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Statistical properties of urn models in response-adaptive designs

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Abstract

In this thesis we analyze the statistical properties of response-adaptive designs, described in terms of two colors urn models, in a clinical trial context. We introduce an urn procedure, the Modified Randomly Reinforced Urn (MRRU) design, whose urn proportion asymptotically targets prespecified values. We prove asymptotic results for the process of colors generated by the urn and for the process of its compositions. An application of the proposed urn model is presented in an estimation problem context. Statistical performances of inferential procedures based on different statistics are investigated. We adopt the MRRU model to improve the performances, from both ethical and statistical point of views, of different tests for comparing the mean effect of two treatments. We apply the MRRU design for implementing the random allocation procedure in a real case study. Finally, we extend the MRRU model to obtain a response adaptive urn design that targets an asymptotic allocation defined as function of unknown parameters modeling the responses distribution.

Introduction

This thesis is focused on mathematical and statistical aspects of urn models used as randomized devices in the field of design of experiments. In particular, we consider the context of clinical trials, where the experimentation involves human subjects. In this framework, a central role is played by the randomization, that is now an essential feature of the scientific method. These procedures randomly assign the subjects that sequentially enter the trial to the treatments under study. The benefit of randomization has been deeply studied in many areas of research, especially in the clinical trial context. The strategy adopted to randomly allocate units to treatments generates different types of experimental designs. In this thesis, we focus on response-adaptive procedures, in which the allocations depend also on the responses given by the subjects previously assigned. This feature enables to create designs that change the probability of assignment of the subjects according to the treatments performances. This factor is very important, especially in clinical experimentation, where the ethical aspect is significant more than in other scientific fields. For this reason, the theory of clinical trials has been always characterized by a trade-off between the individual ethics of the subjects involved in the experiment and the collective ethics of the entire community. The first aims at maximizing the individual probability to receive the best treatment, while the second aims at maximizing the power of the procedure that determines the best treatment.

A large class of response-adaptive randomized designs is based on urn models, since they represent classical tools to guarantee a randomized device. Urn procedures can be characterized by different strategies of reinforcement and in this thesis we consider urn models with random non-negative reinforcements concerning only the extracted color. These designs have been called Play the Winner or Randomly Reinforced Urn (RRU) designs, and they are randomized devices able to asymptotically allocate subjects to the optimal treatment. These procedures had a good success, since their asymptotic behavior maximizes the individual ethics. Nevertheless, these designs are unsatisfactory for the collective ethics, since their statistical properties present some problems. At first, because there are many results for designs whose asymptotic allocation is $\rho \in (0,1)$, that cannot be applied to RRU models since their asymptotic allocation is $\rho \in \{0,1\}$. Moreover, these models generate groups with very different sample sizes. Then, the inferential procedures based on these designs are usually characterized by a very low power in comparing treatments effects. For these reasons, we have modified the reinforcement scheme of the urn to construct a design that asymptotically targets an allocation proportion $\rho \in (0,1)$. The term target indicates the limit of the urn proportion process. We will denote this urn model as the Modified Randomly Reinforced Urn (MRRU) design.

In Chapter 2, we introduce the MRRU model and we prove strong convergence of the urn proportion to the target allocation $\rho \in (0,1)$. Further first-order asymptotic properties of the urn model have been investigated. The study of the asymptotic behavior has been particulary challenging since the modified urn process does not present the sub/supermartingality properties presented by the RRU.

In Chapter 3 we adopt the MRRU model to improve the statistical performance of different tests for comparing the mean effect of two treatments. We show that a response adaptive design as the MRRU for implementing the random allocation procedure enables to get good properties from both ethical and statistical points of view. In particular, we achieve both the goals of increasing the power of the test and of assigning fewer subjects to the inferior treatment. Simulation studies on the statistical performances of this procedure have been conducted. We applied the procedure described in Chapter 3 to a real case study and the results of the analysis have been reported.

In Chapter 4 we investigate the second-order asymptotic properties of the MRRU model. In particular, we compute the rate of convergence of the urn process and we study its asymptotic probability distribution. Then, we compare theoretically and empirically the inferential performances of the MRRU model with the ones provided by the RRU model, whose asymptotic allocation is $\rho \in \{0,1\}$.

In Chapter 5 we construct a randomly reinforced urn model able to target an asymptotic allocation $\rho \in (0,1)$, that is a function of unknown parameters modeling the responses distribution. First-order asymptotic results under different conditions have been investigated. In particular, we prove the couple convergence (almost sure and in probability) of the urn proportion to the desired allocation function of the unknown parameters.

Data analysis and simulations have been carried out using R statistical software [48].

Contents

CHAPTER 1

Response adaptive designs in clinical trial

The principal topic of this thesis is the study of statistical properties of a response-adaptive design, based on an urn model, applied to clinical trials. The general framework consists of the wide area of experimental designs which aim at collecting accurate information, in order to make decisions about real problems, especially in a clinical context. The pursuit of the scientific information can be realized with very different methodologies, and this choice strongly influences both the phase of analysis and the interpretation of the results. We consider experimental designs based on the randomization of units to receive one of the study treatments. The role of randomization is currently an essential feature of the scientific method. Nowadays, most of the areas involving empirical research are adopting randomization techniques. The properties of randomization have been deeply studied in the last few decades. In particular, most of the theoretical research on randomization models has been conducted in the medical context, with a special interest in the application to clinical trials. A clinical trial can be generally defined as an experimental design whose main goal is to determine the positive or negative effects of a new medical treatment or procedure. We focus on the very large class of experimental designs based on the sequential entrance of subjects in the study. In other words, statistical units will be sequentially randomized to one of two or more treatments under study. The clinical trials we are going to consider are basically based on the comparison of two or more treatments, where some of them can be taken as controls. Among the different types of clinical trials, we deal with designs based on urn models having their natural position in therapeutical trials, in which a new therapy or pharmaceutical drug is compared to a conventional one. These kinds of experiments are usually denoted phase III clinical trials, since they correspond to the third phase of a long process that always occurs when a new therapy has to be introduced in the market. Naturally, the new therapy can be a drug or a new procedure as well. Randomization

is strongly adopted in phase III clinical trials, where patients are randomly assigned to study treatments or control.
Why is randomization so important for clinical trials? There are different answers to this question, but the main reason probably is that randomization improves comparability among the study groups. In observational studies, the pursuit of comparability is realized by adjusting for known covariates, without any guarantee of control for other convariates. Besides, this lack of assurance is not even solved asymptotically. However, randomized procedures increase the probability of comparability with respect to unknown covariates that may influence the responses. But randomization has another good property for which is widely used in many areas of experimental design. In fact, randomized designs usually generate a suitable probability model for a complete phase of inferential analysis. The probability structure provided by the adoption of randomized procedure allows the experimenter to consider the observed results with respect to all possible results, and their relative occurrence probability.

There is an important point to be made concerning clinical trials in medicine with respect to experimental designs adopted in other disciplines. Since they involves human beings, in many situations the experimenter can face complex ethical issues which do not exists in other scientific fields. We have to keep in mind this to understand some of the reasons that led us to construct the urn model presented in this thesis. Another issue related to the ethical theme is the fact that randomization uses probability as a method to allocate patients to treatments. As mentioned in [40], in the medical sphere there are some opinions that randomness and probability should have no role in medicine, because only a physician has the right to decide which treatment should be given to a patient. However, all the benefits provided by randomization in clinical trials are now widely known . Naturally, an experiment involving human beings cannot be studied without taking into account the ethical aspects. Randomized procedures in clinical trials always deal with the delicate balance between individual ethics and collective ethics [47]. Individual ethics represents what is the best for the individual patient in the trial. Collective ethics is related to the public healthy status through scientific experimentation. We will see how the models here considered try to optimize the experiment agreement to both individual and collective ethics.

Finally, all clinical trials should be double-masked wherever possible, meaning that neither the patient nor the experimenter should be aware of the treatment randomly assigned to the patient. A procedure that is not double-masked can introduce a bias in the result, called selection bias. To avoid this problem, all the models we are going to see do not introduce any quantity related to the personal feeling or experience of the experimenter.

1.1 General adaptive models

Consider a clinical trial where subjects enter sequentially in the experiment. Let us denote with n the total number of patients that will be involved in the trial. Any of these n patients will sequentially and randomly receive one of two treatments, that we will call R and W. We define a randomization procedure as a vector $\underline{X} = (X_1, ..., X_n)$ where

$X_i \in \{0,1\}$, $i = 1,...,n$. Naturally, $X_i = 1$ means that patient i receives treatment R, while $X_i = 0$ means patient i receives treatment W. By changing the probability distribution of the vector $\underline{X}$, we generate different randomized procedures. Theoretical studies on clinical trials have been often conducted to characterize the asymptotic behavior of the randomization sequence, as the sample size n increases. In particular, most of them focus on the asymptotic properties of the allocation proportions, defined as $N_R(n)/n = \sum_{i=1}^n X_i/n$ and $N_W(n)/n = \sum_{i=1}^n (1-X_i)/n$, respectively. Obviously, $N_R(n) + N_W(n) = n$.

Many designs model the law of the randomized vector $\underline{X}$ depending on responses observed from the patients, so we need to define quantities that model the responses. Let $\underline{M} = (M_1,...,M_n)$ and $\underline{N} = (N_1,...,N_n)$ be vectors of response variables, where M_i and N_i represent the response that would be observed if patient i received treatment R and W, respectively. Notice that because of the randomization, for each patient i, only one element, either M_i or N_i, can be observed. In general, the probability laws of M_i and N_i can be chosen conditionally on X_i and some covariates Y_i. However, in this thesis we will assume that the the vectors $\underline{M}$ and $\underline{N}$ are composed by independent and identically distributed random variables.

Let $\mathcal{F}_n = \sigma(X_1,...,X_n, M_1,...,M_n, N_1,...,N_n, Y_1,...,Y_n)$ be the sigma-algebra generated by the first n treatment allocations, responses and covariates. A randomization procedure is defined by

$$Z_n = \mathbb{E}[X_{n+1}|\mathcal{F}_n] \quad (1.1)$$

where Z_n is a random variable $\mathcal{F}_n$-measurable. We can define Z_n as the conditional probability of assigning treatment R to the patient $n+1$, conditional on the previous n allocations, responses and covariates, and the current patient's covariate vector. We can describe up to five different types of randomization procedures. We have

- complete randomization

$$\mathbb{E}[X_{n+1}|\mathcal{F}_n] = \mathbb{E}[X_{n+1}]$$

The simplest form of randomization procedure is complete randomization, where patients are assigned following a coin-tossing rule. The variables $X_1,...,X_n$ are independent and identically distributed Bernoulli random variables with probability of assignment to treatment R given by $Z_i = \mathbb{E}[X_i] = P(X_i = 1) = 1/2$, $i = 1,...,n$. Complete randomization presents some advantages. The first is that all patients are fully randomized. Moreover, since each subject has the same probability to be assigned correctly or incorrectly, the danger of selection bias is completely overcome. Nevertheless, this procedure is rarely used in practice because it presents a high probability of treatment imbalances in small samples.

- restricted randomization

$$\mathbb{E}[X_{n+1}|\mathcal{F}_n] = \mathbb{E}[X_{n+1}|X_1,...,X_n]$$

Restricted randomization procedures are characterized by the dependence among X_{n+1} and the variables $X_1,...,X_n$. However, the assignments are independent of responses

and covariates. These models are employed when we want to force the allocation of patients to each treatment group to achieve a specific allocation proportion, regardless of the treatment performances. This is usually accomplished by changing the probability of assignment to a treatment according to how many patients have already been allocated to that treatment. The goal often is to have equal numbers of patients assigned to each treatment group, balancing the treatment assignments.
The simplest type of restricted randomization is called the random allocation rule. The main idea is to impose some restrictions on the allocation probabilities, in order to avoid the possible imbalance presented by the complete randomization. Consider the situation where the investigator knows the exact number of subjects n involved in the trial. Then, for n even, the probability that patient i is assigned to treatment R is given by

$$Z_{i-1} = \mathbb{E}[X_i|\mathcal{F}_{i-1}] = \frac{n/2 - N_R(i-1)}{n-(i-1)}, \quad i = 1, ..., n \tag{1.2}$$

Another method to allocate exactly $n/2$ patients to each treatment is to use the complete randomization until one treatment has been assigned to $n/2$ patients. Then, all the further patients will receive the opposite treatment. In [13] Blackwell and Hodges called this model the truncated binomial design. For this design, the probability to allocate the patient i to treatment R is given by

$$Z_{i-1} \; = \; \begin{cases} 1/2 & \text{if} \;\; \max\{N_R(i-i), N_W(i-1)\} < n/2, \\ 0 & \text{if} \;\; N_R(i-1) = n/2, \\ 1 & \text{if} \;\; N_W(i-1) = n/2. \end{cases} \tag{1.3}$$

Positive aspects of the random allocation rule and truncated binomial design are that each patient, at the beginning of the experiment, has the same probability to be assigned to both treatments ($\mathbb{E}[X_i] = 1/2 \; \forall i = 1, ..., n$) and that both groups will be completely balanced ($n/2$ subjects to both treatments). Nevertheless, once $n/2$ patients have been assigned to one treatment, all further treatment allocations are deterministic. Hence, the final assignments are deterministic and predictable, and selection bias can easily occur. Besides, we cannot avoid the possibility of a severe imbalance in the middle of the trial. This is particularly negative in the situation of time-heterogenous covariates related to the responses, because with these designs there is no guarantee of avoiding imbalances between treatment groups with respect those covariates. This type of bias was introduced by Efron in [20], and he denoted it as accidental bias. This issue can be overcome by the adoption of the permuted block designs, that ensure balance throughout the experiment, by introducing some restrictions during the course of the trial. Generally, it is implemented with M blocks, each one containing $m = n/M$ patients. To ensure balance a random allocation rule is typically used to assign patients within each block. Although permutation blocks achieve balanced allocation, when blocks contain few subjects selection bias can result. All these designs require a precise value of the sample size n to be computed. This feature can be a relevant issue in practise, since typically the experimenter does not know n exactly. The following procedures we are going to see overcome this problem, since they consider the allocations as elements of a sequence instead of a vector.

Another very famous restricted randomization procedure is the Efron's biased coin design (see [20]), that is able to balance treatment allocations by changing the probability of a coin-tossing. Let D_i be an increasing function of $N_R(i)$ with $D_i = 0$ if $N_R(i) = i/2$, so that D_i can represent the imbalance between treatments R and W after the first i assignments. Then, for any constant $p \in (0.5, 1]$, the allocation procedure is given by

$$Z_{i-1} = \begin{cases} 1/2 & \text{if } D_{i-1} = 0, \\ p & \text{if } D_{i-1} < 0, \\ 1-p & \text{if } D_{i-1} > 0. \end{cases} \tag{1.4}$$

The biased of the coin p can be chosen arbitrarily before beginning the trial, but is constant, regardless of the degree of imbalance $|D_i|$.

In [53], Wei proposed a modified version of the Efron's biased coin design, such that the degree of imbalance influences the allocation probability. This technique is an adaptive biased coin design which can be describe in terms of urn model. The colors of the balls in the urn represent the treatments to be assigned. Let (R_n, W_n) be the urn composition after n draws, that indicates the number or red and white balls in the urn, respectively. Initially, the urn contains α balls of each type. The allocation procedure can be briefly explained as follows: a ball is drawn and replaced, its color noted, the correspondent treatment is assigned, and β balls of the other color is added in the urn. So doing, the urn composition is skewed to increase the probability of assignment to the treatment that has been selected least often thus far. Then, the probability to assign patient i to treatment R is the proportion of red balls in the urn at time $i-1$, given by

$$Z_{i-1} = \begin{cases} 1/2 & \text{if } i = 1, \\ \frac{\alpha+\beta N_W(i-1)}{2\alpha+\beta(i-1)} & \text{if } i \geq 2. \end{cases} \tag{1.5}$$

Wei's urn design and Efron's biased coin design can be considered as special cases of a more general class of designs, called generalized biased coin designs, characterized by

$$Z_i = \mathbb{E}[X_i|\mathcal{F}_{i-1}] = \phi(i-1) \tag{1.6}$$

where the function $\phi(i) = \phi(N_R(i), N_W(i))$ can be chosen to describe a wide class of models.

In practice, the random allocation rule and truncated binomial design are usually performed within blocks of subject so that balance can be forced throughout the course of the clinical trial. This minimizes the risk of accidental bias. Alternatively, Efron's biased coin design and Wei's urn design adaptively balance the treatment assignments, without forcing perfect balance. In all cases, experiments should be conducted double-masked in order to minimize the risk of selection bias.

- response-adaptive randomization

$$\mathbb{E}[X_{n+1}|\mathcal{F}_n] = \mathbb{E}[X_{n+1}|X_1, ..., X_n, M_1, ..., M_n, N_1, ..., N_n]$$

The response adaptive randomization are procedures characterized by the dependence between the randomized sequence $X_1, ..., X_n$ and the responses collected from the patients. More precisely, the assignment of patient i is based on a probability model that takes into account the past allocations $X_1, ..., X_{i-1}$ and the responses observed from the subjects already allocated $M_1, ..., M_{i-1}$ and $N_1, ..., N_{i-1}$. Response-adaptive designs are usually attractive because they aim to achieve two simultaneous goals, concerning both statistical and ethical points of view: (a) maximizing power in determining the superior treatment, and (b) increasing the allocation of units to the superior treatment. In this thesis we focus on response-adaptive designs that incorporate data on previous treatment assignments and responses to decide the treatment allocation only for the next subject. These procedures are easy to implement but there is no assurance that they are globally optimal. In general, response-adaptive procedures may be constructed with a stopping rule that ends the trial when some optimal criterium has been achieved. In this situations, typical in the context of sequential analysis, the sample size is random. However, we restrict our attention on response-adaptive designs with a sample size fixed in advance, like more and more often occurs in modern clinical trials.
It is possible to distinguish two main classes of response adaptive randomization procedure: the doubly-adaptive biased coin design and the urn models. The former will be briefly described in the next section. The latter will be the main topic of the thesis.

- covariate-adaptive randomization

$$\mathbb{E}[X_{n+1}|\mathcal{F}_n] = \mathbb{E}[X_{n+1}|X_1, ..., X_n, Y_1, ..., Y_n]$$

- covariate-adjusted response-adaptive (CARA) randomization

$$\mathbb{E}[X_{n+1}|\mathcal{F}_n] = \mathbb{E}[X_{n+1}|X_1, ..., X_n, M_1, ..., M_n, N_1, ..., N_n, Y_1, ..., Y_n]$$

Finally, we have covariate-adaptive randomization and covariate-adjusted response-adaptive (CARA) randomization that are two classes of designs used when the goal is to guarantee balance between treatment groups with respect to some known covariates. In these designs, treatment allocations $X_1, ..., X_n$ depend on those covariates observed by the patients. We are not going to discuss these designs in this thesis.

1.2 General doubly-adaptive biased coin design

Designs presented in this section are based on a parametric response model and a target allocation depending on the unknown parameters, that is sequentially substituted with updated estimates of those parameters. The class of doubly-adaptive biased coin design was introduced in [21] and [22], and extends the basic Efron's biased coin design by using an allocation probability that depends on the degree of imbalance. However, unlike Wei's urn model, the doubly-adaptive biased coin design is based on a parametric model that includes the response variables. Let the probability distributions of the responses $M_1, ..., M_n$ and $N_1, ..., N_n$ depend on some parameter vector $\underline{\theta} \in \Theta$. Let $\rho(\underline{\theta}) \in (0, 1)$ be a target allocation, that is the desired proportion of subjects to be assigned to treatment R. Let g be a function from $[0, 1]^2$ to $[0, 1]$ such that the following four regularity conditions hold: (i) g is jointly continuous; (ii) $g(r, r) = r$; (iii) $g(p, r)$ is strictly decreasing in p and strictly increasing in r on $(0, 1)^2$; and (iv) g has bounded derivatives in both arguments. After i assignments, the function g represents the closeness of $N_R(i)/i$ to the current estimate of $\rho(\underline{\theta})$ in some sense. The randomized procedure is the following: the subject $i+1$ is assigned to treatment R with probability given by

$$Z_i = g\left(\frac{N_R(i)}{i}, \rho(\widehat{\underline{\theta}}_i)\right) \tag{1.7}$$

where $\widehat{\underline{\theta}}_i$ is some estimator of θ with observations collected from the first i subjects. Under conditions (i)-(iv) asymptotic properties of the design are investigated. Although of considerable theoretical interest, the design studied in [21] and [22] based on conditions on the function g rather restrictive. In fact, not even the examples provided in those papers satisfy these conditions.

In [44] Melfi, Page and Geraldes proposed an adaptive randomized design that can be included in the class of models described in [21] and [22], but it is much simpler to implement, since the allocation probability is based only on an estimate of the target allocation from the data already gathered

$$Z_i = \rho(\hat{\theta}_i) \tag{1.8}$$

When $\hat{\theta}_i$ represents the MLE estimator of θ, this model is also called sequential maximum likelihood procedure. This particular choice for g does not satisfy conditions (i)-(iv), but good asymptotic properties have been highlighted and the performance of the design is similar to designs proposed in [22].

In [34] Hu and Zhang proposed the following function g for $\gamma \geq 0$:

$$\begin{aligned} g(x,y) &= \frac{y(y/x)^\gamma}{y(y/x)^\gamma + (1-y)((1-y)/(1-x))^\gamma}, \\ g(0,y) &= 1, \\ g(x,0) &= 0. \end{aligned}$$

This function does not satisfy the regularity condition (iv) of [21], but it satisfies alternative conditions that are widely satisfied. In [34] Hu and Zhang (2004) proved strong consistency, a law of the iterated logarithm and asymptotic normality for the new design. Notice that, when $\gamma = 0$ and $\widehat{\underline{\theta}}_i$ is the maximum likelihood estimator of $\underline{\theta}$, the procedure reduces to $Z_i = \rho(\hat{\theta}_i)$, the design studied in [44].

In [31] Hu, Zhang and He proposed a new and simple family of response-adaptive randomization procedures, called Efficient Randomized-Adaptive Design (ERADE). Under some mild conditions, this model is able to asymptotically attain the Cramer-Rao lower bound for the allocation proportion of subjects to both treatment. The allocation probability function of the proposed procedure is discontinuous

$$Z_i = \begin{cases} \alpha\rho(\widehat{\underline{\theta}}_i) & \text{if } N(i)/i > \rho(\widehat{\underline{\theta}}_i), \\ \rho(\widehat{\underline{\theta}}_i) & \text{if } N(i)/i = \rho(\widehat{\underline{\theta}}_i), \\ 1-\alpha(1-\rho(\widehat{\underline{\theta}}_i)) & \text{if } N(i)/i < \rho(\widehat{\underline{\theta}}_i). \end{cases} \tag{1.9}$$

where $\alpha \in [0,1)$ is a constant that indicates the degree of randomization.

In the next section, we will present randomized procedures described in terms of urn models. In general, urn models aim at achieving different goals with respect to the designs presented in this section. In particular, they are not usually designed to target some specific allocation based on unknown parameters.

1.3 Urn models for response-adaptive designs

In this section we explore a large class of response-adaptive randomization procedures based on urn models. Urn models have been investigated for a long time in probability theory, since they generate many interesting stochastic processes. In randomized urn models, balls are replaced according to some probability distributions. The first class of urn models we are going to describe is the generalized Friedman's urn, that basically consists in a generalization of Wei's urn design. Since the randomization is here response-adaptive, balls are added to the urn depending not only on the treatment assigned, but also on the patient's responses. In a generic framework, the randomization of patient i is accomplished as follows: a ball is drawn from the urn and replaced, its color noted ($X_i = 1$ or $X_i = 0$), and the corresponding treatment k is assigned ($k = R$ or $k = W$). After treatment k has been assigned, a response is observed (M_i or N_i) and a random number of balls are added to the urn. We will denote with $D_{R,k}$ or $D_{W,k}$ the number of red balls and white balls respectively, returned in the urn, for $k = R, W$. $D_{R,k}$ and $D_{W,k}$ are measurable functions on the sample space of the responses. The response-adaptive randomization procedure is then given by

$$Z_i = \frac{R_i}{R_i + W_i}$$

where R_i and W_i represent the number of red and white balls, respectively, contained in the urn after the first i assignments. Notice that the probability to allocate the next subject to treatment R is the current proportion of red balls in the urn. Note that if $D_{R,R} = D_{W,W} = 0$ and $D_{W,R} = D_{R,W} = \beta$ we return to the Wei's urn design. Significant theoretical results on the generalized Friedman's urn model have been realized in [5] concerning an urn model with balls of $K > 2$ colors. Let us call $\mathbf{D} = [D_{jk}]$ the random matrix representing the number of balls of type j added to the urn when a ball color k has been sampled. Most of their results based on a matrix defined as the expectation of $\mathbf{H} = \mathbb{E}[\mathbf{D}]$, called generating matrix. Under some regularity conditions, such as $D_{jk} > 0$ and $\mathbb{E}[D_{jk} \log(D_{jk})] < \infty$ for any $j, k = 1, ..., K$, in [5] were proved many important asymptotic properties of the generalized Friedman's urn; they showed that first-order asymptotic properties of the urn depend on the eigen-structure of $\mathbf{H}$. In particular, they prove that both the urn proportion and the proportion of sampled color converge almost surely to the eigenvector associated to the maximum eigenvalue of H. In [52] and [9] it was used a slightly more general setup, calling the model the extended Polya urn. They assume some regularity condition on $\mathbf{H}$ to obtain some second order asymptotic properties on the proportion of sampled color such as $\mathbf{H}$. Among the assumptions, we have that $\mathbf{H}$ has simple eigenvalues and all the rows of $\mathbf{H}$ sum to the same positive constant. They also explore the situation of random generating matrix $\mathbf{H}_i = \mathbb{E}[\mathbf{D}_i | \mathcal{F}_{i-1}]$ converging to a fixed matrix $\mathbf{H}$.

Roughly speaking, all the theory on Friedman's urn models is based on the assumption of irreducible mean replacement matrix $\mathbf{H}$. Under this condition the maximum eigenvalue is unique and the limiting urn proportion will consist in the correspondent strictly positive eigenvector. The rate of convergence and the limiting distribution of the proportion of sampled colors from the urn usually depend on the size of the second greatest eigenvalue with respect to the maximum eigenvalue.

There is another class of urn models that has always played an important role for clinical trials. In [37] Ivanova and Flournoy refer to this class as the ternary urn, since the models admitted only three possible actions:

- a ball is added to the urn
- no ball is neither added nor removed from the urn
- a ball is removed from the urn

Nowadays many of these models have been extended and a random number of balls can be added and removed from the urn. However, the main feature of these designs has remained invariant: the diagonal generating matrix, i.e. any change of the urn composition must involve only the balls of the sampled color.

The first design we see is the birth and death urn model. Consider K treatments and an urn containing balls of K colors. A ball is drawn and replaced and the correspondent treatment is assigned to the patient. Responses are assumed to be binary. When the response is a success a ball is added to the urn, while when a failure occurs a ball is removed from the urn. Then, there is a positive probability that some color disappears because all balls of that color have been removed. To avoid this event, we start with an urn which contains also another type of balls, called immigration balls, as in the [36]. When an immigration ball is sampled, one ball of each type is added to the urn, no patient is treated, and the next ball is drawn. The birth and death urn has a complicated limiting theory that changes according to the magnitude of the highest probability of success (p) among all the treatments under study. If $p > 0.5$ and the maximum is unique, then the proportion of sampled balls of the correspondent color converge in probability to one; otherwise, if $p < 0.5$, the proportion of sampled balls of any color converge in probability to specific values determined by the success probabilities of all K treatments.

The drop-the-loser DL was proposed in [38] for two treatments and binary responses. The urn initially contains balls of type R and W and immigration balls, since also in this model balls can be removed from the urn. In particular, if the response is a failure a ball is removed. Otherwise, the urn composition does not change. When an immigration ball is drawn a ball of each type is added to the urn. If we denote as q_R and q_W the probability of failure to treatment R and W respectively, [38] shows that the proportion of balls of type R sampled from the urn $N_R(n)/n$ converge in probability to $q_W/(q_R + q_W)$. Besides, it provides a central limit theorem with the lowest variance in the class of response-adaptive randomized procedures targeting $q_W/(q_R + q_W)$.
In [33] the Ivanova's DL rule was generalized (GDL), and several asymptotic results are derived, for which Ivanova's results are a special case. In particular, they extended the DL procedure to $K > 2$ treatments. Moreover, the number of balls added to the urn

because of an immigration ball is drawn, becomes a function of the success probabilities. This allows the GDL rule to target any desired allocation theoretically.

In [16] a general class of immigrated urn (IMU) models was proposed that incorporates the immigration mechanism into the generalized Friedman's urn framework. In that paper, theoretical asymptotic properties of the IMU models are investigated. In [16] it was shown that the IMU models have smaller variabilities in allocations than the classical urn models, yielding more powerful statistical inferences. Since the class of IMU models include many popular classical urn models, they offer a unify view of almost all urn processes framework. However, the IMU designs do not include models whose generating matrix H is such that $\mathbf{H}\underline{1} > \underline{1}$, where $\underline{1} = (1, ..., 1)'$, and $\nexists \gamma > 1$ such that $\mathbf{H}\underline{1} = \gamma\underline{1}$. In these models, the total number of balls in the urn gradually increases to infinity and the mean of the total number of balls replaced to the urn at each step changes according to the color of the sample ball. For example, this is the case of generalized Polya urn model with different reinforcement means. These designs will be investigated in the next section.

1.4 The Randomly Reinforced Urn Design

This section focuses on a class of response-adaptive designs, described in terms of two-color generalized Polya urn model, denote as Randomly Reinforced Urn (RRU) design. In all these models, the urn is reinforced every time it is sampled with a random number of balls that are of the same color of the ball that was extracted. Then, the generating matrix **H** is not irreducible, since it is diagonal, and there are no immigration balls. RRU designs have been usually adopted to compare competing treatments in a clinical trial framework, with a special attention on the ethical goal of minimizing the allocation of units to the inferior treatment. Naturally, the attempt is to achieve this aim without losing too much in terms of statistical performance for the inferential analysis devoted to determine the superior treatment.

RRU models were introduced by [17] for binary responses, applied to the dose-finding problems in [18, 19]. Then, they have been extended to the case of continuous responses by [12, 45]. Let us describe the model of a general RRU design. Visualize an urn containing balls of two colors (red,white). Red balls are associated with treatment R, while white balls with treatment W. The urn is sequentially sampled and patients are allocated to treatments according to the colors of the sampled balls. Each time, the extracted ball is reintroduced in the urn together with a random number of balls of the same color. Let us call μ_R and μ_W the probability distributions of the random reinforcements of red and white balls, respectively, and m_R, m_W the corresponding means. The supports of μ_R and μ_W are usually assumed to be bounded and non negative. The sequence $X = (X_n)_{n \in \mathbb{N}}$ ($X_n \in \{0, 1\}$, $n = 1, 2, ..$) represents the colors sampled from the urn and the sequence $Z = (Z_n)_{n \in \mathbb{N}}$ ($Z_n \in (0, 1)$, $n = 0, 1, 2, ..$) the proportion of red balls in the urn.

Theoretical properties of the RRU model have been widely studied in literature. When $m_R = m_W$, the majority of the results have been found in [1–3, 41]. In this case,

the asymptotic distribution of the limiting urn proportion is unknown, except in few particular cases. Consider the case in which $\mu_R = \mu_W = \mu$. In this situation it was proved that the sequence Z converges almost surely to a random variable with no atoms, i.e. $P(\lim_n Z_n = x) = 0$ for any $x \in [0, 1]$. When μ is a point mass at a nonnegative real number m, the RRU degenerates to Polya's urn and the limiting distribution is a $Beta(r_0/m, w_0/m)$. This is also the case for binary responses when m balls are added to the urn after a success is obtained (see [2]). For the general RRU with $\mu_R = \mu_W = \mu$, [3] characterizes the liming distribution of Z as the unique continuous solution, satisfying some boundary conditions, of a specific functional equation in which the unknowns are distribution functions on [0, 1].
When $m_R = m_W$, it may happen that $\mu_R \neq \mu_W$ because of moments of higher order. This is of particular interest because it corresponds to a situation in which the two treatments are considered equivalent in mean. However, in [24] it was proved that $P(\lim_n Z_n = 1) = P(\lim_n Z_n = 0) = 0$, so that asymptotically the urn does not extinguish any color when treatments are equivalent in mean.
When reinforcement means are different ($m_R \neq m_W$), in [45] it is shown that the urn asymptotically is composed almost completely by balls of the color associated to the superior treatment. Formally, they proved that the sequence of the urn proportion of red balls Z converges almost surely to one, when $m_R > m_W$, or to zero, when $m_R < m_W$. As a consequence, the allocation proportion $N_R(n)/n$ converges to the same limit, since in an urn model the probability to assign a subject to a particular treatment is represented by the urn proportion of the corresponding color. Then, an interesting property concerning RRU models is that the probability to allocate units to the best treatment converges to one as the sample size increases, that is a very attractive feature from an ethical point of view. However, because of this asymptotic behavior, RRU models are not in the large class of designs targeting a certain proportion $\rho \in (0, 1)$, that usually is fixed ad hoc or computed by satisfying some optimal criteria. Hence, all the asymptotic desirable properties concerning these procedures presented in literature (for instance in [11,43,44]), are not straightforwardly fulfilled by the RRU designs. For instance, theoretical properties of adaptive estimators of the unknown means must be derived in a different way for a RRU model.
When reinforcement means are the same ($m_R = m_W$), asymptotic behavior of these estimators has been studied in many works (see for instance [44] and the bibliography therein) for adaptive designs with target allocation $\rho \in (0, 1)$ and in [2, 24] for RRU designs.
When reinforcement means are different ($m_R \neq m_W$), the behavior of statistics based on adaptive estimators of unknown parameters has been investigated for instance in [32, 33, 51] for adaptive designs with target allocation $\rho \in (0, 1)$. In a RRU model, asymptotic properties of the adaptive estimators of response means are strictly related to the asymptotic behavior of the urn proportion Z. Important results on second-order asymptotic properties of the urn proportion $(Z_n)_{n\in\mathbb{N}}$ for a RRU model were developed in [24], in the case of reinforcements with different means. In [24] it was proved that the rate of convergence of the process $(Z_n)_{n\in\mathbb{N}}$ to its limit l (either 1 or 0) is equal to $1/n^\gamma$ (with $\gamma = 1 - \frac{\min\{m_W;m_R\}}{\max\{m_W;m_R\}} < 1$). Moreover, the quantity $n^\gamma(l - Z_n)$ converges almost surely to a positive random variable, whose behavior has been studied in [35, 42].
There is another problem with the RRU design, that is especially relevant in the inferen-

tial phase of the trial. In fact, for large samples, a RRU design generates two treatment groups with very different sample sizes, because one is much larger than the other one. Hence, inferential procedures based on this design are usually characterized by a very low power.

In the following chapter, we opportunely change the urn scheme of the RRU design, in order to construct a new urn model that asymptotically target an allocation proportion $\rho \in (0,1)$, still minimizing the number of subjects allocated to the inferior treatment. We study the dynamic of the urn process and we prove first-order asymptotic properties of the urn proportion Z_n and the allocation proportion $N_R(n)/n$. The study of the theoretical properties of these processes has been particulary challenging since the modified urn process does not present the sub/supermartingality properties presented by the RRU.
In Chapter 3 we take advantage of the asymptotic properties of the new urn process to improve the performance of different tests for comparing the mean effect of two treatments. In particular, we achieve both the goals of increasing the power of the test and of assigning fewer subjects to the inferior treatment.
In Chapter 4 we compute the rate of convergence of the urn process and we define its limiting distribution. A comparison study among the inferential performances of tests constructed with different urn designs is conducted.
Finally, in Chapter 5 we propose a randomly reinforced urn design whose urn proportion asymptotically targets a value $\rho \in (0,1)$, which is defined as a function of unknown parameters modeling the responses distributions.

CHAPTER 2

The Modified Randomly Reinforced Urn Design

For the reasons described in the last section, we decided to modify the RRU model and construct a new design that is able to target an asymptotic allocation $\rho \in (0,1)$. In so doing, we increase the power of an inferential procedure applied to the trial and we are allowed to apply the theoretical results adopted in the usual framework $\rho \in (0,1)$. However, we must not forget the initial goal of minimizing the number of subjects assigned to the inferior treatment. Thus, the target allocation must be different depending on which treatment is the best one. Simply, the dichotomy among the possible limits $0-1$ turns to the dichotomy among two values $\delta - \eta$, where $0 < \delta \leq \eta < 1$. This result is obtained by changing opportunely the Randomly Reinforced Urn scheme. The urn process derived in this way is not a sub/supermartingale anymore, so the asymptotic results for the MRRU must be proved by adopting different techniques than the ones used in [45]. The parameter δ will represent the desired limit for $N_R(n)/n$ when W is the superior treatment ($m_R < m_W$), while η will be the desired limit for $N_R(n)/n$ when R is the superior treatment ($m_R > m_W$). All these results proved in this chapter have been gathered in [4, 27].

2.1 The model

Let us consider the response probability laws μ_R and μ_W. In general, we can define an opportune utility function u to turn the responses into values which can be interpretable as urn reinforcements. For ease of notation, in this thesis we will use the identity as utility function, i.e. we will interpret the response distributions to treatment R and W equal to the reinforcement distributions of red and white balls, respectively. The model requires the assumption that the reinforcement probability laws μ_R and μ_W have support contained in $[a, b]$, where $0 < a \leq b < +\infty$. In general, the utility function u can be selected in order to make the reinforcements distributions fulfill that assumption. Moreover, we will consider the superior treatment as the one associated to the color with higher reinforcement mean. Then, if the lower are the responses the better is the treatment, it is necessary to use a decreasing utility function.

Now, let us describe the urn model. Visualize an urn initially containing r_0 balls of color R and w_0 balls of color W. Set

$$R_0 = r_0,\ W_0 = w_0,\ D_0 = R_0 + W_0,\ Z_0 = \frac{R_0}{D_0}.$$

The drawing process from this urn is modeled by a sequence $(U_n)_{n\in\mathbb{N}}$ of independent uniform random variables on $(0, 1)$. At time $n = 1$, a ball is sampled from the urn; its color is $X_1 = \mathbf{1}_{\{U_1<Z_0\}}$, a random variable with Bernoulli(Z_0) distribution. Let M_1 and N_1 be two independent random variables with distribution μ_R and μ_W, respectively; assume that X_1, M_1 and N_1 are independent. Next, if the sampled ball is R i.e. $X_1 = 1$, it is returned in the urn together with M_1 balls of the same color if $Z_0 < \eta$, where $\eta \in (0, 1)$ is a suitable parameter, otherwise the urn composition does not change; if the sampled ball is W i.e. $X_1 = 0$, it is returned in the urn together with N_1 balls of the same color if $Z_0 > \delta$, where $\delta \leq \eta \in (0, 1)$ is a suitable parameter, otherwise the urn composition does not change. So we can update the urn composition in the following way

$$\begin{aligned} R_1 &= R_0 + X_1 M_1 \mathbf{1}_{\{Z_0<\eta\}}, \\ W_1 &= W_0 + (1 - X_1) N_1 \mathbf{1}_{\{Z_0>\delta\}}, \\ D_1 &= R_1 + W_1,\ Z_1 = \frac{R_1}{D_1}. \end{aligned} \tag{2.1}$$

Now iterate this sampling scheme forever. Thus, at time $n + 1$, given the sigma-field $\mathcal{F}_n$ generated by $X_1, ..., X_n, M_1, ..., M_n$ and $N_1, ..., N_n$, let $X_{n+1} = \mathbf{1}_{\{U_{n+1}<Z_n\}}$ be a Bernoulli(Z_n) random variable. Then, assume that M_{n+1} and N_{n+1} are two independent random variables with distribution μ_R and μ_W, respectively. Set

$$\begin{aligned} R_{n+1} &= R_n + X_{n+1} M_{n+1} \mathbf{1}_{\{Z_n<\eta\}}, \\ W_{n+1} &= W_n + (1 - X_{n+1}) N_{n+1} \mathbf{1}_{\{Z_n>\delta\}}, \\ D_{n+1} &= R_{n+1} + W_{n+1}, \\ Z_{n+1} &= \frac{R_{n+1}}{D_{n+1}}. \end{aligned} \tag{2.2}$$

We thus generate an infinite sequence $X = (X_n, n = 1, 2, ..)$ of Bernoulli random variables, with X_n representing the color of the ball sampled from the urn at time n, and a process $(Z, D) = ((Z_n, D_n), n = 0, 1, 2...)$ with values in $(0, 1) \times (0, \infty)$, where D_n represents the total number of balls in the urn before it is sampled for the $(n + 1)$-th time, and Z_n is the proportion of balls of color R; we call X the process of colors generated by the urn while (Z, D) is the process of its compositions. Let us observe that the process (Z, D) is a Markov sequence with respect to the filtration $\mathcal{F}_n$.

2.2 Asymptotic results

In this section we provide some theoretical results that will be used to prove Theorem 2.3.1, which is the main convergence theorem concerning the MRRU design. It states that the urn proportion converges almost surely when the reinforcement means are different. In particular, the limit is η when $m_R > m_W$, or δ when $m_R < m_W$. As mentioned at the beginning of this chapter, since the urn process of a MRRU model is not a sub/supermartingale, the proof of Theorem 2.3.1 can't be straightforwardly derived from the convergence theorem of a RRU design. In the proof we adopt different techniques and we use same auxiliar results, most of them are gathered in this section. Nevertheless, some of these results are presented in a more general framework. All these results have been gathered in [4].

We focus on studying the convergence of a generic adapted bounded process $(Z_n)_n$. Without loss of generality, we will take $Z_n \in [0,1], \forall n$. We will consider the crossing in both directions of a strip $[d,u]$, where $0 < d < u < 1$. More precisely, let $t_{-1} = -1$ and define for every $j \in \mathbb{Z}_+$ two stopping times

$$\begin{aligned} \tau_j &= \begin{cases} \inf\{n > t_{j-1} : Z_n < d\} & \text{if } \{n > t_{j-1} : Z_n < d\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \\ t_j &= \begin{cases} \inf\{n > \tau_j : Z_n > u\} & \text{if } \{n > \tau_j : Z_n > u\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \end{aligned} \tag{2.3}$$

The random interval $(\tau_{j-1}, \tau_j]$ is called the *j-th excursion*, and we denote it by

$$\nu^Z_{[d,u]} = \begin{cases} \sup\{j \colon \tau_j < \infty\} & \text{if } \tau_0 < +\infty; \\ 0 & \text{otherwise,} \end{cases}$$

i.e., $\nu^Z_{[d,u]}$ counts the total number of times that the process Z crosses the strip $[d,u]$ in both directions, i.e., making both an upcrossing and a downcrossing.

Theorem 2.2.1. $(Z_n)_n$ *converges a.s. if and only if, for any* $0 < d < u < 1$,

$$\sum P(\tau_{j+1} = \infty | \tau_j < \infty) = \infty,$$

with the convention that $P(\tau_{j+1} = \infty | \tau_j < \infty) = 1$ *if* $P(\tau_j = \infty) = 1$.

Proof. We first note that

$$\begin{aligned} (Z_n)_n \text{ converges a.s.} &\overset{\forall 0<d<u<1}{\Longleftrightarrow} P(\nu^Z_{[d,u]} = \infty) = 0 \\ &\overset{\forall 0<d<u<1}{\Longleftrightarrow} 0 = \lim_{n\to\infty} P(\nu^Z_{[u,d]} \geq n) \\ &\qquad\qquad = \lim_{n\to\infty} P(\cap_{j=0}^n \{\tau_j < \infty\}) \end{aligned}$$

as a consequence of the countability of $\mathbb{Q}$ in $[0,1]$. Now,

$$P(\{\tau_j < \infty, j = 0, \ldots, n\}) = P(\tau_0 < \infty) \prod_{j=1}^{n} P(\tau_j < \infty | \tau_{j-1} < \infty)$$

and it is well known that, if $(p_j)_j \subseteq (0,1]$ then

$$\lim_{n\to\infty} \prod_{j=1}^{n} p_j = 0 \iff \sum_{j=1}^{\infty}(1-p_j) = \infty.$$

The fact that some $(p_n)_n$ might be zero is controlled by the assumption that $p_n = 0 \Rightarrow p_m = 0, \forall m > n$. □

Now, we will present an interesting property holding for a general class of urn processes. Let $(\Omega, \mathcal{F}, (\mathcal{F}_n)_n, P)$ be a filtered space. Let the vector $(R_n, W_n)_n$ be a $(\mathcal{F}_n)_n$–adapted process, where the sequences $(R_n)_n$ and $(W_n)_n$ are nonnegative and increasing (i.e., $0 \le R_0 \le R_1 \le \ldots R_n \le \ldots$ and $0 \le W_0 \le W_1 \le \ldots W_n \le \ldots$) and $R_0 + W_0 > 0$. The vector (R_n, W_n) represents the urn composition at time n. We denote these processes as *Birth Urn Processes (BUP)*. Let $D_n = R_n + W_n$, for $n \in \mathbb{N}$. The following result connects the number of balls in the urn with the number crossing of the strip (d,u)

Lemma 2.2.2 (Reinforcements during excursions)**.** *For any BUP,* $\forall j \in \mathbb{N}$

$$D_{\tau_j} \ge \left(\frac{u(1-d)}{d(1-u)}\right) D_{\tau_{j-1}} \ge ... \ge \left(\frac{u(1-d)}{d(1-u)}\right)^j D_{\tau_0}$$

Proof. For every $j \in \mathrm{N}_0$ we have that

- $R_{\tau_{j+1}} \ge R_{t_j} \Longrightarrow Z_{\tau_{j+1}} D_{\tau_{j+1}} \ge Z_{t_j} D_{t_j}$
- $W_{t_j} \ge W_{\tau_j} \Longrightarrow (1 - Z_{t_j}) D_{t_j} \ge (1 - Z_{\tau_j}) D_{\tau_j}$

Since $Z_{\tau_j} < d$ and $Z_{t_j} > u$ for every $j \in \mathrm{N}$, we find

- $dD_{\tau_{j+1}} \ge uD_{t_j}$
- $(1-u)D_{t_j} \ge (1-d)D_{\tau_j}$

From this we have immediately the following result

$$D_{\tau_j} \ge \left(\frac{u(1-d)}{d(1-u)}\right) D_{\tau_{j-1}} \ge ... \ge \left(\frac{u(1-d)}{d(1-u)}\right)^j D_{\tau_0}$$

□

Given a sequence of stopping times $(\tau_n)_n$, it is always possible to define the counting process

$$C_n := \begin{cases} \sum_{j=1}^{\infty} 1_{\{\tau_j \le n\}} & \text{if } \tau_0 \le n; \\ -1 & \text{if } \tau_0 > n. \end{cases}$$

Now, consider a BUP $(R_n, W_n)_n$ and a sequence of stopping time $(\tau_n)_n$ such that $(R_n, W_n, C_n)_n$ is a time-homogeneous Markov process. In this case, we will say that the BUP is associated to the sequence $(\tau_n)_n$. Moreover, for any $i \ge 1$ the conditional distribution of τ_{i+1} given $\{\tau_i < \infty\}$ depends only on R_{τ_i}, W_{τ_i} and i, i.e. there exists a function f such that

$$P\left(\tau_{i+1} < \infty | \{\tau_i < \infty\} \bigcap \mathcal{F}_{\tau_i}\right) = f\left(R_{\tau_i}, W_{\tau_i}, i\right) \quad a.s. \tag{2.4}$$

Finally, note that, given a BUP $(R_n, W_n)_n$, it is always possible to define two adapted processes $\{D_n := R_n + W_n, n \in \mathbb{N}\}$ and $\{Z_n := R_n/D_n, n \in \mathbb{N}\}$.

Proposition 2.2.3. *Given a Markov BUP, the process* $(Z_n)_n$ *converges a.s. if, for any* $0 < d < u < 1$*, there exists a function* $g : [0,\infty) \times [0,\infty) \to [0,1]$*,* $(R_n, W_n)_n$ *is associated to the sequence* $(\tau_n)_n$ *defined in* (2.3)*, and*

$$\begin{aligned} & f(x,y,\cdot) \leq g(x',y') && \text{whenever } x+y \geq x'+y', \\ & g(c_1,c_2) = a < 1 && \text{for some } c_1, c_2 > 0 \end{aligned}$$

where f *is given in* (2.4).

Proof. On $\{\tau_0 = \infty\}$, we get $\nu^Z_{[u,d]} = 0$.
On $\{\tau_0 < \infty\}$, fix an integer j such that

$$j \geq \log_{\frac{u(1-d)}{d(1-u)}} \left(\frac{c_1 + c_2}{D_{\tau_0}} \right)$$

So doing, by Lemma 2.2.2 we have that

$$D_{\tau_j} \geq \left(\frac{u(1-d)}{d(1-u)} \right)^j D_{\tau_0} \geq c_1 + c_2$$

Now, using this relation and definition of g we obtain

$$\begin{aligned} P(\tau_{j+1} = \infty | \tau_j < \infty) & \geq 1 \; - \; P(\tau_{j+1} < \infty | \tau_j < \infty) \\ & \geq 1 \; - \sup_{x+y \geq c_1 + c_2} f\,(x,y,i) \\ & \geq 1 \; - \; g(c_1, c_2) \\ & \geq 1 \; - \; a \; > \; 0 \end{aligned}$$

Then, by Theorem 2.2.1 we get the thesis. □

Let us consider the Randomly Reinforced Urn design described in Section 1.4. Because of its strong connection with the MRRU model, the knowledge of RRU properties has been essential to study the asymptotic behavior of the MRRU design. In particular, some results on the Doob decomposition of the RRU process have been applied to prove Theorem 2.3.1. Consider the urn proportion process $(Z_n)_n$ and its Doob decomposition

$$Z_n = Z_0 + M_n + A_n$$

where $(M_n)_n$ is a martingale and $(A_n)_n$ is a predictable process, both null at $n = 0$. Some results on these processes are shown for equal reinforcement means.

Lemma 2.2.4. *Assume* $m_R = m_W = m$*. If* $D_0 \geq 2b$*, then*

$$\begin{aligned} & E(\sup_n |A_n|) \leq \frac{b}{D_0}; \\ & E(\langle M \rangle_\infty - \langle M \rangle_n | \mathcal{F}_n) \leq \frac{b}{D_0}, && \text{for any } n \geq 0. \end{aligned}$$

The first result is provided by [2]. Using Lemma 2.2.4, we get the following result

Lemma 2.2.5. *Assume $m_R = m_W = m$. If $D_0 \geq 2b$, then*

$$P(\sup_n |Z_n - Z_0| \geq h) \leq \frac{b}{D_0}\Big(\frac{4}{h^2} + \frac{2}{h}\Big)$$

for every $h > 0$.

Proof. First note that, since $(M_n)_n$ is a martingale null at $n = 0$, we have, by Lemma 2.2.4 (choosing $n = 0$ in the second inequality) that

$$\lim_{n\to\infty} E(M_n^2) = \lim_{n\to\infty} E(\langle M\rangle_n) \leq \frac{b}{D_0},$$

and hence, by Doob's L^2–inequality,

$$P(\{\sup_n |M_n| \geq h/2\}) \leq \lim_{n\to\infty} \frac{E(M_n^2)}{(h/2)^2} \leq \frac{4b}{h^2 D_0}$$

for any $h > 0$. We easily get

$$\begin{aligned} P(\sup_n |Z_n - Z_0| \geq h) &\leq P(\{\sup_n |M_n| \geq h/2\} \cup \{\sup_n |A_n| \geq h/2\}) \\ &\leq P(\{\sup_n |M_n| \geq h/2\}) + P(\{\sup_n |A_n| \geq h/2\}) \\ &\leq \frac{b}{D_0}\Big(\frac{4}{h^2} + \frac{2}{h}\Big) \end{aligned}$$

□

2.3 Asymptotic target allocation of a Modified Randomly Reinforced Urn

Here, we present the main convergence theorem concerning the MRRU design described in Section 2.1. We have

Theorem 2.3.1. *Consider the MRRU design and assume $m_R \neq m_W$. Then, the sequence of urn proportion of red balls $Z = (Z_n, n = 1, 2, ...)$ converges almost surely and*

$$Z_n \xrightarrow{a.s.} \eta \mathbf{1}_{\{m_R > m_W\}} + \delta \mathbf{1}_{\{m_R < m_W\}} \tag{2.5}$$

Proof. In the proof we frequently use a comparison argument between our model and the RRU model described in Section 1.4. Consider an urn containing at the starting time r_0 red balls and w_0 white balls. Let us consider the case $m_R < m_W$; the opposite case ($m_R > m_W$) is completely analogous. With this assumption, in [45] it was shown that the urn process $(Z_n)_{n\in\mathbb{N}}$ of a RRU design is a super-martingale converging to zero. After introducing the parameters δ and η, the urn proportion is not a super-martingale anymore. Nevertheless, we will prove that the urn process $(Z_n)_{n\in\mathbb{N}}$ of a MRRU design still converges almost surely, but this time the limit is equal to δ.
The thesis is get once we prove the following

(a) $P\,(\,\liminf_{n\to\infty} Z_n \leq \delta\,) \;=\; 1$

(b) $P\,(\,\liminf_{n\to\infty} Z_n \geq \delta\,) \;=\; 1$

(c) $P\left(\exists \lim_{n\to\infty} Z_n \right) \;=\; 1$

Part (a):
First of all, we will prove that

$$\liminf_{n\to\infty} Z_n \leq \delta, \text{a.s}$$

By contradiction, assume there exists $l > \delta$ and $\epsilon > 0$ such that $P(\liminf Z_n \geq l) \geq \epsilon > 0$. Then, there exists n_ϵ such that $P(Z_n > \frac{l+\delta}{2}, \forall n \geq n_\epsilon) = \epsilon/2 > 0$. Nevertheless, on the set $\{Z_n > \frac{l+\delta}{2}, \forall n \geq n_\epsilon\}$ the urn process Z_n evolves as the urn proportion of a RRU with reinforcement means $m_R < m_W$ that tends to 0 a.s. (see [45]). Then, $P(Z_n > \frac{l+\delta}{2}, \text{ev.}) = 0$ and this leads to a contradiction with $P(\liminf Z_n \geq l) \geq \epsilon > 0$. By using this comparison argument with the RRU design, it is possible to show that the process Z_n crosses δ infinite times.

Part (b):
Now, we will prove that

$$\liminf_{n\to\infty} Z_n \geq \delta, \text{a.s}$$

By contradiction, assume there exists $l < \delta$ and $\epsilon > 0$ such that $P(\liminf Z_n \leq l) \geq \epsilon > 0$. Then, with probability ϵ the process Z_n must cross the strip $(\frac{l+\delta}{2}, \delta)$ infinite times. Then, by Lemma 2.2.2, the sequence $(D_n)_n$ tends to infinity. As a consequence, after a sufficiently large number of times, $D_n > b\frac{l+\delta}{\delta-l}$ and therefore, if $k > n$ is any successive downcross of δ,

$$Z_k \geq \frac{R_{k-1}}{D_{k-1}+b} \geq \frac{\delta D_n}{D_n + b} > \frac{l+\delta}{2}$$

since each reinforced is bounded by b and $\frac{R_{k-1}}{D_{k-1}} = Z_{k-1} > \delta$. Then, $P(Z_n < \frac{l+\delta}{2}, \text{ev.}) = 0$ and this leads to a contradiction with $P(\liminf Z_n \leq l) \geq \epsilon > 0$.

Part (c):
Putting together parts (a) and (b), we have shown that $\liminf_n Z_n = \delta$ almost surely. Therefore, if the process $(Z_n)_n$ converges almost surely, then its limit has to be equal to δ.
Let γ, d and u ($\delta < \gamma < d < u$) be three arbitrary values and let $(\tau_i)_i$ and $(t_i)_i$ be two sequences of stopping times as defined in (2.3), in order to apply Proposition 2.2.3.
Let us fix an integer $i \in \mathbb{N}$ satisfying

$$i > \log_{\frac{u(1-d)}{d(1-u)}} \left(b\frac{\max\{1-d;\gamma\}}{D_{\tau_0}(d-\gamma)} \right)$$

so that, by Lemma 2.2.2, we have that

$$D_{\tau_i} > b\frac{\max\{1-d;\gamma\}}{d-\gamma}.$$

To ease of notation, denote by $(\widehat{\cdot}_n)_{n\in\mathbb{N}}$ the renewed process on $\{\tau_i < \infty\}$: $(\widehat{R}_n, \widehat{W}_n) = (R_{\tau_i+n}, W_{\tau_i+n})$, $\widehat{D}_n = \widehat{R}_n + \widehat{W}_n = D_{\tau_i+n}$, $\widehat{Z}_n = \widehat{R}_n/\widehat{D}_n = Z_{\tau_i+n}$, $\widehat{U}_n = U_{\tau_i+n}$.

The Markov property of the original urn ensures that, on $\{\tau_i < \infty\}$, the process $(\widehat{\cdot}_n)_n$ started afresh a new urn with initial composition (R_{τ_i}, W_{τ_i}) and dynamic as in (2.1) and (2.2). Note that $Z_{\tau_i} \in (\gamma, d)$. We denote by $P_i(\cdot) = P(\cdot|\tau_i < \infty)$, and therefore, if

$$t = \begin{cases} \inf\{n : \widehat{Z}_n > u\} & \text{if } \{n : \widehat{Z}_n > u\} \neq \emptyset; \\ +\infty & \text{otherwise,} \end{cases}$$

then we have

$$P(\tau_{i+1} < \infty|\tau_i < \infty) \ \leq \ P_i(t_i < \infty) \ = \ P_i(t < \infty) \tag{2.6}$$

Define the sequences $(t_n^*, \tau_n^*)_n$ of stopping times which indicate the $(\widehat{Z}_n)_n$-crosses of the interval (δ, γ): let $t_0^* = 0$ and define for every $j \geq 1$ two stopping times

$$\begin{aligned} \tau_j^* &= \begin{cases} \inf\{n > t_{j-1}^* : \widehat{Z}_n \leq \delta\} & \text{if } \{n > t_{j-1}^* : \widehat{Z}_n \leq \delta\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \\ t_j^* &= \begin{cases} \inf\{n > \tau_j^* : \widehat{Z}_n > \gamma\} & \text{if } \{n > \tau_j^* : \widehat{Z}_n > \gamma\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \end{aligned} \tag{2.7}$$

Notice that,

$$\begin{array}{l} \dfrac{R}{R+W} \leq \gamma, \\ (R+W) > \dfrac{b(1-d)}{d-\gamma} \end{array} \quad \Longrightarrow \quad \frac{R+x}{R+W+x} < d, \ \forall x \leq b,$$

and hence, since the reinforcements are bounded by b, we have

$$\begin{array}{l} \widehat{Z}_{t_j^*-1} \leq \gamma, \\ \widehat{D}_{t_j^*-1} > \dfrac{b(1-d)}{d-\gamma} \end{array} \quad \Longrightarrow \quad \widehat{Z}_{t_j^*} < d \tag{2.8}$$

For any $j \geq 0$, we can define a process $(\widetilde{Z}_n^j)_{n\in\mathbb{N}}$ to set a new urn, coupled with $(\widehat{Z}_n)_{n\in\mathbb{N}}$, with the following features:

$$\begin{aligned} \widetilde{W}_0^j &= \widehat{W}_{t_j^*} \\ \widetilde{R}_0^j &= \widetilde{W}_{t_j^*} \frac{u+d}{2-u-d} \\ \widetilde{X}_{n+1}^j &= \mathbf{1}_{[0,\widetilde{Z}_n^j]}(\widehat{U}_{t_j^*+n+1}), \\ \widetilde{M}_{n+1}^j &= \widehat{M}_{t_j^*+n+1} + (m_W - m_R) \\ \widetilde{N}_{n+1}^j &= \widehat{N}_{t_j^*+n+1} \\ \widetilde{R}_{n+1}^j &= \widetilde{R}_n^j + \widetilde{X}_{n+1}^j \widetilde{M}_{n+1}^j, \\ \widetilde{W}_{n+1}^j &= \widetilde{W}_n^j + (1-\widetilde{X}_{n+1}^j)\widetilde{N}_{n+1}^j, \\ \widetilde{D}_{n+1}^j &= \widetilde{R}_{n+1}^j + \widetilde{W}_{n+1}^j, \\ \widetilde{Z}_{n+1}^j &= \frac{\widetilde{R}_{n+1}^j}{\widetilde{D}_{n+1}^j}. \end{aligned}$$

Then, $(\widetilde{Z}^j)_{j\in\mathrm{N}}$ is a sequence of urn processes, all starting with $\widetilde{Z}_0^j = \frac{u+d}{2}$ and having nonnegative reinforcements with the same mean m_W. Let us notice that at time n, we have defined only the processes $\widetilde{Z}^j$ such that $t_j^* < n$.

We will prove by induction that, for any $j \in \mathbb{N}$,

$$\widetilde{Z}_n^j > \widehat{Z}_{t_j^*+n}, \qquad \widetilde{W}_n^j \leq \widehat{W}_{t_j^*+n}, \qquad \widetilde{R}_n^j > \widehat{R}_{t_j^*+n} \tag{2.9}$$

for any $n \leq \tau_{j+1}^* - t_j^*$. In other words, we will show that each process $(\widetilde{Z}_n^j)_{n\in\mathrm{N}}$ is always above the original process $(\widehat{Z}_{t_j^*+n})_{n\in\mathrm{N}}$, as long as $\widehat{Z}$ remains above δ (i.e. before the time τ_j^*). In fact, by construction we have that

$$\widetilde{Z}_0^j = \frac{d+u}{2} > d > \widehat{Z}_{t_j^*}, \qquad \widetilde{W}_0^j = \widehat{W}_{t_j^*}$$

which immediately implies $\widetilde{R}_0^j > \widehat{R}_{t_j^*}$. Assume (2.9) by induction hypothesis. Since, for any $n \leq \tau_{j+1}^* - t_j^*$, we have that $\widetilde{X}_{n+1}^j = \mathbf{1}_{[0,\widetilde{Z}_n^j]} \geq \mathbf{1}_{[0,\widehat{Z}_{t_j^*+n}]} = \widehat{X}_{t_j^*+n+1}$ by construction, we get

$$\widehat{R}_{t_j^*+n+1} - \widehat{R}_{t_j^*+n} = \widehat{X}_{t_j^*+n+1}\widehat{M}_{t_j^*+n+1} \leq \widetilde{X}_{n+1}^j\widetilde{M}_{n+1}^j = \widetilde{R}_{n+1}^j - \widetilde{R}_n^j,$$
$$\widehat{W}_{t_j^*+n+1} - \widehat{W}_{t_j^*+n} = (1-\widehat{X}_{t_j^*+n+1})\widehat{N}_{t_j^*+n+1} \geq (1-\widetilde{X}_{n+1}^j)\widetilde{N}_{n+1}^j = \widetilde{W}_{n+1}^j - \widetilde{W}_n^j.$$

that means

$$\widetilde{Z}_{n+1}^j > \widehat{Z}_{t_j^*+n+1}, \qquad \widetilde{W}_{n+1}^j \leq \widehat{W}_{t_j^*+n+1}, \qquad \widetilde{R}_{n+1}^j > \widehat{R}_{t_j^*+n+1} \tag{2.10}$$

for any $n \leq \tau_{j+1}^* - t_j^*$. Note that, for any $j \geq 0$, the process $(\widetilde{Z}_n^j)_{n=0}^{\tau_{j+1}^*-t_j^*}$ is an urn process reinforced with distributions with same means and initial composition $(\widetilde{R}_{t_j^*}, \widetilde{W}_{t_j^*})$. Let us define T_j as the stopping time for $(\widetilde{Z}_n)_n$ to exit from (d,u) before $\tau_{j+1}^* - t_j^*$, i.e.:

$$T_j = \begin{cases} \inf\{n \leq \tau_{j+1}^* - t_j^* : \widetilde{Z}_n^j \leq d \text{ or } \widetilde{Z}_n^j \geq u\} \\ \qquad \text{if } \{n \leq \tau_{j+1}^* - t_j^* : \widetilde{Z}_n^j \leq d \text{ or } \widetilde{Z}_n^j \geq u\} \neq \emptyset; \\ +\infty \qquad \text{otherwise.} \end{cases}$$

Then, since

$$\left\{\widehat{Z}_n > u\right\} \subset \left\{\sup_{j:t_j^*\leq n} \widetilde{Z}_{n-t_j^*}^j > u\right\}.$$

we have stated that

$$P_i(t<\infty) \leq P_i\left(\bigcup_{j=0}^{\infty}\{T_j<\infty\}\right) \leq \sum_{j=0}^{\infty} P_i\left(T_j<\infty\right). \tag{2.11}$$

Now, let us consider a single term of the series. Then, as a consequence of Lemma 2.2.5, if we set $h = \frac{u-d}{2}$, we get

$$P_i(T_j<\infty) \leq P(\sup_n |\widetilde{Z}_{t_j^*+n} - \widetilde{Z}_{t_j^*}| \geq h) \leq \frac{b}{D_{t_j^*}}\Big(\frac{4}{h^2}+\frac{2}{h}\Big).$$

Moreover, by using Lemma 2.2.2, we obtain

$$\frac{b}{D_{t_j^*}}\Big(\frac{4}{h^2}+\frac{2}{h}\Big) \ \le\ \frac{b}{\widehat{D}_{t_0^*}}\left(\frac{\delta(1-\gamma)}{\gamma(1-\delta)}\right)^j\left(\frac{4}{h^2}+\frac{2}{h}\right)$$

Thus define the function $g:[0,\infty)\times[0,\infty)\to[0,1]$ in the following way

$$g(x,y) := \frac{b}{x+y}\Big(\frac{4}{h^2}+\frac{2}{h}\Big)\left(\frac{1-\delta}{1-\delta/\gamma}\right),$$

and note that

$$g\left(8b/h^2\left(\frac{1-\delta}{1-\delta/\gamma}\right)\ ,\ 4b/h\left(\frac{1-\delta}{1-\delta/\gamma}\right)\right) = 1/2$$

and g is monotone in $x+y$. We can apply Proposition 2.2.3 to get the thesis, since, by (5.10) and (2.11), we obtain

$$\begin{aligned} P(\tau_{i+1}<\infty|\tau_i<\infty) \quad &\le \sum_{j=0}^{\infty} P_i\left(T_j<\infty\right) \\ &\le \frac{b}{\widehat{D}_{t_0^*}}\Big(\frac{4}{h^2}+\frac{2}{h}\Big)\sum_{j=0}^{\infty}\left(\frac{\delta(1-\gamma)}{\gamma(1-\delta)}\right)^j \\ &= \frac{b}{D_{\tau_i}}\Big(\frac{4}{h^2}+\frac{2}{h}\Big)\left(\frac{1-\delta}{1-\delta/\gamma}\right) \ =\ g(R_{\tau_i},W_{\tau_i}). \end{aligned}$$

□

Remark 2.3.2. *Notice that in the proof it was never necessary to specify the type of distribution generating the reinforcements. Indeed, we do not need all information about the probability laws, but we deal only with the means of those distributions. In particular, in the proof we only needed to know which of the two reinforcements has the greatest mean. For this reason, all the results still hold if we change the reinforcement probability laws, maintaining fixed the sign of the difference of the means.*

Remark 2.3.3. *Consider a Pólya urn containing initially r_0 red balls and w_0 white balls. Let $X = (X_n)_{n\in N}$ be a generalized urn process of the sampled balls and f the corresponding urn function, i.e. the function f that maps the interval (0,1) to itself and such that the law of X is defined by assuming that X_1 is a Bernoulli$(f(z_0))$, where $z_0 = \frac{r_0}{r_0+w_0}$ and for $n\ge 1$, the conditional distribution of X_{n+1} given $X_1,..,X_n$ is a Bernoulli$(f(Z_n))$, where*

$$Z_n = \frac{r_0+\sum_{i=1}^n X_i}{r_0+w_0+n}$$

If $f(x)=x$ for every $x\in[0,1]$, we obtain the Pólya sequence. Now, consider the urn model described in the introduction, in the particular case in which reinforcements are independent Bernoulli variables, with parameters π_R for the red balls and π_W for the white balls. In this situation, this model is equivalent to a generalized Pólya urn in *which the urn function f can be defined like follows:*

$$f(x) = \frac{x\pi_R 1_{\{x<\eta\}}}{x\pi_R 1_{\{x<\eta\}} + (1-x)\pi_W 1_{\{x>\delta\}}} = \begin{cases} 1 & \text{if } \; x<\delta, \\ \frac{x\pi_R}{x\pi_R+(1-x)\pi_W} & \text{if } \; \delta < x < \eta, \\ 0 & \text{if } \; x>\eta. \end{cases}$$

Looking at the expression above, we can reach to the same convergence result proved in this chapter, by applying the Theorem 4.1. of [30]. The convergence theorem proved in this chapter is more general, because it holds also when reinforcements do not follow Bernoulli distributions.

2.4 Asymptotic properties of stochastic sequences generated by the adaptive design

In this section we study some interesting properties of the urn process. We consider the MRRU design and assume $m_R \neq m_W$. The first result concerns the proportion of colors sampled from the urn. Here we prove that it converges to the same limit of the urn proportion Z_n.

Proposition 2.4.1. *The sequence $(N_R(n)/n, n = 1, 2, ...)$ of the proportion of red balls sampled from the urn converges almost surely and*

$$\frac{N_R(n)}{n} \xrightarrow{a.s.} \eta \mathbf{1}_{\{m_R > m_W\}} + \delta \mathbf{1}_{\{m_R < m_W\}} \tag{2.12}$$

Proof. Let $m_R > m_W$. The proof in the case $m_R < m_W$ is analogous. Let us denote $\xi_n = \frac{Z_{n-1}-X_n}{n}$ for any $n \geq 1$, with $\xi_0 = 0$. Then, $(\xi_n)_{n\in\mathbb{N}}$ is a sequence of random variables adapted with respect to the filtration $(\mathcal{F}_n)_{n\in\mathbb{N}}$ such that

$$\sum_{i=1}^{\infty} \mathbb{E}\left[\xi_i \,|\mathcal{F}_{i-1}\right] \;=\; \sum_{i=1}^{\infty} \mathbb{E}\left[\frac{Z_{i-1}-X_i}{i} \,\Big|\mathcal{F}_{i-1}\right] \;=\; 0$$

$$\sum_{i=1}^{\infty} \mathbb{E}\left[\xi_i^2 \,\Big|\mathcal{F}_{i-1}\right] \;=\; \sum_{i=1}^{\infty} \mathbb{E}\left[\left(\frac{Z_{i-1}-X_i}{i}\right)^2 \,\Big|\mathcal{F}_{i-1}\right] \;\leq\; \sum_{i=1}^{\infty} \frac{1}{i^2} \;<\; \infty$$

Applying Lemma 7 of [2] we have that $\sum \xi_n < \infty$ almost surely.
Now, we have that

$$\frac{1}{n}\sum_{i=1}^{n} Z_{i-1} - X_i \;=\; \frac{1}{n}\sum_{i=1}^{n} i\xi_i \;\xrightarrow{a.s}\; 0,$$

by using Kronecker's lemma, and so

$$\eta - \frac{\sum_{i=1}^{n} X_i}{n} \;=\; \eta - \frac{\sum_{i=1}^{n} Z_{i-1}}{n} \;+\; \frac{\sum_{i=1}^{n} Z_{i-1} - X_i}{n} \;\xrightarrow{a.s.}\; 0$$

where the first term goes to zero thanks to the Toeplitz Lemma, since Z_n converge to η almost surely. □

The following proposition shows the rate of divergence of the total number of balls in the urn.

Proposition 2.4.2. *The sequence* $(D_n/n, n = 0, 1, 2, ...)$ *converges almost surely to the mean of the inferior treatment*

$$\frac{D_n}{n} \stackrel{a.s.}{\longrightarrow} m_W \mathbf{1}_{\{m_R > m_W\}} + m_R \mathbf{1}_{\{m_R < m_W\}} \tag{2.13}$$

Proof. Let $m_R > m_W$. The proof in the case $m_R < m_W$ is analogous. Notice that

$$\begin{aligned}
\frac{\sum_{i=1}^n 1 - X_i}{n} \left[\frac{W_0 + \sum_{i=1}^n (1 - X_i) N_i}{\sum_{i=1}^n 1 - X_i} - m_W \right] &= \\
\frac{\sum_{i=1}^n (1 - X_i) N_i}{n} - m_W \frac{\sum_{i=1}^n 1 - X_i}{n} &= \\
\frac{\sum_{i=1}^n [\, (1 - X_i) N_i - m_W (1 - X_i) \,]}{n} &= \\
\frac{\sum_{i=1}^n (1 - X_i)(N_i - m_W)}{n} &\stackrel{a.s.}{\to} 0
\end{aligned}$$

where the almost sure convergence to zero of the last term can be proved with the same arguments used to prove Proposition 2.4.1. This result implies that

$$\frac{W_0 + \sum_{i=1}^n (1 - X_i) N_i}{\sum_{i=1}^n 1 - X_i} \stackrel{a.s.}{\to} m_W \tag{2.14}$$

since from Proposition 2.4.1 we have that $\frac{\sum_{i=1}^n (1 - X_i)}{n} \stackrel{a.s.}{\to} 1 - \eta$. Then, we have that

$$\frac{W_n}{n} = \frac{W_0 + \sum_{i=1}^n (1 - X_i) N_i}{\sum_{i=1}^n (1 - X_i)} \cdot \frac{\sum_{i=1}^n (1 - X_i)}{n} \stackrel{a.s.}{\to} m_W \cdot (1 - \eta).$$

Since $Z_n \stackrel{a.s.}{\to} \eta$, we get

$$\frac{R_n}{n} = \frac{W_n}{n} \frac{Z_n}{1 - Z_n} \stackrel{a.s.}{\to} \mu_W (1 - \eta) \cdot \frac{\eta}{1 - \eta} = m_W \cdot \eta.$$

Globally we obtain

$$\frac{D_n}{n} = \frac{R_n}{n} + \frac{W_n}{n} \stackrel{a.s.}{\to} m_W \cdot \eta + m_W \cdot (1 - \eta) = m_W.$$

□

Remark 2.4.3. *Notice that in a RRU model the sequence* D_n/n *converges almost surely to the mean of the superior treatment. In fact, in a RRU model, when* $m_R > m_W$*, we have that*

$$\lim_{n \to \infty} \frac{D_n}{n} = \lim_{n \to \infty} \frac{R_n}{n} = \lim_{n \to \infty} \frac{R_0 + \sum_{i=1}^n X_i M_i}{\sum_{i=1}^n X_i} = m_R \tag{2.15}$$

on a set of probability one. The result (2.15) *is proved following the same arguments of* (2.14)

Here, we show that the proportion of times the urn proportion Z_n is under/above its limit converges almost surely to a quantity that depends only on the reinforcement means m_R and m_W.

Proposition 2.4.4. *If* $m_R > m_W$*, then*

$$\frac{\sum_{i=1}^n 1_{\{Z_i<\eta\}}}{n} \overset{a.s.}{\longrightarrow} \frac{m_W}{m_R}. \tag{2.16}$$

If $m_R < m_W$*, then*

$$\frac{\sum_{i=1}^n 1_{\{Z_i>\delta\}}}{n} \overset{a.s.}{\longrightarrow} \frac{m_R}{m_W}.$$

To prove Proposition 2.4.4 we need the following lemma

Lemma 2.4.5. *If* $m_R > m_W$*, then*

$$\frac{\sum_{i=1}^n X_{i+1}1_{\{Z_i<\eta\}}}{\sum_{i=1}^n 1_{\{Z_i<\eta\}}} \overset{a.s.}{\longrightarrow} \eta. \tag{2.17}$$

If $m_R < m_W$*, then*

$$\frac{\sum_{i=1}^n X_{i+1}1_{\{Z_i>\delta\}}}{\sum_{i=1}^n 1_{\{Z_i>\delta\}}} \overset{a.s.}{\longrightarrow} \delta.$$

Proof. Let $m_R > m_W$. The proof in the case $m_R < m_W$ is analogous. Notice that

$$\begin{aligned}
&\frac{\sum_{i=1}^n 1_{\{Z_{i-1}<\eta\}}}{n}\left[\frac{\sum_{i=1}^n X_i 1_{\{Z_{i-1}<\eta\}}}{\sum_{i=1}^n 1_{\{Z_{i-1}<\eta\}}} - \eta\right] &&=\\
&\frac{\sum_{i=1}^n X_i 1_{\{Z_{i-1}<\eta\}}}{n} - \eta\frac{\sum_{i=1}^n 1_{\{Z_{i-1}<\eta\}}}{n} &&=\\
&\frac{\sum_{i=1}^n \left[\, X_i 1_{\{Z_{i-1}<\eta\}} - \eta 1_{\{Z_{i-1}<\eta\}}\,\right]}{n} &&=\\
&\frac{\sum_{i=1}^n [X_i 1_{\{Z_{i-1}<\eta\}} - Z_{i-1}1_{\{Z_{i-1}<\eta\}}]}{n} &&+\\
&\frac{\sum_{i=1}^n [Z_{i-1}1_{\{Z_{i-1}<\eta\}} - \eta 1_{\{Z_{i-1}<\eta\}}]}{n} &&\overset{a.s.}{\to} 0
\end{aligned}$$

where the almost surely convergence to zero of the last terms can be proved with the same arguments used to prove Proposition 2.4.1. Moreover this result implies (2.17) due to the fact that $\frac{\sum_{i=1}^n 1_{\{Z_i<\eta\}}}{n}$ cannot be asymptotically closed to zero. This fact can be proved by contradiction: suppose that

$$P\left(\liminf_{n\to\infty} \frac{\sum_{i=1}^n 1_{\{Z_i<\eta\}}}{n} = 0\right) > 0. \tag{2.18}$$

But we have that

$$\begin{aligned}
&\liminf_{n\to\infty} \frac{\sum_{i=1}^n 1_{\{Z_i<\eta\}}}{n} \geq\\
&\liminf_{n\to\infty} \frac{1}{\beta_R}\frac{R_0 + \sum_{i=1}^n X_{i+1}M_{i+1}1_{\{Z_i<\eta\}}}{\sum_{i=1}^n X_{i+1}1_{\{Z_i<\eta\}}} \cdot \frac{\sum_{i=1}^n X_{i+1}1_{\{Z_i<\eta\}}}{\sum_{i=1}^n 1_{\{Z_i<\eta\}}} \cdot \frac{\sum_{i=1}^n 1_{\{Z_i<\eta\}}}{n} \geq\\
&\liminf_{n\to\infty} \frac{1}{\beta_R}\frac{R_n}{n} = \frac{m_W\eta}{\beta_R} > 0
\end{aligned}$$

on a set of probability one. This contradicts the assumption (2.18).

□

Remark 2.4.6. *By following the same arguments used to prove Proposition 2.4.1 and Lemma 2.4.5, when $m_R > m_W$ it can be proved also that*

$$\frac{R_0 + \sum_{i=1}^{n} X_{i+1} M_{i+1} 1_{\{Z_i<\eta\}}}{\sum_{i=1}^{n} X_{i+1} 1_{\{Z_i<\eta\}}} \xrightarrow{a.s.} \eta \tag{2.19}$$

Proof of the Proposition 2.4.4. Let $m_R > m_W$. The proof in the case $m_R < m_W$ is analogous. Let us observe that on a set of probability one

$$\begin{aligned} 0 \;=\; \lim_{n\to\infty} \eta - Z_n \;=\; \lim_{n\to\infty} \eta - \frac{R_n/n}{R_n/n + W_n/n} \;= \\ \eta \;-\; \frac{m_R \,\cdot\, \eta \,\cdot\, \lim_{n\to\infty} \frac{\sum_{i=1}^{n} 1_{\{Z_i<\eta\}}}{n}}{m_R \,\cdot\, \eta \,\cdot\, \lim_{n\to\infty} \frac{\sum_{i=1}^{n} 1_{\{Z_i<\eta\}}}{n} + m_W \,\cdot\, (1-\eta)} \end{aligned} \tag{2.20}$$

where the last equality is based on the result of Lemma 2.4.5. Finally, we note that the equality (2.20) holds if and only if

$$\frac{\sum_{i=1}^{n} 1_{\{Z_i<\eta\}}}{n} \xrightarrow{a.s.} \frac{m_W}{m_R}$$

□

2.5 An estimation method based on urn model

In this section, we present a simulation study that takes advantage of the convergence theorem proved in Section 2.2. We provide a method to estimate an unknown parameter by only using the result of convergence of the urn process shown in Theorem 2.3.1. Let us consider a treatment W, whose mean effect on subjects is unknown. Let us model the patients' response to the treatment W with a random variable with distribution μ_W. The goal of the study is to estimate its mean effect $m_W = \int x\mu_W(dx)$. Consider another treatment, denoted as R, and suppose that its random effect on patients follows a known distribution μ_R; let us assume that its mean m_R depends on the given dose, that can be suitable modified by the experimenter. We consider a response adaptive design based on the urn model introduced in Section 2.1, with μ_R and μ_W modeling the patients responses to treatment R and W, respectively. The inference on m_W is performed by monitoring along time, the urn composition Z_n.

In this simulation study we consider K urns with the same initial composition (r_0, w_0). Red balls are associated with treatment R, while white balls with treatment W. We denote with $Z^j = (Z_n^j)_{n\in\mathrm{N}}$ the process of the urn proportion in the j^{th} urn, for $j \in \{1, 2, .., K\}$. The reinforced scheme applied to each urn is the one described in Section 2.1. Hence, for each urn Theorem 2.3.1 holds, and then $Z_n^j \xrightarrow{a.s.} \eta\mathbf{1}_{\{m_R>m_W\}} + \delta\mathbf{1}_{\{m_R<m_W\}}$.
When $m_R = m_W$, we do not have the explicit form of the limit distribution of the urn proportion Z_n. Nevertheless, we know that it converges to a random variable Z_e, whose distribution has no atoms and with support $S_e = [\delta, \eta]$.

At the beginning of the experiment, we choose an initial dose for the treatment R. Let us call $m_{R,1}$ the patients responses' mean corresponding to that dose. Then, the reinforcements of red and white balls follow distributions with means, $m_{R,1}$ and m_W respectively. We start K mutually independents urn processes simultaneously. At each step, we draw a ball form each urn and we update the composition of each urn independently, following the model described in Section 2.1. After n draws and reinforcements, we have K urn proportions Z_n^j, $j \in \{1, 2, .., K\}$, that can be used to compute the empirical cumulative distribution function $\widehat{F}_n$ for the random variable Z_n. Thanks to the Theorem 2.3.1, for every $x \in [0, 1]$, $\widehat{F}_n(x)$ must converge to

$$\begin{cases} F_\eta(x) = 1_{\{x \geq \eta\}} & \text{if } m_W < m_{R,1}, \\ \\ F_\delta(x) = 1_{\{x \geq \delta\}} & \text{if } m_W > m_{R,1}. \end{cases}$$

If $m_W = m_{R,1}$, we can compute offline $\widehat{F}_e(x)$, the asymptotic cumulative distribution of Z_e. This calculation requires the simulation of M urn processes with m draws for each one; the number of urns M and the number of draws m can be arbitrarily large. So we have

$$\widehat{F}_e(x) \simeq \frac{1}{M} \sum_{i=1}^{M} 1_{\{Z_m^i < x\}}, \qquad \text{for large m and M.}$$

At each step, once each urn has been reinforced, we use the Wasserstein distance (d_W) to compute the distances between the empirical cumulative distribution function $\widehat{F}_n$ and the three asymptotic possible distributions F_η, $\widehat{F}_e$ and F_δ. When one of these three distances is small enough, we have a good estimate of distribution of the limit proportion Z_n, and so we can state if m_W is less than, equal to, or greater than $m_{R,1}$. Let us define the following quantity

$$\xi := min \left\{ d_W(Z_n, \delta_\eta)\, , d_W(Z_n, Z_e)\, , d_W(Z_n, \delta_\delta) \right\} =$$

$$\min \left\{ \int_0^1 |F_n(x) - F_\eta(x)| dx\ , \int_0^1 |F_n(x) - \widehat{F}_e(x)| dx\ , \int_0^1 |F_n(x) - F_\delta(x)| dx \right\}$$

When ξ is less than a suitable small parameter α, fixed in advance, the drawing process ends and different scenarios are possible. If $\xi = d_W(Z_n, Z_e)$ we conclude that $m_{R,1} = m_W$. Otherwise, if $\xi = d_W(Z_n, \delta_\delta)$ we conclude that m_W is greater than $m_{R,1}$. Hence, we change the given dose for the treatment R to increase the mean effect at a new suitable value $m_{R,2} > m_{R,1}$. If $\xi = d_W(Z_n, \delta_\eta)$ we conclude that m_W is less than $m_{R,1}$, so the dose is changed in order to decrease the mean effect $m_{R,2} < m_{R,1}$. In any case, we can suppose the difference between the two means is decreased ($|m_{R,2} - m_W| < |m_{R,1} - m_W|$). At this point, we start over with K urn processes, with the same initial composition (r_0, w_0). Although the reinforcement scheme applied is the same as before, the probability law of the reinforcements of red balls is not, because the mean is changed.

The whole study goes on until both the conditions $\xi = d_W(Z_n, Z_e)$ and $\xi < \alpha$ are satisfied. Call i_0 the number of times the random responses' mean to treatment R has been changed. Then, m_{R,i_0} is an estimate of the unknown mean m_W. We made some simulation studies and we report here some graphics that illustrate this estimation procedure.

The simulation study was carried out with $K = 40$ urns. Parameters were fixed at $\delta = 0.3$, $\eta = 0.7$ and $\alpha = 0.05$. Responses to treatment W are assumed to be normal random variables with mean m_W and standard deviation $\sigma = 1$. Responses to treatment R are assumed to be normal random variables with mean $m_{R,i}$ and standard deviation $\sigma = 1$. As explained before, the mean is changed every time ξ is less than α. The parameter m_W was sampled by a uniform $(10, 50)$. At the beginning, the responses' mean to treatment R was set equal to 30 ($m_{R,1} = 30$). After changing m_R four times ($i_0 = 5$), the conditions $\xi = d(Z_n, Z_e)$ and $\xi < \alpha$ have been satisfied; this allows us to conclude that $m_W = m_{R,5}$ (see Figure 1-4). The cumulative distribution $\widehat{F}_e$ was computed with $M = 200$ urns and $m = 10^3$ draws for each one. This procedure provided an estimate of $m_W = m_{R,5} = 18.125$. In fact, the result of the started random extraction for m_W was equal to 18.195.

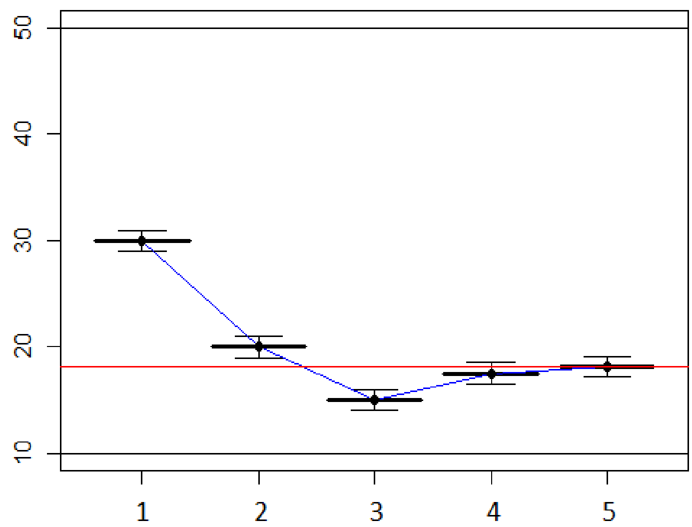

Figure 2.1: *Graphic shows the different values assumed by m_R during the experiment: ($m_{R,1}$, $m_{R,2}$, $m_{R,3}$, $m_{R,4}$, $m_{R,5}$) = (30 , 20 , 15 , 17.5 , 18.125). Five changes were necessary to reach a satisfactory estimate of the mean m_W. x axis represents the number of times m_R was changed, while y axis indicates the responses' means to treatments. The red line represents the unknown mean $m_W = 18.195$. The width of vertical intervals indicates the standard deviation of reinforcement distribution ($\sigma = 1$).*

In this chapter we have constructed a randomly reinforced urn design with asymptotic allocation proportion $\rho \in (0, 1)$. In order to assign a small proportion of subjects to the inferior treatment, the model presents two possible values for the limit of the allocation proportion: δ and η, with $0 < \delta \leq \eta < 1$. In Theorem 2.3.1 we proved

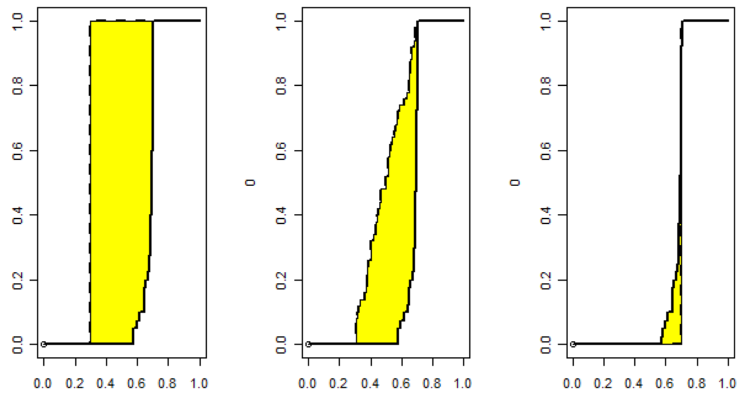

Figure 2.2: *Wasserstein distances (area of yellow zone) for $d_W(Z_n, \delta_\delta)$ (left panel), $d_W(Z_n, Z_e)$ (central panel) and $d_W(Z_n, \delta_\eta)$ (right panel) in the case of $m_{R,1} = 30$ and $m_W = 18.195$ (first iteration). Since $d_W(Z_n, \delta_\eta) < \alpha$ the limit of the process seems to be $\eta = 0.7$.*

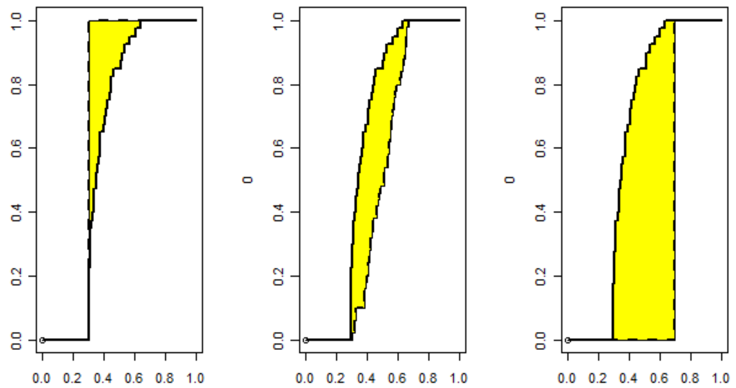

Figure 2.3: *Wasserstein distances (area of yellow zone) for $d_W(Z_n, \delta_\delta)$ (left panel), $d_W(Z_n, Z_e)$ (central panel) and $d_W(Z_n, \delta_\eta)$ (right panel) in the case of $m_{R,3} = 15$ and $m_W = 18.195$ (third iteration). Since $d_W(Z_n, \delta_\delta) < \alpha$ the limit of the process seems to be $\delta = 0.3$.*

that the a.s. limit of the urn process is $\rho = \eta \mathbf{1}_{\{m_R > m_W\}} + \delta \mathbf{1}_{\{m_R < m_W\}}$. Then, this model achieves the ethical goal of assigning an arbitrarily small proportion of subject to the inferior treatment. Moreover, since the limiting proportion is within $(0, 1)$, all the results for designs with asymptotic allocation $\rho \in (0, 1)$ can be applied and the inferential performances are improved.

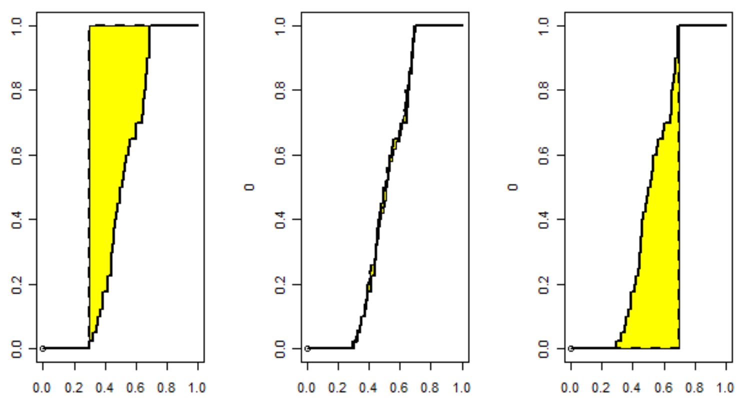

Figure 2.4: *Wasserstein distances (area of yellow zone) for $d_W(Z_n, \delta_\delta)$ (left panel), $d_W(Z_n, Z_e)$ (central panel) and $d_W(Z_n, \delta_\eta)$ (right panel) in the case of $m_{R,5} = 18.125$ and $m_W = 18.195$ (fifth iteration). Since $d_W(Z_n, Z_e) < \alpha$ the limit of the process seems to be Z_e, a random variable with no atoms.*

CHAPTER 3

An urn procedure to construct efficient test for response-adaptive designs

In this chapter we conduct an analysis on the statistical performance of different tests for comparing the mean effect of two treatments ([28, 29]). Given a test $\mathcal{T}_0$, we determine which sample size and allocation proportion guarantee to a test $\mathcal{T}$ to be better than $\mathcal{T}_0$, in terms of (a) higher power and (b) fewer subjects assigned to the inferior treatment. The adoption of a response adaptive design to implement the random allocation procedure is necessary to ensure that both (a) and (b) are satisfied. In particular, we propose to use the Modified Randomly Reinforced Urn design (MRRU) described in Chapter 2 and we show how to perform the model parameters selection for the purpose of this chapter. The opportunity of relaxing some assumptions is examined. Results of simulation studies on the test performance are reported and a real case study is analyzed.

3.1 The *proportion - sample size* space

This section focuses on the statistical properties of the classical hypothesis test aiming at comparing the means of two Gaussian populations. Even if the mathematical framework is very general and the results shown in this section hold for many designs used in different areas, this chapter is set in the context of clinical trials. The goal of the study is the comparison among the response means to two competing treatments, the patients are sequentially assigned to. The allocation rule applied to the sequence of patients depends on the specific experimental design adopted in the trial. Let us fix $p_0 \in (0, 1)$. Consider any procedure able to allocate a proportion of patients p_0 to treatment R, $1-p_0$ to treatment W. Let $n_0 \in \mathbb{N}$ be the total number of subjects involved in the experiment. In what follows, $n_{0,R}$ and $n_{0,W}$ indicate the number of subjects assigned to treatment R

and W, respectively ($n_{0,R} + n_{0,W} = n_0$). Moreover, we denote

- $M_1, M_2, .., M_{n_{0,R}}$: the responses to treatment R, modeled as i.i.d. random variables with distribution μ_R and expected value m_R
- $N_1, N_2, .., N_{n_{0,W}}$: the responses to treatment W , modeled as i.i.d. random variables with distribution μ_W and expected value m_W

We assume the distributions to be Gaussian, i.e. $\mu_R = \mathcal{N}(m_R, \sigma_R^2)$ and $\mu_W = \mathcal{N}(m_W, \sigma_W^2)$, with known variances. Consider the classical hypothesis test

$$H_0 : \ m_R - m_W = 0 \qquad vs \qquad H_1 : \ m_R - m_W \neq 0. \tag{3.1}$$

In this context the critical region and the power curve of the test are well known. Let us first fix

- α : the significance level of the test;
- Δ_0 : the smallest difference among the means detected with high power;
- β_0 : the minimum power for a difference among the means of $\pm\Delta_0$;

Then, once fixed the proportion p_0, it is univocally determined the value of the sample size n_0 which allows the test to satisfy the proprieties required by those parameters. Moreover, we have the following expression for critical region of level α

$$R_\alpha = \left\{ \ |\overline{M}_{n_{0,R}} - \overline{N}_{n_{0,W}}| > \sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}} z_{\frac{\alpha}{2}} \ \right\} \tag{3.2}$$

where $\overline{M}_{n_{0,R}} = \sum_{i=1}^{n_{0,R}} M_i/n_{0,R}$ and $\overline{N}_{n_{0,W}} = \sum_{i=1}^{n_{0,W}} N_i/n_{0,W}$ and $z_{\frac{\alpha}{2}}$ is the quantile of order $1 - \alpha/2$ of a standard normal distribution. Furthermore, the power of the test (4.22), is a function of the real difference $\Delta = m_R - m_W$ (see Figure 3.1 in the case of equal variances), i.e.

$$\beta(\Delta) = P\left(Z < -z_{\frac{\alpha}{2}} - \frac{\Delta}{\sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}}} \right) + P\left(Z > z_{\frac{\alpha}{2}} - \frac{\Delta}{\sqrt{\frac{\sigma_R^2}{n_{0,R}} + \frac{\sigma_W^2}{n_{0,W}}}} \right)$$

Let us call $\mathcal{T}_0$ the test defined in (4.22), with n_0 as sample size and p_0 as proportion of patients allocated to the treatment R. To construct a test with equal parameters (α, Δ_0, β_0) and better statistical performance, the proportion of assignment or the sample size has to be conveniently modified. The test $\mathcal{T}_0$ could be represented in the space $((0,1) \times \mathbb{N})$, that we call *proportion - sample size* space, by the couple (p_0, n_0). Any other test $\mathcal{T}$ can be represented by a point (ρ, n) in the same space. The goal of this section is to point out regions of this space characterized by tests performing better than $\mathcal{T}_0$. A test $\mathcal{T}$ will be considered strictly better than $\mathcal{T}_0$ if it satisfies both the following conditions

(a) $\mathcal{T}$ has a power function uniformly higher than the power function of $\mathcal{T}_0$;

(b) $\mathcal{T}$ assigns to the worst treatment fewer patients than $\mathcal{T}_0$.

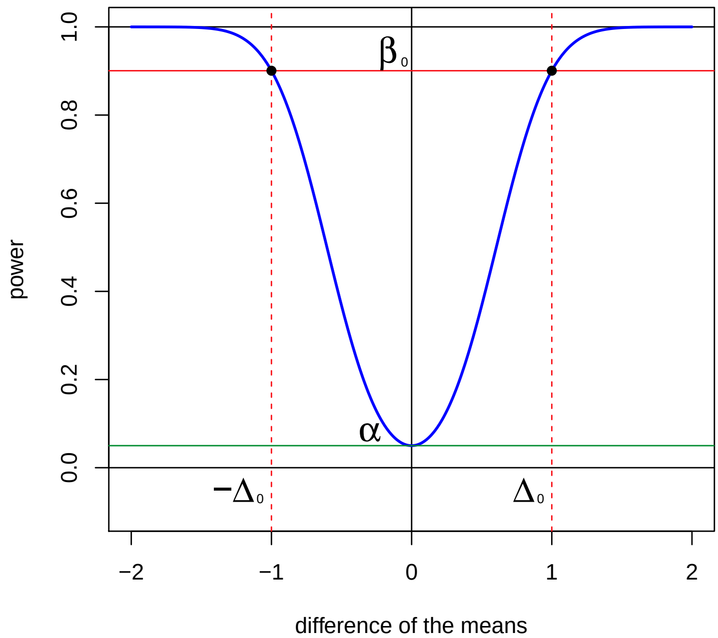

Figure 3.1: *The picture represents the power function* $\beta : \mathbb{R} \to [0,1]$ *of the test defined in* (4.22)*, in the case of* $\alpha = 0.05$ *and* $\beta_0 = 0.9$.

Let us call $\beta_{\mathcal{T}_0}$ and $\beta_{\mathcal{T}}$, the power functions of the tests $\mathcal{T}_0$ and $\mathcal{T}$ respectively. To achieve condition (a) we impose the following constraint

$$\beta_{\mathcal{T}}(\Delta) \geq \beta_{\mathcal{T}_0}(\Delta) \quad \forall \Delta \in \mathbb{R} \Leftrightarrow \frac{\sigma_M^2}{n\rho} + \frac{\sigma_N^2}{n(1-\rho)} \leq \frac{\sigma_M^2}{n_0 p_0} + \frac{\sigma_N^2}{n_0(1-p_0)} \tag{3.3}$$

Now, if we denote as p_{opt} the Neyman allocation proportion $\frac{\sigma_M}{\sigma_M+\sigma_N}$, we can rewrite inequality (3.3) in a more suitable form

$$\frac{{p_{opt}}^2}{n\rho} + \frac{(1-p_{opt})^2}{n(1-\rho)} \leq \frac{{p_{opt}}^2}{n_0 p_0} + \frac{(1-p_{opt})^2}{n_0(1-p_0)} \tag{3.4}$$

Inequality (3.4) divides the *proportion - sample size* space in two regions. The boundary is computed by imposing the equality in (3.4) and expressing the sample size n as a function of the proportion ρ.

$$n_\beta(\rho) = \left(\frac{p_{opt}^2}{\rho} + \frac{(1-p_{opt})^2}{1-\rho}\right)\left(\frac{p_{opt}^2}{n_0 p_0} + \frac{(1-p_{opt})^2}{n_0(1-p_0)}\right)^{-1} \tag{3.5}$$

We refer to function (3.5) as n_β, since it was computed by imposing the condition related with the power of the test β. This relationship between ρ and n is visualized in Figure 3.2 by a red line. Each point over this curve is a test $\mathcal{T}$ with a power uniformly higher than $\mathcal{T}_0$. Points under the red line represent tests with a power uniformly lower than $\mathcal{T}_0$. Notice that the function $n_\beta : (0,1) \to (0,\infty)$ expressed in (3.5) grows boundlessly for proportions close to zero and to one and its global minimum is reached in $\rho = p_{opt}$. This is reasonable as p_{opt} is the allocation proportion which requires the minimum number of patients to get any fixed value of power. Besides, the farther is proportion ρ from p_{opt}, the greater is the number of subjects necessary to get that power. More specifically, the minimum lies on a very interesting curve, which is univocally identified by the parameters of the classical test. Denoting with $g_{min} : (0,1) \to (0,\infty)$ the function associated with that curve, we are able to express it in an analytic form

$$g_{min}(x) \;=\; n_0 \left(\frac{x^2}{p_0} + \frac{(1-x)^2}{1-p_0} \right)^{-1} \qquad \forall x \in (0,1) \tag{3.6}$$

The curve is represented in Figure 3.2 by a red dotted line. The functions n_β and g_{min} cross in two points, in general different, that we denote M and Q. The point M is the minimum of the function n_β and it corresponds to the Neyman allocation proportion

$$M = \left(p_{opt} \;\; , \;\; n_0 \left(\frac{p_{opt}^2}{p_0} + \frac{(1-p_{opt})^2}{1-p_0} \right)^{-1} \right) \tag{3.7}$$

The point Q is the maximum of the function g_{min} and it corresponds to the test $\mathcal{T}_0$: $Q = (p_0, n_0)$. The points M and Q coincide only when $p_0 = p_{opt}$. In this case, the curves n_β and g_{min} are tangents in $M \equiv Q$. Moreover, there are other relevant points highlighted by the function g_{min}. In fact, the curve starts in $X_{W,0} = (0, n_0(1-p_0))$ and ends in $X_{R,0} = (1, n_0 p_0)$. The ordinates of points $X_{W,0}$ and $X_{R,0}$ tell us how many patients have been allocated by the test $\mathcal{T}_0$ to the treatment W and R, respectively.
To satisfy (b) we have to distinguish two different cases, depending on which is the superior treatment

- if $m_R > m_W \Rightarrow$ the superior treatment is R and the condition to be imposed is

$$n(1-\rho) < n_0(1-p_0) \;\;\Leftrightarrow\;\; \rho > 1 - \frac{n_0}{n}(1-p_0); \tag{3.8}$$

- if $m_R < m_W \Rightarrow$ the superior treatment is W and the condition to be imposed is

$$n\rho < n_0 p_0 \;\;\Leftrightarrow\;\; \rho < \frac{n_0}{n} p_0. \tag{3.9}$$

Both these constraints are depicted in blue in the *proportion - sample size* plane. Below each of these lines, the first or the second condition is verified. In conclusion, we divided the *proportion - sample size* space in three regions:

- Region A :

$$A \;=\; \left\{ \; (x,y) \in (0,1) \times (0,\infty) \;:\; n_\beta(x) < y < \frac{p_0}{x} n_0 \; \right\}$$

  tests $\mathcal{T} \in A$ have a power uniformly higher and allocate to treatment R less patients than $\mathcal{T}_0$.

- Region B :

$$B \;=\; \left\{ \; (x,y) \in (0,1) \times (0,\infty) \;:\; y > \max\left\{ \frac{p_0}{x}; \frac{1-p_0}{1-x} \right\} \cdot n_0 \; \right\}$$

  tests $\mathcal{T} \in B$ have a power uniformly higher and allocate to both treatments more patients than $\mathcal{T}_0$.

- Region C :

$$C = \left\{ (x,y) \in (0,1) \times (0,\infty) \ : \ n_\beta(x) < y < \frac{1-p_0}{1-x} n_0 \right\}$$

tests $\mathcal{T} \in C$ have a power uniformly higher and allocate to treatment W less patients than $\mathcal{T}_0$.

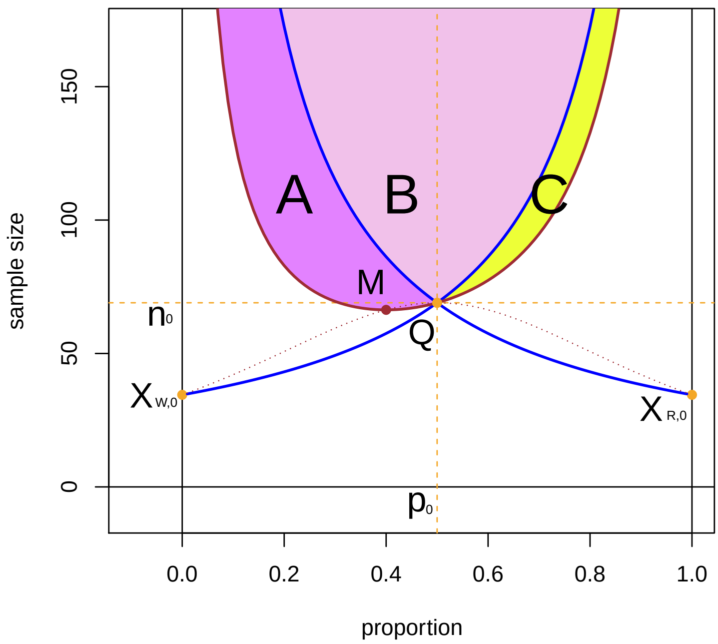

Figure 3.2: *The picture represents the regions A, B and C, on the proportion - sample size plane. The red line represents the function n_β in* (3.5)*; it separates the test $\mathcal{T}$ with power $\beta_{\mathcal{T}}(\Delta) > \beta_{\mathcal{T}_0}(\Delta)$, from the test with power $\beta_{\mathcal{T}}(\Delta) < \beta_{\mathcal{T}_0}(\Delta)$. Blue lines separates tests according on the number of patients allocated to the treatments R and W, with respect to $n_{0,R}$ and $n_{0,W}$. The dotted red line represents the function g_{min} in* (3.6)*.*

Hence, a test $\mathcal{T}$ with better performance than $\mathcal{T}_0$ is a point (ρ, n) in the region A if $m_R < m_W$, or in the region C if $m_R > m_W$. Unfortunately, the experimenter cannot know which is the superior treatment before conducting the trial. For this reason, it could be useful to adopt a response adaptive design to construct the test, since this method is able to target different allocation proportions according to the responses collected during the trial.
Let us introduce a vector $(X_1, X_2, ..., X_n) \in \{0;1\}^n$ composed by the allocations to the treatments according to the adaptive design, i.e. $X_i = 1$ if the subject i receives treatment R or $X_i = 0$ if the subject i receives treatment W. Then, we define the quantities $N_R(n) = \sum_{i=1}^n X_i$ and $N_W(n) = \sum_{i=1}^n (1 - X_i)$, that represent the number of patients allocated to treatments R and W, respectively. Notice that the sample sizes $N_R(n)$ and $N_W(n)$ are random variables. Let us also define the adaptive estimators

based on the observed responses until time n, i.e.

$$\overline{M}(n) = \frac{\sum_{i=1}^{n} X_i M_i}{N_R(n)} \qquad \text{and} \qquad \overline{N}(n) = \frac{\sum_{i=1}^{n}(1-X_i)N_i}{N_W(n)}. \tag{3.10}$$

Then, the test $\mathcal{T}$ is defined by the following critical region

$$R_{\alpha}^{adaptive} = \left\{ \ |\overline{M}(n) - \overline{N}(n)| > \sqrt{\frac{\sigma_R^2}{N_R(n)} + \frac{\sigma_W^2}{N_W(n)}} z_{\frac{\alpha}{2}} \ \right\} \tag{3.11}$$

whose properties depend on the type of adaptive design has been applied in the trial. The authors propose to adopt the *Modified Randomly Reinforced Urn* design (MRRU) described in [4]. The authors propose to adopt the *Modified Randomly Reinforced Urn* design (MRRU) described in 2.

3.2 The parameter selection to construct the test $\mathcal{T}$

Consider the situation presented in Section 3.1. Initially the problem is faced with a classical no-adaptive test. Let us denote this test as $\mathcal{T}_0$. Assume a sample size n higher than the one of the test $\mathcal{T}_0$ (i.e., $n = c \cdot n_0$ with $c > 1$). For any $n \geq n_0$, we can individuate the following intervals

- $I_n^A = \{x \in (0,1) : (x,n) \in A\}$
- $I_n^B = \{x \in (0,1) : (x,n) \in B\}$
- $I_n^C = \{x \in (0,1) : (x,n) \in C\}$

Notice that

- $I_n^A \bigcup I_n^B \bigcup I_n^C \subset (0,1)$
- $I_n^A \bigcap I_n^B = \emptyset$, $I_n^B \bigcap I_n^C = \emptyset$, $I_n^A \bigcap I_n^C = \emptyset$,

The aim is to point out an adaptive test $\mathcal{T}$ represented in the *proportion - sample size* space by a point in region A when R is the inferior treatment, or in the I_n^C when W the inferior one. This goal is achieved when

$$\begin{cases} \frac{N_R(n)}{n} \in I_n^C & \text{if } \int_a^b x\mu_R(dx) > \int_a^b x\mu_W(dx), \\ \\ \frac{N_R(n)}{n} \in I_n^A & \text{if } \int_a^b x\mu_R(dx) < \int_a^b x\mu_W(dx). \end{cases}.$$

Inspired by Proposition 2.4.1, we set $\delta \in I_n^A$ and $\eta \in I_n^C$, so that $\lim_{k\to\infty} \frac{N_R(k)}{k} \in I_n^A$ if $m_R < m_W$ and $\lim_{k\to\infty} \frac{N_R(k)}{k} \in I_n^C$ if $m_R > m_W$. This choice implies that the test $\mathcal{T}$ is in the right region, where both condition (a) and (b) are satisfied. In Figure 3.3 we show how the urn process Z_n converges towards the right region.

The speed of convergence of the urn model is a key point for the success of this procedure. In general, the asymptotic behavior of the urn process $(Z_n)_{n\in\mathbb{N}}$ depends on the reinforcement distributions (μ_R, μ_W) and on the parameters (δ, η). Once the assumptions on the reinforcement probability laws are made and the statistical parameters are

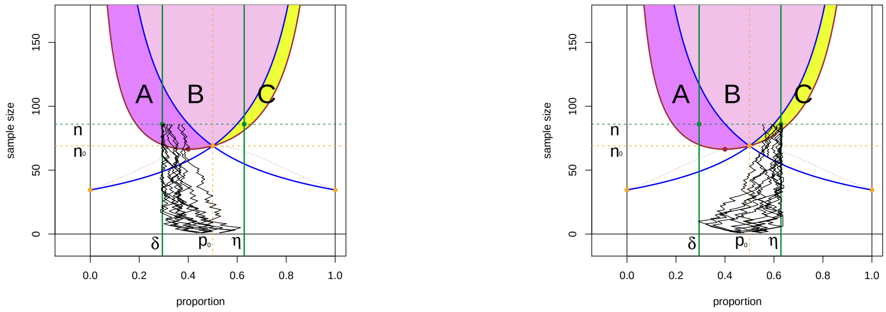

Figure 3.3: *The pictures represents the regions A, B and C, for a particular choice of α, β_0, Δ_0 and p_0. For each fixed sample size n, the parameters of the urn model $\delta, \eta \in (0,1)$ are chosen such that $(\delta, n) \in A$ and $(\eta, n) \in C$. On the left: simulations with $m_R < m_W$. On the right: simulations with $m_R > m_W$. In both pictures, the black lines represent 10 replications of the urn process $(Z_k)_k$.*

fixed, the regions A, B, C can be determined and the rate of convergence depends only on the unknown means m_R and m_W; in particular, the speed of convergence is an increasing function of the mean distance $|\mu_R - \mu_W|$. Moreover, since the value of the sample size n has been computed as a decreasing function of Δ_0, the closeness of the urn proportion Z_n to its limit (η or δ) after n draws, depends mainly on the size of the normalized distance $\frac{|\mu_R - \mu_W|}{\Delta_0}$. If this ratio is large it means that the treatments' performance are very different with respect to the minimum relevant distance $|\Delta_0|$. In this case, the quantity $\frac{N_R(n)}{n}$ will be quickly closed to the limit of the urn process and so the procedure will actually design a test $\mathcal{T}$ which lies in the right region. At the contrary, if $\frac{|\mu_R - \mu_W|}{\Delta_0}$ is small, it means that the difference between the treatments becomes less relevant. The urn proportion $(Z_n)_{n\in\mathbb{N}}$ will be a process which slowly converges to its limit. Therefore, in this situation, the assumption that $\frac{N_R(n)}{n}$ is a good approximation of its limit is less reasonable and so the test $\mathcal{T}$ will be easily found outside the right region. Naturally, it is useless to choose an excessively little value of Δ_0 just to increase the ratio $\frac{|\mu_R - \mu_W|}{\Delta_0}$; in fact, this change would heavy increase the sample size n_0, in order to fulfill the level and power constraint of $\mathcal{T}_0$. As a consequence, the power evaluated at the real difference of the means $\beta(\Delta)$ would be so high that there would be no need to maximize it.

There are other factors which influence the speed of convergence of the process $(Z_n)_{n\in\mathbb{N}}$, like the values of the parameters η and δ. In fact, it is known that the closer to a border point of the interval $(0, 1)$ the limit is, the slower the process converges. This fact is relevant when we propose to improve the approximation of $\frac{N_R(n)}{n}$ with its limit (δ or η) by increasing the sample size n, i.e. using $\tilde{n} = \tilde{c} \cdot n_0$ (with $\tilde{c} >> c$) instead of n. Naturally, since we are using more subjects here, it will be more likely that the urn proportion $Z_{\tilde{n}}$ will be closer to the limit η (or δ), which was previously fixed in the interval I_n^A (or I_n^C). The problem is that the points $(\delta, \tilde{n})$ and $(\eta, \tilde{n})$ could be not in the regions A and C anymore. In fact, when we use the sample size $\tilde{n}$ instead of n, we should locate the parameters η and δ in the intervals $I_{\tilde{n}}^A$ and $I_{\tilde{n}}^C$ instead of I_n^A and I_n^C; so doing, we can be sure that the points $(\delta, \tilde{n})$ and $(\eta, \tilde{n})$ are in the right regions. Moreover, as the sample size n grows the intervals I_n^A and I_n^C become smaller and move towards the border points 0 and 1. This slows down the convergence of the process $(Z_n)_{n\in\mathbb{N}}$ and makes negligible the initial gain obtained by increasing the sample size.

Remark 3.2.1. *The main inferential problem here is a two-sided hypothesis test for comparing the mean effect of two treatments (3.1). It's worth to notice that nothing changes if we consider an one-sided test, where the alternative hypothesis states that one treatment is better than the other one, for instance $H_0 : m_R \leq m_W$ and $H_1 : m_R > m_W$. In this case the goal (b) reduces to assign more patients to treatment W, so we can fix the parameter δ arbitrarily in the interval $(0, \eta)$. In Figure 3.4 we show the partition of the plane proportion - sample size and the choice of the parameters δ and η with an one-sided test.*

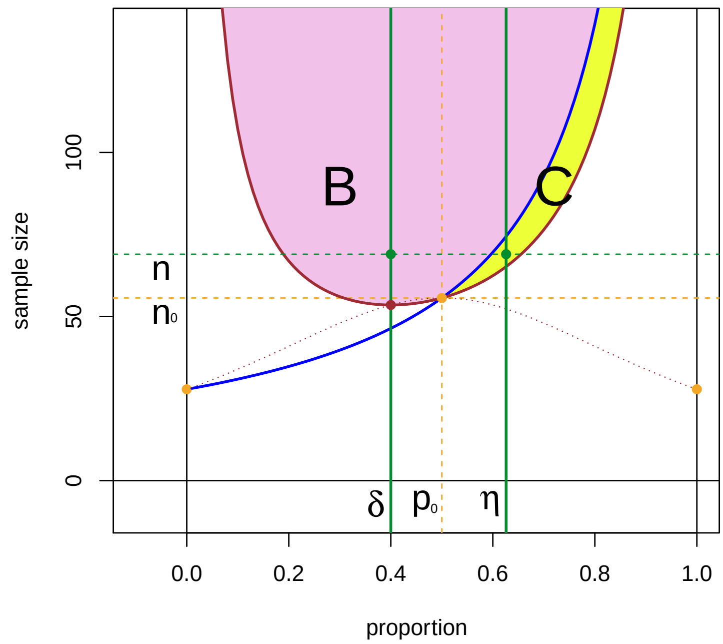

Figure 3.4: *The picture shows the case of an one-sided test. The regions B and C are defined for a fixed level α and a test $\mathcal{T}_0$ characterized by (p_0, n_0). Once fixed a new sample size $n > n_0$, the parameters of the urn model $\delta, \eta \in (0, 1)$ are chosen such that $(\delta, n) \in B$ and $(\eta, n) \in C$*

3.3 Different response distributions

In this section we relax some assumptions on reinforcement distributions. First, we consider the situation with Gaussian laws but unknown variances, then, we discuss the case of non-Gaussian response distributions (exponential and Bernoulli).

In Section 3.1 we made the assumption that the variances of the responses' distributions σ_R^2 and σ_W^2 are known. This hypothesis is very strong and in many cases unrealistic,

since the variability of a new phenomenon is typically unknown and the variance usually has to be estimated through the same observations used to realize the test. Then, a good design should incorporate the possibility of estimating variances, updating them at each step of the procedure and maintaining the good properties obtained with known variances.
First, fix $\delta = \eta = p_0$. Then, we denote as $S^2_R(n)$ and $S^2_W(n)$ the adaptive estimators for the responses' variances, expressed as follows

$$S^2_R(n) = \frac{\sum_{i=1}^n X_i(M_i - \overline{M}(n))^2}{N_R(n) - 1}, \text{ and } S^2_W(n) = \frac{\sum_{i=1}^n (1 - X_i)(N_i - \overline{N}(n))^2}{N_W(n) - 1}. \tag{3.12}$$

So we can replace the true variances σ^2_R and σ^2_W with their estimators $S^2_R(i)$ and $S^2_W(i)$; then, in the critical region (3.11) the quantile of the t-student substitutes the quantile of the Gaussian distribution. Moreover, the function $n_\beta(\cdot)$ introduced in (3.5) has to be redefined as follows

$$n_\beta(\rho; i) \ := \ \left(\frac{\widehat{p}^2_{opt}(i)}{\rho} + \frac{(1 - \widehat{p}_{opt}(i))^2}{1 - \rho} \right) \left(\frac{\widehat{p}^2_{opt}(i)}{n_0 p_0} + \frac{(1 - \widehat{p}_{opt}(i))^2}{n_0(1 - p_0)} \right)^{-1}$$

where $\widehat{p}_{opt}(i) = \frac{S_R(i)}{S_R(i) + S_W(i)}$. This procedure has to be done at every step $i \leq n$, after that a new response is collected and one of the two estimates can be updated. Notice that the function $n_\beta(\cdot; i)$ is random and changes for any $i \leq n$, because now it depends on the observations. As a consequence, also the intervals I^A_i, I^B_i, I^C_i will be random too and we have to recompute them for any $i \leq n$. This leads to two sequences $(\delta_i)_i$, $(\eta_i)_i$ instead of two parameters δ, η, since we need to maintain the property that the parameters of the urn model are chosen in the corresponding intervals: $\delta_i \in I^A_i$ and $\eta_i \in I^C_i$.
In [44] it has been proved that when the sequences $N_R(n)$ and $N_W(n)$ are divergent, adaptive estimators like $S^2_R(n)$ and $S^2_W(n)$ are strongly consistent. This result implies the $n_\beta(t; i) \to_i n_\beta(t)$ almost surely for any $t \in (0, 1)$. This fact ensures that it's always possible to create two convergent sequences $(\delta_i)_i \to \delta$, $(\eta_i)_i \to \eta$ such that $\delta \in I^A$ and $\eta \in I^C$.

When we relax the normality assumption on the reinforcements distribution it is difficult to write the power function of the test in an analytic form. It is not always possible to solve the condition $\beta_{\mathcal{T}}(\Delta) \geq \beta_{\mathcal{T}_0}(\Delta)$ and then to compute the function n_β. Anyway, this task can be realized in simulation and so we will show that the *proportion - sample size* plane can be partitioned again in the regions $A - B - C$ also with non-Gaussian reinforcements. In particular, we focus on two situations: exponential and Bernoulli responses.

Exponential responses:
Let us make the following assumptions on patients' responses

- $M_1, M_2, .., M_{n_{0,R}}$: the responses to treatment R, modeled as i.i.d. random variables with distribution $\mu_R = \mathcal{E}(\lambda_R)$
- $N_1, N_2, .., N_{n_{0,W}}$: the responses to treatment W, modeled as i.i.d. random variables with distribution $\mu_W = \mathcal{E}(\lambda_W)$

Our aim is to perform the following hypothesis test

$$H_0: \ \lambda_R = \lambda_W \qquad vs \qquad H_1: \ \lambda_R \neq \lambda_W. \tag{3.13}$$

We will keep the notation of Section 3.1. We use the likelihood ratio test to compute the critical region. The likelihood function of the whole sample is

$$\begin{aligned} L(\lambda_R, \lambda_W, data) &= \lambda_R^{n_{0,R}} \lambda_W^{n_{0,W}} \exp\left(-\lambda_R \sum_{i=1}^{n_{0,R}} M_i - \lambda_W \sum_{i=1}^{n_{0,W}} N_i\right) \\ &= \left(\lambda_R^{p_0} \lambda_W^{1-p_0} \exp\left(-\lambda_R \overline{M}_{n_{0,R}} p_0 - \lambda_W \overline{N}_{n_{0,W}} (1-p_0)\right) \right)^n \end{aligned}$$

where $\overline{M}_{n_{0,R}} = \sum_{i=1}^{n_{0,R}} M_i / n_{0,R}$ and $\overline{N}_{n_{0,W}} = \sum_{i=1}^{n_{0,W}} N_i / n_{0,W}$. Then, the likelihood ratio test gives us the following critical region

$$\left\{ \frac{\sup_{\lambda_R=\lambda_W \in (0,\infty)} L(\lambda_R, \lambda_W, data)}{\sup_{(\lambda_R,\lambda_W)\in(0,\infty)^2} L(\lambda_R, \lambda_W, data)} \ < \ c_\alpha \right\} = \left\{ \frac{\overline{M}_{n_{0,R}}^{p_0} \ \cdot \ \overline{N}_{n_{0,W}}^{1-p_0}}{\overline{M}_{n_{0,R}} \cdot p_0 + \overline{N}_{n_{0,W}} \cdot (1-p_0)} \ < \sqrt[n]{c_\alpha} \right\}$$

where $c_\alpha \in (0,1)$ can be determined setting the significance level of this critical region to α.

Bernoulli responses:
Let us make the following assumptions on patients' responses

- $M_1, M_2, .., M_{n_{0,R}}$: the sequence of the responses to treatment R, modeled as i.i.d. random variables with distribution $\mu_R = \mathcal{B}(p_R)$
- $N_1, N_2, .., N_{n_{0,W}}$: the sequence of the responses to treatment W, modeled as i.i.d. random variables with distribution $\mu_W = \mathcal{B}(p_W)$

Let us consider now the following hypothesis test

$$H_0: \ p_R = p_W \qquad vs \qquad H_1: \ p_R \neq p_W. \tag{3.14}$$

The likelihood function for two samples of Bernoulli variables is

$$\begin{aligned} &L(p_R, p_W, data) \ = \\ &\left(p_R^{\overline{M}_{n_{0,R}} p_0} (1-p_R)^{(1-\overline{M}_{n_{0,R}}) p_0} p_W^{\overline{N}_{n_{0,W}}(1-p_0)} (1-p_W)^{(1-\overline{N}_{n_{0,W}})(1-p_0)} \right)^n \end{aligned}$$

Then, the likelihood ratio test gives us the following critical region

$$\begin{aligned} &\left\{ \frac{\sup_{p_R=p_W \in (0,1)} L(p_R, p_W, data)}{\sup_{(p_R,p_W)\in(0,1)^2} L(p_R, p_W, data)} \ < \ c_\alpha \right\} \ = \\ &\left\{ \frac{\overline{P}^{\overline{P}} (1-\overline{P})^{1-\overline{P}}}{\overline{M}_{n_{0,R}}^{\overline{M}_{n_{0,R}} p_0} (1-\overline{M}_{n_{0,R}})^{(1-\overline{M}_{n_{0,R}}) p_0} \overline{N}_{n_{0,W}}^{\overline{N}_{n_{0,W}}(1-p_0)} (1-\overline{N}_{n_{0,W}})^{(1-\overline{N}_{n_{0,W}})(1-p_0)}} \ < \sqrt[n]{c_\alpha} \right\} \end{aligned}$$

where

$$\overline{P} = \frac{\sum_{i=1}^{n_{0,R}} M_i + \sum_{i=1}^{n_{0,W}} N_i}{n} = \overline{M}_{n_{0,R}} p_0 + \overline{N}_{n_{0,W}} (1-p_0).$$

Also in this case $c_\alpha \in (0,1)$ can be determined setting the significance level of this critical region to α.

The power function $(\widehat{\beta}_{(p_0,n_0)})$ in both cases (3.13) and (3.14) can be computed through simulations and so we can empirically compute function $n_\beta(\cdot)$ in this way: for any $\rho \in (0,1)$

$$n_\beta(\rho) \ := \ \min\left\{ \ n \geq 1 \ : \ \widehat{\beta}_{(\rho,n)} \geq \widehat{\beta}_{(p_0,n_0)} \ \right\}$$

Now that we have defined the function $n_\beta(\cdot)$, we can partition the *proportion - sample size* plane, introduce the intervals I_n^C and I_n^A and after that fix the parameters η and δ within them. When the urn model is used to allocate the patients the design becomes adaptive and the critical region should be written in a different form, replacing $\overline{M}_{n_{0,R}}$, $\overline{N}_{n_{0,W}}$ and ρ with $\overline{M}(n)$, $\overline{N}(n)$ and $\rho(n)$. As we can see from Figures 3.5 and 3.6, the structure of the regions is the same of those computed in the Gaussian response case.

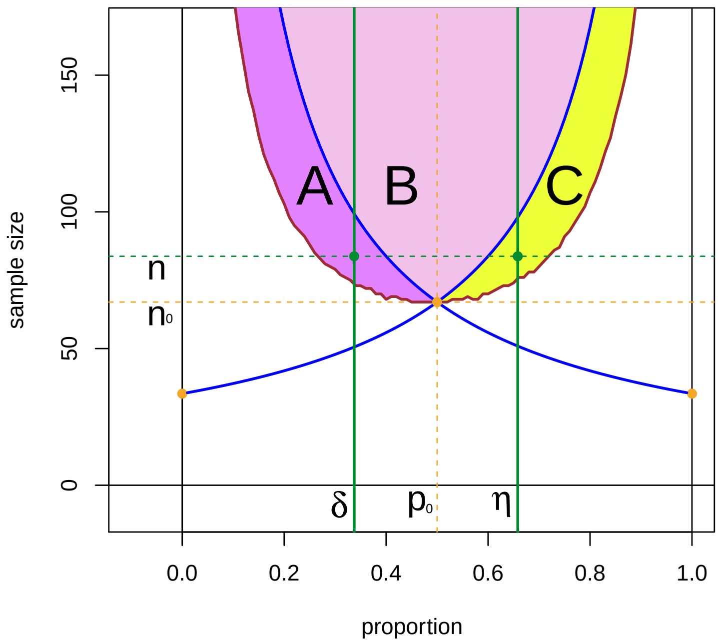

Figure 3.5: *This is an example with exponential distributed responses ($\lambda_R = 2$ and $\lambda_W = 1$). The parameters are: $\alpha = 0.05$, $1-\beta_0 = 0.2$, $\Delta_0 = \Delta = 1/2$. The test $\mathcal{T}_0$ uses an allocation proportion $p_0 = 1/2$ and needs a sample size of $n_0 = 67$. The red line represents the function $n_\beta(\cdot)$ computed by simulation.*

3.4 Simulation Studies

We realized some simulation studies aiming at illustrating the theory presented in this chapter. In this section, we are going to show some of those simulations; in particular, we want to highlight the good properties provided by the use of an adaptive design in

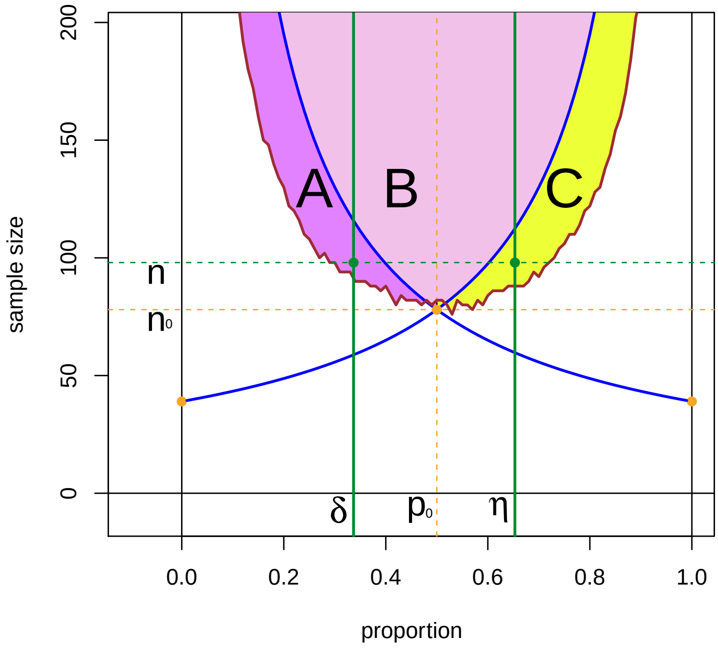

Figure 3.6: *This is an example with Bernoulli distributed responses ($p_R = 0.2$ and $p_W = 0.5$). The parameters are: $\alpha = 0.05$, $1 - \beta_0 = 0.2$, $\Delta_0 = \Delta = 0.3$. The test $\mathcal{T}_0$ uses an allocation proportion $p_0 = 1/2$ and needs a sample size of $n_0 = 76$. The red line represents the function $n_\beta(\cdot)$ computed by simulation.*

the framework of Section 3.1.

Let us consider the two-sided hypothesis test (3.1), for comparing the mean effect of two treatments R and W. We simulated the responses to treatments R and W from two sequences of i.i.d. random variables, with probability laws μ_R and μ_W Gaussian with means m_R and m_W and variances σ_R^2 and σ_W^2, respectively. In all the simulations, $m_W = 10$ and m_R ranges from 5 to 15; we analyze separately the situation of equal variances ($\sigma_R^2 = 1.5^2, \sigma_W^2 = 1.5^2$) and different variances ($\sigma_R^2 = 1, \sigma_W^2 = 4$). We set the significance level $\alpha = 0.05$ and the minimum power $\beta_0 = 0.9$ for a difference of $\Delta_0 = 1$. We assume to have a balanced non adaptive design $p_0 = 0.5$. Then, we compute the right value for the sample size n_0 to fulfill the conditions of significance level and power set in advance, which is $n_0 = 96$ when the variances are equal and $n_0 = 106$ when the variances are different.

At this point, we apply the procedure described in Section 3.1 to get a new adaptive test $\mathcal{T}$ performing better than $\mathcal{T}_0$. The sample size of $\mathcal{T}$ has been increased of a 25% ($n = 1.25 \cdot n_0$), obtaining $n = 120$ in the case of equal variances and $n = 132$ with different variances. In both cases, we can design the regions A, B and C and the corresponding intervals I_n^A, I_n^B and I_n^C; we set δ in the center of I_n^A and η in the center of I_n^A. In particular, we have

- $\sigma_R^2 = 1.5^2, \sigma_W^2 = 1.5^2 \;\;\Rightarrow\;\; I_n^A = (0.127, 0.402),\;\; I_n^C = (0.598, 0.632).$

- $\sigma_R^2 = 1, \sigma_W^2 = 4 \qquad \Rightarrow \quad I_n^A = (0.279, 0.403), \;\; I_n^C = (0.597, 0.721)$

In all simulations, the urn has been initialized with a total number of balls $d_0 = (m_R + m_W)/2$; the initial urn proportion z_0 has been set at the center of the interval (δ, η). Then, for each value of $m_R \in \{5, 7, 9, 9.5, 10.5, 11, 13, 15\}$, we have run 1000 urn processes $(Z_k)_k$ stopped at time n, following the algorithm described in Section 2.1. The results are reported in Table 3.1 (equal variances) and 3.2 (different variances).

m_R	Δ	$\#\{\beta_{\mathcal{T}} \geq \beta_{\mathcal{T}_0}\}$	$\#\{N_R(n) < n_{0,R}\}$	$\#\{N_W(n) < n_{0,W}\}$
5	-5	0.954	(0.766)	0.011
7	-3	0.967	(0.573)	0.057
9	-1	0.970	(0.320)	0.178
9.5	-0.5	0.973	(0.301)	0.201
10.5	0.5	0.969	0.210	(0.283)
11	1	0.976	0.182	(0.319)
13	3	0.961	0.083	(0.486)
15	5	0.962	0.040	(0.608)

Table 3.1: *The table represents the proportion of simulation runs $\mathcal{T}$ performs better feature than $\mathcal{T}_0$. The parenthesis indicate the column of the inferior treatment. For every choice of m_R, 1000 simulations have been realized. Here, the case of equal variances has been reported: $\sigma_R^2 = \sigma_W^2 = 1.5^2$.*

The proportion of simulation runs the test $\mathcal{T}$ has a power higher than $\mathcal{T}_0$ is very high. In other words, it means that most of the simulations yields an allocation proportion after n step such that $(N_R(n)/n, n) \in \{A \bigcup B \bigcup C\}$. Moreover, this result has been found for any values of Δ, that is remarkable since the means are unknown before doing the test. The second goal of this design was minimizing the number of subjects assigned to the inferior treatment. In Table 3.1 we report the proportion of runs $\mathcal{T}$ allocates to each treatment less subjects than $\mathcal{T}_0$. To better understand this aspect of the performance of the MRRU model, we report in Figure 3.7 the flanked boxplots of the number of subjects allocated to the inferior treatment in the 1000 replications of the urn design. The red line indicate the number of subject allocated to the inferior treatment by $\mathcal{T}_0$. Then, the goal is to maximize the number of cases below the red line. The numbers within parenthesis in Table 3.1 represent the proportion of simulation runs that are below the red line in Figure 3.7.
Notice from Figure 3.7 that, the greater is the mean distance $|\Delta| = |m_R - m_W|$, the smaller is the number of subjects allocated to the inferior treatment.

In the case of different variances (Table 3.2), in most of the runs $\mathcal{T}$ has a power greater than $\mathcal{T}_0$. Nevertheless, it seems that the larger is the value of m_R the less is the proportion of times the power of $\mathcal{T}$ is greater than $\mathcal{T}_0$. The reason of this fact is due to the asymmetry of variances: with these values of σ_R^2 and σ_W^2 the length of the interval I_n^C is very small. Then, when the urn process $(Z_k)_k$ overcomes η can occur more often that Z_n goes out from the interval I_n^C, and so does the allocation proportion $N_R(n)/n$. When this happens, we have that $(N_R(n)/n, n) \notin \{A \bigcup B \bigcup C\}$ and so the power of $\mathcal{T}$ will be smaller than the power of $\mathcal{T}_0$.

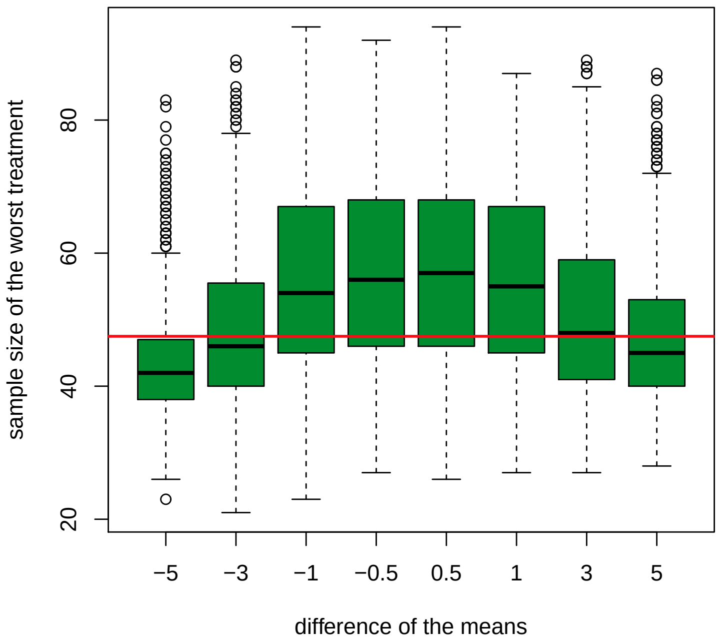

Figure 3.7: *The picture shows, for any* $\Delta \in \{-5, -3, -1, -0.5, 0.5, 1, 3, 5\}$*, the flanked boxplots of the number of subjects allocated to the inferior treatment by* $\mathcal{T}$*. In order to compute the boxpots, 1000 replications of the urn process* $(Z_k)_k$ *have been used. The red line represent the number of subject allocated to the inferior treatment by* $\mathcal{T}_0$*, that in both cases is* $n_0 p_0 = n_0(1 - p_0) = 48$*. Here, the case of equal variances has been reported:* $\sigma_R^2 = \sigma_W^2 = 1.5^2$.

In Table 3.2 we also report the proportion of simulation runs $\mathcal{T}$ allocates to each treatment fewer subjects than $\mathcal{T}_0$. Figure 3.8 shows the boxplots of the number of subjects allocated to the inferior treatment with the 1000 replications of the urn process.
It is easy to note from Figure 3.8 that, even when the variances are different, the greater the mean distance $|\Delta| = |m_R - m_W|$, the smaller the number of subjects allocated to the inferior treatment. In this case, the design performs better when the worst treatment is W. As explained before, this occurs because with these values of σ_R^2 and σ_W^2 the interval I_n^C is very short.

3.5 Real Case Study

In this section we show a real case study, where the application of the methodology presented in this chapter would have improved the performance of a classical test, from both the statistical and ethical point of view. We consider data concerning treatment times of patients affected by ST- Elevation Myocardial. The main rescue procedure for these patients is the Primary Angioplasty. It is well known that to improve the outcome of patients and reduce the in-hospital mortality the time between the arrival at ER (called Door) and the time of intervention (called Baloon) must be reduced as much as possible. So the Door to Baloon time (DB) is our treatment's response. We have two different treatments: the patients managed by the 118 (free-tall number for emergency

m_R	Δ	$\#\{\beta_{\mathcal{T}} \geq \beta_{\mathcal{T}_0}\}$	$\#\{N_R(n) < n_{0,R}\}$	$\#\{N_W(n) < n_{0,W}\}$
5	-5	1.000	(0.895)	0.003
7	-3	0.98	(0.636)	0.042
9	-1	0.928	(0.364)	0.131
9.5	-0.5	0.930	(0.345)	0.136
10.5	0.5	0.887	0.222	(0.232)
11	1	0.876	0.205	(0.265)
13	3	0.847	0.092	(0.361)
15	5	0.799	0.064	(0.447)

Table 3.2: *The table represents the proportion of times the new test $\mathcal{T}$ presented a different feature with respect to the classical test $\mathcal{T}_0$: having higher power of assigning fewer patients to one of the two treatment. The parenthesis indicate the column of the worst treatment. For every choice of m_R, 1000 simulations have been realized. Here, the case of different variances has been considered: $\sigma_R = 1$ and $\sigma_W = 2$.*

in Italy) and the self presented ones. We design our experiment to allocate the majority of patients to treatment performing better, and simultaneously collect evidence in comparing the time distributions of DB times.

We have at our disposal the values of the Door-to-Baloon time (DB) in minutes of 1179 patients. Among them, 657 subjects have been managed by 118, while the others 522 subjects reached the hospital by themselves. We denote the choice of calling 118 as treatment W and the choice of going to the hospital by themselves as treatment R. In this case, since the lower are the responses (DB time) the better is the treatment, a decreasing utility function is necessary. Moreover, the urn model presented in Section 2.1 requires the reinforcements distributions to be positive. Then, we choose the monotonic utility function $u(x) = 6 - log(x)$ to transform responses (DB time) into reinforcement values, in order to satisfy those assumptions. To ease notation, from now on we refer to the responses transformed by the utility function as the responses collected directly from the patients. In this situation, the means and variances computed using all the data at our disposal are taken as the true means and variances of the populations R and W: $m_R = 1.503$, $m_W = 1.996$, $\sigma_R = 0.518$, $\sigma_W = 0.760$. Notice that, since the true difference of the means $\Delta = m_R - m_W = -0.493$ is negative, W is the best treatment. We want to conduct a non-adaptive test and a response adaptive one that aim at determining the best treatment, in order to compare their performance.

Initially, we imagine to conduct a non-adaptive test $\mathcal{T}_0$ to compare the mean effects of treatments R and W. We fix a significance level $\alpha = 0.01$, a minimum power $\beta_0 = 0.95$ for a standard difference of the means $\Delta_0 = 0.5$. Then, we assume responses to treatments R and W are i.i.d random variables with distributions μ_R and μ_W, respectively. Moreover, we assume the laws are Gaussian: $\mu_R = \mathcal{N}(m_R, \sigma_R^2)$ and $\mu_W = \mathcal{N}(m_W, \sigma_W^2)$ (verified by empirical tools). The allocation proportion is set to $p_0 = 0.468$, the empirical one. With these parameters we can conduct a two-sided t-test that requires a total of $n_0 = 119$ subjects, $n_0 p_0 = 56$ allocated to treatment R and $n_0(1 - p_0) = 63$ allocated to treatment W. To compute n_0 we have assumed known variances. The power of this test computed in correspondence to the true difference of the means is $\beta_{\mathcal{T}_0}(\Delta) = 0.945$.

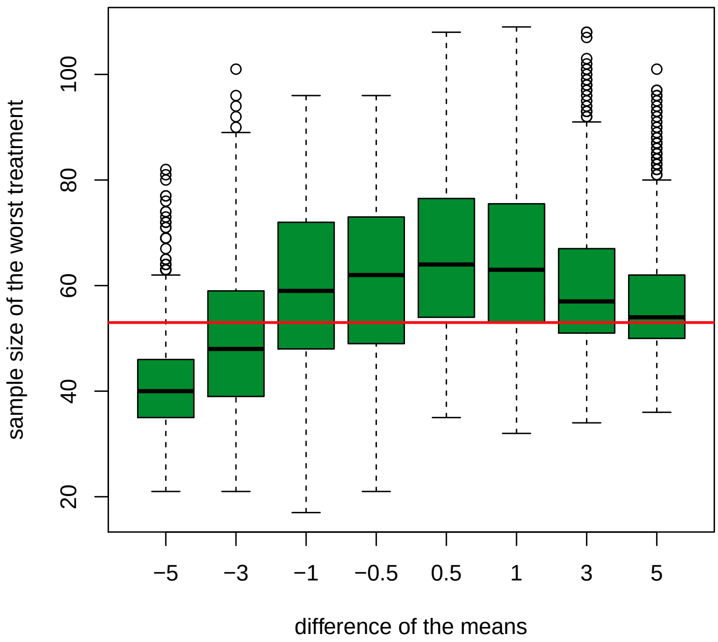

Figure 3.8: *The picture shows, for any* $\Delta \in \{-5, -3, -1, -0.5, 0.5, 1, 3, 5\}$*, the boxplots of the number of subjects allocated to the inferior treatment by* $\mathcal{T}$*. In order to compute the boxplots, 1000 replications of the urn process* $(Z_k)_k$ *have been used. The red line represent the number of subject allocated to the inferior treatment by* $\mathcal{T}_0$*, that in both cases is* $n_0 p_0 = n_0(1 - p_0) = 53$*. Here, the case of different variances has been reported:* $\sigma_R^2 = 1$ *and* $\sigma_W^2 = 4$*.*

Now, consider the urn model presented in Section 2.1 to construct the adaptive test $\mathcal{T}$. $\mathcal{T}$ involves more subject in the experiment than $\mathcal{T}_0$, in particular $n = 1.25 \cdot n_0 = 148$. Nevertheless, since in practice variances are unknown, n_0 and n should be computed from the estimates of the variances. As a consequence, the total number of subjects needed for $\mathcal{T}$ is random, because it depends on the variance estimation. For this reason, we may have replications with different sample size n.
We realize 500 replications of the urn procedure. Since the data at our disposal are much more than the amount of data we need for each trial, by permutating the responses we can take at random different data with a different order in each replication. In Figure 3.9, we represent 10 simulations of the urn proportion process $(Z_n)_n$.

As we can see from Figure 3.9, the urn process seems to target region A, where parameter δ is set. This is because R is the worst treatment in this case. Test $\mathcal{T}$ has higher power and assigns to treatment R less patients than $\mathcal{T}_0$. This is our goal, since we know that R is the worst treatment ($m_R < m_W$).
For each one of the 500 replications we compute analytically the power at the true difference of the means Δ. In general, the power will be different for any simulation because different is the number of subjects assigned to the treatments (N_R and N_W).

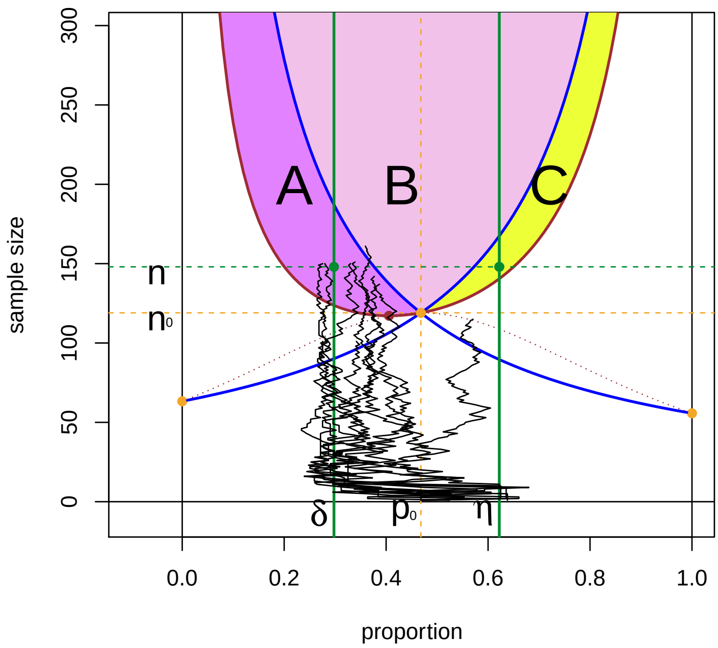

Figure 3.9: *Black lines represent 10 replications of the urn proportion process $(Z_n)_n$. Each replication uses responses taken at random from the data at our disposal. The proportion - sample size space has been partitioned assuming the variances known.*

In Figure 3.10 we show a boxplot with the 500 values of the power computed using the urn model, to be compared with the power obtained with $\mathcal{T}_0$. Moreover, we show for each simulation the number of subjects assigned to treatment R, to be compared with the number of subjects assigned to R by $\mathcal{T}_0$.

From Figure 3.10, we notice that the urn design described in Section 2.1 allows us to construct a test $\mathcal{T}$ with higher power than $\mathcal{T}_0$. This occurs for more than 99% of the replications, and the mean of the power computed overall the runs is

$$\frac{1}{500}\sum_{i=1}^{500}\beta_{\mathcal{T}i}(\Delta) \;=\; 0.975 \;>\; 0.945 \;=\; \beta_{\mathcal{T}_0}(\Delta).$$

Even if $\mathcal{T}$ needs a sample size n larger than $\mathcal{T}_0$, the number of subjects allocated to the inferior treatment R is less for $\mathcal{T}$ for the 52.6% of the runs. Besides, the mean of the number of units assigned to treatment R in all the runs is almost the same of the number computed with $\mathcal{T}_0$

$$\frac{1}{500}\sum_{i=1}^{500} N_{Ri} \;=\; 56.43 \;\simeq\; 56 \;=\; n_0 \cdot p_0.$$

In this chapter we have conducted an analysis on the statistical properties of tests that aim at comparing the means of the responses to two treatments. Starting from any non-

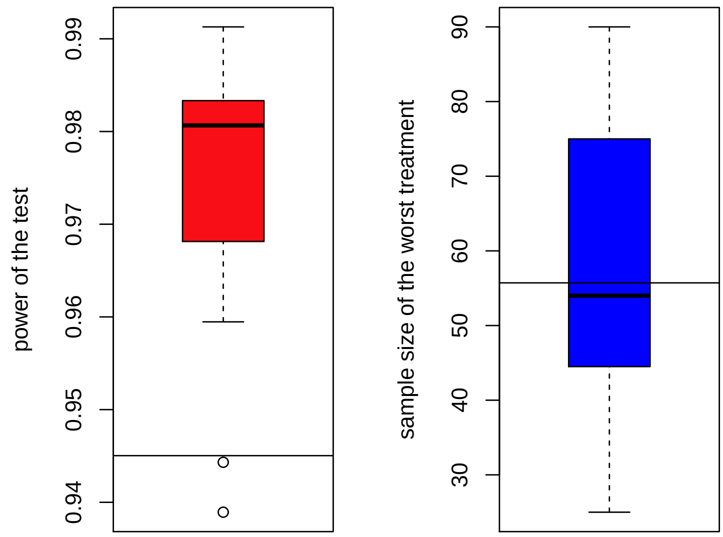

Figure 3.10: *On the left: boxplot representing 500 values of power evaluated at the true difference of the means* $\Delta = -0.493$ *using* $\mathcal{T}$*:* $\beta_{\mathcal{T}}(\Delta)$*. The red line represents the power obtained with* $\mathcal{T}_0$*:* $\beta_{\mathcal{T}_0}(\Delta) = 0.945$*. On the right: boxplot representing 500 values of the number of subjects assigned to treatment* R *by* $\mathcal{T}$*:* N_R*. The red line represents the number of subjects assigned to treatment* R *by* $\mathcal{T}_0$*:* $n_0 \cdot p_0 = 56$*.*

adaptive test $\mathcal{T}_0$, we pointed out the features of an adaptive test $\mathcal{T}$ performing better than $\mathcal{T}_0$. Since the framework here is represented by clinical trials, this goal is achieved when $\mathcal{T}$ has (a) higher power and (b) assigns to the inferior treatment less subjects than $\mathcal{T}_0$. We investigated this task by individuating in the *proportion* - *sample size* space the subregions associated to tests $\mathcal{T}$ performing better than $\mathcal{T}_0$.
The test $\mathcal{T}$ can be implemented by adopting a response adaptive design. We propose an urn procedure (MRRU) that is able to target a fixed allocation proportion in (0,1). Thanks to this property, the urn model can individuate the test $\mathcal{T}$ in different regions depending on which is the inferior treatment, and both goals (a)-(b) can be accomplished. We showed that the assumption of normal responses and known variances can be relaxed and the procedure to partition the *proportion* - *sample size* space and to detect the test $\mathcal{T}$ still holds. We reported simulations and a case study that highlight the goodness of the procedure.

CHAPTER 4

Rate of convergence of urn process to asymptotic proportion

In this chapter we focus on the asymptotic behavior of the urn process $(Z_n)_{n\in\mathbb{N}}$ in the MRRU model ([27]). In Theorem 4.2.2 we prove that the rate of convergence of the process $(Z_n)_{n\in\mathbb{N}}$ to its limit is $1/n$. This asymptotic result has been achieved after defining a particular Markov process denoted $(\tilde{T}_n)_{n\in\mathbb{N}}$, based on the quantities that rule the urn process. The study of stochastic properties of the process $\tilde{T}_n$ (see Section 4.1) has been crucial for proving Theorem 4.2.2. Moreover, Theorem 4.2.2 shows that the sequence $n(\eta - Z_n)$ converges in distribution to a real random variable, whose probability law is related to the unique invariant distribution π of the process $(\tilde{T}_n)_{n\in\mathbb{N}}$.
Section 4.3 is dedicated to the inferential aspects concerning the MRRU design. We deal with a classical hypothesis test comparing the null hypothesis that reinforcement means are equal ($m_R = m_W$) and the one-side alternative hypothesis ($m_R > m_W$). We consider different statistical tests, based either on adaptive estimators of the unknown means or on the urn proportion. We compare statistical properties of tests based on RRU design and tests based on the MRRU design.
In Section 4.4 we illustrate some simulations studies on the probability distribution π and on the statistical properties of the tests described in Section 4.3.

To prove the results shown in this chapter, we need a further assumption on the reinforcement distributions

Assumption 4.0.1. *At least one of these two conditions is satisfied:*

(a) *there exists a closed interval $[a_0, b_0] \subset [a, b]$ such that, $\forall\ x \in [a_0, b_0]$, the measure μ_W is absolutely continuous with respect the Lebesgue measure and the derivative* *is strictly positive, i.e.* $\exists \ \frac{\mu_W(dx)}{dx} \ > \ 0$

(b) *there exists a closed interval* $[a_0, b_0] \subset [a, b]$ *such that,* $\forall \ x \in [a_0, b_0]$*, the measure* μ_R *is absolutely continuous with respect the Lebesgue measure and the derivative is strictly positive, i.e.* $\exists \ \frac{\mu_R(dx)}{dx} \ > \ 0$

Without loss of generality, Condition (a) will be considered true through all this chapter.

In this chapter, we aim at studying the asymptotic behavior of the quantity $n \cdot (\eta - Z_n)$. To do this, let us introduce a new real stochastic process $(T_n)_{n\in\mathbb{N}}$, whose features depend on the random variables ruling the urn process:

$$\begin{cases} T_0 &= \eta W_0 \ - \ (1-\eta)R_0 \\ T_{n+1} &= T_n \ + \ \eta(1-X_{n+1})\ N_{n+1} \ - \ (1-\eta)X_{n+1}\ M_{n+1}\ 1_{\{Z_n<\eta\}} \end{cases} \tag{4.1}$$

$\forall n \in \mathbb{N}$. Let us note that

$$n \cdot (\eta - Z_n) \ = \ \frac{n(\eta - Z_n)D_n}{D_n} \ = \ \frac{\eta W_n - (1-\eta)R_n}{\frac{D_n}{n}} \ = \ \frac{T_n}{\frac{D_n}{n}} \tag{4.2}$$

where $T_n = \eta W_n - (1-\eta)R_n$ satisfies the iterative equations in (4.1).
The process $(Z_n, T_n)_{n\in\mathbb{N}}$ is an homogeneous Markov sequence. Then, there exists the transition probability kernel K for the process T_n such that for any $(z_0, t_0) \ \in \ (0, \eta] \times [0, \infty) \ \cup \ (\eta, 1) \times (-\infty, 0)$ and for any $A \subset \mathbb{R}$

$$P\,(\ T_{n+1} \in A \mid (Z_n, T_n) = (z_0, t_0)\ ) \ = \ \int_A K_{z_0}(t_0, dt)$$

The analytic form of the transition probability kernel is the following

$$\begin{aligned} K_{z_0}(t_0, dt) \quad &= z_0\ \mu_R\left(d\left(\frac{t_0 - t}{1-\eta}\right)\right)\ 1_{\{z_0<\eta\ \wedge\ t<t_0\}} \ + \ z_0\ \delta_{t_0}(t)\ 1_{\{z_0>\eta\}} \\ &+ (1-z_0)\ \mu_W\left(d\left(\frac{t-t_0}{\eta}\right)\right)\ 1_{\{t>t_0\}} \end{aligned} \tag{4.3}$$

If the probability measures μ_R and μ_W are absolutely continuous with respect to the Lebesgue measure, we can write as well

- $\mu_R\left(d\left(\frac{t_0-t}{1-\eta}\right)\right) \ = \ f_R\left(\frac{t_0-t}{1-\eta}\right)\ \frac{1}{1-\eta}\ dt$
- $\mu_W\left(d\left(\frac{t-t_0}{\eta}\right)\right) \ = \ f_W\left(\frac{t-t_0}{\eta}\right)\ \frac{1}{\eta}\ dt$

where $f_R(\cdot)$ and $f_W(\cdot)$ are the Radon Nikodym derivatives of the measures μ_R and μ_W with respect to the Lebesge measure.

4.1 An Harris Chain to study the rate of convergence of urn model

Since the marginal process T_n needs to be coupled with the process Z_n to have a Markov bivariate process (T_n, Z_n), the application of many results on Markov processes in the case of continuous state space it's not straightforward. Then, we define a new auxiliary process $\tilde{T}_n$ strictly related to T_n, in this way:

$$\begin{cases} \tilde{T}_0 & = \eta W_0 \; - \; (1-\eta) R_0 \\ \tilde{T}_{n+1} & = \tilde{T}_n \; + \; \eta(1-\tilde{X}_{n+1}) \; N_{n+1} \; - \; (1-\eta)\tilde{X}_{n+1} \; M_{n+1} \; 1_{\{\tilde{T}_n>0\}} \end{cases} \tag{4.4}$$

$\forall n \in \mathbb{N}$, where $(\tilde{X}_n)_{n\in\mathbb{N}}$ are i.i.d. Bernoulli random variables of parameter η independent of the sequences $(M_n)_{n\in\mathbb{N}}$ and $(N_n)_{n\in\mathbb{N}}$. It's easy to see that $\tilde{T}_n$ is a Markov process. In fact, the transition kernel K_η of $\tilde{T}_n$ is independent of the quantity z_0

$$\begin{aligned} K_\eta(t_0, dt) \quad &= \eta \; \mu_R \left(d\left(\frac{t_0 - t}{1-\eta} \right) \right) \; 1_{\{t_0>0 \,\wedge\, t<t_0\}} \; + \; \eta \; \delta_{t_0}(t) \; 1_{\{t_0<0\}} \\ &+ (1-\eta) \; \mu_W \left(d\left(\frac{t-t_0}{\eta} \right) \right) \; 1_{\{t>t_0\}} \end{aligned} \tag{4.5}$$

Here, we show that the Markov process $\tilde{T}_n$ is an aperiodic recurrent Harris chain. This result will be used in Section 4.2 to investigate the asymptotic behavior of the process T_n, and then obtaining the rate of convergence of the urn process Z_n.
At first, we need a lemma on the dynamic of the process $\tilde{T}_n$

Lemma 4.1.1. *For any $t_0 \in \mathbb{R}$, there exists $\bar{t} > t_0$ such that*

$$\forall \, t > \bar{t}, \quad \forall \, \epsilon > 0, \qquad P\left(\bigcup_{k=1}^{\infty} \left\{ \tilde{T}_k \in [t, t+\epsilon] \right\} \mid \tilde{T}_0 = t_0 \right) \; > \; 0 \tag{4.6}$$

Proof. Let us take $a_1, b_1 \in \mathbb{R}^+$ such that $a_0 < a_1 < b_1 < b_0$. At first, notice that if $t \in (t_0 + a_1\eta, t_0 + b_1\eta)$, then

$$P\left(\; \tilde{T}_1 \in (t, t+dt) \mid \tilde{T}_0 = t_0 \; \right) \; = \; (1-\eta) \; \mu_W \left(d\left(\frac{t-t_0}{\eta} \right) \right) \; > \; 0$$

since $\frac{t-t_0}{\eta} \in (a_1, b_1)$.
For the same reason, for any $k \in \mathbb{N}$, we have that if $t \in (t_0 + ka\eta, t_0 + kb\eta)$, then

$$P\left(\; \tilde{T}_k \in (t, t+dt) \mid \tilde{T}_0 = t_0 \; \right) \; \geq \; (1-\eta)^k \; \mu_W \left(d\left(\frac{t-t_0}{k\eta} \right) \right)^k \; > \; 0$$

Let us introduce the sequence of sets $(A_k)_k$ such that

$$A_k \; = \begin{cases} (\; t_0 + (k-1)b_1\eta \; , \; t_0 + ka_1\eta \;) & \text{if } k < \frac{b_1}{b_1 - a_1}, \\ \\ \emptyset & \text{otherwise} \; . \end{cases}$$

for $k \geq 1$. Then, for any $n \in \mathbb{N}$, we have that if

$$t \; \in \quad (\; t_0 \; , \; t_0 \; + \; nb_1\eta \;) \; / \; \bigcup_{k=1}^{n} A_k,$$

then

$$t \ \in \ \bigcup_{k=1}^{n} (\ t_0 + ka_1\eta\ ,\ t_0 + kb_1\eta\ ),$$

and

$$P\left(\bigcup_{k=1}^{n} \{\tilde{T}_k \in (t, t+dt)\} \mid \tilde{T}_0 = t_0\right) \ \geq \ (1-\eta)^{n_0}\ \mu_W\left(d\left(\frac{t-t_0}{n_0\eta}\right)\right)^{n_0} \ > \ 0,$$

where we choose

$$n_0 = \left[\frac{t-t_0}{b_1\eta}\right] + 1$$

Therefore, a sufficient condition for $P\left(\bigcup_{k=1}^{\infty}\left\{\tilde{T}_k \in [t, t+\epsilon]\right\} |\tilde{T}_0 = t_0\right) > 0$ is

$$t \ \in \ (t_0, \infty) \ / \ \bigcup_{k=1}^{[\frac{b_1}{b_1-a_1}]} (\ t_0 + (k-1)b_1\eta\ ,\ t_0 + ka_1\eta\ ),$$

so the thesis holds for any $\bar{t} \ \geq \ t_0 + \left[\frac{b}{b-a_1}\right] a_1\eta$. ☐

Now, we can use Lemma 4.1.1 to show that $\tilde{T} = (\tilde{T}_n)_{n\in\mathbb{N}}$ is a Harris Chain.

Proposition 4.1.2. *The Markov process $\tilde{T} = (\tilde{T}_n)_{n\in\mathbb{N}}$ on the state space $\mathbb{R}$ is a Harris Chain.*

Proof. Let us start reminding that the Markov process $\tilde{T}_n$ on the state space $\mathbb{R}$ is a *Harris chain* if there exist $A, B \subset \mathbb{R}$, a constant $\epsilon > 0$ and a probability measure ρ with $\rho(B) = 1$, such that

(a) If $\tau^A := inf\{n \geq 0 \ : \ \tilde{T}_n \in A\}$, then $P(\tau^A < \infty \mid \tilde{T}_0 = t_0) > 0$ for any $t_0 \in \mathbb{R}$.

(b) If $t_0 \in A$ and $C \subset B$, then $K_\eta(t_0, C) \geq \epsilon\rho(C)$.

Let us prove the condition (a). Let $A = [0, (b_1 - a_1)\eta]$.

- First case: $t_0 \in [0, (b_1 - a_1)\eta]$

The condition (a) is trivial, since $P(\tau_A = 0 \mid \tilde{T}_0 = t_0 \in A) = 1$.

- Second case: $t_0 > (b_1 - a_1)\eta$

We fix $\bar{t} \ \geq \ t_0 + \left[\frac{b_1}{b_1-a_1}\right] a\eta$ and we define $\bar{n} \in \mathbb{N}$, $I \subset \mathbb{R}$ as follows

$$\bar{n} \ = \ \left[\frac{\bar{t}}{(1-\eta)x_0}\right] + 1,$$

$$I \ = \ [\ \bar{n}(1-\eta)x_0\ ,\ \bar{n}(1-\eta)x_0 + (b_1 - a_1)\eta\ ]\ ,$$

where $x_0 \in [a,b]$ is chosen such that, for every $\epsilon > 0$, $\mu_R([x_0, x_0+\epsilon]) > 0$.
Fixing $\tilde{t} \in I$, we have from the previous lemma that for every $\zeta > 0$

$$P\left(\bigcup_{k=1}^{\infty}\left\{\tilde{T}_k \in [\tilde{t}, \tilde{t}+\zeta]\right\} \mid \tilde{T}_0 = t_0\right) \;>\; 0,$$

since $\tilde{t} \geq \bar{n}(1-\eta)x_0 \geq \bar{t}$. Then, let fix ζ small enough, such that $\tilde{t}+\zeta \in I$. Let

$$\tilde{n} := inf\left\{\; n \geq 1 \;:\; P\left(\bigcup_{k=1}^{n}\left\{\tilde{T}_k \in [\tilde{t}, \tilde{t}+\zeta]\right\} \mid \tilde{T}_0 = t_0 > (b_1-a_1)\eta\right) > 0\;\right\}$$

We can write

$$P(\;\tau^A < \infty \mid \tilde{T}_0 = t_0\;) \;\geq\; P(\;\tilde{T}_{\tilde{n}+\bar{n}} \in (0,(b_1-a_1)\eta) \mid \tilde{T}_0 = t_0\;) \;\geq$$
$$P(\;\tilde{T}_{\tilde{n}+\bar{n}} \in (0,(b_1-a_1)\eta) \mid \tilde{T}_{\tilde{n}} \in [\tilde{t}, \tilde{t}+\zeta]\;) \;\cdot\; P(\;\tilde{T}_{\tilde{n}} \in [\tilde{t}, \tilde{t}+\zeta] \mid \tilde{T}_0 = t_0\;)$$

We have already proved that the second term of this product is strictly positive, so we focus on the first term. Let us call

$$\tilde{t}_{min} := \arg\min_{t \in [\tilde{t}, \tilde{t}+\zeta]} P(\;\tilde{T}_{\tilde{n}+\bar{n}} \in (0,(b_1-a_1)\eta) \mid \tilde{T}_{\tilde{n}} = t\;)$$

we have

$$P(\;\tilde{T}_{\tilde{n}+\bar{n}} \in (0,(b_1-a_1)\eta) \mid \tilde{T}_{\tilde{n}} \in [\tilde{t}, \tilde{t}+\zeta]\;) \;\geq\; P(\;\tilde{T}_{\tilde{n}+\bar{n}} \in (0,(b_1-a_1)\eta) \mid \tilde{T}_{\tilde{n}} = \tilde{t}_{min}\;) \quad \geq$$
$$\prod_{s=1}^{\bar{n}} K_\eta\left(\;\tilde{t}_{min} - (s-1)(1-\eta)x_0 \quad , \quad [\tilde{t}_{min} - s(1-\eta)x_0 ; \tilde{t}_{min} - s(1-\eta)x_0 + dt]\;\right) \quad =$$
$$(\;\eta \cdot \mu_R(dx_0)\;)^{\bar{n}} \;>\; 0$$

because $\tilde{t}_{min} - \bar{n}(1-\eta)x_0 \in (0,(b_1-a_1)\eta)$.

- Third case: $t_0 < 0$

We fix $\bar{t} \;\geq\; \max\left\{\; t_0 + \left[\frac{b_1}{b_1-a_1}\right] a_1\eta \;;\; 0\;\right\}$ and then we follow the same strategy used in the second case ($t_0 > (b_1-a_1)\eta$).

Let us prove the condition (b) Let

$$B \;=\; [\;(b_1-a_1+a_0)\eta\;,\; b_0\eta\;] \subset \mathbb{R}$$

and the probability measure

$$\rho(C) = \frac{1}{(b_0-b_1+a_1-a_0)\eta}\int_C dt$$

for any set $C \subset B$. For every $t_0 \in A$,

$$K_\eta(t_0, C) \;\geq\; \int_C (1-\eta)\,\mu_W\left(d\left(\frac{t-t_0}{\eta}\right)\right) \;\geq\; (1-\eta)\int_C \min_{(t_0,t)\in A\times B}\left[\frac{\mu_W\left(d\left(\frac{t-t_0}{\eta}\right)\right)}{dt}\right]\; dt$$

$$= (1-\eta)\int_C \min_{x\in(a_0,b_0)}\left[\frac{\mu_W(dx)}{dx}\right] dt$$

Now if we define

$$\epsilon = (b_0 - b_1 + a_1 - a_0)\eta(1-\eta)\min_{x\in(a_0,b_0)}\left[\frac{\mu_W(dx)}{dx}\right]$$

we obtain

$$K_\eta(t_0, C) \geq \epsilon \cdot \frac{1}{(b_0 - b_1 + a_1 - a_0)\eta}\int_C dt = \epsilon \cdot \rho(C)$$

□

Now we dedicate on proving the recurrence of the process $\widetilde{T}_n$.
In what follows, for any interval $I \subset \mathbb{R}$, we will refer to $(\tau_i^I)_i$ as the sequence of stopping times

$$\begin{cases} \tau_0^I = 0 \\ \tau_i^I := inf\left\{ n > \tau_{i-1}^I \ : \ \tilde{T}_n \in I \right\}, \ \ i \geq 1 \end{cases}$$

For ease of notation, we will denote τ^I as τ_1^I.

Proposition 4.1.3. *The Harris chain $\tilde{T} = (\tilde{T}_n)_{n\in\mathbb{N}}$ on the state space $\mathbb{R}$ is recurrent .*

Proof. Let us remind that $\tilde{T}_n$ is recurrent if $P(\tau^A < \infty \mid \tilde{T}_0 \in A) = 1$, for any initial probability distribution $\tilde{\lambda}_0$, where $\tau^A := inf\{n \geq 1 \ : \ \tilde{T}_n \in A\}$. In particular, we are able to prove a stronger property, that is $P(\tau^A < \infty \mid \tilde{T}_0 = t_0) = 1$ for any $t_0 \in \mathbb{R}$, which implies the condition we need.

Let

- I be the closed interval defined as

$$I := [-(1-\eta)b, 0],$$

- c be the constant defined as

$$c := \min_{t\in I} P\left(\tau^A < \infty \mid \tilde{T}_0 = t\right)$$

  c is strictly positive because, the process $\tilde{T}_n$ is an Harris chain and so $P(\tau^A < \infty \mid \tilde{T}_0 = t_0) > 0 \ \forall t_0 \in \mathbb{R}$,

- $\tilde{n}$ be the integer defined as

$$\tilde{n} := inf\left\{ n \geq 1 \ : \ \min_{x\in I} P\left(\bigcup_{k=1}^{\tilde{n}}\{\tilde{T}_k \in A\} \mid \tilde{T}_0 = x\right) \geq \frac{c}{2} \right\}$$

Now, we focus on proving that the stopping times $(\tau_i^I)_i$ are almost surely finite:

$$P\left(\tau^I = \infty \mid \tilde{T}_0 = t_0\right) = 0 \tag{4.7}$$

(a) First case: $t_0 \in (0, \infty)$

Looking at the transition kernels (4.3) and (4.5) of the processes T_n and $\tilde{T}_n$ respectively, we note that for any $t_0 \in (0, \infty)$, $P(\tilde{T}_1 \leq T_1 \mid \tilde{T}_0 = T_0 = t_0) \ = \ 1$. This implies that

$$P(\tilde{T}_1 > 0 \mid \tilde{T}_0 = t_0) \ \leq \ P(T_1 > 0 \mid T_0 = t_0) \tag{4.8}$$

Then, we have that

$$\begin{aligned} P\left(\tau^I = \infty \mid \tilde{T}_0 = t_0\right) \quad & = P\left(\tau^{(-\infty,0)} = \infty \mid \tilde{T}_0 = t_0\right) \quad = \\ P\left(\bigcap_{n=1}^{\infty} \left\{\tilde{T}_n > 0\right\} \mid \tilde{T}_0 = t_0\right) \quad & \leq P\left(\bigcap_{n=1}^{\infty} \{T_n > 0\} \mid T_0 = t_0\right) \quad = 0 \end{aligned}$$

where the passage from $\tilde{T}_n$ to T_n is due to the relation (4.8) and the latest probability is equal to zero because $P(T_n < 0 \ \ i.o. \mid T_0 = t_0) = P(Z_n > \eta \ \ i.o. \mid T_0 = t_0) = 1$ for any $t_0 \in \mathbb{R}$.

(b) Second case: $t_0 \in (-\infty, 0]$

Looking at the transition kernels (4.3) and (4.5) we have that for any $t_0 \in (-\infty, 0]$,

$$P(\tilde{T}_1 < 0 \mid \tilde{T}_0 = t_0) \ \leq \ P(T_1 < 0 \mid T_0 = t_0) \tag{4.9}$$

and following the same arguments of the case (a) this leads to

$$P\left(\tau^{(0,\infty)} = \infty \mid \tilde{T}_0 = t_0\right) \ = \ 0 \tag{4.10}$$

Hence, we have

$$\begin{aligned} & P\left(\tau^I = \infty \mid \tilde{T}_0 = t_0\right) && = \\ & P\left(\tau^I = \infty \mid \{\tau^{(0,\infty)} < \infty\} \bigcap \{\tilde{T}_0 = t_0\}\right) && = \\ & P\left(\bigcap_{n=1}^{\infty} \{\tilde{T}_n \notin I\} \mid \{\tau^{(0,\infty)} < \infty\} \bigcap \{\tilde{T}_0 = t_0\}\right) && \leq \\ & P\left(\bigcap_{n=\tau^{(0,\infty)}+1}^{\infty} \{\tilde{T}_n \notin I\} \mid \{\tau^{(0,\infty)} < \infty\} \bigcap \{\tilde{T}_0 = t_0\}\right) && \leq \\ & \sup_{x \in (0,\infty)} P\left(\bigcap_{n=1}^{\infty} \{\tilde{T}_n \notin I\} \mid \tilde{T}_0 = x\right) && = \\ & \sup_{x \in (0,\infty)} P\left(\tau^I = \infty \mid \tilde{T}_0 = x\right) && = 0 \end{aligned}$$

since from the case (a) we have that $\forall t_0 > 0, \ P(\tau^I = \infty \mid \tilde{T}_0 = t_0) = 0$. Therefore, we conclude that $P(\bigcap_{i=1}^{\infty} \tau_i^I < \infty \mid \tilde{T}_0 = t_0) = 1$, which means $(\tau_i^I)_i$ is sequence of stopping times almost surely finite.

Then, let us define the sequence of stopping times

$$\begin{cases} \tau_0 = 0 \\ \tau_i := inf\left\{ n > \tau_{i-1} + \tilde{n} \; : \; \tilde{T}_n \in I \right\}, \quad i \geq 1 \end{cases}$$

Since $\bigcup_{n=1}^{\infty} \tau_n \subset \bigcup_{n=1}^{\infty} \tau_n^I$, the stopping times $(\tau_n, n = 0,1,2,..)$ are almost surely finite.
Therefore, for any $t_0 \in \mathbb{R}$ we have that

$$\begin{aligned}
&P\left(\tau^A = \infty \mid \tilde{T}_0 = t_0\right) \;=\; P\left(\bigcap_{n=1}^{\infty}\{T_n \notin A\} \mid \tilde{T}_0 = t_0\right) && \leq \\
&P\left(\bigcap_{i=0}^{\infty}\bigcap_{n=\tau_i+1}^{\tau_i+\tilde{n}}\{\tilde{T}_n \notin A\} \mid \tilde{T}_0 = t_0\right) && = \\
&\prod_{i=1}^{\infty} P\left(\bigcap_{n=\tau_i+1}^{\tau_i+\tilde{n}}\{\tilde{T}_n \notin A\} \mid \bigcap_{j=0}^{i-1}\bigcap_{n=\tau_j+1}^{\tau_j+\tilde{n}}\{\tilde{T}_n \notin A\}\right) && = \\
&\prod_{i=1}^{\infty}\left[1 - P\left(\bigcup_{n=\tau_i+1}^{\tau_i+\tilde{n}}\{\tilde{T}_n \in A\} \mid \bigcap_{j=0}^{i-1}\bigcap_{n=\tau_j+1}^{\tau_j+\tilde{n}}\{\tilde{T}_n \notin A\}\right)\right] && = \\
&\prod_{i=1}^{\infty}\left[1 - \int_I P\left(\bigcup_{n=\tau_i+1}^{\tau_i+\tilde{n}}\{\tilde{T}_n \in A\} \mid \tilde{T}_{\tau_i} = x\right) P\left(\tilde{T}_{\tau_i} = dx \mid \bigcap_{j=0}^{i-1}\bigcap_{n=\tau_j+1}^{\tau_j+\tilde{n}}\{\tilde{T}_n \notin A\}\right)\right] && = \\
&\prod_{i=1}^{\infty}\left[1 - \int_I P\left(\bigcup_{n=1}^{\tilde{n}}\{\tilde{T}_n \in A\} \mid \tilde{T}_0 = x\right) P\left(\tilde{T}_{\tau_i} = dx \mid \bigcap_{j=0}^{i-1}\bigcap_{n=\tau_j+1}^{\tau_j+\tilde{n}}\{\tilde{T}_n \notin A\}\right)\right] && \leq \\
&\prod_{i=1}^{\infty}\left[1 - \min_{x\in I} P\left(\bigcup_{n=1}^{\tilde{n}}\{\tilde{T}_n \in A\} \mid \tilde{T}_0 = x\right)\right] && \leq \\
&\prod_{i=1}^{\infty}\left[1 - \frac{c}{2}\right] && = 0
\end{aligned}$$

and so the thesis is proved. □

Finally, we show the aperiodicity of the process $\tilde{T}_n$

Proposition 4.1.4. *The recurrent Harris Chain $\tilde{T} = (\tilde{T}_n)_{n\in\mathbb{N}}$ on the state space $\mathbb{R}$ is aperiodic.*

Proof. The recurrent Harris chain $\tilde{T}_n$ is aperiodic if there exists $n_0 \in \mathbb{N}$ such that $P(\tilde{T}_n \in A \mid \tilde{T}_0 \in A) > 0$, for any integer $n \geq n_0$ and for any distribution law $\tilde{\lambda}_0$ on $\tilde{T}_0$.
Let define the stopping time $\tau_1^{A^-}$ as follows

$$\tau^{A^-} := \inf\left\{n > \tau^{(-\infty,0)} \; : \; \tilde{T}_n \in A\right\} \tag{4.11}$$

This stopping time is almost surely finite. In fact, since $P(\tau^{(-\infty,0)} < \infty | \tilde{T}_0 = t_0) = 1$ for any $t_0 \in \mathbb{R}$, we have that

$$P\left(\tau^{A^-} < \infty \mid \tilde{T}_0 \in A\right) = P\left(\tau^{A^-} < \infty \mid \{\tau^{(-\infty,0)} < \infty\} \bigcap \{\tilde{T}_0 \in A\}\right) =$$
$$P\left(\bigcup_{n=\tau^{(-\infty,0)}}^{\infty} \{\tilde{T}_n \in A\} \mid \{\tau^{(-\infty,0)} < \infty\} \bigcap \{\tilde{T}_0 \in A\}\right) \geq$$
$$\min_{x\in(-\infty,0)} P\left(\bigcup_{n=0}^{\infty} \{\tilde{T}_n \in A\} \mid \tilde{T}_0 = x\right) = \min_{x\in(-\infty,0)} P\left(\tau^A < \infty \mid \tilde{T}_0 = x\right) = 1$$

Hence, there exists $n_0 \in \mathbb{N}$ such that $P(\tau^{A^-} = n_0 \mid \tilde{T}_0 \in A) > 0$. We notice also that

$$P\left(\tilde{T}_{n_0} \in A \mid \tilde{T}_0 \in A\right) \geq P\left(\{\tilde{T}_{n_0} \in A\} \bigcap \{\tau^{A^-} = n_0\} \mid \tilde{T}_0 \in A\right) =$$
$$P\left(\tilde{T}_{n_0} \in A \mid \{\tau^{A^-} = n_0\} \bigcap \{\tilde{T}_0 \in A\}\right) \cdot P\left(\tau^{A^-} = n_0 \mid \tilde{T}_0 \in A\right) =$$
$$P\left(\tilde{T}_{\tau^{A^-}} \in A \mid \tilde{T}_0 \in A\right) \cdot P\left(\tau^{A^-} = n_0 \mid \tilde{T}_0 \in A\right) = P\left(\tau^{A^-} = n_0 \mid \tilde{T}_0 \in A\right) > 0$$

Then, for every $n \geq n_0$, we have

$$P\left(\tilde{T}_n \in A \mid \tilde{T}_0 \in A\right) \geq P\left(\tau^{A^-} = n \mid \tilde{T}_0 \in A\right) \geq \eta^{n-n_0} \cdot P\left(\tau^{A^-} = n_0 \mid \tilde{T}_0 \in A\right) > 0$$

and so the thesis is proved. □

4.2 Rate of convergence

In the previous section, we have proved that under Assumption 4.0.1, the Markov process $\tilde{T}_n$ is an aperiodic recurrent Harris chain. So, we can state the following

Proposition 4.2.1. *Let us call π the stationary distribution of the recurrent aperiodic Harris Chain $\tilde{T} = (\tilde{T}_n)_{n\in\mathbb{N}}$. Then, for every $t_0 \in \mathbb{R}$, we have that*

$$\lim_{n\to\infty} \sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(\tilde{T}_n \in C \mid \tilde{T}_0 = t_0) - \pi(C) \,| = 0 \tag{4.12}$$

Proof. The Markov process $\tilde{T}_n$ is a recurrent aperiodic Harris Chain. This result implies that there exists a unique invariant distribution probability π and (4.12) holds for any t_0 such that

$$P(\, \tau^A < \infty \mid \tilde{T}_0 = t_0 \,) = 1 \tag{4.13}$$

where τ^A is defined as follows

$$\tau^A = \begin{cases} \inf\{n \geq 0 \;:\; \tilde{T}_n \in A\} & \text{if } \{n \geq 0 \;:\; \tilde{T}_n \in A\} \neq \emptyset; \\ \infty & \text{otherwise.} \end{cases}$$

The thesis is proved since (4.13) holds for any $t_0 \in \mathbb{R}$. □

Now, we can state the main result

Theorem 4.2.2. *For any initial composition* $(r_0, w_0) \in (0,\infty) \times (0,\infty)$*, we have that*

$$n \cdot (\eta - Z_n) \xrightarrow{\mathcal{D}} \frac{\psi}{m_W} \tag{4.14}$$

where ψ *is a real random variable with probability distribution* π*.*

Proof. Using equation (4.2), Proposition 2.4.2 and Slutsky's theorem we have that it's sufficient to prove that $T_n \overset{\mathcal{D}}{\to} \psi$, where ψ is a real random variable with probability distribution π.

Our aim is to prove that, for any $t_0 \in (-(1-\eta)d_0, \eta d_0)$ (physical bound because $z_0 \in (0,1)$ and $t_0 = d_0(\eta - z_0)$),

$$\lim_{n\to\infty} \sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_n \in C \mid T_0 = t_0) \;-\; \pi(C) \,| = 0. \tag{4.15}$$

To do that, we will prove the following

$$\lim_{n\to\infty} \sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_n \in C \mid T_0 = t_0) \;-\; \int_{\mathbb{R}} K_\eta(t,C) P(T_n = dt \mid T_0 = t_0) \,| = 0 \tag{4.16}$$

since we can show that (4.16) implies (4.15). The proof is so composed by two parts, (a) and (b). Part (a) is dedicated to prove that (4.16) implies (4.15), while in Part (b) we prove (4.16).

Part (a):
Let us denote with p_n the probability law of T_n, conditionally to $\{T_0 = t_0\}$. Then, the goal of Theorem 4.2.2, that is shown in (4.15), can be rewritten as follows

$$\sup_{C\in\mathcal{B}(\mathbb{R})} |\int_C (p_n(dx) - \pi(dx))| \;\to_n\; 0.$$

Now, let us denote with H the operator defined as follows

$$H(t, ds) := 1_{ds}(t) - K_\eta(t, ds)$$

Then, expression (4.16) can be rewritten as follows

$$\sup_{C\in\mathcal{B}(\mathbb{R})} |\int_C \int_{\mathbb{R}} H(t, ds) p_n(dt)| \;\to_n\; 0.$$

Roughly speaking, this means that the sequence of measures p_n is progressively closer to the kernel of the operator H. Formally, we can say there exists a sequence of measures $(\theta_n)_n$ such that

- $\sup_{C\in\mathcal{B}(\mathbb{R})} |\int_C (p_n(dx) - \theta_n(dx))| \to_n 0$,
- $\int_{\mathbb{R}} H(t, ds)\theta_n(dt) = 0$.

Notice that, since π is the unique probability distribution such that $\pi(C) = \int_{\mathbb{R}} K_\eta(t, C)\pi(dt)$ for any $C \in \mathcal{B}(\mathbb{R})$. Hence π is the only measure such that $\int_{\mathbb{R}} H(t, ds)\pi(dt) = 0$

($\pi \in Ker(H)$) and $\int_{\mathbb{R}} \pi(ds) = 1$. As a consequence, since $\int_{\mathbb{R}} p_n(ds) = 1 \; \forall n$, $\theta_n \equiv \pi$ $\forall n$.
Then, we have shown that (4.16) implies (4.15).

Part (b):
To prove (4.16), we are going to define some quantities.
For any t_0 and for any $C \in \mathcal{B}(\mathbb{R})$, let us define

$$F_n(t_0, C) \; := \; \int_{\mathbb{R}} f_n(t, C) P(T_n = dt | T_0 = t_0) \tag{4.17}$$

where

$$f_n(t, C) \; := \; P(T_{n+1} \in C | T_n = t) - P(\widetilde{T}_{n+1} \in C | \widetilde{T}_n = t). \tag{4.18}$$

With these two quantities, we can write

$$\begin{aligned} P(T_{n+1} \in C | T_0 = t_0) \quad &= \int_{\mathbb{R}} P(T_{n+1} \in C | T_n = t) P(T_n = dt | T_0 = t_0) \\ &= \int_{\mathbb{R}} P(\widetilde{T}_{n+1} \in C | \widetilde{T}_n = t) P(T_n = dt | T_0 = t_0) \\ &+ \int_{\mathbb{R}} f_n(t, C) P(T_n = dt | T_0 = t_0) \\ &= \int_{\mathbb{R}} K_\eta(t, C) P(T_n = dt | T_0 = t_0) \\ &+ F_n(t_0, C) \end{aligned}$$

Now, if we define

$$\nu_n(t_0, C) \; := \; P(T_{n+1} \in C | T_0 = t_0) - (T_n \in C | T_0 = t_0). \tag{4.19}$$

we can use this and the previous decomposition of $P(T_{n+1} \in C | T_0 = t_0)$, to obtain

$$\begin{aligned} &\sup_{C \in \mathcal{B}(\mathbb{R})} \mid P(T_n \in C | T_0 = t_0) - \int_{\mathbb{R}} K_\eta(t, C) P(T_n = dt | T_0 = t_0) \mid \\ \le &\sup_{C \in \mathcal{B}(\mathbb{R})} |F_n(t_0, C)| + |\nu_n(t_0, C)| \\ \le &\; F_n(t_0) + \nu_n(t_0). \end{aligned}$$

The thesis is get since in Lemma 4.2.3 and 4.2.4 we show that, for any admissible t_0, $sup_C F_n(t_0, C)$ and $sup_C \nu_n(t_0, C)$ tend to zero as n goes to infinity. $\square$

The first lemma deals with the quantities $F_n(t_0, C)$ and $f_n(t, C)$ defined in the proof of Theorem 4.2.2. The goal is to show $sup_C |F_n(t_0, C)| \le F_n(t_0)$, where $F_n(t_0)$ is a sequence independent of C and that tends to zero for any fixed t_0.

Lemma 4.2.3. *Consider the sequence $F_n(t_0, C)$ defined in* (4.17). *Then, there exists a sequence $F_n(t_0)$ such that $sup_C |F_n(t_0, C)| \le F_n(t_0)$ for any n, and $F_n(t_0) \to_n 0$ for any fixed t_0.*

Proof. At first, let us consider the term $f_n(t_0, C)$ defined in (4.18). We have that

$$\begin{aligned}
|f_n(t_0, C)| \quad &= |\ P(T_{n+1} \in C | T_n = t_0) \ - \ P(\widetilde{T}_{n+1} \in C | \widetilde{T}_n = t_0)\ | \\
&= |\int_C \left(\int_0^1 K_z(t_0, dt) P(Z_n = dz | T_n = t_0) \ - \ K_\eta(t_0, dt) \right) | \\
&= |\int_C \left(\int_0^1 (K_z(t_0, dt) - K_\eta(t_0, dt)) P(Z_n = dz | T_n = t_0) \right) | \\
&= |\int_C \left(\int_0^1 (z - \eta) \ \times \ \left(\mu_R \left(d \left(\frac{t_0 - t}{1 - \eta} \right) \right) 1_{\{t_0 > 0 \ \wedge \ t < t_0\}} \right.\right. \\
&\left.\left. + \ \delta_{t_0}(t)\, 1_{\{t_0 < 0\}} \ - \ \mu_W \left(d \left(\frac{t - t_0}{\eta} \right) \right) 1_{\{t > t_0\}} \right) \ P(Z_n = dz | T_n = t_0) \right) | \\
&\leq \left(\int_0^1 \ |z - \eta| \ P(Z_n = dz | T_n = t_0) \right) \ \times \ 2 \cdot \int_C \ K_{1/2}(t_0, dt) \\
&\leq 2 \ \times \ \mathbb{E}[\ |Z_n - \eta| \ | \ T_n = t_0\ ]
\end{aligned}$$

that is independent of the set C.
Now, let us consider the term $F_n(t_0, C)$. Let us take a sequence $(t_n)_n$, $t_i \in (0, \infty) \forall i$, such that $t_n \to \infty$ and $t_n/n \to 0$. Then, we have that

$$\begin{aligned}
|F_n(t_0, C)| \quad &= |\ \int_{\mathbb{R}} f_n(t, C) P(T_n = dt | T_0 = t_0)\ | \\
&\leq 2 \int_{\mathbb{R}} \mathbb{E}[|Z_n - \eta| | T_n = t] P(T_n = dt | T_0 = t_0) \\
&= 2 \int_{\{T_n > t_n\}} \mathbb{E}[|Z_n - \eta| | T_n = t] P(T_n = dt | T_0 = t_0) \\
&+ 2 \int_{\{T_n \leq t_n\}} \mathbb{E}[|Z_n - \eta| | T_n = t] P(T_n = dt | T_0 = t_0) \\
&\leq 2P(T_n > t_n | T_0 = t_0) \ + \ 2\mathbb{E}[|Z_n - \eta| | T_n = t_n] \\
&= 2P(T_n > t_n | T_0 = t_0) \ + \ 2\mathbb{E}[|Z_n - \eta| | D_n(\eta - Z_n) = t_n]
\end{aligned}$$

The second term tends to zero because D_n/n converge almost surely and in L^1 to a constant.
Let us focus on the first term. To deal with that, notice that if $T_n > t_n$, then $\bigcap_{i=n-[t_n/b]}^{n} \{T_i > 0\}$. Let us introduce the stopping time

$$\tau = \begin{cases} \inf\{\ n \geq 1 \mid Z_n > \eta\ \} & \text{if } \neq \emptyset; \\ \infty & \text{otherwise.} \end{cases}$$

representing the first time $Z_n > \eta$ (i.e. $T_n < 0$). Then, we have

$$\begin{aligned}
P(T_n > t_n | T_0 = t_0) &\leq P\left(\bigcup_{j=0}^{n-[t_n/b]} \left\{ \{T_j < 0\} \bigcap_{i=j+1}^{n} \{T_i > 0\} \right\} \mid T_0 = t_0 \right) \\
&\leq \sum_{j=0}^{n-[t_n/b]} P\left(\{T_j < 0\} \bigcap_{i=j+1}^{n} \{T_i > 0\} \mid T_0 = t_0 \right) \\
&\leq \sum_{j=0}^{n-[t_n/b]} P\left(\bigcap_{i=j+1}^{n} \{T_i > 0\} \mid T_0 = t_0 \bigcap \{T_j < 0\} \right) \\
&= \sum_{j=0}^{n-[t_n/b]} P\left(\bigcap_{i=j+1}^{n} \{Z_i < \eta\} \mid T_0 = t_0 \bigcap \{Z_j > \eta\} \right) \\
&\leq \sum_{j=0}^{n-[t_n/b]} P\left(\, \tau > n-j \mid (Z_0, D_0) = (\eta, d_0) \,\right) \\
&= \sum_{i=[t_n/b]}^{n} P\left(\, \tau > i \mid (Z_0, D_0) = (\eta, d_0) \,\right) \ \to_n \ 0
\end{aligned}$$

since $\mathbb{E}[\tau | Z_0 = z_0] < \infty$ for any $z_0 \in (0, 1)$ (see Lemma 4.2.5).
Therefore, we have that

$$| \int_{\mathbb{R}} f_n(t, C) P(T_n = dt | T_0 = t_0)| = |F_n(t_0, C)| \leq \ F_n(t_0) \ \to \ 0$$

since the limit is independent of C. □

The second lemma deals with the quantity $\nu_n(t_0, C)$ defined in the proof of Theorem 4.2.2. The goal is to show $sup_C |\nu_n(t_0, C)| \leq \nu_n(t_0)$, where $\nu_n(t_0)$ is a sequence independent of C and that tends to zero for any fixed t_0.

Lemma 4.2.4. *Consider the sequence $\nu_n(t_0, C)$ defined in* (4.19)*. Then, there exists a sequence $\nu_n(t_0)$ such that $sup_C |\nu_n(t_0, C)| \leq \nu_n(t_0)$ for any n, and $\nu_n(t_0) \to_n 0$ for any fixed t_0.*

Proof. Let us fix $\epsilon > 0$. We show that there exists $N = N(\epsilon, t_0) \in \mathbb{N}$ (N independent of C) such that

$$|P(T_{n+1} \in C | T_0 = t_0) - (T_n \in C | T_0 = t_0)| < \epsilon$$

for any $n \geq N$.

Let us fix $\epsilon_1 = \epsilon_2 = \epsilon_3 = \epsilon_4 = \epsilon/4$.
Let us denote $I := [-b(1-\eta), 0]$.
Let us take an integer N_2, such that

$$\sup_{t_0 \in I} \sup_{C \in \mathcal{B}(\mathbb{R})} \mid P(\tilde{T}_{k+1} \in C | \tilde{T}_0 = t_0) \ - \ P(\tilde{T}_k \in C | \tilde{T}_0 = t_0) \mid \ < \ \epsilon_1$$

for any $k \geq N_2$. The existence of N_2 is guaranteed by (4.12).
Then, let us take an integer $N_1 \geq N_2$, such that

$$\sup_{t_0 \in I} \sum_{j=1}^{\infty} P\left(\tau > N_1 - N_2 + j \mid T_0 = t_0 \right) < \epsilon_2$$

where τ was the first time $Z_n > \eta$ ($T_n < 0$). The existence of N_1 is guaranteed once we note that $P(\tau > k|T_0 = t_0) \leq P(\tau > k|(Z_0, D_0) = (\eta, d_0))$ for any $t_0 \in I$, and

$$\sum_{j=1}^{\infty} P\left(\tau > j|(Z_0, D_0) = (\eta, d_0)\right) = \mathbb{E}[\,\tau\,|(Z_0, D_0) = (\eta, d_0)] < \infty$$

from Lemma 4.2.5.

Let us define for any $n \geq N_1$ a stopping time $\tau_n \in \mathbb{N}$, such that

$$\tau_n = \begin{cases} \inf\{\, n - N_1 \leq k \leq n - N_2 \mid T_k \in I \,\} & \text{if } \neq \emptyset; \\ \infty & \text{otherwise.} \end{cases}$$

Notice that, for any t_0,

$$\begin{aligned} P(\tau_n = \infty|T_0 = t_0) &= P\left(\bigcap_{j=1}^{n-N_2} \{T_j \notin I\}|T_0 = t_0\right) \\ &+ P\left(\left\{\bigcup_{j=1}^{n-N_1-1} \{T_j \in I\}\right\} \bigcap \bigcap_{j=n-N_1}^{n-N_2} \{T_j \notin I\}|T_0 = t_0\right) \end{aligned}$$

It is easy to show that the first term tends to zero, since $P(T_n \in I, i.o.) = 1$. Then, we can fix $N_3 \in \mathbb{N}$ such that, for any $n \geq N_3$, it is less then ϵ_3.
Now, take the second term, we have

$$\begin{aligned} &= P\left(\bigcup_{j=1}^{n-N_1} \{T_j \in I\} \bigcap_{i=j+1}^{n-N_2} \{T_i \notin I\}|T_0 = t_0\right) \\ &\leq \sum_{j=1}^{n-N_1} P\left(\{T_j \in I\} \bigcap_{i=j+1}^{n-N_2} \{T_i \notin I\}|T_0 = t_0\right) \\ &\leq \sum_{j=1}^{n-N_1} P\left(\bigcap_{i=j+1}^{n-N_2} \{T_i \notin I\}|\{T_0 = t_0\} \bigcap \{T_j \in I\}\right) \\ &\leq \sup_{t_0 \in I} \sum_{j=1}^{n-N_1} P\left(\tau > N_1 - N_2 + j|T_0 = t_0\right) < \epsilon_2 \end{aligned}$$

Then, we can say that, for any $n \geq \max\{N_1; N_3\}$

$$P(\tau_n = \infty|\tilde{T}_0 = t_0) < \epsilon_3 + \epsilon_2$$

Now, putting together all the results we obtain

$$\begin{aligned}
|\nu_n(t_0, C)| &\leq \sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_{n+1}\in C|T_0=t_0) \;-\; P(T_n\in C|T_0=t_0)\,| \\
&\leq \sup_{C\in\mathcal{B}(\mathbb{R})} \sum_{k=N_2}^{N_1} \Big|\, P(T_{n+1}\in C|\tau_n = n-k \bigcap T_0=t_0) \\
&- P(T_n\in C|\tau_n=n-k\bigcap T_0=t_0)\,\Big| \;\times\; P(\tau_n=n-k|\tilde{T}_0=t_0) \\
&+ P(\tau_n=\infty|\tilde{T}_0=t_0)
\end{aligned}$$

Notice that, since $Z_n\to\eta$ a.s., the transition kernels of the processes T and $\widetilde{T}$ become closer as n increases, i.e. $K_{Z_n}(t_0,C)\to K_\eta(t_0,C)$ a.s. This means that, for any fixed $k\in\mathbb{N}$ and for any t_0

$$\lim_{n\to\infty}\sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_{n+k}\in C|T_n=t_0) \;-\; P(\tilde{T}_k\in C|\tilde{T}_0=t_0)\,| \;=\; 0$$

For this reason and because of the closeness of the interval $I=[-b(1-\eta),0]$, we can fix an integer $N_4\in\mathbb{N}$ such that

$$\sup_{t\in I}\sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_{n+k}\in C|T_n=t) \;-\; P(\tilde{T}_k\in C|\tilde{T}_0=t)\,| \;<\; \epsilon_4/2$$

for any $k\leq N_1$ and for any $n\geq N_4$.
Then, for any $n\geq\max\{N_1;N_3;N_4\}$, we have that

$$\begin{aligned}
|\nu_n(t_0, C)| &\leq \sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_{n+1}\in C|T_0=t_0) \;-\; P(T_n\in C|T_0=t_0)\,| \\
&\leq \sup_{t\in I}\sup_{C\in\mathcal{B}(\mathbb{R})} \sum_{k=N_2}^{N_1} \Big|\, P(\tilde{T}_{n+1}\in C|\tilde{T}_{n-k}=t) \\
&- P(\tilde{T}_n\in C|\tilde{T}_{n-k}=t)\,\Big| \;\times\; P(\tau_n=n-k|\tilde{T}_0=t_0) \\
&+ \sum_{k=N_2}^{N_1} \epsilon_4 \;\times\; P(\tau_n=n-k|T_0=t_0) \\
&+ P(\tau_n=\infty|\tilde{T}_0=t_0) \\
&\leq \sup_{t\in I}\sup_{C\in\mathcal{B}(\mathbb{R})} \sum_{k=N_2}^{N_1} \Big|\, P(\tilde{T}_{k+1}\in C|\tilde{T}_0=t) \\
&- P(\tilde{T}_k\in C|\tilde{T}_0=t)\,\Big| \;\times\; P(\tau_n=n-k|T_0=t_0) \\
&+ \epsilon_4 \;+\; \epsilon_3 \;+\; \epsilon_2 \\
&\leq \sum_{k=N_2}^{N_1} \epsilon_1 \times P(\tau_n=n-k|\tilde{T}_0=t_0) \;+\; \epsilon_4 \;+\; \epsilon_3 \;+\; \epsilon_2 \\
&\leq \epsilon_1 \;+\; \epsilon_4 \;+\; \epsilon_3 \;+\; \epsilon_2 \;=\; \epsilon
\end{aligned}$$

For the arbitrary of ϵ, we have that

$$\lim_{n\to\infty}\sup_{C\in\mathcal{B}(\mathbb{R})} |\, P(T_{n+1}\in C|T_0=t_0) \;-\; P(T_n\in C|T_0=t_0)\,| = 0$$

for any t_0. □

Here, we present a lemma that provides a result, concerning the first time the urn process goes above η, that is used in Lemma 4.2.4. Let us denote with τ this stopping time, i.e.

$$\tau = \begin{cases} \inf\{ n \geq 1 \mid Z_n > \eta \} & \text{if } \neq \emptyset; \\ \infty & \text{otherwise.} \end{cases}$$

then we state the following

Lemma 4.2.5. *For any $z_0 \in (0,1)$ and $d_0 \in (0,\infty)$, we have that*

$$\mathbb{E}[\ \tau \mid (Z_0, D_0) = (z_0, d_0)\ ] \ < \ \infty$$

Proof. At first, notice that, for any $0 < x < \eta < y < 1$ and $d_0 > 0$, $\mathbb{E}[\tau|(Z_0, D_0) = (y, d_0)] \leq \mathbb{E}[\tau|(Z_0, D_0) = (x, d_0)]$. Then, consider $0 < z_0 < \eta$ and $d_0 > 0$, we have that

$$\begin{aligned} \mathbb{E}[\tau|(Z_0, D_0) = (z_0, d_0)] &= \sum_{n=1}^{\infty} P(\tau > n|(Z_0, D_0) = (z_0, d_0)) \\ &= \sum_{n=1}^{\infty} P\left(\sup_{j \leq n} Z_j < \eta|(Z_0, D_0) = (z_0, d_0)\right) \\ &< \infty \end{aligned}$$

This is a well known result from the branching process theory ([6]). □

4.3 Testing hypothesis

In this section we focus on the inferential aspects concerning the MRRU design. Let us introduce the classical hypothesis test aiming at comparing the means of two distributions $\mu_R,\ \mu_W$

$$H_0:\ m_R - m_W = 0 \qquad vs \qquad H_1:\ m_R - m_W > 0. \tag{4.20}$$

We approach to the statistical problem (4.20) considering first a no-adaptive design, and then the MRRU model. Let $(M_n)_{n\in\mathbb{N}}$ and $(N_n)_{n\in\mathbb{N}}$ be i.i.d. sequences of random variables with distribution μ_R and μ_W, respectively. For a fixed design with sample sizes n_R and n_W, the usual test statistics is

$$\zeta_0 \ = \ \frac{\overline{M}_{n_R} - \overline{N}_{n_W}}{\sqrt{\frac{s_R^2}{n_R} + \frac{s_W^2}{n_W}}} \tag{4.21}$$

where $\overline{M}_{n_R}$ and $\overline{N}_{n_W}$ are the sample means and s_R^2 and s_W^2 are consistent estimators of the variances. When the no-adaptive design allows both the sample sizes n_R and n_W goes to infinity, by the central limit theorem we have that, under the null hypothesis, ζ_0 converges in distribution to a standard normal variable. Then, fixing a significance level $\alpha \in (0,1)$, we define

$$R_\alpha \ = \ \{\zeta_0 > z_\alpha\} \tag{4.22}$$

as the critical region asymptotically of level α, with z_α as the α-percentage point of the standard Gaussian distribution. Now, let us assume that the rate of divergence of the sample sizes is such that $\frac{n_R}{n_R+n_W} \to \eta$, for some $\eta \in (0,1)$. Then, the power of the test defined in (4.22) can be approximated, for large n_R and n_W, as

$$P\left(Z + \sqrt{n}\frac{m_R - m_W}{\sqrt{\frac{\sigma_R^2}{\eta} + \frac{\sigma_W^2}{1-\eta}}} \ > \ z_\alpha \right), \tag{4.23}$$

where Z is a Gaussian standard random variable.

Now, let us consider an adaptive design described in term of an urn model. Let us denote $N_R(n)$ and $N_W(n)$ as the sample sizes after the firsts n draws, $\overline{M}(n)$ and $\overline{N}(n)$ the corresponding sample means and $s_R^2(n)$ and $s_W^2(n)$ the adaptive consistent estimators. Plugging in (4.21) the corresponding adaptive quantities, we obtain the statistics

$$\zeta_0(n) \ = \ \frac{\overline{M}(n) - \overline{N}(n)}{\sqrt{\frac{s_R^2(n)}{N_R(n)} + \frac{s_W^2(n)}{N_W(n)}}} \tag{4.24}$$

From [44] and Slutsky's Theorem, it can be deduced from the no-adaptive case that for the MRRU model, if $m_R = m_W$, the statistics $\zeta_0(n)$ converges to a standard normal variable. Hence, the critical region (4.22) still defines a test asymptotically of level α. Moreover, calling η the limit of the urn proportion Z_n under the alternative hypothesis, the power of the test defined in (4.22) can be approximated, for large n, as (4.23).

Remark 4.3.1. *The behavior of the statistics ζ_0 defined in* (4.24) *in the case of RRU model was studied in [24]. In that paper, the asymptotic normality of $\zeta_0(n)$ under the null hypothesis was proved; then* (4.22) *defines a test of asymptotic level α also in the RRU case. However, under the alternative hypothesis $\zeta_0(n)$ converges to a mixture of Gaussian distributions, where the mixing variable φ^2 is a strictly positive random variable such that*

$$\frac{N_W(n)}{n^{m_W/m_R}} \ \overset{a.s.}{\to} \ \varphi^2 \tag{4.25}$$

Therefore, it follows that in the RRU case the power of the test defined in (4.22) *can be approximated, for large n, as*

$$P\left(Z + n^{\frac{m_W}{2m_R}}\varphi\frac{m_R - m_W}{\sigma_W} \ > \ z_\alpha \right), \tag{4.26}$$

where Z is a Gaussian standard random variable independent of φ.

Remark 4.3.2. *Let us rewrite the power of the test defined in* (4.22) *as follows*

$$P\left(Z + \sqrt{n}\frac{m_R - m_W}{\sigma_W}\frac{1}{\sqrt{\gamma_n}} \ > \ z_\alpha \right) \tag{4.27}$$

where we have defined a new quantity

$$\gamma_n := \left(\frac{\sigma_R}{\sigma_W}\right)^2 \frac{1}{1 - \frac{N_W(n)}{n}} + \frac{1}{\frac{N_W(n)}{n}}.$$

Let us notice that, γ_n *represents the part in* (4.27) *that depends on the particular adaptive design is applied in the trial. When the RRU design is used, the relation* (4.25) *allows us to approximate the quantity* γ_n *as*

$$\left(\frac{\sigma_R}{\sigma_W}\right)^2 \frac{1}{1-\frac{\varphi^2+o(1)}{n^{1-\frac{m_W}{m_R}}}} + \frac{n^{1-\frac{m_W}{m_R}}}{\varphi^2+o(1)}$$

that diverges as n *goes to infinity. In the same way, when the MRRU design is applied, we can approximate* γ_n *as*

$$\left(\frac{\sigma_R}{\sigma_W}\right)^2 \frac{1}{\eta+o(1)} + \frac{1}{1-\eta+o(1)}$$

that converges to a constant. Therefore, when both MRRU and RRU designs are applied with the same sample size n*, and* n *is large enough, the power of the test* (4.22) *using MRRU design is greater then the one obtained using RRU design.*

A different test statistics based on the urn proportion of a RRU model has been investigated in [25]. Let us denote as $c_\alpha^{(0,1)}$ the α-percentage point of the distribution of the limiting proportion Z_∞ under the null hypothesis in a RRU model. Then, the critical region

$$\{Z_n > c_\alpha^{(0,1)}\} \tag{4.28}$$

defines a test asymptotically of level α. As explained in [25], the power of this test can be approximated, for large n, as

$$P\left(\ \varphi^2 \ < \ (1-c_\alpha^{(0,1)})\frac{m_R}{m_W}n^{1-\frac{m_W}{m_R}}\ \right) \tag{4.29}$$

where φ^2 is the random quantity defined in (4.25).
Now, we consider the statistics Z_n as the urn proportion of a MRRU model, with parameters δ and η. Let us denote as $c_\alpha^{(\delta,\eta)}$ the α-percentage point of the distribution of the limiting proportion Z_∞ when the mean responses are equal. Then, the critical region

$$\{Z_n > c_\alpha^{(\delta,\eta)}\} \tag{4.30}$$

defines a test asymptotically of level α. Under the alternative hypothesis, the asymptotic behavior of the proportion Z_n is shown in Theorem 4.2.2. The power of the test $\{Z_n > c_\alpha^{(\delta,\eta)}\}$ can be approximated, for large n, as

$$P\left(\ \psi \ < \ (\eta - c_\alpha^{(\delta,\eta)})m_W n\ \right) \tag{4.31}$$

where ψ is the random quantity defined in Theorem 4.2.2.

4.4 Simulation study

This section is dedicated to presenting the simulation studies aim at exploring the asymptotic behavior of the urn proportion Z_n. In this section, all the urns are simulated with the following choice of parameters: $\delta = 0.2$ and $\eta = 0.8$. Further studies based on changing the values of δ or η can be of great interest, but this is not the main purpose of the paper.

Initially, we focus on supporting the convergence result shown in Theorem 4.2.2. The reinforcement distributions μ_R and μ_W are chosen to be Gaussian, with means set to $m_R = 10$ and $m_W = 5$ respectively. The variances are assumed to be equal and fixed at $\sigma_R^2 = \sigma_W^2 = 1$. Theorem 4.2.2 shows that, when $m_R > m_W$, the quantity $n(\eta - Z_n)m_W$ converges in distribution to a random variable ψ, whose probability law is π. Through some simulations, we compute the empirical distribution of $n(\eta - Z_n)m_W$ for $n = 10^2$ and $n = 10^4$. The corresponding histograms are presented in Figure 4.1.

In proposition 4.2.1 it was proved that the probability measure π is the unique invariant distribution of the process $(\tilde{T}_n)_{n\in\mathbb{N}}$. This means π is the unique solution of the functional equation

$$\int_{\mathbb{R}} K_\eta(x, dy)\pi(dx) = \pi(dy) \tag{4.32}$$

where K_η is the transition kernel of the process $\tilde{T}_n$ defined in (4.5). Taking the discrete version of (4.32) we compute the density of the measure π, which is superimposed on both the histograms in Figure 4.1. The quite perfect agreement between the empirical distribution of $n(\eta - Z_n)m_W$ and the discrete estimation of π gave to the authors the impetus to prove the convergence result described in Theorem 4.2.2.

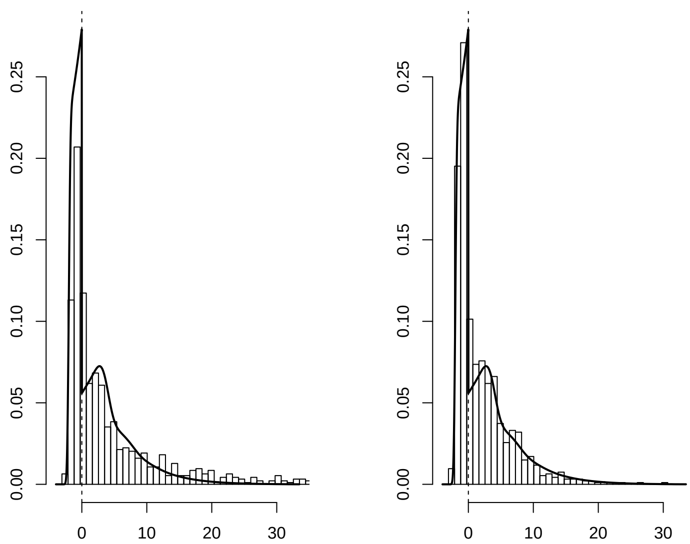

Figure 4.1: *Histograms of ψ obtained simulating the empirical distribution of $n(\eta - Z_n)m_W$ for large n, with superimposed the density of ψ obtained by numerically solving the discrete version of* (4.32). *Left panel: $n = 10^2$. Right panel: $n = 10^4$.*

The simulation study also encouraged the authors to prove some further theoretical results. The first one we present is related to an easy expression for a quantile of the probability law of the limiting variable ψ. In general, the asymptotic distribution of the quantity $n(\eta - Z_n)$ depends on the value η and on the reinforcements distributions μ_R and μ_W. Nevertheless, the following proposition state that 0 is always the $\frac{m_W}{m_R}$-percentage point of the distribution π, regardless η or the types of distributions involved.

Proposition 4.4.1.

$$P(\psi > 0) \;=\; \frac{m_W}{m_R} \tag{4.33}$$

Proof. Since $P(Z_n < \eta) = P(T_n > 0)$ we know that $P(Z_n < \eta)$ is a convergent sequence. In particular

$$\lim_{n\to\infty} P(Z_n < \eta) \;=\; P(\psi > 0) \;=\; \pi([0,\infty))$$

Therefore, by using the dominated convergence theorem, the Toeplitz Lemma and Proposition 2.4.4, we obtain

$$P(\psi > 0) \;=\; \lim_{n\to\infty} P(Z_n < \eta) \;=\; \lim_{n\to\infty} \frac{\sum_{i=1}^{n} P(Z_i < \eta)}{n} \;=$$
$$\lim_{n\to\infty} \frac{\sum_{i=1}^{n} \mathbb{E}[1_{\{Z_i<\eta\}}]}{n} \;=\; \mathbb{E}\left[\lim_{n\to\infty} \frac{\sum_{i=1}^{n} 1_{\{Z_i<\eta\}}}{n}\right] \;=\; \mathbb{E}\left[\frac{m_W}{m_R}\right] \;=\; \frac{m_W}{m_R}$$

□

Another interesting result, that came out from the simulation analysis, concerns the correspondence between the asymptotic distribution of Z_n and a linear transformation of the reinforcement laws. This property is explained in the following proposition

Proposition 4.4.2. *Let Z_n and $\widehat{Z}_n$ be the urn proportions of two MRRU models with reinforcements distributions (μ_R, μ_W) and $(\widehat{\mu}_R, \widehat{\mu}_W)$ respectively. Assume that there exists $c > 0$ such that, for any $a, b \in \mathbb{R}$ with $a < b$*

$$\begin{cases} \widehat{\mu}_R(\,(a,b)\,) & = \; \mu_R(\,(ca,cb)\,) \\ \widehat{\mu}_W(\,(a,b)\,) & = \; \mu_W(\,(ca,cb)\,) \end{cases} \tag{4.34}$$

i.e. $\widehat{M}_n \stackrel{\mathcal{D}}{=} c \cdot M_n$ *and* $\widehat{N}_n \stackrel{\mathcal{D}}{=} c \cdot N_n$ *for any* $n \in \mathbb{N}$.
Then, for any $a, b \in \mathbb{R}$ with $a < b$, we have

$$\widehat{\pi}(\,(a,b)\,) \;=\; \pi(\,(c\cdot a, c\cdot b)\,) \tag{4.35}$$

i.e. $\widehat{\psi} \stackrel{\mathcal{D}}{=} c \cdot \psi$.

Proof. Let us call the initial compositions of the two urn processes as (r_0, w_0) and $(\widehat{r}_0, \widehat{w}_0)$. The proof will be based on the particular choice $\widehat{r}_0 = c \cdot r_0$ and $\widehat{w}_0 = c \cdot w_0$. However, since from Proposition 4.2.1 the invariant distribution π is independent of the initial composition, the generality of the result still holds.

For any $n \geq 1$, by conditioning to the event $\{(\widehat{T}_n, \widehat{Z}_n) = (c \cdot T_n, Z_n)\}$, we have that

$$\begin{aligned}
\widehat{T}_{n+1} &= \widehat{T}_n \;+\; \eta(1-\widehat{X}_{n+1})\widehat{N}_{n+1} \;-\; (1-\eta)\widehat{X}_{n+1}1_{\{\widehat{T}_n>0\}}\widehat{M}_{n+1} \;= \\
&= c \cdot T_n \;+\; \eta(1-\widehat{X}_{n+1})\widehat{N}_{n+1} \;-\; (1-\eta)\widehat{X}_{n+1}1_{\{T_n>0\}}\widehat{M}_{n+1} \;\overset{\mathcal{D}}{=} \\
&\overset{\mathcal{D}}{=} c \cdot T_n \;+\; \eta(1-X_n)c \cdot N_{n+1} \;-\; (1-\eta)X_{n+1}1_{\{T_n>0\}}c \cdot M_{n+1} \;=\; c \cdot T_{n+1}
\end{aligned} \tag{4.36}$$

$$\begin{aligned}
\widehat{Z}_{n+1} &= \frac{\widehat{R}_{n+1}}{\widehat{R}_{n+1}+\widehat{W}_{n+1}} = \\
&= \frac{\widehat{R}_n + \widehat{X}_{n+1}\widehat{M}_{n+1}}{\widehat{R}_n + \widehat{W}_n + \widehat{X}_{n+1}\widehat{M}_{n+1} + (1-\widehat{X}_{n+1})\widehat{N}_{n+1}} = \\
&= \frac{c \cdot R_n + \widehat{X}_{n+1}\widehat{M}_{n+1}}{c \cdot R_n + c \cdot W_n + \widehat{X}_{n+1}\widehat{M}_{n+1} + (1-\widehat{X}_{n+1})\widehat{N}_{n+1}} \overset{\mathcal{D}}{=} \\
&\overset{\mathcal{D}}{=} \frac{R_n + X_{n+1}c \cdot M_{n+1}}{R_n + W_n + X_{n+1}c \cdot M_{n+1} + (1-X_{n+1})c \cdot N_{n+1}} = Z_{n+1}
\end{aligned} \tag{4.37}$$

For ease of notation, let us denote $\lambda_{(T_n,Z_n)}$ and $\lambda_{(\widehat{T}_n,\widehat{Z}_n)}$ as the bivariate laws of the couple of random variables (T_n, Z_n) and $(\widehat{T}_n, \widehat{Z}_n)$ respectively. Then, let us notice that the equivalence of the initial compositions of the two processes Z_n and $\widehat{Z}_n$ implies that the event $\{(\widehat{T}_0, \widehat{Z}_0) = (c \cdot T_0, Z_0)\}$ has probability one. Hence, for any $n \geq 1$, we have

$$\begin{aligned}
\lambda_{(\widehat{T}_n,\widehat{Z}_n)} &= \int_{\mathbb{R}^{n-1}\times(0,1)^{n-1}} \lambda_{(\widehat{T}_n,\widehat{Z}_n)|(\widehat{T}_{n-1},\widehat{Z}_{n-1})} \cdot \lambda_{(\widehat{T}_{n-1},\widehat{Z}_{n-1})|(\widehat{T}_{n-2},\widehat{Z}_{n-2})} \cdots \lambda_{(\widehat{T}_1,\widehat{Z}_1)|(\widehat{T}_0,\widehat{Z}_0)} = \\
&= \int_{\mathbb{R}^{n-1}\times(0,1)^{n-1}} \lambda_{(cT_n,Z_n)|(cT_{n-1},Z_{n-1})} \cdot \lambda_{(cT_{n-1},Z_{n-1})|(cT_{n-2},Z_{n-2})} \cdots \lambda_{(cT_1,Z_1)|(cT_0,Z_0)} = \\
&= \lambda_{(cT_n,Z_n))}
\end{aligned}$$

The thesis is proved since the equivalence $\lambda_{(\widehat{T}_n,\widehat{Z}_n)} = \lambda_{(c \cdot T_n,Z_n)}$ implies that $\widehat{\pi} = \pi$. □

Assumption (4.34) implies also that $\widehat{m}_R = c \cdot m_R$ and $\widehat{m}_W = c \cdot m_W$. Then, from Theorem 4.2.2 we deduce the equivalence between the asymptotic laws of Z_n and $\widehat{Z}_n$. Propositions 4.4.1 and 4.4.2 suggest that urn processes with the same reinforcement means ratio present also similar asymptotic behavior. For this reason, we prefer to use the ratio $\frac{m_R}{m_W}$ as parameter measuring the means' distance, instead of the usual mean difference $m_R - m_W$.

Here we present some simulations concerning the hypothesis test (4.20). In particular, we focus on comparing the power of the tests defined in (4.28) and (4.30). The empirical power is computed using $n = 10^4$ subjects, in correspondence of different values of the ratio $\frac{m_R}{m_W}$. The empirical power functions are reported in Figure 4.2. As shown in Figure 4.2, the MRRU design constructs a test more powerful then the one based on the RRU design with the sample size, for any choice of the reinforcement means. Although this property makes the MRRU design very attractive, the RRU model takes the advantage that, with the same sample size, it allocates less subject to the inferior treatment. Hence, what is really interesting is studing the power functions of the tests (4.28)

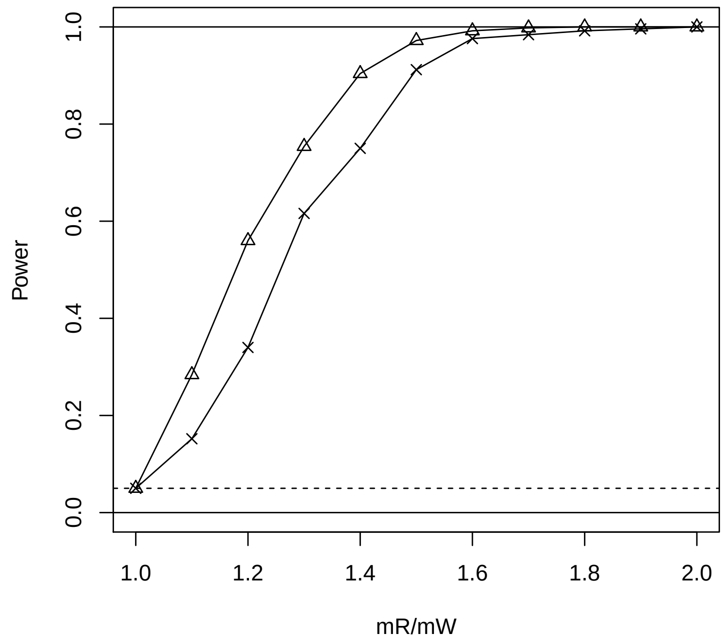

Figure 4.2: *The empirical power functions of test* (4.28) *(line with crosses) and of test* (4.30) *(line with triangles) computed using $n = 10^4$ subjects.*

and (4.30), in correspondence of a different values of N_W, i.e. the number of subjects assigned to the inferior treatment. We compute the empirical power functions for $N_W = 20, 50, 100, 500$ and we report the graphics in Figure 4.3.

From the analysis of the power functions in Figure 4.3, different considerations can be done depending on the size of the ratio $\frac{m_R}{m_W}$. For high values of $\frac{m_R}{m_W}$ the power of the tests (4.28) and (4.30) are very similar. When the ratio $\frac{m_R}{m_W}$ is small the power of the test based on MRRU design seems to be considerable greater, for any value of N_W.

This chapter has been focused on the rate of convergence of the process $(Z_n)_{n\in\mathbb{N}}$ in the MRRU model. In Theorem 4.2.2 we proved that the rate of convergence of the process $(Z_n)_{n\in\mathbb{N}}$ is $1/n$. We recall that in [24] it was proved that the rate of convergence of the RRU process $(Z_n)_{n\in\mathbb{N}}$ is equal to $1/n^{\gamma}$, with $\gamma = 1 - \frac{m_W}{m_R} < 1$ (case $m_R > m_W$) and the quantity $n^{\gamma}(1 - Z_n)$ converges almost surely to a positive random variable. In Theorem 4.2.2 we shows that the sequence $n(\eta - Z_n)$ (case $m_R > m_W$) also converges in distribution to a real random variable, whose probability law is related to the unique invariant distribution π of the process $(\tilde{T}_n)_{n\in\mathbb{N}}$ defined in (4.4).

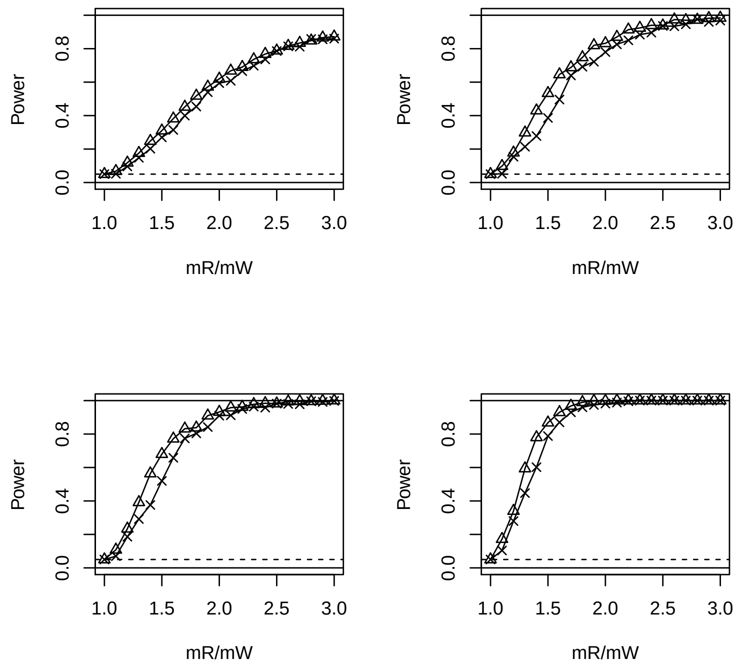

Figure 4.3: *The empirical power functions of test* (4.28) *(line with crosses) and of test* (4.30) *(line with triangles) computed using* $n = 10^4$ *subjects. Top left panel:* $N_W = 20$*. Top right panel:* $N_W = 50$*. Bottom left panel:* $N_W = 100$*. Bottom right panel:* $N_W = 500$*.*

CHAPTER 5

Randomly reinforced urn design with random time-dependent parameters

In this chapter, we modify the urn design described in Chapter 2 to construct a randomization procedure in the framework of parametric models. So far, we used to fix in advance two allocation proportions $\delta, \eta \in (0,1)$, and then we adopted the urn model to target either δ or η, depending on the greatest reinforcement mean: $\rho = \delta \mathbf{1}_{\{m_R < m_W\}} + \eta \mathbf{1}_{\{m_R > m_W\}}$. Even if the MRRU design has been constructed to improve the statistical performance of the RRU design, the ethical goal to allocate to the inferior treatment less patients remained the main goal of the design. Here, we change the urn model in order to achieve other goals more related to the statistical performance of the design, without forget about the ethical context. In particular, we want to construct a model that is able to target an asymptotic allocation proportion $\rho \in (0,1)$, defined as a generic function of some unknown parameters modeling the reinforcements distributions. This is in the spirit of classical response adaptive papers, for instance [49]. This new model has been realized by making the parameters δ and η depend on adaptive estimators of those parameters.

5.1 The model

Let us consider two probability distributions μ_R and μ_W with support contained in $[a,b]$, where $0 < a \leq b < +\infty$. We will interpret μ_R and μ_W as the laws of the responses to treatment R and W, respectively. Then, let us consider a situation with μ_R and μ_W depend on d unknown real parameters. We will call $\underline{\theta} \in \Theta$ (with $\Theta \subset \mathbb{R}^d$) the vector of these unknown parameters. Then, let us define two continuous functions

$f_\delta : \Theta \to (0,1)$ and $f_\eta : \Theta \to (0,1)$ such that

$$\delta^* \ \leq \ f_\delta(\underline{\theta}) \ \leq \ f_\eta(\underline{\theta}) \ \leq \ \eta^* \tag{5.1}$$

for any $\underline{\theta} \in \Theta$, and for some constants δ^* and η^* such that $0 < \delta^* < \eta^* < 1$.
Let us denote as $\widehat{\underline{\theta}}_n \in \Theta$ an estimator of $\underline{\theta}$ after that n responses are collected. To ease of notation, in what follows we will call $\delta = f_\delta(\underline{\theta})$ and $\eta = f_\eta(\underline{\theta})$, $\delta_n = f_\delta(\widehat{\underline{\theta}}_n)$ and $\eta_n = f_\eta(\widehat{\underline{\theta}}_n)$. For those $k \geq 0$ such that the estimator $\widehat{\underline{\theta}}_k$ is not defined, we set δ_k and η_k equal to two arbitrary values such that $0 < \delta_k < \eta_k < 1$. Then, the sequences $(\delta_n)_n$ and $(\eta_n)_n$ are well defined for any $n \geq 0$.

The allocation of the subjects to the treatments is realized through the adoption of a response adaptive design described in term of urn model. The structure of the design is similar to the MRRU design presented in Chapter 2. Visualize an urn initially containing r_0 balls of color R and w_0 balls of color W. Set

$$R_0 = r_0,\ W_0 = w_0,\ D_0 = R_0 + W_0,\ Z_0 = \frac{R_0}{D_0}.$$

The drawing process from this urn is modeled by a sequence $(U_n)_n$ of independent uniform random variables on $(0,1)$. At time $n = 1$, a ball is sampled from the urn; its color is $X_1 = \mathbf{1}_{\{U_1 < Z_0\}}$, a random variable with Bernoulli(Z_0) distribution. Let M_1 and N_1 be two independent random variables with distribution μ_R and μ_W, respectively; assume that X_1, M_1 and N_1 are independent. Next, if the sampled ball is R i.e. $X_1 = 1$, it is returned in the urn together with M_1 balls of the same color if $Z_0 < \eta_0$, where $\eta \in (0,1)$ is a suitable parameter, otherwise the urn composition does not change; if the sampled ball is W i.e. $X_1 = 0$, it is returned in the urn together with N_1 balls of the same color if $Z_0 > \delta_0$, where $\delta < \eta \in (0,1)$ is a suitable parameter, otherwise the urn composition does not change. So we can update the urn composition in the following way

$$\begin{aligned} R_1 &= R_0 + X_1 M_1 \mathbf{1}_{\{Z_0 < \eta_0\}}, \\ W_1 &= W_0 + (1 - X_1) N_1 \mathbf{1}_{\{Z_0 > \delta_0\}}, \\ D_1 &= R_1 + W_1,\ Z_1 = \frac{R_1}{D_1}. \end{aligned} \tag{5.2}$$

Now iterate this sampling scheme forever. Thus, at time $n+1$, given the sigma-field $\mathcal{F}_n$ generated by $X_1, ..., X_n, M_1, ..., M_n$ and $N_1, ..., N_n$, let $X_{n+1} = \mathbf{1}_{\{U_{n+1} < Z_n\}}$ be a Bernoulli(Z_n) random variable. Then, assume that M_{n+1} and N_{n+1} are two independent random variables with distribution μ_R and μ_W, respectively. Set

$$\begin{aligned} R_{n+1} &= R_n + X_{n+1} M_{n+1} \mathbf{1}_{\{Z_n < \eta_n\}}, \\ W_{n+1} &= W_n + (1 - X_{n+1}) N_{n+1} \mathbf{1}_{\{Z_n > \delta_n\}}, \\ D_{n+1} &= R_{n+1} + W_{n+1}, \\ Z_{n+1} &= \frac{R_{n+1}}{D_{n+1}}. \end{aligned} \tag{5.3}$$

Now, let us show an asymptotic result concerning the sequence of the total number of balls in the urn $(D_n)_n$. This result will be used to derive the asymptotic behavior of the urn proportion process.

Proposition 5.1.1. *Let us consider the urn process described in Section 5.1. Then,*

(a) *the sequence $(D_n)_n$ diverge to infinity almost surely*

(b) *there exists a constant C independent of n such that*

$$\mathbb{E}\left[\left(\frac{n}{D_n}\right)^2\right] \leq C \tag{5.4}$$

Proof. To prove (a), notice that for any $n \in \mathbb{N}$

$$\begin{aligned} D_n &= D_0 + \sum_{i=1}^{n} \left[M_i X_i 1_{\{Z_{i-1}<\eta_{i-1}\}} + N_i(1-X_i)1_{\{Z_{i-1}>\delta_{i-1}\}} \right] \\ &\geq D_0 + a \cdot \sum_{i=1}^{n} \left[X_i 1_{\{Z_{i-1}<\eta_{i-1}\}} + (1-X_i)1_{\{Z_{i-1}>\delta_{i-1}\}} \right] \end{aligned}$$

Let us define

$$p^* := \frac{D_0}{D_0+b} \cdot \min\{\delta^*; 1-\eta^*\} \tag{5.5}$$

and note that $P(Z_n \in (p^*, 1-p^*)) = 1$. This is due to the following relation

$$P\left(\inf_{n\in\mathbb{N}}\{\delta_n\} \geq \delta^*\right) = P\left(\sup_{n\in\mathbb{N}}\{\eta_n\} \leq \eta^*\right) = 1.$$

that is implied by Assumption 5.1. and so, as a consequence of assumption (5.1), we have that $P(Z_n \in (p^*, 1-p^*)) = 1$. Then, notice that

$$X_i \mathbf{1}_{\{Z_{i-1}<\eta_{i-1}\}} + (1-X_i)\mathbf{1}_{\{Z_{i-1}>\delta_{i-1}\}} \sim Be(p_i)$$

with $p_i \geq p^* > 0$ for any $i \geq 1$. Now, let us define $Y = (Y_i)_i$ as a sequence of i.i.d. Bernoulli random variable with parameter p_0. Then, we conclude that

$$P\left(\lim_{n\to\infty} D_n = \infty\right) \geq P\left(\lim_{n\to\infty} \sum_{i=1}^{n} Y_i = \infty\right) = 1.$$

Now, let us consider the thesis (b). Using the same arguments used to prove (a), we have that

$$\mathbb{E}\left[\left(\frac{1}{D_n/n}\right)^2\right] \leq \frac{1}{a^2}\mathbb{E}\left[\left(\frac{n}{D_0+\sum_{i=1}^n Y_i}\right)^2\right] = \frac{1}{a^2}\mathbb{E}\left[\left(\frac{n}{D_0+W_n}\right)^2\right]$$

where W_n is a Binomial random variable with parameters n and p^*. So now we have to prove that

$$\limsup_n \mathbb{E}\left[\left(\frac{n}{D_0+W_n}\right)^2\right] < \infty$$

We want to use Theorem 2.1 of [23], with $n_0 = 1$, $p = 2$, $Z_{i,n} = Y_i + D_0/n$ for $i \leq n$. All the assumptions of the theorem are satisfied in our case.

In fact, at first we have $[\bar{Z}_{n_0}^{-2}] < \infty$ because $[(D_0 + Y_1)^{-2}] \leq D_0^{-2} < \infty$.
Secondly, note that $Z_{i,n}$ are identically distributed for all $i \leq n$, since Y_i are i.i.d. Bernoulli of parameter p^*.
Finally, $\bar{Z}_n$ converges in distribution, since $\bar{Z}_n = W_n/n + D_0 \overset{a.s.}{\to} p^* + D_0$.
Then, we can apply the theorem, obtaining that $[\overline{Z}_n^{-2}]$ is uniformly integrable. As a consequence,

$$\limsup_n \ \mathbb{E}\left[\left(\frac{n}{D_0 + W_n}\right)^2\right] \ = \ \limsup_n \ \mathbb{E}\left[\bar{Z}_n^{-2}\right] \ < \ \infty$$

□

Notice that Proposition 5.1.1 is based on Assumption 5.1, but it does not require any assumption on the distribution of the sequence $(\eta_n)_n$ and $(\delta_n)_n$.

5.2 Almost sure Convergence of the urn process

In this section we get the almost sure convergence of the urn proportion Z, concerning the urn model described in Section 5.1. In particular, in Theorem 5.2.1 we show that if the sequences $(\eta_n)_n$ and $(\delta_n)_n$ converge almost surely to some constants η and δ, respectively, then the urn process $(Z_n)_n$ converges almost surely to one of those constants, depending on the order between the reinforcement means. Notice that, in our context, η and δ are not generic constants, but they play a specific role in the adaptive design. In fact, η and δ indicate the functions $f_\eta(\cdot)$ and $f_\delta(\cdot)$ evaluated in the unknown parameters modeling the reinforcement distributions. Moreover, $f_\eta(\underline{\theta})$ and $f_\delta(\underline{\theta})$ represent the desired allocations if the superior treatment is R or W, respectively. Then, Theorem 5.2.1 states that the probability of assignment of the subjects to the treatments, that is modeled by the urn proportion Z_n, converges almost surely to the desired allocation whether the superior treatment is R or W.

Theorem 5.2.1 is based on the assumption (5.6), concerning the almost sure convergence of the adaptive sequences $f_\eta(\widehat{\underline{\theta}}_n)$ and $f_\delta(\widehat{\underline{\theta}}_n)$ to the target $f_\eta(\underline{\theta})$ and $f_\delta(\underline{\theta})$. This condition can be satisfied using various estimators of $\underline{\theta}$ and with different choices of the functions $f_\eta(\cdot)$ and $f_\delta(\cdot)$.
To see that, notice that the assumption (5.1) implies that

$$P\left(\inf_{n\in\mathbb{N}}\{\delta_n\} \ \geq \ \delta^*\right) \ = \ P\left(\sup_{n\in\mathbb{N}}\{\eta_n\} \ \leq \ \eta^*\right) \ = \ 1.$$

Then, taking p^* as defined in (5.5), we have that $P(Z_n \in (p^*, 1-p^*)) = 1$.
As a consequence, both the sequences $N_R(n)$ and $N_W(n)$ diverges as n goes to infinity. In particular, we can show that

$$p^* \ \leq \ \liminf_n \frac{N_R(n)}{n} \ \leq \ \limsup_n \frac{N_R(n)}{n} \ \leq \ 1 - p^* \ \ a.s.$$

$$p^* \ \leq \ \liminf_n \frac{N_W(n)}{n} \ \leq \ \limsup_n \frac{N_W(n)}{n} \ \leq \ 1 - p^* \ \ a.s.$$

Then, if $\widehat{\underline{\theta}}_n$ is the maximum likelihood estimator of $\underline{\theta}$, and the functions $f_\eta(\cdot)$ and $f_\delta(\cdot)$ are continuous, we have that $\eta_n \overset{a.s.}{\to} \eta$ and $\delta_n \overset{a.s.}{\to} \delta$ and so the condition (5.6) is verified.

Theorem 5.2.1. *Assume*

$$\begin{cases} \eta_n \overset{a.s.}{\to} \eta \quad \textit{if} \;\; m_R > m_W, \\ \\ \delta_n \overset{a.s.}{\to} \delta \quad \textit{if} \;\; m_R < m_W. \end{cases} \tag{5.6}$$

Then

$$Z_n \overset{a.s.}{\to} \eta \mathbf{1}_{\{m_R > m_W\}} + \delta \mathbf{1}_{\{m_R < m_W\}} \tag{5.7}$$

Proof. Let us assume that $m_R < m_W$ and $\delta_n \overset{a.s.}{\to} \delta$. The proof of the opposite case is completely analogous. Let Assumption (5.1) holds. Then, the goal is to prove that $Z_n \overset{a.s.}{\to} \delta$.
The thesis is get by proving the following

(a) $P\,(\,\liminf_{n\to\infty} Z_n \geq \delta\,) \;=\; 1$

(b) $P\,(\,\liminf_{n\to\infty} Z_n \leq \delta\,) \;=\; 1$

(c) $P\,(\,\exists \lim_{n\to\infty} Z_n) \;=\; 1$

In this proof we will use the following notation: for any $\rho \in (0,1)$, we define the times

$$\tau_\rho = \begin{cases} \sup\{\, k \geq 0 \;:\; \delta_k \leq \rho \,\} & \text{if } \{\, k \geq 0 \;:\; \delta_k \leq \rho \,\} \neq \emptyset; \\ 0 & \text{otherwise}. \end{cases}$$

$$t_\rho = \begin{cases} \sup\{\, k \geq 0 \;:\; \delta_k > \rho \,\} & \text{if } \{\, k \geq 0 \;:\; \delta_k > \rho \,\} \neq \emptyset; \\ 0 & \text{otherwise}. \end{cases}$$

representing the last time the process $(\delta_n)_n$ is below or above ρ, respectively.

Part (a):
Let us assume there exists $\delta' < \delta$ such that

$$P\left(\liminf_{n\to\infty} Z_n \;<\; \delta'\right) \;\geq\; \epsilon \;>\; 0.$$

Then, $\exists n_\epsilon \in \mathbb{N}$ such that

$$P\left(\tau_{\frac{\delta'+\delta}{2}} \;>\; n_\epsilon\right) \;\leq\; \frac{\epsilon}{2} \tag{5.8}$$

Notice that the existence of n_ϵ is guaranteed by assumption (5.6), since it implies that $P(\tau_{\frac{\delta'+\delta}{2}} < \infty) = 1$. Then, we obtain

$$\begin{aligned} \epsilon \;\leq\; & P(\liminf_{n\to\infty} Z_n < \delta') \\ = \;\; & P\left(\{\liminf_{n\to\infty} Z_n < \delta'\} \bigcap \{\tau_{\frac{\delta'+\delta}{2}} > n_\epsilon\}\right) \;+\; P\left(\{\liminf_{n\to\infty} Z_n < \delta'\} \bigcap \{\tau_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\}\right) \end{aligned}$$

Let us call P_1 and P_2 the two terms of this sum.
At first, consider the term P_1 and by using (5.8) we get that

$$P_1 \;\leq\; P\left(\tau_{\frac{\delta'+\delta}{2}} > n_\epsilon\right) \;\leq\; \frac{\epsilon}{2}$$

Then, consider the term P_2. Let us decompose P_2 in two terms

$$\begin{aligned} P_2 \;=\; & P\left(\{\liminf_{n\to\infty} Z_n < \delta'\} \bigcap \{\tau_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\} \bigcap \left\{\{Z_n > \frac{\delta'+\delta}{2}\} \text{ for infinite indices } n\right\}\right) \\ + \; & P\left(\{\liminf_{n\to\infty} Z_n < \delta'\} \bigcap \{\tau_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\} \bigcap \left\{\{Z_n > \frac{\delta'+\delta}{2}\} \text{ for finite indices n}\right\}\right) \end{aligned}$$

Let us call D_1 and D_2 the events within the two probabilities in the above expression. Consider the second term $P(D_2)$. On the set $\left\{\{Z_n > \frac{\delta'+\delta}{2}\} \text{ for finite indices } n\right\} \supset D_2$ the process Z_n is asymptotically less than $\frac{\delta'+\delta}{2}$. Moreover, on the set $\{\tau_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\} \supset D_2$ we have $\delta_n \geq \frac{\delta'+\delta}{2}$ for any $n \geq n_\epsilon$. Then, $\mathbf{1}_{\{Z_n > \delta_{n-1}\}} \overset{a.s.}{\to} 0$ and asymptotically no white balls are replaced in the urn. As a consequence, the asymptotic behavior of the process $(Z_n)_n$ is the same of a RRU model with $m_R > m_W = 0$, that converges to one as proved in [45]. This is incompatible with the set $\{\liminf_{n\to\infty} Z_n < \delta'\} \supset D_2$. Hence $P(D_2) = 0$.
Consider now the first term $P(D_1)$. Since from Proposition 5.1.1 we have that the sequence $(D_n)_n$ diverges almost surely, then on the set $\left\{\{Z_n > \frac{\delta'+\delta}{2}\} \text{ for infinite indices } n\right\} \supset D_1$ there are infinite indices k such that

$$\begin{cases} Z_k > \frac{\delta'+\delta}{2} \\ \\ D_k > b\frac{\delta+\delta'}{\delta-\delta'}. \end{cases}.$$

For these indices k we have that $P(Z_{k+1} \leq \delta') = 0$. Moreover, on the set $\{\tau_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\} \supset D_1$ we have that $\delta_n \geq \frac{\delta'+\delta}{2}$ for any $n \geq n_\epsilon$. Then, when $Z_n < \frac{\delta'+\delta}{2}$ we have that $\mathbf{1}_{\{Z_n > \delta_{n-1}\}} = 0$ and no white balls are added in the urn. Then, $P(Z_n \leq \delta') = 0$ for any $n \geq n_\epsilon$. This is incompatible with the set $\{\liminf_{n\to\infty} Z_n < \delta'\} \supset D_1$. Hence $P(D_1) = 0$.
Putting all together we have

$$\epsilon \;\leq\; P_1 + P_2 \;\leq\; \epsilon/2 + P(D_1) + P(D_2) \;=\; \epsilon/2$$

that is contradiction.
Then, we can conclude that the event $\{\liminf_{n\to\infty} Z_n \geq \delta\}$ occurs with probability one.

Part (b):
Let us assume there exists $\delta' > \delta$ such that

$$P\left(\liminf_{n\to\infty} Z_n \;>\; \delta'\right) \;\geq\; \epsilon \;>\; 0.$$

Then, $\exists n_\epsilon \in \mathbb{N}$ such that

$$P\left(t_{\frac{\delta'+\delta}{2}} \;>\; n_\epsilon\right) \;\leq\; \frac{\epsilon}{2} \tag{5.9}$$

Notice that the existence of n_ϵ is guaranteed by assumption (5.6), since it implies that $P(t_{\frac{\delta'+\delta}{2}} < \infty) = 1$. Then, we obtain

$$\begin{aligned}
\epsilon \ &\leq \ P(\liminf_{n\to\infty} Z_n > \delta') \\
&= \ P\left(\{\liminf_{n\to\infty} Z_n > \delta'\} \bigcap \{t_{\frac{\delta'+\delta}{2}} > n_\epsilon\}\right) \ + \ P\left(\{\liminf_{n\to\infty} Z_n > \delta'\} \bigcap \{t_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\}\right) \\
&= \ P(D_3) \ + \ P(D_4)
\end{aligned}$$

Let us call D_1 and D_2 the events within the two probabilities in the above expression. At first, consider the term $P(D_3)$ and by using (5.9) we get that

$$P(D_3) \ \leq \ P\left(t_{\frac{\delta'+\delta}{2}} > n_\epsilon\right) \ \leq \ \frac{\epsilon}{2}$$

Then, consider the term $P(D_4)$. On the set $\{\liminf_{n\to\infty} Z_n \geq \delta'\} \supset D_4$, the process Z_n is asymptotically above than δ'. Moreover, on the set $\{t_{\frac{\delta'+\delta}{2}} \leq n_\epsilon\} \supset D_4$, we have $\delta_n \leq \frac{\delta'+\delta}{2}$ for any $n \geq n_\epsilon$. Then, $\mathbf{1}_{\{Z_n > \delta_{n-1}\}} \stackrel{a.s.}{\to} 1$ and so the asymptotic behavior of the process $(Z_n)_n$ is the same of a RRU model with $m_R < m_W$, that converges to zero as proved in [45]. This is incompatible with the set $\{\liminf_{n\to\infty} Z_n > \delta'\} \supset D_4$. Hence $P(D_4) = 0$.

Summarizing, we have that

$$\epsilon \ \leq \ P(D_3) + P(D_4) \ \leq \ \epsilon/2$$

Then, we can conclude that the event $\{\liminf_{n\to\infty} Z_n \geq \delta\}$ occurs with probability one.

Part (c):

Putting together parts (a) and (b), we have shown that $P(\liminf_{n\to\infty} Z_n = \delta) = 1$. Therefore, if the process $(Z_n)_n$ converges almost surely, then its limit has to be equal to δ.

Let δ', γ, d and u ($\delta < \delta' < \gamma < d < u$) be four arbitrary points.

Let $(\tau_i)_i$ and $(t_i)_i$ be two sequences of stopping times as defined in (2.3), in order to apply Proposition 2.2.3.

Notice that if $\inf_n P(\tau_n < \infty) > 0$, then Z_n does not converge almost surely. We will show that, assuming $\inf_n P(\tau_n < \infty) > 0$, we meet a contradiction by proving that Z_n converges almost surely.

Now, let us denote with $t_{\delta'}$ the last time the process δ_n is above δ', i.e.

$$t_{\delta'} = \begin{cases} \sup\{n \geq 1 : \delta_n \geq \delta'\} & \text{if } \{n \geq 1 : \delta_n \geq \delta'\} \neq \emptyset; \\ 0 & \text{otherwise}. \end{cases}$$

Then, fix $\epsilon \in (0, \frac{1}{2})$ and take $n_\epsilon \in \mathbb{N}$ such that

$$P\left(t_{\delta'} > n_\epsilon\right) \ \leq \ \epsilon \cdot \inf_n P(\tau_n < \infty).$$

Let us fix an integer $i \geq n_\epsilon$ satisfying

$$i > \log_{\frac{u(1-d)}{d(1-u)}} b\frac{\max\{1-d;\gamma\}}{D_{\tau_0}(d-\gamma)},$$

so that $\tau_i \geq n_\epsilon$ a.s. and, by Lemma 2.2.2, we have that

$$D_{\tau_i} > b\frac{\max\{1-d;\gamma\}}{d-\gamma} \quad a.s.$$

To ease of notation, denote by $(\widehat{\cdot}_n)_{n\in\mathbb{N}}$ the renewed process on $\{\tau_i < \infty\}$: $(\widehat{R}_n, \widehat{W}_n) = (R_{\tau_i+n}, W_{\tau_i+n})$, $\widehat{D}_n = \widehat{R}_n + \widehat{W}_n = D_{\tau_i+n}$, $\widehat{Z}_n = \widehat{R}_n/\widehat{D}_n = Z_{\tau_i+n}$, $\widehat{U}_n = U_{\tau_i+n}$. Note that $Z_{\tau_i} \in (\gamma, d)$.
We denote by $P_i(\cdot) = P(\cdot|\tau_i < \infty)$, and therefore, if

$$t = \begin{cases} \inf\{n : \widehat{Z}_n > u\} & \text{if } \{n : \widehat{Z}_n > u\} \neq \emptyset; \\ +\infty & \text{otherwise} \end{cases}$$

then we have

$$P(\tau_{i+1} < \infty|\tau_i < \infty) \;\leq\; P_i(t_i < \infty) \;=\; P_i(t < \infty) \tag{5.10}$$

Define the sequences $(t^*_n, \tau^*_n)_n$ of stopping times which indicate the $(\widehat{Z}_n)_n$-crosses of the interval (δ', γ): let $t^*_0 = 0$ and define for every $j \geq 1$ two stopping times

$$\begin{aligned} \tau^*_j &= \begin{cases} \inf\{n > t^*_{j-1} : \widehat{Z}_n \leq \delta'\} & \text{if } \{n > t^*_{j-1} : \widehat{Z}_n \leq \delta'\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \\ t^*_j &= \begin{cases} \inf\{n > \tau^*_j : \widehat{Z}_n > \gamma\} & \text{if } \{n > \tau^*_j : \widehat{Z}_n > \gamma\} \neq \emptyset; \\ +\infty & \text{otherwise.} \end{cases} \end{aligned} \tag{5.11}$$

Notice that,

$$\begin{aligned} &\frac{R}{R+W} \leq \gamma, \\ &(R+W) > \frac{b(1-d)}{d-\gamma} \end{aligned} \qquad \Longrightarrow \qquad \frac{R+x}{R+W+x} < d,\ \forall x \leq b,$$

and hence, since the reinforcements are bounded by b, we have

$$\begin{aligned} &\widehat{Z}_{t^*_j-1} \leq \gamma, \\ &\widehat{D}_{t^*_j-1} > \frac{b(1-d)}{d-\gamma} \end{aligned} \quad \Longrightarrow \quad \widehat{Z}_{t^*_j} < d \tag{5.12}$$

For any $j \geq 0$, we can define a process $(\widetilde{Z}^j_n)_{n\in\mathbb{N}}$ to set a new urn, coupled with $(\widehat{Z}_n)_{n\in\mathbb{N}}$, with the following features:

$$\begin{aligned}
\widetilde{W}_0^j &= \widehat{W}_{t_j^*}\\
\widetilde{R}_0^j &= \widetilde{W}_{t_j^*}\frac{u+d}{2-u-d}\\
\widetilde{X}_{n+1}^j &= \mathbf{1}_{[0,\widetilde{Z}_n^j]}(\widehat{U}_{t_j^*+n+1}),\\
\widetilde{M}_{n+1}^j &= \widehat{M}_{t_j^*+n+1} + (m_W - m_R)\\
\widetilde{N}_{n+1}^j &= \widehat{N}_{t_j^*+n+1}\\
\widetilde{R}_{n+1}^j &= \widetilde{R}_n^j + \widetilde{X}_{n+1}^j\widetilde{M}_{n+1}^j,\\
\widetilde{W}_{n+1}^j &= \widetilde{W}_n^j + (1-\widetilde{X}_{n+1}^j)\widetilde{N}_{n+1}^j,\\
\widetilde{D}_{n+1}^j &= \widetilde{R}_{n+1}^j + \widetilde{W}_{n+1}^j,\\
\widetilde{Z}_{n+1}^j &= \frac{\widetilde{R}_{n+1}^j}{\widetilde{D}_{n+1}^j}.
\end{aligned}$$

Then, $(\widetilde{Z}^j)_{j\in\mathrm{N}}$ is a sequence of urn processes, all starting with $\widetilde{Z}_0^j = \frac{u+d}{2}$ and having nonnegative reinforcements with the same mean m_W. Let us notice that at time n, we have defined only the processes $\widetilde{Z}^j$ such that $t_j^* < n$.

We will prove by induction that, for any $j \in \mathbb{N}$,

$$\widetilde{Z}_n^j > \widehat{Z}_{t_j^*+n}, \qquad \widetilde{W}_n^j \leq \widehat{W}_{t_j^*+n}, \qquad \widetilde{R}_n^j > \widehat{R}_{t_j^*+n} \tag{5.13}$$

for any $n \leq \tau_{j+1}^* - t_j^*$ and $n > t_{\delta'}$.
In other words, we will show that, after the time $t_{\delta'}$, each process $(\widetilde{Z}_n^j)_{n\in\mathrm{N}}$ is always above the original process $(\widehat{Z}_{t_j^*+n})_{n\in\mathrm{N}}$, as long as $\widehat{Z}$ remains above δ' (i.e. before the time τ_j^*). The condition $n > t_{\delta'}$ ensures that, as long as $\widehat{Z}$ remains above δ', both the processes $\widetilde{Z}^j$ and $\widehat{Z}$ are above the process δ_n. By construction we have that

$$\widetilde{Z}_0^j = \frac{d+u}{2} > d > \widehat{Z}_{t_j^*}, \qquad \widetilde{W}_0^j = \widehat{W}_{t_j^*}$$

which immediately implies $\widetilde{R}_0^j > \widehat{R}_{t_j^*}$. Assume (5.13) by induction hypothesis. Since, for any $n \leq \tau_{j+1}^* - t_j^*$, we have that $\widetilde{X}_{n+1}^j = \mathbf{1}_{[0,\widetilde{Z}_n^j]} \geq \mathbf{1}_{[0,\widehat{Z}_{t_j^*+n}]} = \widehat{X}_{t_j^*+n+1}$ by construction, we get

$$\widehat{R}_{t_j^*+n+1} - \widehat{R}_{t_j^*+n} = \widehat{X}_{t_j^*+n+1}\widehat{M}_{t_j^*+n+1} \leq \widetilde{X}_{n+1}^j\widetilde{M}_{n+1}^j = \widetilde{R}_{n+1}^j - \widetilde{R}_n^j,$$
$$\widehat{W}_{t_j^*+n+1} - \widehat{W}_{t_j^*+n} = (1-\widehat{X}_{t_j^*+n+1})\widehat{N}_{t_j^*+n+1} \geq (1-\widetilde{X}_{n+1}^j)\widetilde{N}_{n+1}^j = \widetilde{W}_{n+1}^j - \widetilde{W}_n^j.$$

that means

$$\widetilde{Z}_{n+1}^j > \widehat{Z}_{t_j^*+n+1}, \qquad \widetilde{W}_{n+1}^j \leq \widehat{W}_{t_j^*+n+1}, \qquad \widetilde{R}_{n+1}^j > \widehat{R}_{t_j^*+n+1}$$

for any $n \leq \tau_{j+1}^* - t_j^*$ and $n > t_{\delta'}$.
Note that, for any $j \geq 0$, the process $(\widetilde{Z}_n^j)_{n=0}^{\tau_{j+1}^*-t_j^*}$ is an urn process reinforced with

distributions with same means and initial composition $(\widetilde{R}_{t_j^*}, \widetilde{W}_{t_j^*})$. Let us define T_j as the stopping time for $(\widetilde{Z}_n)_n$ to exit from (d,u) before $\tau_{j+1}^* - t_j^*$, i.e.:

$$T_j = \begin{cases} \inf\{n \leq \tau_{j+1}^* - t_j^* : \widetilde{Z}_n^j \leq d \text{ or } \widetilde{Z}_n^j \geq u\} \\ \qquad \text{if } \{n \leq \tau_{j+1}^* - t_j^* : \widetilde{Z}_n^j \leq d \text{ or } \widetilde{Z}_n^j \geq u\} \neq \emptyset; \\ +\infty \qquad \text{otherwise,} \end{cases}$$

Then, whenever $t_j^* \geq t_{\delta'}$, we have that

$$\left\{\widehat{Z}_n > u\right\} \subset \left\{\sup_{j:t_j^* \leq n} \widetilde{Z}_{n-t_j^*}^j > u\right\}.$$

So, we can obtain

$$\begin{aligned} P(\tau_{i+1} < \infty | \tau_i < \infty) &\leq P_i(t_i < \infty) = P_i(t < \infty) \\ &= P_i\Big(\{t < \infty\} \bigcap \{t_{\delta'} \leq n_\epsilon\}\Big) + P_i\Big(\{t < \infty\} \bigcap \{t_{\delta'} > n_\epsilon\}\Big) \\ &\leq P_i\left(\left\{\bigcup_{j=0}^{\infty} \{T_j < \infty\}\right\} \bigcap \{t_{\delta'} \leq n_\epsilon\}\right) + P_i\left(t_{\delta'} > n_\epsilon\right) \\ &\leq \sum_{j=0}^{\infty} P_i\Big(\{T_j < \infty\} \bigcap \{t_{\delta'} \leq n_\epsilon\}\Big) + \epsilon \end{aligned}$$

Now, let us consider a single term of the series. Then, as a consequence of Lemma 2.2.5, if we set $h = \frac{u-d}{2}$ we get

$$\begin{aligned} P_i\Big(\{T_j < \infty\} \bigcap \{t_{\delta'} \leq n_\epsilon\}\Big) &\leq P\left(\left\{\sup_n |\widetilde{Z}_{t_j^*+n} - \widetilde{Z}_{t_j^*}| \geq h\right\} \bigcap \{t_{\delta'} \leq n_\epsilon\}\right) \\ &\leq \frac{b}{D_{t_j^*}}\Big(\frac{4}{h^2} + \frac{2}{h}\Big) \\ &\leq \frac{b}{\widehat{D}_{t_0^*}}\left(\frac{\delta(1-\gamma)}{\gamma(1-\delta)}\right)^j \Big(\frac{4}{h^2} + \frac{2}{h}\Big) \end{aligned}$$

Thus define the function $g : [0,\infty) \times [0,\infty) \to [0,1]$ in the following way

$$g(x,y) := \frac{b}{x+y}\Big(\frac{4}{h^2} + \frac{2}{h}\Big)\left(\frac{1-\delta}{1-\delta/\gamma}\right) + \epsilon,$$

and note that

$$g\left(8/h^2\left(\frac{1-\delta}{1-\delta/\gamma}\right), 4b/h\left(\frac{1-\delta}{1-\delta/\gamma}\right)\right) = \frac{1}{2} + \epsilon < 1$$

and g is monotone in $x+y$. Then, we can apply Proposition 2.2.3 to get the thesis. □

Remark 5.2.2. *Notice that in the proof of Theorem 5.2.1 we have never used the assumption* (5.1)*. Then, provided that condition* (5.6) *holds, the assumption* (5.1) *is not necessary to get the almost sure convergence of the urn process* $(Z_n)_n$.

5.3 The Convergence in Probability of the urn process

Sometimes the almost sure convergence of the adaptive sequences $f_\eta(\widehat{\underline{\theta}_n})$ and $f_\delta(\widehat{\underline{\theta}_n})$ to the target $f_\delta(\widehat{\underline{\theta}})$ and $f_\delta(\widehat{\underline{\theta}})$ required in the assumption (5.6) can be hard to prove or not even true. In these situations, we may want to have less restrictive conditions on the sequence $f_\eta(\widehat{\underline{\theta}_n})$ and $f_\delta(\widehat{\underline{\theta}_n})$, like assuming that the convergence holds only in probability. Under these conditions, in this section we show the convergence in probability of the urn proportion Z, concerning the urn model described in Section 5.1. In particular, in Theorem 5.3.3 we show that if the sequences $(\eta_n)_n$ and $(\delta_n)_n$ converge in probability to some constants η and δ, respectively, then the urn process $(Z_n)_n$ converges in probability to one of those constants, depending on the order between reinforcement means.

To prove Theorem 5.3.3 we need some auxiliar results gathered in two lemmas. The first one explicit a well-known consequence of the superior/inferior limit of any process

Lemma 5.3.1. *Let $(Y_n)_n$ be a real-value process. Then, for any $l \in \mathbb{R}$*

$$P\left(\{Y_n > l\} \bigcap \left\{ \limsup_{n\to\infty} Y_n < l \right\} \right) \ \to\ 0 \tag{5.14}$$

Proof. If $P(\limsup_n Y_n < l) = 0$, then lemma 5.3.1 is trivially true. Otherwise, we get the thesis once we show that

$$P\left(Y_n > l \mid \limsup_{n\to\infty} Y_n < l \right) \ \to\ 0.$$

Let us introduce the random time τ, representing the last time the process Y_n is above l, i.e.

$$\tau = \begin{cases} \sup\{\, k \geq 0 \mid Y_k > l \,\} & \text{if } \{\, k \geq 0 \mid Y_k > l \,\} \neq \emptyset; \\ -1 & \text{otherwise}. \end{cases}$$

From the definition of superior limit, we have that the event $\{\tau = \infty\}$ implies that $\{\limsup_{n\to\infty} Y_n \geq l\}$. As a consequence, we have that

$$P\left(\tau < \infty \mid \limsup_{n\to\infty} Y_n < l \right) \ =\ 1. \tag{5.15}$$

Then, using (5.15) we get the thesis

$$P\left(Y_n > l \mid \limsup_{n\to\infty} Y_n < l \right) \ =\ P\left(\tau > n \mid \limsup_{n\to\infty} Y_n < l \right) \ \to\ 0.$$

□

Here, we present another lemma that will be used in the proof of Theorem 5.3.3, concerning the conditional expectation of the increments of the urn process.

Lemma 5.3.2. *Let us consider the urn process described in Section 5.1. Then, the following relation holds*

$$\mathbb{E}[Z_{n+1} - Z_n | \mathcal{F}_n] \ =\ \mathbb{E}\left[\frac{M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} - \frac{N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}} |\mathcal{F}_n \right] \tag{5.16}$$

Proof. The proof of Lemma 5.3.2 has been computed following a similar argument applied in the proof of Theorem 2 of [45]. The notation used in [45] is the same adopted in this paper. The presence of the indicator functions $\mathbf{1}_{\{Z_n>\delta_n\}}$ and $\mathbf{1}_{\{Z_n<\eta_n\}}$ is the real difference from the proof in [45]. Nevertheless, since they are $\mathcal{F}_n$-measurable, the same structure of the proof can be proposed here.
Because of the relation

$$Z_{n+1} = X_{n+1}\frac{R_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} + (1-X_{n+1})\frac{R_n}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}$$

and since X_{n+1} is conditionally to $\mathcal{F}_n$ independent of M_{n+1} and N_{n+1}, we can get that

$$\begin{aligned}\mathbb{E}[Z_{n+1}|\mathcal{F}_n] \quad &= \mathbb{E}\left[Z_n\frac{R_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} + (1-Z_n)\frac{R_n}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}|\mathcal{F}_n\right] \\ &= \mathbb{E}\left[Z_n\left(\frac{R_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} + \frac{W_n}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}\right)|\mathcal{F}_n\right]\end{aligned}$$

Analogously, we have that

$$\mathbb{E}[1-Z_{n+1}|\mathcal{F}_n] \;=\; \left[(1-Z_n)\left(\frac{W_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}} + \frac{R_n}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}\right)|\mathcal{F}_n\right].$$

Therefore,

$$\begin{aligned}&\mathbb{E}[Z_{n+1}-Z_n|\mathcal{F}_n] \;=\; \mathbb{E}[(1-Z_n)Z_{n+1} - Z_n(1-Z_{n+1})|\mathcal{F}_n] \\ &= Z_n(1-Z_n)\mathbb{E}\left[\frac{R_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} + \frac{W_n}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}\right. \\ &\quad \left. -\frac{W_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}{D_n + N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}} - \frac{R_n}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}|\mathcal{F}_n\right] \\ &= Z_n(1-Z_n)\left[\frac{M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}}{D_n + M_{n+1}\mathbf{1}_{\{Z_n<\eta_n\}}} - \frac{N_{n+1}\mathbf{1}_{\{Z_n>\delta_n\}}}{D_n + N_{n+1}\mathbf{1}\{Z_n>\delta_n\}}|\mathcal{F}_n\right]\end{aligned}$$

□

Theorem 5.3.3 is based on the assumption (5.17), concerning the convergence in probability of the adaptive sequences $f_\eta(\widehat{\underline{\theta}}_n)$ and $f_\delta(\widehat{\underline{\theta}}_n)$ to the target $f_\eta(\underline{\theta})$ and $f_\delta(\underline{\theta})$. This condition can be satisfied using various estimators of $\underline{\theta}$ and with different choices of the functions $f_\eta(\cdot)$ and $f_\delta(\cdot)$.
As explained for the assumption (5.6) in Section5.2, under Assumption 5.1 both the sequences $N_R(n)$ and $N_W(n)$ diverges as n goes to infinity.
Then, if $\widehat{\underline{\theta}}_n$ is any consistent estimator of $\underline{\theta}$, and the functions $f_\eta(\cdot)$ and $f_\delta(\cdot)$ are continuous, we have that $\eta_n \xrightarrow{p} \eta$ and $\delta_n \xrightarrow{p} \delta$ and so condition (5.17) is verified.

Theorem 5.3.3. *Assume*

$$\begin{cases}\eta_n \xrightarrow{p} \eta \quad \textit{if} \;\; m_R > m_W, \\ \\ \delta_n \xrightarrow{p} \delta \quad \textit{if} \;\; m_R < m_W.\end{cases} \tag{5.17}$$

Then

$$Z_n \;\xrightarrow{p}\; \eta\mathbf{1}_{\{m_R>m_W\}} \;+\; \delta\mathbf{1}_{\{m_R<m_W\}} \tag{5.18}$$

Proof. Let us assume that $m_R < m_W$ and $\delta_n \xrightarrow{p} \delta$. Then, the goal to prove is that $Z_n \xrightarrow{p} \delta$. The proof of the case $m_R > m_W$ is analogous. To prove $Z_n \xrightarrow{p} \delta$, we first show that, $\forall \epsilon > 0$, $P(Z_n - \delta > \epsilon) \to 0$. Then, by using the same argument, we can easily show that, $\forall \epsilon > 0$, $P(Z_n - \delta < -\epsilon) \to 0$ and so we get the thesis.

Let us fix an arbitrary small $\epsilon > 0$ and define $l = \delta + \epsilon$. Our goal is to prove that

$$\lim_{n\to\infty} P(Z_n > l) \;=\; 0.$$

To do that, we fix another constant $\delta' \in (\delta, l)$ and we define the following events

$$A_{sup} = \{\lim \sup_{n\to\infty} Z_n \geq l\}$$

$$A_{inf} = \{\lim \inf_{n\to\infty} Z_n \leq \delta'\}$$

We use these events to decompose the probability of the urn process Z_n to exceed l. So doing, we obtain

$$\begin{aligned} P(Z_n > l) \;\leq\;& P(\,\{Z_n > l\} \,\cap\, A_{sup} \,\cap\, A_{inf}\,) \\ +\;& P(\,\{Z_n > l\} \,\cap\, A_{sup}^C) \\ +\;& P(\,\{Z_n > l\} \,\cap\, A_{inf}^C) \end{aligned}$$

Let us denote with $P_{1,n}$, $P_{2,n}$, $P_{3,n}$ the three probabilities in the previous expression. Then, we get the thesis once we show that $P_{1,n}$, $P_{2,n}$ and $P_{3,n}$ tend to zero as n goes to infinity.

At first, let us consider the term $P_{2,n}$. By using lemma 5.3.1, we immediately get that

$$P_{2,n} \;=\; P(\,\{Z_n > l\} \,\cap\, A_{sup}^C) \;=\; P(\,\{Z_n > l\} \,\cap\, \{\lim \sup_{n\to\infty} Z_n < l\}\,) \;\to_n\; 0.$$

Then, let us consider the term $P_{3,n}$:

$$P_{3,n} \;=\; P(\,\{Z_n > l\} \,\cap\, A_{inf}^C) \;\leq\; P(A_{inf}^C) \;=\; P(\lim \inf_{n\to\infty} Z_n > \delta')$$

In order to prove that $P(\liminf_{n\to\infty} Z_n > \delta') = 0$, we are going to show that if we assume $P(\liminf_{n\to\infty} Z_n > \delta') \geq \epsilon > 0$, then we meet to a contradiction.
At first, let us introduce the random time τ, representing the last time the process Z_n is below δ', i.e.

$$\tau = \begin{cases} \sup\{\, k \geq 0 \mid Z_k < \delta' \,\} & \text{if } \{\, k \geq 0 \mid Z_k < \delta' \,\} \neq \emptyset; \\ 0 & \text{otherwise.} \end{cases}$$

Then, let us define two quantities k_0 and k_1, defined as follows

$$k_0 \;:=\; \inf\left\{\, k \in \mathbb{N} \mid \; P\left(\, \tau < k \mid \liminf_{n\to\infty} Z_n > \delta' \,\right) \;>\; 1/2 \,\right\} \tag{5.19}$$

$$k_1 \;:=\; \inf\{\, k \in \mathbb{N} \mid \forall\, i \geq k,\; P(\delta_i < \delta') > 1 - \epsilon/4 \,\} \tag{5.20}$$

Notice that both k_0 and k_1 are not random times. Moreover, k_0 is finite because $P(\tau < \infty | \liminf_{n\to\infty} Z_n > \delta') = 1$; the proof is an analogous of (5.15) for the inferior limit. Furthermore, k_1 is finite since from the assumption (5.17) we have that $P(\delta_i < \delta') \to 1$. The role of k_0 and k_1 will be clear more ahead in the proof. Then, let us call k_M the maximum between these two times: $k_M = \max\{k_0; k_1\}$ and fix an arbitrary $n_0 \geq k_M$. Now, let us define the stopping time t_{n_0}, which indicates the first time after n_0 that the urn proportion Z_n is below δ'

$$t_{n_0} = \begin{cases} \inf\{\, k \geq n_0 \mid Z_k < \delta' \,\} & \text{if } \{\, k \geq n_0 \mid Z_k < \delta' \,\} \neq \emptyset; \\ -\infty & \text{otherwise.} \end{cases}$$

Finally, for any $n \geq n_0$ we can write

$$\begin{aligned} -1 \quad &\leq \mathbb{E}[Z_{\min\{t_{n_0},n\}} - Z_{n_0}] \;=\; \mathbb{E}\left[\sum_{i=n_0+1}^{\min\{t_{n_0},n\}} (Z_i - Z_{i-1})\right] \\ &= \mathbb{E}\left[\sum_{i=n_0+1}^{n} (Z_i - Z_{i-1})\mathbf{1}_{\{i \leq t_{n_0}\}}\right] \\ &= \mathbb{E}\left[\sum_{i=n_0+1}^{n} \mathbb{E}[Z_i - Z_{i-1}/\mathcal{F}_{i-1}]\mathbf{1}_{\{i \leq t_{n_0}\}}\right] \end{aligned}$$

Here, we apply lemma 5.3.2 to get the relation

$$\mathbb{E}[Z_i - Z_{i-1}|\mathcal{F}_{i-1}] \;=\; \mathbb{E}\left[\frac{M_i\mathbf{1}_{\{Z_{i-1}<\eta_{i-1}\}}}{D_{i-1} + M_i\mathbf{1}_{\{Z_{i-1}<\eta_{i-1}\}}} - \frac{N_i\mathbf{1}_{\{Z_{i-1}>\delta_{i-1}\}}}{D_{i-1} + N_i 1_{\{Z_{i-1}>\delta_{i-1}\}}}|\mathcal{F}_{i-1}\right]$$

So doing, we obtain

$$\begin{aligned} &= \mathbb{E}\left[\sum_{i=n_0+1}^{n} Z_{i-1}(1-Z_{i-1})\mathbb{E}\left[\frac{M_i\mathbf{1}_{\{Z_{i-1}<\eta_{i-1}\}}}{D_{i-1} + M_i\mathbf{1}_{\{Z_{i-1}<\eta_{i-1}\}}} - \frac{N_i\mathbf{1}_{\{Z_{i-1}>\delta_{i-1}\}}}{D_{i-1} + N_i 1_{\{Z_{i-1}>\delta_{i-1}\}}}|\mathcal{F}_{i-1}\right] 1_{\{i \leq t_{n_0}\}}\right] \\ &\leq \mathbb{E}\left[\sum_{i=n_0+1}^{n} Z_{i-1}(1-Z_{i-1})\mathbb{E}\left[\frac{M_i}{D_{i-1} + M_i} - \frac{N_i\mathbf{1}_{\{Z_{i-1}>\delta_{i-1}\}}}{D_{i-1} + N_i}|\mathcal{F}_{i-1}\right] \mathbf{1}_{\{i \leq t_{n_0}\}}\right] \\ &\leq \mathbb{E}\left[\sum_{i=n_0+1}^{n} Z_{i-1}(1-Z_{i-1})\mathbb{E}\left[\frac{b}{D_{i-1}} - \frac{N_i\mathbf{1}_{\{Z_{i-1}>\delta_{i-1}\}}}{D_{i-1} + b}|\mathcal{F}_{i-1}\right] \mathbf{1}_{\{i \leq t_{n_0}\}}\right] \end{aligned}$$

Let us note a simple thing: for any $i \leq t_{n_0}$ the urn proportion Z_i is above δ' and then $\{Z_i > \delta_i\} \supset \{\delta_i < \delta'\}$. For this reason, we write

$$\begin{aligned} &\leq \mathbb{E}\left[\sum_{i=n_0+1}^{n} Z_{i-1}(1-Z_{i-1})\mathbb{E}\left[\frac{M_i}{D_{i-1}} - \frac{N_i\mathbf{1}_{\{\delta_{i-1}<\delta'\}}}{D_{i-1} + b}|\mathcal{F}_{i-1}\right] 1_{\{i \leq t_{n_0}\}}\right] \\ &= \mathbb{E}\left[\sum_{i=n_0+1}^{n} Z_{i-1}(1-Z_{i-1})\mathbb{E}\left[\frac{M_i b + D_{i-1}(M_i - N_i\mathbf{1}_{\{\delta_{i-1}<\delta'\}})}{D_{i-1}(D_{i-1} + b)}|\mathcal{F}_{i-1}\right] 1_{\{i \leq t_{n_0}\}}\right] \end{aligned}$$

Since $E[M_i|\mathcal{F}_{i-1}] = E[M_i] = m_R$ and $E[N_i|\mathcal{F}_{i-1}] = E[N_i] = m_W$ for any $i \in \mathbb{N}$, we have that

$$\leq \mathbb{E}\left[\sum_{i=n_0+1}^{n} \frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}(D_{i-1}+b)} \cdot m_R b \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right]$$
$$+ \mathbb{E}\left[\sum_{i=n_0+1}^{n} \frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}(D_{i-1}+b)} \cdot D_{i-1}(m_R - m_W \mathbf{1}_{\{\delta_{i-1}<\delta'\}}) \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right]$$

By using

$$m_R - m_W \mathbf{1}_{\{\delta_{i-1}<\delta'\}} = (m_R - m_W)\mathbf{1}_{\{\delta_{i-1}<\delta'\}} + m_R \mathbf{1}_{\{\delta_{i-1}>\delta'\}}$$

we decompose the second term, obtaining

$$= \mathbb{E}\left[\sum_{i=n_0+1}^{n} \frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}(D_{i-1}+b)} \cdot m_R b \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right]$$
$$+ \mathbb{E}\left[\sum_{i=n_0+1}^{n} \frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}+b} \cdot (m_R - m_W)\mathbf{1}_{\{\delta_{i-1}<\delta'\}} \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right]$$
$$+ \mathbb{E}\left[\sum_{i=n_0+1}^{n} \frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}+b} \cdot m_R \mathbf{1}_{\{\delta_{i-1}>\delta'\}} \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right]$$

Let us denote with $A_{1,n}$, $A_{2,n}$, $A_{3,n}$ the three quantities in the previous expression.
Let us consider $A_{1,n}$. From Proposition 5.1.1 we get the boundedness of the sequence $\mathbb{E}[(n/D_n)^2]$, obtaining

$$A_{1,n} \leq \frac{m_R b}{4} \sum_{i=n_0}^{n-1} \mathbb{E}\left[\frac{1}{D_i^2}\right] \leq \frac{m_R b}{4} \max_{i \leq n-1} \left\{ \mathbb{E}\left[\frac{1}{(D_i/i)^2}\right] \right\} \cdot \sum_{i=n_0}^{n-1} \frac{1}{i^2} \leq C_1$$

where C_1 is a positive constant.
Now, let us consider the quantity $A_{2,n}$. Let us recall the quantity $p^* \in (0,1)$ introduced in (5.5), such that $P(Z_n \in (p^*, 1-p^*)) = 1$. Then, we can write that

$$\begin{aligned} A_{2,n} &= (m_R - m_W) \sum_{i=n_0+1}^{n} \mathbb{E}\left[\frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}+b} \cdot \mathbf{1}_{\{\delta_{i-1}<\delta'\}} \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right] \\ &\leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \sum_{i=n_0+1}^{n} \mathbb{E}\left[\frac{1}{D_{i-1}+b} \cdot \mathbf{1}_{\{\delta_{i-1}<\delta'\}} \cdot \mathbf{1}_{\{i \leq t_{n_0}\}} \right] \\ &\leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \sum_{i=n_0}^{n-1} \mathbb{E}\left[\frac{1}{D_i+b} \cdot \mathbf{1}_{\{\delta_i<\delta'\}} \cdot \mathbf{1}_{\{t_{n_0}=\infty\}} \right] \end{aligned}$$

where the last passage is due to $\{t_{n_0} = \infty\} \subset \{i \leq t_{n_0}\}$ for any $i \geq n_0$. Moreover, since both the reinforcement distribution have a support contained in $[a, b]$, we have that $D_n \leq D_0 + n \cdot b$ a.s.; then,

$$\leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \sum_{i=n_0}^{n-1} \frac{1}{D_0 + (i+1)b} \, \mathbb{E}\left[\, \mathbf{1}_{\{\delta_i < \delta'\}} \, \cdot \, \mathbf{1}_{\{t_{n_0} = \infty\}} \, \right]$$
$$\leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \frac{n_0}{D_0 + (n_0+1)b} \cdot \sum_{i=n_0}^{n-1} \frac{1}{i} \, P\left(\, \{\delta_i < \delta'\} \bigcap \{t_{n_0} = \infty\} \, \right)$$

Moreover, from definition (5.19) and (5.20) and for any $i \geq n_0$, we get that

$$P\left(\, \{t_{n_0} = \infty\} \bigcap \{\delta_i < \delta'\} \, \right) \; =$$
$$P(t_{n_0} = \infty) \; + \; P(\delta_i < \delta') \; - \; P\left(\, \{t_{n_0} = \infty\} \bigcap \{\delta_i < \delta'\} \, \right) \; \geq$$
$$P(t_{n_0} = \infty) \; + \; P(\delta_i < \delta') \; - \; 1 \; \geq$$
$$P\left(\, t_{n_0} = \infty \mid \liminf_{n \to \infty} Z_n > \delta' \, \right) \cdot P\left(\, \liminf_{n \to \infty} Z_n > \delta' \, \right) \; + \; P(\delta_i < \delta') \; - \; 1 \; =$$
$$P\left(\, \tau < n_0 \mid \liminf_{n \to \infty} Z_n > \delta' \, \right) \cdot P\left(\, \liminf_{n \to \infty} Z_n > \delta' \, \right) \; + \; P(\delta_i < \delta') \; - \; 1 \; \geq$$
$$1/2 \cdot \epsilon \; + \; 1 - \epsilon/4 \; - \; 1 \; = \; \epsilon/4$$

Then, we compute that

$$\begin{aligned} A_{2,n} \quad & \leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \frac{n_0}{D_0 + (n_0+1)b} \cdot \frac{\epsilon}{4} \cdot \sum_{i=n_0}^{n-1} \frac{1}{i} \\ & \leq (m_R - m_W) \cdot p^*(1-p^*) \cdot \frac{k_M}{D_0 + (k_M+1)b} \cdot \frac{\epsilon}{4} \cdot \sum_{i=n_0}^{n-1} \frac{1}{i} \\ & = \; - \; C_2 \cdot \sum_{i=n_0}^{n-1} \frac{1}{i} \end{aligned}$$

where C_2 is a positive constant.

Now, let us consider the quantity $A_{3,n}$.

$$\begin{aligned}
A_{3,n} &= m_R \sum_{i=n_0+1}^{n} \mathbb{E}\left[\frac{Z_{i-1}(1-Z_{i-1})}{D_{i-1}+b} \cdot \mathbf{1}_{\{\delta_{i-1}<\delta'\}} \cdot \mathbf{1}_{\{i \le t_{n_0}\}} \right] \\
&\le m_R \sum_{i=n_0}^{n-1} \mathbb{E}\left[\frac{Z_i(1-Z_i)}{D_i+b} \cdot \mathbf{1}_{\{\delta_i<\delta'\}} \right] \\
&\le m_R \cdot \frac{1}{4} \cdot \sum_{i=n_0}^{n-1} \mathbb{E}\left[\frac{1}{D_i+b} \cdot \mathbf{1}_{\{\delta_i<\delta'\}} \right] \\
&\le m_R \cdot \frac{1}{4} \cdot \sum_{i=n_0}^{n-1} \mathbb{E}\left[\frac{\mathbf{1}_{\{\delta_i<\delta'\}}}{D_i} \right] \\
&\le m_R \cdot \frac{1}{4} \cdot \max_{i \ge n_0} \left\{ \mathbb{E}\left[\frac{1_{\{\delta_i>\delta'\}}}{D_i/i} \right] \right\} \sum_{i=n_0}^{n-1} \frac{1}{i} \\
&= C_3(n_0) \cdot \sum_{i=n_0}^{n-1} \frac{1}{i}
\end{aligned}$$

where $C_3(n_0)$ is a positive sequence, with $n_0 \ge k_M$. By using the Cauchy-Schwartz inequality we write

$$\mathbb{E}\left[\frac{1_{\{\delta_n>\delta'\}}}{D_n/n} \right] \le P\left(\delta_n > \delta'\right)^{\frac{1}{2}} \cdot \mathbb{E}\left[\left(\frac{1}{D_n/n} \right)^2 \right]^{\frac{1}{2}} \to 0$$

where the converge to zero is because $\delta_n \xrightarrow{p} \delta$ from assumption (5.17) and $\mathbb{E}[(\frac{n}{D_n})^2]$ is uniformly bounded from Proposition 5.1.1. Then, the sequence $C_3(n)$ tends to zero as n goes to infinity.
Finally, putting all together and choosing an n_0 large enough such that $C_3(n_0) < C_2$, we obtain

$$-1 \le A_{1,n} + A_{2,n} + A_{3,n} \le C_1 + (C_3(n_0) - C_2) \sum_{i=n_0}^{n-1} \frac{1}{i} \to -\infty$$

Therefore, since we have met a contradiction ($-1 \le -\infty$), we conclude that $P_{3,n} = P(\liminf_{n\to\infty} Z_n > \delta') = 0$.

At this point, it just remains to prove that the first term $P_{1,n}$ tends to zero as n goes to infinity. To do that, we fix an arbitrary small $\epsilon > 0$, and we will prove that asymptotically $P_{1,n} < \epsilon$.

First, we introduce two constants $d, u \in (0,1)$ such that $\delta' < d < u < l$. We are interested in the crossing in both directions of a strip (d, u). In particular, let $t_{-1} = -1$ and define for every $j \in \mathbb{Z}_+$ two stopping times

$$\tau_j = \inf\{n > t_{j-1} : Z_n < d\}$$
$$t_j = \inf\{n > \tau_j : Z_n > u\}$$

Notice that, on the set $A_{sup} \cap A_{inf} = \{\limsup_n Z_n \geq l\} \cap \{\liminf_n Z_n \leq \delta'\}$, both the sequences $(t_n)_n$ and $(\tau_n)_n$ diverge as n goes to infinity. As a consequence, there is no need to define the times τ_j and t_j when the sets are empty.
Let us consider any integer $j_0 \in \mathbb{N}$. A specific value for j_0 will be conveniently chosen more ahead.
Then, for any $n \geq j_0$, we have

$$\begin{aligned} P_{1,n} &= P\Big(\{Z_n > l\} \bigcap \{t_{j_0} > n\} \bigcap A_{sup} \bigcap A_{inf} \Big) \\ &+ P\Big(\{Z_n > l\} \bigcap \{t_{j_0} \leq n\} \bigcap A_{sup} \bigcap A_{inf} \Big) \end{aligned}$$

Because of

$$P\Big(t_{j_0} < \infty \mid A_{sup} \bigcap A_{inf} \Big) \; = \; 1$$

the first term of the sum tends to zero as n goes to infinity for any $j_0 \in \mathbb{N}$. Then, we will consider only the second term.
At first, let us introduce a new object: for any fixed $k \in \mathbb{N}$ we can define an urn process $(\widetilde{Z}_n^k)_n$ coupled with the original process $(Z_n)_n$. The notation of this new urn model is the same of the original process: $\widetilde{R}_n^k$ and $\widetilde{W}_n^k$ are the number of red and white balls, respectively; $\widetilde{Z}_n^k$ is the urn proportion and $\widetilde{D}_n^k$ the total number of balls in the urn; $\widetilde{U}_n^k$ and $\widetilde{X}_n^k$ are the random variables modeling the sampling process, i.e. $\widetilde{U}_n^k \sim U(0,1)$ and $\widetilde{X}_n^k = \mathbf{1}_{\{\widetilde{U}_n^k < \widetilde{Z}_{n-1}^k\}} \sim B(\widetilde{Z}_{n-1}^k)$; $\widetilde{M}_n^k$ and $\widetilde{N}_n^k$ are the possible reinforcements of red and white balls, respectively. The processes $(\widetilde{Z}_n^k)_n$ and $(Z_n)_n$ are coupled in the sense that, for any $n \geq 1$, $U_n^k = \widetilde{U}_{n+k}$, $M_n^k = \widetilde{M}_{n+k}$ and $N_n^k = \widetilde{N}_{n+k}$ almost surely. Moreover, the initial composition is $(\widetilde{R}_0^k, \widetilde{W}_0^k) = (R_k, W_k)$. The urn scheme of the new urn process is, for any $n \geq 1$,

$$\begin{aligned} \widetilde{R}_n^k &= \widetilde{R}_{n-1}^k + \widetilde{X}_n^k M_{n+k}, \\ \widetilde{W}_n^k &= \widetilde{W}_{n-1}^k + (1 - \widetilde{X}_n^k) N_{n+k} 1_{\{\delta_{n-1+k} < \delta'\}}, \\ \widetilde{D}_n^k &= \widetilde{R}_n^k + \widetilde{W}_n^k, \\ \widetilde{Z}_n^k &= \frac{\widetilde{R}_n^k}{\widetilde{D}_n^k}. \end{aligned}$$

Notice that here the indicator function represents a condition on the process $(\delta_n)_n$, and not a condition on the urn proportion $\widetilde{Z}_n^k$ as it was for the original process Z. Moreover, the sequence $(\delta_n)_n$ depends on variables governing the original urn Z (not $\widetilde{Z}$):

$$\delta_n \; = \; f_\delta(\, X_1 M_1 + (1 - X_1) N_1 \, , \; ... \; , \; X_n M_n + (1 - X_n) N_n \,)$$

We have introduced the new urn model $\widetilde{Z}_n^k$ because we have the following relation

$$\bigcap_{i=k}^{n} \{ \; Z_i > \delta' \; \} \quad \subset \quad \Big\{ \; \widetilde{Z}_n^k \; \geq \; Z_{n+k} \; \Big\}$$

holding for all $k \leq n$.

Then, we have that

$$P\Big(\ \{Z_n > l\} \bigcap \{t_{j_0} \le n\} \bigcap\ A_{sup} \bigcap\ A_{inf}\Big)\ \le$$
$$P\left(\ \bigcup_{j=j_0}^{n} \Big\{\{\widetilde{Z}^{t_j}_{n-t_j} > l\} \bigcap \{t_j \le n\}\Big\} \bigcap \{t_{j_0} \le n\} \bigcap\ A_{sup} \bigcap\ A_{inf}\right)\ \le$$
$$\sum_{j=j_0}^{n} P\Big(\ \{\widetilde{Z}^{t_j}_{n-t_j} > l\} \bigcap \{t_j \le n\} \bigcap\ A_{sup} \bigcap\ A_{inf}\Big)$$

where we remind that for any process $(\widetilde{Z}^{t_j}_k)_k$ it holds that $\widetilde{D}^{t_j}_0 = D_{t_j}$.
Now consider a single term of the sum, fixing an integer $j \in \{j_0, ..., n\}$. Naturally $t_j \ge j$ and, because on the set $\{t_j \le n\}$, we also have that $t_j \le n$. Moreover, notice that the increments of the urn proportion $\widetilde{Z}$ becomes smaller as the total number of balls in the urn $\widetilde{D}$ increases. Then, the more balls are contained in the urn, the longer it takes for the urn proportion $\widetilde{Z}^{t_j}$ to goes from u to l. Roughly speaking, when j is large, many balls are in the urn, and then the event $\{\widetilde{Z}^{t_j}_{n-t_j} > l\}$, with n closed to t_j, has probability null to occur. Let us now formalize this idea. Let us denote with $f(j)$ the minimum number of increments that are necessary to $\widetilde{Z}^{t_j}$ to go from $\widetilde{Z}^{t_j}_{t_j}$ to l, i.e.

$$f(j)\ :=\ \min\{\ k \ge 0 \mid P\left(\widetilde{Z}^{t_j}_k > l\right) > 0\ \}$$

After some simple calculus, we can compute $f(j)$ as a function of the minimum value admissible of $\widetilde{D}^{t_j}_0$

$$f(j)\ \ge\ \max\left\{\ \left[\ \frac{\min(D_{t_j})}{b}\frac{1-u}{1-l}\ -\ 1\right]\ ;\ 0\right\}$$

because $\widetilde{D}^{t_j}_0 = D_{t_j}$. Since from Lemma 2.1 of [4] we know that

$$D_{t_j} \ge \left(\frac{u(1-d)}{d(1-u)}\right) D_{t_{j-1}} \ge ... \ge \left(\frac{u(1-d)}{d(1-u)}\right)^j D_{t_0}, \quad a.s. \tag{5.21}$$

we can express $f(j)$ as follows

$$f(j)\ =\ \max\left\{\ \left[\ \left(\frac{u(1-d)}{d(1-u)}\right)^j \frac{D_{t_0}}{b}\frac{1-u}{1-l}\ -\ 1\right]\ ;\ 0\right\}.$$

Then, if $n - j < f(j)$

$$P\Big(\ \{\widetilde{Z}^{t_j}_{n-t_j} > l\} \bigcap \{t_j \le n\} \bigcap\ A_{sup} \bigcap\ A_{inf}\Big)\ =\ 0,$$

so, from now on, suppose j such that $n - j \ge f(j)$. Notice that, for any fixed $j \ge j_0$, this condition is asymptotically satisfied.

Then, we have

$$
\begin{aligned}
& P\Big(\{\widetilde{Z}^{t_j}_{n-t_j} > l\} \bigcap \{t_j \leq n\} \bigcap A_{sup} \bigcap A_{inf} \Big) \\
= & \sum_{i=j}^{n} P\Big(\{\widetilde{Z}^{i}_{n-i} > l\} \bigcap A_{sup} \bigcap A_{inf} \mid t_j = i \Big) P\left(t_j = i\right) \\
\leq & \sup_{j \leq i \leq n} P\Big(\{\widetilde{Z}^{i}_{n-i} > l\} \bigcap A_{sup} \bigcap A_{inf} \mid t_j = i \Big) \\
= & \sup_{j \leq i \leq n-f(j)} P\Big(\{\widetilde{Z}^{i}_{n-i} > l\} \bigcap A_{sup} \bigcap A_{inf} \mid t_j = i \Big)
\end{aligned}
$$

We remind that the last expression is well defined since we are considering an integer j such that $n - f(j) \geq j$.
Now, notice that each process $\widetilde{Z}$ can be seen as a Generalized Polya Urn, with the expected value of reinforcement of white balls greater than the expected value of reinforcement of white balls. Then we can use a result from [7, 14] suggesting that

$$
P(\widetilde{Z}_n \geq l) \leq C_1 \exp(-C_2 2^{log(n)})
$$

where $\widetilde{Z}$ is the urn proportion of a Generalized Polya Urn and C_1 and C_2 are two positive constants depending on the expectation of the initial composition. Using this result in our context, we have

$$
\begin{aligned}
& \sup_{j \leq i \leq n-f(j)} P\Big(\{\widetilde{Z}^{i}_{n-i} > l\} \bigcap A_{sup} \bigcap A_{inf} \mid t_j = i \Big) \\
\leq & \sup_{j \leq i \leq n-f(j)} C_1(i,j) \cdot \exp\left(-C_2(i,j) \cdot 2^{\log(n-i)} \right)
\end{aligned}
$$

where $C_1(i,j)$ and $C_2(i,j)$ indicate that C_1 and C_2 depend on the expectation of the initial conditions of the urn $\widetilde{Z}^i_0$ with $t_j = i$, that is the urn composition (R_i, W_i) with $t_j = i$. Since we know that $\widetilde{Z}^{t_j}_0 = Z_{t_j} \overset{a.s./L^1}{\rightarrow}_j u$ and $\widetilde{D}^{t_j}_0 = D_{t_j} \overset{a.s./L^1}{\rightarrow}_j \infty$, then $C_1(i,j)$ and $C_2(i,j)$ are converging sequence as j increases. As a consequence, we can say that there exists $j_1 \in \mathbb{N}$ and two positive constants $\mathcal{C}_1$ and $\mathcal{C}_2$ such that $C_1(i,j) \leq \mathcal{C}_1$ and $C_2(i,j) \geq \mathcal{C}_2$ for any $i, j \geq j_1$.

Hence, we can write

$$
\begin{aligned}
& \sup_{j \leq i \leq n-f(j)} C_1(i,j) \cdot \exp\left(-C_2(i,j) \cdot 2^{\log(n-i)} \right) \\
\leq & \sup_{j \leq i \leq n-f(j)} \mathcal{C}_1 \cdot \exp\left(-\mathcal{C}_2 \cdot 2^{\log(n-i)} \right) \\
\leq & \, \mathcal{C}_1 \cdot \exp\left(-\mathcal{C}_2 \cdot 2^{\log(f(j))} \right)
\end{aligned}
$$

Notice that since $f(j)$ grows exponentially, there exists a j_2 such that $f(j) \geq j$ for any $j \geq j_2$. Then, by choosing $j_0 > j_2$, we have

$$
\mathcal{C}_1 \cdot \exp\left(-\mathcal{C}_2 \cdot 2^{\log(f(j))} \right) \;\leq\; \mathcal{C}_1 \cdot \exp\left(-\mathcal{C}_2 \cdot 2^{\log(j)} \right)
$$

for any $j \geq j_0$.

Now, coming back to the series. Putting all together, we get that

$$\begin{aligned}
&\sum_{j=j_0}^{n} P\Big(\{\widetilde{Z}^{t_j}_{n-t_j} > l\} \bigcap \{t_j \leq n\} \bigcap A_{sup} \bigcap A_{inf} \Big) \\
&\leq \sum_{j=j_0}^{n} \mathcal{C}_1 \cdot \exp\big(-\mathcal{C}_2 \cdot 2^{\log(j)} \big) \mathbf{1}_{\{j+f(j)\leq n\}} \\
&\leq \sum_{j=j_0}^{n} \mathcal{C}_1 \cdot \exp\big(-\mathcal{C}_2 \cdot 2^{\log(j)} \big)
\end{aligned}$$

for any $j_0 > \max\{j_1; j_2\}$. Notice that in the previous expression we have a convergent series. Then, by choosing j_0 large enough, we can force this series to be smaller than any arbitrary $\epsilon > 0$. This means that we have proved that the term $P_{1,n}$ tends to zero as n goes to infinity, and then also that

$$\lim_{n\to\infty} P(Z_n > \delta + \epsilon) \; = \; 0, \quad \forall \epsilon > 0$$

The proof of

$$\lim_{n\to\infty} P(Z_n < \delta - \epsilon) \; = \; 0, \quad \forall \epsilon > 0$$

is completely analogous.
This conclude the proof that $Z_n \xrightarrow{p} \delta$. □

In this chapter we have presented a randomly reinforced urn model able to target an asymptotic allocation that is a function of unknown parameters modeling the response distributions $\rho = f(\underline{\theta})$. This allows the experimenter to choose functions that in some sense increase the statistical performances of the design, like minimizing a loss function, maximizing the power, ecc.. (collective ethics). Moreover, the design aims also at reducing the proportion of subjects assigned to the inferior treatment (individual ethics). This trade-off is faced in the design through the presence of two possible target allocation functions $f_\delta(\cdot)$ and $f_\eta(\cdot)$. In particular, $f_\delta(\cdot)$ represents the desired allocation if the superior treatment is W, while $f_\eta(\cdot)$ represents the desired allocation if the superior treatment is R.
First-order asymptotic results have been obtained and here reported. In particular, we are able to show, under very mild conditions, the convergence of the urn proportion to the target allocation, function of the unknown parameters. This convergence can be almost sure or in probability according to the choice of the estimators and the allocation functions.

CHAPTER 6

Conclusions and ongoing work

This thesis analyzes statistical properties of urn models for the experimental design in a clinical trail context. In the designs we have considered, subjects are sequentially assigned to two treatments under study (say R and W) according to a response-adaptive randomized procedure, in which the probability of assignment depends on the responses to the treatments observed in the previously allocated patients. We deal with urn models since they are classical procedures to randomize the allocations and to describe the dependence among the probability of assignment of the next subject and the responses previously collected. We focus on urn schemes that at each step reinforce the urn with a random quantity of balls of the color correspondent to the assigned treatment; these models are usually denoted as Randomly Reinforced Urn (RRU) models. These procedures asymptotically allocate subjects to the treatment superior in mean with a probability that converges to 1. They present good ethical properties but poor statistical performance for inferential purposes.
For this reason, in Chapter 2 we propose a new modified randomly reinforced urn design (MRRU) whose allocation proportion converge to a fixed $\rho \in (0,1)$. As a consequence, the performances of inferential procedures adopted in the experiment have been improved. Moreover, the MRRU achieves a goal that typically arises in the clinical trial framework, as it allocates small proportions of subjects to the inferior treatment. This has been obtained by setting two parameters δ and η, with $0 < \delta \leq \eta < 1$, that represent the possible values for the limiting allocation proportion. The target allocation is different depending on which treatment is the superior in mean. In fact, in Theorem 2.3.1 we proved that the almost sure limit of the urn process is $\rho = \eta \mathbf{1}_{\{m_R > m_W\}} + \delta \mathbf{1}_{\{m_R < m_W\}}$. The parameters δ and η are fixed in advance by the experimenter, but the asymptotic allocation ρ is unknown since the response means to the treatments m_R and m_W are unknown. Further asymptotic properties of quantities related to the urn model are proved

and reported in Chapter 2
In Chapter 3 we conduct a statistical study on the properties that follow from the use of the MRRU model to implement a test that aims at comparing the mean effects of the two treatments. We show that a test based on a response adaptive design as the MRRU model presents different desirable properties. In fact, this procedure enables us to increase the power of the test and at the same time to assign fewer subjects to the inferior treatment than a classical non-adaptive test. The analysis of a real case study and simulation studies highlight these results.
In Chapter 4 we compute the rate of convergence and the limiting distribution of the urn process with different reinforcement means. We discuss the asymptotic results in an inferential setting for test procedures using statistics based on both the adaptive estimators and the urn composition. A comparison with the inferential properties of the RRU design whose asymptotic allocation is $\rho \in \{0, 1\}$ has been realized. As we expect, using statistics based on the adaptive estimators, a test implemented with the MRRU design has a power higher than a test implemented with the RRU design.
In Chapter 5 we extend the MRRU model presented in Chapter 2 to obtain an urn design in a sequential estimation framework. In particular, we propose a randomly reinforced urn model whose asymptotic allocation is a function of unknown parameters of the responses probability laws. As a consequence, the choice of that function can be made in order to maximize any statistical goal, and the urn procedure is able to asymptotically target the allocation proportion that achieves that goal. The model is characterized by two functions representing the desired allocation proportions in the cases that the superior treatment in mean is either R or W. The current value of the targets are computed using consistent estimators. This feature allows the experimenter to achieve the ethical goal of reducing the proportion of subjects assigned to the inferior treatment.
The second-order asymptotic results concerning the urn design described in Chapter 5 are the main object of the work in progress naturally in continuity with this thesis. A central limit theorem on the allocation proportion will enable a deeper study of the inferential aspects and a comparison of this model with other parametric response-adaptive designs in a sequential estimating framework. Moreover, a study about operational characteristics of the MRRU model, as the analysis of accidental and selection bias, can be an interesting development to investigate the properties of this urn design.

Bibliography

[1] ALETTI, G., MAY, C. and SECCHI, P. (2007). On the distribution of the limit proportion for a two-color, randomly reinforced urn with equal reinforcement distributions. *Advances in Applied Probability*, 39, 690-707.

[2] ALETTI, G., MAY, C. and SECCHI, P. (2009). A Central Limit Theorem, and related results, for two-color randomly reinforced urn. *Advances in Applied Probability*, 41, 829-844.

[3] ALETTI, G., MAY, C. and SECCHI, P. (2012). A functional equation whose unknown is $P([0;1])$ valued. *Journal of Theoretical Probability*, 25, 4, 1207-1232.

[4] ALETTI, G., GHIGLIETTI, A. and PAGANONI, A.M. (2013). A modified randomly reinforced urn design. *Journal of Applied Probability*, 50, (2), 486-498.

[5] ATHREYA, K.B. and KARLIN, S. (1968). Embedding of Urn Schemes into Continuous Time Markov Branching Processes and Related Limit Theorems. *Annals of Mathematical Statistics*, Vol. 39, No. 6, 1801-1817.

[6] ATHREYA, K.B. and NEY, P.E. (1972). Branching Processes. Springer, New York.

[7] ATHREYA, K.B. and VIDYASHANKAR A.N. (1995) Large deviation rates for branching processes. II. The multitype case. *The Annals of Applied Probability*, 5, (2), 566-576.

[8] BAI, Z. D., HU, F. and ZHANG, L. X. (2002). Gaussian approximation theorems for urn models and their applications. *Annals of Applied Probabability*, 12, 1149-1173.

[9] BAI, Z. D. and HU, F. (2005). Asymptotics in randomized urn models. *Annals of Applied Probabability*, 15, 914-940.

[10] BALDI ANTOGNINI, A. and GIANNERINI, S. (2007). Generalized Polya urn designs with null balance. *Journal of Applied Probability*, 44, 661-669.

[11] BÉLISLE, C. and MELFI, V. (2007). Independent after adaptive allocation. *Statist. Probab. Lett.*, 78, 3, 214-224.

[12] BEGGS, A.W. (2005). On the convergence of reinforcement learning. *Journal of Economic Theory*, 122, 1-36.

[13] BLACKWELL, D. and HODGES, J.L. (1957). Design for control of selection bias. *Annals of Mathematical Statistics*, 28, 449-460.

[14] CHENG, A. and VIDYASHANKAR A.N. (2006) Minimum Hellinger distance estimation for randomized play the winner design *Journal of statistical planning and inference*, 136, 6, 1875-1910.

[15] CHEUNG, Z. D., HU, F. and ZHANG, L. X. (2006). Asymptotic theorems of sequential estimation-adjusted urn models. *Annals of Applied Probabability*, 16, 340-369.

[16] CHEUNG, Z. D., CHAN, W. S., HU, F. and ZHANG, L. X. (2011). Immigrated Urn Models - theoretical properties and applications. *Annals of Statistics*, 39, (1), 643-671.

[17] DURHAM, S.C. and YU, K.F. (1990). Randomized play-the leader rules for sequential sampling from two populations. *Probability in Engineering and Information Science*, 26 (4), 355-367.

[18] DURHAM, S.C., FLOURNOY, N. and LI, W. (1996). Randomized Pólya urn designs. Proc. Biometric Section of the American Statistical Association 166-170. Amer. Statist. Assoc., Alexandria, VA.

[19] DURHAM, S.C., FLOURNOY, N. and LI, W. (1998). A sequential design for maximizing the probability of a response. *The Canadian Journal of Statistics*, 26 (3), 479-495.

[20] EFRON, B. (1971). Forcing a sequential experiment to be balanced. *Biometrika*, 58, 403-417.

[21] EISELE, J.R. (1994). The doubly adaptive biased coin design for sequential clinical trials. *Statistical Planning and Inference*, 38, 249-261.

[22] EISELE, J.R. and WOODROOFE, M.B. (1995). Central limit theorems for doubly adaptive biased coin design. *The Annals of Statistics*, 23, (1), 234-254.

[23] ETEMADI, N., SRIRAM, T.N. and VIDYASHANKAR, A.N. (1997). L^p Convergence of reciprocals of sample means with applications to sequential estimation in linear regression. *Journal of Statistical Planning and Inference*, 65, 1-15

[24] FLOURNOY, N. and MAY, C. (2009). Asymptotics in response-adaptive designs generated by a two-color, randomly reinforced urn. *Annals of Statistics*, 37, 1058-1078.

[25] FLOURNOY, N., MAY, C., MOLER, J.A. and PLO, F. (2009). On testing hypotheses in response-adaptive designs targeting the best treatment. In mODa 9 Advances in Model Oriented Design and Analysis, Contrib. Statist., pp. 81-88. Heidelberg: Physica-Verlag/Springer.

[26] FLOURNOY, N., MAY, C. and SECCHI, P. (2012). Asymptotically Optimal Response-Adaptive Designs for Allocating the Best Treatment: An Overview. *International Statistical Review*, 80, (2), 293-305

[27] GHIGLIETTI, A. and PAGANONI, A. M. (2012). Statistical properties of two-color randomly reinforced urn design targeting fixed allocations. Available as Mox-report 48/2012, Politecnico di Milano. In: *http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/48-2012.pdf*

[28] GHIGLIETTI, A. and PAGANONI, A. M. (2013). Randomly reinforced urn designs whose allocation proportions converge to arbitrary prespecified values. In mODa 10 Advances in Model Oriented Design and Analysis, Contrib. Statist., pp. 99-106. Heidelberg: Physica-Verlag/Springer.

[29] GHIGLIETTI, A. and PAGANONI, A. M. (2013). An urn procedure for efficiently detecting the parameters of an hypothesis test Available as Mox-report /2013, Politecnico di Milano. In: *http://mox.polimi.it/it/progetti/pubblicazioni/quaderni/60-2013.pdf*

[30] HILL, B.M., LANE, D. and SUDDERTH, W. (1980). A Strong Law for Some Generalized Urn Processes. *The Annals of probability*, 8, 214-226.

[31] HE, X., HU, F. and ZHANG, L. (2009). Efficient randomized-adaptive design. *The Annals of Statistics*, 37, (5A), 2543-2560

[32] HU, F. and ROSENBERGER, W. F. (2003). Optimality, variability, power: Evaluating responseadaptive randomization procedures for treatment comparisons. *Journal of American Statistical Society*, 98, 671-678.

[33] HU, F. and ROSENBERGER, W. F. (2006). The Theory of Response-Adaptive Randomization in Clinical Trials. Wiley, Hoboken, NJ.

[34] HU, F. and ZHANG, L. (2004). Asymptotic proprieties of doubly adaptive biased coin designs for multitreatment clinical trials. *The Annals of Statistics*, 32, 1, 268-301.

[35] HUANG, P. (2007). A numerical study of a randomized reinforced urn design for binary responses. Technical report, Univ. Missouri Columbia. A Masters' project available from N. Flournoy upon request.

[36] IVANOVA, A., ROSENBERGER, W.F., DURHAM S.D. and FLOURNOY, N. (2000). A birth and death urn for randomized clinical trials. *Sankhya B*, 62, 104-118.

[37] IVANOVA, A. and FLOURNOY, N. (2001). A birth and death urn for ternary outcomes: stochastic processes applied to urn models. *Advances in Statistical Theory* - A Volume in Honor of Theophilos Cacoulous. (Charalambides, C, Koutras, MV, Balakrishnan, N, eds.). Florida: CRC Press/Chapman and Hall.

[38] IVANOVA, A (2003). A play-the-winner-type urn design with reduced variability. *Metrika*, 58, 1-13

[39] JANSON, S.(2004). Functional limit theorems for multitype branching processes and generalized Pólya urns. *Stochastic Process. Appl.*, 110, 177-245

[40] LACHIN, J. M. and ROSENBERGER, W. F. (2002). Randomization in Clinical Trials. Wiley, New York.

[41] MAY, C., PAGANONI, A.M. and SECCHI, P. (2005). On a two-color generalized Polya urn. *Metron*, LXIII, (1), 115-134.

[42] MAY, C., PAGANONI, A.M. and SECCHI, P. (2007). Response-adaptive designs targeting the best treatment for clinical trials with continuous responses. In S. Co. 2007 Fifth Conference Complex Models and Computational Intensive Methods for Estimation and Prediction Book of Short Papers 326-331. Cleup, Padova.

[43] MELFI, F. and PAGE, C. (2000). Estimation after adaptive allocation. *J. Statist. Plann. Inference*, 87, 353-363.

[44] MELFI, F., PAGE, C. and GERALDES, M. (2001). An adaptive randomized design with application to estimation. *The Canadian Journal of Statistics*, 29, 107-116.

[45] MULIERE, P., PAGANONI, A.M. and SECCHI, P. (2006). A randomly reinforced urn. *Journal of Statistical Planning and Inference*, 136, 1853-1874.

[46] PAGANONI, A.M. and SECCHI, P. (2007). A numerical study for comparing two response-adaptive designs for continuous treatment effects. *Statistical Methods and Applications*, 16, 321-346.

[47] PALMER, C.R. and ROSENBERGER, W. F. (1999). Ethics and practice: alternative designs for phase III randomized clinical trials. *Controlled Clinical Trials*, 20, 172-86.

[48] R DEVELOPMENT CORE TEAM (2011). A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

[49] ROSENBERGER, W. F., STALLARD, N., IVANOVA, A., HARPER, C.N. and RICKS, M.L. (2001). Optimal adaptive design for binary response trials. *Biometrics*, 57, 3, 909-913.

[50] ROSENBERGER, W. F. (2002). Randomized urn models and sequential design. *Sequential Analysis*, 21(1&2), 1-28.

[51] ROSENBERGER, W. F. and ZHANG, L. (2006). Response-adaptive randomization for clinical trials with continuous responses. *Biometrics*, 62, 562-569.

[52] SMYTHE, R.T. (1996). Central limit theorems for urn models. *Stochastic Processes and their Application*, 65, 115-137

[53] WEI, L.J. (1978). An application of an urn model to the design of sequential controlled clinical trials *Journal of American Statistical Association*, 73, 559-563.