Up-and-Down Designs
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Chapter 1
The Probability Structure of a Random Walk Rule

In a general first order Markovian procedure, the probability of transiting from dose $x_i$ for the $n$th subject (or cohort of subjects) to dose $x_j$ for the $n+1$st subject (or cohort of subjects) only depends on the dose $x_i$ and the outcome(s) observed for the $n$th subject (cohort) at that dose. A random walk procedure is a first order Markovian procedure in which the next dose assignment is never more than one dose distant from the current assignment. Advantages of these procedures are that they use information from a prior subject or cohort in a very predictable manner which makes them easy to implement and straightforward to explicitly characterize. In addition, random walk procedures are so intuitive that they repeatedly arise spontaneously in many scientific disciplines, so it is important to understand their behavior.

From dose $x_i$, the transition probability in one trial and in $n \geq 0$ trials, respectively, are

$$p_{ik} = P \{ X(n+1) = x_k | X(n) = x_i \}; \quad (1.1)$$
$$p_{ik}(n) = P \{ X(n+1) = x_k | X(1) = x_i \}; \quad (i, k) = 1, \ldots, K. \quad (1.2)$$

Of course, $p_{ik}(0) = \delta_{ik}$, where $\delta_{ik}$ is Kronecker’s delta function, and because the transitions are assumed to follow a random walk, $p_{ij} = 0$ for $|i - j| > 1$. Thus, given the sample space $\mathcal{X} = \{ x_1 < x_2 < \cdots < x_K \}$ and the initial dose $X(1)$, the random walk rule is determined by

1. $p_{ij, j-1}$, the probability of decreasing the dose from $x_j$ to $x_{j-1}$,
2. $p_{ij, j+1}$, the probability of increasing the dose from $x_j$ to $x_{j+1}$, and
3. $p_{jj}$, the probability to performing another trial at $x_j$;
4. $p_{ij, j-1} + p_{jj} + p_{ij, j+1} = 1$ for all $k$.

The transition probabilities $\{ p_{ij, |x_i - x_j| \leq 1} \}$ will depend on the definition of a particular up-and-down rule and on the probability of response at the current dose $x_i$. In theory, the number of doses can be unlimited, but in reality there is a min-
imum \( x_1 \) and a maximum \( x_K \) that are finite and the random walk rule will need special conditions to deal with treatment assignments that would otherwise go outside the boundary to insure that \( p_{i0} = p_{K,K+1} = 0 \). For simplicity, in this chapter the treatment space is assumed to be finite and adjustments at the boundaries are not described explicitly for each rule.

The elements \( \{p_{ij}\} \) comprise the transition probability matrix:

\[
P = \begin{pmatrix}
p_{11} & p_{12} & 0 & \cdots & \cdots & 0 \\
p_{21} & p_{22} & p_{23} & 0 & \ddots & \vdots \\
0 & \ddots & \ddots & \ddots & \ddots & \vdots \\
\vdots & \ddots & \ddots & \ddots & \ddots & 0 \\
\vdots & \ddots & 0 & p_{K-1,K-2} & p_{K-1,K-1} & p_{K-1,K} \\
0 & \cdots & 0 & p_{K,K-1} & p_{K} & p_{KK}
\end{pmatrix}.
\]  

(1.3)

The \((i,k)\) element of \( P^n \) is \( p_{ik}(n) \).

### 1.1 The Asymptotic Treatment Distribution Generated by an Up-and-Down Rule

If the treatment allocation rule allows each dose to be reached, eventually, from every other dose, the matrix \( P \), and hence the up-and-down rule, is called regular. When the transition probabilities \( \{p_{i,i-1}\} \) and \( \{p_{i,i+1}\} \) are non-degenerate functions of an increasing response function \( F(x) \) which is bounded away from 0 and 1 and if at least one \( \{p_{ii}\} \) is nonzero so that the treatment allocation process will not be not periodic, then the treatment allocation rule will be regular.

#### 1.1.1 Consistency and Asymptotic Normality of the Treatment Frequencies.

For regular procedures and any initial treatment distribution \( p \), the asymptotic allocation probabilities \( \lim_{n \to \infty} P^n \{X(n) = x_k\} = w_k \) exist and are unique. [cf. Kemeny and Snell (pp. 70 – 71, [25]) and Karlin and Taylor (pp. 60, 106 – 107, [24])].

The empirical treatment probabilities, \( W_j(n) \), for regular Markov procedures also converge to \( w_j \) as \( n \to \infty \) by the law of large numbers for regular Markov chains. Hence the limiting treatment proportions equal the asymptotic allocation probabilities and \( w \) is called the asymptotic treatment distribution. In addition, \( \lim_{n \to \infty} E(W_j(n)) = w_j, j = 1, \ldots, K \) because \( nW_j(n) \) is a Cesaro sum, and by the central limit theorem for regular Markov chains,
1.2 Deriving the Asymptotic Treatment Distribution from the Transition Probability Matrix.

\[
\sqrt{n}(W_1(n), \ldots, W_K(n) - w) \xrightarrow{n \to \infty} \mathcal{N}(0, \text{diag} (\sigma_1^2(P), \ldots, \sigma_K^2(P))).
\]

So the rate of convergence of \(W_k(n)\) to \(w_k\) is of order \(O(1/\sqrt{n})\) for all \(k\). [The rate of convergence is determined by the second largest eigenvalue in the absolute value of the transition matrix (cf. Mira, 2001 [29]).]

Bortot and Giovagnoli ([7]) present an expression for \(\sigma_k(P)\), the variance of \(W_k\), given in (1.1.1), as a special case of a representation given by Peskun [30]:

\[
\sigma_k(P) = w_k^2 \sum_{i=1}^{K} \frac{1 + \lambda_{ij}}{1 - \lambda_{ij}} \left(v_{k[i]}\right)^2, \quad k = 1, \ldots, K, \tag{1.4}
\]

where \(\lambda_{ij}\) denotes the \(i\)th largest eigenvalue of \(P\) in absolute value and \(v_{k[i]}\) denotes the \(k\)th component of the corresponding normalized left eigenvector of \(P\), \(i, k = 1, \ldots, K\).

1.2 Deriving the Asymptotic Treatment Distribution from the Transition Probability Matrix.

For Markov chains, \(\{w_k\}\) can be written in terms of the elements of \(P\) by solving \(K\) linear equations that describe how each dose can be reached in one step:

\[
\sum_{i=1}^{K} w_i p_{ik} = w_k, \quad k = 1, \ldots, K. \tag{1.5}
\]

These equations are called the balance equations. In the case of random walk rules, the balance equations,

\[
w_k = w_{k-1} p_{k-1,k} + w_k p_{kk} + w_{k+1} p_{k+1,k}, \quad k = 1, \ldots, K,
\]

yield the explicit solution:

\[
w_k = \prod_{j=1}^{k} \lambda_j, \quad \lambda_j = \frac{p_{j,j-1}}{p_{j,j+1}}, \quad k = 2, \ldots, K; \quad \lambda_1^{-1} = 1 + \sum_{k=2}^{K} \prod_{j=2}^{k} \lambda_j. \tag{1.6}
\]

The formula for \(\lambda_1\) standardizes all the asymptotic assignment probabilities so they sum to one.

Define \(\Pi = \text{we}\), where \(\text{e} = (1 \cdots 1)\). Then it can also be shown (pg 22, [25]) that \(P^n - \Pi \to 0\) as \(n \to \infty\), so numerical values of \(w\) for a specific \(P\) can be found using software such as Matlab [2] as follows: multiply \(P\) times itself until all the rows of the resulting matrix are identical to each other to as many decimal places as you care about. Suppose this requires \(P\) to be raised to the \(\tau\)th power. Then each row vector of the resulting matrix \(P^\tau\) is equal to \(w\) to the chosen number of decimal points.
1.3 Unimodality of the Asymptotic Treatment Distribution

Equations (1.6) can be exploited in the development of treatment allocation rules to control the location and spread of the resulting treatment distribution. Durham and Flournoy [14] give conditions under which $w$ will be unimodal:

**Durham-Flournoy Unimodality Condition.** If $\{\lambda_j\}$ decreases with $j$, then $w$ will be unimodal with

$$
\begin{align*}
  w_j < w_{j+1} & \quad \text{so long as } \lambda_j > 1, \\
  & \quad \text{or equivalently, if } p_{j-1,j} > p_{j,j-1}; \\
  w_j = w_{j-1} & \quad \text{if } \lambda_j = 1; \\
  & \quad \text{or equivalently, if } p_{j-1,j} = p_{j,j+1}; \\
  w_j > w_{j+1} & \quad \text{when } \lambda_j < 1 \\
  & \quad \text{or equivalently, if } p_{j-1,j} < p_{j,j+1}.
\end{align*}
$$

(1.7)

If $\lambda_j \geq 1$ for all $j$, $w$ is increasing with mode at the upper boundary of $X$; if $\lambda_j \leq 1$ for all $j$, $w$ is decreasing with mode at the lower boundary of $X$. If $\{\lambda_j\}$ decreases with $j$ and $\lambda_1 \geq 1 \geq \lambda_K$, and the mode of the asymptotic treatment distribution will be

$$
\max\{x_j \in X : p_{j-1,j} \geq p_{j,j-1}\}
$$

(1.8)

Typically, equality cannot be obtained exactly because of the discreteness of $X$, (1.8), but even when $x_j : p_{j,j-1} = p_{j,j+1}$ is not in $X$, this equality provides a very useful approximation that is used to construct rules that have treatment modes in prespecified locations.

If there is one or more $j$ for which the equality $\lambda_j = 1$ holds exactly, the mode of the treatment distribution will be comprised of the corresponding collection of doses. Then the set of adjacent doses that are equally most frequent is called the modal set.

The mode is not a commonly used measure of central tendency, but in the case of random walk rules, it is useful because it can be explicitly linked to quantiles of the response function. However, for the mode, or modal set, to be useful as a measure of central tendency, the treatment distribution for the particular treatment allocation rule must be shown to be unimodal. To determine unimodality, the Durham-Flournoy condition (1.7) may be applied. Another feature of random walk rules that makes the asymptotic mode useful is the exponential rate of convergence of the trial frequencies to the asymptotic proportions as described in section (1.4). See [23].

1.4 Expected Trial Frequencies

Various functions of the treatment moments may be of interest in a particular application, such that the expected number of subjects treated at a high dose level.
The results in this section and the next can be used to find exact expressions for the mean and variance of these functions. Illustrations are given in sections for specific allocation rules.

For notational simplicity, the subscript \( p \) in \( P_i(\cdot), E_i(\cdot) \), etc., indicates that the probabilities and expectations are taken with respect to the distribution \( p \) of \( X(1) \); in the special case in which the initial dose is not random (i.e., \( p \) is degenerate), the subscript \( i \) indicates that the probabilities are conditional on a fixed initial dose \( X(1) = x_i \). The expected relative treatment frequencies are

\[
E_i(W_k(n)) = \frac{1}{n} E\left( \sum_{m=1}^{n} I(X(m) = x_k | X(1) = x_i) \right) \\
= \frac{1}{n} \sum_{m=1}^{n} p_{ik}(m) = \frac{1}{n} \left( \delta_{ik} + \sum_{m=2}^{n} p_{ik}(m) \right), \quad k = 1, 2, \ldots, K. \quad (1.9)
\]

Let \( \tilde{W}(n) \) denote the \( K \times K \) dimensional matrix with \( i \)th row vector \( E_i(W(n)) \). Then

\[
E_p(W(n)) = \sum_{i=1}^{K} E_i(W_k(n)) p_i(1), \quad \text{or}
\]

\[
E_p(W(n)) = p(1) \tilde{W}(n)
\]

when \( X(1) \) is random with probability distribution \( p(1) \). When the initial distribution is the asymptotic distribution, (1.4) becomes \( E_w(W(n)) = \Pi \), where \( \Pi \) the \( K \times K \) matrix whose rows are all \( w \).

By the Markov property of the allocation rules, (1.9) can be expressed as a recursion for serial computation:

\[
nE_i(W_k(n)) = p_{ik}(1) + \sum_{m=2}^{n} \sum_{l=1}^{K} p_{il} p_{lk}(m - 1) \\
= \delta_{ik} + \sum_{l=1}^{K} p_{il} \sum_{m=2}^{n} p_{lk}(m - 1) \\
= \delta_{ik} + \sum_{l=1}^{K} p_{il} \sum_{m=1}^{n} p_{lk}(m) \\
= \delta_{ik} + (n - 1) \sum_{l=1}^{K} p_{il} E_i(W_k(n - 1)), \quad k = 1, \ldots, K.
\]

Expressing this recursion in matrix notation is useful for computing with software such as Matlab:

\[
nW(n) = I + P\tilde{W}(n - 2) \\
= I + P + P^2 + \cdots + P^{n-2} + P^{n-1}.
\]
1.5 A Graphical Tool for Evaluating when n is Large Enough for Asymptotic Approximations

Because \( \Pi = w^T e \), where \( e = (1 \cdots 1) \), \( \Pi^n = \Pi \) for all \( n \), and since \( P^n - \Pi \to 0 \) as \( n \to \infty \), it follows (see Kemeny and Snell (pg 22, [25])) that

\[
\lim_{n \to \infty} n(W(n) - \Pi) = \lim_{n \to \infty} \left( I + \sum_{m=1}^{n} (P^m - \Pi) \right) = (I + (P - \Pi))^{-1}.
\]

(1.10)

The matrix

\[
Z = (z_{ik}) = (I + (P - \Pi))^{-1}
\]

is called the fundamental matrix for regular Markov chains. It follows from (1.10), that when any particular starting level is chosen, say \( i \), \( nE_i(W_k(n)) - nw_k \to z_{ik} - w_k \) as \( n \to \infty \). Thus for large \( n \),

\[
E_i(W_k(n)) \approx \frac{z_{ik} + nw_k}{n}.
\]

(1.11)

To calculate 1.11, use the definition of a particular up-and-down design to calculate the transition probabilities \( \{p_{ij}\} \); then use (1.6) to calculate the asymptotic treatment distribution \( w \) which are the rows of \( \Pi \). \( Z \) can then be calculated using a standard matrix inversion routine.

Furthermore, it follows from (1.4) and (1.10) that for any initial distribution \( p(1) \),

\[
\lim_{n \to \infty} E_p n(W(n) - \Pi) = \lim_{n \to \infty} np(1) \sum_{m=1}^{n} (P^m - \Pi) = p(1)(Z - \Pi) = p(1)Z - \Pi.
\]

(1.12)

By (1.10) for large \( n \), the difference between \( E_n(W_k(n) - nw_k) \) is approximately equal to the constant \( z_{ik} - w_k \). Thus a plot of \( E_i(N_k(n) - nw_k) \) by \( n \) approaching this constant can serve as a tool for deciding when large sample approximations will be satisfactory.

1.6 Covariances between Trial Frequencies on Different Treatments

When the initial dose is fixed at \( x_i \), the covariances between trial frequencies are sums over trials of the covariances between doses, and the covariances between doses can be calculated from the transition probabilities. After \( n \) trials when \( X(1) \) was fixed at \( x_i \), the covariances between trial frequencies for \( n \geq 1 \) at levels \( k, l = 1, \ldots, K \) are
where the covariance between using dose $x_k$ at trial $s$ and $x_l$ at trial $t$ is

$$\text{Cov}_t(W_k(n), W_l(n)) = \frac{1}{n^2} \sum_{s=1}^{n} \sum_{t=1}^{n} \text{Cov}_t(I(X(s) = x_k), I(X(t) = x_l)),$$

where the covariance between using dose $x_k$ at trial $s$ and $x_l$ at trial $l$ is

$$\text{Cov}_l(I(X(s) = x_k), I(X(t) = x_l))$$

$$= \begin{cases} 
\mu_{k}(s-t)\mu_{l}(t) - \mu_{k}(s)\mu_{l}(t) & \text{if } s > t, \\
\mu_{l}(t-s)\mu_{k}(s) - \mu_{l}(s)\mu_{k}(t) & \text{if } s < t, \\
\mu_{l}(t)\delta_{ik} - \mu_{l}(t) & \text{if } s = t.
\end{cases}$$

Then for any trial $n \geq 1$ when $X(1)$ is selected with probability $p(1)$,

$$\text{Cov}_p(W_k(n), W_l(n)) = \frac{1}{n^2} \sum_{s=1}^{n} \sum_{t=1}^{n} \text{Cov}_p(I(X(s) = x_k), I(X(t) = x_l)),$$

where the covariance between using dose $x_k$ at trial $s$ and $x_l$ at trial $l$ is

$$\text{Cov}_p(I(X(s) = x_k), I(X(t) = x_l))$$

$$= \begin{cases} 
\mu_{k}(s-t)\mu_{l}(t) - \sum_{i=1}^{K} \mu_{i}(s)\mu_{l}(t)\mu_{l}(1) & \text{if } s > t, \\
\mu_{l}(t-s)\mu_{k}(s) - \sum_{i=1}^{K} \mu_{i}(s)\mu_{l}(t)\mu_{l}(1) & \text{if } s < t, \\
\sum_{i=1}^{K} \mu_{l}(t)\delta_{ik} - \mu_{l}(t)\mu_{l}(1) & \text{if } s = t.
\end{cases}$$

To evaluate large sample properties of these covariances it is helpful to define a $K \times K$ matrix $C$ with elements

$$c_{kl} = \lim_{n \to \infty} n\text{Cov}_W(W_k(n), W_l(n)).$$

Since $\lim_{n \to \infty} E_p(\cdot) = \lim_{n \to \infty} E_W(\cdot)$ for all initial treatment distributions $p(1)$, for $n$ sufficiently large it is sufficient to consider $X(1)$ to be random with asymptotic probability distribution $W$. Thus $c_{kl}$ provides a large sample approximation to $n\text{Cov}_p(W_k(n), W_l(n))$ that is independent of $p(1)$.

Let $D = \text{diag}(w_1, w_2, \ldots, w_K)$. Expressing $c_{kl}$ in terms of the asymptotic probabilities and the fundamental matrix (1.10) makes them easily computable:

$$C = D - w'w + D_w(Z - I) + (Z' - I)D_w.$$

A proof of this relationship can be found in Kemeny and Snell [25]. So a tractable large sample approximation to $\text{Cov}_W(W_k(n), W_l(n))$ that is independent of $p(0)$ is suggested by (1.6), namely,

$$\text{Cov}_W(W_k(n), W_l(n)) \approx c_{kl}/n.$$
1.7 A Graphical Tool for Determining when n is Large Enough for Asymptotic Results to Hold.

Durham, Flournoy and Montazer-Haghighi [16] showed that the increment in the covariance between treatment frequencies is approximately constant for large \( n \):

\[
n^2 (\text{Cov}_W (W_k(n+1), W_l(n+1)) - \text{Cov}_W (W_k(n), W_l(n))) \rightarrow c_{kl} \text{ as } n \rightarrow \infty \tag{1.13}
\]

This greatly simplifies the required recursive computation for large \( n \). It also provides a tool for determining when the large sample approximation in (1.6) is suitable in that the number of trials required can be read off from where a plot of the increment versus \( n \) approaches a constant.
Chapter 2
Up-and-Down Rules

2.1 The Classical Up–and–Down Rule for Estimating $x_{0.50}$

Given $X(n) = x_j$, the $n + 1$st treatment assignment is

$$X(n + 1) = \begin{cases} x_{j-1} & \text{if } Y(n) = 1; \\ x_{j+1} & \text{if } Y(n) = 0. \end{cases}$$

$j = 2, \ldots, K - 1$. On the interior of $\mathcal{X}$, this rule is periodic, but the rule can easily be made regular with the adjustments at the boundaries. For example, the adjustments

$$X(n + 1) = \begin{cases} x_1 & \text{if } Y(n) = 1 \text{ and } X(n) = x_1 \\ x_K & \text{if } Y(n) = 0 \text{ and } X(n) = x_K \end{cases}$$

allow all doses to be reached by every other dose eventually.

The transition probabilities on the interior of $\mathcal{X}$ are

$$p_{j,j-1} = P\{Y(n) = 1|x_j\}$$
$$p_{j,j+1} = P\{Y(n) = 0|x_j\}.$$ 

When $F(x) = P\{Y(n) = 1|x\}$ is a nondecreasing function for $x \in \mathcal{X}$, then $\{\lambda_j = (1 - F(x_j))/F(x_j)\}$ (1.6) is a non-increasing function and so, by (1.7), the asymptotic treatment distribution is unimodal. Furthermore, by (1.8), the mode of the treatment distribution is $\max\{x_j : F(x_j) \geq 1 - F(x_j)\}$, or approximately the solution to the equation $F(x) = 1 - F(x)$. So the Classical Up-and-Down Rule will cluster treatments around $x_q : q = 0.50$.

This rule was studied independently by Wilson and Worester (1943) [37] and [36], Von Békésy (1947) [6] and Dixon and Mood (1948) [12] who were involved with bioassays, experiments of biophysical reactions and explosives testing, respectively. This classical procedure is still being used [10] in explosives testing just as when it first came to the attention of Dixon and Mood. Other recent applications include fatigue testing in metallurgy and material science [28], testing restorative
dental materials [32], estimation of breakdown voltages [26] and animal toxicity [13].

Animal laboratories resisted adopting $UD(1, 0, 1)$ to estimate $x_{0.50}$ for classifying toxic substances for labeling purposes. They argued that it was too burdensome to handle animals individually, until toxicologists at Proctor and Gamble began experimenting with the procedure. Enthusiastic reports by Bruce (1985, 1987)[9], [8] and Yam, Reer and Bruce (1991) [38] stimulated the application of this procedure and it was presented to the European Union Ministry of Public Health and the Environment, together with start-up and stopping rules, for consideration by Bonnyns, Delcour and Vral (1990) [1].

In the United States, Proctor and Gamble scientists worked with the Environmental Protection Agency (EPA) to bring $UD(1, 0, 1)$, with starting and stopping rules, to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for evaluation. ICCVAM’s mission is to facilitate development, validation and regulatory acceptance of new and revised regulatory test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment. Members of ICCVAM include the Agency for Toxic Substances and Disease Registry, the Consumer Product Safety Commission, the Departments of Agriculture, Defense, Energy, Interior, Transportation, the EPA, the Food and Drug Administration, the National Cancer Institute, National Institute of Environmental Health Sciences, National Institute of Occupational Safety and Health the National Institutes of Health (Offices of Scientific Affairs and Laboratory Animal Welfare), the National Library of Medicine and the Occupational Safety and Health Administration. ICCVAM convened a working group to draft guidelines for use of the up-and-down method, including start-up and stopping rules, for applications spread across the purviews of the committees’ members.

The 2001 final report, following revisions incorporating suggestions made by a peer panel and a public meeting, is cited in the references along with the background review document. The EPA organized training sessions and on-line aids for toxicologists. Concerns about the burden of sequentially handling individual animals were not borne out, and the up-and-down method has reportedly become the method of choice for acute oral toxicity testing among chemical toxicologists.

2.2 Biased Coin Rules

In many experimental settings, including single center clinical trials, assigning treatments to subjects one at a time may be natural and/or necessary. Strategies that make use of a biased coin to shift the mode of the treatment distribution to cluster treatments around an arbitrary were proposed by Derman [11], Durham and Flournoy [14], [15], [17], Durham, Flournoy and Rosenberger [18] and generalized by Giovagnoli and Pintacuda (1998) [23], [7].
2.2 Biased Coin Rules

For dose-finding in clinical toxicity studies, Derman’s rule [11] reduces a dose following a toxic response, which is unappealing. Durham and Flournoy [14] eliminated this feature. In presenting several up-and-down strategies, they exemplified how to use the balance equations to control the treatment distribution. They are given here for the same purpose. Each procedure assumes subject \( n \) has received dose \( x_j, j = 2, \ldots, K \) and that appropriate adjustments to the rule are made at \( K = 0 \) and 1.

2.2.1 Derman’s BCR.

Derman [11] employed Markov chain theory to theoretically validate the performance of the classical up-and-down rule. While doing so, he generalized it to cluster doses around an arbitrary \( x_q \).

Derman’s procedure can be conceptualized with the introduction of a coin with \( P(\text{heads}) = b \): If \( X(n) = x_j \), then

\[
X(n+1) = \begin{cases} 
  x_{j-1} & \text{if } Y(n) = 1 \text{ and a coin flip results in heads;} \\
  x_{j+1} & \text{if } Y(n) = 1 \text{ and a coin flip results in tails;} \\
  x_j & \text{or } Y(n) = 0.
\end{cases}
\]

The transition probabilities from \( \{x_j\} \) on the interior of \( \mathcal{X} \) are

\[
p_{j,j-1} = P\{Y(n) = 1 | X(n) = x_j \} P(\text{heads}) = F(x_j)b \\
p_{j,j+1} = P\{Y(n) = 1 | X(n) = x_j \} P(\text{tails}) + P\{Y(n) = 0\} = 1 - F(x_j)b.
\]

If \( F(x_j) = P\{Y(n) = 1 | x_j\} \) is nondecreasing in \( j \), the Durham-Flournoy unimodality condition holds, that is, \( p_{j,j-1}/p_{j,j+1} = bF(x_j)/[(1 - F(x_j))] \) is nonincreasing. So the asymptotic treatment distribution is unimodal with mode at \( \max\{x_j : bF(x_j) \geq [(1 - bF(x_j))]\} \). By (1.8), the mode of the treatment distribution is approximately located where the probability of increasing the dose equals the probability of decreasing the dose. That is, the mode is approximately the solution to the equation

\[
F(x) b = F(x) (1 - bF(x)).
\]

So if the coin has bias \( b = 0.50q^{-1} \), the treatment mode will be approximately \( x_q, 0.50 \leq q < 1.0 \).

A reflection of the procedure produces modes near \( x_q \) for \( q, 0 < q \leq 0.50 \):

\[
X(n+1) = \begin{cases} 
  x_{j-1} & \text{if } Y(n) = 1; \\
  x_j & \text{or } Y(n) = 0 \text{ and a coin flip results in tails;} \\
  x_{j+1} & \text{if } Y(n) = 0 \text{ and a coin flip results in heads.}
\end{cases}
\]

In this case, (1.8) is
1 − P\{no response & heads\} = P\{no response & heads\},

or approximately, 1 − (1 − F(x))b = (1 − F(x))b. So setting $b = 0.5(1 − q)^{-1}$ with this reflected rule clusters doses around $q, 0 < q ≤ 0.50$.

### 2.3 Durham & Flournoy’s BCR

Unaware of Derman’s BCR, Durham and Flournoy rediscovered how to use a biased coin to shift the treatment distribution around the target quantile, and proposed [14] the following procedure: Let a coin have $P\{\text{heads}\} = b$. The $(n + 1)$th subject is assigned as

\[
X(n + 1) = \begin{cases} 
  x_{j-1} & \text{if } Y(n) = 1; \\
  x_{j+1} & \text{if } Y(n) = 0 \& \text{heads}; \\
  x_j & \text{if } Y(n) = 0 \& \text{tails.}
\end{cases}
\]

So if $F(x_j) = P\{Y(n) = 1|x_j\}$ is non-increasing, $\lambda_j = F(x_j)/[b(1 − F(x_j))]$ is non-increasing assuring that the asymptotic treatment distribution is unimodal. By (1.8), the mode is $x_j : F(x_j) = b(1 − F(x_j))b$ if such an $x_j$ exists and setting $b = q/(1 − q)$ causes the asymptotic treatment mode to be approximately $x_q, 0 < q ≤ 0.5$.

The procedure can be reflected for $q : 0.5 < q ≤ 1.0$:

\[
X(n + 1) = \begin{cases} 
  x_{j-1} & \text{if } Y(n) = 0; \\
  x_{j+1} & \text{if } Y(n) = 1 \& \text{heads}; \\
  x_j & \text{if } Y(n) = 1 \& \text{tails.}
\end{cases}
\]

and setting $b = (1 − q)/q$ yields $q$ an asymptotic treatment mode near $x_q, q : 0.5 < q ≤ 1.0$.

Durham, Flournoy and Montazer-Haghighi [17] provide an example of using exact treatment moments of treatment frequencies to calculate (without simulation) the probability of treating at high doses. An expository presentation of BCD with illustrations is given by Durham, Flournoy and Rosenberger [18].

### 2.3.1 Asymptotic Treatment Distribution of BCR with a Logistic Response Function

Additional characteristic of the asymptotic treatment distribution are obtained when the the probability of positive response follows a logistic distribution function, i.e., $1 − F(x) = (1 + \exp(\alpha + \beta x))^{-1}$ and doses are equally spaced: $\mathcal{X} = \{x_1 < x_1 + \Delta, x_1 + 2\Delta < \cdots < x_K\}$. 

Definition 2.1. Let $Z$ be a random variable that is defined on a set of discrete real valued points, namely, $\mathcal{X}$. Let $\phi(z)$ denote $P\{Z = z\}$. Then $Z$ is said to have a Discrete Normal Distribution if

$$
\phi(z_j) = \frac{\exp\left(-\frac{1}{2}z_j^2\right)}{\sum_{k=1}^{K} \exp\left(-\frac{1}{2}z_k^2\right)}, \quad z_k \in \mathcal{X}.
$$

(2.1)

Durham and Flournoy [14] show that the asymptotic treatment distribution is a mixture of two discrete normal distributions for which the mixing parameter is $q$. In particular,

$$
w_j = \lim_{n \to \infty} \frac{W_k(n)}{n} = (1-q)\phi\left(\frac{x_j - (x_q - 0.5\Delta)}{\sigma}\right) + q\phi\left(\frac{x_j - (x_q + 0.5\Delta)}{\sigma}\right),
$$

(2.2)

where $\sigma = \Delta/\beta$. Note that the modes of the two discrete normal distributions are separated only by one stepsize $\Delta$. If $q = 0.5$, the component discrete normal distributions are equally weighted. Whereas if $q$ is very small, the asymptotic distribution is dominated by a single discrete normal distribution. Because many common response function models are very similar, except in the extreme tails, this result will hold in general, approximately, and it provides insight into the treatment distributions to be expected when running BCR. In addition, the asymptotic treatment probabilities can be written as a mixture of treatment probabilities conditioned on the responses:

$$
w_j = (1-q)P\{X(n) = x|Y(n) = 0\} + qP\{X(n) = x|Y(n) = 1\}, \quad j = 1, \ldots, K.
$$

In general, the mode of $\{w_j\}$ is bounded within $x_q \pm \Delta$. But as a consequence of (2.2), the difference between the mode of $\{w_j\}$ and $x_q$ can be bounded more tightly. Let $\kappa = \max\{j \lambda_j > 1\}$. Then $x_q$ is bounded as

$$
x_{\kappa} - \Delta < x_q < x_{\kappa} + 0.5\Delta, 0.0 \leq q \leq 0.5
$$

$$
x_{\kappa} - 0.5\Delta < x_q < x_{\kappa} + \Delta, 0.5 \leq q \leq 1.0.
$$

Controlling the Spread of the Asymptotic Distribution

The spread of the treatment distribution can be controlled by the selection of $\Delta$ as given by [14], cf. [18].

2.3.2 Durham & Flournoy’s, (1995) BCD-II

To show there are multiple ways to use a biased coin in the treatment allocation procedure to shift the treatment distribution around the desired target quantile, Durham and Flournoy [15] describe BCD-II: Let a coin have $P\{\text{heads}\} = b$. The $(n+1)$st subject is assigned as
\[ X(n+1) = \begin{cases} x_{j-1} & \text{if } Y(n) = 1 \text{ & tails;} \\ x_{j+1} & \text{if } Y(n) = 0 \text{ & heads;} \\ x_j & \text{if } Y(n) = 1 \text{ & heads.} \end{cases} \]

By (1.8), the asymptotic treatment mode is the solution to \( P\{Y(n) = 1|X(n) = x_j\} = P\{\text{tails}\} = P\{\text{heads}\} \), which is approximately \( F(x)(1-b) = b \). So fixing the coin bias at \( b = q/(1+q) \) will cluster treatments around \( x_q, 0 < q \leq 0.5 \). The procedure can be reflected for 0.5 \( q < 1.0 \).

### 2.3.3 Durham, Flournoy & Rosenberger’s BCD

Another example is provided by Durham, Flournoy, and Rosenberger [20]. Let a coin have \( P\{\text{heads}\} = b \). The \((n+1)\)st subject is assigned as

\[ X(n+1) = \begin{cases} x_{j-1} & \text{if tails;} \\ x_{j+1} & \text{if } Y(n) = 0 \text{ & heads;} \\ x_j & \text{if } Y(n) = 1 \text{ & heads.} \end{cases} \]

The asymptotic treatment mode is \( \max\{x_j\} : P\{\text{tails}\} \geq P\{Y(n) = 0|X(n) = x_j\} P\{\text{heads}\} \), which is approximately \( x : (1-b) = (1-F(x))b \). So fixing the coin bias at \( b = 1/(2-q) \) will cluster treatments around \( x_q, 0 < q \leq 0.5 \) and the procedure can be reflected for larger \( q \).

### 2.3.4 Bortot & Giovagnoli’s Generalized BCD

Because there is so much flexibility in constructing biased coin designs that will cluster treatments around \( x_q \), Bortot and Giovagnoli [7] developed a generalized approach in order to study their properties: Let there be two coins having \( P\{\text{heads}\} \) equal to \( b_1 \) and \( b_2 \). Then

\[ X(n+1) = \begin{cases} x_{j-1} & \text{if } Y(n) = 1 \text{ and coin 1 yields heads;} \\ x_{j+1} & \text{if } Y(n) = 0 \text{ and coin 2 yields heads;} \\ x_j & \text{if } Y(n) = 1 \text{ and coin 1 yields tails or } Y(n) = 0 \text{ and coin 2 yields tails.} \end{cases} \]

The mode of the treatment distribution is

\[ \max\{x_j\} : P\{Y(n) = 1|X(n) = x_j\} b_1 \geq P\{Y(n) = 0|X(n) = x_j\} b_2, \quad (2.3) \]
2.4 A Second Order Biased Coin Rule

Bortot and Giovagnoli ([7]) developed a second order Markovian up-and-down rule in which the next dose allocation is based on the last two outcomes. This procedure uses more information than do the first order random walk rules, but retains the elegant Markov chain theory for characterizing the procedure and for analyzing options. Because Durham and Flourney’s BCD has superior performance characteristics to other BCD, Bortot and Giovagnoli provide a natural extension of it. Let two coins have \( P\{\text{heads}\} \) equal to \( b_1 \) and \( b_2 \). For \( 0 < q \leq 0.5 \),

\[
X(n+1) = \begin{cases} 
  x_{j+1} & \text{if } Y(n) = 0, Y(n-1) = 0 \text{ and coin 1 yields heads} \\
  x_{j-1} & \text{if } Y(n) = 1 \\
  x_j & \text{else}
\end{cases}
\]

Bortot and Giovagnoli derive the asymptotic treatment distribution which is unimodal for increasing \( F(x) \) by the Durham-Flourney condition and, if \( (1-q)b_1 + qb_2 = q/1-q \), then the treatment mode \( x_M \) is such that \( x_{M-1} < x_q \leq x_{M+1} \).

Their simulations reinforce the value of Durham and Flourney’s BCD, in that adding the information from an additional prior subject did not provide much enhancement in performance.
2.5 Randomized Biased Coin Rules

The fully sequential biased coin designs require responses to be observed for a subject before the next one can be treated. One way to gather information faster is to run parallel up-and-down procedures. Flournoy [19] proposed the use of an urn model to integrate such parallel trial runs. This strategy is also useful when clinical trials are performed at different locations.

2.6 Group Random Walk Rules

Sometimes it is inconvenient to treat individual subjects sequentially and other times there is resistance to assigning dose in a way that relies on the flip of a coin. Group up-and-down rules are viable alternatives in these circumstances. Tsutakawa [33] and [34] analyzed group up-and-down rules with the goal of estimating \( q = 0.50 \). These were generalized for a large class of quantiles by Gezmu and Flournoy [22].

Let subjects be treated in cohorts of size \( s \). Let \( Y(m) \) be the number of positive responses in the \( m \)th cohort. Let \( c_L \) and \( c_U \) be two integers such that \( 0 \leq c_L < c_U \leq s \). Given the \( m \)th cohort is treated at \( X(m) = x_j \) on the interior of \( \mathcal{X} \), the \( m+1 \)st cohort of \( s \) subjects is assigned to

\[
X(m+1) = \begin{cases} 
  x_{j-1} & \text{if } Y(m) \geq c_U; \\
  x_{j+1} & \text{if } Y(m) \leq c_L; \\
  x_j & \text{if } c_L < Y(m) < c_U.
\end{cases}
\]  

(2.4)

Given the \( m \)th cohort is treated at \( X(m) = x_j \) on the interior of \( \mathcal{X} \), \( Y(m) \) has a binomial distribution with parameters \( s \) and \( q_0 \). So the transition probabilities are the tails of this binomial distribution:

\[
p_{j,j-1} = \sum_{r=c_L}^{s} \binom{s}{r} F(x_j)^r (1 - F(x_j))^{s-r} \\
= \frac{\int_0^c \mu^{c_L} (1 - \mu)^{s-c_L} d\mu}{\int_0^c \sum_{r=0}^{c_L} \mu^{c_L} (1 - \mu)^{s-c_L} d\mu}
\]

\[
p_{j,j+1} = \sum_{r=0}^{c_L} \binom{s}{r} F(x_j)^r (1 - F(x_j))^{s-r},
\]

where the second equality in the expression for \( p_{j,j-1} \), following from the relationship between the binomial distribution and the incomplete beta function (cf. Abramowitz and Stegun, 1964 [4]), shows that \( \{p_{j,j-1}\} \) increases with \( j \). Then \( \{p_{j,j+1}\} \) decreases with \( j \) and the Durham-Flournoy condition for unimodality is met. Because the treatment mode is \( \max_j : p_{j,j-1} \geq p_{j,j+1} \), any combination of \( c_L \), \( c_U \) and \( s \) such that
2.6 Group Random Walk Rules

\[ \sum_{r=c_U}^{s} \binom{s}{r} q^r (1-q)^{s-r} = \sum_{r=0}^{c_L} \binom{s}{r} q^r (1-q)^{s-r}, \]  

(2.5)

will cause the treatment distribution to be unimodal with mode approximately \( x_q \).

Ivanova, Flournoy and Chung [5] give an alternate proof of unimodality. This design is denoted \( UD(s,c_L,c_U) \).

Gezmu and Flournoy [22] and Ivanova, Flournoy and Chung [5] table combinations of \( s, c_L, \) and \( c_U \) with the values of \( q \) satisfying (2.5). They are easy to recreate from this equation.

For example, the rule is to go up if all responses in the cohort are negative and go down if one or more is positive, then the balance equation becomes

\[ q = \sqrt[3]{1/2}. \]  

(2.6)

The only fully sequential version of the \( UD(s,c_L,c_U) \) is \( UD(1,0,1) \) which clusters subjects around \( q = 0.50 \), which can also be targeted by, for example, \( UD(3,1,2), UD(3,0,3), UD(4,1,3), UD(4,0,4), UD(5,2,3), UD(5,1,4), UD(5,0,5), UD(6,2,4), UD(6,1,5) \) and \( UD(6,0,6) \). Tradeoffs in such choices between designs are conjectured and illustrated by Gezmu and Flournoy (2005).

### 2.6.1 The 3+3 Rule

The 3+3 Rule (Korn et al, 1994 [27]) can be viewed as a truncated mixture of two group up-and-down designs. \( X(m) \) denotes the dose assigned to the \( m \)th cohort of 3 subjects.

1. Begin at a safe dose: \( X(1) = x_1 \).
2. If \( X(m) = x_j \),

\[
X(m+1) = \begin{cases} 
  x_{j+1} & \text{if 0 of 3 subjects respond positively; go to 2;} \\
  x_j & \text{if 1 of 3 subjects respond positively; go to 3;} \\
  \text{stop the trial} & \text{if at least 2 of 3 have responded positively.}
\end{cases}
\]

3. Evaluate an additional cohort of 3 patients at \( x_j \):

\[
X(m+2) = \begin{cases} 
  x_{j+1} & \text{if 1 of 6 respond positively; go to 2} \\
  \text{stop the trial} & \text{if at least 2 of 6 respond positively.}
\end{cases}
\]

(2.7)

When the trial is stopped, say at \( x_k, \hat{x}_q = x_{k-1} \).

Some protocols make the following modification: if only 3 patients were evaluated at selected dose, then an additional 3 are entered, and that process proceeds downward if at least 2 of the 6 respond positively.
This design can be constructed as a combination of and with a change over rule and a stopping rule. Reiner, Paoletti and O’Quigley (1999) [31] analyzed this design and concluded that ”the risk of choosing an incorrect level is large”.

2.6.2 A Biased Coin Group Up-and-Down Rule


2.6.3 Comparing Group Designs

There can be several group designs with the same group size $s$ to use for the same target toxicity rate. Both $UD(6,1,2)$ with target $q = -0.264$ and $UD(6,0,3)$ with target $q = -0.264$ can be used when the target toxicity rate is $q^* = 0.25$. Alternatively, $UD(6,2,4)$ and $UD(6,1,5)$ both target $q^* = 0.50$. Guidelines for selecting the best decision rule given a fixed cohort size are needed.

Because a group design induces a Markov chain on $\mathcal{X}$, Markov chain theory suggests some measures of comparison

- the ”peakedness” of the asymptotic distribution

- the rate of convergence to the asymptotic distribution

For two designs with asymptotic distributions and $\mathbf{w}$ and $\mathbf{w}$ with the same mode, Giovagnoli and Pintacuda, [23] define $\mathbf{w}$ to be ”more peaked”, if it grows more quickly to the left of the mode and decreases more quickly to the right of the mode. That is, if the mode is at $x_j$, $\bar{w}_i/\bar{w}_{i-1} \geq w_i/w_{i-1} \geq 1$ for $i = 1,\ldots,j$, and $\bar{w}_{i+1}/\bar{w}_i \geq w_{i+1}/w_i \leq 1$ for $i = j,\ldots,K$.

Both the peakedness and the rate of convergence to a asymptotic distribution for a group design depend on $F(x)$. Thus we suggest comparing two group rules that approximately the same treatment modes in a trial with $K$ dose levels by assuming a large number (for example 10,000) of different scenarios $\{F(x_j), j = 1,\ldots,K\}$ and summarizing the results. To simplify the comparison, Ivanova et al. constructed scenarios in such a way that one of the possible doses in $\mathcal{X}$ has positive response rate exactly equal to $q$.

For the majority of group rules studied by Gezmu and Flournoy [22] and Ivanova, Flournoy and Chung [5], the rule that converges faster has a asymptotic distribution that is less peaked. So Ivanova et al. based their comparisons on a finite sample statistic instead. For each scenario, they compared rules based on the expected proportion of subjects assigned to $x_q$ in a trial with $n$ cohorts, with a uniform initial treatment distribution $\mathbf{p}$. 
2.7 A-B rules

The measure is calculated (not simulated) by averaging the elements of the matrix \((I + P + \cdots + P^{n-1})/n\) in the column corresponding to the location of \(x_q\), where \(P\) is the transition matrix for the scenario (2.8) and \(I\) is an identity matrix. This produces an average over all possible “starting” doses which, when averaged over all 10,000 scenarios, is called the average expected proportion allocated to \(q\).

This summary characteristic was used to select group rules for construction of the cumulative cohort design [5]. The choice of the total number of groups, \(n\), to use in each trial is guided by the number of doses \(K\). One wants \(n > K - 1\) so that dose allocations can move from one level to the other levels even if these levels are far apart. Ivanova, et al took \(n = K\). Scenarios were generated with the \(x_q\) being equally likely at any of the \(K\) treatment levels. That is, about \(1/K\) of all scenarios had \(q\) at \(x_1\), \(1/K\) scenarios at \(x_2\), etc. Let \(q_{\text{max}}\) denote expert opinion regarding the maximum possible positive response rate at \(x_K\). Positive response rates below \(x_q\) were generated as ordered uniform random variables on \((0,q)\), and above \(q\) as ordered uniform random variables on \((q,q_{\text{max}})\) with \((q < q_{\text{max}} \leq 1)\). For example, if \(x_q\) for a particular scenario was \(x_2\), the positive response rate at \(x_1\) was generated as the uniform random variable on \((0,q)\), and positive response rates at \(x_3, \ldots, x_K\) were generated as \(K - 2\) ordered uniform random variables on \((q,q_{\text{max}})\).

Ivanova et al.[5] compared group rules with \(K = 6\) equally spaced doses. For all possible group rules producing treatment modes approximately \(x_{0.25}\) with each cohort size \(s = 3, \ldots, 25\), the average expected proportion of subjects allocated to \(x_q\) was computed. The group rule with the largest average expected proportion allocated to \(x_q\) for \(s = 3, \ldots, 25\) are

\[
\begin{align*}
\text{UD(3,0,2)}, & \quad \text{UD(4,0,2),UD(5,0,2)}, \quad \text{UD(6,0,3),UD(7,1,3)}, \\
\text{UD(8,1,3)}, & \quad \text{UD(9,1,4),UD(10,1,4)}, \quad \text{UD(11,1,4),UD(12,1,5)}, \\
\text{UD(13,2,5)}, & \quad \text{UD(14,2,5),UD(15,2,6)}, \quad \text{UD(16,2,6),UD(17,2,6)}, \\
\text{UD(18,2,7)}, & \quad \text{UD(19,3,7),UD(20,3,7)}, \quad \text{UD(21,3,8),UD(22,3,8)}, \\
\text{UD(23,3,8)}, & \quad \text{UD(24,4,8,UD(25,4,9))}.
\end{align*}
\]

For example, \(\text{UD(6,0,3)}\) and \(\text{UD(6,1,2)}\) are the only two group designs with \(s = 6\) and modes close to \(x_{0.25}\). The average expected proportion allocated to the treatment mode using \(\text{UD(6,0,3)}\) and \(\text{UD(6,1,2)}\) are 0.28 and 0.26, respectively. Hence \(\text{UD(6,0,3)}\) is said to be the best group rule for \(x_{0.25}\) and \(s = 6\).

2.7 A-B rules

To be added.
2.8 \( k \)-in-a-Row Rules

There is new information on this, including a recent dissertation by A. Oron, University of Washington. So this material is very incomplete.

From the balance equations for the classical \( UD(1,0,1) \), Wetherill [35] inferred that the asymptotic treatment distribution was approximately symmetric over equally spaced treatment levels, and hence that \( \lim_{n \to \infty} E(W(n)) = 0.50 \). Aiming to shift the treatment distribution to center around other quantiles, Wetherill proposed so called transformed rules in which changes in treatment levels are determined by a consecutive series of observations at the current \( x_j \).

Let \( T(F(x)) \) denote a monotonic transformation of the response function. Then, Wetherill argued, the average treatment level allocated by a rule for which \( p_j, j - 1 = T(F(x_j)) \) and \( p_j, j + 1 = 1 - T(F(x_j)) \) will be approximately equal to

\[ x : T(\{F(x)\}) = 0.50. \]

The most popular such transformation yields the \( k \)-in-a-row rule in which exactly \( k \) consecutive successes must be observed before the dose level is increased:

\[
X(n + 1) = \begin{cases} 
  x_{j-1} & \text{if } Y(n) = 1 \\
  x_{j+1} & \text{if } Y(n) = \cdots = Y(n - s + 1) = 0 \\
  x_j & \text{otherwise}
\end{cases} \quad (2.8)
\]

Viewed as a truncation of the \( UD(s,0,1) \) group rule, the \( k \)-in-a-row rule has appeal because the entire cohort does not need to be completed after a positive response. However, introducing this random rule for truncating a cohort fundamentally changes the resulting treatment distribution.

The probability of increasing and decreasing dose appears to be \( (1 - F(x))^k \) and \( F(x) \), respectfully. Naively, equating these probabilities as has been done with the biased coin and group up-and-down rules suggests that the asymptotic treatment distribution will have the same possible modes as does the \( UD(s,0,1) \) rules, namely, \( x_q : q = 0.500, 0.293, 0.206, 0.159, \ldots \) for \( s = 1, 2, 3, 4, \ldots \). However, an expression for the asymptotic distribution of treatments must take into account the possible replications at each level. Indeed, as stated, the \( k \)-in-a-row rule does not generate a first order Markov chain because the probability of increasing the dose depends, not just on the last dose and its outcome, but on up to \( k \) prior outcomes. Before using balance equations to help characterize this rule, Gezmu [21] extended the treatment space to create a first order Markov chain.

In particular, let \( x_{j,E_1} \) denote dose \( x_j \) when reached following a positive response from \( x_{j+1} \) or from the last of \( k \) negative responses from \( x_{j-1} \) and let \( x_{j,E_i} \) denote dose \( x_j \) when reached by a replication following a negative response from \( x_{j,E(i-1)} \), \( i = 2, \ldots, k \). Conceptually, the sample space of the experiment is extended to

\[
\mathcal{B}_k = \{ x_{1,E1},x_{1,E2},\ldots,x_{1,Ek},\ldots,x_{k,E1},x_{k,E2},\ldots,x_{k,Ek} \}.
\]
Transitions on this extended sample space form a Markov chain with probabilities $p_{ij}, (i, j) = (1, E1), \ldots, (1, Ek), \ldots, (K, E1), \ldots, (K, Ek)$.

For example, repeating a dose on the boundary when the rule for interior doses would assign a dose outside of $\mathcal{X}$ and defining $\bar{F}_i = F_i, i = 1, \ldots, K$ with maximum cohort size $k = 2$ and $K = 6$ possible doses, the transition probability matrix is on the extended treatment space is

$$P = \begin{bmatrix}
F_1 & F_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
F_1 & 0 & F_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
F_2 & 0 & 0 & F_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
F_2 & 0 & 0 & 0 & F_2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & F_3 & 0 & 0 & F_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & F_3 & 0 & 0 & F_3 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & F_3 & 0 & 0 & F_3 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & F_4 & 0 & F_4 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & F_4 & 0 & F_4 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & F_4 & 0 & F_4 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & F_6 & 0 & F_6 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & F_6 & 0 & F_6 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & F_6 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & F_6 \\
\end{bmatrix}$$

Balance equations on the interior of the extended state space are ([21])

$$w_{j,E1} = w_{j-1,E1}F_{j-1} + \left(w_{j+1,E1} + w_{j+1,E2} + \cdots + w_{j+1,Ek}\right)\bar{F}_{j+1}, j = 2, \ldots, K;$$

$$w_{j,Ei} = w_{j-1,E(i-1)}\bar{F}_i.$$

Gezmu derived a recursive algorithm for the asymptotic treatment probabilities in order to transform them onto the original treatment space:

$$w_{j,E1} = w_{1,E1}\prod_{i=2}^{j} \lambda_i, i = 1, \ldots, K;$$

$$w_{j,Ei} = w_{j,E1}\bar{F}_{j-1}^{i-1} \prod_{i=2}^{j} \lambda_i, i = 2, \ldots, k, j = 2, \ldots, K.$$

where

$$\lambda_i = \frac{\bar{F}_{i-1}^k}{1 - F_i^k}.$$  \hspace{1cm} (2.9)

Again, $\lambda_i$ standardizes the probabilities so that they sum to one. When $F(x)$ is increasing, $\bar{F}_{i-1}$ decreases with $i$ while $1 - F_i^k$ increases. The Durham-Flournoy unimodality condition of decreasing $\lambda_i$ is met for the $i$th subset of doses $\{w_{j,Ei}, j = 2, \ldots, K\}, i = 1, \ldots, k$.

Because the actual treatment frequency at $x_j$ is

$$w_j = w_{j,E1} + w_{j,E2} + \cdots + w_{j,Ek}, j = 1, \ldots, K,$$

the asymptotic treatment distribution on the actual treatment space is
\[ w_j = w_1 \left( \frac{F_1}{1 - F_1^k} \right) \left( \frac{1 - F_j^k}{F_k} \right) \prod_{i=2}^{j} \lambda_i, \quad j = 2, \ldots, K; \quad (2.10) \]

\[ w_1 = \frac{F_1^k}{1 - F_1^k + F_1 \left( \sum_{j=2}^{K} \frac{1 - F_j^k}{F_k} \prod_{i=2}^{j} \lambda_i \right)} \]

The product of \( \lambda \)s produces a unimodal function as in the Durham-Flournoy unimodality condition 1.7, while set

\[ \left( \frac{1 - F_j^k}{F_k} \right) = \sum_{j=0}^{x_1} F_j^f \]

is a geometric series, giving a decreasing set of terms. Thus treatment distribution is the product of two unimodal functions, one of which has its mode at \( x_1 \). The product of two unimodal functions can be bivariate, rather than univariate.

Because the product of two unimodal distributions may not itself be unimodal the behavior of this rule is distinctly different from others described in this section. There has been no general characterization of the conditions under which the treatment distribution bifurcates into one with two modes. Furthermore, the relationship between the mode(s) of the treatment distribution and a target set by solving the balance equations has not been obtained.
3. Abramowitz, M., Stegun, I.A.: Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables, ninth dover printing, tenth gpo printing edn. Dover, New York (1964)