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RISK-EFFICIENT ESTIMATION OF THE MEAN OF THE LOGISTIC RESPONSE FUNCTION USING THE SPEARMAN-KARBER ESTIMATOR

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Abstract: In this paper we study the asymptotic properties of the sequential risk-efficient rule developed for the estimation of the mean of the logistic response function based on the quantal responses observed at equally spaced dose levels. The Spearman-Karber (S-K) and Spearman-type variance (S-T-V) estimator are used for the mean and variance, respectively, in the sequential estimation.

Key words and phrases: Logistic regression, lethal dosage 50, sequential estimation, Spearman-Karber estimator, optimal properties.

1. Introduction and Notation

Spearman (1908), Karber (1931), Finney (1952), Berkson (1955), Brown (1961), Miller (1973) and Church and Cobb (1973) have investigated the theoretical merits of the Spearman mean estimator. Miller (1973) also showed that the Spearman-Karber estimator is in terms of efficiency, the best estimator among all nonparametric estimators (see also Govindarajulu and Lindgvist (1986)). Church and Cobb (1973) showed that, asymptotically, for small dose span, the Spearman-Karber estimator is equivalent to the maximum likelihood estimator. Epstein and Churchman (1944), Cornfield and Mantel (1950) and Chmiel (1976) have investigated the theoretical merits of the Spearman-type variance estimator. For some other details the reader is referred to Govindarajulu (1988). The sequential methods for estimation of parameters were first proposed by Wald. The methods commonly in use are fixed-width method, fixed-precision method and risk-efficient plus sampling cost method. Anscombe (1953), Ray (1957), Robbins (1959), Starr (1966) have extensively studied the theoretical merits of these sequential procedures. Robbins (1959) estimates the mean of the iid random variables using the quadratic loss function. Starr (1966) considers a more general loss function, in the risk-efficient estimation. For some details on these contributions see Govindarajulu (1987, §5.1). Here we are concerned with the risk-efficient estimation of the mean of a logistic regression model within the context of a quantal bioassay model. We describe our approach as follows.

In the usual quantal bioassay model, the mean (or median) of a distribution function $F(x)$ is estimated by selecting $2k+1$ doses on the x-scale $x_{-k}, x_{-k+1}, x_{-k+2}, \ldots, x_0, \ldots, x_{k-1}, x_k$ and then observing n experimental units at each dose level. The positive responses are recorded as 1's and the negative responses as 0's. We consider the probability of positive response to be the logistic distribution function given by

$$F(x) = \left[1 + e^{-(x-\theta)/\beta}\right]^{-1}.$$

The location and scale parameters θ and β are estimated respectively by the Spearman-Karber (S-K) estimator given by

$$\hat{\theta}_k = \left(x_0 + \frac{d}{2}\right) - \frac{d}{n}\sum_{-k}^{0} r_i + \frac{d}{n}\sum_{1}^{k}(n - r_i), \tag{1.1}$$

and the Spearman-type variance (S-T-V) estimator given by

$$\hat{\beta}_k^2 = \frac{3}{\pi^2}\left\{\left(x_0 + \frac{d}{2}\right)^2 - \frac{2d}{n}\sum_{-k}^{0} x_i r_i + \frac{2d}{n}\sum_{1}^{k} x_i(n - r_i) - (\hat{\theta}_k)^2\right\}, \tag{1.2}$$

where

$$\begin{aligned} x_0 &= \text{the initial dose level}, \\ x_i &= x_0 + id, \ i = 0, \pm 1, \pm 2, \ldots, \pm k, \\ r_i &= \text{number of positive responses at } x_i, \\ d &= \text{dose span}, \\ n &= \text{number of experimental units at each dose level.} \end{aligned}$$

We study the almost sure convergence of the S-K estimator, the sequential S-K estimator, S-T-V estimator and the sequential S-T-V estimator. Using the asymptotic properties of these estimators we establish the "asymptotic efficiency" of the sequential procedure given by (2.5), as the dose span $d(= \frac{d_0}{m})$ tends to zero (analogously as $m \to \infty$).

Later on we show that if the cost of sampling per unit c is of the form $c = O(d^{1+\eta})$ where $\eta > 1$ and a certain regularity condition holds, then the sequential procedure given by (2.5) is risk-efficient.

2. The Sequential Procedure

First, the initial dose level x_0 is chosen at random (uniformly) between 0 and d, where d is a specified small positive number. The other dose levels are selected according to the formula $x_i = x_0 + id$, $i = 0, \pm 1, \pm 2, \ldots, \pm k$. At each dose level, n experimental units are placed and the individual responses are recorded as 1 *or* 0 according as the unit gives a positive *or* negative response. The experiment begins by placing n experimental units at each of the dose levels x_{-i} and x_i at the $(i+1)$th stage until the experiment is stopped according to a risk-efficient rule $(i = m^*, m^*+1, \ldots)$.

The risk-efficient rule is derived in such a way that at the stopping stage, the mean squared error of the estimator plus the sampling cost is at the minimum. Assume that the cost per experimental unit is c, where c may be a function of the dose span d. Let

$$\begin{aligned} R &= \text{Risk} + \text{Cost} \\ &= \text{Var}(\hat{\theta}_k) + \Big(\text{bias}(\hat{\theta}_k)\Big)^2 + (2k+1)cn. \end{aligned} \tag{2.1}$$

Note that

$$\begin{aligned} \text{Var}(\hat{\theta}_k) &= \sigma^2_{\hat{\theta}_k} = E\Big(\text{Var}(\hat{\theta}_k|x_0)\Big) + \text{Var}\Big(E(\hat{\theta}_k|x_0)\Big) \\ &= \frac{d\beta}{n}\left\{G\left(\frac{kd-\theta}{\beta}\right) + G\left(\frac{kd+\theta}{\beta}\right) - 1\right\} + o(d^2), \end{aligned} \tag{2.2}$$

where $G(x) = (1+e^{-x})^{-1}$.

The bias of $\hat{\theta}_k$ is

$$\begin{aligned} B &= E(\hat{\theta}_k) - \theta = E\Big(E(\hat{\theta}_k|x_0)\Big) - \theta \\ &= E\left\{\left(x_0 + \frac{d}{2}\right) - \frac{d}{n}\sum_{-k}^{0} n \cdot F(x_i) + \frac{d}{n}\sum_{1}^{k} n\Big(1 - F(x_i)\Big)\right\} - \theta \\ &= \beta\int_{(kd+\theta)/\beta}^{(kd+d-\theta)/\beta} (1 - G(u))du \\ &\approx \beta\frac{e^{-(kd+\theta)/\beta} - e^{-((k+1)d-\theta)/\beta}}{1 + e^{-((k+1)d-\theta)/\beta}}. \end{aligned} \tag{2.3}$$

This leads to the objective function R (after ignoring $o(d^2)$) as

$$\begin{aligned} R = {} & \left(\frac{d\beta}{n}\right)\left\{\left[1 + e^{-(kd-\theta)/\beta}\right]^{-1} + \left[1 + e^{-(kd+\theta)/\beta}\right]^{-1} - 1\right\} \\ & + \beta^2\left\{e^{-(kd+\theta)/\beta} - e^{-((k+1)d-\theta)/\beta}\right\}^2 \cdot \left\{1 + e^{-((k+1)d-\theta)/\beta}\right\}^{-2} + (2k+1)cn. \end{aligned}$$

In order to find the value of k that minimizes R, we set the partial derivative of R with respect to k equal to zero and then solve for k. In order to show that the optimum value of k thus obtained will in fact minimize R, we show that the second (partial) derivative of R with respect to k is positive when evaluated at the optimizing value of k (see Nanthakumar (1989)).

Now to derive the rule, let $\alpha = e^{\theta/\beta}$, $\gamma = e^{-d/\beta}$, $\Delta = \frac{d}{n}$ and $\tilde{T} = (4 + \frac{2\Delta}{\beta} + \frac{4c/\beta}{\Delta})\gamma + \frac{c/\beta}{\Delta}(\alpha^2\gamma^2 + \frac{1}{\alpha^2})$. If terms of order $e^{-3kd/\beta}$ and higher can be neglected, the stopping value of k that minimizes the cost plus the risk is: stop taking dose levels when

$$\frac{kd}{\beta} \geq \log_e J(\theta, \beta, c, d, n), \tag{2.4}$$

where

$$J(\theta,\beta,c,d,n) = \frac{4\beta(\Delta + \frac{4c}{\Delta})^{-1}\left\{(\alpha\gamma + \frac{1}{\alpha}) - \tilde{T}(\alpha\gamma + \frac{1}{\alpha})^{-1}\right\}}{1 + \left\{1 + \frac{16c\beta}{\Delta}(\Delta + \frac{4c}{\Delta})^{-2}\left[1 - \tilde{T}(\alpha\gamma + \frac{1}{\alpha})^{-2}\right]\right\}^{1/2}}.$$

However, since θ and β are unknown, we use the following adaptive rule. That is, stop taking observations at the $(K+1)$th stage, where K is given by

$$K = \inf\left\{k; k \geq m^*,\ \frac{kd}{\hat{\beta}_k} \geq \log_e J(\hat{\theta}_k, \hat{\beta}_k, c, d, n)\right\}, \tag{2.5}$$

where $\hat{\theta}_k$ and $\hat{\beta}_k$ denote the S-K estimator and S-T-V estimator, respectively, and $J(\hat{\theta}_k, \hat{\beta}_k, c, d, n)$ is the quantity corresponding to $J(\theta, \beta, c, d, n)$ when θ and β are replaced by $\hat{\theta}_k$ and $\hat{\beta}_k$, respectively. These estimators are strongly consistent under some regularity assumptions and are easily computable.

If θ and β are known then the stopping value of k is given by

$$k^* = (\beta/d)\log_e J(\theta, \beta, c, d, n). \tag{2.6}$$

3. Finite Termination of the Stopping Rule

In this section, the finite termination of the stopping rule is considered. We show that the experiment terminates with probability one when the dose span d is bounded away from zero.

Note that from (2.5),

$$\begin{aligned}\{K > k\} &\subseteq \left\{\hat{\beta}_k J(\hat{\theta}_k, \hat{\beta}_k, c, d) > kd\right\} \\ &\subseteq \left\{\hat{\beta}_k \log_e\left[4\hat{\beta}_k\left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1}\left(e^{(\hat{\theta}_k - d)/\hat{\beta}_k} + e^{-\hat{\theta}_k/\hat{\beta}_k}\right)\right] > kd\right\}.\end{aligned} \tag{3.1}$$

This implies that

$$P(K > k) \leq P\left\{\hat{\beta}_k \log_e\left[4\hat{\beta}_k\left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1}\left(e^{(\hat{\theta}_k - d)/\hat{\beta}_k} + e^{-\hat{\theta}_k/\hat{\beta}_k}\right)\right] > kd\right\} \tag{3.2}$$

and by applying Markov's inequality, we get

$$P\{K > k\} \leq \left(\frac{1}{kd}\right) E\left\{\hat{\beta}_k \log_e \left[4\hat{\beta}_k \left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1} \left(e^{(\hat{\theta}_k - d)/\hat{\beta}_k} + e^{-\hat{\theta}_k/\hat{\beta}_k}\right)\right]\right\}. \quad (3.3)$$

This inequality can be further reduced to

$$\begin{aligned} P\{K > k\} &\leq \left(\frac{1}{kd}\right) E\left\{\hat{\beta}_k \log_e \left[8\hat{\beta}_k \left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1} e^{\hat{\theta}_k/\hat{\beta}_k}\right]\right\} \\ &\leq \left(\frac{1}{kd}\right) E\left\{\hat{\beta}_k \left[\log_e \hat{\beta}_k + \log_e \left(8\left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1}\right)\right] + \hat{\theta}_k\right\} \\ &\leq \left(\frac{1}{kd}\right)\left\{E(\hat{\beta}_k^2) + \log_e \left[8\left(\frac{d}{n} + \frac{4nc}{d}\right)^{-1}\right] E(\hat{\beta}_k) + E(\hat{\theta}_k)\right\}. \quad (3.4) \end{aligned}$$

Note that $E(\hat{\beta}_k^2) < \infty$, $E(\hat{\theta}_k) < \infty$ (see Lemma 8 of the Appendix). Hence, $P\{K > k\} \to 0$ as $k \to \infty$. This shows the finite termination of the risk-efficient stopping rule for fixed values of c, d and n.

4. Asymptotic Results

In this section, the asymptotic properties of the S-K estimator, S-T-V estimator and the stopping rule will be stated and the proofs deferred to the appendix. In order to assert the almost sure convergence of the estimators, we take the initial number of stages to be $m^* + 1$ where $m^* = m^*(d) = O(d^{-1}\log_e(d^{-1}))$ as $d \to 0$, where d is the dose span such that $d = \frac{d_0}{m}$ for some d_0 (> 0) and positive integer m. For convenience, we choose the initial number of stages $m^* = m \log_e m$.

Theorem 4.1 deals with the asymptotic properties of the stopping rule, sequential S-K estimator and the sequential S-T-V estimator while Theorem 4.2 focuses on the risk-efficiency of the stopping rule.

Theorem 4.1. *For the stopping rule given by* (2.5), *we have*
(i) $K(d) \to \infty$ *as* $d \to 0$.
(ii) $E(K(d)) \to \infty$ *as* $d \to 0$.
(iii) $\hat{\theta}_{K(d)} \to \theta$ *a.s. as* $d \to 0$, $d = \frac{d_0}{m}$.
(iv) $\beta_{K(d)} \to \beta$ *a.s. as* $d \to 0$, $d = \frac{d_0}{m}$.
(v) $\frac{K(d)}{k^*(d)} \to 1$ *as* $d \to 0$, $d = \frac{d_0}{m}$ *and* $k^*(d)$ *is the value of* k *satisfying* (2.4).
(vi) $E\{\frac{K(d)}{k^*(d)}\} \to 1$ *as* $d \to 0$.

Note: *Property* (vi) *is known as asymptotic efficiency.*

Theorem 4.2. *For the stopping rule given by* (2.5), *if* $c = O(d^{1+\eta})$ *for some* η (> 1) *and* $e^{-(K(d)-k^*(d))d}$ *is uniformly integrable, then the rule is risk-efficient as* d *tends to zero.*

5. Numerical Results

Consider the following dose response problem. Suppose that the response is quantal (or binary) and its occurrence or non-occurrence depends upon the intensity of the stimulus administered. Let us assume that at each dose level, $n = 3$ experimental units are placed and the responses are measured at each dose level. Here the number of positive responses follow a binomial distribution with $n = 3$ and the probability of success is the distribution function of the intensity levels. Letting x denote the dose level and $P(x) = [1 + e^{-(x-\theta)/\beta}]^{-1}$ the probability of success at x, we estimate θ sequentially using the risk-efficient stopping rule.

In the case that $c = O(\Delta^{1+\eta})$ where $\Delta = \frac{d}{n}$ and $\eta > 1$, the stopping rule given by equations (2.4) and (2.5) can be approximated respectively by

$$k^* \doteq \frac{\beta}{d} \log_e \left\{ 2\beta^{1/2} \left(\frac{d}{n}\right)^{-\eta/2} \left(e^{|\theta|/\beta} - e^{-|\theta|/\beta}\right) \right\}, \tag{5.1}$$

$$K \doteq \inf \left\{ k;\ k > \frac{\hat\beta_k}{d} \log_e \left[2\hat\beta_k^{1/2} \left(\frac{d}{n}\right)^{-\eta/2} \left(e^{|\hat\theta_k|/\hat\beta_k} - e^{-|\hat\theta_k|/\hat\beta_k}\right) \right] \right\}. \tag{5.2}$$

To simplify the numerical computation, we use equations (5.1) and (5.2) in the place of (2.4) and (2.5), respectively. In the computations $c = \frac{1}{15}(\frac{d}{n})^{1+\eta}$ with $\eta = 1.98$.

As we see, when the dose span d goes up in value, K and k^* go down in value, and as d goes to zero, EK/k^* tends to one.

An example

In order to demonstrate the application of the risk-efficient procedure, we generate a random sample from the logistic distribution with $\theta = 0.625$, $\beta = 0.5$ and $\eta = 1.98$, $d = 0.2$ and $n = 3$. When $c = (1/15)d^{1+\eta} = 0.00055$, the rule is to stop according to (5.2). We obtain the following results.

Hence $K = 8$ and the data is $(0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 1, 2, 1, 2, 2, 2, 3)$. We also compute k^* using (5.1) as $k^* = 10.48 \doteq 11$.

Table 5.1. Risk-efficient procedure results

θ	β	d	$E(K)$	k^*	$E(K/k^*)$	R_K/R_{k^*}
2	1	0.2	26.8	27	0.992	0.996
2	1	0.15	40.5	38	1.060	1.033
2	1	0.1	61.6	61	1.010	1.018
−2	1	0.2	29.1	27	1.078	1.081
−2	1	0.15	40.1	38	1.056	1.074
−2	1	0.1	57	61	0.934	0.972
2	2	0.2	40.3	43	0.937	1.053
2	2	0.15	63.2	64	0.987	0.972
2	2	0.1	105	106	0.991	0.997
−2	2	0.2	45.6	43	1.066	1.066
−2	2	0.15	64.2	64	1.003	0.923
−2	2	0.1	106	106	1.000	1.000
1	1	0.2	17.4	22	0.791	1.043
1	1	0.15	26.8	31	0.865	0.919
1	1	0.1	44.6	50	0.892	1.043
−1	1	0.2	21.6	22	0.982	1.094
−1	1	0.15	28.7	31	0.926	0.944
−1	1	0.1	47.8	50	0.956	1.058
3	0.5	0.20	21.5	23	0.935	0.958
3	0.5	0.15	29.6	31	0.955	1.021
3	0.5	0.10	47.2	49	0.963	0.999
−3	0.5	0.20	21.2	23	0.922	0.906
−3	0.5	0.15	30.2	31	0.974	1.045
−3	0.5	0.10	49	49	1.00	1.007

k	$\hat{\theta}_k$	$\hat{\beta}_k$	R.HS of (5.1) with $\beta = \hat{\beta}_k$ and $\theta = \hat{\theta}_k$
1	0.216	0.103	2.241
2	0.283	0.137	3.043
3	0.416	0.207	4.756
4	0.483	0.243	5.646
5	0.550	0.284	6.628
6	0.616	0.328	7.676
7	0.616	0.328	7.676
8	0.616	0.328	7.676
9	0.616	0.328	7.676
10	0.616	0.328	7.676

Appendix

Here certain mathematical details of the proofs of Theorems 4.1 and 4.2 are presented. Note that $d = \frac{d_0}{m}$, where $d_0 > 0$ and m is a positive integer. In order to prove Theorem 4.1, we need the following lemmas. In the proofs of the lemmas, for simplicity K is used (since $K(d) = K(m) = K$) in place of $K(d)$ or $K(m)$. We use uniform probability bounds in several places in the proofs. Note that (A.6) and similar inequalities are very useful in this regard.

Lemma 1. *Let X be a continuous random variable with distribution function $F(\cdot)$ and $E(X) = \theta$. Then for any $x_0 \in (0, d)$*

$$\left|\theta - \left(x_0 + \frac{d}{2}\right) + d\sum_{-\infty}^{0} F(x_0 + id) - d\sum_{1}^{\infty}(1 - F(x_0 + id))\right| \leq \frac{d}{2}.$$

Proof. One can write

$$\begin{aligned}\theta &= \int_{-\infty}^{\infty} xdF(x) = \sum_{-\infty}^{\infty} \int_{x_0+id}^{x_0+(i+1)d} xdF(x) \\ &= \sum_{-\infty}^{\infty} x_i^*\{F(x_{i+1}) - F(x_i)\} \text{ for some } x_i^* \qquad \text{(A.1)}\end{aligned}$$

such that $x_i \leq x_i^* \leq x_{i+1}$. Note that (A.1) can be written as

$$\theta = \sum_{-\infty}^{\infty} \left(x_i^* - x_i - \frac{d}{2}\right)\{F(x_{i+1}) - F(x_i)\} + \sum_{-\infty}^{\infty} \left(x_i + \frac{d}{2}\right)\{F(x_{i+1}) - F(x_i)\}.$$

From the identity $\sum_{-\infty}^{\infty} i\{F(x_{i+1}) - F(x_i)\} = -\sum_{-\infty}^{0} F(x_i) + \sum_{1}^{\infty}(1 - F(x_i))$ we have

$$\sum_{-\infty}^{\infty} \left(x_i + \frac{d}{2}\right)\{F(x_{i+1}) - F(x_i)\} = x_0 + \frac{d}{2} - d\sum_{-\infty}^{0} F(x_i) + d\sum_{1}^{\infty}(1 - F(x_i)).$$

Since $|\sum_{-\infty}^{\infty}(x_i^* - x_i - \frac{d}{2})(F(x_{i+1}) - F(x_i))| \leq \frac{d}{2}$, the proof readily follows.

Lemma 2. *Let $y_m = \sup_{k\geq 1} m^{-1}|\sum_{-k}^{k}(p_i - P_i)|$ where p_i's are independent (for a given x_0) binomial proportions with $E(p_i|x_0) = P_i = [1 + e^{-(x_i-\theta)/\beta}]^{-1}$ and x_0 is uniformly distributed on $(0, d)$. Then $y_m \overset{\text{a.s.}}{\to} 0$ as $m \to \infty$, where $P_i = P_i(m) = [1 + e^{-(x_i-\theta)/\beta}]^{-1}$ and $d = d_0/m$ for some $d_0 > 0$.*

Proof. Note that

1. $E(p_i - P_i|x_0) = 0.$

2. $E((p_i - P_i)^4|x_0) = n^{-3}P_i(1-P_i)\{3nP_i(1-P_i) - 6P_i(1-P_i) + 1\} < \infty.$

So we have, after using the inequality for sub-martingales, (see, for instance, Woodroofe (1982, p.8) or Hall and Heyde (1980, p.14))

$$P\left\{\sup_{1\le k\le N}\left|\sum_{-k}^{k}(p_i - P_i)\right| > \epsilon \mid x_0\right\} \le \frac{1}{\epsilon^4}E\left\{\sum_{-N}^{N}(p_i - P_i)\Big|x_0\right\}^4. \tag{A.2}$$

It is easy to show the identity

$$\begin{aligned}\left(\sum a_i\right)^4 &= \sum a_i^4 + 4\sum_{i\ne j}\sum a_i^3 a_j + 3\sum_{i\ne j}\sum a_i^2 a_j^2 \\ &\quad +6\sum_{i\ne j\ne k}\sum\sum a_i^2 a_j a_k + \sum_{i\ne j\ne k\ne l}\sum\sum\sum a_i a_j a_k a_l \end{aligned} \tag{A.3}$$

since $P_i(1-P_i) \le \frac{1}{4}$, we have

$$3nP_i(1-P_i) - 6P_i(1-P_i) + 1 < 2n. \tag{A.4}$$

Also $P_i(1-P_i) = \beta f(x_0 + id)$ where $f(\cdot)$ is the logistic density function. Using the Euler-MacLaurin integral sum formula we can write

$$\begin{aligned}\sum_{-N}^{N} f(x_0 + id) &= \frac{1}{2}\Big\{f(x_0 + Nd) + f(x_0 - Nd)\Big\} + \int_{-N}^{N} f(x_0 + xd)dx \\ &\quad - d\int_{-N}^{N} H_1(x) f'(x_0 + xd)dx, \end{aligned} \tag{A.5}$$

where

$$H_1(x) = \begin{cases} [x] - x + \frac{1}{2}, & \text{if } x \text{ is a non-integer;} \\ 0, & \text{if } x \text{ is an integer,}\end{cases}$$

and $f'(x) = \frac{df(x)}{dx}$. Note that $|H_1(x)| \le \frac{1}{2}$. From (A.5), it follows that

$$d\sum_{-N}^{N} P_i(1-P_i) \le \beta\left(1 + \frac{3d}{2\beta}\right). \tag{A.6}$$

By combining (A.2), (A.3), (A.4), (A.5), (A.6) we obtain

$$\begin{aligned}&P\left\{\sup_{1\le k\le N}\left|\sum_{-k}^{k} d(p_i - P_i)\right| > \epsilon \mid x_0\right\} \\ &\le \epsilon^{-4}\left\{2n^{-2}m^{-3}\beta d_0^3\left(1 + \frac{3d}{2\beta}\right) + 3n^{-2}m^{-2}\beta^2 d_0^2\left(1 + \frac{3d}{2\beta}\right)^2\right\}. \end{aligned} \tag{A.7}$$

Now by integrating over x_0 and then taking the limit as $N \to \infty$ we get

$$P\left\{ \sup_{k\geq 1} \left| \sum_{-k}^{k} d(p_i - P_i) \right| > \epsilon \right\}$$
$$\leq \epsilon^{-4}\left\{ 2n^{-2}m^{-3}\beta d_0^3\left(1+\frac{3d}{2\beta}\right) + 3n^{-2}m^{-2}\beta^2 d_0^2\left(1+\frac{3d}{2\beta}\right)^2\right\} \qquad \text{(A.8)}$$

and hence $\sum_{m=1}^{\infty} P\{\sup_{k\geq 1} | \sum_{-k}^{k} d(p_i - P_i) > \epsilon\} < \infty$.

Lemma 3.

$$\hat{\theta}_k \overset{\text{a.s.}}{\to} \theta \text{ as } m \to \infty, \text{ and } k \to \infty, \text{ such that } km^{-1} \to \infty.$$

Proof. One can write

$$\hat{\theta}_k - \theta = \left(x_0 + \frac{d}{2}\right) - d\sum_{-k}^{0} p_i + d\sum_{1}^{k}(1-p_i) - \left(x_0 + \frac{d}{2}\right) + d\sum_{-\infty}^{0} P_i - d\sum_{1}^{\infty}(1-P_i)$$
$$+\left(x_0 + \frac{d}{2}\right) - d\sum_{-\infty}^{0} P_i + d\sum_{1}^{\infty}(1-P_i) - \theta.$$

So,

$$|\hat{\theta}_k - \theta| \leq \left| d\sum_{-k}^{k}(p_i - P_i)\right| + \left|\left(x_0 + \frac{d}{2}\right) - d\sum_{-\infty}^{0} P_i + d\sum_{1}^{\infty}(1-P_i) - \theta\right|$$
$$+ d\sum_{-\infty}^{-k-1} P_i + d\sum_{k+1}^{\infty}(1-P_i).$$

Since $d\sum_{-\infty}^{0} P_i$ and $d\sum_{1}^{\infty}(1-P_i)$ are converging sums, $d\sum_{-\infty}^{-k-1} P_i$ and $d\sum_{k+1}^{\infty}(1-P_i)$ tend to zero as $d = \frac{d_0}{m} \to 0$ and $k \to \infty$, such that $kd \to \infty$. This result together with lemmas 1 and 2 prove the lemma.

Corollory 1. *For any stopping time $K(m)$ such that $K(m)m^{-1} \to \infty$ as $m \to \infty$, $\hat{\theta}_{K(m)} \to \theta$ as $m \to \infty$.*

Lemma 4. *If $F(x)$ denotes a logistic distribution function with location and scale parameters θ and β respectively then for some positive constant C_1,*

$$\left| \frac{\pi^2\beta^2}{3} + \theta^2 - \left(x_0 + \frac{d}{2}\right)^2 + 2d\sum_{-\infty}^{0} x_i F(x_i) - 2d\sum_{1}^{\infty} x_i(1-F(x_i))\right| \leq C_1 d,$$

where $x_0 \in (0, d)$ and C_1 is free of x_0.

Proof. It is well known that

$$\begin{aligned}\frac{\pi^2\beta^2}{3}+\theta^2 &= \int_{-\infty}^{\infty} x^2 dF(x) = \sum_{-\infty}^{\infty}\int_{x_i}^{x_{i+1}} x^2 dF(x) \\ &= \sum_{-\infty}^{\infty}(x_i^*)^2\{F(x_{i+1})-F(x_i)\}\end{aligned}$$

for some x_i^* such that $x_i \le x_i^* \le x_{i+1}$.

So, one can write

$$\begin{aligned}\frac{\pi^2\beta^2}{3}+\theta^2 &= \sum_{-\infty}^{\infty}\left(x_i+\frac{d}{2}\right)^2\{F(x_{i+1})-F(x_i)\} \\ &\quad+\sum_{-\infty}^{\infty}\left\{x_i^{*2}-\left(x_i+\frac{d}{2}\right)^2\right\}\cdot\{F(x_{i+1})-F(x_i)\}.\end{aligned}$$

It can be shown that

$$\sum_{-\infty}^{\infty}\left(x_i+\frac{d}{2}\right)^2\{F(x_{i+1})-F(x_i)\} = \left(x_0+\frac{d}{2}\right)^2-2d\sum_{-\infty}^{0}x_iF(x_i)+2d\sum_{1}^{\infty}x_i(1-F(x_i)).$$

Also $x_i^* = x_i+\lambda d$ for some λ such that $0\le\lambda\le 1$ and therefore

$$\begin{aligned}x_i^{*2}-\left(x_i+\frac{d}{2}\right)^2 &= (x_i+\lambda d)^2-\left(x_i+\frac{d}{2}\right)^2 \\ &= \left(2x_i+\lambda d+\frac{d}{2}\right)\left(\lambda-\frac{1}{2}\right)d \\ &= x_i(2\lambda-1)d+\left(\lambda^2-\frac{1}{4}\right)d^2.\end{aligned}$$

So,

$$\begin{aligned}&\sum_{-\infty}^{\infty}\left|x_i^{*2}-\left(x_i+\frac{d}{2}\right)^2\right|\{F(x_{i+1})-F(x_i)\} \\ &\le |2\lambda-1|d\sum_{-\infty}^{\infty}|x_i|\{F(x_{i+1})-F(x_i)\}+\left|\lambda^2-\frac{1}{4}\right|d^2 \\ &= O(d).\end{aligned}$$

Hence the lemma.

Lemma 5. *Let* $Z_m = \sup_{k\ge1} m^{-1}|\sum_{-k}^{k} x_i(p_i-P_i)|$ *where* p_i, P_i *and* x_i *are as defined in Lemma 2.*

Then $Z_m \overset{\text{a.s.}}{\to} 0$ *as* $m \to \infty$.

Proof. Similar to the proof of Lemma 2, except for changing $p_i - P_i$ to $x_i(p_i - P_i)$.

Lemma 6. $\hat{\beta}_k \overset{\text{a.s.}}{\to} \beta$ *as* $m \to \infty$, $k \to \infty$ *such that* $km^{-1} \to \infty$.

Proof. From (1.2) and Lemma 4, we have

$$\begin{aligned}
& -C_1 d - 2d\sum_{-k}^{k} x_i(p_i - P_i) + 2d \sum_{-\infty}^{-k-1} x_i P_i - 2d \sum_{k+1}^{\infty} x_i(1 - P_i) \\
\leq\ & \frac{\pi^2}{3}(\hat{\beta}_k^2 - \beta^2) + \hat{\theta}_k^2 - \theta^2 \\
\leq\ & C_1 d - 2d\sum_{-k}^{k} x_i(p_i - P_i) + 2d \sum_{-\infty}^{-k-1} x_i P_i - 2d \sum_{k+1}^{\infty} x_i(1 - P_i).
\end{aligned}$$

Note that $2d\sum_{-\infty}^{-k-1} x_i P_i$ and $2d\sum_{k+1}^{\infty} x_i(1 - P_i)$ tend to zero as $m \to \infty$, $k \to \infty$ such that $km^{-1} \to \infty$. Also by Lemma 3, $\hat{\theta}_k \to \theta$ and by Lemma 5, $d\sum_{-k}^{k} x_i(p_i - P_i)$ tend to zero. Hence the lemma.

Corollory 2. *For any stopping time* $K(m)$ *such that* $K(m)m^{-1} \to \infty$ *as* $m \to \infty$, $\hat{\beta}_{K(m)} \to \beta$ *as* $m \to \infty$.

Proof. The proof can be given along the same lines as the proof of Lemma 6.

Lemma 7. *If* $P_i = [1 + e^{-(x_i - \theta)/\beta}]^{-1}$ *with* $x_i = x_0 + id$ *where* $x_0 \in (0, d)$ *then for any stopping time* K
(i) *for the* S-K *estimator* $\hat{\theta}_K$, $E(\hat{\theta}_K^2) < \infty$
(ii) *for the Spearman type variance estimator* $\frac{\pi^2}{3}\hat{\beta}_K^2$, $E(\hat{\beta}_K^2) < \infty$.

Proof. For the sequential Spearman-Karber estimator given by $\hat{\theta}_K = (x_0 + \frac{d}{2}) - d\sum_{-K}^{0} p_i + d\sum_{1}^{K}(1 - p_i)$, let $X_K = d\sum_{-K}^{0} p_i + d\sum_{1}^{K}(1 - p_i)$. Then $|\hat{\theta}_K| \leq x_0 + \frac{d}{2} + X_K$.

To show that $E(\hat{\theta}_K^2) < \infty$, it suffices to show that $E(X_K^2) < \infty$. Now consider

$$E(X_K) = E\left(d\sum_{-K}^{0} p_i\right) + E\left(d\sum_{1}^{K}(1 - p_i)\right).$$

Now the p_i's are conditionally independent with respect to x_0 and thus by Wald's generalized equation

$$E(X_K) = E\left(E\left(d\sum_{-K}^{0} p_i | x_0\right)\right) + E\left(E\left(d\sum_{1}^{K}(1 - p_i) | x_0\right)\right)$$

$$
\begin{aligned}
&= E\left(d\sum_{-K}^{0} P_i\right) + E\left(d\sum_{1}^{K}(1-P_i)\right) \quad \text{where } P_i = E(p_i|x_0) \\
&< E\left(d\sum_{-\infty}^{0} P_i + d\sum_{1}^{\infty}(1-P_i)\right) \\
&< \infty.
\end{aligned}
$$

Also

$$
\begin{aligned}
\mathrm{Var}(X_K) &= \mathrm{Var}\left\{d\sum_{-K}^{0} p_i + d\sum_{1}^{K}(1-p_i)\right\} \\
&= \mathrm{Var}\left(E\left\{d\sum_{-K}^{0} p_i + d\sum_{1}^{K}(1-p_i)|x_0\right\}\right) \\
&\quad + E\left(\mathrm{Var}\left\{d\sum_{-K}^{0} p_i + d\sum_{1}^{K}(1-p_i)|x_0\right\}\right) \\
&< E\left\{\left[d\sum_{-\infty}^{0} P_i + d\sum_{1}^{\infty}(1-P_i)\right]^2\right\} + (d^2/n)E\left\{\sum_{-\infty}^{\infty} P_i(1-P_i)\right\} \\
&< \infty.
\end{aligned}
$$

That is, $E(X_K^2) < \infty$ and this implies $E(\hat{\theta}_K^2) < \infty$.

To prove (ii), use the fact that

$$
\begin{aligned}
\pi^2\hat{\beta}_K^2/3 \leq\ & (17/4)d^2 - 2d\sum_{-\infty}^{-1}(i+1)d\left\{1 + e^{-((i+1)d-\theta)/\beta}\right\}^{-1} \\
& + 2d\sum_{1}^{\infty}(i+1)d\left\{1 - \left[1 + e^{((i+1)d-\theta)/\beta}\right]^{-1}\right\} + \hat{\theta}_K^2
\end{aligned}
$$

and this implies $E(\hat{\beta}_K^2) < \infty$.

Lemma 8. *For any finite k*
(i) $E(\hat{\theta}_k^2) < \infty$.
(ii) $E(\hat{\beta}_k^2) < \infty$.

Proof. It is similar to the proof of Lemma 7.

Now we are ready to prove Theorem 4.1.

Proof of Theorem 4.1. (i) and (ii) are obvious. (iii) follows from Corollory 1. (iv) follows from Corollory 2. To prove (v) and (vi), let

$$\begin{aligned}
\alpha &= e^{\theta/\beta}, \quad \gamma = e^{-d/\beta}, \quad \Delta = d/n, \quad y = \alpha\gamma + 1/\alpha \\
\rho &= 4 + 2\Delta/\beta + 4c/\Delta\beta, \quad T = \rho\gamma + (c/\Delta\beta)(\alpha^2\gamma^2 + 1/\alpha^2), \\
\hat{\alpha}_k &= e^{\hat{\theta}_k/\hat{\beta}_k}, \quad \hat{\gamma}_k = e^{-d/\hat{\beta}_k}, \quad \hat{y}_k = \hat{\alpha}_k\hat{\gamma}_k + 1/\hat{\alpha}_k \\
\hat{\rho}_k &= 4 + 2\Delta/\hat{\beta}_k + 4c/\Delta\hat{\beta}_k, \quad T_k = \hat{\delta}_k\hat{\gamma}_k + (C/\Delta\hat{\beta}_k)(\hat{\alpha}_k^2\hat{\gamma}_k^2 + \hat{\alpha}_k^{-2}) \\
u &= (16c/\Delta\beta)(\Delta + 4c/\Delta)^{-2}(1 - Ty^{-2}) \text{ and} \\
u_k &= (16c/\Delta\hat{\beta}_k)(\Delta + 4c/\Delta)^{-2}(1 - T_k y_k^{-2}).
\end{aligned}$$

From (2.5), we have

$$\frac{(K/\hat{\beta}_K) - (k^*/\beta)}{(k^*/\beta)} \geq \log_e \left\{ \frac{\hat{\beta}_K(y_K - T_K y_K^{-1})[1 + u_K^{\frac{1}{2}}]}{\beta(y - Ty^{-1})[1 + u^{\frac{1}{2}}]} \right\} \Big/ \log_e(J(\theta, \beta, c, d, n)) \tag{A.9}$$

and

$$\begin{aligned}
&\frac{((K-1)/\hat{\beta}_{K-1}) - (k^*/\beta)}{(k^*/\beta)} \\
&< \log_e \left\{ \frac{\hat{\beta}_{K-1}(y_{K-1} - T_{K-1} y_{K-1}^{-1})[1 + u_{K-1}^{\frac{1}{2}}]}{\beta(y - Ty^{-1})[1 + u^{\frac{1}{2}}]} \right\} \Big/ \log_e(J(\theta, \beta, c, d, n))
\end{aligned} \tag{A.10}$$

where $J(\theta, \beta, c, d, n)$ is as defined in (2.4).

Note that $\hat{\theta}_{K(m)} \xrightarrow{\text{a.s.}} \theta$, $\hat{\beta}_{K(m)} \xrightarrow{\text{a.s.}} \beta$ as $m \to \infty$. This implies that $y_{K(m)} \xrightarrow{\text{a.s.}} y$, $T_{K(m)} \xrightarrow{\text{a.s.}} T$, $u_{K(m)} \xrightarrow{\text{a.s.}} u$ as $m \to \infty$, and this in turn implies (v), since the cost $c = O(d^{1+\eta})$ for some $\eta > 1$.

To prove (vi), use the facts that

$$\frac{(K-1)\beta}{k^*\hat{\beta}_{K-1}} < \frac{\log_e \left\{ 4\hat{\beta}_{K-1}(\Delta + \frac{4c}{\Delta})^{-1} y_{K-1} \right\}}{\log_e \left\{ \frac{4\beta(\Delta + \frac{4c}{\Delta})^{-1}}{1 + (1+u)^{\frac{1}{2}}}(y - Ty^{-1}) \right\}}$$

and $\log_e(\hat{\beta}_{K-1}) < \hat{\beta}_{K-1}$, and obtain

$$\frac{K-1}{k^*} < \frac{\beta^{-1}\left\{ \hat{\beta}_{K-1} \log_e \left[4(\Delta + \frac{4c}{\Delta})^{-1} \right] + \hat{\beta}_{K-1}^2 + 2|\hat{\theta}_{K-1}| \right\}}{\log_e \left[4(\Delta + \frac{4c}{\Delta})^{-1} \right] + \log_e \left[\frac{4\beta(y - Ty^{-1})}{1 + u^{\frac{1}{2}}} \right]}. \tag{A.11}$$

However, $E(\hat{\beta}_{K-1}^2) < \infty$ and $E(|\hat{\theta}_{K-1}|) < \infty$ (see Lemma 7 for the proof). Therefore the expected value of the right hand side of (A.11) is finite. So, by the dominated convergence theorem and part (v) of Theorem 4.1, we obtain $E\{\frac{K(m)}{k^*(m)}\} \to 1$ as $m \to \infty$.

Risk Efficiency

Let R_K and R_{k^*} denote the mean squared error plus the sampling cost associated with K and k^* respectively. We assume that the sampling cost per unit $c = O(d^{1+\eta})$ where d is the dose span and $\eta > 1$. In this section we show that $\frac{R_K}{R_{k^*}} \to 1$ as $c \to 0$. Towards this we need the following lemmas.

Lemma 9. $\sup_{k\geq 1}\{(k^*d)(d\sum_{-k}^{k}(p_i - P_i))\} \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.

Proof. By the sub-martingale inequality

$$P\left\{\sup_{1\leq k\leq N}(k^*d)d\left|\sum_{-k}^{k}(p_i - P_i)\right| > \epsilon \mid x_0\right\} \leq \epsilon^{-4}(k^*d)^4 d^4 E\left\{\left[\sum_{-N}^{N}(p_i - P_i)\right]^4 |x_0\right\}$$

and it is easy to show that

$$\begin{aligned} &E\left[\left\{\sum_{-N}^{N}(p_i - P_i)\right\}^4 |x_0\right] \\ &= \sum_{-N}^{N} E\left\{(p_i - P_i)^4|x_0\right\} + 3\sum_{i\neq j}^{N}\sum^{N} E\left\{\sum_{-N}^{N}(p_i - P_i)^2|x_0\right\}E\left\{\sum_{-N}^{N}(p_j - P_j)^2|x_0\right\} \\ &\leq\; 2n^{-2}\sum_{-N}^{N} P_i(1-P_i) + 3n^{-2}\left[\sum_{-N}^{N} P_i(1-P_i)\right]^2. \end{aligned}$$

Also from (A.6) $d\sum_{-N}^{N} P_i(1-P_i) \leq \beta(1+\frac{3d}{2\beta})$. Therefore

$$\begin{aligned} &P\left\{\sum\sup_{1\leq k\leq N}(k^*d)d\left|\sum_{-k}^{k}(p_i - P_i)\right| > \epsilon \mid x_0\right\} \\ &\leq\; \epsilon^{-4}(k^*d)^4\left\{2n^{-2}\beta d^3\left(1+\frac{3d}{2\beta}\right) + 3n^{-2}\beta^2 d^2\left(1+\frac{3d}{2\beta}\right)^2\right\}. \end{aligned}$$

Now by letting $N \to \infty$ and then integrating over x_0 we obtain

$$\begin{aligned} &P\left\{\sum_{k\geq 1}(k^*d)\left|d\sum_{-K}^{K}(p_i - P_i)\right| > \epsilon\right\} \\ &\leq\; \epsilon^{-4}(k^*d)^4\left\{2n^{-2}\beta d^3\left(1+\frac{3d}{2\beta}\right) + 3n^{-2}\beta^2 d^2\left(1+\frac{3d}{2\beta}\right)^2\right\}. \end{aligned}$$

However from (2.4) it follows that when $c = O(d^{1+\eta})$ for some $\eta > 1$, $k^*d = O(\log_e d^{-1})$ and therefore as $d = \frac{d_0}{m} \to 0$, the result follows.

Lemma 10. *For K and k^* given by (2.5) and (2.6)*
(i) $k^* d(\sum_{-K}^{K}(p_i - P_i)) \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.
(ii) $Kd(d\sum_{-K}^{K}(p_i - P_i)) \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.

Proof. (i) follows from Lemma 9 and (ii) follows from (i) and the fact that $\frac{K}{k^*} \overset{\text{a.s.}}{\to} 1$ as $d = \frac{d_0}{m} \to 0$.

Lemma 11. *For K and k^* given by (2.5) and (2.6)*
(i) $k^* d(d\sum_{-K}^{K} x_i(p_i - P_i)) \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.
(ii) $Kd(d\sum_{-k}^{k} x_i(p_i - P_i)) \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.

Proof. The proof is analogous to the proof of Lemma 9 except for changing $p_i - P_i$ to $x_i(p_i - P_i)$.

Lemma 12. $(K - k^*)d \overset{\text{a.s.}}{\to} 0$ *as* $d = \frac{d_0}{m} \to 0$.

Proof. From (2.5) and (2.6) we have

$$\begin{aligned} &\hat{\beta}_K \log_e\Big(J(\hat{\theta}_K, \hat{\beta}_K, c, d, n)\Big) - \beta \log_e\Big(J(\theta, \beta, c, d, n)\Big) \\ \leq\ & (K - k^*)d < d + \hat{\beta}_{K-1} \log_e\Big(J(\hat{\theta}_{K-1}, \hat{\beta}_{K-1}, c, d, n)\Big) - \beta \log_e(J(\theta, \beta, c, d, n)) \end{aligned}$$

and both the right hand side and left hand side tend to zero almost surely as $d = \frac{d_0}{m} \to 0$. Hence the lemma.

The following lemmas are used to show the risk-efficiency of the stopping rule.

Lemma 13. *According to the set-up of the experimentation, we have the risk plus the sampling cost of estimation for $\hat{\theta}_k$ and $\hat{\theta}_K$ denoted by R_k and R_K respectively are as follows.*

$$\begin{aligned} 1.\quad R_k &= E(\hat{\theta}_k - \theta)^2 + (2k+1)cn \\ &= \Delta\Big\{1 - \alpha e^{-kd/\beta} + \alpha^2 e^{-2kd/\beta} - \alpha^{-1} e^{-kd/\beta}(1 - \alpha^{-1} e^{-kd/\beta})\Big\} \\ &\quad + \beta^2\Big(\alpha - \frac{1}{\alpha}\Big)^2 \frac{e^{-2kd/\beta}}{(1 + \alpha e^{-kd/\beta})^2} + (2k+1)nc \end{aligned}$$

for any finite k.

$$
\begin{aligned}
2.\ R_K &= E(\hat{\theta}_K-\theta)^2+E((2K+1)cn)\\
&= \beta\Delta E\Big\{1-\alpha e^{-Kd/\beta}+\alpha^2 e^{-2Kd/\beta}-\alpha^{-1}e^{-Kd/\beta}\Big(1-\frac{1}{\alpha}e^{-Kd/\beta}\Big)\Big\}\\
&\quad+\beta^2\Big(\alpha-\frac{1}{\alpha}\Big)^2 E\Big\{e^{-2Kd/\beta}[1+\alpha e^{-Kd/\beta}]^{-2}\Big\}\\
&\quad-2\beta E\Big\{\Big[d\sum_{-K}^{K}(p_i-P_i)\Big]\Big[\int_{(x_0+(K+1)d-\theta)/\beta}^{-(x_0+(K+1)d-\theta)/\beta}(1-G(u))du\Big]\Big\}\\
&\quad+\beta\Delta E\Big\{\int_{(Kd-\theta)/\beta}^{(x_0+Kd-\theta)/\beta}g(u)du+\int_{-(x_0+Kd+\theta)/\beta}^{-(Kd+\theta)/\beta}g(u)du\Big\}\\
&\quad+E\Big\{[T^*(x_0)]^2\Big\}-2E\Big\{\Big[dT^*(x_0)\sum_{-K}^{K}(p_i-P_i)\Big]\Big\}\\
&\quad+2\beta E\Big\{T^*(x_0)\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+Kd+\theta)/\beta}(1-G(u))du\Big\}+E((2K+1)cn)+o(d)
\end{aligned}
$$

where

$$
\begin{aligned}
T^*(x_0) &= \frac{d}{2}\Big\{1-F(x_0+(K+1)d)-F(x_0-(K+1)d)\Big\}\\
&\quad+d^2\int_{K+1}^{\infty}H_1(x)f(x_0+xd)dx+d^2\int_{-\infty}^{-K-1}H_1(x)f(x_0+xd)dx+Ad
\end{aligned}
$$

for some $A=A(x_0)$ *such that* $-\frac{1}{2}\le A\le\frac{1}{2}$. *Also* $\Delta=\frac{d}{n}$, $F(\cdot)$ *is the logistic c.d.f.,* $f=\frac{dF}{dx}$, G *is the logistic c.d.f. in the standard form,* $g=\frac{dG}{dx}$ *and* $H_1(x)$ *is defined as*

$$
H_1(x)=\begin{cases}[x]-x+0.5, & x \text{ is a non-integer};\\ 0, & x \text{ is an integer.}\end{cases}
$$

Proof. The proof of 1 is straightforward. The proof of 2 is as follows.

Note that

$$
\hat{\theta}_K-\theta=-d\sum_{-K}^{K}(p_i-P_i)+\beta\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+(K+1)d+\theta)/\beta}(1-G(u))du+T^*(x_0). \quad \text{(A.12)}
$$

Equation (A.12) follows from Equation (A.1) and the random version of the Euler-MacLaurin formula. Now by squaring both sides and then taking expectations, we obtain

$$
E(\hat{\theta}_K-\theta)^2 = E\Big\{d\sum_{-K}^{K}(p_i-P_i)\Big\}^2
$$

$$+E\left\{\beta\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+(K+1)d+\theta)/\beta}(1-G(u))du\right\}^2+E\left\{(T^*(x_0))^2\right\}$$
$$-2\beta E\left\{d\left[\sum_{-K}^{K}(p_i-P_i)\right]\left[\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+(K+1)d+\theta)/\beta}(1-G(u))du\right]\right\}$$
$$-2E\left\{T^*(x_0)\left[d\sum_{-K}^{K}(p_i-P_i)\right]\right\}$$
$$+2\beta E\left\{T^*(x_0)\left[\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+(K+1)d+\theta)/\beta}(1-G(u))du\right]\right\}. \qquad (A.13)$$

However, by the generalized Wald's equation (see Wolfowitz (1947)), we have

$$\begin{aligned}E\left\{d^2\left[\sum_{-K}^{K}(p_i-P_i)\right]^2\right\} &= d^2E\left\{E\left[\sum_{-K}^{K}(p_i-P_i)\right]^2|x_0\right\}\\ &= \left(\frac{d^2}{n}\right)E\left\{E\left(\sum_{-K}^{K}P_i(1-P_i)\right)|x_0\right\}\\ &= \beta\left(\frac{d}{n}\right)E\left\{\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+Kd+\theta)/\beta}g(u)du\right\}+o(d). \quad (A.14)\end{aligned}$$

The last step of (A.14) follows from the random version of the Euler-MacLaurin formula. Next, using simple algebra, one can complete the proof.

Lemma 14. *If $c=O(\Delta^{1+\eta})$ with $\Delta=\frac{d}{n}$ for some $\eta>1$ and $e^{-2(K-k^*)\frac{d}{\beta}}$ is uniformly integrable then*
(i) $\Delta^{-1}E(e^{-2K\frac{d}{\beta}})\to 0$ *as* $\Delta\to 0$.
(ii) $E\{(\sum_{-K}^{K}(p_i-P_i))(\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+Kd+\theta)/\beta}(1-G(u))du)\}\to 0$ *as* $\Delta\to 0$ *where* p_i, P_i *are as defined in Lemma 2 and* $G(u)=(1+e^{-u})^{-1}$.
(iii) $E\{T^*(x_0)(\sum_{-K}^{K}(p_i-P_i))\}\to 0$ *as* $\Delta\to 0$.
(iv) $E\{\Delta^{-1}T^*(x_0)\int_{(x_0+(K+1)d-\theta)/\beta}^{(-x_0+Kd+\theta)/\beta}(1-G(u))du\}\to 0$ *as* $\Delta\to 0$ *where* $T^*(x_0)$ *is as defined in Lemma 12.*

Proof. To prove (i), note that

$$\Delta^{-1}e^{-2Kd/\beta}=\Delta^{-1}e^{-2k^*d/\beta}e^{-2(K-k^*)d/\beta}.$$

If $c=O(\Delta^{1+\eta})$ then $\Delta^{-1}e^{-2k^*\frac{d}{\beta}}=O(\Delta^{\eta-1})$.

From Lemma 12, we have $(K-k^*)d\overset{\text{a.s.}}{\to}0$ as $\Delta\to 0$ and this implies $e^{-2(K-k^*)\frac{d}{\beta}}\overset{\text{a.s.}}{\to}1$ as $\Delta\to 0$. This shows that $\Delta^{-1}e^{-2K\frac{d}{\beta}}\overset{\text{a.s.}}{\to}0$ as $\Delta\to 0$. Since

$e^{-2(K-k^*)\frac{d}{\beta}}$ is uniformly integrable, $\Delta^{-1}e^{-2K\frac{d}{\beta}}$ is uniformly integrable and therefore

$$\Delta^{-1}E\left(e^{-2K\frac{d}{\beta}}\right) \to 0 \text{ as } \Delta \to 0.$$

Parts (ii), (iii) and (iv) can be shown by using Cauchy-Schwarz inequality, noting the fact that $E\left(\sqrt{d}\sum_{-K}^{K}(p_i - P_i)\right)^2 < \infty$.

Proof of Theorem 4.2. From lemmas 12 and 13, we obtain that $\Delta^{-1}R_K \to 1$ as $\Delta \to 0$ and $\Delta^{-1}R_{k^*} \to 1$ as $\Delta \to 0$. These results establish that $\frac{R_K}{R_{k^*}} \to 1$ as $\Delta \to 0$.

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