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OPTIMALITY OF RANDOM ALLOCATION DESIGN FOR THE CONTROL OF ACCIDENTAL BIAS IN SEQUENTIAL EXPERIMENTS*

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Abstract: In comparing two treatments, suppose the suitable subjects arrive sequentially and must be treated at once. Known or unknown to the experimenter there may be nuisance factors systematically affecting the subjects. Accidental bias is a measure of the influence of these factors in the analysis of data. We show in this paper that the random allocation design minimizes the accidental bias among all designs that allocate n, out of $2n$, subjects to each treatment and do not prefer either treatment in the assignment. When the final imbalance is allowed to be nonzero, optimal and efficient designs are given. In particular the random allocation design is shown to be very efficient in this broader setup.

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1. Introduction

In comparing two treatments suppose that eligible subjects are available one at a time and must be treated at once. In this context, a statistical design is simply an allocation rule, which determines how the treatment for the $(m+1)$th subject is chosen, given the first m assignments. In this paper we are concerned with finding optimal designs assuming that the total number of subjects is predetermined (taken as $N=2n$) and that prognostic factors are not used in the assignment procedure. These assumptions are admittedly restrictive for direct practical applications. The designs studied here may hopefully provide further insights for the more complex situations.

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Most previous work in this area is based on the concept of selection bias. It is argued that if the experimenter is aware of or guesses which treatment will be assigned next, he may consciously or unconsciously bias the experiment by such decision as who is or is not a suitable experimental subject. Blackwell and Hodges (1957) defined selection bias as the number of correct guesses made by the experimenter. Using selection bias as the risk of the design, they formulated the design problem as the one of choosing a strategy in a two-person game and proved that the truncated binomial design is the statistician's minimax strategy. If n subjects are to be assigned to each treatment, the truncated binomial is such that the statistician S assigns treatment A or B to the subject with probability $\frac{1}{2}$ each, independently of all other assignments, until n of one of the treatments have been used.

In their game-theoretic formulation, Blackwell and Hodges assumed that the experimenter E tries consciously to bias the experiment. Stigler (1969) criticized this assumption and argued that in realistic situations E will tend to be timid either consciously or unconsciously. He proposed a model to quantify this tendency to timidity and based on it proved an optimality result for the random allocation design (RAD). According to this design, the statistician picks, at random without replacement, n of the first $2n$ integers and gives treatment A to the subjects corresponding to the integers selected.

Wei (1978) defined a different criterion by assuming that the outcome of the experiment can be affected via a linear model, by the experimenter's guess of which treatment will be assigned. He then proved that the random allocation design is better than the truncated binomial design in the minimax sense under the new criterion. No optimality property for the random allocation was claimed.

The use of selection bias or its modifications as design criterion can be criticized on the basis that bureaucratic devices, such as making the list of assignments inaccessible to the experimenters, are very successful in drastically reducing the selection bias. We think that the accidental bias, given in Section 2, is a more suitable criterion. It measures the amount of protection to statistical analysis provided by a design against some unknown prognostic factors associated with the subjects. In Section 3 we prove a general result, which, when specialized in the above context, says that the random allocation design minimizes the accidental bias among all designs satisfying condition (2.1) and assigning n out of $2n$ to each treatment, which include the truncated binomial design. When the perfect balance assumption is relaxed, optimal and efficient designs are found. The random allocation design is shown to be highly efficient in this broader setup.

2. Accidental bias as a design criterion

Known or unknown to the experimenter there may be nuisance factors affecting systematically the subjects in a trial. One way of measuring the influence of these factors in the analysis of data was introduced by Efron (1971) as follows.

Let $T_m = 1$ or -1 as the mth subject is assigned to treatment A or B, and let $\boldsymbol{T} = (T_1, \ldots, T_N)'$. To avoid designs that prefer either treatment, we shall restrict our attention to designs such that

$$E(\boldsymbol{T}) = \mathbf{0}. \tag{2.1}$$

Let $\boldsymbol{t}$ be a realization of $\boldsymbol{T}$. Suppose the responses of the subjects are described by the linear model $\boldsymbol{y} = \mu\boldsymbol{e} + \alpha\boldsymbol{t} + \beta\boldsymbol{z} + \boldsymbol{\varepsilon}$, where α is the treatment effect, $\boldsymbol{e}' = (1, \ldots, 1)$, $\boldsymbol{\varepsilon}$ is distributed as $\mathrm{N}(\mathbf{0}, \sigma^2 I_N)$ and $\boldsymbol{z}$ is some nuisance factor. For efficient inference about α, it would be desirable to have $\boldsymbol{t}$ orthogonal to $\boldsymbol{z}$. Being a realization of the random vector $\boldsymbol{T}$ with mean $\mathbf{0}$ and covariance matrix Σ, $\boldsymbol{t}$ cannot always be made orthogonal to $\boldsymbol{z}$. Instead we look at $E(\boldsymbol{z}'\boldsymbol{T})^2 = \boldsymbol{z}'\Sigma\boldsymbol{z}$. Since $\boldsymbol{z}$ is typically unknown, Efron (1971) proposed the largest eigenvalue of Σ as a measure of the vulnerability of a design to unknown nuisance factors and called it the *accidental bias*. Perhaps a more informative name would be 'lurking-variable bias'.

The assumption of assigning exactly n subjects, out of $2n$, to each treatment is unnecessarily restrictive as shown by Pocock (1979). It will be relaxed in the next section.

3. A complete class theorem for extended random allocation designs

In this section we show that if we want to choose a design based on its accidental bias we can restrict ourselves to the class of extended random allocation designs (ERAD). An ERAD is obtained in the following way: a distribution on the final imbalance is prescribed and then all the sequences of assignments, which lead to the same final imbalance, are forced to occur equally likely. The random allocation design is obtained by choosing zero final imbalance. An ERAD is implemented as follows. Select an integer according to the final imbalance distribution and denote it by $2x$. Then $n+x$ of the $2n$ subjects are randomly selected and assigned to treatment A, the remaining $n-x$ to treatment B.

Let Ω be the class of designs satisfying (2.1). Theorem 1 shows that if $\Omega_I \subset \Omega$ is the family of designs in Ω with I as the final imbalance distribution, then, within Ω_I, the corresponding ERAD is the design with the lowest accidental bias.

Lemma 1. *Let I be the final imbalance distribution. The corresponding extended random allocation design has accidental bias given by*

$$\frac{\operatorname{var}(I)}{2n} \text{ if } w > 0 \quad \text{and} \quad \frac{4n^2 - E(I^2)}{2n(2n-1)} \text{ if } w \le 0, \tag{3.1}$$

where

$$w = \frac{E(I^2) - 2n}{2n(2n-1)} - \left\{\frac{E(I)}{2n}\right\}^2.$$

Proof. From the definition of extended random allocation design it is obvious that

$$\mathrm{pr}(T_i=-1, T_j=1 \mid I=2x)=(n+x)(n-x)/2n(2n-1).$$

Therefore

$$C=\mathrm{pr}(T_i=-1, T_j=1)=\sum_{x=-n}^{n}\mathrm{pr}(T_i=-1, T_j=1 \mid I=2x)\,\mathrm{pr}(I=2x)$$
$$=\{n^2-E(I^2)/4\}/2n(2n-1).$$

Let $D_1=\mathrm{pr}(T_i=1, T_j=1)$ and $D_2=\mathrm{pr}(T_i=-1, T_j=-1)$, $i\neq j$. Then $D_1+D_2+2C=1$ and $E(T_iT_j)=D_1+D_2-2C=1-4C=\{E(I^2)-2n\}/2n(2n-1)$. Analogously it can be shown that $\mathrm{pr}(T_i=1)=1-\mathrm{pr}(T_i=-1)=\frac{1}{2}+E(I)/4n$ and so $\mathrm{cov}(T_i, T_j)=w$ given by (3.1) and $y=\mathrm{var}(T_i)=1-(E(I)/2n)^2$. Therefore Σ, the covariance matrix of $T=(T_1,\ldots,T_{2n})'$ where T_i is the ith assignment under the ERAD, is given by $\Sigma=w\boldsymbol{e}\boldsymbol{e}'+(y-w)I_{2n}$, where $\boldsymbol{e}=(1,\ldots,1)'$ and I_{2n} is the identity matrix of order $2n$. The eigenvalues of Σ are (Rao, 1973, p. 67) $y+(2n-1)w=\mathrm{var}(I)/2n$ with multiplicity 1 and $y-w=(4n^2-E(I^2))/(4n^2-2n)$ with multiplicity $2n-1$, thus completing the proof.

Lemma 2. *Let d be a design in Ω, and I_d its final imbalance distribution. Let $\lambda(1)\leq\cdots\leq\lambda(2n)$ be the eigenvalues of Σ. Then $\mathrm{tr}(\Sigma)=2n$, which implies $\lambda(1)\leq 1$ and $\lambda(2n)\geq 1$ and $2n\lambda(1)\leq\mathrm{var}(I_d)\leq 2n\lambda(2n)$.*

This can be easily proved by noting two facts. Under (2.1) $\mathrm{var}(T_i)=1$, for all i, implies $\mathrm{tr}(\Sigma)=2n$. Since $I_d=\boldsymbol{e}'T_d$, $\mathrm{var}(I_d)=\boldsymbol{e}'\Sigma\boldsymbol{e}$ and $\|\boldsymbol{e}\|^2=2n$.

Theorem 1. *Let $\Omega_I\subset\Omega$ be the family of all designs in Ω for which I is the final imbalance distribution. In Ω_I the corresponding ERAD is the design with the lowest accidental bias.*

Proof. Let d be a design in Ω_I. Two cases should be considered:

(i) $\mathrm{var}(I)<2n$.

By Lemma 2, $\lambda(1)$ is such that $\lambda(1)\leq\mathrm{var}(I)/2n<1$. Since $\mathrm{tr}(\Sigma)=2n$, $\lambda(2n)$, the accidental bias of d, satisfies $\lambda(2n)\geq\{2n-\lambda(1)\}/(2n-1)$ or $\lambda(2n)\geq\{4n^2-\mathrm{var}(I)\}/2n(2n-1)$, which is the accidental bias of the corresponding ERAD by Lemma 1.

(ii) $\mathrm{var}(I)\geq 2n$.

By Lemma 2, $\lambda(2n)$ satisfies $\lambda(2n)\geq\mathrm{var}(I)/2n\geq 1$. From Lemma 1 the corresponding ERAD has accidental bias $\mathrm{var}(I)/2n$, thus proving the result.

Corollary 1. *Let Ω_0 be the design in Ω with zero final imbalance. The random allocation design is the design with minimum accidental bias among all designs in Ω_0.*

While it is not possible to obtain a closed form for the accidental bias of the truncated binomial design, numerical results are easily obtained. Table 1 compares the values of the accidental bias and selection bias for the random allocation design and the truncated binomial design. The selection bias results are taken from Table 1 of Blackwell and Hodges (1957). The improvement in accidental bias of the random allocation over the truncated binomial is substantial, while the loss in selection bias of the former over the latter is slight. Note that the accidental bias of the random allocation decreases as n increases as predicted by Lemma 1, while the accidental bias of the truncated binomial increases as n increases. For large n the random allocation design is definitely superior.

Table 1
Accidental bias and selection bias of the random allocation design and the truncated binomial design

N	Selection bias		Accidental bias	
	Truncated binomial	Random allocation	Truncated binomial	Random allocation
10	6.23	6.53	2.36	1.111
20	11.76	12.24	3.05	1.053
30	17.17	17.96	3.62	1.034
40	22.51	23.49	4.11	1.026
50	27.81	28.95	4.54	1.020

4. Optimum and efficient designs

Based on the complete class theorem of Section 3, the search for optimal designs for minimizing accidental bias can be confined to the ERAD. Efron (1971) showed that within Ω the smallest accidental bias is 1 and can be attained by the complete randomization ($\Sigma = I_N$). This fact and Lemma 1, Theorem 1 imply that any ERAD with

$$E(I^2) = \mathrm{var}(I) = 2n \tag{4.1}$$

is optimal in Ω. Many ERAD can be constructed to satisfy (4.1).

In practice it is usually desirable to place a bound on the final imbalance distribution,

$$|I| \le a. \tag{4.2}$$

The maximum value var(I) can take under (4.2) is a^2. If $a^2 \ge 2n$, there are several optimal designs satisfying (4.2). In more typical situations the maximal imbalance a in (4.2) is small or moderate and $2n > a^2$ holds. There is no optimal design. The best choice is to pick the final imbalance distribution

$$I = \begin{cases} a \\ -a \end{cases} \text{ with probability } \tfrac{1}{2} \tag{4.3}$$

to maximize var(I) subject to (4.2). This design has high efficiency as will be shown later.

So far we have used the ERAD mainly because they happen to form the complete class for minimizing accidental bias. Despite this strong theoretical appeal, its use in practice is hindered by the somewhat artificial imposition of a probability distribution on the final imbalance. The random allocation design with $a=0$ remains the most natural one. Although it is not optimal, we would like to know how efficient it is. From (3.1), its accidental bias is $1+(2n-1)^{-1}$ and the loss of efficiency is only $(2n-1)^{-1}$. For $2n=30$, it is less than 4%. The design (4.3) with $0<a^2<2n$ is more efficient than the random allocation ($a=0$) and therefore is highly efficient. Since there is a broad range of ERAD with high efficiency, we recommend RAD for its simplicity and high efficiency. If selection bias is also a concern, an ERAD given in (4.3) might be a good choice. It can be implemented by picking a or $-a$ with probability $\frac{1}{2}$. The value chosen, denoted x, should not be made available to the experimenter in order to reduce selection bias. Given x, the allocation can be done sequentially. If, after the ith assignment, j A's and $i-j$ B's have been assigned, then the next assignment is A with probability $p=\max\{0,(n+x-j)/(2n-i)\}$ and B with $1-p$.

5. Remarks

Theorem 1 is not true outside Ω. Consider the family of designs such that $e'T_d=a$ with probability 1. The corresponding extended random allocation design has accidental bias

$$\frac{2n}{(2n-1)}-\frac{a^2}{2n(2n-1)},$$

but the design that concentrates on just one sequence with final imbalance a has zero accidental bias. The assumption $E(\boldsymbol{T})=\mathbf{0}$,(2.1), is essential to our result and more basically to the original definition of accidental bias. It can be argued that, without it, accidental bias should depend on both Cov($\boldsymbol{T}$) and $E(\boldsymbol{T})$. This suggests that the study of sequential designs with fixed imbalance would depend on a new definition of accidental bias, which is beyond the scope of our paper.

Other design criteria could be used for comparison. For example, in Ω_0 the random allocation design is also the design that maximizes the entropy, a common measure of randomness. Klotz (1979) gave an application of this measure in the design of clinical trials.

Our assumption that the total sample size N is known may be unrealistic in situations like clinical trials. For N unknown, sequential designs have been proposed by Efron (1971), Wei (1977), Soares and Wu (1983), and others. (Most of them satisfy $E(\boldsymbol{T})=\mathbf{0}$.) But very often a lower bound for N is available, or better still, in situations like cloud seeding experiments N may indeed be known.

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