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Randomized Urn Models revisited using Stochastic Approximation

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Abstract

This paper presents the link between stochastic approximation and clinical trials based on randomized urn models investigated in [4, 5, 6]. We reformulate the dynamics of both the urn composition and the assigned treatments as standard stochastic approximation (*SA*) algorithms with remainder. Then, we derive the *a.s.* convergence and the asymptotic normality (*CLT*) of the normalized procedure under less stringent assumptions by calling upon the *ODE* and *SDE* methods. As a second step, we investigate a more involved family of models, known as multi-arm clinical trials, where the urn updating depends on the past performances of the treatments. By increasing the dimension of the state vector, our *SA* approach provides this time a new asymptotic normality result.

Keywords *Stochastic approximation, extended Pòlya urn models, nonhomogeneous generating matrix, strong consistency, asymptotic normality, multi-arm clinical trials.*

2010 AMS classification: 62L20, 62E20, 62L05 secondary: 62F12, 62P10.

1 Introduction

The aim of this paper is to illustrate the efficiency of Stochastic Approximation (*SA*) Theory by revisiting several recent results on randomized urn models applied to clinical trials (especially [4, 5, 6]). We will first retrieve the *a.s.* convergence (strong consistency) and asymptotic normality results obtained in these papers under less stringent assumptions. Then we will take advantage of this more synthetic approach to establish a new Central Limit Theorem (*CLT*) in the more sophisticated randomized urn model known as “multi-arm clinical test”. In this model, the urn updating which produces the adaptive design is based on statistical estimators of the past efficiency of the assigned treatments.

In these adaptive models, the starting point is the equation which governs the urn composition updated after each new treated patient. Basically, we will show that a normalized version of this urn composition can be formulated as a classical recursive stochastic algorithm with step $\gamma_n = \frac{1}{n}$

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which classical Stochastic Approximation Theory deals with. Doing so we will be in position to establish the *a.s.* convergence of the procedure by calling upon the so-called Ordinary Differential Equation Method (*ODE* method) and to derive the asymptotic normality - a *CLT*, to be precise - from the standard *CLT* for stochastic algorithms (sometimes called the Stochastic Differential Equation Method (*SDE* method), see *e.g.* [12, 8]). These two main theoretical results are recalled in a self-contained form in the Appendix. They can be found in all classical textbooks on *SA* ([8], [12], [19]) and go back to [18] and [10].

Clinical trials essentially deal with the asymptotic behaviour of the patient allocation to several treatments during the procedure. Adaptive designs in clinical trials aim at detecting “on line” which treatment should be assigned to more patients, while keeping randomness enough to preserve the basis of treatments. This adaptive approach relies on the cumulative information provided by the responses to treatments of previous patients in order to adjust treatment allocation to the new patients. To this end, many urn models have been suggested in the literature (see [17], [23], [22], [13] and [20]). The most widespread random adaptive model is the Generalized Friedman Urn (*GFU*) (see [2]), also called Generalized Pólya Urn (*GPU*). The idea of this modeling is that the urn contains balls of d different types representative of the treatments. All random variables involved in the model are supposed to be defined on the same probability space $(\Omega, \mathcal{A}, \mathbb{P})$. Denote $Y_0 = (Y_0^i)_{i=1, \dots, d} \in \mathbb{R}_+^d \setminus \{0\}$ the initial composition of the urn, where Y_0^i denotes the number of balls of type i , $i = 1, \dots, d$. The allocation of the treatments is sequential and the urn composition at draw n is denoted by $Y_n = (Y_n^i)_{i=1, \dots, d}$. When the n^{th} patient presents, one draws randomly (*i.e.* uniformly) a ball from the urn with instant replacement. If the ball is of type i , then the treatment i is assigned to the n^{th} patient, $i = 1, \dots, d$, $n \geq 1$. The response of the n^{th} patient to the treatment is modeled by a random variable ξ_n . The urn composition is updated by taking into account the efficiency of the assigned treatment, namely by adding $D_n^{ij} = \varphi^{ij}(\xi_n)$ balls of type j , $j = 1, \dots, d$, where φ^{ij} is a (Borel) function such that $D_n^{ij} \in L^1(\mathbb{P})$. No independence assumption is made on the sequence $(\xi_n)_{n \geq 1}$ *a priori*. The procedure is iterated as long as patients present. Consequently the larger the number of balls of a given type is, the more efficient the treatment is. The urn composition at n , modelled by an \mathbb{R}^d -valued vector Y_n satisfies the following recursive procedure:

$$Y_n = Y_{n-1} + D_n X_n, \quad Y_0 \in \mathbb{R}_+^d \setminus \{0\}, \quad (1.1)$$

with $D_n = (D_n^{ij})_{1 \leq i, j \leq d}$ is the addition rule matrix and X_n is the result of the n^{th} draw and $X_n : (\Omega, \mathcal{A}, \mathbb{P}) \rightarrow \{e^1, \dots, e^d\}$ models the selected treatment ($\{e^1, \dots, e^d\}$ denotes the canonical basis of \mathbb{R}^d and e^i stands for treatment i). We model the drawing in the urn by setting

$$X_n = \sum_{i=1}^d \mathbb{1}_{\left\{ \frac{\sum_{\ell=1}^{i-1} Y_{n-1}^\ell}{\sum_{\ell=1}^d Y_{n-1}^\ell} < U_n \leq \frac{\sum_{\ell=1}^i Y_{n-1}^\ell}{\sum_{\ell=1}^d Y_{n-1}^\ell} \right\}} e^i, \quad n \geq 1, \quad (1.2)$$

where $(U_n)_{n \geq 1}$ is i.i.d., independent of $(\xi_n)_{n \geq 1}$, with distribution $U_1 \stackrel{\mathcal{L}}{\sim} \mathcal{U}_{[0,1]}$. Let $\mathcal{F}_n = \sigma(Y_0, U_k, \xi_k, 1 \leq k \leq n)$ be the filtration of the procedure. The *generating matrices* are defined as the \mathcal{F}_n -compensator of the additions rule sequence $i; e$.

$$H_n = (\mathbb{E} [D_n^{ij} | \mathcal{F}_{n-1}])_{1 \leq i, j \leq d}, \quad n \geq 1.$$

The first designs under consideration were the homogeneous *GFU* models where the addition rules D_n are i.i.d. and the so-called generating matrices $H_n = H = \mathbb{E} D_n$ are identical, non-random,

nonnegative and irreducible. Hence by the Perron-Frobenius theorem H has a unique and positive maximal eigenvalue and an eigenvector with positive components (see [2, 3, 15, 16]). But the homogeneity of the generating matrix is often not satisfied in practice and inhomogeneous GFU models have been introduced (see [4]) in which H_n are not random but converge to a deterministic limit H , under the assumption that the total number of balls added at each stage is constant. As a third step, the homogeneous Extended Pòlya Urn (EPU) models have been introduced in [21] in which only the mean total number of balls added at each stage is constant.

Finally, in [5] the authors proposed a nonhomogeneous EPU model because in applications, the addition rule D_n depends on the past history of previous trials (see [1]), so that the general generating matrix H_n is usually random. Thus the entries of H may not be all nonnegative (*e.g.*, when there is no replacement after the draw), and they assume that the matrix H has a unique maximal eigenvalue λ with associated (right) eigenvector $v^* = (v^{*,i})_{i=1,\dots,d}$ with $\sum_{i=1}^d v^{*,i} = 1$. Furthermore the conditional expectation of the total number of balls added at each stage were constant.

The first theoretical investigations on these models focused on the asymptotic properties of the urn composition (consistency and asymptotic normality). However, for practical matter, it is clear that the asymptotic behaviour of the vector $N_n := \sum_{k=1}^n X_k$ which stores the treatment allocation among the first n patients is of high interest, especially its variance structure in order to compare several adaptive designs. Thus, in [5] is proved the strong consistency of both (normalized) quantities Y_n/n and N_n/n (under a summability assumption on the generating matrices).

By considering an appropriate recursive procedure for the normalized urn composition derived from (1.1) we prove by the *ODE* method its *a.s.* convergence toward v^* under a significantly less stringent assumption, namely the minimal requirement that $H_n \xrightarrow[n \rightarrow \infty]{a.s.} H$. The *a.s.* convergence of the treatment allocation frequency $\frac{N_n}{n} := \frac{1}{n} \sum_{k=1}^n X_k$ toward the same v^* .

As concerns asymptotic normality, separate results these two quantities are obtained in [5] under an additional assumption on the rate of convergence of the generating matrices H_n toward H . On our side we propose to consider a stochastic approximation procedure with remainder satisfied by the higher dimensional vector $(\frac{Y_n}{n}, \frac{N_n}{n})$. Then, the standard *CLT* for *SA* procedures with remainder directly provides the expected asymptotic normality result for the whole vector under an assumption on the L^2 -rate of convergence of the generating matrices towards their limit (namely *i.e.* $\|H_n - H\| = o(n^{-\frac{1}{2}})$) which is again slightly less stringent than the original one. As a result, we obtain the asymptotic joint distribution with an explicit global covariance structure matrix.

In the end of [5], an application to multi-arm clinical trials randomized urn models is proposed. This adaptive design has already been introduced in [6] with first consistency results. This kind of models is clearly the most interesting for practitioners since it takes into account the past results of the assigned treatments in the addition rule matrices, denoted S_n at time n (S_n^i denotes the number of cured patients by treatment i among the N_n^i treated ones). The above strong consistency results apply but none of the asymptotic normality works as stated since the generating matrices H_n do not – in fact *cannot* as we will emphasize – converge at the requested rate since they themselves satisfy a *CLT*. However by increasing again the structural dimension of the problem by considering the triplet $(\frac{Y_n}{n}, \frac{N_n}{n}, \frac{S_n}{n})$ which can be shown again to satisfy a *SA* algorithm with remainder for which *a.s.* convergence and the *CLT* hold (provided the limiting generating matrix is still irreducible, etc). Thus we illustrate on this example that *SA* Theory is a powerful tool to investigate this kind

of adaptive design problem. The main difficulty is to exhibit the appropriate form for the recursion by making *a priori* the balance between significant asymptotic terms and remainder terms.

The paper is organized as follows. We rewrite the dynamics (1.1) of the urn composition as a stochastic approximation procedure with state variable for $\tilde{Y}_n := \frac{Y_n}{n}$ in Section 2.1. In Section 2.2 the *a.s.* convergence of $\frac{1}{n} \sum_{i=1}^d Y_n^i$ is established which implies the one of \tilde{Y}_n and $\frac{N_n}{n}$ by using the *ODE* method of *SA* (see [8], [11]). The rate of convergence is after studied in Section 2.3: we obtain a *CLT* under some slightly more stringent assumptions on the limit generating matrix H . In particular we retrieve the main result in [5]. In Section 2.3 we present an example from [4] the generating matrices H_n are not random. Section 3 is devoted to the multi-arm clinical trials where we use the precedent result to prove the strong consistency and prove a new *CLT* for this example, when the generating matrix H_n satisfies itself a *CLT*.

NOTATIONS $\forall u = (u^i)_{i=1, \dots, d} \in \mathbb{R}^d$, $\|u\|$ denotes the canonical Euclidean norm of the column vector u on \mathbb{R}^d , $\text{Tr}(u) = \sum_{k=1}^d u^k$ denotes its “trace”, u^t denotes its transpose; $\|A\|$ denotes the operator norm of the matrix $A \in \mathcal{M}_{d,q}(\mathbb{R})$ with d rows and q columns with respect to canonical Euclidean norms. When $d = q$, $\text{Sp}(A)$ denotes the set of eigenvalues of A . $\mathbf{1} = (1 \cdots 1)^t$ denotes the unit column vector in \mathbb{R}^d and I_d denotes the $d \times d$ identity matrix.

2 Convergence and first rate result

With the notations and definitions described in the introduction, we then formulate the main assumptions to establish the *a.s.* convergence of the urn composition.

(A1) The generating matrices $H_n = (H_n^{ij})_{1 \leq i, j \leq d}$, $n \geq 1$, satisfies *a.s.*

$$\forall i, j \in \{1, \dots, d\}, \quad H_n^{ij} \geq 0 \quad \text{and} \quad \forall j \in \{1, \dots, d\}, \quad \sum_{i=1}^d H_n^{ij} = c > 0. \quad (2.3)$$

We may assume up to a renormalization of Y_n without loss of generality that $c = 1$.

(A2) The addition rule D_n is conditionally independent of the drawing procedure X_n given \mathcal{F}_{n-1} and satisfies

$$\forall 1 \leq j \leq d, \quad \sup_{n \geq 1} \mathbb{E} \left[\|D_n^j\|^2 \mid \mathcal{F}_{n-1} \right] < \infty. \quad (2.4)$$

(A3) Assume that there exists an irreducible $d \times d$ matrix H (with non-negative entries) such that

$$H_n \xrightarrow[n \rightarrow \infty]{a.s.} H. \quad (2.5)$$

H is called the limit generating matrix.

This assumption guarantees by the Perron-Frobenius Theorem (see [9]) that 1 is the maximal eigenvalue of H and that the components of its right eigenvector v can be chosen all positive. Therefore, we may normalize this vector v^* such that $\text{Tr}(v^*) = 1$.

2.1 The dynamics as a stochastic approximation procedure

Our aim in this section is to reformulate the dynamics (1.1)-(1.2) into a recursive stochastic algorithm. Then we aim at applying the most powerful tools of *SA*, namely the “*ODE*” and the “*SDE*” methods to elucidate the asymptotic properties (*a.s.* convergence and weak rate) of both the urn composition and the treatment allocation. We start from (1.1) with $Y_0 \in \mathbb{R}_+^d \setminus \{0\}$.

$$Y_{n+1} = Y_n + D_{n+1}X_{n+1} = Y_n + \mathbb{E}[D_{n+1}X_{n+1} | \mathcal{F}_n] + \Delta M_{n+1}, \quad (2.6)$$

where

$$\Delta M_{n+1} := D_{n+1}X_{n+1} - \mathbb{E}[D_{n+1}X_{n+1} | \mathcal{F}_n]$$

is an \mathcal{F}_n -martingale increment. By the definition of the generating matrix H_n , we have

$$\begin{aligned} \mathbb{E}[D_{n+1}X_{n+1} | \mathcal{F}_n] &= \sum_{i=1}^d \mathbb{E}[D_{n+1} \mathbb{1}_{\{X_{n+1}=e^i\}} e^i | \mathcal{F}_n] = \sum_{i=1}^d \mathbb{E}[D_{n+1} | \mathcal{F}_n] \mathbb{P}(X_{n+1} = e^i | \mathcal{F}_n) e^i \\ &= H_{n+1} \sum_{i=1}^d \frac{Y_n^i}{\text{Tr}(Y_n)} e^i = H_{n+1} \frac{Y_n}{\text{Tr}(Y_n)} \end{aligned}$$

so that
$$Y_{n+1} = Y_n + H_{n+1} \frac{Y_n}{\text{Tr}(Y_n)} + \Delta M_{n+1}.$$

Now we can derive a stochastic approximation for the normalized urn composition Y_n . First we have for every $n \geq 1$,

$$\frac{Y_{n+1}}{n+1} = \frac{Y_n}{n} + \frac{1}{n+1} \left(H_{n+1} \frac{Y_n}{\text{Tr}(Y_n)} - \frac{Y_n}{n} \right) + \frac{\Delta M_{n+1}}{n+1}.$$

Consequently, $\tilde{Y}_n = \frac{Y_n}{n}$, $n \geq 1$, satisfies a canonical recursive stochastic approximation procedure

$$\begin{aligned} \tilde{Y}_{n+1} &= \tilde{Y}_n + \frac{1}{n+1} (H_{n+1} - I_d) \tilde{Y}_n + \frac{1}{n+1} \left(\Delta M_{n+1} + \left(\frac{n}{\text{Tr}(Y_n)} - 1 \right) H_{n+1} \tilde{Y}_n \right) \\ &= \tilde{Y}_n - \frac{1}{n+1} (I_d - H) \tilde{Y}_n + \frac{1}{n+1} (\Delta M_{n+1} + r_{n+1}) \end{aligned} \quad (2.7)$$

with step $\gamma_n = \frac{1}{n}$ and a remainder term given by

$$r_{n+1} := \left(\frac{n}{\text{Tr}(Y_n)} - 1 \right) H_{n+1} \tilde{Y}_n + (H_{n+1} - H) \tilde{Y}_n. \quad (2.8)$$

Furthermore, in order to establish the *a.s.* boundedness of $(\tilde{Y}_n)_{n \geq 0}$ we will rely on the following recursive equation satisfied by $\text{Tr}(Y_n)$:

$$\text{Tr}(Y_{n+1}) = \text{Tr}(Y_n) + \frac{\text{Tr}(H_{n+1}Y_n)}{\text{Tr}(Y_n)} + \text{Tr}(\Delta M_{n+1}).$$

By the properties of the generating matrix H_{n+1} , we obtain

$$\text{Tr}(H_{n+1}Y_n) = \sum_{i=1}^d (H_{n+1}Y_n)_i = \sum_{i=1}^d \sum_{j=1}^d H_{n+1}^{ij} Y_n^j = \sum_{j=1}^d \left(\sum_{i=1}^d H_{n+1}^{ij} \right) Y_n^j = \text{Tr}(Y_n).$$

Consequently

$$\text{Tr}(Y_{n+1}) = \text{Tr}(Y_n) + 1 + \text{Tr}(\Delta M_{n+1}). \quad (2.9)$$

2.2 Convergence results

Theorem 2.1. *Under the assumptions (A1), (A2) and (A3),*

$$(a) \frac{\text{Tr}(Y_n)}{n} \xrightarrow[n \rightarrow \infty]{a.s.} 1 \text{ and } \frac{Y_n}{\text{Tr}(Y_n)} \xrightarrow[n \rightarrow \infty]{a.s.} v^*.$$

$$(b) \tilde{N}_n := \frac{N_n}{n} = \frac{1}{n} \sum_{k=1}^n X_k \xrightarrow[n \rightarrow \infty]{a.s.} v^*.$$

Remarks. • We simply need that $H_n \xrightarrow[n \rightarrow \infty]{a.s.} H$ whereas the assumption in [5], namely

$$\sum_{n \geq 1} \frac{\|H_n - H\|_\infty}{n} < \infty \quad a.s.$$

• Assumption (A3) is not necessary to prove that $\frac{\text{Tr}(Y_n)}{n} \xrightarrow[n \rightarrow \infty]{a.s.} 1$.

Proof. We will first prove that (a) \Rightarrow (b), then we will prove (b).

(a) \Rightarrow (b). We have

$$\mathbb{E}[X_n | \mathcal{F}_{n-1}] = \sum_{i=1}^d \frac{Y_{n-1}^i}{\text{Tr}(Y_{n-1})} e^i = \frac{Y_{n-1}}{\text{Tr}(Y_{n-1})}$$

and, by construction $\|X_n\|^2 = 1$ so that $\mathbb{E}[\|X_n\|^2 | \mathcal{F}_{n-1}] = 1$. Hence the martingale

$$\tilde{M}_n = \sum_{k=1}^n \frac{X_k - \mathbb{E}[X_k | \mathcal{F}_{k-1}]}{k} \xrightarrow[n \rightarrow \infty]{a.s. \& L^2} \tilde{M}_\infty \in L^2,$$

and by the Kronecker Lemma we obtain

$$\frac{1}{n} \sum_{k=1}^n X_k - \frac{1}{n} \sum_{k=1}^n \frac{Y_{k-1}}{\text{Tr}(Y_{k-1})} \xrightarrow[n \rightarrow \infty]{a.s.} 0.$$

This yields the announced implication owing to the Cesaro Lemma.

(a) FIRST STEP: We have

$$D_{n+1} X_{n+1} = \sum_{j=1}^d D_{n+1}^j e^j \mathbf{1}_{\{X_{n+1}=e^j\}}$$

where $D_{n+1}^j = (D_{n+1}^{ij})_{i=1, \dots, d}$. Therefore

$$\|D_{n+1} X_{n+1}\|^2 = \sum_{j=1}^d \left\| D_{n+1}^j \right\|^2 \mathbf{1}_{\{X_{n+1}=e^j\}},$$

$$\begin{aligned} \text{so that } \mathbb{E}[\|D_{n+1} X_{n+1}\|^2 | \mathcal{F}_n] &= \sum_{j=1}^d \mathbb{E} \left[\left\| D_{n+1}^j \right\|^2 | \mathcal{F}_n \right] \mathbb{P}(X_{n+1} = e^j | \mathcal{F}_n) \\ &\leq d \sup_{n \geq 0} \sup_{1 \leq j \leq d} \mathbb{E} \left[\left\| D_{n+1}^j \right\|^2 | \mathcal{F}_n \right] < \infty \quad a.s. \end{aligned}$$

Consequently $\sup_{n \geq 1} \mathbb{E} \left[\|\Delta M_{n+1}\|^2 \mid \mathcal{F}_n \right] < \infty$. Therefore thanks to the strong law of large numbers for conditionally L^2 -bounded martingale increments, we have $\frac{M_n}{n} \xrightarrow[n \rightarrow \infty]{a.s.} 0$. Consequently it follows from (2.9) that

$$\frac{\text{Tr}(Y_n)}{n} = 1 + \frac{\text{Tr}(Y_0) - 1}{n} + \frac{\text{Tr}(M_n)}{n} \xrightarrow[n \rightarrow \infty]{a.s.} 1. \quad (2.10)$$

SECOND STEP: Since the components of \tilde{Y}_n are non-negative and $\text{Tr}(\tilde{Y}_n) = \frac{\text{Tr}(Y_n)}{n} \xrightarrow[n \rightarrow \infty]{a.s.} 1$, it is clear that $(\tilde{Y}_n)_{n \geq 0}$ is *a.s.* bounded and that *a.s.* the set \mathcal{V}_∞ of all its limiting value is contained in

$$\mathcal{V} = \text{Tr}^{-1}\{1\} = \left\{ u \in \mathbb{R}_+^d \mid \text{Tr}(u) = 1 \right\}.$$

So we may try applying the ODE method (see Appendix Theorem A.1). Since \tilde{Y}_n and $H_{n+1}\tilde{Y}_n$ are *a.s.* bounded, (2.10) and (A3) imply that $r_n \xrightarrow[n \rightarrow \infty]{a.s.} 0$.

The ODE associated to the recursive procedure reads

$$ODE_{I_d - H} \equiv \dot{y} = -(I_d - H)y.$$

Owing to Assumption (A3), $I_d - H$ admits v^* as unique zero in \mathcal{V} . The restriction of $ODE_{I_d - H}$ to the affine hyperplane \mathcal{V} is the linear system $\dot{z} = -(I_d - H)z$, where $z = y - v^*$ takes values in $\mathcal{V}_0 = \{u \in \mathbb{R}^d \mid \text{Tr}(u) = 0\}$. Since $\text{Sp}((I_d - H)|_{\mathcal{V}_0}) \subset \{\lambda \in \mathbb{C}, \text{Re}(\lambda) > 0\}$, owing to Assumption (A3). As a consequence v^* is a uniformly stable equilibrium for the restriction of $ODE_{I_d - H}$ to \mathcal{V} , the whole hyperplane, as an attracting area. The fundamental result derived from the ODE method (see Theorem A.1 in Appendix) yields the expected result

$$\tilde{Y}_n \xrightarrow[n \rightarrow \infty]{a.s.} v^*. \quad \square$$

Remark: If we assume that the addition rule matrices $(D_n)_{n \geq 1}$ satisfy (A1), then we can directly write a stochastic approximation for $\frac{Y_n}{\text{Tr}(Y_n)}$ in which the remainder simply reads $(H_{n+1} - H)\frac{Y_n}{\text{Tr}(Y_n)}$ and prove the *a.s.* convergence under the same assumptions.

COMMENTS. We could apply directly the ODE method because we first proved that $(\tilde{Y}_n)_{n \geq 0}$ is *a.s.* bounded without using the standard Lyapunov machinery developed in SA Theory. That is why the assumption on the remainder sequence $(r_n)_{n \geq 1}$ simply reads

$$r_n \xrightarrow[n \rightarrow \infty]{a.s.} 0.$$

Another approach is the martingale one. It relies on the existence of a Lyapunov function $V : \mathbb{R}^d \rightarrow \mathbb{R}_+$ associated to the algorithm satisfying

$$\exists a > 0, \quad \forall y \in \mathbb{R}^d, \quad \langle \nabla V \mid I_d - H \rangle (y) > 0 \quad \text{and} \quad \langle \nabla V \mid I_d - H \rangle > a |\nabla V|^2. \quad (2.11)$$

In this framework the existence of a Lyapunov function can be established. Hence, the natural condition on the remainder sequence $(r_n)_{n \geq 1}$ reads (see [11])

$$\sum_{n \geq 1} \frac{\|r_n\|^2}{n} < +\infty \text{ a.s.}$$

In that perspective, the assumption on the generating matrices would read $\sum_{n \geq 1} \frac{\|H_n - H\|^2}{n} < \infty$ *a.s.* which is still slightly less stringent than assumption on the generating matrices made in [5].

2.3 Rate of convergence

In the previous section we proved the *a.s.* convergence of both quantities of interest, namely \tilde{Y}_n and \tilde{N}_n , toward v^* . In this section we establish a “joint *CLT*” for the couple $\theta_n := (\tilde{Y}_n, \tilde{N}_n)^t$ with an explicit asymptotic joint normal distribution (including covariances). To this end we will show that θ_n satisfies a *SA* recursive procedure which (*a.s.* converges toward $\theta^* = (v^*, v^*)^t$ and) fulfils the assumptions of the *CLT* Theorem A.2 for *SA* algorithms (see Appendix), with a special attention paid to Condition (A.21) about the remainder term. As concerns \tilde{Y}_n , we derive from (2.7) that

$$\forall n \geq 1, \quad \tilde{Y}_{n+1} = \tilde{Y}_n - \frac{1}{n+1} \left(I_d - (2 - \text{Tr}(\tilde{Y}_n))H \right) \tilde{Y}_n + \frac{1}{n+1} (\Delta M_{n+1} + \tilde{r}_{n+1}),$$

where
$$\tilde{r}_{n+1} := \left(\frac{H_{n+1} - H}{\text{Tr}(\tilde{Y}_n)} + \frac{(\text{Tr}(\tilde{Y}_n) - 1)^2}{\text{Tr}(\tilde{Y}_n)} H \right) \tilde{Y}_n.$$

For \tilde{N}_n we have, still for every $n \geq 1$,

$$\tilde{N}_{n+1} = \tilde{N}_n - \frac{1}{n+1} \left(\tilde{N}_n - (2 - \text{Tr}(\tilde{Y}_n))\tilde{Y}_n \right) + \frac{1}{n+1} \left(\Delta \tilde{M}_{n+1} + \tilde{r}_{n+1} \right)$$

with $\Delta \tilde{M}_{n+1} := X_{n+1} - \mathbb{E}[X_{n+1} | \mathcal{F}_n] = X_{n+1} - \frac{Y_n}{\text{Tr}(\tilde{Y}_n)}$ and $\tilde{r}_{n+1} := \frac{(\text{Tr}(\tilde{Y}_n) - 1)^2}{\text{Tr}(\tilde{Y}_n)} \tilde{Y}_n$.

Thus, we obtain a new recursive *SA* procedure, still with step $\gamma_n = \frac{1}{n}$, namely

$$\theta_{n+1} = \theta_n - \frac{1}{n+1} h(\theta_n) + \frac{1}{n+1} (\Delta \mathbf{M}_{n+1} + R_{n+1}), \quad n \geq 1,$$

with $\Delta \mathbf{M}_{n+1} := \begin{pmatrix} \Delta \tilde{M}_{n+1} \\ \Delta \tilde{M}_{n+1} \end{pmatrix}$, $R_{n+1} := \begin{pmatrix} \tilde{r}_{n+1} \\ \tilde{r}_{n+1} \end{pmatrix}$ and

$$\forall \theta = \begin{pmatrix} y \\ \nu \end{pmatrix}, y \in \mathbb{R}^d, \nu \in \mathbb{R}^d, \quad h(\theta) := \begin{pmatrix} (I_d - (2 - \text{Tr}(y))H)y \\ \nu - (2 - \text{Tr}(y))y \end{pmatrix} \quad \text{with} \quad h(\theta^*) = 0.$$

The function h is differentiable on \mathbb{R}^{2d} and its differential at point θ^* is given by

$$Dh(\theta^*) = \begin{pmatrix} I_d - H + v^* \mathbf{1}^t & 0_{\mathcal{M}_d(\mathbb{R})} \\ v^* \mathbf{1}^t - I_d & I_d \end{pmatrix}.$$

To establish a *CLT* for the sequence $(\theta_n)_{n \geq 1}$ we need to make the following additional assumptions:

(A4) The addition rules D_n *a.s.* satisfy

$$\forall 1 \leq j \leq d, \quad \begin{cases} \sup_{n \geq 1} \mathbb{E} \left[\|D_n^j\|^{2+\delta} | \mathcal{F}_{n-1} \right] \leq C < \infty \quad \text{for a } \delta > 0, \\ \text{Cov} \left[D_n^j (D_n^j)^t | \mathcal{F}_{n-1} \right] \xrightarrow{n \rightarrow \infty} C^j, \end{cases}$$

where $C^j = (C_{il}^j)_{1 \leq i, l \leq d}$, $j = 1, \dots, d$, are $d \times d$ positive definite matrices.

(A5) The matrix H satisfies

$$n \mathbb{E} [\|H_n - H\|^2] \xrightarrow[n \rightarrow \infty]{} 0. \quad (2.12)$$

Theorem 2.2. Assume (A1), (A3), (A4) and (A5) and

$$\mathcal{R}e(\text{Sp}(H) \setminus \{1\}) < 1/2 \quad (2.13)$$

Then, $\theta_n \rightarrow \theta^*$ a.s. as $n \rightarrow \infty$ and

$$\sqrt{n}(\theta_n - \theta^*) \xrightarrow[n \rightarrow \infty]{\mathcal{L}} \mathcal{N}(0, \Sigma) \quad \text{with} \quad \Sigma = \int_0^{+\infty} e^{u(Dh(\theta^*) - \frac{I}{2})} \Gamma e^{u(Dh(\theta^*) - \frac{I}{2})^t} du$$

$$\text{and} \quad \Gamma = \begin{pmatrix} \sum_{k=1}^d v^{*k} C^k & H(\text{diag}(v^*) - v^*(v^*)^t) \\ (\text{diag}(v^*) - v^*(v^*)^t)^t H^t & \text{diag}(v^*) - v^*(v^*)^t \end{pmatrix} = a.s.-\lim_{n \rightarrow \infty} \mathbb{E} [\Delta \mathbf{M}_n \Delta \mathbf{M}_n^t | \mathcal{F}_{n-1}]. \quad (2.14)$$

Proof. We will check the three assumptions of the *CLT* for *SA* algorithms recalled in the Appendix (Theorem A.2). Firstly, the condition (A.22) on the spectrum of $D(h(\theta^*))$ requested for algorithms with step $\frac{1}{n}$ in Theorem A.2 reads $\mathcal{R}e(\text{Sp}(Dh(\theta^*))) > \frac{1}{2}$. This follows from our Assumption (2.13) since by decomposing $\mathbb{R}^d = \mathbb{R}v^* \oplus \text{Ker}(\text{Tr})$, one checks that

$$\text{Sp}(Dh(\theta^*)) = \{1\} \cup \{1 - \lambda, \lambda \in \text{Sp}(H)\}.$$

Secondly Assumption (A4) ensures that Condition (A.20) is satisfied since

$$\sup_{n \geq 1} \mathbb{E} [\|\Delta \mathbf{M}_n\|^{2+\delta} | \mathcal{F}_{n-1}] < +\infty \quad a.s. \quad \text{and} \quad \mathbb{E} [\Delta \mathbf{M}_n \Delta \mathbf{M}_n^t | \mathcal{F}_{n-1}] \xrightarrow[n \rightarrow \infty]{a.s.} \Gamma \quad \text{as} \quad n \rightarrow \infty,$$

where Γ is the symmetric nonnegative matrix given by (2.14) as established below. To this end we have to determine three blocks since Γ reads

$$\Gamma = \begin{pmatrix} \Gamma_1 & \Gamma_{12} \\ \Gamma_{12}^t & \Gamma_2 \end{pmatrix} \quad \text{where} \quad \Gamma_1, \Gamma_2, \Gamma_{12} \in \mathcal{M}_d(\mathbb{R}).$$

Computation of Γ_1 .

$$\begin{aligned} \mathbb{E} [\Delta M_{n+1} \Delta M_{n+1}^t | \mathcal{F}_n] &= \sum_{q=1}^d \mathbb{P}(X_{n+1} = e^q | \mathcal{F}_n) (\mathbb{E} [D_{n+1}^q (D_{n+1}^q)^t | \mathcal{F}_n] - \mathbb{E} [D_{n+1} X_{n+1} | \mathcal{F}_n] \mathbb{E} [D_{n+1} X_{n+1} | \mathcal{F}_n]^t) \\ &= \sum_{q=1}^d \frac{Y_n^q}{\text{Tr}(Y_n)} \text{Cov}(D_{n+1}^q (D_{n+1}^q)^t | \mathcal{F}_n) \xrightarrow[n \rightarrow \infty]{a.s.} \Gamma_1 = \sum_{q=1}^d v^{*q} C^q. \end{aligned}$$

Computation of Γ_2 .

$$\begin{aligned} \mathbb{E} [\Delta \widetilde{M}_{n+1} \Delta \widetilde{M}_{n+1}^t | \mathcal{F}_n] &= \mathbb{E} [X_{n+1} X_{n+1}^t | \mathcal{F}_n] - \frac{Y_n}{\text{Tr}(Y_n)} \left(\frac{Y_n^q}{\text{Tr}(Y_n)} \right)^t \\ &= \text{diag} \left(\frac{Y_n}{\text{Tr}(Y_n)} \right) - \frac{Y_n}{\text{Tr}(Y_n)} \left(\frac{Y_n^q}{\text{Tr}(Y_n)} \right)^t \xrightarrow[n \rightarrow \infty]{a.s.} \Gamma_2 = \text{diag}(v^*) - v^*(v^*)^t. \end{aligned}$$

Computation of Γ_{12} .

$$\begin{aligned}
\mathbb{E} \left[\Delta M_{n+1} \Delta \widetilde{M}_{n+1}^t \mid \mathcal{F}_n \right] &= \mathbb{E} \left[D_{n+1} X_{n+1} X_{n+1}^t \mid \mathcal{F}_n \right] - \mathbb{E} \left[D_{n+1} X_{n+1} \mid \mathcal{F}_n \right] \mathbb{E} \left[X_{n+1} \mid \mathcal{F}_n \right]^t \\
&= \mathbb{E} \left[D_{n+1} \mid \mathcal{F}_n \right] \mathbb{E} \left[X_{n+1} X_{n+1}^t \mid \mathcal{F}_n \right] - \mathbb{E} \left[D_{n+1} \mid \mathcal{F}_n \right] \mathbb{E} \left[X_{n+1} \mid \mathcal{F}_n \right] \mathbb{E} \left[X_{n+1} \mid \mathcal{F}_n \right]^t \\
&= H_{n+1} \text{diag} \left(\frac{Y_n}{\text{Tr}(Y_n)} \right) - H_{n+1} \frac{Y_n}{\text{Tr}(Y_n)} \left(\frac{Y_n}{\text{Tr}(Y_n)} \right)^t \\
&\xrightarrow[n \rightarrow \infty]{a.s.} \Gamma_{12} = H \left(\text{diag}(v^*) - v^* (v^*)^t \right).
\end{aligned}$$

Finally, it remains to check that the remainder sequence $(R_n)_{n \geq 1}$ satisfies (A.21) for an $\epsilon > 0$:

$$\mathbb{E} \left[(n+1) \|R_{n+1}\|^2 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \epsilon\}} \right] \xrightarrow[n \rightarrow \infty]{} 0. \quad (2.15)$$

We note that $\|R_{n+1}\|^2 = \|\bar{r}_{n+1}\|^2 + \|\tilde{r}_{n+1}\|^2$. It follows from the definition of \bar{r}_{n+1} and the elementary facts $\|\tilde{Y}_n - v^*\| \leq \|\theta_n - \theta^*\|$ and $\text{Tr}(\tilde{Y}_n) \geq \|\tilde{Y}_n\|$ that

$$\begin{aligned}
\|\bar{r}_{n+1}\|^2 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} &\leq 2 \left(\frac{(\text{Tr}(\tilde{Y}_n) - 1)^4}{\frac{\|v^*\|}{2}} + \frac{\|H_{n+1} - H\|^2}{\frac{\|v^*\|}{2}} \right) \frac{3}{2} \|v^*\| \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} \\
&\leq 6 \left((\text{Tr}(\tilde{Y}_n) - 1)^4 + \|H_{n+1} - H\|^2 \right) \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}}.
\end{aligned}$$

But $\text{Tr}(\tilde{Y}_n) - 1 = \frac{\text{Tr}(\Delta M_n)}{n}$ where $\sup_{n \geq 0} \mathbb{E} \left[|\text{Tr}(\Delta M_{n+1})|^{2+\delta} \mid \mathcal{F}_n \right] \leq C'$, $\delta > 0$, owing to (A4). Now using that $|\text{Tr}(y)| \leq C_d \|y\|$,

$$\mathbb{E} \left[n \left| \text{Tr}(\tilde{Y}_n) - 1 \right|^4 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} \right] \leq C_\delta^* n \mathbb{E} \left[\left| \text{Tr}(\tilde{Y}_n) - 1 \right|^{2+\delta} \right] = \frac{C_d}{n^{1+\delta}} \mathbb{E} \left[|\text{Tr}(\Delta M_n)|^{2+\delta} \right] \leq \frac{C'_d}{n^{1+\delta}},$$

where $C_\delta^* > 0$ is a real constant. Consequently

$$\mathbb{E} \left[\left| \text{Tr}(\tilde{Y}_n) - 1 \right|^4 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} \right] = o\left(\frac{1}{n}\right).$$

Thus, by (A5) we obtain

$$\mathbb{E} \left[\|\bar{r}_{n+1}\|^2 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} \right] = o\left(\frac{1}{n}\right).$$

The same argument yields $\mathbb{E} \left[\|\tilde{r}_{n+1}\|^2 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \frac{\|v^*\|}{2}\}} \right] = o\left(\frac{1}{n}\right)$, therefore (2.15) is satisfied. \square

Example. We consider here the example presented in [4, 5] and named adaptive allocation rules associated with covariates. Let $(\xi_n)_{n \geq 1}$ be i.i.d. random vectors representing covariates observed on the patients and $(T_n)_{n \geq 1}$ be random variables such that $T_n = 1$ if the response of the subject n is a success and 0 otherwise. We consider that the probability of success of treatments depends upon some observable covariates on the patients and the result of the treatment, *i.e.* for each n , T_n is Bernoulli distributed conditionnally to X_n and ξ_n , namely

$$\forall n \geq 1, p_n^i = p^i(\xi_n) = \mathbb{P}(T_n = 1 \mid X_n = e^i, \xi_n), \quad 1 \leq i \leq d,$$

where $X_n = e^i$ indicates that a ball of type i is drawn at the n^{th} stage. Thus, for a given ξ_n , the addition rule could be $D(\xi_n)$, the generating matrices

$$H_n = \mathbb{E}[D(\xi_n) | \mathcal{F}_{n-1}] = \mathbb{E} D(\xi_n) = \mathbb{E} D(\xi_1) = H.$$

Here we illustrate the results by considering the case $d = 2$. Consider the generalized play-the-winner rule (see [4]) and set $p^i = \mathbb{E}[p^i(\xi_n)]$, $i = 1, 2$. Then the addition rule matrices read

$$D(\xi_n) = \begin{pmatrix} p^1(\xi_n) & 1 - p^2(\xi_n) \\ 1 - p^1(\xi_n) & p^2(\xi_n) \end{pmatrix} \quad \text{and} \quad H_n = H = \begin{pmatrix} p^1 & q^2 \\ q^1 & p^2 \end{pmatrix},$$

where $0 \leq p^i(\xi_n) \leq 1$ and $q^i = 1 - p^i$ for $i = 1, 2$. It is easy to see that

$$\lambda_{max} = 1, \quad \lambda_{min} = p^1 + p^2 - 1 \quad \text{and} \quad v^* = \begin{pmatrix} \frac{q^2}{q^1 + q^2} \\ \frac{q^1}{q^1 + q^2} \end{pmatrix}.$$

3 Urn models for multi-arm clinical trials

We consider now the model introduced in [6] (and considered again in [5]) where balls are added depending on the success probabilities of each treatment. Define a success indicator as follows: let $(T_n^i)_{n \geq 1}$, $1 \leq i \leq d$, be d independent sequences of i.i.d. $\{0, 1\}$ -valued Bernoulli trials, independent of the i.i.d. *sampling* sequence $(U_n)_{n \geq 1}$ so that

$$\forall 1 \leq i \leq d, \quad \mathbb{P}(T_n^i = 1 | \sigma(Y_0, U_1, \dots, U_n, X_n)) = p^i, \quad 0 < p^i < 1.$$

The convention is to set $T_n^i = 1$ to indicate that the response of the i^{th} treatment in the n^{th} trial is a success ($T_n^i = 0$ otherwise). In this framework one considers the filtration $\mathcal{F}_n = \sigma(Y_0, U_k, T_k, 1 \leq k \leq n)$, $n \geq 0$. Let $N_n = (N_n^1, \dots, N_n^d)^t$ and $S_n = (S_n^1, \dots, S_n^d)^t$, where $N_n^i = N_{n-1}^i + X_n^i$, $n \geq 1$, still denotes the number of times the i^{th} treatment is selected among the first n stages and

$$S_n^i = S_{n-1}^i + T_n^i X_n^i, \quad n \geq 1,$$

denotes the *number of successes* of the i^{th} treatment among these N_n^i trials, $i = 1, \dots, d$. However, to avoid degeneracy of the procedure, we will make the following initialization assumption

$$N_0^i = 1, \quad S_0^i = 1, \quad i = 1, \dots, d$$

(which makes the above interpretation of these quantities correct “up to one unit”).

Define $Q_n = (Q_n^1, \dots, Q_n^d)^t$, where $Q_n^i = \frac{S_n^i}{N_n^i}$, $i = 1, \dots, d$ and $E_n = \sum_{i=1}^d Q_n^i$. We consider the following addition rule matrices

$$D_{n+1} = \begin{pmatrix} T_{n+1}^1 & \frac{Q_n^1(1-T_{n+1}^2)}{E_n - Q_n^2} & \dots & \frac{Q_n^1(1-T_{n+1}^d)}{E_n - Q_n^d} \\ \frac{Q_n^2(1-T_{n+1}^1)}{E_n - Q_n^1} & T_{n+1}^2 & \dots & \frac{Q_n^2(1-T_{n+1}^d)}{E_n - Q_n^d} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{Q_n^d(1-T_{n+1}^1)}{E_n - Q_n^1} & \frac{Q_n^d(1-T_{n+1}^2)}{E_n - Q_n^2} & \dots & T_{n+1}^d \end{pmatrix},$$

i.e. at stage $n + 1$, if the response of the i^{th} treatment is a success, then one ball of type i is added in the urn. Otherwise, $\frac{Q_n^j}{E_n - Q_n^i}$ balls of type j , $j \neq i$, are added. Then, one easily checks that the generating matrices are given by

$$H_{n+1} = \mathbb{E}[D_{n+1} | \mathcal{F}_n] = \begin{pmatrix} p^1 & \frac{Q_n^1}{E_n - Q_n^2} q^2 & \cdots & \frac{Q_n^1}{E_n - Q_n^d} q^d \\ \frac{Q_n^2}{E_n - Q_n^1} q^1 & p^2 & \cdots & \frac{Q_n^2}{E_n - Q_n^d} q^d \\ \vdots & \vdots & \ddots & \vdots \\ \frac{Q_n^d}{E_n - Q_n^1} q^1 & \frac{Q_n^d}{E_n - Q_n^2} q^2 & \cdots & p^d \end{pmatrix}.$$

In this case, the matrices H_n are random and *a.s.* converging (see [6] or Lemma 3.1 below) to

$$H = \begin{pmatrix} p^1 & \frac{p^1}{E - p^2} q^2 & \cdots & \frac{p^1}{E - p^d} q^d \\ \frac{p^2}{E - p^1} q^1 & p^2 & \cdots & \frac{p^2}{E - p^d} q^d \\ \vdots & \vdots & \ddots & \vdots \\ \frac{p^d}{E - p^1} q^1 & \frac{p^d}{E - p^2} q^2 & \cdots & p^d \end{pmatrix} \quad \text{where } E = p^1 + \cdots + p^d.$$

For the strong consistency (*a.s.* convergence) of the sequences $(\tilde{Y}_n)_{n \geq 0}$ and $(\tilde{N}_n)_{n \geq 0}$, we can apply Theorem 2.1. However Theorem 2.2 does not apply in this case because Assumption **(A5)** is not satisfied and, as we will see, cannot be satisfied since $H_n - H$ satisfies a *CLT*. In [5] is established a weak rate of convergence of Y_n toward its expectation $\mathbb{E}Y_n$, namely

$$\frac{Y_n - \mathbb{E}Y_n}{\sqrt{n}} \xrightarrow[n \rightarrow \infty]{\mathcal{L}} \mathcal{N}(0, \Sigma^\infty).$$

Unfortunately, in this setting the bias $\mathbb{E}Y_n - nv^*$ is of order \sqrt{n} . The authors add that as soon as

$$\sum_{n \geq 1} \frac{\|H_n - H\|_\infty}{\sqrt{n}} < \infty \quad \textit{a.s.}, \quad (3.16)$$

$\mathbb{E}Y_n$ can be replaced by nv^* to provide a *CLT*. But they cannot fulfil Condition (3.16) since they only show that $\|H_n - H\|_\infty = o(n^{-\frac{1}{4}})$ *a.s.* (see [6]).

Nevertheless by “over-vectorizing” our algorithm, we can prove a *CLT* in this framework: this is the subject of the next section.

3.1 Rate of convergence for multi-arm clinical trials

To establish the *CLT* we must write a new recursive procedure by including the \mathbb{R}_+^d -valued quantity $\tilde{S}_n = \frac{S_n}{n}$ and by noticing that the generating matrix H_{n+1} may be written as a function depending on \tilde{S}_n and \tilde{N}_n , *i.e.* $H_{n+1} = \Phi(\tilde{S}_n, \tilde{N}_n)$, where $\Phi : \mathbb{R}_+^d \times (0, \infty)^d \rightarrow \mathcal{M}_d(\mathbb{R})$ is a differentiable function defined by

$$\Phi(s, \nu) = (\Phi^{ij})_{1 \leq i, j \leq d} \quad \text{where} \quad \begin{cases} \Phi^{ii} = p^i & 1 \leq i \leq d \\ \Phi^{ij} = \frac{s^i \nu^i}{\sum_{k \neq j} s^k \nu^k} q^j & 1 \leq i, j \leq d, i \neq j. \end{cases}$$

We define for every $n \geq 1$ the new state vector $\tilde{\theta}_n := (\tilde{Y}_n, \tilde{N}_n, \tilde{S}_n)^t$ and its expected limit $\tilde{\theta}^* := (v^*, v^*, u^*)^t$ where $u^* = \text{diag}(p)v^*$.

Theorem 3.1. *Assume that (A1), (A4), (A5) and (2.13) hold. Then*

$$\tilde{\theta}_n \xrightarrow[n \rightarrow \infty]{a.s.} \tilde{\theta}^* \quad \text{and} \quad \sqrt{n} \left(\tilde{\theta}_n - \tilde{\theta}^* \right) \xrightarrow[n \rightarrow \infty]{\mathcal{L}} \mathcal{N} \left(0, \tilde{\Sigma} \right),$$

with

$$\tilde{\Sigma} = \int_0^{+\infty} e^{u(D\tilde{h}(\tilde{\theta}^*) - \frac{I}{2})} \tilde{\Gamma} e^{u(D\tilde{h}(\tilde{\theta}^*) - \frac{I}{2})^t} du$$

where $\tilde{\Gamma} = a.s. \lim_{n \rightarrow +\infty} \mathbb{E} \left[\Delta \tilde{M}_{n+1} \Delta \tilde{M}_{n+1}^t \mid \mathcal{F}_n \right]$ (with $(\Delta \tilde{M}_n)_{n \geq 1}$ a sequence of martingale increments defined in the proof below) reads

$$\tilde{\Gamma} = \begin{pmatrix} \sum_{k=1}^d v^{*k} C^k & H \left(\text{diag}(v^*) - v^*(v^*)^t \right) & \left(\text{diag}(v^*) - v^*(v^*)^t \right) \text{diag}(p) \\ \left(\text{diag}(v^*) - v^*(v^*)^t \right)^t H^t & \text{diag}(v^*) - v^*(v^*)^t & \left(\text{diag}(v^*) - v^*(v^*)^t \right) \text{diag}(p) \\ \text{diag}(p) \left(\text{diag}(v^*) - v^*(v^*)^t \right)^t & \text{diag}(p) \left(\text{diag}(v^*) - v^*(v^*)^t \right)^t & \text{diag}(p) \left(v^* - v^* v^{*t} \text{diag}(p) \right) \end{pmatrix}.$$

Proof. STEP 1 (Strong consistency).

Lemma 3.1. *If the assumptions (1.1), (2.3), (2.4) hold, then,*

$$Q_n \xrightarrow[n \rightarrow \infty]{a.s.} p = (p^1, \dots, p^d) \quad \text{as } n \rightarrow \infty$$

so that Assumption (2.5) holds i.e. $H_n \xrightarrow[n \rightarrow \infty]{a.s.} H$.

Proof of the lemma. *Step 1.* It follows from the dynamics (1.1) and the definition of D_{n+1} and H_{n+1} that, for every $n \geq 0$, $\text{Tr}(Y_n) = \text{Tr}(Y_0) + n$ and that, for every $i \in \{1, \dots, d\}$,

$$Y_{n+1}^i = Y_n^i + \sum_{j=1}^d H_{n+1}^{ij} \frac{Y_n^j}{\text{Tr} Y_n} + \Delta M_{n+1}^i$$

where $(\Delta M_n^i)_{n \geq 1}$ is a sequence of martingale increments satisfying $\sup_n \mathbb{E} [|\Delta M_n^i|^2 \mid \mathcal{F}_{n-1}] < +\infty$ owing to (2.4). Now using that $S_0^i = N_0^i = 1$ by convention, one derives that

$$\forall i \neq j, H_{n+1}^{ij} \geq \frac{\kappa_0}{n}, \quad \text{with } \kappa_0 = \frac{1}{2d} \min_{1 \leq i \leq d} (p^i, q^i) > 0$$

so that, using that $H_{n+1}^{ii} = p^i$, there exists a deterministic integer n_0 such that for every $n \geq n_0$,

$$\begin{aligned} Y_{n+1}^i &\geq \left(1 + \frac{p_i}{n} - \frac{\kappa_0}{n \text{Tr} Y_n} \right) Y_n^i + \frac{\kappa_0}{n} + \Delta M_{n+1}^i \\ &\geq \left(1 + \frac{p_i}{2 \text{Tr}(Y_n)} \right) Y_n^i + \frac{\kappa_0}{n} + \Delta M_{n+1}^i. \end{aligned}$$

Standard computations show that, setting $a_n^i = \prod_{k=n_0}^{n-1} (1 + \frac{p_i}{2\text{Tr}(Y_n)})$, $i = 1, \dots, d$,

$$\forall n \geq n_0, \quad \frac{Y_n^i}{a_n^i} \geq \frac{Y_{n_0}^i}{a_{n_0}^i} + \sum_{k=n_0+1}^n \frac{\kappa_0}{a_k^i} + \sum_{k=n_0+1}^n \frac{\Delta M_k^i}{a_k^i}$$

Since there exists $\kappa_1, \kappa_2 > 0$ such that $\kappa_1 n^{\frac{p_i}{2}} \leq a_n^i \leq \kappa_2 n^{\frac{p_i}{2}}$, one has

$$\forall \eta > 0, \quad \sum_{k=n_0+1}^n \frac{\Delta M_k^i}{a_k^i} = o(n^{\frac{1-p_i+\eta}{2}}).$$

Finally, there exists a positive real constant c' such that, for every $i = 1, \dots, d$,

$$Y_n^i \geq c' n^{\frac{p_i}{2}} \sum_{k=n_0+1}^n k^{-\frac{p_i}{2}} + o(n^{\frac{1+\eta}{2}})$$

so that

$$\forall i \in \{1, \dots, d\}, \quad \liminf_n \tilde{Y}_n^i \geq c' \int_0^1 u^{-\frac{p_i}{2}} du > 0$$

and, as a consequence, $\sum_{n \geq 1} \tilde{Y}_n^i = +\infty$ -a.s. Now using that for every $i = 1, \dots, d$,

$$N_n^i = \sum_{k=1}^n \mathbf{1}_{\{X_k=e^i\}} \quad \text{and} \quad \mathbb{P}(X_n = e^i | \mathcal{F}_{n-1}) = \tilde{Y}_{n-1}^i \left(1 - \frac{\text{Tr}(Y_0)}{\text{Tr}(Y_{n-1})}\right), \quad n \geq 1,$$

we get by the conditional Borel-Cantelli Lemma that $N_\infty^i = \lim_n N_n^i = +\infty$ a.s.

Step 2. First we note that

$$Q_n^i = \frac{\sum_{k=1}^n T_k^i \Delta N_k^i}{N_n^i}$$

and we introduce the sequence $(\tilde{Q}_n)_{n \geq 1}$ defined by

$$\tilde{Q}_n^i = \sum_{k=1}^n (T_k^i - p^i) \frac{\Delta N_k^i}{N_{k-1}^i + 1}, \quad n \geq 1.$$

It is an \mathcal{F}_n -martingale since, T_k^i being independent of \mathcal{F}_{k-1} and X_k ,

$$\mathbb{E}\left((T_k^i - p^i) \Delta N_k^i | \mathcal{F}_{k-1}\right) = \mathbb{E}(T_k^i - p^i) \mathbb{P}(X_k = e^i | \mathcal{F}_{k-1}) = 0.$$

It has bounded increments since $|T_k^i - p^i| \leq 1$ and

$$\langle \tilde{Q}^i \rangle_n \leq \sum_{k=1}^n \frac{\mathbb{E}((\Delta N_k^i)^2 | \mathcal{F}_{k-1})}{(N_{k-1}^i + 1)^2}.$$

It follows, using $(\Delta N_k^i)^2 = \Delta N_k^i$, that, for every $n \geq 1$,

$$\mathbb{E}\langle \tilde{Q}^i \rangle_n \leq \mathbb{E}\left(\sum_{k=1}^n \frac{\Delta N_k^i}{(N_{k-1}^i + 1)^2}\right) \leq \mathbb{E}\left(\sum_{k=1}^n \frac{\Delta N_k^i}{N_{k-1}^i N_k^i}\right) \leq \frac{1}{N_0^i} = 1.$$

Consequently $\tilde{Q}_n^i \rightarrow \tilde{Q}_\infty^i \in L^1(\mathbb{P})$ a.s. as $n \rightarrow \infty$. This in turn implies by Kronecker's Lemma that

$$Q_n^i \xrightarrow{a.s.} p^i \quad \text{as } n \rightarrow \infty$$

since $N_n^i \rightarrow \infty$ by the first step. \square

It follows from the lemma and Theorem 2.1 that $(\tilde{Y}_n, \tilde{N}_n) \rightarrow (v^*, v^*)$. Furthermore $\text{diag}(\tilde{S}_n) = \text{diag}(Q_n)\tilde{N}_n \rightarrow \text{diag}(p)v^* = u^*$ so that $\tilde{\theta}_n \rightarrow \tilde{\theta}^*$ as $n \rightarrow \infty$.

STEP 2 (*Asymptotic normality*). We will show now that $(\tilde{\theta}_n)_{n \geq 1}$ satisfies an appropriate recursion to apply Theorem A.2 (*CLT*). First, we write a recursive procedure for \tilde{S}_n . Having in mind that $S_n = 1 + \sum_{1 \leq k \leq n} \text{diag}(T_k)X_k$, we get

$$\begin{aligned} \tilde{S}_{n+1} &= \tilde{S}_n - \frac{1}{n+1} \left(\tilde{S}_n - \text{diag}(T_{n+1})X_{n+1} \right) \\ &= \tilde{S}_n - \frac{1}{n+1} \left(\tilde{S}_n - \text{diag}(p) \frac{\tilde{Y}_n}{\text{Tr}(\tilde{Y}_n)} \right) + \frac{1}{n+1} \Delta \widehat{M}_{n+1} \\ &= \tilde{S}_n - \frac{1}{n+1} \left(\tilde{S}_n - \text{diag}(p)(2 - \text{Tr}(\tilde{Y}_n))\tilde{Y}_n \right) + \frac{1}{n+1} \left(\Delta \widehat{M}_{n+1} + \widehat{r}_{n+1} \right) \end{aligned} \quad (3.17)$$

where $\Delta \widehat{M}_{n+1} := \text{diag}(T_{n+1})X_{n+1} - \mathbb{E}[\text{diag}(T_{n+1})X_{n+1} | \mathcal{F}_n] = \text{diag}(T_{n+1})X_{n+1} - \text{diag}(p) \frac{\tilde{Y}_n}{\text{Tr}(\tilde{Y}_n)}$

is an \mathcal{F}_n -martingale increment and $\widehat{r}_{n+1} = \text{diag}(p) \frac{(\text{Tr}(\tilde{Y}_n) - 1)^2}{\text{Tr}(\tilde{Y}_n)} \tilde{Y}_n$. Then we rewrite the dynamics satisfied by \tilde{Y}_n as follows

$$\tilde{Y}_{n+1} = \tilde{Y}_n - \frac{1}{n+1} \left(I_d - (2 - \text{Tr}(\tilde{Y}_n))H_{n+1} \right) \tilde{Y}_n + \frac{1}{n+1} (\Delta M_{n+1} + \check{r}_{n+1}), \quad (3.18)$$

where $\check{r}_{n+1} := \frac{(\text{Tr}(\tilde{Y}_n) - 1)^2}{\text{Tr}(\tilde{Y}_n)} H_{n+1} \tilde{Y}_n$. Finally, we get the following recursive procedure for $\tilde{\theta}_n$

$$\tilde{\theta}_{n+1} = \tilde{\theta}_n - \frac{1}{n+1} \tilde{h}(\tilde{\theta}_n) + \frac{1}{n+1} \left(\Delta \widetilde{M}_{n+1} + \widetilde{R}_{n+1} \right), \quad n \geq 1,$$

where, for every $\tilde{\theta} = (y, \nu, s)^t \in \mathbb{R}_+^{3d}$,

$$\tilde{h}(\tilde{\theta}) := \begin{pmatrix} (I_d - (2 - \text{Tr}(y))\Phi(s, \nu))y \\ \nu - (2 - \text{Tr}(y))y \\ s - (2 - \text{Tr}(y))\text{diag}(p)y \end{pmatrix}, \quad \Delta \widetilde{M}_{n+1} := \begin{pmatrix} \Delta M_{n+1} \\ \Delta \widehat{M}_{n+1} \\ \Delta \widehat{M}_{n+1} \end{pmatrix} \quad \text{and} \quad \widetilde{R}_{n+1} := \begin{pmatrix} \check{r}_{n+1} \\ \check{r}_{n+1} \\ \check{r}_{n+1} \end{pmatrix}.$$

The function Φ being differentiable at the equilibrium point $\tilde{\theta}^*$, we have

$$D\tilde{h}(\tilde{\theta}^*) = \begin{pmatrix} I_d - H + v^* \mathbf{1}^t & -\frac{\partial}{\partial \nu} (\Phi(s, \nu)y)|_{\tilde{\theta}=\tilde{\theta}^*} & -\frac{\partial}{\partial s} (\Phi(s, \nu)y)|_{\tilde{\theta}=\tilde{\theta}^*} \\ v^* \mathbf{1}^t - I_d & I_d & 0_{\mathcal{M}_d(\mathbb{R})} \\ \text{diag}(p)(v^* \mathbf{1}^t - I_d) & 0_{\mathcal{M}_d(\mathbb{R})} & I_d \end{pmatrix}$$

which is invertible since by Schur complement we have $\det(D\tilde{h}(\tilde{\theta}^*)) = \det(I_d - H + v^* \mathbf{1}^t)$ thanks to $\frac{\partial}{\partial v} (\Phi(s, \nu)y)|_{\tilde{\theta}=\tilde{\theta}^*} = -\text{diag}(p) \frac{\partial}{\partial s} (\Phi(s, \nu)y)|_{\tilde{\theta}=\tilde{\theta}^*}$.

At this stage, the proof follows the lines of that of Theorem 2.2: the computation of the covariance matrix $\tilde{\Gamma}$ and the treatment of the remainder term uses the same tools as before. The details are left to the reader. \square

Remarks. • The asymptotic variances of \tilde{Y}_n and \tilde{N}_n in Theorem 3.1 are different from those in Theorem 2.2 because the differential matrices $Dh(\theta^*)$ and $D\tilde{h}(\tilde{\theta}^*)$ are not the same.

• In the SA Theory, there also exists some results on the rate of convergence without CLT. For the sake of simplicity, in this paper we only treat the case where $L > \frac{1}{2}$, with $L = \min \{\text{Re}(\lambda); \lambda \in \text{Sp}(Dh(\theta^*))\}$.

When $L = \frac{1}{2}$, \sqrt{n} can be replaced by $\sqrt{\frac{n}{(\ln n)^\alpha}}$, $\alpha > 0$, and when $L < \frac{1}{2}$, we have an *a.s.* convergence toward a finite random variable at a rate n^{-L} (see [12]).

Corollary 3.1. *Under the assumptions of Theorem 3.1,*

$$\sqrt{n}(H_n - H) \xrightarrow[n \rightarrow \infty]{\mathcal{L}} \mathcal{N}(0; \Gamma_H)$$

where Γ_H is a $d^2 \times d^2$ matrix given by $\Gamma_H = D\Phi(u^*, v^*)[\tilde{\Sigma}_{i+d, j+d}]_{1 \leq i, j \leq 2d} D\Phi(u^*, v^*)^t$.

Proof. This is an easy consequence of the so-called Δ -method since

$$H_n = \Phi(\tilde{S}_n, \tilde{N}_n) = \Phi(u^*, v^*) + D\Phi(u^*, v^*) \cdot (\tilde{S}_n - u^*, \tilde{N}_n - v^*) + \|\tilde{\varepsilon}(\tilde{S}_n, \tilde{N}_n)\| \varepsilon(\tilde{S}_n, \tilde{N}_n)$$

with $\lim_{y \rightarrow (u^*, v^*)} \varepsilon(y) = 0$. Consequently

$$\sqrt{n}(H_n - H) = D\Phi(u^*, v^*) \cdot (\sqrt{n}(\tilde{S}_n - u^*), \sqrt{n}(\tilde{N}_n - v^*)) + \varepsilon_{\mathbb{P}}(n)$$

where $\varepsilon_{\mathbb{P}}(n)$ goes to 0 in probability (as the product of a tight sequence and an *a.s.* convergent sequence). This concludes the proof. \square

Remark. This corollary shows *a posteriori* that it was hopeless to try applying Theorem 2.2 in its standard form to establish asymptotic normality for multi-arm clinical trials since the assumption $\mathbb{E}\|H_n - H\|^2 = o(n^{-1})$ cannot be satisfied. Our global SA approach breaks the vicious circle.

NUMERICAL EXAMPLE: MULTI-ARM CLINICAL TEST. We consider the case $d = 2$, so v^* as the same form as in the example in Subsection 2.3.

Appendix

A Basic tools of Stochastic Approximation

Consider the following recursive procedure defined on a filtered probability space $(\Omega, \mathcal{A}, (\mathcal{F}_n)_{n \geq 0}, \mathbb{P})$

$$\forall n \geq n_0, \quad \theta_{n+1} = \theta_n - \gamma_{n+1} h(\theta_n) + \gamma_{n+1} (\Delta M_{n+1} + r_{n+1}), \quad (\text{A.19})$$

where $h : \mathbb{R}^d \rightarrow \mathbb{R}^d$ is a locally Lipschitz continuous function, θ_{n_0} an \mathcal{F}_{n_0} -measurable finite random vector and, for every $n \geq n_0$, ΔM_{n+1} is an \mathcal{F}_n -martingale increment and r_n is an \mathcal{F}_n -adapted remainder term.

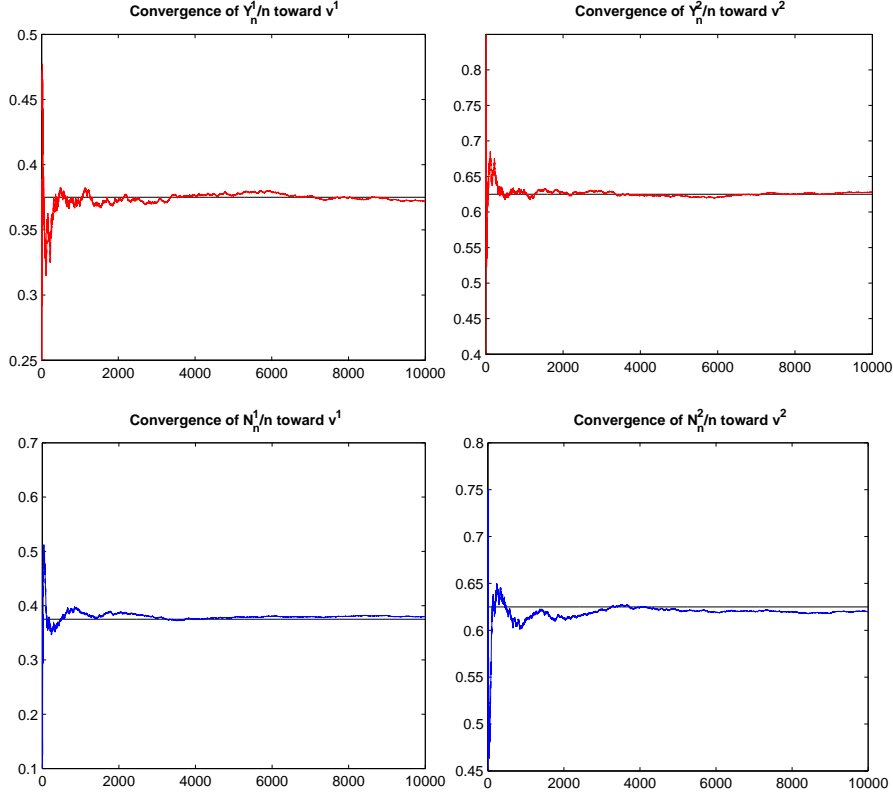


Figure 1: Convergence of $\frac{Y_n}{n}$ toward v^* (up-windows) and of $\frac{N_n}{n}$ toward v^* (down-windows): $d = 2$, $n = 10^4$, $p^1 = 0.5$, $p^2 = 0.7$, $Y_0 = (0.5, 0.5)^t$ and $N_0 = (0, 0)^t$.

Theorem A.1. (a.s. convergence with ODE method, see e.g. [8, 12, 19, 14, 7]). Assume that h is locally Lipschitz, that

$$r_n \xrightarrow[n \rightarrow \infty]{a.s.} 0 \quad \text{and} \quad \sup_{n \geq n_0} \mathbb{E} \left[\|\Delta M_{n+1}\|^2 \mid \mathcal{F}_n \right] < +\infty \quad a.s.,$$

and that $(\gamma_n)_{n \geq 1}$ is a positive sequence satisfying

$$\sum_{n \geq 1} \gamma_n = +\infty \quad \text{and} \quad \sum_{n \geq 1} \gamma_n^2 < +\infty.$$

Then the set Θ^∞ of its limiting values as $n \rightarrow +\infty$ is a.s. a compact connected set, left stable by the flow of

$$ODE_h \equiv \dot{\theta} = -h(\theta).$$

Furthermore if $\theta^* \in \Theta^\infty$ is a uniformly stable equilibrium on Θ^∞ of ODE_h , then

$$\theta_n \xrightarrow[n \rightarrow \infty]{a.s.} \theta^*.$$

COMMENTS. By uniformly stable we mean that

$$\sup_{\theta \in \Theta^\infty} |\theta(\theta_0, t) - \theta^*| \longrightarrow 0 \quad \text{as } t \rightarrow +\infty,$$

where $\theta(\theta_0, t)_{\theta_0 \in \Theta^\infty, t \in \mathbb{R}_+}$ is the flow of ODE_h on Θ^∞ .

Theorem A.2. (CLT see e.g. [8, 12, 19]). Let θ^* be an equilibrium point of $\{h = 0\}$. Assume that the function h is differentiable at θ^* and all the eigenvalues of $Dh(\theta^*)$ have positive real parts. Assume that for some $\delta > 0$,

$$\sup_{n \geq n_0} \mathbb{E} \left[\|\Delta M_{n+1}\|^{2+\delta} \mid \mathcal{F}_n \right] < +\infty \text{ a.s.}, \quad \mathbb{E} \left[\Delta M_{n+1} \Delta M_{n+1}^t \mid \mathcal{F}_n \right] \xrightarrow[n \rightarrow \infty]{\text{a.s.}} \Gamma, \quad (\text{A.20})$$

where Γ is a nonrandom symmetric definite positive matrix and for an $\epsilon > 0$,

$$\mathbb{E} \left[(n+1) \|r_{n+1}\|^2 \mathbf{1}_{\{\|\theta_n - \theta^*\| \leq \epsilon\}} \right] \xrightarrow[n \rightarrow \infty]{} 0. \quad (\text{A.21})$$

Specify the gain parameter sequence as follows

$$\forall n \geq 1, \quad \gamma_n = \frac{\alpha}{n}, \quad \alpha > \frac{1}{2\mathcal{R}e(\lambda_{\min})} \quad (\text{A.22})$$

where λ_{\min} denotes the eigenvalue of $Dh(\theta^*)$ with the lowest real part. Then, the above a.s. convergence is ruled on the convergence set $\{\theta_n \rightarrow \theta^*\}$ by the following Central Limit Theorem

$$\sqrt{n} (\theta_n - \theta^*) \xrightarrow[n \rightarrow \infty]{\mathcal{L}} \mathcal{N}(0, \alpha \Sigma),$$

with $\Sigma := \int_0^{+\infty} \left(e^{-\left(Dh(\theta^*) - \frac{I_d}{2\alpha}\right)u} \right)^t \Gamma e^{-\left(Dh(\theta^*) - \frac{I_d}{2\alpha}\right)u} du$.

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