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Randomized group up and down experiments

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Abstract An up and down (U&D) procedure is a sequential experiment used in binary response trials for identifying the treatment corresponding to a prespecified probability of positive response. Recently, a group version of U&D procedures has been proposed whereby at each stage a group of units is treated at the same level and the number of observed positive responses determines the treatment assigned to the next group. The deterministic nature of this algorithm leads to some limitations that in this paper we propose to overcome by introducing a randomization mechanism. A broad class of randomized group U&D's is presented, giving the conditions for targeting the treatment level of interest. In addition, we study how the properties of the design change as we vary the method of randomization within this general class and find randomization schemes which guarantee desirable results in terms of the asymptotic behavior of the experiment.

Keywords Dose-response problems · Phase I clinical trials · Markov chain · Random walk · Sequential experiments · Stochastic ordering · Stationary distribution

1 Introduction

In recent years the attention of the statistical literature on experimental design, especially in the area of biomedical applications, has focused on sequential methods. In sequential experiments at each stage the decision on whether

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to continue the trial and how to carry out the next observation or group of observations is taken in light of the results obtained up to that point. So the next treatment allocation may depend on what treatments have been previously allocated and/or on what outcomes have been observed. This dependence may either extend to all the past allocations and/or responses, as, for example, in Maximum Likelihood designs (see Rosenberger & Lachin, 2002), or be limited to the most recent ones, the so-called Markovian experiments as defined by Giovagnoli (2004). Sometimes, a supplementary randomization mechanism may also come into play: typical examples of the latter type of experiments are the Biased Coin Design proposed by Efron (1971) and the Urn Designs (see for instance Rosenberger, 2002, Baldi Antognini, 2005).

When the treatment levels are ordered and the response is binary, a common problem is finding the treatment corresponding to a given probability of positive response, like for instance LD(50), the dose that is lethal for 50% of the population under trial. In this context, a possible sequential experiment is the so-called up-and-down procedure (U&D), mainly developed for dose-response problems (Phase I clinical trials, see for instance Piantadosi, 1997), where the probability of a toxicity is an increasing function of the dose and the aim is to identify a target dose μ having a prescribed probability Γ of toxicity. In a Markovian U&D design, at each stage we either increase or decrease the treatment by one level with respect to the previous stage, or keep it at the same level, according to the most recently observed responses. In the classical U&D algorithm proposed by Dixon & Mood (1948), the target dose was LD(50) and the experiment simply consisted in decreasing the treatment level if the response was positive and increasing it if negative. Later, a randomization mechanism of the Biased Coin type (see for instance Derman, 1957, Durham & Flournoy, 1994) was introduced to cope with values of Γ different from 0.5. Other approaches for identifying a target dose μ can also be found: for example, alternatives to the non-parametric solution of U&D procedures are the parametric methods discussed by O'Quigley (2002) and Mugno, Zhus & Rosenberger (2004).

Most of the literature on Markovian U&D designs (Dixon & Mood, 1948, Derman, 1957, Durham & Flournoy, 1994, 1995, Durham, Flournoy & Rosenberger, 1997, Giovagnoli & Pintacuda, 1998, Stylianou & Flournoy, 2002; Ivanova, Montazer-Haghighi, Mohanti & Durham, 2003, Bortot & Giovagnoli, 2005) deals with the case of one observation at a time: at each stage just one statistical unit is observed and the single response used to choose the next treatment allocation. Recently, starting from an idea of Tsutakawa (1967) and also from the observation of common practice in clinical trials (see Storer, 1998), Gezmu & Flournoy (2006) have studied a "group" version of U&D experiments, which we will denote by GF–GU&D. At each stage a group of m units is treated at the same dose level and the responses are observed. If the number of observed toxicities within the group is less than or equal to a given threshold s the dosage is increased by one level and if it is greater than or equal to another threshold t then it is decreased by one level; otherwise it stays the same. This is a deterministic algorithm which, for appropriate values of the group size and

thresholds s and t, can be shown to allocate a large percentage of the treatments around the target dose. However, this is possible only for some values of the probability of toxicity Γ, but not for all. We will show that this problem may be solved by randomizing the experiment, similarly to what is done for U&D designs of the single type, i.e. $m = 1$ (see Giovagnoli & Pintacuda, 1998).

The discussion of various types of randomization for group U&D experiments is the main concern of this paper. Besides showing how randomization can be used to overcome the limitation of the GF–GU&D mentioned above, we will study how the properties of the design vary as we change the method of randomization and address the identification of randomization schemes which guarantee optimal results in terms of the asymptotic behaviour of the experiment. In Sect. 2 a general randomization mechanism for group U&D's is presented and its properties are discussed, focussing on the conditions that allow the design to target a dose μ with a prescribed toxicity probability. Sect. 3 considers special cases of the general randomized group U&D design which are of particular interest for their practical and theoretical features. The optimality properties of these special cases are studied in Sect. 4.

2 The randomized group U&D design

With the aim of overcoming some limitations of the GF–GU&D that are due to its deterministic nature, we propose a general randomized version of a group U&D design, which we will denote by Rand–GU&D. The basic idea is to associate to each number of observed positive responses the probabilities of increasing or decreasing the dose level according to two functions. Obviously, some constraints on the two functions are necessary to target the design on the dose with prescribed toxicity rate.

Suppose there is a set D of available doses. Assume in addition that the response to a given dose $X = x$ is a binary random variable, for which the probability of positive response is a continuous and strictly increasing function $Q(x)$ of the assigned dose x, $Q : \mathbb{R} \to [0;1]$. The aim is to find the unknown target dose μ such that $\Gamma = Q(\mu)$ for a given probability of toxicity $\Gamma \in (0,1)$. Suppose further that the experimenter knows the probability of positive response at two doses d_1 and d_M, such that $Q(d_1) < \Gamma < Q(d_M)$. Then, we can assume without loss of generality that $D = \{d_1 < d_2 < \ldots < d_M\}$ and

$$Q(d_1) = 0 \quad \text{and} \quad Q(d_M) = 1\,,$$

since other cases can be reduced to this setup by applying a straightforward linear transformation of $Q(\cdot)$, as in Giovagnoli & Pintacuda (1998).

Let $Q(d_i) = Q_i$ for $i = 1, \ldots, M$. A possible scheme of randomization consists in introducing two functions $\alpha(\cdot)$ and $\beta(\cdot)$ on $\{0, \ldots, m\}$, which give the probabilities of, respectively, increasing and decreasing the dose by one level in terms of the number of observed toxicities. We want the probability of increasing the dose not to go up as the number of observed toxicities increases, and vice versa

for the probability of decreasing the dose. Also, when there are no toxicities, we require that the probability of increasing is higher than the probability of decreasing the dose level, and conversely when the number of toxicities is a maximum. More precisely, the randomization mechanism is defined as follows.

Let $\alpha(\cdot)$ and $\beta(\cdot)$ be two functions from $\{0,\dots,m\}$ onto $[0,1]$, such that

- $\alpha(k)+\beta(k)\le 1$ for any $k\in\{0,\dots,m\}$.
- $\alpha(\cdot)$ is non-increasing, $\beta(\cdot)$ is non-decreasing.
- $\alpha(0)\ge\beta(0)$ and $\alpha(m)\le\beta(m)$.

We will refer to $\alpha(\cdot)$ and $\beta(\cdot)$ as the *generating functions* of the design. At each step n, given a dose level $X_n=d_i$ $(i=2,\dots,M-1)$ and a response $Y_n=k\in\{0,\dots,m\}$, the next dose level will be chosen according to

$$\begin{aligned}
\Pr\left(X_{n+1}=d_{i+1}\mid Y_n=k;X_n=d_i\right) &= \alpha(k)\\
\Pr\left(X_{n+1}=d_{i-1}\mid Y_n=k;X_n=d_i\right) &= \beta(k)\\
\Pr\left(X_{n+1}=d_i \mid Y_n=k;X_n=d_i\right) &= 1-\alpha(k)-\beta(k)
\end{aligned}\tag{1}$$

and for the extreme doses d_1 and d_M

$$\Pr\left(X_{n+1}=d_2\mid X_n=d_1\right)=\Pr\left(X_{n+1}=d_{M-1}\mid X_n=d_M\right)=1\,.$$

The latter condition ensures that we do not "waste" observations on d_1 and d_M where the response is assumed to be known (see also Sect. 4 of Giovagnoli & Pintacuda, 1998). This assumption is likely to be satisfied in practice; however, alternative boundary rules will be desirable if this requirement is not met.

We now show how this randomized version of a group U&D can be used to target a dose μ associated to a given probability of toxicity Γ and how different choices of $\alpha(\cdot)$ and $\beta(\cdot)$ give rise to different properties of the algorithm. At each step n, conditionally on $X_n=d_i$ $(i=1,\dots,M)$, the distribution of Y_n is Binomial $B(m,Q_i)$ and depends on n only through the dose which has been assigned. For any choice of $\alpha(\cdot)$ and $\beta(\cdot)$ the sequence $\{X_n\}$ is a random walk on the state space D. Let $E[g(B(m,p))]$ denote the expected value of the transformation $g(\cdot)$ of the Binomial random variable $B(m,p)$, for any real measurable function $g(\cdot)$ and $0<p<1$. The transition probabilities of $\{X_n\}$ are, for $i=2,\dots,M-1$,

$$\begin{aligned}
p_i &= E[\alpha(B(m,Q_i))]=\sum_{k=0}^{m}\alpha(k)\binom{m}{k}Q_i^k\,(1-Q_i)^{m-k}\\
q_i &= E[\beta(B(m,Q_i))]=\sum_{k=0}^{m}\beta(k)\binom{m}{k}Q_i^k\,(1-Q_i)^{m-k}\\
r_i &= 1-p_i-q_i
\end{aligned}\tag{2}$$

with boundary condition $p_1=q_M=1$. The chain $\{X_n\}$ is irreducible and positive recurrent, with a unique stationary distribution $\boldsymbol{\pi}=\{\pi(d_i),\,i=1,\dots,M\}$ given by the equilibrium equations

$$\pi(d_i) = \pi(d_{i-1})\lambda_i \qquad i = 2, \ldots, M$$
$$\pi(d_1) = \left[1 + \sum_{j=2}^{M} \prod_{i=2}^{j} \lambda_i\right]^{-1}, \tag{3}$$

where $\lambda_i = p_{i-1}/q_i$, namely,

$$\begin{aligned} \lambda_2 &= \frac{1}{E[\beta(B(m, Q_2))]}, \\ \lambda_i &= \frac{E[\alpha(B(m, Q_{i-1}))]}{E[\beta(B(m, Q_i))]}, \qquad i = 3, \ldots, M-1, \\ \lambda_M &= E[\alpha(B(m, Q_{M-1}))]. \end{aligned} \tag{4}$$

Proposition 1 *Under the randomized group U&D, the stationary distribution* $\boldsymbol{\pi}$ *is unimodal with mode* d_K*, where*

$$K = \max\{i \in \{2, \ldots, M\} \text{ such that } \lambda_i > 1\}. \tag{5}$$

Furthermore, if $0 < \Gamma < 1$ *and* $\alpha(\cdot)$ *and* $\beta(\cdot)$ *satisfy*

$$E[\alpha(B(m, \Gamma))] = E[\beta(B(m, \Gamma))], \tag{6}$$

then the mode of $\boldsymbol{\pi}$ *is such that*

$$d_{K-1} < \mu < d_{K+1}. \tag{7}$$

Proof Since the set D of doses is ordered and the dose-response function $Q(\cdot)$ is strictly increasing, then $Q_1 < \ldots < Q_M$. Let $\leq_{st}$ be the usual stochastic ordering of random variables; since $\alpha(\cdot)$ is non-increasing and $\beta(\cdot)$ non-decreasing,

$$\begin{aligned} \alpha\left(B(m, Q_1)\right) &\geq_{st} \ldots \geq_{st} \alpha\left(B(m, Q_M)\right) \\ \beta\left(B(m, Q_1)\right) &\leq_{st} \ldots \leq_{st} \beta\left(B(m, Q_M)\right). \end{aligned} \tag{8}$$

From (2), applying a well-known property of the stochastic ordering $\leq_{\mathrm{st}}$ (see Ross, 1996), the sequence $\{q_i\}_{\{i=2,\ldots,M\}}$ is non-decreasing and $\{p_i\}_{\{i=1,\ldots,M-1\}}$ is non-increasing. Thus, the sequence $\{\lambda_i\}_{\{i=2,\ldots,M\}}$ in (4) is non-increasing with $\lambda_2 > 1$, so that the stationary distribution $\boldsymbol{\pi}$ is unimodal with mode d_K (see Durham & Flournoy, 1994). For any fixed m, condition (6) leads to an equation in Γ, where the left-hand side $E[\alpha(B(m, \Gamma))]$ is a continuous and decreasing function of Γ varying between 1 and 0, and the right-hand side $E[\beta(B(m, \Gamma))]$ is a continuous and increasing function of Γ varying between 0 and 1. Thus, Eq. (6) admits a unique solution Γ^* in $(0, 1)$ and the proof follows from Theorem 1 of Durham & Flournoy (1994): see also Proposition 2 in Giovagnoli & Pintacuda (1998). Observe that we cannot have $\mu = d_{K+1}$ since $Q(\cdot)$ is assumed to be strictly increasing and continuous.

This result offers a solution to the problem of estimating μ. The empirical distribution of the assigned treatments can be used as an approximation of the invariant distribution $\boldsymbol{\pi}$. Thus, if Rand–GU&D satisfies condition (6), by virtue of (7) the mode of the empirical dose distribution is a valid candidate as an estimator of μ (see Giovagnoli & Pintacuda, 1998). Alternative estimators have also been proposed, see for example Stylianou & Flournoy (2002).

3 Special cases of the randomized group U&D design

In this section we analyze some special cases of Rand–GU&D. Their properties in terms of the asymptotic behavior of the design will be studied in Sect. 4.

Without loss of generality, from now on we assume $\Gamma \in (0; 0.5]$, which is the most relevant case for toxicology studies. The case $\Gamma \in (0.5, 1)$, most frequently encountered in efficacy experiments and adaptive testing, for example, can be derived analogously.

3.1 Giovagnoli and Pintacuda

When $m = 1$ the group U&D becomes fully sequential. Then the randomized U&D defined in this paper becomes the general U&D rule proposed by Giovagnoli & Pintacuda (1998) with

$$\begin{aligned} &\alpha(0) = \alpha, \quad \alpha(1) = \alpha', \\ &\beta(0) = \gamma', \quad \beta(1) = \gamma, \end{aligned} \tag{9}$$

where $0 < \alpha' \leq \alpha \leq 1$ and $0 < \gamma' \leq \gamma \leq 1$.

3.2 Gezmu and Flournoy

The U&D rule defined by Gezmu & Flournoy (2006) is

$$\begin{aligned} &\text{if } X_n = d_i \ (i = 2, \ldots, M-1), \text{ then} \\ &\qquad X_{n+1} = d_{i+1}, \quad \text{if } Y_n \leq s \\ &\qquad X_{n+1} = d_i, \quad \text{if } s < Y_n < t \\ &\qquad X_{n+1} = d_{i-1}, \quad \text{if } Y_n \geq t, \\ &\text{if } X_n = d_1, \text{then} \\ &\qquad X_{n+1} = d_2, \quad \text{if } Y_n \leq s \\ &\qquad X_{n+1} = d_1, \quad \text{if } Y_n > s, \\ &\text{if } X_n = d_M, \text{then} \\ &\qquad X_{n+1} = d_M, \quad \text{if } Y_n < t \\ &\qquad X_{n+1} = d_{M-1}, \quad \text{if } Y_n \geq t, \end{aligned}$$

where s and t are integer values satisfying $0 \leq s < t \leq m$. This algorithm corresponds to choosing the functions

$$\alpha(k) = \begin{cases} 1, & k \leq s \\ 0, & \text{otherwise} \end{cases} \quad \text{and} \quad \beta(k) = \begin{cases} 1, & k \geq t \\ 0, & \text{otherwise} \end{cases}. \tag{10}$$

Gezmu and Flournoy do not assume the response function $Q(\cdot)$ to be strictly increasing, thus their targeting condition leads to

$$d_{K-1} \leq \mu \leq d_{K+1}$$

instead of the strict inequalities in (7). The GF–GU&D algorithm is appropriate under further assumptions (see the Theorem in Sect. 3 of Gezmu & Flournoy, 2006), which correspond to knowing two values of the response $Q(\cdot)$, either Q_1 and Q_2 or Q_{M-1} and Q_M. In addition, as mentioned in the Introduction, one limitation of GF–GU&D is that, for a given probability Γ and group size m, there might not exist integers s and t such that the targeting condition (6) is satisfied.

3.3 Randomized extension of the GF–GU&D design

A simple way of randomizing the GF–GU&D design is as follows. With suitable adjustments for the extreme doses, at each step if the number of positive responses is less or equal to s, then the next dose is increased with probability $0 < \alpha \leq 1$, whereas if the number of positive responses is greater or equal to t the dose is decreased with probability $0 < \beta \leq 1$. Within the class of Rand–GU&D's, this rule corresponds to the following choice of the generating functions

$$\alpha(k) = \begin{cases} \alpha, & k \leq s \\ 0, & \text{otherwise} \end{cases} \quad \text{and} \quad \beta(k) = \begin{cases} \beta, & k \geq t \\ 0, & \text{otherwise} \end{cases}.$$

The random walk $\{X_n\}$ generated by this algorithm has transition probabilities given by

$$\begin{aligned} p_i &= \alpha \sum_{k=0}^{s} \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} \\ q_i &= \beta \sum_{k=t}^{m} \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} \\ r_i &= 1 - p_i - q_i \end{aligned} \tag{11}$$

for $i = 2, \ldots, M-1$, with $p_1 = q_M = 1$.

As regards the stationary distribution of the chain, from (4) we derive

$$\begin{aligned}\lambda_2 &= \frac{1}{\beta \Pr\left(B(m, Q_2) \geq t\right)}, \\ \lambda_i &= \frac{\alpha \Pr\left(B(m, Q_{i-1}) \leq s\right)}{\beta \Pr\left(B(m, Q_i) \geq t\right)}, \qquad i = 3, \ldots, M-1, \\ \lambda_M &= \alpha \Pr\left(B(m, Q_{M-1}) \leq s\right). \end{aligned} \tag{12}$$

The targeting condition (6) becomes

$$\alpha \sum_{k=0}^{s} \binom{m}{k} \Gamma^k (1-\Gamma)^{m-k} = \beta \sum_{k=t}^{m} \binom{m}{k} \Gamma^k (1-\Gamma)^{m-k} \tag{13}$$

and is satisfied for fixed m, s, t and toxicity rate Γ if

$$\alpha = \beta \frac{\Pr\left(B(m, \Gamma) \geq t\right)}{\Pr\left(B(m, \Gamma) \leq s\right)}, \tag{14}$$

and β is chosen in the interval $S = (0, \beta^*)$, where

$$\beta^* = \min\left\{1; \frac{\Pr\left(B(m, \Gamma) \leq s\right)}{\Pr\left(B(m, \Gamma) \geq t\right)}\right\}. \tag{15}$$

Thus, for any values of Γ and m this randomized rule admits a parameter setting that satisfies the targeting condition.

3.4 Linear generating functions

Condition (6) and the selection of a rule that targets the dose μ having a prescribed toxicity probability Γ are greatly simplified if the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ are linear, that is if the probability of increasing (decreasing) the dose level, given the current dose and outcomes, is proportional to the number of observed toxicities. For any $k = 0, \ldots, m$, let

$$\alpha(k) = a\left(1 - \frac{k}{m}\right) \qquad \text{and} \qquad \beta(k) = 1 + b\left(\frac{k}{m} - 1\right), \tag{16}$$

where $0.5 \leq a \leq b \leq 1$. In this algorithm if we observe 0 toxicities then the probability of increasing the dose level is greater than 0.5; if we observe m toxicities, than at the next step the dose level will be decreased with probability 1.

From the linearity of the generating functions, the transition probabilities of the random walk $\{X_n\}$ are

$$\begin{aligned} p_i &= E[\alpha(B(m, Q_i))] = (1 - Q_i)a \\ q_i &= E[\beta(B(m, Q_i))] = 1 - (1 - Q_i)b \\ r_i &= (1 - Q_i)(b - a) \end{aligned} \tag{17}$$

for $i = 2, \ldots, M - 1$, with $p_1 = q_M = 1$, and the stationary distribution can be derived from (3) with

$$\begin{aligned} \lambda_2 &= \frac{1}{1 - (1 - Q_2)b}, \\ \lambda_i &= \frac{(1 - Q_{i-1})a}{1 - (1 - Q_i)b}, \qquad i = 3, \ldots, M - 1, \\ \lambda_M &= (1 - Q_{M-1})a\,. \end{aligned} \tag{18}$$

Under this procedure, the targeting condition (6) becomes

$$a + b = \frac{1}{1 - \Gamma}, \tag{19}$$

which implies

$$\begin{aligned} \lambda_2 &= \frac{1}{1 - (1 - Q_2)b}, \\ \lambda_i &= \frac{(1 - Q_{i-1})\left(\frac{1}{1-\Gamma} - b\right)}{1 - (1 - Q_i)b}, \qquad i = 3, \ldots, M - 1, \\ \lambda_M &= (1 - Q_{M-1})\left(\frac{1}{1 - \Gamma} - b\right). \end{aligned} \tag{20}$$

Thus the stationary distribution of the targeting design does not depend on m.

3.5 Complementary generating functions

Consider now the class of Rand–GU&D's for which $r_i = 0$ for any i, i.e. the dose level changes at each step. More precisely, let the generating functions satisfy

$$\alpha(k) + \beta(k) = 1 \qquad k = 0, \ldots, m. \tag{21}$$

We call this a *complementary* group U&D. Examples of this type of algorithm can be found in each of the special cases previously analyzed, for instance, within the GF–GU&D class by letting $t = s + 1$, or in the linear generating function scheme for $a = b$.

For a complementary group U&D, from (2)

$$p_i = \sum_{k=0}^{m} \alpha(k) \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} = 1 - q_i \qquad i = 2, \ldots, M-1, \tag{22}$$

and the target condition (6) becomes

$$E[\alpha(B(m, \Gamma))] = \sum_{k=0}^{m} \alpha(k) \binom{m}{k} \Gamma^k \, (1 - \Gamma)^{m-k} = \frac{1}{2} \, . \tag{23}$$

For example, consider the GF–GU&D with $t = s + 1$. In this case Eq. (23) becomes

$$\sum_{k=0}^{s} \binom{m}{k} \Gamma^k \, (1 - \Gamma)^{m-k} = \frac{1}{2} \, ,$$

so that the integer s must be chosen as the median of $B(m, \Gamma)$. For $\Gamma = 0.5$ any combination of an integer s and a group size $m = 2s + 1$ satisfies the target condition, as shown by Gezmu & Flournoy (2006) by the following examples $(m, s) = (1, 0)$, $(3, 1)$, $(5, 2)$ and $(7, 3)$.

Consider now linear generating functions with $a = b$. From (23) the target condition becomes

$$E[\alpha(B(m, \Gamma))] = (1 - \Gamma) b = \frac{1}{2}$$

i.e.

$$a = b = \frac{1}{2(1 - \Gamma)} \, .$$

Thus the linear complementary design is uniquely determined. Substituting in (20), the stationary distribution can be derived in terms of Γ and the quantile function $Q(\cdot)$.

3.6 Symmetric U&D

We end this section with a remark on symmetric generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ satisfying

$$\alpha(k) = \beta(m - k) \qquad k = 0, \ldots, m. \tag{24}$$

Lemma 1 *For symmetric generating functions, the only dose μ which can be targeted corresponds to $\Gamma = \frac{1}{2}$.*

Proof Under (24),

$$E[\alpha(B(m,\Gamma))] = \sum_{k=0}^{m} \alpha(k) \binom{m}{k} \Gamma^k (1-\Gamma)^{m-k}$$
$$= \sum_{k=0}^{m} \beta(m-k) \binom{m}{k} \Gamma^k (1-\Gamma)^{m-k} = E[\beta(B(m,1-\Gamma))], \tag{25}$$

so that the target Eq. (6) becomes

$$E[\beta(B(m,1-\Gamma))] = E[\beta(B(m,\Gamma))]\,. \tag{26}$$

As a function of Γ, the left-hand side is a continuous and decreasing function from $(0,1)$ in $[0,1]$, and the right-hand side is a continuous and increasing function from $(0,1)$ in $[0,1]$. Thus, equation (26) has a unique solution in $(0,1)$, which is obviously $\Gamma = 0.5$, so that the only target dose which can be located by this procedure is $\mu = Q^{-1}(0.5)$.

4 Optimality of randomized group U&D experiments

An asymptotic criterion was given in Giovagnoli & Pintacuda (1998) to compare two U&D algorithms, $\mathrm{UD}^{(1)}$ and $\mathrm{UD}^{(2)}$, both targeted on the same dose level μ. We say that the stationary distribution $\boldsymbol{\pi}^{(1)}$ is more peaked around μ than $\boldsymbol{\pi}^{(2)}$ if, for $i = 2, \ldots, M-1$,

$$Q_i < \Gamma \text{ implies } \lambda_i^{(1)} \geq \lambda_i^{(2)} \quad \text{and} \quad Q_i \geq \Gamma \text{ implies } \lambda_{i+1}^{(1)} \leq \lambda_{i+1}^{(2)}\,, \tag{27}$$

where $\lambda_i^{(j)} = \pi^{(j)}(d_i)/\pi^{(j)}(d_{i-1})$ and $j = 1, 2$.

We will use this comparison rule in the present setting to choose the "optimal" design within each subclass of the Rand–GU&D algorithm that has been described in Sect. 3.

4.1 Randomized extension of the GF–GU&D rule

From Eq. (12) we see that, if m, s and t are fixed and the randomization parameters α and β are chosen to satisfy (14) and (15), then different choices of β in S lead to the same stationary distribution. Thus we cannot specialize β in order to improve on the " peakedness" of the stationary distribution. However, it may be observed that the same arguments of Bortot & Giovagnoli (2005) can be applied, namely we can compare the speed of convergence of different rules having the same stationary distribution. By virtue of these results, the optimal

value of β is the one associated to the algorithm that moves fastest, i.e.

$$\beta^* = \min\left\{1; \frac{\Pr\left(B(m,\Gamma) \leq s\right)}{\Pr\left(B(m,\Gamma) \geq t\right)}\right\},$$

while α is obtained from (14).

4.2 Linear generating functions

From (20), the stationary distribution of a linearly randomized group U&D targeted on $\Gamma \in (0; 0.5]$ can be expressed in terms of b. The following result gives the optimal choice of b with respect to the shape of the stationary distribution, while a is given by (19).

Proposition 2 *For linearly randomized group U&D algorithms satisfying* (19)*, a choice of b as large as possible optimizes the design according to criterion* (27)*.*

Proof By taking the derivative in (20) with respect to b, it is easy to see that λ_i increases for all integers i such that $Q_i < \Gamma$ and decreases for i such that $Q_i \geq \Gamma$.

Because of conditions $0.5 \leq a \leq b \leq 1$ and of (19), the best possible value for b is thus

$$b = \min\left\{1; \frac{1}{1-\Gamma} - \frac{1}{2}\right\}.$$

4.3 Complementary group U&D designs

Within the class of complementary group U&D rules consider the special case

$$\tilde{\alpha}(k) = \begin{cases} 1, & k \leq \lfloor m\Gamma \rfloor \\ 0, & \text{otherwise} \end{cases} \qquad \text{and} \qquad \tilde{\beta}(k) = 1 - \tilde{\alpha}(k), \tag{28}$$

where $\lfloor z \rfloor$ stands for the integer part of z. This rule falls within the GF–GU&D family with $s = \lfloor m\Gamma \rfloor$ and $t = s + 1$. The rationale is identical to Dixon and Mood and consists of increasing the dose level if the observed number of toxicities is less than $m\Gamma$, the expected number at the target dose, and decreasing it otherwise. From (22), under procedure (28) the transition probabilities of the Markov chain $\{X_n\}$ are given by

$$\tilde{p}_i = \sum_{k=0}^{\lfloor m\Gamma \rfloor} \binom{m}{k} Q_i^k \left(1 - Q_i\right)^{m-k} = 1 - \tilde{q}_i \qquad i = 2, \ldots, M-1, \tag{29}$$

with $\tilde{p}_1 = \tilde{q}_M = 1$, and the target condition (23) becomes

$$E[\tilde{\alpha}(B(m,\Gamma))] = \sum_{k=0}^{\lfloor m\Gamma \rfloor} \binom{m}{k} \Gamma^k (1-\Gamma)^{m-k} = \frac{1}{2}\,. \tag{30}$$

Given a target toxicity rate Γ, the group size m must be chosen as the integer solution of Eq. (30). Thus this algorithm may not target some Γ's exactly.

Proposition 3 *For a toxicity rate* Γ *and group size m, rule* (28) *is optimal by criterion* (27) *within the class of complementary group U&D's that can target* Γ *with the same group size.*

Proof Consider a complementary group U&D targeted on Γ, namely with generating function $\alpha(\cdot)$ satisfying (23). Let $\{X_n\}$ be the corresponding random walk with transition probabilities $\{p_i\}$ defined in (22). Observe that for any $i = 2, \ldots, M-1$

$$\begin{aligned} p_i &= \sum_{k=0}^{m} \alpha(k) \binom{m}{k} Q_i^k (1-Q_i)^{m-k} \\ &= \sum_{k=0}^{m} \alpha(k) \binom{m}{k} \left\{ Q_i^k (1-Q_i)^{m-k} - \Gamma^k (1-\Gamma)^{m-k} \right\} + \frac{1}{2} \\ &= \sum_{k=0}^{m} \alpha(k) \binom{m}{k} C_i(k) + \frac{1}{2}\,, \end{aligned}$$

with $C_i(k) = Q_i^k (1-Q_i)^{m-k} - \Gamma^k (1-\Gamma)^{m-k}$. From condition (27), it is sufficient to show that

$$p_i \le \tilde{p}_i \quad \text{for} \quad Q_i < \Gamma \ \text{ and } \ p_i \ge \tilde{p}_i \quad \text{for} \quad Q_i \ge \Gamma\,.$$

Case 1 If $0 \le Q_i < \Gamma$, then $C_i(k) \ge 0$ for any $k = 0, \ldots, \lfloor m\tau_i \rfloor$, where

$$\tau_i = \frac{\ln\left\{\dfrac{1-\Gamma}{1-Q_i}\right\}}{\ln\left\{\dfrac{Q_i(1-\Gamma)}{\Gamma(1-Q_i)}\right\}} \in (0;\Gamma).$$

Since $\alpha(k) \in [0;1]$ for $k = 0, \ldots, m$, then

$$\sum_{k=0}^{m} \alpha(k) \binom{m}{k} C_i(k) \le \sum_{k=0}^{\lfloor m\tau_i \rfloor} \binom{m}{k} C_i(k)$$

and thus

$$
\begin{aligned}
p_i &= \sum_{k=0}^{m} \alpha(k) \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} \leq \sum_{k=0}^{\lfloor m\tau_i \rfloor} \binom{m}{k} C_i(k) + \frac{1}{2} \\
&\leq \sum_{k=0}^{\lfloor m\Gamma \rfloor} \binom{m}{k} C_i(k) + \frac{1}{2} = \sum_{k=0}^{\lfloor m\Gamma \rfloor} \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} \\
&= \sum_{k=0}^{m} \tilde{\alpha}(k) \binom{m}{k} Q_i^k \, (1 - Q_i)^{m-k} = \tilde{p}_i \, .
\end{aligned}
$$

Case 2 If $\Gamma \leq Q_i \leq 1$, we must show that $p_i \geq \tilde{p}_i$ and the proof is similar to that of Case 1.

5 Conclusions

In this paper we have discussed a general randomization mechanism for group U&D experiments aimed at overcoming the limitations of the group U&D proposed by Gezmu & Flournoy (2006). We introduce a very broad class of randomized U&D's, giving conditions that allow the designs to target a given dose μ with a prescribed probability of positive response. We have focussed on special methods of randomization which are of particular interest for their practical and theoretical features, showing some of their properties. Further, we have indicated which randomization schemes guarantee "optimized" results in terms of the asymptotic behaviour of the experiment.

Several questions remain to be answered, for example regarding the effect of randomization on the speed of convergence of these experiments to their stationarity. We point out that a fully satisfactory criterion for comparing all U&D experiments remains to be found.

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