

# An Overview of Adaptive Designs

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February 24, 2021

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# Introduction

- ▶ Response-adaptive designs, or response-adaptive randomization procedures, are designs that **change allocation away** from 50/50 based on responses observed so far in the trial.
- ▶ The desired allocation proportion is usually motivated by an **ethical consideration of assigning more patients to better treatments**.
- ▶ In this presentation, we discuss several classes of response-adaptive designs and the advantages and disadvantages of these designs, and the analysis of clinical trials based on adaptive designs.

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# Goals of Response Adaptive Designs

The two main goals of response-adaptive designs are :-

1. To maximize the individual patient's personal experience in a trial under certain restrictions.
2. To reduce the overall number of patients (sample size) of a randomized clinical trial.

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# Different Families of Response Adaptive Designs

- ▶ The early ideas of adaptive designs can be traced back to Thompson and Robbins. Since then, two main families of response-adaptive designs have been proposed :-
- ▶ **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
- ▶ Few examples of these type of designs are (**Urn Models**) :-
  1. Play-the-winner rule.
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# Notations and Basic Assumptions

- ▶ Let  $p_A$  be the probability of a success on treatment  $A$  and let  $p_B$  be the success probability of treatment  $B$ , with  $q_A = 1 - p_A$  and  $q_B = 1 - p_B$ .
- ▶ In addition, let  $n$  be the total number of patients in a trial, let  $n_A$  be the number of patients assigned to treatment  $A$ , and let  $n_B$  be the number of patients assigned to  $B$ , so that  $n_A + n_B = n$ .
- ▶ We here assume that the outcome can be observed relatively quickly.
- ▶ Here we consider the simplest situation where two independent treatments “A” and “B” with binary outcomes (Success or failure) are compared in the course of a trial.

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# Play-The-Winner Rule

- ▶ This is one of the first response-adaptive designs, proposed by Zelen.
- ▶ The first patient is equally likely to receive one of the two treatments.
- ▶ The subsequent patient is assigned to the **same** treatment following a **successful** outcome, and to the **opposite** treatment following a **failure**.



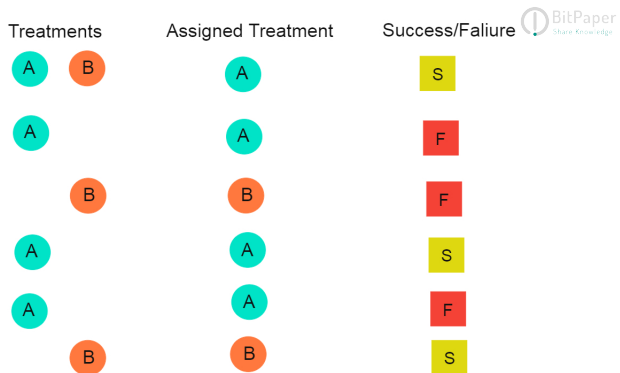
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# Diagram illustrating Play-The-Winner Rule



# Play-The-Winner Rule

- ▶ On average, the proportion of patients  $\frac{n_A}{n}$  assigned to treatment A is  $\frac{q_B}{q_A+q_B}$ .
- ▶ We simulate using R,  $10^3$  samples following Play-The-Winner Procedure where we consider  $p_A = 0.3$  and  $p_B = 0.6$ .
- ▶ Since, here we have taken  $p_A = 0.3, p_B = 0.6$ , the simulated allocation proportion for treatment A must converge to  $\frac{q_B}{q_A+q_B} = \frac{0.4}{1.1} = \frac{4}{11} \approx 0.364$ .
- ▶ We try to validate the above statements using simulation and plot the allocation proportions for both Treatment A & B as a function of increasing sample size  $n$ .

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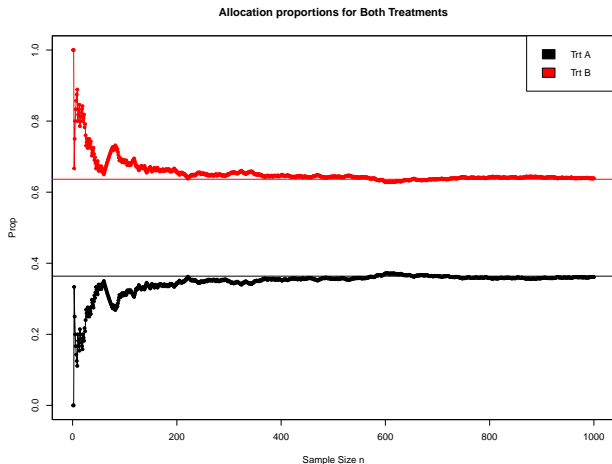


Figure: Plot of  $n_A/n$  and  $n_B/n$  as a function of  $n$



# Randomized play-the-winner Rule

- ▶ This rule was suggested by Wei and Durham and Wei.
- ▶ In this rule, the procedure is generally started with an urn containing one ball of each type corresponding to the two treatments.
- ▶ When a patient arrives, a ball is drawn from the urn and then replaced.
- ▶ The patient receives corresponding treatment.
- ▶ If the outcome is a **success**, **one ball of that type** is added to the urn.
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# Diagram illustrating Randomized play-the-winner Rule



Click/tap or press [1] for toolbars

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- ▶ This design has the **same limiting allocation proportion** as the play-the-winner rule i.e  $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$ .
- ▶ We simulate for the parameter values  $p_A = 0.2, p_B = 0.4$ .
- ▶ So from theoritical perspective, the observed allocation proportion for Treatment A must get closer to  $\frac{q_B}{q_A+q_B} = \frac{0.6}{1.4} \approx 0.429$  and for Treatment B, closer to  $\frac{q_A}{q_A+q_B} \approx 0.571$ .



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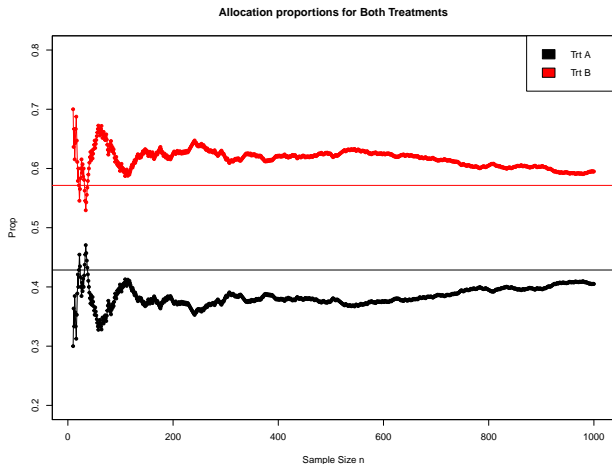


Figure:  $n_A/n$  and  $n_B/n$  as a function of  $n$

# Drop-The-Loser Rule

- ▶ According to this rule, the urn starts with **one** ball of **each treatment type** and **one** ball of the so-called **immigration type**.
- ▶ When a patient arrives to be randomized to a treatment, a ball is taken from the urn.
- ▶ If it is an immigration ball, the ball is replaced and two additional balls (one of each treatment type) are added to the urn.
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Treatments	Ball Drawn	Assigned Treatment	Success/Faliure
		None	None
		A	
		B	
		A	
		B	

-  Treatment A
-  Treatment B
-  Immigration Ball

Click/tap or press [1] for toolbars



# Drop-The-Loser Rule

- ▶ If response is a **failure**, the **ball is not returned** to the urn.
- ▶ If response is a **success**, the ball is **returned** to the urn (hence the urn composition remains unchanged).
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# Advantages of Designs Based on Urn Models

1. We can stop the trial early or come to conclusions early.
2. Because of early decision and greater flexibility it can reduce the potential cost.
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# Neyman Allocation

- ▶ Response-adaptive designs were introduced following the ethical goal to maximize an individual patient's personal experience in the trial.
- ▶ Another important goal is to maximize the power of treatment comparison.
- ▶ These two goals usually compete with each other.
- ▶ Optimal allocation proportions are usually determined through some multiple-objective optimality criteria.
- ▶ Consider the situation when two binomials are compared and the measure of interest is  $p_A - p_B$ .

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# Neymann Allocation

- ▶ Let  $\hat{p}_A$  and  $\hat{p}_B$  be the corresponding maximum likelihood estimators of  $p_A$  and  $p_B$ . The allocation that minimizes the variance of  $\hat{p}_A - \hat{p}_B$  is the **Neymann Allocation** with :-

$$\frac{n_A}{n} = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}}$$

- ▶ An interesting fact about the **Neymann Allocation** scheme is that for some values of  $p_A$  and  $p_B$  it will assign more patients to the inferior treatment. Since, then

$$p_A \geq p_B \Rightarrow \frac{\sqrt{p_A q_A}}{\sqrt{p_B q_B}} \geq 1 \quad \forall p_A, p_B \in (0, 1)$$

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$$\frac{n_A}{n} = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}}$$

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- ▶ Another goal, a compromise between the ethical goal and efficiency, is to minimize the expected number of failures for a fixed variance of  $\hat{p}_A - \hat{p}_B$ . The optimal allocation for this goal is :-

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$$\sqrt{\frac{p_A}{p_B}} \geq 1 \implies (n_A)_{opt} \geq (n_B)_{opt}$$

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# Target-Based Response-Adaptive Designs

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# Sequential Maximum Likelihood Procedure

- ▶ To start, allocate  $n_0 \geq 2$  patients to both treatments  $A$  and  $B$ .
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- ▶ We plot the simulated allocation proportion for both Treatment A & B with  $p_A = 0.3, p_B = 0.7$  with increasing value of  $n$  :-
- ▶ So, theoretical the limiting proportions must be equal to  $\frac{\sqrt{0.3}}{\sqrt{0.3} + \sqrt{0.7}} \approx 0.396$  and  $\frac{\sqrt{0.7}}{\sqrt{0.3} + \sqrt{0.7}} \approx 0.604$  for Treatments A & B respectively.

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# Allocation Proportion in SML Procedure

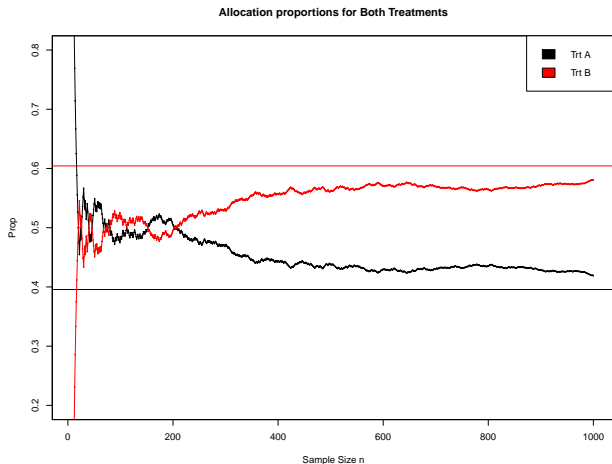


Figure:  $n_A/n$  and  $n_B/n$  as a function of  $n$



# Doubly Adaptive Biased Coin Design

- ▶ This procedure is a generalization of the sequential maximum likelihood procedure.
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- ▶ Now, we simulate the Doubly Adaptive Biased Coin Design for different two pairs of  $(p_A = 0.3, p_B = 0.7)$  &  $(p_A = 0.6, p_B = 0.7)$  and also plot the allocation proportions for different values of  $\gamma$  parameter.

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At the extreme, when  $\gamma = 0$ , we have the sequential maximum likelihood procedure, which has maximum variability :-

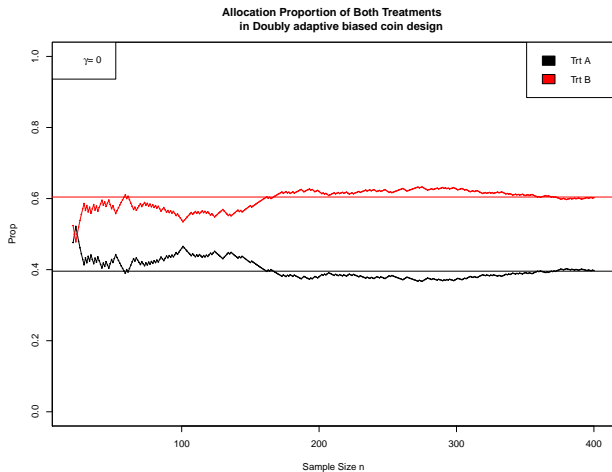


Figure:  $p_A = 0.3, p_B = 0.7, \gamma = 0$

As  $\gamma$  increases, the procedure becomes more deterministic resulting in a reduction of variance using simulation this can be shown :-

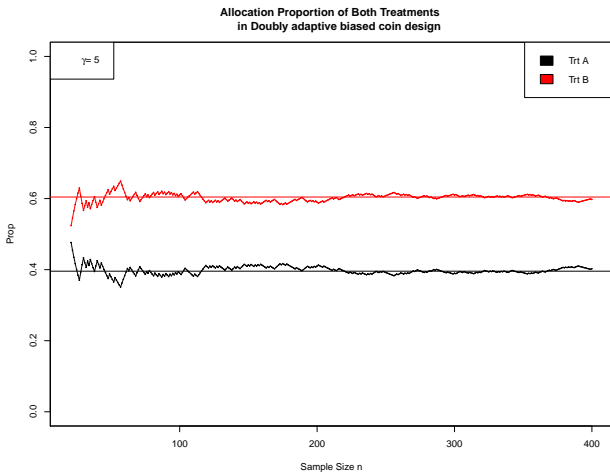


Figure:  $p_A = 0.3, p_B = 0.7, \gamma = 5$

For quite large values of  $\gamma (= 10)$ , the variability further decreases :-

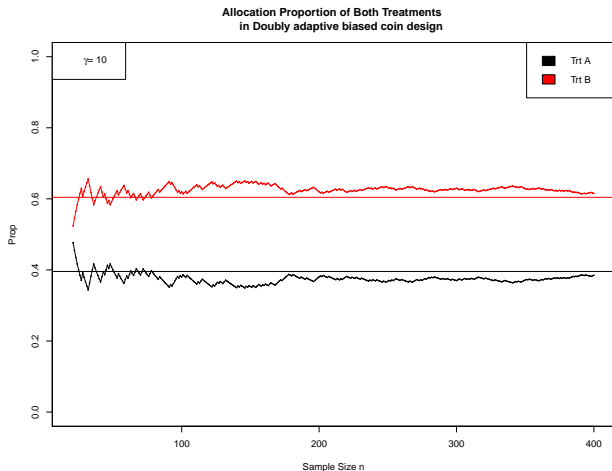
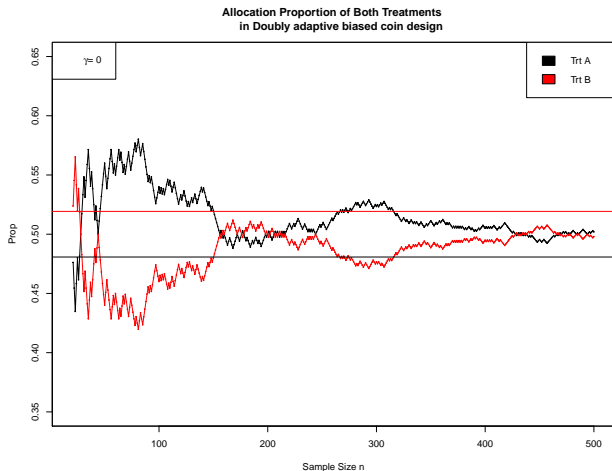


Figure:  $p_A = 0.3, p_B = 0.7, \gamma = 10$

Smaller the difference between  $p_A$  and  $p_B$  , larger is the variability of the procedure as we can notice it even doesn't seem to converge to the desired limits :-



**Figure:**  $p_A = 0.6, p_B = 0.7, \gamma = 0$



So to stabilize the procedure, we require even larger values of  $\gamma$ , say  $\gamma = 20$  as we can see in the simulated plot :-

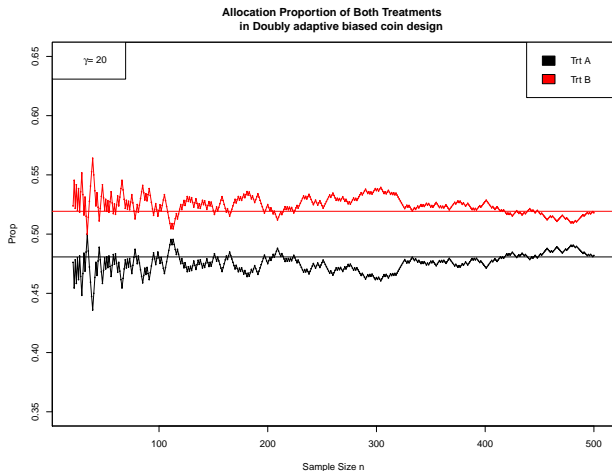


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# Variability and Power of Using Adaptive Designs

- ▶ When using response-adaptive designs in clinical trials, the number of patients assigned to each treatments ( $n_A$  &  $n_B$ ) are random variables.
- ▶ Therefore the power  $P$  (rejecting  $\mathcal{H}_0 | \mathcal{H}_0$  false) (for most testing hypotheses and alternatives) is also a random variable. Here we generally consider hypothesis like :-

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- ▶ Hu and Rosenberger show that the **average power of a randomization procedure** is a **decreasing function** of the **variability of the procedure**.

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  - ▶ It is flexible in terms of targeting any desired allocation.
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- ▶ As  $\gamma$  becomes smaller, we have more randomization, but also more variability.
- ▶ Overall, the doubly adaptive biased coin procedure is the most favorable design as :-
  - ▶ It is flexible in terms of targeting any desired allocation.
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# Sample Size of Adaptive Designs

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# Applying Adaptive Designs

- ▶ The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygenation (ECMO) study.
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  - ▶ A trial of crystalloid preload in hypotension for cesarean patients.
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- ▶ In the above discussion, we assume that individual patient outcome will be immediately available.
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# Acknowledgement

We would like to express our **special thanks of gratitude** to our respected **Prof. Arunangshu Biswas** for helping us through the presentation work and also for giving us this wonderful opportunity as we learned many things during the making of this presentation.