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PhD THESIS

"RESPONSE - ADAPTIVE CLINICAL TRIALS"

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To my father, my mother,

my sister, Teresa and

my brother, Antonio.

We are always

in the same stem.

And in this journey,

you all have

made the utmost

difference.

Abstract

The question we posed at the beginning of this thesis was whether, in the presence of a clinical superiority of one of two possible treatments, it was possible to find an appropriate statistical methodology that would allow us to reach this goal. We were thus led to explore many possibilities to carry out this analysis and randomly assign patients to the two treatments, as required by the particular nature of these experiments. Specifically, we made a close examination of the methods of randomization, especially appreciating the flexibility of the adaptive responses, and could see the strengths of urn models. We started with the study of the urn for excellence, Polya's urn. Next, we analyzed some extensions and generalizations, focusing especially on two kinds of urns with random reinforcement. We exposed the results obtained throughout simulations concerning the convergence of the proportion of the best treatment, which came from the comparison of the models studied. In the end, we showed how the urn model works in a real case, comparing two treatments with continuous response in one ICU trial on Melatonin. We'll see how the properties demonstrated in theory are confirmed in practice. The project ends by giving a hint of a new adaptive model that we have started to idealize in collaboration with the team of Prof. Parmigiani and Prof. Trippa of the "Biostatistics and Computational Biology" Department, Harvard T.H. Chan School of Public Health.

Contents

List of Figures

Introduction

In the mankind history, human people has been afflicted by disease and has attempted to plan treatments to cure or improve the suffering of the afflicted. So, it is desirable knowing which treatments work, which do not, and whether one treatment is better than another.

When a clinical researcher wants to evaluate the treatment efficacy or the safety of one therapy that is under investigation, he runs a clinical trial. There are many kinds of experiments, but in these years randomized controlled clinical trials (RCT) have become established as the method which investigators must use to assess new treatments. They are characterized by two key features:

1. At the same time, the new treatment is given to a group of patients (the *the treated group*) and the another treatment, often the one most widely used, is given to another group of patients (the *the control group*).

2. Patients are allocated to one group or another by *randomization*. This

mechanism can be thought of as deciding on the treatment to be given by tossing a coin.

Usually, the standard tool for patients allocation is the *equal randomization* that assures the balanced assignment. In this case the sample size is fixed in advanced and chosen on the basis of statistical power.

However, a condition of initial balance is not always the optimal solution. Indeed, there is an ethical concern to treat as many subjects as possible with the best treatment. Indeed, when the treatment is clearly lower / higher than the other one, it is not acceptable to allocate randomly to that treatment in less than 50 percent of cases. Moreover, the responses to treatments can differ greatly, in the sense that not all the patients will react in the same way to the treatment.

The study of these issues has stimulated the birth in the 70's of a new allocation policy to the treatments: the *Response Adaptive Randomization* (RAR). We dedicated the first chapter to them. First, we will focus on some considerations about the randomization process and then we will explain briefly the two main areas of study: the optimal and the sequential designs.

The second chapter is devoted to the presentation of a particular kind of adaptive design, the urn models. This method was introducted by Polya in 1923 to describe the spread of some diseases and very soon it became

the prototype for many statistical models in the clinical setting. Thanks to the luck of its application, the Polya urn has been subjected to many generalizations. In the models that we will examine, we will see that the drawing rule could be different. These rules will have the possibility to add the balls to the urn in the various stages of the experiment and will also define a specific law for certain balls to change the color. In addition, once one ball is randomly drawn, it can be assumed that any other ball is equally likely to draw. After giving a brief idea of reinforcement, we will present one of the models most used in clinical urn until now, the *Randomized Play the Winner Rule*.

In the third chapter, we focus on a specific urn model that included for the first time a distribution on the reinforcement. This model, the *Reinforced Urn Model*, was presented by Muliere et al. in 2006 and was born as an evolution of the *Randomized Play the Winner Rule*. The new idea based on this method is to vary the number of balls in the urn inserted according to the responses of the patient, creating change proportion much faster than using the constant reinforcement. We will presente the model, explaining in detail the variables that comes into play. Then we will focus on the asymptotic results and inference problems.

The fourth chapter is dedicated to a generalization of the RRU model introduced by Ghiglietti and Paganoni in 2013. We analyzed the theory and

the application of this evolution pattern, including some thresholds within the proportion of one type of treatment varies. At the end of the chapter, we will performe several simulations to compare different properties of the two models with the random reinforcement. In particular, we focus on the convergence of the proportion of the balls that represents the best treatment.

In the last chapther, we show some practical applications. We present the application on the dataset of one study about the use of melatonin in ICU patients. The dataset is from the study on the use of melatonin on ICU patients conducted in the "San Paolo Hospital - University Campus", Milan, by the Doctors Iapichino and Mistraletti. We have re-designed the study and resorted a way of allocation using the RRU models. We performed some simulations to see if the new model is able to achieve the two main objectives: determine the best treatment and minimize (maximize) the patient's number with the worst (best) treatment.

Finally, we conclude giving a hint of a new adaptive model that we have started to idealize in collaboration with the team of Prof. Parmigiani and Prof. Trippa of the "Biostatistics and Computational Biology" Department, Harvard T.H. Chan School of Public Health.

In the appendix we have been inserted the R code for the different simulations.

Chapter 1

Adaptive Clinical Trials

In the clinical trials the patients enter sequentially and then they are randomly allocate to one or more treatments. Typically, this study is divided in three parts: design, run, analysis. Now, we focus on the first aspect and we attempt to change the randomization rule during the allocation process.

1.1 Randomization Process

The *randomization* has many properties and its huge use in the clinical context is justified by the fact that it promotes the comparability among the study groups and it provides a probabilistic basis for the inference.

On the other hand, the use of randomization in medicine has raised up many ethical discussions. Many scientists agree upon the fact that it is

ethical to use the randomization in a state of pure equilibrium, where the patient has supply to their consent to be investigated and is fully informed about the potential risks and benefits of treatments.

Moreover we need to consider the delicate balance between *individual* and *collective* ethics. The first one regards as optimal the individual health, the second one has as main goal the public health. Some researchers argue that this balance occurs only in stage I and stage II studies. In general the question is controversial, but nowadays the randomization was accepted as a good standard.

The second importat issue when one researcher runs the clinical trial is about the *sample size*. Large sample size gives more information and ensures a good level of statistical power, but it requires also higher costs. So, in this case, we have to respond to statistical and economic needs at the same time.

Let us consider a clinical trial with n patients and k possible treatments.

Definition 1.1. A random sequence is a matrix (Kxn)

$$\mathbf{T} = (T_1...T_n)'$$

where $\mathbf{T}_i = \mathbf{e}_j \ j = 1, ..., K$ and $i = 1, ..., n$ with $\mathbf{e}_j$ the identity vector.

In general, we are interested in the properties of the random sequence and, in particular, in the asympotic properties of the *allocation proportion*.

Definition 1.2. Let be n patients and k treatments. The allocation proportion will be

$$\frac{\mathbf{N}(n)}{n}$$

where the matrix $\mathbf{N}(n) = (N_1(n), ..., N_k(n))$ e $N_j(n) = \Sigma_{i=1}^{n} T_{ij}$

And necessary it has to be

$$||\mathbf{N}(n)|| = \sum_{j=1}^{K} N_j(n) = n$$

where $||\mathbf{N}(n)||$ is the *norm* of N.

Now, let us consider a *response variables* matrix

$$\mathbf{X} = (\mathbf{X}_1, ..., \mathbf{X}_n)$$

with

$$\mathbf{X}_i = (X_{i1}, ..., X_{iK})$$

where $\mathbf{X}_i$ is the observed responses sequence when the *i-th* patient is independent assigned to the treatment. We will consider only the models for $\mathbf{X}_i$ conditionally to T_i.

Let us indicate

$$\Im_n = \sigma\{\mathbf{T}_1, ..., \mathbf{T}_n\}$$

the sigma - algebra generated by the first n treatment assigned;

$$\mathcal{X}_n = \sigma\{\mathbf{X}_1, ..., \mathbf{X}_n\}$$

the sigma - algebra generated by the first n responses;

$$Z_n = \sigma\{\mathbf{Z}_1, ..., \mathbf{Z}_n\}$$

the sigma - algebra generated by the first n covariates.

Definition 1.3. Let

$$\mathcal{F}_n = \Im_n \otimes \mathcal{X}_n \otimes Z_{n+1}$$

be one random procedure defined by

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1})$$

where ϕ_n is $\mathcal{F}_n$ measurable.

We indicate ϕ_n the conditional probability of the treatments $(1, 2, ..., K)$ for the *n-th* patient conditionally to the first $(n-1)$ responses to the treatments and covariates.

Following this idea, we detect five different kinds of randomization

Complete Randomization when

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1}) = E(\mathbf{T}_n)$$

Restricted Randomization when

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1}) = E(\mathbf{T}_n|\Im_{n-1})$$

Response Adaptive Randomization when

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1}) = E(\mathbf{T}_n|\Im_{n-1}, \mathcal{X}_{n-1})$$

Covariate Adaptive Randomization when

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1}) = E(\mathbf{T}_n|\Im_{n-1}, Z_n)$$

Adjusted-Covariate Response Adaptive Randomization when

$$\phi_n = E(\mathbf{T}_n|\mathcal{F}_{n-1}) = E(\mathbf{T}_n|\Im_{n-1}, \mathcal{X}_{n-1}, Z_n)\,.$$

1.2 Response Adaptive Randomization

In this work we focus on one of the randomization processes above presented, the *Response Adaptive Randomization - RAR*. This method uses the information gathered during the trial to sequentially change the allocation probability to one treatment.

The main reason for our choice is the ethical concern. Indeed, using this method we try to simultaneously meet both an individual ethical component, providing for the individual patient the best care possible, and a collective ethical one, providing for the population suffering from a disease sufficient proof of a drug.

The *RAR* strength is the fact of being more flexible to the changes that the researcher might meet during an experiment and to be able to absorb the information even modifying the initial design for scientific needs. The reasons that led us to study this strategy are different. First, the adaptive models

exploit the information available at present and to the past, permitting the reconstruction of a trend at each instant and, therefore, understanding the evolution of the entire process. So, we will have a combination of past and present data. We can work with continous and binary data. Our main objectives are two: determine the best treatment and maximize the number of patients in the experiment that receives the best treatment.

1.2.1 The Optimal Designs

The *RAR* is part of a particular kind of methodology: the *Optimal Design*. The main purpose of these designs is to allocate the patients in a optimal manner, in the sense that they meet certain properties. The principal idea is finding the experiment that minimize the loss of information. The *Optimal Designs* contain a wide range of models. In the clinical context the most commonly used are the D - *Optimal* ones, where D means the determinant, as this method minimizes the determinant of the variance/covariance matrix of the estimates of parameters. These strategies aim to maximize the information matrix $D = |X'X|$. The principal objectives of these designs are obtaining precise estimates and assigning as many patients as possible to the treatment that it is proving to do the best. The idea is to identify the best treatment and increase the probability that this is could be chosen. The

main components of the adaptive processes are: the identification of variables assessed at regular intervals during the treatment, the development of alternative treatment options and modifications, the specification of the algorithms that link the changes on the variables to the treatment modification, the inclusion of the patients preferences.

The most important problem in this context is to achieve the *optimal allocation*, as mentioned before. We start from a homogeneous population in which the responses of patients assigned to the same treatment have the same probability distribution. We suppose to have K treatments and the sample size equal to $n = (n_1, ..., n_K)$ such that $n1' = n$ and the probability distributions of the responses depend on the parameter $\theta \in \Theta$. Then, we have a constrained optimization problem which include the sample size $\omega(\theta)n'$, where $\omega(\theta) = (\omega_1(\theta), ..., \omega_K(\theta))$ are the possible positive weights probability and $\eta(\eta, \theta)$ is the sample variance. So, our optimization problem is given by

$$\min_{n_1,...,n_K} \omega(\theta)n'$$

$$\text{sub}\, \eta(\eta, \theta) = C$$

where C is a constant value. Now, let us consider two competitive treatments, called R and G, with binary responses. In particular, we know that p_R is the success probability to the treatment R and p_G is the success probability to

the treatment G, with $q_R = 1 - p_R$ and $q_G = 1 - p_G$. We suppose to have one fixed allocation n_R for R and n_G for G, with $n_R + n_G = n$ and suppose that we want to measure the difference between the two treatments observing the probability allocation of each of them. We run, then, a bilateral hypothesis test where we compare the null hypothesis that the difference between the two treatments is statistically insignificant. That is

$$H_0 : p_R - p_G = 0$$

versus

$$H_1 : p_R - p_G \neq 0$$

The Wald test gives us

$$Z = \frac{\hat{p}_R - \hat{p}_G}{\sqrt{\frac{\hat{p}_R \hat{q}_R}{n_R} + \frac{\hat{p}_G \hat{q}_G}{n_G}}}$$

where $\hat{p}_R, \hat{p}_G, \hat{q}_R, \hat{q}_G$ are the estimators. Our problem is about the sample size needed to observe a significant difference between the two treatments. One solution can be fixing the test variance of the alternative hypothesis and looking at the allocation $n = (n_R, n_G)$ which minimizes the total sample size. To simplify, we can set $\omega_1(\theta) = \omega_2(\theta) = 1$ and the unknown parameter $\theta = (p_R, p_G)$. The test for the variance becomes

$$\eta(\eta, \theta) = \frac{p_R q_R}{n_R} + \frac{p_G q_G}{n_G}$$

Knowing that $\eta(\eta, \theta) = C$ and substituting $\rho(\theta) = \frac{n_R}{n}$, we have

$$\frac{p_R q_R}{\rho n} + \frac{p_G q_G}{(1-\rho)n} = C$$

and solving for n

$$n = \frac{p_R q_R}{\rho C} + \frac{p_G q_G}{(1-\rho)C}.$$

Now, minimizing respect to ρ, we obtain

$$-\frac{p_R q_R}{\rho^2} + \frac{p_G q_G}{(1-\rho)^2} = 0$$

and then

$$\rho = \frac{\sqrt{p_R q_R}}{\sqrt{p_R q_R} + \sqrt{p_G q_G}}$$

This is the *Neyman allocation*, as in the balanced design trial. In this case, we can take advantage from the balanced trial in which the power of the test is maximized. According to Rosenberger and Lachin (2005), the power of the test is maximized when the equal allocation produces the response variables to the treatment with same variance. When the variance of the response variables is different, the power of the test should be maximized with the allocation of patients to the treatment with higher variance. The weak point of this procedure is when $p_R + p_G > 1$ the Neyman allocation directs a greater number of patients to lower treatment. If we set $\omega_1(\theta) = q_R$, $\omega_2(\theta) = q_G$ we

have the *RSIHR* allocation (Rosenberger 2010)

$$\rho = \frac{\sqrt{p_R}}{\sqrt{p_R} + \sqrt{p_G}}$$

As we can see, the optimal allocation ρ_θ depends on unknown parameters. We can overcome the problem by replacing the data parameters, using the methodology of the sequential design.

In general, when we run the response adaptive designs we have to consider the correlation between the assigned treatments that can increase the variability and adversely affect the power of the test. Shortly, we have to face the main problem of minimizing worst treatments and avoiding wasting power. For Rosenberger and Hu (2003), this can happen imposing the normality assumption on the allocation proportions to the treatments. Infact, in this case tha best allocation is the Neyman allocation.

1.2.2 The Sequential Designs

As we exposed before, the *RAR* procedures include a dynamic process that assigns one patient to a given treatment following the probability that is function of the respenses to the treatment and, consequently, will change during the trial. The alternative way to the *Optimal Designs* to randomize sequentially patients considering their responses, and then implement the randomization of adaptive responses, it is a family of procedures based on

sequential estimation.

The first procedure was introducted by Eisele (1994) and it is called the *doubly adaptive coin design.* This design has inspired the research of many authors and, thanks to the changes proposed by Hu and Zhang (2004), it gave birth to one great part of the family of the procedures of adaptive responses. This family includes all the procedures that have goals of allocations based on unknown parameters of the model answers and that since the data increase, sequentially updated estimates of these parameters.

Let us consider a generic clinical study with K possible treatments and let us suppose that the patients are sequentially randomized and we can immediately observe the responses to these treatments. When we randomized the *i-th* patient and observed his response, the *i + 1-th* patient is allocated to the k treatment with probability $\{\phi_{i+1,k}\}$, with $k = 1, ..., K$.

Let $T_i = (T_{i1}, ..., T_{iK})$ be the vector that represents the outcome of the *i-th* assignment, X_i the response of the *i-th* patient and N_i the allocation after the *i-th* patient. Now, let us imagine that the proportion allocation of the patients required, assigned to each treatment, is a function of some unknown parameter of the answer X. A major purpose of this allocation scheme is to get that the proportion allocation of the patients tents asymptotically to a predetermined target allocation, considered optimal, the value of which is a function of unknown parameters of the distribution of responses. Mathe-

matically, we want to have

$$\frac{N_n}{n} \longrightarrow \upsilon = \rho(\Theta)$$

for $n \to \infty$ where $\rho(z) = (\rho_1(z), ..., \rho_k(z)) : R^{d\times K} \to (0,1)^K$ is a vector of a function such that $\rho(z)' = 1$, where $\Theta = (\theta_1, ..., \theta_K)$ is a vector $R^{d\times K}$ and $\theta_k = (\theta_{k1}, ..., \theta_{kd})$ is a vector of unknown parameters of the distribution $X_{1,k}$ with $k = 1, ..., K$. Imposing Θ_0 as the first estimate of the sample size Θ. When m patients are assigned and their responses are observed, we use the sample mean to estimate θ_k, $k = 1, ..., K$

$$\hat{\theta}_{ik} = \frac{\Sigma_{j=1}^{i} T_{j,k} X_{j,k} + \theta_{0,k}}{N_{i,k} + 1}$$

and, consequently, $\hat{\Theta}_{i,k} = (\hat{\theta}_{i,1}, ..., \hat{\theta}_{i,K})$. The estimation of Θ_0 could be a hypothesized value of Θ or an estimation of Θ obtained from the previous trials.

Chapter 2

The Classical Urn Models

2.1 The idea of reinforcement

The urn models play an important role in studies adaptive response, primarily because they ensure the randomization of the allocations. The first use of the urn process in the clinical field is with the *Polya Urn*, exploited in the past to study the contagious disease. Over the years, generalizations and modifications of this particular method have affected different aspects of medical research, particularly for the clinical trials. The model introduced by Polya consists of an urn with two colors.

Let us consider an urn initially containing $r_0 \geq 0$ red balls and $g_0 \geq 0$ green balls. At stage $n = 1, 2, ...$ one ball is drawn from the urn and we assign to the patient the treatment represented by that ball. In this way, we

modify the urn composition following a particular rule.

The main assumption on the replacing process is that number of the balls $m > 0$ added to each stage is constant. And this is the first idea of the *reinforcement*. Following the definition

Definition 2.1. Muliere and Walker (2000).

Let $(X_1, X2, ...)$ be one sequence of random variables distributed as Bernoulli. The observations are reinforced if

$$P(X_2 = 1|X_1 = 1) \geq P(X_1 = 1)$$

and

$$P(X_2 = 0|X_1 = 0) \geq P(X_1 = 0)$$

and, for every $n \geq 1$ and $x_1, ..., x_n \in \{0, 1\}$

$$P(X_{n+2} = 1|X_1 = x_1, ..., X_n = x_n, X_{n+1} = 1) \geq P(X_{n+1} = 1|X_1 = x_1, ..., X_n = x_n)$$

This implies that

$$P(X_{n+2} = 0|X_1 = x_1, ..., X_n = x_n, X_{n+1} = 0) \geq P(X_{n+1} = 0|X_1 = x_1, ..., X_n = x_n)$$

and, for every $n \geq 1$ and $x_1, ..., x_n \in \{0, 1\}$.

Then we have a random variables sequence $\{X_n\}$ each of which will be 0 or 1 depending on red or white ball drawn at the stage n. Moreover, for every $n \geq 1$, we indicate R_n and G_n as the number of red and green balls,

respectively, in the urn at stage $n+1$. We are interested in the law of the process of $\{X_n\}$ and in the limit behavior of the quantities that are functions of R_n and G_n, as, for example, the red balls proportion in the urn before the $n+1$ stage defined as

$$Z_n = \frac{R_n}{R_n + G_n} \tag{2.1}$$

At the stage $n \geq 1$, a ball is randomly chosen from the urn and replaced together with other $m \geq 1$ balls of the same color.

Now, let us examine the dynamics of the processes $\{X_n\}$, $\{R_n\}$ and $\{G_n\}$. $\{X_1\}$ is distributed as

$$Bernoulli\left(\frac{r_0}{r_0 + g_0}\right) \tag{2.2}$$

For every $n \geq 1$, conditionally to $X_1, ..., X_n$,

$$X_{n+1} = \begin{cases} 0 \ with \ prob \ \frac{G_n}{R_n+G_n} \\ 1 \ with \ prob \ \frac{R_n}{R_n+G_n} \end{cases} \tag{2.3}$$

where

$$(R_{n+1}, G_{n+1}) = \begin{cases} (R_n, G_n + m) \ with \ prob \ \frac{G_n}{R_n+G_n} \\ (R_n + m, G_n) \ with \ prob \ \frac{R_n}{R_n+G_n} \end{cases} \tag{2.4}$$

One of the most important on the proportion of Z is expressed by the following

Theorem 2.1.1. *In a Polya Urn, when n goes to infinity, the red balls proportion*

$$Z_n = \frac{R_n}{R_n + G_n}$$

converges almost surely to a random limit.

Moreover, the limit distribution is a $Beta(\frac{r_0}{m}, \frac{g_0}{m})$.

2.2 Randomized Play-the-Winner Rule

The first application of a urn model in a clinical trial is due to Zelen (1969), who exposed his theory in a paper on a rule winning (*Play-the-Winner-Rule*) for controlled clinical trials. We want to run a clinical trial in which two treatments, labeled as 0 and 1, are compared and patients are accrued sequentially. The success or failure of the test result depends only on the assigned treatment. In this way, the success of a treatment generates another study on the same treatment with a new patient, while the failure generates a study on the competitive treatment. Although the Zelen rule is deterministic and, consequently, includes the typical biases of models not randomized, it is noteworthy because it represents the first known case of urn models used as sequential designs in clinical trials. His idea also inspired later Wei and Durham (1978), which altering the original rule, have created

a random strategy (*Randomized Play-the-Winner Rule - RPW*).

In the original expression, we have Y_0 balls of type A and B. Each time that a patient is ready to be randomized, a ball is drawn and put back into the urn. If we observe one A ball, it is assigned the corresponding treatment. If the patient response is a success, then other balls of the same type are added into the urn, while if it is register an unsuccessful, balls corresponding to the opposite treatment are added into the urn.

Let $N_{A,n}$ be the number of patients to the treatment A, after n patients are observed, and $N_{B,n} = n - N_{A,n}$. If $p_A = P\{Success|TreatmentA\}$, $p_B = P\{Success|TreatmentB\}$, $q_A = 1 - p_A$ and $q_B = 1 - p_B$, then the limit allocation $N_{A,n}/N_{B,n}$ is q_B/q_A and it is a meausure of the relative risk for $n \to \infty$.

It can be noted how this rule was not built on the basis of some optimal criterion and the allocation limit is not particularly attractive, as it tends to be allocated according to the relative risk. Being the RPW a completely randomized design, it benefits from the same characteristics of any randomized procedure. In particular, we do not expect a selection bias, but an accumulation one (Rosenberger, 1996), given by those subjects who become available to be recruited in the later stages of the study to benefit the impact of previous results, as the first subjects have a higher likelihood of being sent to treatment lower. For this reason it prefers a blind study, in which

subjects do not know their succession in the study. However, in the studies about emergency therapies, such as emergency surgery techniques, this type of distortion is irrelevant.

Actually, it does resort to the use of RPW very rarely, as in the past has raised strong criticism of the fact that in a clinical trial on ECMO therapy (Bartlett et al., 1985) had been assigned to the control group only one subject. Yao and Wei have tried to overcome this problem thinking to update the structure of the urn only after a certain period. Furthermore, RPW has been replaced by other adaptive strategies also in several survival studies (Hallstrom et al. 1996, Rosenberger et al. 1997, Sverlov et al. 2014). So, although in theory it would seem an ideal tool for clinical trials, in practice it is good to think of other instruments.

Chapter 3

Reinforced Urn Model

As mentioned in the previous chapter, the *RPW* procedure has aroused a lot of skepticism in practice. Among the many adaptive strategies in growth in the last decade, we have focused on urn models that include a random reinforcement. The idea is to vary the number of balls in the urn inserted according to the responses of the patient, thus creating a proportion Z is changed much faster than using the constant reinforcement. We are talking about the so-called *Randomly Reinforced Urn - (RRU)*. The *RRUs* were born as an evolution of the *Randomized Play the Winner Rule - (RPTW)* and have been introduced by Durham and Yu in 1990. Initially, it interested in experiments with binary outcomes (success / failure) and were used mainly to find the optimal dosage of a therapy. Subsequently, Muliere et al. (2006) and Beggs (2005), have extended the application of the *RRU* also experimented

with continuous responses.

3.1 The Model

Let us consider two treatments to be assessed, R and G. The subjects come sequentially in the study and allocated to two treatments randomly, according to a RRU design. The variables of interest are

- **Allocations** (X_i). The strategy used to assign subjects to one of two treatments is through a process urn, which is supposed to be independent of the answers.

- **Treatments Responses** (Y_i). Random vectors *i.i.d.* with discrete or continuous marginal distributions on $\Re$. It will be observed only one answer for every patient.

- **Reinforcement** $(U(Y_i))$. For each draw, after observing the response, a variable number of balls is replaced into the urn following a probability distribution, called transformation function.

- **Proportion** (Z). The proportion of red balls is the parameter of the Bernoulli r. v. of the color of the ball (allocation).

Now, we look at the description of the process. Let us consider an urn containing a non-negative number of red (r_0) and green (g_0) balls, so that

a red ball represents the treatment R and a green one the treatment G. We impose the first condition

$$R_0 = r_0 \quad and \quad G_0 = g_0 \tag{3.1}$$

from which we derive

$$D_0 = R_0 + G_0 \quad and \quad Z_0 = R_0/D_0 \tag{3.2}$$

where D_0 is the urn composition at time $n = 0$ and Z_0 is the proportion of red balls at same time.

Let us imagine that at time $n = 1$ one ball is drawn from urn and it is observed the color. The color of the ball will be an independent random variable of the answers equal to 1 if a red ball is drawn, equal to 0 if it is a green ball, then it is a *Bernoulli* random variable with parameter equal to the proportion of red balls, that is $Bernoulli(Z_0)$ distribution denoted by X_1.

Regarding the reinforcement distribution, we have to focus on the responses: if it is drawn a red ball, then it will be replaced with a random number of the balls of the same color, depending on the previous responses. Let $M_1 \in \mu$ and $N_1 \in \nu$ be two independent r. v. representing the function of the response variable on the ball drawn, and let suppose that M_1, N_1 and X_1 are independent. Subsequently, the ball drawn will be replaced into the

urn with

$$X_1 M_1 + (1 - X_1) N_1$$

balls of the same color. M_1 and N_1 are the functions of the responses corresponding respectively to the red and green balls, also called *transformation functions*, because they capture the effect of responses and turn it into random reinforcement. The reinforcement, for example, could be linked to the survival functions: the greater the survival, the greater the reinforcement, and then the number of balls added in the urn. This implies that, if we drawn a red ball, the urn will be reinforced by the r. v. M_1, belonging to μ, instead, if it is extracted a green ball, the urn will be reinforced by the r. v. N_1, belonging to ν. Generally, M_1 and N_1 are represented as

$$U(Y_i(n+1))$$

where U is a monotonic function, which could be equal to an identity function when the distributions of the responses have non-negative limited support. The new composition of the urn will be equal to

$$R_1 = R_0 + X_1 M_1$$

$$G_1 = G_0 + (1 - X_1) N_1$$

$$D_1 = R_1 + G_1$$

$$Z_1 = R_1 / D_1$$

The process is iterated following the same rule. Each draw will be assigned the patient to the treatment following the allocation strategy given by

$$X_{n+1}U(Y_R(n+1)) + (1 - X_{n+1})U(Y_G(n+1)) \tag{3.3}$$

where X_{n+1} is a Bernoulli r. v. with parameter

$$Z_n = \frac{R_n}{R_n + G_n}$$

and $U(Y_R(n+1) = M_{n+1}$ and $U(Y_G(n+1) = N_{n+1}$. The responses will be

$$Y(n) = X_n Y_R(n) + (1 - X_{n+1})Y_G(n)$$

At the stage $n+1$ we will have a sigma-algebra $\Im$ generated by $X_1, ..., X_n$, $M_1, ..., M_n$ and $N_1, ..., N_n$. The process will generate the following variables

$$R_{n+1} = R_n + X_{n+1}M_{n+1}$$

$$G_{n+1} = G_n + (1 - X_{n+1})N_{n+1}$$

$$D_{n+1} = R_{n+1} + G_{n+1}$$

$$Z_{n+1} = R_{n+1}/D_{n+1}$$

So, we have one finite sequence $X = (X_n : n \geqslant 1)$ of Bernoulli r. v., where X_n is the color drawn at *n-th* time or, equally, the *n-th* allocation and the process $(Z, D) = ((Z_n, D_n), n = 0, 1, 2, ...)$, where D_n is the total number of the balls in the urn at time n and $Z = (Z_n : n \geqslant 0)$ the sequence of r. v.

in $[0, 1]$ representing the proportion of red balls present in the urn at each step. The total number of the subjects will be

$$N_R(n) = \sum_{i=1}^{n} X_i$$

and

$$N_G(n) = \sum_{i=1}^{n} (1 - X_i)$$

with $N_R(n) + N_G(n) = n$. R_n and G_n are the cumulative responses observed and transformed by the utility function U, that is

$$\begin{cases} R_n = r_0 + \sum_{i=1}^{n} X_i U(Y_R(i)) \\ G_n = g_0 + \sum_{i=1}^{n} (1 - X_i) U(Y_G(i)) \end{cases} \tag{3.4}$$

3.2 Asymptotic Results

At this point we show the reasons why the use of this strategy is optimal for clinical studies. Recall that the main objective is to assign the highest number of patients to the treatment superiors, that is to say that the probability of being assigned to the best treatment converges to one, so that the proportion of the best treatment is asymptotically converged to one.

We distinguish now the average of the transformed response from non-transformed, i. e. with no reinforcement effect. We indicate the average reinforcements of the urn as

$$m_R = \int U(y) Y_R dy$$

$$m_G = \int U(y) Y_G dy$$

Li et al. (1996) proved the following very important result for the binary responses. If $m_R > m_G$ then

$$\lim_{n \to \infty} Z_n = 1$$

almost surely.

This result was then extended to the general case by Beggs (2005), Muliere et al. (2006a) and Aletti et al. (2009a). Consequently, the contrary is also true: the probability of assigning one patient to G treatment tends asymptotically to 0. Based on this property, we try to apply this case in a trial in which you want to demonstrate the effectiveness of R respect to G when the first treatment mean is bigger then the second one. Let us consider, then, the finite mean responses from non-transformed random reinforcement, i. e.

$$\mu_R = \int y Y_R dy$$

$$\mu_G = \int y Y_G dy$$

It has to choose an appropriate transformation function, in the sense that the following conditions must be simultaneously hold on

$$\mu_R > \mu_G \quad \text{if and only if} \quad m_R > m_G$$

$$\mu_R = \mu_G \quad \text{if and only if} \quad m_R = m_G$$

ensuring in this way the convergence to the best treatment with probability one when $n \to 1$.

To decide which transformation function is the most appropriate is a delicate point, because it influences the rate of convergence and the distribution of the allocations. Certainly, the best option should be one that takes into account a good tradeoff between ethics and accuracy of the analysis. We emphasize that, both in the case in which there is a superior treatment, and both in the case where they are equal, the proportion of subjects designed for the two treatments has the same limit of the composition of the urn

$$\lim_{n\to\infty} \frac{N_R(n)}{n} = Z_\infty \qquad \text{a. s.}$$

and

$$\lim_{n\to\infty} \frac{N_G(n)}{n} = 1 - Z_\infty \quad \text{a. s.}$$

Consequently, the proportion of subjects placed at the best treatment converges to one. Let us now concentrate on the more delicate case: *when the means responses are the same how it will be the behavior of the proportion Z?* Recalling the achievements Muliere et al. (2006*a*), we know that the process is a limited super or sub martigale. When the treatments give the same results, the sequence of the proportion

$$Z_n : n \geq 0 \quad \text{converges a. s. to the random limit} \quad Z_\infty \quad \text{in} \quad [0, 1].$$

The delicate point of this condition is that, until now, the distribution of Z_1 is unknown. According to the results obtained by Aletti et al. (2007, 2009a), we are only sure about that, under certain conditions, its distribution will continue. In general, the problem of equality of the responses is particularly important when you have to test effectiveness of treatments under the null hypothesis that these are equal. In fact, there are special cases studied in the literature in which the distribution of Z_1 is known.

Now, we can sum up all the considerations.

1. **The responses distributions are the same**. When $Y_R = Y_G$ then even distributions of reinforcement will be the same, $U(Y_R) = U(Y_G) = \gamma$. If responses to treatment are random variables constant, that is, γ is a grounding point, the RRU degenerates to the classic design of Polya (Eggenberger, Polya, 1923): an urn initially contains r red balls and g green balls and the reinforcement It is a constant m. In this case the distribution of Z_1 we know that is a $Beta(r/m, g/m)$.

2. **Random reinforcement different for success and failure**. If in a RRU design, we define the random reinforcement as a non-negative number m for the success and zero for the failure, the distribution of Z_1 is still a Beta. It is about a result which follows from Aletti et al. (2007) in which it is shown that the distribution of Z_∞ doesn't change

when $U(Y_R) \neq U(Y_G)$.

It should be noted that when the treatments are equal, the moments higher than the first of the reinforcements are different

$$\int U(y)^h Y_R dy \neq \int U(y)^h Y_G dy \quad \text{for} \quad h \geqslant 1$$

In this case, although the treatments are equal, the distributions of the reinforcements are different.

3.3 Inference

Let us consider the case where we want to estimate mean $\{\mu_R, \mu_G\}$ and variance $\{\sigma_R^2, \sigma_G^2\}$of the distributions of the responses. Following the method of May and Flournoy (2009), we define the estimators based on the observed responses of the n subjects with a random sample size $N_R(n)$ and $N_G(n)$

$$\hat{Y}_R(n) = \frac{\Sigma_{i=1}^n X_i Y_R(i)}{N_R(n)}$$

$$\hat{Y}_G(n) = \frac{\Sigma_{i=1}^n (1 - X_i) Y_G(i)}{N_G(n)}$$

$$\hat{\sigma}_R^2(n) = \frac{\Sigma_{i=1}^n X_i (Y_R(i) - \hat{Y}_R(n))^2}{N_R(n)}$$

$$\hat{\sigma}^2_G(n) = \frac{\Sigma_{i=1}^n (1 - X_i)(Y_G(i) - \hat{Y}_G(n))^2}{N_G(n)}.$$

In May et al. (2012) it proves the strict consistency of $\hat{Y}_R(n)$, $\hat{Y}_G(n)$, $\hat{\sigma}^2_R(n)$ and $\hat{\sigma}^2_G(n)$ for μ_R, μ_G, σ^2_R and σ^2_G respectively. Furthermore, the two estimators are asymptotically jointly distributed as *Normal*, despite of the randomness of $N_R(n)$ and $N_G(n)$, its dependence and the no convergence of $\frac{N_R(n)}{n}$ and $\frac{N_G(n)}{n}$ to a constant in $(0, 1)$. Now suppose you want to build a hypothesis tests on the means.

$$H_0 : \mu_R = \mu_G \qquad \text{versus} \qquad H_1 : \mu_R > \mu_G.$$

In the literature there are cases in which the asymptotic normality occurs only when the proportion of allocations converges to a fixed $\rho \in (0, 1)$ and cases applicable to the RRU in general, that is, when both the averages are the same and when both are different.

A work worthy of attention is the paper of Paganoni and Secchi (2007), in which it is presented a new guideline to compare an adaptive design with one no adaptive, i. e. one balanced study. At the end of the paper, you can find the regions useful for discriminating the use of either strategy. These considerations have been effectively used for the comparison of two studies adaptive (Bandyopadhyay and Biswas, 2001; Biswas and Basu, 2001).

Chapter 4

Modified Reinforced Urn Model

In recent years, the RRU models have become under study, in particular, has aroused our curiosity a change made in 2013 by Ghiglietti, Aletti and Paganoni. Significant steps have been made with regard to the convergence of the proportion of balls. One of the first results will be presented, in fact, the convergence theorem. The most important change is the introduction of two *thresholds* in which falls the allocation proportion. Practically, the previously values 0 and 1 are replaced with the thresholds. The main reason is that we want to avoid a concentration of one color of balls and, in particular, the extreme case where the composition of the urn asymptotically collapses towards a type of ball which, as we have seen before in the case of RPW,

turns out to be not attractive in practice of clinical studies.

4.1 The Model

Let us imagine that we are in a clinical trial in which you want to compare two treatments R and G. The subjects in the study sequentially enter and are allocated to the two treatments randomly, according to a *Reinforced Modified Random Urn - (MRRU)* design. The variables of interest are the same of the RRU model, but with a modification in the reinforcement process.

Let us consider an urn containing a non-negative number of red (r_0) and green (g_0) balls, so that a red ball represents the treatment R and a green one the treatment G. At time 0 the process will be

$$R_0 = r_0, \quad G_0 = g_0, \quad D_0 = R_0 + G_0, \quad Z_0 = R_0/D_0. \tag{4.1}$$

At time $n = 1$, one ball is drawn from the urn and its color is a $Bernoulli(Z_0)$

$$X_1 = \mathbf{1}_{[0,Z_0]}(U_1)$$

Let M_1 and N_1 be two independent random variables having distributions μ_R and μ_G with the support on $[\alpha, \beta]$, where $0 \leqslant \alpha \leqslant \beta < \infty$. These variables represent the responses to the treatments R and G, where (U_1) is a sequence of independent Uniform r. v. in $(0, 1)$. Moreover, we assume that X_1, M_1 and N_1 are independent. Now, we have in this situation a different

type of reinforcement, including two limit thresholds to avoid an excessive concentration of red balls. We could have 4 different scenarios. If we drawn one red ball, then it will be replaced into the urn with a random number $X_1 M_1$ of the same balls if $Z_0 < \eta$, with $\eta \in (0,1)$ a parameter decided a priori. Otherwise, the urn composition doesn't update. Instead, when we drawn one green ball, it will be replaced into the urn with a random number $(1 - X_1)N_1$ balls of the same color only if $Z_0 > \delta$, with $\delta < \eta \in (0,1)$; on the contrary nothing changes. The updating process then becomes

$$R_1 = R_0 + X_1 M_1 \mathbf{1}_{[Z_0 < \eta]},$$

$$G_1 = G_0 + (1 - X_1) N_1 \mathbf{1}_{[Z_0 > \delta]},$$

$$D_1 = R_1 + G_1,$$

$$Z_1 = R_1 / D_1.$$

As we can see, while in the previous case there was always an update of the urn, now sometimes we could find in deadlock situations in which there shall be no adjustment to the process. This happens when $\delta < Z_0 < \eta$. Now, we can iterate infinite the strategy and at time $n+1$, given the sigma-algebra $\mathcal{F}_n$ generated by $X_1, ..., X_n$, $M_1, ..., M_n$ and $N_1, ..., N_n$, the new process will be

$$R_{n+1} = R_n + X_{n+1} M_{n+1} \mathbf{1}_{[Z_n < \eta]},$$

$$G_{n+1} = G_n + (1 - X_{n+1})N_{n+1}\mathbf{1}_{[Z_n>\delta]},$$

$$D_{n+1} = R_{n+1} + G_{n+1},$$

$$Z_{n+1} = R_{n+1}/D_{n+1}.$$

We have, thus, generated an infinite succession of $X = (X_n, n = 1, 2, ...)$ Bernoulli r. v., with X_n equal to the color of the drawn ball at time n, and one 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 before the $n-th$ ball was drawn and Z_n is always the proportion of red balls. X will be the color process generated by the urn, and (Z, D) the process of its composition. We highlight that (Z, D) a Markov sequence respect to the filtration $\mathcal{F}_n$.

As mentioned above, also for the convergence it has been achieved an important result. Infact, we have the following

Theorem 4.1.1 (Aletti et al.)**.** *The sequence of the proportions* $Z = (Z_n, n = 1, 2, ...)$ *of the MRRU process converges almost surely to the following limit*

$$\lim_{n\to\infty} Z_n = \begin{cases} \eta \text{ if } \int_\alpha^\beta x\mu_R dx > \int_\alpha^\beta x\mu_G dx \\ \delta \text{ if } \int_\alpha^\beta x\mu_R dx < \int_\alpha^\beta x\mu_G dx \end{cases}$$

For the proof we refer to Aletti, Ghiglietti, Paganoni (2013).

The strength of this result is not only the proof of the convergence of proportion, but the fact that when this convergence exists we know what that

is, and its value is exactly equal to the two thresholds introduced in the construction of the urn process with random reinforcement.

The two thresholds, defined in advance at the beginning of the study and decided based on the experience of the researcher, are nothing more than a fixed target of allocation, introduced to avoid extreme cases where the proportion collapses to 1 or 0. Note that we are evaluating probability distributions with different means, then treatments with well-defined outcomes. A further advantage of the introduction of two thresholds is that the probability of allocation of patients to different treatments can be chosen by the researcher in order to ensure full control of the evolution of the urn. However, at this juncture nothing it is said on the speed of convergence, aspect that will be treated in the simulation, in which will be taken a higher number of urns to increase the convergence's speed.

As regards the case in which means are equal, that is the two treatments are perceived as similar, a result was achieved by the following

Lemma 4.1.2. *We assume that $m_R = m_G = m$. If $D_0 \geqslant 2\beta$, then*

$$E\left(\sup_n |A_n\right) \leqslant \frac{\beta}{D_0}$$

$$E\left(\langle M\rangle_\infty - \langle M\rangle_n | \mathcal{F}_n\right) \leqslant \frac{\beta}{D_0}, \qquad \forall n \geq 0.$$

Consequently, we have

Lemma 4.1.3. *We assume that* $m_R = m_G = m$. $D_0 \geqslant 2\beta$, *then*

$$P\left(\sup_n |Z_n - Z_0| \geq h\right) \leq \frac{\beta}{D_0}\left(\frac{4}{h^2} + \frac{2}{h}\right) \forall h > 0.$$

In general, when the means are equal, that is when the treatments have the same effects, we don't have the explicit form of the asymptotic distribution of proportion Z_n. The only important information that we know is that the proportion converges to a continuous distribution.

In some special cases, however, we can know what is the distribution of responses (Flournoy, May, Secchi, 2012). Saying that the distribution of the responses are equal is the same to say that the distribution of the reinforcement is equal. When the distribution of responses and reinforcements are equal to a discrete distribution, the responses to the treatment have a constant reinforcement, then the *RRU* degenerates to classical *Polya Urn*. In this case we already shown that Z_∞ follows a $Beta(r/m, g/m)$. We have the same result also for the *RRU* in the case of binary responses, where m is the random number of balls added when success happens and 0 when we have a failure (Aletti, 2007).

It should be noted that when the treatments are perceived equally, in the sense of having the same mean responses, the moments higher than the first of the reinforcements are different. This consideration may be of interest when the treatments are identical, but the distributions of the reinforcement

not. The conclusion we reach is that the total number of balls increases exponentially: this result depends on the reinforcements, then the balls that are adding to the urn, which are random in the sense that change based on the responses from patients. We have to underline the fact that the number of balls will never decrease because the ball drawn, in any color, it will always be reinserted into the urn, with or without reinforcement by using the upper and lower thresholds. The goodness of a treatment is identified with its expected value, or mean. The greater the mean of the responses, the better the treatment and the greater the reinforcement in terms of balls added to the urn, so as to reach at the end the convergence at the upper end.

4.2 Convergence Theorem: some simulations

Now let us see how to use in practice the convergence theorem presented before, based on the idea proposed by Aletti et al. (2011). An interesting way is to use it for finding the mean of the responses of one treatment in a two arms clinical trial. We imagine that you want to design a clinical trial in which we know only one treatment R and we want to figure out the mean effect on patients of the introduction of a new treatment G. In statistical terms, we want to know the mean of the distribution of the responses of patients to the new treatment. Knowing well the competitive treatment

allows us to make adjustments during the trial and change the mean of treatment R properly.

Let us consider K urns with the same unknown initial composition (r_0, g_0). We use a greater number of urns because we want to see faster the empirical convergence. As before, the red ball is associated to the known treatment R, the new treatment to the green G. We indicate with $Z^j = (Z_n^j)_{n \in N}$ the process of the proportion in the *j-th* urn, with $j \in \{1, 2, ..., K\}$. For every urn, the convergence theorem says us

$$\lim_{n \to \infty} Z_n = \begin{cases} \eta \text{ if } m_R > m_G \\ \\ \delta \text{ if } m_R < m_G \end{cases}$$

Now, we see that we can use the result of convergence for the *MRRU* model to estimate the mean m_G when this is unknown and it is instead known m_R. For this purpose, it will be sufficient to repeat several times the simulation with different values of m_R, at each step the simulation is calculated by the empirical cumulative function $\hat{F}$ and evaluated as the Wasserstein distance between it and the three sample functions $F_\delta(x) = 1_{x \geqslant \delta}$, $F_\eta(x) = 1_{x \geqslant \eta}$ and the cumulative function F_e of the asymptotic distribution that is obtained in the case of reinforcements with the same mean m_R. Given that we unknow the latter is not known except for some case particularly (when, for example , the reinforcements are constant we know that Z_∞ is a $Beta(r_0/m, g_0/m)$ we have empirically determined this function run an other

simulation. When the Wasserstein distance between the function and one of the empirical cumulative functions sample becomes less of a tolerance α fixed a priori, the simulation ends. In such case there will be one of the following situations:

- the sample function with the Wasserstein distance minimum is F_δ, then $m_R < m_G$. It will proceed with the experiment, and then will be performed another simulation in which the reinforcements of red balls will have the mean m_R greater than that used for this iteration;

- the sample function with the minimum Wasserstein distance is F_η, then $m_R > m_G$. It will be performed another simulation in which the reinforcements of red balls will have mean m_R lower than that used for this iteration;

- the sample function with the minimum Wasserstein distance is F_e, this happens when $m_R \backsim m_G$. Only in this case we can terminate the experiment, since we have found an estimate of m_G.

We performed two types of experiments using the first as a *normal* distribution reinforcements variance always equals equals 1, and the second constant reinforcement (classical Polya Urn). The next figures show the results produced in the two cases. In both situations they are taken $m_G = 17$ and $m_R = 30, 20, 15, 17.5$.

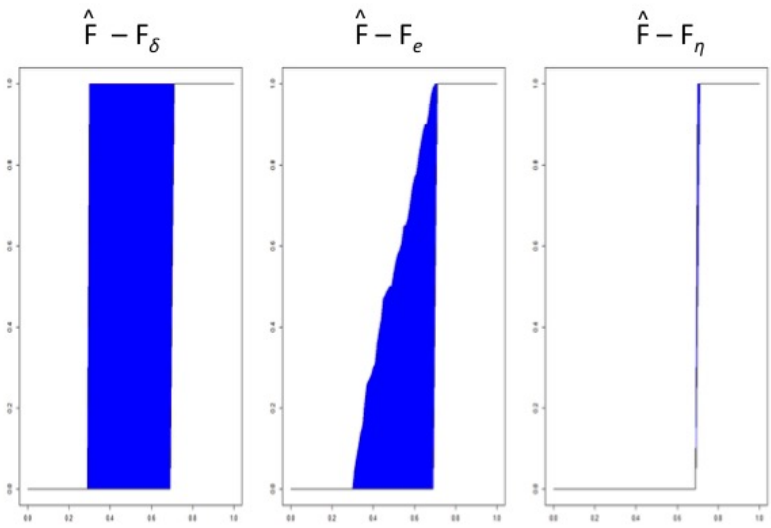

Figure 4.1: Normal Reinforcement, $m_R = 30$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

In both experiments, it is observed that for $m_R = 30, 20$ the function that realizes the minimum Wasserstein distance is F_η, in the case $m_R = 15$, the minimum is realized by F_δ, in the case $m_R = 17.5$ the minimum distance is obtained by F_e.

In conclusion we have seen that thanks to the *convergence theorem* we can calculate the unknown mean, regardless of the assumptions imposed on the reinforcements. The fact remains that, as anticipated above, in the case

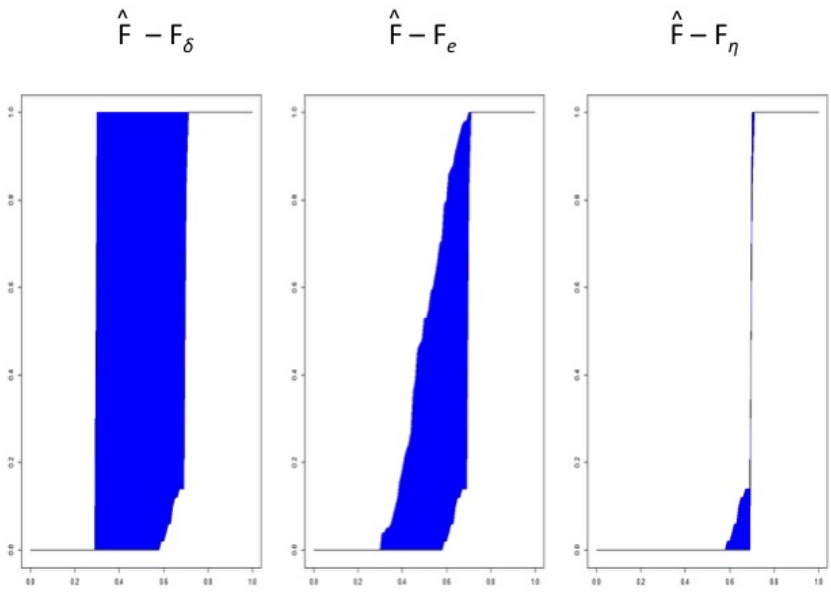

Figure 4.2: Normal Reinforcement, $m_R = 20$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

of reinforcements constants, and therefore the case of the Classical Polya Urn, the distribution of the proportion of the balls is known to be a Beta distribution, but this is not proved for $MRRU$ model.

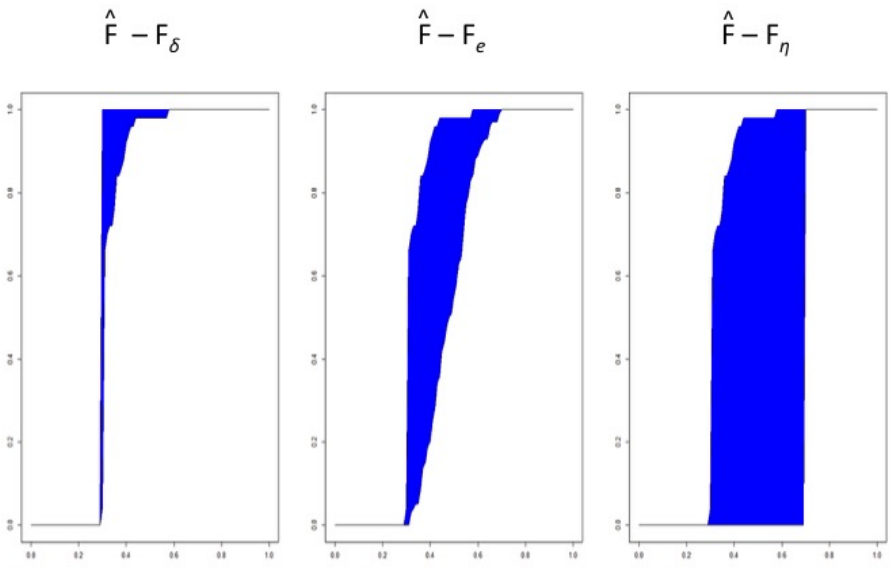

Figure 4.3: Normal Reinforcement, $m_R = 15$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

4.3 Hypothesis Tests

A very important aspect concerns the power of hypothesis testing and the determination of the sample size. Suppose that we run a clinical trial in which patients were assigned n_0 to two treatments R and G, with p_0 the proportion of patients assigned to R. We want to test the hypothesis

$$H_0 : m_R = m_G$$

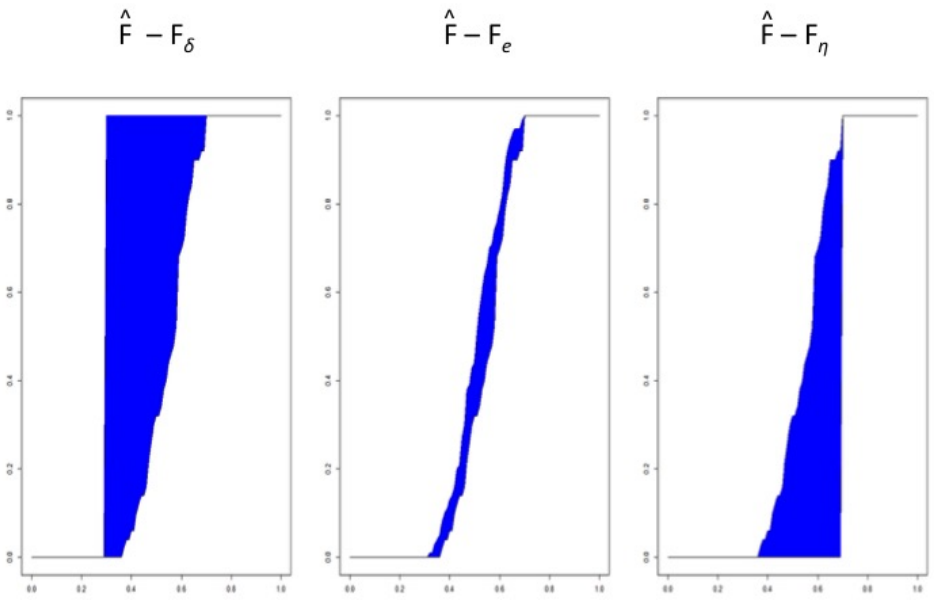

Figure 4.4: Normal Reinforcement, $m_R = 17.5$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

versus

$$H_1 : m_R \neq m_G$$

with significance level equal to α. From the theoretical results we know that the statistic

$$\zeta_0 = \frac{\bar{X}_R - \bar{X}_G - (m_R - m_G)}{\sqrt{\frac{\sigma_R^2}{N_R} + \frac{\sigma_G^2}{N_G}}},$$

where N_R and N_G are the patients assigned to treatment R and G, respec-

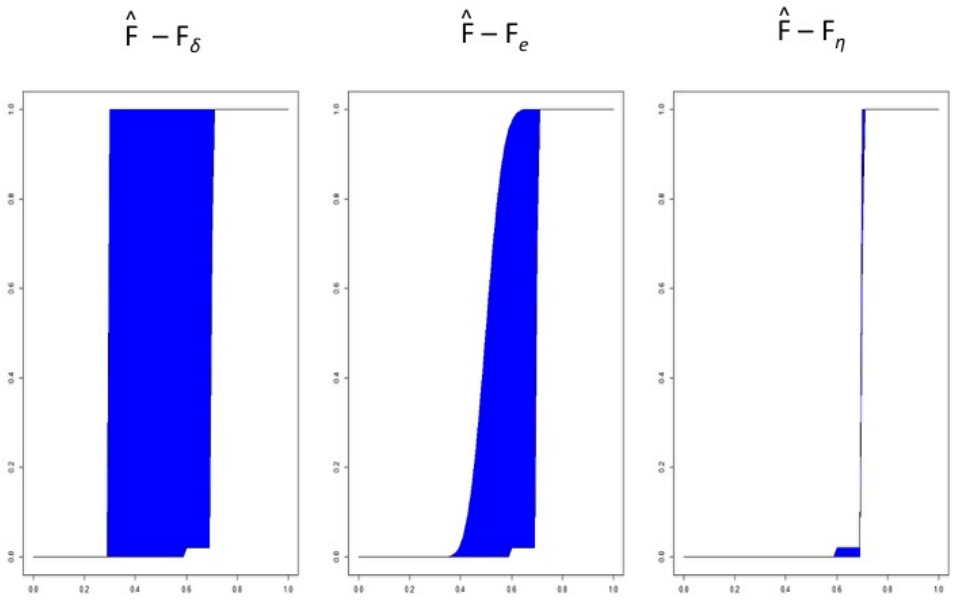

Figure 4.5: Constant Reinforcement, $m_R = 30$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

tively, and

$$\overline{X}_R = \frac{\Sigma_{i=0}^{n} X_i M_i}{N_R},$$

$$\overline{X}_G = \frac{\Sigma_{i=0}^{n} (1 - X_i) N_i}{N_G},$$

are distributed ad a standard Normal. Then, the critical region of level α is

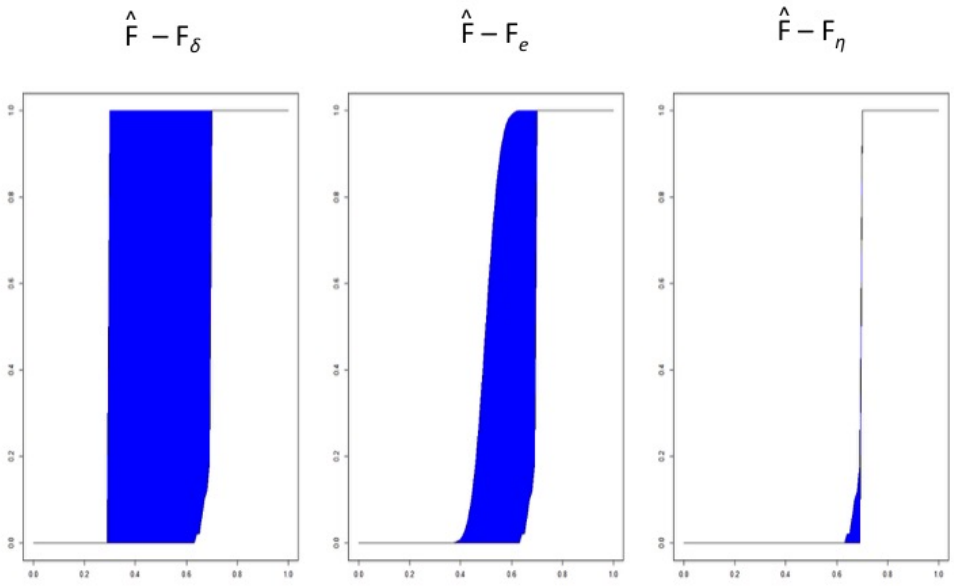

Figure 4.6: Constant Reinforcement, $m_R = 20$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

represented by

$$R_\alpha = \left\{ |\overline{X}_R - \overline{X}_G| > \sqrt{\frac{\sigma_R^2}{N_R} + \frac{\sigma_G^2}{N_G}} \cdot z_{\alpha/2} \right\}.$$

In general, one difference Δ_0 between two treatments is clinically relevant if it is greater than a fixed quantity. We denoted by $1-\beta_0$ the minimum power of the test we want to achieve at Δ_0. We we have fixed α, Δ_0, knowing p_0 and n_0, we can compute the unique value of β_0.

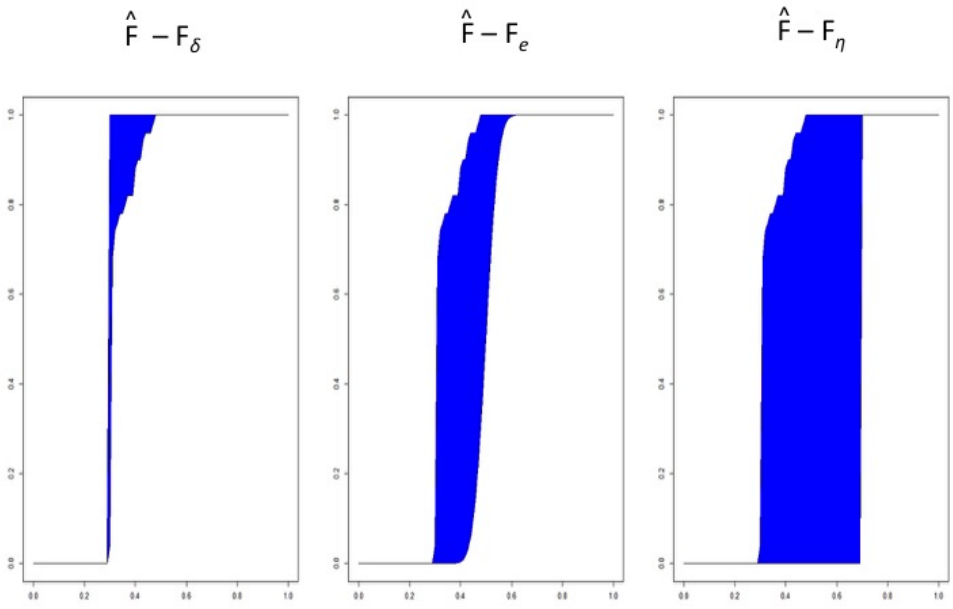

Figure 4.7: Constant Reinforcement, $m_R = 15$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

For example, we impose $\alpha = 0.05$, $\Delta_0 = 0.2$, $p_0 = 0.5$, $n_0 = 198$, then we have $1 - \beta_0 = 0.8$.

Now, we want to undestand how finding a new test (n, p) so that it is uniformly most powerful test (p_0, n_0) and that it assigns less patients to the worse treatment. One can verify that this happens when the pair (p, n) is located in one of these following three regions.

A REGION In this region the tests are uniformly most powerful test (p_0, n_0)

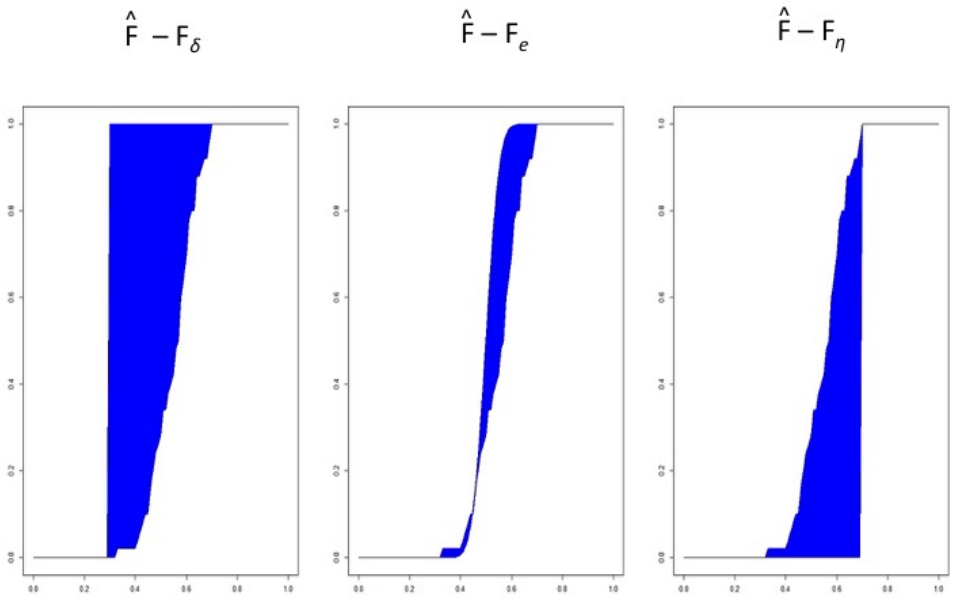

Figure 4.8: Constant Reinforcement, $m_R = 17.5$, $m_G = 17$, $\delta = 0.3$, $\eta = 0.7, r_0 = w_0 = 200$

and fewer patients assigned to treatment R

$$A = \left\{ (p, n) \in (0, 1) \times (0, +\infty) : n_\beta(p) < n < \frac{p_0 n_0}{p} \right\},$$

where $n_\beta(p)$ is defined as the following reasoning. Called $p_{opt} = \frac{\sigma_R}{\sigma_R + \sigma_G}$,

$$n_\beta(p) = \left(\frac{p_{opt}^2}{p} + \frac{(1 - p_{opt})^2}{(1 - p)} \right) \cdot \left(\frac{p_{opt}^2}{n_0 p} + \frac{(1 - p_{opt})^2}{n_0 (1 - p)} \right)^{-1}.$$

B REGION The tests in this region are uniformly most powerful of the

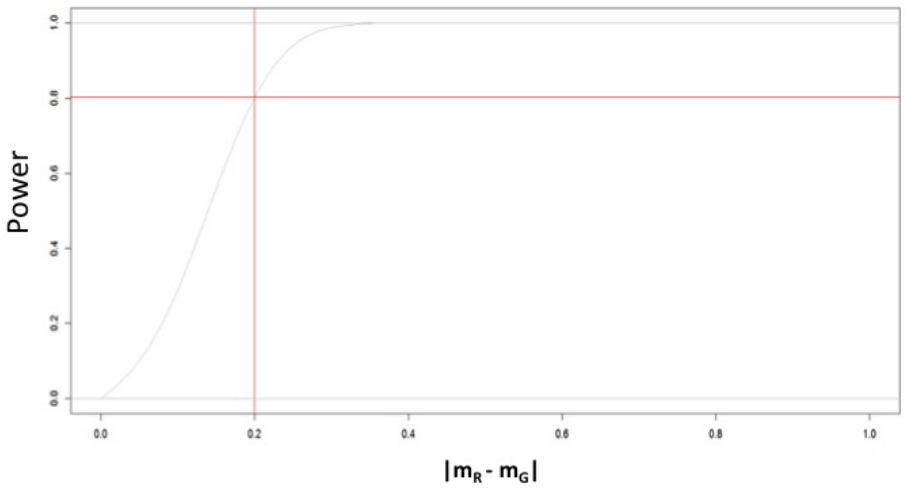

Figure 4.9: Power of the test of the mean difference when $\alpha = 0.05$, $\Delta_0 = 0.2$, $p_0 = 0.5$, $n_0 = 198$

test (p_0, n_0) and they assign fewer patients to either treatment

$$B = \left\{ (p,n) \in (0,1) \times (0,+\infty) : n > \max\left\{ \frac{p_0}{p}, \frac{1-p_0}{1-p} \right\} \cdot n_0 \right\} \quad (4.2)$$

C REGION The tests in this region are uniformly most powerful of the test and assign less patients to treatment G

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

It is clear that the allocation of patients to the two treatments should be

made so that, if $m_R < m_G$, $(p, n) \in A$, if instead $m_R < m_G$, then $(p, n) \in C$. In this way it can use an allocation method based on an $MRRU$ urn, with δ and η appropriately chosen.

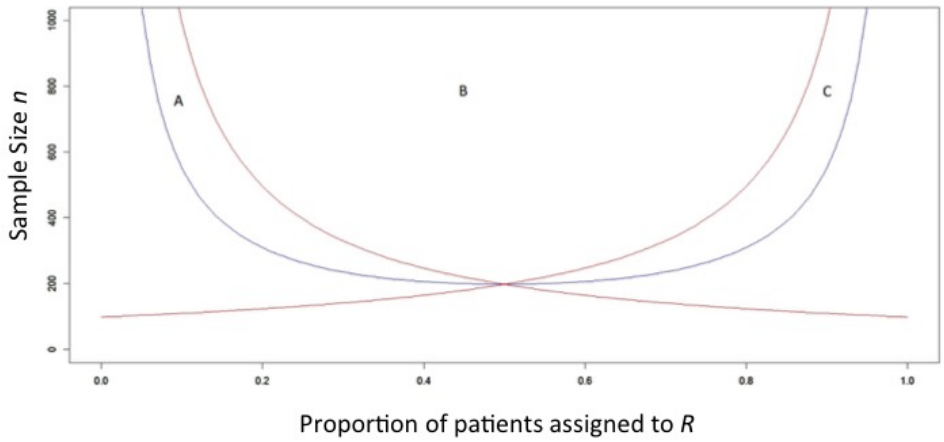

Figure 4.10: A, B, C regions when $n_0 = 198, p_0 = 0.5, \sigma_R = \sigma_G = 0.5$

Doing the test we find that when $n = 300$, $n_0 = 198$, $p_0 = 0.5$, then it has to be

$$\delta \in [0.2084512, 0.33] \qquad \eta \in [0.67, 0.7915488]$$

To verify empirically the properties of this test, we run $K = 200$ urn processes with intervals $[\delta_1, \eta_1] = [0.33, 0.67]$ and $[\delta_2, \eta_2] = [0.2084512, 0.7915488]$.

To do this we have run K urn processes and, using the properties exposed before, compute the *mean power* (the mean of all the powers obtained by all the K test when $\Delta = |m_R - m_G|$), the *empirical power* (the mean of the results of the K test computed assuming of assigning 0 when the hypothesis H_0 is accepted, 1 when the hypothesis H_1) and the times in which the power of each test was higher than the power of the test classic.

We run the simulation, assuming $K = 200$, $m_R = 1.25$, $m_G = 1$, and we see that for both intervals the "improved" power (number of times in which the power of the new test was superior to that of the reference test) is 1. Moreover, we register the following the results registered in the **table 4.1**.

Interval	Calculated Power	Empirical Power	Mean N_R	Mean N_G
$[\delta_1, \eta_1]$	0.9760361	0.9	127	122
$[\delta_2, \eta_2]$	0.9905799	0.91	157	143

Table 4.1: Different values of δ and η

4.4 RRU versus MRRU

At this point we are able to make some comparisons between the two methods proposed. First of all, we have carried out simulations to see the

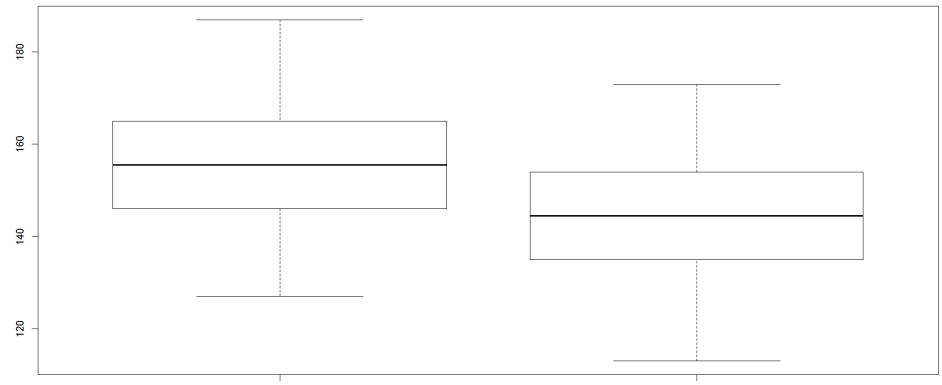

Figure 4.11: Patients assigned to the treatments R and G when $[\delta_1, \eta_1]$

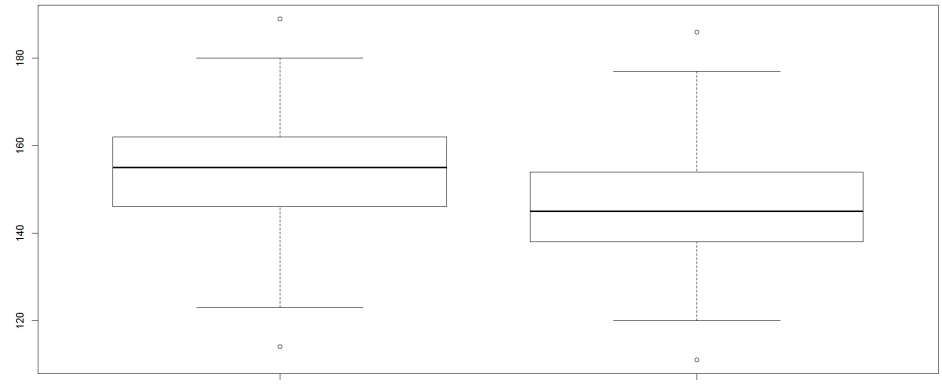

Figure 4.12: Patients assigned to the treatments R and G when $[\delta_2, \eta_2]$

different trend of the proportion of red balls depending on whether you are in the case where the thresholds are present or not. Initially we performed

simulations using three different distributions for the reinforcement: normal, exponential and constant reinforcements. With this choice, it was verified empirically that the convergence results seen previously for the two urn processes does not depend on the particular distribution of the reinforcements, but only by their mean. In all cases, it is taken as an initial composition of the urn $r_0 = 200, g_0 = 200$.

The figures **4.13**, **4.14** and **4.15** report the graphs in the case without thresholds, that is with $\delta = 0$ and $\eta = 1$, the numerical simulations for 10000 extractions with reinforcements following normal distribution.

In the figures **4.16**, **4.17** and **4.18**, we present the results obtained with inserting the thresholds, in particulare we impose $\delta = 0.3$ and $\eta = 0.7$.

As we can see in the figures above, consistent with the theoretical results, when we run the RRU model the sequence Z_n converges to 0 if $m_R < m_G$, to 1 if $m_R < m_G$, instead when we run the $MRRU$ model the sequence Z_n converges to δ if $m_R < m_G$, to η if $m_R < m_G$. When, instead of the means of reinforcements are equal, the result is ambiguous. To better assess what happens when the averages are equal, we have modified the functions used in the simulations presented before for K independent urns. In this case listed the histograms for the different distributions of the reinforcements. We show only the results for the RRU model, first with constant reinforcements (figures **4.19**, **4.20** and **4.21**), and after with normal reinforcement (figures

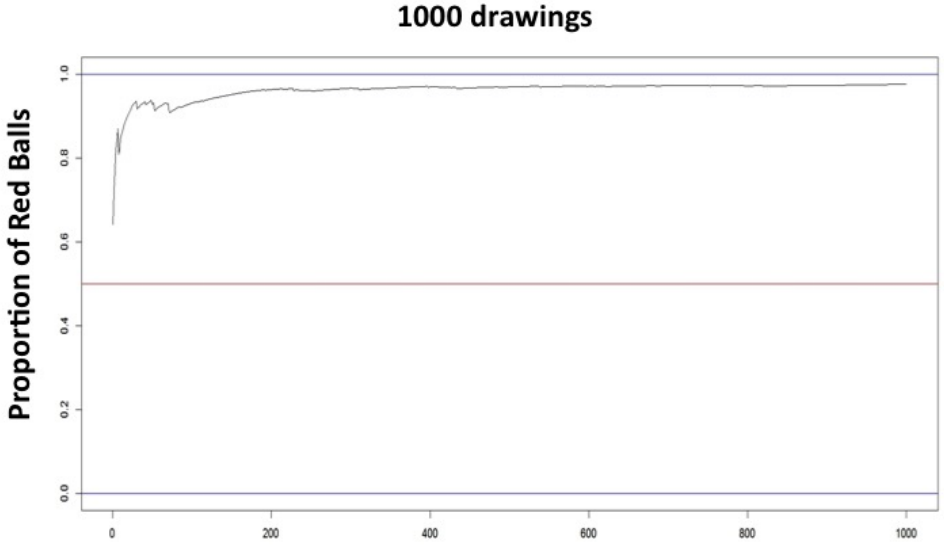

Figure 4.13: Normal Reinforcement with $m_R = 4$ and $m_G = 2$ for 10000 drawings

4.22, **4.23** and **4.24**).

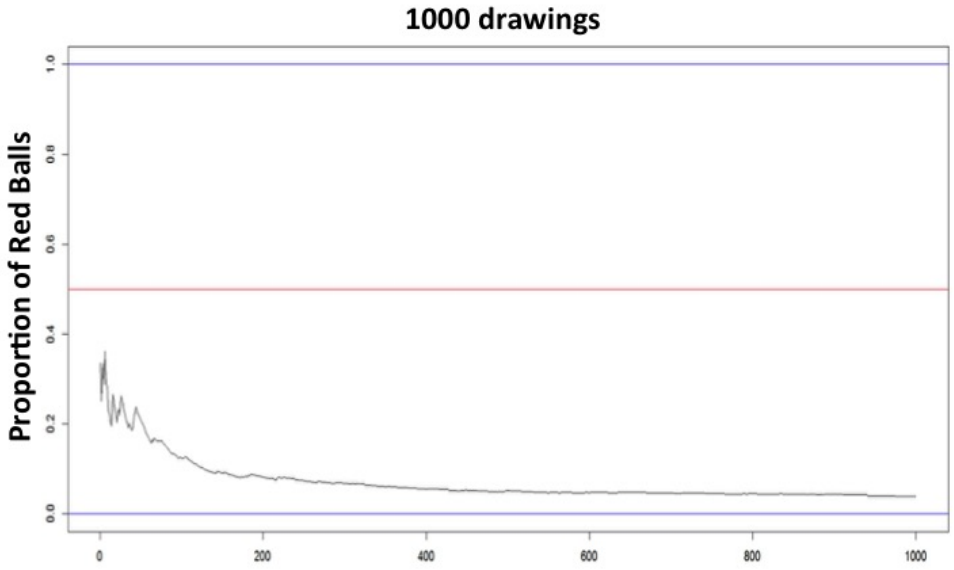

Figure 4.14: Normal Reinforcement with $m_R = 2$ and $m_G = 4$ for 10000 drawings

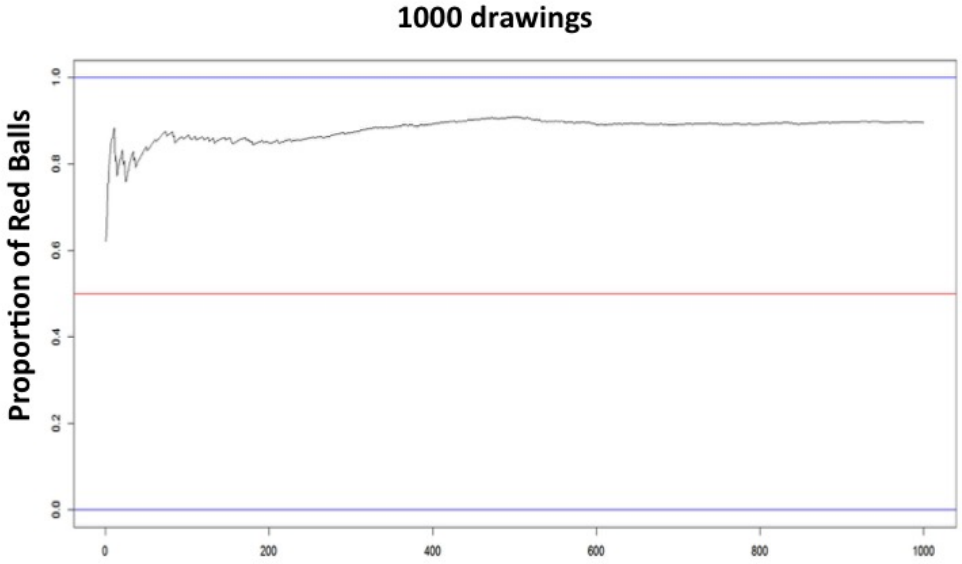

Figure 4.15: Normal Reinforcement with $m_R = m_G = 3$ for 10000 drawings

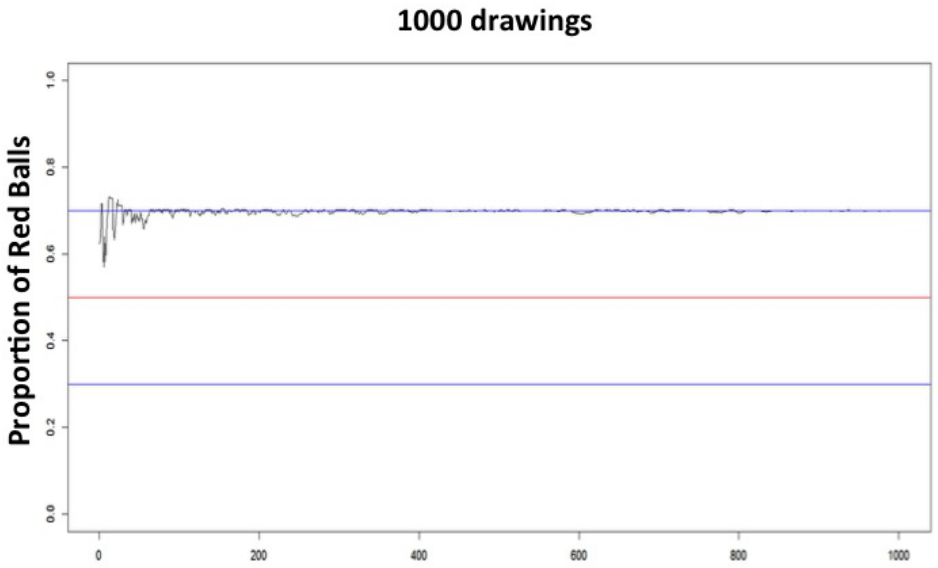

Figure 4.16: Normal Reinforcement with $m_R = 4$ and $m_G = 2$ for 10000 drawings, $\delta = 0.3$ and $\eta = 0.7$

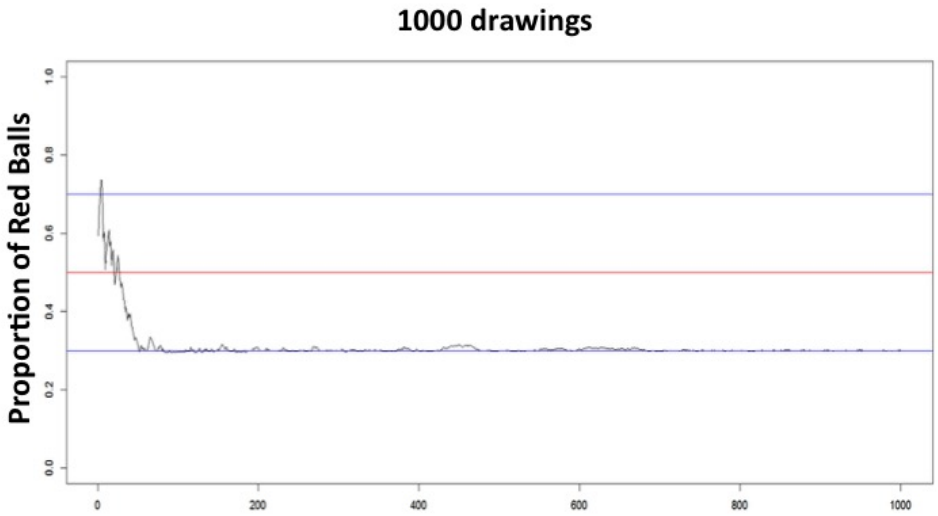

Figure 4.17: Normal Reinforcement with $m_R = 2$ and $m_G = 4$ for 10000 drawings, $\delta = 0.3$ and $\eta = 0.7$

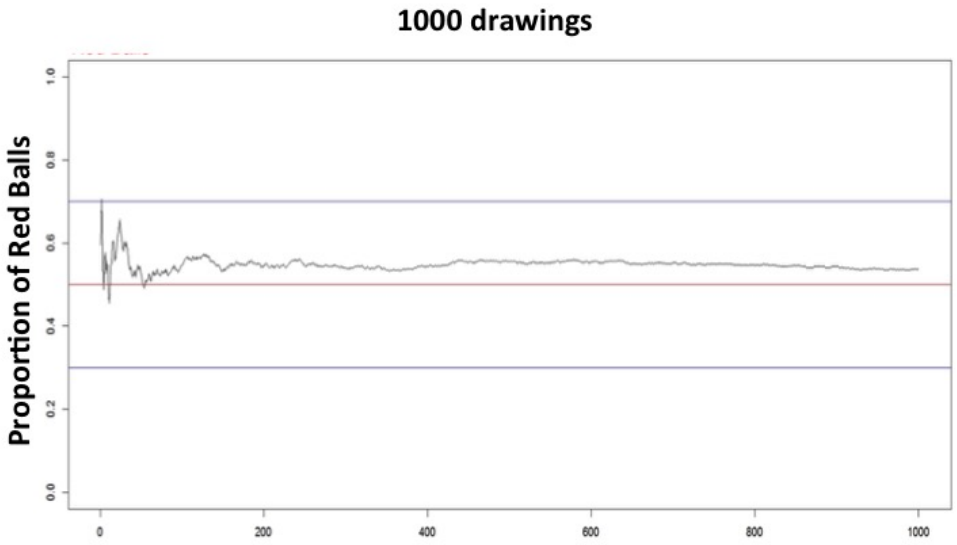

Figure 4.18: Normal Reinforcement with $m_R = m_G = 3$ for 10000 drawings, $\delta = 0.3$ and $\eta = 0.7$

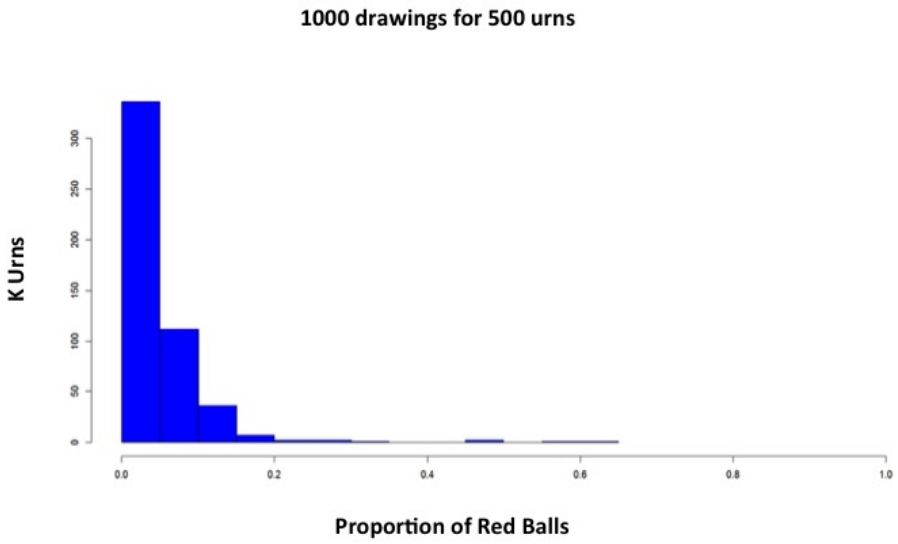

Figure 4.19: Constant Reinforcements, $m_R = 2$, $m_G = 4$, $r_0 = g_0 = 200$, 500 urns.

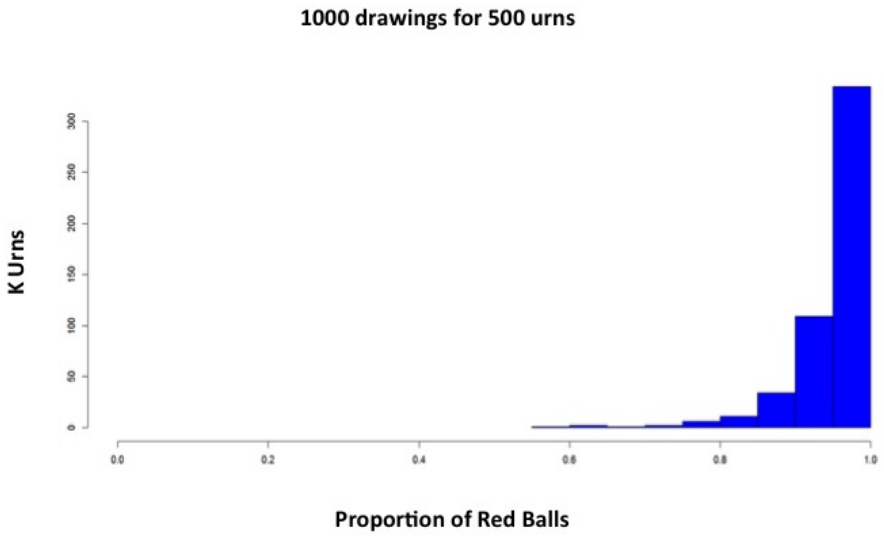

Figure 4.20: Constant Reinforcements, $m_R = 4$, $m_G = 2$, $r_0 = g_0 = 200$, 500 urns.

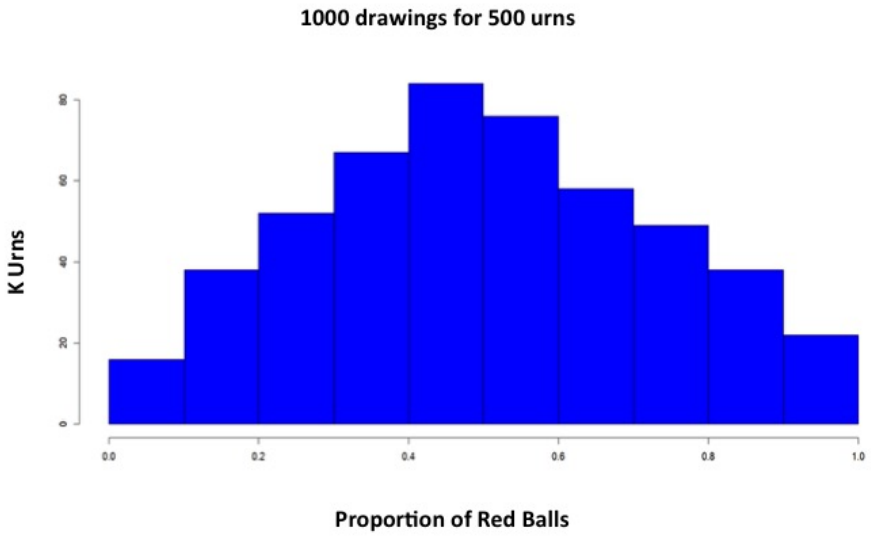

Figure 4.21: Constant Reinforcements, $m_R = 3$, $m_G = 3$, $r_0 = g_0 = 200$, 500 urns.

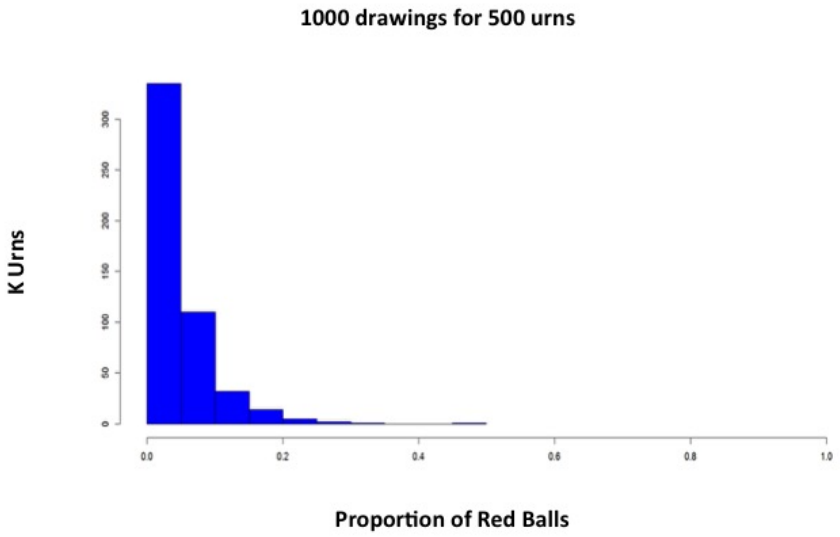

Figure 4.22: Normal Reinforcements, $m_R = 2$, $m_G = 4$, $r_0 = g_0 = 200$, 500 urns.

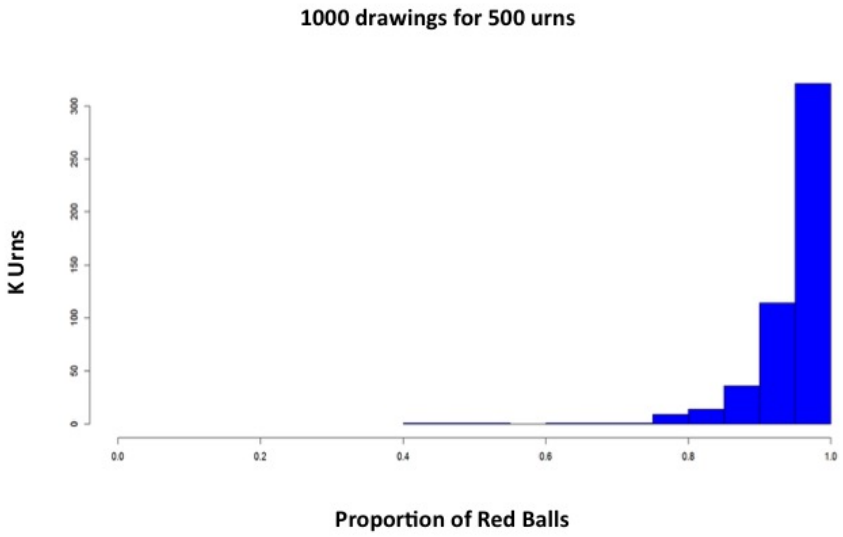

Figure 4.23: Normal Reinforcements, $m_R = 4$, $m_G = 2$, $r_0 = g_0 = 200$, 500 urns.

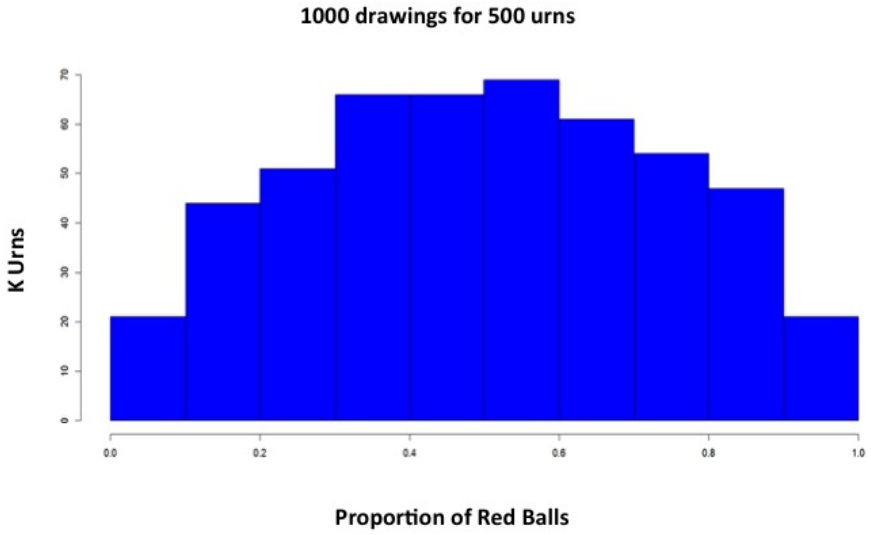

Figure 4.24: Normal Reinforcements, $m_R = 3$, $m_G = 3$, $r_0 = g_0 = 200$, 500 urns.

Chapter 5

Real Case: The Melatonin Study

In this chapter we are going to evaluate the models exposed before in the real context. As we proved in first chapters, the urn models work well in the simulation, now we want to see their behavior in the practical context. In the next sections, we present the results obtained after applied the urn designs to one real experiment.

In this chapter we use the dataset from the study "Melatonin reduces the need for sedatives in high-risk critically ill patients" conducted in the "San Paolo Hospital - University Campus", Milan, by the Doctors Iapichino G. and Mistraletti G., from Institute of Anesthesiology and Intensive Care. A single-center, double-blind randomized placebo-controlled trial was carried

out from July 2007 to May 2010. We use the information gathered from this study to re-design a new imaginary trial in which we use the Response Adaptive Design.

5.1 The original study

The original study is aimed to estimate if the administration of oral melatonin in ICU patients is able to regularize the sleep-waking rhythm, improving sleep quality and reducing episodes of agitation/mental confusion.

The main objectives are: assessment of sleep quality, prevalence of mental confusion/agitation, amount of daily sedative drugs administered and modification of redox status. The **primary outcome** measures is the overall sedatives daily doses. The **secondary outcome** measures are: prevalence of delirium assessed with CAM-ICU, prevalence of mental disorders, ICU length of stay, ICU mortality, hospital mortality, sleep quantity assessed by wrist actigraphy.

At the admission in ICU, obtained the informed consent, the patients, who were high-risk critically ill, will be randomly assigned to the "Treatment" group receiving melatonin 3mg BID by oral route (or nasogastric tube) or to the "Control" group receiving placebo. The sedation will be performed according to clinical standard.

The study was a randomized, controlled, double-blind. Of the 1158 patients admitted to ICU and treated with conscious enteral sedation, 82 critically ill with mechanical ventilation ¿ 48h and Simplified Acute Physiology Score II ¿ 32 points were randomized 1:1 to receive, at eight p.m. and midnight, melatonin (3+3mg) or placebo, from the third ICU day until ICU discharge.

The results of the analysis have shown that melatonin treated patients received lower amount of enteral hydroxyzine. Other neurological indicators (amount of some neuroactive drugs, pain, agitation, anxiety, sleep observed by nurses, need for restraints, need for extra sedation, nurse evaluation of sedation adequacy) seemed improved, with reduced cost for neuroactive drugs. Post - traumatic stress disorder prevalence did not differ between groups, nor did ICU or hospital mortality. There are some study limitations, including the differences between groups before intervention, the small sample size, and the single-center observation.

They concluded that long term enteral melatonin supplementation may result in a decreased need for sedation, with improved neurological indicators and cost reduction. Further multicenter evaluations are required to confirm these results with different sedation protocols.

5.2 The ICU trial on Melatonin reinterpreted according to RRU Model

We have re-designed the study and resorted a way of allocation using the urn with random reinforcement studied previously. The two objectives that we set were:

1. determine the best treatment,

2. minimize (maximize) the patient's number with the worst (best) treatment.

We know that, in this case, patients come sequentially in the experiment and each time a new subject arrives, a ball is drawn and the patient is assigned to one of two treatments, based on the color of the ball that represents the treatment. In our case, we indicate red balls for the melatonin (R treatment) and green balls for the placebo (G treatment). Later, we will see the response to the assigned treatment and we will replace in the urn other balls of the same color of the drawn one, whose quantities will be a function of the observed response. We repeat the procedure until of the next patient. In this way, the composition of urn changes every time a new response is observed, and then with it the probability of allocating of patients to treatments.

To achieve the first goal we use the bootstrap method and run 200 sim-

ulations of the responses from the empirical distribution obtained by the responses of the original study. As you can see from **Figure 5.1**, the urn process is able to identify the best treatment. Particularly, among the simulations we ran, 169 times the urn assigned the largest number of patients to melatonin (the best treatment), and only 31 times to placebo treatment. Moreover, the proportion of the R balls representing the melatonin treatment tends to 1, in particular to 0.98. Then, also the convergence is assured.

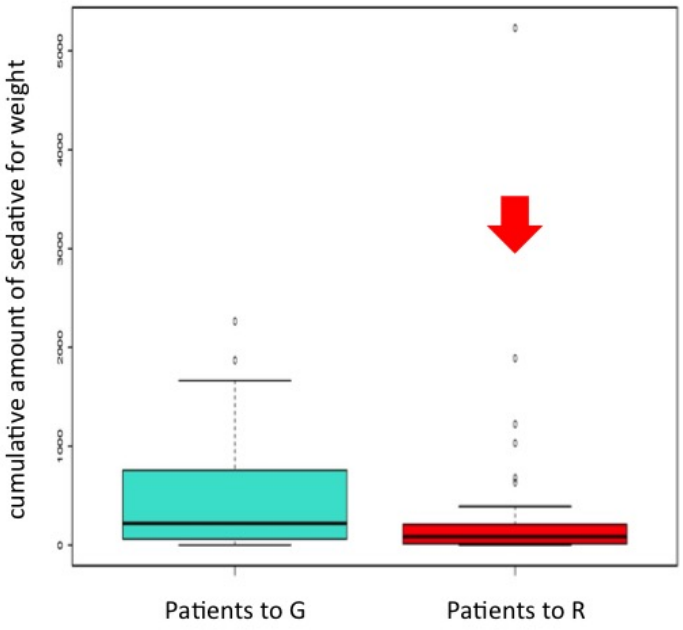

Figure 5.1: Number of patients assigned to placebo treatment (G) and melatonin treatment (R) with RRU method.

The second goal is to compare the performance statistics of the original clinical trial, that was randomized controlled, with those of a test based on RRU design. Now, we want to show that a response adaptive clinical trial is able to lead to a statistical test as the most powerful and to assign less patients to the less effective treatment, in our case the placebo group.

We considere three cases, based on a different sample sizes: sample = 82, sample = 102, sample = 122. For each of these cases, we run 10000 simulations of the experiment. In each simulation, we have a virtual urn whose drawings set the assignments of patients to treatments, and in general, the two sample sizes at the end of the experiment will be different every time. The patients responses to treatments, that are used to update the urn's composition, are randomly drawn from the data collected for testing with the randomization controlled. The RRU design generates two samples with different numerosity in the different experiments.

In **Figure 5.2** we reported the boxplots for the number of patients assigned to the lower treatment (placebo - G) in the three cases with different sample sizes. As we can notice, in all the three cases, more than 50 percent of the times the adaptive model assigns fewer patients to treatment G. Moreover, this happens even when the number of total patients used in the experiment is greater than the original one. For each simulation performed, we have realized a t - test at the significance level of 5 percent to test whether

the mean difference was significantly different in the two samples (Placebo vs Melatonin).

For each scenario, we reported the power of the test obtained as the proportion of the number of times that the test has encountered such difference between the means. In **Figure 5.2**, each power is been shown under the corresponding boxplot and next to each boxplot we have shown the patient's number for each group in the balanced trial. We have calculated the power of the original test obtained by the method of the randomization controlled, equal to 0.8. This value is calculated evaluating the theoretical power function of the t- tests at the values of the observed sample means. We can therefore see that in second and third case, the response adaptive model is able to build a statistical test with a power equal to or greater than the original test.

After all these considerations, we can conclude that the RRU method confirms the theoretical results also in practice.

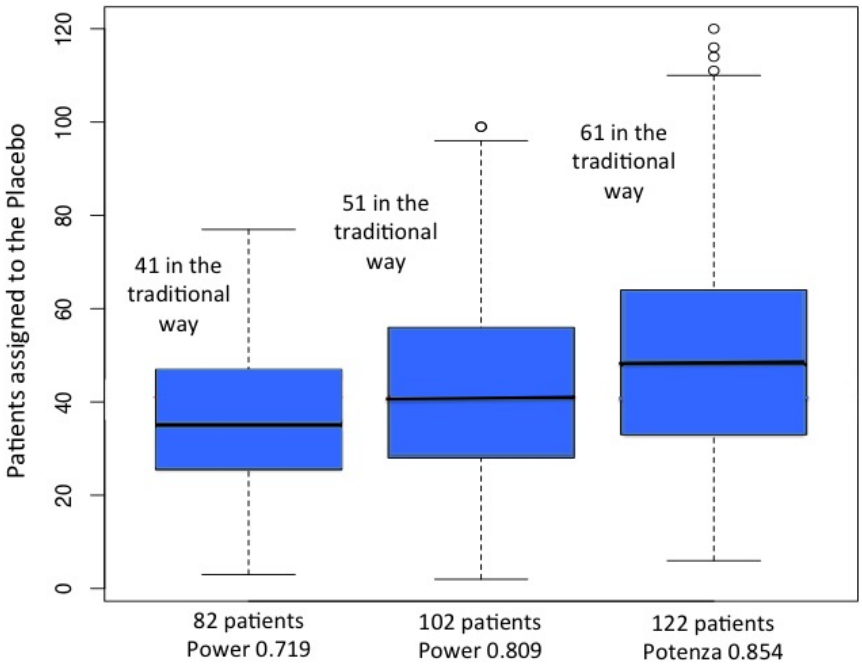

Figure 5.2: Boxplots of the number of patients assigned to lower treatment (placebo) in the three cases: sample size = 82, sample size = 102, sample size = 122. Next to each boxplot it is indicate the number of patients assigned in the classical controlled trial. Below is shown the power of the test to the adaptive response obtained in the simulation.

Chapter 6

Conclusions

In this thesis we interested in the use of adaptive models in clinical trials, especially on the strategies based on the urn models. These techniques used not only for binary responses, but also for the continue ones. We have seen that the use of these methods allows to maintain a certain degree of randomization, useful for the purposes of statistical analysis. Starting with the Polya's Urn, we analyzed the main changes, focusing on designs with random reinforcement. In this case the urn has the ability to change its composition depending of the reinforcements, that is, the effects of the treatments on the patients. This means that all patients will be allocated to the asymptotically best treatment, thereby offering subjects in the sample the best care among those in the study. Our analysis focused on those models that have an asymptotic target set for the proportion urn. This value represents the

limit to which the proportion of patients assigned to different treatments in the study, will converge asymptotically.

Although these models exhibit many advantages, one of the weaknesses is the delay of the answers that could lead to an increase in time analysis. Different solutions may be used: resorting to a multi-center trial, using a Bayesian approach considering the distribution of answers as a priori or considering the covariates.

A number of scientific questions arise with the use of Bayesian Adaptive Randomization (BAR). Because the variability of an estimator of a comparative effect between the two treatments is lower when there is balance in allocations, especially in the case of BAR, the ethical goal is in contrast with that of optimizing the statistical accuracy.

Another weakness is the fact that the characteristics of the patients in the study could change systematically over time, a phenomenon known as "drift", and this could cause a impractical procedure. While the use of a model for covariates reduces the probability of this problem, the drift caused by the effects of latent variables is a very delicate aspect. In regards to this several methods were created to manage "drift" (Karrison et al. 2003). In general, a very controversial and typical issue in the design of a Bayesian clinical trial is the choice of the prior distribution.

It is this approach that we decided to follow to continue our research.

In fact, an evolution of these adaptive models in Bayesian key are being studied, mainly thanks to the recent period at Department of "Biostatistics and Computational Biology" of the Harvard T.H. Chan School of Public Health, working with the group of Professor Parmigiani and Professor Trippa. We started working on a new adaptive model that combines cross-over design , thus taking into account the possibility for a person to change treatment, and Bayesian Adaptive Randomization. The aim is to define the method to be able to compare with the design of the urn models and to generalize these methods to a multiarm clinical trial with continous responses.

So, this is only the springboard to new insights. It is not one ending, but the new starting.

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R Code

.1 RRU versus MRRU

In this appendix we report the R code used for all the simulation in this thesis.

The following `one_step` make a step from the process urn, when we know the current composition of the urn and a set of parameters that define the type of reinforcement to be applied.

```
one_step = function(r, g, mr, mg, tipo_rinforzo, delta, eta) {
    z = r / (r + g);
    x = rbinom(1, 1, z);
    if(tipo_rinforzo == 'n') {
        m = rnorm(1, mr);
        n = rnorm(1, mg);
    } else if (tipo_rinforzo == 'c') {
```

```
        m = mr;
        n = mg;
    } else if (tipo_rinforzo == 'e') {
        m = rexp(1, mr);
        n = rexp(1, mg);
    }
    if(z < eta)
        r = r + x*m;
    if(z > delta)
        g = g + (1-x)*n;
    z = r / (r + g);
    cat("Palline rosse: ", r, "\n");
    cat("Palline bianche: ", g, "\n");
    cat("Proporzione: ", z, "\n");
    return(c(r, w, z));
}
```

The function `simulation` simulates an entire urn process calling up the function `one_step`

```
simulation = function(r0, g0, mr, mg, n_iterazioni, +
        + tipo_rinforzo, delta = 0, eta = 1) {
```

```
    r = r0;
    g = g0;
    proporzione = rep(0, n_iterazioni);
    for(i in c(1 : n_iterazioni)) {
        output = one_step(r, g, mr, mg, tipo_rinforzo, delta, eta);
        r = output[1];
        w = output[2];
        proporzione[i] = output[3];
    }
    windows();
    plot(proporzione, type='l', ylim = c(0, 1), +
    + main=paste('Simulazione di ', n_iterazioni, ' estrazioni'), +
    + xlab = "", ylab = "Zn");
    abline(h=delta,col='blue')
    abline(h=(eta+delta)/2,col='red')
    abline(h=eta,col='blue')
}
```

We note that the two functions lend themselves to run simulations using three different distributions for the reinforcements: *normal* reinforcements, *exponential* reinforcements and *constant* reinforcements, depending on the

value assumed by the parameter `tipo_rinforzo`. With this choice, we want verify empirically that the convergence results, seen previously for the two processes urn, do not depend on the particular distribution of the reinforcements, but only by their means.

.1.1 Different independent urns

The following are the modified functions for k independent urns.

```
one_step_vectors = function(r, g, mr, mg, tipo_rinforzo, delta, eta) {
    z = r / (r + g);
    k = length(r);
    if(tipo_rinforzo == 'n') {
        m = rnorm(k, mr);
        n = rnorm(k, mg);
    } else if (tipo_rinforzo == 'c') {
        m = rep(mr, k);
        n = rep(mg, k);
    } else if (tipo_rinforzo == 'e') {
        m = rexp(k, mr);
        n = rexp(k, mg);
    }
```

```
    x = rep(0, k);
    for(i in c(1:k)) {
        x[i] = rbinom(1, 1, z[i]);
        if(z[i] < eta)
            r[i] = r[i] + x[i]*m[i];
        if(z[i] > delta)
            g[i] = g[i] + (1-x[i])*n[i];
    }
    cat("Palline estratte: ", x, "\n");
    cat("Palline rosse: ", r, "\n");
    cat("Palline bianche: ", w, "\n");
    z = r / (r + w);
    cat("Nuova composizione delle urne: ", z, "\n");
    return(list(r, g, z));
}
```

and

```
simulation_vectors = function(r0, g0, mr, mg, n_iterazioni, tipo_rinforzo, +
+ k, delta = 0, eta = 1) {
    r = rep(r0, k);
    g = rep(g0, k);
```

```
    proporzione = matrix(nrow = k, ncol = n_iterazioni);
    for(i in c(1 : n_iterazioni)) {
        output = one_step_vectors(r, g, mr, mg, tipo_rinforzo, delta, eta);
        r = output[[1]];
        w = output[[2]];
        proporzione[, i] = output[[3]];
    }
    hist(proporzione[,n_iterazioni], col = "blue", +
    + main=paste('Simulazione di ', n_iterazioni, ' estrazioni per ', k, " urne"
    + xlab="", ylab="", xlim=c(0,1))
}
```

.1.2 Application of Convergence Theorem

We shown below the code for the application of the Convergence Theorem.

```
simulation_test = function(r0, g0, mr, mg, tipo_rinforzo, alpha = 0.001,
+ passo = 0.01, n_iterazioni = 10000, k = 500, delta = 0, eta = 1) {
    r = rep(r0, k);
    g = rep(g0, k);
    ascisse = seq(from=0, to=1, by=passo);
    F_delta = ifelse(ascisse >= delta, 1, 0);
```

```
    F_eta = ifelse(ascisse >= eta, 1, 0);

    F_e = fe(r0, g0, mr, tipo_rinforzo, passo, delta, eta);

    F = rep(0, length(ascisse));

    errore = 1;

    j = 0;

    while(errore > alpha && j < n_iterazioni) {

        j = j + 1;

        output = one_step_vectors(r, w, mr, mw, tipo_rinforzo, delta, eta);

        r = output[[1]];

        w = output[[2]];

        z = output[[3]];

        for(i in c(1:length(ascisse))) {

            F[i] = (sum(z < ascisse[i])) / k;

        }

        int1 = passo*sum(abs(F - F_delta));

        int2 = passo*sum(abs(F - F_e));

        int3 = passo*sum(abs(F - F_eta));

        errore = min(int1, int2, int3);

    }


    par(mfrow=c(1,3));
```

```
    plot(ascisse,F_delta,type = 'n', ylab = '', xlab = '')
    lines(ascisse, F_delta)
    lines(ascisse, F)
    polygon(c(ascisse, rev(ascisse)),
    + c(F_delta, rev(F)), col = "blue", border = NA)

    plot(ascisse,F_e,type = 'n', ylab = '', xlab = '')
    lines(ascisse, F_e)
    lines(ascisse, F)
    polygon(c(ascisse, rev(ascisse)),
    + c(F_e, rev(F)), col = "blue", border = NA)

    plot(ascisse,F,type = 'n', ylab = '', xlab = '')
    lines(ascisse, F)
    lines(ascisse, F_eta)
    polygon(c(ascisse, rev(ascisse)),
    + c(F, rev(F_eta)), col = "blue", border = NA)

}
```

We can observe that into the function `simulation_test` it is called one function `fe`, that makes an other simulation for determining empirically F_e, or it gives a Beta with appropriate parameters when we have constant reinforcements.

```
fe = function(r0, g0, m, tipo_rinforzo, passo, delta, eta) {
    n_iterazioni = 10000;
    k = 100;
    r = rep(r0, k);
    g = rep(g0, k);
    ascisse = seq(from=0, to=1, by=passo);
    ordinate = rep(0, length(ascisse));
    if(tipo_rinforzo != 'c') {
        for(i in c(1:n_iterazioni)) {
            output = one_step_vectors(r, g, m, m, tipo_rinforzo,
            + delta, eta);
            r = output[[1]];
            g = output[[2]];
        }
        z = output[[3]];
        for(i in c(1: length(ascisse))) {
```

```
            ordinate[i] = (sum(z < ascisse[i])) / k;
        }
    } else {
        for(i in c(1:length(ascisse))) {
            if(ascisse[i] < delta)
                ordinate[i] = 0;
            if(ascisse[i] > eta)
                ordinate[i] = 1;
            if(ascisse[i] >= delta && ascisse[i] <= eta)
                ordinate[i] = pbeta((ascisse[i] - delta)/(eta-delta),
                + r0/m, g0/m);
        }
    }
    return(ordinate)
}
```

.2 Power

In this section we display the function built to find the minimun power.

```
potenza = function(alpha, delta0, n0, p0 = 0.5, +
+ sigmaR = 0.5, sigmaG = 0.5) {
```

```
    z = qnorm(1 - alpha/2);
    ascisse = seq(from=0, to=2, length=100);
    err = pnorm(-z-ascisse/(sqrt(sigmaR*sigmaR/(n0*p0) +
    + sigmaG*sigmaG/(n0*(1-p0))))) +
    + pnorm(z-ascisse/(sqrt(sigmaR*sigmaR/(n0*p0) +
    + sigmaG*sigmaG/(n0*(1-p0)))))
    potenza = 1 - err
    plot(ascisse, potenza, type="l", col = "Grey", +
    + xlab = "Delta", ylab = "Potenza", xlim = c(0, 1))
    abline(v = delta0, col = "Red")
    abline(h = 0, col = "Grey")
    abline(h = 1, col = "Grey")
    potenza_minima = 1 - pnorm(-z-delta0/(sqrt(sigmaR*sigmaR/(n0*p0) +
    + sigmaG*sigmaG/(n0*(1-p0))))) +
    - pnorm(z-delta0/(sqrt(sigmaR*sigmaR/(n0*p0) +
    + sigmaG*sigmaG/(n0*(1-p0)))))
    abline(h = potenza_minima, col = "Red")
    return(potenza_minima);
}
```

Now we show the function `regions` that produces the graph of regions

A, B, C.

```
regions = function(n0, p0 = 0.5, sigmaR = 0.5, sigmaG = 0.5) {
    p_opt = sigmaR / (sigmaR + sigmaG);
    ascisse = seq(from=0, to=1, length=100);
    n = (p_opt*p_opt/ascisse + (1-p_opt)*(1-p_opt)/(1-ascisse)) +
    + / (p_opt*p_opt/(n0*p0) + (1-p_opt)*(1-p_opt)/(n0*(1-p0)));
    A_limit = p0 * n0 / ascisse
    C_limit = (1 - p0) * n0 / (1 - ascisse)
    plot(ascisse, n, type = "l", col = "Blue", +
    + ylim = c(0, 1000), xlab = "p", ylab = "n")
    par(new="T")
    plot(ascisse, A_limit, type = "l", col = "Red", +
    + ylim = c(0, 1000), xlab = "", ylab = "")
    par(new="T")
    plot(ascisse, C_limit, type = "l", col = "Red", +
    + ylim = c(0, 1000), xlab = "", ylab = "")
}
```

The function `delta_eta` computes for a fixed n the intervals in which δ and η have to vary in order that the tests belong to the proper region.

```
delta_eta = function(n, n0, p0 = 0.5, +
```

```
+ sigmaR = 0.5, sigmaG = 0.5) {
    nn = function(x) {
        p_opt = sigmaR / (sigmaR + sigmaG);
        return((p_opt*p_opt/x + (1-p_opt)*(1-p_opt)/(1-x)) +
        + / (p_opt*p_opt/(n0*p0) + (1-p_opt)*(1-p_opt) +
        + /(n0*(1-p0)))-n);
    }
    delta_inf = uniroot(nn, c(0.1, p0));
    delta_sup = n0 * p0 / n;
    eta_inf = 1 - n0 * (1 - p0) / n;
    eta_sup = uniroot(nn, c(p0, 0.9));
    return(c(delta_inf, delta_sup, eta_inf, eta_sup))
}

simulation_power = function(alpha, n0, p0, n, delta, eta, +
+ K, mr, mg, sigmaR = 0.5, sigmaG = 0.5, r0 = 200, g0 = 200) {
    z = qnorm(1 - alpha/2);
    potenza = function(n, p) {
        differenza = abs(mr - mg);
        return(1 - pnorm(-z-differenza/(sqrt(sigmaR*sigmaR/(n*p) +
        + sigmaG*sigmaG/(n*(1-p))))) +
```

```
    - pnorm(z-differenza/(sqrt(sigmaR*sigmaR/(n*p) +
    + sigmaG*sigmaG/(n*(1-p))))))
}
Ra = function(p) {
    return(sqrt(sigmaR*sigmaR/(n*p) +
    + sigmaG*sigmaG/(n*(1-p)))*z)
}
Nr = rep(0, K);
Ng = rep(0, K);
P = rep(0, K);
Xr = rep(0, K);
Xg = rep(0, K);
Potenza = rep(0, K);
Test = rep(0, K);
for(j in c(1: K)) {
    r = r0;
    g = g0;
    xr = 0;
    xg = 0;
    nr = 0;
    ng = 0;
```

```
        for(i in c(1 : n)) {
            output = one_step_test(r, w, mr, mg, 'n',
            + delta, eta, xr, xg, nr, ng);
            r = output[1];
            g = output[2];
            xr = output[3];
            xg = output[4];
            nr = output[5];
            ng = output[6];
        }
        Nr[j] = nr;
        Ng[j] = ng;
        P[j] = nr / n;
        Xr[j] = xr / nr;
        Xg[j] = xg / ng;
        Potenza[j] = potenza(n, P[j]);
        Test[j] = ifelse(abs(Xr[j] - Xw[j]) > Ra(P[j]), 1, 0);
    }
    cat("Potenza calcolata: ", mean(Potenza), "\n");
    cat("Potenza empirica: ", mean(Test), "\n");
    cat("Potenza migliorata: ", +
```

```
    + sum(Potenza>potenza(n0, p0))/K, "\n");
    cat("Media del numero di pazienti assegnati +
    + al primo trattamento: ", mean(Nr), "\n");
    cat("Media del numero di pazienti assegnati +
    + al secondo trattamento: ", mean(Ng), "\n");
}
```

The function `simulation_power` uses the function `one_step_test`. This is the R code.

```
one_step_test = function(r, g, mr, mg, tipo_rinforzo, +
+ delta, eta, xr, xg, nr, ng) {
    z = r / (r + g);
    x = rbinom(1, 1, z);
    if(tipo_rinforzo == 'n') {
        m = rnorm(1, mr);
        n = rnorm(1, mg);
    } else if (tipo_rinforzo == 'c') {
        m = mr;
        n = mg;
    } else if (tipo_rinforzo == 'e') {
        m = rexp(1, mr);
```

```
        n = rexp(1, mg);
    }
    if(z < eta)
        r = r + x*m;
    if(z > delta)
        w = w + (1-x)*n;
    if(x == 0){
        xg = xg + n;
        ng = ng + 1;
    }
    else{
        xr = xr + m;
        nr = nr + 1;
    }
    return(c(r, w, xr, xg, nr, ng));
}
```

.3 Melased

Upload of the dataset.

```
dataset = read.csv("mela.csv", header=TRUE, sep=";", dec=".")
```

Outcome construction: cumulative amount of sedative

```
poat_paz = sapply(split(dataset$poat, dataset$id), sum)

pobz_paz = sapply(split(dataset$pobz, dataset$id), sum)

poal_paz = sapply(split(dataset$poal, dataset$id), sum)

evpr_paz = sapply(split(dataset$evpr, dataset$id), sum)

evbz_paz = sapply(split(dataset$evbz, dataset$id), sum)

evop_paz = sapply(split(dataset$evop, dataset$id), sum)


somma_sed_paz = poat_paz + pobz_paz + poal_paz + evpr_paz + evbz_paz + evop_paz

MAX = floor(max(somma_sed_paz))


id_paz = unique(dataset$id)

index_paz = match(id_paz, dataset$id)

gruppi_paz = dataset$gruppo[index_paz]

somma_sed_inv = MAX - somma_sed_paz
```

Final dataset with new id (repeated mesaures)

```
dataset_rev = data.frame(id_paz, gruppi_paz, somma_sed_paz, somma_sed_inv)

somma_sed_0 <- dataset_rev$somma_sed_inv[(dataset_rev$gruppi_paz==0)&(is.na(data

somma_sed_1 <- dataset_rev$somma_sed_inv[(dataset_rev$gruppi_paz==1)&(is.na(data

n_1 <- length(somma_sed_1)
```

```
n_0 <- length(somma_sed_0)
```

We made some graphical checks on the distribution of the responses.

```
plot(density(dataset_rev$somma_sed_paz[dataset_rev$gruppi_paz=="0"], main="Densi
plot(density(dataset_rev$somma_sed_paz[dataset_rev$gruppi_paz=="1"], main="Densi


plot(dataset_rev$somma_sed_paz[dataset_rev$gruppi_paz=="0"], main="Density on Pl
plot(dataset_rev$somma_sed_paz[dataset_rev$gruppi_paz=="1"], main="Density on Me


windows()
hist(somma_sed_1)
windows()
hist(somma_sed_0)


t.test(somma_sed_1,somma_sed_0)


hist(somma_sed_0, main = 'Cumulative Sedative for Placebo')


hist(somma_sed_1, main = 'Cumulative Sedative for Melatonin')
```

Descriptive analysis.

```
summary(dataset_rev)
```

```
sd(dataset_rev$gruppi_paz)
```

To compare the results between the RRU test and the classical one, we need to compute the test on the controlled randomized trial.

```
simulazione_Ttest = function(dataset, nr, ng, Npazienti, Nsimulazioni, alpha, cu
output = inizializza(dataset, cutoff);
listaPazienti0 = output$pazienti0
listaPazienti1 = output$pazienti1
pazienti1 = c()
potenza1 = 0
for(i in 1:Nsimulazioni) {
output = simulazione_bootstrap(dataset, nr, ng, Npazienti[1], listaPazienti0, li
pazienti1[i] = output$pazienti0
potenza1 = potenza1 + output$test
}
potenza1 = potenza1 / Nsimulazioni
pazienti2 = c()
potenza2 = 0
for(i in 1:Nsimulazioni) {
output = simulazione_bootstrap(dataset, nr, ng, Npazienti[2], listaPazienti0, li
pazienti2[i] = output$pazienti0
```

```
potenza2 = potenza2 + output$test
}
potenza2 = potenza2 / Nsimulazioni
pazienti3 = c()
potenza3 = 0
for(i in 1:Nsimulazioni) {
output = simulazione_bootstrap(dataset, nr, ng, Npazienti[3], listaPazienti0,
listaPazienti1, alpha, cutoff)
pazienti3[i] = output$pazienti0
potenza3 = potenza3 + output$test
}
potenza3 = potenza3 / Nsimulazioni

boxplot(pazienti1, pazienti2, pazienti3, names=c(paste(Npazienti[1],
"pazienti\nPotenza", 1-potenza1), paste(Npazienti[2], "pazienti\nPotenza", 1-pot
"pazienti\nPotenza", 1-potenza3)), col=c("cornflowerblue", "cornflowerblue", "co
abline(h=41,col='red')
}
```

Classical test with the bootstrap method.

```
test_rct <- rep(0,ripetizioni)
```

```
for (j in 1:ripetizioni) {

M <- u_inv(F_1(n_1))

N <- u_inv(F_0(n_0))

m_R <- mean(M)

m_G <- mean(N)

s_R <- sqrt( sum( (M-m_R)^2 ) / (n_1-1) )

s_G <- sqrt( sum( (N-m_G)^2 ) / (n_0-1) )

nu <- ( (s_R^2/n_1) +

(s_G^2/n_0) )^2 / ( (s_R^2/n_1)^2/(n_1-1) + (s_G^2/n_0)^2/(n_0-1) )

RC[j] <- sqrt( (s_R^2/n_1) + (s_G^2/n_0) ) * qt(alpha/2,nu,0,FALSE)

test_rct[j] <- abs(mean(M) - mean(N)) > RC[j]

}
```

R code for the boxplots.

```
pow <- sum(pow_t)/10000


par(mfrow=c(1,3))

boxplot(n_G, col='blue', main='SAMPLE = 82', ylab='Patients assigned

to Placebo', xlab='power = 0.80', ylim=c(0,150))


boxplot(n_G, col='forestgreen', main='SAMPLE = 102',ylab='Patients assigned
```

```
to Placebo', xlab='power = 0.85', ylim=c(0,150))


boxplot(n_G, col='forestgreen', main='SAMPLE = 122',ylab='Patients assigned
 to Placebo', xlab='power = 0.89', ylim=c(0,150))
```