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### THE TREATMENT VERSUS EXPERIMENTATION DILEMMA IN DOSE-FINDING STUDIES

By

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מרכז לחקר הרציונליות

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# The Treatment Versus Experimentation Dilemma in Dose-finding Studies

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## Abstract

Phase I clinical trials are conducted in order to find the maximum tolerated dose (MTD) of a given drug from a finite set of doses. For ethical reasons, these studies are usually sequential, treating patients or group of patients with the best available dose according to the current knowledge. However, it is proved here that such designs, and, more generally, designs that concentrate on one dose from some time on, cannot provide consistent estimators for the MTD unless very strong parametric assumptions hold. We describe a family of sequential designs that treat individuals with one of the two closest doses to the estimated MTD, and prove that such designs, under general conditions, concentrate eventually on the two closest doses to the MTD and estimate the MTD consistently. It is shown that this family contains randomized designs that assign the MTD with probability that approaches 1 as the size of the experiment goes to infinity. We compare several designs by simulations, studying their performances in terms of correct estimation of the MTD and the proportion of individuals treated with the MTD.

## 1 Introduction

It is generally believed that increasing the dosage of a certain drug increases both the probability of a toxic reaction and efficacy. It is therefore important to determine the maximum tolerated dose (MTD) of a given drug, that is, the highest dose of a drug that does not cause unacceptable proportion of toxic reactions. This is particularly important in severe diseases, typically cancer, where strong and even lethal side effects may be present. MTD-finding studies, conducted as part of phase I clinical trials, are usually performed sequentially for reasons of efficiency and due to ethical requirements, and have the following two different purposes:

1. Treatment: ideally, treat each subject with the MTD; since it is unknown, use the best available estimate of the MTD at the time of treatment.
2. Experimentation: obtain a good estimate for the MTD at the end of the study.

The choice between the two is called the treatment versus experimentation dilemma in [Bartroff and Lai \(2010\)](#). Purpose 1 is an ethical consideration that does not allow to treat subjects with doses that may have a high toxicity rate or doses with low efficacy. In the words of [Shu and O’Quigley \(2008\)](#): “being optimal for anything other than the best estimated treatment for the next patient, or group of patients, to be included in the study is not acceptable”. Purpose 2 is the core of MTD studies, but may require to treat subjects with high doses in order to find the MTD as fast as possible.

In the case of a continuous response that follows a simple linear regression model and a continuous dose space, [Lai and Robbins \(1982\)](#) show that this dilemma can be resolved asymptotically by treating each subject with the estimated MTD based on a truncated version of the least squares estimators. The aim of the current paper is to examine if and how this dilemma can be resolved in the more common phase I framework of a finite dose space, under minimal assumptions on the dose-response curve.

The statistical literature regarding phase I clinical trials is quite rich; see, e.g., the review papers of [Rosenberger and Haines \(2002\)](#) and [Potter \(2006\)](#). Most of the methods, such as the continual reassessment method (CRM) ([O’Quigley et al. \(1990\)](#)) and escalation with overdose control ([Babb et al. \(1998\)](#)), assume a functional parametric model for the dose-response curve and adaptively estimate the parameters and the MTD; doses are assigned to patients according to the current estimate of the MTD. Such parametric methods are consistent only for certain dose-response curves ([Shen and O’Quigley \(1996\)](#); [Zacks et al. \(1998\)](#)), where consistency means that the estimator of the MTD is strongly consistent.

Several non-parametric methods were suggested in the literature of phase I trials. [Gasparini et al. \(2000\)](#) propose a Bayesian scheme, where each subject or cohort is treated with the estimated MTD according to the posterior distribution. Limitations and problems of this method are discussed by [O’Quigley \(2002\)](#) and by [Cheung \(2002\)](#) who shows that, for certain dose-response curves, there is a non-negligible probability of treating each subject with a dose that differs from the MTD. [Leung and Wang \(2001\)](#) consider a similar, albeit frequentist design, and [Ivanova and Wang \(2004\)](#) extend the procedure to two-dimensional dose-finding trials. [Ivanova et al. \(2007\)](#) present a non-parametric approach where the current dose is repeated if the estimated toxicity rate at this dose is close to the target level; otherwise the dose assigned to the next subject decreases or increases. Recently, [Oron et al. \(2010\)](#) classified the set of dose-response curves for which the latter method is consistent. All these methods focus on the ‘Treatment’ purpose, requiring that each subject be treated with the estimated MTD. We show in [Section 2](#) that they fail to satisfy the ‘Experimentation’ purpose, and that such designs cannot yield consistent estimators for all response curves.

Methods that do not require treatment at the current estimated MTD can yield consistent estimators. The classical non-parametric up and down methods ([Dixon and Mood \(1948\)](#); [Derman \(1957\)](#)) provide consistent estimators, but use only part of the available data at each step to determine the next dose, and therefore have undesirable properties ([O’Quigley and Zohar \(1990\)](#)). [Ivanova et al. \(2003\)](#) suggest an improved up and down method that estimates the dose-response curve by isotonic regression. To the best of our knowledge, this is the only method in the statistical literature of phase I that provides consistent estimator for the MTD for every increasing dose-response curve and that uses all available data at each step. Isotonic regression was considered previously in the framework of stochastic approximation on a lattice by [Mukerjee \(1981\)](#) who proves consistency of a method which eventually concentrates on two doses.

In view of the treatment versus experimentation dilemma, we show in [Section 2](#) that a design that assigns doses according to the estimated MTD has a non negligible probability of concentrating on

the wrong dose. This implies that the practice of assigning sequentially the current estimated MTD is statistically undesirable. Instead, it seems preferable to alternate in some fashion between the two estimated closest doses to the desired level. In Section 3 we present a modification of Mukerjee’s design and prove that it yields a consistent sequence of estimators for the MTD. We then generalize the result to a broader family of designs of which Ivanova et al. (2003)’s design is a special case. Though it is not possible to assign the MTD from a certain stage of the sequential experiment and on, one can assign the MTD with probability that goes to 1 as the experiment grows. We introduce in Section 3 a new design, which is a special case of the above family, that accomplishes this. Properties of several designs for small and moderate sample sizes are studied via simulations in Section 4. Concluding remarks are given in Section 5. All proofs are given in the Appendix.

## 2 Treatment Versus Experimentation Dilemma

Let  $x$  be a dose of a given drug and let  $y$  be a binary outcome, where  $y = 1$  ( $y = 0$ ) represents a toxic (non-toxic) response. Let  $m(x) := P(y = 1|x)$  be the probability of a toxic response at dose  $x$ , where  $m : \mathbb{R}^+ \rightarrow (0, 1)$  is an unknown strictly increasing function. Typically, the dose range  $D$  consists of only a few doses,  $d_1 < d_2 < \dots < d_K$ , and one aims at finding the dose  $d_{j^*}$  having toxicity that is closest to a prescribed target toxicity level  $m^*$ , i.e.,  $j^* = \arg \min_j |m(d_j) - m^*|$ . The dose  $d_{j^*}$  is called the MTD. Note that no assumptions on  $m$  are made besides being an increasing function;  $m$  is estimable only at  $K$  points, and thus the relevant parameter space is of finite dimension.

We consider sequential designs and denote by  $x_n$  and  $y_n$  the dose assigned to the  $n$ ’th subject and his response, respectively, and by  $\mathcal{F}_{n-1} := \sigma\{(x_1, y_1), (x_2, y_2), \dots, (x_{n-1}, y_{n-1})\}$  the available data prior to the decision on the  $n$ ’th subject’s dose. We assume for  $n \geq 2$  that

$$x_n \in \mathcal{F}_{n-1} \quad , \quad y_n | \mathcal{F}_{n-1} \sim \text{Bernoulli}(m(x_n)). \quad (1)$$

The sequence  $\{x_n\}_{n=1}^\infty$  is called a *design*; a sequence of estimators  $\{\widehat{MTD}_n\}_{n=1}^\infty$  is said to be *strongly consistent* with respect to a given design if  $\widehat{MTD}_n \rightarrow d_{j^*}$  a.s. for all increasing functions  $m$ .

**Theorem 1.** *Assuming (1), there exists no design that satisfies for all increasing functions  $m$*

$$P(\exists N \text{ s.t. } \forall n \geq N : x_n = d_{j^*}) = 1, \quad (2)$$

or equivalently that  $P(x_n \neq d_{j^*} \text{ i.o.}) = 0$ .

The idea of the proof is that a design that concentrates eventually on one dose, say  $d_j$ , can yield a consistent estimator for  $m(d_j)$ , but cannot estimate well  $m(d_i)$  for  $i \neq j$ ; therefore, such a design may miss the MTD. (Proofs are given in the Appendix.)

**Corollary 1** (Treatment versus experimentation dilemma). *Let  $\{\widehat{MTD}_n\}_{n=1}^\infty$  be any sequence of estimators of the MTD. If for all  $n$ ,  $x_{n+1} = \widehat{MTD}_n$  then  $\{\widehat{MTD}_n\}_{n=1}^\infty$  is not strongly consistent.*

Corollary 1 has important implications for phase I studies because many designs, including the CRM and the non-parametric methods mentioned in Section 1, assign the estimated MTD to the next subjects. Such designs cannot yield consistent estimation of the MTD unless severe parametric

assumptions on  $m$  are imposed. Hence, in our framework, it is not obvious that the aforementioned ethical requirement of Shu and O’Quigley should be accepted.

In the sequel, we construct sampling designs, and consider estimators  $\hat{m}_n(d)$  of  $m(d)$  and  $\widehat{MTD}_n$  of the MTD, such that the  $(n+1)$ st treatment is at one of the two doses  $d_j$  or  $d_{j+1}$ , where  $j$  is such that  $\hat{m}_n(d_j) < m^* < \hat{m}_n(d_{j+1})$ , and the sequence  $\widehat{MTD}_n$  is strongly consistent. Although ideal treatment at the MTD is not guaranteed, we have with probability 1 that  $j = j'$  where  $m(d_{j'}) < m^* < m(d_{j'+1})$  for large enough  $n$ ; in words, subjects are treated “almost” with the estimated MTD, and in the long run they are treated “almost” with the true MTD.

We shall use the isotonic regression estimator of  $m$ , which maximizes the likelihood  $\prod_{i=1}^n m(x_i)^{y_i} [1 - m(x_i)]^{1-y_i}$  under the restriction that  $m$  is nondecreasing (Barlow et al. (1972), p. 38). Specifically, for any  $r, s \in D$  such that  $r \leq s$ , define

$$\begin{aligned} \mathcal{N}_n(d_r, d_s) &= \sum_{i=1}^n I(x_i \in [d_r, d_s]), \\ \bar{y}_n(d_r, d_s) &= \begin{cases} \frac{1}{\mathcal{N}_n(d_r, d_s)} \sum_{i=1}^n y_i I(x_i \in [d_r, d_s]) & \mathcal{N}_n(d_r, d_s) > 0 \\ 0 & \mathcal{N}_n(d_r, d_s) = 0 \end{cases}. \end{aligned}$$

The estimator for  $m$  at stage  $n$  is

$$\hat{m}_n(d_j) = \max_{r \leq j} \min_{s \geq j} \bar{y}_n(d_r, d_s) \quad j = 1, \dots, K.$$

The corresponding estimator of the MTD is defined as follows. Let  $j$  be the maximal element in  $\{1, \dots, K-1\}$  that satisfies  $\hat{m}_n(d_j) \leq m^*$  (if no  $j$  satisfies this, set  $j = 1$ ); our estimator of the MTD is

$$\widehat{MTD}_n = \begin{cases} d_j & m^* \leq \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2} \\ d_{j+1} & m^* > \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2}. \end{cases} \quad (3)$$

The next section presents designs ( $\{x_n\}_{n \geq 1}$ ) under which the estimators above are strongly consistent. The results hold also for other sequences of estimators as detailed below.

### 3 Mukerjee’s design and generalizations

Mukerjee (1981) suggested a stochastic approximation method on a lattice, which is the basis of the family of designs we introduce. We describe the method with the necessary adjustments to a finite dose space, and provide a different proof of consistency.

Mukerjee’s design (MUK) assigns doses in pairs according to the current estimate of  $m$ , obtained by isotonic regression. The doses for subjects  $(2n+1)$  and  $(2n+2)$  are assigned as follows:

1. If  $\hat{m}_{2n}(d_K) < m^*$  then  $x_{2n+1} = x_{2n+2} = d_K$ .
2. If  $\hat{m}_{2n}(d_1) > m^*$  then  $x_{2n+1} = x_{2n+2} = d_1$ .
3. If  $\hat{m}_{2n}(d_j) \leq m^* \leq \hat{m}_{2n}(d_{j+1})$  for some  $j \in \{1, \dots, K-1\}$  then  $x_{2n+1} = d_j$ ,  $x_{2n+2} = d_{j+1}$ . (if more than one  $j$  satisfies the condition - an arbitrary one is chosen.)

**Theorem 2.** Assuming (1), if  $m(d_{j'}) < m^* < m(d_{j'+1})$  for some  $j' \in \{1, \dots, K-1\}$ , then Mukerjee's design satisfies

I.  $P(\exists N_1 \text{ s.t. } \forall n \geq N_1 : x_{2n+1} = d_{j'}, x_{2n+2} = d_{j'+1}) = 1$

II. The sequence of estimators defined in (3) satisfies  $P(\exists N_2 \text{ s.t. } \forall n \geq N_2 : \widehat{MTD}_n = j^*) = 1$ , i.e.,  $\widehat{MTD}_n$  is strongly consistent.

Part I of the theorem ensures that the design eventually assigns the two closest doses to  $m^{-1}(m^*)$  (one smaller and one larger than  $m^{-1}(m^*)$ ). One of these two doses is the MTD, and Part II asserts that it is estimated consistently.

**Remark 1.** By a similar argument as in the proof of Theorem 2, Mukerjee's design satisfies

i. If  $m^* = m(d_{j^*})$  then  $P(\exists N \text{ s.t. } \forall n \geq N : x_n \in \{d_{j^*-1}, d_{j^*}, d_{j^*+1}\}) = 1$ .

ii. If  $m^* < m(d_1)$  then  $P(\exists N \text{ s.t. } \forall n \geq N : x_n = d_1) = 1$ .

iii. If  $m^* > m(d_K)$  then  $P(\exists N \text{ s.t. } \forall n \geq N : x_n = d_K) = 1$ .

In all three cases,  $\widehat{MTD}_n$  is strongly consistent.

Together, Theorem 2 and Remark 1 show consistency for any increasing  $m$ . The interesting and important case is the one described in the theorem. Case (i) of Remark 1 is unlikely to occur, and in cases (ii) and (iii) the dose range is irrelevant for finding the MTD.

Because of the dependence of  $x_n$  on previous observations, and the dependence of  $y_n$  on  $x_n$ , the observations are not independent, hence standard convergence laws do not apply. Therefore, for the proof of Theorem 2 we transform the data into a martingale and apply a martingale convergence theorem.

The proof of Theorem 2 does not use the special features of isotonic regression and can be applied also to other estimators and designs as in the following remark.

**Remark 2.** Suppose that  $m(d_{j'}) < m^* < m(d_{j'+1})$  for some  $j' \in \{1, \dots, K-1\}$ . Let  $\tilde{m}_n(\cdot)$  be a consistent sequence of estimators in the sense that  $\tilde{m}_n(d_j) \rightarrow m(d_j)$  a.s. on  $\{\mathcal{N}_n(d_j) \rightarrow \infty\}$ ,  $j = 1, \dots, K$ , where  $\mathcal{N}_n(d_j) := \mathcal{N}_n(d_j, d_j)$ . Any design with the properties:

- $P(\exists j \in \{1, \dots, K-1\} \text{ s.t. } \{x_n = d_j \text{ i.o.}\} \cap \{x_n = d_{j+1} \text{ i.o.}\}) = 1$ .
- $\{m^* < \tilde{m}_n(d_j) \text{ i.o.}\} \subseteq \{x_n = d_{j+1} \text{ i.o.}\}^c \quad j = 1, \dots, K-1$ .
- $\{m^* > \tilde{m}_n(d_j) \text{ i.o.}\} \subseteq \{x_n = d_{j-1} \text{ i.o.}\}^c \quad j = 2, \dots, K$ .

(the inclusions are up to a null set) satisfies

$$P(\exists N \text{ s.t. } \forall n \geq N : x_n \in \{d_{j'}, d_{j'+1}\}) = 1.$$

The sequence  $\widehat{MTD}_n$  as defined in (3) is not necessarily consistent as  $\tilde{m}_n$  is not restricted to be monotone. This can be resolved in an obvious way, e.g., the sequence of estimators  $\widehat{MTD}_n$  defined as in (3) with  $j = \arg \max\{\mathcal{N}_n(d_j, d_{j+1})\}$  is strongly consistent.

A special case satisfying Remark 2 is the design of Ivanova et al. (2003) (IVA) with the isotonic regression estimator for  $m$ , where it is assumed that  $m^* = 1 - 0.5^{1/k}$  for some integer  $k$  (but consistency holds for any  $m^*$ ). At stage  $n$ ,  $\hat{m}_n$  is calculated and a higher (lower) dose is assigned if  $\hat{m}_n(x_n)$  is smaller (larger) than  $m^*$  and there are no (there is at least one) toxicity responses among the last  $k$  subjects. Otherwise, the same dose is assigned to the next subject. One can check that this design satisfies the conditions of Remark 2, and therefore the sequence of estimators defined in (3) is consistent.

**Remark 3.** Mukerjee's design described in the beginning of this section assigns doses to a pair of patients in each step. A similar design that assigns one dose at a time can yield consistent estimators and is more flexible. Specifically, we prescribe the doses  $d_K$  to one patient in the case  $\hat{m}_n(d_K) < m^*$ ,  $d_1$  once in the case  $\hat{m}_n(d_1) > m^*$ , and in the case  $\hat{m}_n(d_j) \leq m^* \leq \hat{m}_n(d_{j+1})$  for some  $j \in \{1, \dots, K-1\}$ , we assign only one of the doses  $d_j$  or  $d_{j+1}$  to a single patient in such a way that both would be assigned infinitely often if  $\hat{m}_n(d_j) \leq m^* \leq \hat{m}_n(d_{j+1})$  occurs infinitely often. Remark 2 implies that such a design concentrates eventually on a pair of doses, one of which is the MTD, and the corresponding estimator of the MTD is strongly consistent. Optimality of the proportion of choosing between  $d_j$  or  $d_{j+1}$  requires further study. In general, Mukerjee's suggestion of equal proportions may not be optimal under suitable criteria.

Constructing a design that (with probability 1) for large enough  $n$  satisfies  $x_n = d_{j^*}$  is impossible by Theorem 1. However, by randomly choosing  $d_j$  or  $d_{j+1}$  when  $\hat{m}_n(d_j) \leq m^* \leq \hat{m}_n(d_{j+1})$ , it is possible to provide a rule such that the probability of the event  $x_n = d_{j^*}$  approaches 1. Such a design 'almost' resolves the treatment versus experimentation dilemma.

Specifically, as in Remark 3, if  $m^* < \hat{m}_n(d_1)$  ( $m^* > \hat{m}_n(d_K)$ ) the proposed randomized allocation design (RAD) assigns  $x_{n+1} = d_1$  ( $x_{n+1} = d_K$ ). Otherwise, if  $B_n(d_j) := \{\hat{m}_n(d_j) \leq m^* \leq \hat{m}_n(d_{j+1})\}$  occurs, the RAD randomly chooses  $d_j$  or  $d_{j+1}$  according to the following rule:

$$\begin{aligned} & \text{if } m^* \leq (>) \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2} \text{ then} \\ & x_{n+1} = \begin{cases} d_j & \text{with probability } 1 - \frac{1}{k} \quad \left(\frac{1}{k}\right) \\ d_{j+1} & \text{with probability } \frac{1}{k} \quad \left(1 - \frac{1}{k}\right), \end{cases} \end{aligned} \quad (4)$$

where  $k := k(n, j) = \sum_{i=1}^n B_i(d_j)$ . Note that if  $m^* \leq \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2}$ , then  $d_j$  is the estimated MTD and  $x_{n+1} = d_j$  with large probability. The design is constructed in such a way that if  $B_n(d_j)$  occurs infinitely often then the probability of choosing the estimated MTD tends to one (if  $m(d_j) \leq m^* \leq m(d_{j+1})$ ), and both  $\{x_n = d_j\}$  and  $\{x_{n+1} = d_{j+1}\}$  occur infinitely often. Thus, in the RAD, non MTD treatment occurs asymptotically only rarely (though it occurs infinitely often) and the probability of treatment at the true MTD approaches one. The properties of this design are summarized in the following theorem.

**Theorem 3.** Assume that  $m(d_{j'}) < m^* < m(d_{j'+1})$ . The RAD (4) satisfies

- I.  $P(\exists N \text{ s.t. } \forall n \geq N : I(B_n(d_{j'})) = 1) = 1$ .
- II. The sequence  $\widehat{MTD}_n$  is strongly consistent.
- III.  $P(x_n = d_{j^*}) \rightarrow 1$ .



**Remark 4.** *As in the Mukerjee’s design, the resulting sequence of estimators of the MTD is strongly consistent also for the other three cases that are described in Remark 1.*

**Remark 5.** *Theorem 3 guarantees large probability of optimal treatment for large  $n$ , and treatment at one of the two closest doses to the MTD with probability 1 from some time on (Part I). However, for practical purposes (small  $n$ ), we found that the algorithm performs better when the rate of choosing the estimated MTD is reduced. For example, replacing  $k$  in (4) with  $a \cdot k + 2$ , where  $a$  is a (small) constant, yields better small sample performance. Thus, the choice between  $d_j$  and  $d_{j+1}$  is done with probability  $\frac{1}{a \cdot k + 2}$  which is  $\approx 0.5$  for small  $a$ . This modification does not change the asymptotic behavior of the estimator given in Theorem 3, while improving the learning rate of the response curve in early stages of the experiment.*

## 4 A Simulation study

In this section, we compare the small sample performance of several designs under the following dose-response curves:

A.  $(m(d_1), \dots, m(d_6)) = (0.1, 0.13, 0.15, 0.17, 0.25, 0.3)$ ;

B.  $(m(d_1), \dots, m(d_6)) = (0.07, 0.11, 0.23, 0.43, 0.84, 0.98)$ .

Scenario B is taken from Table 4 of O’Quigley et al. (1990). Scenario A represents a dose-response curve with a much smaller slope. For scenario A, we considered  $m^* = 0.2$  and  $m^* = 0.22$  (MTD= $d_3$  and MTD= $d_4$ , respectively), and for scenario B, we considered  $m^* = 0.2$  and  $m^* = 0.3$  (MTD= $d_3$  in both cases).

We compare the randomized allocation design (RAD) (4), the up and down design of Ivanova et al. (2003) (IVA), the design of Mukerjee described in Section 3 (MUK), and the parametric CRM design (Shen and O’Quigley (1996)) with maximum likelihood as the estimation approach. Three different versions of the RAD are studied according to different choices of  $a$  (see Remark 5):  $a = (10 - 2)/30$ ,  $(10 - 2)/50$ , and  $(10 - 2)/100$ , denoted RAD1, RAD2, and RAD3, respectively; these values correspond to 0.9 chance of assigning the estimated MTD for  $k = 30, 50$ , and 100.

The CRM assumes the one parameter working model  $P(y = 1|x = d_j) = \xi_j^\alpha$ , where  $\xi_j$  ( $j = 1, \dots, 6$ ) are the constants suggested by O’Quigley et al. (1990), and  $\alpha$  is the unknown parameter. The CRM approach assigns the next dose according to the maximum likelihood estimate of the MTD. Note that the two dose-response curves we consider do not satisfy the working model for the CRM; the ‘nearest’ curves in the standard Euclidean metric are

$$(0.001, 0.005, 0.025, 0.063, 0.202, 0.437) , (0.135, 0.213, 0.341, 0.448, 0.628, 0.786)$$

for scenarios A and B, respectively. However, scenario B with  $m^* = 0.2$  satisfies the conditions given by Cheung and Chappell (2002), conjectured to be sufficient for consistency of the CRM.

All methods started with  $x_1 = d_1$  and assigned  $x_{n+1} = d_{(x_n+1) \wedge K}$  until the first toxicity response was observed, and continued according to the specific rules described above. We conducted 10,000 replications from each scenario and ran the experiment for a maximum of 500 individuals. For better comparison, we coupled all designs in a manner that is akin to the notion of antithetic variables in the following way: the  $n$ ’th subject in the  $r$ ’th replication was associated with a uniform random



variable  $U_{n,r}$  (independent of all other random variables); if the  $n$ 'th subject in the  $r$ 'th replication was assigned with the dose  $d_j$  then he had toxicity response if  $U_{n,r} \leq m(d_j)$ . Thus, when individual  $n$  in replication  $r$  had the outcome  $y = 1$  in one design, then the same outcome ( $y = 1$ ) was obtained in all designs that assigned the same or a higher dose (to individual  $n$  in replication  $r$ ). Similarly for the outcome  $y = 0$ .

The performances of the designs were measured according to the different purposes of the treatment versus experimentation dilemma, that is, the probability of finding the true MTD at stage  $n$  and the proportion of subjects treated with the true MTD. For CRM, the MTD was estimated according to the maximum likelihood approach; for the other methods, (3) was used. The results for small sample sizes are given in Tables 1 and 2; Figures 1 and 2 present the results for all sample sizes.

Overall, the performances under scenario B are much better than under scenario A. This is expected, as the response-curve of the latter is much flatter. Also of note is the small probability of correct estimation for  $n \leq 50$ , which are the typical sample sizes of MTD studies. This is a known problem in such studies – the probability of selecting the true MTD is more often than not smaller than 0.5.

When comparing the designs on the basis of the probability of finding the true MTD, we found that IVA and MUK outperformed the others for large  $n$ . The CRM performed well only in scenario B with  $m^* = 0.2$  as suggested by the consistency considerations mentioned above. The randomized designs and especially RAD3 estimated the MTD relatively well for small  $n$ . This is because the allocation probability is close to one half in these stages. For small  $n$ , the performances of all designs except the CRM are comparable, though, it seems that Mukerjee's and Ivanova's designs are over all the best when aiming at estimating the MTD.

Looking at the proportion of subjects treated with the true MTD, we see that the RADs perform the best for large  $n$  for all scenarios except scenario B with  $m^* = 0.2$  in which CRM is better. Generally, RAD3, which has the smallest  $a$ , is the best among the RADs, though, in scenario B with  $m^* = 0.3$ , RAD1 and RAD2 perform somewhat better. For small  $n$ , it seems that the best design depends on the specific dose-response curve and on  $m^*$ .

The CRM performs very well in scenario B, but performs poorly under scenario A. This demonstrates the potential benefit and risk of using parametric models. No single method among the nonparametric approaches outperforms the others. Further study is needed in order to understand the operating characteristics of the different designs under different scenarios.

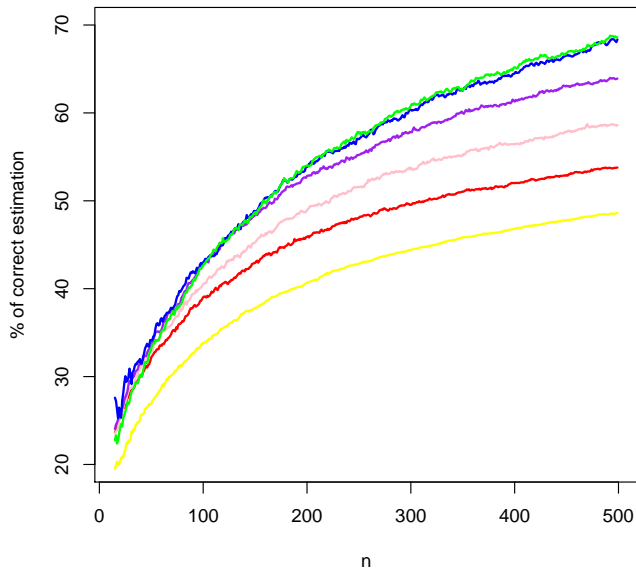
Table 1: The percent of correct estimation (standard errors) at stage  $n$  for  $n = 20, 30, 40, 50$  based on 10,000 replications; the best designs are shown in bold.

% of correct estimation					
Scenario	Design	n=20	n=30	n =40	n=50
$A(m^* = 0.2)$	RAD1	25.6(0.47)	28.3(0.45)	30.1(0.46)	32.2(0.47)
	RAD2	25.4(0.43)	28.6(0.45)	31.1(0.47)	33.1(0.47)
	RAD3	<b>25.9(0.44)</b>	29.3(0.45)	31.4(0.46)	33.4(0.47)
	MUK	25.6(0.47)	<b>30.1(0.46)</b>	<b>31.5(0.46)</b>	<b>34.1(0.47)</b>
	IVA	24.2(0.43)	27.8(0.45)	30.2(0.46)	33.2(0.47)
	CRM	20.5(0.40)	22.8(0.42)	25.6(0.47)	26.9(0.44)
$A(m^* = 0.22)$	RAD1	24.3(0.43)	26.3(0.44)	27.8(0.45)	29.6 (0.46)
	RAD2	24.6(0.43)	27.5(0.45)	29.1(0.45)	30.7(0.46)
	RAD3	<b>25.4(0.43)</b>	<b>28.8(0.45)</b>	30.0(0.46)	31.7(0.46)
	MUK	23.8(0.47)	26.6(0.44)	<b>30.1(0.46)</b>	<b>32.5(0.47)</b>
	IVA	21.4(0.41)	24.4(0.43)	27.1(0.44)	30.1(0.46)
	CRM	22.9(0.42)	24.1(0.43)	25.4(0.43)	26.3(0.44)
$B(m^* = 0.2)$	RAD1	44.8(0.45)	49.2(0.50)	52.2(0.50)	53.6(0.50)
	RAD2	45.6(0.50)	50.470(0.50)	54.2(0.50)	56.3(0.50)
	RAD3	<b>46.3(0.50)</b>	52.6(0.50)	55.8(0.50)	58.8(0.49)
	MUK	45.9(0.50)	<b>53.9(0.50)</b>	<b>58.6(0.49)</b>	<b>62.0(0.49)</b>
	IVA	46.3(0.50)	51.9(0.50)	56.9(0.50)	60.8(0.49)
	CRM	42.1(0.49)	49.9(0.50)	55.1(0.50)	59.3(0.49)
$B(m^* = 0.3)$	RAD1	47.9(0.50)	55.8(0.50)	61.7(0.49)	65.5(0.47)
	RAD2	48.7(0.50)	56.3(0.50)	62.0(0.48)	66.1(0.47)
	RAD3	47.7(0.50)	55.9(0.50)	61.2(0.49)	65.5(0.47)
	MUK	48.8(0.50)	55.4(0.50)	59.9 (0.49)	63.47(0.48)
	IVA	<b>51.2(0.50)</b>	<b>60.2(0.49)</b>	<b>65.4(0.48)</b>	<b>69.49(0.46)</b>
	CRM	50.6(0.50)	58.3(0.49)	63.0(0.49)	65.2(0.48)

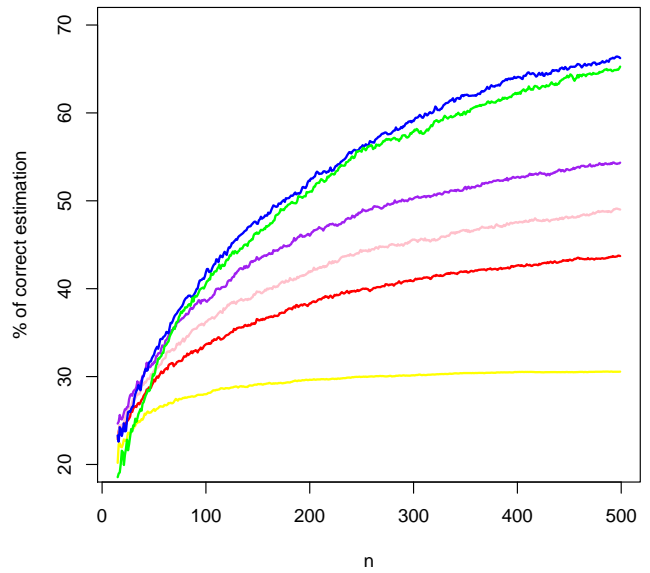
Table 2: The proportion of subjects treated with the true MTD (standard errors) for  $n = 20, 30, 40, 50$  based on 10,000 replications; the best designs are shown in bold.

Proportion of subjects treated with the true MTD					
Scenario	Design	n=20	n=30	n =40	n=50
$A(m^* = 0.2)$	RAD1	0.190(0.0021)	0.212(0.0023)	0.229(0.0025)	0.244(0.0026)
	RAD2	0.187(0.0020)	0.209(0.0021)	0.227(0.0023)	0.243(0.0024)
	RAD3	0.187(0.0019)	0.207(0.0020)	0.225(0.0021)	0.240(0.0021)
	MUK	0.198(0.0016)	0.214(0.0017)	0.227(0.0017)	0.239(0.0017)
	IVA	<b>0.202(0.0018)</b>	<b>0.220(0.0018)</b>	<b>0.234(0.0018)</b>	<b>0.246(0.0018)</b>
	CRM	0.173(0.0022)	0.188(0.0025)	0.202(0.0027)	0.214(0.0029)
$A(m^* = 0.22)$	RAD1	0.192(0.0020)	0.217(0.0022)	0.233(0.0023)	0.245(0.0024)
	RAD2	0.194(0.0019)	0.221(0.0020)	0.239(0.0021)	0.252(0.0022)
	RAD3	0.202(0.0019)	0.230(0.0019)	0.249(0.0020)	0.263(0.0020)
	MUK	<b>0.207 (0.0016)</b>	<b>0.235(0.0017)</b>	<b>0.254(0.0017)</b>	<b>0.269(0.0017)</b>
	IVA	0.157(0.0015)	0.183(0.0016)	0.203(0.0016)	0.218(0.0016)
	CRM	0.170(0.0023)	0.191(0.0027)	0.205(0.0030)	0.216(0.0031)
$B(m^* = 0.2)$	RAD1	0.325(0.0023)	0.361(0.0024)	0.389(0.0025)	0.411(0.0027)
	RAD2	0.324(0.0022)	0.361(0.0022)	0.389(0.0023)	0.413(0.0023)
	RAD3	0.314(0.0020)	0.351(0.0020)	0.381(0.0020)	0.405(0.0020)
	MUK	0.312(0.0017)	0.339(0.0015)	0.360(0.0014)	0.375(0.0013)
	IVA	<b>0.333(0.0018)</b>	<b>0.367(0.0017)</b>	0.391(0.0016)	0.409(0.0015)
	CRM	0.310(0.0023)	0.360(0.0025)	<b>0.402(0.0027)</b>	<b>0.437(0.0028)</b>
$B(m^* = 0.3)$	RAD1	0.335(0.0023)	0.382(0.0024)	0.422(0.0025)	0.456(0.0026)
	RAD2	0.330(0.0022)	0.376(0.0022)	0.414(0.0022)	0.446(0.0023)
	RAD3	0.318(0.0020)	0.359(0.0020)	0.393(0.0019)	0.423(0.0019)
	MUK	0.312(0.0016)	0.337(0.0014)	0.356(0.0013)	0.371(0.0013)
	IVA	0.362(0.0017)	0.403(0.0017)	0.433(0.0016)	0.456(0.0015)
	CRM	<b>0.372(0.0021)</b>	<b>0.434(0.0022)</b>	<b>0.478(0.0022)</b>	<b>0.512(0.0022)</b>

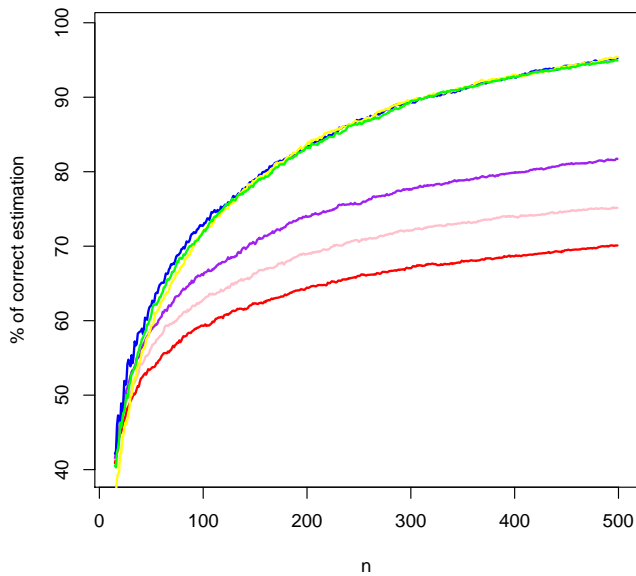
Figure 1: The percent of finding the true MTD at stage  $n$  for  $n = 20 \dots 500$  based on 10,000 replications. The following designs were compared: RAD1 (red), RAD2 (pink), RAD3 (purple), Mukerjee (blue), Ivanova et al. (2003) (green) and CRM (yellow).



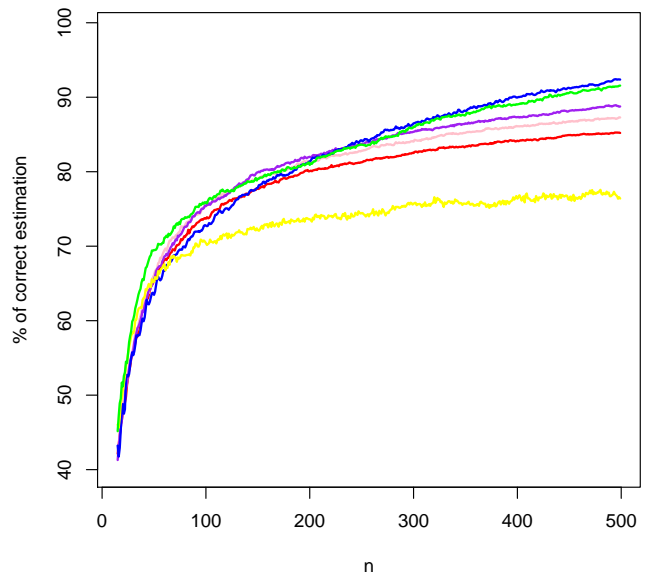
(a) Scenario A ( $m^* = 0.2$ )



(b) Scenario A ( $m^* = 0.22$ )

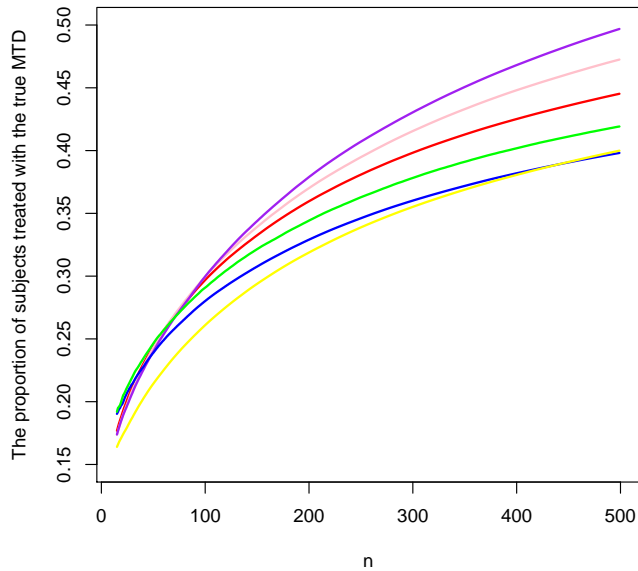


(c) Scenario B ( $m^* = 0.2$ )

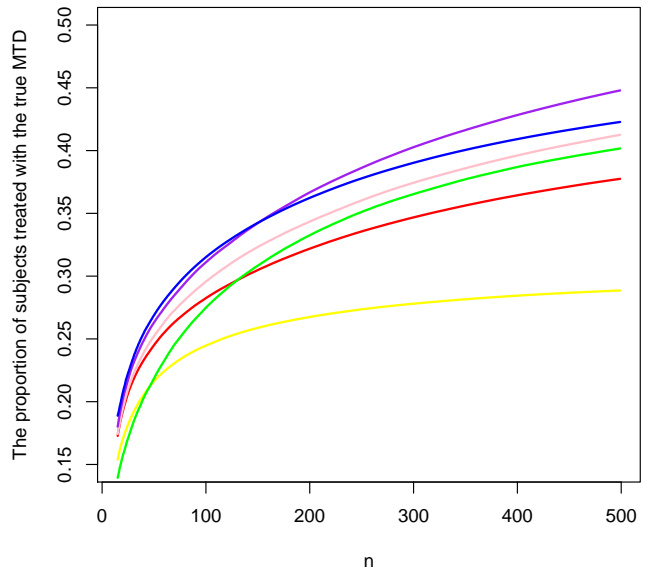


(d) Scenario B ( $m^* = 0.3$ )

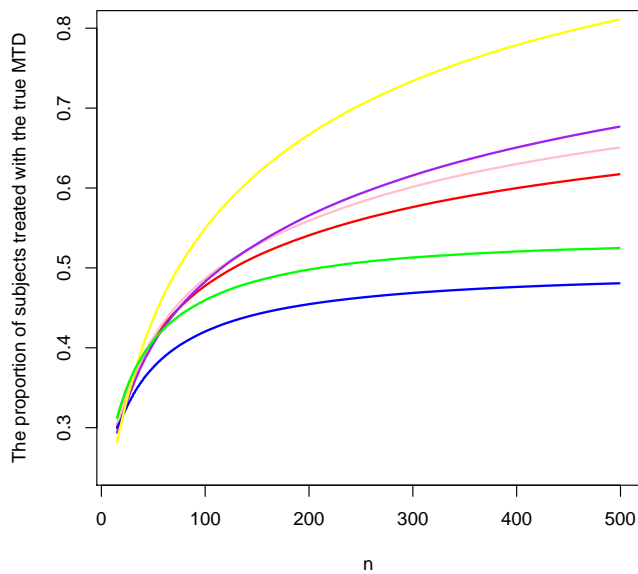
Figure 2: The proportion of subjects treated with the true MTD for  $n = 20 \dots 500$  based on 10,000 replications. The following designs were compared: RAD1 (red), RAD2 (pink), RAD3 (purple), Mukerjee (blue), [Ivanova et al. \(2003\)](#) (green) and CRM (yellow).



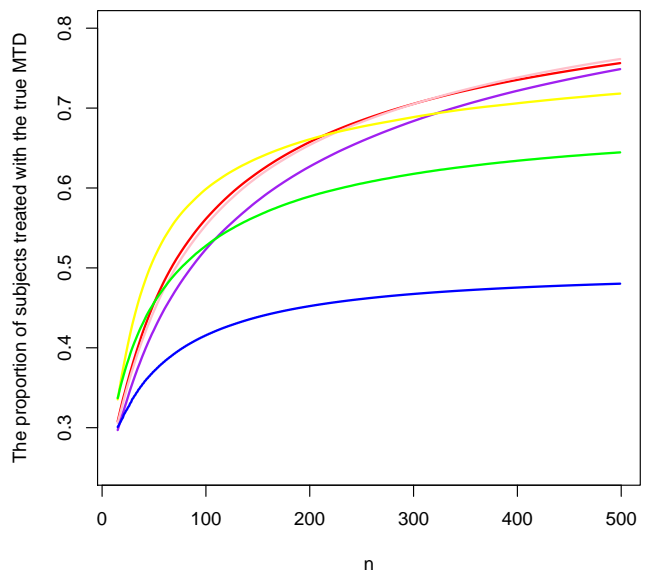
(a) Scenario A ( $m^* = 0.2$ )



(b) Scenario A ( $m^* = 0.22$ )



(c) Scenario B ( $m^* = 0.2$ )



(d) Scenario B ( $m^* = 0.3$ )

## 5 Conclusions

Most designs considered in the literature of phase I clinical trials follow the premise that subjects must be treated with the estimated MTD. This paper shows that without parametric assumptions on the response curve, such an approach yields inconsistent estimators. In other words, one cannot achieve simultaneously the two goals in the treatment versus experimentation dilemma, i.e, finding the MTD and treating the subjects in an optimal way. This finding necessitates a second thought about the way doses should be assigned in phase I studies. In particular, this result may imply that one should try to learn the responses in the two closest doses to the desired level, rather than the closest one.

A similar result can be proved in parametric models where the dimension of the parameter space is two or larger. The basic idea of the proof of Theorem 1 is valid also for such models. A design that concentrates eventually on one dose can yield a consistent estimator for the probability of a toxic response at that dose only, but knowing the response curve in a single dose cannot yield a consistent estimator for the unknown parameters, unless the dimension is one. Therefore, Corollary 1 is also relevant for parametric models involving more than one parameter: assigning the estimated MTD to the next subject at each stage may be undesirable also in this seemingly simpler case. Shen and O’Quigley (1996) and Shu and O’Quigley (2008), make a similar argument in favor of a one parameter model as a working model for the CRM.

Following Mukerjee (1981), we suggest to treat each subject with one of the two closest doses to the estimated desired level. Mukerjee proposes to use each of these doses with equal proportions. We show that a broader family of choices still yields consistent estimators. Further study is required in order to achieve optimality under suitable definitions.

The randomized allocation design in which the MTD is assigned to the  $n$ ’th subject with increasing probability, treats subject ‘almost’ in an optimal way for large  $n$ . However, for small and moderate sample sizes, this design does not estimate the MTD as well as other designs, as it aims mainly at the treatment part of the dilemma. This implies that, even though the MTD can be consistently estimated, a price is being paid in the experimentation part.

## Appendix

### Proof of Theorem 1

A sequential design is a sequence of rules or functions:  $f_n(x_1, y_1, \dots, x_{n-1}, y_{n-1}) \in D$ , where  $f_n = x_n$  is the dose assigned to the  $n$ ’th subject. Assume that  $\{f_n\}_{n=1}^\infty$  satisfies (2) for all increasing  $m$ ’s. We will show that such a sequence does not exist. Let  $m$  and  $m'$  differ only at one value in  $D$ , say  $d_3$ , and suppose, for example, that  $j^* = 2$  and  $j'^* = 3$  are the MTD’s associated with  $m$  and  $m'$ . It is easy to construct such  $m$  and  $m'$ . Consider two probability measures,  $P$  and  $P'$ , generated by  $m$  and  $m'$ , defined on the measurable space  $(\Omega, \mathcal{F})$ , where  $\Omega$  is the sample space of the experiment and  $\mathcal{F}$  is the sigma-field generated by the union of all  $\mathcal{F}_n$ .

Let  $A_n$  be the event that from the  $n$ ’th subject on we always choose  $d_2$ . By the assumption of consistency of the given decision rule  $f_n$  under  $P$  (that is, under  $m$ ), there is an index  $n_0$  such that  $P(A_{n_0}) > 0$ . Consequently, there exists a vector  $(x_1^0, y_1^0, \dots, x_{n_0-1}^0, y_{n_0-1}^0)$  such that

$$\tilde{A} := \{\omega \in \Omega : (x_1, y_1, \dots, x_{n_0-1}, y_{n_0-1})(\omega) = (x_1^0, y_1^0, \dots, x_{n_0-1}^0, y_{n_0-1}^0)\} \subseteq A_{n_0},$$

and  $P(\tilde{A}) > 0$ .

By finiteness we also have  $P'(\tilde{A}) > 0$ , since the  $n_0 - 1$  outcomes that lead to  $A_{n_0}$  also have positive probability under  $P'$ . Therefore,  $P'(A_{n_0}) \geq P'(\tilde{A}) > 0$  so that on a set of positive measure,  $A_{n_0}$ , we sample  $d_2$  from  $n_0$  on, while the MTD under  $m'$  is  $d_3$ .  $\square$

## Proof of Theorem 2

For the proof, we first need a lemma.

**Lemma 1.** *Mukerjee's design satisfies*

I.  $\bar{y}_n(d_j) \rightarrow m(d_j)$  a.s. on  $\{\mathcal{N}_n(d_j) \rightarrow \infty\}$ ,  $j = 1, \dots, K$ , where  $\bar{y}_n(d_j) := \bar{y}_n(d_j, d_j)$ .

II.  $\hat{m}_n(d_j) \rightarrow m(d_j)$  a.s. on  $\{\mathcal{N}_n(d_j) \rightarrow \infty\}$ ,  $j = 1, \dots, K$ .

**Proof.** I.  $\hat{m}_n := \sum_{i=1}^n I(x_i = d_j)(y_i - m(d_j))$  is a square integrable martingale with respect to the filtration  $\mathcal{F}_n$ , with quadratic variation  $\sum_{i=1}^n [I(x_i = d_j)]^2 \cdot m(d_j) \cdot [1 - m(d_j)] = m(d_j) \cdot [1 - m(d_j)] \mathcal{N}_n(d_j)$ , where  $\mathcal{N}_n(d_j) = \sum_{i=1}^n I(x_i = d_j)$ . Therefore, by the strong law of large numbers for square integrable martingales, ([Shiryaev \(1996\)](#) p. 519, Theorem 4)

$$\frac{1}{\mathcal{N}_n(d_j)} \sum_{i=1}^n I(x_i = d_j)(y_i - m(d_j)) \rightarrow 0 \quad \text{a.s. on } \{\mathcal{N}_n(d_j) \rightarrow \infty\}.$$

Since  $\bar{y}_n(d_j) = m(d_j) + \frac{1}{\mathcal{N}_n(d_j)} \sum_{i=1}^n I(x_i = d_j)(y_i - m(d_j))$ , the first part of the lemma follows.

II. We first consider the case  $j \in \{2, \dots, K-1\}$ . Mukerjee's design has the property that if  $\mathcal{N}_n(d_j) \rightarrow \infty$  then either  $\mathcal{N}_n(d_{j+1}) \rightarrow \infty$  or  $\mathcal{N}_n(d_{j-1}) \rightarrow \infty$  (or both); without loss of generality, we assume that  $\mathcal{N}_n(d_{j+1}) \rightarrow \infty$ , and we condition on the event  $\{\mathcal{N}_n(d_j) \rightarrow \infty\} \cap \{\mathcal{N}_n(d_{j+1}) \rightarrow \infty\}$ .

Recall that  $\hat{m}_n(d_j) = \max_{r \leq j} \min_{s \geq j} \bar{y}_n(d_r, d_s)$ . We first show that for every  $r \leq j$  and  $s > j$

$$\bar{y}_n(d_r, d_s) > \bar{y}_n(d_r, d_j), \tag{5}$$

eventually, with probability 1, i.e., for almost all  $\omega \in \Omega$  (where the probability space is  $(\Omega, \mathcal{F}, P)$  as defined in the proof of Theorem 1) there exists  $N(\omega)$  such that (5) holds for all  $n \geq N(\omega)$  and where the random variables are evaluated at  $\omega$ . To see that, write

$$\bar{y}_n(d_r, d_j) = \sum_{k=r}^j \frac{\mathcal{N}_n(d_k)}{\mathcal{N}_n(d_r, d_j)} \bar{y}_n(d_k),$$

and recall that  $\mathcal{N}_n(d_r, d_j) > \mathcal{N}_n(d_j) \rightarrow \infty$ . If  $\lim_n \mathcal{N}_n(d_k) < \infty$  then the corresponding term in the sum above has zero limit; if  $\lim_n \mathcal{N}_n(d_k) = \infty$  then, by part I of the lemma,  $\lim_n \bar{y}_n(d_k) = m(d_k)$  a.s., and in particular,  $\lim_n \bar{y}_n(d_j) = m(d_j)$  a.s.. Thus,  $\limsup_n \bar{y}_n(d_r, d_j) \leq m(d_j)$  a.s.. A similar argument shows that  $\liminf_n \bar{y}_n(d_{j+1}, d_s) \geq m(d_{j+1})$  a.s., and therefore, for large enough  $n$ , with probability 1,  $\bar{y}_n(d_{j+1}, d_s) > \bar{y}_n(d_r, d_j)$ . The inequality (5) follows, as

$$\begin{aligned} \bar{y}_n(d_r, d_s) &= \frac{\mathcal{N}_n(d_r, d_j)}{\mathcal{N}_n(d_r, d_s)} \bar{y}_n(d_r, d_j) + \frac{\mathcal{N}_n(d_{j+1}, d_s)}{\mathcal{N}_n(d_r, d_s)} \bar{y}_n(d_{j+1}, d_s) > \\ &\frac{\mathcal{N}_n(d_r, d_j)}{\mathcal{N}_n(d_r, d_s)} \bar{y}_n(d_r, d_j) + \frac{\mathcal{N}_n(d_{j+1}, d_s)}{\mathcal{N}_n(d_r, d_s)} \bar{y}_n(d_r, d_j) = \bar{y}_n(d_r, d_j). \end{aligned}$$



In view of (5) and the definition of  $\hat{m}_n$ , for large enough  $n$ , with probability 1,  $\hat{m}_n(d_j) = \max_{r \leq j} \bar{y}_n(d_r, d_j)$ . Now, since  $\limsup_n \bar{y}_n(d_r, d_j) \leq m(d_j)$  a.s. for  $r < j$ , and  $\lim_n \bar{y}_n(d_j, d_j) = m(d_j)$  a.s., the second part of the lemma follows for  $j \in \{2, \dots, K-1\}$ .

If  $j = 1$  (the case  $j = K$  is similar), then if  $\mathcal{N}_n(d_2) \rightarrow \infty$  the proof is the same, otherwise  $d_1$  is the only dose that is assigned infinitely often and therefore, for every  $j$

$$\bar{y}_n(d_1, d_j) = \sum_{k=1}^j \frac{\mathcal{N}_n(d_k)}{\mathcal{N}_n(d_r, d_j)} \bar{y}_n(d_k) \rightarrow m(d_1) \text{ a.s.}$$

because for  $k = 1$  the limit is  $m(d_1)$ , and for  $k > 1$ , the  $k$ 'th term has limit zero; since  $\hat{m}_n(d_1) = \min_{j \geq 1} \bar{y}_n(d_1, d_j)$  the lemma follows.

**Proof of Theorem 2.** *I.* For an even  $n$  and  $j < K$ , denote by  $B_n(d_j)$  the event that  $x_{n+1} = d_j, x_{n+2} = d_{j+1}$ , and by  $B'_n(d_1)$  ( $B'_n(d_K)$ ) the event that  $x_{n+1} = d_1, x_{n+2} = d_1$  ( $x_{n+1} = d_K, x_{n+2} = d_K$ ). We show by contradiction that the only  $j$  satisfying that  $\{B_n(d_j)\}$  occurs infinitely often is  $j = j'$ .

Assume that  $j$  satisfies  $j > j'$  and  $\{B_n(d_j)\}$  occurs infinitely often. By Lemma 1, there exists  $N$  such that  $\hat{m}_n(d_j) > m^*$  for all  $n > N$ , with probability 1. Then,  $I(B_n(d_j)) = 0$  for  $n > N$  in contradiction to  $\{B_n(d_j)\}$  occurring infinitely often. A similar argument shows that  $\{B_n(d_j)\}$  does not occur infinitely often for  $j < j'$ , nor do  $\{B'_n(d_1)\}$  and  $\{B'_n(d_K)\}$ ; hence, for large enough  $n$ , with probability 1,  $x_{2n+1} = d_{j'}$ ,  $x_{2n+2} = d_{j'+1}$ .

*II.* The first part of the theorem ensures that the design will concentrate eventually on the two closest doses to  $m^{-1}(m^*)$  and both of these doses will be chosen infinitely often. By Lemma 1,  $\hat{m}_n(d_{j'})$  and  $\hat{m}_n(d_{j'+1})$  are strongly consistent. This implies that for large enough  $n$ , with probability 1,  $\widehat{MTD}_n = j^*$ .  $\square$

## Proof of Theorem 3

For the purposes of this theorem we define  $x_{n+1}$  for each  $n$  as

$$\begin{aligned} \text{if } m^* \leq \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2} & \text{ then } x_{n+1} = d_j I(U_{n+1} \leq \frac{k-1}{k}) + d_{j+1} I(U_{n+1} > \frac{k-1}{k}); \\ \text{if } m^* > \frac{\hat{m}_n(d_j) + \hat{m}_n(d_{j+1})}{2} & \text{ then } x_{n+1} = d_j I(U_{n+1} \leq \frac{1}{k}) + d_{j+1} I(U_{n+1} > \frac{1}{k}), \end{aligned}$$

where  $\{U_i\}_{i=1}^\infty$  are i.i.d uniform  $[0, 1]$  random variables independent of the  $y$ 's;  $j$  is such that  $I(B_n(d_j)) = 1$  and  $k = \sum_{i=1}^n B_i(d_j)$ .

*I.* The proof is similar to the proof of Theorem 2 after showing that if  $j \in \{1, \dots, K-1\}$  satisfies that  $B_n(d_j)$  occurs infinitely often, then both  $\{x_n = d_j\}$  and  $\{x_n = d_{j+1}\}$  occur infinitely often, with probability 1.

Let  $\{n_k\}_{k=1}^\infty$  be the (random) subsequence in which  $I(B_{n_k}(d_j)) = 1$ . The design implies  $\{x_{n_k+1} = d_j\} \supseteq \{U_{n_k+1} < \frac{1}{k}\}$ , and  $\{U_{n_k+1}\}_{k=1}^\infty$  are i.i.d. (since  $n_k = \min\{n : I(B_n(d_j)) = 1, n > n_{k-1}\}$  is a stopping time for all  $k$ ; see Lemma 2 below). As,  $\sum_k P(U_{n_k+1} < \frac{1}{k}) = \sum_k \frac{1}{k} = \infty$ , the second Borel-Cantelli lemma shows that  $\{U_{n_k+1} < \frac{1}{k}\}$ , and hence  $\{x_{n_k+1} = d_j\}$  occur infinitely often. Similar arguments show that  $\{x_n = d_{j+1}\}$  occur infinitely often.

*II.* This follows from the same arguments as in the proof of Part *II* of Theorem 2.

III. The MTD,  $d_{j^*}$ , is either  $d_{j'}$  or  $d_{j'+1}$ . Assume that  $d_{j^*} = d_{j'}$  (the argument is symmetric). For any  $n \geq k_0 \geq 1$ , define the set

$$A_{n,k_0} = B_n(d_{j'}) \cap \{\widehat{MTD}_n = d_{j'}\} \cap \{k(n, j') \geq k_0\}.$$

For any fixed  $k_0$  and large enough  $n$  (so that  $A_{n,k_0}$  is not null),

$$P(x_{n+1} = d_{j'}) \geq P(x_{n+1} = d_{j'} | A_{n,k_0}) P(A_{n,k_0}) \geq \frac{k_0 - 1}{k_0} P(A_{n,k_0}),$$

since  $P(x_{n+1} = d_{j'}) = P(U_{n+1} \leq \frac{k-1}{k}) \geq P(U_{n+1} \leq \frac{k_0-1}{k_0})$  on  $A_{n,k_0}$ . For any fixed  $k_0$ ,  $P(A_{n,k_0}) \rightarrow 1$  by Parts I and II, so that  $\liminf_n P(x_n = d_{j'}) \geq \frac{k_0-1}{k_0}$ . As this is true for all  $k_0$ , the claim follows.

**Lemma 2.** Let  $\{U_n\}_{n=1}^\infty$  be a sequence of i.i.d random variables with distribution  $F$ , and let  $\{\tau_n\}_{n=1}^\infty$  be an increasing sequence of finite stopping times with respect to  $\mathcal{G}_n \supseteq \sigma(U_1, \dots, U_n)$ . Assume that  $U_{n+k} | \mathcal{G}_n \sim F$  for all  $k \geq 1$  and  $n$ . Then  $\{U_{\tau_n+1}\}_{n=1}^\infty$  is also a sequence of i.i.d random variables with distribution  $F$ .

Lemma 2 is quite standard, we include a proof for completeness.

**Proof.** For any subset of indices  $n_1 < n_2 < \dots < n_l$  and any measurable sets  $A_1, \dots, A_l$ ,

$$\begin{aligned} P\left(\bigcap_{1 \leq k \leq l} \{U_{\tau_{n_k}+1} \in A_k\}\right) &= E\left[\prod_{1 \leq k \leq l} I(U_{\tau_{n_k}+1} \in A_k)\right] = E\left[E\left[\prod_{1 \leq k \leq l} I(U_{\tau_{n_k}+1} \in A_k) | \mathcal{G}_{\tau_{n_l}}\right]\right] \\ &= E\left[\prod_{1 \leq k \leq l-1} I(U_{\tau_{n_k}+1} \in A_k) E[I(U_{\tau_{n_l}+1} \in A_l) | \mathcal{G}_{\tau_{n_l}}]\right] \\ &= E\left[\prod_{1 \leq k \leq l-1} I(U_{\tau_{n_k}+1} \in A_k)\right] P(U_1 \in A_l) = \dots = \prod_{1 \leq k \leq l} P(U_1 \in A_k); \end{aligned}$$

hence the random variables  $\{U_{\tau_n+1}\}_{n=1}^\infty$  are i.i.d. □

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