An Efficient *R*-Estimator for the ED50

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Analogues of *R*-estimators are defined for the problem of estimating the median of a symmetric tolerance distribution in quantal bioassay. Asymptotic distributions are derived, and it is shown that the logistic scores estimator is, in a certain sense, asymptotically efficient. A Monte Carlo study is conducted to investigate the small-sample behavior of this estimator in relation to 10 competing estimators. The results suggest that the logistic scores estimator merits further consideration.

KEY WORDS: Quantal bioassay; Median effective dose; Spearman-Kärber; Trimmed Spearman-Kärber; Logistic scores estimator; Asymptotic efficiency.

1. INTRODUCTION

In the past few years, several authors have considered the problem of extending the techniques used in robust estimation of location parameters, based on samples of iid random variables, to the problem of estimating the median effective dose (ED50) in quantal bioassay. Hamilton, Russo, and Thurston (1977), after criticizing the lack of robustness of classical methods based on the probit and logit models, suggested using trimmed Spearman-Kärber estimators, which are analogues of the trimmed means of iid theory. Hamilton (1979) compared 10 estimators in terms of simulated mean squared error (MSE), finding the trimmed Spearman-Kärber estimator to be especially reliable in the sense that it reached a good balance of efficiency, calculability, and robustness (insensitivity to an anomalous response). In his study, he considered estimators based on logits, as well as various trimmed means and analogues of some of the *M*-estimators of iid theory.

Miller and Halpern (1980) generalized Hamilton's definitions, defining *L*- and *M*-estimators of the ED50 to be explicit or implicit functionals of the empirical tolerance distribution, the functionals being the same as those applied to the empirical distribution function in the iid case. They then determined the asymptotic distribution of *L*- and *M*-estimators and looked at efficiencies of some of these estimators for various underlying symmetric tolerance distributions, including both bounded and heavy-tailed distributions, as well as standard and contaminated normal and logistic distributions. Among the estimators considered were the Spearman-Kärber estimator, trimmed means, and the Tukey biweight.

In this article we study analogues of *R*-estimators in the quantal bioassay case. Since, in the iid case, *R*-estimators of the median of a symmetric distribution can also be defined as functionals applied to the empirical distribution function, we obtain *R*-estimators of the ED50 by applying these same functionals to a version of the empirical tolerance distribution. It will be seen that the "logistic scores" estimator is, in a certain sense, asymptotically efficient when the underlying distribution is symmetric.

In order to obtain some idea of the performance of the logistic scores estimator for small samples, we conducted a Monte Carlo study along the lines of Hamilton's. As a result, sample MSE's were obtained for various estimators, including estimators based on probits and logits, several trimmed Spearman-Kärber estimators, and two *R*-estimators: the logistic scores estimator and the analogue of the Hodges-Lehmann estimator.

Section 2 sets up the model we use throughout the article. *R*-estimators are defined in Section 3, and the concept of asymptotic efficiency is discussed in Section 4, which considers questions of optimality and defines the logistic scores estimator. The framework and results of the simulations are given in Section 5, which also contains comments and suggestions for further study. The formal statement of the theorem on the asymptotic distribution of *R*-estimators, together with an outline of its proof, is given in the Appendix.

2. THE PROBABILISTIC MODEL

We use the same model as Miller and Halpern (1980). We assume that n subjects are to be tested at each of $2k + 1$ equally spaced dose levels, $x_{-k}, \ldots, x_{-1}, x_0, x_1, \ldots, x_k$, where in practice the x_i usually represent logarithms of actual dosages. There is no particular reason for considering only an odd number of dose levels, besides the notational convenience of having a middose x_0; if we let d be the dose spacing, that is, $d = x_1 - x_0 > 0$, then $x_i = x_0 + id \ \forall\ i$. The number of subjects responding at dose level x_i will be denoted by r_i. We assume

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that the r_i's are independent and that r_i has a binomial distribution with parameters n and $p_i = F(x_i)$, where $F(x)$ is the probability of getting a positive response at dose level x from a subject chosen at random from the population at large. We assume also that F is a distribution function on the real line, symmetric about θ. We call F the *tolerance distribution* and θ the *median effective dose* (ED50).

The natural estimator of p_i is $\hat{p}_i = r_i/n$. But in the estimation of the tolerance distribution, or at least of the vector $\mathbf{p} = (p_{-k}, \ldots, p_0, \ldots, p_k)$, the vector $\hat{\mathbf{p}}$ is not a possible value of $\mathbf{p}$ unless the $\hat{p}_i$ are nondecreasing in i. In fact, the maximum likelihood estimator of $\mathbf{p}$ is the monotonized version of $\hat{\mathbf{p}}$ defined by

$$\tilde{p}_i = \max_{s \le i} \min_{t \ge i} \frac{\sum_{u=s}^{t} \hat{p}_u}{(t - s + 1)}.$$

See, for example, Barlow et al. (1972, p. 19). The vector $(\tilde{p}_{-k}, \ldots, \tilde{p}_0, \ldots, \tilde{p}_k)$ is called the isotonic regression of $\hat{\mathbf{p}}$.

In his study of robust estimates of θ, Hamilton considered seven nonparametric estimators, all of them functions of the monotonized version of $\mathbf{p}$. In fact, all of them were functions of an estimate of F obtained by linearly connecting the points of a graph $(x_i, \tilde{p}_i)$. Hamilton dealt only with small n and hoped to observe $\hat{p}_{-k} = 0$ and $\hat{p}_k = 1$. If this condition were violated, the Spearman-Kärber estimator, for example, was said to be not calculable. However, since we will be considering the behavior of estimators as $n \to \infty$, we will follow Miller and Halpern and adopt the frequently used convention that defines $\hat{p}_{-k-1} = 0$ and $\hat{p}_{k+1} = 1$. Our version of the empirical tolerance distribution is then, the piecewise linear function defined by the following:

$$\begin{aligned}
\tilde{F}(x) &= \tilde{p}_i, && \text{if } x = x_i,\ -k \le i \le k \\
&= 0, && \text{if } x \le x_{-k-1} = x_0 - (k+1)d \\
&= 1, && \text{if } x \ge x_{k+1} = x_0 + (k+1)d \\
&= \text{linear} && \text{and continuous in } [x_i, x_{i+1}]\ \forall\ i.
\end{aligned}$$

Note that if F is strictly increasing in the interval where it takes on values >0 and <1, then for a fixed dose mesh $(x_{-k}, \ldots, x_k)$ the vector $(\tilde{p}_{-k}, \ldots, \tilde{p}_k)$ will equal $\hat{\mathbf{p}}$ for n sufficiently large (with probability one).

3. *R*-ESTIMATORS

In the iid case, *R*-estimators can be obtained from two-sample rank tests. Suppose first that $X_1, \ldots, X_n$ and $Y_1, \ldots, Y_n$ are two independent samples from symmetric distributions differing only in location, with the X_i's having common symmetric distribution F and the Y_j's common distribution G satisfying $G(x) = F(x - \Delta)$. A test of the hypothesis H: $\Delta = 0$ versus the alternative K: $\Delta \neq 0$ can be based on the score function $J(t)$, $0 < t < 1$, by using as test statistic

$$S_n = \frac{1}{n} \sum_{i=1}^{n} J\left(\frac{R_i}{2n + 1}\right),$$

where R_i is the rank of X_i in the combined sample. If $J(1 - t) = -J(t)$ and J is nondecreasing, then S_n will take on a value near zero when the two samples are well intermixed, and one will reject H when $|S_n|$ is large.

Now, if $X_1, \ldots, X_n$ is a single sample from a symmetric distribution F, one can obtain an estimator of the center of symmetry of F by choosing that value of θ for which the two "samples" $X_1 - \theta, \ldots, X_n - \theta$ and $-(X_1 - \theta), \ldots, -(X_n - \theta)$ are well intermixed, in the sense that the test statistic $S_n(\theta)$ based on the two samples is equal to zero, or at least approximately so. The test statistic can also be based on the samples $X_1, \ldots, X_n$ and $2\theta - X_1, \ldots, 2\theta - X_n$, so that (if there are no ties in the combined sample) $R_i = n[F_n(X_i) + 1 - F_n(2\theta - X_i)]$, where F_n is the empirical df of the sample $X_1, \ldots, X_n$. Therefore, the estimator $\hat{\theta}$ will satisfy

$$\begin{aligned}
0 \approx S_n(\hat{\theta}) &\approx \frac{1}{n} \sum_{i=1}^{n} J\left(\frac{n[F_n(X_i) + 1 - F_n(2\hat{\theta} - X_i)]}{2n + 1}\right) \\
&\approx \int_{-\infty}^{\infty} J\left(\frac{F_n(x) + 1 - F_n(2\hat{\theta} - x)}{2}\right) dF_n(x).
\end{aligned}$$

Thus the *R*-estimator based on J is customarily defined in the iid case to be $T(F_n)$, where $T(F)$ is the solution of the equation

$$\int J\left(\frac{F(x) + 1 - F(2T(F) - x)}{2}\right) dF(x) = 0.$$

Examples of such *R*-estimators are the median, which corresponds to the score function of the sign test: $J(t) = -1$ for $t < \frac{1}{2}$, $J(t) = +1$ for $t > \frac{1}{2}$; the Hodges-Lehmann estimator, obtained from the score function of the Wilcoxon test: $J(t) = t - \frac{1}{2}$; and the normal scores estimator, obtained from the score function of the same name: $J(t) = \Phi^{-1}(t)$, where Φ is the standard normal distribution function.

We now extend this definition to quantal bioassay.

Definition 1. Let J be a nondecreasing integrable function defined on (0, 1), such that $J(1 - t) = -J(t)$ and J is not identically equal to zero. The *R*-estimator $\hat{\theta}$ based on J is the solution of the equation

$$h(\tilde{F}, \theta) \overset{\text{def}}{=} \int_{-\infty}^{\infty} J\left(\frac{\tilde{F}(x) + 1 - \tilde{F}(2\theta - x)}{2}\right) d\tilde{F}(x) = 0, \tag{3.1}$$

if a unique solution exists. If not, define

$$\hat{\theta} = \frac{\sup\{\theta: h(\tilde{F}, \theta) > 0\} + \inf\{\theta: h(\tilde{F}, \theta) < 0\}}{2}.$$

One notes that since $h(\tilde{F}, \theta)$ is a nonincreasing, con-

tinuous function of θ and

$$\lim_{\theta \to -\infty} h(\tilde{F}, \theta) = \int_{-\infty}^{\infty} J\left(\frac{\tilde{F}(x) + 1}{2}\right) d\tilde{F}(x)$$

$$= 2 \int_{1/2}^{1} J(t)dt > 0,$$

$$\lim_{\theta \to \infty} h(\tilde{F}, \theta) = 2 \int_{0}^{1/2} J(t)dt < 0,$$

$\hat{\theta}$ is well defined. (Note that continuity and the preceding limits are consequences of the facts that

$$\left| J\left(\frac{\tilde{F}(x) + 1 - \tilde{F}(2\theta - x)}{2}\right) \right|$$

$$\leq \left| J\left(\frac{\tilde{F}(x)}{2}\right) \right| + \left| J\left(\frac{\tilde{F}(x) + 1}{2}\right) \right|,$$

$\tilde{F}$ is continuous, and J has at most a countable set of discontinuity points, which together with a change of variables under an integral allow application of the Dominated Convergence Theorem (DCT).) The Appendix (Lemma 1) shows that the equation $h(\tilde{F}, \theta) = 0$ has a unique solution if $\tilde{F}$ is strictly increasing in the interval in which it takes on values greater than zero and less than one.

4. ASYMPTOTIC EFFICIENCY AND THE LOGISTIC SCORES ESTIMATOR

As defined in the previous section, the R-estimator $\hat{\theta}$ based on the score function J satisfies $h(\tilde{F}, \hat{\theta}) = 0$. For a fixed dose mesh $x_{-k}, \ldots, x_0, \ldots, x_k$, with distance d between successive doses, $\hat{\theta}$ is not necessarily a consistent estimator of θ (it will be if $x_0 = \theta$). In fact, as $n \to \infty$, the empirical tolerance distribution $\tilde{F}$ converges uniformly to the piecewise linear distribution function F_D defined by

$$F_D(x) = p_i, \quad \text{if} \quad x = x_i, i = -k - 1, \ldots, k + 1$$

$$= 0, \quad \text{if} \quad x \leq x_{-k-1} = x_0 - (k + 1)d$$

$$= 1, \quad \text{if} \quad x \geq x_{k+1} = x_0 + (k + 1)d$$

$$= p_{i-1} + \frac{(x - x_{i-1})}{d}(p_i - p_{i-1}),$$

$$\text{if} \quad x_{i-1} \leq x \leq x_i, i = -k, \ldots, k + 1.$$

Here we have adopted the convention $p_{-k-1} = 0, p_{k+1} = 1$.

So we would expect $\hat{\theta}$ to be a consistent estimator of θ_D, defined to satisfy the equation $h(F_D, \theta_D) = 0$. (That this is in fact the case follows from Lemma 3 of the Appendix, under regularity conditions on J.) We call θ_D the "discretized version" of θ based on J. The letter D is used as a mnemonic device to remind us of the dependence on the dose mesh.

It is not our purpose to consider ways of reducing the asymptotic bias $\theta_D - \theta$. Rather we follow Miller and Halpern (1980) in obtaining the asymptotic distribution of $(n/d)^{1/2}(\hat{\theta} - \theta_D)$ as first $n \to \infty$, and then the dose mesh becomes dense in the real line in the sense that $d \to 0$, $x_k \to +\infty$, and $x_{-k} \to -\infty$. Of course, this order of taking the limits is not the ideal one. It would be more reasonable to take $n \to \infty$ and $d \to 0$ simultaneously, but we chose the present method because of its mathematical convenience.

Since $\theta_D \to \theta$ as the dose mesh becomes dense (see Lemma 3 of the Appendix), the variance of this asymptotic distribution is used as an inverse measure of asymptotic efficiency. *We emphasize that the asymptotic efficiency defined here is really a measure of the precision with which $\hat{\theta}$ estimates θ_D.*

Definition 2. Suppose that when F is the tolerance distribution, $(n/d)^{1/2}(\hat{\theta} - \theta_D) \xrightarrow{\mathcal{D}} N(0, \sigma_J^2(F))$ as first $n \to \infty$ and then $d \to 0$, $x_k \to \infty$, and $x_{-k} \to -\infty$. Let $\sigma_0^2(F)$ be the smallest possible asymptotic variance of an R-estimator under F. Then $\sigma_0^2(F)/\sigma_J^2(F)$ is the *asymptotic efficiency* of the R-estimator based on J when F is the tolerance distribution.

See the Appendix for the proof, under regularity conditions on J and F, of the result

$$(n/d)^{1/2}(\hat{\theta} - \theta_D) \xrightarrow{\mathcal{D}} N(0, \sigma_J^2(F)),$$

where (with f denoting the density of F)

$$\sigma_J^2(F) = \frac{\int_{-\infty}^{\infty} (J'(F(x)))^2 f^2(x)F(x)(1 - F(x))dx}{\left(\int_{-\infty}^{\infty} J'(F(x))f^2(x)dx\right)^2}. \quad (4.1)$$

Let $\mathcal{J}$ be the class of score functions that satisfy the regularity conditions of the Appendix, and, for notational convenience, let $\sigma_J^2(F)$ be defined by the right side of (4.1) for all differentiable score functions J (not just those in $\mathcal{J}$). We will now show that among these general J,

$$\inf_J \sigma_J^2(F) = \left[\int \frac{f^2(x)}{F(x)(1 - F(x))} dx\right]^{-1} \stackrel{\text{def}}{=} I^{-1}(F), \quad (4.2)$$

with the infimum attained by any score function J satisfying $J'(t) = c/[t(1 - t)]$, where $c > 0$. That is, if the score function is of the form

$$J(t) = c \log \frac{t}{1 - t}, \quad (4.3)$$

then it attains the infimum.

Note that if J satisfies (4.3), then $\sigma_J^2(F) = I^{-1}(F)$, and so it remains to check "$\geq$" in (4.2). If $I(F)$ is infinite, which occurs for example when F is uniform, then the infimum is 0. So suppose $I(F) < \infty$. It is sufficient to restrict attention to those J such that the numerator in (4.1) is finite (note that both the numerator and denominator are strictly positive). In this case, the Cauchy-

Schwarz inequality implies

$$\left(\int_{-\infty}^{\infty} J'(F(x))f^2(x)dx\right)^2 \leq I(F) \cdot \int_{-\infty}^{\infty} (J'(F(x)))^2 f^2(x)F(x)(1 - F(x))dx,$$

which completes the proof of (4.2).

Now let $J_0(t) = \log(t/(1 - t))$. Then J_0 is just the logit function, or the "log odds." Since it equals the inverse G^{-1} of the standard logistic distribution function defined by $G(x) = e^x/(1 + e^x)$, the rank test on which the estimator is based can be called the logistic scores test. Therefore, we shall call the estimator $\hat{\theta}$ corresponding to the score function J_0, the *logistic scores estimator*.

We note that $J_0 \notin \mathcal{J}$, since it is unbounded, and so it is not yet known whether the logistic scores estimator is asymptotically efficient. However, it is a natural candidate in the search for an efficient estimator. We point out that one can easily obtain a sequence $\{J_m\}$ of score functions with $J_m \in \mathcal{J}$ for all m and $\lim_{m\to\infty} \sigma_{J_m}^2(F) = I^{-1}(F)$. For this, one need only truncate the values of J at m and smooth the resulting bounded function. Thus by choosing m sufficiently large, one can find an estimator with guaranteed asymptotic efficiency of, say, at least 99% under all 11 distributions considered in the next section.

The smallest possible asymptotic variance, given by (4.2), equals the reciprocal of the Fisher information about the location parameter in an infinite dose mesh experiment with randomized middose x_0, as defined in Brown (1961, especially formula (7.3)). This is exactly what Miller and Halpern found in the cases of L- and M-estimators.

The most surprising point about this result is that the score function that minimizes (4.1) does not depend on the underlying distribution F. The optimal L- and M-estimators found by Miller and Halpern depend on F, and one would expect such dependence here too.

5. A MONTE CARLO COMPARISON

The asymptotic results given in Section 4 suggest that the logistic scores estimator may be an efficient estimator when the number of individuals tested at each level is large and the dose mesh is sufficiently dense. To determine its efficiency in practical situations, however, one would hope to be able to calculate its mean squared error for small samples, which in our model means a small number of doses with few individuals tested at each dose. Unfortunately, this is not practicable; in fact, the only estimator we consider whose MSE is easy to calculate for small samples is Spearman-Kärber. Therefore, our study parallels Hamilton's in comparing sample MSE's of several estimators under various experimental conditions.

5.1 Estimators Compared

The 11 estimators we compare are of three types: R-estimators, trimmed and untrimmed Spearman-Kärber estimators, and parametric estimators based on the probit and logit methods. Their descriptions follow.

R-estimators. $\hat{\theta}_{LS}$ is the logistic scores estimator. $\hat{\theta}_{HL}$ is the analogue of the Hodges-Lehmann estimator of iid theory, obtained via the score function $J(t) = t - \frac{1}{2}$; in this case, the solution of the equation $h(\tilde{F}, \theta) = 0$ is also the solution of

$$\int_{-\infty}^{\infty} \tilde{F}(2\theta - x)d\tilde{F}(x) = \frac{1}{2},$$

and the Hodges-Lehmann estimator is the median of $(X + Y)/2$, where X and Y are independent random variables having common distribution $\tilde{F}$.

In both cases, (3.1) was solved by first capturing the solution in an interval of the type $[\theta_j, \theta_{j+1}]$, with $\theta_j = x_0 + (jd)/2$, and then finding the solution within the interval. Computing the value of $h(\tilde{F}, \theta)$ initially at points θ_j has two advantages: (a) ease in computation, since in this case the argument of the function J is linear in the intervals $[x_i, x_{i+1}]$; and (b) if J is strictly increasing, then $h(\tilde{F}, \theta)$ is strictly decreasing in $[\theta_j, \theta_{j+1}]$, unless $h(\tilde{F}, \theta_j) = h(\tilde{F}, \theta_{j+1})$. Thus if $h(\tilde{F}, \theta_j) > 0 > h(\tilde{F}, \theta_{j+1})$ for some j, then the unique solution of the equation lies in (θ_j, θ_{j+1}). Of course, if $h(\tilde{F}, \theta_j) = 0$ for some j, then one must check for zeroes at neighboring points, taking an average if such zeroes are found.

After pinning down the interval containing $\hat{\theta}_{LS}$, the solution was obtained by iteration, using linear interpolation to determine successive iterates. The procedure was said to converge as soon as the distance between the last two iterates was less than 10^{-5}, with the last iterate then used as the estimate. The Hodges-Lehmann estimate was calculated by solving a quadratic equation in $\Delta = (\hat{\theta} - \theta_j)/(\theta_{j+1} - \theta_j)$, as described in James and James (1979, Sec. 5).

Trimmed and Untrimmed Spearman-Kärber. $\hat{\theta}_{SK}$, the Spearman-Kärber estimator, is the mean of the empirical tolerance distribution, so that

$$\hat{\theta}_{SK} = \int x d\tilde{F}(x) = \sum_{i=-k+1}^{k} (\tilde{F}(x_{i+1}) - \tilde{F}(x_i))(x_i + d/2)$$
$$= x_k + d/2 - d\sum \tilde{p}_i = x_k + d/2 - d\sum \hat{p}_i.$$

$\hat{\theta}_{SK\alpha\%}$ is the $\alpha\%$-trimmed Spearman-Kärber estimator, which is defined by trimming $\alpha\%$ from each tail of the empirical tolerance distribution and taking the mean of the (appropriately normalized) remaining central part of the distribution:

$$\theta_{SK\alpha\%} = \frac{\int_{\tilde{F}^{-1}(\alpha/100)}^{\tilde{F}^{-1}(1-\alpha/100)} x\, d\tilde{F}(x)}{1 - (\alpha/50)}, \quad 0 \leq \alpha < 50.$$

We used $\alpha = 5$, 10, and 20. $\hat{\theta}_{SK50\%}$ is the median, which is the limit of the $\alpha\%$-trimmed Spearman-Kärber estimator as $\alpha \to 50$.

Estimators Based on Probits and Logits. $\hat{\theta}_{PR}$ and $\hat{\theta}_L$ are the estimators of the ED50 obtained by probit and logit analysis; that is, the maximum likelihood estimators (MLE's) of θ under the assumptions of normal and logistic tolerance distributions.

The values of the probit and logit MLE's were obtained by similar methods. First, the data were screened for two special cases, in which the MLE's are usually considered incalculable: that in which the $\hat{p}_i$ consisted only of a sequence of zeroes followed by a sequence of ones, and that in which only one value, $\hat{p}_j$, was different from zero and one, with zeroes to the left and ones to the right. In the former case, the MLE is indeterminate, whereas in the latter case, the supremum of the likelihood function can be obtained by a limit process, which yields x_j and zero as MLE's of the mean and variance of the tolerance distribution. However, this definition is highly artificial, and, as Hamilton did, we decided to treat both cases as leading to incalculable MLE's.

After screening, an iterative procedure was used to approximate the value of the estimate. The procedure was considered to have converged when the difference between successive iterates of $\hat{\theta}$ was less than 10^{-5}, with the estimates being called incalculable if convergence was not reached within 20 iterations.

$\hat{\theta}_{MLC}$ is a minimum logit chi-squared estimator based on the empirical logits $l_i = \log\{(r_i + \frac{1}{2})/(n - r_i + \frac{1}{2})\}$ and empirical weights $w_i = 1/\{(r_i + \frac{1}{2})^{-1} + (n - r_i + \frac{1}{2})^{-1}\}$, for $-k \le i \le k$. If more than one dose level yielded no response, only the largest was assigned a positive weight, the others being assigned weight $w_i = 0$. Similarly, if more than one dose level yielded n responses, only the smallest was assigned positive weight. This definition is slightly different from that of Hamilton, who set $w_i = 0$ if either $r_{-k} = \cdots = r_{i+1} = 0$ or $r_{i-1} = \cdots = r_k = n$. Our method of calculation was chosen to keep outliers in heavy-tailed and contaminated distributions from having their effects eliminated by smoothing, the point being to let the minimum logit chi-squared estimator show its pronounced sensitivity to contamination when it is based on raw response data. Finally, $\hat{\theta}_{MLCM}$ is a minimum logit chi-squared estimator based on the monotonized sequence $\tilde{F}(x_{-k}), \ldots, \tilde{F}(x_k)$, and is equal to the MLCSM of Hamilton (1979, Sec. 2.2.3).

5.2 Set-up of the Simulations

Two large simulation experiments were performed, corresponding to $n = 10$ and $n = 20$ individuals at each dose level. The calculations were carried out on an IBM 3032 computer at Brazil's Census Bureau (IBGE), with programs written in PL/I. Each experiment consisted of generating bioassays with the 11 dose levels 1, 2, . . . , 11, so that $k = 5$ and $x_0 = 6$. An odd number of dose levels was chosen for convenience.

We based each experiment on 1,800 replications of data sets consisting of $11n$ pseudo-random uniform variates, generated by the multiplicative congruential method with modulus 2^{31} and multiplier 65539. Each data set yielded 121 estimates, corresponding to the evaluation of 11 estimators at each of 11 tolerance distributions. The binomial response frequencies r_i were calculated for each data set and each distribution F by counting the number of members of the ith block of n uniform variates in the data set that took on values less than or equal to $F(x_i)$. We chose 1,800 as the number of replications to agree, for the purpose of comparison, with Hamilton's study. As in that study, all tolerance distributions were assumed to be symmetric about x_0 (so that 6 was the true value of the ED50) and the scale parameters were adjusted so that 98% of the distribution fell between the third smallest and third largest doses (3 and 9 in our case). Finally, we calculated the sample MSE's for each estimator at each underlying distribution, based on the pseudosamples of size 1,800.

The underlying distributions (models) used were the nine considered by Miller and Halpern (1980), plus contaminated logistic and normal distributions with 10% contamination. The contamination used was that of the basic distribution with 100 times the variance. For example, the logistic distribution with 10% contamination, called 10% Contam Logistic in the tables, was a weighted average consisting of 90% of a basic logistic distribution with mean 6, and 10% of a contaminating logistic distribution with the same mean and 100 times the variance. Miller and Halpern considered 5% contamination with the same factor of 100 for the variance of the contaminating distribution.

To aid in the interpretation of the empirical results, Table 1 presents asymptotic efficiencies of the seven L- and R-estimators for each of the 11 tolerance distributions. The efficiency given is the ratio between the reciprocal of the Fisher information, $I^{-1}(F)$, and the asymptotic variance of the estimator (or its formal value, as represented by $\sigma_J^2(F)$), as obtained from the results given in Miller and Halpern (1980) and James and James (1979). Asymptotic efficiencies were not calculated for

Table 1. Asymptotic Efficiencies

Distribution	Estimator						
	$\hat{\theta}_{SK}$	$\hat{\theta}_{SK5\%}$	$\hat{\theta}_{SK10\%}$	$\hat{\theta}_{SK20\%}$	$\hat{\theta}_{SK50\%}$	$\hat{\theta}_{LS}$	$\hat{\theta}_{HL}$
Cauchy	0	.74	.84	.71	0	1.00	.88
Logistic	1.00	.90	.80	.60	0	1.00	.83
Normal	.98	.86	.75	.55	0	1.00	.80
Uniform	0	0	0	0	0	—[a]	0
Laplace	.96	.90	.82	.67	0	1.00	.87
5% Contam Logistic	.75	.96	.88	.67	0	1.00	.89
10% Contam Logistic	.63	.94	.91	.72	0	1.00	.91
5% Contam Normal	.75	.95	.85	.63	0	1.00	.87
10% Contam Normal	.63	.97	.90	.68	0	1.00	.90
Angular	.81	.68	.58	.24	0	1.00	.67
Slash	0	.80	.88	.79	0	1.00	.94

[a] Indeterminate (= 0/0).

the parametric estimators, but it can be shown that the logit MLE has the same asymptotic variance as Spearman-Kärber. This is not surprising, since it is well known that the two estimators are similar in their behavior.

5.3 Numerical Results

Table 2 compares the sample MSE's obtained for the two cases $n = 10$ and $n = 20$. The third column gives the theoretical MSE of the Spearman-Kärber estimator, which can be compared with the empirical value immediately following it. The fifth column gives the approximate two-tailed p values for testing the differences between the empirical and theoretical MSE's of Spearman-Kärber. The sample variance of the MSE was used to estimate the true variance, and the p values were taken from tables of the normal distribution.

The other estimators are compared directly with Spearman-Kärber via relative efficiencies, so that the value given in the table is the inverse ratio of the sample MSE's. For each estimator and each distribution, the sample MSE was based on the number of data sets for which the estimator was calculable. All estimators but the probit and logit MLE's were calculable for all data sets. These two estimators turned out to be incalculable for the same distributions and data sets; except for one or two pathological exceptions, all incalculable estimates belonged to the second case described in Section 5.1. The number of data sets for which the probit and logit MLE's were calculable can be found in the last column of Table 2.

The significance of the differences among the sample MSE's is analyzed in Table 3. In order not to reduce our data base, the probit and logit MLE's were omitted from this analysis. This was no great loss as far as the logit MLE was concerned, because of its similarity with Spearman-Kärber. In fact, we calculated the sample correlation coefficient between the logit MLE and Spearman-Kärber for each distribution for $n = 10$ and $n = 20$, based on the data sets for which the logit MLE was calculable, and found that it never fell below .998.

The analysis was performed by obtaining simultaneous approximate level .05 confidence intervals for the 36 differences between the true MSE's of the 9 estimators, for each of the tolerance distributions. Bonferroni confidence intervals were obtained as described in Miller (1966, p. 200, formula (50)), but the normal distribution was used in place of the t. For each distribution, Table 3 lists the estimators whose MSE's were not distinguishable at the overall 5% level. In other words, each entry under a given estimator corresponds to another estimator such that the confidence interval for the difference of the MSE's contained zero.

5.4 Remarks

The simulation results obtained here, although based on a small number of special models in which the underlying distribution was symmetric about the central dose, do suggest that the logistic scores estimator merits further study and should be considered a candidate to estimate the ED50 in many real bioassays. Even in the case $n = 10$, its relative efficiency with respect to the best of the 11 estimators was never lower than .85 for the distributions considered, and it was superior to the other estimators in this respect. Also, it was the most efficient estimator for virtually all the heavy-tailed and contaminated distributions, being significantly better than the other estimators in the case $n = 20$. Since all estimators studied here are unbiased under our models, this leads us to believe that the logistic scores estimator performs well in relation to the other estimators, in terms of the variance, even with fairly small sample sizes. We believe,

Table 2. Sample Relative Efficiencies Based on All Calculable Estimates

Distribution		Theoretical MSE of $\hat{\theta}_{SK}$	Sample MSE of $\hat{\theta}_{SK}$	p-value	Sample Efficiency Relative to $\hat{\theta}_{SK}$										Data Sets
					$\hat{\theta}_{SK5\%}$	$\hat{\theta}_{SK10\%}$	$\hat{\theta}_{SK20\%}$	$\hat{\theta}_{SK50\%}$	$\hat{\theta}_{LS}$	$\hat{\theta}_{HL}$	$\hat{\theta}_{PR}$	$\hat{\theta}_{L}$	$\hat{\theta}_{MLC}$	$\hat{\theta}_{MLCM}$	
Cauchy	$n = 10$	.0384	.0379	.65	1.074	.972	.791	.691	1.075	.936	.667	.907	.231	.344	1388
	$n = 20$	.0192	.0189	.63	1.144	.994	.750	.588	1.302	.996	.688	1.007	.164	.257	1701
Logistic	$n = 10$	.0653	.0624	.16	.938	.871	.747	.636	.851	.791	.990	.996	.779	.812	1791
	$n = 20$	.0326	.0317	.40	.951	.886	.743	.526	.889	.796	.969	1.000	.866	.889	1800
Normal	$n = 10$	.0728	.0710	.46	.918	.841	.703	.555	.883	.777	1.025	.997	.875	.873	1797
	$n = 20$	.0364	.0348	.18	.923	.835	.693	.452	.882	.758	1.011	.998	.883	.887	1800
Uniform	$n = 10$	.1003	.1019	.63	.864	.740	.545	.340	1.199	.775	1.094	.986	.663	.663	1800
	$n = 20$	.0502	.0495	.68	.866	.750	.551	.260	1.266	.803	1.085	.987	.699	.708	1800
Laplace	$n = 10$	.0582	.0554	.12	.963	.899	.768	.660	.860	.809	.950	.991	.696	.745	1770
	$n = 20$	.0291	.0278	.16	.986	.949	.780	.568	.913	.844	.924	1.002	.751	.804	1800
5% Contam	$n = 10$	.0376	.0368	.52	1.057	.954	.775	.677	1.069	.923	.671	.903	.239	.344	1345
Logistic	$n = 20$	.0188	.0186	.76	1.126	.978	.739	.581	1.295	.985	.690	1.005	.169	.253	1684
10% Contam	$n = 10$	.0386	.0371	.25	1.037	.946	.770	.671	1.043	.907	.717	.911	.311	.390	1380
Logistic	$n = 20$	.0193	.0188	.40	1.122	.983	.740	.578	1.257	.978	.731	1.019	.228	.291	1711
5% Contam	$n = 10$	.0362	.0357	.68	1.045	.939	.763	.670	1.094	.918	.652	.890	.238	.336	1262
Normal	$n = 20$	.0181	.0177	.53	1.118	.955	.721	.568	1.359	.981	.671	1.005	.151	.226	1645
10% Contam	$n = 10$	.0385	.0374	.38	1.037	.949	.773	.674	1.033	.908	.725	.911	.336	.399	1386
Normal	$n = 20$	.0193	.0188	.48	1.121	.983	.740	.579	1.246	.977	.740	1.019	.245	.301	1704
Angular	$n = 10$	.0859	.0863	.89	.888	.783	.619	.442	.978	.756	1.065	.993	.784	.777	1799
	$n = 20$	.0430	.0411	.19	.896	.794	.624	.346	.981	.755	1.054	.994	.838	.842	1800
Slash	$n = 10$	.0384	.0379	.63	1.074	.972	.790	.690	1.075	.936	.667	.907	.232	.344	1388
	$n = 20$	.0192	.0189	.57	1.143	.993	.749	.587	1.299	.995	.688	1.006	.164	.256	1703

NOTE: Sample MSE's of $\hat{\theta}_{PR}$ and $\hat{\theta}_{L}$ were based on number of data sets appearing in the last column. Those of all other estimators were based on all 1,800 data sets.

Table 3. Estimators Not Distinguishable at 5% Level

Distribution		Estimator							
		$\hat{\theta}_{SK}$	$\hat{\theta}_{SK5\%}$	$\hat{\theta}_{SK10\%}$	$\hat{\theta}_{SK20\%}$	$\hat{\theta}_{SK50\%}$	$\hat{\theta}_{LS}$	$\hat{\theta}_{HL}$	$\hat{\theta}_{MLC}$
Cauchy	$n = 10$	SK10%	LS	—	—	—	—	—	—
	$n = 20$	SK10%, HL	—	HL	—	—	—	—	—
Logistic	$n = 10$	—	—	LS, MLC, MLCM	MLC, MLCM	—	MLC, MLCM	MLC, MLCM	MLCM
	$n = 20$	—	—	LS, MLC, MLCM	—	—	MLC, MLCM	—	—
Normal	$n = 10$	—	LS, MLC	LS, MLC, MLCM	—	—	MLC, MLCM	—	MLCM
	$n = 20$	—	LS, MLC, MLCM	LS	—	—	MLC, MLCM	—	MLCM
Uniform	$n = 10$	—	—	—	—	—	—	—	MLCM
	$n = 20$	—	—	—	—	—	—	—	MLCM
Laplace	$n = 10$	—	—	LS	MLC, MLCM	MLC	—	MLC, MLCM	MLCM
	$n = 20$	SK5%, SK10%	—	LS	MLC, MLCM	—	—	MLCM	—
5% Contam	$n = 10$	SK10%	LS	—	—	—	—	—	—
Logistic	$n = 20$	SK10%, HL	—	HL	—	—	—	—	—
10% Contam	$n = 10$	SK5%, SK10%, LS	LS	—	—	—	—	—	—
Logistic	$n = 20$	SK10%, HL	—	HL	—	—	—	—	—
5% Contam	$n = 10$	SK5%, SK10%	—	—	—	—	—	—	—
Normal	$n = 20$	SK10%, HL	—	—	—	—	—	—	—
10% Contam	$n = 10$	SK5%, SK10%, LS	LS	—	—	—	—	—	—
Normal	$n = 20$	SK10%, HL	—	HL	—	—	—	—	—
Angular	$n = 10$	LS	—	HL, MLC, MLCM	—	—	—	MLC, MLCM	MLCM
	$n = 20$	LS	—	—	—	—	—	—	MLCM
Slash	$n = 10$	SK10%	LS	—	—	—	—	—	—
	$n = 20$	SK10%, HL	—	HL	—	—	—	—	—

NOTE: Ordered pairs of estimators with indistinguishable MSE's are presented by listing the second estimator of the pair under the column headed by the first. The order used is that of Table 2, without the probit and logit MLE's. For convenience, only the subscripts of the estimators are listed.

as does Hamilton (1979, Section 4.2), that for well-behaved estimators the contribution of the bias to the MSE will be small when the dose mesh is not symmetric about the ED50. It would be desirable, however, to have theoretical, or at least Monte Carlo, confirmation of this belief. We are presently looking at this problem.

As for the other estimators, 5%-trimmed Spearman-Kärber was quite good in our study, except when the tolerance distribution was uniform. The performance of the logit MLE was good, although this must be taken with a grain of salt because of the problem of calculability. Also, our results support Hamilton's conclusion that the minimum logit chi-squared estimator should not be used without first monotonizing the $\hat{p}_i$.

A comparison of the simulation results with Table 1 shows that the estimators lined up in approximately the same order, in terms of efficiency, as they obey asymptotically. The logistic scores estimator was significantly better than the other estimators under the uniform distribution, where its asymptotic efficiency relative to the others is infinite. The median had uniformly poor performance, as could be expected from its asymptotic efficiency of zero.

Note that the p values presented in Table 2 lend some credibility to our results, since none of the sample MSE's of Spearman-Kärber was significantly different from the true MSE at the 10% level.

APPENDIX

In the following, the function J is assumed to satisfy the conditions of Definition 1. F, F_1, F_2, . . . , denote distribution functions, not necessarily symmetric unless explicitly assumed so. The interval $\{x: 0 < F(x) < 1\}$ is called the "support interval" of F.

Lemma 1. If F is continuous and is strictly increasing in its support interval, then the solution of

$$h(\theta) \overset{\text{def}}{=} \int J\left(\frac{F(x) + 1 - F(2\theta - x)}{2}\right) dF(x) = 0$$

exists and is unique.

Proof. Suppose for convenience that J is strictly increasing (the lemma holds without this assumption, but the proof is more complicated). It will be shown that, in this case, the function h is strictly decreasing in the interval in which it attains neither its supremum nor its infimum, that is, in

$$\left\{\theta: 2\int_0^{1/2} J(t)dt < h(\theta) < 2\int_{1/2}^1 J(t)dt\right\}$$

(see Section 3).

Suppose that θ_1 and θ_2 both belong to this interval, with $\theta_1 < \theta_2$. It then follows by the discussion in Section 3 that there exists a point x_0 in the support interval of F such that $0 < F(2\theta_1 - x_0) < 1$ (if there were no such point, one of the extreme values of h would be attained at θ_1). Since F is continuous and strictly increasing in a neighborhood of $2\theta_1 - x_0$, there is a neighborhood of x_0 in which $0 < F(2\theta_1 - x) < F(2\theta_2 - x) \leq 1$. Therefore, for x in that neighborhood of x_0 we have

$$J\left(\frac{F(x) + 1 - F(2\theta_1 - x)}{2}\right) > J\left(\frac{F(x) + 1 - F(2\theta_2 - x)}{2}\right).$$

Since "$\geq$" holds in place of "$>$" in the preceding inequality for all x, the lemma follows.

Lemma 2. Suppose that F is a member of a location parameter family $\{F_\theta: \theta \in \mathbf{R}\}$, where F_θ is continuous, symmetric about θ, and strictly increasing in its support interval. If $(n/d)^{1/2}(\hat{\theta} - \theta_D)$ has a limit distribution when $\theta = 0$, where the limit is taken as first $n \to \infty$ and then $d \to 0$, $x_k \to +\infty$ and $x_{-k} \to -\infty$, then that distribution is the limit distribution regardless of the true value of θ.

Proof. The middose x_0 is not held fixed as the dose mesh becomes dense in the line, and so if all the dose meshes are simultaneously shifted by a fixed amount δ, the limit distribution will be the same when $\theta = 0$. Since shifting the distribution by an amount δ does not change the distribution of $\hat{\theta} - \theta_D$ if the dose mesh is also shifted by δ, the limit distribution is the same under F_θ.

Lemma 3. Suppose that $F_n \xrightarrow{w} F_0$ as $n \to \infty$, where F_0 and F_n are continuous and are strictly increasing in their support intervals. If the score function J has a bounded derivative in (0, 1), then

$$\theta_J(F_n) \to \theta_J(F_0) \quad \text{as} \quad n \to \infty,$$

where $\theta_J(F)$ is defined by

$$\int J\left(\frac{F(x) + 1 - F(2\theta_J(F) - x)}{2}\right) dF(x) = 0.$$

Proof. By Lemma 1, $\theta_J(F_0)$ and $\theta_J(F_n)$ are uniquely defined. For $i = 0, 1, 2, \ldots$ and $\theta \in \mathbf{R}$, let

$$h_i(\theta) = \int_{-\infty}^{\infty} J\left(\frac{F_i(x) + 1 - F_i(2\theta - x)}{2}\right) dF_i(x).$$

Because of the monotonicity of the functions h_i and the uniqueness of the solutions of $h_i(\theta) = 0$, it is sufficient to show that, for all θ, $h_n(\theta) \to h_0(\theta)$ as $n \to \infty$. (If this condition is satisfied, then for $\theta < \theta_J(F_0)$ one has $h_0(\theta) > 0$, $h_n(\theta) > 0$ for n sufficiently large, and consequently $\theta < \theta_J(F_n)$ for n sufficiently large, with a similar argument holding for $\theta > \theta_J(F_0)$.)

Since J' is bounded and F_n converges uniformly to F_0, the integrand involved in the definition of $h_n(\theta)$ converges uniformly to that involved in the definition of $h_0(\theta)$. Together with the Helly-Bray theorem, this implies the convergence of $h_n(\theta)$ to $h_0(\theta)$.

In order to prove that $\hat{\theta}$ is asymptotically normal, we adopt the following conditions of regularity:

Regularity conditions on the tolerance distribution F.

F0: F is symmetric about θ.
F1: F is strictly increasing in its support interval.
F2: F has a bounded density, f, which is continuous almost everywhere.
F3: There exists an L such that f is nondecreasing in $(-\infty, L]$ and nonincreasing in $[L, \infty)$.

Regularity conditions on the score function J. (These conditions include those given in Definition 1.)

J1: J is continuous and nondecreasing in (0, 1).
J2: J is twice differentiable in (0, 1), with bounded second derivative J''.
J3: J is antisymmetric about 1/2, that is, $J(t) = -J(1 - t)$, so that $J(1/2) = 0$, $J'(t) = J'(1 - t)$, and $\int_0^1 J(t)dt = 0$.
J4: J is not constantly equal to zero.

Theorem. Under the above regularity conditions on F and J,

$$(n/d)^{1/2}(\hat{\theta} - \theta_D) \xrightarrow{\mathcal{D}} N\left(0, \frac{\int (J'(F(x)))^2 f^2(x)F(x)(1-F(x))dx}{\left(\int J'(F(x))f^2(x)dx\right)^2}\right),$$

where the limit is taken as first $n \to \infty$ and then $d \to 0$, $x_k \to +\infty$, and $x_{-k} \to -\infty$. The integrals given in the numerator and denominator of the asymptotic variance are strictly positive and finite.

Proof. Both integrals in the expression for the asymptotic variance are finite because the integrands are bounded by a constant times the density f (J2 implies that J' is bounded). The integrals are positive, by J4, and, being invariant under shifts, do not depend on the parameter θ. By Lemma 2, it is enough to prove the theorem under the assumption $\theta = 0$, which we make for the remainder of the proof.

The method we use is an adaptation of that used by Hodges and Lehmann (1963). First note that by F1, J1, J4, and Lemma 1, the equation $h(\tilde{F}, \theta) = 0$ will, with probability one, eventually have a unique solution $\hat{\theta}$. Since $h(\tilde{F}, \theta)$ is nonincreasing in θ, this implies that for any sequence of constants $\{c_n\}$, $\hat{\theta} \le c_n$ if and only if $h(\tilde{F}, c_n) \le 0$, at least for n sufficiently large (with probability one). Therefore,

$$\begin{aligned}\lim_{n\to\infty} P((n/d)^{1/2}(\hat{\theta} - \theta_D) \le a) &= \lim_{n\to\infty} P(\hat{\theta} \le \theta_D + a(d/n)^{1/2}) \\ &= \lim_{n\to\infty} P((n/d)^{1/2}h(\tilde{F}, \theta_D + a(d/n)^{1/2}) \le 0),\end{aligned}$$

provided this last limit exists. Letting the dose mesh become finer, we see that

$$\lim P((n/d)^{1/2}(\hat{\theta} - \theta_D) \le a) = \lim P((n/d)^{1/2}h(\tilde{F}, \theta_D + a(d/n)^{1/2}) \le 0), \quad \text{(A.1)}$$

if the latter limit exists, where the limits are taken as first $n \to \infty$ and then $d \to 0$, $x_k \to +\infty$ and $x_{-k} \to -\infty$.

Now recall that

$$\int J\left(\frac{F_D(x) + 1 - F_D(2\theta_D - x)}{2}\right) dF_D(x) = 0,$$

and write

$$(n/d)^{1/2}h(\tilde{F}, \theta_D + a(d/n)^{1/2}) = \mathrm{I} + \mathrm{II} + \mathrm{III},$$

where

$$\text{I} = (n/d)^{1/2} \int \left[J\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) - J\left(\frac{F_D(x) + 1 - F_D(2\theta_D - x)}{2}\right)\right] dF_D(x),$$

$$\text{II} = (n/d)^{1/2}\left\{ \int \left[J\left(\frac{\tilde{F}(x) + 1 - \tilde{F}(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) - J\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right)\right] dF_D(x) + \int J\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) \times d(\tilde{F}(x) - F_D(x))\right\},$$

$$\text{III} = (n/d)^{1/2} \int \left[J\left(\frac{\tilde{F}(x) + 1 - \tilde{F}(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) - J\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right)\right] \times d(\tilde{F}(x) - F_D(x)).$$

The theorem will follow from proofs of the following:

(i) $\text{I} \to -a \int J'(F(x))f^2(x)dx$,

(ii) $\text{II} \xrightarrow{\mathcal{D}} N(0, \int (J'(F(x)))^2 f^2(x)F(x)(1 - F(x))dx)$, and

(iii) $\text{III} \to 0$ in probability.

To see that (i) through (iii) imply the theorem, note that they imply

$$(n/d)^{1/2} h(\tilde{F}, \theta_D + a(d/n)^{1/2}) \xrightarrow{\mathcal{D}} N\left(-a \int J'(F(x))f^2(x)dx, \int (J'(F(x)))^2 f^2(x)F(x)(1 - F(x))dx\right),$$

and therefore (from (A.1)),

$$\lim P((n/d)^{1/2}(\theta - \theta_D) \le a) = \Phi\left(\frac{a \int J'(F(x))f^2(x)dx}{\left(\int (J'(F(x)))^2 f^2(x)F(x)(1 - F(x))dx\right)^{1/2}}\right),$$

where Φ is the standard normal distribution function. Thus, $(n/d)^{1/2}(\hat{\theta} - \theta_D)$ has, asymptotically, the normal distribution stated in the theorem.

We now sketch the proof of (i), (ii), and (iii). Details can be found in James and James (1979). It is important to keep in mind that we are assuming $\theta = 0$, so that in particular F0 implies $f(x) = f(-x)\ \forall\ x$.

Part (i) is a consequence of the DCT, which first yields (by J2)

$$\lim_{n\to\infty} \text{I} = -a \int J'\left(\frac{F_D(x) + 1 - F_D(2\theta_D - x)}{2}\right) \times F_D'(2\theta_D - x)dF_D(x),$$

and then, together with F2, F3, and J2, yields the desired result when $d \to 0$, $x_k \to +\infty$, and $x_{-k} \to -\infty$.

Part (iii) can be proved by using the definitions of $\tilde{F}$ and F_D, applying the Central Limit Theorem to the resulting $\tilde{p}_i - p_i$, and noting that the integrand in III is bounded (by J2) and converges to zero a.s.

To prove (ii), start by using Taylor expansion for J in the first integral. The integrand is essentially equal to

$$J'\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) \times \frac{(\tilde{F}(x) - F_D(x) - (\tilde{F}(2\theta_D + 2a(d/n)^{1/2} - x) - F_D(2\theta_D + 2(d/n)^{1/2} - x)))}{2},$$

since the error term is asymptotically negligible as $n \to \infty$ (use F1 and J2). Now integrate the second integral by parts; it equals

$$-\int \frac{(\tilde{F}(x) - F_D(x))}{2} \times J'\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) \times (F_D'(x) + F_D'(2\theta_D + 2a(d/n)^{1/2} - x))dx.$$

Then add the two integrals. Since $dF_D(x) = F_D'(x)dx$, the first term of each integral will cancel out. The second terms are equal, as can be seen by the change of variables $y = 2\theta_D + 2a(d/n)^{1/2} - x$ in the second term of the first integral, together with the fact that $J'(t) = J'(1 - t)$, from J3. Therefore, II is asymptotically equivalent to

$$-(n/d)^{1/2} \int J'\left(\frac{F_D(x) + 1 - F_D(2\theta_D + 2a(d/n)^{1/2} - x)}{2}\right) \times F_D'(2\theta_D + 2a(d/n)^{1/2} - x)(\tilde{F}(x) - F_D(x))dx.$$

Using F2, F3, J2, and the definitions of $\tilde{F}$ and F_D, it can be shown to be a consequence of the Central Limit Theorem, the DCT, and Slutsky's theorem, that as $n \to \infty$

$$\text{II} \xrightarrow{\mathcal{D}} N\left(0, 1/d \sum_{i=-k}^{k} p_i(1 - p_i)\left[\int_{x_{i-1}}^{x_i} \times J'\left(\frac{F_D(x) + 1 - F_D(2\theta_D - x)}{2}\right) F_D'(2\theta_D - x)\right]^2\right),$$

where we have ignored another asymptotically negligible term. Part (ii) then follows by a calculus argument when $d \to 0$, $x_k \to +\infty$, and $x_{-k} \to -\infty$.

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