Bernoulli **21**(2), 2015, 881–908
DOI: 10.3150/13-BEJ591

On the almost sure convergence of adaptive allocation procedures

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In this paper, we provide some general convergence results for adaptive designs for treatment comparison, both in the absence and presence of covariates. In particular, we demonstrate the almost sure convergence of the treatment allocation proportion for a vast class of adaptive procedures, also including designs that have not been formally investigated but mainly explored through simulations, such as Atkinson's optimum biased coin design, Pocock and Simon's minimization method and some of its generalizations. Even if the large majority of the proposals in the literature rely on continuous allocation rules, our results allow to prove via a unique mathematical framework the convergence of adaptive allocation methods based on both continuous and discontinuous randomization functions. Although several examples of earlier works are included in order to enhance the applicability, our approach provides substantial insight for future suggestions, especially in the absence of a prefixed target and for designs characterized by sequences of allocation rules.

Keywords: Biased Coin Designs; CARA Procedures; minimization methods; Response-Adaptive designs; sequential allocations

1. Introduction

The past five decades have witnessed a sizeable amount of statistical research on adaptive randomized designs in the context of clinical trials for treatment comparison. These are sequential procedures where at each step the accrued information is used to make decisions about the way of randomizing the allocation of the next subject.

Starting from the pioneering work of Efron's Biased Coin Design (BCD) [12], several authors have suggested adaptive procedures that, by taking into account at each step only previous assignments, are aimed at achieving balance between two available treatments (see, e.g., [4,38–40,43]). We shall refer to these as Assignment-Adaptive methods. Since clinical trials usually involve additional information on the experimental units, expressed by a set of important covariates/prognostic factors, Pocock and Simon [28] and other authors (see, for instance, [1,6,9,41]) proposed Covariate-Adaptive designs. These methods modify the allocation probabilities at each step according to the assignments and the characteristics of previous statistical units, as well as those of the present subject, in order to ensure balance between the treatment groups among covariates for reducing possible sources of heterogeneity.

Motivated by ethical demands, another different viewpoint is the Response-Adaptive randomization methods. These are allocation rules introduced with the aim of skewing the assignments

towards the treatment that appears to be superior at each step (see, e.g., [2]) or, more generally, of converging to a desired target allocation of the treatments which combines inferential and ethical concerns [5,42]. The above mentioned framework has been recently extended in order to incorporate covariates, which has led to the introduction of the so-called Covariate-Adjusted Response-Adaptive (CARA) procedures, that is, allocation methods that sequentially modify the treatment assignments on the basis of earlier responses and allocations, past covariate profiles and the characteristics of the subject under consideration. See [35,45] and the cornerstone book by Hu and Rosenberger [20].

In general, given a desired target it is possible to adopt different procedures converging to it, such as the Sequential Maximum Likelihood design [26], the Doubly-adaptive BCD [13,21] and their extensions with covariates given by Zhang *et al.*'s CARA design [45] and the Covariate-adjusted Doubly-adaptive BCD [46], having well established asymptotic properties. However, in the absence of a given target one of the main problems lies in providing the asymptotic behaviour of the suggested procedure. This is especially true in the presence of covariates, where theoretical results seem to be few and the properties of the suggested procedures have been explored extensively through simulations; indeed, as stated by Rosenberger and Sverdlov [34] "very little theoretical work has been done in this area, despite the proliferation of papers". For instance, even if Pocock and Simon's minimization method is widely used in the clinical practice, its theoretical properties are still largely unknown (indeed, Hu and Hu's results [23] do not apply to this procedure), as well as the properties of several extensions of the minimization method and of Atkinson's Biased Coin Design [1].

Moreover, although the large majority of the proposals are based on continuous and prefixed allocation rules, updated step by step on the basis of the current allocation proportion and some estimates of the unknown parameters (usually based on the sufficient statistics of the model), the recent literature tends to concentrate on discontinuous randomization functions, such as the Efficient Randomized-Adaptive Design (ERADE) [22], because of their low variability.

In this paper, we provide some general convergence results for adaptive allocation procedures both in the absence and presence of covariates, continuous or categorical. By combining the concept of downcrossing (originally introduced in [19]) and stopping times of stochastic processes, we demonstrate the almost sure convergence of the treatment allocation proportion for a large class of adaptive procedures, even in the absence of a given target, and thus our approach provides substantial insight for future suggestions as well as for several existing procedures that have not been theoretically explored [18,36]. In particular, we prove that Pocock and Simon's minimization method [28] is asymptotically balanced, both marginally and jointly, showing also the convergence to balance of Atkinson's BCD [1]. The suggested approach allow to prove through a unique mathematical framework the convergence of continuous and discontinuous randomization functions (like e.g., the Doubly-Adaptive Weighted Differences design [15], the Reinforced Doubly-adaptive BCD [7], ERADE [22] and Hu and Hu's procedure [23]), taking also into account designs based on Markov chain structures, such as the Adjustable BCD [4] and the Covariate-adaptive BCD [6], that can be characterized by sequences of allocation rules. Moreover, by removing some unessential conditions usually assumed in the literature, our results allow to provide suitable extensions of several existing procedures.

The paper is structured as follows. Even if Assignment-Adaptive and Response-Adaptive procedures can be regarded as special cases of CARA designs, we will treat them separately for

the sake of clarity, in order to describe the general proof scheme in a simple setting, whereas Covariate-Adaptive methods will be discussed as particular case of CARA rules. To treat CARA rules in the presence of solely categorical covariates we need to extend the concept of down-crossing in a vectorial framework; this generalization is not used for CARA procedures with continuous prognostic factors and therefore these two cases will be analyzed separately. Starting from the notation in Section 2, Section 3 deals with Assignment-Adaptive designs, while Section 4 discusses Response-Adaptive procedures. Sections 5 and 6 illustrate the asymptotic behavior of CARA methods in the case of continuous and categorical covariates, respectively. Section 7 discusses the relationship between the proposed methodology and the theory of Stochastic Approximation. To avoid cumbersome notation, the paper mainly deals with the case of just two treatments, but the suggested methodology is shown to extend to more than two (see Section 3.1).

2. Notation

Suppose that patients come to the trial sequentially and are assigned to one of two treatments, A and B, that we want to compare. At each step $i \geq 1$, a subject will be assigned to one of the treatments and a response Y_i will be observed. Typically, the outcome Y_i will depend on the treatment, but it may also depend on some characteristics of the subject expressed by a vector $\mathbf{Z}_i$ of covariates/concomitant variables. We assume that $\{\mathbf{Z}_i\}_{i\geq 1}$ are i.i.d. covariates that are not under the experimenters' control, but they can be measured before assigning a treatment, and, conditionally on the treatments and the covariates (if present), patients' responses are assumed to be independent. Let δ_i denote the ith allocation, with $\delta_i = 1$ if the ith subject is assigned to A and 0 otherwise; also, $\widetilde{N}_n = \sum_{i=1}^{n} \delta_i$ is the number of allocations to A after n assignments and π_n the corresponding proportion, that is, $\pi_n = n^{-1}\widetilde{N}_n$.

In general, adaptive allocation procedures can be divided in four different categories according to the experimental information used for allocating the patients to the treatments. Suppose that the $(n+1)$st subject is ready to be randomized; if the probability of assigning treatment A depends on:

(i) the past allocations, that is, $\Pr(\delta_{n+1} = 1|\delta_1, \ldots, \delta_n)$, we call such a procedure Assignment-Adaptive (AA);
(ii) earlier allocations and responses, that is, $\Pr(\delta_{n+1} = 1|\delta_1, \ldots, \delta_n; Y_1, \ldots, Y_n)$, then the design is Response-Adaptive (RA);
(iii) the previous allocations and covariates, as well as the covariate of the present subject, that is, $\Pr(\delta_{n+1} = 1|\delta_1, \ldots, \delta_n; \mathbf{Z}_1, \ldots, \mathbf{Z}_n, \mathbf{Z}_{n+1})$, the procedure is Covariate-Adaptive (CA);
(iv) the assignments, the outcomes and the covariates of the previous statistical units, as well as the characteristics of the current subject that will be randomized, that is, $\Pr(\delta_{n+1} = 1|\delta_1, \ldots, \delta_n; Y_1, \ldots, Y_n; \mathbf{Z}_1, \ldots, \mathbf{Z}_{n+1})$, then the rule is called Covariate-Adjusted Response-Adaptive (CARA).

From now on, we will denote with $\Im_n$ the σ-algebra representing the natural history of the experiment up to step n associated with a given procedure belonging to each category (with $\Im_0$ the trivial σ-field). For instance, in the case of AA rules, $\Im_n = \sigma\{\delta_1, \ldots, \delta_n\}$, whereas for RA designs $\Im_n = \sigma\{\delta_1, \ldots, \delta_n; Y_1, \ldots, Y_n\}$.

The sequence of allocations is a stochastic process and a general way of representing it is by the sequence of the conditional probabilities of assigning treatment A given the past information at every stage, that is, $\Pr(\delta_{n+1} = 1|\Im_n)$ for $n \in \mathbb{N}$, which is called the allocation function. Even if the large majority of suggested procedures assume continuous allocation rules, in this paper, we take also into account designs with discontinuous randomization functions, provided that their set of discontinuities is nowhere dense.

3. Assignment-Adaptive designs

Assignment adaptive rules, which depend on the past history of the experiment only through the sequence of previous allocations, were proposed as a suitable trade-off between balance (i.e., inferential optimality) and unpredictability in the context of randomized clinical trials. Indeed, if the main concern is maximum precision of the results (without ethical demands), as is well-known under the classical linear model assumptions, balanced design is *universally optimal* [37], since it minimizes the most common inferential criteria for estimation and maximizes the power of the classical statistical tests. The requirement of balance is considered particularly cogent for phase III trials, where patients are sequentially enrolled and the total sample size is often a-priori unknown, so that keeping a reasonable degree of balance at each step, even for small/moderate samples, is crucial for stopping the experiment at any time under an excellent inferential setting.

The simplest sequential randomized procedure that approaches balance is the completely randomized (CR) design, where every allocation is to either treatment with probability $1/2$ independently on the previous steps; thus, $\delta_1, \delta_2, \ldots$ are i.i.d. Be$(1/2)$ so that, as n tends to infinity, $\pi_n \to 1/2$ almost surely from the SLLN for independent r.v.'s. Although CR could represent an ideal trade-off between balance and unpredictability, this holds only asymptotically. In fact, CR may generate large imbalances for small samples, since $n^{-1/2}\pi_n$ is asymptotically normal, and this may induce a consistent loss of precision. For this reason, starting from the pioneering work of Efron [12], AA rules were introduced in the literature in order to force the allocations at each step towards balance maintaining, at the same time, a suitable degree of randomness.

In this section, we shall deal with AA procedures such that

$$\Pr(\delta_{n+1} = 1|\Im_n) = \varphi^{\mathrm{AA}}(\pi_n), \qquad \text{for } n \geq 1, \tag{3.1}$$

where $\varphi^{\mathrm{AA}} : [0; 1] \to [0; 1]$.

Definition 3.1. *For any function $\psi : [0; 1] \to [0; 1]$, a point $t \in [0; 1]$ is called a* downcrossing *of $\psi(\cdot)$ if*

$$\forall x < t, \qquad \psi(x) \geq t \quad \textit{and} \quad \forall x > t, \qquad \psi(x) \leq t.$$

Note that if the function $\psi(x)$ is decreasing, then there exists a single downcrossing $t \in (0; 1)$ and if the equation $\psi(x) = x$ admits a solution then the downcrossing coincides with it. Clearly, if $\psi(\cdot)$ is a continuous and decreasing function, then t can be found directly by solving the equation $\psi(x) = x$.

Theorem 3.1. *If the allocation function* $\varphi^{\mathrm{AA}}(\cdot)$ *in* (3.1) *has a unique downcrossing* $t \in (0; 1)$, *then* $\lim_{n\to\infty} \pi_n = t$ *a.s.*

Proof. By using a martingale decomposition of the number of assignments to treatment A, we will show that the asymptotic behavior of the allocation proportion π_n coincides with that of the sequence of downcrossing points of the corresponding allocation function (i.e., a constant sequence in the case of AA procedures). The same arguments will be generalized in the Appendix to the case of RA and CARA rules for random sequences of downcrossings.

At each step $n \geq 1$,

$$\widetilde{N}_n = \sum_{i=1}^{n} \delta_i = \sum_{i=1}^{n} \big\{\delta_i - E(\delta_i|\Im_{i-1})\big\} + \sum_{i=1}^{n} E(\delta_i|\Im_{i-1}) = \sum_{i=1}^{n} \Delta M_i + \sum_{i=1}^{n} \varphi^{\mathrm{AA}}(\pi_{i-1}), \quad (3.2)$$

where $\Delta M_i = \delta_i - E(\delta_i|\Im_{i-1})$, $\Im_n = \sigma\{\delta_1, \ldots, \delta_n\}$ and $\pi_0 = 0$. Then $\{\Delta M_i; i \geq 1\}$ is a sequence of bounded martingale differences with $|\Delta M_i| \leq 1$ for any $i \geq 1$; thus the sequence $\{M_n = \sum_{i=1}^{n} \Delta M_i; \Im_n\}$ is a martingale with $\sum_{k=1}^{n} E[(\Delta M_i)^2|\Im_{k-1}] \leq n$, so that as n tends to infinity $n^{-1}M_n \to 0$ a.s. Let $l_n = \max\{s\colon\ 1 \leq s \leq n, \pi_s \leq t\}$, with $\max \varnothing = 0$, then at each step $i > l_n$ we have $\varphi^{\mathrm{AA}}(\pi_i) \leq t$. Note that

$$\begin{aligned}
\widetilde{N}_n &= \widetilde{N}_{l_n+1} + \sum_{k=l_n+2}^{n} \Delta M_k + \sum_{k=l_n+2}^{n} E(\delta_k|\Im_{k-1}) \\
&\leq \widetilde{N}_{l_n} + 1 + M_n - M_{l_n+1} + \sum_{k=l_n+2}^{n} \varphi^{\mathrm{AA}}(\pi_{k-1}) \\
&\leq \widetilde{N}_{l_n} + 1 + M_n - M_{l_n+1} + \sum_{k=l_n+2}^{n} t
\end{aligned}$$

and, since $\widetilde{N}_{l_n} \leq l_n t$, then

$$\widetilde{N}_n - nt \leq M_n - M_{l_n+1} + 1 - t,$$

namely

$$\pi_n - t \leq \frac{M_n - M_{l_n+1} + 1 - t}{n}. \quad (3.3)$$

As $n \to \infty$, then $l_n \to \infty$ or $\sup_n l_n < \infty$, and in either case the r.h.s. of (3.3) goes to 0 a.s. Thus $[\pi_n - t]^+ \to 0$ a.s. and, analogously, $[(1 - \pi_n) - (1 - t)]^+ \to 0$ a.s. Therefore, $\lim_{n\to\infty} \pi_n = t$ a.s. □

Example 3.1. The completely randomized design is defined by letting $\Pr(\delta_{n+1} = 1|\Im_n) = 1/2$ for every n. This corresponds to assume $\varphi^{\mathrm{CR}}(x) = 1/2$ for all $x \in [0; 1]$, which is continuous and does not depend on x; therefore, $\varphi^{\mathrm{CR}}(\cdot)$ has a single downcrossing $t = 1/2$ and thus $\pi_n \to 1/2$ a.s. as $n \to \infty$. Clearly, this procedure can be naturally extended to any given desirable target allocation that is a-priori known.

Example 3.2. Efron's BCD [12] is defined by

$$\Pr(\delta_{n+1}=1|\Im_n)=\begin{cases} p, & \text{if } D_n<0,\\ 1/2, & \text{if } D_n=0,\\ 1-p, & \text{if } D_n>0,\end{cases} \qquad \text{for } n\geq 1,$$

where $D_n = 2\widetilde{N}_n - n$ is the difference between the allocations to A and B after n steps and $p \in [1/2; 1]$ is the bias parameter. Since $\operatorname{sgn} D_n = \operatorname{sgn}(\pi_n - 1/2)$, then Efron's rule corresponds to

$$\varphi^E(x)=\begin{cases} p, & \text{if } x<1/2,\\ 1/2, & \text{if } x=1/2,\\ 1-p, & \text{if } x>1/2,\end{cases} \tag{3.4}$$

which has a single downcrossing $t = 1/2$ and therefore $\lim_{n\to\infty}\pi_n = 1/2$ a.s. Clearly, Theorem 3.1 allows to provide suitable extensions of Efron's coin converging to any given desired target $t^* \in (0; 1)$, namely

$$\varphi^{\tilde{E}}(x)=\begin{cases} p_2, & \text{if } x<t^*,\\ t^*, & \text{if } x=t^*,\\ p_1, & \text{if } x>t^*,\end{cases} \tag{3.5}$$

where $0 \leq p_1 \leq t^* \leq p_2 \leq 1$ and at least one of these inequalities must hold strictly.

Remark 3.1. Note that, from Theorem 3.1, for the convergence to a given desired target t^*:

(i) the allocation function should be decreasing; this condition is quite intuitive, since it corresponds to assume that, at each step, if the current allocation proportion π_n is greater than t^*, then the next allocation is forced to treatment B with probability greater than t^* and this probability increases as the difference $\pi_n - t^*$ grows;

(ii) the continuity of the allocation rule is not required and therefore it is possible to consider discontinuous randomization functions like, for example, (3.4) and (3.5);

(iii) condition $\varphi^{\mathrm{AA}}(t^*) = t^*$ is not requested; moreover, structures of symmetry of the allocation function are not needed (e.g., in (3.5) condition $p_2 = 1 - p_1$ is not required), even if they are typically assumed in order to treat A and B in the same way. For instance, the following AA procedure

$$\varphi^{\mathrm{AA}^*}(x)=\begin{cases} 1, & \text{if } x\leq 1/2,\\ 1/2, & \text{if } x>1/2,\end{cases}$$

is asymptotically balanced, that is, $\pi_n \to 1/2$ a.s. as n tends to infinity.

Corollary 3.1. *Suppose that φ^{AA} is a composite function such that $\varphi^{\mathrm{AA}}(x) = h_1[h_2(x)]$, where $h_1 : D \subseteq \mathbb{R} \to [0; 1]$ is decreasing and $h_2 : [0; 1] \to D$ is continuous and increasing. If $d \in D$ is such that $h_1(d) = h_2^{-1}(d)$, then $\lim_{n\to\infty}\pi_n = h_2^{-1}(d)$ a.s.*

Proof. The proof follows easily from Theorem 3.1. Indeed, $\varphi^{\mathrm{AA}}(\cdot)$ is a decreasing function with $\varphi^{\mathrm{AA}}[h_2^{-1}(d)] = h_1(d) = h_2^{-1}(d)$ and therefore $\varphi^{\mathrm{AA}}(\cdot)$ has a single downcrossing in $h_2^{-1}(d)$. □

Example 3.3. Wei [43] defined his Adaptive BCD by letting

$$\Pr(\delta_{n+1} = 1|\Im_n) = \mathfrak{f}(2\pi_n - 1), \qquad \text{for } n \geq 1, \tag{3.6}$$

where $\mathfrak{f}:[-1;1] \to [0;1]$ is a continuous and decreasing function s.t. $\mathfrak{f}(-x) = 1 - \mathfrak{f}(x)$. Set $g(w) = 2w - 1 : [0;1] \to [-1;1]$, Wei's allocation function is $\varphi^W(x) = \mathfrak{f}[g(x)]$. Since $g^{-1}(w) = (w+1)/2$ for all $w \in [0;1]$, then $g^{-1}(0) = 1/2 = \mathfrak{f}(0)$, that is, $1/2$ is the only downcrossing of $\varphi^W(\cdot)$. Therefore, from Corollary 3.1 it follows that $\pi_n \to 1/2$ a.s. as $n \to \infty$.

Remark 3.2. Note that Theorem 3.1 still holds even if we assume different randomization functions at each step by letting $\Pr(\delta_{n+1} = 1|\Im_n) = \varphi_n^{\mathrm{AA}}(\pi_n)$, provided that $t \in (0;1)$ is the unique downcrossing of $\varphi_n^{\mathrm{AA}}(\cdot)$ for every $n \geq 1$.

Example 3.4. The Adjustable Biased Coin Design (ABCD) proposed by Baldi Antognini and Giovagnoli [4] is defined as follows. Let $F(\cdot):\mathbb{R} \to [0;1]$ be a decreasing function such that $F(-x) = 1 - F(x)$, the ABCD assigns the $(n+1)$st subject to treatment A with probability $\Pr(\delta_{n+1} = 1|\Im_n) = F(D_n)$, for $n \geq 1$. This corresponds to let

$$\varphi_n^{\mathrm{ABCD}}(x) = F\big[n(2x-1)\big], \qquad n \geq 1,$$

and, from the properties of $F(\cdot)$, at each step n the function $\varphi_n^{\mathrm{ABCD}}(\cdot)$ is decreasing with $\varphi_n^{\mathrm{ABCD}}(1/2) = 1/2$. Thus $t = 1/2$ is the only downcrossing of $\varphi_n^{\mathrm{ABCD}}(\cdot)$ for every n, so that $\lim_{n\to\infty} \pi_n = 1/2$ a.s.

3.1. The case of several treatments

Now we briefly discuss AA procedures in the case of several treatments in order to show how the proposed downcrossing methodology can be extended to $K > 2$ treatments. Even if the same mathematical structure could also be applied to the other types of adaptive rules that will be presented in Sections 4–6, we restrict the presentation of multi-treatment adaptive procedures only for AA designs, for the sake of simplicity regarding the notation.

At each step $i \geq 1$, let $\delta_{iJ} = 1$ if the ith patient is assigned to treatment J (with $J = 1, \ldots, K$) and 0 otherwise, and set $\boldsymbol{\delta}_i^t = (\delta_{i1}, \ldots, \delta_{iK})$ with $\boldsymbol{\delta}_i^t \mathbf{1}_K = 1$ (where $\mathbf{1}_K$ is the K-dim vector of ones). After n steps, let $\widetilde{N}_{nJ} = \sum_{i=1}^n \delta_{iJ}$ be the number of allocations to treatment J and π_{nJ} the corresponding proportion, i.e. $\pi_{nJ} = n^{-1}\widetilde{N}_{nJ}$; also, set $\widetilde{\mathbf{N}}_n^t = (\widetilde{N}_{n1}, \ldots, \widetilde{N}_{nK})$ and $\boldsymbol{\pi}_n^t = (\pi_{n1}, \ldots, \pi_{nK})$, where $\widetilde{\mathbf{N}}_n^t \mathbf{1}_K = n$ and $\boldsymbol{\pi}_n^t \mathbf{1}_K = 1$.

In this setting, we consider a class of AA designs that assigns the $(n+1)$st patient to treatment J with probability

$$\Pr(\delta_{n+1,J} = 1|\Im_n) = \varphi_J^{\mathrm{AA}}(\boldsymbol{\pi}_n), \qquad \text{for } n \geq 1, \tag{3.7}$$

where $\Im_n = \sigma(\boldsymbol{\delta}_1, \ldots, \boldsymbol{\delta}_n)$, φ_J^{AA} is the allocation function of the Jth treatment and from now on we set $\boldsymbol{\varphi}^{\mathrm{AA}}(\boldsymbol{\pi}_n) = (\varphi_1^{\mathrm{AA}}(\boldsymbol{\pi}_n), \ldots, \varphi_K^{\mathrm{AA}}(\boldsymbol{\pi}_n))$.

Definition 3.2. *Let* $\mathbf{x} = (x_1, \ldots, x_K)$, *where* $x_J \in [0; 1]$ *for any* $J = 1, \ldots, K$, $\psi_J(\mathbf{x}) : [0; 1]^K \to [0; 1]$ *and set* $\boldsymbol{\psi}(\mathbf{x}) = (\psi_1(\mathbf{x}), \ldots, \psi_K(\mathbf{x}))$. *Then* $\mathbf{t} = (t_1, \ldots, t_K) \in [0; 1]^K$ *is called a* vectorial downcrossing *of* $\boldsymbol{\psi}$ *if for any* $J = 1, \ldots, K$

$$\text{for all } x_J < t_J, \qquad \psi_J(\mathbf{x}) \geq t_J \quad \text{and} \quad \text{for all } x_J > t_J, \qquad \psi_J(\mathbf{x}) \leq t_J.$$

Clearly, if $\psi_J(\mathbf{x})$ is decreasing in $\mathbf{x}$ (i.e., componentwise) for any J, then the vectorial downcrossing $\mathbf{t}$ is unique, with $\mathbf{t} \in (0; 1)^K$; furthermore $\boldsymbol{\psi}(\mathbf{t}) = \mathbf{t}$, provided that the solution exists.

Theorem 3.2. *At each step* n, *suppose that* $\varphi_J^{\mathrm{AA}}(\boldsymbol{\pi}_n)$ *is decreasing in* $\boldsymbol{\pi}_n$ (*componentwise*) *for any* $J = 1, \ldots, K$, *then* $\lim_{n\to\infty} \boldsymbol{\pi}_n = \mathbf{t}$ *a.s.*

Proof. The proof follows easily from the one in Appendix A.3, where K treatments should be considered instead of the strata induced by the categorical covariates. □

Example 3.5. In order to achieve balance, that is, $\pi_J^* = K^{-1}$ for any $J = 1, \ldots, K$, Wei *et al.* [44] considered the following allocation rules:

$$\Pr(\delta_{n+1,J} = 1 | \Im_n) = \frac{\pi_{nJ}^{-1} - 1}{\sum_{k=1}^K (\pi_{nk}^{-1} - 1)}, \tag{3.8}$$

and

$$\Pr(\delta_{n+1,J} = 1 | \Im_n) = \frac{1 - \pi_{nJ}}{K - 1}. \tag{3.9}$$

Both rules are decreasing in π_{nJ} ($J = 1, \ldots, K$) and it is straightforward to see that $\mathbf{t} = K^{-1}\mathbf{1}_K$ is the only vectorial downcrossing of the functions $\boldsymbol{\psi}^{W_1}$ and $\boldsymbol{\psi}^{W_2}$ given by:

$$\psi_J^{W_1}(\mathbf{x}) = \frac{x_J^{-1} - 1}{\sum_{k=1}^K (x_k^{-1} - 1)} \quad \text{and} \quad \psi_J^{W_2}(\mathbf{x}) = \frac{1 - x_J}{K - 1}$$

and therefore, by Theorem 3.2, $\lim_{n\to\infty} \pi_{nJ} = K^{-1}$ a.s. for any $J = 1, \ldots, K$.

Note that, under rule (3.9), $\psi_J^{W_2}(\mathbf{x}) = \psi_J^{W_2}(x_J)$ (i.e., at each step the allocation probability of each treatment depends only on the current allocation proportion of that treatment); in such a case it is sufficient to solve the system of equations $\psi_J^{W_2}(x_J) = x_J$ ($J = 1, \ldots, K$).

4. Response-Adaptive designs

RA rules, which change at each step the allocation probabilities on the basis of the previous assignments and responses, were originally introduced as a possible solution to local optimality problems in a parametric setup, where there exists a desired target allocation depending on the unknown model parameters [31]. Recently, they have been also suggested in the context of

sequential clinical trials where ethical purposes are of primary importance, with the aim of maximizing the power of the test and, simultaneously, skewing the allocations towards the treatment that appears to be superior (e.g., minimizing exposure to the inferior treatment) [13,15,32].

Suppose that the probability law of the responses under treatments A and B depends on a vector of unknown parameters $\boldsymbol{\gamma}_A$ and $\boldsymbol{\gamma}_B$, respectively, with $\boldsymbol{\gamma}^t = (\boldsymbol{\gamma}_A^t, \boldsymbol{\gamma}_B^t) \in \Omega$, where Ω is an open convex subset of $\mathbb{R}^k$. Starting with m observations on each treatment, usually assigned by using restricted randomization, an initial non-trivial parameter estimation $\hat{\boldsymbol{\gamma}}_{2m}$ is derived. Then, at each step $n \geq 2m$ let $\hat{\boldsymbol{\gamma}}_n$ be the estimator of the parameter $\boldsymbol{\gamma}$ based on the first n observations, which is assumed to be consistent in the i.i.d. case (i.e., $\lim_{n\to\infty} \hat{\boldsymbol{\gamma}}_n = \boldsymbol{\gamma}$ a.s.). Obviously, the speed of convergence of the allocation proportion is strictly related to the convergence rate of the chosen estimators; however, their consistency is sufficient in order to establish the almost sure convergence of π_n.

In this section, we shall deal with RA procedures such that

$$\Pr(\delta_{n+1} = 1 | \Im_n) = \varphi^{\mathrm{RA}}(\pi_n; \hat{\boldsymbol{\gamma}}_n), \qquad \text{for } n \geq 2m. \tag{4.1}$$

The following definition will help illustrate the asymptotic behaviour of RA rules and also CARA designs with continuous covariates treated in Section 5.

Definition 4.1. *Let* $\dot{\psi}(x; \mathbf{y}) : [0; 1] \times \mathbb{R}^d \to [0; 1]$. *The function* $t(\mathbf{y}) : \mathbb{R}^d \to [0; 1]$ *is called a* generalized downcrossing *of* $\dot{\psi}$ *if for any given* $\mathbf{y} \in \mathbb{R}^d$ *we have*

$$\forall x < t(\mathbf{y}), \qquad \dot{\psi}(x; \mathbf{y}) \geq t(\mathbf{y}) \quad \textit{and} \quad \forall x > t(\mathbf{y}), \qquad \dot{\psi}(x; \mathbf{y}) \leq t(\mathbf{y}).$$

If the function $\dot{\psi}(x, \mathbf{y})$ is decreasing in x, then the generalized downcrossing $t(\mathbf{y})$ is unique and $t(\mathbf{y}) \neq \{0; 1\}$ for any $\mathbf{y} \in \mathbb{R}^d$. Moreover, if there exists a solution of the equation $\dot{\psi}(x, \mathbf{y}) = x$, then $t(\mathbf{y})$ coincides with this solution.

Theorem 4.1. *Suppose that at each step* n *the allocation rule* $\varphi^{\mathrm{RA}}(\pi_n; \hat{\boldsymbol{\gamma}}_n)$ *is decreasing in* π_n. *If the only generalized downcrossing* $t(\hat{\boldsymbol{\gamma}}_n)$ *is a continuous function, then* $\lim_{n\to\infty} \pi_n = t(\boldsymbol{\gamma})$ *a.s.*

Proof. See Appendix A.1. □

Example 4.1. Geraldes *et al.* [15] introduced the Doubly Adaptive Weighted Differences Design (DAWD) for binary response trials. Let $\boldsymbol{\gamma} = (p_A, p_B)^t$ be the vector of the probabilities of success of A and B and $\hat{\boldsymbol{\gamma}}_n = (\hat{p}_{An}, \hat{p}_{Bn})^t$ the corresponding estimate after n steps. When the $(n + 1)$st patient is ready to be randomized, the DAWD allocates him/her to treatment A with probability

$$\Pr(\delta_{n+1} = 1 | \Im_n) = \rho g_1(\hat{p}_{An} - \hat{p}_{Bn}) + (1 - \rho) g_2(2\pi_n - 1), \qquad \text{for } n \geq 2m, \tag{4.2}$$

where $\rho \in [0; 1)$ represents an "ethical weight" and $g_1, g_2 : [-1, 1] \to [0, 1]$ are continuous functions s.t.

(i) $g_1(0) = g_2(0) = 1/2$ and $g_1(1) = g_2(-1) = 1$;

(ii) $g_1(-x) = 1 - g_1(x)$ and $g_2(-x) = 1 - g_2(x)$ $\forall x \in [-1; 1]$;
(iii) $g_1(\cdot)$ is non decreasing and $g_2(\cdot)$ is decreasing.

Regarded as a function of π_n and $\hat{\boldsymbol{\gamma}}_n$, rule (4.2) corresponds to

$$\varphi^{\mathrm{DAWD}}(\pi_n; \hat{\boldsymbol{\gamma}}_n) = \rho g_1\big((1; -1)\hat{\boldsymbol{\gamma}}_n\big) + (1 - \rho) g_2(2\pi_n - 1),$$

which is decreasing in π_n, so that the equation $\varphi^{\mathrm{DAWD}}(\pi_n; \hat{\boldsymbol{\gamma}}_n) = \pi_n$ has a unique solution $t(\hat{\boldsymbol{\gamma}}_n)$, i.e. the generalized downcrossing, which is continuous in $\hat{\boldsymbol{\gamma}}_n$ (see [15]). Thus $\lim_{n\to\infty} \pi_n = t(\boldsymbol{\gamma})$ a.s.

Often there is a desired target allocation π^* to treatment A that depends on the unknown model parameters, i.e. $\pi^* = \pi^*(\boldsymbol{\gamma})$, where $\pi^* : \Omega \to (0; 1)$ is a mapping that transforms a k-dim vector of parameters into a scalar one. Thus, Theorem 4.1 still holds even if, instead of (4.1), we assume

$$\Pr(\delta_{n+1} = 1 | \Im_n) = \breve{\varphi}^{\mathrm{RA}}\big(\pi_n; \pi^*(\hat{\boldsymbol{\gamma}}_n)\big), \qquad \text{for } n \geq 2m,$$

provided that $\pi^*(\cdot)$ is a continuous function. In this case the generalized downcrossing could be more properly denoted by $t(\hat{\boldsymbol{\gamma}}_n) = t(\pi^*(\hat{\boldsymbol{\gamma}}_n))$.

Example 4.2. The Doubly-adaptive Biased Coin Design (DBCD) [13,21] is one of the most effective families of RA procedures aimed at converging to a desired target $\pi^*(\boldsymbol{\gamma}) \in (0, 1)$ that is a continuous function of the model parameters. The DBCD assigns treatment A to the $(n + 1)$st subject with probability

$$\Pr(\delta_{n+1} = 1 | \Im_n) = \breve{\varphi}^{\mathrm{DBCD}}\big(\pi_n; \pi^*(\hat{\boldsymbol{\gamma}}_n)\big), \qquad \text{for } n \geq 2m, \tag{4.3}$$

where the allocation function $\breve{\varphi}$ needs to satisfy the following conditions:

(i) $\breve{\varphi}^{\mathrm{DBCD}}(x; y)$ is continuous on $(0; 1)^2$;
(ii) $\breve{\varphi}^{\mathrm{DBCD}}(x; x) = x$;
(iii) $\breve{\varphi}^{\mathrm{DBCD}}(x; y)$ is decreasing in x and increasing in y;
(iv) $\breve{\varphi}^{\mathrm{DBCD}}(x; y) = 1 - \breve{\varphi}^{\mathrm{DBCD}}(1 - x; 1 - y)$ for all $x, y \in (0; 1)^2$.

The DBCD forces the allocation proportion to the target since from conditions (ii) and (iii), when $x > y$ then $\breve{\varphi}^{\mathrm{DBCD}}(x, y) < y$, whereas if $x < y$, then $\breve{\varphi}^{\mathrm{DBCD}}(x, y) > y$. However, condition (i) is quite restrictive since it does not include several widely-known proposals based on discontinuous allocation functions, such as Efron's BCD and its extensions [22], while condition (iv) simply guarantees that A and B are treated symmetrically.

Since $\breve{\varphi}^{\mathrm{DBCD}}(x; y)$ is decreasing in x with $\breve{\varphi}^{\mathrm{DBCD}}(x; x) = x$, then the generalized downcrossing is unique, given by $t(\pi^*(\hat{\boldsymbol{\gamma}}_n)) = \pi^*(\hat{\boldsymbol{\gamma}}_n)$. Thus, from the continuity of the target $\pi^*(\cdot)$ it follows that $\lim_{n\to\infty} \pi_n = \pi^*(\boldsymbol{\gamma})$ a.s.

Example 4.3. In the same spirit of Efron's BCD, Hu, Zhang and He [22] have recently introduced the ERADE, which is a class of RA procedures based on discontinuous randomization functions. Let again $\pi^*(\boldsymbol{\gamma}) \in (0, 1)$ be the desired target, that is assumed to be a continuous

function of the unknown model parameters, the ERADE assigns treatment A to the $(n+1)$st patient with probability

$$\Pr(\delta_{n+1}=1|\Im_n)=\begin{cases}\alpha\pi^*(\hat{\boldsymbol{\gamma}}_n), & \text{if } \pi_n>\pi^*(\hat{\boldsymbol{\gamma}}_n),\\ \pi^*(\hat{\boldsymbol{\gamma}}_n), & \text{if } \pi_n=\pi^*(\hat{\boldsymbol{\gamma}}_n),\\ 1-\alpha\big(1-\pi^*(\hat{\boldsymbol{\gamma}}_n)\big), & \text{if } \pi_n<\pi^*(\hat{\boldsymbol{\gamma}}_n),\end{cases} \tag{4.4}$$

where $\alpha\in[0;1)$ governs the degree of randomness. Clearly, rule (4.4) corresponds to

$$\breve{\varphi}^{\mathrm{ERADE}}(x;y)=\begin{cases}\alpha y, & \text{if } x>y,\\ y, & \text{if } x=y,\\ 1-\alpha(1-y), & \text{if } x<y,\end{cases}$$

which has a single generalized downcrossing $t(y)=y$; therefore $\lim_{n\to\infty}\pi_n=\pi^*(\boldsymbol{\gamma})$ a.s.

Remark 4.1. Contrary to the DBCD in (4.3) and the ERADE in (4.4), from Theorem 4.1 conditions $\breve{\varphi}^{\mathrm{RA}}(x;x)=x$ and $\breve{\varphi}^{\mathrm{RA}}(x;y)=1-\breve{\varphi}^{\mathrm{RA}}(1-x;1-y)$ are not requested for guaranteeing the convergence to the chosen target $\pi^*(\boldsymbol{\gamma})$. For instance, if we let

$$\breve{\varphi}^{\mathrm{RA}}\big(\pi_n;\pi^*(\hat{\boldsymbol{\gamma}}_n)\big)=\begin{cases}\pi^*(\hat{\boldsymbol{\gamma}}_n)^{\tau}, & \text{if } \pi_n>\pi^*(\hat{\boldsymbol{\gamma}}_n),\\ \pi^*(\hat{\boldsymbol{\gamma}}_n)^{1/\tau}, & \text{if } \pi_n\le\pi^*(\hat{\boldsymbol{\gamma}}_n),\end{cases}$$

where the parameter $\tau\ge1$ controls the degree of randomness, then $\pi_n\to\pi^*(\boldsymbol{\gamma})$ a.s. as $n\to\infty$.

5. CARA designs with continuous covariates

Since in the actual clinical practice information on patients' covariates or prognostic factors is usually collected, in some circumstances it may not be suitable to base the allocation probabilities only on earlier responses and assignments. This is particularly true when ethical demands are cogent and the patients have different profiles that induce heterogeneity in the outcomes.

Starting from the pioneering work of Rosenberger *et al.* [35], there has been a growing statistical interest in the topic of CARA randomization procedures. These designs change at each step the probabilities of allocating treatments by taking into account all the available information, namely previous responses, assignments and covariates, as well as the covariate profile of the current subject, with the aim of skewing the allocations towards the superior treatment or, in general, of converging to a desired target allocation depending on the covariates [45].

Within this class of procedures, if past outcomes are not taken into account in the allocation process, then the corresponding class of rules are called Covariate-Adaptive. The direct application of CA designs regards clinical trials without ethical demands, where the experimental aim consists in balancing the assignments of the treatments across covariates in order to optimize inference [6].

Due to the fact that the proof scheme for CARA rules with categorical covariates requires the extension of the concept of downcrossing in a vectorial framework, which is not used under CARA procedures with continuous prognostic factors, we will treat these cases separately and the former will be analyzed in the next section.

From now on, we deal with CARA designs such that

$$\Pr(\delta_{n+1}=1|\Im_n, \mathbf{Z}_{n+1}=\mathbf{z}_{n+1}) = \varphi^{\mathrm{CARA}}\big(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{z}_{n+1})\big), \qquad n \geq 2m, \tag{5.1}$$

where $\Im_n = \sigma(\delta_1, \ldots, \delta_n; Y_1, \ldots, Y_n; \mathbf{Z}_1, \ldots, \mathbf{Z}_n)$, $f(\cdot)$ is a known vector function of the covariates of the $(n+1)$st patient (usually f is the identity function, but it can also incorporate cross-products to account for interactions among covariates), $\hat{\boldsymbol{\gamma}}_n$ depends on earlier allocations, covariates and responses, while $\mathbf{S}_n = \mathbf{S}(\mathbf{z}_1, \ldots, \mathbf{z}_n)$ is a function of the covariates of the previous patients. In general, it is a vector of sufficient statistics of the covariate distribution that incorporates the information on $\mathbf{Z}$ after n steps, and from now on we always assume that, as $n \to \infty$,

$$\mathbf{S}_n = \mathbf{S}(\mathbf{Z}_1, \ldots, \mathbf{Z}_n) \to \boldsymbol{\varsigma} \qquad \text{a.s.} \tag{5.2}$$

Often, $\mathbf{S}_n$ contains the moments up to a given order of the covariate distribution, and (5.2) is satisfied provided that these moments exist.

Theorem 5.1. *At each step n, suppose that the allocation function φ^{CARA} in (5.1) is decreasing in π_n and let*

$$\tilde{\varphi}_{\mathbf{Z}}(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = E_{\mathbf{Z}_{n+1}}\big[\varphi^{\mathrm{CARA}}\big(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{Z}_{n+1})\big)\big].$$

If the only generalized downcrossing $\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n)$ of $\tilde{\varphi}_{\mathbf{Z}}$ is jointly continuous, then

$$\lim_{n\to\infty} \pi_n = \tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) \qquad a.s. \tag{5.3}$$

Proof. See Appendix A.2. □

Example 5.1. Consider the linear homoscedastic model with treatment/covariate interactions in the following form

$$E(Y_i) = \delta_i \mu_A + (1-\delta_i)\mu_B + z_i\big[\delta_i \beta_A + (1-\delta_i)\beta_B\big], \qquad i \geq 1,$$

where μ_A and μ_B are the baseline treatment effects, $\beta_A \neq \beta_B$ are different regression parameters and z_i is a scalar covariate observed on the ith individual, which is assumed to be a standard normal. Under this model, adopting "the-larger-the-better" scenario, treatment A is the best for patient $(n+1)$ if $\mu_A + z_{n+1}\beta_A > \mu_B + z_{n+1}\beta_B$; thus, if only ethical aims are taken into account it could be reasonable to consider the following allocation rule:

$$\varphi^{\mathrm{ETH}}\big(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{z}_{n+1})\big) = \mathbb{1}_{\{\hat{\mu}_{An} - \hat{\mu}_{Bn} + z_{n+1}(\hat{\beta}_{An} - \hat{\beta}_{Bn}) > 0\}}, \tag{5.4}$$

where $\mathbb{1}_{\{\cdot\}}$ is the indicator function and $\hat{\boldsymbol{\gamma}}_n = (\hat{\mu}_{An}, \hat{\mu}_{Bn}, \hat{\beta}_{An}, \hat{\beta}_{Bn})^t$ is the least square estimator of $\boldsymbol{\gamma} = (\mu_A, \mu_B, \beta_A, \beta_B)^t$ after n steps. Thus,

$$\begin{aligned} &E_{\mathbf{Z}_{n+1}}\big[\varphi^{\mathrm{ETH}}\big(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{Z}_{n+1})\big)\big] \\ &\quad = \Pr\big\{\hat{\mu}_{An} - \hat{\mu}_{Bn} + Z_{n+1}(\hat{\beta}_{An} - \hat{\beta}_{Bn}) > 0\big\} = 1 - \Phi\left(\frac{\hat{\mu}_{Bn} - \hat{\mu}_{An}}{|\hat{\beta}_{An} - \hat{\beta}_{Bn}|}\right), \end{aligned} \tag{5.5}$$

where $\Phi(\cdot)$ is the cdf of Z. Note that (5.5) is constant in π_n, so it has a single generalized downcrossing and from Theorem 5.1,

$$\lim_{n\to\infty} \pi_n = 1 - \Phi\left(\frac{\mu_B - \mu_A}{|\beta_A - \beta_B|}\right).$$

Clearly, (5.4) is a deterministic allocation function that at each step assigns the treatment that appears to be superior for the current subject. Excluding degenerate cases, even if both treatments are explored over the covariate domain (which is due to the random nature of the covariates), this rule is improper for clinical applications, since a random component in the assignments is fundamental and a suitable compromise between ethical demands and inferential efficiency is usually needed. This dilemma, usually known in the clinical literature as "individual versus collective ethics" [5], corresponds to the trade-off between "exploitation" and "exploration" of the Bandits literature [3,16]. Although Adaptive randomization [33] and Bandits methodology are very different approaches, since under the latter a deterministic policy (i.e., a sequence of allocations) is usually selected in a finite time horizon in order to maximize a total expected reward over all the possible sequences (often made in a Bayesian setting), similar conclusions as those of the present example have been recently developed by Pavlidis *et al.* [27] in the case of Multi-Armed Bandits with linear reward in the presence of covariates.

Example 5.2. As in the case of RA procedures, also for CARA rules there is often a desired target allocation π^* to treatment A that is a function of the unknown model parameters and the covariates, that is, $\pi^* = \pi^*(\boldsymbol{\gamma}, \mathbf{z})$, which is assumed to be continuous in $\boldsymbol{\gamma}$ for any fixed covariate level $\mathbf{z}$. In particular, Zhang *et al.* [45] assumed a generalized linear model setup and suggested to allocate subject $(n+1)$ to A with probability

$$\Pr(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = \mathbf{z}_{n+1}) = \pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_{n+1}), \qquad \text{for } n \geq 2m, \tag{5.6}$$

which represents an analog of the Sequential Maximum Likelihood design [26] in the presence of covariates. Assuming that the target function π^* is differentiable in $\boldsymbol{\gamma}$, under the expectation, with bounded derivatives, the authors showed that $\lim_{n\to\infty} \pi_n = E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$ a.s.

Clearly, allocation rule (5.6) is constant in π_n and therefore $\tilde{\varphi}_{\mathbf{Z}}(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = E_{\mathbf{Z}_{n+1}}[\pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{Z}_{n+1})]$ is also constant in π_n. Thus, the generalized downcrossing of $\tilde{\varphi}_{\mathbf{Z}}$ is unique and obviously $\lim_{n\to\infty} \pi_n = E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$ a.s.

Remark 5.1. Some authors (see for instance [8]) suggested CARA designs that incorporate covariate information in the randomization process, but ignoring the covariate of the current subject. Note that these methods can be regarded as special cases of φ^{CARA} in (5.1) and therefore Theorem 5.1 can still be applied by taking into account the generalized downcrossing of φ^{CARA} directly.

Even if Theorem 5.1 proves the convergence of CARA designs in the case of continuous covariates, it could be difficult to obtain an analytical expression for $\tilde{\varphi}_{\mathbf{Z}}$ and therefore to find the corresponding generalized downcrossing. Nevertheless, the following lemma allows to obtain the generalized downcrossing in a simple manner in some circumstances.

Lemma 5.1. *Let* $\varphi^{\mathrm{CARA}}(\pi_n; \hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{z}_{n+1}))$ *be jointly continuous and, assuming that* $\varphi^{\mathrm{CARA}}(x; \boldsymbol{\gamma}, \boldsymbol{\varsigma}, f(\mathbf{Z}))$ *is decreasing in* x, *let* $t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$ *be the unique solution of equation*

$$\varphi^{\mathrm{CARA}}\big(x; \boldsymbol{\gamma}, \boldsymbol{\varsigma}, E_{\mathbf{Z}}\big[f(\mathbf{Z})\big]\big) = x.$$

If $\varphi^{\mathrm{CARA}}(t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}, f(\mathbf{Z}))$ *is linear in* $f(\mathbf{Z})$ *and* $t^*_{\mathbf{Z}}$ *is jointly continuous, then* (5.3) *still holds with* $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) = t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$.

Proof. Assume that $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) < t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$. From the properties of φ^{CARA}, the function $\tilde{\varphi}_{\mathbf{Z}}(x; \boldsymbol{\gamma}, \boldsymbol{\varsigma})$ is jointly continuous and decreasing in x, so that $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) = \tilde{\varphi}_{\mathbf{Z}}(\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}) > \tilde{\varphi}_{\mathbf{Z}}(t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma})$. However,

$$\tilde{\varphi}_{\mathbf{Z}}\big(t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}\big) = \varphi^{\mathrm{CARA}}\big(t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}, E_{\mathbf{Z}}\big[f(\mathbf{Z})\big]\big) = t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}),$$

since $\varphi^{\mathrm{CARA}}(t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}, f(\mathbf{Z}))$ is linear in $f(\mathbf{Z})$, contradicting the assumption. Analogously if we assume $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) > t^*_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$. □

Example 5.3. The Covariate-adjusted Doubly-adaptive Biased Coin Design introduced by Zhang and Hu [46] is a class of CARA procedures intended to converge to a desired target $\pi^*(\boldsymbol{\gamma}, \mathbf{z})$. When the $(n+1)$st subject with covariate $\mathbf{Z}_{n+1} = \mathbf{z}_{n+1}$ is ready to be randomized, he/she will be assigned to A with probability

$$\begin{aligned}&\Pr(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = \mathbf{z}_{n+1}) \\ &\quad = \frac{\pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_{n+1})(\hat{\rho}_n/\pi_n)^{\nu}}{\pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_{n+1})(\hat{\rho}_n/\pi_n)^{\nu} + [1 - \pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_{n+1})]((1-\hat{\rho}_n)/(1-\pi_n))^{\nu}},\end{aligned} \tag{5.7}$$

where $\hat{\rho}_n = n^{-1} \sum_{i=1}^{n} \pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_i)$. Assuming that

$$\Pr(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = \mathbf{z}) \to \pi^*(\boldsymbol{\gamma}, \mathbf{z}) \qquad \text{a.s.} \tag{5.8}$$

the authors proved that $\lim_{n\to\infty} \pi_n = E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$ a.s.

Note that rule (5.7) can be regarded as special case of φ^{CARA} after the transformation $(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n, f(\mathbf{z}_{n+1})) \mapsto (\hat{\rho}_n, \pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{z}_{n+1}))$ and thus, even if we remove condition (5.8), Lemma 5.1 can be applied to the allocation function

$$\breve{\varphi}^{\mathrm{ZH}}(x; a, b) = \left\{1 + \frac{1-b}{b}\left[\frac{(1-a)x}{a(1-x)}\right]^{\nu}\right\}^{-1},$$

which is decreasing in x and continuous in all the arguments. Indeed, since both $\hat{\rho}_n$ and $E_{\mathbf{Z}_{n+1}}[\pi^*(\hat{\boldsymbol{\gamma}}_n, \mathbf{Z}_{n+1})]$ converge to $E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$ a.s., the solution of the equation $\breve{\varphi}^{\mathrm{ZH}}(x; E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})], E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]) = x$ is $t^*_{\mathbf{Z}} = E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$. Furthermore, since $\breve{\varphi}^{\mathrm{ZH}}(E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]; E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})], \pi^*(\boldsymbol{\gamma}, \mathbf{Z})) = \pi^*(\boldsymbol{\gamma}, \mathbf{Z})$, then $\lim_{n\to\infty} \pi_n = E_{\mathbf{Z}}[\pi^*(\boldsymbol{\gamma}, \mathbf{Z})]$ a.s.

Remark 5.2. Theorem 5.1 and Lemma 5.1 can be naturally applied to CA designs in the presence of continuous covariates by considering, instead of (5.1), the following class of allocation rules:

$$\Pr(\delta_{n+1}=1|\Im_n, \mathbf{Z}_{n+1}=\mathbf{z}_{n+1}) = \varphi^{\mathrm{CA}}\big(\pi_n; \mathbf{S}_n, f(\mathbf{z}_{n+1})\big),$$

with $\Im_n = \sigma(\delta_1,\dots,\delta_n; \mathbf{Z}_1,\dots,\mathbf{Z}_n)$. Clearly, $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma},\boldsymbol{\varsigma})$ and $t^*_{\mathbf{Z}}(\boldsymbol{\gamma},\boldsymbol{\varsigma})$ should be replaced by $\tilde{t}_{\mathbf{Z}}(\boldsymbol{\varsigma})$ and $t^*_{\mathbf{Z}}(\boldsymbol{\varsigma})$, respectively.

6. CARA designs with categorical covariates

We now provide a convergence result for CARA designs in the case of categorical covariates. In order to avoid cumbersome notation, from now on we assume without loss of generality two categorical covariates, i.e. $\mathbf{Z}=(T,W)$, with levels t_j $(j=0,\dots,J)$ and w_l $(l=0,\dots,L)$, respectively. Also, let $\mathbf{p}=[p_{jl}\colon\ j=0,\dots,J; l=0,\dots,L]$ be the joint probability distribution of the categorical covariates, with $p_{jl}>0$ for any $j=0,\dots,J$ and $l=0,\dots,L$ and $\sum_{j=0}^{J}\sum_{l=0}^{L} p_{jl}=1$.

After n steps, let $N_n(j,l)=\sum_{i=1}^{n}\mathbb{1}_{\{Z_i=(t_j,w_l)\}}$ be the number of subjects within the stratum (t_j,w_l), $\widetilde{N}_n(j,l)=\sum_{i=1}^{n}\delta_i\mathbb{1}_{\{Z_i=(t_j,w_l)\}}$ the number of allocations to A within this stratum and $\pi_n(j,l)$ the corresponding proportion, that is, $\pi_n(j,l)=N_n(j,l)^{-1}\widetilde{N}_n(j,l)$, for any $j=0,\dots,J$ and $l=0,\dots,L$. Also, let $\boldsymbol{\pi}_n=[\pi_n(j,l)\colon\ j=0,\dots,J; l=0,\dots,L]$.

After an initial stage with m observations on each treatment, performed to derive a non-trivial parameter estimation, we consider a class of CARA designs that assigns the $(n+1)$st patient with covariate profile $\mathbf{Z}_{n+1}=(t_j,w_l)$ to A with probability

$$\Pr\big(\delta_{n+1}=1|\Im_n, \mathbf{Z}_{n+1}=(t_j,w_l)\big)=\varphi_{jl}(\boldsymbol{\pi}_n;\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n), \qquad \text{for } n\geq 2m, \tag{6.1}$$

where $\Im_n=\sigma(\delta_1,\dots,\delta_n; Y_1,\dots,Y_n; \mathbf{Z}_1,\dots,\mathbf{Z}_n)$ and φ_{jl} is the allocation function of the stratum (t_j,w_l).

Let $\boldsymbol{\varphi}(\boldsymbol{\pi}_n;\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n)=[\varphi_{jl}(\boldsymbol{\pi}_n;\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n)\colon\ j=0,\dots,J; l=0,\dots,L]$, often the allocation rule at each stratum does not depend on the entire vector of allocation proportions $\boldsymbol{\pi}_n$ involving all the strata, but depends only on the current allocation proportion of this stratum, that is,

$$\varphi_{jl}(\boldsymbol{\pi}_n;\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n)=\varphi_{jl}\big(\pi_n(j,l);\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n\big), \qquad \forall j=0,\dots,J; l=0,\dots,L. \tag{6.2}$$

However, note that (6.2) does not correspond in general to a stratified randomization, due to the fact that the estimate $\hat{\boldsymbol{\gamma}}_n$ usually involves the information accrued from all the strata up to that step, and thus the evolutions of the procedure at different strata are not independent.

Definition 6.1. *Let* $\mathbf{x}=[x_1,\dots,x_{\mathcal{K}}]$, *where* $x_\iota\in[0;1]$ *for any* $\iota=1,\dots,\mathcal{K}$ *and* $\mathcal{K}$ *is a positive integer. Also, let* $\ddot{\psi}_\iota(\mathbf{x};\mathbf{y}):[0;1]^{\mathcal{K}}\times\mathbb{R}^d\to[0;1]$ *and set* $\ddot{\boldsymbol{\psi}}(\mathbf{x};\mathbf{y})=[\ddot{\psi}_1(\mathbf{x};\mathbf{y}),\dots,\ddot{\psi}_{\mathcal{K}}(\mathbf{x};\mathbf{y})]$. *Then* $\mathbf{t}(\mathbf{y})=[t_1(\mathbf{y}),\dots,t_{\mathcal{K}}(\mathbf{y})]$, *with* $t_\iota(\mathbf{y}):\mathbb{R}^d\to[0;1]$ *for* $\iota=1,\dots,\mathcal{K}$, *is called a* vectorial generalized downcrossing *of* $\ddot{\boldsymbol{\psi}}$ *if for all* $\mathbf{y}\in\mathbb{R}^d$ *and for any* $\iota=1,\dots,\mathcal{K}$

$$\textit{for all } x_\iota<t_\iota(\mathbf{y}), \qquad \ddot{\psi}_\iota(\mathbf{x};\mathbf{y})\geq t_\iota(\mathbf{y}) \quad \textit{and} \quad \textit{for all } x_\iota>t_\iota(\mathbf{y}), \qquad \ddot{\psi}_\iota(\mathbf{x};\mathbf{y})\leq t_\iota(\mathbf{y}).$$

Clearly, if the function $\ddot{\psi}_\iota(\mathbf{x};\mathbf{y})$ is decreasing in $\mathbf{x}$ (i.e., componentwise) for any ι, then the vectorial generalized downcrossing $\mathbf{t}(\mathbf{y})$ is unique, with $\mathbf{t}(\mathbf{y}) \in (0;1)^{\mathcal{K}}$ for any $\mathbf{y} \in \mathbb{R}^d$; furthermore $\ddot{\boldsymbol{\psi}}(\mathbf{t}(\mathbf{y});\mathbf{y}) = \mathbf{t}(\mathbf{y})$, provided that the solution exists. Moreover, note that if $\ddot{\psi}_\iota(\mathbf{x};\mathbf{y}) = \ddot{\psi}_\iota(x_\iota;\mathbf{y})$ for any $\iota = 1,\dots,\mathcal{K}$, then each component $t_\iota(\mathbf{y})$ of $\mathbf{t}(\mathbf{y})$ is simply the single generalized downcrossing of $\ddot{\psi}_\iota(x_\iota;\mathbf{y})$, which can be found by solving the equation $\ddot{\psi}_\iota(x;\mathbf{y}) = x$ (if the solution exists).

Theorem 6.1. *At each step n, suppose that for any given stratum (t_j, w_l) the allocation function $\varphi_{jl}(\boldsymbol{\pi}_n;\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n)$ is decreasing in $\boldsymbol{\pi}_n$ (componentwise). If the unique vectorial generalized downcrossing $\mathbf{t}(\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n) = [t_{jl}(\hat{\boldsymbol{\gamma}}_n,\mathbf{S}_n)\colon\ j = 0,\dots,J; l = 0,\dots,L]$ is a continuous function and $\boldsymbol{\varphi}(\mathbf{t}(\boldsymbol{\gamma},\boldsymbol{\varsigma});\boldsymbol{\gamma},\boldsymbol{\varsigma}) = \mathbf{t}(\boldsymbol{\gamma},\boldsymbol{\varsigma})$, then*

$$\lim_{n\to\infty} \boldsymbol{\pi}_n = \mathbf{t}(\boldsymbol{\gamma},\boldsymbol{\varsigma}) \quad \textit{and} \quad \lim_{n\to\infty} \pi_n = E_{\mathbf{Z}}\big[\mathbf{t}(\boldsymbol{\gamma},\boldsymbol{\varsigma})\big] = \sum_{j=0}^{J}\sum_{l=0}^{L} t_{jl}(\boldsymbol{\gamma},\boldsymbol{\varsigma})\, p_{jl} \qquad a.s.$$

Proof. See Appendix A.3. □

Example 6.1. The Reinforced Doubly-adaptive Biased Coin Design (RDBCD) is a class of CARA procedures recently introduced by Baldi Antognini and Zagoraiou [7] in the case of categorical covariates intended to target any desired allocation proportion

$$\boldsymbol{\pi}^*(\boldsymbol{\gamma}) = \big[\pi^*(j,l)\colon\ j = 0,\dots,J; l = 0,\dots,L\big]\colon \Omega \to (0,1)^{(J+1)\times(L+1)},$$

which is a continuous function of the unknown model parameters. Starting with a pilot stage performed to derive an initial parameter estimation, at each step $n \geq 2m$ let $\hat{\pi}^*_n(j,l)$ be the estimate of the target within stratum (t_j, w_l) obtained using all the collected data up to that step and $\hat{p}_{jln} = n^{-1}N_n(j,l)$ the estimate of p_{jl}; when the next patient with covariate $\mathbf{Z}_{n+1} = (t_j, w_l)$ is ready to be randomized, the RDBCD assigns him/her to A with probability

$$\Pr\big(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = (t_j, w_l)\big) = \varphi_{jl}\big(\pi_n(j,l); \hat{\pi}^*_n(j,l), \hat{p}_{jln}\big),$$

where the function $\varphi_{jl}(x;y,z)\colon (0,1)^3 \to [0,1]$ satisfies the following conditions:

(i) φ_{jl} is decreasing in x and increasing in y, for any $z \in (0,1)$;
(ii) $\varphi_{jl}(x;x,z) = x$ for any $z \in (0,1)$;
(iii) φ_{jl} is decreasing in z if $x < y$, and increasing in z if $x > y$;
(iv) $\varphi_{jl}(x;y,z) = 1 - \varphi_{jl}(1-x;1-y,z)$ for any $z \in (0,1)$.

First, observe that for the RDBCD (6.2) holds and thus, from (i) and (ii), at each stratum (t_j, w_l) the only generalized downcrossing of φ_{jl} is simply given by $\hat{\pi}^*_n(j,l)$. Therefore, by Theorem 6.1, $\lim_{n\to\infty}\pi_n(j,l) = \pi^*(j,l)$ a.s. for any $j = 0,\dots,J$ and $l = 0,\dots,L$, due to the continuity of the target, that is, $\lim_{n\to\infty}\boldsymbol{\pi}_n = \boldsymbol{\pi}^*(\boldsymbol{\gamma})$ a.s.

6.1. Covariate-Adaptive designs with categorical covariates

Theorem 6.1 can be naturally applied to CA procedures in the case of categorical covariates by assuming, instead of (6.1), the following class of allocation rules:

$$\Pr(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = \mathbf{z}_{n+1}) = \varphi_{jl}(\boldsymbol{\pi}_n; \mathbf{S}_n), \tag{6.3}$$

where now $\Im_n = \sigma(\delta_1, \ldots, \delta_n; \mathbf{Z}_1, \ldots, \mathbf{Z}_n)$. Moreover, from now on we let $\mathbf{t}^B = [1/2\colon\ j = 0, \ldots, J; l = 0, \ldots, L]$.

Example 6.2. The Covariate-Adaptive Biased Coin Design (C-ABCD) [6] is a class of stratified randomization procedures intended to achieve joint balance. For any stratum (t_j, w_l), let $F_{jl}(\cdot)\colon \mathbb{R} \to [0, 1]$ be a non-increasing and symmetric function with $F_{jl}(-x) = 1 - F_{jl}(x)$; the C-ABCD assigns the $(n+1)$st patient with profile $\mathbf{Z}_{n+1} = (t_j, w_l)$ to A with probability

$$\Pr\big(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = (t_j, w_l)\big) = F_{jl}\big[D_n(j, l)\big], \tag{6.4}$$

where $D_n(j, l) = N_n(j, l)[2\pi_n(j, l) - 1]$ is the imbalance between the two groups after n steps within stratum (t_j, w_l). As showed in Remark 3.2 and Example 3.4 in the case of AA procedures, Theorem 6.1 still holds even if we assume different randomization functions at each step, provided that the unique vectorial generalized downcrossing is the same for any n. Indeed, it is trivial to see that rule (6.4) corresponds to

$$\varphi_{jln}(\boldsymbol{\pi}_n; \mathbf{S}_n) = \varphi_{jln}\big(\pi_n(j, l); \mathbf{S}_n\big) = F_{jl}\big\{n\big[2\pi_n(j, l) - 1\big]\hat{p}_{jln}\big\},$$

and, from the properties of F_{jl}, φ_{jln}'s have $1/2$ as unique downcrossing for any n; thus $\lim_{n\to\infty} \boldsymbol{\pi}_n = \mathbf{t}^B$, which clearly implies marginal balance.

Moreover, when the covariate distribution is known Baldi Antognini and Zagoraiou [6] suggested the following class of randomization rules:

$$F^q_{jl}(x) = \big\{x^{q(p_{jl})} + 1\big\}^{-1}, \qquad x \geq 1,$$

where $q(\cdot)$ is a decreasing function with $\lim_{t\to 0^+} q(t) = \infty$. Clearly, the above mentioned arguments and Theorem 6.1 guarantee the convergence to balance even if the covariate distribution is unknown, by replacing at each step p_{jl} with its current estimate.

Examples 6.1 and 6.2 deal with procedures such that, at every step n, the allocation rule φ_{jl} depends only on the current allocation proportion $\pi_n(j, l)$, namely satisfying (6.2). We now present additional examples where φ_{jl} is a function of the whole vectorial allocation proportion $\boldsymbol{\pi}_n$.

Example 6.3. Minimization methods [28,41] are stratified randomization procedures intended to achieve the so-called marginal balance among covariates. In general, they depend on the definition of a measure of overall imbalance among the assignments which summarizes the imbalances between the treatment groups for each level of every factor. Assuming the well-known

variance method proposed by Pocock and Simon [28], the $(n+1)$st subject with covariate profile $\mathbf{Z}_{n+1} = (t_j, w_l)$ is assigned to treatment A with probability

$$\Pr\big(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = (t_j, w_l)\big) = \begin{cases} p, & D_n(t_j) + D_n(w_l) < 0, \\ \frac{1}{2}, & D_n(t_j) + D_n(w_l) = 0, \\ 1-p, & D_n(t_j) + D_n(w_l) > 0, \end{cases} \tag{6.5}$$

where $p \in [1/2; 1]$, $D_n(t_j)$ is the imbalance between the two arms within the level t_j of T and, similarly, $D_n(w_l)$ represents the imbalance at the category w_l of W. At each step n, note that $\operatorname{sgn}\{D_n(t_j)\} = \operatorname{sgn}\{n^{-1} D_n(t_j)\}$ where

$$n^{-1} D_n(t_j) = \sum_{l=0}^{L} \big[2\pi_n(j,l) - 1\big] \hat{p}_{jln}, \qquad \text{for any } j = 0, \ldots, J \tag{6.6}$$

and analogously for $D_n(w_l)$. Thus, allocation rule (6.5) corresponds to

$$\varphi_{jl}^{\mathrm{PS}}(\boldsymbol{\pi}_n; \mathbf{S}_n) = \begin{cases} p, & \displaystyle\sum_{l=0}^{L} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} + \sum_{j=0}^{J} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} < 0, \\ \frac{1}{2}, & \displaystyle\sum_{l=0}^{L} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} + \sum_{j=0}^{J} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} = 0, \\ 1-p, & \displaystyle\sum_{l=0}^{L} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} + \sum_{j=0}^{J} \left[\pi_n(j,l) - \frac{1}{2}\right] \hat{p}_{jln} > 0, \end{cases}$$

and therefore the problem consists in finding the vectorial generalized downcrossing of $\boldsymbol{\varphi}^{\mathrm{PS}}(\boldsymbol{\pi}_n; \mathbf{S}_n) = [\varphi_{jl}^{\mathrm{PS}}(\boldsymbol{\pi}_n; \mathbf{S}_n)\colon\ j = 0, \ldots, J; l = 0, \ldots, L]$. Since at each step n, $\varphi_{jl}^{\mathrm{PS}}(\boldsymbol{\pi}_n; \mathbf{S}_n)$ is decreasing in $\pi_n(j,l)$ for any $j = 0, \ldots, J$ and $l = 0, \ldots, L$, then the vectorial generalized downcrossing is unique. It is straightforward to see that $\boldsymbol{\varphi}^{\mathrm{PS}}(\mathbf{t}^B; \boldsymbol{\varsigma}) = \mathbf{t}^B$ for every n and thus $\lim_{n\to\infty} \boldsymbol{\pi}_n = \mathbf{t}^B$ a.s.

Example 6.4. In order to include minimization methods and stratified randomization procedures in a unique framework, Hu and Hu [23] have recently suggested to assign subject $(n+1)$ belonging to the stratum (t_j, w_l) to A with probability

$$\Pr\big(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = (t_j, w_l)\big) = \begin{cases} p, & \bar{D}_n(j,l) < 0, \\ \frac{1}{2}, & \bar{D}_n(j,l) = 0, \\ 1-p, & \bar{D}_n(j,l) > 0, \end{cases} \tag{6.7}$$

where the overall measure of imbalance

$$\bar{D}_n(j,l) = \omega_g D_n + \omega_T D_n(t_j) + \omega_W D_n(w_l) + \omega_s D_n(j,l)$$

is a weighted average of the three types of imbalances actually observed (global, marginal and within-stratum), with non-negative weights ω_g (global), ω_T and ω_W (covariate marginal) and ω_s (stratum) chosen such that $\omega_g + \omega_T + \omega_W + \omega_s = 1$.

By choosing the weights $\omega_g, \omega_T, \omega_W$ such that

$$(JL + J + L)\omega_g + J\omega_W + L\omega_T < 1/2, \tag{6.8}$$

the authors proved that the probabilistic structure of the within stratum imbalance is that of a positive recurrent Markov chain and this implies that procedure (6.7) is asymptotically balanced, both marginally and jointly. However, as stated by the authors, only strictly positive choices of the stratum weight ω_s satisfy (6.8), and thus their result cannot be applied to Pocock and Simon's minimization method.

The asymptotic behaviour of Hu and Hu's design can be illustrated in a different way by applying Theorem 6.1. Since $\operatorname{sgn}\{\bar{D}_n(j,l)\} = \operatorname{sgn}\{n^{-1}\bar{D}_n(j,l)\}$ and

$$n^{-1}D_n = 2\pi_n - 1 = \sum_{j=0}^{J}\sum_{l=0}^{L}\big[2\pi_n(j,l) - 1\big]\hat{p}_{jln}, \tag{6.9}$$

from (6.6) it follows that

$$\begin{aligned}\operatorname{sgn}\big\{n^{-1}\bar{D}_n(j,l)\big\} = \operatorname{sgn}\Bigg\{&\omega_g \sum_{j=0}^{J}\sum_{l=0}^{L}\left[\pi_n(j,l) - \frac{1}{2}\right]\hat{p}_{jln} + \omega_T \sum_{l=0}^{L}\left[\pi_n(j,l) - \frac{1}{2}\right]\hat{p}_{jln}\\ &+ \omega_W \sum_{j=0}^{J}\left[\pi_n(j,l) - \frac{1}{2}\right]\hat{p}_{jln} + \omega_s\left[\pi_n(j,l) - \frac{1}{2}\right]\hat{p}_{jln}\Bigg\}.\end{aligned}$$

Thus, at each step n procedure (6.7) corresponds to an allocation rule $\varphi_{jl}^{\mathrm{HH}}(\boldsymbol{\pi}_n; \mathbf{S}_n)$ which is decreasing in $\pi_n(j,l)$ for any $j = 0, \ldots, J$ and $l = 0, \ldots, L$. Since $\boldsymbol{\varphi}^{\mathrm{HH}}(\mathbf{t}^B; \boldsymbol{\varsigma}) = \mathbf{t}^B$, then the unique vectorial generalized downcrossing is $\mathbf{t}^B$ for any n and therefore $\lim_{n\to\infty}\boldsymbol{\pi}_n = \mathbf{t}^B$ a.s.

Under the same arguments, it can be easily proved the convergence to balance of several extensions of minimization methods (see, e.g., [18,36]), since at each step n every type of imbalance (global, marginal and within-stratum) is a linear combination of the allocation proportions $\pi_n(j,l)$'s.

Example 6.5. Assuming the liner homoscedastic model without treatment/covariate interaction in the form

$$E(Y_i) = \delta_i\mu_A + (1-\delta_i)\mu_B + \widetilde{f}(\mathbf{z}_i)^t\boldsymbol{\beta}, \qquad i \geq 1, \tag{6.10}$$

where $\widetilde{f}(\cdot)$ is a known vector function and $\boldsymbol{\beta}$ is a vector of common regression parameters.

Put $\mathcal{F}_n = [\widetilde{f}(\mathbf{z}_i)^t]$ and $\mathbb{F}_n = [\mathbf{1}_n : \mathcal{F}_n]$, Atkinson [1] introduced his biased coin design by assigning the $(n+1)$st patient to A with probability

$$\begin{aligned}&\Pr(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1})\\ &\quad = \frac{\{1 - (1; \widetilde{f}(\mathbf{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n\}^2}{\{1 - (1; \widetilde{f}(\mathbf{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n\}^2 + \{1 + (1; \widetilde{f}(\mathbf{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n\}^2},\end{aligned} \tag{6.11}$$

where $\mathbf{b}_n^t = (2\delta_1 - 1, \ldots, 2\delta_n - 1)\mathbb{F}_n$ is usually called the imbalance vector.

As showed in [6], in the presence of all interactions among covariates we obtain

$$\mathbf{b}_n^t = \big(D_n, D_n(t_1), \ldots, D_n(t_J), D_n(w_1), \ldots, D_n(w_L), D_n(1,1), \ldots, D_n(J,L)\big)$$

and Atkinson's procedure (6.11) becomes a stratified randomization rule with

$$\begin{aligned} &\Pr\big(\delta_{n+1} = 1 | \Im_n, \mathbf{Z}_{n+1} = (t_j, w_l)\big) \\ &\quad = \frac{(1 - D_n(j,l)/N_n(j,l))^2}{(1 - D_n(j,l)/N_n(j,l))^2 + (1 + D_n(j,l)/N_n(j,l))^2}. \end{aligned} \tag{6.12}$$

Clearly, procedure (6.12) corresponds to

$$\varphi_{jl}(\boldsymbol{\pi}_n; \mathbf{S}_n) = \frac{[1 - \pi_n(j,l)]^2}{[1 - \pi_n(j,l)]^2 + \pi_n(j,l)^2},$$

so (6.2) holds; thus, by Theorem 6.1, $\lim_{n\to\infty} \boldsymbol{\pi}_n = \mathbf{t}^B$.

When the model is not full, then $\mathbf{b}_n$ contains all the imbalance terms corresponding to the included interactions. Thus, from (6.6) and (6.9), $(1; \widetilde{f}(\mathbf{z}_{n+1})^t)(\mathbb{F}_n^t \mathbb{F}_n)^{-1}\mathbf{b}_n$ is a linear function of the allocation proportion $\boldsymbol{\pi}_n$, so that Theorem 6.1 can be applied by the previous arguments.

7. Downcrossing and stochastic approximation methods

By combining the concept of downcrossing and stopping times of stochastic processes, we demonstrated the almost sure convergence of the treatment allocation proportion for a vast class of adaptive procedures. In general, this is due to the fact that the asymptotic behavior of π_n coincides with that of the sequence of downcrossing points of the corresponding allocation function. An alternative way to characterize the same large-sample behavior is provided by the Stochastic Approximation (SA) methods (see, e.g., [10,11,24,25]) and the asymptotic theory of supermartingales [17]. Indeed, considered now the AA procedures of Section 3, from (3.2) at each step $n \geq 1$,

$$\begin{aligned} \pi_{n+1} &= \pi_n\left(\frac{n}{n+1}\right) + \frac{1}{n+1}\big\{\Delta M_{n+1} + \varphi^{\mathrm{AA}}(\pi_n)\big\} \\ &= \pi_n - \frac{1}{n+1}\big\{\pi_n - \varphi^{\mathrm{AA}}(\pi_n)\big\} + \frac{\Delta M_{n+1}}{n+1}. \end{aligned} \tag{7.1}$$

Therefore, the allocation proportion follows the classical Robbins–Monro [29] recursive relation:

$$\pi_{n+1} = \pi_n - a_n H(\pi_n) + a_n \Delta M_{n+1}, \tag{7.2}$$

where $H(x) = x - \varphi^{\mathrm{AA}}(x)$ and $a_n = (n+1)^{-1}$. Note that:

- $\{\Delta M_n\}$ is a sequence of bounded martingale differences, so that for any n

$$E[\Delta M_{n+1} | \Im_n] = 0 \quad \text{and} \quad E\big[\Delta M_{n+1}^2 | \Im_n\big] = \varphi^{\mathrm{AA}}(\pi_n)\big[1 - \varphi^{\mathrm{AA}}(\pi_n)\big] \leq 1;$$

- $\lim_{n\to\infty} a_n = 0$, $\sum_{i=1}^{\infty} a_i = \infty$ and $\sum_{i=1}^{\infty} a_i^2 < \infty$;
- the function $H(\cdot)$ is increasing, since $\varphi^{\mathrm{AA}}(\cdot)$ is assumed to be decreasing, and furthermore $(x-t)H(x) > 0$ since t is the unique downcrossing of $\varphi^{\mathrm{AA}}(\cdot)$.

Therefore, it follows that $\pi_n \to t$ a.s.

The same asymptotic result can be obtained via a super-martingale approach since, from (7.1)

$$E\big[(\pi_{n+1}-t)^2|\Im_n\big] = (\pi_n - t)^2 - 2a_n(\pi_n - t)H(\pi_n) + a_n^2\big\{H^2(\pi_n) + E\big[\Delta M_{n+1}^2|\Im_n\big]\big\},$$

where the last term of the r.h.s. is asymptotically negligible, due to the properties of a_n, $H(\cdot)$ and ΔM_{n+1}, and $(\pi_n - t)H(\pi_n)$ is always non-negative. Thus, the quantity

$$(\pi_n - t)^2 \text{ is a non-negative almost super-martingale,} \tag{7.3}$$

namely it is asymptotically equivalent to a non-negative super-martingale; therefore it converges almost surely and, in our setting, it vanishes asymptotically. If we further assume φ^{AA} differentiable, then

$$\left.\frac{\partial \varphi^{\mathrm{AA}}(x)}{\partial x}\right|_{x=t} = \varphi'(t) < 0,$$

so that from Fabian's theorem [14]

$$\sqrt{n}(\pi_n - t) \hookrightarrow N\left(0; \frac{t(1-t)}{1-2\varphi'(t)}\right), \tag{7.4}$$

since $\lim_{n\to\infty} E[\Delta M_{n+1}^2|\Im_n] = \varphi^{\mathrm{AA}}(t)[1-\varphi^{\mathrm{AA}}(t)] = t(1-t)$ (due to the continuity of φ^{AA}). The asymptotic variance in (7.4) could help distinguish between different AA rules intended to achieve the same target allocation proportion; clearly, this variance increases as $\varphi'(t)$ grows (i.e. as the random component in the assignments increases).

Example 7.1. Adopting Wei's Adaptive BCD in (3.6) with $\mathfrak{f}(\cdot)$ differentiable, then

$$\lim_{n\to\infty} \pi_n = \frac{1}{2} \quad \text{a.s.} \quad \text{and} \quad \sqrt{n}\left(\pi_n - \frac{1}{2}\right) \hookrightarrow N\left(0; \frac{1}{4[1-2\mathfrak{f}'(1/2)]}\right). \tag{7.5}$$

While assuming CR design

$$\lim_{n\to\infty} \pi_n = \frac{1}{2} \quad \text{a.s.} \quad \text{and} \quad \sqrt{n}\left(\pi_n - \frac{1}{2}\right) \hookrightarrow N\left(0; \frac{1}{4}\right),$$

namely under CR the asymptotic variance of the allocation proportion is always greater than Wei's one (since $\mathfrak{f}$ is decreasing). This reduction in terms of asymptotic variance lies in the fact that Wei's rule favors at each step the assignments of the under-represented treatment, that is, it is adapted to the sequence of previous allocations.

Remark 7.1. Even if SA theory can be applied in the context of adaptive procedures, we would like to stress some differences between them:

- in the classical Robbins–Monro scheme, there is a controllable design variable taking values in $\mathbb{R}$ that follows itself the SA recursion, while in our setting the design space is discrete, since $\delta_n \in \{0; 1\}$, and only the allocation proportions π_ns follow (7.2);
- within SA framework the function $H(\cdot)$ is analytically unknown and it cannot be observed directly, but it could be observed only with a stochastic perturbation; whereas in our setting the allocation function is the only ingredient chosen by the experimenter and thus it is completely known (while the assignments δ_ns are randomly generated by the allocation rule).

As regards the other types of adaptive procedures, (7.3) is still a non-negative almost supermartingale provided that the downcrossing t of $\varphi^{\mathrm{AA}}(\cdot)$ is substituted by the generalized (vectorial) downcrossing of the corresponding allocation function. For instance, in the RA case $t \mapsto t(\hat{\boldsymbol{\gamma}}_n)$ and the asymptotic behavior of π_n coincides with that of $t(\hat{\boldsymbol{\gamma}}_n)$; therefore, assuming $t(\cdot)$ continuous, as n grows $\pi_n \to t(\boldsymbol{\gamma})$ a.s. Furthermore, by adding suitable continuity and differentiability conditions for $t(\cdot)$ and the allocation function, it is possible to derive the asymptotic normality of the allocation proportions as in (7.5) (see, e.g., [21] for RA procedures and [45] for CARA designs). Note that the case of CARA designs with categorical covariates is a multidimensional SA scheme where, at each step n, (i) the evolution at each stratum depends, in general, on the information gathered up to that step from all the strata and (ii) the constant a_n should be replaced by the random vector $\mathbf{a}_n = [N_{n+1}(j,l)^{-1}\mathbb{1}_{\{Z_i=(t_j,w_l)\}}, j = 0,\dots,J; l = 0,\dots,L]$ and therefore the Robbins–Siegmund's lemma (1971) should be applied (see [25, 30]).

Appendix

A.1. Proof of Theorem 4.1

At each step n, consider the squared integrable martingale process $\{M_n; \Im_n\}$, where $M_n = \sum_{i=1}^n \Delta M_i = \sum_{i=1}^n \{\delta_i - E(\delta_i|\Im_{i-1})\}$ and $\Im_n = \sigma(\delta_1,\dots,\delta_n; Y_1,\dots,Y_n)$.

Let $\lambda_n = \max\{s\colon 2m+1 \le s \le n, \pi_s \le t(\hat{\boldsymbol{\gamma}}_s)\}$, with $\max \varnothing = 2m$. Thus at each step $i > \lambda_n$, $\varphi^{\mathrm{RA}}(\pi_i; \hat{\boldsymbol{\gamma}}_i) \le t(\hat{\boldsymbol{\gamma}}_i)$ and therefore

$$\widetilde{N}_n = \widetilde{N}_{\lambda_n+1} + \sum_{k=\lambda_n+2}^{n} \Delta M_k + \sum_{k=\lambda_n+2}^{n} \varphi^{\mathrm{RA}}(\pi_{k-1}; \hat{\boldsymbol{\gamma}}_{k-1})$$

$$\le \widetilde{N}_{\lambda_n} + 1 + M_n - M_{\lambda_n+1} + \sum_{k=\lambda_n+2}^{n} t(\hat{\boldsymbol{\gamma}}_{k-1}).$$

Since $\widetilde{N}_{\lambda_n} \le \lambda_n t(\hat{\boldsymbol{\gamma}}_{\lambda_n})$ we obtain

$$\widetilde{N}_n - nt(\hat{\boldsymbol{\gamma}}_n) \le \left(\lambda_n t(\hat{\boldsymbol{\gamma}}_{\lambda_n}) - \sum_{k=2}^{\lambda_n+1} t(\hat{\boldsymbol{\gamma}}_{k-1})\right) + M_n - M_{\lambda_n+1} + 1 - t(\hat{\boldsymbol{\gamma}}_0) - \left(nt(\hat{\boldsymbol{\gamma}}_n) - \sum_{k=1}^{n} t(\hat{\boldsymbol{\gamma}}_{k-1})\right),$$

where $t(\hat{\boldsymbol{\gamma}}_0) = t_0 \in [0; 1]$ is a constant depending on the initial stage. Furthermore, as $n \to \infty$, at least one of the number of assignments to the treatments, $\widetilde{N}_n$ and $(n - \widetilde{N}_n)$, tends to infinity a.s. As showed in [22], in either case $\hat{\boldsymbol{\gamma}}_n$ has finite limit so that, from the properties of $t(\hat{\boldsymbol{\gamma}}_n)$, almost surely there exists a v such that

$$t(\hat{\boldsymbol{\gamma}}_n) \to v \qquad \text{a.s.} \tag{A.1}$$

and so $\lim_{n\to\infty} t(\hat{\boldsymbol{\gamma}}_n) - n^{-1}\sum_{k=1}^{n} t(\hat{\boldsymbol{\gamma}}_{k-1}) = 0$ a.s. As $n \to \infty$, then $\lambda_n \to \infty$ or $\sup_n \lambda_n < \infty$; in either case, $\lim_{n\to\infty} n^{-1}\lambda_n[t(\hat{\boldsymbol{\gamma}}_{\lambda_n}) - \lambda_n^{-1}\sum_{k=1}^{\lambda_n} t(\hat{\boldsymbol{\gamma}}_k)] = 0$ a.s. and therefore

$$\left[\pi_n - t(\hat{\boldsymbol{\gamma}}_n)\right]^+ \to 0 \qquad \text{a.s.} \tag{A.2}$$

Analogously,

$$\left[(1-\pi_n) - \left(1 - t(\hat{\boldsymbol{\gamma}}_n)\right)\right]^+ \to 0 \qquad \text{a.s.} \tag{A.3}$$

From (A.2) and (A.3), as n tends to infinity $\pi_n - t(\hat{\boldsymbol{\gamma}}_n) \to 0$ a.s. and by (A.1) $\lim_{n\to\infty} \pi_n = \lim_{n\to\infty} t(\hat{\boldsymbol{\gamma}}_n) = v$ a.s. Since $0 < v < 1$, then $0 < 1 - v < 1$ and thus $\lim_{n\to\infty} \widetilde{N}_n \to \infty$ a.s. and $\lim_{n\to\infty}(n - \widetilde{N}_n) \to \infty$ a.s. Therefore, $\lim_{n\to\infty} \hat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma}$ a.s. and from the continuity of the downcrossing $\lim_{n\to\infty} t(\hat{\boldsymbol{\gamma}}_n) = t(\boldsymbol{\gamma}) = v$ a.s., that is, $\lim_{n\to\infty} \pi_n = t(\boldsymbol{\gamma})$ a.s.

A.2. Proof of Theorem 5.1

If φ^{CARA} is decreasing in π_n, then $\tilde{\varphi}_{\mathbf{Z}}$ is also decreasing in π_n, so that the generalized downcrossing is unique and lies in $(0; 1)$. Letting now $\Im_n = \sigma(\delta_1, \ldots, \delta_n; Y_1, \ldots, Y_n; \mathbf{Z}_1, \ldots, \mathbf{Z}_n)$, then $E(\delta_i|\Im_{i-1}) = E_{\mathbf{Z}_i}[\varphi(\pi_{i-1}; \hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1}, f(\mathbf{Z}_i))]$ and $\Delta M_i = \delta_i - E(\delta_i|\Im_{i-1})$. Then $\{\Delta M_i; i \ge 1\}$ is a sequence of bounded martingale differences with $|\Delta M_i| \le 1$ for any $i \ge 1$; thus $\{M_n = \sum_{i=1}^{n} \Delta M_i; \Im_n\}$ is a martingale with $\sum_{k=1}^{n} E[(\Delta M_i)^2|\Im_{k-1}] \le n$. Let $\zeta_n = \max\{\vartheta\colon\ 2m + 1 \le \vartheta \le n, \pi_\vartheta \le \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_\vartheta, \mathbf{S}_\vartheta)\}$, with $\max \varnothing = 2m$. So that $\forall i > \zeta_n$ we have $\tilde{\varphi}_{\mathbf{Z}}(\pi_i; \hat{\boldsymbol{\gamma}}_i, \mathbf{S}_i) \le \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_i, \mathbf{S}_i)$. Note that

$$\widetilde{N}_n = \widetilde{N}_{\zeta_n+1} + \sum_{k=\zeta_n+2}^{n} \Delta M_k + \sum_{k=\zeta_n+2}^{n} E(\delta_k|\Im_{k-1})$$

$$\le \widetilde{N}_{\zeta_n} + 1 + M_n - M_{\zeta_n+1} + \sum_{k=\zeta_n+2}^{n} \tilde{\varphi}_{\mathbf{Z}}(\pi_{k-1}; \hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1})$$

$$< \widetilde{N}_{\zeta_n} + 1 + M_n - M_{\zeta_n+1} + \sum_{k=\zeta_n+2}^{n} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1})$$

$$= \widetilde{N}_{\zeta_n} + 1 + M_n - M_{\zeta_n+1} + \sum_{k=1}^{n} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1}) - \sum_{k=1}^{\zeta_n+1} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1}).$$

Since $\widetilde{N}_{\zeta_n} \leq \zeta_n \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{\zeta_n}, \mathbf{S}_{\zeta_n})$, then

$$\widetilde{N}_n - n\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) \leq \left(\zeta_n \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{\zeta_n}, \mathbf{S}_{\zeta_n}) - \sum_{k=2}^{\zeta_n+1} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1}) \right)$$
$$+ M_n - M_{\zeta_n+1} + 1 - \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_0, \mathbf{S}_0) - \left(n\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) - \sum_{k=1}^{n} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1}) \right).$$

Moreover, as $n \to \infty$, at least one of the number of assignments to the treatments, $\widetilde{N}_n$ and $(n - \widetilde{N}_n)$, tends to infinity a.s. In either case from the properties of $\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n)$, almost surely there exists a $\tilde{\upsilon}$ such that

$$\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) \to \tilde{\upsilon} \qquad \text{a.s.} \tag{A.4}$$

and so

$$\tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) - \frac{1}{n} \sum_{k=1}^{n} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{k-1}, \mathbf{S}_{k-1}) \to 0 \qquad \text{a.s.}$$

As $n \to \infty$, then $\zeta_n \to \infty$ or $\sup_n \zeta_n < \infty$; in either case,

$$\frac{\zeta_n}{n} \left\{ \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_{\zeta_n}, \mathbf{S}_{\zeta_n}) - \frac{1}{\zeta_n} \sum_{k=1}^{\zeta_n} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_k, \mathbf{S}_k) \right\} \to 0 \qquad \text{a.s.}$$

and therefore

$$\left[\pi_n - \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) \right]^+ \to 0 \qquad \text{a.s.} \tag{A.5}$$

Analogously,

$$\left[(1 - \pi_n) - \left(1 - \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) \right) \right]^+ \to 0 \qquad \text{a.s.} \tag{A.6}$$

From (A.5) and (A.6), $\lim_{n\to\infty} \pi_n - \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = 0$ a.s. and therefore by (A.4) $\lim_{n\to\infty} \pi_n = \lim_{n\to\infty} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = \tilde{\upsilon}$ a.s. Since $0 < \tilde{\upsilon} < 1$, then $0 < 1 - \tilde{\upsilon} < 1$ and $\lim_{n\to\infty} \widetilde{N}_n \to \infty$ a.s. and $\lim_{n\to\infty} (n - \widetilde{N}_n) \to \infty$ a.s. Therefore, $\lim_{n\to\infty} \hat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma}$ a.s. and also $\lim_{n\to\infty} \mathbf{S}_n \to \boldsymbol{\varsigma}$ a.s., so that from the continuity of the downcrossing $\lim_{n\to\infty} \tilde{t}_{\mathbf{Z}}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = \tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) = \tilde{\upsilon}$ a.s., namely $\lim_{n\to\infty} \pi_n = \tilde{t}_{\mathbf{Z}}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$ a.s.

A.3. Proof of Theorem 6.1

At each step n, let $M_n(j,l) = \sum_{i=1}^n \Delta M_i(j,l) = \sum_{i=1}^n \{\delta_i - E(\delta_i|\mathfrak{G}_{i-1})\}\mathbb{1}_{\{Z_i=(t_j,w_l)\}}$, where $\mathfrak{G}_i = \sigma(\Im_i, \mathbf{Z}_{i+1})$. Therefore, at each stratum (t_j, w_l), $\{\Delta M_i(j,l); i \geq 1\}$ is a sequence of bounded martingale differences with $|\Delta M_i(j,l)| \leq 1$ for any $i \geq 1$ and thus, $\{M_n(j,l); \mathfrak{G}_n\}$ is a squared integrable martingale with $\sum_{k=1}^n E[(\Delta M_i(j,l))^2|\mathfrak{G}_{k-1}] \leq n$.

Let $\xi_n(j,l) = \max\{s\colon 2m+1 \leq i \leq n, \pi_i(j,l) \leq t_{jl}(\hat{\boldsymbol{\gamma}}_i, \mathbf{S}_i)\}$, with $\max \varnothing = 2m$, then there exists a given stratum $(t_{j'}, w_{l'})$ such that $\xi_n(j',l') = \max_{jl} \xi_n(j,l)$. Therefore, for any $i > \xi_n(j',l')$, at each stratum $\pi_i(j,l) > t_{jl}$ and, by Definition 6.1, $\varphi_{jl}(\boldsymbol{\pi}_i; \hat{\boldsymbol{\gamma}}_i, \mathbf{S}_i) \leq t_{jl}(\hat{\boldsymbol{\gamma}}_i, \mathbf{S}_i)$. Thus

$$
\begin{aligned}
\widetilde{N}_n(j',l') &= \widetilde{N}_{\xi_n(j',l')+1}(j',l') + \sum_{i=\xi_n(j',l')+2}^{n} \Delta M_i(j',l') + \sum_{i=\xi_n(j',l')+2}^{n} E(\delta_i|\mathfrak{G}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \\
&\leq \widetilde{N}_{\xi_n(j',l')}(j',l') + 1 + M_n(j',l') - M_{\xi_n(j',l')+1}(j',l') \\
&\quad + \sum_{i=\xi_n(j',l')+2}^{n} \varphi_{j'l'}(\boldsymbol{\pi}_{i-1}; \hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \\
&< \widetilde{N}_{\xi_n(j',l')}(j',l') + 1 + M_n(j',l') - M_{\xi_n(j',l')+1}(j',l') \\
&\quad + \sum_{i=\xi_n(j',l')+2}^{n} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \\
&= \widetilde{N}_{\xi_n(j',l')}(j',l') + 1 + M_n(j',l') - M_{\xi_n(j',l')+1}(j',l') \\
&\quad + \sum_{i=1}^{n} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \\
&\quad - \sum_{i=1}^{\xi_n(j',l')+1} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}}.
\end{aligned}
$$

Moreover, since $\widetilde{N}_{\xi_n(j',l')}(j',l') \leq N_{\xi_n(j',l')}(j',l')t_{j'l'}(\hat{\boldsymbol{\gamma}}_{\xi_n(j',l')}, \mathbf{S}_{\xi_n(j',l')})$, then

$$
\begin{aligned}
&\widetilde{N}_n(j',l') - N_n(j',l')t_{j'l'}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) \\
&\quad \leq M_n(j',l') - M_{\xi_n(j',l')+1}(j',l') + 1 \\
&\qquad + \left(N_{\xi_n(j',l')}(j',l')t_{j'l'}(\hat{\boldsymbol{\gamma}}_{\xi_n(j',l')}, \mathbf{S}_{\xi_n(j',l')}) - \sum_{i=1}^{\xi_n(j',l')+1} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \right) \\
&\qquad - \left(N_n(j',l')t_{j'l'}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) - \sum_{i=1}^{n} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1})\mathbb{1}_{\{Z_i=(t_{j'},w_{l'})\}} \right).
\end{aligned}
$$

Since $p_{jl} > 0$, then as $n \to \infty$

$$N_n(j,l) \to \infty \quad \text{and} \quad \frac{M_n}{N_n(j,l)} \to 0 \qquad \text{a.s.} \qquad \forall j = 0, \dots, J; l = 0, \dots, L.$$

Moreover, as $n \to \infty$ at least one of $\widetilde{N}_n(j',l')$ and $[N_n(j',l') - \widetilde{N}_n(j',l')]$ tends to infinity a.s. Therefore $\hat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma}$ a.s. and, from (5.2), $\mathbf{S}_n \to \boldsymbol{\varsigma}$ a.s. Thus, as $n \to \infty$

$$t_{j'l'}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) - \frac{\sum_{i=1}^{n} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1}) \mathbb{1}_{\{Z_i = (t_{j'}, w_{l'})\}}}{\sum_{i=1}^{n} \mathbb{1}_{\{Z_i = (t_{j'}, w_{l'})\}}} \to 0 \qquad \text{a.s.}$$

Furthermore, as $n \to \infty$

$$t_{j'l'}(\hat{\boldsymbol{\gamma}}_{\xi_n(j',l')}, \mathbf{S}_{\xi_n(j',l')}) \frac{N_{\xi_n(j',l')}(j',l')}{N_n(j',l')} - \frac{\sum_{i=1}^{\xi_n(j',l')+1} t_{j'l'}(\hat{\boldsymbol{\gamma}}_{i-1}, \mathbf{S}_{i-1}) \mathbb{1}_{\{Z_i = (t_{j'}, w_{l'})\}}}{\sum_{i=1}^{n} \mathbb{1}_{\{Z_i = (t_{j'}, w_{l'})\}}} \to 0 \qquad \text{a.s.}$$

and therefore $\lim_{n\to\infty} [\pi_n(j',l') - t_{j'l'}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n)]^+ = 0$ a.s.

Analogously, $\lim_{n\to\infty} \{[1 - \pi_n(j',l')] - [1 - t_{j'l'}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n)]\}^+ = 0$ a.s. and thus

$$\lim_{n\to\infty} \pi_n\big(j',l'\big) = t_{j'l'}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) \qquad \text{a.s.} \tag{A.7}$$

Since $\exists!\, \mathbf{t}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n) = [t_{jl}(\hat{\boldsymbol{\gamma}}_n, \mathbf{S}_n)\colon\ j = 0, \dots, J; l = 0, \dots, L]$ which is continuous and $\boldsymbol{\varphi}(\mathbf{t}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}); \boldsymbol{\gamma}, \boldsymbol{\varsigma}) = \mathbf{t}(\boldsymbol{\gamma}, \boldsymbol{\varsigma})$, then from (A.7) follows that

$$\lim_{n\to\infty} \pi_n(j,l) = t_{jl}(\boldsymbol{\gamma}, \boldsymbol{\varsigma}) \qquad \text{a.s.} \qquad \text{for every } (j,l) \neq \big(j',l'\big)$$

and Theorem 6.1 follows directly.

Acknowledgements

We are grateful to the referees and the associate editor for their comments and suggestions, which led to a substantially improved version of the paper.

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Received March 2013 and revised November 2013