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# BLOCK DESIGNS FOR EARLY-STAGE CLINICAL TRIALS

Paul Deheuvels\* & Gérard Derzko†

## ABSTRACT

We provide a commented list of uniform on periods incomplete block designs appropriate for early-stage clinical trials. The optimality of these designs with respect to the NN1 and NN2 nearest-neighbour correlation models studied by Kiefer and Wynn (1981) and Morgan and Chakravarti (1988) is discussed.

AMS 1980 *subject classification*. 62K10.

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## 1 Preliminaries and notation.

### 1.1 Introduction

This paper provides a selection of experimental designs, appropriate for *early-stage* clinical trials, where  $2 \leq v \leq 7$  treatments are applied to  $b$  subjects over  $2 \leq k \leq 5$  time-periods. We consider only *proper binary equireplicated block designs* [PBERD], where the subject  $i \in \{1, \dots, b\}$  receives  $k$  distinct treatments  $j(i, 1), \dots, j(i, k)$  over the time-periods  $1, \dots, k$ , each treatment being replicated  $r$  times (Rasch and Herrendörfer [RH] (1986)). A design  $\mathbf{D}$  is described by its  $b \times k$  *design matrix*  $J_{\mathbf{D}}$ , whose  $i$ -th line is  $(j(i, 1), \dots, j(i, k))$ .

### 1.2 Uniformity on periods and efficiency

Let  $\lambda_{j'j''}$  be the number of times that the pair  $(j', j'')$  of treatments is allocated to the same subject, and  $\lambda_{j'j'} = r_{j'}$  for  $1 \leq j' \neq j'' \leq v$ . Among PBERD's, a special role is played by *balanced incomplete block designs*

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\*L.S.T.A., Université Paris VI, 4 Place Jussieu, F-75252 Paris Cedex 05, France.

†Sanofi-Aventis R&D, 371, rue du Professeur Joseph Blayac, 34184 Montpellier Cedex 04, France

[BIBD], denoted by  $\text{BIBD}(v, b, r, k, \lambda)$ , for which  $\lambda_{j'j''} = \lambda$  is independent of  $1 \leq j' \neq j'' \leq v$ . *Partially balanced incomplete block designs* [PBIBD] with  $K$  associated classes are PBERD's such that  $\lambda_{j'j''}$  take  $K$  distinct values for  $1 \leq j' \neq j'' \leq v$  (see e.g. Raghavarao (1971)). For combinations of  $v, b, k$  and  $r$  for which a BIBD does not exist, the class of PBIBD's (Clatworthy (1973)) may provide some useful alternatives. We refer to Street and Street (1987), Fisher and Yates (1963), Sprott (1962) and Mathon and Rosa (1985) for methods of construction and lists of designs covering the most usual values of  $v, b, r, k$  and  $\lambda$ . A PBERD is connected if  $\text{rank}(\mathbf{C}) = v - 1$ , where  $\mathbf{C} = r\mathbf{I}_v - k^{-1}\mathbf{A}$ ,  $\mathbf{I}_v$  is the  $v \times v$  identity matrix, and  $\mathbf{A} = (\lambda_{j'j''})$ , or equivalently if there exist unbiased estimates of the treatment elementary contrasts (RH (1986) pp. 39-40 and John (1980), pp. 9-13). Let  $\Omega_{v,b,k}$  denote the class of connected PBERD's. For  $\mathbf{D} \in \Omega_{v,b,k}$  the yield of subject  $i$  in period  $h$  is assumed to be

$$Y_{ih} = \mu + \beta_i + \tau_{j(i,h)} + \pi_h + \epsilon_{ih} \text{ for } 1 \leq i \leq b \text{ and } 1 \leq h \leq k \quad (1)$$

where  $\mu$  is the mean effect,  $\beta_i$  the  $i$ -th subject effect,  $\tau_j$  the  $j$ -th treatment effect,  $\pi_h$  the  $h$ -th time-period effect, and  $\sum_i \beta_i = \sum_j \tau_j = \sum_h \pi_h = 0$ . The residuals  $\{\epsilon_{ih}\}$  form a Gaussian array with  $\mathcal{N}(0, \sigma^2)$  marginals. The assumption that these residuals are *uncorrelated* [UC] being often unrealistic, the following models have been introduced to account for within-block dependence, assuming no between-block dependence. For  $0 \leq m \leq k - 1$ , it is assumed in  $m$ -th *nearest-neighbour* [NN or NNm] models that

$$\mathbb{E}(\epsilon_{ip}\epsilon_{iq}) = \sigma^2 \rho_{|p-q|} \text{ for } 1 \leq i \leq b \text{ and } 1 \leq p, q \leq k \quad (2)$$

where  $\rho_0 = 1, \dots, \rho_m, \rho_{m+1} = \dots = \rho_{k-1} = 0$ .

The *geometric correlation* [GC or GC(R)] model is a special case of NN(k-1) with

$$\mathbb{E}(\epsilon_{ip}\epsilon_{iq}) = \sigma^2 R^{|p-q|} \text{ for } 1 \leq i \leq b \text{ and } 1 \leq p, q \leq k \quad (3)$$

The NNm and GC(R) models become UC for  $m = R = 0$  and are appropriate for analysis of *repeated measurements experiments* (Hedayat and Asfarinejad (1975, 1978), Jones and Kenward (1989). NN1-dependence was studied by Kiefer and Wynn [KW] (1981), Cheng (1983), NN2-dependence, by Morgan (1983), Morgan and Chakravarti (1988), GC-dependence, by Patterson and Hunter (1983), Kunert (1985). For general or special forms of NN(k-1)-dependence we refer to Azzalini and Giovagnoli (1987), Williams (1985, 1986), Ipinyomi (1986), Wild and Williams (1987), Russel and Eccleston (1987a, b), Martin and Eccleston (1991) and the references therein.

One may further specialize (1) by introducing for  $1 \leq j \leq v$  the first-order residual (or carryover) effect  $\gamma_j$  of the treatment  $j$  once administered, and

setting (Kunert (1984, 1985))

$$Y_{ih} = \mu + \beta_i + \tau_{j(i,h)} + \pi_h + \gamma_{j(i,h-1)} + \epsilon_{ih} \text{ for } 1 \leq i \leq b \text{ and } 1 \leq h \leq k \quad (4)$$

In early stage clinical trials, primarily aimed to study treatment effects, it is desirable for the *best linear unbiased estimator* [BLUE]  $\hat{\tau} = \{\hat{\tau}_j\}$  of  $\tau = \{\tau_j\}$  with respect to ordinary least squares [OLS] to be uncorrelated with the BLUE of the other parameters. This requires any design of interest to be *uniform on periods*, each treatment being then allocated  $b/v$  times over each time period (Patterson (1951, 1952)), in which case the OLS BLUE  $\hat{\tau}$  of  $\tau$  under (1) coincides with that obtained assuming  $\pi_h = 0$  for  $1 \leq h \leq k$ . Uniformity on periods requires that  $v$  divides  $b$ , denoted  $v|b$ , and conversely one has (Agrawal (1966a, b)), Chapter 6 of Raghavarao (1971))

**Theorem 1** (Agrawal (1966a, b)) *For any  $\mathbf{D} \in \Omega_{v,b,k}$  with  $v|b$ , the treatment sequences can be rearranged for each subject to obtain a design uniform on periods.*

Uniform on periods PBERD's are often called *Latin rectangles* if  $v = b > k$ , and Latin square designs of order  $v$  if  $v = b = k$  in which case  $J_{\mathbf{D}}$  is a  $v \times v$  Latin square. Youden (1937) proved a special case of theorem 1 for symmetrical BIBD's (with  $v = b$  and  $k = r$ ), which, when rearranged, are best-known as *Youden squares* (Shrikhande (1951)). In the sequel, the designs  $\mathbf{D} \in \Omega_{v,b,k}$  are rearranged when possible to be uniform on periods.

Among the various forms of optimality with respect to estimation of  $\tau$  (Kiefer (1975)), *A-optimality* is the most appropriate when treatments play symmetrical roles. For  $\mathbf{D} \in \Omega_{v,b,k}$  and under (1), the OLS BLUE  $u'\hat{\tau}$  of a contrast  $u'\tau$  satisfies  $\text{var}(u'\hat{\tau}) = \sigma^2 u'(\mathbf{C} + a\mathbf{J}_v)^{-1}u$ , where  $\mathbf{J}_v$  is a  $v \times v$  matrix of ones,  $a \neq 0$  and  $\mathbf{J}_v u = 0$ . *A-optimality* corresponds to a maximal value of the *efficiency factor*, averaging the variances of elementary contrasts and given by

$$E = \left\{ \frac{r}{\sigma^2(v-1)} \sum_{1 \leq j' < j'' \leq v} \text{var}(\hat{\tau}_{j'} - \hat{\tau}_{j''}) \right\}^{-1} = \frac{2}{v-1} \sum_{1 \leq j \leq v-1} \theta_j^{-1} \leq \frac{vr-b}{r(v-1)} \leq 1 \quad (5)$$

$\theta_1, \dots, \theta_{v-1}$  being the non-zero characteristic roots of  $\mathbf{C}$  (Raghavarao (1971)), pp. 58-59). The upper bound  $\frac{vr-b}{k(v-1)}$  for  $E$  in (5) is reached iff  $\mathbf{D} \in \Omega_{v,b,k}$  is a BIBD( $v, b, r, k, \lambda$ ) (Kiefer (1958), Kshirsagar (1958), Mote (1958) and Roy (1958)), in which case (John (1980), p. 15)

$$E = \frac{v(k-1)}{r(v-1)} = \frac{\lambda v}{rk}, \quad bk = rv, \quad \lambda(v-1) = r(k-1) \text{ and } b \geq v \quad (6)$$

Whenever the subclass  $\Omega_{v,b,k}^*$  of  $\text{BIBD}(v, b, r, k, \lambda)$  is not empty, it is therefore advisable to select  $\mathbf{D} \in \Omega_{v,b,k}^*$  within  $\Omega_{v,b,k}^*$  as to optimize other forms of optimality discussed below.

### 1.3 Minimal NN1 and NN2-optimal designs

For  $\text{NN}(k-1)$ -dependence, efficiency can be assessed either under *generalized least square* [GLS], assuming that  $\{\rho_r, 1 \leq r \leq k-1\}$  is known, or under *ordinary least squares* [OLS]. GLS is theoretically more efficient than OLS, but bears the disadvantage to require inference or prior knowledge on within-blocks dependence. On the other hand, OLS coincide with GLS in the UC model and is of standard use. The choice of a design is further complicated by the fact that optimal designs with respect to OLS may not be optimal with respect to GLS and conversely (Martin and Eccleston (1991)). In spite of the fact that our approach is primarily OLS-oriented with respect to NN1- and NN2-dependence, the properties of the designs we consider are, at times, also appropriate for GLS-optimality at the price of weak additional conditions on  $\{\rho_r\}$ . This point will not be discussed further.

Weak OLS universal optimality for NN1- and NN2-dependence was characterized by Kiefer and Wynn (1981), Morgan (1983) and Morgan and Chakravarti (1988) as follows. Let  $N_{j',j''}^t$  be the number of times that  $j'$  and  $j''$  are allocated to the same subject as  $t$ -th neighbours,  $e_{j',j''}$  the number of times that  $j'$  and  $j''$  are allocated to the same subject, with  $j'$  or  $j''$  on an end plot ( $h = 1$  or  $k$ ) (counted twice when both  $j'$  and  $j''$  are on an end plot), and  $f_{j',j''}$  the number of times that  $j'$  and  $j''$  are allocated to the same subject with at least one of  $j'$  and  $j''$  on a next-to-end plot ( $h = 2$  or  $k-1$ ) (counted twice if both  $j'$  and  $j''$  are on next-to-end plots).

**Theorem 2** (Kiefer and Wynn (1981)) *For  $k \geq 2$ , a  $\text{BIBD}(v, b, r, k, \lambda)$  is weakly universally optimum within  $\Omega_{v,b,k}^*$  for the NN1 model if*

$$kN_{j',j''}^1 + e_{j',j''} \text{ is independent of } 1 \leq j' \neq j'' \leq v \quad (7)$$

**Theorem 3** (Morgan and Chakravarti (1988)) *For  $k \geq 3$ , a  $\text{BIBD}(v, b, r, k, \lambda)$  is weakly universally optimum within  $\Omega_{v,b,k}^*$  for the NN2 model if*

$$\begin{aligned} (i) \quad & kN_{j',j''}^1 + e_{j',j''} \text{ is independent of } 1 \leq j' \neq j'' \leq v \\ (ii) \quad & kN_{j',j''}^2 + e_{j',j''} + f_{j',j''} \text{ is independent of } 1 \leq j' \neq j'' \leq v \end{aligned} \quad (8)$$

For  $k = 3$  (resp.  $k = 2$ ), (i) and (ii) are (resp. (i) is) equivalent to

$$N_{j',j''}^1 \text{ is independent of } 1 \leq j' \neq j'' \leq v \quad (9)$$

For complete designs ( $v = k$ ), weak universal optimality within  $\Omega_{v,b,k}^*$  with respect to the NN1 (resp. NN2) models holds iff  $N_{j'j''}^1$  is (resp.  $N_{j'j''}^1$  and  $N_{j'j''}^2$  are) independent of  $1 \leq j' \neq j'' \leq v$

We provide in section 2 for  $2 \leq k \leq 5$  and  $2 \leq v \leq 7$  a series of designs  $\mathbf{D} \in \Omega_{v,b,k}^*$  which are NN1- (resp. NN2-) *optimal* in the sense of theorem 2-3, and *minimal*, meaning that they correspond to the minimal possible value of  $b$  given  $k$  and  $v$ . The superposition  $\mathbf{D}_1 + \mathbf{D}_2$  of two NN1- (resp. NN2-) optimal BIBD's  $\mathbf{D}_1$  and  $\mathbf{D}_2$  of parameters  $(v, b_1, r_1, k, \lambda_1)$  and  $(v, b_2, r_2, k, \lambda_2)$  and design matrices  $J_{\mathbf{D}_1}$  and  $J_{\mathbf{D}_2}$  is an NN1- (resp. NN2-) optimal BIBD's of parameters  $(v, b_1 + b_2, r_1 + r_2, k, \lambda_1 + \lambda_2)$  and design matrix  $(J_{\mathbf{D}_1}, J_{\mathbf{D}_2})'$ , suitable superposition of minimal optimal designs enable to generate optimal designs for each admissible value of  $b$ .

A BIBD is *minimal or irreducible* if not the superposition of two BIBD's. Irreducible component of minimal optimal BIBD's are provided in section 2.

**Remark 1** If  $\mathbf{D} \in \Omega_{v,b,k}^*$  is NN1- (or NN2-) optimal, we obtain another NN1- (or NN2-) optimal BIBD by replacing in  $\mathbf{D}$ , for some selected subjects, the original sequence of treatments by the sequence of reverse order (this modification leaves unchanged  $N_{j'j''}^t$ ,  $e_{j'j''}$  and  $f_{j'j''}$ ). However this may affect uniformity on periods.

**Remark 2** For a BIBD( $v, b, r, k, \lambda$ ), Kiefer and Wynn (1981) showed that equality of all  $N_{j'j''}^1$  imply  $k|4\lambda$ . By theorem 2.12 and corollary 2.13 of Morgan (1983), and by theorem 2.2 of Morgan and Chakravarti (1988), an NN1 optimal BIBD( $v, b, r, k, \lambda$ ) satisfies  $k|4\lambda$  (and  $k|2\lambda$  if either  $k \neq 0 \pmod{4}$ ,  $v = 2$  or  $v = 3 \pmod{4}$ ). An NN2 optimal BIBD( $v, b, r, k, \lambda$ ) satisfies  $k(k-1)|4\lambda$  (and  $k(k-1)|2\lambda$  if either  $k \neq 0 \pmod{4}$ ,  $v = 2$  or  $v = 3 \pmod{4}$ ). Morgan and Chakravarti (1988) showed that the minimal value of  $b$  for which there exists a complete NN1- (resp. NN2-) optimal design with  $v = k$  is  $b = v$  (resp.  $b = \frac{1}{2}v(v-1)$ ).

#### 1.4 Optimal designs for the GC model

$\mathbf{D} \in \Omega_{v,b,k}^*$  is called an *equi-neighbourhood balanced incomplete block design* [EBIBD] (or a Williams design), when  $N_{j'j''}^1$  is independent of  $1 \leq j' \neq j'' \leq v$  (Kunert (1985), Williams (1949, 1950)). These designs have been investigated by Kiefer and Wynn (1981) (Street and Street (1987) pp. 333-337). A Latin square design  $\mathbf{D}$  is called *complete* (resp. *quasi-complete*) (Bailey (1984)) if every ordered (resp. unordered) pair of treatments appears once (resp. twice) in the rows and once (resp. twice) in the columns.

Williams (1949) proved the existence of a complete (resp. quasi-complete) Latin square of order  $2m$  (resp.  $2m + 1$ ) for each integer  $m$ . By theorem 3, a quasi-complete (resp. complete) Latin square design is an NN1-optimal EBIBD. A design is called *equi-neighboured* [ED] if  $N_{j',j''}^t$  is independent of  $1 \leq j' \neq j'' \leq v$  for each  $t = 1, \dots, t - 1$  (Ipinoyomi (1986)). By theorem 3, an ED is NN2-optimal if  $k = v$  or  $k = 3$  and NN1-optimal for  $k = 2$ , but needs not be NN2-optimal in general when  $4 \leq k \leq v$ .

A design  $\mathbf{D}$  has *balanced end pairs* [BEP] if the number  $N_{j',j''}^k$  of subjects receive  $j'$  and  $j''$  on end-plots is independent of  $1 \leq j' \neq j'' \leq v$ . When  $k = v$ , optimality of designs with respect to estimation of  $\tau$  and the GC model (Kunert (1985), Kiefer (1975)) is characterized as follows.

**Theorem 4** (Kunert (1985)) *Under the GC model, the universally optimal designs are characterized when  $k = v$  by the conditions:*

$$\begin{aligned} (i) \quad & kN_{j',j''}^1 + e_{j',j''} \text{ is independent of } 1 \leq j' \neq j'' \leq v \\ (ii) \quad & kN_{j',j''}^k + e_{j',j''} + f_{j',j''} \text{ is independent of } 1 \leq j' \neq j'' \leq v \end{aligned} \quad (10)$$

Cheng and Wu (1980) and Kunert (1984) considered optimality for estimation of weighted least squares [WLS] with respect to the first order carry-over UC model (4).

**Theorem 5** (Kunert (1984)) *For a first order carry-over model with uncorrelated residuals, and for  $k = v \geq 3$ , designs such that the number of times that the treatments  $j'$  is administered to a subject prior to the treatment  $j''$  is independent of  $1 \leq j' \neq j'' \leq v$  are universally optimal with respect to WLS in  $\Omega_{v,v,v}^*$ .*

For  $k \leq v$ , we refer to Martin and Eccleston (1991) for a discussion of optimality in the NN( $k - 1$ ) model (2), which includes the GC model (3).

## 1.5 Higher neighbour balancing

With the exception of (4), the models above do not consider effects due to the ordering of treatment sequences (see Remark 1). This observation leads to introducing *pairwise balanced* EBIBD's [PB] where the number of times that each ordered pair  $(j', j'')$  is allocated to the same subject in adjacent positions is independent of  $1 \leq j' \neq j'' \leq v$ . A PB-EBIBD may be generated by superposition of an arbitrary EBIBD with its *mirror-image* obtained by reversing the order of treatments for each subject.

An equi-neighboured BIBD is said to be *universally balanced* (resp. *totally balanced*), denoted by UBIBD (resp. TBIBD) if the number of times an ordered (resp. unordered) pair  $(j', j'')$  is allocated to the same subject over

the time periods  $h'$  and  $h''$  is independent of  $1 \leq j' \neq j'' \leq v$  and  $1 \leq h' \neq h'' \leq v$ . TBIBD's (resp. UBIBD's) are related to *strongly directionally equi-neighbourled designs* [SDEN] (resp. *transitive designs*) (Martin and Eccleston (1991)), *orthogonal arrays of type II of strength 2*, and *semi-balanced arrays of strength 2* (Rao (1961, 1973)). By Ipinoyomi (1986) and Martin and Eccleston (1991) TBIBD's and UBIBD's possess general properties of optimality with respect to OLS or GLS and under weak restrictions upon  $\{\rho_r, 1 \leq r \leq k-1\}$ . A UBIBD( $v, b = \frac{v!}{(v-k)!}, r = \frac{k(v-1)!}{(v-k)!}, k, \lambda = \frac{k(k-1)(v-2)!}{2(v-k)!}$ ) is generated by allocating all ordered sequences of  $k$  treatments taken among  $\{1, \dots, v\}$ . The resulting *trivial design* is uniform on periods, but requires a large number of subjects and is minimal only in special cases.

## 1.6 Cyclic designs

The *cyclic designs*  $C_v(j_1, \dots, j_k)$  (John (1981, 1987)), allocating to the  $i$ -th subject the residuals mod.  $v$  of  $\{j_1 + i - 1, \dots, j_k + i - 1\}$ , is uniform over periods with  $b = v$  and  $\lambda_{j'j''} = \lambda_{|j'-j''|}$ , where  $\lambda_1, \dots, \lambda_{v-1}$  satisfy (John (1987), pp. 64-65)

$$\lambda_m = \lambda_{v-m} \text{ for } m = 1, \dots, v-1 \quad (11)$$

By (11), cyclic designs, denoted by  $C(v, k)$ , are BIBD's for  $v = 2, 3$ , PBIBD's with  $K \leq 2$  for  $v = 4, 5$ , and  $K \leq 3$  for  $v = 5, 6$ . For connected cyclic designs (John (1987), p. 65),

$$E = \frac{k-1}{k} - \frac{1}{rk} \sum_{j=1}^{v-1} \lambda_j \cos\left(\frac{2j\pi}{v}\right) \quad (12)$$

Most optimal BIBD's in section 2 are superpositions of cyclic designs and listed as such.  $E$  is obtained, for each cyclic component, by (12) if connected, or by  $E = \infty$  if not connected.

## 1.7 Conclusion

In section 2 below, we tabulate a series of optimal designs obtained by miscellaneous techniques, including trial and error arguments. Applications of these designs will be presented elsewhere.

## 2 Some useful balanced designs

In all cases, we have the following implications.



- (i)  $UBIBD \Rightarrow TBIBD \Rightarrow ED \Rightarrow EBIBD$  and  $BEP$ ;
- (ii)  $UBIBD \Rightarrow PB, EBIBD \Rightarrow BIBD$ ;
- (iii)  $TBIBD \Rightarrow NN2\text{-optimality} \Rightarrow NN1\text{-optimality}$ ;
- (iv)  $EBIBD$  and  $k = v \Leftrightarrow NN1\text{-optimality}$ ,  $ED$  and  $k = v \Rightarrow NN2\text{-optimality}$ ;
- (v)  $UBIBD \Rightarrow$  Uniformity on periods.

(13)

Here NN1 (resp. NN2-) optimality is meant in the sense of theorems 2 and 3, and holds within  $\Omega_{v,b,k}$ . A BIBD may be either NN1-optimal, NN2-optimal, EBIBD, ED or TBIBD without being uniform on periods. Minimality is meant with respect to  $b$  in a given class. For example, a minimal UBIBD has the least possible value of  $b$  among all possible UBIBD's, given  $v$  and  $k$ , and an irreducible BIBD will be said a *minimal BIBD*. In view of (13), and to avoid repetitions, we only mention minimality with respect to the less stringent condition. For example, if a design is both a minimal UBIBD and a minimal BIBD, we only mention the latter property.

When possible, designs are listed as superpositions of cyclic designs with the notation of section 1. When such decomposition do not exist, designs  $\mathbf{D}$  are given by listing lines of  $J_{\mathbf{D}}$ . Tables are ordered by increasing values of  $k \in 2, \dots, 5$ , and for a fixed  $k$ , by increasing values of  $v \in \{k, \dots, 7\}$ . Designs which are not uniform on periods are labeled by a “\*”. The following tables give the least possible number of subjects required to obtain NN1- (resp. NN2-) optimal BIBD's with the number (#) of the corresponding design.

NN1	$v = 2$	$v = 3$	$v = 4$	$v = 5$	$v = 6$	$v = 7$
$k = 2$	$b = 2$ (#1)	$b = 3$ (#2a)	$b = 12$ (#3a)	$b = 10$ (#4a)	$b = 30$ (#5a)	$b = 21$ (#6a)
$k = 3$		$b = 3$ (#7a)	$b = 12$ (#8a, b)	$b = 10$ (#9a, b, c)	$b = 30$ (#10a)	$b = 21$ (#11a)
$k = 4$			$b = 4$ (#12a)	$b = 10$ (#13a, b)	$b = 30$ (#14a)	$b = 14$ (#15a)
$k = 5$				$b = 5$ (#16a)	$b = 30$ (#17a)	$b = 21$ (#18a)

**Table 1.** Minimal value of  $b$  for uniform on period NN1-optimal BIBD's

NN2	$v = 3$	$v = 4$	$v = 5$	$v = 6$	$v = 7$
$k = 3$	$b = 3$ (#7a)	$b = 12$ (#8a, b)	$b = 10$ (#9a, b, c)	$b = 30$ (#10a)	$b = 21$ (#11a)
$k = 4$		$b = 6$ (#12a)	$b = 10$ (#13a, b)	$b = 30$ (#14a)	$b = 14$ (#15b)
$k = 5$			$b = 10$ (#16b)	$b = 60$ (#17b)	$b = 21$ (#18b)

**Table 2.** Minimal value of  $b$  for uniform on period NN2-optimal BIBD's (\*)

TBIBD	$v = 2$	$v = 3$	$v = 4$	$v = 5$	$v = 6$	$v = 7$
$k = 2$	$b = 2$ (#1)	$b = 3$ (#2a)	$b = 12$ (#3a)	$b = 10$ (#4a)	$b = 30$ (#5a)	$b = 21$ (#6a)
$k = 3$		$b = 3$ (#7a)	$b = 12$ (#8a, b)	$b = 10$ (#9a, b, c)	$b = 30$ (#10a)	$b = 21$ (#11a)
$k = 4$			$b = 12$ (#12g)	$b = 10$ (#13a, b)	$b = 60$ (#14d)	$b = 21$ (#15b)
$k = 5$				$b = 10$ (#16b)	$b = 60$ (#17b)	$b = 21$ (#18a)

**Table 3.** Minimal value of  $b$  for uniform on period TBIBD's (\*)

UBIBD	$v = 2$	$v = 3$	$v = 4$	$v = 5$	$v = 6$	$v = 7$
$k = 2$	$b = 2$ (#1)	$b = 6$ (#2b)	$b = 12$ (#3a)	$b = 20$ (#4d)	$b = 30$ (#5a)	$b = 42$ (#6e)
$k = 3$		$b = 6$ (#7b)	$b = 24$ (#8c)	$b = 20$ (#9d)	$b = 60$ (#10e)	$b = 42$ (#11b)
$k = 4$			$b = 24$ (#12h)	$b = 20$ (#13c)	$b = 60$ (#14d)	$b = 42$ (#15c)
$k = 5$				$b = 20$ (#16e)	$b = 120$ (#17c)	$b = 42$ (#18b)

**Table 4.** Minimal value of  $b$  for uniform on period UBIBD's (\*)

(\*) Minimality of designs in Tables 1, 2, 3 is proved, with exception of Design #17b in Table 2, Design #14b in Table 3 and Design #17c in Table 4.

## 2.1 Designs for $k=2$

Minimal BIBD's are obtained here by listing all treatment pairs  $\{1, \dots, v\}$ . NN2-optimality is meaningless, NN1-optimality  $\Leftrightarrow$  ED  $\Leftrightarrow$  EBIBD  $\Leftrightarrow$  BEP  $\Leftrightarrow$  BIBD  $\Leftrightarrow$  TBIBD, and PB  $\Leftrightarrow$  UBIBD. Therefore, we only mention whether the design is uniform on periods, TBIBD, UBIBD or not.

**Design 1**  $v = 2 : UBIBD(v = 2, b = 2, r = 2, k = 2, \lambda = 2), E = 100\%$ .  
 $C_2(1, 2)$

This minimal BIBD is a complete Latin square design.

**Design 2a**  $v = 3 : TBIBD(v = 3, b = 3, r = 2, k = 2, \lambda = 1), E = 75\%$ .  
 $C_3(1, 2)$

This minimal BIBD is symmetrical. The superposition of this design with its mirror-image yields a minimal UBIBD (design 2b).

**Design 2b**  $v = 3 : UBIBD(v = 3, b = 6, r = 4, k = 2, \lambda = 2), E = 75\%$ .  
 $C_3(1, 2) + C_3(1, 3)$ .

**Design 3a**  $v = 4 : UBIBD(v = 4, b = 12, r = 6, k = 2, \lambda = 2), E = 2/3 \approx 67\%$ .

$C_4(1, 2) + C_4(1, 3) + C_4(1, 4)$

This minimal uniform on periods TBIBD is superposition of two (non uniform over periods) minimal TBIBD's (Designs 3b, c).

**Design 3b\***  $v = 4 : TBIBD(v = 4, b = 6, r = 3, k = 2, \lambda = 1), E = 2/3 \approx 67\%$ .

$(1, 2), (1, 3), (4, 1), (2, 3), (2, 4), (4, 3)$

**Design 3c\***  $v = 4 : TBIBD(v = 4, b = 6, r = 3, k = 2, \lambda = 1), E = 2/3 \approx 67\%$ .

$(2, 1), (3, 1), (1, 4), (3, 2), (4, 2), (3, 4)$

Among the three components (Design 3d,e,f) of design 3a, Design 3d is not connected.

**Design 3d**  $v = 4 : C(v = 4, k = 2), E = 50\%$

$C_4(1, 2)$

**Design 3e**  $v = 4 : C(v = 4, k = 2), E = \infty$

$c_4(1, 3)$

**Design 3f**  $v = 4 : C(v = 4, k = 2), E = 50\%$

$c_4(1, 4)$

**Design 4a**  $v = 5 : TBIBD(v = 5, b = 10, r = 4, k = 2, \lambda = 1), E = 5/8 \approx 62\%$ .

$C_5(1, 2) + C_5(1, 3)$

This minimal BIBD is superposition of two cyclic designs (designs 4b,c).

**Design 4b**  $v = 5 : C(v = 5, k = 2)$

$C_5(1, 2)$

**Design 4c**  $v = 5 : C(v = 5, k = 2)$

$C_5(1, 3)$

The superposition of design 4 with its mirror image yields a minimal UBIBD (design 4d).

**Design 4d**  $v = 5 : UBIBD(v = 5, b = 20, r = 8, k = 2, \lambda = 2), E = 5/8 \approx 62\%$ .

$C_5(1, 2) + C_5(1, 3) + C_5(1, 4) + C_5(1, 5)$ .

**Design 5a**  $v = 6 : UBIBD(v = 6, b = 30, r = 10, k = 2, \lambda = 2), E = 60\%$ .

$C_6(1, 2) + C_6(1, 3) + C_6(1, 4) + C_6(1, 5) + C_6(1, 6)$ .

This minimal uniform on periods BIBD is superposition of two minimal (non uniform on periods) BIBD's (Designs 5b,c). Among the five cyclic components (Designs 5d,e,f,g,h) of Design 5a, Design 5e,f,g are not connected.

**Design 5b\***  $v = 6 : TBIBD(v = 6, b = 15, r = 5, k = 2, \lambda = 1), E = 60\%$ .

$(1, 2), (1, 3), (1, 4), (5, 1), (6, 1), (3, 2), (2, 4), (2, 5), (2, 6), (3, 4), (5, 3), (6, 3), (4, 5), (4, 6), (5, 6)$ .

**Design 5c\***  $v = 6 : EBIBD(v = 6, b = 15, r = 5, k = 2, \lambda = 1), E = 60\%$ .

$(2, 1), (3, 1), (4, 1), (1, 5), (1, 6), (2, 3), (4, 2), (5, 2), (6, 2), (4, 3), (3, 5), (3, 6), (5, 4), (6, 4), (6, 5)$ .

**Design 5d**  $v = 6 : C(v = 6, k = 2)$ .

$C_6(1, 2)$ .

**Design 5e**  $v = 6 : C(v = 6, k = 2), E = \infty$ .

$C_6(1, 3)$ .

**Design 5f**  $v = 6 : C(v = 6, k = 2), E = \infty$ .

$C_6(1, 4)$ .

**Design 5g**  $v = 6 : C(v = 6, k = 2), E = \infty$ .

$C_6(1, 5)$ .

**Design 5h**  $v = 6 : C(v = 6, k = 2)$ .

$C_6(1, 6)$ .

**Design 6a**  $v = 7 : TBIBD(v = 7, b = 21, r = 6, k = 2, \lambda = 1), E = 7/12 \approx 58\%$ .

$C_7(1, 2) + C_7(1, 3) + C_7(1, 4)$

This minimal BIBD is the superposition of three cyclic designs (Designs 6b,c,d).

**Design 6b**  $v = 7 : C(v = 7, k = 2)$ .

$C_7(1, 2)$ .

**Design 6c**  $v = 7 : C(v = 7, k = 2)$ .

$C_7(1, 3)$ .

**Design 6d**  $v = 7 : C(v = 7, k = 2)$ .

$C_7(1, 4)$ .

The superposition of Design 6a with its mirror image yields a minimal UBIBD (Design 6e).

**Design 6e**  $v = 7 : UBIBD(v = 7, b = 42, r = 12, k = 2, \lambda = 2), E = 7/12 \approx 58\%$ .

$C_7(1, 2) + C_7(1, 3) + C_7(1, 4) + C_7(1, 5) + C_7(1, 6) + C_7(1, 7)$

## 2.2 Designs for $k=3$

By theorem 4.15 in RH (1986) (Hannani (1961)), (6) is here sufficient for existence of a  $BIBD(v, b, r, k, \lambda)$ . By (13) and theorem 1.3, NN1-optimality  $\Leftrightarrow$  NN2-optimality  $\Leftrightarrow$  EBIBD, and ED  $\Leftrightarrow$  EBIBD and BEP. Theorem 5.2 of Kiefer and Wynn (1981) shows that an NN1-optimal  $BIBD(v, b, r, k, \lambda)$  exists iff  $\lambda = 3m$ ,  $b = mv(v - 1)/2$  and  $r = 3m(v - 1)/2$ , whence the minimum value of  $b$  given  $v$  is  $b = v(v - 1)/2$  for odd  $v$  and  $b = v(v - 1)$  for even  $v$ . We only mention below whether the design is uniform on periods, EBIBD, ED, TBIBD or UBIBD.

**Design 7a**  $v = 3 : TBIBD(v = 3, b = 3, r = 3, k = 3, \lambda = 3), E = 100\%$

$C_3(1, 2, 3)$

This minimal TBIBD is a quasi-complete Latin square design of order 3. The superposition of this design with its mirror image yield a minimal UBIBD (Design 7b).

**Design 7b**  $v = 3 : UBIBD(v = 3, b = 6, r = 6, k = 3, \lambda = 6), E = 100\%$   
 $C_3(1, 2, 3) + C_3(1, 3, 2)$

**Design 8a**  $v = 4 : TBIBD(v = 4, b = 12, r = 9, k = 3, \lambda = 6), E = 8/9 \approx 89\%$   
 $C_4(1, 2, 3) + C_4(1, 3, 2) + C_4(1, 4, 2)$

**Design 8b**  $v = 4 : TBIBD(v = 4, b = 12, r = 9, k = 3, \lambda = 6), E = 8/9 \approx 89\%$   
 $C_4(1, 2, 4) + C_4(1, 3, 4) + C_4(1, 4, 3)$

Designs 8a,b are minimal TBIBD's. Each cyclic component  $C_4(1, 2, 3)$ ,  $C_4(1, 3, 2)$ ,  $C_4(1, 4, 2)$ ,  $C_4(1, 2, 4)$ ,  $C_4(1, 3, 4)$ ,  $C_4(1, 4, 3)$  is an irreducible BIBD( $v = 4, b = 4, r = 3, k = 3, \lambda = 2$ ) with  $E \approx 89\%$ . The superposition of Designs 8a,b is a minimal UBIBD (Design 8c).

**Design 8c**  $v = 4 : UBIBD(v = 4, b = 24, r = 18, k = 3, \lambda = 12), E = 8/9 \approx 89\%$   
 $C_4(1, 2, 3) + C_4(1, 3, 2) + C_4(1, 4, 2) + C_4(1, 2, 4) + C_4(1, 3, 4) + C_4(1, 4, 3)$

**Design 9a**  $v = 5 : TBIBD(v = 5, b = 10, r = 6, k = 3, \lambda = 3), E = 5/6 \approx 83\%$   
 $C_5(1, 2, 3) + C_5(1, 3, 5)$ .

**Design 9b**  $v = 5 : TBIBD(v = 5, b = 10, r = 6, k = 3, \lambda = 3), E = 5/6 \approx 83\%$   
 $C_5(1, 2, 4) + C_5(1, 4, 5)$ .

**Design 9c**  $v = 5 : TBIBD(v = 5, b = 10, r = 6, k = 3, \lambda = 3), E = 5/6 \approx 83\%$   
 $C_5(1, 3, 4) + C_5(1, 2, 5)$ .

Designs 9a,b,c are minimal BIBD's. Each is superposition of designs of efficiency  $E \approx 83\%$

**Design 9d**  $v = 5 : UBIBD(v = 5, b = 20, r = 12, k = 3, \lambda = 6), E = 5/6 \approx 83\%$   
 $C_5(1, 2, 3) + C_5(1, 3, 5) + C_5(1, 4, 2) + C_5(1, 5, 4)$ .

Design 9d is minimal UBIBD with TBIBD components  $C_5(1, 2, 3) + C_5(1, 3, 5)$  and  $C_5(1, 4, 2) + C_5(1, 5, 4)$ .

**Design 10a**  $v = 6 : TBIBD(v = 6, b = 30, r = 15, k = 3, \lambda = 6), E = 4/5 = 80\%$

(Design 10b) + (Design 10c) + (Design 10d).

This minimal period-balanced BIBD is superposition of Designs 10b,c,d. Each is an irreducible BIBD, but neither is uniform on periods, nor with balanced end pairs. Up to permutations of treatments within each subject, designs 10b,c,d coincide with a design given on p. 170 in RH (1986) and in Example 3.1.5 of Morgan (1983). The superposition of design 10a with its mirror image yields a minimal UBIBD (Design 10e).

**Design 10b\***  $v = 6 : BIBD(v = 6, b = 10, r = 5, k = 3, \lambda = 2), E = 4/5 = 80\%$

(1, 2, 5), (1, 2, 6), (1, 3, 4), (1, 3, 6), (1, 4, 5), (2, 3, 4), (2, 3, 5), (2, 4, 6), (3, 5, 6), (4, 5, 6)

**Design 10c\***  $v = 6 : BIBD(v = 6, b = 10, r = 5, k = 3, \lambda = 2), E = 4/5 = 80\%$

(5, 1, 2), (6, 1, 2), (4, 1, 3), (6, 1, 3), (5, 1, 4), (4, 2, 3), (5, 2, 3), (6, 2, 4), (6, 3, 5), (6, 4, 5)

**Design 10d\***  $v = 6 : BIBD(v = 6, b = 10, r = 5, k = 3, \lambda = 2), E = 4/5 = 80\%$

(2, 5, 1), (2, 6, 1), (3, 4, 1), (3, 6, 1), (4, 5, 1), (3, 4, 2), (3, 5, 2), (4, 6, 2), (5, 6, 3), (5, 6, 4)

**Design 10e**  $v = 6 : UBIBD(v = 6, b = 60, r = 30, k = 3, \lambda = 12), E = 4/5 = 80\%$

(1, 2, 5), (1, 2, 6), (1, 3, 4), (1, 3, 6), (1, 4, 5), (2, 3, 4), (2, 3, 5), (2, 4, 6), (3, 5, 6), (4, 5, 6)  
(5, 2, 1), (6, 2, 1), (4, 3, 1), (6, 3, 1), (5, 4, 1), (4, 3, 2), (5, 3, 2), (6, 4, 2), (6, 5, 3), (6, 5, 4)  
(5, 1, 2), (6, 1, 2), (4, 1, 3), (6, 1, 3), (5, 1, 4), (4, 2, 3), (5, 2, 3), (6, 2, 4), (6, 3, 5), (6, 4, 5)  
(2, 1, 5), (2, 1, 6), (3, 1, 4), (3, 1, 6), (4, 1, 5), (3, 2, 4), (3, 2, 5), (4, 2, 6), (5, 3, 6), (5, 4, 6)  
(2, 5, 1), (2, 6, 1), (3, 4, 1), (3, 6, 1), (4, 5, 1), (3, 4, 2), (3, 5, 2), (4, 6, 2), (5, 6, 3), (5, 6, 4)  
(1, 5, 2), (1, 6, 2), (1, 4, 3), (1, 6, 3), (1, 5, 4), (2, 4, 3), (2, 5, 3), (2, 6, 4), (3, 6, 4), (4, 6, 5)

**Design 11a**  $v = 7 : TBIBD(v = 7, b = 21, r = 9, k = 3, \lambda = 3), E = 7/9 \approx 78\%$

$C_7(1, 2, 4) + C_7(1, 5, 6) + C_7(1, 3, 7)$  also  $C_7(1, 3, 4) + C_7(1, 2, 6) + C_7(1, 5, 7)$

Design 11a is a minimal TBIBD. Each of its three components is a symmetrical irreducible BIBD( $v = 7, b = 7, r = 3, k = 3, \lambda = 1$ ) with  $E = 7/9 \approx 78\%$ . The superposition of Design 11a with its mirror image yields a minimal UBIBD (Design 11b).

**Design 11b**  $v = 7 : UBIBD(v = 7, b = 42, r = 18, k = 3, \lambda = 6), E = 7/9 \approx 78\%$

$C_7(1, 2, 4) + C_7(1, 5, 6) + C_7(1, 3, 7) + C_7(1, 6, 5) + C_7(1, 7, 3) + C_7(1, 4, 2)$

also

$C_7(1, 3, 4) + C_7(1, 2, 6) + C_7(1, 5, 7) + C_7(1, 7, 5) + C_7(1, 4, 3) + C_7(1, 6, 2)$

### 2.3 Designs for $k=4$

By Theorem 4.15 in RH (1986) (Hanani (1961, 1970, 1972)), (6) is here sufficient for existence of a BIBD( $v, b, r, k, \lambda$ ).

**Design 12a**  $v = 4 : EBIBD(v = 4, b = 4, r = 4, k = 4, \lambda = 4), E = 100\%$   
 $C_4(1, 2, 3, 4)$

This minimal NN1-optimal, symmetrical, PB, irreducible EBIBD is a complete Latin square design. On the other hand, it is not NN2-optimal, nor BEP, nor TBIBD.

**Design 12b**  $v = 4 : EBIBD(v = 4, b = 4, r = 4, k = 4, \lambda = 4), E = 100\%$   
 $C_4(1, 2, 4, 3)$

**Design 12c**  $v = 4 : EBIBD(v = 4, b = 4, r = 4, k = 4, \lambda = 4), E = 100\%$   
 $(1, 4, 3, 2), (2, 3, 4, 1), (3, 1, 2, 4), (4, 2, 1, 3)$

**Design 12d**  $v = 4 : EBIBD(v = 4, b = 4, r = 4, k = 4, \lambda = 4), E = 100\%$   
 $(1, 2, 3, 4), (2, 4, 1, 3), (3, 1, 4, 2), (4, 3, 2, 1)$

Designs 12b,c,d are minimal NN1-optimal symmetrical EBIBD's. Neither is NN2-optimal nor with balanced end pairs. Design 12b is cyclic, whereas Designs 12c,d are not.

**Design 12e\***  $v = 4 : EBIBD(v = 4, b = 6, r = 6, k = 4, \lambda = 6), E = 100\%$   
 $(1, 2, 3, 4), (3, 1, 4, 2), (1, 4, 3, 2), (3, 1, 2, 4), (1, 2, 4, 3), (4, 1, 3, 2)$

**Design 12f\***  $v = 4 : EBIBD(v = 4, b = 6, r = 6, k = 4, \lambda = 6), E = 100\%$   
 $(2, 4, 1, 3), (4, 3, 2, 1), (2, 3, 4, 1), (4, 2, 1, 3), (2, 3, 1, 4), (3, 4, 2, 1)$

Designs 12e,f are minimal NN2-optimal symmetrical and irreducible EBIBD's. However, neither is uniform on periods.



**Design 12g**  $v = 4 : TBIBD(v = 4, b = 12, r = 12, k = 4, \lambda = 12), E = 100\%$

(Design 12b) + (Design 12c) + (Design 12d) = (Design 12e) + (Design 12f)

This design is minimal uniform on periods NN2-optimal EBIBD. By remark 2, for  $v = 4$ , an NN2-optimal design with  $k = v$  requires at least  $b = v(v - 1)/2 = 6$  subjects. However, in this case  $v = 4$  does not divide  $b = 6$  so that uniformity on periods cannot hold. Therefore, Designs 12e,f being NN2-optimal EBIBD's, cannot be rearranged to be uniform over periods.

**Design 12h**  $v = 4 : UBIBD(v = 4, b = 24, r = 24, k = 4, \lambda = 24), E = 100\%$

$C_4(1, 2, 3, 4), C_4(1, 2, 4, 3), C_4(1, 3, 2, 4), C_4(1, 3, 4, 2), C_4(1, 4, 2, 3), C_4(1, 4, 3, 2)$

This design is minimal UBIBD.

**Design 13a**  $v = 5 : TBIBD(v = 5, b = 10, r = 8, k = 4, \lambda = 6), E = 15/16 \approx 94\%$ .

$C_5(1, 2, 3, 4) + C_5(1, 3, 5, 2)$ .

**Design 13b**  $v = 5 : TBIBD(v = 5, b = 10, r = 8, k = 4, \lambda = 6), E = 15/16 \approx 94\%$ .

$C_5(1, 5, 4, 3) + C_5(1, 4, 2, 5)$ .

Designs 13a,b are minimal NN2- (and NN1-) optimal BIBD's, each being superposition of two symmetrical irreducible BIBD( $v = 5, b = 5, r = 4, k = 4, \lambda = 3$ )'s. The superposition of Designs 13a,b yields a minimal UBIBD (Design 13c). There does not exist an NN1-optimal BIBD( $v = 5, b = 5, r = 4, k = 4, \lambda = 3$ ), as follows from Lemma 4.9 of Morgan (1983) which implies (6) cannot be satisfied for  $\lambda = 3$  and  $k = 4$ .

**Design 13c**  $v = 5 : UBIBD(v = 5, b = 20, r = 16, k = 4, \lambda = 12), E = 15/16 \approx 94\%$ .

$C_5(1, 2, 3, 4) + C_5(1, 3, 5, 2) + C_5(1, 5, 4, 3) + C_5(1, 4, 2, 5)$ .

**Design 14a**  $v = 6 : EBIBD(v = 6, b = 30, r = 20, k = 4, \lambda = 12), E = 90\%$ .

$C_6(1, 6, 2, 4) + C_6(1, 6, 5, 3) + C_6(1, 2, 4, 3) + C_6(1, 4, 5, 2) + C_6(1, 3, 6, 2) =$   
Design 14b + Design 14c.

This minimal NN2 (and NN1-) optimal BIBD is ED and superposition of two irreducible non uniform on periods BIBD's (Designs 14b,c) (Cheng (1983), p246). It is not a TBIBD.

**Design 14b\***  $v = 6 : BIBD(v = 6, b = 15, r = 10, k = 4, \lambda = 6), E = 90\%$ .

(1, 6, 2, 4), (2, 1, 3, 5), (3, 2, 4, 6), (4, 3, 5, 1), (5, 4, 6, 2), (6, 5, 1, 3), (1, 2, 4, 3), (2, 3, 5, 4), (3, 4, 6, 5), (4, 5, 1, 6), (5, 6, 1, 2), (6, 1, 3, 2), (1, 4, 5, 2), (2, 5, 6, 3), (3, 6, 1, 4).

**Design 14c\***  $v = 6 : BIBD(v = 6, b = 15, r = 10, k = 4, \lambda = 6), E = 90\%$ .

(1, 6, 5, 3), (2, 1, 6, 4), (3, 2, 1, 5), (4, 3, 2, 6), (5, 4, 3, 1), (6, 5, 4, 2), (1, 3, 6, 2), (2, 4, 1, 3), (3, 5, 2, 4), (4, 6, 3, 5), (5, 1, 4, 6), (6, 2, 5, 1), (4, 1, 2, 5), (5, 2, 3, 6), (6, 3, 4, 1).

**Design 14d**  $v = 6 : UBIBD(v = 6, b = 60, r = 40, k = 4, \lambda = 24), E = 90\%$ .

$C_6(1, 6, 2, 4) + C_6(1, 6, 5, 3) + C_6(1, 2, 4, 3) + C_6(1, 4, 5, 2) + C_6(1, 3, 6, 2)$   
 $+ C_6(1, 5, 3, 4) + C_6(1, 3, 4, 5) + C_6(1, 2, 6, 5) + C_6(1, 4, 3, 6) + C_6(1, 5, 2, 6)$

This minimal UBIBD, superposition of Design 14a with its mirror image, is conjectured to be a minimal TBIBD.

**Design 15a**  $v = 7 : EBIBD(v = 7, b = 14, r = 8, k = 4, \lambda = 4), E = 7/8 \approx 88\%$ .

$C_7(1, 2, 7, 4) + C_7(1, 2, 5, 3)$ .

This minimal NN1-optimal BIBD, superposition of two irreducible EBIBD( $v = 7, b = 7, r = 4, k = 4, \lambda = 2$ )'s, is obtained via the construction pp. 749-750 in KW (1981). By example 5.1 of KW (1981) there does not exist an NN1-optimal BIBD( $v = 7, b = 7, r = 4, k = 4, \lambda = 2$ ). The following five designs share the properties of Design 15a.

$C_7(1, 2, 7, 4) + C_7(1, 2, 5, 3), C_7(1, 2, 3, 6) + C_7(1, 3, 5, 2), C_7(1, 3, 2, 5) + C_7(1, 3, 6, 2),$   
 $C_7(1, 2, 7, 5) + C_7(1, 2, 6, 3), C_7(1, 3, 2, 6) + C_7(1, 2, 4, 7)$ .

**Design 15b**  $v = 7 : TBIBD(v = 7, b = 21, r = 12, k = 4, \lambda = 6), E = 7/8 \approx 88\%$ .

$C_7(1, 2, 4, 5) + C_7(1, 4, 3, 6) + C_7(1, 3, 7, 2)$ .

This minimal NN2-optimal BIBD is superposition of three designs of efficiency  $E \approx 85\%$ , neither of which is a BIBD (see Theorem 3.6 of Morgan (1983), Patterson (1951), Jones and Kenward (1989) p. 200). Minimality follows from Corollary 3.9 of Morgan (1983).

**Design 15c**  $v = 7 : UBIBD(v = 7, b = 42, r = 24, k = 4, \lambda = 12), E = 7/8 \approx 88\%$ .

$$C_7(1, 2, 4, 5) + C_7(1, 4, 3, 6) + C_7(1, 3, 7, 2) + C_7(1, 7, 5, 4) + C_7(1, 5, 6, 3) + C_7(1, 6, 2, 7).$$

This minimal UBIBD is superposition of design 15a with its mirror image. The following three designs are also UBIBD( $v = 7, b = 42, r = 24, k = 4, \lambda = 12$ ).

$$C_7(1, 2, 3, 4) + C_7(1, 4, 7, 3) + C_7(1, 3, 5, 7) + C_7(1, 7, 6, 5) + C_7(1, 5, 2, 6) + C_7(1, 6, 4, 2)$$

$$C_7(1, 4, 2, 5) + C_7(1, 3, 4, 6) + C_7(1, 2, 6, 7) + C_7(1, 5, 7, 4) + C_7(1, 6, 5, 3) + C_7(1, 7, 3, 2)$$

$$C_7(1, 3, 2, 4) + C_7(1, 2, 5, 6) + C_7(1, 4, 6, 2) + C_7(1, 6, 7, 5) + C_7(1, 7, 4, 3) + C_7(1, 5, 3, 7)$$

## 2.4 Designs for $k=5$

By theorem 4.15 in RH (1986) (Hanani (1972)), for  $k = 5$ , the necessary condition (6) for existence of a BIBD( $v, b, r, k, \lambda$ ) are sufficient for  $v \leq 14$ . By remark 2, an NN1-optimal uniform on periods BIBD( $v = 7, b, r, k = 5, \lambda$ ) requires  $v|b$  and (6), and hence  $\lambda = 5m, b = vq$  and  $r = 5q$ , with  $m(v - 1) = 4q$ . Likewise, an NN2-optimal uniform on periods BIBD( $v = 7, b, r, k = 5, \lambda$ ) requires  $\lambda = 10m, b = vq$  and  $r = 5q$  with  $m(v - 1) = 2q$ .

**Design 16a**  $v = 5 : EBIBD(v = 5, b = 5, r = 5, k = 5, \lambda = 5), E = 100\%$ .  
(1, 2, 3, 4, 5), (2, 5, 4, 1, 3), (3, 4, 2, 5, 1), (4, 1, 5, 3, 2), (5, 3, 1, 2, 4).

This NN1-optimal BIBD is ED and a quasi-complete Latin square design.

**Design 16b**  $v = 5 : TBIBD(v = 5, b = 10, r = 10, k = 5, \lambda = 10), E = 100\%$ .

Design 16c + Design 16d.

This minimal NN2-optimal BIBD is superposition of two quasi-complete Latin squares, Designs 16c,d, neither of whom is TBIBD, NN1-optimal, or BEP. The superposition of Design 16b with its mirror image yields a minimal UBIBD (Design 16e).

**Design 16c**  $v = 5 : EBIBD(v = 5, b = 5, r = 5, k = 5, \lambda = 5), E = 100\%$ .  
 $C_5(1, 3, 4, 5, 2)$ .

**Design 16d**  $v = 5 : EBIBD(v = 5, b = 5, r = 5, k = 5, \lambda = 5), E = 100\%$ .

$C_5(1, 2, 5, 3, 4)$ .

**Design 16e**  $v = 5 : UBIBD(v = 5, b = 20, r = 20, k = 5, \lambda = 20), E = 100\%$ .

$$C_5(1, 3, 4, 5, 2) + C_5(1, 2, 5, 3, 4) + C_5(1, 4, 3, 2, 5) + C_5(1, 5, 2, 4, 3).$$

**Design 17a**  $v = 6 : EBIBD(v = 6, b = 30, r = 25, k = 5, \lambda = 20), E = 24/25 \approx 96\%$ .

$$C_6(1, 2, 6, 4, 5) + C_6(1, 3, 6, 2, 5) + C_6(1, 4, 5, 6, 2) + C_6(1, 5, 6, 3, 4) + C_6(1, 6, 4, 3, 5).$$

This design is a minimal NN1-optimal BIBD, superposition of five cyclic BIBD( $v = 6, b = 6, r = 5, k = 5, \lambda = 4$ )'s with  $E \approx 96\%$ .

**Design 17b**  $v = 6 : TBIBD(v = 6, b = 60, r = 50, k = 5, \lambda = 40), E = 24/25 \approx 96\%$ .

$$C_6(1, 2, 6, 4, 5) + C_6(1, 3, 6, 2, 5) + C_6(1, 4, 5, 6, 2) + C_6(1, 5, 6, 3, 4) + C_6(1, 6, 4, 3, 5) \\ C_6(1, 2, 4, 5, 6) + C_6(1, 3, 5, 2, 4) + C_6(1, 4, 3, 5, 6) + C_6(1, 5, 6, 4, 2) + C_6(1, 6, 3, 2, 5).$$

This design is NN2-optimal and a minimal TBIBD.

**Design 17c**  $v = 6 : UBIBD(v = 6, b = 120, r = 100, k = 5, \lambda = 80), E = 24/25 \approx 96\%$ .

$$C_6(1, 2, 6, 4, 5) + C_6(1, 3, 6, 2, 5) + C_6(1, 4, 5, 6, 2) + C_6(1, 5, 6, 3, 4) + C_6(1, 6, 4, 3, 5) \\ C_6(1, 2, 4, 5, 6) + C_6(1, 3, 5, 2, 4) + C_6(1, 4, 3, 5, 6) + C_6(1, 5, 6, 4, 2) + C_6(1, 6, 3, 2, 5) \\ C_6(1, 6, 2, 4, 3) + C_6(1, 4, 2, 5, 3) + C_6(1, 5, 4, 3, 6) + C_6(1, 6, 3, 2, 4) + C_6(1, 3, 2, 5, 6) \\ C_6(1, 6, 5, 3, 2) + C_6(1, 5, 2, 6, 4) + C_6(1, 6, 4, 5, 2) + C_6(1, 5, 3, 4, 2) + C_6(1, 4, 6, 3, 2).$$

This design is conjectured to be minimal UBIBD.

**Design 18a**  $v = 7 : TBIBD(v = 7, b = 21, r = 15, k = 5, \lambda = 10), E = 14/15 \approx 93.3\%$ .

$$C_7(1, 4, 3, 2, 5) + C_7(1, 3, 7, 4, 6) + C_7(1, 2, 4, 6, 7).$$

This minimal uniform on periods NN2- (and NN1-) optimal BIBD is irreducible. The component cyclic designs are not BIBD's but have nearly optimal efficiency  $E \approx 93.3\%$ .

**Design 18b**  $v = 7 : UBIBD(v = 7, b = 42, r = 30, k = 5, \lambda = 20), E = 14/15 \approx 93.3\%$ .

$$C_7(1, 4, 3, 2, 5) + C_7(1, 3, 7, 4, 6) + C_7(1, 2, 4, 6, 7) \\ C_7(1, 5, 6, 7, 4) + C_7(1, 6, 2, 5, 3) + C_7(1, 7, 5, 3, 2).$$

This design is a minimal UBIBD.

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