MODELLISTICA E CALCOLO SCIENTIFICO
MODELING AND SCIENTIFIC COMPUTING

MOX–Report No. 09/2007

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Asymptotics in response-adaptive designs generated by a two-color, randomly reinforced urn

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April 27, 2007

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Abstract

This paper illustrates asymptotic properties for a response-adaptive design generated by a two-color, randomly reinforced urn model. The design considered is optimal in the sense that it assigns patients to the best treatment with probability converging to one. An approach to show the joint asymptotic normality of the estimators of the mean responses to the treatments is provided in spite of the fact that allocation proportions converge to zero and one. Results on the rate of convergence of the number of patients assigned to each treatment are also obtained. Finally, we study the asymptotic behavior of a suitable test statistic.

Keywords: Generalized Pólya urn, Adaptive designs, Asymptotic normality, Rate of convergence, Optimal allocation, Estimation and inference, Clinical trials, Ethical allocation, Testing mean differences, Treatment allocation, Stable convergence.

MSC 2000: Primary: 62L05; secondary: 60F15, 60F05

*Part of the work of the first author has been done at MOX– Modellistica e Calcolo Scientifico, Dipartimento di Matematica "F. Brioschi", Politecnico di Milano , via Bonardi 9, 20133 Milano, Italy, under the supervision of Prof. Piercesare Secchi. She wishes to thank for the support and the warm hospitality.

1 Introduction

The present paper is devoted to studying asymptotic properties of sequential, response-adaptive designs generated by a two-color, generalized Pólya urn that is reinforced every time it is sampled with a random number of balls that are the same color as the ball that was extracted. The model is based on the the two-color randomly reinforced urn studied in Muliere, Paganoni and Secchi (2006a) and for conciseness we will denote it by the acronym RRU. A RRU generalizes to discrete or continuous responses the urn models proposed initially in Durham and Yu (1990) and Li, Durham and Flournoy (1996) for dichotoumus responses, and which was also applied to select an optimal dosage in Durham, Flournoy and Li (1998). This work has been stimulated by the fact that a design driven by a RRU allocates units to the best response with a probability that converges to one. In the context of a response-adaptive design used to allocate patients in a clinical trial, this property is desirable from an ethical point of view; for this reason, the results obtained in this work will be illustrated within a clinical trial framework. However, the reader should note that response-adaptive designs are of fundamental importance in many areas of applications, for instance in industrial problems.

The experimenter has two simultaneous goals: collecting evidence to determine the superior treatment, and biasing the allocations toward the better treatment in order to reduce the proportion of subjects in the experiment that receive the inferior treatment. Patients enter the experiment sequentially and are allocated randomly to a treatment, according to a rule that depends on the previous allocations and the previous observed responses. A vast number of adaptive designs have been proposed in recent years; an informed review is found in Rosenberger and Lachin (2002). Many of them are based on generalized urn models; see, for instance, Rosenberger (2002), who traces an historical development of generalized urn models, their properties and applications in sequential designs. Although in the past many response-adaptive designs have been focused on binary responses, more attention recently has been given to continuous outcomes: among others, we note the procedures proposed by Hu and Zhang (2004), Atkinson and Biswas (2005) and Zhang and Rosenberger (2006).

Consider a clinical trial conducted to compare two competing treatments, say B and W, and a response-adaptive design. Indicate with $N_B(n)$ and $N_W(n)$ the number of patients allocated through the n-th patient to treatment B and W, respectively. Many of these designs allocate patients targeting a certain proportion $\rho \in (0, 1)$; the proportions of patients $N_B(n)/n$ and $N_W(n)/n$ allocated to each treatment converge almost surely to ρ and $1 - \rho$, respectively, where ρ may be ad hoc or may be determined by some optimality criteria which are usually a function of the unknown parameters of the outcomes. The adaptive design considered in this paper is different, since its optimality property is to assign patients to the best treatment with a proportion that converges almost surely to 1, while the proportion of patients allocated to the inferior treatment converges to 0. When the two treatments are equivalent, the design allocates the proportion of patients with a random limit in $[0, 1]$.

After the specification of the model and the provision of preliminary results in Section 2, the first part of this work, included in Section 3, is dedicated to the study of the exact rate of convergence to infinity of the sample sizes $N_B(n)$ and $N_W(n)$. Because the treatment given corresponds to the color of the ball that is drawn, $N_B(n)$ and $N_W(n)$ also correspond to the number of balls of each color sampled from a RRU through the n-th draw. Moreover we obtain the order of convergence of the process representing the proportion of black balls contained in the urn at every stage.

The asymptotic properties of response-adaptive designs studied in literature are usually based on the hypothesis that the target allocation ρ is a determined value $(0, 1)$. In some of those procedures, despite the randomness of the number of patients $N_B(n)$ and $N_W(n)$ allocated to treatment B and W, respectively, and the complex dependence structure of the random variables involved, it has been proved that joint normality of the estimators of the mean responses based on the observed responses still holds. An important contribution is given in Melfi and Page (2000), where they provide a general method to prove consistency and an easy, general, non-martingale approach to prove asymptotic normality of estimators based on adaptively observed allocations. As they show, their method can be applied to a wide class of adaptive designs targeting an allocation proportion $\rho \in (0, 1)$. Although their basic framework covers the adaptive design considered in this paper, and strong consistency of the adaptive estimators of the parameters involved is derived from it, their method can't work for proving asymptotic normality when ρ is exactly equal to one or has a random behavior as in our procedure. Therefore, in Section 4, we prove that the joint asymptotic normality of the estimators of the mean responses still holds, both when the two treatments are equivalent and when one treatment is superior. The argument used resorts to a martingale technique that involves the concept of stable convergence; stable convergence is required to obtain the distribution of our test statistic.

In Section 5, we consider the following hypothesis test: the experimenter wants to test the null hypothesis that the two treatments are equivalent, in the sense that the mean responses μ_B and μ_W are equal, against the alternative hypothesis that $\mu_B > \mu_W$. For this reason, we are interested in the distribution of the usual test statistic ζ_0 for comparing the difference of the means, based on the observed responses, both under the null and the alternative hypothesis. When the target allocation is a value ρ in $(0,1)$, from the joint normality of the estimators of the means, it can be deduced using Slutsky's Theorem, that the test statistic ζ_0 still has an asymptotic normal distribution. Also under the alternative hypothesis, ζ_0 has the same asymptotic noncentrality parameter as in the classical case in which the sample sizes n_B and n_W are deterministic. For a review of the approach to these situations see Hu and Rosenberger (2003) and Zhang and Rosenberger (2006).

In the response-adaptive procedure considered in this paper, since the limit allocation is a random variable under the null hypothesis, we can't apply Slutsky's Theorem to derive the asymptotic normality of the test statistic ζ_0 from the joint normality result of estimators. Notwithstanding this, it is proved that under the null hypothesis the asymptotic normality of ζ_0 holds in this procedure. The proof uses the stability of the convergence showed in Section 4. Moreover, under the alternative hypothesis, it is showed that ζ_0 is a specific mixture of normal distributions. A final discussion concludes the paper.

2 Model specification and preliminary results

Let $\{(Y_B(n), Y_W(n)) : n \geq 1\}$ be a sequence of independent and identically distributed random response vectors with marginal distributions $\mathcal{L}_B$ and $\mathcal{L}_W$, discrete or continuous on $\mathbb{R}$. Consider an urn containing initially b black balls and w white balls, where b and w are two strictly positive real numbers. With the arrival of the first patient ($n = 1$), a ball is drawn at random from the urn and its color is observed: we define a random variable δ_1 that we assume to be independent of the potential response vector $(Y_B(i), Y_W(i))$ for every $i \geq 1$ such that $\delta_1 = 1$ if the extracted ball is black; while $\delta_1 = 0$ if the extracted ball is white. So δ_1 is a Bernoulli random variable with parameter $Z_0 = b/(b+w)$. After the ball is extracted, if it is black, it is replaced in the urn together with $u(Y_B(1))$ black balls. Otherwise, if it is white, is replaced in the urn together with $u(Y_W(1))$ white balls, where u is an arbitrary measurable function such that $u(Y_B(1))$ and $u(Y_W(1))$ have distribution on a nonnegative and bounded real set. (Note that u may be chosen as the identity function when the distributions $\mathcal{L}_B$ and $\mathcal{L}_W$ have nonnegative and bounded support).

This process is then reiterated at every instant $n+1$, $n \geq 1$: a ball is extracted and we define a random variable δ_{n+1} indicating its color: $\delta_{n+1} = 1$ if the ball extracted is black, while $\delta_{n+1} = 0$ if the ball extracted is white. We always assume that δ_{n+1} is independent of the potential response vector $(Y_B(i), Y_W(i))$ for every $i \geq n+1$. After the ball is extracted, it is replaced in the urn together with

$$\delta_{n+1}u(Y_B(n+1)) + (1-\delta_{n+1})u(Y_W(n+1))$$

balls of the same color. So, given the σ-algebra

$$\mathcal{F}_n = \sigma\left(\delta_1, \delta_1 Y_B(1) + (1-\delta_1)Y_W(1), \ldots, \delta_n, \delta_n Y_B(n) + (1-\delta_n)Y_W(n)\right), \quad (2.1)$$

δ_{n+1} is Bernoulli distributed with parameter

$$Z_n = \frac{B_n}{B_n + W_n},$$

where

$$\begin{cases} B_n = b + \sum_{i=1}^n \delta_i u(Y_B(i)) \\ W_n = w + \sum_{i=1}^n (1-\delta_i)u(Y_W(i)). \end{cases}$$

We thus generate the following processes: the sequence $\{\delta_n : n \geq 1\}$ of Bernoulli random variables and the sequence $\{Z_n : n \geq 0\}$ of random variables in $[0,1]$ representing the proportion of black balls present in the urn at every stage. Now the number of black balls and white balls that have been extracted from the urn through the nth treatment allocation can be written as $N_B(n) = \sum_{i=1}^n \delta_i$ and $N_W(n) = \sum_{i=1}^n (1-\delta_i)$, respectively; clearly $N_B(n) + N_W(n) = n$. Also note that B_n and W_n are the cumulative (transformed) observed responses to treatment B and W, respectively, adjusted by the initial numbers of balls in the urn. We call B_n and W_n *cumulative responses* for short.

Let $m_B = \int u(y)\mathcal{L}_B(dy)$ and $m_W = \int u(y)\mathcal{L}_W(dy)$. Then from Beggs (2005) and Muliere, Paganoni and Secchi (2006a), we have the following limit for the proportion of black balls in the urn:

2.2 **Theorem**. *If $m_B > m_W$, then $\lim_{n\to\infty} Z_n = 1$, almost surely.*

The *RRU* model can be used to drive the allocations of a sequential experiment that is conducted, for instance, to compare two competing treatments in a clinical trial. The allocation procedure is given by the sequence $\{\delta_n\}$: when δ_n is 1, allocate the n-th patient to the first treatment, say treatment B, and let the random variable $Y_B(n)$ be the potential response of n-th patient to treatment B; when δ_n is 0, allocate the n-th patient to the second treatment, say treatment W, and let $Y_W(n)$ be the potential response of n-th patient to treatment W. Only one response will be actually observed, so we write the response $Y(n)$ of n-th patient as $\delta_n Y_B(n) + (1-\delta_n)Y_W(n)$.
Suppose now that the sequences of responses $\{Y_B(n)\}$ and $\{Y_W(n)\}$ have finite means $\mu_B = \int y\mathcal{L}_B(dy)$ and $\mu_W = \int y\mathcal{L}_W(dy)$ and that, for instance, the treatment B is preferred to the treatment W if $\mu_B > \mu_W$. Then, choosing a function

u such that $\mu_B > \mu_W$ if and only if $m_B > m_W$ and $\mu_B = \mu_W$ if and only if $m_B = m_W$, Theorem 2.2 ensures that a *RRU*-design allocates patients to the superior treatment with probability converging to one as n goes to infinity.

2.3 **Remark**. As suggested in Muliere, Paganoni and Secchi (2006b), the existence of a bounded function u such that

$$\int y\mathcal{L}_B(dy) > \int y\mathcal{L}_W(dy) \Leftrightarrow \int u(y)\mathcal{L}_B(dy) > \int u(y)\mathcal{L}_W(dy)$$

and

$$\int y\mathcal{L}_B(dy) = \int y\mathcal{L}_W(dy) \Leftrightarrow \int u(y)\mathcal{L}_B(dy) = \int u(y)\mathcal{L}_W(dy)$$

is guaranteed by the theory of utility. In the situation illustrated in this paper, the experimenter expresses a preference among the distributions of responses in terms of the ordering of their means. Indeed, he may express also a different preference between $\mathcal{L}_B$ and $\mathcal{L}_W$: the theory of utility gives conditions which guarantee the existence of a bounded utility function u such that the expected utilities of the elements of a class of probability distributions on $\mathbb{R}$ are ordered in the same way as a certain preference among the probability distributions; see, for instance, Berger (1980). ■

2.1 Preliminary results

The process $\{Z_n : n \geq 0\}$ of the proportions of black balls is of primary interest for the study of stochastic processes generated by this particular generalization of Pólya urn. Moreover, in a *RRU*-design, Z_n represents the conditional probability of allocating the nth patient to treatment B; the asymptotic behavior of this process is also essential for analyzing the asymptotic normality of estimators for these designs, as it will be made clear in the next sections.

Muliere, Paganoni and Secchi (2006a) provide the following general result:

2.4 **Proposition**. *The sequence of proportions $\{Z_n : n \geq 0\}$ is eventually a bounded super or sub-martingale; therefore, it converges almost surely to a random limit Z_∞ in $[0,1]$.*

When the the urn is reinforced by the random variables $u(Y_B(n))$ and $u(Y_W(n))$ with means m_B and m_W such that $m_B > m_W$, then, as given by Theorem 2.2, the limit Z_∞ is equal to 1 almost surely.

Consider the case in which $\mathcal{L}_B = \mathcal{L}_W$ so that the urn reinforcements $u(Y_B(n))$ and $u(Y_W(n))$ have the same distribution, say μ. In May, Paganoni and Secchi

(2005), it is showed that in this situation $P(Z_\infty = x) = 0$ for every $x \in [0,1]$; however, the exact distribution of Z_∞ is unknown except in a few particular cases. When μ is a point mass at a non-negative real number m, the *RRU* degenerates to Polya's urn, in which case Z_∞ has a Beta$(b/m, w/m)$ distribution. For the general *RRU* with $\mathcal{L}_B = \mathcal{L}_W$, Aletti, May and Secchi (2006), characterize the distribution of Z_∞ as the unique continuous solution, satisfying some boundary conditions, of a specific functional equation in which the unknowns are distribution functions on $[0,1]$.

When $m_B = m_W$, it may happen that $\int u(y)^k \mathcal{L}_B(dy) \neq \int u(y)^k \mathcal{L}_W(dy)$ for some $k \geq 2$ and then $u(Y_B(n))$ and $u(Y_W(n))$ may have different distributions; this is of particular interest in this paper, since it corresponds to a situation in which the two treatments are considered equivalent. In the next section, we prove a fundamental property of Z_∞ when $m_B = m_W$, that is, $P(Z_\infty = 1) = P(Z_\infty = 0) = 0$ in this case.

The following preliminary result regarding the limiting sample sizes on B and W is important for showing the asymptotic normality of the common statistic for testing differences in mean responses:

2.5 **Proposition**. *$N_B(n)$ and $N_W(n)$ converge to infinity almost surely as $n \to \infty$.*

Proof. Following Theorem 2 in Muliere, Paganoni and Secchi (2006a), if $\tau = \inf\{n \geq 1 : \delta_n = 0\}$, then, for $k \geq 1$,

$$P(\tau > k) \leq \frac{b}{b+w}\frac{b+\beta}{b+w+\beta}\cdots\frac{b+(k-1)\beta}{b+w+(k-1)\beta} = \exp\left(\sum_{n=0}^{k-1}\log\left(\frac{b+n\beta}{b+w+n\beta}\right)\right).$$

Since $\sum_{n=0}^{\infty}\log[(b+n\beta)/(b+w+n\beta)] = -\infty$, it follows that $\lim_{k\to\infty} P(\tau > k) = 0$, and hence $P(\tau < \infty) = 1$. From the strong Markov property we obtain that

$$P(\delta_n = 0, i.o.) = 1,$$

and then $N_W(n) \to \infty$, a.s. The proof for $N_B(n)$ is similar. ∎

Now let

$$\tau_n = \inf\{k : \sum_{i=1}^{k}\delta_i = n\} \quad \text{and} \quad \nu_n = \inf\{k : \sum_{i=1}^{k}(1-\delta_i) = n\};$$

thus, $\tau_n = j$ indicates that the nth observed response to treatment B occurs for patient j, and $\{Y_B(\tau_n)\}$ is the subsequence of the potential responses $\{Y_B(n)\}$ that is given by the observed responses to B; similarly, $\nu_n = j$ indicates that the nth observed response to treatment W occurs for patient j, and the subsequence of potential responses $\{Y_W(n)\}$ to W that are given by the observed responses is $\{Y_W(\nu_n)\}$. Melfi and Page (2000) prove independence properties of the sequences of observed responses, so that the strong consistency of estimators based on those sequences can be deduced:

2.6 **Proposition**. *The sequences $\{Y_B(\tau_n)\}$ and $\{Y_W(\nu_n)\}$ are i.i.d. with distributions $\mathcal{L}_B$ and $\mathcal{L}_W$, respectively, and are independent one of each other.*

As a consequence of this proposition, we can model the observed responses of random sizes $N_B(n)$ and $N_W(n)$ to treatments B and W as samples from two i.i.d. populations generated by $\mathcal{L}_B$ and $\mathcal{L}_W$, respectively. Assume that $\mathcal{L}_B$ and $\mathcal{L}_W$ depend on unknown parameters θ_B and θ_W. We have the following

2.7 **Corollary**. *Suppose that $\widetilde{\theta}_B$ and $\widetilde{\theta}_W$ are estimators of θ_B and θ_B based on n-dimensional samples from two independent i.i.d. sequences generated by $\mathcal{L}_B$ and $\mathcal{L}_W$, respectively. Let $\hat{\theta}_B$ and $\hat{\theta}_W$ be the correspondent estimators computed on observed responses through time n in the RRU-design (which have random sample sizes $N_B(n)$ and $N_W(n)$, respectively). If $\widetilde{\theta}_B$ and $\widetilde{\theta}_W$ converges a.s. to θ_B and θ_W, respectively, then also $\hat{\theta}_B$ and $\hat{\theta}_W$ converge a.s. to θ_B and θ_W.*

3 Rates of convergence of $N_B(n)$ and $N_W(n)$

The aim of this section is to study the rate of convergence to infinity of the sample size sequences $N_B(n) = \sum_{i=1}^n \delta_i$ and $N_W(n) = \sum_{i=1}^n (1-\delta_i)$ defined in Section 2. We will also obtain the rate of the convergence of the process Z_n given in Theorem 2.2. First we have the following result:

3.8 **Proposition**.

$$\lim_{n\to\infty} \frac{N_B(n)}{n} = Z_\infty, \quad a.s. \quad \textit{and} \quad \lim_{n\to\infty} \frac{N_W(n)}{n} = 1 - Z_\infty, \quad a.s., \tag{3.9}$$

where Z_∞ is the limit of the process $\{Z_n\}$ representing the proportion of black balls in the urn.

Proof. Since $\mathbf{E}(\delta_i | \mathcal{F}_{i-1}) = Z_{i-1}$ and (from Proposition 2.5) $\sum_{i=1}^n \delta_i \to \infty$ almost surely, it follows from from Levy's extension of the Borel-Cantelli Lemma that, almost surely,

$$\sum_{i=1}^n Z_{i-1} \to \infty \quad \text{and} \quad \frac{\sum_{i=1}^n \delta_i}{\sum_{i=1}^n Z_{i-1}} \to 1.$$

Using Cesaro's Lemma, $\lim_{n\to\infty} Z_n = Z_\infty$, almost surely, implies that $(\sum_{i=1}^n Z_{i-1})/n$ converges to Z_∞; hence also $(\sum_{i=1}^n \delta_i)/n$ converges almost surely to Z_∞. ■

The next theorem gives the exact rate of convergence to infinity of $N_B(n)$ and $N_W(n)$.

3.10 **Theorem**. *If $m_B > m_W$, then*

(i) $\lim_{n\to+\infty} \dfrac{N_B(n)}{n} = 1$, *a.s.;*

(ii) there exist a random variable η^2 with $P(0 < \eta^2 < \infty) = 1$ such that

$$\lim_{n\to+\infty} \frac{N_W(n)}{n^{m_W/m_B}} = \eta^2, \quad a.s.$$

If $m_B = m_W$, then $P(Z_\infty = 0) = P(Z_\infty = 1) = 0$ and there exist two random variables ${\lambda_i}^2$, $i = 1, 2$, with $P(0 < {\lambda_i}^2 < 1) = 1$, such that

(iii) $\lim_{n\to+\infty} \dfrac{N_B(n)}{n} = \lambda_1^2$, *a.s.;*

(iv) $\lim_{n\to+\infty} \dfrac{N_W(n)}{n} = \lambda_2^2$, *a.s..*

Part (i) of Theorem 3.10 follows immediately from Theorem 2.2 and Proposition 3.8, since when $m_B > m_W$, then $Z_\infty = 1$ almost surely and $N_B(n)/n$ converges to Z_∞. To obtain the rest of the Theorem, that is the main result of this section, we will first prove an auxiliary result concerning the relative convergence rates of the cumulative responses to treatments B and W which holds both when $m_B = m_W$ and $m_B > m_W$.

3.11 **Theorem**. *$B_n/({W_n}^{m_B/m_W})$ converges almost surely to a random variable with support in $(0, \infty)$.*

In order to prove Theorem 3.11 we need the following two Lemmas.

3.12 **Lemma**. *If $m_B > m_W$, then*

(i) the rate of convergence of B_n is n, almost surely;

(ii) the rate of convergence of W_n is greater then n^γ for some real costant $\gamma > 0$, almost surely.

If $m_B = m_W$, then

(iii) the rate of convergence of $B_n + W_n$ is n, almost surely;

(iv) the rates of convergence of both B_n and W_n are greater than n^γ, almost surely, for some real costant $\gamma > 0$.

Proof.

(i) This is an immediate consequence of Corollary 2.7 and of the fact that when $m_B > m_W$ then $N_B(n)/n \to 1$ (using Proposition 3.8 and Theorem 2.2):

$$\lim_{n\to+\infty} \frac{B_n}{n} = \lim_{n\to+\infty} \frac{b}{n} + \frac{\sum_{i=1}^n \delta_i u(Y_B(i))}{n} = \lim_{n\to+\infty} \frac{b}{n} + \frac{\sum_{i=1}^n \delta_i u(Y_B(i))}{N_B(n)} \frac{N_B}{n} = m_B,$$

almost surely.

(ii) Let's consider the conditional increments of the process $B_n/{W_n}^\kappa$, for some $\kappa > m_B/m_W$.

$$\begin{aligned}
\mathbf{E}\left(\frac{B_{n+1}}{{W_{n+1}}^\kappa} - \frac{B_n}{{W_n}^\kappa}|\mathcal{F}_n\right) &= \frac{B_n}{B_n+W_n}\mathbf{E}\left(\frac{B_n + u(Y_B(n+1))}{{W_n}^\kappa} - \frac{B_n}{{W_n}^\kappa}|\mathcal{F}_n\right) \\
&+ \frac{W_n}{B_n+W_n}\mathbf{E}\left(\frac{B_n}{(W_n + u(Y_W(n+1)))^\kappa} - \frac{B_n}{{W_n}^\kappa}|\mathcal{F}_n\right) \\
&= \frac{B_n}{B_n+W_n}\frac{\mathbf{E}(u(Y_B))}{{W_n}^\kappa} + \\
&+ \frac{W_nB_n}{B_n+W_n}\mathbf{E}\left(\frac{1}{(W_n + u(Y_W(n+1)))^\kappa} - \frac{1}{{W_n}^\kappa}|\mathcal{F}_n\right).
\end{aligned}$$

By a Taylor expansion of the function $f(x) = 1/(a+x)^\kappa$ with $x = u(Y_W(n+1))$ and $a = W_n$, we can choose a constant c such that whenever $W_n \geq 1$

$$\mathbf{E}\left(\frac{1}{(W_n + u(Y_W(n+1)))^\kappa}|\mathcal{F}_n\right) \leq \frac{1}{{W_n}^\kappa} - \frac{\kappa}{{W_n}^{\kappa+1}}\left(\mathbf{E}(u(Y_W)) - \frac{c}{W_n}\right).$$

Thus we obtain that

$$\mathbf{E}\left(\frac{B_{n+1}}{{W_{n+1}}^\kappa} - \frac{B_n}{{W_n}^\kappa}|\mathcal{F}_n\right) \leq \frac{B_n}{B_n+W_n}\frac{1}{{W_n}^\kappa}\left(\mathbf{E}(u(Y_B)) - \kappa\,\mathbf{E}(u(Y_W)) + \frac{\kappa c}{W_n}\right). \tag{3.13}$$

From inequality (3.13), note that if $\kappa > \mathbf{E}(u(Y_B))/\,\mathbf{E}(u(Y_W))$, then the process $B_n/{W_n}^\kappa$ is (eventually) a positive supermartingale, and then it converge almost surely to a finite limit. Since from part (i) of the Lemma $B_n/n \to m_B$ a.s., it follows that also $n/{W_n}^\kappa$ converges almost surely to a finite limit. Hence, for every $\varepsilon > 0$, $n/{W_n}^{\kappa+\varepsilon}$ converges a.s. to 0. This means that ${W_n}^{\kappa+\varepsilon} > n$ eventually, that is, $W_n > n^{\frac{1}{\kappa+\varepsilon}}$ a.s., eventually.

(iii) If $m_B = m_W$, we have that $\lim_{n\to+\infty} \dfrac{B_n + W_n}{n} = m_B$ almost surely because

$$\begin{aligned}\frac{B_n + W_n}{n} &= \lim_{n\to+\infty} \frac{b+w}{n} + \frac{\sum_{i=1}^n \delta_i u(Y_B(i))}{n} + \frac{\sum_{i=1}^n (1-\delta_i) u(Y_W(i))}{n} \\ &= \lim_{n\to+\infty} \frac{b+w}{n} + \frac{\sum_{i=1}^n \delta_i u(Y_B(i))}{N_B(n)} \frac{N_B(n)}{n} + \\ &+ \frac{\sum_{i=1}^n (1-\delta_i) u(Y_W(i))}{N_W(n)} \frac{N_W(n)}{n}.\end{aligned}$$

Using Corollary 2.7 and Proposition 3.8, this converges almost surely to $m_B Z_\infty + m_W(1 - Z_\infty)$. Since $m_B = m_W$, this is equal to m_B.

(iv) From the part (iii) of the Lemma, it follows that, eventually, $B_n + W_n > n \cdot m_B/2$ on a set of probability one. Consequently, at least B_n or W_n are greater then $n \cdot m_B/4$; without loss of generality, suppose

$$B_n > n \cdot m_B/4, \text{ a.s., eventually.} \tag{3.14}$$

Further, using the same argument as in the proof of part (ii) of this Lemma, we can obtain from equation (3.13) that for $k > 1$ the process $B_n/{W_n}^\kappa$ is (eventually) a positive supermartingale, and then it converges almost surely to a finite limit. This implies that, for every $\varepsilon > 0$, $B_n/{W_n}^{\kappa+\varepsilon}$ converges to 0 and then

$$B_n/{W_n}^{\kappa+\varepsilon} < 1, \text{ a.s., eventually.} \tag{3.15}$$

Combining (3.14) and (3.15) we deduce that $n/{W_n}^{\kappa+\varepsilon} \cdot m_B/4 < 1$, a.s., that is, $W_n > n^{\frac{1}{\kappa+\varepsilon}} \cdot (m_B/4)^{\frac{1}{\kappa+\varepsilon}}$ a.s., eventually. ■

The second Lemma is a general fact about convergence of random sequences; for lack of a better reference, see Lemma 3.2 in Pemantle and Volkov (1999).

3.16 **Lemma**. *Let $\{\xi_n : n \geq 0\}$ be a random sequence that is measurable with respect to a filtration $\{\mathcal{F}_n\}$. Define*

$$\Delta_n = \mathbf{E}(\xi_{n+1} - \xi_n | \mathcal{F}_n); \qquad Q_n = \mathbf{E}((\xi_{n+1} - \xi_n)^2 | \mathcal{F}_n).$$

If $\sum_n \Delta_n < +\infty$ and $\sum_n Q_n < +\infty$ on a set of probability one, then ξ_n converges to a finite random variable almost surely as n goes to infinity.

Proof of Theorem 3.11. We apply Lemma 3.16 to the process

$$\xi_n = \log \frac{B_n}{{W_n}^{m_B/m_W}}$$

in order to prove that it converges almost surely to a finite random variable. This implies that $B_n/({W_n}^{m_B/m_W})$ converges almost surely to a strictly positive and finite random variable.

$$\begin{aligned}
\Delta_n = \mathbf{E}\left(\xi_{n+1}-\xi_n|\mathcal{F}_n\right) &= \mathbf{E}\left(\log B_{n+1}-\log B_n|\mathcal{F}_n\right)-\frac{m_B}{m_W}\mathbf{E}\left(\log W_{n+1}-\log W_n|\mathcal{F}_n\right)\\
&= \frac{B_n}{B_n+W_n}\mathbf{E}\left(\log(B_n+u(Y_B(n+1)))-\log B_n|\mathcal{F}_n\right)\\
&- \frac{m_B}{m_W}\frac{W_n}{B_n+W_n}\mathbf{E}\left(\log(W_n+u(Y_W(n+1)))-\log W_n|\mathcal{F}_n\right)\\
&= \frac{B_n}{B_n+W_n}\mathbf{E}\left(\int_0^{u(Y_B(n+1))}\frac{1}{B_n+t}\,dt|\mathcal{F}_n\right)\\
&- \frac{m_B}{m_W}\frac{W_n}{B_n+W_n}\mathbf{E}\left(\int_0^{u(Y_W(n+1))}\frac{1}{W_n+t}\,dt|\mathcal{F}_n\right).
\end{aligned}$$

By a Taylor expansion of the function $f(x)=1/(x+t)$ we have that, for B_n sufficiently large, there exist constants c_1 and c_2 such that for every t

$$\frac{1}{B_n}-c_2\frac{t}{B_n^2}\leq\frac{1}{B_n+t}\leq\frac{1}{B_n}-\frac{t}{B_n^2}+c_1\frac{t^2}{B_n^3}\,, \tag{3.17}$$

and similarly for $1/(W_n+t)$. Hence we obtain

$$-\frac{1}{B_n+W_n}\left(\frac{h_1}{B_n}+\frac{h_2}{W_n^2}\right)\leq\Delta_n\leq\frac{1}{B_n+W_n}\left(\frac{k_1}{B_n^2}+\frac{k_2}{W_n}\right) \tag{3.18}$$

for some constant k_1,k_2,h_1,h_2. Thanks to the rates of convergence of B_n and W_n shown in Lemma 3.12, we obtain that $\sum_n\Delta_n<+\infty$, a.s.

$$\begin{aligned}
Q_n = \mathbf{E}\left((\xi_{n+1}-\xi_n)^2|\mathcal{F}_n\right) &= \frac{B_n}{B_n+W_n}\mathbf{E}\left((\log(B_n+u(Y_B(n+1)))-\log B_n)^2|\mathcal{F}_n\right)\\
&+ \frac{W_n}{B_n+W_n}\mathbf{E}\left((\log(W_n+u(Y_W(n+1)))-\log W_n)^2|\mathcal{F}_n\right)\\
&= \frac{B_n}{B_n+W_n}\mathbf{E}\left(\left(\int_0^{u(Y_B(n+1))}\frac{1}{B_n+t}\,dt\right)^2|\mathcal{F}_n\right)\\
&+ \left(\frac{m_B}{m_W}\right)^2\frac{W_n}{B_n+W_n}\mathbf{E}\left(\left(\int_0^{u(Y_W(n+1))}\frac{1}{W_n+t}\,dt\right)^2|\mathcal{F}_n\right).
\end{aligned}$$

Since, for positive t, $\dfrac{1}{B_n+t}\leq\dfrac{1}{B_n}$ and $\dfrac{1}{W_n+t}\leq\dfrac{1}{W_n}$, we obtain

$$Q_n \leq \mathbf{E}\ \frac{B_n}{B_n+W_n}\left(\frac{E(u(Y_B)^2)}{{B_n}^2}\right)+\left(\frac{\mu_B}{m_W}\right)^2\frac{W_n}{B_n+W_n}\left(\frac{E(u(Y_W)^2)}{{W_n}^2}\right);$$

hence $\sum_n Q_n < +\infty$, a.s. ■

Proof of Theorem 3.10. Let $m_B > m_W$. Observe that

$$\begin{aligned}\lim_{n\to+\infty}\frac{B_n}{{W_n}^{m_B/m_W}} &= \lim_{n\to+\infty}\frac{b+\sum_{i=1}^n \delta_i u(Y_B(i))}{(w+\sum_{i=1}^n(1-\delta_i)u(Y_W(i)))^{m_B/m_W}}\\ &= \lim_{n\to+\infty}\frac{\sum_{i=1}^n \delta_i u(Y_B(i))/N_B(n)}{(\sum_{i=1}^n(1-\delta_i)u(Y_W(i))/N_W(n))^{m_B/m_W}}\frac{N_B(n)}{N_W(n)^{m_B/m_W}}.\end{aligned}$$

From Theorem 3.11, we know that this limit is in $(0,\infty)$. From Corollary 2.7, we have that $\sum_{i=1}^n \delta_i u(Y_B(i))/N_B(n)$ and $\sum_{i=1}^n(1-\delta_i)u(Y_W(i))/N_W(n)$ converge a.s. to m_B and m_W, respectively, and $N_B(n)/n$ converges a.s. to 1. So it follows that also $N_W(n)^{m_B/m_W}/n$ converges a.s. to a random variable in $(0,\infty)$. Hence we obtain part (ii) of the theorem.

Let $m_B = m_W$. From Proposition 3.8 we know that, almost surely, $N_B(n)/n \to Z_\infty$ and $N_W(n)/n \to 1-Z_\infty$. Since, from Theorem 3.11, B_n/W_n converges a.s. to a limit in $(0,+\infty)$, it follows that

$$Z_n = \frac{B_n}{B_n+W_n} = \frac{B_n/W_n}{B_n/W_n+1}$$

converges a.s. to a limit in $(0,1)$, that is,

$$P(Z_\infty = 0) = P(Z_\infty = 1) = 0; \tag{3.19}$$

setting ${\lambda_1}^2 = Z_\infty$ and ${\lambda_2}^2 = 1-Z_\infty$, we obtain also part (iii) and (iv) of the Theorem. ■

Finally we prove a relevant consequence of Theorem 3.10, that is, when $m_B > m_W$, we find the exact order of convergence of the proportion of white balls in the urn to be the same as was obtained for the proportion of patients allocated to treatment W in Theorem 3.10(ii).

3.20 **Corollary**. *Let η^2 be the random variable given by Theorem 3.10. If $m_B > m_W$, then*

$$\lim_{n\to+\infty}\frac{1-Z_n}{n^{m_W/m_B-1}} = \frac{m_W}{m_B}\eta^2, \quad a.s.$$

Proof.

$$\frac{1-Z_n}{n^{m_W/m_B-1}} = \frac{1}{n^{m_W/m_B-1}} \frac{W_n}{B_n+W_n}$$

$$= \frac{1}{n^{m_W/m_B-1}} \frac{w+\sum_{i=1}^n (1-\delta_i)u(Y_W(i))}{b+w+\sum_{i=1}^n \delta_i u(Y_B(i)) + \sum_{i=1}^n (1-\delta_i)u(Y_W(i))}$$

$$= \frac{1}{n^{m_W/m_B-1}}$$

$$\cdot \frac{w+(\sum_{i=1}^n (1-\delta_i)u(Y_W(i))/N_W(n))N_W(n)}{b+w+(\sum_{i=1}^n \delta_i u(Y_B(i))/N_B(n))N_B(n) + (\sum_{i=1}^n (1-\delta_i)u(Y_W(i))/N_W(n))N_W(n)}$$

$$= \frac{w/n^{m_W/m_B} + \sum_{i=1}^n (1-\delta_i)u(Y_W(i))/N_W(n)\cdot N_W(n))/n^{m_W/m_B}}{(b+w)/n + \sum_{i=1}^n \delta_i u(Y_B(i))/N_B(n)\cdot N_B(n)/n + \sum_{i=1}^n (1-\delta_i)u(Y_W(i))/N_W(n)\cdot N_W(n)/n}.$$

Now, using Corollary 2.7 and Theorem 3.10, the numerator of the last equality converges almost surely to $\eta^2 m_W$, while the denominator converges almost surely to m_B. ■

3.21 **Remark**. Theorem 3.11 has been inspired by some ideas contained in Pemantle and Volkov (1999). Actually, even when $m_B > m_W$, Theorem 3.11 doesn't follow from their Lemma 3.5 readapted to our case, which would assert that $\log W_n/\log B_n \to m_W/m_B$ as $n \to +\infty$, almost surely. As a counterexample consider the case in which the rate of convergence of B_n is n, while the rate of convergence of W_n is $n^{m_W/m_B}\log n$. (This is also a counterexample to the fact that their true Theorem 2.2 is not a consequence of their Lemma 3.5.) ■

4 Asymptotic normality

Consider estimation of the means μ_B and μ_W of the responses to treatments. We define the following estimators based on the observed responses through patient n, with random sample sizes $N_B(n)$ and $N_W(n)$, respectively:

$$\hat{Y}_B(n) = \frac{\sum_{i=1}^n \delta_i Y_B(i)}{N_B(n)} \quad \text{and} \quad \hat{Y}_W(n) = \frac{\sum_{i=1}^n (1-\delta_i) Y_W(i)}{N_W(n)} . \tag{4.22}$$

Corollary 2.7 and the strong law of large numbers ensure that the (4.22) are strongly consistent. In this section we will show that these estimators, appropriately standardized, are jointly asymptotically normal, despite the randomness of $N_B(n)$ and $N_W(n)$, their dependence, and the fact that they don't satisfy the classical assumption, as also is required in Theorem 3.2 of Melfi and Page (2000), that $N_B(n)/n$ and $N_W(n)/n$ converge in probability to a constant in $(0, 1)$.

Before proceeding, we need to recall the concept of *stable convergence*, which was introduced by Renyi (1963) and provides a particularly elegant approach to martingale central limit theory (see Hall and Heyde, 1980 and Heyde, 1997). The stability of the convergence in the next result will be essential to our study of the asymptotic distribution of the test statistic in the next section.

4.23 **Definition**. *Consider a sequences of random vectors* $\mathbf{Y}_n = (Y_1(n), ..., Y_p(n))$ *on a probability space* $(\Omega, \mathcal{F}, P)$ *that converges in distribution to* $\mathbf{Y} = (Y_1, ..., Y_p)$*; we say that the convergence is stable if for every point* $\mathbf{y}$ *of continuity for the distribution function of* $\mathbf{Y}$ *and for every event* $E \in \mathcal{F}$*, the limit*

$$\lim_{n\to\infty} P\{Y_1(n) \leq y_1, ..., Y_p(n) \leq y_p, E\} = Q_{\mathbf{y}}(E)$$

exists and $Q_{\mathbf{y}}(E) \to P(E)$ *as* $y_i \to \infty$ *for* $i = 1, ..., p$.

During this section and the next one, we will assume that the distributions of the responses $\mathcal{L}_B$ and $\mathcal{L}_W$ have finite variances, which we indicate by ${\sigma_B}^2$ and ${\sigma_W}^2$. In the following theorem, we now obtain asymptotic distributions for the two-dimensional potential response process using three different standardizations.

4.24 **Theorem**.

(a) Assume $H_0 : \mu_B = \mu_W$ *is true; then the standardized two-dimensional process of potential responses*

$$\mathbf{Q}_n = \left(\frac{1}{\sigma_B} \frac{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)}{\sqrt{n}}, \frac{1}{\sigma_W} \frac{\sum_{i=1}^n (1 - \delta_i)(Y_W(i) - \mu_W)}{\sqrt{n}} \right) \tag{4.25}$$

converges stably in distribution to the normal mixture vector $(N_1\sqrt{Z_\infty}, N_2\sqrt{1 - Z_\infty})$*, where* N_1 *and* N_2 *are independent standard normal variables, independent of the limit of the proportion of black balls* Z_∞.

(b) Assume $H_1 : \mu_B > \mu_W$ *is true; then the standardized two-dimensional process of potential responses*

$$\mathbf{Q}_n = \left(\frac{1}{\sigma_B} \frac{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)}{\sqrt{n}}, \frac{1}{\sigma_W} \frac{\sum_{i=1}^n (1 - \delta_i)(Y_W(i) - \mu_W)}{\sqrt{n^{\mu_W/\mu_B}}} \right) \tag{4.26}$$

converges stably in distribution to the normal mixture vector $(N_1, \eta^2 N_2)$*, where* η^2 *is the random variable defined in Theorem 3.10 and* N_1 *and* N_2 *are independent standard normal variables, independent of* η^2.

(c) *Under both the null and the alternative hypothesis, the standardized two-dimensional process of potential responses*

$$\left(\frac{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)}{\sqrt{\sum_{i=1}^n \delta_i^2 (Y_B(i) - \mu_B)^2}}, \frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i) - \mu_W)}{\sqrt{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i) - \mu_W)^2}} \right)$$

converges in distribution to a standard Gaussian vector $\mathcal{N}(\mathbf{0}, \mathbf{I}_2)$.

Proof. Consider the filtration $\{\mathcal{F}_n\}$ given by equation (2.1), with $\mathcal{F}_0$ being the trivial σ-field. The components of processes (4.25) and (4.26) are martingales, since $Y_B(i)$ and $Y_W(i)$ are independent of $\mathcal{F}_{i-1}$ and of δ_i:

$$\begin{aligned} &\mathbf{E}\left(\delta_i (Y_B(i) - \mu_B) | \mathcal{F}_{i-1}\right) = \mathbf{E}(Y_B(i) - \mu_B)\, \mathbf{E}\left(\delta_i | \mathcal{F}_{i-1}\right) = 0, \\ &\mathbf{E}\left((1-\delta_i)(Y_W(i) - \mu_W) | \mathcal{F}_{i-1}\right) = \mathbf{E}(Y_W(i) - \mu_W)\, \mathbf{E}\left((1-\delta_i) | \mathcal{F}_{i-1}\right) = 0, \end{aligned} \tag{4.27}$$

for every $i \geq 1$.

Assume first that $\mu_B = \mu_W$. We apply Theorem 12.6 of Heyde (1997) to the two-dimensional martingale of potential responses

$$\mathbf{S}_n = \left(\frac{1}{\sigma_B} \sum_{i=1}^n \delta_i (Y_B(i) - \mu_B), \frac{1}{\sigma_W} \sum_{i=1}^n (1-\delta_i)(Y_W(i) - \mu_W) \right)$$

with non-random normalizing vector $\mathbf{k_n} = (\sqrt{n}, \sqrt{n})$. Because $\delta_i(1-\delta_i) = 0$, the quadratic variation matrix $[\mathbf{S}]_n$ is diagonal:

$$[\mathbf{S}]_n = \operatorname{diag}\left(\frac{1}{\sigma_B{}^2} \sum_{i=1}^n \delta_i{}^2 (Y_B(i) - \mu_B)^2, \frac{1}{\sigma_W{}^2} \sum_{i=1}^n (1-\delta_i)^2 (Y_W(i) - \mu_W)^2 \right).$$

We need to verify the following three conditions:

(i) $\frac{1}{\sqrt{n}} \max_{i \leq n} |\delta_i (Y_B(i) - \mu_B)| \to^P 0$ and $\frac{1}{\sqrt{n}} \max_{i \leq n} |(1-\delta_i)(Y_W(i) - \mu_W)| \to^P 0$;

(ii) $\operatorname{diag}\left(\frac{1}{\sigma_B{}^2} \frac{\sum_{i=1}^n \delta_i{}^2 (Y_B(i) - \mu_B)^2}{n}, \frac{1}{\sigma_W{}^2} \frac{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i) - \mu_W)^2}{n} \right) \to^P \mathbf{s}^2$,

where $\mathbf{s}^2$ is a random nonnegative definite matrix;

(iii) $\mathbf{E}\left(\operatorname{diag}\left(\frac{1}{\sigma_B{}^2} \frac{\sum_{i=1}^n \delta_i{}^2 (Y_B(i) - \mu_B)^2}{n}, \frac{1}{\sigma_W{}^2} \frac{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i) - \mu_W)^2}{n} \right) \right) \to \mathbf{\Sigma}$, where $\mathbf{\Sigma}$ is a positive definite matrix.

Condition (i) can be verified using the Chebycev inequality. Condition (ii) is a consequence of Corollary 2.7 and of Proposition 3.8:

$$
\begin{aligned}
&\operatorname{diag}\left(\frac{1}{{\sigma_B}^2}\frac{\sum_{i=1}^n {\delta_i}^2 (Y_B(i)-\mu_B)^2}{n}, \frac{1}{{\sigma_W}^2}\frac{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i)-\mu_W)^2}{n}\right)\\
&= \operatorname{diag}\left(\frac{1}{{\sigma_B}^2}\frac{\sum_{i=1}^n \delta_i (Y_B(i)-\mu_B)^2}{N_B(n)}\frac{N_B(n)}{n}, \frac{1}{{\sigma_W}^2}\frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i)-\mu_W)^2}{N_W(n)}\frac{N_W(n)}{n}\right)\\
&\longrightarrow \mathbf{s}^2 = \operatorname{diag}\left(Z_\infty, 1-Z_\infty\right), \ a.s.
\end{aligned}
$$

Condition (iii) is verified observing that the process $\{Z_n\}$ converges also in mean and then, using Cesaro Lemma, $\sum_{i=1}^n \mathbf{E}(Z_{i-1})/n \to \mathbf{E}(Z_\infty)$ and $\sum_{i=1}^n \mathbf{E}(1-Z_{i-1})/n \to \mathbf{E}(1-Z_\infty)$; hence

$$
\begin{aligned}
&\mathbf{E}\left(\operatorname{diag}\left(\frac{1}{{\sigma_B}^2}\frac{\sum_{i=1}^n {\delta_i}^2 (Y_B(i)-\mu_B)^2}{n}, \frac{1}{{\sigma_W}^2}\frac{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i)-\mu_W)^2}{n}\right)\right)\\
&= \operatorname{diag}\left(\frac{\sum_{i=1}^n \mathbf{E}(\delta_i)}{n}, \frac{\sum_{i=1}^n \mathbf{E}(1-\delta_i)}{n}\right) = \operatorname{diag}\left(\frac{\sum_{i=1}^n \mathbf{E}(Z_{i-1})}{n}, \frac{\sum_{i=1}^n \mathbf{E}(1-Z_{i-1})}{n}\right)\\
&\longrightarrow \mathbf{\Sigma} := \operatorname{diag}\left(\mathbf{E}(Z_\infty), \mathbf{E}(1-Z_\infty)\right).
\end{aligned}
$$

We can then conclude from Theorem 12.6 of Heyde that the normalized martingale $\mathbf{k}_n \cdot \mathbf{S}_n = \mathbf{Q}_n$ converges stably in distribution to the normal mixture with joint characteristic function

$$
\varphi(t_1,t_2) = \mathbf{E}\exp\left(-\frac{1}{2}\,(t_1,t_2)\,\mathbf{s}^2\,(t_1,t_2)^T\right) = \mathbf{E}\exp\left(-\frac{1}{2}\left({t_1}^2 Z_\infty + {t_2}^2(1-Z_\infty)\right)\right),
$$

that is assertion (a). Since, from Theorem 3.10, $P\{Z_\infty = 0\} = P\{Z_\infty = 1\} = 0$, we have that $\det(\mathbf{s}^2) > 0$ a.s., and so we also obtain assertion (c) under the null hypothesis.

Assume now that $\mu_B > \mu_W$. Condition (iii) of Theorem 12.6 of Heyde is not easy to verify in this case; for this reason we use the Cramer-Wold device. Let $\mathbf{c} = (c_1, c_2)'$ be a vector of real constants, and consider

$$
S_{\mathbf{c}}(n) \;=\; c_1\frac{1}{\sigma_B}\frac{\sum_{i=1}^n \delta_i (Y_B(i)-\mu_B)}{\sqrt{n}} + c_2\frac{1}{\sigma_W}\frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i)-\mu_W)}{\sqrt{n^{m_W/m_B}}}.
$$

Since equation (4.27) holds, $S_{\mathbf{c}}(n)$ is a martingale; consider the martingale array differences:

$$
{X_{ni}}^{\mathbf{c}} = c_1\frac{1}{\sigma_B}\frac{\delta_i (Y_B(i)-\mu_B)}{\sqrt{n}} + c_2\frac{1}{\sigma_W}\frac{(1-\delta_i)(Y_W(i)-\mu_B)}{\sqrt{n^{m_W/m_B}}}, \quad i = 1,\dots,n
$$

and the σ-fields $\mathcal{F}_{ni} = \sigma(\delta_1, \delta_1 Y_B(1) + (1-\delta_1)Y_W(1), \dots, \delta_i, \delta_i Y_B(i) + (1-\delta_i)Y_W(i))$. In order to apply Theorem 3.2 of Hall and Heyde (1980), we need to verify the following three conditions:

(i) $\max_{1\le i\le n}|X_{ni}{}^{\mathbf{c}}| \to^P 0$;

(ii) $\sum_{i=1}^n (X_{ni}{}^{\mathbf{c}})^2$ converges a.s. to a strictly positive random variable;

(iii) $\mathbf{E}\left(\max_{1\le i\le n}(X_{ni}{}^{\mathbf{c}})^2\right)$ is bounded in n.

Condition (i) can be verified by observing that

$$\max_{1\le i\le n}|X_{ni}{}^{\mathbf{c}}| \le c_1\frac{1}{\sigma_B}\max_{1\le i\le n} \mid \frac{(Y_B(i)-\mu_B)}{\sqrt{n}} \mid + c_2\frac{1}{\sigma_W}\max_{1\le i\le n}|\frac{(Y_W(i)-\mu_W)}{\sqrt{n^{m_W/m_B}}}|;$$

using the Chebycev inequality for both members of the sum, we obtain that they converge to zero in probability. Since $\delta_i(1-\delta_1)=0$, we have that

$$\begin{aligned}\sum_{i=1}^n (X_{ni}{}^{\mathbf{c}})^2 &= \sum_{i=1}^n \left(c_1{}^2\frac{1}{\sigma_B{}^2}\frac{\delta_i{}^2(Y_B(i)-\mu_B)^2}{n} + c_2{}^2\frac{1}{\sigma_W{}^2}\frac{(1-\delta_i)^2(Y_W(i)-\mu_B)^2}{n^{m_W/m_B}}\right)\\ &= c_1{}^2\frac{1}{\sigma_B{}^2}\frac{\sum_{i=1}^n\delta_i(Y_B(i)-\mu_B)^2}{N_B(n)}\frac{N_B(n)}{n} + c_2{}^2\frac{1}{\sigma_W{}^2}\frac{\sum_{i=1}^n(1-\delta_i)(Y_W(i)-\mu_W)^2}{N_W(n)}\frac{N_W(n)}{n^{m_W/m_B}};\end{aligned}$$

using Proposition 2.7 and Theorem 3.10, this converges to $c_1{}^2 + c_2{}^2\eta^2$, proving condition (ii).

Finally we observe that

$$\begin{aligned}\mathbf{E}(\max_{1\le i\le n}(X_{ni}{}^{\mathbf{c}})^2) &\le c_1{}^2\frac{1}{\sigma_B{}^2}\,\mathbf{E}\left(\max_{1\le i\le n}\frac{(Y_B(i)-\mu_B)^2}{n}\right)\\ &+ c_2{}^2\frac{1}{\sigma_W{}^2}\,\mathbf{E}\left(\max_{1\le i\le n}\frac{(Y_W(i)-\mu_W)^2}{n^{m_W/m_B}}\right),\end{aligned}$$

and it can be proved that both terms converge to 0 for $n\to+\infty$, yielding also condition (iii). In fact, if $\mathcal{L}_B$ and $\mathcal{L}_W$ are distributions with bounded support, this is immediate; otherwise we can compute the distribution function and then the density of $\mathcal{Y}_T = \max_{1\le i\le n}(Y_T(i)-\mu_T)^2$, $T=B,W$; inverting the order of limit and expectation, we obtain the convergence to 0 since the distribution functions of $\mathcal{L}_B$ and $\mathcal{L}_W$ are in $[0,1)$.

Now, from Theorem 3.2 of Hall and Heyde, it follows that

$$S_{\mathbf{c}}(n) \longrightarrow^d Z_{\mathbf{c}} \quad \text{(stably)}, \tag{4.28}$$

where $Z_{\mathbf{c}}$ has characteristic function $\varphi_{Z_{\mathbf{c}}}(t) = \mathbf{E}\exp(-\frac{1}{2}(c_1{}^2+c_2{}^2\eta^2)t^2)$. This means that $Z_{\mathbf{c}} = c_1N_1 + c_2N_2\eta$, where N_1 and N_2 are independent standard normal variables, independent of η. Using the Cramer-Wold device, the proof of part (b) of the Theorem is concluded. The remaining part (c) follows from the definition of stable convergence as in Theorem 12.6 of Heyde (1997). ■

4.29 **Remark**. It is interesting to note that when the distributions of the sequences $\{Y_B(n)\}$ and $\{Y_W(n)\}$ belong to exponential families, it follows that the components of the martingale $\mathbf{S}_n$ are the score functions, that is, the partial derivatives, on μ_B and μ_W respectively, of the logarithm of the likelihood function $L_n(\mu_B, \mu_W)$ associated with all the observations until time n. In this interpretation the quadratic variation matrix $[\mathbf{S}]_n$ represents the observed Fisher information. ■

We can now prove the joint asymptotic normality of estimators (4.22).

4.30 **Theorem**. *Under the null and the alternative hypotesis, the joint vector*

$$\left(\sqrt{N_B(n)}\left(\hat{Y}_B(n) - \mu_B\right), \sqrt{N_W(n)}\left(\hat{Y}_W(n) - \mu_W\right)\right)$$

converges in distribution to a Gaussian vector $\mathcal{N}(\mathbf{0}, \Xi)$, *with* $\boldsymbol{\Xi} = diag\,({\sigma_B}^2, {\sigma_W}^2)$.

Proof. Observe that

$$\left(\frac{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)}{\sqrt{\sum_{i=1}^n {\delta_i}^2 (Y_B(i) - \mu_B)^2}}, \frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i) - \mu_W)}{\sqrt{\sum_{i=1}^n (1-\delta_i)^2 (Y_W(i) - \mu_W)^2}}\right)$$
$$= \left(\frac{\left(\hat{Y}_B(n) - \mu_B\right) N_B(n)}{\sqrt{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)^2}}, \frac{\left(\hat{Y}_W(n) - \mu_W\right) N_W(n)}{\sqrt{\sum_{i=1}^n (1-\delta_i)(Y_W(i) - \mu_W)^2}}\right)$$
$$= \left(\frac{\sqrt{N_B(n)}\left(\hat{Y}_B(n) - \mu_B\right)}{\sqrt{\sum_{i=1}^n \delta_i (Y_B(i) - \mu_B)^2 / N_B(n)}}, \frac{\sqrt{N_W(n)}\left(\hat{Y}_W(n) - \mu_W\right)}{\sqrt{\sum_{i=1}^n (1-\delta_i)(Y_W(i) - \mu_W)^2 / N_W(n)}}\right).$$

From Theorem 4.24 (c), this vector converges to a standard Gaussian vector $\mathcal{N}(\mathbf{0}, \mathbf{I}_2)$. Using Corollary 2.7, the denominators of the last equation converge almost surely to ${\sigma_B}^2$ and ${\sigma_W}^2$, respectively. Then, from Slutsky's Theorem, we obtain the thesis. ■

5 Testing hypothesis

In this section we consider the hypothesis test

$$H_0 : \mu_B = \mu_B \quad \text{versus} \quad H_1 : \mu_B > \mu_W.$$

We characterize the classical statistic for two samples $\{Y_B(n)\}$ and $\{Y_W(n)\}$, i.i.d. and with law $\mathcal{L}_B$ and $\mathcal{L}_W$, respectively, when applied to the response-adaptive design that motivates this paper.

First consider the usual test statistic observed in a fixed design with sample sizes n_B and n_W, respectively:

$$\zeta_0 = \frac{\bar{Y}_B(n_B) - \bar{Y}_W(n_W)}{\sqrt{\dfrac{{\sigma_B}^2}{n_B} + \dfrac{{\sigma_W}^2}{n_W}}}, \tag{5.31}$$

where $\bar{Y}_B(n_B)$ and $\bar{Y}_W(n_W)$ are the sample means. Suppose that, for some $\rho \in (0,1)$, $n_B/(n_B+n_W) \to \rho$, $n_W/(n_B+n_W) \to 1-\rho$ as n_B and $n_W \to \infty$; then from the classical central limit theorem:

$$\left(\frac{\sqrt{n_B}}{\sigma_B} \left(\bar{Y}_B(n_B) - \mu_B\right), \frac{\sqrt{n_W}}{\sigma_W} \left(\bar{Y}_W(n) - \mu_W\right) \right) \longrightarrow^d \mathcal{N}(\mathbf{0}, I). \tag{5.32}$$

We can deduce that ζ_0 converges in distribution to a standard normal random variable under the null hypothesis, while it is asymptotically normal with noncentrality parameter

$$\phi = \frac{\mu_B - \mu_W}{\sqrt{\dfrac{{\sigma_B}^2}{n_B} + \dfrac{{\sigma_W}^2}{n_W}}} \approx \sqrt{n} \frac{\mu_B - \mu_W}{\sqrt{\dfrac{{\sigma_B}^2}{\rho} + \dfrac{{\sigma_W}^2}{1-\rho}}} \tag{5.33}$$

under the alternative hypothesis.

Now consider a response-adaptive procedure with random sample sizes such that $N_B(n)/n \to \rho$ and $N_W(n)/n \to (1-\rho)$, where ρ is a determined value in $(0,1)$, even if unknown *a priori*. If the result (5.32), with $N_B(n)$ and $N_W(n)$ replacing n_B and n_W, still holds, it can be deduced, similarly to the classical case and using Slutsky's Theorem, that the test statistic ζ_0 (with $N_B(n)$ and $N_W(n)$ replacing n_B and n_W), still has asymptotic normal distribution, and the same asymptotic noncentrality parameter under the alternative hypothesis.

Examine now the *RRU*-design considered in this paper: under the null hypothesis $N_B(n)/n$ and $N_W(n)/n$ converge to random limits: Z_∞ and $(1-Z_\infty)$, respectively. So we can't apply Slutsky's Theorem and we can't derive the asymptotic normality of the test statistic ζ_0 from the joint normality result proved in Theorem 4.30. Notwithstanding this, the asymptotic normality of ζ_0 holds in this procedure, as it will be proved in Theorem 5.34.

Also, under the alternative hypothesis we find a different situation: $N_B(n)/n \to 1$ and $N_W(n)/n \to 0$, almost surely. This implies that, asymptotically, $\zeta_0(n)$ carries information about the value of the mean of one only treatment. Notwithstanding this loss of balance, the use of the test statistic ζ_0 is still reasonable because the rates of $N_B(n)$ and $N_W(n)$ carry information about the difference between μ_B and μ_W.

5.34 **Theorem**. *The random process*

$$\zeta(n) = \frac{\hat{Y}_B(n) - \hat{Y}_W(n) - (\mu_B - \mu_W)}{\sqrt{\dfrac{{\sigma_B}^2}{N_B(n)} + \dfrac{{\sigma_W}^2}{N_W(n)}}} \tag{5.35}$$

converges in distribution to a standard normal variable, both under the null and under the alternative hypothesis.

Proof. *First case: assume H_0 true.* Suppose first ${\sigma_B}^2 = {\sigma_W}^2 = \sigma^2$. We shall prove preliminary that

$$\left(\frac{\hat{Y}_B(n) - \mu_B}{\sigma\sqrt{\dfrac{1}{N_B(n)} + \dfrac{1}{N_W(n)}}}, \frac{\hat{Y}_W(n) - \mu_W}{\sigma\sqrt{\dfrac{1}{N_B(n)} + \dfrac{1}{N_W(n)}}} \right) \longrightarrow^d \left(N_1\sqrt{1 - Z_\infty}, N_2\sqrt{Z_\infty} \right), \tag{5.36}$$

where N_1, N_2 and Z_∞ are as in the assertion (a) of Proposition 4.24. Rewrite the first component as follows:

$$\begin{aligned} \frac{\hat{Y}_B(n) - \mu_B}{\sigma\sqrt{\dfrac{1}{N_B(n)} + \dfrac{1}{N_W(n)}}} &= \frac{1}{\sigma}\frac{\sum_{i=1}^n \delta_i(Y_B(i) - \mu_B)}{N_B(n)}\sqrt{\frac{N_B(n)N_W(n)}{n}} \\ &= \frac{1}{\sigma}\frac{\sum_{i=1}^n \delta_i(Y_B(i) - \mu_B)}{\sqrt{n}}\sqrt{\frac{n}{N_B(n)} - 1}. \end{aligned}$$

From Proposition 4.24 (a), we have that

$$S_1(n) = \frac{1}{\sigma}\frac{\sum_{i=1}^n \delta_i(Y_B(i) - \mu_B)}{\sqrt{n}} \longrightarrow^d N_1\sqrt{Z_\infty} \quad \text{(stably)};$$

using Theorem 3.1 of Hall and Heyde (1980), this implies that for any bounded r.v. X, $\mathbf{E}\left(\exp(itS_1(n))X\right) \longrightarrow \mathbf{E}(\exp(-\frac{1}{2}Z_\infty t^2)X)$, for any real t. Let $X = \exp(iu\sqrt{\frac{1-Z_\infty}{Z_\infty}})$; it follows that the joint characteristic function of $\left(S_1(n), \sqrt{\frac{1-Z_\infty}{Z_\infty}}\right)$ converges to that of $\left(N_1\sqrt{Z_\infty}, \sqrt{\frac{1-Z_\infty}{Z_\infty}}\right)$. Since $\sqrt{\dfrac{n}{N_B(n)} - 1}$ converges a.s. to $\sqrt{\frac{1-Z_\infty}{Z_\infty}}$, using Slutsky's Theorem we obtain that

$$S_1(n)\sqrt{\frac{n}{N_B(n)} - 1} = \frac{1}{\sigma}\frac{\sum_{i=1}^n \delta_i(Y_B(i) - \mu_B)}{\sqrt{n}}\sqrt{\frac{n}{N_B(n)} - 1} \longrightarrow^d N_1\sqrt{1 - Z_\infty},$$

completing the assertion (5.36) for the first component. Similarly, we can obtain convergence of the second component in assertion (5.36) and their joint convergence stably in distribution then follows from Proposition 4.24 (a).

Thus, (5.36) ensures that

$$\zeta(n) = \frac{\hat{Y}_B(n) - \mu_B}{\sigma\sqrt{\frac{1}{N_B(n)} + \frac{1}{N_W(n)}}} - \frac{\hat{Y}_W(n) - \mu_W}{\sigma\sqrt{\frac{1}{N_B(n)} + \frac{1}{N_W(n)}}} \longrightarrow^d N_1\sqrt{1 - Z_\infty} - N_2\sqrt{Z_\infty}.$$

The thesis then is obtained, since N_1 and N_2 are independent standard normal r.v., independent of Z_∞:

$$P\{N_1\sqrt{1 - Z_\infty} - N_2\sqrt{Z_\infty} \le x\} = \mathbf{E}(P\{N_1\sqrt{1 - Z_\infty} - N_2\sqrt{Z_\infty} \le x | Z_\infty\}) = \mathbf{E}(\Phi(x)) = \Phi(x).$$

The case ${\sigma_B}^2 \neq {\sigma_W}^2$ is only slightly different. Similarly to (5.36) it can be proved that

$$\left(\frac{\hat{Y}_B(n) - \mu_B}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)} + \frac{{\sigma_W}^2}{N_W(n)}}}, \frac{\hat{Y}_W(n) - \mu_W}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)} + \frac{{\sigma_W}^2}{N_W(n)}}} \right) \tag{5.37}$$
$$\longrightarrow^d \left(N_1\sqrt{\frac{{\sigma_B}^2(1 - Z_\infty)}{{\sigma_B}^2(1 - Z_\infty) + {\sigma_W}^2 Z_\infty}}, N_2\sqrt{\frac{{\sigma_W}^2 Z_\infty}{{\sigma_W}^2 Z_\infty + {\sigma_B}^2(1 - Z_\infty)}} \right),$$

with N_1, N_2 and Z_∞ as in the assertion (a) of Proposition 4.24, ensuring that $\zeta(n)$ converges in distribution to a standard normal. This complete the proof of the Theorem under the null hypothesis.

Second case: assume H_1 true.

$$\begin{aligned} \zeta(n) &= \frac{\hat{Y}_B(n) - \mu_B}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)} + \frac{{\sigma_W}^2}{N_W(n)}}} - \frac{\hat{Y}_W(n) - \mu_W}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)} + \frac{{\sigma_W}^2}{N_W(n)}}} = \\ &= \sqrt{N_B(n)}\left(\hat{Y}_B(n) - \mu_B\right)\frac{1}{\sqrt{{\sigma_B}^2 + {\sigma_W}^2\frac{N_B(n)}{N_W(n)}}} \\ &- \sqrt{N_W(n)}\left(\hat{Y}_W(n) - \mu_W\right)\frac{1}{\sqrt{{\sigma_B}^2\frac{N_W(n)}{N_B(n)} + {\sigma_W}^2}}; \end{aligned}$$

since $N_B(n)/N_W(n) \to +\infty$ a.s., from Slutsky's Theorem the first member of the sum in the last equation converges to 0 in distribution, while the second term converges to the limit distribution of $\sqrt{N_W(n)}(\hat{Y}_W(n) - \mu_W)/\sigma_W$. Using again Slutsky's Theorem and Theorem 4.30, it follows that $\zeta(n)$ converges to a standard normal variable. ∎

Let us examine the distribution of the test statistic

$$\zeta_0(n) = \frac{\hat{Y}_B(n) - \hat{Y}_W(n)}{\sqrt{\dfrac{{\sigma_B}^2}{N_B(n)} + \dfrac{{\sigma_W}^2}{N_W(n)}}}.$$

When H_0 is true, $\zeta_0(n)$ is equal to $\zeta(n)$ and hence, from Theorem 5.34, it is asymptotically normal. So one can then construct the following critical region with asymptotic level of significance α:

$$C_\alpha = \{\zeta_0(n) > z_{1-\alpha}\}.$$

When the alternative hypothesis is true, $\mu_B > \mu_W$ and we have that $\zeta_0(n) = \zeta(n) + \phi(n)$, where

$$\phi(n) = \frac{\mu_B - \mu_W}{\sqrt{\dfrac{{\sigma_B}^2}{N_B(n)} + \dfrac{{\sigma_W}^2}{N_W(n)}}} \tag{5.38}$$

is the noncentrality parameter. Let η be the positive square root of η^2. The following Theorem establishes that, in this case, the test statistic $\zeta_0(n)$ is a mixture of normal distributions and characterizes its representation.

5.39 **Theorem**. *Under the alternative hypothesis, the conditional distribution of $\zeta_0(n)$ given the random variable η^2 defined in Theorem 3.10, is asymptotically normal with mean equal to $\sqrt{n^{m_B/m_W}}\,\eta\,\dfrac{\mu_B - \mu_W}{\sigma_W}$ and unit variance.*

Proof. When $\mu_B > \mu_W$, for Theorem 3.10 we have that $N_B(n)/n^{m_W/m_B} \to \infty$ and $N_W(n)/n^{m_W/m_B} \to \eta^2$ almost surely, and then, for n large, we can approximate the noncentrality parameter as follows:

$$\phi(n) = \frac{\mu_B - \mu_W}{\sqrt{\dfrac{{\sigma_B}^2}{N_B(n)} + \dfrac{{\sigma_W}^2}{N_W(n)}}} \approx \sqrt{n^{m_W/m_B}}\sqrt{\eta^2}\,\frac{\mu_B - \mu_W}{\sigma_W}.$$

We then prove a fact that reinforces the statement of Theorem 5.34, that is: if $\mu_B > \mu_W$, then $\zeta(n)$ converges in distribution to a normal random variable independent of η^2. In fact,

$$\begin{aligned}
\zeta(n) &= \frac{\hat{Y}_B(n)-\mu_B}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)}+\frac{{\sigma_W}^2}{N_W(n)}}} - \frac{\hat{Y}_W(n)-\mu_W}{\sqrt{\frac{{\sigma_B}^2}{N_B(n)}+\frac{{\sigma_W}^2}{N_W(n)}}} = \\
&= \frac{\sum_{i=1}^n \delta_i (Y_B(i)-\mu_B)}{N_B(n)\sqrt{\frac{{\sigma_B}^2}{N_B(n)}+\frac{{\sigma_W}^2}{N_W(n)}}} - \frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i)-\mu_W)}{N_W(n)\sqrt{\frac{{\sigma_B}^2}{N_B(n)}+\frac{{\sigma_W}^2}{N_W(n)}}} \\
&= \frac{\sum_{i=1}^n \delta_i (Y_B(i)-\mu_B)}{\sigma_B\sqrt{n}}\sqrt{\frac{n}{N_B(n)}}\left(\sqrt{1+\frac{\sigma_W^2}{\sigma_B^2}\frac{N_B(n)}{N_W(n)}}\right)^{-1} \\
&- \frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i)-\mu_W)}{\sigma_W\sqrt{n^{m_W/m_B}}}\sqrt{\frac{n^{m_W/m_B}}{N_W(n)}}\left(\sqrt{1+\frac{\sigma_B^2}{\sigma_W^2}\frac{N_W(n)}{N_B(n)}}\right)^{-1}.
\end{aligned}$$

Consider now the two terms of the sum in the last equality above. Applying Slutsky's theorem, the first one converges to zero, in fact: using part (b) of Theorem 4.24, $Q_1(n) = \frac{\sum_{i=1}^n \delta_i (Y_B(i)-\mu_B)}{\sigma_B\sqrt{n}}$ converges in distribution to a normal random variable, while from Theorem 3.10, $\sqrt{n/N_B(n)}$ converges a.s. to 1 and

$$\left(\sqrt{1+\frac{\sigma_W^2}{\sigma_B^2}\frac{N_B(n)}{N_W(n)}}\right)^{-1}$$

converges a.s. to zero.

We claim that the second term of the sum converges to a normal random variable independent of η^2. In fact, $Q_2(n) = \frac{\sum_{i=1}^n (1-\delta_i)(Y_W(i)-\mu_W)}{\sigma_W\sqrt{n^{m_W/m_B}}}$ converges stably in distribution to the normal mixture ηN_2, where N_2 is a standard normal random variable independent of η^2. It follows, using Theorem 3.1 of Hall and Heyde (1980), that for any bounded random variable X, $\mathbf{E}(e^{itQ_2(n)}X)$ converges to $\mathbf{E}(e^{-1/2\eta^2 t)}X)$. If we choose $X = e^{iu\eta}$, $u \in \mathbb{R}$, we can deduce that the joint characteristic function of $(Q_2(n), \eta)$ converges to that of $(\eta N_2, \eta)$, where N_2 is a standard normal r.v. independent of η. This implies that

$$\eta^{-1} Q_2(n) \longrightarrow^d N_2,$$

and, since from Theorem 3.10

$$\sqrt{\frac{n^{m_W/m_B}}{N_W(n)}}\left(\sqrt{1+\frac{\sigma_B^2}{\sigma_W^2}\frac{N_W(n)}{N_B(n)}}\right)^{-1}$$

converge a.s. to η^{-1}, using Slutsky's Theorem we have proved the claim. Since $\zeta_0(n) = \zeta(n) + \phi(n)$, this completes the proof. ■

5.40 **Remark**. We conjecture that the random variable η^2 is not a constant. This would prove, for Theorem 5.39, that the test statistic $\zeta_0(n)$ is not asymptotically normal under the alternative hypothesis. An open problem, also in order to evaluate theoretically the power the test considered, is the distribution of η^2. The power of the test considered in this section has been studied via simulations in Paganoni and Secchi (2007). ■

6 Conclusions

The results obtained lead us to some considerations. In Section 3, we have proved that the rate of convergence of the number of patients assigned to the worst treatment is determined by the ratio of m_W and m_B: the smaller the value of this quantity, the more slowly $N_W(n)$ increases. However for smaller values of m_W/m_B, the probability of assigning patients to the best treatment converges to one faster. On the other hand, the study of the noncentrality parameter in Section 5 shows that small values of m_W/m_B cause a lost of the power of the test for treatment mean differences. This observation generates interesting research questions regarding the best choice for the function u that determines the values of m_B and m_W.

Paganoni and Secchi (2007) and Muliere, Paganoni and Secchi (2006b) have studied the performance of the response-adaptive urn designs considered in this paper through numerical simulations, when responses to treatments have normal distributions. Their results show that such designs look to be a viable alternative to a standard, randomized, non-adaptive design only when the difference $\Delta = \mu_B - \mu_W$ between the mean responses to treatments have moderate or large values. In our work we have solved some problems of asymptotic theory generated by the fact that a *RRU*-design has a very desirable property that can't be approached with the usual methods presented in literature. We wish that this study may offer a contribution to development of research in response-adaptive, optimal designs.

7 Acknoweledgments

Special thanks to Piercesare Secchi, Giacomo Aletti and Jose Moler for many useful discussions and suggestions that have been an essential contribution to this work.

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