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# A LOCAL LIMIT THEOREM FOR A BIASED COIN DESIGN FOR SEQUENTIAL TESTS

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In a clinical comparison of responses to two treatments, patients are admitted sequentially and given one of the two treatments. The allocation is determined randomly, to decrease the possibility of personal bias in the selection of subjects for the test. To balance the assignments, the probability of receiving one treatment is a function of the proportion of patients previously assigned to that treatment. A local limit theorem for the distribution of the number of patients assigned to the first treatment is developed.

**1. Introduction.** Consider a sequential medical trial in which two treatments are compared. Each subject is assigned to one of the two treatments. In most statistical tests, it is desirable that an equal number of patients are assigned to the two treatments. However, in a sequential test, this balance is not easily obtained. For example, patients may be assigned to treatments by a completely random rule, by flipping a fair coin. Since the sample size in a sequential test is sometimes small, there may be a sizeable imbalance in the number of subjects assigned to each treatment. Alternatively, a deterministic scheme may be used, with assignments strictly alternating between the two treatments. But the experimenter then knows the treatment to be given to a subject, possibly before that subject has entered the trial. Thus, either consciously or unknowingly, the experimenter may bias the test in favor of one of the two treatments (e.g., by not admitting difficult cases when that treatment is to be administered). The allocation bias of an allocation scheme is defined to be the probability of correctly guessing the next patient's assignment, given all previous assignments (Blackwell and Hodges, 1957; Stigler, 1969). With the deterministic scheme, the allocation bias is equal to one, the worst possible value. With the completely random scheme, the bias is one-half, the optimal value.

Efron (1971) and Wei (1978) have proposed alternative allocation schemes. Let $\delta_i = 1$ if the $i$th patient has received one treatment, 0 if the other. Let

$$D_n = 2 \textstyle\sum_1^n \delta_i - n, \tag{1}$$

the difference in the number of patients assigned to the treatments. These schemes require that

$$P\{\delta_{n+1} = 1 \mid \delta_1, \cdots, \delta_n\} = h(D_n/n), \tag{2}$$

where $h$ is a nonincreasing function with $h(0) = ½$. Efron considers a class of

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functions for which the asymptotic allocation bias (as the number of assignments approaches infinity) is greater than one-half. Wei's schemes, in which $h$ satisfies certain smoothness conditions, have asymptotic allocation bias equal to one-half. In addition, in Wei's scheme, $n^{-1/2}D_n$ converges in distribution to a normal, mean zero random variable with variance depending on $h$. Theorem 1 below, a local limit theorem for $n^{-1/2}D_n$, is an extension of Wei's result. This theorem can be used to study the properties of a sequential test comparison of two treatments, using the described allocation scheme, as the expected sample size approaches infinity. The asymptotic joint distribution of the stopping time and the proportion of patients assigned to one of the treatments at this stopping time, in addition to the Type I error probability have been determined in the sequential probability ratio test and in the test of a simple hypothesis in a one-parameter exponential family (Heckman, 1982, 1985).

The sequence, $D_n$, $n \geq 1$, has been studied extensively in the context of urn models. In particular, the sequence generated in the case $h(x) = ½ - x/2$ can be described by a Friedman urn model (1949). In this case, Freedman (1965) has shown that $n^{-1/2}D_n$ converges in distribution to a normal random variable. Hill, Lane, and Sudderth (1980) have studied the convergence of $D_n/n$ where $D_n$ is generated by a continuous function, $h$, from the unit interval to $[0, 1]$. Their results relate the support of the limiting random variable to simple properties of $h$.

**2. A local limit theorem.** Let $h$ be a function from $[-1, 1]$ to $[0, 1]$ satisfying

(i) $h$ is nonincreasing,
(ii) $h(x) = 1 - h(-x)$,
(iii) $h(x) = ½ + h'(0)x + B(x)x^2$
where $\sup_{|x| \leq 1} |B(x)| < \infty$.

Suppose that $m = m_n$ is a sequence of integers with $m - n$ even. Let $x$ be a real number and suppose that $mn^{-1/2}$ converges to $x$ as $n$ approaches infinity. Let $D_0 = 0$ and let $D_n$ be as defined in (1) and (2). Then

THEOREM 1. *$\lim_{n\to\infty} n^{1/2}P\{D_n = m_n\} = 2\phi(x/\tau)/\tau$, where $\phi$ is the standard normal density and $\tau^2 = [1 - 4h'(0)]^{-1}$.*

The proof of the theorem uses the following results of Wei (1978). Under the assumptions of Theorem 1,

THEOREM 2. *$\sup_n E\,|\,n^{-1/2}D_n\,|^j < \infty$ for all $j$ greater than one.*

THEOREM 3. *The distribution of $n^{-1/2}D_n$ converges to a normal distribution with mean zero and variance $\tau^2$.*

In the special case that $h(x) = ½$, the $\delta_i$ are independent and identically distributed, and Theorem 3 is simply the central limit theorem with $\tau^2 = 1$. It is thus possible to reduce the asymptotic variance of $n^{-1/2}D_n$ from the case, $h(x) = 1/2$, by making the slope of $h$ steeper at $x = 0$.

PROOF OF THEOREM 1. By Fourier inversion,

$$n^{1/2}P\{D_n = m\} = n^{1/2}\pi^{-1}\int_{-\pi/2}^{\pi/2} e^{-itm}\psi_n(t)\,dt, \tag{3}$$

where $\psi_n(t) = E(\exp(itD_n))$. Theorem 3 and the continuity theorem (Feller, 1971) imply that

$$\psi_n(n^{-1/2}t) \to \exp(-\tau^2t^2/2).$$

So,

$$\lim_{A\to\infty}\lim_{n\to\infty} 1/\pi \int_{-An^{-1/2}}^{An^{-1/2}} n^{1/2}\psi_n(t)e^{-itm}\,dt$$

$$= 1/\pi\int_{-\infty}^{\infty}\exp(-\tau^2s^2/2)\exp(-isx)\,ds = 2\phi(x/\tau)/\tau.$$

Therefore it suffices to show that, in (3), the integral over $t$, $An^{-1/2} \le |t| \le \pi/2$, converges to zero as first $n$, then $A$, approaches infinity.

Theorem 1 follows from Lemma 2 below, after first expressing $\psi_n(t)$ in the form given in Lemma 1, with $j = [n\varepsilon]$. ([ ] denotes the greatest integer function.)

LEMMA 1. *For* $1 \le j \le n$,

$$\psi_n(t) = \psi_{n-j}(t)\cos^j t$$
$$+\, 2h'(0)\sin t \textstyle\sum_{k=1}^{j} \psi'_{n-k}(t)\cos^{k-1}t/(n-k) - \sum_{k=1}^{j} f_{n-k}(t)\cos^{k-1}t$$

*where* $|f_{n-k}(t)| \le K\sin t/(n-k)$, *for some constant* $K$.

*In addition, there exists* $C$ *depending only on* $h$ *such that, for all* $t \in [-\pi/2, \pi/2]$ *and for all* $n$,

$$|\psi_n(t)| \le \cos^j t + C(n-j)^{-1/2}|t|^{-1}, \quad \textit{for all} \quad j < n.$$

PROOF. By conditioning on $D_{n-1}$ and using condition (iii)

$$\psi_n(t) = \psi_{n-1}(t)\cos t + 2h'(0)\sin t \cdot \psi'_{n-1}(t)/(n-1) + f_{n-1}(t)$$

where

$$f_{n-1}(t) = 2i\sin tE\{e^{itD_{n-1}}D_{n-1}^2B(\bar{D}_{n-1})\}/(n-1)^2.$$

The first part of the lemma follows by iterating. The bound on $f_{n-k}(t)$ follows from Theorem 2 and the boundedness of $B$.

The bound for $\psi_n(t)$ follows from Theorem 2, since

$$(n-k)^{-1/2}|\psi'_{n-k}(t)| \le E|(n-k)^{-1/2}D_{n-k}|.$$

LEMMA 2. *For all* $\varepsilon$ *in* (0, 1),

$$\lim_{n\to\infty} n^{1/2} \int_{-\pi/2\le t\le\pi/2} \left| \sum_{k=1}^{[n\varepsilon]} f_{n-k}(t)\cos^{k-1}t e^{-itm} \right| dt = 0,$$

$$\lim_{A\to\infty} \lim_{n\to\infty} n^{1/2} \int_{An^{-1/2}\le|t|\le\pi/2} \psi_{n-[n\varepsilon]}(t)\cos^{[n\varepsilon]}t\, dt = 0,$$

$$\lim_{\varepsilon\to 0} \lim_{A\to\infty} \lim_{n\to\infty} n^{1/2}$$

$$\sum_{k=1}^{[n\varepsilon]} \left\{ (n-k)^{-1} \int_{An^{-1/2}\le|t|\le\pi/2} e^{-itm} \psi'_{n-k}(t) \sin t \cos^{k-1} t\, dt \right\} = 0.$$

The first statement follows immediately from the bound on $f_{n-k}$ in Lemma 1. The second statement follows by bounding $|\psi_{n-[n\varepsilon]}(t)|$ by one. To prove the third statement, integrate each term in the sum by parts with $u = \sin t \cos^{k-1} t e^{-itm}$, sum, and use the bound on $\psi_{n-k}$ given in Lemma 1.

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