Adaptive Designs
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UP-AND-DOWN DESIGNS I: STATIONARY TREATMENT DISTRIBUTIONS

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Abstract

The primary objective of experiments motivating this work is to estimate the unknown amout μ of treatment that has a probability of response equal to a fixed value $\Gamma, 0 \leq \Gamma \leq 1$. We further assume that it is desirable to 'center' the distribution of treatments around the unknown quantile. This is accomplished by sequentially assigning treatment levels to subjects using *up-and-down rules*, that is, rules by which the treatment used in the next trial is restricted to be one level higher, one level lower, or the same as it is for the current trial. We describe two such rules that asymptotically result in a unimodal distribution of treatment assignments with mode as close to μ as is possible given the discreteness of the treatment levels permitted. Responses are assumed to follow an extreme value function and a logistic function to illustrate how a parametric stationary treatment distribution can be determined by pairing a response function model with an up-and-down design. The designs are shown to be robust with respect to the form of the response function.

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1. Introduction. Consider experiments in which a treatment or stimulus is given, or a stress is applied, at a finite number of levels, and the number of responses at each level is observed. Quantile estimation is one important objective of such experiments in many areas of application, including toxicology, item response analysis, and material stress analysis. In these applications, the unknown response function is commonly monotone, but nonlinear. Because quantile estimation is an important problem in many areas of application, a variety of statistical approaches have been developed. For fixed experimental designs, probit analysis and logistic regression are two standard methods used for quantile estimation.

For nonlinear response functions, however, the optimal design depends on the unknown parameters, and therefore, an optimal design cannot be set forth a priori. In order to improve efficiency, several sequential approaches have been proposed in which levels of the treatment are changes as information accumulates. Methods involving multistage or sequential optimal design by Tsutakawa (1967), Chiang (1990), Flournoy (1993), and Awartani (1993). In the spirit of stochastic approximation, Wu (1985) proposed sequential maximum likelihood estimation be used to produce a sequence of treatments that converges to a target quantile. Bayesian approaches have been proposed by Freedman (1970), Zellner and Rossi (1984) and O'Quigley, Pepe and Fisher (1990).

This paper considers a class of rules that are up-and-down designs. Anderson, McCarthy and Tukey (1946) first brought these designs to the attention of the statistical community. Dixon and Mood (1948) analyzed a more tractable version of such designs, namely one specifically designed for estimating the 50th percentile of the response function. Up-and-down designs have been studied by many, including Wetherill (1963), Dixon (1965), Tsutakawa (1967), Wetherill and Glazebrook (1986), Storer (1989), Flournoy (1990), and Durham and Flournoy (1993, 1994), among others.

The primary objective of experiments motivating this work is to estimate the unknown amount μ of treatment, stimulus, or stress that has a probability of response equal to a fixed value $\Gamma, 0 \leq \Gamma < 1$. We call Γ the *target probability of response*, and we call μ *the target quantile.* We further assume that it is desirable to center the distribution of treatments around the unknown quantile. This is accomplished by sequentially assigning treatment levels to subjects using up-and-down rules, that is, rules by which the treatment used in the next trial is

restricted to be one level higher, one level lower, or the same as it is for the current trial. We describe rules that asymptotically result in a unimodal distribution of treatment assignments with mode as close to μ as is possible given the discreteness of the treatment levels used.

Let $Y(n)$, $n = 0, 1, 2, \ldots$, be Bernoulli random variables with $Y(n) = 1$ indicating that the *outcome* of the nth *trial* was a response, and $Y(n) = 0$ indicating no response. This notation derives from thinking of the response as being toxicity, so that a *response* connotes *failure* and *no response* connotes *success*. Let $\Omega_{\mathbf{x}} = \{x_0, x_1, \ldots, x_K\}$ be a sample space of ordered treatments. Assume that the interval $\triangle$ between treatments is constant, so that $x_k = x_0 + k\triangle$, where x_0 is the smallest treatment. Assuming also that the sample size is fixed, an experimental design is defined by the rule that assigns treatments to subjects. Often arbitrary outcomes and treatments will be denoted by Y and X, respectively, without explicit mention of their position in the sequence of trials. The probability of response given x is denoted by $Q(x) \equiv P\{Y = 1 \mid X = x\}$, with $P(x) \equiv 1 - Q(x)$. The *response function* $Q(x)$ is taken to be strictly increasing in x, but given x, $Q(x)$ is assumed to be constant over all trials $n = 0, 1, 2, \ldots$.

Two up-and-down designs are described in Section 2. Then the effect of these designs on the asymptotic distribution of treatments is examined. The theory for deriving the asymptotic treatment distributions is reviewed in Section 3, and some nonparametric properties of asymptotic treatment distributions are discussed.

Responses are assumed to follow an extreme value function and a logistic function in Sections 4 and 5, respectively, to illustrate how a parametric stationary treatment distribution can be determined by pairing a response function model with an up-and-down design. In order to make some comparisons between the performance of the designs with different underlying response functions, parameters for the logistic and extreme value models are chosen so that they coincide at the 10th and 50th percentiles; specifically $Q(2.50) = 0.10$ and $Q(6.21) = 0.50$ for both models. The resulting value of the shape parameter β for the logistic response function is equal to the prior for β that was elicited by Flournoy (1994) for estimating optimal treatment levels in a phase I clinical trial. The location parameter α and the number of dose levels (namely, 9) in the treatment space are then selected so that the response function is just slightly greater than zero at the lowest dose level and just slightly less than one at the highest dose level. That control over the location of the stationary treatment distribution can be effected

using the biased coin up-and-down designs is demonstrated targeting the 10th and the 33rd percentiles. In Section 6, the robustness of the two designs given different response functions is discussed.

To summarize, given a proportion Γ, we consider designs that will create a distribution about the treatment μ for which $P(Y = 1 \mid X = \mu) = \Gamma$. Two biased coin up-and-down designs are given that accomplish this asymptotically can be seen in Figure 1. Here we illustrate, given underlying, unknown logistic and extreme value response functions, that a distribution centered about the 33rd percentile of the response function is obtained when fixing $\Gamma = 0.33$; whereas when fixing $\Gamma = 0.10$, a distribution centered about the 10th percentile of the response function is obtained. It is important to note that many ad hoc up-and-down procedures have been used [for example, see Flournoy (1993) and Storer (1989)] without theoretical analysis of their consequences.

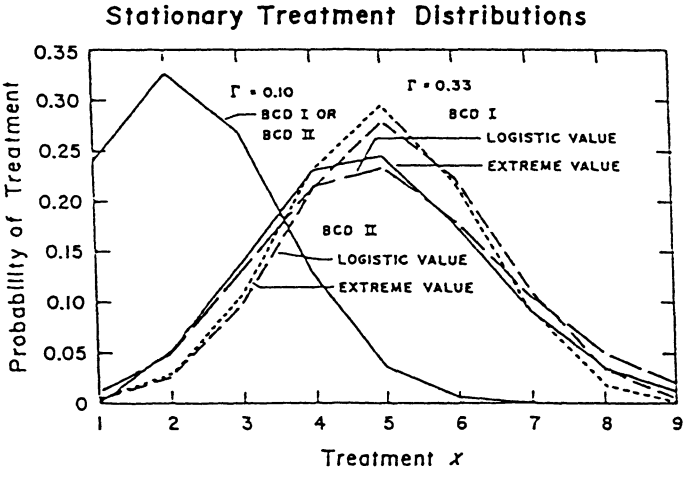

Fig. 1. Stationary treatment distributions using BCD I and BCD II to target $\Gamma = 0.10$ and $\Gamma = 0.33$ when $Q(x)$ is logistic value $\cdot Q(x) = 1 - [1 + \exp(-3.569 + 0.549x)]^{-1}$ and $Q(x)$ is extreme value $\cdot Q(x) = 1 - \exp\{-\exp\{(x - 6.931)/1.97\}\}$.

2. Biased coin up-and-down designs. Figure 2 depicts two biased coin designs that are each defined so that the resulting transition probabilities define a random walk on the non-negative integers.

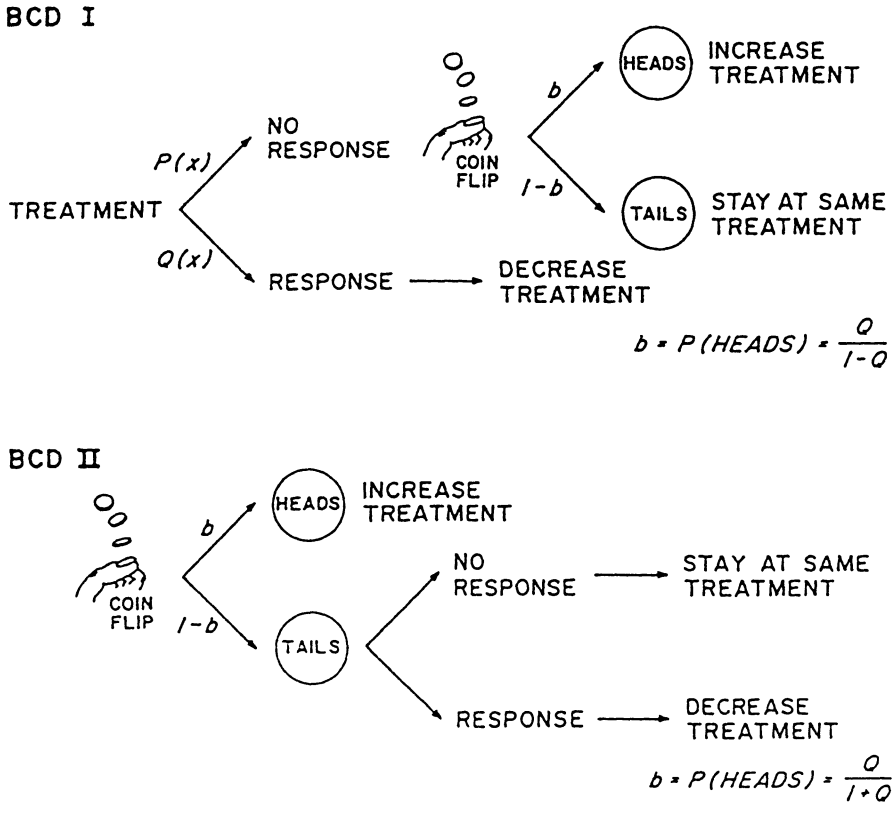

FIG. 2. BIASED COIN RULES

The initial treatment $X(0)$ may be fixed or random. In up-and-down designs, subsequent treatments $X(n+1)$ depend on the current treatment $X(n)$ by definition. However, we place the random walk in a random environment by making it depend on the experimental outcome $Y(n)$ as well. Additional randomness is introduced in order to provide a mechanism for controlling the location of the treatment distribution. When this randomness results from the toss of a biased coin, we say that the treatment allocation procedure follows a *biased coin*

up-and-down rule. Therefore, the treatments $X(n)$, $n > 0$, are random variables assuming values in the treatment space $\Omega_{\mathbf{x}}$. Let b denote the probability that the result of a biased coin flip is heads. Let p_k, q_k, and r_k denote the probabilities that the treatment dosages will move up from level k to $k+1$, down from level k to $k-1$, and stay at level k, respectively. Of course, $p_k + q_k + r_k = 1$, $0 < k < K$. Strict boundaries on the dosage to be used in the experiment are fixed by requiring that $q_0 = 0$ and $p_K = 0$.

BIASED COIN DESIGN I (BCD I). *Fix the target quantile* Γ *between 0 and 1, and assume that a treatment has been given at level* k. *Toss the coin with probability of heads equal to* $b \equiv \Gamma/(1+\Gamma), 0 \leq b \leq 1/2$. *If heads is observed, treat the next subject at level* $k+1$. *If tails is observed and there is no response, treat the next subject at level* k, *whereas if there is a response, treat the next subject at level* $k-1$.

The transition probabilities for treatment x_k are

$$
\begin{array}{lll}
p_0 = b, & q_0 = 0, & r_0 = 1-b, \\
(1)\quad p_k = b & q_k = (1-b)\,Q(x_k), & r_k = (1-b)\,P(x_k), \\
p_K = 0, & q_K = (1-b)\,Q(x_K), & r_K = 1-(1-b)\,Q(x_K),
\end{array}
$$

where $k = 1, \ldots, K-1$.

To implement BCD I for a particular target, one needs to compute the coin bias. Suppose the 33rd percentile is targeted. Then $\Gamma = .33$, and so $b = \Gamma/(1+\Gamma) = 1/4$ and the transition probabilities (1) become

$$
\begin{array}{lll}
p_0 = \frac{1}{4}, & q_0 = 0, & r_o = \frac{3}{4}, \\
(2)\quad p_k = \frac{1}{4}, & q_k = \frac{3}{4}Q(x_k), & r_k = \frac{3}{4}P(x_k), \\
p_K = 0, & q_K = \frac{3}{4}Q(x_K), & r_K = \frac{3}{4}P(x_K),
\end{array}
$$

where $k = 1, \ldots, K-1$. However if the 10th percentile is targeted, $\Gamma = 0.10$ and $b = \Gamma/(1+\Gamma) = 1/11$ and the transition probabilities (1) become

$$
\begin{array}{lll}
p_0 = \frac{1}{11}, & q_0 = 0, & r_0 = \frac{10}{11} \\
(3)\quad p_k = \frac{1}{11}P(x_k), & q_k = \frac{10}{11}Q(x_k), & r_k = \frac{10}{11}P(x_k), \\
p_K = 0, & q_k = \frac{10}{11}Q(x_k), & r_K = \frac{1}{11}P(x_K),
\end{array}
$$

where $k = 1, \ldots, K-1$.

BIASED COIN DESIGN II (BCD II). *Assume that a treatment has just been given at level* k. *For* $0.0 \leq \Gamma \leq 0.5$, *let the bias* $b \equiv \Gamma/(1-\Gamma)$ *equal the odds ratio at the target quantile. If not response is observed and the toss of a biased coin yields heads, then increase the level to* $k+1$; *if no response is observed and the coin toss yields tails, then leave the label at level* k; *if a response is observed, then decrease the level to* $k-1$.

The transition probabilities for the treatments that result from using BCD II can be expressed in terms of the coin bias and the probability of response:

$$
\begin{array}{lll}
p_0 = bP(x_0), & q_0 = 0, & r_0 = 1 - bP(x_0), \\
p_k = bP(x_k), & q_k = Q(x_k), & r_k = (1-b)P(x_k), \\
p_K = 0, & q_K = Q(x_K), & r_0 = P(x_K);
\end{array} \tag{4}
$$

where $k = 1, \ldots, K-1$.

In the special case that $\Gamma = 0.5$, $b \equiv 1$ (the coin is deterministic); then BCD II is equivalent to the up-and-down method introduced by Dixon and Mood (1948) for estimating the 50th percentile. However, suppose the 33rd percentile is targeted; then the coin bias to use is $b = \Gamma/(1-\Gamma) = (1/3)(2/3) = 1/2$. With $b = 1/2$, the transition probabilities (4) are

$$
\begin{array}{lll}
p_0 = \frac{1}{2}P(x_0), & q_0 = 0, & r_0 = 1 - \frac{1}{2}P(x_0), \\
p_k = \frac{1}{2}P(x_k), & q_k = Q(x_k), & r_k = \frac{1}{2}P(x_k), \\
p_K = 0, & q_k = Q(x_K), & r_0 = P(x_K);
\end{array} \tag{5}
$$

where $k = 1, \ldots, K-1$, whereas if the 10th percentile is targeted, $b = \Gamma/(1-\Gamma) = 1/9$ and (4) becomes

$$
\begin{array}{lll}
p_0 = \frac{1}{9}P(x_0), & q_0 = 0, & r_0 = 1 - \frac{1}{9}P(x_0), \\
p_k = \frac{1}{9}P(x_k), & q_k = Q(x_k), & r_k = \frac{8}{9}P(x_k), \\
p_K = 0, & q_k = Q(x_K), & r_0 = P(x_K).
\end{array} \tag{6}
$$

where $k = 1, \ldots, K-1$.

3. The stationary treatment distribution. Let treatments be allocated according to BCD I or BCD II. It can be verified that these designs describe irreducible recurrent random walks, and thus

well-known theory guarantees that the *stationary treatment distribution* $\boldsymbol{\pi} \equiv (\pi_0, \pi_1, \ldots, \pi_K)$ exists [for example, see Feller (1950) or Harris (1952)]. The elements of $\boldsymbol{\pi}$ are called *stationary treatment probabilities*, and so long as $r_k > 0$, $k = 0, \ldots, K$,

$$\pi_k = \lim_{n \to \infty} P\{X(n) = x_k\}.$$

Let $N_k(n)$ denote the number of times treatment x_k has been used during the first $n+1$ trials. Then, π_k is also the asymptotic proportion of trials at x_k, that is,

$$\pi_k = \lim_{n \to \infty} N_k(n) / (n+1) > 0, \; k = 0, 1, \ldots, K.$$

It is also well-known that the stationary treatment distribution can be obtained by solving the *balance equations*, $\pi_k = \pi_{k-1} p_{k-1} + \pi_k r_k + \pi_{k+1} q_{k+1}$, $k = 0, 1, \ldots, K$, (where for convenience, we define $p_{-1} = q_{K+1} \equiv 0$) to obtain

(7)

$$\pi_k = \prod_{j=0}^{k} \lambda_j; \; \lambda_0^{-1} \equiv 1 + \sum_{k=1}^{K} \prod_{j=1}^{k} \lambda_j; \; \lambda_k \equiv \frac{p_{k-1}}{q_k}; \; k = 1, \ldots, K.$$

To see that (7) is indeed a solution, rewrite the balance equations as

$$\pi_k (p_k + q_k) = \pi_{k-1} p_{k-1} + \pi_{k+1} q_{k+1}.$$

Then insert $\prod_{j=0}^{k} \lambda_j$ for π_k to obtain

$$(p_k + q_k) \prod_{j=0}^{k} \lambda_j = p_{k-1} \prod_{j=0}^{k-1} \lambda_j + q_{k+1} \prod_{j=0}^{k+1} \lambda_j.$$

Cancel the terms in common on both sides of the equals sign and insert $\lambda_k \equiv p_{k-1}/q_k$ and $\lambda_{k+1} \equiv p_k/q_{k+1}$ to obtain the identity $(p_k + q_k)\, p_{k-1}/q_k = p_{k-1} + q_{k+1}\; p_{k-1}/q_k\; p_k/q_{k+1}$.

Now assume that the response function $Q(x)$ is monotone increasing. Then it can be seen from (1) and (4) that the probabilities

$\{q_0, q_1, \ldots, q_K\}$ form a monotone decreasing set using either BCD I or BCD II, whereas the probabilities $\{p_0, p_1, \ldots, p_K\}$ form a monotone increasing set. Let κ denote the largest treatment level such that $\lambda_\kappa \geq 1$. Durham and Flournoy (1994) showed that, using an up-and-down rule for which $\{q_0, q_1, \ldots, q_K\}$ is a monotone decreasing set and $\{p_0, p_1, \ldots, p_K\}$ is a monotone increasing set, the stationary treatment distribution $\boldsymbol{\pi}$ has a single mode at x_κ, except when $\lambda_\kappa = 1$ in which case the model of $\boldsymbol{\pi}$ spans $x_{\kappa-1}$ as well. For large samples, this result justifies considering the sample mode as a non-parametric measure of central tendency for the treatment distribution. For simplicity, x_κ is called the *mode of the stationary treatment distribution*, or simply the *mode of* $\boldsymbol{\pi}$, although it is possible that $x_{\kappa-1}$ is a mode as well. Durham and Flournoy (1994) also showed that the target quantile μ is bounded within $\pm\Delta$ of x_κ when using BCD II. This result holds for both designs as is stated in the following theorem without proof.

THEOREM 1. *If BCD I or BCD II is used when the response function is monotone increasing in* x, *with* $q_1 < p_0$ *and* $q_K > p_{K-1}$, *then* $|\mu - x_K| < \Delta$.

This result suggests using the empirical mode of the treatment distribution as a nonparametric estimate of μ.

Parametric models of the treatment distribution may be obtained by inserting parametric models of the response functions into (1) and (4) for BCD I and BCD II, respectively, and then inserting these results into (7). The resulting limiting treatment distributions are expressions involving the unknown response function. In particular, since

$$\lambda_k \equiv \frac{p_{k-1}}{q_k} = \begin{cases} \dfrac{\Gamma}{Q(x_k)} & \text{for BCD I,} \\ \dfrac{\Gamma}{Q(x_k)} \dfrac{P(x_{k-1})}{1-\Gamma} & \text{for BCD II,} \end{cases} \qquad k = 1, \ldots, K,$$

it follows from the law of total probability that $\pi_0 = \lambda_0$, and for $k = 1, \ldots, K$,

(8)

$$\pi_k = \prod_{j=0}^{k} \lambda_j = \lambda_0 \prod_{j=1}^{k} \pi_k = \begin{cases} \lambda_0 \dfrac{\Gamma^k}{\prod_{j=1}^{k} Q(x_k)} & \text{for BCD I,} \\ \lambda_0 \left(\dfrac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \dfrac{P(x_{k-1})}{Q(x_k)} & \text{for BCD II,} \end{cases}$$

where

$$\lambda_0^{-1} = 1 + \sum_{j=1}^{K} \pi_j/\lambda_0 = \begin{cases} 1 + \sum_{j=1}^{K} \dfrac{\Gamma^j}{\prod_{i=1}^{j} Q(x_i)} & \text{for BCD I,} \\ 1 + \sum_{j=1}^{K} \left(\dfrac{\Gamma}{1-\Gamma}\right)^j \prod_{i=1}^{j} \dfrac{P(x_{i-1})}{Q(x_i)} & \text{for BCD II.} \end{cases}$$

Parametric models for the limiting treatment distribution now can be evaluated explicitly by inserting a parametric model for the response function into (8). Examples are given assuming an extreme value response function in Section 4 and a logistic response function in Section 5.

4. Biased coin rules with an extreme value response function. Suppose the underlying, unknown response function is an extreme value function, namely, $Q(x) = 1 - \exp\{-\exp\{(x-\alpha)/\beta\}\}$, $\beta > 0$. Since the probability of no response is

$$P(x) = 1 - Q(x) = exp\{-exp\{(x-\alpha)/\beta\}\},$$

$$(x-\alpha)/\beta = log\left\{log\left(P(x)\right)^{-1}\right\}$$

which, evaluated at the target quantile $x = \mu$, yields

$$\alpha = \mu + \beta log\left\{log\ \left(P(\mu)\right)^{-1}\right\}.$$

Consequently, the probability of no response can be written in terms of the target percentile as

$$P(x) = \exp\{-\exp\{(x-\alpha)/\beta\}\}$$

$$= \exp\left\{-\exp\left\{\left(x - \left(\mu + \beta\ log\left\{log\ \ (1-\Gamma)^{-1}\right\}\right)\right)/\beta\right\}\right\}$$
$$= \exp\left\{log\,(1-\Gamma)\exp\left\{(x-\mu)/\beta\right\}\right\}.$$

Now if (8) is evaluated for treatments that are allocated according to BCD I, the limiting distribution of treatments is given by $\pi_0 = \lambda_0$ and for $k = 1, \ldots, K$,

(9)

$$\pi_k = \lambda_0 \frac{\Gamma^k}{\prod_{j=1}^{k} Q(x_j)} = \lambda_0 \frac{\Gamma^k}{\prod_{j=1}^{k} \left(1 - \exp\left\{log\,(1-\Gamma)\exp\left\{(x_j-\mu)/\beta\right\}\right\}\right)},$$

where

$$\lambda_0^{-1} \equiv 1 + \sum_{k=1}^{K} \left(\frac{\Gamma^k}{\prod_{j=1}^{k} Q(x_j)} \right)$$

$$= 1 + \sum_{k=1}^{K} \left(\frac{\Gamma^k}{\prod_{j=1}^{k} \left(1 - \exp\left\{log\,(1-\Gamma)\exp\left\{(x_j-\mu)/\beta\right\}\right\}\right)} \right)$$

For illustrative purposes, suppose that the extreme value response function has parameters $\alpha = 6.931$ and $\beta = 1.97$. Selected percentiles of this response function are $Q(2.5) = 0.10$, $Q(5.15) = 0.33$, and $Q(6.21) = 0.50$. For a design in which $\Omega_{\mathbf{x}} = \{1, 2, \ldots, 9\}$, the stationary treatment distribution (9) is shown in Figure 1 targeting $\mu = 5.15$ (for which $\Gamma = 0.33$) and $\mu = 2.50$ for which $\Gamma = 0.10$.

The stationary treatment distribution has moments

$$E_{\boldsymbol{\pi}}(X) = \textstyle\sum_{k=0}^{K} x_k \pi_k$$

and

$$Var_{\boldsymbol{\pi}}(X) = \textstyle\sum_{k=1}^{K} x^2 \pi_k - \left(\sum_{k=0}^{K} x_k \pi_k\right)^2,$$

which can be calculated directly from (9). As shown in Tables 1 and 2, for our exemplary response model, $E_{\boldsymbol{\pi}}(X)$ is 4.79 when $\Gamma = 0.33$

Table 1.
Targeting $\Gamma = 0.33$
when $Q(2.50) = 0.10$ and $Q(6.21) = 0.50$

Response Function	Extreme Value		Logistic	
Biased Coin Design	BCD I	BCD II	BCD I	BCD II
Target μ	5.15	5.15	5.24	5.24
$E_{\pi}(X)$	4.79	4.91	4.96	5.07
$\mu - E_{\pi}(X)$	0.36	0.24	0.28	0.17
$SD_{\pi}(X)$	1.61	1.34	1.66	1.42

and 2.43 when $\Gamma = 0.10$ with standard deviations 1.61 and 1.12, respectively. Note that in both cases, $\mu - E_{\pi}(X)$ is less than $0.5\,\triangle$. It is interesting that the standard deviation of the stationary treatment distribution is smaller when Γ is close to the boundary of Ω_x and the distribution becomes skewed.

Alternatively, if treatments are allocated according to BCD II, the limiting distribution of the treatments is given by $\pi_0 = \lambda_0$ and for $k = 1, \ldots, K$,

(10)

$$\pi_k = \lambda_0 \left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \frac{P(x_{k-1})}{Q(x_k)}$$

$$= \lambda_0 \left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \frac{\left(\exp\left\{log\,(1-\Gamma)\, e^{(x_{j-1}-\mu)/\beta}\right\}\right)}{\left(1-\exp\left\{log\,(1-\Gamma)\, e^{(x_j-\mu)/\beta}\right\}\right)},$$

where

$$\lambda_0^{-1} \equiv 1 + \sum_{k=1}^{K} \left(\left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \frac{P(x_{k-1})}{Q(x_k)} \right)$$

$$= 1 + \sum_{k=1}^{K} \left(\left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \frac{\left(\exp\left\{log\,(1-\Gamma)\, e^{(x_{j-1}-\mu)/\beta}\right\}\right)}{\left(1-\exp\left\{log\,(1-\Gamma)\, e^{(x_j-\mu)/\beta}\right\}\right)} \right).$$

For the extreme value response function with parameters $\alpha = 6.931$ and $\beta = 1.970$, the stationary treatment distribution (10) is also shown

Table 2.
Targeting $\Gamma = 0.10$
when $Q(2.50) = 0.10$ and $Q(6.21) = 0.50$

Response Functions Biased Coin Design	Extreme Value and Logistic BCD I and BCD II
Target μ	2.50
$E_{\pi}(X)$	2.43
$\mu - E_{\pi}(X)$	0.07
$\mathrm{SD}_{\pi}(X)$	1.12

in Figure 1 targeting $\mu = 5.15$ when $\Gamma = 0.33$ and $\mu = 2.50$ when $\Gamma = 0.10$. When $\Gamma = 0.10$, the stationary treatment distributions for BCD I and BCD II are indistinguishable.

Recall that the unknown target quantile is 2.5, and note that the stationary treatment distribution has a mode at 2. Alternatively, when $\Gamma = 0.33$, the unknown target quantile is 5.15 and the mode of the treatment distribution is seen to be 5 for both up-and-down designs. Thus, as expected from Theorem 1, this mode is as close to the target as is possible given that the design is discrete.

The $E_{\pi}(X)$ calculated from (10) for our exemplary response model is 4.91 for $\Gamma = 0.33$ and 2.43 when $\Gamma = 0.10$ with standard deviations 1.34 and 1.12, respectively. Although for both up-and-down designs and both targets, the expected treatment is less than the targeted percentile, the difference between the expected treatment and the targeted percentile is less than half the interval between treatments. As was noted for BCD I, the standard deviation of the stationary treatment distribution for BCD II is smaller when Γ is further out in the tail of the response function. For $\Gamma = 0.10$, the difference between the target percentile and the center of the treatment distribution as measured by its mean is $\mu - E(x) = 0.07$ for both up-and-down designs; this is just a small fraction of the interval between treatments.

5. Biased coin rules with a logistic response function. We now consider the case in which $Q(x)$ is a logistic response function, that is, $Q(x) = \exp(\alpha + \beta x) / (1 + \exp(\alpha + \beta x))$, so that at $x = \mu$, $\alpha + \beta\mu = \log(\Gamma / (1 - \Gamma))$. In terms of Γ we have

$$P(x) = (1 + \exp(\alpha + \beta x))^{-1} = \left(1 + \frac{\Gamma}{1 - \Gamma} \exp(\beta(x - \mu))\right)^{-1}.$$

For example, if $\Gamma = 0.33$, $\alpha + \beta\mu = \log\left(\frac{1}{3}/\frac{2}{3}\right) = \log\left(\frac{1}{2}\right)$, and

$$P(x) = \left(1 + \tfrac{1}{2}\exp\left(\beta\left(x - \mu\right)\right)\right)^{-1}.$$

If treatments are allocated according to BCD I, the limiting distribution of the treatments given by (8) becomes $\pi_0 = \lambda_0$ and for $k = 1, \ldots, K$,

(11)

$$\pi_k = \lambda_0 \frac{\Gamma^k}{\prod_{j=1}^{k} Q(x_j)} = \lambda_0 \Gamma^k \prod_{j=1}^{k} \left(\frac{1 + \frac{\Gamma}{1-\Gamma}\exp\left(\beta\left(x_j - \mu\right)\right)}{\frac{\Gamma}{1-\Gamma}\exp\left(\beta\left(x_j - \mu\right)\right)} \right),$$

where

$$\lambda_0^{-1} \equiv 1 + \sum_{k=1}^{K} \left(\frac{\Gamma^k}{\prod_{j=1}^{k} Q(x_j)} \right)$$

$$= 1 + \sum_{k=1}^{K} \left[\Gamma^k \prod_{j=1}^{k} \left(\frac{1 + \frac{\Gamma}{1-\Gamma}\exp\left(\beta\left(x_j - \mu\right)\right)}{\frac{\Gamma}{1-\Gamma}\exp\left(\beta\left(x_j - \mu\right)\right)} \right) \right].$$

For the logistic response function with parameters $\alpha = -3.569$ and $\beta = 0.549$, the stationary treatment distribution (11) is shown in Figure 1 targeting $\mu = 5.24$ when $\Gamma = 0.33$ and $\mu = 2.50$ when $\Gamma = 0.10$. The stationary treatment distributions have expectation $E_{\boldsymbol{\pi}}(X) = \sum_{k=0}^{K} x_k \pi_k$ and $\mathrm{Var}_{\boldsymbol{\pi}}(X) = \sum_{k=1}^{K} x_k^2 \pi_k - \left(\sum_{k=0}^{K} x_k \pi_k\right)^2$ which can be calculated directly from (11). As shown in Tables 1 and 2, using BCD I with this exemplary response model, $E_{\boldsymbol{\pi}}(X) = 4.96$ when $\Gamma = 0.33$ and $E_{\boldsymbol{\pi}}(X) = 2.43$ when $\Gamma = 0.10$ with standard deviations 1.66 and 1.12, respectively.

The limiting treatment distribution that results from using BCD II is also shown in Figure 1 for the same targets and response function. This distribution is given by $\pi_0 = \lambda_0$ and for $k = 1, \ldots, K$,

$$(12)\pi_0 = \lambda_0 \left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \frac{P(x_{k-1})}{Q(x_k)}$$

$$= \lambda_0 \left(\frac{\Gamma}{1-\Gamma}\right)^k \prod_{j=1}^{k} \left(\frac{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_j-\mu))}{\frac{\Gamma}{1-\Gamma}\exp(\beta(x_j-\mu))}\right) \times \left(\frac{1}{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_{j-1}-\mu))}\right)$$

$$= \lambda_0 \left(\frac{\Gamma}{1-\Gamma}\right)^k \left[\frac{\Gamma}{1-\Gamma}\exp\left(\beta\sum_{j=1}^{k} x_j - k\mu\right)\right]^{-1} \times \left(\frac{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_K-\mu))}{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_0-\mu))}\right),$$

where

$$\lambda_0^{-1} \equiv 1 + \sum_{K=1}^{k}\left(\left(\frac{\Gamma}{1-\Gamma}\right)^k \sum_{j=1}^{k} \frac{P(x_{k-1})}{Q(x_k)}\right)$$

$$= 1 + \sum_{K=1}^{k}\left(\frac{\Gamma}{1-\Gamma}\right)^k \left[\frac{\Gamma}{1-\Gamma}\exp\left(\beta\sum_{j=1}^{k} x_j - k\mu\right)\right]^{-1} \times \left(\frac{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_K-\mu))}{1+\frac{\Gamma}{1-\Gamma}\exp(\beta(x_0-\mu))}\right)$$

For the logistic response function with parameters $\alpha = -3.569$ and $\beta = 0.549$, the stationary treatment distribution (12) is also shown in Figure 1 targeting $\mu = 5.24$ when $\Gamma = 0.33$ and $\mu = 2.50$ when $\Gamma = 0.10$. As shown in Tables 1 and 2, the $E_{\boldsymbol{\pi}}(X)$ calculated from (12) for this exemplary response model is 5.07 for $\Gamma = 0.33$ and 2.43 when $\Gamma = 0.10$ with standard deviations 1.42 and 1.12, respectively. Again for both up-and-down designs and both targets, the expected treatment is less than the targeted percentile, the difference between the expected treatment and the targeted percentile is less than half the interval between treatments. As was noted for BCD I, the standard deviation of the stationary treatment distribution for BCD II is smaller when Γ is further out in the tail of the response function. Again for $\Gamma = 0.10$, the targeted percentile and the mean of the treatment distribution differ only by $\mu - E(x) = 0.07$ for both up-and-down designs.

For the stationary treatment distribution given by (12), Durham and Flournoy (1993, 1994) showed that, if the range of treatment is unbounded, $\pi_0 \to 0$ as $x_0 \to -\infty$ and $\pi_K \to 0$ as $x_0 \to \infty$. In this situation, since the stationary treatment distribution has its mode at $x_k \in \Omega_{\mathbf{x}} = \{x_0, x_1, \ldots, x_K\}$, it may be possible to arrange $\Omega_{\mathbf{x}}$ so that frequencies in the tails of the treatment distribution are small. When $\Omega_{\mathbf{x}}$ is arranged in such a fashion, Durham and Flournoy (1994) showed that (12) can be written as a mixture of two *discrete normal distributions* with location parameters $\mu \pm 0.5\triangle$, the same scale parameter $\triangle/\beta$, and mixing parameter $\Gamma \equiv P(Y = 1 \mid X = \mu)$, that is, $k = 0, \ldots, K$,

(13)

$$\pi_k \approx (1 - \Gamma)\,\psi\left(\frac{x_k - (\mu - .5\triangle)}{\sqrt{\triangle/\beta}}\right) + \Gamma\,\psi\left(\frac{x_k - (\mu + .5\triangle)}{\sqrt{\triangle/\beta}}\right),$$

where

$$\psi(z_k) = \frac{\exp(-z_k^2/2)}{\sum_{k=0}^{K} \exp(-z_k^2/2)}.$$

However in many applications, x_0 is bounded below by 0, even when x_K may be freely controlled by design. Consider the shapes of the stationary distributions shown in Figure 1. Using BCD II, when $\Gamma = 0.33$, the stationary treatment distribution is concentrated in the center of $\Omega_{\mathbf{x}}$ with 98.88% of the probability mass occurring between $X = 2$ and $X = 8$, inclusively, and 92.668% of the mass between $X = 3$ and $X = 7$, inclusively. Using BCD I, the probability mass is even slightly more concentrated, and either up-and-down design produces a stationary treatment distribution that is reasonably bell-shaped. The shape of the stationary treatment distribution differs markedly when $\Gamma = 0.10$, in which case it is strikingly skewed to the right with 24.06% of the probability mass at $X = 1$ and only 0.08% of the mass at $X \geq 7$. Thus for an experiment on $\Omega_{\mathbf{x}} = \{1, \ldots, 9\}$ when the response function is logistic with parameters $\alpha = -3.569$ and $\beta = 0.549$, (13) should provide a much better approximation when $\Gamma = 0.33$ than when $\Gamma = 0.10$. A more comprehensive evaluation of the goodness of fit of the

approximation (13) to (12) and its usefulness in designing experiments is currently in progress.

6. Conclusions. Both BCD I and BCD II center the stationary treatment distribution around the unknown targeted percentile in the sense that the mode occurs as close to μ as is possible given the distance between treatments. When the response function is modeled parametrically, the stationary treatment probabilities may be given explicitly. They are derived for extreme value and logistic responses.

In order to compare the effect of having different response functions on the stationary treatment distributions, the parameters that were used for illustrative purposes in Section 3 for the logistic response function and in Section 4 for the extreme value response function were chosen so that both response functions would agree at $Q(2.5) = 0.10$ and $Q(6.7) = 0.50$. This yields $\alpha = 6.931$ and $\beta = 1.970$ for extreme value responses with $Q(5.15) = 0.33$ and $\alpha = -3.569$ and $\beta = 0.549$ for logistic responses with $Q(5.24) = 0.33$.

When targeting the 10th percentile of the response functions, the resulting stationary treatment distributions agree to 4 decimal points for both up-and-down designs and both extreme value and logistic response functions.

Using BCD I to target the 33rd percentile of the response functions, the stationary treatment distribution has expectation 4.79 when the response function is extreme value and 4.96 when it is logistic, with standard deviations 1.62 and 1.66, respectively. If BCD II is used instead to target the 33rd percentile, the stationary treatment distribution has expectation 4.91 when the response function is extreme value and 5.07 when it is logistic, with standard deviations 1.62 and 1.66, respectively.

Thus, both BCD I and BCD II seem robust with respect to the exact shape of the response function because changing the form of the model while controlling its location and spread has little effect relative to the difference between successive treatments.

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