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ESTIMATION FOLLOWING A GROUP SEQUENTIAL TEST FOR DISTRIBUTIONS IN THE ONE-PARAMETER EXPONENTIAL FAMILY

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Abstract: We consider unbiased estimation following a group sequential test for distributions in a one-parameter exponential family. We show that, for an estimable parameter function, there exists uniquely an unbiased estimator depending on the sufficient statistic and based on the truncation-adaptation criterion (Liu and Hall (1999)); moreover, this estimator is identical to one based on the Rao-Blackwell method. When completeness fails, we show that the uniformly minimum-variance unbiased estimator may not exist or might possess undesirable performance. A Phase-II clinical trial application with exponentially distributed responses is included.

Key words and phrases: Clinical trials, completeness, Laplace transform, minimum variance, truncation-adaptation, unbiased estimation.

1. Introduction

Group sequential testing procedures have been widely used in Phase II and III clinical trials due to ethical, administrative, and cost concerns. In a group sequential test regarding a null hypothesis, sampling data are examined in cumulative groups at a number of time points, with a stopping region specified for the test statistic at each time point. "Time" may be specified in terms of real calendar time, or sample size, or Fisher information. If at a certain time point, the test statistic reaches the stopping region, then the sampling process is terminated and a decision is made as to whether or not the null hypothesis should be rejected. Popular designs for comparing two treatment groups are the Pocock (1977) and O'Brien and Fleming (1979) designs, and the more flexible error spending designs developed by Lan and DeMets (1983) that allow for unequal group sizes and unspecified inspection times. Other group sequential designs, such as Simon's (1989) optimal two-stage tests, have been developed to evaluate patient response to a drug treatment. Jennison and Turnbull (2000) is an excellent reference for the design and analysis of such trials, focusing on theory with normally distributed outcomes. All such designs are special cases of

one-at-a-time sequential sampling for which stopping opportunities are limited and the sample size is bounded.

Parameter estimation after a sequential test is important, especially in clinical trials, since the magnitude of the treatment effect is always of interest to the medical investigators. However, conventional estimators that are efficient in non-sequential settings (fixed sample size) lose statistical properties such as unbiasedness and minimum variance when used in sequential settings (e.g., Cox (1952), Siegmund (1978), Whitehead (1986) and Chang, Wieand and Chang (1989)). For group sequential designs with normal variables, Emerson and Fleming (1990) proposed a Rao-Blackwell type unbiased estimator of the normal mean. Liu and Hall (1999) later showed that there exist infinitely many unbiased estimators of the normal mean and none has uniform minimum variance. They further proposed a truncation-adaptable criterion, and showed that Emerson and Fleming's (1990) estimator has uniform minimum variance among all truncation-adaptable unbiased estimators.

Much of the work on estimation in sequential designs dates back over fifty years. For sequential sampling with Bernoulli trials, Girshick, Mosteller and Savage (1946) considered unbiased estimation of the success probability p and found necessary and also certain sufficient conditions for completeness, enabling conclusions about uniform minimum variance for associated unbiased estimators. Wolfowitz (1946) and Savage (1947) derived necessary and sufficient conditions for bounded completeness, and Blackwell (1947) introduced what we call the Rao-Blackwell method in the context of sequential sampling. These works were extended by Lehmann and Stein (1950) in two directions: first, they presented a necessary condition for completeness of a sufficient statistic from a general distribution, and second, they found a necessary and sufficient condition for completeness — without the boundedness condition — when sampling sequentially from Bernoulli, Poisson or rectangular distributions. To our knowledge, however, no further development or extension has occurred with respect to unbiased estimation and completeness in a general sequential sampling setting. Popularity of group sequential designs has re-generated interest in sequential estimation.

In this paper, we consider unbiased estimation following a group sequential test for distributions in a one-parameter exponential family. Extending results in Liu and Hall (1999), we derive two unbiased estimators depending on the sufficient statistic, one based on their truncation-adaptation criterion and the other on the Rao-Blackwell Theorem, and show these two estimators to be identical. The estimator has uniform minimum variance among all unbiased estimators if the sufficient statistic has a complete family of distributions. When completeness fails — for which we give a sufficient condition and examples — we show that the uniform minimum-variance unbiased estimator may not exist, or when

it does, may possess an undesirable property. This enables our conclusion that the Rao-Blackwell estimator may perform well regardless of the completeness of the sufficient statistic.

The results have potential application in clinical trials and other fields, for example, in a Phase II clinical trial where the parameter of a single distribution is evaluated; see the example in Section 5.

Proofs of all theorems are in an appendix.

2. Group Sequential Designs for Distributions in an Exponential Family

We consider a random variable X, continuous or discrete, whose density is a member of the one-parameter exponential family, having the form

$$f_\theta(x) = h(x)\exp\{\theta x - a(\theta)\} \tag{2.1}$$

with respect to some measure μ; for a density with $\theta t(x)$ instead of θx for some monotone function t, consider the density of $t(X)$ which has the form (2.1). The parameter θ takes values in an open interval Θ, and the support $\mathcal{X}$ of X is either a real interval or a set of integers containing 0. Examples of such distributions include the normal, exponential, gamma, and beta for continuous variables and the Bernoulli, Poisson and geometric for discrete distributions. For simplicity, we take μ to be Lebesgue measure on $\mathcal{R}$ or $\mathcal{R}^+$ and write integrals dx rather than $d\mu(x)$; alternatively, μ is counting measure on a countable set — here restricted to integers — and integrals need to be replaced by sums.

When considering a random sample $X_1, \ldots, X_n$ from X, we write S_n for the cumulative sum; it is a minimal sufficient statistic for inference on θ, and is well-known to have a density of the form (2.1), say

$$f_{n,\theta}(s) = h_n(s)\exp\{\theta s - na(\theta)\} \tag{2.2}$$

$(d\mu)$; let $\mathcal{X}_n$ denote the support. (See Lehmann and Casella (1998), for example.)

Since $f_{n,\theta}(s)$ integrates (or sums) to unity, we have, for each integer n,

$$\exp\{na(\theta)\} = \int_{\mathcal{X}_n} h_n(s)\exp(s\theta)d\mu(s). \tag{2.3}$$

That is, $\exp\{na(\theta)\}$ is the Laplace transform (Widder (1941)) of $h_n(s)$ on $\mathcal{X}_n$ with respect to measure μ, or $h_n(s)$ is the (unique) inverse Laplace transform of $\exp\{na(\theta)\}$. We will repeatedly use these concepts.

We consider a group sequential design for testing hypotheses about θ, based on the sufficient statistic S_n with K (> 1) possible analyses. Suppose that the kth analysis $(k = 1, \ldots, K)$ is conducted after n_k observations are observed, with

stopping region $\mathcal{B}_k \neq \emptyset$ and continuation region $\mathcal{C}_k$ (with $\mathcal{C}_k \neq \emptyset$ for $k < K$ and $\mathcal{C}_K = \emptyset$). In clinical trial settings, the stopping regions are normally the union of one or two (or possibly three) disjoint intervals; see Section 5 for an example. The sampling process stops when S_n first falls into a stopping region, and some terminal inference for the test is made. The details about the test are irrelevant here since our focus is on estimation of some function of θ once a stopping region has been reached; thus, the test may be one- or two-sided, and may or may not have inner stopping boundaries, etc.

We can and will assume that each $\mathcal{C}_k$ and $\mathcal{B}_k$ has been reduced to a *reachable* version; that is, for each k and any subset Δ (with positive measure with respect to μ) of $\mathcal{C}_k \cup \mathcal{B}_k$, $P_\theta\{S_{n_i} \in \mathcal{C}_i \text{ for } i < k \text{ and } S_{n_k} \in \Delta\} > 0$. Write $m_k = n_k - n_{k-1}$ ($n_0 = 0$) for the incremental sample size at stage k. Then the stopping and continuation regions have the following relationships: $\mathcal{C}_1 \cup \mathcal{B}_1 = \mathcal{X}_{m_1}$ and $\mathcal{C}_k \cup \mathcal{B}_k = \mathcal{C}_{k-1} \oplus \mathcal{X}_{m_k}$ for $k > 1$, where the operator $\oplus$ on sets Δ_1 and Δ_2 is defined by $\Delta_1 \oplus \Delta_2 = \{x : \ x = x_1 + x_2 \text{ for some } x_1 \in \Delta_1 \text{ and } x_2 \in \Delta_2\}$.

Remark. Although $\mathcal{C}_K$ is required to be empty to ensure that stopping eventually occurs, $\mathcal{B}_K$ may be only a proper subset of $\mathcal{X}_{n_K}$; this generally occurs when $\mathcal{X}$ is bounded, and often occurs if it is only bounded below or above. For example, with Poisson sampling, $0 \in \mathcal{B}_k$ for some $k < K$ implies $0 \notin \mathcal{B}_K$; also see Section 5.

Let M be the (random) number of analyses performed when a stopping region is first reached, and let $S = S_{n_M}$ be the sample sum upon stopping. Since, for each n, S_n is sufficient for θ with respect to the sample space of $(X_1, \ldots, X_n)$, the statistic (M, S) is jointly sufficient (Blackwell (1947)) for θ with respect to the sample space $\{S_{n_1} \in \mathcal{B}_1\} \cup [\cup_{k=2}^{K}\{S_{n_i} \in \mathcal{C}_i,\, i < k, S_{n_k} \in \mathcal{B}_k\}]$.

We now derive the joint density $g_\theta(k, s)$ of (M, S). Obviously $g_\theta(1, s) = f_{n_1,\theta}(s)\, 1_{\mathcal{B}_1}(s)$, the latter factor being the indicator of $s \in \mathcal{B}_1$. For $M = k > 1$, the k increments $S_{n_1}, S_{n_2} - S_{n_1}, \ldots, S_{n_k} - S_{n_{k-1}}$ are independently distributed with respective densities $f_{m_1,\theta}, f_{m_2,\theta}, \ldots, f_{m_k,\theta}$. We then find the joint density of $(S_{n_1}, \ldots, S_{n_k})$ at a point $(s_1, \ldots, s_k)$ in its support to be

$$f_{m_1,\theta}(s_1) f_{m_2,\theta}(s_2 - s_1) \ldots f_{m_k,\theta}(s_k - s_{k-1}) = \tilde{r}_k(s_k; s_1, \ldots, s_{k-1}) f_{n_k,\theta}(s_k),$$

say, where

$$\tilde{r}_k(s_k; s_1, \ldots, s_{k-1}) = \frac{1}{h_{n_k}(s_k)} h_{m_1}(s_1) h_{m_2}(s_2 - s_1) \ldots h_{m_k}(s_k - s_{k-1});$$

or, recursively,

$$\tilde{r}_k(s_k; s_1, \ldots, s_{k-1}) = \frac{h_{n_{k-1}}(s_{k-1})}{h_{n_k}(s_k)} h_{m_k}(s_k - s_{k-1}) \tilde{r}_{k-1}(s_{k-1}; s_1, \ldots, s_{k-2}). \quad (2.4)$$

This then yields the joint density

$$g_\theta(k,s) = \frac{d}{ds} P_\theta(S_{n_i} \in \mathcal{C}_i,\ i<k,\ S_{n_k} \le s,\ S_{n_k} \in \mathcal{B}_k) = r_k(s) f_{n_k,\theta}(s),$$

where $r_1(s) = 1_{\mathcal{B}_1}(s)$ and, for $k > 1$,

$$\begin{aligned} r_k(s) &= \int \dots \int_{\{u_i \in \mathcal{C}_i, i<k\}} \tilde{r}_k(s; u_1, u_2, \dots, u_{k-1}) du_1 \dots du_{k-1} \\ &= \frac{1_{\mathcal{B}_k}(s)}{h_{n_k}(s)} \int_{u \in \mathcal{C}_{k-1}} r_{k-1}(u) h_{n_{k-1}}(u) h_{m_k}(s-u) du. \end{aligned} \tag{2.5}$$

We thus conclude that the density function of the sufficient statistic (M, S) at (k, s) is

$$g_\theta(k,s) = r_k(s) f_{n_k,\theta}(s) = r_k(s)\, h_{n_k}(s) \exp\{\theta s - n_k a(\theta)\} \tag{2.6}$$

with $r_k(s)$ given recursively in (2.5). The family of densities (2.6) is a *curved exponential family*, with natural parameters $\theta_1 = -a(\theta)$ and $\theta_2 = \theta$ —curved since the two parameters θ_1 and θ_2 lie on a curve in 2-space (Efron (1975)).

Formula (2.6) provides the basis for computing the expectation of a statistic $W = w(M, S)$:

$$E_\theta(W) = \sum_{k=1}^{K} \int_{\mathcal{B}_k} w(k,s) r_k(s) f_{n_k,\theta}(s) ds. \tag{2.7}$$

In particular, if $\mathcal{R}_k \subset \mathcal{B}_k$ $(k = 1 \dots, K)$ define rejection sets for some null hypothesis about θ, then the power of the test is given by (2.7) upon setting $w(k,s) = 1_{\mathcal{R}_k}(s)$. For power, sample size and other design issues, see Lai and Shih (2003).

3. Unbiased Estimation of Parameters

Suppose we want to estimate $\eta = \eta(\theta)$, a real-valued (but not constant) function of the natural parameter θ. We consider unbiased estimation of η, and assume throughout that an unbiased estimator, based on a random sample of size m for some $m \le n_1$, exists; we say η is m-estimable. This implies n-estimability for any $n > m$, and indeed for any group sequential design with $n_1 \ge m$.

Typically, many functions are m-estimable, even for $m = 1$; what is required is that $\eta(\theta) \exp\{m\, a(\theta)\}$ be a Laplace transform. However, in the Bernoulli case, only polynomials of degree m are m-estimable, and in the Poisson case, functions with a power series are 1-estimable. We will not pursue these issues further here.

Nonsequentially, let $\hat{\eta}_n(S_n)$ be the unique unbiased estimator of η based on the complete sufficient statistic S_n. After stopping in a group sequential

design, the estimator $\tilde{\eta}(M,S) = \hat{\eta}_{n_M}(S_{n_M})$ is biased, and sometimes badly so (Whitehead (1986), Emerson and Fleming (1990) and Chang, Wieand and Chang (1989)). The expectation of this estimator can be obtained from (2.7) and compared with $\eta(\theta)$ to evaluate the bias.

To control variance as well as eliminate bias, we seek unbiased estimators depending only on the sufficient statistic (M,S). We consider two methods, (i) that of Rao-Blackwell starting from a first-stage estimator and (ii) the truncation-adaptation approach, introduced by Liu and Hall (1999), that requires the estimator to be independent of future stopping regions. The two criteria were developed from quite different perspectives, but interestingly lead to the same unbiased estimator depending on the sufficient statistic — the uniform minimum-variance truncation-adaptable unbiased estimator.

3.1. The Rao-Blackwell unbiased estimator

Let $\hat{\eta}_{n_1}(S_{n_1})$ be the unique sufficient-statistic-based unbiased estimator of η for a non-sequential sample size n_1. As in Blackwell (1947) and Emerson and Fleming (1990), we define a Rao-Blackwell estimator as

$$\hat{\eta}_u(M,S) = E\{\hat{\eta}_{n_1}(S_{n_1})|(M,S)\}. \tag{3.1}$$

Then $\hat{\eta}_u$ is parameter-free, unbiased for η, and with reduced variance.

If sampling stops at the first analysis, then $\hat{\eta}_u(1,S) = \hat{\eta}_{n_1}(S_{n_1})$. For $M > 1$, $\hat{\eta}_u(M,S)$ can in general only be computed numerically, but see Blackwell (1947) for algorithms when estimating the Bernoulli or Poisson parameter. Here we derive a general recursive formula for $\hat{\eta}_u$.

Similar to the derivation of (2.7), we find that the conditional density of S_{n_1} given (M,S), upon writing it as the ratio of the joint density and the density of the condition, is

$$1_{\mathcal{B}_k}(s)\frac{f_{n_k,\theta}(s)}{g_\theta(k,s)}\int\dots\int_{s_i\in\mathcal{C}_i,1<i<k}\tilde{r}_k(s;s_1,s_2,\dots,s_{k-1})ds_2\dots ds_{k-1},$$

and the ratio in front of the integrals is $1/r_k(s)$. It follows from (3.1) that

$$\hat{\eta}_u(k,s) = \frac{1_{\mathcal{B}_k}(s)}{r_k(s)}\int\dots\int_{s_i\in\mathcal{C}_i,1\le i\le k-1}\hat{\eta}_{n_1}(s_1)\tilde{r}_k(s;s_1,s_2,\dots,s_{k-1})ds_1\dots ds_{k-1}.$$

Utilizing (2.5), we obtain the following recursive expression for the Rao-Blackwell estimator (3.1): $\hat{\eta}_u(1,s) = 1_{\mathcal{B}_{n_1}}(s)\,\hat{\eta}_{n_1}(s)$ and, for $k \ge 1$,

$$\hat{\eta}_u(k+1,s) = \frac{1_{\mathcal{B}_{k+1}}(s)}{r_{k+1}(s)h_{n_{k+1}}(s)}\int_{\mathcal{C}_k}\hat{\eta}_u(k,u)r_k(u)h_{n_k}(u)h_{m_{k+1}}(s-u)du. \tag{3.2}$$

Computation in (3.2) can be quite extensive, often involving multiple integrals that can only be numerically evaluated. For normal distributions, Emerson (1993) and Emerson and Kittelson (1997) discussed the complexity of the computation issues and proposed simpler programs for numerical computation. Section 5 below presents an illustrative example with exponential distributions.

3.2. Truncation-adaptable unbiased estimators

The truncation-adaptation concept was proposed by Liu and Hall (1999), formalizing an observation in Emerson (1993), and related comments in Emerson and Fleming (1990), that it is desirable for an inference after a stopped sequential test to be free of dependence on future stopping boundaries.

Specifically, consider an estimator $\tilde{\eta}$, possibly depending on the whole sampling path $\{X_1, \ldots, X_{n_M}\}$, of $\eta = \eta(\theta)$ that is unbiased when using a particular group sequential design $\mathcal{D}$, with stopping regions $\mathcal{B}_k$. For each $k < K$, consider a truncated design $\mathcal{D}^k$, obtained by retaining the first $k-1$ stopping regions and closing the kth stopping region; that is, replacing $\mathcal{B}_k$ by $\mathcal{B}_k \cup \mathcal{C}_k = \mathcal{C}_{k-1} \oplus \mathcal{X}_{m_k}$. We say $\tilde{\eta}$ is a *truncation-adaptable unbiased estimator of* η if, for each k, there exists an extension of $\tilde{\eta}$ to the domain $\mathcal{C}_k$ so that the resulting estimator is unbiased for η in the truncated design $\mathcal{D}^k$.

To help clarify this concept, we first consider Bernoulli sampling with parameter p. As in Blackwell (1947), the Rao-Blackwell unbiased estimator of p^r (for $r \leq n_1$) is found to be the ratio of two counts of paths — in Pascal triangle fashion — to the stopping point, expressed as (s, f) with $f = n - s$. The numerator count is from $(r, 0)$ to (s, f), and the denominator count from $(0, 0)$ to (s, f). It is easy to see that, in truncation from a maximum sample size of n_K to $n_K - 1$, the path counts to stopping points common to both designs are unaffected, and so the unbiased estimator can be preserved by appropriate path counting to new boundary points. The same holds for further truncation. Hence, this estimator is truncation adaptable. Lehmann and Stein (1950) showed that this estimator is unique among sufficient-statistic-based unbiased estimators in sequential designs with every continuation set an interval. For other designs, it is not unique, and others may have smaller variance for limited ranges of p. Only the Rao-Blackwell estimator is truncation adaptable, however (see Theorem 1).

A small example of Bernoulli sampling that illustrates lack of adaptability is as follows. Consider a design with stopping points $(s, f) = (3, 0)$, $(2, 1)$, $(1, 1)$, $(1, 2)$ and $(0, 3)$, with $n = 2$ or 3 ($k = 1, 2$). The Rao-Blackwell estimator of p has values 1, 1, 1/2, 0, 0, respectively. But a statistic with values 0, c, $-c/2$, c, 0 has 0 expectation uniformly (and only these statistics). Hence, $\hat{p}_c$, with values 1, $1 + c$, $(1 - c)/2$, c, 0, for any c are the only unbiased estimators. Upon truncating to $n = 2$, a truncation-adaptable estimate must not change at

the $n = 2$ boundary point (1,1), but the only unbiased estimator when $n = 2$ has value $1/2$ at this point; hence, $\hat{p}_c$ is truncation-adaptable unbiased only when $c = 0$, which corresponds to the Rao-Blackwell estimators (the omitted details are straightforward, but sometimes tedious). Moreover, for any c with $0 < |c| < 2/3$, $\hat{p}_c$ has smaller variance than $\hat{p}_0$ over a sub-interval of p but not uniformly over the unit interval, and for any given $c \neq 0$ (not necessarily with $0 < |c| < 2/3$), $\hat{p}_0$ has smaller variance than $\hat{p}_c$ in a neighborhood of $p = 1/2$, hence a uniform minimum-variance unbiased estimator does not exist. This is in keeping with the fact that the continuation set $\{(2, 0), (0, 2)\}$ is not an interval. Note also that $\hat{p}_c$ is not confined to the unit interval except when $c = 0$.

Returning to the exponential family generally, slight modification of the proof of Lemma 2 of Liu and Hall (1999) to the case of exponential families will show that, if $\tilde{\eta}$ is truncation-adaptable unbiased for η, then so is $E\{\tilde{\eta}|(M, S)\}$, and with reduced variance. We therefore can limit attention to sufficient-statistic-based estimators.

We show in the Appendix how to construct, stage by stage, a truncation-adaptable unbiased estimator $\hat{\eta}_{ta}(M, S)$ of η, verifying uniqueness along the way. We thus have

Theorem 1. *In a group-sequential design, for any m-estimable ($m \leq n_1$) function $\eta = \eta(\theta)$, there exists at most one truncation-adaptable unbiased estimator based on (M, S), and it is identical to the Rao-Blackwell estimator $\hat{\eta}_u(M, S)$.*

Therefore, for an m-estimable η, both Rao-Blackwell and truncation-adaptable criteria lead to the unique uniform minimum-variance truncation-adaptable unbiased estimator.

Remark. In defining the truncation-adaptable concept, we could allow truncation at some intermediate stage, say after n observations for some $n_k < n < n_{k+1}$, but have used the simpler definition here.

4. Minimum Variance and Completeness

In the previous section, we showed that the Rao-Blackwell estimator (3.1) has minimum variance among all truncation-adaptable unbiased estimators. If (M, S) is complete, the truncation-adaptable restriction can be removed. We now consider whether this estimator, or other estimators, if any, has minimum variance among all unbiased estimators. To do so, we investigate situations where the sufficient statistic (M, S) is not complete and investigate the performance of the uniform minimum-variance unbiased estimator, if any, in these situations.

For each fixed n, the family of distributions of S_n is complete (Lehmann and Casella (1998)); we say simply that S_n is complete. Hence, there exists at most one unbiased estimator depending on S_n of an m-estimable ($m \leq n$) parameter

function $\eta = \eta(\theta)$. However, the completeness property may not be inherited when data are examined sequentially since the distribution of (M, S) is from a curved exponential family, as noted following (2.6). (See Lehmann and Stein (1950) for the case of Bernoulli, Poisson and normal distributions; see also the $n \leq 3$ Bernoulli example above.)

Consider $W = w(M, S)$ such that $E_\theta(W) = 0$ for all θ in an open interval. Then, from (2.6) and (2.7), we have, equivalently,

$$\sum_{k=1}^{K} \exp\{-n_k a(\theta)\} \mathcal{L}_{w_k}(\theta; \mathcal{B}_k) = 0, \tag{4.1}$$

where $w_k(s) = w(k, s) r_k(s) h_{n_k}(s)$ and $\mathcal{L}_g(\theta; \Delta) = \int_\Delta g(s) \exp\{\theta s\} ds$, the Laplace transform of a function g on support Δ.

Note that $r_k(s) > 0$ for all k and $s \in \mathcal{B}_k$, and $h_n(s) > 0$ for all n and $s \in \mathcal{X}_n$. Hence the equation $E_\theta(W) = 0$ holds only for the null function if and only if (4.1) holds only for the null function, i.e., for each k, $w_k(s) = 0$ for all $s \in \mathcal{B}_k$.

Theorem 2. *Consider a K-analysis group sequential design for a density having form* (2.1)*, with* (*reachable*) *stopping regions $\mathcal{B}_k$ ($k \leq K$). If, for some $1 \leq i < j \leq K$ and some positive-measure subset $\mathcal{B}_i^o$ of $\mathcal{B}_i$,*

$$\mathcal{B}_i^o \oplus \mathcal{X}_{n_j - n_i} \subseteq \mathcal{B}_j, \tag{4.2}$$

then the sufficient statistic (M, S) is not complete.

The condition in Theorem 2 is not necessary for completeness to fail, however (but not shown here).

Remark. When $\mathcal{B}_i^o = \mathcal{B}_i$, (4.2) is a special case of part (i) of Lehmann and Stein's (1950) theorem; it suffices to note that our $\mathcal{C}_m \oplus \mathcal{X}_{p-m}$ is their W_p^m. This implies, in the Bernoulli sampling case (with bounded sample size), that completeness requires every continuation set to be an interval.

Note that, for each $i < K$, $\mathcal{B}_i \oplus \mathcal{X}_{n_K - n_i} \subseteq \mathcal{X}_{n_i} \oplus \mathcal{X}_{n_K - n_i} = \mathcal{X}_{n_K}$.

Corollary 1. *If $\mathcal{B}_K = \mathcal{X}_{n_K}$, then (M, S) is not complete.*

Case 1. If the support of (2.1) is $(-\infty, \infty)$, then $\mathcal{B}_K = (-\infty, \infty)$ and thus (M, S) is not complete. A special case is that of normal sampling with known variance (Lehmann and Stein (1950) and Liu and Hall (1999)).

Case 2. Suppose the support of (2.1) is $\mathcal{X} = (0, \infty)$, such as for an exponential distribution. If $(0, c) \subset \mathcal{C}_{K-1}$, for some $c > 0$, then $\mathcal{B}_K = \mathcal{C}_{K-1} \oplus \mathcal{X}_{n_K - n_{K-1}} = \mathcal{X} = \mathcal{X}_{n_K}$, and thus (M, S) is not complete.

Case 3. Suppose the support of (2.1) is $\mathcal{X} = \{0, 1, \ldots\}$, such as for a Poisson distribution. If $0 \in \mathcal{C}_{K-1}$, then, as in Case 2, $\mathcal{B}_K = \mathcal{X} = \mathcal{X}_{n_K}$, and thus (M, S) is not complete.

Remark. The origin may be shifted in Cases 2 and 3.

When (4.2) holds, and hence completeness fails, there exist infinitely many unbiased estimators of η, since we can construct infinitely many zero-mean statistics each of which yields an unbiased estimator when added to the Rao-Blackwell estimator (3.1). (See (A.2) in the appendix; also, recall the $n \leq 3$ Bernoulli example above.) But is there a uniform minimum-variance one among them? We show below that, when existent, it may have an undesirable property, and we give a simple sufficient condition for non-existence.

Often, a parameter function $\eta(\theta)$ of practical interest is *distinguishable* in the sense that over no open intervals of Θ is the function constant. Two particular parameter functions, the natural parameter θ itself and the mean parameter $E(X) = a'(\theta)$, are both monotone functions (noting that $Var(X) = a''(\theta) > 0$), and thus are distinguishable. Functions with a finite number of inverses — such as pq in the Bernoulli case — remain distinguishable. An estimator $\hat{\eta} = \hat{\eta}(M, S)$ is said to be *distinguishable* if for no non-singleton interval of any $\mathcal{B}_k$ is $\hat{\eta}$ constant. It is natural to prefer that a distinguishable parameter function be estimated by distinguishable estimators, just like the restriction that a bounded parameter be estimated by a bounded estimator (Wolfowitz (1946) and Savage (1947)). In the discrete case, this requirement that an estimator is not constant on any two adjacent boundary points may need relaxing somewhat since, it may be shown that, in every curtailed Bernoulli sampling design, $\mathcal{B}_{n_K}$ consists of two adjacent points where the uniform minimum-variance estimate is constant.

The following results show that when completeness fails, a uniform minimum-variance unbiased estimator of η is often not distinguishable, and hence may be of less practical interest (assuming η is distinguishable).

Theorem 3. *Assume that* (4.2) *holds for some* $1 \leq i < j \leq K$ *and* $\mathcal{B}_i^o$ *contains an open interval. If* $\hat{\eta}(M, S)$ *is a uniform minimum-variance unbiased estimator of* η*, then for each* $s \in \mathcal{B}_i^o \oplus \mathcal{X}_{n_j - n_i}$*,* $\hat{\eta}(i, t) = \hat{\eta}(j, s)$ *for all* $t \in \mathcal{B}_i^o$ *such that* $s - t \in \mathcal{X}_{n_j - n_i}$*. Moreover,* $\hat{\eta}$ *is not distinguishable.*

For discrete variables, the 'open interval' requirement should be omitted.

Consequently, in extension to a result of Liu and Hall (1999) for sampling normal variables with known variance, we have

Corollary 2. *If the support* $\mathcal{X}$ *of (2.1) is* $\mathcal{R}$*, then for any estimable non-constant parameter function* η*, a uniform minimum-variance unbiased estimator does not exist.*

Proof. Suppose $\hat{\eta}(M,S)$ is such an estimator. Since $\mathcal{X}=\mathcal{R}$ implies $\mathcal{X}_n=\mathcal{R}$, we have, for each $1\le i<K$, $\mathcal{B}_i\oplus\mathcal{X}_{n_K-n_i}=\mathcal{R}=\mathcal{X}_{n_K}$. It follows from Theorem 3 that $\hat{\eta}(i,t)=\hat{\eta}(K,s)$ for all $t\in\mathcal{B}_i$ and all $s\in\mathcal{X}_{n_K}$. Hence $\hat{\eta}$ is a constant, a contradiction to its unbiasedness.

5. Exponential Distributions and an Application to Clinical Trials

In this section, we investigate the completeness of the sufficient statistic for a class of group sequential designs when sampling from an exponential distribution.

We first briefly describe a clinical trial example for which the exponential distribution assumption of the outcome measurement is appropriate. A new treatment for asthma using magnesium is being evaluated. Before a large Phase III trial is carried out to compare it with the standard treatment, investigators plan to conduct a Phase II study to assess the efficacy and feasibility of magnesium. The primary clinical outcome is the forced expiratory volume (FEV), measured by having the patient exhale into a spirometer which is calibrated to measure the amount of air exhaled in one second. The measurements are assumed to follow an exponential distribution. The study was designed to have two stages, allowing early stopping of the trial if the observed mean FEV at the first stage is too low.

This example involves group sequential designs for exponential distributions, whose densities have the form (2.1) with $h(x)=1_{[0,\infty)}(x)$ and $a(\theta)=-\log(-\theta)$ with $\theta<0$; hence $h_{n+1}(s)=1_{[0,\infty)}(s)\,s^n/n!$. We confine consideration to three types of boundaries.

Type 1. (upper-boundary) The first type are those designs having only an upper boundary at each stage: $\mathcal{B}_k=[l_k,\infty)$ with $l_k>0$, $1\le k<K$ and $\mathcal{B}_K=[0,\infty)$ to ensure eventual stopping. Such a design may be appropriate when larger values of observation indicate an adverse effect. In this case, completeness fails, as argued in Case 2 of Section 4.

Type 2. (lower-upper-boundary) If a trial needs to be stopped early for either large or small values of observations, then each stage of the design may have both a lower and an upper boundary, that is, $\mathcal{B}_k=[l_{1k},u_{1k})\cup[l_{2k},\infty)$ with $l_{11}=0$, $l_{1k}<u_{1k}<l_{2k}$ for $1\le k<K$, and $\mathcal{B}_K=[l_{1K},\infty)$. Boundaries being reachable requires $0=l_{11}<u_{11}=l_{12}<u_{12}=\ldots=l_{1K-1}<u_{1K-1}=l_{1K}$. Now $u_{1K-1}<l_{2K-1}$ implies $[l_{2K-1},\infty)\oplus[0,\infty)=[l_{2K-1},\infty)\subset[u_{1K-1},\infty)=\mathcal{B}_K$, and hence completeness fails by Theorem 2. This Type can be extended to allow an additional inner stopping boundary, resulting in two continuation intervals; the same conclusion holds.

Type 3. (lower-boundary) Now each stage has only a lower boundary, that is $\mathcal{B}_k = [l_k, u_k)$, starting with $l_1 = 0$, and reachability requires

$$0 = l_1 < u_1 = l_2 < u_2 = \ldots = l_{K-1} < u_{K-1} = l_K < u_K = \infty. \tag{4.3}$$

The asthma clinical trial described above uses this type of design (with $K = 2$) to allow early stopping for small values of observations. For this type of design, condition (4.2) is obviously not satisfied. Indeed, we have the following result, in contrast to the other two types of designs.

Theorem 4. *Following a group sequential design for an exponential distribution having lower boundaries only (Type 3), the sufficient statistic (M, S) is complete.*

Consequently the Rao-Blackwell estimator $\hat{\eta}_u(M, S)$ is the uniform minimum-variance unbiased estimator of the estimable parameter function $\eta = \eta(\theta)$.

Computation of the estimator involves numerical evaluation of multiple integrals when $M \geq 3$. For illustration, consider estimation of $E(X) = -1/\theta$ at $M = 1, 2, 3$. The functions r_k in (2.5) are given recursively by $r_1(s) = 1_{[0,u_1)}(s)$,

$$\begin{aligned}
r_2(s) &= \frac{1}{h_{n_2}(s)} \int_{u_1}^{\infty} h_{n_1}(u) h_{m_2}(s-u) du \\
&= 1_{[u_1,u_2)}(s) \frac{(n_2-1)!}{s^{n_2-1}} \int_{u_1}^{s} \frac{u^{n_1-1}(s-u)^{m_2-1}}{(n_1-1)!(m_2-1)!} du, \\
r_3(s) &= \frac{1}{h_{n_3}(s)} \int_{u_2}^{\infty} r_2(u) h_{n_2}(u) h_{m_3}(s-u) du \\
&= 1_{[u_2,u_3)}(s) \frac{(n_3-1)!}{s^{n_3-1}} \int_{u_2}^{s} \frac{r_2(u) u^{n_2-1}(s-u)^{m_3-1}}{(n_2-1)!(m_3-1)!} du.
\end{aligned}$$

At $M = 1$, the Rao-Blackwell estimator of η is $\hat{\eta}(1, s) = s/n_1$. For $M = 2, 3$, (3.2) yields

$$\begin{aligned}
\hat{\eta}(2, s) &= \frac{1}{r_2(s) h_{n_2}(s)} \int_{u_1}^{\infty} \hat{\eta}(1, u) r_1(u) h_{n_1}(s) h_{m_2}(s-u) du \\
&= \frac{1}{r_2(s) h_{n_2}(s)} \int_{u_1}^{s} \frac{u^{n_1}(s-u)^{m_2-1}}{(n_1)!(m_2-1)!} du, \\
\hat{\eta}(3, s) &= \frac{1}{r_3(s) h_{n_3}(s)} \int_{u_2}^{\infty} \hat{\eta}(2, u) r_2(u) h_{n_2}(s) h_{m_3}(s-u) du \\
&= \frac{\displaystyle\int_{u_2}^{s} \hat{\eta}(2, u) r_2(u) u^{n_2-1}(s-u)^{m_3-1} du}{\displaystyle\int_{u_2}^{s} r_2(u) u^{n_2-1}(s-u)^{m_3-1} du}.
\end{aligned}$$

For $k = 2$, the integrals in $r_k(s)$ and $\hat{\eta}(k, s)$ are incomplete beta functions, commonly available in software packages, but $\hat{\eta}(3, s)$ will require a numerical integration, for both the numerator and denominator.

6. Summary and Discussion

We have investigated unbiased estimation following group sequential sampling for distributions in a one-parameter exponential family. The restrictions to bounded sequential sampling and to exponential family distributions allowed us to utilize Laplace transforms and their inverses to obtain conditions for completeness of the sufficient statistic to fail. The latter restriction covers most distributions in Lehmann and Stein (1950), but rules out distributions like the rectangular distribution.

We showed that the sufficient statistic (M, S) possesses truncation-adaptable properties, similar to completeness, and the Rao-Blackwell estimator (3.1) has minimum variance among truncation-adaptable unbiased estimators. With completeness of the sufficient statistic, minimum variance among all unbiased estimators is assured. We suspect that this estimator remains a strong candidate regardless of completeness. When completeness fails, the uniform minimum-variance unbiased estimator, if it exists, may remain constant over an open interval, an undesirable property when the parameter function of interest is *distinguishable* (a monotone function, for example).

To what extent our results can be extended to other distributions and more general types of stopping regions is not clear, as the Laplace transform methods used in the paper are specific to the exponential family.

Lehmann and Stein (1950) found, for Bernoulli and Poisson distributions, necessary and sufficient conditions for the sequential sampling scheme to be complete. For exponential distributions, we found a sub-class of group sequential procedures that are complete (Section 5). It remains an unsolved problem to find a necessary and sufficient condition for a general sequential sampling scheme to be complete with a general distribution, within or beyond the exponential family.

As commented earlier in Section 3.1, computation of the unbiased estimators can be complex and extensive, especially when K, the number of looks, is relatively large (≥ 4). For normal distributions, these estimators are available in the software S+SeqTrial by Emerson, Hesterberg and Bruce (2002). Extension of this program to accommodate other distributions of the exponential family is necessary. Note that the computation for $K \leq 3$ is relatively simple and closed forms are often available for $K = 2$. If the trial stops at a stage $k \geq 4$, one can approximate the unbiased estimators by retaining only the most recent one or two stages and computing the estimators as if these were the only stages before stopping. Some limited numerical results show this strategy to work well for

normally distributed variables with various stopping boundaries (Hall, Ding and Liu (2002)).

Appendix A. Proofs of Theorems

Proof of Theorem 1. Without ambiguity, we use the notation $\hat{\eta}_{ta}(M,S)$ for both the estimator (defined for $s \in \mathcal{B}_M$) and its extension to $s \in \mathcal{C}_M$. By definition, $\hat{\eta}_{ta}(M,S)$ is unbiased for η under each truncated design $\mathcal{D}^k$ $(k<K)$. For each $\mathcal{D}^k$, the density of (M,S) is still given by (2.6), except with $\mathcal{B}_k$ in the indicator in $r_k(s)$ being replaced by $\mathcal{B}_k \cup \mathcal{C}_k = \mathcal{C}_{k-1} \oplus \mathcal{X}_{m_k}$. It follows that

$$\sum_{i=1}^{k-1} \int_{\mathcal{B}_i} \hat{\eta}_{ta}(i,s) r_i(s) f_{n_i,\theta}(s) ds + \int_{\mathcal{B}_k \cup \mathcal{C}_k} \hat{\eta}_{ta}(k,s) r_k(s) f_{n_k,\theta}(s) ds = \eta(\theta), \quad \text{(A.1)}$$

with the sum term omitted when $k=1$.

We derive recursive formulas for $\hat{\eta}_{ta}$ by induction. Since $\mathcal{D}^1$ is a non-sequential design with sample size n_1, the completeness of S_n implies a unique $\hat{\eta}_{ta}(1,s) = \hat{\eta}_{n_1}(s)$ in (A.1).

Suppose $\hat{\eta}_{ta}(j,s), s \in \mathcal{B}_j \cup \mathcal{C}_j$, $j = 1, \cdots, k < K$, have been determined to satisfy (A.1). Then $\hat{\eta}_{ta}(k+1,s)$ must satisfy the equation

$$\int_{\mathcal{B}_{k+1} \cup \mathcal{C}_{k+1}} \hat{\eta}_{ta}(k+1,s) r_{k+1}(s) f_{n_{k+1},\theta}(s) ds = \int_{\mathcal{C}_k} \hat{\eta}_{ta}(k,s) r_k(s) f_{n_k,\theta}(s) ds,$$

which, from (2.3) and the convolution of Laplace transforms, becomes

$$\begin{aligned} &\int_{\mathcal{B}_{k+1} \cup \mathcal{C}_{k+1}} \hat{\eta}_{ta}(k+1,s) r_{k+1}(s) h_{n_{k+1}}(s) \exp\{s\theta\} ds \\ &= \int_{\mathcal{X}_{m_{k+1}}} h_{m_{k+1}}(s) \exp\{s\theta\} ds \int_{\mathcal{C}_k} \hat{\eta}_{ta}(k,s) r_k(s) h_{n_k}(s) \exp\{s\theta\} ds \\ &= \int_{\mathcal{B}_{k+1} \cup \mathcal{C}_{k+1}} \delta(k+1,s) \exp\{s\theta\} ds, \end{aligned}$$

where

$$\begin{aligned} \delta(k+1,s) &= \int_{\mathcal{C}_k} h_{m_{k+1}}(s-u) \hat{\eta}_{ta}(k,u) r_k(u) h_{n_k}(u) du \\ &= \int_{\mathcal{X}_{m_{k+1}}} h_{m_{k+1}}(u) \hat{\eta}_{ta}(k,s-u) r_k(s-u) h_{n_k}(s-u) du. \end{aligned}$$

By uniqureness of Laplace transforms, this leads to (3.2).

Since each step of the induction has only one solution, estimators satisfying (A.1) are unique.

Proof of Theorem 2. The theorem follows from the fact that a class of zero-mean statistics can be constructed based on (4.2), as demonstrated below. Let $w(i,s)$ be such a function on $\mathcal{B}_i$ that takes the value 0 on $\mathcal{B}_i \setminus \mathcal{B}_i^o$, and define

$$w(j,s) = -1_{\mathcal{B}_{ij}^o}(s)\frac{1}{r_j(s)h_{n_j}(s)}\int_{\mathcal{B}_i^o(s;j)} w(i,t)r_i(t)h_{n_i}(t)h_{n_j-n_i}(s-t)dt$$

and

$$\mathcal{B}_i^o(s;j) = \mathcal{B}_i^o \cap \{t : s-t \in \mathcal{X}_{n_j-n_i}\}, \quad \mathcal{B}_{ij}^o = \mathcal{B}_i^o \oplus \mathcal{X}_{n_j-n_i}. \tag{A.2}$$

Now consider $W_o = w_o(M,S)$ where, for $s \in \mathcal{B}_k$, $w_o(k,s) = w(k,s)$ if $k = i$ or j and $= 0$ otherwise. Then $E_\theta(W_o) = 0$ for θ in an open interval.

Proof of Theorem 3. An unbiased estimator $\hat{\eta}$ has uniform minimum variance among all unbiased estimators of η if and only if it is uncorrelated with every zero-mean statistic (Lehmann and Casella (1998), Theorem 1.7). Thus for every zero-mean W_o constructed above, $E_\theta(W_o\,\hat{\eta}) = 0$ for θ in an open interval which, along with (2.3) and the uniqueness of Laplace transforms, yields, for each $s \in \mathcal{B}_{ij}^o$,

$$\hat{\eta}(j,s)w_o(j,s)r_j(s)h_{n_j}(s) = -\int_{\mathcal{B}_i^o(s;j)} \hat{\eta}(i,t)w_o(i,t)r_i(t)h_{n_i}(t)h_{n_j-n_i}(s-t)dt.$$

By construction of w_o after (A.2) above, we have

$$\int_{\mathcal{B}_i^o(s;j)} \{\hat{\eta}(j,s) - \hat{\eta}(i,t)\}w(i,t)r_i(t)h_{n_i}(t)h_{n_j-n_i}(s-t)dt = 0 \tag{A.3}$$

for every $s \in \mathcal{B}_{ij}^o$ and $t \in \mathcal{B}_i^o(s;j)$, and every function $w(i,t)$ defined on $\mathcal{B}_i^o$. Setting $w(i,t) = \hat{\eta}(j,s) - \hat{\eta}(i,t)$ in (A.3) hence yields $\hat{\eta}(j,s) = \hat{\eta}(i,t)$ for every $s \in \mathcal{B}_{ij}^o$ and $t \in \mathcal{B}_i^o(s;j)$.

We now show that $\hat{\eta}$ is not distinguishable if $\mathcal{B}_i^o$ contains an open interval. We first note that, if the distribution is absolutely continuous, then there exists at least one $s \in \mathcal{B}_{ij}^o$ such that $\mathcal{B}_i^o(s;j)$ also contains an open interval $\mathcal{I}$, since $\mathcal{X}_{n_j-n_i}$ contains an open interval. Hence $\hat{\eta}$ is constant on $\mathcal{I}$, upsetting distinguishability.

If the distribution is discrete, then $\mathcal{B}_i^o$ contains a reachable point, say a (an integer). Because $\mathcal{X}_{n_j-n_i}$ is a set of (at least two) integers, $\{a\} \oplus \mathcal{X}_{n_j-n_i}$ has a one-to-one mapping on $\mathcal{X}_{n_j-n_i}$. Therefore, for each $s \in \{a\} \oplus \mathcal{X}_{n_j-n_i}$, $s-a \in \mathcal{X}_{n_j-n_i}$, $\hat{\eta}(j,s) = \hat{\eta}(i,a)$, again upsetting distinguishability.

Proof of Theorem 4. Let $W = w(M,S)$ be such that $E_\theta(W) = 0$ for all $\theta < 0$, and write $m_k' = n_K - n_k$. Then, with Type 3 boundaries, (4.1) becomes

$$\int_{l_{1K}}^{\infty} w_K(s)\exp\{\theta s\}ds = -\sum_{k=1}^{K-1}\exp\{m_k' a(\theta)\}\int_{l_k}^{u_k} w_k(s)\exp\{\theta s\}ds,$$

with w_k being defined as in (4.1).

Apply (2.3) and the convolution of Laplace transforms to obtain

$$\int_{l_{1K}}^{\infty} w_K(s)\exp\{\theta s\}ds = -\sum_{k=1}^{K-1}\int_0^{\infty} h_{m'_k}\exp\{\theta s\}ds\int_{l_k}^{u_k} w_k(s)\exp\{\theta s\}ds$$
$$= -\sum_{k=1}^{K-1}\int_{l_k}^{\infty}\tilde{w}_k(s)\exp\{\theta s\}ds, \tag{A.4}$$

where

$$\tilde{w}_k(s) = \int_{\{u:\, l_k\le u\le u_k, s-u\le 0\}} w_k(u)h_{m'_k}(s-u)du = \int_{l_k}^{min(u_k,s)} w_k(u)h_{m'_k}(s-u)du.$$

We first show that $w(1,s)=0$ for all $s\in\mathcal{B}_1=[0,u_1)$. Recall (5.1). By the uniqueness of Laplace transforms, $\tilde{w}_1(s)=0$ for every $0\le s\le l_2=u_1$, that is, for every such s,

$$\int_0^s w_1(u)h_{m'_1}(s-u)du = 0. \tag{A.5}$$

Repeatedly differentiating the left side of (A.5) up to m'_k times yields $w_1(s)=0$, thus implying $w(1,s)=0$.

Now, with the first term eliminated, the right side of (A.4) reduces to $K-2$ terms. Using the above approach again, we can then show $w(2,s)=0$ for every $s\in[l_2,u_2)$, and then go on to show sequentially that $w(k,s)=0$ for $3\le k\le K-1$ for $s\in[l_k,u_k)$. Hence $w(K,s)=0$ for $s\ge l_K$.

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