A RANDOM HORIZON MODEL FOR SEQUENTIAL CLINICAL TRIALS

by

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Summary

The risk in a trial to compare two medical treatments is borne by the patients who receive the inferior treatment during the experimental phase and by those treated after the experimental phase who receive the inferior treatment if the results are misleading. Under the assumption that the total number of treated patients is random, a precise model is described and the exact stopping rule is derived which tells how to stop the experimental phase so as to maximize the expected number of successfully treated patients. Many results are derived which precisely describe the statistical properties of this optimally designed sequential clinical trial.

AMS 1980 *subject classifications*: Primary 60G40, 62C10, 62L05.

Key words and phrases: Clinical trials, Bayes rules, optimal stopping, Markov states.

* This research was supported by the National Sience Foundation Grant DMS-8400602.

1. Introduction.

Consider the task of assigning two possible treatments to a random number of patients who suffer from the same illness. The nominal objective is to assign the treatment with the larger probability of success to as many patients as possible. The assignment procedure begins with a *testing phase*, during which both treatments are to be used, and ends with a *utility phase*, during which the most promising treatment is to be used for all remaining patients (if any). Throughout the testing phase, the treatments are to be assigned randomly to patients in pairs, with the patients in each pair receiving distinct treatments. It is assumed the response time is short, depending on the patient accrual rate, so that a decision to switch to the utility phase can be made in a timely manner.

Many variants of this model have been described in the literature, but typically with a "fixed horizon", i.e., with a *fixed number of patients, known in advance*. Needless to say, this is an unnatural assumption, and it has met with much criticism. The assumption used here, of a random number of patients (a "random horizon"), is intended to overcome such criticism.

Let p_1 and p_2 denote the probabilities of success for the the first and second treatments, respectively, and assume the pair (p_1, p_2) has an exchangeable prior distribution; the clinical trial begins with neither treatment preferred. Further, let M denote the random number of *pairs* of patients who are to be treated. It is assumed here that M has a known distribution, and that it is independent of the responses of the patients to their treatments, and independent of (p_1, p_2). (A more realistic assumption might be that the distribution of M depends on the perceived superiority of the preferred treatment when the utility phase begins, or depends on how this perception evolves during the utility phase. More simply, its distribution might just depend on the value of (p_1, p_2).) Importantly, it is *not* assumed the value of M is known in advance; the decision to continue or stop the testing phase, at each stage, is to be made without knowing how many pairs of patients remain to be treated.

The task is to find the rule for stopping the testing phase which minimizes the "expected successes lost" due to ignorance of the sign of $p_1 - p_2$. Mathematically, this is the expectation of the product of $|p_1 - p_2|$ and the total number of patients assigned, by the stopping rule, to the inferior treatment *during both treatment phases*. Here, "expectation" includes integration with respect to the priors on M [illegible]

The main objective in this paper is to describe a detailed theory for a special case: "two-point symmetric priors" and geometrically distributed M. The presumption is that this theory reveals important aspects of the general case. This is more than wishful thinking. Berry (1978) has shown, for a two-armed bandit context, that symmetric priors can be replaced by two-point symmetric priors with little adverse affect. And Simons (1986) has provided evidence that Berry's observations are valid in the present setting when M is a known constant, i.e., for the case of a fixed horizon.

Section 2 describes a general mathematical formulation. This is specialized in Section 3 to the case of a two-point symmetric prior, and the optimal stopping rule is described qualitatively (Theorem 1). The detailed theory, referred to above, appears in Section 4. It includes many results that are valid for all values of $E(M)$. Many of the theorems and corollaries contain asymptotic results as well (as $E(M) \to \infty$). These provide additional information, or information that is easier to interpret. Moreover, it is anticipated that the asymptotic results are valid for a much wider (but yet to be determined) context.

2. General mathematical formulation.

Since some of what follows requires M to have a finite expectation, it will be assumed hereafter that $E(M) < \infty$.

It is convenient to think in terms of "time n", $n = 0,1,\cdots$. At time n, one knows either: (i) $M \geq n$ and the responses of n pairs of patients under the testing phase, or (ii) $M < n$ and the responses of M pairs of patients under the testing phase. At time n, the conditional expected successes lost (so far) is $E_n\{(n \wedge M)\cdot|p_1-p_2|\}$, where E_n denotes conditional expectation given the information available at time n, and $n \wedge M$ denotes the minimum of n and M. If one switches to the utility phase at time n, all of the remaining $2(M-n)^+$ patients will be given the more promising treatment, and their conditional expected successes lost will be $2E_n\{(M-n)^+\cdot(p_1-p_2)^+\}$ or $2E_n\{(M-n)^+\cdot(p_1-p_2)^-\}$, whichever is smaller. Here, the superscripts "+,-" refer, as usual, to positive and negative parts, respectively. Thus the "posterior Bayes risk" becomes

$$E_n\{(n\wedge M)\cdot|p_1-p_2|\} + 2\cdot\min(E_n\{(M-n)^+\cdot(p_1-p_2)^+\},E_n\{(M-n)^+\cdot(p_1-p_2)^-\}).$$

Conveniently, this can be rewritten as

$$E_n(M|p_1-p_2|) - |E_n(M-n)^+(p_1-p_2)|.$$

Since the first term is a martingale in n, it has no bearing on the question of optimal stopping. Consequently, the problem of optimal stopping can be recast in terms of a *reward* sequence defined by

$$R_n = |E_n(M-n)^+(p_1-p_2)|. \tag{1}$$

Let $t_n = 1$ or 0 as $M \geq n$ or $M < n$, respectively. The value of R_n depends intimately on the value of t_n. Clearly, $R_n = 0$ when $t_n = 0$. When $t_n = 1$,

$$R_n = \delta_n|E_n(p_1-p_2)|,$$

where

$$\delta_n = E(M - n|M \geq n). \tag{2}$$

Thus, in general,

$$R_n = t_n\cdot\delta_n\cdot|E_n(p_1-p_2)|. \tag{3}$$

When computing the third factor on the right side of (3), one is free to act as if $t_n = 1$, and, hence, to reinterpret "E_n" as a *conditional expectation given the hypothetical* responses of n pairs of patients, taken *from an infinite pool of patients, all treated under a testing phase*; the joint distribution of the sequence $R_0, R_1, R_2, \cdots$ will be unaltered. This new interpretation will be used hereafter unless stated otherwise. In particular, the processes $\{t_n : n \geq 0\}$ and $\{E_n(p_1 - p_2) : n \geq 0\}$ can be viewed as independent of each other.

A simple argument shows, for the present level of generality, that *the functional equation rule* σ, defined by Chow, Robbins and Siegmund (1971, page 63), *is finite and optimal*: R_n is bounded above by the product $t_n \cdot \delta_n$, which is a uniformly integrable supermartingale in n (because $E(M) < \infty$). Thus the value V of the optimal stopping problem is bounded above by $E(t_0 \cdot \delta_0) = E(M)$. In particular, V is finite. Moreover, condition (d) of their Theorem 4.10 holds. Consequently, σ is optimal *in the extended class of stopping times*. But it is easily seen that $\sigma \leq M$. Thus σ is finite and optimal.

The process $\{E_n(p_1 - p_2) : n \geq 0\}$ is Markovian with a state parameter (n,r,s), where r and s denote the numbers of successes, produced by n pairs of patients under the testing phase, for the first and second treatments, respectively.

Likewise, the process $\{t_n : n \geq 0\}$ is Markovian with a state parameter (n,t). The transition $(n,0) \to (n+1,0)$ occurs with probability one for all n, and the transition $(n,1) \to (n+1,1)$ occurs with probability

$$\gamma_n = P(M \geq n+1 \mid M \geq n). \tag{4}$$

Thus $\{R_n : n \geq 0\}$ is Markovian with a state parameter (n,r,s,t).

Notice, R_n has the form $t \cdot R^*(n,r,s)$, where the second factor is independent of "t". And it is easy to see that the maximum expected reward, for optimal stopping from the initial state (n,r,s,t), has the similar form $t \cdot S^*(n,r,s)$. The relationship between the factors R^* and S^* is described by the "dynamic equation":

$$S^*(n,r,s) = \max\{R^*(n,r,s), \gamma_n \cdot \sum_{i=0}^{1} \sum_{j=0}^{1} u_{ij}(n,r,s) \cdot S^*(n+1,r+i,s+j)\},\ n,r,s \geq 0, \quad (5)$$

where the transition $(n,r,s) \rightarrow (n+1,r+i,s+j)$ has probability $u_{ij}(n,r,s)$. Thus, with the factor γ_n included in (5), the component "t" can be dropped, and the state parameter of interest can be taken to be (n,r,s).

The factor γ_n can be thought of as a "discount factor". But such an interpretation will not be pursued here.

Notice that the testing phase begins in state $(n,r,s) = (0,0,0)$ with $t = 1$. So the expected successes lost under the optimal stopping rule takes the form $E(M|p_1-p_2|) - S^*(0,0,0)$. For a general stopping rule, $S^*(0,0,0)$ must be replaced by an appropriate analogue.

The point (n,r,s) is an *optimal stopping point* if $S^*(n,r,s) = R^*(n,r,s)$. It is an *optimal continuation point* if $S^*(n,r,s) > R^*(n,r,s)$ or if

$$\gamma_n \cdot \sum_{i=0}^{1} \sum_{j=0}^{1} u_{ij}(n,r,s) \cdot S^*(n+1,r+i,s+j) = R^*(n,r,s).$$

In the latter case, both appellations will be used.

3. Two-point symmetric priors.

Now suppose the prior G for (p_1, p_2) assigns probability 1/2 to each of two symmetric points (a,b) and (b,a), $0<b<a<1$. Then $R^*(n,r,s)$ becomes (see (3))

$$R^*(n,r,s) = (a-b)\cdot\delta_n\cdot\tanh|r-s|\alpha,$$

where

$$\alpha = \frac{1}{2}\log\{a(1-b)/(1-a)b\}. \qquad (\alpha > 0) \tag{6}$$

The Markovian state (n,r,s) can be replaced by the simpler Markovian state

$$(n,k) = (n, r-s). \tag{7}$$

Then $(a-b)^{-1}R^*(n,r,s)$ becomes

$$R(n,k) = \delta_n\cdot\tanh|k|\alpha. \tag{8}$$

Moreover, $S^*(n,r,s)$ takes the form $(a-b)\cdot S(n,k)$ and the dynamic equation can be written as

$$S(n,k) = \max\{R(n,k), \gamma_n\cdot[u_k\cdot S(n+1,k-1) + v\cdot S(n+1,k) + w_k\cdot S(n+1,k+1)]\}, \tag{9}$$

where

$$\left.\begin{array}{l} u_k = \dfrac{\beta\cdot\cosh(k-1)\alpha}{\cosh k\alpha}, \quad w_k = \dfrac{\beta\cdot\cosh(k+1)\alpha}{\cosh k\alpha}, \\ v = ab + (1-a)(1-b), \quad \beta = \{ab(1-a)(1-b)\}^{1/2}. \end{array}\right\} \tag{10}$$

Observe, for future use, that

$$\left.\begin{aligned} \beta e^{\alpha} &= a(1-b), \quad \beta e^{-\alpha} = b(1-a), \\ 2\beta\cdot\sinh\alpha &= a-b, \quad 2\beta\cdot\cosh\alpha = 1-v. \end{aligned}\right\} \qquad (11)$$

The notions of *optimal stopping* and *optimal continuation points* (n,k) are defined as for (n,r,s) above, with the appropriate changes. A simple qualitative description of the class of optimal stopping points can be stated:

Theorem 1. *Depending on* a, b *and the distribution of* M, *there is a sequence* $\{\kappa_n, n\geq 0\}$ *of nonnegative integers such that* (n,k) *is an optimal stopping point if and only if* $|k| \geq \kappa_n$. *Necessarily,* $\kappa_{n+1} - \kappa_n \geq -1$, $n \geq 0$. ($\kappa_{n+1} - \kappa_n$ *does not appear to have a universal upper bound.*)

Proof. It is enough to show this result for $k \geq 0$ (due to symmetry), and when M is bounded above. For then, the general result can be obtained by applying standard truncation techniques. However, it is necessary to show, for each fixed n, that there is a stopping point (n,k), $k \geq 0$: The value $k = 0$ will suffice when $P(M > n) = 0$. If $P(M > n) > 0$, then $\delta_n > \gamma_n\cdot\delta_{n+1}$. Consequently, $R(n,k) > \gamma_n\cdot\delta_{n+1}$ for a sufficiently large k, and, for this k, (n,k) is an optimal stopping point. This follows from the fact, noted earlier, that $t_n\cdot\delta_n$ is a supermartingale in n. If (n,k) were not an optimal stopping point, then $S(n,k)$ would be bounded above by $E_n(t_{n+1}\cdot\delta_{n+1}) = \gamma_n\cdot\delta_{n+1}$. This is impossible since $S(n,k) \geq R(n,k)$.

So suppose $P(M > m) = 0$. Then, clearly, $\kappa_n = 0$ for $n \geq m$. Let $Q(n,k) = S(n,k) - R(n,k)$, and observe that $Q(n,k) \geq 0$, with equality holding whenever (n,k) is an optimal stopping point. From (9), one obtains

$$Q(n,k) = \begin{cases} \gamma_n \cdot Q^*(n,0) + (a-b)\cdot\gamma_n\cdot\delta_{n+1} & \text{for } k = 0, \\ \max(0, \gamma_n \cdot Q^*(n,k) - (1-\gamma_n)\cdot\tanh k\alpha) & \text{for } k > 0, \end{cases}$$

where

$$Q^*(n,k) = u_k \cdot Q(n+1,k-1) + v\cdot Q(n+1,k) + w_k \cdot Q(n+1,k+1).$$

It is enough to establish that $Q(n,k)$ is a nonincreasing function in k ($k \geq 0$) for each $n \leq m$. For then, if (n,k) is an optimal stopping point, so is $(n,k+1)$. Moreover, since $Q(n+1,k) = 0$ for $k \geq \kappa_{n+1}$, $Q^*(n,\kappa_{n+1}+1) = 0$, and hence, $\kappa_n \leq \kappa_{n+1} + 1$.

A straightforward backward induction argument establishes that the function $Q(n,k)$ is nonincreasing in k for $n \leq m$. Clearly, $Q(m,k) = 0$ for $k \geq 0$. The elementary inequalities $u_k \geq u_{k+1}$, $w_k < w_{k+1}$, and $v > u_1$ are needed for the induction step. The details are omitted. □

4. Two-point symmetric priors with geometrically distributed M.

In addition to the assumption that G is a two-point symmetric prior on (a,b) and (b,a) $(0<b<a<1)$, it will be assumed throughout this section that M has a geometric distribution with parameter γ, $0<\gamma<1$, so that $P(M=n) = \gamma^n(1-\gamma)$, $n \geq 0$. This substantially simplifies the theory, and it makes it possible to obtain many detailed results. Two small simplifications are: $\gamma_n = \gamma$ and $\delta_n = E(M) = \gamma/(1-\gamma)$ for $n \geq 0$. The next theorem details a major simplification; the sequence $\{\kappa_n, n\geq 0\}$, appearing in Theorem 1, is constant.

Theorem 2. *It is optimal to stop the testing phase as soon as* $\frac{\sinh |k|\alpha}{\cosh |k|\theta} \geq \frac{\sinh (|k|+1)\alpha}{\cosh (|k|+1)\theta}$, *where* $\theta > \alpha$ *is defined by*

$$\cosh \theta = \frac{1 - \gamma\cdot v}{2\cdot\beta\cdot\gamma}. \tag{12}$$

Proof. Since

$$\cosh \theta - \cosh \alpha = \frac{1 - \gamma v}{2\beta\gamma} - \frac{1 - v}{2\beta} = \frac{1-\gamma}{2\beta\gamma} = \frac{1}{2\beta E(M)}, \tag{13}$$

there is a unique $\theta > \alpha$ that satisfies (12). One can write $R(n,k) = E(M)\cdot\mathcal{R}(k)$ and $S(n,k) = E(M)\cdot\mathcal{S}(k)$, where $\mathcal{R}(k) = \tanh(|k|\alpha)$ and $\mathcal{S}$ satisfy the recursive relationship

$$\mathcal{S}(k) = \max(\mathcal{R}(k), \gamma\{u_k\cdot\mathcal{S}(k-1) + v\cdot\mathcal{S}(k) + w_k\cdot\mathcal{S}(k+1)\}). \tag{14}$$

Notice, $\mathcal{S}$ has to be a symmetric function. In the "continuation region", $\mathcal{S}(k) = \gamma\{u_k\cdot\mathcal{S}(k-1) + v\cdot\mathcal{S}(k) + w_k\cdot\mathcal{S}(k+1)\}$, so $\mathcal{S}(k) = c\,\frac{\cosh k\theta}{\cosh k\alpha}$ for some constant $c>0$. Since $\mathcal{S}(k) = \mathcal{R}(k) = \tanh(|k|\alpha)$ has to hold in the "stopping region", the constant c must have the form $c = \frac{\sinh \ell\alpha}{\cosh \ell\theta}$ for some integer $\ell > 0$. Since $c \to 0$ as $\ell \to \infty$, there must be a value of ℓ which maximizes c. Hereafter, let ℓ be a maximizing value. Then it is easily checked that

$$\mathcal{S}(k) = \begin{cases} \frac{\sinh \ell\alpha}{\cosh \ell\theta}\cdot\frac{\cosh k\theta}{\cosh k\alpha} & \text{for } |k| < \ell, \\ \tanh |k|\alpha \quad (= \mathcal{R}(k)) & \text{for } |k| \geq \ell, \end{cases}$$

is the unique solution to (14) . If the maximizing value ℓ is unique, then the optimal stopping rule is unique and the optimal stopping points are those points (n,k) for which $|k| \geq \ell$. There may be two adjacent integers ℓ which maximize c, in which case there will be points (n,k) which are both optimal continuation and optimal stopping points. In any event, the stopping rule described in the statement of the theorem is of the form "stop as soon as $|k| = \ell$". So it is an optimal stopping rule as asserted. □

Theorem 2 describes a "sequential probability ratio test with random truncation" (imposed by M). The positive integer ℓ will be called the *optimal level*.

It seems obvious the optimal level ℓ goes to infinity as $E(M) \to \infty$. It does, but at a pleasantly slow rate:

Corollary 2. *For possibly variable* α *(defined in* (6)) *and difference* $a - b$ $(\alpha > 0,\ 0 < a-b < 1)$,

$$|\ell - \ell^*| \leq .5 + o(1) \quad \textit{as} \quad \nu \to \infty, \tag{15}$$

where,

$$\ell^* = (2\alpha)^{-1}\log\{4\cdot\sinh\alpha\cdot(a-b)\cdot E(M)\} \quad \textit{and} \quad \nu = \alpha\cdot\tanh^2\alpha\cdot(a-b)\cdot E(M). \tag{16}$$

Interpretation. Besides asserting that (15) holds when the prior G is fixed and $E(M) \to \infty$, the corollary states that ℓ is well approximated by ℓ^* *whenever* ν *is sufficiently large.* Numerical evidence indicates $|\ell - \ell^*| \leq .51$ whenever $\nu \geq 45$. No bound smaller than .5 could be expected since ℓ is integer-valued. The corollary has content even when $E(M)$ is bounded above.

Proof of upper bound: $\ell \le \ell^* + .5 + o(1)$ as $\nu \to \infty$.

Since ℓ is an optimal level, $\frac{\sinh \ell\alpha}{\cosh \ell\theta} \ge \frac{\sinh(\ell-1)\alpha}{\cosh(\ell-1)\theta}$, which can be rewritten as $\frac{\cosh(\ell-1)\theta}{\cosh \ell\theta} \ge \frac{\sinh(\ell-1)\alpha}{\sinh \ell\alpha}$. Expanding this with hyperbolic identities, one obtains:

$$(\cosh\theta - \cosh\alpha)(\coth \tfrac{1}{2}(\theta+\alpha) - 1) \le \frac{2e^{-2\ell\alpha}\sinh\alpha}{1-e^{-2\ell\alpha}} + \frac{2e^{-2\ell\theta}\sinh\theta}{1+e^{-2\ell\theta}}.$$

Since $\theta > \alpha > 0$ and $\cosh\theta - \cosh\alpha = \frac{1}{2\beta E(M)} = \frac{\sinh\alpha}{(a-b)\cdot E(M)}$, one obtains

$$\frac{\sinh\alpha\cdot e^{-\theta}}{\sinh\theta\cdot(a-b)\cdot E(M)} \le (\cosh\theta - \cosh\alpha)(\coth\tfrac{1}{2}(\alpha+\theta) - 1) \le \frac{4e^{-2\ell\alpha}\sinh\theta}{1-e^{-2\ell\alpha}}.$$

Thus

$$2\alpha\ell \le \log(4\cdot\frac{\sinh^2\theta}{\sinh\alpha}\cdot(a-b)\cdot E(M)\cdot e^{\theta} + 1)$$
$$\le 2\alpha\ell^* + \theta + 2\log(\frac{\sinh\theta}{\sinh\alpha}) + \frac{e^{-\alpha}}{4\cdot\sinh\alpha\cdot(a-b)\cdot E(M)}.$$

It remains to show: (i) $\theta = \alpha + o(\alpha)$, (ii) $\log\sinh\theta = \log\sinh\alpha + o(\alpha)$, and (iii) $e^{-\alpha}/\{4\cdot\sinh\alpha\cdot(a-b)\cdot E(M)\} = o(\alpha)$ as $\nu \to \infty$.

Equation (iii) is trivial. Equations (i) and (ii) easily follow from consequences of the mean value theorem:

$$\theta - \alpha \le \frac{\cosh\theta - \cosh\alpha}{\sinh\alpha} = \frac{1}{(a-b)\cdot E(M)} \tag{17}$$

and

$$\log\sinh\theta - \log\sinh\alpha \le (\cosh\theta - \cosh\alpha)\cdot\frac{\cosh\alpha}{\sinh^2\alpha} = \frac{1}{\tanh\alpha\cdot(a-b)\cdot E(M)}. \quad \square$$

Proof of lower bound: $\ell \geq \ell^* - .5 - o(1)$ as $\nu \to \infty$.

Here one begins with the inequality $\frac{\sinh \ell\alpha}{\cosh \ell\theta} \geq \frac{\sinh(\ell+1)\alpha}{\cosh(\ell+1)\theta}$ and proceeds in much the same way as with the upper bound to obtain

$$e^{-2\ell\alpha} + e^{-2\ell\theta} \leq \frac{e^{\alpha}}{2\cdot \sinh \alpha \cdot (a-b)\cdot E(M)}. \tag{18}$$

It remains to show the left side equals $2\cdot e^{-2\ell\alpha+o(\alpha)}$, i.e., $\ell\theta = \ell\alpha + o(\alpha)$ as $\nu \to \infty$. For this, one needs the *upper* bound for ℓ and (17). The key step is:

$$\begin{aligned}2\alpha^{-1}\ell^*(\theta-\alpha) &\leq \frac{\log\{4\cdot \sinh \alpha\cdot (a-b)\cdot E(M)\}}{\alpha^2\cdot (a-b)\cdot E(M)}\\ &= \nu^{-1}\alpha^{-1}\tanh^2\alpha\cdot\{\log(4\nu) + \log\cosh\alpha - \log(\alpha\cdot\tanh\alpha)\}\\ &= \alpha^{-1}\cdot\tanh^2\alpha\ \{1 + \log\cosh\alpha - \log(\alpha\cdot\tanh\alpha)\}\cdot o(1).\end{aligned}$$

The expression preceding the "o(1)" is a bounded function of α, $\alpha>0$. So $2\ell^*(\theta-\alpha) = o(\alpha)$ as $\nu \to \infty$. □

This result is not "best possible". The same proof works if ν is replaced by "$f(\alpha)\cdot(a-b)\cdot E(M)$", where f is any positive and continuous function with $f(\alpha) = O(\alpha)$ as $\alpha \to \infty$ and $f(\alpha) = O(\alpha^2/\log(1/\alpha))$ as $\alpha \to 0$ (big O's).

This corollary suggests that one can probably determine the optimal level ℓ (that one needs) with no more than a crude estimate of $E(M)$. To illustrate, suppose $a = .6$ and $b = .4$, so $\alpha \doteq .405$. For ℓ = 6,7,8,9,10,11, the possible integer estimates of $E(M)$ are:

TABLE 1

ℓ	Estimate of E(M)
6	273-602
7	603-1,337
8	1,338-2,984
9	2,985-6,684
10	6,685-15,002
11	15,003-33,712

Thus, for instance, with an estimate "E(M) = 10,000", one would choose (from the table) $\ell = 10$. If the true expected number of pairs is between 6,685 and 15,002, then the choice $\ell = 10$ still will be optimal.

The actual situation is even more favorable than this. To illustrate with the same example, suppose the true expectation were E(M) = 5,000, half of what was estimated. Then the optimal level ℓ is nine, not 10. Nevertheless, the expected successes lost due this suboptimal choice ($\ell = 10$) is a mere .25; one could expect .25 patients out of an expected total of 5,000 pairs to be adversely affected. If, on the other hand, the true expectation were twice the estimate, the expected number of adversely affected patients would be .33 out of an expected total of 20,000 pairs. And even if the true expectation were *three* times the estimate, the expected number of adversely affected patients would be only one patient out of an expected total of 30,000 pairs! To summarize, numerical evidence suggests *one can safely choose the optimal level* ℓ, *for an estimated value of* E(M), *without worrying about how poor the estimate is, as long as the error is not truly gross.* However, the size of the difference one is trying to detect does make a difference; a better estimate is needed when a-b is quite small. Consider an extreme example: $a = .51$ and $b = .49$. If one estimates $E(M) = 10{,}000$ and, in fact, $E(M) = 20{,}000$, then one will choose $\ell = 42$ instead of the actual optimal level $\ell = 51$. This can be expected to adversely affect 3.85 patients out of an expected 20,000 pairs of patients.

The cost of choosing ℓ incorrectly can be deduced from the following theorem.

Theorem 3. *Suppose one stops the testing phase with the possibly suboptimal rule "stop as soon as* $|k| = \ell'$." *Then the expected successes lost will be* $(a-b)\cdot E(M)\cdot\left\{\frac{\sinh \ell\alpha}{\cosh \ell\theta} - \frac{\sinh \ell'\alpha}{\cosh \ell'\theta}\right\}$, *where* ℓ *is the optimal level (described in the proof of* Theorem 2), α *is defined in* (6) *and* θ *is defined in* (12).

Proof. The quantity $(a-b)\cdot E(M)\cdot\frac{\sinh \ell\alpha}{\cosh \ell\theta}$ is simply $S^*(n,r,s)$ with $(n,r,s) = (0,0,0)$, the state one begins in; before any patients have been treated; the third factor $\frac{\sinh \ell\alpha}{\cosh \ell\theta}$ can be identified as $\varphi(0)$ in the proof of Theorem 2. Now $S^*(0,0,0)$ is the maximal expected reward for *optimal* stopping, beginning in state $(0,0,0)$. Likewise, $(a-b)\cdot E(M)\cdot\frac{\sinh \ell'\alpha}{\cosh \ell'\theta}$ is the expected reward, beginning in state $(0,0,0)$, if one uses the possibly suboptimal rule based on ℓ'. This can be checked; one can argue as in the proof of Theorem 4 below. Finally, since the original optimal stopping problem is concerned with "expected successes lost", the difference $(a-b)\cdot E(M)\cdot\left\{\frac{\sinh \ell\alpha}{\cosh \ell\theta} - \frac{\sinh \ell'\alpha}{\cosh \ell'\theta}\right\}$ is precisely the expected successes lost for acting suboptimally. □

The testing phase can be stopped in two ways. Normally, the stopping rule stops the testing phase, and the utility phase is begun. But the testing phase can be stopped prematurely simply by running out of patients. In the first case, the testing phase will be said to be *completed*. And in the second case, it will be said to be *truncated.* Something akin to *truncation* is well-known in practice; protocols are sometimes abandoned for a lack of suitable patients.

Theorem 4. *For the stopping rule described in* Theorem 3, *the testing phase is completed with probability* $\cosh \ell'\alpha/\cosh \ell'\theta$.

Proof. Let $X = \{X(t),\ t=0,1,\cdots\}$ be a Markov chain on the integers which is independent of M and has transition probabilities from state k to $k-1$, k, $k+1$ given by u_k, v, w_k, respectively. (See (10).) Further, let T be the first passage time to $\pm\ell'$, and set $e(k) = P(M\geq T|X(0)=k)$, $|k| \leq \ell'$. The assertion is established by showing $e(0) = \frac{\cosh \ell'\alpha}{\cosh \ell'\theta}$. Clearly, $e(\pm\ell') = 1$. For $|k| < \ell'$,

$$e(k) = \gamma\{u_k\cdot e(k-1) + v\cdot e(k) + w_k\cdot e(k+1)\},$$

because the geometric random variable M has the "memoryless property." Notice, $e(k)$ is symmetric in k. So $e(k) = c\,\frac{\cosh k\theta}{\cosh k\alpha}$ for some constant $c>0$. But then, $e(0) = c = e(\ell')\,\frac{\cosh \ell'\alpha}{\cosh \ell'\theta} = \frac{\cosh \ell'\alpha}{\cosh \ell'\theta}$. □

Corollary 4. *For the optimal stopping rule described in* Theorem 2, *the probability of truncation goes to zero like* $\frac{\log E(M)}{2(a-b)\cdot\alpha\cdot E(M)} + O(E(M)^{-1})$ *as* $E(M)\to\infty$ (*when* a *and* b *are held fixed*).

Proof. The assertion is concerned with the behavior of $1 - \cosh \ell\alpha/\cosh \ell\theta$ as $E(M) \to \infty$. From Corollary 2, one obtains $e^{-2\ell\alpha} = O(E(M)^{-1})$ and

$$\frac{\ell}{(a-b)\cdot E(M)} = \frac{\log E(M)}{2(a-b)\cdot\alpha\cdot E(M)} + O(E(M)^{-1}) \quad \text{as} \quad E(M) \to \infty. \tag{19}$$

Thus

$$\left|e^{-\ell(\theta-\alpha)} - \frac{\cosh \ell\alpha}{\cosh \ell\theta}\right| \le e^{-2\ell\alpha} = O(E(M)^{-1}) \quad \text{as} \quad E(M) \to \infty.$$

So the task is to show $1 - e^{-\ell(\theta-\alpha)} = \frac{\ell}{(a-b)\cdot E(M)} + O(E(M)^{-1})$ as $E(M) \to \infty$. But (17) and (19) give

$$1 - e^{-\ell(\theta-\alpha)} \le \ell(\theta-\alpha) \le \frac{\ell}{(a-b)\cdot E(M)}$$

and

$$1 - e^{-\ell(\theta-\alpha)} \ge \ell(\theta-\alpha) - \ell^2(\theta-\alpha)^2/2 \ge \ell(\theta-\alpha) - O(E(M)^{-1})$$

as $E(M) \to \infty$. Thus it remains to show $\ell(\theta-\alpha) \ge \frac{\ell}{(a-b)\cdot E(M)} - O(E(M)^{-1})$ as $E(M) \to \infty$. But this follows from the lemma below. □

Lemma 1. $\frac{\sinh \theta - \sinh \alpha}{\sinh \theta} \le \frac{1-v}{(a-b)^2\cdot E(M)}$, $\theta-\alpha \ge \frac{1}{(a-b)\cdot E(M)} - \frac{1-v}{(a-b)^3\cdot E(M)^2}$.

Proof. The mean value theorem, (11) and (13) yield

$$\sinh \theta - \sinh \alpha \le (\cosh \theta - \cosh \alpha)\cdot\coth \alpha = \frac{\cosh \alpha}{(a-b)\cdot E(M)},$$

and hence,

$$\frac{\sinh \theta - \sinh \alpha}{\sinh \theta} \le \frac{1-v}{(a-b)^2\cdot E(M)}.$$

In turn,

$$\theta - \alpha \geq \frac{\cosh\theta - \cosh\alpha}{\sinh\theta} = \frac{1}{(a-b)\cdot E(M)} - \frac{\sinh\theta - \sinh\alpha}{\sinh\theta\cdot(a-b)\cdot E(M)}$$
$$\geq \frac{1}{(a-b)\cdot E(M)} - \frac{1-v}{(a-b)^3\cdot E(M)^2}. \qquad \square$$

The next theorem describes how the available patients are divided between the testing and utility phases.

Theorem 5. *For the stopping rule described in* Theorem 3, *the expected number of pairs of patients treated during the utility phase is* $E(M)\cdot\frac{\cosh \ell'\alpha}{\cosh \ell'\theta}$, *where,* α *is defined in* (6) *and* θ *is defined in* (12). *For the optimal stopping rule described in* Theorem 2, *the expected number of pairs of patients treated in the testing phase grows like* $\frac{\log E(M)}{2(a-b)\alpha} + O(1)$ *as* $E(M) \to \infty$ *(with* a *and* b *held fixed).*

Proof. For the first assertion, proceed as in the proof of Theorem 4 but with $e(k)$ redefined as $E((M-T)^+|X(0)=k)$, $|k| \leq \ell'$. The expected number of pairs of patients is $e(0) = E(M)\cdot\frac{\cosh \ell'\alpha}{\cosh \ell'\theta}$. The second assertion is concerned with the behavior of $E(M)\cdot\{1 - \cosh \ell\alpha/\cosh \ell\theta\}$ as $E(M) \to \infty$, and follows as in the proof of Corollary 4. $\square$

It is now possible to examine how, under the optimal rule, the expected successes lost are divided between the testing and utility phases. It turns out that the patients treated during the testing phase are forced to assume most of the burden:

Theorem 6. *Under the optimal stopping rule, the expected successes lost during the testing and utility phases are,* $(a-b)\cdot E(M)\cdot\{1-\frac{\cosh \ell\alpha}{\cosh \ell\theta}\}$ *and* $(a-b)\cdot E(M)\cdot e^{-\ell\alpha}/\cosh \ell\theta$*, respectively. The former grows like* $(2\alpha)^{-1}\log E(M) + O(1)$ *and the latter remains bounded as* $E(M)\to\infty$ *(with* a *and* b *held fixed).*

Proof. The expected successes lost is the expectation of the product of $|p_1-p_2|$ and the total number of patients assigned, by the optimal stopping rule, to the inferior treatment during both treatment phases. So each pair of patients treated during the testing phase contributes an amount "a-b" to the expected successes lost. Since the expected number of such pairs is $E(M)\cdot\{1 - \frac{\cosh \ell\alpha}{\cosh \ell\theta}\}$ and grows with $E(M)$ like $\frac{\log E(M)}{2(a-b)\alpha} + O(1)$, the assertions pertaining to the testing phase follow. Now the actual expected successes lost is

$$E(M|p_1-p_2|) - S^*(0,0,0) = (a-b)\cdot E(M)\cdot\{1 - \frac{\sinh \ell\alpha}{\cosh \ell\theta}\}.$$

Thus the expected successes lost during the utility phase is

$$(a-b)\cdot E(M)\cdot\{1 - \frac{\sinh \ell\alpha}{\cosh \ell\theta}\} - (a-b)\cdot E(M)\cdot\{1 - \frac{\cosh \ell\alpha}{\cosh \ell\theta}\}$$
$$= (a-b)\cdot E(M)\cdot e^{-\ell\alpha}/\cosh \ell\theta,$$

as asserted. Finally, since $(a-b)\cdot E(M)\cdot e^{-\ell\alpha}/\cosh \ell\theta \le 2(a-b)\cdot E(M)\cdot e^{-2\ell\alpha}$ and $2(a-b)\cdot E(M)\cdot e^{-2\ell^*\alpha} = (2\cdot\sinh\alpha)^{-1}$ (see Corollary 2), it follows that the expected successes lost during the utility phase stays bounded as $E(M)\to\infty$. □

So the expected successes lost that are borne by testing-phase patients approaches 100% as $E(M) \to \infty$. Surprisingly, the same thing occurs as $E(M) \to 0$: For small values of $E(M)$, the optimal level ℓ is fixed at 1, and the ratio of expected successes lost, between the testing and utility phases, becomes $\frac{e^{\alpha}\cdot \sinh \alpha}{(a-b)\cdot E(M)}$. This goes to infinity as $E(M) \to 0$. It appears, based upon some numerical evidence, that the minimal percentage occurs when $\ell = 1$ just before $E(M)$ becomes large enough to make $\ell = 2$.

It should be emphasized that Theorem 6 describes the expected successes lost during the utility phase *from an a priori vantage point*, before any patients have been treated. *From the vantage point of a just completed testing phase*, $2E(M)$ additional patients are expected, not $2E(M)\cdot\frac{\cosh \ell\alpha}{\cosh \ell\theta}$ as suggested by Theorem 5, and these are expected to result in $(a-b)\cdot E(M)\cdot e^{-\ell\alpha}/\cosh \ell\alpha$ more successes lost.

Frequentists are likely to be interested in the operating characteristics of the optimal rule, i.e., in the probability a particular treatment is rejected for use in the utility phase. The first (second) treatment is *rejected*, when the treatment phase is completed or terminated, if the parameter $k < 0$ ($k > 0$), and is *selected* if $k > 0$ ($k < 0$). Recall, k is the excess of successes produced by the first treatment. It is mathematically convenient to reject each treatment with probability one-half when $k = 0$. The occurrence of the value $k = 0$ is usually very unlikely; it never occurs when the treatment phase is completed.

A Bayesian result will be given first.

Theorem 7. *For the stopping rule described in* Theorem 3, *the better treatment is rejected with probability*

$$B(a,b) = \frac{1}{2} - \frac{\sinh \alpha}{2\cdot \sinh \theta}\cdot \tanh \ell'\theta, \qquad (0<b<a<1). \tag{20}$$

For the optimal stopping rule described in Theorem 2,

$$B(a,b) \le \frac{1-v + a(1-b)}{2(a-b)^2\cdot E(M)}. \tag{21}$$

PROOF. Proceed as in the proof of Theorem 4, but with $e(k)$ defined as the probability the better treatment is rejected starting in the state k. Thus $B(a,b) = e(0)$. It is easily seen that $e(\pm\ell') = (1 + e^{2\ell'})^{-1}$, and $e(k)$ satisfies the nonhomogeneous second order difference equation

$$e(k) = \gamma\cdot\{u_k\cdot e(k-1) + v\cdot e(k) + w_k\cdot e(k+1)\} + (1-\gamma)\cdot(1 + e^{2|k|})^{-1} \tag{22}$$

for $|k| < \ell'$. It is shown in the lemma below that the unique solution is given by

$$e(k) = (1 + e^{2|k|})^{-1} - \frac{\sinh \alpha\cdot \sinh (\ell' - |k|)\theta}{2\cdot \sinh \theta\cdot \cosh k\alpha\cdot \cosh \ell'\theta}. \tag{23}$$

Then (20) follows immediately.

When $\ell' = \ell$, Lemma 1, (18) and (11) yield

$$B(a,b) \le \frac{\sinh\theta - \sinh\alpha}{2\cdot\sinh\theta} + \frac{1-\tanh \ell\theta}{2} \le \frac{1-v}{2(a-b)^2\cdot E(M)} + e^{-2\ell\theta}$$
$$\le \frac{1-v}{2(a-b)^2\cdot E(M)} + \frac{e^{\alpha}}{4\cdot \sinh\alpha\cdot (a-b)\cdot E(M)} = \frac{1-v + a(1-b)}{2(a-b)^2\cdot E(M)}. \qquad \square$$

Inequality (21) is "asymptotically tight" in that

$$\limsup_{E(M)\to\infty} 2(a-b)^2 \cdot E(M) \cdot B(a,b) = 1-v + a(1-b).$$

COROLLARY 7. *For the stopping rule described in* Theorem 3, *and for fixed success probabilities* p_1 *and* p_2, *the first treatment is rejected with probability*

$$\pi(p_1,p_2) = \frac{1}{2} - \frac{\sinh \alpha' \cdot \tanh \ell'\theta'}{2\cdot\sinh\theta'}, \qquad (24)$$

where

$$\alpha' = \frac{1}{2}\log\left\{\frac{p_1\cdot(1-p_2)}{p_2\cdot(1-p_1)}\right\}$$

and $\theta' > 0$ *is defined by*

$$\cosh\theta' = \frac{1-\gamma\cdot v'}{2\cdot\beta'\cdot\gamma},$$

and where

$$v' = p_1\cdot p_2 + (1-p_1)\cdot(1-p_2),\ \beta' = \{p_1 p_2 (1-p_1)\cdot(1-p_2)\}^{1/2}.$$

For the optimal stopping rule described in Theorem 2,

$$\pi(p_1,p_2) = O(\max[E(M)^{-1}, E(M)^{-\alpha'/\alpha}]) \quad \text{as} \quad E(M)\to\infty \qquad (25)$$

for $p_1 > p_2$. *Thus* $\pi(p_1,p_2) = 1 - \pi(p_2,p_1) = 1 - O(\max[E(M)^{-1}, E(M)^{-\alpha'/\alpha}])$ *as* $E(M)\to\infty$ *for* $p_1 < p_2$.

PROOF. It is easily seen that $\pi(p_1,p_2) = B(p_1,p_2)$ when $p_1 > p_2$, and equals $B(p_2,p_1)$ when $p_1 \le p_2$. The values of α and θ, defined in (6) and (12), become α' and θ', respectively, when $p_1 > p_2$. And it is easily seen that (24) is still correct when $p_1 \le p_2$.

When $\ell' = \ell$, the bound described in (25) can be obtained as for (21):

$$\pi(p_1,p_2) \le \frac{\sinh\theta' - \sinh\alpha'}{2\cdot\sinh\theta'} + \frac{1-\tanh\ell\theta'}{2} \le \frac{1-v'}{2(p_1-p_2)^2\cdot E(M)} + e^{-2\ell\theta'},$$

and by (18),

$$e^{-2\ell\theta'} = \{e^{-2\ell\theta}\}^{\theta'/\theta} = \{e^{-2\ell\theta}\}^{\alpha'/\alpha}\cdot\{1+o(1)\}$$
$$\le \left\{\frac{a(1-b)}{2(a-b)^2\cdot E(M)}\right\}^{\alpha'/\alpha}\cdot\{1+o(1)\} = E(M)^{-\alpha'/\alpha}$$

as $E(M) \to \infty$. □

LEMMA 2. *Equation* (23) *is the unique solution to the difference equation shown in* (22) *which satisfies the boundary conditions* $e(\pm\ell') = (1+e^{2\ell'})^{-1}$.

PROOF. The "uniqueness of solution" requires a standard argument and will not be given. With the substitution $f(k) = 2\cdot\cosh k\alpha\cdot e(k)$, equations (22) and (23) become

$$f(k) = \gamma\cdot\{\beta\cdot f(k-1) + v\cdot f(k) + \beta\cdot f(k+1)\} + (1-\gamma)\cdot e^{-|k|\alpha}, \qquad |k|<\ell',$$

and

$$f(k) = e^{-|k|\alpha} - \frac{\sinh\alpha\cdot\sinh(\ell'-|k|)\theta}{\sinh\theta\cdot\cosh\ell'\theta}, \qquad |k|\le\ell'. \qquad (23')$$

The former can be rewritten as (see (12) and (13))

$$f(k) = (2\cdot\cosh\theta)^{-1}\cdot\{f(k-1)+f(k+1)\} + \left(1 - \frac{\cosh\alpha}{\cosh\theta}\right)\cdot e^{-|k|\alpha}, \qquad |k|<\ell'. \qquad (22')$$

Clearly (23′) satisfies the transformed boundary conditions $f(\pm\ell') = e^{-\ell'\alpha}$. And it is a matter of using elementary hyperbolic identities to show (23′) satisfies (22′). □

5. Concluding comments.

It is hoped that the theory presented in Section 4 becomes a stimulus for future research. Clearly the assumptions made in this section were designed for mathematical convenience. In their defense, it could argued that they are no stronger than those that have been made for fixed horizon versions of the model. And a random horizon does appear more reasonable. Most importantly, they lead to precisely describable results. But it is not clear yet whether the conclusions drawn fairly approximate reality.

There are many important theoretical questions that were not addressed. For instance, one should probably assign a cost to the treatments administered during the testing phase. What effect would this have? It's inclusion would probably cause a shift of the "expected successes lost" from treatment-phase patients to utility-phase patients. (See Theorem 6.) But how big would the shift be? It should be possible to address such a question theoretically within a convenient mathematical context.

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