An Overview of Adaptive Designs

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Contents

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.
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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 faliure) 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**.
- On average, the proportion of patients $\frac{n_A}{n}$ assigned to treatment A is $\frac{q_B}{q_A+q_B}$.

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Play-The-Winner Rule

- 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 as a function of increasing sample size n.

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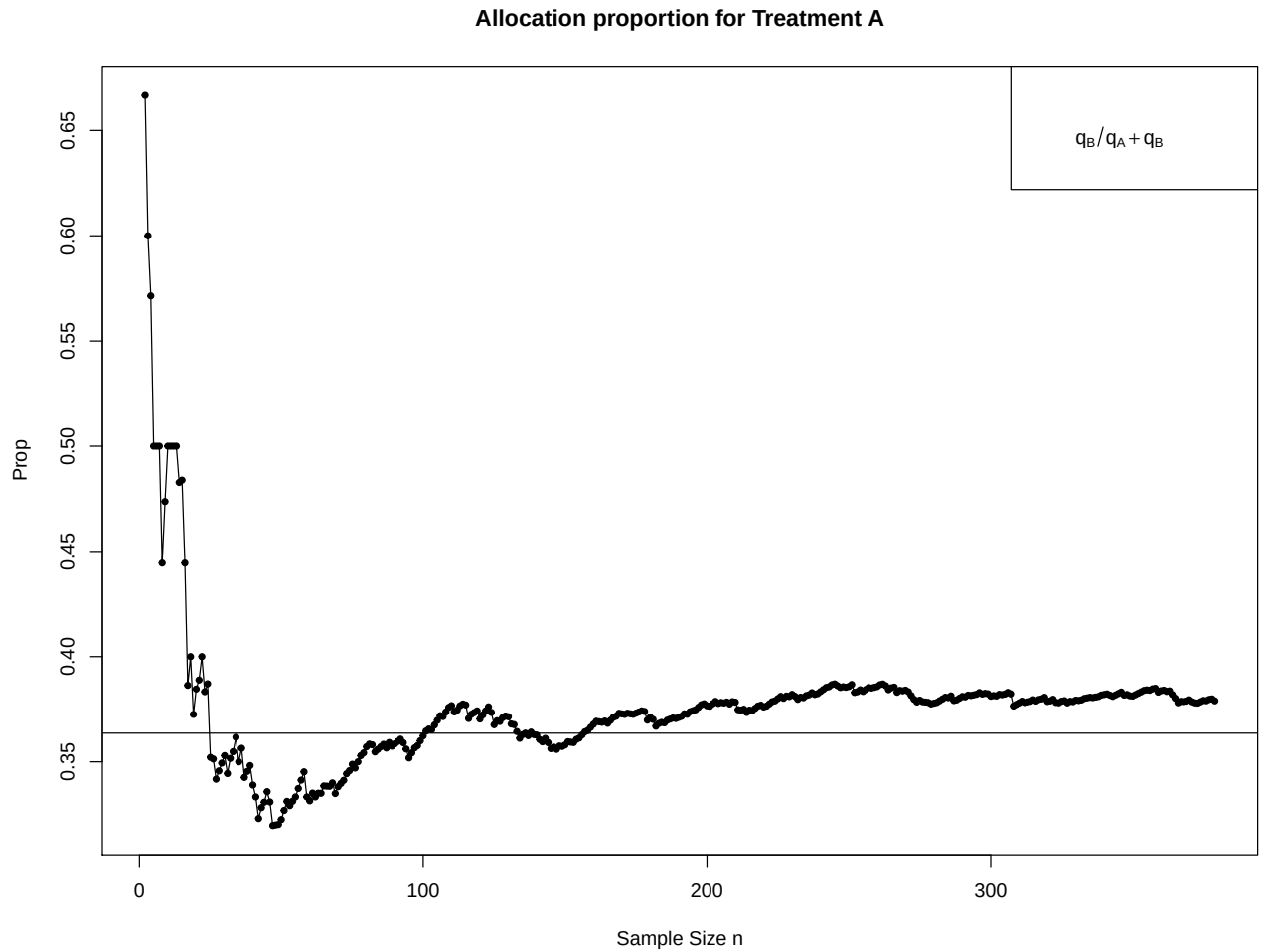

Figure: Plot of n_A/n as a function of n

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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- 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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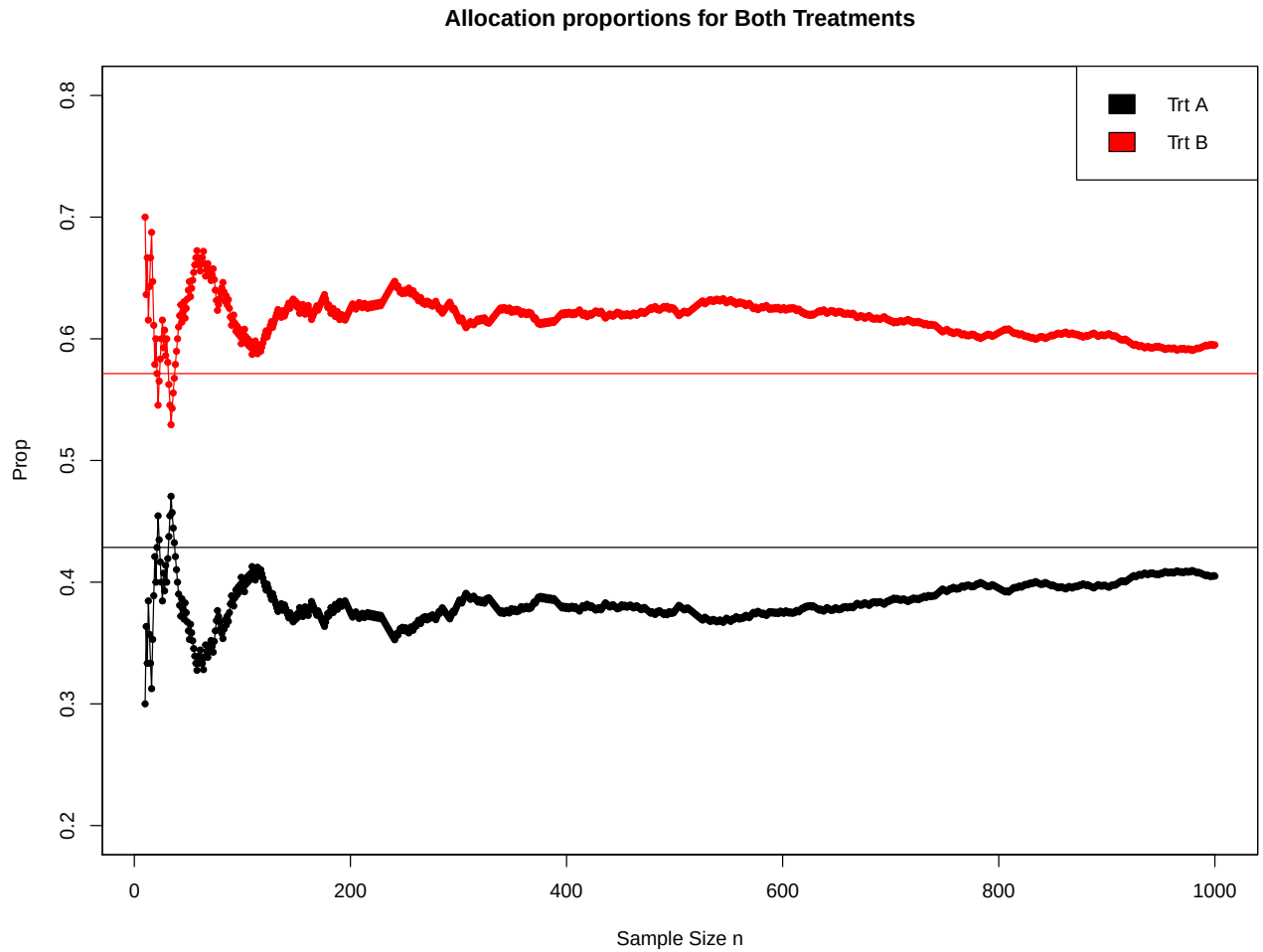

Figure: n_A/n and n_B/n as a function of n

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

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

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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.
3. Urn models are intuitive and easy to implement in clinical trials.
4. They shift the allocation probability to better treatments.

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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.
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- Consider the situation when two binomials are compared and the measure of interest is $p_A - p_B$.

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Optimal Allocation

- 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 :-

1. They shift the allocation probability to better treatments.

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

- 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

$$\frac{n_A}{n_B} = \frac{\sqrt{p_A q_A}}{\sqrt{p_B q_B}} > 1 \not\Longrightarrow p_A > p_B \forall\, p_A, p_B \in (0,1)$$

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Optimal Allocations

- 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 :-

$$\frac{n_A}{n_B} = \sqrt{\frac{p_A}{p_B}}$$

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 !!

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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.
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Allocation Proportion in SML Procedure

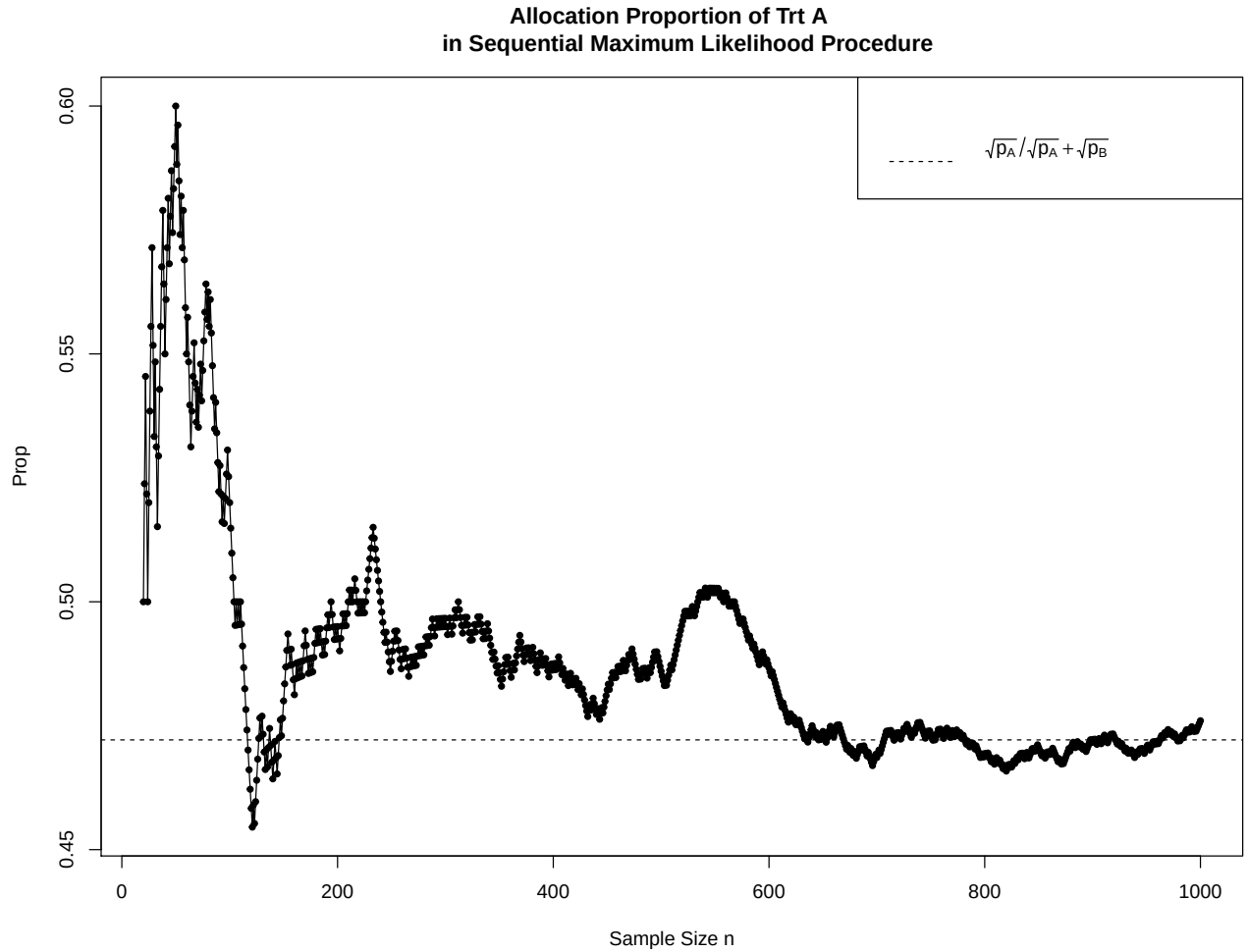

Figure: n_A/n as a function of n

Doubly Adaptive Biased Coin Design

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- Here g is an allocation function belonging to the family of functions :-

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

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

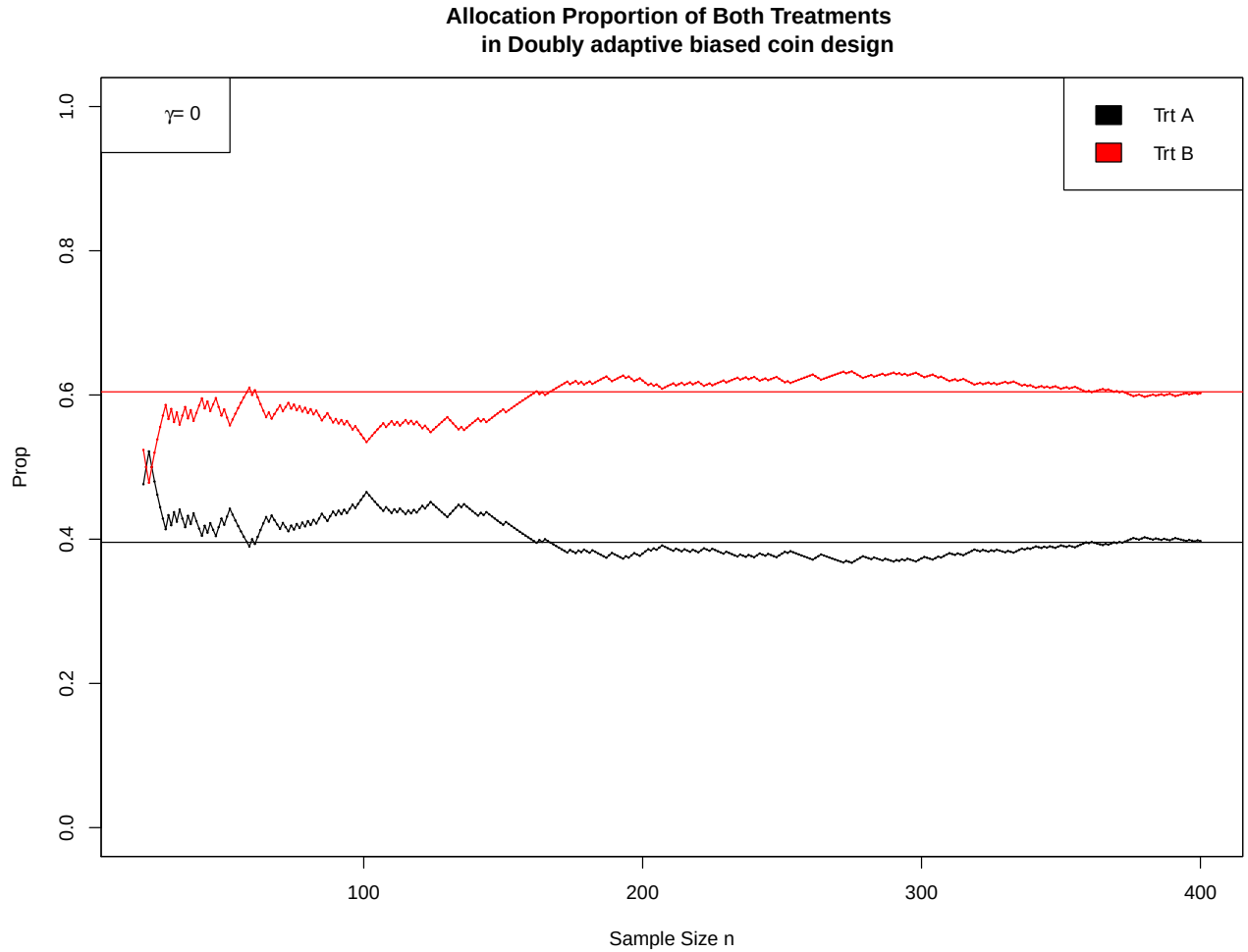


Figure: $p_A = 0.3, p_B = 0.7, \gamma = 0$

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

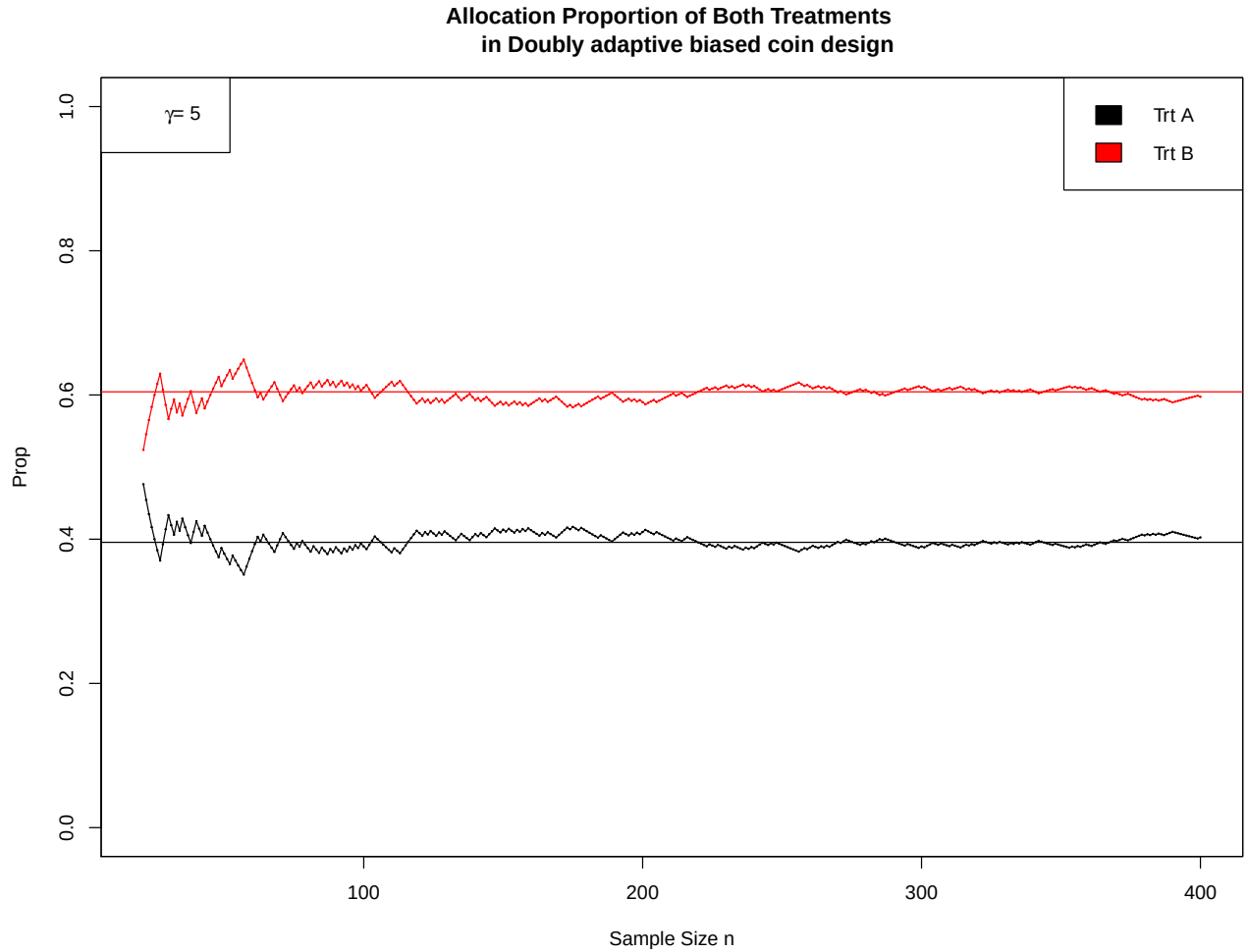
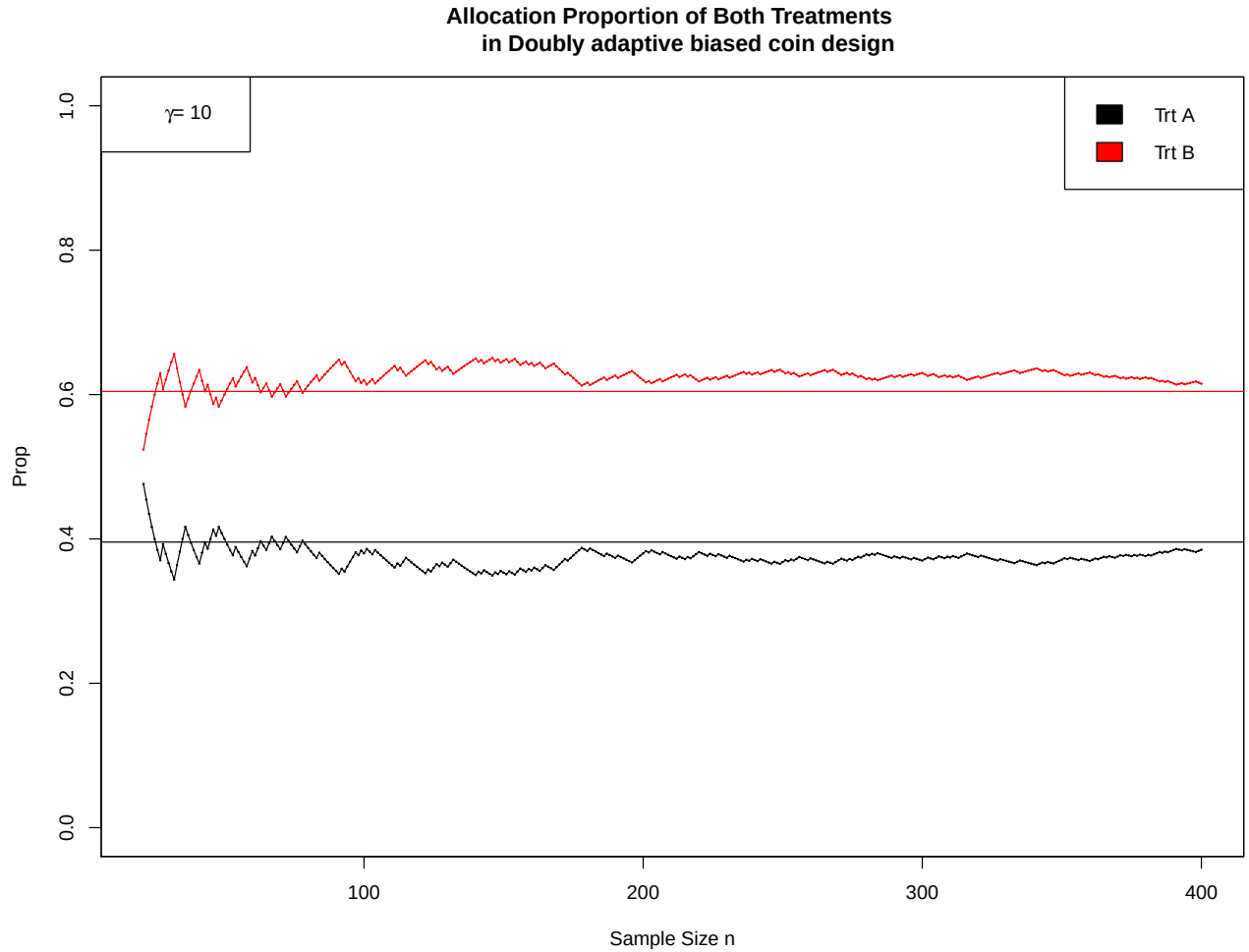


Figure: $p_A = 0.3, p_B = 0.7, \gamma = 5$

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



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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 :-

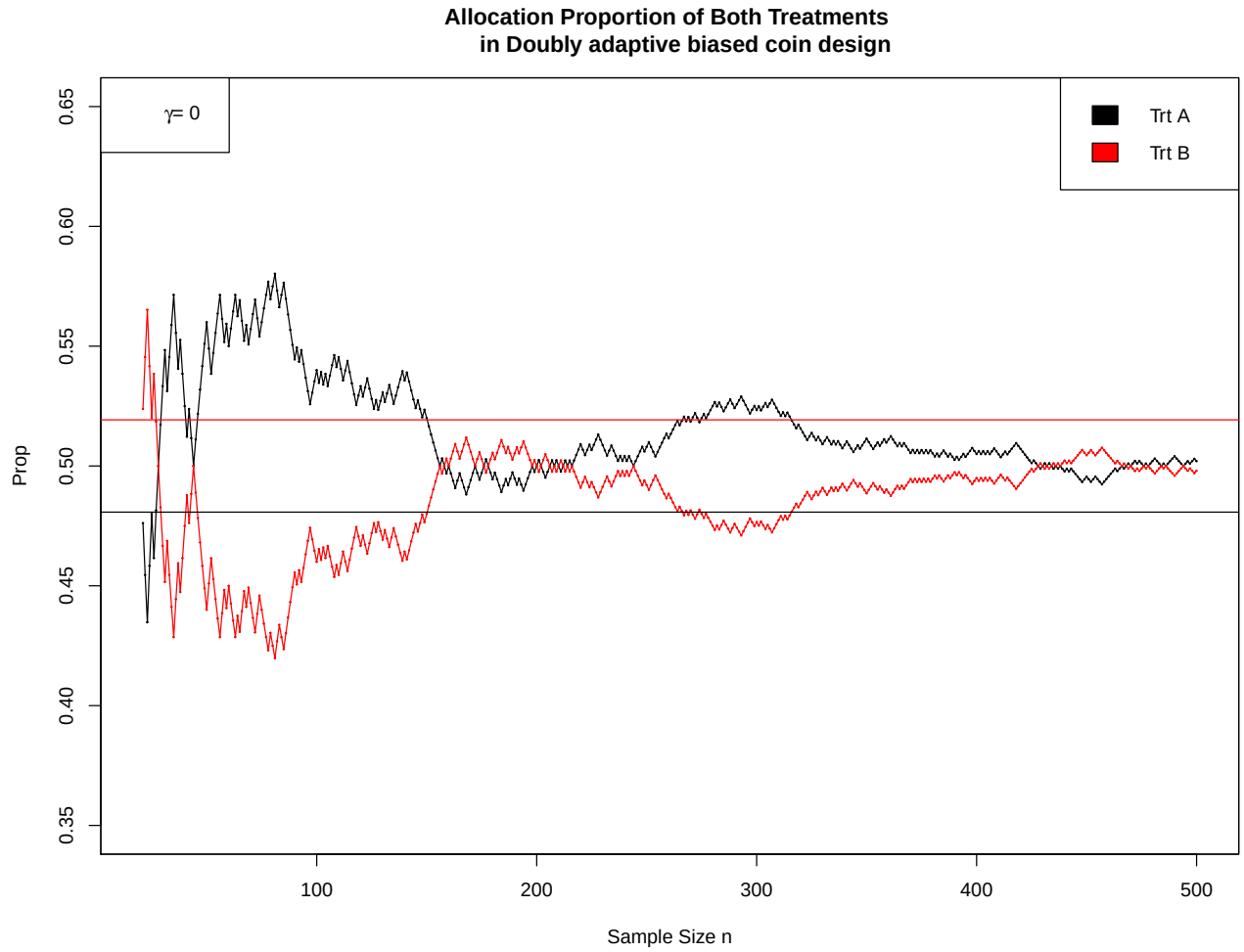
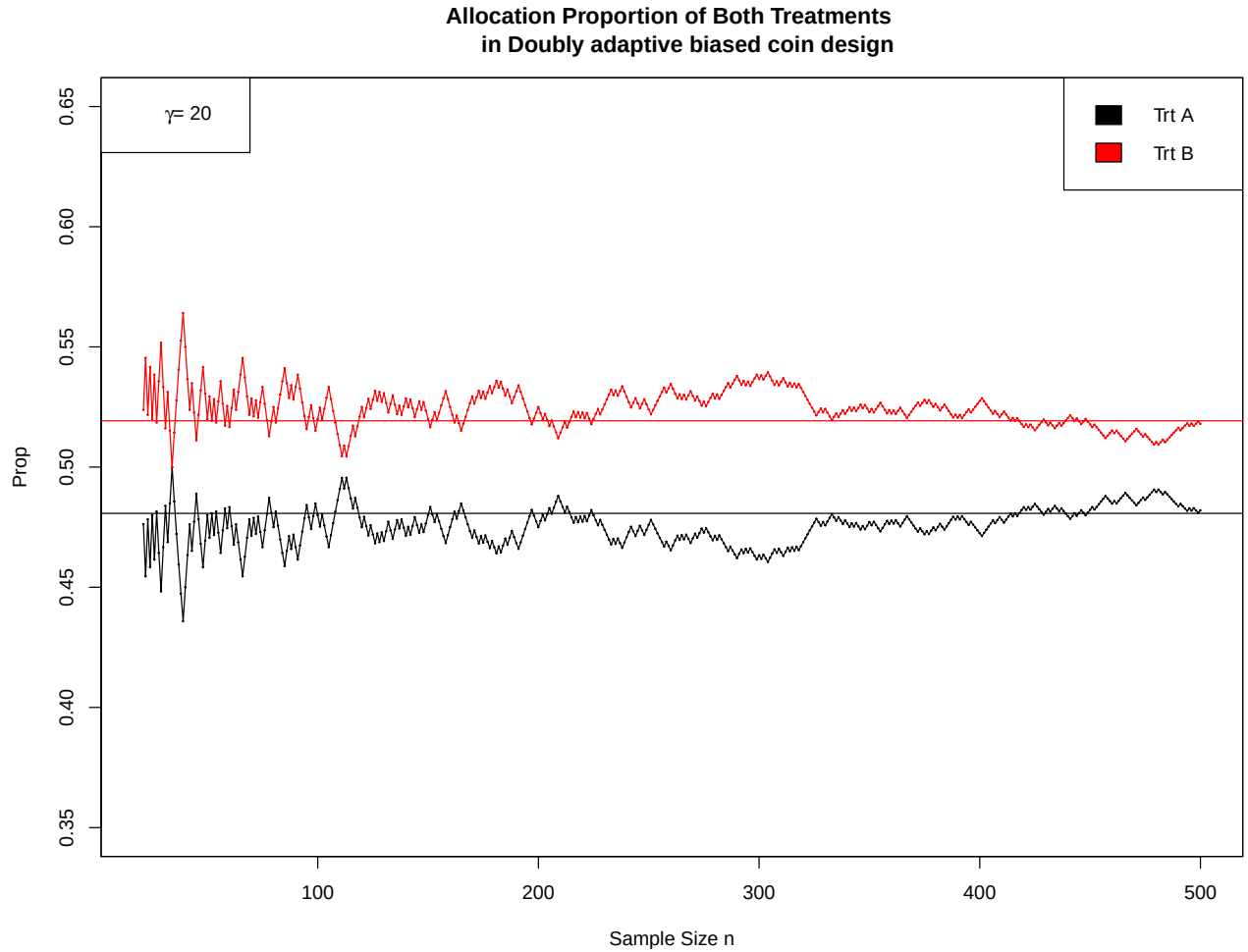


Figure: $p_A = 0.6, p_B = 0.7, \gamma = 10$

So to stabilize the procedure, we require even larger values of γ, 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 $\mathscr{H}_0 | \mathscr{H}_0$ false) (for most testing hypotheses and alternatives) is also a random variable. Here we generally consider hypothesis like :-

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Acknowledgement

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