THE COVARIATE-ADAPTIVE BIASED COIN DESIGN FOR BALANCING CLINICAL TRIALS IN THE PRESENCE OF PROGNOSTIC FACTORS.

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The present paper deals with sequential designs aimed at balancing the allocations of two competing treatments in the presence of prognostic factors. After giving a theoretical framework on the optimality of different balanced designs that can arise when some covariates are taken into account, we address the problem of finding covariate-adaptive procedures which are fully randomized and high order efficient from an inferential viewpoint. We propose a new family of covariate-adaptive randomized designs that can be regarded as a suitable extension of Efron's biased coin and it represents the higher order approximation to balance treatments, both globally and also across covariates. Ergodic Markov chains and martingale methods are used to establish the optimal properties of the suggested designs, in terms of loss of precision and predictability. The performances of this proposal are also illustrated through a simulation study and compared with those of other procedures suggested in the literature.

1. Introduction. In the biomedical and pharmaceutical research for treatment comparisons randomized clinical trials are commonly considered to be the gold standard, since a randomization component in the assignments tends to mitigate several types of bias, including the accidental bias due to unknown confounders/disturbances and the selection bias induced by the investigators. Often, another important requirement is that the trial should be balanced in order to optimize inference about the treatment effects. This is particularly true in the contest of phase-III clinical trials, where patients are sequentially assigned to one of two available treatments, say A and B, and "nearly balanced" groups are always deemed to be desirable since they allow to stop the experiment at any time in an excellent inferential setting.

To obtain a valid compromise between these goals, Efron (1971) introduced his Biased Coin Design (BCD), namely a sequential allocation rule randomized by means of the flipping of a biased coin which at each step favors the under represented treatment. Let $\delta_1, \ldots, \delta_n, \ldots$ denote the allocation sequence, with $\delta_n = 1$ if the n-th subject is assigned to treatment A,

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and 0 otherwise, Efron defined the BCD(p) by letting

$$\Pr(\delta_{n+1} = 1 \mid \delta_1, \ldots, \delta_n) = \begin{cases} p & D_n < 0 \\ \frac{1}{2} & D_n = 0 \\ 1-p & D_n > 0 \end{cases}, \qquad n \geq 1, \tag{1.1}$$

where $D_n = 2\sum_{i=1}^{n} \delta_i - n$ represents the difference between the two groups after n steps (with $D_0 = 0$) and $p \geq 1/2$ is the bias parameter. The choice $p = 1$ corresponds to a permuted block design (PBD) with size 2, i.e. the allocations are perfectly balanced at each step but 50% of the assignments are deterministic, while for $p = 1/2$ the design is completely randomized (CR). To obtain a valid trade-off between balance and predictability (i.e. "lack of randomness"), Efron suggested $p = 2/3$.

Several extensions of Efron's BCD have been proposed in the literature (see e.g. Wei (1978a), Atkinson (1982), Soares and Wu (1983), Smith (1984a) and Chen (1999)). In particular, Wei (1978a) introduced the Adaptive Biased Coin Design by assigning the $(n+1)$-th patient to A with probability

$$\Pr(\delta_{n+1} = 1 \mid \delta_1, \ldots, \delta_n) = f(D_n/n), \qquad n \geq 1, \tag{1.2}$$

where $f : [-1; 1] \to [0; 1]$ is a continuous and decreasing function with $f(x) = 1 - f(-x)$. Adopting this class of procedures, which are based on the probabilistic structure of non-homogeneous Markov chains, the allocations are asymptotically balanced, namely $\lim_{n\to\infty} D_n/n = 0$ *a.s.* Also, assuming that $f(\cdot)$ is continuously differentiable with bounded derivative at 0, Wei showed that $D_n/\sqrt{n}$ is asymptotically normal (see also Smith (1984a)).

Clearly, Efron's coin cannot be regarded as a special case of the Adaptive Biased Coin Design, since the allocation probability function in (1.1) is discontinuous. A proper generalization of the BCD(p) has been recently introduced by Baldi Antognini and Giovagnoli (2004), who define the Adjustable Biased Coin Design (ABCD) by letting

$$\Pr(\delta_{n+1} = 1 \mid \delta_1, \ldots, \delta_n) = F(D_n), \qquad n \geq 1,$$

where $F : \mathbb{Z} \to [0; 1]$ is a decreasing and symmetric function with $F(x) = 1 - F(-x)$, so that at every step the tendency towards balance is stronger the more we move away from it. Ergodic random walks represent the underlined probabilistic structure of the ABCD, which is asymptotically balanced and also, unless $F(\cdot)$ is constant (namely the CR), $D_n/\sqrt{n} \to 0$ in probability. Thus the BCD(p), and more in general the ABCD class, represents a high order approximation to balance and this is one of the main reasons for which

Efron's coin is still the topic of several papers. Indeed, as showed recently by Hu and Rosenberger (2003) and Chen (2006), the inferential precision - in terms of both power of the test or variance of parameter estimates - decreases as the variability of the randomized design increases, so that the ABCD (and in particular Efron's coin) is asymptotically the best procedure for balancing the allocations of two treatments, since the balance is targeted with minimum variance (see Baldi Antognini (2008), Hu et al. (2009) and Markaryan and Rosenberger (2010)).

One of the major drawbacks of the ABCD is that ignores covariates or prognostic factors, which are usually taken into account in comparative clinical trials. To overcome this disadvantage, several allocation rules have been suggested aimed to achieve balance among the set of covariates of interest. Following Rosenberger and Lachin (2002), these procedures fall into the class of covariate-adaptive randomization, since the allocation probability at each step depends on the assignments and the covariates of previous subjects and on the current patient's covariate, but does not depend on the observed responses (see Hu and Rosenberger, 2006). For instance, adopting an approach based on optimal design theory, Atkinson (1982) and Smith (1984a; 1984b) assume the classical linear model without treatment-covariate interactions and propose allocation rules aimed at balancing the allocations across the covariates in order to minimize the variance of the estimated difference between the treatment effects. See also Begg and Iglewicz (1980) for a simplified version of these proposals.

Although Smith and Atkinson's procedures can be applied for any type of prognostic factors, in the large majority of practical situations the covariates of interest are categorical and, even in the quantitative case, these are often categorized by adopting suitable thresholds. Thus, such trials are usually stratified with respect to the chosen set of prognostic factors and in this setting one of the most popular technique is the minimization method proposed by Pocock and Simon (1975). Originally introduced by Taves (1974) in a deterministic version, this procedure is aimed to achieve the so-called *marginal balance*, so that the balance between the treatment groups is forced within each level of every covariate. Since non-randomized allocations are subject to several types of bias, this proposal has been later modified by introducing a random mechanism based on a biased coin (Wei, 1978b); moreover, minimization methods have been recently modified in order to differentiate the role of the covariates and, consequently, the need for balance between the levels of the considered factors, motivated by the fact that in practical situations some factors may have a major/minor impact on the outcome with respect to others (see Signorini et al. (1993) and Heritier et al. (2005)).

An alternative approach is represented by stratified randomization methods, which are aimed to achieve the so called *joint balance* or balance within-strata, i.e. within each combination of the levels of the prognostic factors. Under these procedures a separate randomization sequence is generated within each stratum, usually based on CR or PBD (Zelen, 1974). However, as is well-known, CR may induce strong departures from balance, in particular for small sample trials, whereas permuted block designs are not fully randomized and tend to be high predictable. Furthermore, these procedures could induce a significant loss of precision as the number of covariates grows, so that they may be unsuitable for practical situations.

In general, there are only few theoretical results aimed at justifying minimization methods and stratified randomization procedures. To our knowledge, until now only Wei (1978b) showed that under the linear model without interactions (both treatment-covariate and among covariates) the bias term of the MSE of the BLUE of the parameters vanishes if the design is marginally balanced. Moreover, stratified randomization methods are solely based on intuition, since the requirement of joint balance does not have a formal mathematical justification (see Rosenberger and Sverdlov (2008)). Furthermore, the properties of the entire class of covariate-adaptive procedures as well as the comparisons of different methods have been approached almost exclusively through simulations.

The aim of this paper is to give a theoretical analysis of sequential randomized designs aimed at balancing the allocations of two competing treatments in the presence of prognostic factors, also addressing the problem of finding covariate-adaptive procedures which are fully randomized and optimal from an inferential viewpoint. After giving a theoretical discussion on the optimality of different balanced designs that can arise when some covariates are taken into account in the planning phase, we introduce and analyze a new class of stratified randomization methods, called the Covariate-Adaptive Biased Coin Design (C-ABCD), aimed at achieving the balance of treatments both marginally and within-strata. The suggested procedure is quite simple to implement, very flexible and allows to diversify the role of the covariates in order to force in a different way the balance between strata and between the different levels of the involved factors. Through the martingale limit theory and the properties of ergodic Markov chains we prove that the C-ABCD is asymptotically high order efficient, since it represents the higher order approximation of balance (jointly, marginally and also globally) with respect to the chosen set of covariates. We analyze the loss of precision induced by the experiment, showing that under the C-ABCD such loss tends to 0 asymptotically, independently of the number of factors taken into

consideration. Moreover, we show some properties of Smith and Atkinson's procedures, stressing similarities and differences between our proposal and these methods. Finally, a simulation study is performed in order to compare the C-ABCD with the minimization method proposed by Pocock and Simon (1975) and Atkinson's rules. To avoid cumbersome notation, in this paper we restrict ourselves to the case of two covariates (without loss of generality). The extension to several prognostic factors is straightforward.

The paper is organized as follows. Starting from the terminology in Section 2, Section 3 deals with the optimality of different types of balanced designs. Section 4 introduces the C-ABCD, while Section 5 describes properties of the suggested procedure in terms of both loss and predictability. Section 6 provides a brief discussion about the choice of the randomization functions, which may be useful for the practitioners and in Section 7 the properties of the C-ABCD are compared with those of other procedures through a simulation study. Some of the technical proofs are given in the Appendix.

2. The Linear Model with Covariates. Let A and B be two competing treatments. We suppose that for each subject entering the trial we observe a vector $\boldsymbol{Z}$ of concomitant variables, which may be quantitative or categorical (block effects): thus we take each observed covariate to stand either for a numerical value or a vector of indicators of the levels. We assume the covariates to be random, i.e. they are not under the experimenters' control, but they can be measured before assigning a treatment. Then, the treatments are assigned according to a given randomization rule and a response Y is observed. Conditionally on the covariates and the treatments, patients' responses are assumed to be independent.

Let Y_i denote the outcome for the i-th subject, a common model for the response is the homoscedastic linear model which, conditionally on the covariates and the treatment, is given by

$$\begin{aligned} E(Y_i) &= \delta_i\ \mu_A + (1-\delta_i)\ \mu_B + \boldsymbol{f}(\boldsymbol{z}_i)^t\boldsymbol{\beta} \\ V(Y_i) &= \sigma^2 \qquad i = 1,\dots,n, \end{aligned} \tag{2.1}$$

where δ_i is a treatment indicator variable, with $\delta_i = 1$ or 0 if the i-th subject is assigned to treatment A or B respectively, μ_A and μ_B are the treatment effects, $\boldsymbol{z}_i$ is the vector of covariates observed on the i-th individual, $\boldsymbol{f}(\cdot)$ is a known vector function which may include interactions among the covariates, and $\boldsymbol{\beta}$ is a q-dim vector of covariate effects.

At the end of the trial, suppose that n assignments of either treatment A or B have been made to patients with i.i.d. covariates $\mathbf{Z}_1,\dots,\mathbf{Z}_n$. Letting $\boldsymbol{Y} = (Y_1,\dots,Y_n)^t$, $\boldsymbol{\delta} = (\delta_1,\dots,\delta_n)^t$ and $\mathbf{F} = (\boldsymbol{f}(\boldsymbol{z}_i)^t)$, model (2.1) can be

written as follows

$$E(\boldsymbol{Y}) = \mathbf{X}\boldsymbol{\gamma} = \boldsymbol{\delta}\ \mu_A + (\mathbf{1}-\boldsymbol{\delta})\ \ \mu_B + \mathbf{F}\boldsymbol{\beta}, \quad V(\boldsymbol{Y}) = \sigma^2\mathbf{I}_n,$$

where $\mathbf{X} = (\boldsymbol{\delta}; \mathbf{1}-\boldsymbol{\delta}; \mathbf{F})$, $\boldsymbol{\gamma} = (\mu_A, \mu_B, \boldsymbol{\beta})^t$ denotes the vector of unknown parameters and $\mathbf{I}_n$ is the $n-$dim identity matrix. Let $\hat{\boldsymbol{\gamma}}$ be the least square estimator of $\boldsymbol{\gamma}$, then if $(\mathbf{X}^t\mathbf{X})^{-1}$ exists, given the covariates $\mathbf{Z}_1, \ldots, \mathbf{Z}_n$ and the design $\boldsymbol{\delta}$, the variance-covariance matrix is

$$V(\hat{\boldsymbol{\gamma}}) = \sigma^2(\mathbf{X}^t\mathbf{X})^{-1} = \frac{\sigma^2}{n}\mathbf{M}^{-1} \tag{2.2}$$

with $\mathbf{M}$ the average (*per observation*) Fisher information matrix

$$\begin{aligned}\mathbf{M} &= \frac{1}{n}\begin{pmatrix} \boldsymbol{\delta}^t\boldsymbol{\delta} & \boldsymbol{\delta}^t(\mathbf{1}-\boldsymbol{\delta}) & \boldsymbol{\delta}^t\mathbf{F} \\ (\mathbf{1}-\boldsymbol{\delta})^t\boldsymbol{\delta} & (\mathbf{1}-\boldsymbol{\delta})^t(\mathbf{1}-\boldsymbol{\delta}) & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \\ \mathbf{F}^t\boldsymbol{\delta} & \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) & \mathbf{F}^t\mathbf{F} \end{pmatrix} \\ &= \frac{1}{n}\begin{pmatrix} n_A & 0 & \boldsymbol{\delta}^t\mathbf{F} \\ 0 & n_B & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \\ \mathbf{F}^t\boldsymbol{\delta} & \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) & \mathbf{F}^t\mathbf{F} \end{pmatrix},\end{aligned} \tag{2.3}$$

where $n_A = \boldsymbol{\delta}^t\boldsymbol{\delta} = \boldsymbol{\delta}^t\mathbf{1}$ and $n_B = (\mathbf{1}-\boldsymbol{\delta})^t(\mathbf{1}-\boldsymbol{\delta}) = (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{1} = n - n_A$ denote the number of subjects assigned to A and B, respectively.

For numerical covariates, $\mathbf{M}^{-1}$ exists if no serious collinearity among them arises. When some of the covariates are categorical $\mathbf{M}$ may be singular, but with some care $\mathbf{M}^{-1}$ may be replaced by the Moore-Penrose inverse $\mathbf{M}^{-}$.

3. Balance and optimality. As is well-known, for any fixed sample size, balancing the covariates is a desirable property for inference and now we provide a brief explanation for this. According to Optimal Design Theory (see, for instance, Pukelsheim (2005)), the problem lies in finding the design that minimizes the loss of information expressed by a suitably chosen real function Φ of matrix argument, usually called optimality criterion.

Under model (2.1), i.e. in the absence of treatment-covariate interaction, the covariates affect the treatment responses in the same way for all patients with the same covariate profile $\boldsymbol{z}$. Indeed, the expected difference between the treatment effects is $\mu_A - \mu_B$, so that the superiority of treatment A on B (or vice versa) is *uniformly* constant over the covariates. In this case it is customary to regard the vector $\boldsymbol{\beta}$ as nuisance parameter, so that the inferential interest typically lies in estimating $\mu_A - \mu_B$, or μ_A and μ_B, as precisely as possible. Consequently, the design for optimal inference consists in allocating A and B so as to minimize one of the following criteria:

C1 trace-optimality: $\mathrm{tr}V\left(\hat{\mu}_A;\hat{\mu}_B\right)= \mathrm{tr}\left(n^{-1}\sigma^2\mathbf{\Lambda}^t\mathbf{M}^{-1}\mathbf{\Lambda}\right)$,
C2 D-optimality: $\det V\left(\hat{\mu}_A;\hat{\mu}_B\right) = \det\left(n^{-1}\sigma^2\mathbf{\Lambda}^t\mathbf{M}^{-1}\mathbf{\Lambda}\right)$,

where $\mathbf{\Lambda}^t = (\mathbf{I}_2;\mathbf{0}_{2\times q})$, $\mathbf{0}_{2\times q}$ denotes the $(2\times q)-$dim matrix of zero's, and $\mathbf{M}^{-1}$ replaced by $\mathbf{M}^{-}$ if needed.

For given covariates a *balanced design*, namely an allocation vector $\boldsymbol{\delta}$ which satisfies both the following properties

B1: $\boldsymbol{\delta}^t\boldsymbol{\delta} = (\mathbf{1}-\boldsymbol{\delta})^t(\mathbf{1}-\boldsymbol{\delta})$,
B2: $\boldsymbol{\delta}^t\mathbf{F} = (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} = \frac{1}{2}\mathbf{1}^t\mathbf{F}$,

is optimal for model (2.1) with respect to any convex criterion Φ of the information matrix $\mathbf{M}$, which is invariant with respect to permutation of the first two rows and two columns simultaneously, like for instance **C1** and **C2**. To see this, assume that conditions **B1**+**B2** hold for the information matrix $\mathbf{M}^*$, so that

$$\mathbf{M}^* = \frac{1}{2n}\begin{pmatrix} n & 0 & \mathbf{1}^t\mathbf{F} \\ 0 & n & \mathbf{1}^t\mathbf{F} \\ \mathbf{F}^t\mathbf{1} & \mathbf{F}^t\mathbf{1} & 2\mathbf{F}^t\mathbf{F} \end{pmatrix}. \tag{3.1}$$

For any information matrix $\mathbf{M}$ of the type (2.3), by the simultaneous permutation of the first two rows and two columns we obtain the information matrix $\tilde{\mathbf{M}}$ corresponding to the design which switches treatments A and B. Clearly $\Phi(\tilde{\mathbf{M}}) = \Phi(\mathbf{M})$ and

$$\begin{aligned}\frac{1}{2}\mathbf{M}+\frac{1}{2}\tilde{\mathbf{M}} &= \\ = \frac{1}{2n}\begin{pmatrix} n_A & 0 & \boldsymbol{\delta}^t\mathbf{F} \\ 0 & n_B & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \\ \mathbf{F}^t\boldsymbol{\delta} & \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) & \mathbf{F}^t\mathbf{F} \end{pmatrix} &+ \frac{1}{2n}\begin{pmatrix} n_B & 0 & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \\ 0 & n_A & \boldsymbol{\delta}^t\mathbf{F} \\ \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) & \mathbf{F}^t\boldsymbol{\delta} & \mathbf{F}^t\mathbf{F} \end{pmatrix} \\ &= \frac{1}{2n}\begin{pmatrix} n & 0 & \mathbf{1}^t\mathbf{F} \\ 0 & n & \mathbf{1}^t\mathbf{F} \\ \mathbf{F}^t\mathbf{1} & \mathbf{F}^t\mathbf{1} & 2\mathbf{F}^t\mathbf{F} \end{pmatrix} = \mathbf{M}^*,\end{aligned}$$

then by convexity

$$\Phi(\mathbf{M}^*) = \Phi\left(\frac{1}{2}\mathbf{M}+\frac{1}{2}\tilde{\mathbf{M}}\right) \le \frac{1}{2}\Phi(\mathbf{M})+\frac{1}{2}\Phi(\tilde{\mathbf{M}}) = \Phi(\mathbf{M}).$$

REMARK 3.1. *An alternative model that accounts for treatment-covariate interactions is*

$$E(\boldsymbol{Y}) = \boldsymbol{\delta}\mu_A + (\mathbf{1}-\boldsymbol{\delta})\mu_B + \mathbf{\Delta}\mathbf{F}\boldsymbol{\beta}_A + (\mathbf{I}_n-\mathbf{\Delta})\mathbf{F}\boldsymbol{\beta}_B, \quad V(\boldsymbol{Y}) = \sigma^2\mathbf{I}_n$$

where $\boldsymbol{\Delta} = diag(\boldsymbol{\delta})$ *and* $\boldsymbol{\beta}_A$, $\boldsymbol{\beta}_B$ *are* q*-dim vectors of possibly different regressor parameters for* A *and* B*, respectively. Under this model the relative performance of the treatments depends on the patient's covariates, so that both* (μ_A, μ_B) *and* $(\boldsymbol{\beta}_A, \boldsymbol{\beta}_B)$ *are of interest. Letting* $\boldsymbol{\gamma} = (\mu_A, \mu_B, \boldsymbol{\beta}_A, \boldsymbol{\beta}_B)^t$*, (2.2) still holds with*

$$\mathbf{M} = \frac{1}{n} \begin{pmatrix} n_A & 0 & \boldsymbol{\delta}^t\mathbf{F} & \mathbf{0} \\ 0 & n_B & 0 & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \\ \mathbf{F}^t\boldsymbol{\delta} & \mathbf{0} & \mathbf{F}^t\boldsymbol{\Delta}\mathbf{F} & \mathbf{0} \\ \mathbf{0} & \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) & \mathbf{0} & \mathbf{F}^t(\mathbf{I}_n-\boldsymbol{\Delta})\mathbf{F} \end{pmatrix}$$

and an important issue lies in choosing the design in order to minimize $\log\det V(\hat{\boldsymbol{\gamma}})$*. Furthermore, in addition to* ***C1****-****C2****, other relevant criteria are now* $\det V(\hat{\boldsymbol{\beta}}_A, \hat{\boldsymbol{\beta}}_B)$*,* $\det V(\hat{\boldsymbol{\beta}}_A - \hat{\boldsymbol{\beta}}_B)$*,* $trV(\hat{\boldsymbol{\beta}}_A, \hat{\boldsymbol{\beta}}_B)$ *and* $trV(\hat{\boldsymbol{\beta}}_A - \hat{\boldsymbol{\beta}}_B)$*. These criteria are convex functions of* $\mathbf{M}$*, invariant with respect to permutations of the bottom two block rows and the two right-hand block columns of* $\mathbf{M}$*. Thus, if conditions* ***B1*** *and* ***B2*** *hold the ensuing information matrix*

$$\mathbf{M}^{**} = \frac{1}{2n} \begin{pmatrix} n & 0 & \mathbf{1}^t\mathbf{F} & \mathbf{0} \\ 0 & n & \mathbf{0} & \mathbf{1}^t\mathbf{F} \\ \mathbf{F}^t\mathbf{1} & \mathbf{0} & 2\mathbf{F}^t\mathbf{F} & \mathbf{0} \\ \mathbf{0} & \mathbf{F}^t\mathbf{1} & \mathbf{0} & 2\mathbf{F}^t\mathbf{F} \end{pmatrix}$$

is invariant wrt permutations of the bottom two block rows and the two right-hand block columns, as well as the first two rows and columns. Therefore $\mathbf{M}^{**}$ *is optimal wrt the aforementioned criteria by the same argument as above.*

3.1. *What kind of "balance" is desirable?.* To clarify the different types of balance that can arise in the presence of covariates and their properties it may be useful to explain the meaning of the definition of balanced allocation made by **B1**+**B2**. Letting $\mathbb{F}_n = (\mathbf{1}\,;\mathbf{F})$, conditions **B1**+**B2** can be simply rewritten as follows

$$(2\boldsymbol{\delta} - \mathbf{1})^t\mathbb{F}_n = \mathbf{0}_n^t, \tag{3.2}$$

where $\mathbf{b}_n^t = (2\boldsymbol{\delta}-\mathbf{1})^t\mathbb{F}_n$ is usually called the *imbalance vector*. Condition **B1** guarantees simply that $D_n = (2\boldsymbol{\delta}-\mathbf{1})^t\mathbf{1} = 0$, namely the two treatments are *globally* equireplicated in the trial. As regards **B2**, consider two covariates $\boldsymbol{Z} = (T, W)$ and let either

- $\boldsymbol{f}(\boldsymbol{z}) = (t, w)^t$, without interactions among covariates,

or

- $\boldsymbol{f}(\boldsymbol{z}) = (t, w, tw)^t$, which includes the interaction effect.

When both covariates are quantitative the notation is unambiguous and condition **B2** means the equality of the sums of the covariates in the groups assigned to A and B, respectively. Together with **B1**, it ensures that for each covariate the averages in the two treatment groups are the same. With interactions, condition **B2** also implies that the sums of the cross products in the two groups are equal, so that **B1**+**B2** imply equal covariances.

In the case of categorical covariates the notation and the interpretation are quite different. For instance, suppose that the covariate T is categorized into $t_0, t_1, \ldots, t_J$ levels, so that it can be represented by a J-dim vector $\mathbb{T}$ of dummy variables; analogously, let $w_0, w_1, \ldots, w_L$ the levels of W, which can be represented by a L-dim vector $\mathbb{W}$ of dummies (where t_0 and w_0 are the reference categories). In this setting tw corresponds to the vector $\mathbb{T} \otimes \mathbb{W}$ (similarly if one of the covariates is quantitative and the other one categorical). After n assignments, let $D_n(t_j)$ denote the imbalance between the two arms within the level t_j of T ($j = 0, \ldots, J$) and, analogously, $D_n(w_l)$ represent the imbalance at the category w_l of W ($l = 0, \ldots, L$). Moreover, $D_n(t_j, w_l)$ is the imbalance within the row-column intersection (*stratum*) identified by the pair of categories (t_j, w_l) (for $j = 0, \ldots, J$ and $l = 0, \ldots, L$). In the absence of interactions among covariates, condition (3.2) becomes

$$\mathbf{b}_n^t = (D_n, D_n(t_1), \ldots, D_n(t_J), D_n(w_1), \ldots, D_n(w_L)) = \mathbf{0}_n^t \,,$$

stating that A and B are equally replicated at every level of each blocking factor, i.e. the so-called *marginal balance* of the covariates. On the other hand, if the considered model contains all the interactions, $\mathbf{b}_n$ includes also all the imbalance terms $D_n(t_j, w_l)$ associated with each stratum (excepting those related to the reference categories t_0 and w_0), i.e.

$$\mathbf{b}_n^t = (D_n, D_n(t_1), \ldots, D_n(t_J), D_n(w_1), \ldots, D_n(w_L), D_n(t_1, w_1), \ldots, D_n(t_J, w_L)) \,.$$

Thus, condition (3.2) means that A and B are equally replicated also within every stratum, the so-called *joint balance* or *balance within strata*, which clearly implies marginal balance. When the model is not full, then $\mathbf{b}_n$ contains all the imbalance terms corresponding to the included interactions.

3.2. *Allocation rules and loss of precision.* Under model (2.1), the inferential interest typically lies in estimating the difference $\mu_A - \mu_B$ between the treatment effects as precisely as possible. Thus it is customary to adopt **C1** and, assuming $\mathbb{F}_n^t \mathbb{F}_n$ non-singular, this criterion can be rewritten as follows

$$\mathrm{tr}V\left(\hat{\mu}_A; \hat{\mu}_B\right) = \frac{\sigma^2}{n}\left(1 - \frac{L_n}{n}\right)^{-1} \,, \tag{3.3}$$

where

$$L_n = \mathbf{b}_n^t \left(\mathbb{F}_n^t \mathbb{F}_n\right)^{-1} \mathbf{b}_n = \mathbf{b}_n^t \begin{pmatrix} n & \mathbf{1}^t\mathbf{F} \\ \mathbf{F}^t\mathbf{1} & \mathbf{F}^t\mathbf{F} \end{pmatrix}^{-1} \mathbf{b}_n \tag{3.4}$$

is the loss associated with an experiment involving n patients.

By assuming the D_A-optimality criterion, Atkinson (1982) introduced his biased coin design which is aimed, under model (2.1), at minimizing (3.3) sequentially. As showed by Smith (1984b) such procedure, denoted by D_A-BCD, assigns the $(n+1)$-st patient to treatment A with probability

$$\frac{[1-(1;\boldsymbol{f}(\boldsymbol{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n]^2}{[1-(1;\boldsymbol{f}(\boldsymbol{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n]^2+[1+(1;\boldsymbol{f}(\boldsymbol{z}_{n+1})^t)(\mathbb{F}_n^t\mathbb{F}_n)^{-1}\mathbf{b}_n]^2}. \tag{3.5}$$

On the other hand, Smith (1984a) by assuming the covariate distribution a-priori known and, by approximating $\mathbb{F}_n^t\mathbb{F}_n \simeq n\mathbb{Q}$ with $\mathbb{Q} = \lim_{n\to\infty} n^{-1}\mathbb{F}_n^t\mathbb{F}_n$ non-singular, analysed a modified version of the D_A-BCD which assigns A with probability

$$\psi(n^{-1}\boldsymbol{f}(\boldsymbol{z}_{n+1})^t\mathbb{Q}^{-1}\mathbf{b}_n)\,, \tag{3.6}$$

where $\psi(\cdot):[-1,1]\to[0,1]$ is a non-increasing function, twice continuously differentiable, with $\psi(-x)=1-\psi(x)$.

Observe that, analogously to criterion **C1** in (3.3), L_n represents a fundamental measure of loss of precision even if the inferential goal consists in the joint estimation of the treatment effects, as the following proposition shows.

PROPOSITION 3.2. *Assuming model (2.1), the D-optimality criterion **C2** can be rewritten as*

$$\det V\left(\hat{\mu}_A;\hat{\mu}_B\right) = \frac{4\sigma^4}{n\left[n-\mathbf{1}^t\mathbf{F}(\mathbf{F}^t\mathbf{F})^{-1}\mathbf{F}^t\mathbf{1}\right]}\left(1-\frac{L_n}{n}\right)^{-1}.$$

PROOF. See Appendix A. □

Thus, adopting either criteria **C1** or **C2**, the inferential precision depends on the design only through the loss L_n in (3.4), which depends on the allocations and the covariates and it is identically zero if condition (3.2) holds.

As mentioned previously, several designs have been suggested in the literature aimed to achieve marginal balance between the treatments. In the case of two prognostic factors, a *marginal procedure* can be described as follows: when the $(n+1)$-th patient with profile (t_j, w_l) arrives, a weighted sum $\widetilde{D}_n = \omega_1 D_n(t_j) + \omega_2 D_n(w_l)$ is computed and treatment A is assigned with

probability $p \geq 1/2$ if $\widetilde{D}_n < 0$, $1/2$ if $\widetilde{D}_n = 0$ and $(1-p)$ if $\widetilde{D}_n > 0$ (for several covariates, $\widetilde{D}_n$ is a weighted sum of all marginal imbalances corresponding to the patient's profile). The choice $p = 1$ corresponds to Taves's (1974) minimization method, while Pocock and Simon (1975) analyzed $p = 3/4$. However, in the presence of interactions among covariates, marginal balance can have a critical impact in terms of loss, as the following example shows.

EXAMPLE 3.3. *Assume model (2.1) with $\boldsymbol{Z} = (T, W)$, where T and W are binary covariates potentially interacting. If the adopted design is only marginally balanced (but not jointly), then $\boldsymbol{b}_n^t = (0, 0, 0, D_n(t_1, w_1))$ and straightforward calculations show that the loss in (3.4) becomes*

$$L_n = D_n^2(t_1, w_1)\left(\frac{1}{N_n(t_0, w_0)} + \frac{1}{N_n(t_1, w_0)} + \frac{1}{N_n(t_0, w_1)} + \frac{1}{N_n(t_1, w_1)}\right),$$

where $N_n(t_j, w_l)$ denotes the number of subjects within this stratum after n assignments ($j, l = 0, 1$). Since the design is marginally balanced, then $|D_n(t_j, w_l)|$ is constant for $j, l = 0, 1$. Moreover, letting $k_n = \min_{jl} N_n(t_j, w_l)$ note that $1 \leq |D_n(t_j, w_l)| \leq k_n$ and thus

$$L_n \leq k_n^2\left(2^2/k_n\right) = 4k_n.$$

As a numerical example, set for instance $n = 100$ with $D_{100}(t_1, w_1) = 10$. When $N_{100}(t_0, w_0) = 30$, $N_{100}(t_1, w_0) = 20$ and $N_{100}(t_0, w_1) = 40$ we have $L_{100}/100 \simeq 0,208$, while if $N_{100}(t_0, w_0) = N_{100}(t_0, w_1) = N_{100}(t_1, w_0) = 10$ then $L_{100}/100 \simeq 0,314$. It is worth noticing that there are several marginally unbalanced designs that perform better when compared to marginally balanced ones. For instance, setting as previously $n = 100$ and $D_{100}(t_1, w_1) = 10$, an allocation s.t. $D_{100}(t_0, w_0) = D_{100}(t_0, w_1) = 4$ and $D_{100}(t_1, w_0) = 6$, with $N_{100}(t_0, w_0) = N_{100}(t_0, w_1) = N_{100}(t_1, w_0) = 10$, gives $L_{100}/100 \simeq 0,082$.

Thus, in the absence of balance within-strata, the loss of precision may have a significant impact even if the design is marginally balanced; furthermore, this loss can be amplified by the random nature of the covariates.

4. The C-ABCD. Since marginal balance does not always promote efficiency, ensuring balance within every stratum could be a crucial issue. In this Section we describe the natural modification of the ABCD in the presence of covariates and from now on we name this procedure *Covariate-Adaptive Biased Coin Design* (C-ABCD).

Let again $\boldsymbol{Z} = (T, W)$ be the covariates of interest, with levels (or codes) t_j ($j = 0, \ldots, J$) and w_l ($l = 0, \ldots, L$) respectively, and assume that $\{\boldsymbol{Z}_i,\ i =$

$1, 2, \ldots\}$ is a sequence of i.i.d. random vectors, where each $\boldsymbol{Z}_i$ is distributed in the population of interest according to a given (joint) pdf

$$\Pr(\boldsymbol{Z}_i = (t_j, w_l)) = p_{jl}, \qquad \text{for } j = 0, \ldots, J \text{ and } l = 0, \ldots, L,$$

where $p_{jl} > 0$ and $\sum_{j=0}^{J} \sum_{l=0}^{L} p_{jl} = 1$. For any given stratum identified by the pair (j, l) $(j = 0, \ldots, J; l = 0 \ldots, L)$, let $F_{jl}(\cdot) : \mathbb{Z} \to [0, 1]$ be a non-increasing and symmetric function with $F_{jl}(-x) = 1 - F_{jl}(x)\ \forall x \in \mathbb{Z}$, where $F_{jl}(\cdot)$'s are called generating functions and govern the request of balance within each covariate profile.

Let $\Im_n = \sigma(\boldsymbol{Z}_1, \ldots, \boldsymbol{Z}_n; \delta_1, \ldots, \delta_n)$ be the sigma-field generated by the sequence of assignments and patients' covariates; when the $(n+1)$-th subject is ready to be randomized and its covariate profile $\boldsymbol{Z}_{n+1} = (t_j, w_l)$ is recorded, it will be assigned to treatment A with probability

$$\Pr\left(\delta_{n+1} = 1 | \Im_n, \boldsymbol{Z}_{n+1} = (t_j, w_l)\right) = F_{jl}(D_n(t_j, w_l)) \quad \text{for any } (j, l). \tag{4.1}$$

Clearly, different choices of the generating functions for each covariate pattern meet the need for more or less balance at different population strata, as it will be further explained in the following sections.

4.1. *Probabilistic structure.* Within each stratum (j, l), for any choice of the generating function $F_{jl}(\cdot)$ the sequence $\{D_n(t_j, w_l)\}_{n \in \mathbb{N}}$ is a time-homogeneous Markov chain on the integers $\mathbb{Z}$ with $D_0(t_j, w_l) = 0$ and transition probabilities

$$\Pr\left(D_{n+1}(t_j, w_l) = k \mid D_n(t_j, w_l) = x\right) = \begin{cases} p_{jl} F_{jl}(x) & k = x + 1 \\ 1 - p_{jl} & k = x \\ p_{jl} F_{jl}(-x) & k = x - 1 \end{cases}.$$

Unless the degenerate case $F_{jl}(x) = 1/2$ for any x (namely the complete randomization), the chain is ergodic, time-reversible and aperiodic with stationary distribution $\boldsymbol{\xi}_{jl}$ given by the equilibrium equations

$$\begin{aligned} &\xi_{jl}(x) = \xi_{jl}(x-1)\lambda_{jl}(x) \qquad \forall x \in \mathbb{Z} \\ &\xi_{jl}(0) = \left[1 + \sum_{s=1}^{\infty} \prod_{x=1}^{s} \lambda_{jl}(x) + \sum_{s=1}^{\infty} \prod_{x=1}^{s} (\lambda_{jl}(1-x))^{-1}\right]^{-1}, \end{aligned} \tag{4.2}$$

where for any integer x

$$\lambda_{jl}(x) = \frac{p_{jl} F_{jl}(x-1)}{p_{jl} F_{jl}(-x)} = \frac{F_{jl}(x-1)}{F_{jl}(-x)}. \tag{4.3}$$

Since

$$\lambda_{jl}(x) = (\lambda_{jl}(1-x))^{-1} \quad \forall \quad x \geq 1, \tag{4.4}$$

the stationary distribution $\boldsymbol{\xi}_{jl}$ in (4.2) is symmetric with $\xi_{jl}(x) = \xi_{jl}(-x)$ for any $x \in \mathbb{Z}$, and also unimodal, due to the fact that the sequence $\{\lambda_{jl}(x)\}_{x\in\mathbb{Z}}$ is non-increasing. Thus, 0 represents both the expectation and the mode of $\boldsymbol{\xi}_{jl}$, where from (4.4)

$$\xi_{jl}(0) = \left[1 + 2\sum_{s=1}^{\infty}\prod_{x=1}^{s}\lambda_{jl}(x)\right]^{-1}. \tag{4.5}$$

Observe that $\{D_n(t_0, w_0), \ldots, D_n(t_j, w_l)\}_{n\in\mathbb{N}}$ is a multidimensional process in $\mathbb{Z}^{J\times L}$ where each component is an ergodic random walk and at each step only one of them is activated on the basis of the random entry of a given patient with a specific covariate profile.

REMARK 4.1. *From (4.3), within each stratum (j, l) the stationary law $\boldsymbol{\xi}_{jl}$ does not depend on the probability distribution of the covariates. Thus, the asymptotic behavior of the stratum imbalance, as well as its asymptotic variability, depends only on the chosen generating function $F_{jl}(\cdot)$. Nevertheless, the covariate distribution plays a central role in terms of convergence towards stationarity, since the more a given stratum is over-represented, the more the corresponding chain evolves rapidly.*

After n assignments, for any given level t_j of the covariate T the marginal imbalance is given by $D_n(t_j) = \sum_{l=0}^{L} D_n(t_j, w_l)$. Therefore, $\{D_n(t_j)\}_{n\in\mathbb{N}}$ is a time-homogeneous Markov chain on the integers $\mathbb{Z}$ with $D_0(t_j) = 0$ and

$$\Pr\left(D_{n+1}(t_j) = k \mid D_n(t_j) = x\right) = \begin{cases} \sum_{l=0}^{L} p_{jl}F_{jl}(x) & k = x+1 \\ 1 - \sum_{l=0}^{L} p_{jl} & k = x \\ \sum_{l=0}^{L} p_{jl}F_{jl}(-x) & k = x-1 \end{cases},$$

which is also ergodic, aperiodic and time-reversible, with stationary distribution $\boldsymbol{\xi}_j$ that can be easily derived from the equilibrium equations. Analogously, the marginal imbalance for any level w_l of W is $D_n(w_l) = \sum_{j=0}^{J} D_n(t_j, w_l)$ and its probabilistic structure can be derived as previously.

Also, let $D_n = \sum_{j=0}^{J}\sum_{l=0}^{L} D_n(t_j, w_l)$ be the global imbalance between the two treatments after n steps, then $\{D_n\}_{n\in\mathbb{N}}$ is time-homogeneous Markov chain on $\mathbb{Z}$ with $D_0 = 0$ and transition probabilities

$$\Pr\left(D_{n+1} = k \mid D_n = x\right) = \begin{cases} \sum_{j=0}^{J}\sum_{l=0}^{L} p_{jl}F_{jl}(x) & k = x+1 \\ \sum_{j=0}^{J}\sum_{l=0}^{L} p_{jl}F_{jl}(-x) & k = x-1 \end{cases}.$$

This chain is ergodic and time-reversible so that the stationary distribution $\boldsymbol{\xi}$ exists and can be easily derived as previously. However, since the chain is periodic, with period 2, it does not converge in law to $\boldsymbol{\xi}$.

Contrary to the asymptotic behavior of the stratum imbalance, where $\boldsymbol{\xi}_{jl}$ depends only on the chosen generating function $F_{jl}(\cdot)$, the stationary distributions $\boldsymbol{\xi}_j$ and $\boldsymbol{\xi}$ of the marginal imbalance $\{D_n(t_j)\}_{n\in\mathbb{N}}$ and the global one $\{D_n\}_{n\in\mathbb{N}}$ depend also on the probability distribution of the covariates.

REMARK 4.2. *Choosing the same generating function for every stratum by letting $F_{jl}(\cdot) = F(\cdot)$ for any $j = 0\ldots, J$ and $l = 0, \ldots, L$, (4.1) becomes*

$$\Pr\left(\delta_{n+1} = 1 | \Im_n, \boldsymbol{Z}_{n+1} = (t_j, w_l)\right) = F(D_n(t_j, w_l)) \quad \forall (j, l),$$

so that the C-ABCD does not coincide with the ABCD (Baldi Antognini and Giovagnoli, 2004). Under this choice the asymptotic behavior of the strata imbalance will be the same for every stratum, coinciding also with that of the marginal and global imbalance. Indeed, for any $j = 0\ldots, J;\ l = 0, \ldots, L$ $\{D_n(t_j, w_l)\}_{n\in\mathbb{N}}$, $\{D_n(t_j)\}_{n\in\mathbb{N}}$, $\{D_n(w_l)\}_{n\in\mathbb{N}}$ and $\{D_n\}_{n\in\mathbb{N}}$ are chains having the same stationary distribution $\boldsymbol{\xi}$ given by

$$\xi(0) = \left[1 + 2\sum_{s=1}^{\infty}\prod_{x=1}^{s}\lambda(x)\right] \qquad \text{and} \qquad \xi(x) = \xi(x-1)\lambda(x) \quad \forall x \in \mathbb{Z},$$

where $\lambda(x) = F(x-1)/F(-x)$ for any integer x.

4.2. *Balance.* Starting from the probabilistic structure of ergodic random walks it is possible to prove that the optimal balancing properties of the ABCD still hold even in the presence of covariates, showing that the C-ABCD is asymptotically balanced within each stratum, within each level of the covariates and also globally.

THEOREM 4.3. *For any choice of the generating functions, as n tends to infinity the C-ABCD is jointly balanced*

$$\frac{D_n(t_j, w_l)}{N_n(t_j, w_l)} \to 0 \quad a.s. \quad \forall j = 0, \ldots, J;\ l = 0, \ldots, L.$$

Furthermore, for each covariate the C-ABCD is asymptotically balanced within each level

$$\frac{D_n(t_j)}{N_n(t_j)} \to 0 \quad a.s. \quad \forall j = 0, \ldots, J \quad \text{and} \quad \frac{D_n(w_l)}{N_n(w_l)} \to 0 \quad a.s. \quad \forall l = 0, \ldots, L$$

and also globally

$$\frac{D_n}{n} \to 0 \quad a.s.$$

PROOF. See Appendix B. □

In the absence of covariates, as showed by Baldi Antognini and Giovagnoli (2004) and recently recalled by Hu et al. (2009) and Markaryan and Rosenberger (2010) for the special case of Efron's coin, the ABCD is high order efficient since it converges to balance faster than other coin designs. This can also be extended to the present setting, as the following corollary shows:

COROLLARY 4.4. *Within each stratum (j,l), for any choice of the generating function $F_{jl}(\cdot)$ of the C-ABCD*

$$\lim_{n\to\infty} n^{-1/2} D_n(t_j, w_l) = 0 \quad \textit{in prob.} \qquad \forall j = 0,\dots,J; l = 0,\dots,L. \tag{4.6}$$

Thus the same order convergence to balance still hold marginally, i.e.

$$\lim_{n\to\infty} n^{-1/2} D_n(t_j) = 0 \quad \textit{in prob.} \qquad \forall j = 0,\dots,J$$

and also globally:

$$\lim_{n\to\infty} n^{-1/2} D_n = 0 \qquad \textit{in prob.}$$

PROOF. It is sufficient to prove (4.6) since the other statements can be easily derived from it. Observe that for any $j = 0,\dots,J$ and $l = 0,\dots,L$

$$\frac{D_n(t_j, w_l)}{\sqrt{n}} = \frac{D_n(t_j, w_l)}{N_n(t_j, w_l)} \cdot \frac{N_n(t_j, w_l)}{\sqrt{n}},$$

where from Theorem 4.3

$$\lim_{n\to\infty} \frac{D_n(t_j, w_l)}{N_n(t_j, w_l)} = 0 \qquad a.s.$$

Thus, statement (4.6) follows directly from the asymptotic normality of $N_n(t_j, w_l)/\sqrt{n}$ due to the CLT for iid r.v.'s. □

From Corollary 4.4 it is obvious that, adopting the C-ABCD

$$\frac{D_n(t_j, w_l)}{\sqrt{N_n(t_j, w_l)}} \to 0 \quad \text{in prob.} \quad \forall j = 0,\dots,J; l = 0,\dots,L,$$

since

$$\frac{D_n(t_j, w_l)}{\sqrt{N_n(t_j, w_l)}} = \frac{D_n(t_j, w_l)}{\sqrt{n}} \cdot \frac{\sqrt{n}}{\sqrt{N_n(t_j, w_l)}}$$

and

$$\lim_{n\to\infty}\left(\frac{N_n(t_j,w_l)}{n}\right)^{-\frac{1}{2}}=(p_{jl})^{-\frac{1}{2}}\quad\text{a.s.}\qquad\forall j=0,\dots,J;l=0,\dots,L.$$

Analogously, for any $j=0,\dots,J$ and $l=0,\dots,L$

$$\frac{D_n(t_j)}{\sqrt{N_n(t_j)}}\to 0\qquad\text{and}\qquad\frac{D_n(w_l)}{\sqrt{N_n(w_l)}}\to 0\quad\text{in prob.}$$

Clearly, from (4.1) it is possible to extend in a natural way other restricted randomization procedures into a stratified randomization, such as the Adaptive Biased Coin Design proposed by Wei (1978a) in (1.2) by letting

$$P\left(\delta_{n+1}=1|\Im_n,\boldsymbol{Z}_{n+1}=(t_j,w_l)\right)=f_{jl}\left(\frac{D_n(t_j,w_l)}{N_n(t_j,w_l)}\right)\quad\forall\,(j,l),\tag{4.7}$$

where $f_{jl}(\cdot):[-1,1]\to[0,1]$ is non-increasing, twice continuously differentiable function, with $f_{jl}(-x)=1-f_{jl}(x)$. However, the fact that the imbalance terms may satisfy a CLT property (see for instance Smith (1984b) and the following Section 5) ensures that these procedures represent an order of convergence towards balance which is worst wrt the C-ABCD.

A stronger result about the optimal balancing properties of the C-ABCD is provided by the next Theorem.

THEOREM 4.5. *Adopting the C-ABCD, within each stratum (j,l) and for any choice of the generating function $F_{jl}(\cdot)$*

$$D_n(t_j,w_l)=o(n^\nu)\quad\textit{in } L_1\qquad\textit{for any } \nu>0.$$

PROOF. See Appendix C. □

A straightforward consequence of Theorem 4.5 is that, for any $\nu>0$

(i) $D_n(t_j)=o(n^\nu)$ in L_1 $\forall\ j=0,\dots,J$
(ii) $D_n(w_l)=o(n^\nu)$ in L_1 $\forall\ l=0,\dots,L$
(iii) $D_n=o(n^\nu)$ in L_1.

5. Properties of the C-ABCD.

5.1. *Loss function.* As is well-known, a good design should achieve high levels of balance, both globally and among the prognostic factors, in order to optimize the inferential precision, guaranteeing at the same time a suitable degree of randomness in the allocations. Within this framework the loss L_n in (3.4) is commonly considered the fundamental tool for comparing different design strategies and, since it is a random variable, several authors have investigated its behaviour mainly through simulation studies (see e.g. Begg and Iglewicz, 1980; Atkinson 1982, 1999, 2002; Heritier *et al.* 2005). In particular, Atkinson shows that under the D_A-BCD the expected loss converges to $(q+1)/5$, to $(q+1)$ for the complete randomization and to 0 for the Efron's BCD. However, there are only few theoretical results about the distribution of the loss, mainly due to Smith (1984a, 1984b), who shows that adopting (3.6) the imbalance vector $\mathbf{b}_n$ is asymptotically normal, so that the expected loss converges to $(q+1)/(1-4\psi'(0))$. Thus, excluding Efron's coin, the asymptotic precision decreases as the number of prognostic factors, as well as the levels of the covariates and interaction effects, grows.

THEOREM 5.1. *Under model (2.1) with categorical covariates, adopting the Covariate-Adaptive Biased Coin Design*

$$\lim_{n\to\infty} L_n = 0 \quad \textit{in prob.}$$

PROOF. Observe that from (3.4), the loss L_n can be rewritten as follows:

$$L_n = n^{-1/2}\mathbf{b}_n^t \left(n^{-1}\mathbb{F}_n^t\mathbb{F}_n\right)^{-1} n^{-1/2}\mathbf{b}_n\,.$$

Since the categorical covariates are i.i.d. with $p_{jl} > 0$ for any $j = 0,\dots,J$ and $l = 0,\dots,L$, then there exists a symmetric and nonsingular matrix $\mathbb{Q} = \lim_{n\to\infty} n^{-1}\mathbb{F}_n^t\mathbb{F}_n$. Thus, the result follows from the continuous mapping theorem and Corollary 4.4, since adopting the C-ABCD $n^{-1/2}\mathbf{b}_n \to \mathbf{0}$ in probability. □

Observe that Theorem 5.1 does not depend on the presence or absence of interactions among covariates. However, in the former case it is possible to derive a simple expression for the loss, showing also that the D_A-BCD proposed by Atkinson and Smith's class are stratified randomization rules. Indeed, let $\boldsymbol{Z} = (T, W)$ categorical and assume model (2.1) containing all the interaction effects, the loss in (3.4) becomes (see Appendix D):

$$L_n = \sum_{j=0}^{J}\sum_{l=0}^{L} \frac{D_n^2(t_j, w_l)}{N_n(t_j, w_l)}\,. \tag{5.1}$$

Furthermore, Atkinson's D_A-BCD in (3.5) is a special case of (4.7) with

$$f_{jl}(x) = \frac{(1-x)^2}{(1-x)^2 + (1+x)^2} \qquad \forall j = 0, \dots J; l = 0, \dots, L,$$

(see Appendix E) and Smith's procedure (3.6) is also a restricted randomization, similar to (4.7), where $f_{jl}(\cdot) = \psi(\cdot)\ \forall\,(j,l)$ and each $N_n(t_j, w_l)$ is approximated by np_{jl}.

5.2. *Predictability.* Selection bias of sequential designs refers to a particular type of bias that can be introduced by the experimenter in the composition of the treatment groups due to the possibility to predict the sequence of assignments on the basis of the available information. For a biased coin design, in the absence of covariates the allocations at each step depend on the actual degree of imbalance between the treatment groups, which summarizes the useful information for guessing the next assignment. In this setting, Blackwell and Hodges (1957) suggest to measure the selection bias (i.e. predictability or lack of randomness) by the expected percentage of correct guesses when the best strategy is used, namely to pick the underrepresented treatment without preference in case of a tie. Let $G_i = 1$ if the i-th assignment is guessed correctly, and 0 otherwise, then $\bar{G}_n = n^{-1} \sum_{i=1}^{n} G_i$ represents the proportion of correct guesses after n steps, so that the selection bias indicator is

$$SB_n = E[\bar{G}_n] = \frac{1}{n} \sum_{i=1}^{n} \Pr(G_i = 1). \tag{5.2}$$

Adapting this approach in the presence of covariates, by (4.1) the allocation of the next subject depends on its covariate profile, which identifies the stratum of interest, and the actual degree of imbalance within this stratum. Thus, when the i-th patient is ready to be randomized, the probability of correctly guessing his/her treatment allocation given the optimal strategy is

$$\Pr(G_i = 1 \mid \boldsymbol{Z}_i = (t_j, w_l), \Im_{i-1}) = F_{jl}(-|D_{i-1}(t_j, w_l)|).$$

Then

$$\Pr(G_i = 1) = \sum_{j=0}^{J} \sum_{l=0}^{L} \sum_{x=0}^{i-1} F_{jl}(-x) \Pr(|D_{i-1}(t_j, w_l)| = x) p_{jl}\,,$$

since for any stratum (j,l)

$$\Pr(|D_{i-1}(t_j, w_l)| \leq i-1) = 1 \qquad \forall i \geq 1\,,$$

so that

$$SB_n = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=0}^{J}\sum_{l=0}^{L}\sum_{x=0}^{i-1} F_{jl}(-x)\Pr(|D_{i-1}(t_j,w_l)| = x)p_{jl}\ .$$

THEOREM 5.2. *Adopting the C-ABCD,*

$$\bar{G}_n = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=0}^{J}\sum_{l=0}^{L} F_{jl}(-|D_{i-1}(t_j,w_l)|)p_{jl} + o(n) \quad a.s.$$

and thus

$$\lim_{n\to\infty}\bar{G}_n = \frac{1}{2}\left(\sum_{j=0}^{J}\sum_{l=0}^{L}\xi_{jl}(0)p_{jl} + 1\right) \quad a.s.$$

PROOF. See Appendix F. □

A straightforward consequence of Theorem (5.2) is that

$$\lim_{n\to\infty} SB_n = \frac{1}{2}\left(\sum_{j=0}^{J}\sum_{l=0}^{L}\xi_{jl}(0)p_{jl} + 1\right)\ ,$$

namely the asymptotic excess of selection bias is simply given by

$$\frac{1}{2}\sum_{j=0}^{J}\sum_{l=0}^{L}\xi_{jl}(0)p_{jl}\ ,$$

which depends only on an overall measure (over the strata) of the asymptotic balance induced by the design.

6. Choice of the generating functions. The flexibility of the C-ABCD lies in the fact that allows the experimenter to choose the generating function $F_{jl}(\cdot)$ in every stratum on the basis of the different need for balance within each combination of the levels of the prognostic factors. As showed in Remark 4.2, if we assume the same randomization function for each stratum by letting $F_{jl}(\cdot) = F(\cdot)$ for any $j = 0\ldots, J$, $l = 0,\ldots, L$, then the closeness to balance will be forced in the same way for each covariate pattern. In this setting, a suitable class of generating functions is given by

$$F^a(x) = \begin{cases} 1/2, & \text{if } 0 \le x \le 1, \\ (x^a+1)^{-1}, & \text{if } x > 1, \end{cases} \tag{6.1}$$

where the parameter $a > 0$ governs the degree of randomness: if a tends to 0 at each step the assignment tends to be completely randomized, whereas as a grows the allocation becomes more deterministic. This class of functions ensures a good trade-off between balance and predictability even for small samples, since the allocations are completely randomized when the treatment imbalance is 0 or 1 (i.e. in the case of perfect balance under an even or an odd number of steps) and the balance is forced in all the other situations (see Baldi Antognini and Giovagnoli, 2004).

Otherwise, different generating functions $F_{jl}(\cdot)$ can be chosen according to the major/minor importance of some patterns, e.g. the diffusion of the disease taken into consideration in certain high risk groups/patterns.

However, the evolution of the imbalance within each stratum (and thus its convergence properties) depends on the number of subjects belonging to this pattern and therefore it is strictly related to the distribution of the covariates in the population of interest. Furthermore, as mentioned previously, the loss is a r.v. depending on the random nature of both the covariates and the design and to stress the impact on L_n due to the allocations, instead of (5.1) it may be useful to take into account the following expression

$$\widetilde{L}_n = \sum_{j=0}^{J} \sum_{l=0}^{L} \frac{D_n^2(t_j, w_l)}{np_{jl}},$$

obtained by approximating $N_n(t_j, w_l) \simeq np_{jl}$ (this corresponds to consider $E_{\mathbf{Z}}(\mathbf{M})$ instead of $\mathbf{M}$ in (2.3) or, equivalently, $n\mathbb{Q}$ instead of $\mathbb{F}_n^t \mathbb{F}_n$ in (3.4)). Thus, strongly departures from balance may not have a great impact on the loss if observed at populous covariate profiles, while they could induce a significant loss of precision if observed at under-represented strata. Indeed

$$E\left(\widetilde{L}_n\right) = \sum_{j=0}^{J} \sum_{l=0}^{L} \frac{V(D_n(t_j, w_l))}{np_{jl}},$$

since at each step n the distribution of $D_n(t_j, w_l)$ is symmetric around 0 (for any $j = 0 \ldots, J$ and $l = 0, \ldots, L$). Thus, when the covariate distribution is known a-priori the generating functions $F_{jl}(\cdot)$ can be chosen in order to force the convergence towards balance on the basis of the different representativeness of the population patterns. For instance, we can adopt

$$F_{jl}^{g}(x) = \begin{cases} 1/2, & \text{if } 0 \leq x \leq 1 \\ (x^{g(p_{jl})} + 1)^{-1}, & \text{if } x > 1 \end{cases}, \qquad \forall\, (j, l) \tag{6.2}$$

where $g(\cdot)$ is a decreasing function with $\lim_{x \to 0^+} g(t) = \infty$.

7. Finite sample properties. In this Section we compare the performances of the C-ABCD, Atkinson's D_A-BCD and Pocock and Simon's minimization method (with constant weights), in terms of loss and selection bias in the case of binary covariates. We take into account several situations: model (2.1) with two and four factors and in the presence or absence of interactions; moreover, in the case of two covariates two different scenarios are investigated: a uniform distribution, where each stratum is equally represented in the population, and a non-uniform one. Concerning our allocation rule, in what follows we consider:

- the C-ABCD(F^g_{jl}) with different randomization functions $F^g_{jl}(\cdot)$ defined in (6.2), where we set $g(p_{jl}) = p_{jl}^{-1} - 1$;
- the C-ABCD(F^a), i.e. assuming the same generating function $F^a(\cdot)$ in (6.1) for each stratum, where $a = t^{-1} - 1$ and t is the reciprocal of the number of strata (clearly, if the covariate distribution is uniform C-ABCD(F^a) coincides with C-ABCD(F^g_{jl})).

The results come from 1000 simulations with sample sizes $n = 150$, 500 and 1000. In the case of two prognostic factors, Tables 1-4 show the behaviour of the loss L_n in (3.4) and the selection bias indicator SB_n in (5.2) for model (2.1) in the full version (Tables 1 and 2) and in the absence of interactions (Tables 3 and 4), under two different covariate distributions. Moreover, Tables 5-6 are related to the case of four binary covariates with uniform distribution (i.e. every stratum is equally represented in the population with probability 2^{-4}), under (2.1) in the full version (Table 5) and without interactions (Table 6).

TABLE 1

Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, under model (2.1) in the full version with $p_{00} = 0.2$, $p_{01} = 0.4$, $p_{10} = 0.3$, $p_{11} = 0.1$.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	1.09	0.70	1.02	0.71	0.99	0.71
	(1.7392)	(0.0011)	(1.8610)	(0.0003)	(1.8694)	(0.0002)
Atkinson's D_A-BCD	0.82	0.55	0.81	0.53	0.81	0.52
	(0.3458)	(0.0010)	(0.3308)	(0.0003)	(0.3003)	(0.0001)
C-ABCD(F^g_{jl})	0.24	0.61	0.07	0.61	0.04	0.61
	(0.0213)	(0.0013)	(0.0018)	(0.0004)	(0.0005)	(0.0002)
C-ABCD(F^a)	0.26	0.61	0.08	0.61	0.04	0.61
	(0.0296)	(0.0014)	(0.0026)	(0.0004)	(0.0006)	(0.0002)

TABLE 2
Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, under model (2.1) in the full version with $p_{00} = p_{01} = p_{10} = p_{11} = 0.25$.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	1.10	0.70	1.09	0.71	1.03	0.71
	(1.7304)	(0.0010)	(2.1684)	(0.0003)	(1.8483)	(0.0002)
Atkinson's D_A-BCD	0.81	0.54	0.80	0.53	0.81	0.52
	(0.3242)	(0.0009)	(0.3314)	(0.0003)	(0.3380)	(0.0001)
C-ABCD($F_{jl}^g = F^a$)	0.20	0.61	0.06	0.62	0.03	0.62
	(0.0127)	(0.0013)	(0.0011)	(0.0004)	(0.0002)	(0.0002)

TABLE 3
Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, under model (2.1) without interactions with $p_{00} = 0.2$, $p_{01} = 0.4$, $p_{10} = 0.3$, $p_{11} = 0.1$.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	0.13	0.70	0.04	0.71	0.02	0.71
	(0.0237)	(0.0009)	(0.0029)	(0.0003)	(0.0006)	(0.0002)
Atkinson's D_A-BCD	0.62	0.55	0.61	0.53	0.61	0.52
	(0.2459)	(0.0009)	(0.2802)	(0.0003)	(0.2685)	(0.0001)
C-ABCD(F_{jl}^g)	0.17	0.61	0.05	0.61	0.02	0.61
	(0.0167)	(0.0012)	(0.0013)	(0.0004)	(0.0004)	(0.0002)
C-ABCD(F^a)	0.18	0.61	0.05	0.62	0.02	0.62
	(0.0175)	(0.0014)	(0.0015)	(0.0004)	(0.0003)	(0.0002)

TABLE 4
Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, under model (2.1) without interactions with $p_{00} = p_{01} = p_{10} = p_{11} = 0.25$.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	0.13	0.70	0.04	0.71	0.02	0.71
	(0.0243)	(0.0011)	(0.0017)	(0.0003)	(0.0004)	(0.0002)
Atkinson's D_A-BCD	0.62	0.54	0.60	0.53	0.59	0.52
	(0.2394)	(0.0009)	(0.2471)	(0.0003)	(0.2382)	(0.0001)
C-ABCD($F_{jl}^g = F^a$)	0.14	0.61	0.04	0.61	0.02	0.62
	(0.0103)	(0.0014)	(0.0009)	(0.0004)	(0.0002)	(0.0002)

TABLE 5

Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, for model (2.1) in the full version with four covariates, under the uniform distribution.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	11.98	0.70	11.46	0.72	11.22	0.73
	(22.9593)	(0.0010)	(22.7962)	(0.0003)	(22.3261)	(0.0002)
Atkinson's D_A-BCD	3.40	0.54	3.28	0.52	3.28	0.52
	(1.4823)	(0.0009)	(1.4093)	(0.0003)	(1.3761)	(0.0001)
C-ABCD($F_{jl}^g = F^a$)	2.86	0.60	0.80	0.61	0.39	0.62
	(0.5685)	(0.0014)	(0.0398)	(0.0004)	(0.0095)	(0.0002)

TABLE 6

Expectation and variance (within brackets) of L_n and SB_n, for $n = 150$, 500 and 1000, for model (2.1) with four covariates without interactions, under the uniform distribution.

	L_{150}	SB_{150}	L_{500}	SB_{500}	L_{1000}	SB_{1000}
Pocock & Simon	0.39	0.70	0.11	0.72	0.06	0.73
	(0.0984)	(0.0009)	(0.0094)	(0.0003)	(0.0021)	(0.0002)
Atkinson's D_A-BCD	1.04	0.54	1.04	0.53	1.00	0.52
	(0.4446)	(0.0009)	(0.3994)	(0.0003)	(0.3672)	(0.0001)
C-ABCD($F_{jl}^g = F^a$)	0.82	0.61	0.23	0.61	0.12	0.62
	(0.2385)	(0.0013)	(0.0199)	(0.0004)	(0.0045)	(0.0002)

When the model is full, the C-ABCD yields a significant improvement in terms of loss than Pocock and Simon's procedure and Atkinson's D_A-BCD, due to the fact that it ensures balance within every stratum, whereas it has slightly higher predictability with respect to the latter rule. Moreover, the C-ABCD is still efficient even in the absence of interactions, since L_n tends to 0 asymptotically (see Theorem (5.1)). Observe that the C-ABCD(F_{jl}^g) has slightly better performances than the C-ABCD(F^a) and this gain increases the more we move away from the uniform distribution (as further simulations, omitted here for brevity, have shown).

In the absence of interactions among covariates (Tables 3 and 4), the above comparisons between our proposal and the D_A-BCD are essentially similar, while Pocock and Simon's procedure yields a big improvement in terms of loss (since in this case L_n depends only on the marginal imbalances). However, the C-ABCD still ensures good performances wrt both L_n and SB_n, whereas Pocock and Simon's minimization method is high predictable (SB_n is always greater than 0.7). Furthermore, as Tables 5 and 6 show, the previous comments are still valid even in the case of several covariates.

Appendix A: Proof of Proposition 3.2. For simplicity of notation in this Appendix we omit the subscript n, neglecting the dependence on the number of assignments. From the properties on the inverse of partitioned matrices, the loss L in (3.4) can be written as:

$$L = \mathbf{b}^t \left(\begin{array}{c|c} 0 & \mathbf{0} \\ \hline \mathbf{0} & \boldsymbol{\Omega}^{-1} \end{array} \right) \mathbf{b} + \frac{1}{n - \mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x}} \mathbf{b}^t \begin{pmatrix} 1 \\ -\boldsymbol{\Omega}^{-1}\mathbf{x} \end{pmatrix} \begin{pmatrix} 1 & -\mathbf{x}^t \boldsymbol{\Omega}^{-1} \end{pmatrix} \mathbf{b} \,,$$

where $\mathbf{x}^t = \mathbf{1}^t \mathbf{F}$ and $\boldsymbol{\Omega} = \mathbf{F}^t \mathbf{F}$. Also, letting $\widetilde{\mathbf{b}}^t = (2\boldsymbol{\delta} - \mathbf{1})^t \mathbf{F}$ the imbalance vector can be rewritten as $\mathbf{b}^t = (D; \widetilde{\mathbf{b}}^t)$ and consequently

$$L = \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}} + \frac{\left[D - \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \mathbf{x} \right]^2}{n - \mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x}}. \tag{7.1}$$

Letting $\widetilde{\mathbf{M}} = n\mathbf{M}$, criterion **C2** can be rewritten as $\sigma^4 \det\left(\boldsymbol{\Lambda}^t \widetilde{\mathbf{M}}^{-1} \boldsymbol{\Lambda} \right)$, where

$$\widetilde{\mathbf{M}} = \left(\begin{array}{c|c} \boldsymbol{\Upsilon} & \mathbf{U}^t \\ \hline \mathbf{U} & \boldsymbol{\Omega} \end{array} \right)$$

with $\boldsymbol{\Upsilon} = diag\,(n_A, n_B) = \frac{1}{2}\, diag\,(n + D, n - D)$ and

$$\mathbf{U}^t = \begin{pmatrix} \boldsymbol{\delta}^t \mathbf{F} \\ (\mathbf{1} - \boldsymbol{\delta})^t \mathbf{F} \end{pmatrix} = \frac{1}{2} \begin{pmatrix} \mathbf{x}^t + \widetilde{\mathbf{b}}^t \\ \mathbf{x}^t - \widetilde{\mathbf{b}}^t \end{pmatrix}.$$

Consequently, $\det\left(\boldsymbol{\Lambda}^t \widetilde{\mathbf{M}}^{-1} \boldsymbol{\Lambda} \right) = \left[\det(\boldsymbol{\Upsilon} - \mathbf{U}^t \boldsymbol{\Omega}^{-1} \mathbf{U}) \right]^{-1}$, where

$$\mathbf{U}^t \boldsymbol{\Omega}^{-1} \mathbf{U} = \frac{1}{4} \left(\begin{array}{c|c} (\mathbf{x}^t + \widetilde{\mathbf{b}}^t) \boldsymbol{\Omega}^{-1} (\mathbf{x} + \widetilde{\mathbf{b}}) & (\mathbf{x}^t + \widetilde{\mathbf{b}}^t) \boldsymbol{\Omega}^{-1} (\mathbf{x} - \widetilde{\mathbf{b}}) \\ \hline (\mathbf{x}^t - \widetilde{\mathbf{b}}^t) \boldsymbol{\Omega}^{-1} (\mathbf{x} + \widetilde{\mathbf{b}}) & (\mathbf{x}^t - \widetilde{\mathbf{b}}^t) \boldsymbol{\Omega}^{-1} (\mathbf{x} - \widetilde{\mathbf{b}}) \end{array} \right).$$

Thus,

$$\det(\boldsymbol{\Upsilon} - \mathbf{U}^t \boldsymbol{\Omega}^{-1} \mathbf{U}) = \left[\left(\frac{n}{2} - \frac{\mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x} + \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}}}{4} \right) + \left(\frac{D_n - \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \mathbf{x}}{2} \right) \right] \times$$
$$\left[\left(\frac{n}{2} - \frac{\mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x} + \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}}}{4} \right) - \left(\frac{D_n - \widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \mathbf{x}}{2} \right) \right] - \left(\frac{\widetilde{\mathbf{b}}^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}} - \mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x}}{4} \right)^2,$$

so that from (7.1), after simple algebra

$$\det(\boldsymbol{\Upsilon} - \mathbf{U}^t \boldsymbol{\Omega}^{-1} \mathbf{U}) = (n - \mathbf{x}^t \boldsymbol{\Omega}^{-1} \mathbf{x})\,(n - L)\,/4\,.$$

Appendix B: Proof of Theorem 4.3. Let $\mathbb{1}_{\{\cdot\}}$ denote the indicator function, for any given stratum (t_j, w_l)

$$\frac{D_n(t_j,w_l)}{n} = 2\left(\frac{1}{n}\sum_{i=1}^{n}\delta_i \mathbb{1}_{\{Z_i=(t_j,w_l)\}}\right) - \frac{N_n(t_j,w_l)}{n}, \quad j=0,\dots,J; l=0,\dots L,$$

where

$$\frac{1}{n}\sum_{i=1}^{n}\delta_i \mathbb{1}_{\{Z_i=(t_j,w_l)\}} = \frac{1}{n}\sum_{i=1}^{n}\left(\delta_i \mathbb{1}_{\{Z_i=(t_j,w_l)\}} - E[\delta_i \mathbb{1}_{\{Z_i=(t_j,w_l)\}} \mid \Im_{i-1}]\right) +$$
$$+ \frac{1}{n}\sum_{i=1}^{n} F_{jl}(D_{i-1}(t_j,w_l))\Pr(Z_i=(t_j,w_l)) = \frac{1}{n}\sum_{i=1}^{n} Q_i + p_{jl}\left[\frac{1}{n}\sum_{i=1}^{n} F_{jl}(D_{i-1}(t_j,w_l))\right]$$

and $\Im_0$ represents the trivial σ-field. Thus, $\mathcal{Q}_n = \sum_{i=1}^{n} Q_i$ is a centered martingale with

$$|Q_i| \le 1 \quad a.s. \qquad \text{and} \qquad \sum_{i=1}^{\infty} i^{-2}\, E\left[Q_i^2 \mid \Im_{i-1}\right] < \infty\,,$$

and hence from Theorem 2.18 in Hall and Heyde (1980)

$$\lim_{n\to\infty}\frac{\mathcal{Q}_n}{n} = 0 \qquad a.s.$$

From the Strong Law of Large Numbers for ergodic Markov chains

$$\frac{1}{n}\sum_{i=1}^{n} F_{jl}(D_{i-1}(t_j,w_l)) \to E_{\boldsymbol{\xi}_{jl}}[F_{jl}] = \sum_{x=-\infty}^{\infty} F_{jl}(x)\xi_{jl}(x) = \frac{1}{2} \quad a.s.$$

since the stationary law $\boldsymbol{\xi}_{jl}$ is symmetric around 0. Furthermore, from the SLLN for independent random variables

$$\lim_{n\to\infty}\frac{N_n(t_j,w_l)}{n} = p_{jl} \qquad a.s.$$

so that

$$\lim_{n\to\infty}\frac{D_n(t_j,w_l)}{n} = 2\left(0+\frac{p_{jl}}{2}\right) - p_{jl} = 0 \qquad a.s.$$

and therefore the results follow easily from the continuous mapping theorem.

Appendix C: Proof of Theorem 4.5. The sequence $\{|D_n(t_j, w_l)|\}_{n\in\mathbb{N}}$ is an homogeneous Markov chain on $\mathbb{N}$ starting at $|D_0(t_j, w_l)| = 0$ with

$$\Pr\left(|D_{n+1}(t_j, w_l)| = k \mid |D_n(t_j, w_l)| = x\right) = \begin{cases} p_{jl}F_{jl}(x) & k = x+1 \\ 1 - p_{jl} & k = x \\ p_{jl}F_{jl}(-x) & k = x-1 \end{cases} \qquad \forall x \geq 1$$

and boundary conditions

$$\Pr\left(|D_{n+1}(t_j, w_l)| = k \mid |D_n(t_j, w_l)| = 0\right) = \begin{cases} p_{jl} & k = 1 \\ 1 - p_{jl} & k = 0 \end{cases}.$$

Since the process $\{|D_n(t_j, w_l)|\}_{n\in\mathbb{N}}$ is ergodic (see e.g. Karlin and McGregor (1959)), it is sufficient to show that

$$\lim_{n\to\infty} E\left[|D_n(t_j, w_l)|\right] = \sum_{x=0}^{\infty} x\xi_{jl}^{+}(x) < \infty$$

where $\boldsymbol{\xi}_{jl}^{+}$ denotes the stationary distribution of $\{|D_n(t_j, w_l)|\}_{n\in\mathbb{N}}$. Clearly, $\boldsymbol{\xi}_{jl}^{+}$ can be easily derived from the symmetric property of $\boldsymbol{\xi}_{jl}$ in (4.2) since

$$\xi_{jl}^{+}(0) = \xi_{jl}(0) \quad \text{and} \quad \xi_{jl}^{+}(x) = 2\xi_{jl}(x) \qquad \text{for any } x \geq 1, \tag{7.2}$$

and therefore

$$\sum_{x=0}^{\infty} x\xi_{jl}^{+}(x) = 2\xi_{jl}(0)\sum_{x=1}^{\infty} x\left(\prod_{s=1}^{x}\lambda_{jl}(s)\right).$$

Let $\gamma = \min\{n \in \mathbb{N} \; s.t. \; F_{jl}(-\gamma) > 1/2\}$, then $1 \leq \gamma < \infty$ from the definition of $F_{jl}(\cdot)$; also, note that $\lambda_{jl}(1) = \ldots = \lambda_{jl}(\gamma - 1) = 1$, while $1 > \lambda_{jl}(\gamma) \geq \lambda_{jl}(\gamma + 1) \geq \ldots$, since $\{\lambda_{jl}(x)\}$ is non-increasing. Thus,

$$\begin{aligned}\sum_{x=1}^{\infty} x\left(\prod_{s=1}^{x}\lambda_{jl}(s)\right) &= \sum_{x=1}^{\gamma-1} x\left(\prod_{s=1}^{x}\lambda_{jl}(s)\right) + \sum_{x=\gamma}^{\infty} x\left(\prod_{s=1}^{x}\lambda_{jl}(s)\right) \\ &= \frac{\gamma(\gamma-1))}{2} + \sum_{x=\gamma}^{\infty} x\left(\prod_{s=\gamma}^{x}\lambda_{jl}(s)\right) < \frac{\gamma(\gamma-1))}{2} + \sum_{x=\gamma}^{\infty} x\lambda_{jl}(\gamma)^{x-\gamma+1} < \infty\,.\end{aligned}$$

Appendix D: proof of equation (5.1). For the sake of simplicity in this Appendix all the quantities without subscripts are intended evaluated after n steps. Let $\boldsymbol{f}(\boldsymbol{z})^t = (\mathbb{T}^t, \mathbb{W}^t, \mathbb{T}^t \otimes \mathbb{W}^t)$ be the $(J+L+J\times L)$-dim vector including all interactions, where $\mathbb{T}$ and $\mathbb{W}$ are the J-dim vector and L-dim

vector of dummies associated with T and W, respectively. From (7.1) it is sufficient to simplify the quantities $\widetilde{\mathbf{b}}^t\boldsymbol{\Omega}^{-1}\widetilde{\mathbf{b}}$, $\mathbf{x}^t\boldsymbol{\Omega}^{-1}\mathbf{x}$ and $\widetilde{\mathbf{b}}^t\boldsymbol{\Omega}^{-1}\mathbf{x}$, where

$$\mathbf{x}^t = \mathbf{1}^t\mathbf{F} = (\mathbf{N}^t_{\mathbb{T}}, \mathbf{N}^t_{\mathbb{W}}, \mathbf{N}^t_{\mathbb{T}\otimes\mathbb{W}}) \quad \text{and} \quad \widetilde{\mathbf{b}}^t = (2\boldsymbol{\delta}-\mathbf{1})^t\mathbf{F} = (\mathbf{D}^t_{\mathbb{T}}, \mathbf{D}^t_{\mathbb{W}}, \mathbf{D}^t_{\mathbb{T}\otimes\mathbb{W}}),$$

with $\mathbf{N}^t_{\mathbb{T}\otimes\mathbb{W}} = (N(t_1,w_1),\ldots,N(t_1,w_L),\ldots,N(t_J,w_1),\ldots,N(t_J,w_L))$, $\mathbf{N}^t_{\mathbb{T}} = (N(t_1),\ldots,N(t_J))$, $\mathbf{N}^t_{\mathbb{W}} = (N(w_1),\ldots,N(w_L))$ and, analogously, $\mathbf{D}^t_{\mathbb{T}\otimes\mathbb{W}} = (D(t_1,w_1),\ldots,D(t_1,w_L),\ldots,D(t_J,w_1),\ldots,D(t_J,w_L))$, $\mathbf{D}^t_{\mathbb{T}} = (D(t_1),\ldots,D(t_J))$ and $\mathbf{D}^t_{\mathbb{W}} = (D(w_1),\ldots,D(w_L))$. Also, letting $\mathbf{N}^t_{t_j\otimes\mathbb{W}} = (N(t_j,w_1),\ldots,N(t_j,w_L))$, the matrix $\boldsymbol{\Omega} = \mathbf{F}^t\mathbf{F}$ can be partitioned as follows

$$\boldsymbol{\Omega} = \left(\begin{array}{c|c} \mathbf{A} & \mathbf{B} \\ \hline \mathbf{B}^t & \mathbf{C} \end{array}\right),$$

where

$$\mathbf{A} = diag\,(\mathbf{N}_{\mathbb{T}}, \mathbf{N}_{\mathbb{W}}) + \left(\begin{array}{ccc|c} & \mathbf{0}_{J\times J} & & \mathbf{N}^t_{t_1\otimes\mathbb{W}} \\ & & & \vdots \\ & & & \mathbf{N}^t_{t_J\otimes\mathbb{W}} \\ \hline \mathbf{N}_{t_1\otimes\mathbb{W}} & \ldots & \mathbf{N}_{t_J\otimes\mathbb{W}} & \mathbf{0}_{L\times L} \end{array}\right),$$

$$\mathbf{B} = \begin{pmatrix} \mathbf{N}^t_{t_1\otimes\mathbb{W}} & \mathbf{0} & \mathbf{0} & \ldots & \mathbf{0} \\ \mathbf{0} & \mathbf{N}^t_{t_2\otimes\mathbb{W}} & \mathbf{0} & \ldots & \mathbf{0} \\ \vdots & & \ddots & & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \ldots & & \mathbf{N}^t_{t_J\otimes\mathbb{W}} \\ diag(\mathbf{N}_{t_1\otimes\mathbb{W}}) & diag(\mathbf{N}_{t_2\otimes\mathbb{W}}) & \ldots & & diag(\mathbf{N}_{t_J\otimes\mathbb{W}}) \end{pmatrix}$$

and $\mathbf{C} = diag(\mathbf{N}_{\mathbb{T}\otimes\mathbb{W}})$. Thus,

$$\boldsymbol{\Omega}^{-1} = \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array}\right) + \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\, -\mathbf{B}\mathbf{C}^{-1}\right), \tag{7.3}$$

where $\boldsymbol{\Gamma} = \mathbf{A} - \mathbf{B}\mathbf{C}^{-1}\mathbf{B}^t = diag\,(\mathbf{N}_{\mathbb{T}\otimes w_0}\,,\, \mathbf{N}_{t_0\otimes\mathbb{W}})$. Note that $\boldsymbol{\Omega}$ is nonsingular if and only if $\mathbf{C}$ and $\boldsymbol{\Gamma}$ are nonsingular, i.e. there is at least one patient for each stratum. Hence, from (7.3) it follows that

$$\widetilde{\mathbf{b}}^t\boldsymbol{\Omega}^{-1}\widetilde{\mathbf{b}} = \widetilde{\mathbf{b}}^t \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array}\right) \widetilde{\mathbf{b}} + \widetilde{\mathbf{b}}^t \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\, -\mathbf{B}\mathbf{C}^{-1}\right) \widetilde{\mathbf{b}}$$

where

$$\widetilde{\mathbf{b}}^t \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array}\right) \widetilde{\mathbf{b}} = \sum_{j=1}^{J}\sum_{l=1}^{L} \frac{D^2(t_j,w_l)}{N(t_j,w_l)}$$

and

$$\begin{aligned}\widetilde{\mathbf{b}}^t \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \mathbf{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\, -\mathbf{B}\mathbf{C}^{-1}\right) \widetilde{\mathbf{b}} &= \\ = \left[\left(\mathbf{D}_{\mathbb{T}}^t\,,\, \mathbf{D}_{\mathbb{W}}^t\right) - \mathbf{D}_{\mathbb{T}\otimes\mathbb{W}}^t \mathbf{C}^{-1}\mathbf{B}^t\right] \mathbf{\Gamma}^{-1} \left[\begin{pmatrix} \mathbf{D}_{\mathbb{T}} \\ \mathbf{D}_{\mathbb{W}} \end{pmatrix} - \mathbf{B}\mathbf{C}^{-1}\mathbf{D}_{\mathbb{T}\otimes\mathbb{W}}\right] \\ = \sum_{j=1}^{J} \frac{D^2(t_j, w_0)}{N(t_j, w_0)} + \sum_{l=1}^{L} \frac{D^2(t_0, w_l)}{N(t_0, w_l)}\,,\end{aligned}$$

since $(\mathbf{D}_{\mathbb{T}}^t, \mathbf{D}_{\mathbb{W}}^t) - \mathbf{D}_{\mathbb{T}\otimes\mathbb{W}}^t \mathbf{C}^{-1}\mathbf{B}^t = (\mathbf{D}_{\mathbb{T}\otimes w_0}^t\,,\, \mathbf{D}_{t_0\otimes\mathbb{W}}^t)$. Therefore,

$$\widetilde{\mathbf{b}}^t \mathbf{\Omega}^{-1} \widetilde{\mathbf{b}} = \sum_{j=1}^{J}\sum_{l=1}^{L} \frac{D^2(t_j, w_l)}{N(t_j, w_l)} + \sum_{j=1}^{J} \frac{D^2(t_j, w_0)}{N(t_j, w_0)} + \sum_{l=1}^{L} \frac{D^2(t_0, w_l)}{N(t_0, w_l)}\,.$$

Similarly,

$$\widetilde{\mathbf{b}}^t \mathbf{\Omega}^{-1} \mathbf{x} = \widetilde{\mathbf{b}}^t \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array}\right) \mathbf{x} + \widetilde{\mathbf{b}}^t \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \mathbf{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\, -\mathbf{B}\mathbf{C}^{-1}\right) \mathbf{x}\,,$$

where

$$\widetilde{\mathbf{b}}^t \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array}\right) \mathbf{x} = \sum_{j=1}^{J}\sum_{l=1}^{L} D(t_j, w_l)$$

and

$$\begin{aligned}\widetilde{\mathbf{b}}^t \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \mathbf{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\, -\mathbf{B}\mathbf{C}^{-1}\right) \mathbf{x} &= \\ = \left[\left(\mathbf{D}_{\mathbb{T}}^t\,,\, \mathbf{D}_{\mathbb{W}}^t\right) - \mathbf{D}_{\mathbb{T}\otimes\mathbb{W}}^t \mathbf{C}^{-1}\mathbf{B}^t\right] \mathbf{\Gamma}^{-1} \left[\begin{pmatrix} \mathbf{N}_{\mathbb{T}} \\ \mathbf{N}_{\mathbb{W}} \end{pmatrix} - \mathbf{B}\mathbf{C}^{-1}\mathbf{N}_{\mathbb{T}\otimes\mathbb{W}}\right] \\ = \sum_{j=1}^{J} D(t_j, w_0) + \sum_{l=1}^{L} D(t_0, w_l).\end{aligned}$$

Thus,

(7.4)
$$\widetilde{\mathbf{b}}^t \mathbf{\Omega}^{-1} \mathbf{x} = \sum_{j=1}^{J}\sum_{l=1}^{L} D(t_j, w_l) + \sum_{j=1}^{J} D(t_j, w_0) + \sum_{l=1}^{L} D(t_0, w_l) = D - D(t_0, w_0).$$

Analogously, by (7.3)

(7.5)
$$\begin{aligned}\mathbf{x}^t \mathbf{\Omega}^{-1} \mathbf{x} &= \mathbf{N}_{\mathbb{T}\otimes\mathbb{W}}^t \mathbf{C}^{-1} \mathbf{N}_{\mathbb{T}\otimes\mathbb{W}} + \left(\mathbf{N}_{\mathbb{T}\otimes w_0}^t\,,\, \mathbf{N}_{t_0\otimes\mathbb{W}}^t\right) \mathbf{\Gamma}^{-1} \begin{pmatrix} \mathbf{N}_{\mathbb{T}\otimes w_0} \\ \mathbf{N}_{t_0\otimes\mathbb{W}} \end{pmatrix} \\ &= \sum_{j=1}^{J}\sum_{l=1}^{L} N(t_j, w_l) + \sum_{j=1}^{J} N(t_j, w_0) + \sum_{l=1}^{L} N(t_0, w_l) = n - N(t_0, w_0)\end{aligned}$$

and hence the loss in (5.1) follows from (7.1) after simple algebra.

Appendix E: simplification of Atkinson's procedures. As in Appendix D we let $\boldsymbol{f}(\boldsymbol{z})^t = (\mathbb{T}^t, \mathbb{W}^t, \mathbb{T}^t \otimes \mathbb{W}^t)$ and the aim is to simplify the allocation rule (3.5) of Atkinson's D_A-BCD, where for the sake of simplicity all the quantities without subscripts are intended evaluated after n steps. By (7.4) and (7.5), observe that

$$
\begin{aligned}
\left(1, \boldsymbol{f}(\boldsymbol{z}_{n+1})^t\right) \left(\mathbb{F}^t\mathbb{F}\right)^{-1} \mathbf{b} &= \left(1\,,\ \boldsymbol{f}(\boldsymbol{z}_{n+1})^t\right) \begin{pmatrix} n & \mathbf{x}^t \\ \mathbf{x} & \boldsymbol{\Omega} \end{pmatrix}^{-1} \mathbf{b} \\
&= \boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}} + \frac{\left[1 - \boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1}\mathbf{x}\right] \left[D - \mathbf{x}^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}}\right]}{n - \mathbf{x}^t \boldsymbol{\Omega}^{-1}\mathbf{x}} \\
&= \boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}} + \frac{D(t_0, w_0)}{N(t_0, w_0)} \left[1 - \boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1}\mathbf{x}\right].
\end{aligned} \tag{7.6}
$$

From (7.3), it follows that

$$
\begin{aligned}
&\boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1} \widetilde{\mathbf{b}} = (\mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \mathbf{C}^{-1} \mathbf{D}_{\mathbb{T}\otimes\mathbb{W}} + \\
&\quad + (\mathbb{T}^t_{n+1}, \mathbb{W}^t_{n+1}, \mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\ -\mathbf{B}\mathbf{C}^{-1}\right) \widetilde{\mathbf{b}} \\
&\quad = \sum_{j=1}^{J} \sum_{l=1}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_j, w_l)\}} \frac{D(t_j, w_l)}{N(t_j, w_l)} + \left[(\mathbb{T}^t_{n+1}, \mathbb{W}^t_{n+1}) - (\mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \mathbf{C}^{-1} \mathbf{B}^t\right] \times \\
&\quad \times \left(\frac{D(t_1, w_0)}{N(t_1, w_0)}, \ldots, \frac{D(t_J, w_0)}{N(t_J, w_0)}, \frac{D(t_0, w_1)}{N(t_0, w_1)}, \ldots, \frac{D(t_0, w_L)}{N(t_0, w_L)}\right)^t \\
&\quad = \sum_{j=1}^{J} \sum_{l=1}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_j, w_l)\}} \frac{D(t_j, w_l)}{N(t_j, w_l)} + \sum_{j=1}^{J} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_j, w_0)\}} \frac{D(t_j, w_0)}{N(t_j, w_0)} + \\
&\quad + \sum_{l=1}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_0, w_l)\}} \frac{D(t_0, w_l)}{N(t_0, w_l)}.
\end{aligned}
$$

Similarly,

$$
\begin{aligned}
&\boldsymbol{f}(\boldsymbol{z}_{n+1})^t \boldsymbol{\Omega}^{-1} \mathbf{x} = (\mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \mathbf{C}^{-1} \mathbf{N}_{\mathbb{T}\otimes\mathbb{W}} + \\
&\quad + (\mathbb{T}^t_{n+1}, \mathbb{W}^t_{n+1}, \mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} \left(\mathbf{I}_{J+L}\,,\ -\mathbf{B}\mathbf{C}^{-1}\right) \mathbf{x} \\
&\quad = (\mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \mathbf{1}_{J\times L} + \left[\left(\mathbb{T}^t_{n+1}, \mathbb{W}^t_{n+1}\right) - (\mathbb{T}^t_{n+1} \otimes \mathbb{W}^t_{n+1}) \mathbf{C}^{-1} \mathbf{B}^t\right] \mathbf{1}_{J+L} \\
&\quad = \sum_{j=1}^{J} \sum_{l=1}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_j, w_l)\}} + \sum_{j=1}^{J} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_j, w_0)\}} + \sum_{l=1}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1} = (t_0, w_l)\}},
\end{aligned}
$$

and hence (7.6) becomes

$$\left(1, \boldsymbol{f}(\boldsymbol{z}_{n+1})^t\right) \left(\mathbb{F}^t\mathbb{F}\right)^{-1} \mathbf{b} = \sum_{j=0}^{J}\sum_{l=0}^{L} \mathbb{1}_{\{\boldsymbol{Z}_{n+1}=(t_j,w_l)\}} \frac{D(t_j,w_l)}{N(t_j,w_l)}\,.$$

Thus, when the $(n+1)$-th subject with covariate $\boldsymbol{Z}_{n+1} = (t_j, w_l)$ is ready to be randomized, it will be assigned to treatment A with probability

$$P\left(\delta_{n+1} = 1 | \Im_n, \boldsymbol{Z}_{n+1} = (t_j, w_l)\right) = \frac{\left(1 - \frac{D_n(t_j,w_l)}{N_n(t_j,w_l)}\right)^2}{\left(1 - \frac{D_n(t_j,w_l)}{N_n(t_j,w_l)}\right)^2 + \left(1 + \frac{D_n(t_j,w_l)}{N_n(t_j,w_l)}\right)^2}\,.$$

Appendix F: Proof of Theorem 5.2. Notice that

$$\begin{aligned}\bar{G}_n =& \frac{1}{n}\sum_{i=1}^{n}\left(G_i - E[G_i \mid \Im_{i-1}]\right) + \frac{1}{n}\sum_{i=1}^{n} E[G_i \mid \Im_{i-1}] \\ =& \frac{1}{n}\sum_{i=1}^{n} A_i + \sum_{j=1}^{J}\sum_{l=1}^{L}\left[\frac{1}{n}\sum_{i=1}^{n} F_{jl}(-|D_{i-1}(t_j,w_l)|)\right] p_{jl}\,,\end{aligned}$$

where the centered martingale $\mathcal{A}_n = \sum_{i=1}^{n} A_i = o(n)$ $a.s.$, since

$$|A_i| \le 1 \quad a.s. \text{ for any } i \ge 1 \quad \text{and} \quad \sum_{i=1}^{\infty} i^{-2} E\left[A_i^2 \mid \Im_{i-1}\right] < \infty.$$

Thus, from the ergodic theorem for Markov chains,

$$\frac{1}{n}\sum_{i=1}^{n} F_{jl}(-|D_{i-1}(t_j,w_l)|) \to \sum_{x=0}^{\infty} F_{jl}(-x)\xi_{jl}^{+}(x) \qquad a.s. \qquad \forall (j,l)$$

where $\boldsymbol{\xi}_{jl}^{+}$ is the stationary distribution of $\{|D_n(t_j,w_l)|\}_{n\in\mathbb{N}}$ defined in (7.2), and hence from the dominated convergence theorem

$$\lim_{n\to\infty} \bar{G}_n = \sum_{j=0}^{J}\sum_{l=0}^{L}\sum_{x=0}^{\infty} F_{jl}(-x)\xi_{jl}^{+}(x)\,.$$

Notice that, from (4.2),

$$\begin{aligned}\sum_{x=0}^{\infty} F_{jl}(-x)\xi_{jl}^{+}(x) =& \frac{1}{2}\xi_{jl}(0) + 2\sum_{x=1}^{\infty} F_{jl}(-x)\xi_{jl}(x) \\ =& \xi_{jl}(0)\left\{\frac{1}{2} + 2\sum_{x=1}^{\infty} F_{jl}(-x)\prod_{s=1}^{x}\lambda_{jl}(s)\right\},\end{aligned}$$

where, by (4.3),

$$\sum_{x=1}^{\infty} F_{jl}(-x) \prod_{s=1}^{x} \lambda_{jl}(s) = F_{jl}(-1)\lambda_{jl}(1) + \sum_{x=2}^{\infty} F_{jl}(-x) \prod_{s=1}^{x} \lambda_{jl}(s)$$
$$= \frac{1}{2} + \sum_{x=2}^{\infty} F_{jl}(x-1) \prod_{s=1}^{x-1} \lambda_{jl}(s) = \frac{1}{2} + \sum_{x=1}^{\infty} F_{jl}(x) \prod_{s=1}^{x} \lambda_{jl}(s)\,.$$

Thus,

$$\frac{1}{2} = \sum_{x=1}^{\infty} [F_{jl}(-x) - F_{jl}(x)] \prod_{s=1}^{x} \lambda_{jl}(s) = \sum_{x=1}^{\infty} [1 - 2F_{jl}(x)] \prod_{s=1}^{x} \lambda_{jl}(s)$$

and, from (4.5), $2\sum_{x=1}^{\infty} \prod_{s=1}^{x} \lambda_{jl}(s) = \xi_{jl}(0)^{-1} - 1$. Therefore,

$$\sum_{x=1}^{\infty} F_{jl}(x) \prod_{s=1}^{x} \lambda_{jl}(s) = \frac{1}{2}\left(\frac{1}{2\xi_{jl}(0)} - 1\right),$$

namely $\sum_{x=1}^{\infty} F_{jl}(-x)\xi_{jl}(x) = 1/4$, and thus

$$\sum_{x=0}^{\infty} F_{jl}(-x)\xi_{jl}^{+}(x) = [\xi_{jl}(0) + 1]/2.$$

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