An Overview of Adaptive Designs

Niranjan Dey

Contents

1 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.

2 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.
   (a) To reduce the overall number of patients (sample size) of a randomized clinical trial.

3 Different Families of Response Adaptive Designs

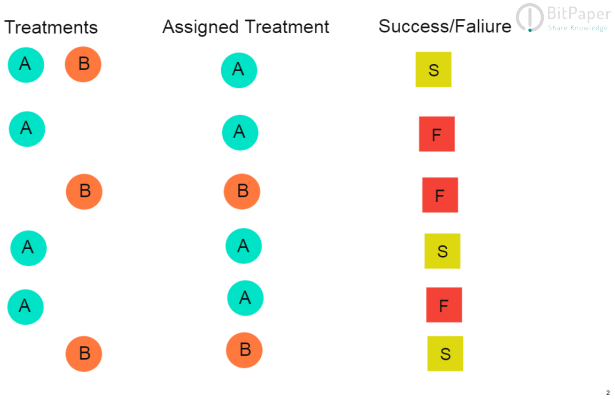
- The early ideas of adaptive designs can be traced back to Thompson and Robbins. Since then, two main families of response-adaptive designs have been proposed :-
  - **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
  - Few examples of these type of designs are (**Urn Models**) :-
    1. Play-the-winner rule.
    2. Randomized play-the-winner rule.
    3. Drop-the-loser rule.
- **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
  - Different examples of Target Based Adaptive Designs are :-
    1. Sequential maximum likelihood procedure.
    2. Doubly adaptive biased coin design.
- 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 faliure) are compared in the course of a trial.

4 Urn Models

- One large class of response-adaptive designs is based on urn models which are specifically design driven , are based on Urn Models.
  - Following the ethical imperative, the Urn Models basically change the allocation in the course of a trial so that **more patients receive** the **treatment performing better** thus far in the trial.

4.1 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**.



- 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 $p_A = 0 \cdot 3$ and $p_B = 0 \cdot 6$.
  - Since, here we have taken $p_A = 0 \cdot 3, p_B = 0 \cdot 6$, the simulated allocation proportion for treatment A must converge to $\frac{q_B}{q_A+q_B} = \frac{0 \cdot 4}{1 \cdot 1} = \frac{4}{11} \approx 0 \cdot 364$.
  - 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.

4.2 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.
  - Otherwise, **one ball** of the **opposite type** is added to the urn.

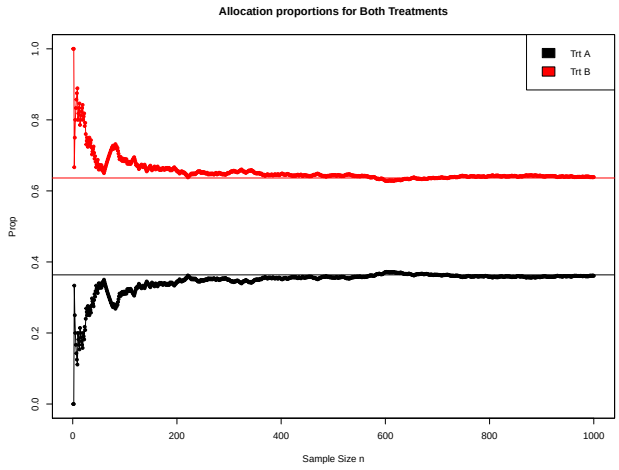
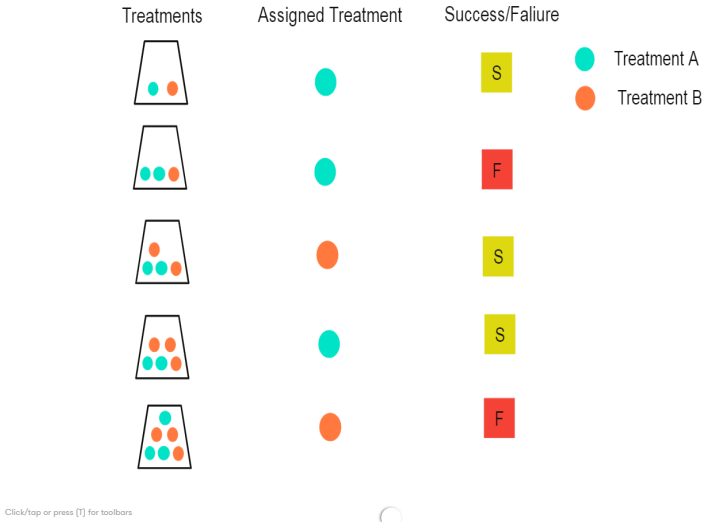


Figure 1: Plot of $^{n_A}/_n$ and $^{n_B}/_n$ as a function of n



- 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 $\frac{q_A}{q_A+q_B} \approx 0.571$.

4.3 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.

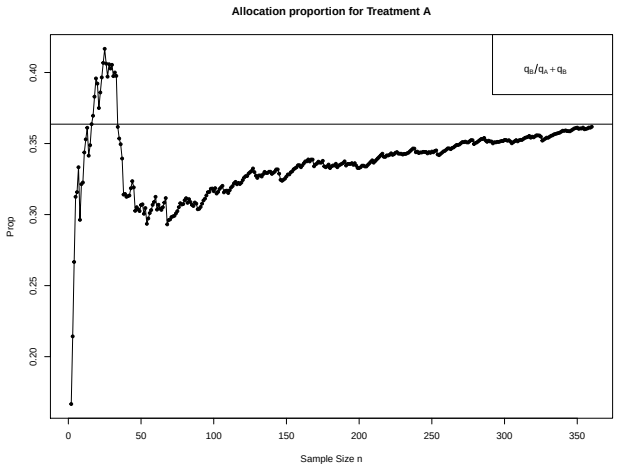
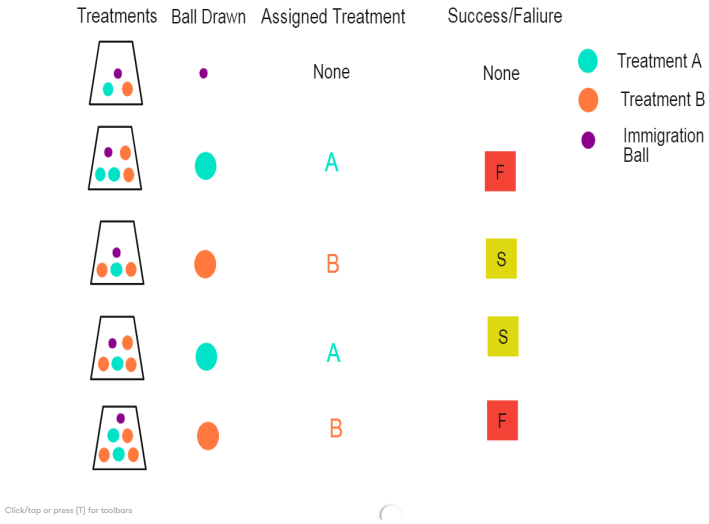


Figure 2: n_A/n and n_B/n as a function of n

– If it is an actual treatment ball, a patient is assigned to corresponding treatment and response is observed.



- 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).
  - In this case also, the **limiting allocation proportion** is equal to $\frac{q_B}{q_A+q_B}$.

4.4 Advantages of Designs Based on Urn Models

1. We can stop the trial early or come to conclusions early.
   (a) Because of early decision and greater flexibility it can reduce the potential cost.
   (b) Urn models are intuitive and easy to implement in clinical trials.
   (c) They shift the allocation probability to better treatments.

4.5 Some Drawbacks of Designs Based on Urn Models

1. In most of the models, we can see that it can only target a specific allocation proportion. This allocation is usually not optimal in a formal sense.

   (a) It can only be applied to the clinical trials with binary or multinomial responses only. Modifications are necessary to apply urn models to clinical trials with continuous responses or survival responses.

5 Neyman Optimal Allocations

- 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 $p_A - p_B$.

- Let $\widehat{p}_A$ and $\widehat{p}_B$ be the corresponding maximum likelihood estimators of p_A and p_B. The allocation that minimizes the variance of $\widehat{p}_A - \widehat{p}_B$ 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

$$p_A \gtrless p_B \not\Longrightarrow \frac{\sqrt{p_A q_A}}{\sqrt{p_B q_B}} \gtrless 1 \ \forall \ p_A, p_B \in (0,1)$$
$$\implies p_A \gtrless p_B \not\Longrightarrow (n_A)_{Neymann} \gtrless (n_B)_{Neymann} \ \forall \ p_A, p_B \in (0,1)$$

    (which is obviously not desirable in terms of the ethical goal)

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

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

  - This allocation also has the advantage of allocating more patients to better treatment as :-

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

    so it serves both the goals simultaneously which is much desired.
  - For more than 2 treatments i.e k treatments in general, it is still unclear how to find optimal allocations for general K treatment clinical trials !!

6 Target-Based Response-Adaptive Designs

- Because optimal allocation usually **depends on** some **unknown parameters**, we **cannot implement** it in practice, unless we **estimate** the **unknown parameters sequentially**.
  - In this section, we introduce two allocation procedures that use **sequential estimation** of **unknown parameters**.
  - We consider the case of comparing two treatments with binary responses.
  - We also suppose that the **optimal allocation** is the **target proportion**.

6.1 Sequential Maximum Likelihood Procedure

- To start, allocate $n_0 \geq 2$ patients to both treatments A and B.
  - Assume that we have assigned j $(j \geq 2n_0)$ patients in the trial and their responses have been observed.
  - Let $\widehat{p}_A$ and $\widehat{p}_B$ be the corresponding maximum likelihood estimators of p_A and p_B based on the j responses.
  - Then we allocate the $(j+1)^{th}$ patient to treatment A with probability :-

$$\frac{\sqrt{\widehat{p}_A}}{\sqrt{\widehat{p}_A} + \sqrt{\widehat{p}_B}}$$

- From the invariance property of MLE, we can show that this allocation proportion, in a limiting sense, converges to the desired optimal allocation proportion $\frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$.
  - Using simulation we can give evidence that the limiting allocation proportion gets closer to the optimal allocation proportion $\frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$ for Trt A and $\frac{\sqrt{p_B}}{\sqrt{p_A}+\sqrt{p_B}}$ for Trt B :-
  - We plot the simulated allocation proportion for both Treatment A & B with $p_A = 0 \cdot 3, p_B = 0 \cdot 7$ with increasing value of n :-
  - So, theoritical the limiting proportions must be equal to $\frac{\sqrt{0 \cdot 3}}{\sqrt{0 \cdot 3}+\sqrt{0 \cdot 7}} \approx 0 \cdot 396$ and $\frac{\sqrt{0 \cdot 3}}{\sqrt{0 \cdot 3}+\sqrt{0 \cdot 7}} \approx 0 \cdot 604$ for Treatments A & B respectively.

6.2 Doubly Adaptive Biased Coin Design

- This procedure is a generalization of the sequential maximum likelihood procedure.
  - At first, allocate $n_0 \geq 2$ patients to both treatments A and B.
  - Suppose that we have assigned j $(j \geq 2n_0)$ patients in the trial and their responses have been observed.
  - Let $\rho = \frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$ be the desired allocation.
- Let $\widehat{\rho}$ be the desired allocation, replaced by current estimates $\widehat{p}_A$ and $\widehat{p}_B$.
  - Let j_A/j and j_B/j be the current proportions of patients that have already been allocated to A and B, respectively.

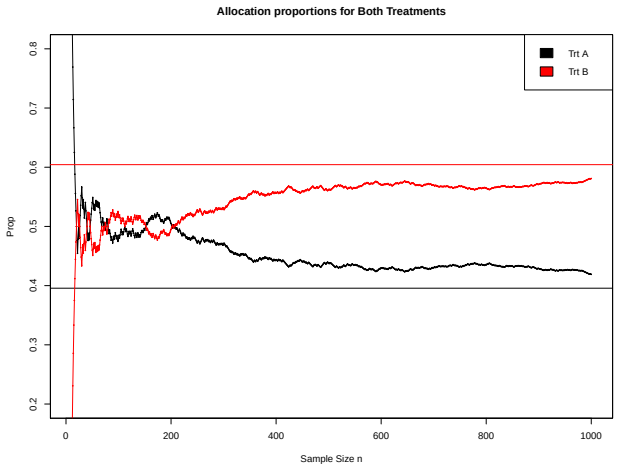


Figure 3: ${}^{n_A}/_{n}$ and ${}^{n_B}/_{n}$ as a function of n

- Then we assign patient $j+1$ to treatment A with probability $g\left({}^{j_A}/_{j}, \widehat{\rho}\right)$.
- Here g is an allocation function belonging to the family of functions :-

$$g\left(x, y\right) = \frac{y\left({}^{y}/_{x}\right)^{\gamma}}{y\left({}^{y}/_{x}\right)^{\gamma} + \left(1-y\right)\left({}^{1-y}/_{1-x}\right)^{\gamma}} \text{ where } \gamma \geq 0$$

- Suppose the $(j+1)^{th}$ patient is allocated to Treatment A.
  - Then we update the estimates $\widehat{p}_A, \widehat{p}_B$ and then the optimal allocation estimate $\widehat{\rho}$ accordingly.
  - Then we allocate the $(j+2)^{th}$ patient to Treatment A with probability $g\left(\left(j+1\right)_A / \left(j+1\right), \widehat{\rho}\right)$ where $\left(j+1\right)_A = j_A + 1$.
  - Now, we simulate the Doubly Adaptive Biased Coin Design for different two pairs of $(p_A = 0\cdot 3, p_B = 0\cdot 7)$ & $(p_A = 0\cdot 6, p_B = 0\cdot 7)$ and also plot the allocation proportions for different values of γ parameter.

6.2.1 Role of Parameter γ in Determining Variability of The Procedure

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

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

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

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 :-

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

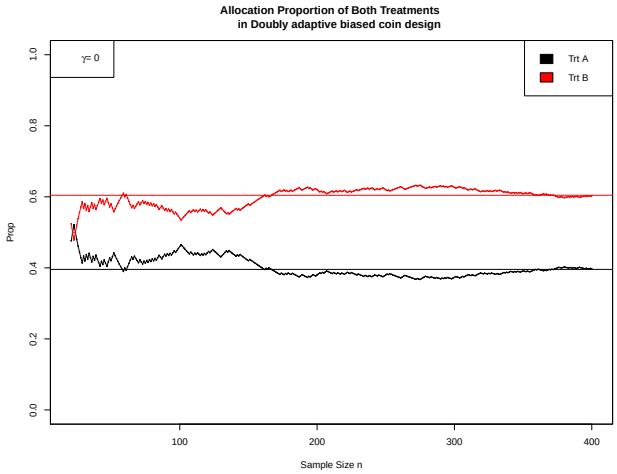


Figure 4: $p_A = 0 \cdot 3, p_B = 0 \cdot 7, \boldsymbol{\gamma = 0}$

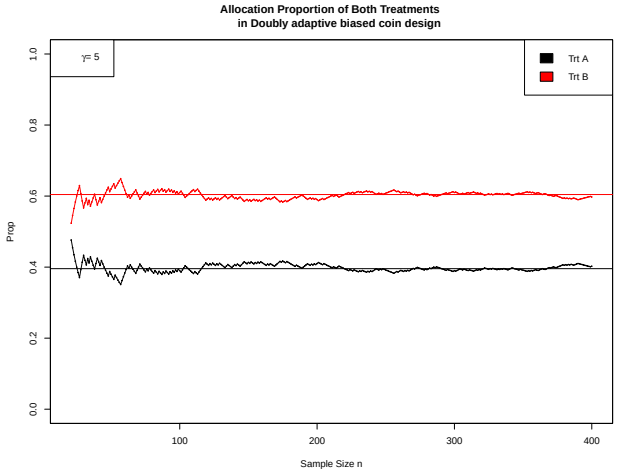


Figure 5: $p_A = 0 \cdot 3, p_B = 0 \cdot 7, \boldsymbol{\gamma = 5}$

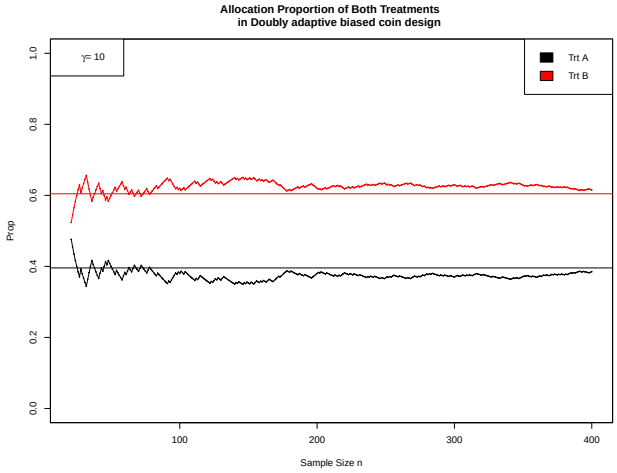


Figure 6: $p_A = 0 \cdot 3, p_B = 0 \cdot 7, \boldsymbol{\gamma = 10}$

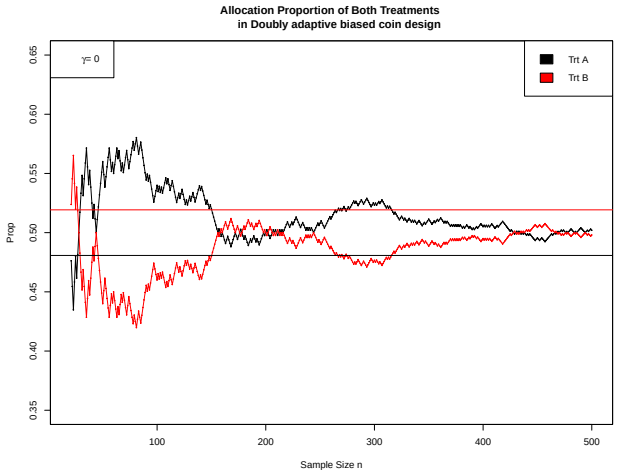


Figure 7: $p_A = 0 \cdot 6, p_B = 0 \cdot 7, \boldsymbol{\gamma = 0}$

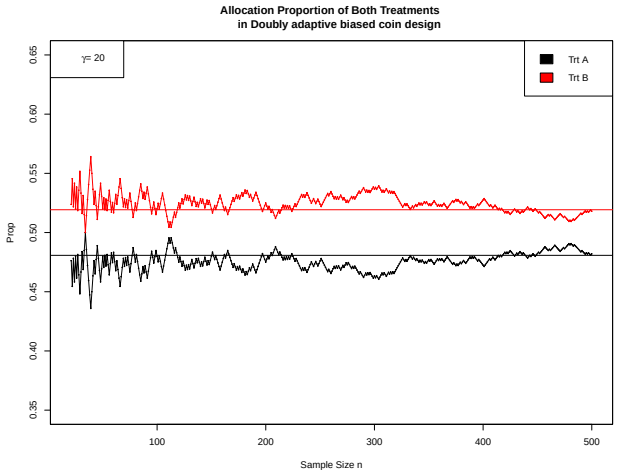


Figure 8: $p_A = 0.6, p_B = 0.7, \boldsymbol{\gamma = 20}$

7 Important Issues in Adaptive Design

7.1 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 $\mathscr{H}_0|\mathscr{H}_0$ false) (for most testing hypotheses and alternatives) is also a random variable. Here we generally consider hypothesis like :-

$$\mathscr{H}_0 : p_A = p_B$$
$$\mathscr{H}_1 : p_A \neq p_B$$

  - The variability of allocation has a strong effect on the power.
  - Hu and Rosenberger show that the **average power of a randomization procedure** is a **decreasing function** of the **variability of the procedure**.

- The drop-the-loser rule has minimum variability (lower bound) in the class of all response-adaptive procedures targeting urn allocation $\frac{q_B}{q_A+q_B}$.
  - The doubly adaptive biased coin design can directly target any given allocation (may depend on unknown parameters).
  - At the extreme, when $\gamma = 0$, we have the sequential maximum likelihood procedure, which has the highest variability.

- As γ tends to ∞, we have a procedure that attains the lower bound of any randomization procedure targeting the same allocation.
  - As γ 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.
    - It can be applied to different types of responses.
    - One can tune the parameter γ to reflect the **tradeoff** between the **power** and **variability**, and the tradeoff between **degree of randomization** and **expected treatment successes**.

7.2 Sample Size of Adaptive Designs

- It is usually difficult to determine the required sample size for response-adaptive designs.
  - This is because the allocation probabilities keep changing during a clinical trial when using response-adaptive design.
  - For a fixed sample size, the number of patients assigned to each treatment is a random variable.
  - Therefore the power is also a random variable for a fixed sample size.
  - In the literature, sample sizes of response-adaptive designs are calculated by ignoring the randomness of the allocations.

8 Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygenation (ECMO) study.
  - Adaptive designs have been implemented in several clinical trails such as :-
    - A trial of crystalloid preload in hypotension for cesarean patients.
    - A trial of fluoxetine vs. placebo in depression patients.
    - A four-arm trial in depression.
  - Adaptive designs have also been used extensively in adaptive learning algorithms, game theory, as well as dynamical systems.

9 Some Important Issues Regarding Adaptive Designs

- In the above discussion, we assume that individual patient outcome will be immediately available.
  - For clinical trials with delayed responses, we can update the urn when the response becomes available.
  - For doubly adaptive biased coin designs, the unknown parameters are estimated sequentially and the delayed responses effect these estimators.
  - The properties of doubly adaptive biased coin design with delayed responses are unknown, and this is a topic of future research.