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A BAYESIAN COMPARISON OF GROUP SEQUENTIAL DESIGNS

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A Bayesian approach to group sequential designs is illustrated for Anscombe's formulation of the problem of comparing two treatments in a medical trial. It is shown that an adjusted continuous time stopping boundary is a good approximation to the optimal group sequential stopping boundary. The Bayes risk and efficiency of the group sequential designs, using both the optimal and adjusted continuous time boundaries, are computed.

1. Introduction. In long-term clinical trials, where patients are entering sequentially, the strict application of fixed sample size designs is unjustified on ethical grounds. On the other hand, fully sequential designs may be impractical due to the need for continuous assessment of accumulating data. The planned use of group sequential designs has been advocated as a convenient approach to the monitoring of clinical trials. In the literature there are many ad-hoc group sequential designs, for example in Pocock (1977), O'Brien and Fleming (1979), and Lan and Demets (1983). For a good review, one can consult Simon (1991) and Whitehead (1997). Recently Lewis and Berry (1994) and Eales and Jennison (1995) gave some comparisons of different types of group sequential designs.

In this manuscript we will focus on the following issues:

(a) In a Bayesian framework, how a continuous-time version of the group sequential problem, where the data arrive as a Wiener process, can approximate the discrete-time group sequential procedure.

(b) How good the continuous-time "optimal" stopping boundary (with proper adjustment) is as an approximation to the "optimal" discrete-time group sequential stopping boundary.

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This paper is organized as follows. In Section 2 some relevant results in the fully sequential setting are recalled in enough detail to motivate the group sequential analogues which are introduced and analyzed in Section 3. The Bayes risk and Bayes efficiency of the group sequential designs are investigated in Section 4.

2. Background: fully sequential tests. Anscombe (1963) introduced a decision-theoretic approach to clinical trials. He assumed that the patients are treated in pairs during the experimental phase of the study, with one member of the pair assigned to treatment 1 and the other assigned to treatment 2. The difference in patient response (treatment 1 - treatment 2) is assumed to be normally distributed with mean μ and standard deviation σ^2. Here μ is unknown and σ^2 is assumed to be known. Throughout the current paper the treatment differences are assumed to be independent. It is also assumed that N, the total number of patients ever to receive either of the treatments, is known.

Anscombe (1963) uses the loss function defined by $|\mu|$ times the number of patients receiving the poorer treatment. For $n < N/2$, let S_n denote the sum of the response differences after n pairs of patient responses have been observed. In Anscombe (1963) it is assumed that the remaining $N - 2n$ patients would be treated according to the sign of S_n: If $S_n > 0$ then the remaining patients will receive treatment 1; otherwise, the remaining patients will receive treatment 2.

In this section some relevant results due to Chernoff (1972) and Chernoff and Petkau (1981, 1985), are presented. These references may be consulted for further details. The notation follows that of Chernoff and Petkau (1981).

In the Bayesian setting, the posterior expected loss can be written as

$$nE[|\mu|] + (N - 2n)E[\max(0, -\text{sgn}(S_n)\mu)], \tag{2.1}$$

where sgn represents the sign function and the expectation is taken with respect to the posterior distribution of μ after observing S_n.

Throughout this section, the prior distribution of μ is assumed to be a normal distribution with mean μ_0 and variance σ_0^2. After observing the treatment differences $X_1, \ldots, X_n$, the posterior distribution of μ is normal with mean Y_n^* and variance s_n^*, where

$$Y_n^* = \frac{\sigma_0^{-2}\mu_0 + \sigma^{-2}\sum_{i=1}^n X_i}{\sigma_0^{-2} + n\sigma^{-2}} \quad \text{and} \quad s_n^* = (\sigma_0^{-2} + n\sigma^{-2})^{-1}. \tag{2.2}$$

Chernoff (1972) showed that for $n \geq m \geq 0$, the conditional distribution of $Y_n^* - Y_m^*$ given Y_m^* is normal with mean 0 and variance $s_m^* - s_n^*$, and $Y_n^* - Y_m^*$ is independent of Y_m^*. Therefore $\{Y_n^*\}$ behaves like a Gaussian process with independent increments starting from $Y_0^* = \mu_0$.

Since the choice of treatment for the remaining $N-2n$ patients is determined by the sign of Y_n^*, the expected loss or posterior risk associated with stopping after treating n pairs of patients is given by

$$nE[|\mu|] + (N - 2n)E[\max(0, -\text{sgn}(Y_n^*)\mu)], \tag{2.3}$$

where the expectation is taken with respect to the posterior distribution of μ given Y_n^*. Let ϕ and Φ represent the standard normal density and cumulative distribution functions respectively, and let $\psi(u) = \phi(u) + u\{\Phi(u) - 1/2\}$. Then the posterior risk can be expressed as

$$N\sqrt{s_n^*}\psi(Y_n^*/\sqrt{s_n^*}) - (1/2)(N-2n)|Y_n^*|. \tag{2.4}$$

Using (2.2) the posterior risk can be written as $d_1(Y_n^*, s_n^*)$, where

$$d_1(y^*, s^*) = N\sqrt{s^*}\psi(y^*/\sqrt{s^*}) - \sigma^2(s_*^{-1} - s^{*^{-1}})|y^*|, \tag{2.5}$$

and $s_*^{-1} = \sigma_0^{-2} + (1/2)N\sigma^{-2}$. It is of interest to find the stopping time τ that minimizes the expected risk $E\{d_1(Y_\tau^*, s_\tau^*)\}$, where the expectation is taken over the distribution of τ.

A continuous-time approximation to the above problem is to replace the sequence of partial sums $\{\sum_{i=1}^k X_i : 0 \le k \le n\}$ by a continuous-time Wiener process $\{X(t^*) : 0 \le t^* \le N/2\}$ with drift μ and variance σ^2 per unit in the t^* scale. The posterior distribution of μ given $X(t'), 0 \le t' \le t^*$ is normal with mean Y^* and variance s^*, where

$$Y^* = Y^*(s^*) = \frac{\sigma_0^{-2}\mu_0 + \sigma^{-2}X(t^*)}{\sigma_0^{-2} + t^*\sigma^{-2}} \qquad \text{and} \qquad s^* = (\sigma_0^{-2} + t^*\sigma^{-2})^{-1}. \tag{2.6}$$

It is shown in Chernoff (1972) that $\{Y^*(s^*)\}$ is a Wiener process with drift 0 and variance 1 per unit in the $-s^*$ scale with $Y^*(s_0^*) = \mu_o$ where $s_0^* = \sigma_0^2$. In Chernoff and Petkau (1981) it is shown that the posterior risk corresponding to stopping at (Y^*, s^*) can be written as $d_1(Y^*, s^*)$, with d_1 given by (2.5).

A convenient normalization follows by setting $Y = aY^*$ and $s = a^2 s^*$. Algebra yields the expression

$$d_1(y^*, s^*) = (N/a)\sqrt{s}\psi\left(y/\sqrt{s}\right) - a\sigma^2((a^2 s_*)^{-1} - s^{-1})|y|. \tag{2.7}$$

Call the function on the right-hand-side of (2.7) $d_2(y, s)$.

Choosing $a^2 = \sigma_0^{-2} + (1/2)N\sigma^{-2} = (s_*)^{-1}$, defining $s_0 = a^2\sigma_0^2$, and performing some algebra yields the expression

$$d_2(y, s) = \sigma^2(ss_0\sigma_0^{-2})^{1/2}\left[2(1 - s_0^{-1})\psi\left(y/\sqrt{s}\right) - (1 - s^{-1})|y/\sqrt{s}|\right]. \tag{2.8}$$

3. Group sequential designs. The group sequential setting can be described as follows. The total number of pairs of patients $N/2$ is split into K groups of m pairs of patients, so that $Km = N/2$. Stopping is allowed only at the values $n = im$ for $i = 1, \ldots, K$, and stopping is enforced when $n = Km = N/2$.

3.1. *The loss function.* The model of the previous section translates as follows. We have K observations (the mean differences for the K groups) which are independent

and normally distributed with mean μ and (known) variance $\overline{\sigma}^2 = \sigma^2/m$. Here μ is assumed to have a prior normal distribution with mean μ_0 and variance σ_0^2. As in Section 2, the posterior risk associated with stopping after the ith group is computed to be

$$miE(|\mu|) + 2m(K-i)E[\max(0, -\mathrm{sgn}(Y_n^*)\mu)]. \tag{3.1}$$

Note the similarity with (2.3). If m is set equal to 1, i is replaced by n, and K is replaced by $N/2$, then the expressions are equal. The theory of the previous section can thus be applied easily in the group sequential setting.

As in the previous section, one can introduce a continuous-time version of the problem. For this version, one can write the posterior cost of stopping at (Y^*, s^*) to be $d^*(Y^*, s^*)$, where

$$d^*(y^*, s^*) = m\left[2K\sqrt{s^*}\psi(y^*/\sqrt{s^*}) - \overline{\sigma}^2(s_*^{-1} - s^{*^{-1}})|y^*|\right], \tag{3.2}$$

where $s_* = (\sigma_0^{-2} + \overline{\sigma}^{-2}K)$. Again use the transformation $Y(s) = aY^*(s^*)$ and $s = a^2 s^*$ to rewrite the posterior cost of stopping as

$$d^*(y^*, s^*) = m\left[2Ka^{-1}\sqrt{s}\psi(y/\sqrt{s}) - \overline{\sigma}^2 a((a^2 s_*)^{-1} - s^{-1})|y|\right]. \tag{3.3}$$

Call this $d^{**}(y, s)$. Use the value $a^2 = (\sigma_0^{-2} + \overline{\sigma}^{-2}K) = (s_*)^{-1}$ to get the expression

$$d^{**}(y, s) = \sigma^2(ss_0\sigma_0^{-2})^{1/2}\left[2(1 - s_0^{-1})\psi(y/\sqrt{s}) - (1 - s^{-1})|y/\sqrt{s}|\right]. \tag{3.4}$$

where $s_0 = \sigma_0^2 a^2$ as before.

Note that, for the original group sequential problem, stopping is allowed at the points

$$s_{im} = \frac{\sigma_0^{-2} + mK\sigma^{-2}}{\sigma_0^{-2} + mi\sigma^{-2}}. \tag{3.5}$$

Also note that since both σ^2 and σ_0^{-2} are constant, they will not affect the optimal stopping boundary, so we will set both equal to one and use the following stopping cost:

$$d(y, s) = (ss_0)^{1/2}\left[2(1 - s_0^{-1})\psi(y/\sqrt{s}) - (1 - s^{-1})|y/\sqrt{s}|\right]. \tag{3.6}$$

3.2. *Computation of boundaries.* Let $\rho(y, s)$ be the risk corresponding to the cost $d(y, s)$ for the optimal stopping rule starting at (y, s). One can compute $\rho(y, s)$ by using the following backward induction algorithm:

$$\rho(y, s_{Km}) = d(y, s_{Km}) \tag{3.7}$$

$$\rho(y, s_{im}) = \min\{d(y, s_{im}), E(\rho(y + z\sqrt{\Delta s_{im}}, s_{(i+1)m}))\} \tag{3.8}$$

where i ranges over the values $0, \ldots, K-1$, z is a standard normal random variable, and $\Delta s_{im} = s_{im} - s_{(i+1)m}$. If $\rho(y, s_{im}) = d(y, s_{im})$ than (y, s_{im}) is a stopping point, otherwise it is a continuation point. The risk $\rho(0, s_0)$ is the Bayes risk for the whole procedure. For a procedure P, it will be denoted by ρ_P.

TABLE 1

Optimal boundaries $\tilde{\alpha}_{opt}$ for various group sequential designs, all with $s_0 = 10^4$

Stage	$K = 5$	$K = 10$	$K = 15$	$K = 20$
0	0.865	1.143	1.296	1.401
1	0.581	0.917	1.085	1.185
2	0.443	0.760	0.949	1.075
3	0.232	0.657	0.850	0.968
4	0.089	0.569	0.775	0.894
5	0.000	0.495	0.693	0.800
6		0.387	0.632	0.767
7		0.335	0.547	0.710
8		0.179	0.511	0.632
9		0.095	0.465	0.604
10		0.000	0.408	0.566
11			0.343	0.519
12			0.268	0.465
13			0.186	0.433
14			0.097	0.418
15			0.000	0.346
16				0.268
17				0.250
18				0.190
19				0.097
20				0.000

The optimal standardized boundary, denoted by $\tilde{\alpha}_{opt}$, is tabulated in Table 1 for $s_0 = 10^4$ and for various values of the number of groups, K.

One can use the optimal continuous-time Bayes boundary and use the correction developed in Chernoff and Petkau (1986) to get an approximate optimal group sequential boundary as follows. Let $\tilde{\alpha}(s) = \tilde{y}/\sqrt{s}$, where $\tilde{y}$ is the optimal continuous-time boundary. Then one can adjust the continuous-time boundary to approximate the group sequential boundary, obtaining $\tilde{\alpha}_{adj}$ as follows:

$$\tilde{\alpha}_{adj}(s_{im}) = \tilde{\alpha}(s_{im}) - 0.5826\sqrt{\Delta s_{im}/s_{im}}. \tag{3.9}$$

Using the values of $\tilde{\alpha}(s)$ from Table 1 of Chernoff and Petkau (1981) leads to the values of $\tilde{\alpha}_{adj}(s_{im})$ tabulated in Table 2.

4. Comparison of designs. The results of Section 3 are now applied to investigate the performance of various group sequential designs.

4.1. *Bayes risk.* Since for any boundary $b_{im}\sqrt{s_{im}}$ leading to a stopping time τ of the form

TABLE 2

Optimal boundary, adjusted continuous-time boundary and Bayes risk. The parameter s_0 is taken to be 10^4 throughout. Also note that the argument of the functions is $t = 1/s$.

	t	$\tilde{\alpha}_{opt}(t)$	$\tilde{\alpha}_{adj}(t)$	$b_{adj}(0,t)$	$\rho(0,t)$
$K = 5$	1.000	0.000	0.000	79.780	79.780
	0.800	0.089	0.109	89.177	89.591
	0.600	0.232	0.286	92.697	92.415
	0.400	0.443	0.468	95.776	95.288
	0.200	0.581	0.724	98.401	97.861
	10^{-4}	0.862	3.129	1596.292	1579.143
$K = 10$	1.000	0.000	0.000	79.780	79.780
	0.800	0.179	0.176	86.226	85.940
	0.600	0.387	0.357	89.772	89.235
	0.400	0.506	0.543	91.824	91.222
	0.200	0.760	0.800	91.298	90.556
	10^{-4}	1.140	3.129	799.605	791.026
$K = 15$	1.000	0.000	0.000	79.780	79.780
	0.800	0.268	0.208	85.656	85.311
	0.600	0.387	0.393	89.127	88.660
	0.400	0.569	0.584	90.915	90.059
	0.200	0.805	0.845	89.684	88.768
	10^{-4}	1.293	3.129	534.367	528.644
$K = 20$	1.000	0.000	0.000	79.780	79.780
	0.800	0.268	0.229	85.430	85.099
	0.600	0.465	0.415	88.832	87.956
	0.400	0.633	0.610	90.514	89.391
	0.200	0.850	0.875	88.968	87.777
	10^{-4}	1.398	3.129	401.928	397.639
$K = 100$	1.000	0.000	0.000	79.780	79.780
	0.800	0.358	0.305	84.981	83.528
	0.600	0.542	0.502	88.174	84.628
	0.400	0.759	0.713	89.456	85.363
	0.200	1.029	1.009	87.221	82.519
	10^{-4}	1.944	3.131	86.509	85.550

(4.1) $$\tau = \inf\{i \mid Y(s_{im}) \geq b_{im}\sqrt{s_{im}}\}$$

one can compute the exact Bayes risk $b(y, s)$ at (y, s) by using the following recursive formula:

$$\begin{aligned} b(y, s_{Km}) &= d(y, s_{Km}); \\ b(y, s_{im}) &= E\left[d(y + z(\sqrt{\Delta s_{im}}), s_{(i+1)m})\right], \quad \text{for } y < b_{im}\sqrt{s_{im}}; \\ b(y, s_{im}) &= d(y, s_{im}), \quad \text{for } y \geq b_{im}\sqrt{s_{im}}; \end{aligned}$$

where i ranges from 0 through $K - 1$.

We can therefore compute the Bayes risk of the optimal group sequential and the adjusted continuous-time boundaries. The risk for the optimal group sequential boundaries for various values of K and s_0 are given in Table 3 and the Bayes risk for the approximate boundary for $s_0 = 10^4$ are given in the column labeled $b_{adj}(0, t)$ in Table 2. Comparing the values for $s_0 = 10^4$ in Table 3 and the entries for $t = 0$ in Table 2, we see that there is little loss in terms of Bayes risk if one uses the adjusted continuous-time boundary in place of the optimal boundary.

TABLE 3

Risk for the optimal boundary. The Bayes Efficiency with respect to the $K = 100$ design is given in parentheses below the Bayes risk.

	s_0				
	10^1	10^2	10^3	10^4	10^5
$K = 5$	2.33	16.80	158.86	1579.1	15781.4
	(0.73)	(0.3)	(0.09)	(0.05)	(0.05)
$K = 10$	1.97	9.74	80.86	791.0	7892.2
	(0.86)	(0.52)	(0.17)	(0.12)	(0.10)
$K = 15$	1.89	7.63	55.18	528.6	5262.8
	(0.90)	(0.66)	(0.25)	(0.16)	(0.15)
$K = 20$	1.85	6.68	42.51	397.6	3948.2
	(0.91)	(0.75)	(0.33)	(0.21)	(0.20)
$K = 100$	1.69	5.04	14.10	85.5	795.7
	(1.00)	(1.00)	(1.00)	(1.00)	(1.00)

4.2. *Loss of efficiency due to grouping.* For any two procedures P_1 and P_2, we define the Bayes Efficiency (BE) as the ratio of their posterior risks:

(4.2) $$BE(P_1, P_2) = \rho_{P_1}/\rho_{P_2}.$$

In Table 3 the posterior risks of some group sequential designs are given, along with their Bayes Efficiency with respect to the group sequential design with $K = 100$.

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