

A new “biased coin design” for the sequential allocation of two treatments¹

Un nuovo metodo di randomizzazione ristretta per l’allocazione sequenziale di due trattamenti

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Riassunto: Il “Biased Coin Design” introdotto da Efron è una nota tecnica di randomizzazione che consente di neutralizzare la prevedibilità propria di un esperimento clinico sequenziale, forzando il disegno ad una forma di bilanciamento. Molti autori hanno proposto estensioni di questa procedura, facendo particolare attenzione alle proprietà asintotiche. Introducendo un “Adjustable Biased Coin Design” abbiamo reso il disegno di Efron maggiormente flessibile; dopo averne analizzato le proprietà asintotiche mostriamo come, per piccoli campioni, tale procedura risulti essere quasi sempre preferibile rispetto alle altre tecniche sequenziali randomizzate prese in considerazione.

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1. Introduction

Assume we want to carry out a clinical trial to compare the efficacy of two alternative treatments of some minor ailment, like the common cold. No major ethical issue is at stake, and the main concern is maximum precision of our results. In the great majority of experiments two requirements are: a) the need for a certain amount of randomization to protect against several types of bias, including selection bias arising from being able to guess the treatment allocation, and b) some type of optimality. Assuming a linear homoscedastic model, a common, perhaps implicit, optimality criterion is seeking to minimize the variances of the estimated treatment effects and this translates into a request for balance. Suppose also that subjects arrive sequentially at an experimental site and are assigned immediately to either treatment. A classical statistical design problem is how to assign patients to treatments in order to avoid predictability and to keep a reasonable degree of balance between the treatments even for all sample sizes. These are, as is to be expected, conflicting demands.

This problem was brought to the fore in an authoritative paper by Efron (1971), who proposed his - by now widely known - BCD (*Biased Coin Design*). Several authors have extended his suggestion to more complex algorithms, see e.g. Wei (1978) and Atkinson (1982). In Smith (1984) some asymptotic properties of such designs are studied.

We define a new extension of Efron's coin: the Adjustable Biased Coin Design (ABCD). This is a class of designs where the probability of selecting the under-represented treat-

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ment at step n is a decreasing function of the difference between the two treatment allocations up to n . We compare its properties with those of the other randomized sequential mechanisms and show that in small size experiments suitable designs can be chosen within the class of ABCD's with a better trade-off between predictability and expected imbalance than most of the other biased coins. Here we present a summary of the results without the proofs, which can be found in Baldi Antognini and Giovagnoli (2001). Similar comparisons have been performed applying different indicators in Baldi Antognini and Bodini (2001), which also seem to indicate that the ABCD is preferable.

2. Various types of biased coin designs

Various suggestions have been made in the literature for restricted randomization sequential mechanisms based on the hypothetical tossing of a biased coin that force the experiments back towards more equal assignments of the treatments and at the same time minimize the predictability of the next assignments. Let $\delta_n = 1$ if the n -th patient is allocated to T_1 , $\delta_n = -1$ otherwise and $D_n = \sum_{i=1}^n \delta_i = N_1 - N_2$ the difference between the two groups after n assignments. Let $p(N_1, N_2) = \Pr(\delta_{n+1} = 1 \mid n, D_n)$ be the conditional probability that the next patient is allocated to T_1 .

Efron's Biased Coin Design Let $1/2 \leq p \leq 1$, the BCD(p) has:

$$p(N_1, N_2) = \begin{cases} p & \text{if } N_1 < N_2 \\ 1 - p & \text{if } N_1 > N_2 \\ 1/2 & \text{if } N_1 = N_2 \end{cases}$$

For $p = 1$ the design is deterministic and the balance is strongest ($T_1 T_2 T_1 \dots$ or $T_2 T_1 T_2 \dots$) while for $p = 1/2$ the design is completely randomized. Efron's choice is $p = 2/3$.

Adjustable Biased Coin Design The ABCD suggested by us consists in making $p(N_1, N_2)$ a decreasing function of D_n , so that the tendency towards balance is stronger the more we move away from it. Let $\bar{F} : \mathbb{Z} \rightarrow [0, 1]$ be a decreasing function on $\mathbb{Z}$, the set of integers, such that $\bar{F}(-x) = 1 - \bar{F}(x)$. Such a function $\bar{F}(\cdot)$ generates an ABCD letting: $p(N_1, N_2) = \bar{F}(N_1 - N_2)$. Efron's coin is obviously a special case. A particularly interesting class of functions is:

$$\bar{F}_a(x) = \begin{cases} \frac{|x|^a}{|x|^a + 1} & \text{if } x \leq -1 \\ \frac{1}{2} & \text{if } x = 0 \\ \frac{1}{x^a + 1} & \text{if } x \geq 1 \end{cases}, \quad a \in \mathbb{R}^+ \cup \{0\}. \quad (1)$$

The rationale behind this choice is to treat the case of a difference = 1 between the treatments as if the design was balanced, and to redress the balance in all the other cases. Observe that a expresses the slope of the generating function $\bar{F}(x)$ at $x = 1$, since $a = -4\bar{F}'(1)$; $a = 0$ gives the completely randomized design and as a increases the tendency to balance becomes stronger.

Other coin designs A small difference between N_1 and N_2 may be less significant the larger the size of the experiment is, thus some authors define algorithms that favour

allocation to the under-represented treatment increasingly as $|D_n|/n$ grows. In particular Wei's designs are defined by:

$$p(N_1, N_2) = f\left(\frac{N_1 - N_2}{N_1 + N_2}\right) = f(D_n/n) \quad (2)$$

where $f : [-1, 1] \rightarrow [0, 1]$ is decreasing and $f(-x) = 1 - f(x)$. This includes Efron's BCD(p) when $f(x) = \frac{1}{2} + \text{sgn}(x)(\frac{1}{2} - p)$. Special cases are also $f(x) = \frac{1-x}{2}$ and $f(x) = \frac{(1-x)^2}{(1-x)^2 + (1+x)^2}$, which correspond, respectively, to the two coin designs suggested by Atkinson:

$$p(N_1, N_2) = \frac{N_2}{N_1 + N_2} \quad \text{and} \quad p(N_1, N_2) = \frac{N_2^2}{N_1^2 + N_2^2}.$$

3. Imbalance and predictability of biased coin designs

Imbalance A natural way to measure lack of balance of the design after n steps is simply $|D_n| = |N_1 - N_2|$. Since the designs are randomized so too is the imbalance indicator $|D_n|$. We evaluate the performance of the design by calculating its expected value $E(|D_n|)$ after n steps. A perfectly balanced design will have this value = 0 or = 1 according to whether n is even or odd.

Predictability Let $J_k = 1$ if the k -th assignment is guessed correctly, $J_k = 0$ otherwise. For all the designs introduced so far, the optimal guessing strategy consists, at each step, of picking the under-represented treatment, while indifference is expressed in case of a tie. Selection bias of the design can be measured by the expected percentage of correct guesses when this strategy is used. The expected value is:

$$\begin{aligned} SB_n &= E\left(\frac{1}{n} \sum_{k=1}^n J_k\right) = \frac{1}{n} \sum_{k=1}^n \Pr(J_k = 1) \\ &= \frac{1}{n} \sum_{k=1}^n \sum_{h=0}^{k-1} \Pr(J_k = 1 \mid |D_{k-1}| = h) \Pr(|D_{k-1}| = h) \end{aligned} \quad (3)$$

For a completely randomized design any strategy is useless and the expected percentage of correct guesses is = 1/2 for any n ; this is then the optimal value of SB_n .

4. Properties of the ABC Designs

Asymptotic properties For any choice of $\bar{F}(\cdot) \in \mathfrak{F}$, the sequence $\{|D_n|, n = 0, 1, \dots, D_o = 0\}$ is a homogeneous Markov chain of period 2 on non-negative integers. The stationary distribution $\pi(\cdot)$ of the chain exists, has a maximum at $j = 1$ and is strictly decreasing for $j > 1$. We have shown that under the ABCD conditions the probabilities of perfect balance after an even or an odd number of steps, respectively $\{\Pr(|D_{2m}| = 0)\}$ and $\{\Pr(|D_{2m+1}| = 1)\}$, are decreasing in m . Since:

$$\lim_{m \rightarrow \infty} \Pr(|D_{2m}| = 0) = 2\pi(0) \quad \text{and} \quad \lim_{m \rightarrow \infty} \Pr(|D_{2m+1}| = 1) = 2\pi(1).$$

these probabilities are even greater for small values of m .

As regards predictability, the probability of guessing correctly at stage $n + 1$ given $|D_n|$ is $\bar{F}(-|D_n|)$ and

$$\lim_{n \rightarrow \infty} SB_n(\text{ABCD}) = \sum_{h=0}^{\infty} \bar{F}(-h)\pi(h); \quad (4)$$

in particular for Efron's coin:

$$\lim_{n \rightarrow \infty} SB_n(\text{BCD}(p)) = \frac{1}{2} + \frac{1}{4p}(2p - 1). \quad (5)$$

This indicates, for example, that the ABCD generated by (1) with $a = 1$ is asymptotically less predictable than the BCD(2/3) since:

$$\lim_{n \rightarrow \infty} SB_n(\text{ABCD}(\bar{F}_1)) = 0.592 \leq \lim_{n \rightarrow \infty} SB_n(\text{BCD}(2/3)) = 0.625.$$

Small sample properties Our results indicate that the ABC algorithm generated by $\bar{F}_a$ keeps the experiment fairly balanced right from the very first allocations since all the probability concentrates on the small values of $|D_n|$; the balance gets stronger as the value of a in (1) increases. We have compared values of $E[|D_n|]$ of the ABCD with those of Efron's BCD(2/3) and of (2) and the procedure ABC is seen to be preferable when $n > 8$ because $E[|D_n|]$ is smaller.

Moving on to selection bias, comparison of SB_n for designs with “similar” degrees of balance, namely BCD(2/3), the ABCD generated by $\bar{F}_2$ and the first of Atkinson's designs shows that the design ABC is less predictable for all $n \leq 18$.

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