Response-Adaptive Randomization (RAR) in Clinical Trials

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Outline

- Motivating examples.
- Overview of the problem.
- Brief review of adaptive randomization.
- Power and variability.
- Best randomization procedures.
- Doubly-adaptive biased coin designs.
- Some recent developments.
- Further topics.
- Future of RAR.

1 One Motivating Example.

Example 1. HIV transmission. Connor et al. (1994, The New England Journal of Medicine) report a clinical trial to evaluate the drug AZT in reducing the risk of maternal-infant HIV transmission.

50-50 randomization scheme is used:

- AZT Group—239 pregnant women (**20 HIV positive infants**).
- placebo group—238 pregnant women (**60 HIV positive infants**).

Given the seriousness of the outcome of this study, it is reasonable to argue that 50-50 allocation was **unethical**. As accruing information favoring (albeit, not conclusively) the AZT treatment became available, allocation probabilities should have been **shifted from 50-50 allocation proportional to weight of evidence for AZT**. Designs which attempt to do this are called *Response-Adaptive designs (Response-Adaptive Randomization).*

If the treatment assignments had been done with the **randomized play the winner rule (RPW rule)** (Zelen 1969, JASA, Wei and Durham,1978, JASA):

- AZT Group— 360 patients
- placebo group—117 patients

then, only **60 (instead of 80)** infants would be HIV positive.

Example 2 (ECMO Trial). Extracorporeal membrane oxygenation (ECMO) is an external system for oxygenating the blood based on techniques used in cardiopulmonary bypass technology developed for cariac surgery. In the literature, there are three well-document clinical trials on evaluating the clinical effectiveness of ECMO:
(i) the Michigan ECMO study (Bartlett, *et al.* 1985);
(ii) the Boston ECMO study (Ware, 1989);
(iii) the UK ECMO trial (UK Collaborative ECMO Trials Group, 1996).

The UK ECMO trial:

50-50 randomization scheme is used:

- ECMO Group—93 infants (**28 deaths**).
- Conventional group—92 infants (**54 deaths**).

If ERADE (Hu, Zhang and He, 2007) is used, then

- ECMO Group—121 infants (**36 deaths**).
- Conventional group—64 infants (**38 deaths**).

2 Overview of the Problem.

Clinical Trials: Complex with multiple (competitive) objectives

- maximizing power to detect clinically relevant difference;
- minimizing the expected total number of failures;
- maximizing the individual patient's experience in the trial;
- minimizing total monetary cost of trial;
- etc.

Randomized designs should be used to remove the potential bias in clinical trial.

Example 3. Binary response: treatment A and B.

- p_A: $P(success|A)$, $q_A = 1 - p_A$;
- p_B: $P(success|B)$, $q_B = 1 - p_B$;
- n_A: number of patients on A;
- n_B: number of patients on B, $n = n_A + n_B$.

Some important functions:

1. An objective function, $\phi(n_A, n_B)$, power or noncentral parameter;
2. Sample size $n_A + n_B$ or total number of failures $q_A n_A + q_B n_B$;
3. Allocation proportion to treatment A, $\rho(p_A, p_B) \sim n_A/n$;

Approach 1:
With fixed $\phi(n_A, n_B)$, to minimizing sample size, $n = n_A + n_B$, the solution is called *Neyman allocation*:

$$\rho(p_A, p_B) = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}}.$$

Approach 2:
With fixed $\phi(n_A, n_B)$, to minimizing total number of failures, $q_A n_A + q_B n_B$, the solution is called *optimal allocation* (see Rosenberger et al. (2001, biometrics)):

$$\rho(p_A, p_B) = \frac{\sqrt{p_A}}{\sqrt{p_A} + \sqrt{p_B}}.$$

Tymofyeyev, Rosenberger and Hu (2007, JASA) propose a general framework to find optimal ρ.

Usually $\rho(p_A, p_B)$ depends on **unknown** parameters, how to implement these optimal allocations?

Solution: Response-Adaptive Randomization can be applied to achieve above objectives.

Three-step approach:

1. Find the optimal allocation;
2. Use sequential estimation, substituting estimates from the data accrued thus far into the optimal allocation;
3. Find an appropriate randomization procedure that will result in optimal allocation.

We call the resulting randomization procedure a *response-adaptive randomization procedure*, because the probability of assignment to treatments will depend on previous patient responses.

3 Brief review of Adaptive Randomization

3.1 Adaptive Randomization for Balancing

Complete randomization: Assign next patient to A with probability 0.5.

Disadvantages: **unbalance** among A and B (usually not powerful).

Some important designs:

- Truncated binomial design.
- Permuted block designs.
- Efron's biased coin design (Efron, 1971, Biometrika): Assign next patient to A (or B) with probability $2/3$, if there are more patients in B (or A). Use complete randomization, if equal.
- Wei's urn design (Wei, 1977, JASA and Wei, 1978, Annals).
- Generalized biased coin design (Smith, 1984, JRSSB).

3.2 Response-Adaptive Randomization

The preliminary ideas: Thompson (1933, Biometrika) and Robbins (1952, Bulletin of AMS).

Play-the-winner (PW) rule (Zelen, 1969, JASA): Assign the next patient to the same treatment if a success; assign the next patient to the opposite treatment if a failure.

Asymptotic properties:

$$n_A/n \to q_B/(q_A + q_B)$$

Disadvantages: **Not a randomized design**.

Randomized play-the-winner (RPW) rule (Wei and Durham,1978, JASA).

Begin with c balls of A and c balls of B in an urn.

- Draw A:
  - assign patient to A;
  - replace ball;
  - add 1 type A ball if treatment A is successful;
  - add 1 type B ball if treatment A is failure.
- Draw B:
  - assign patient to B;
  - replace ball;
  - add 1 type B ball if treatment B is successful;
  - add 1 type A ball if treatment B is failure.

Two main families:

(i) Urn models: PW rule; RPW rule; Generalized Friedman's urn models (Wei, 1979, JASA; Smythe, 1996, Stochastic Process. Appl.; Bai, Hu and Shen, 2002, JMVA); Randomized Polya Urn (Durham, Flournoy, and Li, 1998, CJS); Ternary Urn (Ivanova and Flournoy, 2001); Drop-the-Loser rule (Ivanova, 2003, Metrika); Generalized drop-the-Loser rule (Zhang, Chan, Cheung and Hu, 2007, Statistic Sinica), etc.

(ii) Doubly adaptive biased coin designs: Eisele and Woodroofe (1995, Annals of Statistics), Hu and Zhang (2004, Annals of Statistics), Hu and Rosenberger (2003, JASA). ERADE (Hu, Zhang and He, 2007).

Example: Extracorporeal Membrane Oxygenation (ECMO) trial using RPW rule:

The RPW rule was used in a clinical trial of extracorporeal membrane oxygenation (ECMO; Bartlett, *et al.* 1985, Pediatrics), a surgical procedure for newborns with respiratory failure.

Total 12 patients.

- ECMO group– 11 patients, all survived.
- Conventional therapy– 1 patient, died.

Valid of this trial??? No statistical conclusion.

Why??? Power and variability.

Another ECMO trial at England, 185 patients (93 in ECMO and 92 in control), 82 patients died.

In literature, researchers focused on:
(i) proposing new response-adaptive designs;
(ii) studying some properties;
(iii) comparing designs by simulations.

Some important questions:

- What is relationship among the power, expected failures and the design?
- How to compare different designs?
- What is a good design?
- etc.

4 Power and Variability

Let $\Delta = p_A - p_B$ and consider

$$H_0 : \Delta = 0 \text{ versus } H_A : \Delta \neq 0.$$

The Wald test is given by

$$Z = \frac{\hat{p}_A - \hat{p}_B}{\sqrt{\frac{\hat{p}_A \hat{q}_A}{n_A} + \frac{\hat{p}_B \hat{q}_B}{n_B}}}.$$

Under H_0, Z^2 is asymptotically chi-square with 1 degree of freedom.

Under the H_A, power is an increasing function of the the noncentrality parameter:

$$\phi = \frac{(p_A - p_B)^2}{p_A q_A/n_A + p_B q_B/n_B}$$
$$= \frac{n(p_A - p_B)^2}{\frac{p_A q_A}{\rho + (n_A/n - \rho)} + \frac{p_B q_B}{(1-\rho) - (n_A/n - \rho)}}.$$

Now we define a function

$$f(x) = \frac{(p_A - p_B)^2}{p_A q_A/[\rho + x] + p_B q_B/[(1-\rho) - x]}.$$

We have the following expansion:

$$f(x) = f(0) + f'(0)x + f''(0)x^2/2 + o(x^2).$$

After some calculation, we obtain

$$f'(0) = (p_A - p_B)^2 \frac{(p_A q_A (1-\rho)^2 - p_B q_B \rho^2)}{(p_A q_A (1-\rho) + p_B q_B \rho)^2}$$

and

$$f''(0) = -2(p_A - p_B)^2 \frac{p_A q_A p_B q_B}{((1-\rho)\rho)^3}.$$

The non-centrality parameter is

$$n^{-1}\phi = \frac{(p_A - p_B)^2}{p_A q_A/\rho + p_B q_B/(1-\rho)}$$

$$+(p_A - p_B)^2 \frac{(p_A q_A (1-\rho)^2 - p_B q_B \rho^2)}{(p_A q_A (1-\rho) + p_B q_B \rho)^2}(n_A/n - \rho)$$

$$-(p_A - p_B)^2 \frac{p_A q_A p_B q_B}{((1-\rho)\rho)^3}(n_A/n - \rho)^2$$

$$+o((n_A/n - \rho)^2)$$

$$= (I) + (II) + (III) + o((n_A/n - \rho)^2)$$

The first term (I) is determined by ρ, and represents the non-centrality parameter for a fixed design (with ρ as the target allocation proportion). Note that Neyman allocation maximizes this term.

The second term (II) represents the bias of the actual allocation from the optimal allocation. With the design shifting to different side from the target proportion ρ, the non-centrality parameter will increase or decrease according the coefficient

$$(p_A - p_B)^2 \frac{(p_A q_A (1-\rho)^2 - p_B q_B \rho^2)}{(p_A q_A (1-\rho) + p_B q_B \rho)^2}.$$

It is interesting to see that this coefficient equals 0 if and only if $p_A q_A (1-\rho)^2 - p_B q_B \rho^2 = 0$, that is

$$\rho = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}},$$

i.e., Neyman allocation.

Most procedures will be asymptotically unbiased, so we can assume

$$E(n_A/n - \rho) = 0$$

for large n. Assuming this, the average power lost of the procedure is then a function of

$$-(p_A - p_B)^2 \frac{p_A q_A p_B q_B}{((1-\rho)\rho)^3} E(n_A/n - \rho)^2,$$

which is a direct function of the variability of the design.

So we now have the precise link between power and the variability of the design. Thus we can use the

$$Var(n_A/n)$$

to compare different response-adaptive designs (with same allocation limit ρ).

The variance of n_A/n as small as possible! (Hu and Rosenberger, 2003, JASA)

5 Best Adaptive Randomization Procedures

Lower Bound of $Var(n_A/n)$?

Let $I(p_A, p_B, n_A)$ be the Fisher's information, where the expectation is taken conditional on n_A, for estimating p_A and p_B. Suppose the following some regularity conditions hold. Then the lower bound of $Var(n_A/n)$ is given by

$$\left(\frac{\partial \rho(p_A, p_B)}{\partial p_A} \;\; \frac{\partial \rho(p_A, p_B)}{\partial p_B}\right) I^{-1}(p_A, p_B, \rho(n, p_A, p_B))$$

$$\left(\frac{\partial \rho(p_A, p_B)}{\partial p_A} \;\; \frac{\partial \rho(p_A, p_B)}{\partial p_B}\right)'.$$

We refer to a response-adaptive design that attains the lower bound as **asymptotically best** for that particular target allocation $\rho(p_A, p_B)$.

If

$$\rho(p_A, p_B) = q_B/(q_A + q_B),$$

then the lower bound is

$$\frac{q_A q_B (p_A + p_B)}{(q_A + q_B)^3}.$$

For general cases, see Hu and Rosenberger (2003, JASA) and Hu, Rosenberger and Zhang (2006, JSPI) for details.

Asymptotic properties ($p_A + p_B < 1.5$) of RPW rule:

$$n_A/n \to q_B/(q_A + q_B)$$

and

$$\sqrt{n}(n_A/n - q_B/(q_A + q_B)) \to_D N(0, \sigma^2).$$

Where

$$\sigma^2 = \frac{q_A q_B[5 - 2(q_A + q_B)]}{[2(q_A + q_B) - 1](q_A + q_B)^2}.$$

Not attain the lower bound

RPW rule (urn models)

- targets the urn allocation $q_B/(q_A + q_B)$;
- applies to binary responses only.
- does not attain the lower bound.

Can we find a design that

- can target any given allocation ρ;
- attain the low bound;
- and apply to other types of responses?

Yes.

6 Doubly-Adaptive Biased Coin Design

Doubly-adaptive biased coin design (DBCD) (Eisele and Woodroofe, 1995, Annals of Statist, Hu and Zhang, 2004, Annals of Statist).

Let g be a function from $[0,1] \times [0,1]$ to $[0,1]$ satisfied certainly conditions. The procedure then allocates patient j to treatment A with probability

$$g(\frac{n_A(j-1)}{j-1}, \hat{\rho}).$$

How to choose function g?

Eisele and Woodroofe (1995) use

$$g(x,\rho) = [1 - (\frac{1}{\rho} - 1)x]_+.$$

Eisele and Woodroofe's conditions (1995):

(i) g is jointly continuous;

(ii) $g(x,x) = x$ for all $x \in [0,1]$;

(iii) $g(x,y)$ is strictly decreasing in x and strictly increasing in y on $(0,1) \times (0,1)$;

(iv) $g(x,y)$ has bounded partial derivatives in both x and y and $\partial g(x,y)/\partial x|_{x=\rho,y=\rho} \neq 0$;

(v) There are positive constants C and γ for which

$$\frac{1}{\rho} + \frac{1}{1-\rho} \leq C(\|E(\xi_A)\|^\gamma + \|E(\xi_B)\|^\gamma);$$

(vi) ρ is a continuous function and it is twice continuously differentiable on a small neighborhood of (p_A, p_B).

In fact, as pointed out by Melfi, Page and Geraldes (2001), Eisele and

Woodroofe's $g(x, \rho)$ violated their regularity conditions (iv) and (v).

Recently, Hu and Zhang (2004) proposed ($\gamma \geq 0$)

$$g(x,\rho) = \frac{\rho(\rho/x)^\gamma}{\rho(\rho/x)^\gamma + (1-\rho)((1-\rho)/(1-x))^\gamma}$$

- $\gamma = 0$, the $g(x, \rho) = \rho$ (the SMLE);
- $\gamma = \infty$, determined design.

(vii) There exists $\delta > 0$, such that $g(x, y)$ satisfies

$$g(x,y) = g(\rho,\rho) + (x-\rho)\frac{\partial g}{\partial x}|_{(\rho,\rho)}$$

$$+(y-\rho)\frac{\partial g}{\partial y}|_{(\rho,\rho)} + o(|x-\rho|^{1+\delta}) + o(|y-\rho|^{1+\delta})$$

as $(x, y) \to (\rho, \rho)$.

Let

$$\lambda = \partial g/\partial x\big|_{(\rho,\rho)},\ \eta = \partial g/\partial y\big|_{(\rho,\rho)}$$

and

$$\nabla(\rho) = (\frac{\partial \rho}{\partial p_A}, \frac{\partial \rho}{\partial p_B})'$$

. Also let

$$\sigma_3^2 = \big(\nabla(\rho)|_\Theta\big)' V \nabla(\rho)|_\Theta \text{ and } \sigma_1^2 = \rho(1-\rho).$$

Where $\Theta = (p_A, p_B)$ and

$$V = diag(\frac{Var(\xi_A)}{\rho}, \frac{Var(\xi_B)}{1-\rho}).$$

Theorem. If (i)-(iii), (vi) and (vii) are satisfied, and

$$E\|\xi_A\|^{2+\epsilon} + E\|\xi_B\|^{2+\epsilon} < \infty$$

for some $\epsilon > 0$, then

$$n^{1/2}(n_A/n - \rho) \to N(0, \sigma^2) \tag{1}$$

in distribution. Where

$$\sigma^2 = \frac{\sigma_1^2}{1-2\lambda} + \frac{2\eta^2\sigma_3^2}{(1-\lambda)(1-2\lambda)}$$

Main Techniques used: Martingale, Gaussian Approximation and Matrix theory.

For binary responses with ($\rho = q_B/(q_A + q_B)$),

$$n^{1/2}(n_A/n - \rho) \to N(0, \sigma^2_{DBCD})$$

in distribution, whenever $\lambda < 1/2$, where

$$\sigma^2_{DBCD} = \frac{q_1 q_2}{(1-2\lambda)(q_1+q_2)^2} + \frac{2\eta^2}{(1-\lambda)(1-2\lambda)} \frac{q_1 q_2 (p_1+p_2)}{(q_1+q_2)^3}$$

If

$$g(x,\rho) = \frac{\rho(\rho/x)^\gamma}{\rho(\rho/x)^\gamma + (1-\rho)((1-\rho)/(1-x))^\gamma},$$

then

$$\sigma^2_{DBCD} = \frac{q_1 q_2 (p_1+p_2)}{(q_1+q_2)^3} + \frac{2q_1q_2}{(1+2\gamma)(q_1+q_2)^3}.$$

- $\gamma = 0$, $\sigma^2_{DBCD} = \frac{q_1 q_2 (p_1+p_2+2)}{(q_1+q_2)^3}$.
- $\gamma = \infty$, $\sigma^2_{DBCD} = \frac{q_1 q_2 (p_1+p_2)}{(q_1+q_2)^3}$ (Lower bound).
- $\gamma = 2$, $\sigma^2_{DBCD} = \frac{q_1 q_2 (p_1+p_2+.4)}{(q_1+q_2)^3}$.

7 Some recent developments

To compare different designs, it is important to obtain the asymptotic distribution and asymptotic variance of n_A/n.

- Generalized Friedman's urn models (K treatments):
  - Athreya and Karlin (1968, Annals of Mathematical Statistics) obtained the consistent of n_A/n; They conjectured the asymptotic of n_A/n.
  - Bai and Hu (2005, Annals of Applied Probability) obtained the asymptotic normality and asymptotic variance of n_A/n.
  - Zhang, Hu and Cheung (2006, Annals of Applied Probability) proposed estimation-adjusted urn models that can target any given allocation and also apply to different responses.
- Optimal allocation and implementing DBCD
  - Two treatments: Binary responses (Rosenberger *et al*, 2001,

Biometrics, Rosenberger and Hu, 2004, Clinical Trial), Continuous responses (Zhang LJ and Rosenberger, 2006, Biometrics).

- K treatments: Binary responses (Tymofyeyev, Rosenberger and Hu, 2007, JASA). Continuous responses (Zhu and Hu, 2007).

- Delayed Responses
  - Generalized Friedman's urn: Bai, Hu and Rosenberger (2002, Annals of Statistics), Hu and Zhang (2004, Bernoulli).
  - Drop-the-loser rule: Zhang, Chan, Cheung and Hu (2007, Statistic Sinica).
  - DBCD: Hu, Zhang, Cheung and Chan (2007).
- Non-homogeneous Responses
  - Generalized Friedman's urn: Bai and Hu (1999, 2005, Annals of Applied Probability).
  - DBCD: Duan and Hu (2007).

8 Further Topics

- Sample size of randomized design.
  - Power is a random variable (Hu (2004) for $K = 2$, two-arm trials);
  - For $K > 2$, unknown.
- Using covariate information in adaptive designs.
  - Some preliminary results: Zhang, Hu, Cheung and Chan (2007, Annals of Statistics) and Gwise's Thesis;
  - D-optimal designs (Gwise, Hu and Hu, 2006);
  - A lot of research problems.
- Best adaptive randomizations.
  - Fully randomized procedure (best) that targets any allocation? Hu, Zhang and He (2007, Submitted)

  - Best adaptive randomization for multi-arm trials.

- Fixing power and minimizing expected failures.
  - Simulation studies of $K = 2$ (Rosenberger and Hu (2004, Clinical Trial));
  - General cases; unknown.
- Survival responses.
- Balance covariates in clinical trials.

9 Future of RAR

- White Papers on Response-Adaptive Randomization for FDA (2007).
- Adaptive Trials in the future (The Wall Street Journal, July 10, 2006).
- Hu and Rosenberger's book: *The Theory of Response Adaptive Randomization in Clinical Trials*, John Wiley, 2006.

- 63rd Deming Conference on Applied Statistics (Bio-pharmaceutical Section of ASA). Over 100 Bio-statisticians will attend the three hour session about RAR (Dec 4, 2007).

Thank You!