MULTI-ARM CLINICAL TRIALS WITH FINITE RESPONSE AND NON HOMOGENEOUS URN FUNCTION

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Abstract. An adaptive design for a clinical trial with prognostic factors and more than two treatments is described using a generalised urn model in a random environment. Patients arrive sequentially and treatments are applied according to a function of the urn composition. This function may change at each stage. Patient's response is immediate and discrete, with a finite number of possible values. The evolution of the urn composition is expressed by a recurrence equation that fits the Robbins-Monro scheme of stochastic approximation. In this setting, we obtain asymptotic properties for the performance of each treatment and we illustrate the application of the rule with an example.

Keywords: Adaptive designs; Urn models; Robbins-Monro algorithm; ODE method

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§1. Introduction

A sequential design is called adaptive design or response-driven design when, in each stage, the sequential allocation is made depending on the past allocations and outcomes. In the context of clinical trials, the use of accruing information can help to limit the number of patients that are exposed to treatments with high probability of failure. Randomised urn models are the techniques commonly used to perform adaptive designs (see [3] and [8] and the references therein).

The randomised Play-The-Winner rule introduced in [9], is a well-known adaptive design used in clinical trials. In [1] this rule is modified to include prognostic factors. In [6], their model is modified in several ways. First, more than two treatments are considered in the trial. Second, the replacement matrices and the success probability functions are general. Third, a modulation of the allocation rule is allowed by means of an urn function and, fourth, the asymptotic results for the statistics that measure the performance of the treatments are obtained without assumptions on the success probabilities of the treatments.

In this paper, the design introduced in [6] is generalized in two ways. First, by assuming finite responses of the patients, instead of dichotomous, and second, by permitting a different allocation rule in each step, that is, by considering a sequence of urn functions.

In order to obtain these results, the evolution of the urn composition is expressed by a recurrence equation that fits the Robbins-Monro scheme of stochastic approximation. Stochastic

approximation theory (see, for example, [2]) appears as an adequate framework to study some stochastic processes generated in an adaptive design.

This paper is organised as follows. In section 2, the adaptive design is described by means of a Pólya urn model in a random environment. Conditions on this urn model that guarantee convergence results of the urn composition are established. In section 3, estimators of the treatments performance are proposed, their asymptotic behaviour is studied and an example is included to illustrate the previous results.

§2. Adaptive design with finite response and non homogeneous urn function.

We are interested in an adaptive design of a clinical trial to compare $L \geq 2$ treatments with finite response, where the patients arrive sequentially and they can be classified according to a prognostic factor with $K+1$ levels $0, \ldots, K$.

For each n, let $\delta_n = (\delta_{1n}, \ldots, \delta_{Ln})$ be an L-dimensional random vector of indicator variables such that $\delta_{hn} = 1$ if treatment h has been applied to the n-th patient and 0 otherwise, $h = 1, \ldots, L$.

Let $\{\xi_n\}$ be a sequence of random variables independent and identically distributed, such that, for each n, ξ_n represents the level of the n-th patient. We denote $P(\xi_1 = i) = \pi_i$, $0 < \pi_i < 1$, $i = 0, \ldots, K$.

In order to assign treatments, we consider an urn that contains balls of L different types. Let $\mathbb{X}_n = (X_{1n}, \ldots, X_{Ln})$ be the proportion of balls of each type in the urn after stage n. For $i = 1, \cdots, L$, we consider $X_{i0} > 0$ and we denote $T_0 = \sum_{i=0}^{L} X_{i0}$. As it will be seen later, the urn replacement policy guarantees that for all n, $\mathbb{X}_n \in \Delta_{L-1}$, where $\Delta_{L-1} = \{\mathbf{x} \in \mathbb{R}^L : \sum_{i=1}^{L} x_i = 1,\ x_i > 0\}$. We consider, for each n, a measurable function $\varphi_n : \Delta_{L-1} \to \Delta_{L-1}$, and $\varphi_n(\mathbb{X}_n) = (\varphi_{1n}(\mathbb{X}_n), \ldots, \varphi_{Ln}(\mathbb{X}_n))$. The n-th patient, independently of his level, is assigned to treatment h with probability $\varphi_{hn}(\mathbb{X}_{n-1})$, $h = 1, \ldots, L$.

The patient gives, in each stage n, an immediate and discrete response Z_n that can take J different values: $j = 1, \ldots, J$. The composition of the urn is modified in the following way: given that the treatment assigned is h and the patient's level is i, if the response is j then $c_{(Jh-(j-1));t}(i) \geq 0$ balls of type t are added to the urn, $t = 1, \ldots, L$. Observe that the first subscript, $Jh-(j-1)$, indicates that for each treatment applied, h, there are J different replacement vectors, depending on the response given j. So that, taking each replacement vector as a row of a $JL \times L$ non-negative matrix, we have $C(i) = (c_{rt}(i))$, $i = 0, \ldots, K$, $r = 1, \ldots, JL$, $t = 1, \ldots, L$. We assume that

[A1] $C(i)\mathbf{1}^t = s\mathbf{1}^t,\ i = 0, \ldots, K,$

where $\mathbf{1}^t$ is the column vector of ones and s is a positive real number. Obviously, the total number of balls added to the urn in every stage is s. Then, the total number of balls in the urn after the n-th replacement, T_n, is $T_0 + ns$.

At each stage n, we consider $\gamma_n = (\gamma_{1n}, \ldots, \gamma_{Ln})$, where $\gamma_{jn} = 1$ if $Z_n = j$ and 0 otherwise. The replacement policy is modelled by a random replacement matrix, $C(\xi_n)$, and by the random vector:

$$A_n := (\delta_{1n}\gamma_{1n}, \ldots, \delta_{1n}\gamma_{Jn}, \ldots, \delta_{Ln}\gamma_{1n}, \ldots, \delta_{Ln}\gamma_{Jn}),$$

which takes a value from the set $\{e_i\}_{i=1,\ldots,JL}$, the natural basis of $\mathbb{R}^{JL}$. So that, in the n-th

replacement, balls of each colour are added to the urn according to the vector $A_nC(\xi_n)$. The evolution of the process $\{\mathbb{X}_n\}$ is represented by means of the recursion

$$\mathbb{X}_{n+1} = \frac{T_n\mathbb{X}_n + A_{n+1}C(\xi_{n+1})}{T_{n+1}} = \mathbb{X}_n + \frac{A_{n+1}C(\xi_{n+1}) - s\mathbb{X}_n}{T_{n+1}}. \tag{1}$$

The process $\{(\mathbb{X}_n,\, \xi_n,\, A_n)\}$ is a generalised Pólya urn model of the clinical trial and we denote its natural filtration by $\{\mathcal{F}_n\}$. The process $\{\xi_n\}$ can be seen as the random environment of the urn.

The random environment is supposed to be independent of the past history of the process. That is:

[A2] For each $n \geq 1$, ξ_{n+1} is independent of $\mathcal{F}_n$.

The response variable, Z_n, depends on both the treatment assigned δ_n and the type of patient ξ_n, and it is independent of the previous history of the clinical trial. That is,

$$P(Z_n = j \mid \delta_{hn} = 1,\, \xi_n = i,\, \mathcal{F}_{n-1}) = P(Z_n = j \mid \delta_{hn} = 1, \xi_n = i), \quad j = 1, \ldots, J \tag{2}$$

for $h = 1, \ldots, L$ and $i = 0, \ldots, K$.

Besides, given a treatment h and a patient's level i, the probability distribution of Z_n does not depend on n, and we denote

$$p_{hi}(j) := P(Z_n = j \mid \delta_{hn} = 1, \xi_n = i), \quad h = 1, \cdots, L, \quad i = 0, \ldots, K, \quad j = 1, \ldots, J. \tag{3}$$

where $0 < p_{hi}(j) < 1$, for all h, i and j. Then, for $h = 1, \ldots, L$, $i = 0, \ldots, K$ and $r = 0, \ldots, J-1$ we have

$$\begin{aligned} P(A_n = e_{(Jh-r)} | \mathcal{F}_{n-1}, \xi_n = i) &= P(\delta_{hn} = 1,\ Z_n = J - r | \mathcal{F}_{n-1}, \xi_n = i) \\ &= P(Z_n = J - r \mid \delta_{hn} = 1,\, \mathcal{F}_{n-1},\, \xi_n = i) \\ &\quad \times P(\delta_{hn} = 1 \mid \mathcal{F}_{n-1}, \xi_n = i) \\ &= \varphi_{hn}(\mathbb{X}_{n-1}) p_{hi}(J - r) \end{aligned} \tag{4}$$

Therefore, if we consider the matrices

$$Q(i) = \begin{pmatrix} p_{1i}(1) & p_{1i}(2) & \ldots & p_{1i}(J) & 0 & \ldots & 0 & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \ldots & p_{Li}(1) & p_{Li}(2) & \ldots & p_{Li}(J) \end{pmatrix},$$

for $i = 0, \ldots, K$, we have,

$$P(A_n = e_j | \mathcal{F}_{n-1}, \xi_n) = (\varphi_n(\mathbb{X}_{n-1}) Q(\xi_n))_j, \quad j = 1, \ldots, JL. \tag{5}$$

The recursive equation (1) suggests the following result.

Proposition 1. *The urn process* $\{(\mathbb{X}_n,\, \xi_n,\, A_n)\}$ *verifying* **[A1]** *and* **[A2]** *fits the stochastic approximation scheme*

$$\mathbb{X}_{n+1} = \mathbb{X}_n + \gamma_{n+1}(F_{n+1}(\mathbb{X}_n) + \varepsilon_{n+1}) \tag{6}$$

where:

1.- $\{\gamma_n\}$ *is a sequence of positive real numbers such that* $\sum \gamma_n = \infty$ *and* $\sum \gamma_n^2 < \infty$.
2.- $F_{n+1}(\mathbf{x}) = \varphi_{n+1}(\mathbf{x})H - s\mathbf{x}$, *where* H *is a* $L \times L$ *non-negative matrix.*
3.- $\{\varepsilon_n\}$ *is a sequence of martingale differences relative to the filtration* $\{\mathcal{F}_n\}$.

Proof. Since

$$\mathbb{X}_{n+1} = \mathbb{X}_n + \frac{A_{n+1}C(\xi_{n+1}) - s\mathbb{X}_n}{T_{n+1}},$$

then

$$\begin{aligned} E[\mathbb{X}_{n+1} \mid \mathcal{F}_n] &= \mathbb{X}_n + \frac{1}{T_{n+1}}(E[A_{n+1}C(\xi_{n+1}) \mid \mathcal{F}_n] - s\mathbb{X}_n) \\ &= \mathbb{X}_n + \frac{1}{T_{n+1}}(E[E[A_{n+1}C(\xi_{n+1}) \mid \mathcal{F}_n, \xi_{n+1}] \mid \mathcal{F}_n] - s\mathbb{X}_n) \\ &= \mathbb{X}_n + \frac{1}{T_{n+1}}(\varphi_{n+1}(\mathbb{X}_n)E[Q(\xi_{n+1})C(\xi_{n+1}) \mid \mathcal{F}_n] - s\mathbb{X}_n) \\ &= \mathbb{X}_n + \frac{1}{T_{n+1}}(\varphi_{n+1}(\mathbb{X}_n)E[Q(\xi_{n+1})C(\xi_{n+1})] - s\mathbb{X}_n) \end{aligned}$$

where we have applied (5) in the third equality and **[A2]** in the fourth.
Thus, denoting $H = E[Q(\xi_1)C(\xi_1)]$, the urn process can be expressed as

$$\begin{aligned} \mathbb{X}_{n+1} &= E[\mathbb{X}_{n+1} \mid \mathcal{F}_n] + (\mathbb{X}_{n+1} - E[\mathbb{X}_{n+1} \mid \mathcal{F}_n]) \\ &= \mathbb{X}_n + \frac{1}{T_{n+1}}[(\varphi_{n+1}(\mathbb{X}_n)H - s\mathbb{X}_n) + \varepsilon_{n+1}]. \end{aligned}$$

where

$$\begin{aligned} \varepsilon_{n+1} &= T_{n+1}(\mathbb{X}_{n+1} - E[\mathbb{X}_{n+1} \mid \mathcal{F}_n]) \\ &= A_{n+1}C(\xi_{n+1}) - \varphi_{n+1}(\mathbb{X}_n)H. \end{aligned}$$

Denoting

$$\gamma_{n+1} = \frac{1}{T_{n+1}},$$

and

$$F_{n+1}(\mathbb{X}_n) = \varphi_{n+1}(\mathbb{X}_n)H - s\mathbb{X}_n$$

the result follows. □

Remark 1. When φ is continuous, F is continuous too and the scheme of Proposition 2.1 is the classical Robbins-Monro stochastic approximation scheme (see [5] or [2]).

In order to obtain asymptotic results for the process $\{\mathbb{X}_n\}$, the ODE (Ordinary Differential Equation) method will be applied (see [5]). This method relates the asymptotic behaviour of a stochastic recursive process with the asymptotics of the associated ODE. A broader discussion of this method applied to generalised Pólya urn models can be seen in [4] and an application to an adaptive design with dichotomous response in [6]. The following proposition will be crucial in the application of the ODE method to the process $\{\mathbb{X}_n\}$.

Proposition 2. *Let the urn process* $\{(\mathbb{X}_n,\, \xi_n,\, A_n)\}$ *be under assumptions* **[A1]** *and* **[A2]***and let* F_{n+1} *be the function obtained in Proposition 2.1. If there exists an* $L \times L$ *irreducible non-negative matrix* C *verifying* $C\mathbf{1}^t = s\mathbf{1}^t$, $s > 0$, *such that*

$$\|F_{n+1}(\mathbb{X}_n) - \mathbb{X}_n(C - sI)\| \to 0 \qquad a.s.$$

and if $\mathbf{u}$ *is the normalised left eigenvector of* C *associated with the eigenvalue* s, *then*

$$\mathbb{X}_n \to \mathbf{u}, \quad a.s.$$

Proof. Equation (6) can be written as

$$\mathbb{X}_{n+1} = \mathbb{X}_n + \gamma_{n+1}((\mathbb{X}_n - \mathbf{u})(C - sI) + \varepsilon_{n+1} + \beta_{n+1}) \tag{7}$$

where

$$\beta_{n+1} = F_{n+1}(\mathbb{X}_n) - \mathbb{X}_n(C - sI) \tag{8}$$

so that $\{\beta_n\}$ converges a.s. to 0.

Moreover, from Corollary A.1 in [4] , the conditions of the Theorem 5.2.1 in [5] are fulfilled. Hence, the result follows. □

Observe that $\sum_{j=1}^{n} \delta_{hj}/n$ represents the proportion of balls of type h extracted up to n. The following corollary establishes its relationship with the a.s. limit of $\{\mathbb{X}_n\}$.

Corollary 3. *In the conditions of Proposition 2 and assuming that* $\{\varphi_n\}$ *is a sequence of continuous functions that converges uniformly with the supremum norm to* φ, *then the process* $\{\delta_n\}$ *satisfies that*

$$\frac{1}{n}\sum_{j=1}^{n} \delta_j \to \varphi(\mathbf{u}), \qquad a.s.$$

Proof. Observe that for each h, $h = 1, \ldots, L$, and each j:

$$\begin{aligned} E[\delta_{hj}|\mathcal{F}_{j-1}] &= E[E[\delta_{hj}|\mathcal{F}_{j-1},\, \xi_j]|\mathcal{F}_{j-1}] \\ &= E[\varphi_{hj}(\mathbb{X}_{j-1})|\mathcal{F}_{j-1}] \\ &= \varphi_{hj}(\mathbb{X}_{j-1}) \end{aligned}$$

>From the extension of Lévy of the Borel-Cantelli lemma (see, for instance, [7] Corollary VII-2-6) the convergence

$$\frac{\displaystyle\sum_{j=1}^{n} \delta_{hj}}{\displaystyle\sum_{j=1}^{n} \varphi_{hj}(\mathbb{X}_{j-1})} \to 1,\ a.s. \tag{9}$$

is established on the set $\{\sum_{j=1}^{\infty} \varphi_{hj}(\mathbb{X}_{j-1}) = \infty\}$ for each h, $h = 1, \ldots, L$.

Moreover, as φ_n converges uniformly to φ, for all $\varepsilon > 0$ there exists n_1 such that $\forall n \geq n_1$ and $\forall \mathbf{x} \in \Delta_{L-1}$ we have that $|\varphi_{hn}(\mathbf{x}) - \varphi_h(\mathbf{x})| < \varepsilon/2$. Besides, as φ is continuous and, from

Proposition 2, $\mathbb{X}_n \to \mathbf{u},\ a.s.$, there exists n_2 such that $\forall n \geq n_2$ we have that $|\varphi_h(\mathbb{X}_{n-1}) - \varphi_h(\mathbf{u})| < \varepsilon/2,\ a.s.$ Then, $\forall n \geq max\{n_1, n_2\}$ we have the following a.s. inequalities

$$|\varphi_{hn}(\mathbb{X}_{n-1}) - \varphi_h(\mathbf{u})| \leq |\varphi_{hn}(\mathbb{X}_{n-1}) - \varphi_h(\mathbb{X}_{n-1})| + |\varphi_h(\mathbb{X}_{n-1}) - \varphi_h(\mathbf{u})| \leq \varepsilon \tag{10}$$

Therefore, $\{\varphi_n(\mathbb{X}_{n-1})\}$ converges a.s. to $\varphi(\mathbf{u})$.

As $\varphi_h(\mathbf{u}) > 0$ for each h, $h = 1, \ldots, L$, then $\sum_{j=1}^{\infty} \varphi_{hj}(\mathbb{X}_{j-1}) = \infty$ a.s., $\sum_{j=1}^{n} \varphi_{hj}(\mathbb{X}_{j-1})/n$ converges a.s. to $\varphi_h(\mathbf{u})$ and the result follows. □

§3. Asymptotic results.

In order to obtain inference results for the adaptive design described in section 2, we consider the urn model of the clinical trial in the conditions of Proposition 2 and assuming that φ is continuous. Given a treatment h and a patient's level i, the probability distribution of Z_n does not depend on n (see (2) and (3)). We denote

$$\mu_{hi} = E[Z_n|\delta_{hn} = 1,\, \xi_n = i] \quad \text{and} \quad \sigma^2_{hi} = Var[Z_n|\delta_{hn} = 1,\, \xi_n = i]$$

Let

$$g_{hn} = \frac{T_{hn}}{N_{hn}}, \quad h = 1, \ldots, L \tag{11}$$

where

$$T_{hn} = \sum_{k=1}^{n} f_h(\xi_k) Z_k \delta_{hk}, \qquad N_{hn} = \sum_{k=1}^{n} \delta_{hk}, \tag{12}$$

with $f_h(i) = \dfrac{\mu_{h0}}{\mu_{hi}}$, $h = 1, \ldots, L$, $i = 0, \ldots, K$.

In the following proposition we obtain asymptotic results for g_{hn}.

Proposition 4. *Consider the urn model of the clinical trial in the conditions of Proposition 2 and assume the conditions of Corollary 3. Let g_{hn} be as in (11), then*

$$g_{hn} \to \mu_{h0} \quad \textit{a.s.}$$

and the random vector $\sqrt{n}(g_{1n} - \mu_{10}, \ldots, g_{Ln} - \mu_{L0})$ converges in distribution to a multivariate normal distribution with zero mean vector and a diagonal variance and covariance matrix Σ, where

$$\Sigma_{hh} = \frac{A_h}{\varphi_h(\mathbf{u})}, \quad h = 1, \ldots, L$$

and $A_h = \sum_{i=0}^{K} \sigma^2_{hi} \pi_i / \mu^2_{hi}$.

Proof. >From Corollary 3 we have that $N_{hn} = \sum_{k=1}^{n} \delta_{hk}$ diverges a.s. for $h = 1, \ldots, L$. Besides, $N_{hn}/n \to \varphi_h(\mathbf{u})$, a.s. Then, using martingale techniques as in Proposition 3.1 and 3.2 in [6], the result follows. □

Example. We consider an adaptive design for a clinical trial where the allocation rule is given by $\varphi_{h(n+1)}(\mathbb{X}_n) = \alpha_n + (1 - L\alpha_n)X_{hn}$ for $h = 1, \ldots, L$, $\{\alpha_n\}$ is a sequence of real numbers such that $0 \leq \alpha_n \leq 1/L$, $\alpha_n \to \alpha$ as $n \to \infty$ and, therefore, $0 \leq \alpha \leq 1/L$. It is immediate that φ_n converges uniformly to φ, where $\varphi_h(\mathbf{x}) = \alpha + (1 - L\alpha)x_h$, $h = 1, \ldots, L$. It is not difficult to see that F_{n+1} in the Proposition 1 is

$$F_{n+1}(\mathbf{x}) = \mathbf{x}([\alpha_n \mathbf{1}^t\mathbf{1} + (1 - L\alpha_n)I]H - sI),$$

and then, from Proposition 2, the process $\{\mathbb{X}_n\}$ converges to $\mathbf{u}$ and the proportion of times that treatment h is applied converges to $\varphi_h(\mathbf{u})$, where $\mathbf{u}$ is the normalised left eigenvector associated to the eigenvalue s of the matrix $C = [\alpha\mathbf{1}^t\mathbf{1} + (1 - L\alpha)I]H$, provided that C is irreducible. This occurs when H is irreducible. In fact, if $\alpha = 0$, then $C = H$ and $\mathbf{u}$ is the eigenvector of H associated to s. If $\alpha = 1/L$, then $\mathbf{u}$ is the eigenvector of $(1/L)\mathbf{1}^t\mathbf{1}H$ associated to s, namely, $\mathbf{u} = 1/(Ls)(\beta_1, \ldots, \beta_L)$, where $\beta_j = \sum_{i=1}^{L} h_{ij}$.

A particular case of this situation, when $\alpha_n = \alpha$ for each n and the response is dichotomous, can be seen as example 4.2 in [6].

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