{k=1}^{n_j} t_{jk} x_{jk}\right)\right\} \\ &\quad = \left[\frac{n_0 + \rho/\mu}{n_\cdot + \rho/\mu}\right]^{x_{0\cdot}+\rho} \left[1 - \frac{1}{n_\cdot + \rho/\mu} \sum_{j=1}^{r} \sum_{k=1}^{n_j} \exp(it_{jk})\right]^{-(x_{0\cdot}+\rho)} \end{aligned}$$

Therefore the characteristic function of U is obtained as follows.

$$\phi_U(t) = E\left\{\exp\left(it \sum_{j=1}^{r} c_j \sum_{k=1}^{n_j} x_{jk}\right)\right\} = E\left\{\exp\left(i \sum_{j=1}^{r} \sum_{k=1}^{n_j} c_j t x_{jk}\right)\right\}$$

$$= \left[\frac{n_0 + \rho/\mu}{n_\cdot + \rho/\mu} \right]^{x_0\cdot+\rho} \left[1 - \frac{1}{n_\cdot + \rho/\mu} \sum_{j=1}^{r} \sum_{k=1}^{n_j} \exp(ic_j t) \right]^{-(x_0\cdot+\rho)}$$

$$= \left[\frac{n_0 + \rho/\mu}{n_\cdot + \rho/\mu} \right]^{x_0\cdot+\rho} \left[1 - \frac{1}{n_\cdot + \rho/\mu} \sum_{j=1}^{r} n_j \exp(ic_j t) \right]^{-(x_0\cdot+\rho)}$$

Thus denoting the k-th cumulant of U by β_k, the cumulant generating function of U is

$$\begin{aligned}
\psi_U(t) &= \log \phi_U(t) \\
&= -(x_0\cdot + \rho)\log\left\{ 1 + \frac{1}{1!}\left(-\frac{1}{n_0 + \rho/\mu} \sum_{j=1}^{r} n_j c_j \right)(it) + \cdots \right. \\
&\qquad \left. + \frac{1}{k!}\left(-\frac{1}{n_0 + \rho/\mu} \sum_{j=1}^{r} n_j c_j^k \right)(it)^k + \cdots \right\} \\
&= -(x_0\cdot + \rho)\log\left\{ 1 + \frac{\alpha_1}{1!}(it) + \cdots + \frac{\alpha_k}{k!}(it)^k + \cdots \right\} \\
&= \frac{\beta_1}{1!}(it) + \cdots + \frac{\beta_k}{k!}(it)^k + \cdots ,
\end{aligned}$$

where

$$\alpha_k = -\frac{1}{n_0 + \rho/\mu} A_k \quad \text{and} \quad A_k = \sum_{j=1}^{r} n_j c_j^k \quad (k = 1, 2, \ldots) .$$

Furthermore expanding logarithmic function using the relation of the cumulants and the moments (see for example, Kendall and Stuart (1977), p. 72), we have by putting $\nu=(x_0\cdot+\rho)/(n_0+\rho/\mu)$ and $\gamma=1/(n_0+\rho/\mu)$

$$\begin{aligned}
\beta_1 &= -(x_0\cdot + \rho)\alpha_1 = \nu A_1 , \\
\beta_2 &= -(x_0\cdot + \rho)(\alpha_2 - \alpha_1^2) = \nu(A_2 + \gamma A_1^2) , \\
\beta_3 &= -(x_0\cdot + \rho)(\alpha_3 - 3\alpha_2\alpha_1 + 2\alpha_1^3) \\
&= \nu(A_3 + 3\gamma A_2 A_1 + 2\gamma^2 A_1^3) , \\
\beta_4 &= -(x_0\cdot + \rho)(\alpha_4 - 4\alpha_3\alpha_1 - 3\alpha_2^2 + 12\alpha_2\alpha_1^2 - 6\alpha_1^4) \\
&= \nu(A_4 + 4\gamma A_3 A_1 + 3\gamma A_2^2 + 12\gamma^2 A_2 A_1^2 + 6\gamma^3 A_1^4) , \\
\beta_5 &= -(x_0\cdot + \rho)(\alpha_5 - 5\alpha_4\alpha_1 - 10\alpha_3\alpha_2 + 20\alpha_3\alpha_1^2 + 30\alpha_2^2\alpha_1 \\
&\quad - 60\alpha_2\alpha_1^3 + 24\alpha_1^5) \\
&= \nu(A_5 + 5\gamma A_4 A_1 + 10\gamma A_3 A_2 + 20\gamma^2 A_3 A_1^2 + 30\gamma^2 A_2^2 A_1 \\
&\quad + 60\gamma^3 A_2 A_1^3 + 24\gamma^4 A_1^5) , \\
\beta_6 &= -(x_0\cdot + \rho)(\alpha_6 - 6\alpha_5\alpha_1 - 15\alpha_4\alpha_2 + 30\alpha_4\alpha_1^2 - 10\alpha_3^2 \\
&\quad + 120\alpha_3\alpha_2\alpha_1 - 120\alpha_3\alpha_1^3 + 30\alpha_2^3 - 270\alpha_2^2\alpha_1^2 \\
&\quad + 360\alpha_2\alpha_1^4 - 120\alpha_1^6)
\end{aligned}$$

$$= \nu(A_6 + 6\gamma A_5A_1 + 15\gamma A_4A_2 + 30\gamma^2 A_4A_1^2 + 10\gamma A_3^2 + 120\gamma^2 A_3A_2A_1 + 120\gamma^3 A_3A_1^3 + 30\gamma^2 A_2^3 + 270\gamma^3 A_2^2A_1^2 + 360\gamma^4 A_2A_1^4 + 120\gamma^5 A_1^6)\ .$$

Now we represent each A_k by using $B_k=\sum_{j=1}^{r} n_j d_j^k$ $(k=1, 2,\dots, 6)$.

$$A_1 = \sum_{j=1}^{r} n_j c_j = \frac{n_0 + \rho/\mu}{\tilde{n}} B_1\ ,$$

$$A_2 = \sum_{j=1}^{r} n_j c_j^2 = B_2 + \frac{-2\tilde{n} + (n\cdot - n_0)}{\tilde{n}^2} B_1^2\ ,$$

$$\vdots$$

$$A_6 = \sum_{j=1}^{r} n_j c_j^6 = B_6 - 6\frac{1}{\tilde{n}} B_5B_1 + 15\frac{1}{\tilde{n}^2} B_4B_1^2 - 20\frac{1}{\tilde{n}^3} B_3B_1^3 + 15\frac{1}{\tilde{n}^4} B_2B_1^4 + \frac{-6\tilde{n} + (n\cdot - n_0)}{\tilde{n}^6} B_1^6\ .$$

Then the cumulants of U are obtained as follows.

$$\beta_1 = \frac{x_0\cdot + \rho}{n\cdot + \rho/\mu} B_1 \quad (=E_0(U\,|\,\underline{x}_0))\ ,$$

$$\beta_2 = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}(B_2 - B_1^2/\tilde{n}) \quad (=V_0(U\,|\,\underline{x}_0))\ ,$$

$$\beta_3 = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}(B_3 - B_1^3/\tilde{n}^2)\ ,$$

$$\beta_4 = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}(B_4 - B_1^4/\tilde{n}^3) + 3\frac{1}{x_0\cdot + \rho}\beta_2^2\ ,$$

$$\beta_5 = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}(B_5 - B_1^5/\tilde{n}^4) + 10\frac{1}{x_0\cdot + \rho}\beta_3\beta_2\ ,$$

$$\beta_6 = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}(B_6 - B_1^6/\tilde{n}^5) + 15\frac{1}{x_0\cdot + \rho}\beta_4\beta_2 + 10\frac{1}{x_0\cdot + \rho}\beta_3^2 - 15\frac{1}{(x_0\cdot + \rho)^2}\beta_2^3\ .$$

From the cumulants of U, it is straightforward to obtain the cumulants of S.

Appendix 2

Proof of Theorem

Define $\lambda_{nj}=H(a+\xi_n d_j)$, $\xi_n=\delta/n\cdot^{1/2}$, $\lambda=\lambda_0=H(a)$, then under H_{1n} the conditional expectation and variance of T_E conditioned on λ are

$$E_n(T_E\,|\,\lambda) = n\cdot\{\Sigma\eta_j(d_j - \theta_n\Sigma\eta_k d_k)(\lambda_{nj} - \lambda) + (1-\theta_n)(\lambda - \mu)\Sigma\eta_j d_j\}\ ,$$

$$V_n(T_E\,|\,\lambda) = n\cdot\{\Sigma\eta_j(d_j - \theta_n\Sigma\eta_k d_k)^2\lambda_{nj} + \eta_0(\theta_n\Sigma\eta_j d_j)^2\lambda\}\ .$$

Define

$$A_n = V_n(T_E\,|\,\lambda)/n\cdot C_n\ ,$$

$$R_n = E_n(T_E\,|\,\lambda)/(n\cdot C_n)^{1/2}\ ,$$

$$C_n = \frac{x_0\cdot + \rho}{n_0 + \rho/\mu}\{\Sigma\eta_j d_j^2 - \theta_n(\Sigma\eta_j d_j)^2\} \quad (=V_0(T_E|\underline{x}_0)/n\cdot)\ ,$$

$$U_n = \{T_E - E_n(T_E\,|\,\lambda)\}/\{V_n(T_E\,|\,\lambda)\}^{1/2}\ ,$$

then we may express

$$S = U_n A_n^{1/2} + R_n\ .$$

(a) For ρ fixed, clearly $\theta_n \to 1$ as $n\cdot\to\infty$, and

$$\lim_{n\cdot\to\infty}\Pr\{S \ge z_\alpha\} = E[\lim_{n\cdot\to\infty}\Pr\{U_n \ge (z_\alpha - R_n)/A_n^{1/2}\,|\,\lambda\}]\ .$$

Now since

$$n\cdot^{1/2}(1-\theta_n) = n\cdot^{1/2}\frac{\rho/\mu}{n\cdot + \rho/\mu} \to 0\ ,$$

$$n\cdot^{1/2}(\lambda_{nj} - \lambda) = n\cdot^{1/2}\{H(a + d_j\delta/n\cdot^{1/2}) - H(a)\} \to d_j\delta H'(a)\ , \quad \text{and}$$

$$(x_0\cdot + \rho)/(n_0 + \rho/\mu) \to \lambda\ ,$$

in probability as $n\cdot\to\infty$, we have conditionally

$$\begin{aligned} R_n &\to \delta H'(a)\,\{\Sigma\eta_j d_j^2 - (\Sigma\eta_j d_j)^2\}^{1/2}/\lambda^{1/2} \\ &= \delta H'(H^{-1}(\lambda))\,B(1)/\lambda^{1/2}\ , \end{aligned}$$

and $A_n \to 1$ in probability as $n\cdot\to\infty$. Thus

$$\begin{aligned} &\lim_{n\cdot\to\infty}\Pr\{U_n \ge (z_\alpha - R_n)/A_n^{1/2}\,|\,\lambda\} \\ &\quad = \Phi[\{\delta H'(H^{-1}(\lambda))\,B(1)/\lambda^{1/2} - z_\alpha\}\,|\,\lambda]\ . \end{aligned}$$

Therefore, the result follows.

(b) When $\rho \to \infty$ as $n\cdot \to \infty$, the conditioning is not needed. It is immediate to see

$$\lambda \to \mu \quad \text{and} \quad (x_{0\cdot} + \rho)/(n_0 + \rho/\mu) \to \mu$$

in probability and that U_n converges to the standard normal distribution unconditionally as $n\cdot \to \infty$. We first suppose $\theta_n \to 0$ or 1 as $n\cdot \to \infty$. Since

$$E\{n\cdot^{1/2}(1-\theta_n)(\lambda-\mu)\} = 0 ,$$

$$E\{n\cdot^{1/2}(1-\theta_n)(\lambda-\mu)\}^2 = \theta_n(1-\theta_n)\mu ,$$

we have

$$\lambda_{nj} \to \mu \quad \text{and} \quad n\cdot^{1/2}(1-\theta_n)(\lambda-\mu) \to 0 \quad \text{as} \quad n\cdot \to \infty .$$

Further

$$n\cdot^{1/2}(\lambda_{nj}-\lambda) \to d_j\delta H'(a) \quad \text{as} \quad n\cdot \to \infty .$$

Therefore, putting

$$R = \delta H'(a)\,\{\Sigma\eta_j d_j^2 - \theta(\Sigma\eta_j d_j)^2\}/\mu^{1/2} = \delta H'(H^{-1}(\mu))\; B(\theta)/\mu^{1/2} ,$$

it follows that $A_n \to 1$ and $R_n \to R$ as $n\cdot \to \infty$. Thus

$$\lim_{n\cdot\to\infty} \Pr\{U_n \geq (z_\alpha - R_n)/A_n^{1/2}\}$$
$$= \Phi\{\delta H'(H^{-1}(\mu))\; B(1)/\mu^{1/2} - z_\alpha\} .$$

Next we suppose that $\theta_n \to \theta$ $(0<\theta<1)$ as $n\cdot \to \infty$. We have

$$A_n \to \frac{\Sigma\eta_j d_j^2 - \theta(2-\theta)(\Sigma\eta_j d_j)^2}{\Sigma\eta_j d_j^2 - \theta(\Sigma\eta_j d_j)^2} = A \quad \text{as} \quad n\cdot \to \infty$$

and R_n is asymptotically equivalent to

$$BV_n + R ,$$

where

$$B = \{\theta(1-\theta)\}^{1/2}(\Sigma\eta_j d_j)\,\{\Sigma\eta_j d_j^2 - \theta(\Sigma\eta_j d_j)^2\}^{-1/2} ,$$

$$V_n = \{n\cdot(1-\theta)\}^{1/2}(\lambda-\mu)/(\mu\theta)^{1/2} .$$

Therefore S is asymptotically equivalent to W_n+R, where

$$W_n = A^{1/2}U_n + BV_n .$$

Since U_n and V_n are asymptotically standard normal variates, it follows that W_n is also asymptotically standard normal variate. Thus

$$\begin{aligned}\lim_{n\to\infty} \Pr\{S \geq z_\alpha\} &= \lim_{n\to\infty} \Pr\{W_n + R \geq z_\alpha\} \\ &= \Phi\{\delta H'(H^{-1}(\mu))\, B(\theta)/\mu^{1/2} - z_\alpha\} .\end{aligned}$$

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