An Overview of Adaptive Designs

Ritwick Mondal Kalpesh Chatterjee
Niranjan Dey Spandan Ghoshal

February 23, 2021

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.

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.

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.

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.

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.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

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 :-

1. **Target-based**, which is based on an optimal allocation target, where a **specific criterion** is **optimized** based on a **population model**.
2. Different examples of Target Based Adaptive Designs are :-
   2.1 Sequential maximum likelihood procedure.
   2.2 Doubly adaptive biased coin design.
3. **Design-driven**, where designs are driven by intuition and are **not optimal** in a formal sense.
4. Few examples of these type of designs are (**Urn Models**) :-
   4.1 Play-the-winner rule.
   4.2 Randomized play-the-winner rule.
   4.3 Drop-the-loser rule.

Origins of the test

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

Origins of the test

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

Origins of the test

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

Origins of the test

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

Origins of the test

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

Origins of the test

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

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**.

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**.

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**.

Play-The-Winner Rule

- On average, the proportion of patients $\frac{n_A}{n}$ assigned to treatment A is $\frac{q_B}{q_A+q_B}$.
- Therefore this design assigned more patients to the better treatment.
- We simulate two treatments A and B with success probabilities $p_A = 0.3$ & $p_B = 0.6$ and plot the allocation proportion for A :-

Play-The-Winner Rule

- On average, the proportion of patients $\frac{n_A}{n}$ assigned to treatment A is $\frac{q_B}{q_A+q_B}$.
- Therefore this design assigned more patients to the better treatment.
- We simulate two treatments A and B with success probabilities $p_A = 0.3$ & $p_B = 0.6$ and plot the allocation proportion for A :-

Play-The-Winner Rule

- On average, the proportion of patients $\frac{n_A}{n}$ assigned to treatment A is $\frac{q_B}{q_A+q_B}$.
- Therefore this design assigned more patients to the better treatment.
- We simulate two treatments A and B with success probabilities $p_A = 0.3$ & $p_B = 0.6$ and plot the allocation proportion for A :-

Play-The-Winner Rule

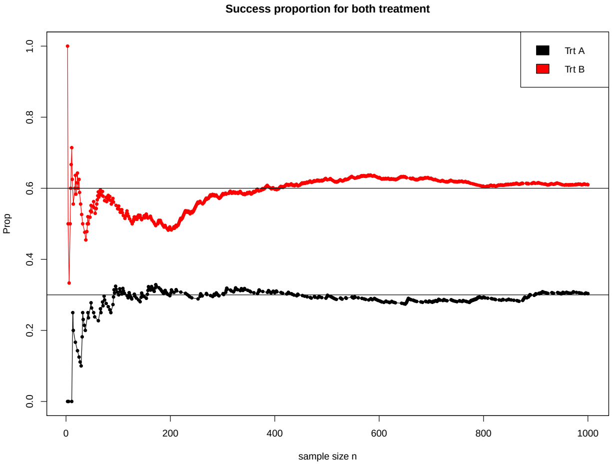


Figure: Plot of $\widehat{p}_A$ and $\widehat{p}_B$ where $p_A = 0.3, p_B = 0.6$

Play-The-Winner Rule

- We also know that the allocation proportion for treatment A converges to $\frac{q_B}{q_A+q_B}$.
- 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 as a function of increasing sample size n.

Play-The-Winner Rule

- We also know that the allocation proportion for treatment A converges to $\frac{q_B}{q_A+q_B}$.
- 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 as a function of increasing sample size n.

Play-The-Winner Rule

- We also know that the allocation proportion for treatment A converges to $\frac{q_B}{q_A+q_B}$.
- 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 as a function of increasing sample size n.

Play-The-Winner Rule

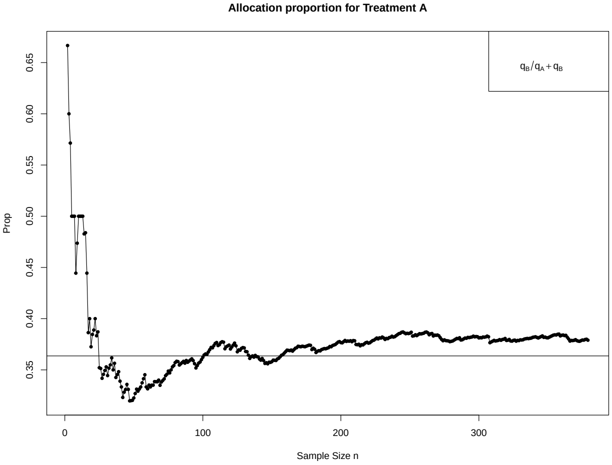


Figure: Plot of n_A/n as a function of n

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.
- Otherwise, **one ball** of the **opposite type** is added to the urn.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

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.
- This design has the **same limiting allocation proportion** as the play-the-winner rule i.e $\frac{n_A}{n} \xrightarrow{P} \frac{q_B}{q_A+q_B}$.

Randomized play-the-winner Rule

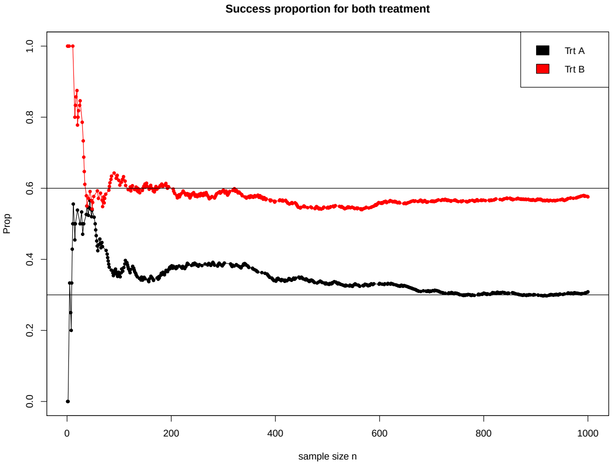


Figure: Plot of both $\widehat{p}_A$ and $\widehat{p}_B$ as a function of n

Randomized play-the-winner Rule

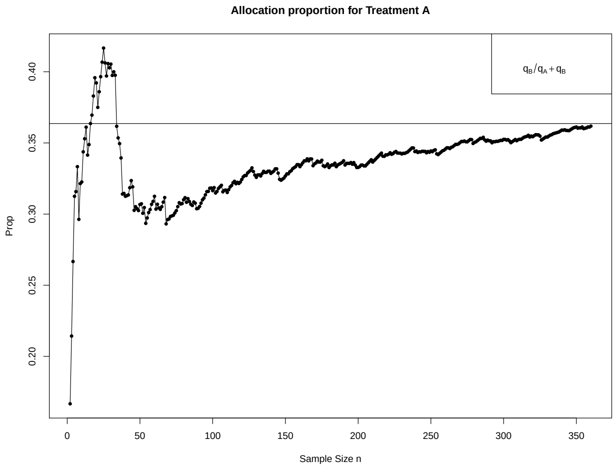


Figure: Plot of n_A/n as a function of n

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

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

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

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

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

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

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

Generalized Urn Model

- For clinical trials with K treatment$(K \geq 2)$, an important family of urn models is the generalized Friedman's urn.
- In general the basic notions of the Friedman's Urn Scheme contains $\alpha_1, \alpha_2, \ldots, \alpha_k$ number of balls for each of the k treatments. One ball is drawn at random and a balls of the same type are added to the urn and b of the other types each are added as well.
- We can note that all the urn schemes discussed before , can be treated as a special case of the above.

Generalized Urn Model

- For clinical trials with K treatment$(K \geq 2)$, an important family of urn models is the generalized Friedman's urn.
- In general the basic notions of the Friedman's Urn Scheme contains $\alpha_1, \alpha_2, \ldots, \alpha_k$ number of balls for each of the k treatments. One ball is drawn at random and a balls of the same type are added to the urn and b of the other types each are added as well.
- We can note that all the urn schemes discussed before , can be treated as a special case of the above.

Generalized Urn Model

- For clinical trials with K treatment$(K \geq 2)$, an important family of urn models is the generalized Friedman's urn.
- In general the basic notions of the Friedman's Urn Scheme contains $\alpha_1, \alpha_2, \ldots, \alpha_k$ number of balls for each of the k treatments. One ball is drawn at random and a balls of the same type are added to the urn and b of the other types each are added as well.
- We can note that all the urn schemes discussed before , can be treated as a special case of the above.

Advantages of Designs Based on Urn Models

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

Advantages of Designs Based on Urn Models

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

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.
2. Tt 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.

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.
2. Tt 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.

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 $p_A - p_B$.

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 $p_A - p_B$.

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 $p_A - p_B$.

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 $p_A - p_B$.

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 $p_A - p_B$.

Optimal Allocations

- 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

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

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

Optimal Allocations

- 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

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

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

Optimal Allocations

- 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

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

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

Optimal Allocations

- 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

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

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

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 !!

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 !!

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 !!

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**.

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**.

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**.

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**.

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 :-

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

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 :-

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

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 :-

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

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 :-

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

Sequential Maximum Likelihood Procedure

- 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 $\frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$:-
- We plot the allocation proportion for Treatment A with increasing value of n :-

Sequential Maximum Likelihood Procedure

- 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 $\frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$:-
- We plot the allocation proportion for Treatment A with increasing value of n :-

Sequential Maximum Likelihood Procedure

- 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 $\frac{\sqrt{p_A}}{\sqrt{p_A}+\sqrt{p_B}}$:-
- We plot the allocation proportion for Treatment A with increasing value of n :-

Allocation Proportion in SML Procedure

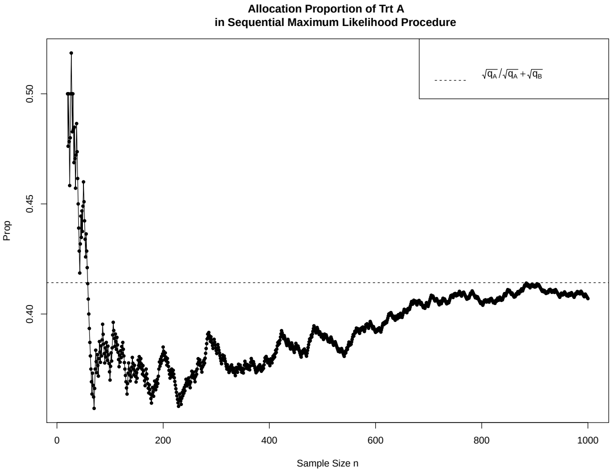


Figure: ${n_A}/{n}$ as a function of n

Doubly Adaptive Biased Coin Design

- This procedure is a generalization of the sequential maxi- mum 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.

Doubly Adaptive Biased Coin Design

- This procedure is a generalization of the sequential maxi- mum 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.

Doubly Adaptive Biased Coin Design

- This procedure is a generalization of the sequential maxi- mum 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.

Doubly Adaptive Biased Coin Design

- This procedure is a generalization of the sequential maxi- mum 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.

Doubly Adaptive Biased Coin Design

- 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.
- Then we assign patient j 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 :-

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

Doubly Adaptive Biased Coin Design

- 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.
- Then we assign patient j 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 :-

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

Doubly Adaptive Biased Coin Design

- 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.
- Then we assign patient j 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 :-

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

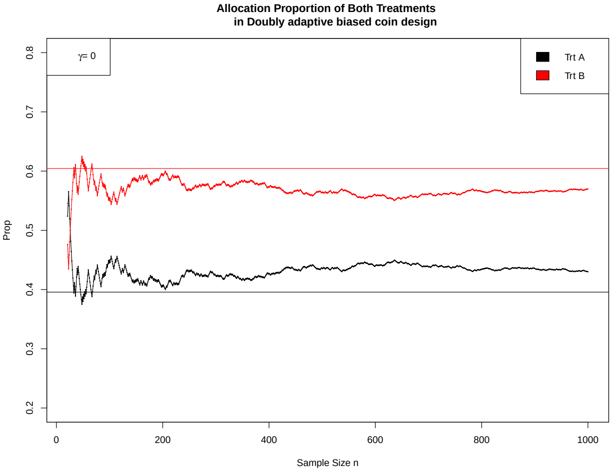
Doubly Adaptive Biased Coin Design

- 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.
- Then we assign patient j 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 :-

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

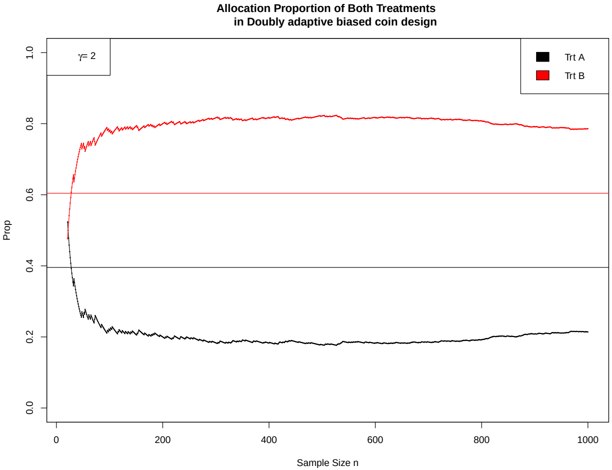
Role of Parameter γ in Determining Variability of The Procedure

At the extreme, when $\gamma = 0$, we have the sequential maximum likelihood procedure, which converges to the desired optimal allocation values :-



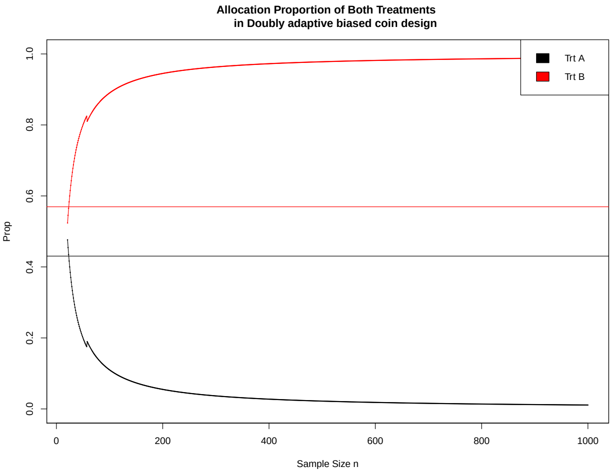
Role of Parameter γ in Determining Variability of The Procedure

As γ increases, the procedure becomes more deterministic (allocates more patients to better treatments) using simulation this can be shown :-



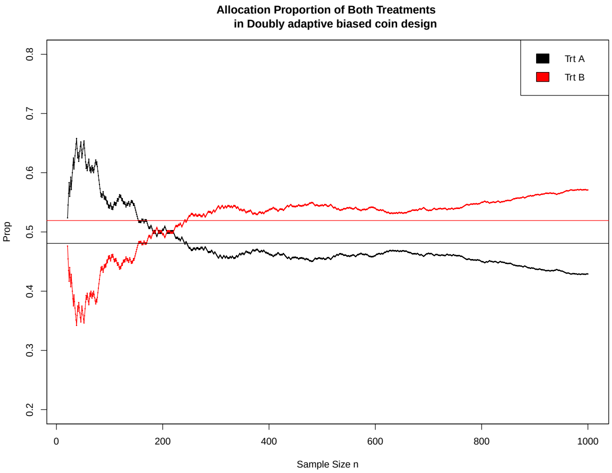
Role of Parameter γ in Determining Variability of The Procedure

For quite large values of $\gamma\,(=10)$, the procedure becomes more deterministic :-



Role of Parameter γ in Determining Variability of The Procedure

Smaller the difference between the success probabilities, larger is the variability (randomness) of the procedure :-



Variability and Power of Using Adaptive Designs

- When using response-adaptive designs in clinical trials, the number of patients assigned to each treatments are random variables.
- Therefore the power $P\,(\text{rejecting } \mathscr{H}_0 | \mathscr{H}_0 \text{ false})$ (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**.

Variability and Power of Using Adaptive Designs

- When using response-adaptive designs in clinical trials, the number of patients assigned to each treatments are random variables.
- Therefore the power $P\,(\text{rejecting } \mathscr{H}_0|\mathscr{H}_0 \text{ false})$ (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**.

Variability and Power of Using Adaptive Designs

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

$$
\begin{aligned}
\mathscr{H}_0 :& p_A = p_B \\
\mathscr{H}_1 :& p_A \neq p_B
\end{aligned}
$$

- 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**.

Variability and Power of Using Adaptive Designs

- When using response-adaptive designs in clinical trials, the number of patients assigned to each treatments 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**.

Variability and Power of Using Adaptive Designs

- 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.

Variability and Power of Using Adaptive Designs

- 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.

Variability and Power of Using Adaptive Designs

- 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.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

Variability and Power of Using Adaptive Designs

- 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 **degree of randomization** and **variability**, and the tradeoff between **power** and **expected treatment successes**.

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.

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.

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.

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.

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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

Applying Adaptive Designs

- The randomized play-the-winner rule was used in the highly controversial extracorporeal membrane oxygena- tion (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.

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.
- It is also unclear how delayed responses will affect the birth-and-death urn and the treatment effective mapping.

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.
- It is also unclear how delayed responses will affect the birth-and-death urn and the treatment effective mapping.

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.
- It is also unclear how delayed responses will affect the birth-and-death urn and the treatment effective mapping.

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.
- It is also unclear how delayed responses will affect the birth-and-death urn and the treatment effective mapping.

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.
- It is also unclear how delayed responses will affect the birth-and-death urn and the treatment effective mapping.