

A dose-finding sequential method for targeting a given mean response: Up&Down experiments ^(*)

Un metodo sequenziale per la ricerca della dose corrispondente ad un'assegnata risposta media: esperimenti di tipo Up-and-Down

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Riassunto: Tradizionalmente, gli studi dose-risposta sono esperimenti di tipo binario volti a stimare un determinato “quantile” di interesse di una curva di risposta. In questo lavoro si considera il caso in cui la risposta osservata sia una generica variabile aleatoria reale, non necessariamente dicotomica, e lo scopo dell’esperimento consiste nello stimare la dose target associata ad una preassegnata risposta media. Ripercorrendo i risultati di Giovagnoli e Pintacuda (1998) e Baldi Antognini *et al* (2006), viene proposta ed analizzata un’estensione randomizzata dell’algoritmo up-and-down, fornendo inoltre una procedura di stima della risposta media basata sul metodo di massima verosimiglianza.

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1. Introduction

Dose-response experiments are sequential methods widely used in a vast area of biomedical fields, e.g. toxicology and pharmacology, for estimating the relationship between a set of ordered doses of a drug or a toxin and the effect on a response variable. Traditionally, these studies are binary response trials where the probability of positive response (toxicity) is assumed to be an increasing function of the given dose level and the aim consists in estimating the target dose at which a pre-specified probability of positive response is associated. Classical examples are the median dose, usually denoted by LD_{50} , or the maximum tolerated dose (MTD) of phase I clinical trials.

When the set of available ordered doses is fixed in advance, the up-and-down designs (U&D) provide a possible solution for dose-finding problems. Originally, the U&D algorithm was introduced for estimating LD_{50} (von Békésy, 1947; Dixon and Mood, 1948). Later, several authors have extended this procedure by introducing a randomization component, which is particularly desirable in clinical trials and allows one to target any quantile of interest (e.g. Derman, 1957; Durham and Flournoy, 1994 and 1995; Durham *et al*, 1997; Giovagnoli and Pintacuda, 1998; Ivanova *et al*, 2003; Bortot and Giovagnoli, 2005; Baldi Antognini *et al*, 2006). These algorithms provide a non-parametric estimate of the target. However, assuming a parametric model for the response curve other authors have analyzed the properties of MLE under U&D designs (see Durham *et al*, 1997).

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Other possible strategies for dose-finding problems include adaptive urn randomization (Rosenberger and Grill, 1997; Mugno *et al*, 2004), the maximum likelihood method (Wu, 1985) and the continual reassessment method (O’Quigley *et al*, 1990). For recent literature on this topic see also Gasparini and Eisele (2000), Zhu and Wong (2000, 2001), O’Quigley (2002), Hardwick *et al* (2003) and Cheung (2005).

However, in several experimental fields the responses are not necessarily binary. This can occur in toxicological or pharmaceutical trials, since often the original outcomes are measurements, say of some physiological aspects, and they become dichotomized by adopting suitable thresholds, and also in many other areas such as industrial experimentation, material stress analysis, etc.

In this paper we assume that the response to a given stimulus is a real random variable whose expected value is an increasing function of the level of the stimulus, and the aim of the experiment is finding the unknown target level which induces a pre-specified *mean response*. Adapting the theoretical results of Giovagnoli and Pintacuda (1998) and Baldi Antognini *et al* (2006), we show that in the case of general outcomes too a U&D algorithm can be found that clusters the treatment distribution around the target. Furthermore, if assume that the observed responses belong to the exponential family, under this U&D design the MLE’s of the expected values retain the strong consistency and asymptotical normality properties. Note that this does not involve any parametric assumptions on the response curve.

After setting the notation in Section 2, Section 3 of the paper describes the proposed randomized up-and-down design. Section 4 discusses some special cases, which seem to be of particular interest for their practical and theoretical features. In Section 5 we suggest a group version of the proposed procedure and Section 6 describes some examples. Section 7 deals with the problem of asymptotic parametric inference and Section 8 discusses the properties of the special designs presented in Section 4.

2. Notation and Model

Suppose there is a finite set of ordered treatment levels and assume that the response Y to a given dose $X = x$ is a real random variable with expected value $Q(x)$, where $Q(\cdot)$ is a continuous and strictly increasing function of the assigned level x , which from now on we will refer to as a “dose”. Let us denote by $F(\cdot; Q(x))$ the cumulative distribution function (*cdf*) of Y given $X = x$ and by $\mathcal{Y}$ the set of the possible values of Y , with $\inf \mathcal{Y} = a$ and $\sup \mathcal{Y} = b$. Set $I = [a; b]$, assume further that $F(y; \gamma)$ is decreasing⁽¹⁾ in γ for each fixed y (i.e. the family $\{F(\cdot; \gamma), \gamma \in I\}$ is stochastically ordered; see Ross, 1996) and the experimental purpose consists in finding the unknown target level μ such that $\Gamma = Q(\mu)$ for a given *mean response* $\Gamma \in I^{(2)}$.

If the response Y is binary, this setting roughly corresponds to the classical dose-response problems of phase I clinical trials.

We will suppose that the experimenter knows the expected response at two doses, denoted by d_1 and d_M , such that $Q(d_1) < \Gamma < Q(d_M)$; thus, we can assume without loss of generality that the set of doses is given by $D = \{d_1 < d_2 < \dots < d_M\}$ with doses not necessarily uniformly-spaced, and we let $Q(d_i) = Q_i$ for any $i = 1, \dots, M$.

⁽¹⁾ The terms “decreasing” and “increasing” are not meant in a strict sense.

⁽²⁾ Clearly, if the extremes a and b are not finite we assume that $I = (a; b)$.

3. A Randomized U&D Design to target a given mean response

3.1. Definition

Up-and-Down designs are experiments in which at each stage one or more statistical units are observed at the same dose level and, on the basis of these outcomes we either increase or decrease it by one level, or maintain the same dose. We start by introducing a randomized U&D procedure in a fully sequential setting, namely only one outcome is observed at each stage. A straightforward extension to the case when groups of units are observed each time will be discussed in Section 5. We follow the same approach of (Baldi Antognini *et al*, 2006), in which the outcome at each stage is a binomial response.

At each step we define probabilities of, respectively, increasing and decreasing the dose by one level in terms of the single outcome. We do not want the probability of increasing the dose to go up when the response increases, and vice versa for the probability of decreasing the dose. More precisely, let $\alpha(\cdot)$ and $\beta(\cdot)$ be two functions from $\mathcal{Y}$ onto $[0, 1]$ such that:

- $\alpha(y) + \beta(y) \leq 1$ for any $y \in \mathcal{Y}$;
- $\alpha(\cdot)$ is decreasing and $\beta(\cdot)$ is increasing;
- $\lim_{y \rightarrow a} \alpha(y) \geq \lim_{y \rightarrow a} \beta(y)$ and $\lim_{y \rightarrow b} \alpha(y) \leq \lim_{y \rightarrow b} \beta(y)$.

As in (Baldi Antognini *et al*, 2006), we will refer to $\alpha(\cdot)$ and $\beta(\cdot)$ as the *generating functions* of the design.

At each step n , given the dose $X_n = d_i$ ($i = 2, \dots, M - 1$) and the corresponding response $Y_n = y$, the next dose level will be chosen according to

$$\begin{aligned} X_{n+1} &= d_{i+1} \text{ with probability } \alpha(y) \\ X_{n+1} &= d_{i-1} \text{ with probability } \beta(y) \\ X_{n+1} &= d_i \text{ with probability } 1 - \alpha(y) - \beta(y) \end{aligned} \tag{3.1}$$

and for the extreme doses d_1 and d_M

$$\begin{aligned} X_{n+1} &= d_2 \quad \text{given } X_n = d_1 \\ X_{n+1} &= d_{M-1} \quad \text{given } X_n = d_M. \end{aligned}$$

Remark 3.1. From now on we take into account only non-trivial generating functions. More precisely, if ν_γ is the probability measure with *cdf* $F(\cdot; \gamma)$, we exclude the case in which there exists some γ such that

$$\alpha(y) = c \quad \nu_\gamma - a.s. \quad \text{or} \quad \beta(y) = c \quad \nu_\gamma - a.s. \quad \text{with } c \in [0; 1],$$

since otherwise the design might not be data-dependent.

3.2. Properties of the Randomized U&D Design

It is easy to show that for any choice of the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ the sequence $\{X_n\}$ is a random walk on the state space D , with transition probabilities given by (see Port, 1994)

$$\begin{aligned} p_i &= P(X_{n+1} = d_{i+1} | X_n = d_i) = E[\alpha(Y_n) | X_n = d_i] = \int \alpha(y) F(dy; Q_i), \\ q_i &= P(X_{n+1} = d_{i-1} | X_n = d_i) = E[\beta(Y_n) | X_n = d_i] = \int \beta(y) F(dy; Q_i), \\ r_i &= P(X_{n+1} = d_i | X_n = d_i) = 1 - p_i - q_i, \end{aligned}$$

for $i = 2, \dots, M - 1$, with boundary conditions

$$\begin{aligned} p_1 &= P(X_{n+1} = d_2 \mid X_n = d_1) = 1, \\ q_M &= P(X_{n+1} = d_{M-1} \mid X_n = d_M) = 1. \end{aligned}$$

Hence (see for instance Giovagnoli and Pintacuda, 1998) the Markov chain $\{X_n\}$ is irreducible and positive recurrent, with a unique stationary distribution $\pi = (\pi(d_1), \dots, \pi(d_M))$ given by the equilibrium equations

$$\begin{aligned} \pi(d_i) &= \pi(d_{i-1})\lambda_i \quad i = 2, \dots, M \\ \pi(d_1) &= \left[1 + \sum_{j=2}^M \prod_{i=2}^j \lambda_i \right]^{-1}, \end{aligned} \quad (3.2)$$

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

$$\begin{aligned} \lambda_2 &= \left[\int \beta(y) F(dy; Q_2) \right]^{-1} > 1, \\ \lambda_i &= \frac{\int \alpha(y) F(dy; Q_{i-1})}{\int \beta(y) F(dy; Q_i)}, \quad i = 3, \dots, M - 1, \\ \lambda_M &= \int \alpha(y) F(dy; Q_{M-1}) < 1. \end{aligned} \quad (3.3)$$

Proposition 3.2. *The stationary distribution π is unimodal with mode d_K , where*

$$K = \max \{i \in \{2, \dots, M - 1\} \text{ such that } \lambda_i > 1\}. \quad (3.4)$$

Proof. Since $Q(\cdot)$ is strictly increasing and the doses are ordered, then

$$i < j \Rightarrow F(y; Q_i) \geq F(y; Q_j) \quad \forall y \in \mathbb{R}.$$

Therefore, since $\alpha(\cdot)$ is decreasing and $\beta(\cdot)$ is increasing, it easily follows that the sequence $\{p_i\}_i$ is decreasing and the sequence $\{q_i\}_i$ is increasing. Thus, $\{\lambda_i\}_{i=2, \dots, M}$ is decreasing and we can apply the Lemma in Giovagnoli and Pintacuda (1998). $\square$

The next result shows how this design can be used to target the unknown dose μ associated to a pre-specified Γ .

Proposition 3.3. *For any given $\Gamma \in I$, let the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ be chosen so that*

$$\int [\alpha(y) - \beta(y)] F(dy; \Gamma) = 0 \quad (\text{“target condition”}). \quad (3.5)$$

If Γ is the unique solution of the following equation

$$\int [\alpha(y) - \beta(y)] F(dy; \gamma) = 0 \quad (3.6)$$

then

$$d_{K-1} < \mu \leq d_{K+1} \quad (3.7)$$

where μ is the target dose and K is defined by (3.4).

Proof. It is sufficient to prove

$$d_{j-1} < \mu \leq d_j \Rightarrow p_{j-1} > q_{j-1} \quad \text{and} \quad p_j \leq q_j \quad (3.8)$$

after which we can go on as in the proof of Proposition 2 in Giovagnoli and Pintacuda (1998). In order to prove (3.8), let us observe that, since $Q(\cdot)$ is strictly increasing, we have

$$Q_{j-1} = Q(d_{j-1}) < Q(\mu) = \Gamma \leq Q(d_j) = Q_j$$

Moreover, since $F(y; \cdot)$ is decreasing, $\alpha(\cdot)$ is decreasing and $\beta(\cdot)$ is increasing, then the function

$$\gamma \mapsto \int [\alpha(y) - \beta(y)] F(dy; \gamma) \quad (3.9)$$

is decreasing. Therefore, we have

$$p_j - q_j = \int [\alpha(y) - \beta(y)] F(dy; Q_j) \leq \int [\alpha(y) - \beta(y)] F(dy; \Gamma) = 0$$

and, since Γ is the unique solution of (3.6), we have

$$p_{j-1} - q_{j-1} = \int [\alpha(y) - \beta(y)] F(dy; Q_{j-1}) > 0 .$$

□

Remark 3.4. If the cdf $F(y; \gamma)$ is strictly decreasing in the expected value γ for any fixed $y \in [a; b]$ (this is the most usual case, e.g. binomial, normal, exponential distribution), then the functions

$$\gamma \mapsto \int \alpha(y) F(dy; \gamma) \quad \text{and} \quad \gamma \mapsto \int \beta(y) F(dy; \gamma)$$

are strictly monotone and so, if the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ satisfy the target condition, then Γ is the unique solution of (3.6). Furthermore, the sequence $\{\lambda_i\}_{i=2, \dots, M}$ is strictly decreasing, so that the modal set $M(\pi)$ of π is contained in $\{d_K; d_{K+1}\}$.

Proposition 3.3 also provides a solution to the problem of estimating μ . In fact, let $N_j(n)$ denote the number of observations that are allocated to the dose d_j after n steps, then $\pi_j(n) = n^{-1}N_j(n)$ will be the proportion of allocations to d_j and from the Strong Law of Large Numbers for Markov chains we have

$$\lim_{n \rightarrow \infty} \pi_j(n) = \pi(d_j) \quad a.s. \quad \forall j = 1, \dots, M \quad (3.10)$$

Thus, for n sufficiently large the mode of the empirical distribution $\pi(n) = (\pi_1(n), \dots, \pi_M(n))$ is a valid candidate as an estimator of μ . Some of its properties are discussed in (Giovagnoli and Pintacuda, 1998).

4. Special Cases

In this section we analyze some special U&D designs also considered in Baldi Antognini *et al* (2006).

4.1. Stepwise generating functions

Let us consider the following generating functions:

$$\alpha(y) = \alpha I_{]-\infty, s]}(y) \quad \beta(y) = \beta I_{]t, +\infty[}(y),$$

with $0 < \alpha \leq 1$, $0 < \beta \leq 1$ and $a < s < t < b$. In this case we have

$$\int [\alpha(y) - \beta(y)] F(dy; \gamma) = \alpha F(s; \gamma) - \beta [1 - F(t; \gamma)].$$

Thus, from the target condition

$$\alpha = \frac{\beta [1 - F(t; \Gamma)]}{F(s; \Gamma)} \quad (4.1)$$

and therefore, for any given pair of thresholds (s, t) , β must be chosen in $(0, \beta^*]$, where

$$\beta^* = \min \left\{ 1; F(s; \Gamma) [1 - F(t; \Gamma)]^{-1} \right\}.$$

4.2. Symmetric case

Proposition 4.1. *If the cdf $F(\cdot; \Gamma)$ satisfies the symmetric condition*

$$F(y; \Gamma) = 1 - F(2\Gamma - y; \Gamma) \quad \forall y \in \mathbb{R} \quad (4.2)$$

then, for every choice of the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ such that

$$\alpha(y) = \beta(2\Gamma - y) \quad \text{for each } y \in \mathcal{Y} \quad (4.3)$$

the target condition (3.5) is satisfied.

Proof. Condition (4.2) implies that $F(\cdot; \Gamma)$ is continuous. Indeed, for each $y \in \mathbb{R}$

$$\begin{aligned} \Delta F(y; \Gamma) &= F(y; \Gamma) - \lim_n F(y - 1/n; \Gamma) \\ &= F(y; \Gamma) - \lim_n [1 - F(2\Gamma - y + 1/n; \Gamma)] \\ &= F(y; \Gamma) - 1 + F(2\Gamma - y; \Gamma) = 0. \end{aligned}$$

Moreover, if Y has cdf $F(\cdot; \Gamma)$ and we set $Z = 2\Gamma - Y$, then

$$\begin{aligned} P(Z \leq z) &= P(2\Gamma - Y \leq z) = P(Y \geq 2\Gamma - z) \\ &= 1 - F(2\Gamma - z; \Gamma) = F(z; \Gamma), \quad \text{for any } z \in \mathbb{R} \end{aligned}$$

and so Y and Z are identically distributed. Consequently, it is immediate to verify the following equalities:

$$\int \alpha(y) F(dy; \Gamma) = \int \beta(2\Gamma - y) F(dy; \Gamma) = \int \beta(z) F(dz; \Gamma).$$

□

4.3. Linear generating functions

Suppose that $a = \inf \mathcal{Y}$ and $b = \sup \mathcal{Y}$ are finite and consider now the case in which the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ are linear, that is the probabilities of increasing and decreasing the dose are proportional to the observed response. Formally, for any $y \in \mathcal{Y}$ we let

$$\alpha(y) = \alpha \left(1 - \frac{y}{b}\right) \quad \beta(y) = 1 - \beta \left(1 - \frac{y}{b}\right),$$

with $0 < \alpha \leq \beta \leq (1 - a/b)^{-1}$ and $(\alpha + \beta)(1 - a/b) \geq 1$.

From the linearity of the generating functions, the target condition becomes:

$$\alpha(1 - \Gamma/b) = 1 - \beta(1 - \Gamma/b).$$

Thus, if we set $\alpha = (1 - \Gamma/b)^{-1} - \beta$, from the previous inequalities β must be chosen in such a way that

$$[2(1 - \Gamma/b)]^{-1} \leq \beta \leq (1 - a/b)^{-1}.$$

Observe that in this case $\Gamma \leq (a + b)/2$. This means that with such generating functions we can only target $\Gamma \in [a, (a + b)/2]$.

4.4. Complementary generating functions

Consider now the family of U&D algorithms under which the dose level changes at each step (i.e. $r_i = 0$ for any $i = 2, \dots, M - 1$), namely the designs for which the generating functions satisfy

$$\alpha(y) + \beta(y) = 1 \quad \forall y \in \mathcal{Y}.$$

Under any complementary U&D procedure,

$$\int [\alpha(y) - \beta(y)] F(dy; \gamma) = 2 \int \alpha(y) F(dy; \gamma) - 1 \quad \text{for any } \gamma \in I,$$

so that the target condition (3.5) becomes

$$\int \alpha(y) F(dy; \Gamma) = 1/2.$$

For example, the stepwise generating functions with $\alpha = \beta = 1$ and $s = t$ become complementary and the target condition is $F(t; \Gamma) = 1/2$. Whereas, the linear case with $\alpha = \beta$ becomes complementary and the target condition is $\alpha = \beta = [2(1 - \Gamma/b)]^{-1}$.

5. Randomized Group U&D Design

Most of the literature on U&D designs (Dixon and Mood, 1948; Derman, 1957; Durham and Flournoy, 1994 and 1995; Durham *et al*, 1997; Giovagnoli and Pintacuda, 1998; Stylianou and Flournoy, 2002; Ivanova *et al*, 2003; Bortot and Giovagnoli, 2005) deals with the fully sequential case: at each stage just one statistical unit is observed and the single response is used to choose the next treatment allocation. However this is not the common practice in clinical trials (e.g. Storer, 1998).

Recently, Gezmu and Flournoy (2006) and Baldi Antognini *et al* (2006) have studied a group version of U&D experiments by assuming that at each stage a group of m independent units is treated at the same dose level.

In this setting, if we replace in the randomized U&D design described above the single observation $Y_n = y$ by the empirical mean $\bar{Y}_n = \bar{y}$ of m independent observations, then all the preceding results still hold. Indeed, let $G(\cdot; \gamma)$ be the *cdf* of the empirical mean of m i.i.d random variables with common *cdf* $F(\cdot; \gamma)$. Since the family $\{F(\cdot; \gamma), \gamma \in I\}$ is stochastically ordered, then $\{G(\cdot; \gamma), \gamma \in I\}$ is stochastically ordered too (see Ross, 1996).

6. Some Examples

6.1. Binary responses

When the responses are binary and at each stage one unit is observed, then the randomized U&D design becomes the U&D rule proposed by Giovagnoli and Pintacuda (1998) with

$$\begin{aligned} \alpha(0) &= \alpha, & \alpha(1) &= \alpha', \\ \beta(0) &= \gamma', & \beta(1) &= \gamma, \end{aligned} \tag{6.1}$$

where $\max\{\alpha + \gamma', \alpha' + \gamma\} \leq 1$, $\max\{\alpha', \gamma'\} \leq \min\{\alpha, \gamma\}$ and $\sigma = \alpha - \alpha' + \gamma - \gamma' > 0$.

If at each stage a group of $m > 1$ statistical units is treated at the same dose level, this procedure corresponds to the randomized group U&D design proposed by Baldi Antognini *et al* (2006).

6.2. Gaussian case

For each fixed $m \geq 1$, assume now that the distribution of the response given the dose x is the Gaussian distribution $\mathcal{N}(Q(x), \sigma^2)$. Then the distribution of the empirical mean is $\mathcal{N}(Q(x), \sigma^2/m)$, so that $G(y; \gamma) = \Phi(\frac{y-\gamma}{\sigma} \sqrt{m})$, where Φ denotes the *cdf* of $\mathcal{N}(0, 1)$.

Observe that, for each Γ the *cdf* $G(\cdot; \Gamma)$ satisfies condition (4.2). Therefore, for $\epsilon \geq 0$ if we set

$$\begin{aligned} \alpha(y) &= \alpha I_{]-\infty, \Gamma - \epsilon]}(y) \\ \beta(y) &= \alpha I_{[\Gamma + \epsilon, +\infty[}(y), \end{aligned}$$

by Proposition 4.1 the target condition (3.5) is satisfied $\forall \alpha \in (0; 1]$. Indeed, in this case condition (3.5) becomes

$$\Phi\left(\frac{-\epsilon}{\sigma} \sqrt{m}\right) = 1 - \Phi\left(\frac{\epsilon}{\sigma} \sqrt{m}\right),$$

which is always satisfied because $\Phi(\cdot)$ is symmetric. Furthermore, since the function

$$\gamma \mapsto \int [\alpha(y) - \beta(y)] G(dy; \gamma) = \alpha \left[\Phi\left(\frac{\Gamma - \epsilon - \gamma}{\sigma} \sqrt{m}\right) - 1 + \Phi\left(\frac{\Gamma + \epsilon - \gamma}{\sigma} \sqrt{m}\right) \right]$$

is strictly decreasing, then Γ is the unique solution of equation (3.5).

7. Asymptotic Inference for U&D Experiments

In binary response trials, several estimators of the target have been considered for U&D experiments. One possibility is the mode of the empirical distribution, as seen before, which is non parametric. Parametric estimation requires care, because of the sequential nature of the design. Since the U&D procedure is response-adaptive, the observations generated by such a design are not independent.

Durham *et al* (1997) assumed an underlying parametric model for the binary-response curve (e.g. the two parameter logistic model or a location-scale model) and analyzed the properties of the maximum likelihood estimators under the U&D Biased Coin Design (BCD) introduced by Durham and Flournoy (1994), showing that the MLE's retain the asymptotical normality properties. Recently, Stylianou and Flournoy (2002) have proposed an estimate of the target based on a linearly interpolated isotonic regression; adopting the BCD, they show the performance of the proposed estimator by simulations.

In this Section we adopt a semi-parametric approach, assuming a parametric model for the responses with no parametric restrictions for the function $Q(\cdot)$, and consider estimating the unknown target μ by Maximum Likelihood. Since the U&D procedures are response-adaptive experiments, the responses generated by such a design are not independent, so that the theoretical properties of the proposed estimators may be analyzed together with the adopted procedure.

Suppose that the response Y to a given dose $X = x$ is a real random variable with distribution function belonging to the regular exponential family

$$Y \sim \exp \left\{ \frac{u(\theta_x)y - v(\theta_x)}{\phi_x} + w(y, \phi_x) \right\}, \quad (7.1)$$

with $u(\cdot)$ and $v(\cdot)$ twice continuously differentiable, where $\theta_x \in \mathbb{R}$ is the parameter of interest and $\phi_x \in \mathbb{R}^+$ is a nuisance parameter (for more details see Brown, 1986). Special cases are normal, Poisson, exponential and Bernoulli models.

Since the family in (7.1) can always be parameterized in such a way that the parameter of interest is the expected value, from now on we assume without loss of generality that

$$\theta_x = E[Y | X = x] = Q(x).$$

At each step n , for any given dose d_j the current MLE $\hat{Q}_j(n)$ of Q_j is the sample mean

$$\hat{Q}_j(n) = \frac{S_j(n)}{N_j(n)}, \quad \text{for } j = 1, \dots, M, \quad (7.2)$$

where $S_j(n)$ denotes the sum of the observation that are allocated to the dose d_j up to n .

Let $\hat{\mathbf{Q}}(n) = (\hat{Q}_1(n), \dots, \hat{Q}_M(n))$ be the MLE's of $\mathbf{Q} = (Q_1, \dots, Q_M)$, from Theorem 5.1 of Baldi Antognini and Giovagnoli (2005) and the results of Section 3 the following asymptotic results are easily established.

Theorem 7.1. *Under any randomized U&D experiment, as $n \rightarrow \infty$*

- *the empirical treatment distribution $\pi(n)$ converges almost surely to the stationary law π ;*
- *$\hat{\mathbf{Q}}(n) \rightarrow \mathbf{Q}$ a.s.*

- $\sqrt{n} \left(\hat{Q}(n) - Q \right) \hookrightarrow N(0; \Sigma) \quad \text{in law,}$

where

$$\Sigma = \text{diag} \left(\frac{\text{Var}[Y \mid X = d_j]}{\pi(d_j)} \right)_{j=1, \dots, M}. \quad (7.3)$$

For any given Γ , if the generating functions $\alpha(\cdot)$ and $\beta(\cdot)$ satisfy the assumption of Proposition 3.3, by (3.7) the target μ lies in a closed neighborhood of the mode d_K of the stationary distribution π and the asymptotic precision of the MLE's at the target dose is high. Furthermore, Eq. (7.3) shows that the precision increases as the peak of the stationary distribution rises. Thus, for n sufficiently large the maximum likelihood method provides a valid estimation procedure and the unknown target μ can be estimate by adjusting the MLE's through suitable algorithm of the classical isotonic regression method (e.g. the pair-adjacent violators algorithm; see Robertson *et al*, 1988).

8. On the Optimality of U&D Experiments

8.1. A suitable criterion for comparing U&D's

From Optimal Design Theory the U&D design is not asymptotically optimal, since the *ideal* stationary law π would be a Dirach-distribution with probability 1 at the unknown target μ . However, we can use the criterion based on the peakedness of the corresponding stationary distribution for comparing different U&D methods targeting the same target dose μ .

According to the *peakedness* definition of Giovagnoli and Pintacuda (1998), given two U&D experiments $UD^{(1)}$ and $UD^{(2)}$, both targeted on the same dose level μ , we say that the stationary distribution $\pi^{(1)}$ of $UD^{(1)}$ is more peaked than the stationary distribution $\pi^{(2)}$ of $UD^{(2)}$ if, for any $i = 2, \dots, M - 1$,

$$Q_i < \Gamma \text{ implies } \lambda_i^{(1)} \geq \lambda_i^{(2)} \quad \text{and} \quad Q_i \geq \Gamma \text{ implies } \lambda_{i+1}^{(1)} \leq \lambda_{i+1}^{(2)}, \quad (8.1)$$

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

In the following are some examples that show how the above criterion can be applied

8.2. Stepwise generating functions

In this case we have:

$$\begin{aligned} \lambda_2 &= \frac{1}{\beta[1 - F(t; Q_2)]}, \\ \lambda_i &= \frac{\alpha[F(s; Q_{i-1})]}{\beta[1 - F(t, Q_i)]}, \quad i = 3, \dots, M - 1, \\ \lambda_M &= \alpha F(s; Q_{M-1}). \end{aligned}$$

If α and β satisfy the target condition (4.1), λ_i does not depend on α and β for any $i = 3, \dots, M - 1$. Thus, the peakedness depends only on λ_2 and λ_M and if $\beta^{(1)} \leq \beta^{(2)}$, then $\pi^{(1)}$ is more peaked than $\pi^{(2)}$.

8.3. Linear generating functions

In this case we have:

$$\begin{aligned}\lambda_2 &= \frac{1}{1 - \beta(1 - Q_2/b)}, \\ \lambda_i &= \frac{\alpha(1 - Q_{i-1}/b)}{1 - \beta(1 - Q_i/b)}, \quad i = 3, \dots, M-1, \\ \lambda_M &= \alpha(1 - Q_{M-1}/b).\end{aligned}$$

The target condition implies $\alpha = (1 - \Gamma/b)^{-1} - \beta$. If we substitute this expression for α in the above equalities, by taking the derivative of λ_i with respect to β it is easy to see that λ_i is increasing with respect to β for all integers i such that $Q_i < \Gamma$ and it is decreasing for any i such that $Q_i \geq \Gamma$. By virtue of what we have observed in Subsection 4.3, we obtain that the best possible value for β is $(1 - a/b)^{-1}$.

References

- Baldi Antognini, A. and Giovagnoli, A.(2005). On the large sample optimality of sequential designs for comparing two or more treatments, *Sequential Analysis*, **24**(2), 205–217.
- Baldi Antognini, A., Bortot, P. and Giovagnoli, A.(2006). Randomized Group Up and Down Experiments, *Annals of the Institute of Statistical Mathematics*, under revision.
- Bortot, P. and Giovagnoli, A.(2005). Up and Down experiments of first and second order, *Journal of Statistical Planning and Inference*, **134**, 236–253.
- Brown, L.(1986). *Fundamentals of Statistical Exponential Families*, Institute of Mathematical Statistics, Hayward, CA.
- Cheung, Y.K.(2005). Coherence principles in dose-finding studies, *Biometrika*, **92**, 863–873.
- Derman, C.(1957). Non-parametric up-and-down experimentation, *Annals of Mathematical Statistics*, **28**, 795–799.
- Dixon, W.J. and Mood, A.M.(1948). A method for obtaining and analyzing sensitivity data, *Journal of the American Statistical Association*, **43**, 109–126.
- Durham, S.D. and Flournoy, N.(1994). Random walks for quantile estimation, *Statistical Decision Theory and Related Topics*, **V**, 467–476.
- Durham, S.D. and Flournoy, N.(1995). Up and down design: stationary treatment distributions, *Adaptive designs* (eds. Flournoy N. and Rosenberger W.F.), 139–157, IMS Lecture Notes **25**, Hayward CA.
- Durham, S.D., Flournoy, N. and Rosenberger, W.F.(1997). A random walk rule for phase I clinical trials, *Biometrics*, **53**, 745–760.
- Gasparini, M. and Eisele, J.(2000). A curve-free method for phase I clinical trials, *Biometrics*, **56**, 609–615.
- Gezmu, M. and Flournoy, N.(2006). Group up-and-down designs for dose-finding, *Journal of Statistical Planning and Inference*, **136**, 1749–1764.
- Giovagnoli, A. and Pintacuda, N.(1998). Properties of frequency distributions induced by general ‘up-and-down’ methods for estimating quantiles, *Journal of*

Statistical Planning and Inference, **74**, 51–63.

Hardwick, J., Meyer, C.M. and Stout, Q.F.(2003). Directed walk designs for dose response problems with competing failure modes, *Biometrics*, **59**, 229–236.

Ivanova, A., Montazer-Haghighi, A., Mohanti S.G. and Durham, S.D.(2003). Improved up-and-down designs for phase I trials, *Statistics in Medicine*, **22**, 69–82.

Mugno, R., Zhu, W. and Rosenberger, W.F.(2004). Adaptive urn designs for estimating several percentages of a dose-response curve, *Statistics in Medicine*, **23**, 2137–2150.

O’Quigley, J., Pepe, M. and Fisher, L.(1990). Continual Reassessment method: a practical design for phase I clinical trials in cancer, *Biometrics*, **46**, 33–48.

O’Quigley, J.(2002). Curve-free and Model-Based Continual Reassessment method Designs, *Biometrics*, **58**, 245–249.

Port, S.C.(1994). *Theoretical probability for applications*, Wiley, New York.

Robertson, T., Wright, F.T. and Dykstra, R.L.(1988). *Order Restricted Statistical Inference*, Wiley, New York.

Rosenberger, W.F. and Grill, S.E.(1997). A sequential design for psychophysical experiments: an application to estimating timing of sensory events, *Statistics in Medicine*, **16**, 2245–2260.

Ross, S.(1996). *Stochastic Processes*, Wiley & Sons, New York.

Storer, B.E.(1998). Phase I trials, *Encyclopedia of Biostatistics*, (eds. Armitage, P. and Colton, T.), 3365–3370, Wiley, New York.

Stylianou, M. and Flournoy, N.(2002). Dose finding using the biased coin up-and-down design and isotonic regression, *Biometrics*, **58**, 171–177.

von Békésy, G.(1947). A new audiometer, *Acta Otolaryngology*, **35**, 411–422.

Wu, C.F.J.(1985). Efficient sequential design with binary data, *Journal of the American Statistical Association*, **85**, 156–162.

Zhu, W. and Wong, W.K.(2000). Multiple-objective designs in a dose response experiment, *Journal of Biopharmaceutical Statistics*, **10**, 1–14.

Zhu, W. and Wong, W.K.(2001). Bayesian optimal designs for estimating a set of symmetrical quantiles, *Statistics in Medicine*, **20**, 123–137.