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NONPARAMETRIC TESTING FOR DOSE-RESPONSE CURVES SUBJECT TO DOWNTURNS: ASYMPTOTIC POWER CONSIDERATIONS

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Dose-response experiments are widely used in scientific research and nonmonotone dose-response curves are commonly observed. A class of nonparametric tests for dose-response curves subject to downturns at high doses is examined via its asymptotic properties. This class includes the well-known Jonckheere–Terpstra test as a limiting case. The analysis indicates that the Jonckheere–Terpstra test lacks robustness to a downturn in the dose-response, and that other members of the class provide superior overall performance. A result concerning U statistics in locally asymptotically normal families of distributions facilitates the derivation of the asymptotic power function for the class of tests under consideration. This result may also be used to obtain asymptotic power functions for other tests based on U statistics, for instance, the Mann–Whitney–Wilcoxon test. The accuracy of the asymptotic approximation is examined via Monte Carlo simulation and is found to be quite good for moderate sample sizes, suggesting that the approximation might reasonably be used for sample-size determinations.

1. Introduction. Dose-response experiments are widespread in scientific research. By exposing the experimental units to a range of doses of a treatment, the experimenter hopes to gain assurance that a positive result reflects the phenomenon of interest, and that failure to obtain such a result is not due simply to an unfortunate selection of a single test dose. In these experiments the test agent at times can have more than one effect and nonmonotone dose-response relationships can occur. For example, in an agricultural experiment, increasing the amount of irrigation can enhance crop yields up to a certain level, but it can produce rot and reduced yields at higher levels. Similarly, in the Ames test [Ames, McCann and Yamasaki (1975)], mutagenicity of a test chemical is reflected in an increasing relationship between the chemical dose and the frequency of visible colonies among plated salmonella bacteria, but cellular toxicity at high doses can reduce the population of microbes on the plate and lower the frequency of visible colonies [Margolin, Kaplan, and Zeiger, 1981; Vollmar (1981)].

A dose-response that rises monotonically at low to moderate doses and decreases monotonically at high doses poses an important inferential question: How can these two different effects of the treatment be separated when one is not certain a priori that there is a downturn or at what dose it commences? In the Ames test, for example, it is essential to assess the significance of any initial

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mutagenic increase in the dose-response and yet to minimize the influence on this inference of any downturn at higher doses. Nondirectional procedures like the F-test for homogeneity fail to achieve this separation. Parametric statistical modeling offers one appealing approach. Ideally the science suggests an appropriate model [e.g., Margolin, Kaplan and Zeiger (1981)]; however, this is not commonly the case.

Nonparametric dose-response testing offers an alternative approach. Terpstra (1952), Jonckheere (1954), Chacko (1963), Puri (1965), Shorack (1967) and others have studied nonparametric tests for monotone trends. The test of Terpstra (1952) and Jonckheere (1954), in particular, is well-known, as evidenced by its discussion in a number of recent publications [Potter and Sturm (1981); Boyd (1982); Harding (1984); Thakur (1984); Hoop and Mohebalian (1985)]. Simpson and Margolin (1986) proposed a class of recursive nonparametric tests for increasing dose-response when a downturn is possible at high doses. Their Monte Carlo results indicate a substantial improvement in power relative to the Jonckheere–Terpstra test and the nonparametric test of Chacko (1963) and Shorack (1967) if a downturn is present. This appears to be at a modest cost in power for a monotone dose-response. Simpson and Dallal (1989) provided software for these tests.

The main purpose of the present paper is to investigate the tests of Simpson and Margolin (1986) via their asymptotic properties. These tests are indexed by a user-specified tuning parameter $q \in [0, 1)$ and include the Jonckheere–Terpstra test as the limiting case $q = 0$. The effect of q on the power for different dose-response configurations is of particular interest here. Section 2 provides a formulation of the testing problem and a description of the tests under consideration. Section 3 is concerned with the consistency of these tests. Section 4 is general in scope and provides the joint limiting distribution in a local asymptotic setting of a collection of U statistics with respect to different partitions of the data. Section 5 uses these results to obtain asymptotic power functions for the class of tests under study and to draw general conclusions about the impact of the tuning parameter. Section 6 examines the agreement between the asymptotic and (Monte Carlo) finite-sample power functions.

2. Preliminaries. Assume that the experimental units are arranged in m ordered dose groups and that the ith dose group yields independent, identically distributed observations $X_{i1}, \ldots, X_{in_i}$. The hypotheses of interest are stated nonparametrically in terms of stochastic orderings. For $i = 1, \ldots, m$, let $F_i(t) = P(X_{i1} \leq t)$, $t \in R^1$. The hypothesis of no dose-response effect is

$$H\colon F_1(\cdot) = \cdots = F_m(\cdot), \tag{1}$$

but it is expanded here to include

$$H'\colon F_1(\cdot) \leq \cdots \leq F_m(\cdot), \tag{2}$$

the hypothesis that the dose-response is nonincreasing. The alternative hypothe-

ses of interest have the form:

$$F_1(\cdot) \geq \cdots \geq F_h(\cdot) \leq \cdots \leq F_m(\cdot), \tag{3}$$

where $h \in \{2, \ldots, m\}$ and $F_1(t) > F_h(t)$ for some $t \in R^1$, reflecting an initial monotone increase in the dose-response through dose h followed by a monotone decrease through dose m. [For a decreasing dose-response with a possible upturn, one reverses all inequalities in (2) and (3).] Tests of (1) versus (3) with $h = m$ are studied in Terpstra (1952), Jonckheere (1954), Chacko (1963), Puri (1965) and Shorack (1967). Mack and Wolfe (1981) and Hettmansperger and Norton (1987) proposed tests of (1) against (3) with $h \in \{1, \ldots, m\}$, but these tests are inappropriate for the testing problem considered here, because they include H' $(h = 1)$ in the alternative space and because they do not separate the different effects of the treatment in testing for significance.

The Jonckheere–Terpstra statistic and the recursive test statistics are functions of

$$R_j = \sum_{i=1}^{j-1} \sum_{u=1}^{n_i} \sum_{v=1}^{n_j} \Psi(X_{iu}, X_{jv}), \qquad j = 2, \ldots, m,$$

where

$$\Psi(x, y) = \begin{cases} 0, & \text{if } x > y, \\ \frac{1}{2}, & \text{if } x = y, \\ 1, & \text{if } x < y. \end{cases}$$

Observe that R_j is simply the two-sample Mann–Whitney–Wilcoxon statistic for comparing the aggregate of groups 1 through $j - 1$ with group j. If $R_2, \ldots, R_m$ are large there is evidence of an increasing dose-response relationship among groups 1 through m. The Jonckheere–Terpstra test is based on the sum

$$S = R_2 + R_3 + \cdots + R_m,$$

which, when appropriately standardized, may also be interpreted as an index of the association between dose and response. It has been observed that $R_2, \ldots, R_m$ are stochastically independent under H [Terpstra (1952); Dwass (1960)]. Hence, letting

$$S_j = R_2 + \cdots + R_j, \qquad j = 2, \ldots, m,$$

it follows that $S_j = S_{j-1} + R_j$ is a decomposition into components S_{j-1} and R_j independent under H $(j = 3, \ldots, m)$. This suggests adapting recursively to the downturn in the dose-response by using R_j to choose between the potential trend test statistics S_j and S_{j-1} $(j = m, m - 1, \ldots)$. Simpson and Margolin (1986) proposed basing the test for trend on S_M with the index M determined by the data according to the rule

$$M = \max\{j \in (2, \ldots, m): R_j \geq c_j(q)\},$$

where $c_2(q) = 0$ and where, for some prespecified $q \in [0, 1)$, $c_j(q)$ is a q quantile of the distribution of R_j under H $(j = 3, \ldots, m)$. This test, denoted by $S_M(q)$ to

emphasize the dependence on the tuning parameter, has critical regions of the form

$$(S_M \geq d_M) = \bigcup_{i=2}^{m} \{R_i \geq c_i(q), S_i \geq d_i\} \bigcap_{j=i+1}^{m} \{R_j < c_j(q)\}.$$

We shall take $d_i = d_i(p)$ to be a $(1-p)$ quantile of the distribution of S_i under H $(i = 2, \ldots, m)$, where $p \in (0,1)$. This ensures that the critical regions for different test sizes are nested and reduces specification of $d_2, \ldots, d_m$ to specification of p. For fixed q and a desired size α under (1), a conservative choice of p is

$$p = \alpha(1-q)/(1-q^{m-1}) \tag{4}$$

[Simpson and Margolin (1986)].

In the asymptotic investigation to be presented the well-known marginal asymptotic normality of R_j and S_j provides critical values

$$c_j(q) = \mu_0(R_j) + \sigma_0(R_j)\Phi^{-1}(q), \qquad j = 3, \ldots, m, \tag{5}$$

and

$$d_j(p) = \mu_0(S_j) + \sigma_0(S_j)\Phi^{-1}(1-p), \qquad j = 2, \ldots, m, \tag{6}$$

where μ_0 and σ_0 denote expectation and standard deviation under H, and Φ is the standard normal distribution function. Letting $N_j = n_1 + \cdots + n_j$, $j = 1, \ldots, m$,

$$\mu_0(R_j) = \tfrac{1}{2}N_{j-1}n_j, \qquad \sigma_0^2(R_j) = N_{j-1}n_j(N_j+1)/12, \qquad \mu_0(S_j) = \sum_{i=2}^{j} \mu_0(R_i)$$

and, using the independence,

$$\sigma_0^2(S_j) = \sum_{i=2}^{j} \sigma_0^2(R_j), \qquad j = 2, \ldots, m.$$

3. Regions of consistency. A sequence of tests with critical regions ω_N is consistent for a given configuration of distributions if $P(\omega_N) \to 1$ as $N \to \infty$. Reasonable nondirectional tests of (1) are consistent for any fixed alternative, so consistency results provide little insight for such tests. On the other hand, directional tests are designed for narrower classes of alternatives, so it is informative to determine the regions over which they are consistent; see, for instance, Hollander (1967) and Barlow, Bartholomew, Bremner and Brunk (1972), page 210. This section is concerned with the consistency of the recursive tests.

Let $Y_i = (R_i - \mu_0(R_i))/\sigma_0(R_i)$ and $Z_i = (S_i - \mu_0(S_i))/\sigma_0(S_i)$, $i = 2, \ldots, m$. Let $M = \max\{2, (i\colon Y_i \geq y)\}$, where $y = \Phi^{-1}(q)$ and let $z = \Phi^{-1}(1-p)$. Then (5) and (6) yield the critical region

$$(Z_M \geq z) = \left((Z_2 \geq z) \bigcap_{j=3}^{m} (Y_j < y)\right) \cup \left(\bigcup_{i=3}^{m} (Z_i \geq z, Y_i \geq y) \bigcap_{j=i+1}^{m} (Y_j < y)\right).$$

For convenience write N for N_m. It is assumed that $X_{11}, \ldots, X_{mn_m}$ are independent, that $F_1, \ldots, F_m$ are absolutely continuous and that $n_i/N \to a_i \in (0,1)$ as $N \to \infty$, $i = 1, \ldots, m$.

THEOREM 1. (i) *If* (2) *holds, then* $\limsup_{N\to\infty} P(Z_M \geq z) \leq \alpha$, $0 \leq q < 1$.
(ii) *Consistency of* $S_M(0)$ *implies consistency of* $S_M(q)$, $0 < q < 1$.
(iii) *If* (3) *holds, then* $S_M(q)$ *is consistent*, $0 < q < 1$.

An outline of the proof is in the Appendix. Property (i) establishes that it is meaningful to compare the regions of consistency of the tests $S_M(q)$. Moreover, this property distinguishes the tests $S_M(q)$ from nondirectional tests, like the Kruskal–Wallis test [Kruskal (1952); Kruskal and Wallis (1952)] and from the tests of Mack and Wolfe (1981) and Hettmansperger and Norton (1987). For these tests the probabilities of rejection converge to 1 if the dose-response is strictly decreasing. Result (ii) implies that one never loses consistency by using $S_M(q)$, $0 < q < 1$, instead of the ordinary Jonckheere–Terpstra test. On the other hand, examples of alternatives in (3) for which the Jonckheere–Terpstra test fails to be consistent are easily constructed.

4. Local asymptotic normality and U statistics. In developing asymptotic results for $S_M(q)$ it is useful to observe that Y_j, as defined in Section 3, is a standardized U statistic with respect to a three-group partition of the data

$$\left\{\left(X_{11}, \ldots, X_{j-1,n_{j-1}}\right), \left(X_{j1}, \ldots, X_{jn_j}\right), \left(X_{j+1,1}, \ldots, X_{mn_m}\right)\right\}, \qquad j = 2, \ldots, m.$$

In this section the standard theory of locally asymptotically normal (LAN) families of distributions is applied to obtain the joint limiting distribution under alternatives contiguous to (1) for a vector of U statistics with respect to different partitions of the data. A general account of LAN families can be found in Ibragimov and Has'minskii (1981).

Suppose $\{F_t, t \in \Theta\}$ is a dominated family of distributions and suppose $f_t = f(\cdot; t)$ is a density for F_t. We assume the mapping from t to $f_t^{1/2}$ is continuously differentiable in L_2, that is, there are functions ℓ_t $(t \in \Theta)$ such that

$$\int \ell_t^2 f_t < \infty, \int \left\{ f_{t+\delta}^{1/2} - f_t^{1/2} - \tfrac{1}{2}\delta \ell_t f_t^{1/2} \right\}^2 = o(\delta^2) \tag{7}$$

and

$$\int \left\{ \ell_{t+\delta} f_{t+\delta}^{1/2} - \ell_t f_t^{1/2} \right\}^2 = o(1) \tag{8}$$

as $\delta \to 0$, where the integrals are with respect to the dominating measure. In standard cases $\ell_t(x) = (\partial/\partial t) \log f(x; t)$. If (7) holds, F_t is said to have finite Fisher information $J(t) = \int \ell_t^2 f_t$. If (8) holds, $J(t)$ is continuous in t. Conditions (7) and (8) imply the following LAN condition [Ibragimov and Has'minskii (1981), pages 118–120]: If $\xi_1, \xi_2, \ldots$ are independent replicates of $\xi \sim F_t$ and if

$t_n \to t$ and $n^{1/2}\beta_n \to \beta$ as $n \to \infty$, then

$$(9)\quad \log \prod_{i=1}^{n} f(\xi_i; t_n + \beta_n)/f(\xi_i; t_n) = n^{-1/2}\beta \sum_{i=1}^{n} \ell_t(\xi_i) - \tfrac{1}{2}\beta^2 J(t) + o_p(1)$$

as $n \to \infty$ and, moreover, the log-likelihood ratio is asymptotically normal with mean $-\frac{1}{2}\beta^2 J(t)$ and variance $\beta^2 J(t)$.

Specializing to the m-sample problem, let $X_1, X_2, \ldots$ be a sequence of independent random variables, let $N_0 = 0$ and $N_i = n_1 + \cdots + n_i$, $i = 1, \ldots, m$, and let $G = \{G_1, \ldots, G_m\}$ be the partition of the indices $\{1, 2, \ldots, N = N_m\}$ into the sets $G_i = \{N_{i-1} + 1, \ldots, N_i\}$, $i = 1, \ldots, m$. For $j \in G_i$ let $F_i(x) = P(X_j \le x)$. We consider the hypotheses

$$H_N\colon F_i(\cdot) = F(\cdot; \theta)$$

and

$$K_N\colon F_i(\cdot) = F\big(\cdot; \theta + N^{-1/2}\beta_i\big), \qquad i = 1, \ldots, m,$$

where

$$\sum_{i=1}^{m} n_i \beta_i = 0$$

and where $\{F_\theta\}$ satisfies (7) and (8). The parameter θ may be a location parameter, but other families of distributions are also covered by the development. Let L_N denote the log-likelihood ratio for K_N versus H_N:

$$(10)\qquad L_N = \sum_{i=1}^{m} \sum_{j \in G_i} \log\Big\{ f\big(X_j; \theta + N^{-1/2}\beta_i\big)/f\big(X_j; \theta\big)\Big\}.$$

The conditions on F_θ and (9) imply that under H_N,

$$(11)\qquad L_N = N^{-1/2} \sum_{i=1}^{m} \beta_i \sum_{j \in G_i} \ell_\theta\big(X_j\big) - \tfrac{1}{2} J(\theta) N^{-1} \sum_{i=1}^{m} n_i \beta_i^2 + o_p(1)$$

and K_N is contiguous to H_N.

For $j = 1, \ldots, s$, let $H_j = \{H_{j1}, \ldots, H_{jm_j}\}$ be a partition of $\{1, 2, \ldots, N\}$ consisting of unions of sets in G, the basic partition. Let U_j be an m_j sample U statistic of order $\{r_{j1}, \ldots, r_{jm_j}\}$ with respect to H_j, $j = 1, \ldots, s$. Then U_j has the form

$$(12)\qquad U_j = C_j^{-1} \sum_{A_1} \cdots \sum_{A_{m_j}} \Psi_j\Big(X(A_1); \ldots; X\big(A_{m_j}\big)\Big),$$

where the sums are over the distinct subsets $A_k = (\alpha_1, \ldots, \alpha_{r_{jk}})$ of size r_{jk} that can be selected without replacement from H_{jk}, $k = 1, \ldots, m_j$, C_j is the number of terms in the sum and $X(A)$ means $(X_{\alpha_1}, \ldots, X_{\alpha_r})$ if $A = (\alpha_1, \ldots, \alpha_r)$. The kernel function Ψ_j is assumed without loss of generality to be symmetric in its first r_{j1} arguments, its next r_{j2} arguments and so on.

We approximate $U_1, \ldots, U_s$ by their projections. Suppose that $E_\theta \Psi_j = 0$ and $E_\theta \Psi_j^2 < \infty$, and that $n_i/N \to a_i \in (0, 1)$ as $N \to \infty$, $i = 1, \ldots, m$. For $k =$

$1, \ldots, m_j$ let

$$\Psi_{jk}(x) = E_\theta \Psi_j\big(X(B_1); \ldots; x, X(B_k); \ldots; X(B_{m_j})\big),$$

where B_u $(u \neq k)$ is a subset of size r_{ju} from H_{ju} and B_k is a subset of size $r_{jk} - 1$ from H_{jk}. By a standard result [Hoeffding (1948); Lehmann (1951)],

$$U_j = V_j + o_p(N^{-1/2}) \tag{13}$$

under H_N, where

$$V_j = \sum_{k=1}^{m_j} \frac{r_{jk}}{n_{jk}} \sum_{i \in H_{jk}} \Psi_{jk}(X_i) \tag{14}$$

and n_{jk} is the cardinality of H_{jk}.

To obtain the joint limiting distribution of $V_2, \ldots, V_s$, and hence of $U_1, \ldots, U_s$, it is useful to rewrite (14) in terms of the basic partition G. Let

$$\lambda_{jk}(x) = \sum_{u=1}^{m_j} I\{G_k \subseteq H_{ju}\} \Psi_{ju}(x),$$

where $I\{\cdot\} = 1$ if its argument is true, $= 0$ otherwise, $k = 1, \ldots, m$. Rearranging the sum in (14) and noting that

$$I\{G_k \subseteq H_{ju}\} \lambda_{jk}(x) = I\{G_k \subseteq H_{ju}\} \Psi_{ju}(x)$$

yields

$$V_j = N^{-1} \sum_{i=1}^{m} b_{ji} \sum_{k \in G_i} \lambda_{ij}(X_k), \tag{15}$$

where

$$b_{ji} = N \sum_{k=1}^{m_j} I\{G_i \subseteq H_{jk}\} r_{jk}/n_{jk}, \qquad j = 1, \ldots, s.$$

The approximations (11) and (13)–(15) yield the following result, which is proved in the Appendix.

THEOREM 2. *Suppose* $\{F_t\}$ *satisfies* (7) *and* (8). *Let* $U_1, \ldots, U_s$ *be as in* (12) *and suppose* $E_\theta \Psi_j = 0$ *and* $E_\theta \Psi_j^2 < \infty$, $j = 1, \ldots, s$. *Assume* $n_i/N \to a_i \in (0, 1)$ *as* $N \to \infty$, $i = 1, \ldots, m$. *Then*

$$\mathcal{L}\{(N^{1/2}U_1, \ldots, N^{1/2}U_s)\} \to N(\mu, \Gamma)$$

under K_N, *where* $\mu = (\mu_1, \ldots, \mu_s)$ *with*

$$\mu_j = \sum_{i=1}^{m} a_i \beta_i b_{ji}^0 E_\theta\big[\ell_\theta(X) \lambda_{ij}(X)\big]$$

and $b_{uv}^0 = \lim_{N \to \infty} b_{uv}$ *and where* $\Gamma = ((\gamma_{jk}))$ *with*

$$\gamma_{jk} = \sum_{i=1}^{m} a_i b_{ji}^0 b_{ki}^0 E_\theta\big[\lambda_{ji}(X) \lambda_{ki}(X)\big], \qquad j = 1, \ldots, s,\ k = 1, \ldots, s.$$

Theorem 2 provides an asymptotic distribution for $(R_2, \ldots, R_m)$ under K_N. The Mann–Whitney–Wilcoxon statistic R_2 is handled as a special case. Let $U_j = N_{j-1}^{-1} n_j^{-1} R_j - \frac{1}{2}$ and note that

$$U_j = N_{j-1}^{-1} n_j^{-1} (N - N_j)^{-1} \sum_{\alpha_1 \in H_{j1}} \sum_{\alpha_2 \in H_{j2}} \sum_{\alpha_3 \in H_{j3}} \Psi(X_{\alpha_1}, X_{\alpha_2}),$$

where $H_{j1} = G_1 \cup \cdots \cup G_{j-1}$, $H_{j2} = G_j$ and $H_{j3} = G_{j+1} \cup \cdots \cup G_m$, $j = 2, \ldots, m$, and where

$$\Psi(x, y) = \begin{cases} -\frac{1}{2}, & \text{if } x > y, \\ 0, & \text{if } x = y, \\ \frac{1}{2}, & \text{if } x < y, \end{cases} \qquad j = 2, \ldots, m.$$

If F_θ is absolutely continuous, then

$$\Psi_{ju}(x) = \begin{cases} \frac{1}{2} - F_\theta(x), & \text{if } u = 1, \\ F_\theta(x) - \frac{1}{2}, & \text{if } u = 2, \\ 0, & \text{if } u = 3. \end{cases}$$

Moreover, $\lambda_{jk}(x) = \Psi_{ju}(x)$ if $G_k \subseteq H_{ju}$, $u = 1, 2, 3$, and b_{jk} takes the value N/N_{j-1}, N/n_j or $N/(N - N_j)$ depending on whether G_k is contained in H_{j1}, H_{j2} or H_{j3}, respectively. Using Theorem 2 and simplifying shows that $(N^{1/2}U_2, \ldots, N^{1/2}U_m)$ is asymptotically normal (μ, Γ) under K_N, where $\mu = (\mu_2, \ldots, \mu_m)$ and $\Gamma = \operatorname{diag}(\gamma_{22}, \ldots, \gamma_{mm})$ with

$$\mu_j = (\beta_j - \bar{\beta}_{j-1}) E_\theta[F_\theta(X) \ell_\theta(X)], \qquad \bar{\beta}_k = N_k^{-1} \sum_{i=1}^{k} n_i \beta_i$$

and

$$\gamma_{jj} = NN_j/(12 n_j N_{j-1}).$$

The exact variance of $N^{1/2}U_j$ under H_N is $N(N_j + 1)/(12 n_j N_{j-1})$, which can replace γ_{jj} in the asymptotic approximation.

In the asymptotic distribution of $(R_2, \ldots, R_m)$, the only quantity that depends on the form of the sampling distribution is the constant $E_\theta F_\theta \ell_\theta$. This fact will be exploited in the next section. For continuous families of distributions, differentiating the relation

$$E_\theta[F_\theta(X)] = \tfrac{1}{2}$$

yields the identity

$$E_\theta[F_\theta(X) \ell_\theta(X)] = -E_\theta\left[\frac{\partial}{\partial \theta} F_\theta(X)\right].$$

If θ is a location parameter, the right side reduces to the familiar expression $E_\theta[f(X - \theta)] = \int f^2$. Table 1 gives the form of the constant $E_\theta F_\theta \ell_\theta$ for several families of distributions.

TABLE 1
The constant $E_\theta F_\theta \ell_\theta$ for several choices of F_θ.

Distribution (F_θ)	$E_\theta F_\theta \ell_\theta$
Normal [mean = θ, variance = $\sigma^2(\theta)$]	$\{2\sigma(\theta)\pi^{1/2}\}^{-1}$
Logistic (mean = θ, scale = σ)	$(6\sigma)^{-1}$
Cauchy (median = θ, scale = σ)	$(2\pi\sigma)^{-1}$
Exponential (mean = θ)	$(4\theta)^{-1}$

5. Asymptotic power. In the nonparametric testing literature it is common to derive the asymptotic relative efficiency between a nonparametric test and an analogous parametric test. Here interest is focused instead on comparisons within the class of nonparametric tests $S_M(q)$. The relative performances of the tests depend on the direction of deviation from H, so no overall measure of asymptotic relative efficiency is available. Useful insight is obtained, however, by direct comparison of the asymptotic power functions [cf. Puri (1965)].

Assume $\{F_\theta\}$ satisfies the LAN conditions of the previous section and let Y_j and Z_j be as defined in Section 3. The results of Section 4 imply that, under K_N, $Y = (Y_2, \ldots, Y_m)$ is asymptotically normal with mean $\eta = (\eta_2, \ldots, \eta_m)$, where

$$\eta_j = N^{-1/2}\sigma_0^{-1}(R_j)N_{j-1}n_j(\beta_j - \bar{\beta}_{j-1})E_\theta F_\theta \ell_\theta, \tag{16}$$

and with covariance equal to the $(m-1)\times(m-1)$ identity matrix. This asymptotic distribution for Y and the representation

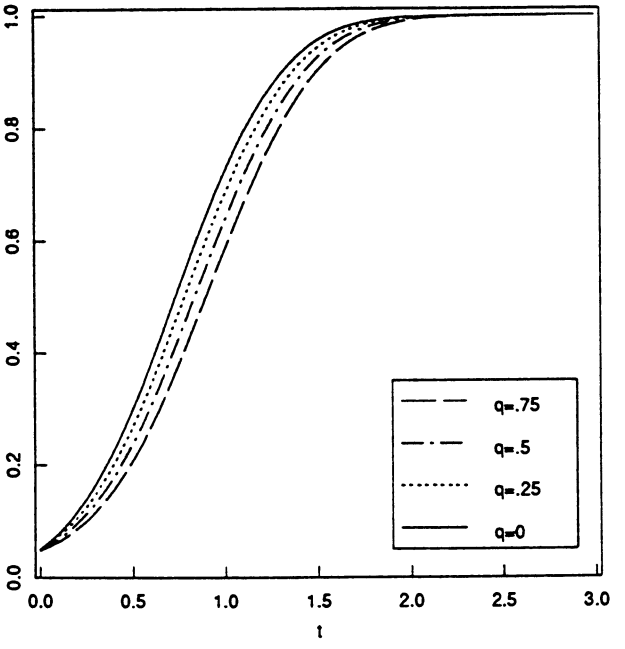
$$Z_j = \sigma_0^{-1}(S_j)\sum_{i=2}^{j}\sigma_0(R_i)Y_i, \qquad j = 2, \ldots, m,$$

yield an asymptotic power function for $S_M(q)$. Let $z = \Phi^{-1}(1-p)$ and $y = \Phi^{-1}(q)$, where p and q are as in (4), and let $M = \max\{2, (j = Y_j \geq y)\}$. Then the power $P(Z_M > z)$ for alternatives in K_N can be approximated by

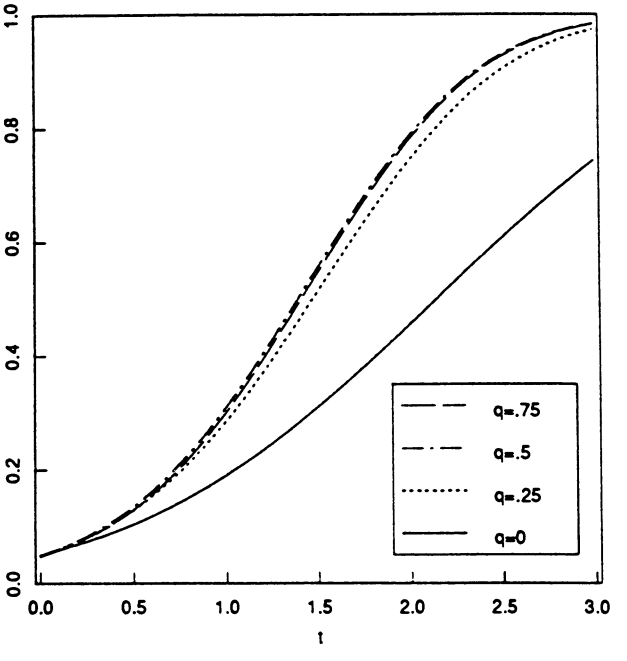
$$\begin{aligned}&\{1 - \Phi(z - \nu_2)\}\prod_{k=3}^{m}\Phi(y - \eta_k)\\ &\quad + \sum_{j=3}^{m}\bar{\Phi}_2(z - \nu_j, y - \eta_j; \rho_j)\prod_{k=j+1}^{m}\Phi(y - \eta_k),\end{aligned} \tag{17}$$

where $\nu_j = \{\sigma_0(R_2)\eta_2 + \cdots + \sigma_0(R_j)\eta_j\}/\sigma_0(S_j)$ and $\rho_j = \sigma_0(R_j)/\sigma_0(S_j)$, $j = 2, \ldots, m$, and where $\bar{\Phi}_2(u, v; \rho) = P(U > u, V > v)$ if (U, V) is a bivariate normal random variable with mean $(0, 0)$, unit variances and correlation ρ. If $q = 0$, one obtains the asymptotic power function for the Jonckheere–Terpstra test:

$$1 - \Phi(\Phi^{-1}(1-\alpha) - \nu_m). \tag{18}$$



(a)



(b)

FIG. 1. *Asymptotic power* ($\alpha = 0.05$) *of* $S_M(q)$ *for* $F_i(x) + \Phi(x - t\Delta_i)$, $i = 1, \ldots, 6$, $q = 0(0.25)0.75$: (a) $\Delta = (0.0, 0.25, 0.5, 0.75, 1.0, 1.25)$; (b) $\Delta = (0.0, 0.25, 0.5, 0.75, 0.75, 0.25)$.

For specified F_θ and $n_1, \ldots, n_m$, one uses (16)–(18) to approximate power for alternatives of the form $F_i(\cdot) = F(\cdot; \theta_i^*)$, $i = 1, \ldots, m$, by setting

$$\theta = N^{-1} \sum_{i=1}^{m} n_i \theta_i^* \quad \text{and} \quad \beta_i = N^{1/2}(\theta_i^* - \theta).$$

Figures 1 through 4 plot asymptotic power of $S_M(q)$ as a function of the tuning parameter q and another quantity t that parametrizes various paths through the space of $\theta^* = (\theta_1^*, \ldots, \theta_m^*)$. These plots are scaled to predict power for normal mean shift alternatives with unit variance, $m = 6$ and $n_1 = \cdots = n_6 = 5$. Other choices for F_θ would produce similar plots, because the sampling distribution appears only in the constant $E_\theta F_\theta \ell_\theta$ in (16). IMSL routines MDBNOR, MDNOR and MDNRIS facilitated computation of (17) and (18). Critical values for nominal test size 0.05 were determined from (5) and (6).

Figure 1(a) and (b) considers $\theta^* = \theta^*(t) = (\theta_1^*(t), \ldots, \theta_6^*(t))$, where $\theta_i^*(t) = t\Delta_i$, $i = 1, \ldots, 6$, and plot asymptotic power of $S_M(q)$, $q = 0(0.25)0.75$ versus t. Figure 1(a), in which $\Delta = (\Delta_1, \ldots, \Delta_6) = (0.0, 0.25, 0.50, 0.75, 1.0, 1.25)$, illustrates the cost in power for a monotone trend of using $S_M(q)$, $q = 0.25, 0.5, 0.75$, instead of the Jonckheere–Terpstra test $S_M(0)$. Figure 1(b), in which $\Delta = (0.0, 0.25, 0.50, 0.75, 0.75, 0.25)$, demonstrates that using $S_M(q)$, $q > 0$, instead of the Jonckheere–Terpstra test can yield a sizeable gain in power if there is a moderate downturn.

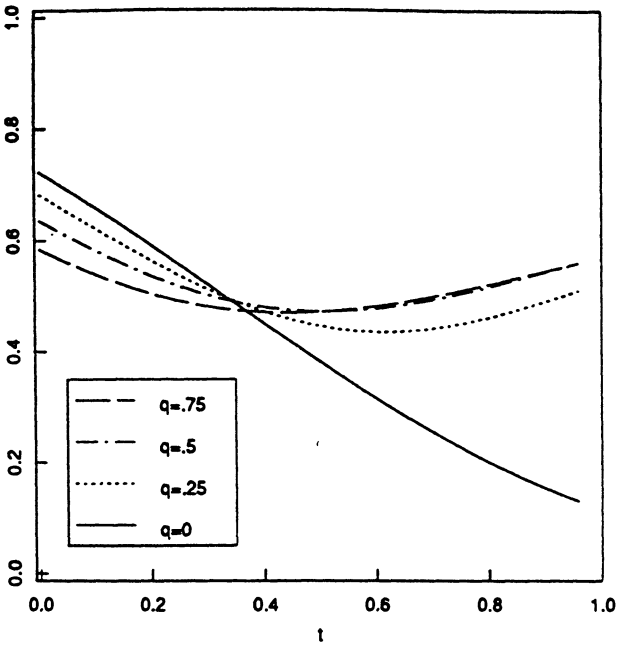


FIG. 2. *Asymptotic power* ($\alpha = 0.05$) *of* $S_M(q)$ *for* $F_i(x) = \Phi(x - (1 - t)\Delta_{Li} - t\Delta_{Qi})$, $i = 1, \ldots, 6$, $q = 0(0.25)0.75$, *where* $\Delta_L = (0.0, 0.25, 0.5, 0.75, 1.0, 1.25)$ *and* $\Delta_Q = (0.0, 0.5, 1.0, 1.25, 1.0, 0.0)$.

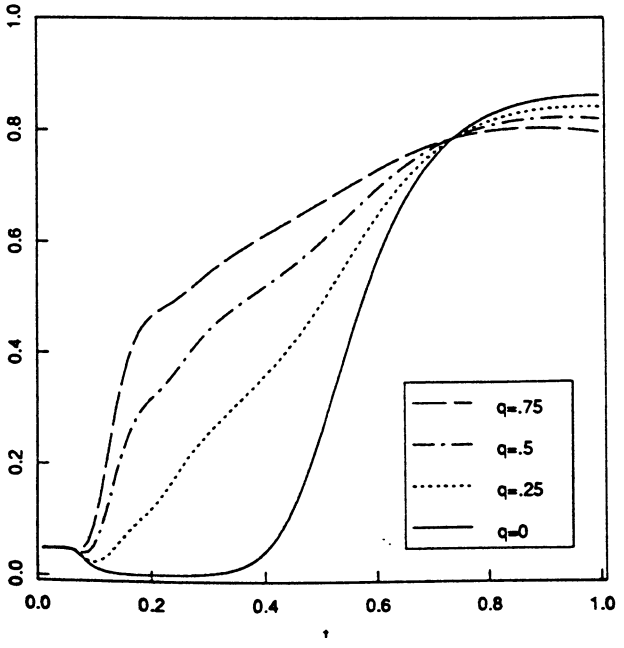
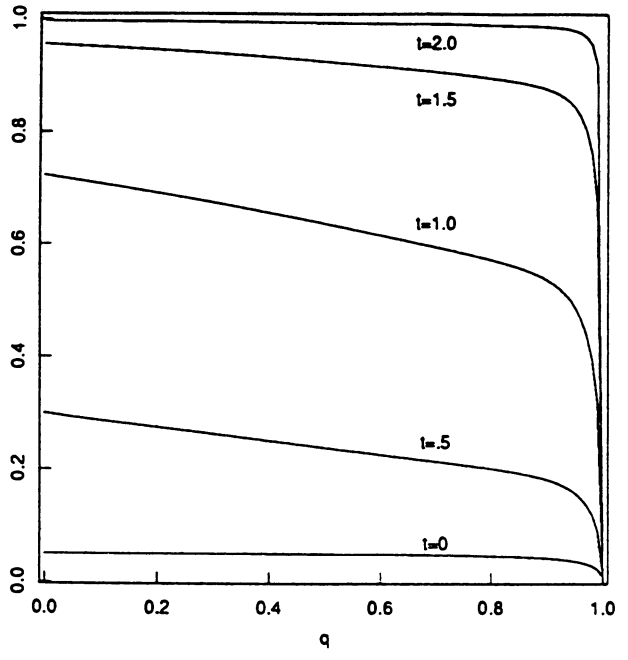


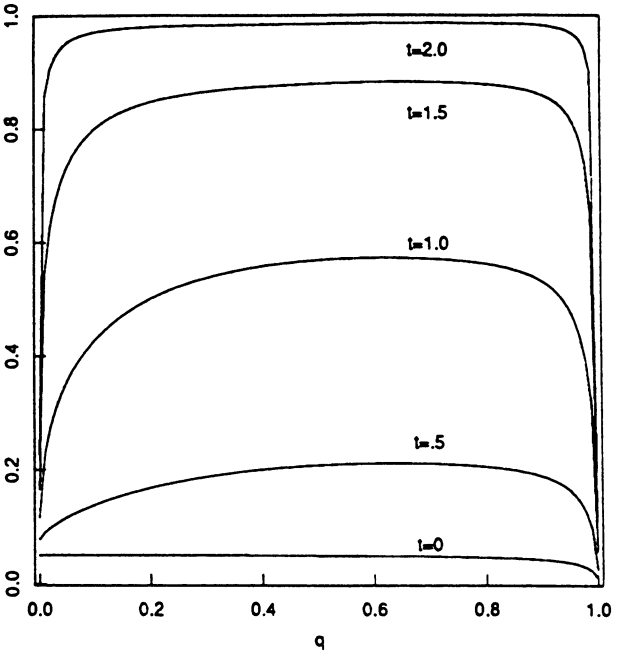
FIG. 3. *Asymptotic power* ($\alpha = 0.05$) *of* $S_M(q)$ *for* $F_i(x) = \Phi(x - 1.5g(\Delta_i, t, 2))$, $i = 1, \ldots, 6$, $q = 0(0.25)0.75$, *where* $\Delta = (0, 0.2, 0.4, 0.6, 0.8, 1.0)$ *and* $g(s, t, u) = (s/t)\exp\{u^{-1}(1 - (s/t)^u)\}$.

To show the tradeoff directly, Figure 2 considers the configurations $\theta^*(t) = (1 - t)\Delta_L + t\Delta_Q$, where $\Delta_L = (0.0, 0.25, 0.5, 0.75, 1.0, 1.25)$ and $\Delta_Q = (0,0, 0.5, 1.0, 1.25, 1.0, 0.0)$ for $t \in [0, 1]$. The lower extreme is a linear trend in the parameter values; the upper extreme is a roughly quadratic trend that drops back to the zero level at the highest dose. The power curves for $S_M(\frac{1}{2})$ and $S_M(0)$ cross at $t \simeq 0.34$, which corresponds to $\theta^* \simeq (0.0, 0.34, 0.67, 0.92, 1.0, 0.83)$.

Figure 3 illustrates the effect of the location of the downturn. Define $g(x, t, u) = (x/t)\exp\{u^{-1}(1 - (x/t)^u)\}$. For fixed positive t and u, $g(x, t, u)$ is a nonnegative, unimodal function of x on $[0, \infty)$ that increases from $g(0, t, u) = 0$ to $g(t, t, u) = 1$ and decreases thereafter to zero. The larger u is, the sharper the downturn beyond t. By varying t one can study asymptotic power as a function of the point of downturn. Figure 3 considers $\theta_i^*(t) = 1.5g(\Delta_i, t, 2)$, $i = 1, \ldots, 6$, with $\Delta = (0, 0.2, 0.4, 0.6, 0.8, 1.0)$ and $q = 0(0.25)0.75$. For $t = 1$ the dose-response is monotone over the sampled doses. The crossing point $t \simeq 0.73$ corresponds to $\theta^* \simeq (0, 0.65, 1.17, 1.45, 1.49, 1.33)$. To get an idea of the steepness of the downturn note that $g(2t, t, 2) = 2e^{-3/2} \simeq 0.45$, $g(3t, t, 2) = 3e^{-4} \simeq 0.055$ and so on. The power of the Jonckheere–Terpstra test drops substantially below $\alpha = 0.05$ if t is in the range $(0.07, 0.4)$. Less pronounced drops are apparent for $S_M(0.25)$ and $S_M(0.5)$ when t is near 0.1. Otherwise the tests tend to have greater power for later downturns, which is to be expected because of the larger effective sample sizes for testing the initial upward trend.



(a)



(b)

FIG. 4. *Asymptotic power* ($\alpha = 0.05$) *of* $S_M(q)$ *as a function of* q *for* $F_i(x) = \Phi(x - t\Delta_i)$, $i = 1, \ldots, 6$, $t = 0(0.5)2$: (a) $\Delta = (0.0, 0.25, 0.5, 0.75, 1.0, 1.25)$; (b) $\Delta = (0.0, 0.5, 1.0, 1.25, 1.0, 0.0)$.

Plotting power as a function of q shows directly the effect of this tuning parameter. Figure 4(a) and (b) gives plots of this type for two dose-response configurations, one linear and one with a downturn. The performance is clearly poor for $q > 0.95$; the corresponding tests do not use enough of the data. At the other extreme, q near zero results in poor robustness to a downturn. Away from these extremes the performance appears to be relatively stable across a range of choices for q. We recommend $q = \frac{1}{2}$ as a compromise that provides robustness to a downturn without sacrificing much power to detect a monotone dose-response. It is also easy to compute: If $q = \frac{1}{2}$ the cutoff value for R_j is simply $C_j = \frac{1}{2}n_jN_{j-1}$, the median under (1).

These conclusions are essentially invariant to the choice of F_θ in K_N, so the LAN theory provides a useful simplication. The accuracy of the resulting approximation, which clearly depends on the choice of F_θ, is examined in the next section.

TABLE 2

Monte Carlo and asymptotic power (nominal $\alpha = 0.05$) for the Jonckheere–Terpstra test (J) and $S_M(0.5)$ ($m = 6$, $n_1 = \cdots = n_6 = 5$): (a) Normal deviates with unit variance; (b) Logistic deviates with unit scale; (c) Cauchy deviates with unit scale; (d) Exponential deviates; (e) Normal deviates with variance equal to the mean.

						Monte Carlo power			Asymptotic power		
						J	$S_M(0.5)$	ratio	J	$S_M(0.5)$	ratio
(a) Normal means											
0.00	0.25	0.50	0.75	1.00	1.25	0.722	0.613	1.18	0.723	0.636	1.14
0.00	0.25	0.50	0.75	0.75	0.25	0.174	0.281	0.62	0.190	0.310	0.61
0.00	0.50	1.00	1.50	1.75	2.00	0.969	0.947	1.02	0.977	0.961	1.02
0.00	0.50	1.00	1.50	1.00	0.00	0.093	0.623	0.15	0.129	0.671	0.19
(b) Logistic means											
0.00	0.25	0.50	0.75	1.00	1.25	0.371	0.281	1.32	0.374	0.300	1.25
0.00	0.25	0.50	0.75	0.75	0.25	0.117	0.146	0.81	0.117	0.160	0.73
0.00	0.50	1.00	1.50	1.75	2.00	0.682	0.578	1.18	0.694	0.620	1.12
0.00	0.50	1.00	1.50	1.00	0.00	0.079	0.301	0.26	0.090	0.311	0.29
(c) Cauchy medians											
0.00	0.25	0.50	0.75	1.00	1.25	0.327	0.259	1.26	0.351	0.281	1.25
0.00	0.25	0.50	0.75	0.75	0.25	0.111	0.149	0.74	0.113	0.152	0.74
0.00	0.50	1.00	1.50	1.75	2.00	0.592	0.506	1.17	0.660	0.584	1.13
0.00	0.50	1.00	1.50	1.00	0.00	0.086	0.252	0.34	0.088	0.290	0.30
(d) Exponential means											
1.00	1.25	1.50	1.75	2.00	2.25	0.356	0.288	1.24	0.336	0.268	1.25
1.00	1.25	1.50	1.75	1.75	1.25	0.118	0.167	0.71	0.122	0.170	0.72
1.00	1.50	2.00	2.50	2.75	3.00	0.500	0.434	1.14	0.450	0.381	1.18
1.00	1.50	2.00	2.50	2.00	1.00	0.037	0.224	0.16	0.085	0.266	0.32
(e) Normal means (= variances)											
1.00	1.25	1.50	1.75	2.00	2.25	0.401	0.333	1.20	0.394	0.318	1.24
1.00	1.25	1.50	1.75	1.75	1.25	0.117	0.190	0.62	0.135	0.195	0.69
1.00	1.50	2.00	2.50	2.75	3.00	0.529	0.490	1.08	0.528	0.453	1.16
1.00	1.50	2.00	2.50	2.00	1.00	0.036	0.300	0.12	0.090	0.318	0.28

6. Asymptotic versus simulated power. Monte Carlo and asymptotic power approximations were computed for the tests $S_M(0)$ and $S_M(\frac{1}{2})$. Table 2 shows results for equivariant (scale = 1) location shift trends for normal, logistic and Cauchy deviates, for trends in the means for exponential deviates and for normal deviates with variance equal to the mean. The results are for six doses and $n_i = 5$, $i = 1, \ldots, 6$. Critical values for a nominal test size of $\alpha = 0.05$ were computed using (5) and (6). The Monte Carlo results are each based on 5000 replications using IMSL routines GGAMR, GGCAY, GGNML and GGUBS. Under a binomial sampling assumption for the proportion of rejections, the maximal standard deviation of the power estimate from 5000 Monte Carlo replications is roughly 0.007, occurring when the power is 0.5.

For the normal and logistic families the agreement between the Monte Carlo and asymptotic results are rather good; most of the differences are within Monte Carlo sampling error. For the Cauchy family the asymptotic results appear mildly optimistic, but the agreement is still good, especially given the reputation of the Cauchy distribution. The agreement is also rather good for the exponential distribution and the normal distribution with mean equal to the variance. For these latter distributions the sum-to-zero constraint on the β_i is crucial; $E_\theta F_\theta \ell_\theta$ in (16) must be evaluated at the average value of the parameter, as described in Section 5.

This modest study suggests that the asymptotic power function for $S_M(q)$ is quite accurate for moderate sample sizes and that it might reasonably be used for sample size determinations. That relative efficiencies appear to be well predicted lends support to the theoretical conclusions of Section 5.

APPENDIX

PROOF OF THEOREM 1. Let Y_i, Z_i, $i = 2, \ldots, m$, and M be as in Section 3. Let $\pi_{ij} = P(X_{i1} \le X_{j1}) = \int F_i(t)\, dF_j(t)$, $1 \le i, j \le m$. Let δ_k and τ_k denote the weighted averages

$$\delta_k = N_{k-1}^{-1} \sum_{j=1}^{k-1} n_j \pi_{jk} \quad \text{and} \quad \tau_k = \sum_{i=2}^{k} n_i N_{i-1} \delta_i \Big/ \sum_{j=2}^{k} n_j N_{j-1}, \qquad k = 2, \ldots, m.$$

For fixed m and assuming $n_i/N \to a_i \in (0,1)$ as $N \to \infty$, known results concerning the Mann–Whitney and Jonckheere–Terpstra statistics imply that, for finite y and z, $P(Y_i \ge y) \to 1$ $(\to 0)$ if and only if $\delta_i > \frac{1}{2}$ $(< \frac{1}{2})$ in the limit and $P(Z_i \ge z) \to 1$ $(\to 0)$ if and only if $\tau_i > \frac{1}{2}$ $(< \frac{1}{2})$ in the limit. Using these facts, the proof of (i) is straightforward. The proofs of (ii) and (iii) proceed by checking the conditions of the following lemma, which says that the test $S_M(q)$ will be consistent if at least one of the tests $Z_i \ge z$, $i = 2, \ldots, m$, is consistent and if the probability of selecting an inconsistent test becomes negligible in large samples.

LEMMA 1. *Let* $A = \{i \in (2, \ldots, m): \tau_i > \frac{1}{2}\}$ *and* $b = \max\{i \in A: \delta_i > \frac{1}{2}\}$. *Suppose* (i) A *is nonempty and* (ii) $j \ge b$ *and* $j \in A^c$ *imply* $\delta_j < \frac{1}{2}$. *Then* $S_M(q)$, $0 < q < 1$, *is consistent.*

PROOF. For finite y and z,

$$\liminf P(Z_M \geq z) = \liminf \sum_{i \in A,\, i \geq b} P\left(Y_i \geq y, \bigcap_{j=i+1}^{m} (Y_j < y)\right), \tag{19}$$

because $P(Z_i \geq z) \to 1$ for $i \in A$ and $\to 0$ for $i \in A^c$, and because $P(Y_b < y) \to 0$. Moreover,

$$1 = P\left\{\bigcap_{j=2}^{m} (Y_j < y)\right\} + \sum P\left(Y_i \geq y, \bigcap_{j=i+1}^{m} (Y_j < y)\right), \tag{20}$$

where the sum is over the disjoint sets $\{i = 2, \ldots, b-1\}$, $\{i \in A^c, i \geq b\}$ and $\{i \in A, i \geq b\}$. The first term on the right in (20) converges to zero as $N \to \infty$, as do the summations over $\{i = 2, \ldots, b-1\}$ and $\{i \in A^c, i \geq b\}$ in the second term. Hence, the result follows from (19) and (20). □

PROOF OF THEOREM 2. Theorem 2 follows from a result of Le Cam [see Hajek and Sidak (1967), page 208] and the following lemma.

LEMMA 2. *Suppose the conditions of Theorem 2 hold and let L_N be as in (10). Then $(L_N, N^{1/2}U_1, \ldots, N^{1/2}U_s)$ converges in distribution under H_N to a multivariate normal random vector with mean $\left(-\frac{1}{2}\sigma^2, 0, \ldots, 0\right)$ and covariance*

$$D = \begin{pmatrix} \sigma^2 & \mu \\ \mu' & \Gamma \end{pmatrix},$$

where μ and Γ are as in Theorem 2 and

$$\sigma^2 = J(\theta) \sum_{i=1}^{m} a_i \beta_i^2.$$

PROOF. Using (13), (15) and Chebyshev's inequality,

$$N^{1/2}\left(U_j - V_j^0\right) = o_p(1),$$

where

$$V_j^0 = N^{-1} \sum_{i=1}^{m} b_{ji}^0 \sum_{k \in G_i} \lambda_{ij}(X_k), \qquad j = 1, \ldots, s.$$

Hence, using also (11),

$$\left(L_N + \tfrac{1}{2}\sigma^2, N^{1/2}U_1, \ldots, N^{1/2}U_s\right) = \left(\Lambda_N, N^{1/2}V_1^0, \ldots, N^{1/2}V_s^0\right) + o_p(1),$$

where

$$\Lambda_N = N^{-1/2} \sum_{i=1}^{m} \beta_i \sum_{j \in G_i} \ell_\theta(X_j).$$

Fix an arbitrary $\alpha = (\alpha_0, \alpha_1, \ldots, \alpha_s) \in R^{s+1}$. Then

$$\alpha_0 \Lambda_N + N^{1/2} \sum_{j=1}^{s} \alpha_j V_j^0 = \sum_{i=1}^{m} a_i^{1/2} n_i^{-1/2} \sum_{j \in G_i} \left\{ \alpha_0 \beta_i \ell_\theta(X_j) + \sum_{k=1}^{s} \alpha_k b_{ki}^0 \lambda_{ki}(X_j) \right\} + o_p(1).$$

This converges in distribution to $\Sigma a_i^{1/2} W_i$, where $W_1, \ldots, W_m$ are independent and $W_i \sim N(0, \alpha D_i \alpha')$, and where D_i has (j, k)th element d_{ijk}, $j = 0, \ldots, s$, $k = 0, \ldots, s$, with $d_{i00} = \beta_i^2 J(\theta)$, $d_{i0k} = d_{ik0} = \beta_i b_{ki}^0 E_\theta \ell_\theta \lambda_{ki}$ and $d_{ijk} = d_{ikj} = b_{ji}^0 b_{ki}^0 E_\theta \lambda_{ji} \lambda_{ki}$, $j \neq 0$, $k \neq 0$. Note that D_i is finite by the Cauchy–Schwarz inequality, because $J(\theta)$ and $E_\theta \Psi_j^2$ are both finite. The result follows because $\Sigma a_i^{1/2} W_i \sim N(0, \alpha D \alpha')$ and α was arbitrary. □

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