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BLOCK DESIGNS FOR SYMMETRIC PARALLEL LINE ASSAYS WITH BLOCK SIZE ODD

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SUMMARY. In a parallel line assay, there are three treatment contrasts of major importance. Block designs allowing the estimability of all the three contrasts free from block effects, called L-designs, necessarily have the block sizes even. For odd block sizes, we provide here a class of highly efficient designs, called nearly L-designs. These nearly L-designs have been constructed by establishing a link with linear and nearly linear trend-free designs.

1. **Introduction**

Biological assays or bioassays involve two stimuli applied to subjects. One preparation of the stimulus, called the *standard* preparation, has a known effect on subjects, while the other preparation of the stimulus, called the *test* preparation, has an unknown strength. A major purpose of a bioassay is to estimate the potency of the test relative to the standard preparation. The relative potency is defined as the ratio of two equivalent doses of the standard to the test preparation. In a bioassay, we thus have two groups of treatments, one for standard preparation and the other for test preparation. Often, within each group, the treatment effect is represented by a polynomial in the logarithm of the dose. In particular, when the polynomial has degree one and both the groups share the same slope, then the assay is called a parallel line assay. If the number of doses of both the preparations are same, then the parallel line assay is called *symmetric*, otherwise, it is called *asymmetric*. In the context of parallel line assays, three treatment contrasts (contrasts among dose effects) are of major importance. The first two, the preparation contrast and the combined regression contrast, provide an estimate of the relative potency and the third one, the parallelism contrast, is used to test the parallelism of the two regression lines. For an excellent description of the theory and application of bioassays, the reader is referred to Finney (1978).

If a block design is used for the assay, it is desirable that the design allows

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the estimability of these three contrasts with full efficiency. For symmetric parallel line assays, an equireplicate block design is called an L-design if the three contrasts of importance are estimated with full efficiency. L-designs have been studied quite extensively; see the review by Gupta and Mukerjee (1996) where more references can be found. Most of these L-designs are for even number of doses of each of the preparations. Gupta and Mukerjee (1990) suggested a somewhat unified method of construction of L-designs. They provided a (i) complete solution of L-designs for even number of doses, and (ii) table of L-designs for all odd number (≤ 15) of doses. However, there are situations where it is impossible to construct an L-design. For such situations, Chai and Das (2001) introduced a class of designs, called nearly L-designs for symmetric parallel line assays. Recall that a necessary condition for the existence of an L-design is that the block size be even. The designs of of Chai and Das (2001) also require the block size to be even.

Thus, it appears that a systematic study for obtaining efficient block designs for parallel line assays with *odd* block sizes has not been attempted. In this paper we propose a class of designs, called nearly L-designs, with odd block sizes. In Section 2, some preliminaries on linear trend-free designs are given. Nearly L-designs are introduced in Section 3 and a link between linear trend-free (nearly linear trend-free) designs and nearly L-designs is established. With the help of this connection, a necessary and sufficient condition for the existence of nearly L-designs as well as a construction method is provided. The proposed designs are shown to be highly efficient.

2. **Linear trend-free designs**

Throughout, $D(v,b,k,r)$ will denote the class of all connected block designs with v treatments each replicated r times and arranged in b blocks each of size $k \geq 2$. Similarly, $D(v,b,k,r_1,\ldots,r_v)$ will denote the class of all connected block designs with v treatments, b blocks each of size $k \geq 2$ and the ith treatment replicated r_i times, $1 \leq i \leq v$.

Trend-free block designs were introduced by Bradley and Yeh (1980). The setup they considered involves v treatments and b blocks each of size k (≥ 2), where, the k experimental units within each block are linearly ordered over time and space. Thus each block has k periods, numbered $1,2,\ldots,k$. Suppose that, in addition to treatment and block effects, there is a common polynomial trend effect within each block. The postulated model for an observation in period l of block j is

$$y_{jl} = \mu + \sum_{i=1}^{v} \delta_{jl}^{i} \tau_i + \beta_j + \sum_{\alpha=1}^{p} \phi_\alpha(l)\theta_\alpha + \epsilon_{jl}, \tag{2.1}$$

where μ is a general mean, $\tau_1,\ldots,\tau_v$, the treatment effects, $\beta_1,\ldots,\beta_b$, the block effects and $\theta_1,\ldots,\theta_p$, the trend effects. Moreover, for $1 \leq \alpha \leq p$, $\phi_\alpha(l)$, is an orthogonal polynomial of degree α, based on $1,2,\ldots,k$, with $\sum_{l=1}^{k}\phi_\alpha(l) = 0$ and $\sum_{l=1}^{k}\phi_\alpha(l)\phi_{\alpha'}(l) = \delta_{\alpha\alpha'}$, $\delta_{\alpha\alpha'}$ being the

Kronecker delta, $\alpha, \alpha' = 1, \dots, p$. Also,

$$\delta_{jl}^{i} = \begin{cases} 1, & \text{if treatment } i \text{ is applied in period } l \text{ of block } j, \\ 0, & \text{otherwise,} \end{cases}$$

with $\sum_{i=1}^{v} \delta_{jl}^{i} = 1$.

Let $\boldsymbol{\tau} = (\tau_1, \dots, \tau_v)'$, $\boldsymbol{\beta} = (\beta_1, \dots, \beta_b)'$ and $\boldsymbol{\theta} = (\theta_1, \dots, \theta_p)'$. A trend-free block design has the property that the presence of trend effect in a treatment-block model does not affect the analysis of the treatment effects. A design d is said to be p-trend-free if

$$R_d(\boldsymbol{\tau}|\mu, \boldsymbol{\beta}, \boldsymbol{\theta}) = R_d(\boldsymbol{\tau}|\mu, \boldsymbol{\beta}), \tag{2.2}$$

where $R_d(\boldsymbol{\tau}|\mu, \boldsymbol{\beta}, \boldsymbol{\theta})$ denotes the adjusted treatment sum of squares under (2.1) and $R_d(\boldsymbol{\tau}|\mu, \boldsymbol{\beta})$ denotes $R_d(\boldsymbol{\tau}|\mu, \boldsymbol{\beta}, \boldsymbol{\theta})$ when $\boldsymbol{\theta} = \mathbf{0}$ in (2.1).

If $p = 1$, then a design $d \in D(v, b, k, r)$ satisfying (2.2) is called a linear trend-free block design. Equivalently, d is called a linear trend-free block design if

$$\sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l = \frac{r(k+1)}{2}, \quad 1 \leq i \leq v.$$

Clearly, a necessary condition for a design $d \in D(v, b, k, r)$ to be linear trend-free is

$$r(k+1) \equiv 0 \pmod 2. \tag{2.3}$$

Stufken (1988) showed that (2.3) is both necessary and sufficient for the existence of a linear trend-free block design. The result of Stufken (1988) has recently been generalized by Chai (2002), who shows that a linear trend-free design exists in $D(v, b, k, r_1, \dots, r_v)$ if and only if $r_i(k+1) \equiv 0 \pmod 2$ for each i, $1 \leq i \leq v$. In $D(v, b, k, r)$, when k is even and r is odd, Yeh, Bradley and Notz (1985) defined a class of designs, called nearly linear trend-free design. We give a more general definition of a nearly linear trend-free design belonging to $D(v, b, k, r_1, \dots, r_v)$.

Definition 1. *For a design belonging to $D(v, b, k, r_1, \dots, r_v)$, suppose k is even and at least one of the r_i's is odd. Then $d \in D(v, b, k, r_1, \dots, r_v)$ is called a nearly linear trend-free block design if for $1 \leq i \leq v$, $\sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l$ equals (a) either $\frac{r_i(k+1)-1}{2}$ or $\frac{r_i(k+1)+1}{2}$, if r_i is odd and, (b) $\frac{r_i(k+1)}{2}$, if r_i is even.*

We have the following result which shows that a nearly linear trend-free design, as per Definition 1, always exists. A proof of Theorem 1 appears in the Appendix.

Theorem 1. *Suppose k is even and at least one of r_i's is odd. Then a nearly linear trend-free block design exists in $D(v, b, k, r_1, ..., r_v)$.*

For the purpose of obtaining designs for parallel line assays, we need to consider a class of nearly linear trend-free designs with the following parametric structure : there are $v \equiv 0 \pmod 4$ treatments which can be split into two sets, say S_1 and S_2, both with cardinality $\frac{1}{2}v$. Furthermore, each treatment in S_1 has replication $r_1 \equiv 1 \pmod 2$ and each treatment belonging to S_2 has replication $r_2 \equiv 0 \pmod 2$. Then, since $\sum_{i \in S_1} \sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l = vr_1(k+1)/4$, it is easy to see that for $\frac{1}{4}v$ treatments in S_1, $\sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l = \frac{r_1(k+1)-1}{2}$ and for the remaining $\frac{1}{4}v$ treatments in S_1, $\sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l = \frac{r_1(k+1)+1}{2}$. Also, for each treatment $i \in S_2$, $\sum_{j=1}^{b} \sum_{l=1}^{k} \delta_{jl}^{i} l = \frac{r_2(k+1)}{2}$.

3. Nearly L-designs

The three contrasts of major importance in the context of parallel line assays are *preparation* (L_p), *combined regression* (L_1) and *parallelism* (L_1'). The three contrasts, $L_p,\ L_1,\ L_1{}'$, in the context of symmetric parallel line assays, can be explicitly written as

$$L_p = m^{-1}(\mathbf{1}_m', -\mathbf{1}_m')\boldsymbol{\tau},\ \ L_1 = \delta_0(\boldsymbol{w}', \boldsymbol{w}')\boldsymbol{\tau},\ \ L_1' = 2\delta_0(\boldsymbol{w}', -\boldsymbol{w}')\boldsymbol{\tau}, \tag{3.1}$$

where $v = 2m$, $\mathbf{1}_s$ is a $s \times 1$ vector of all ones, $\delta_0 = 6/\{\theta_0 log\ h\}$, $\theta_0 = m(m^2-1)$ and $\boldsymbol{w} = (1, 2, \ldots, m)' - \frac{1}{2}(m+1)\mathbf{1}_m$.

Suppose a symmetric parallel line assay involving m doses of each of the preparations is conducted in b blocks each of size k. As mentioned earlier, there are $v = 2m$ treatments, in which the first m treatments represent the doses of standard preparation and the last m treatments represent the doses of the test preparation. Each treatment is replicated $r = bk/v$ times. Let N_d be the incidence matrix of $d \in D(v = 2m, b, k, r)$. We postulate a fixed effects additive model for the data collected through d, making the usual assumption that errors are independent with mean zero and variance σ^2. Under such a model the information matrix of the reduced normal equations for estimating contrasts among dose effects, using a design d, is $C_d = rI - k^{-1}N_dN_d'$ where I is the identity matrix. Every contrast among dose effects is estimable via d if and only if $\text{Rank}(C_d) = v - 1$ and in such a case the design d is called connected. Note that N_d may be partitioned as $N_d = (N_{1d}', N_{2d}')'$, where $N_{1d}(N_{2d})$ is the $m \times b$ incidence matrix for the m doses of the standard (test) preparation. Hence we have

$$\mathbf{1}_m' N_{1d} + \mathbf{1}_m' N_{2d} = k\mathbf{1}_b', \tag{3.2}$$

$$N_{id}\mathbf{1}_b = r\mathbf{1}_m\ ,\ \ i = 1, 2. \tag{3.3}$$

From Lemma 3.1 of Gupta and Mukerjee (1996), a design $d \in D(v = 2m, b, k, r)$ retains full information on L_p, L_1 and $L_1{}'$ if and only if

$$\begin{bmatrix} \mathbf{1}_m' & -\mathbf{1}_m' \\ \boldsymbol{w}' & \boldsymbol{w}' \\ \boldsymbol{w}' & -\boldsymbol{w}' \end{bmatrix} \begin{bmatrix} N_{1d} \\ N_{2d} \end{bmatrix} = \mathbf{0}, \tag{3.4}$$

where $\mathbf{0}$ is a null matrix (or, vector) of appropriate order.

A block design $d \in D(v = 2m, b, k, r)$ satisfying (3.4) is called an L-design. It follows from (3.2) - (3.4), that $d \in D(v = 2m, b, k, r)$ is an L-design if and only if

$$\mathbf{1}'_m N_{1d} = \mathbf{1}'_m N_{2d} = \frac{1}{2} k \mathbf{1}'_b; \quad \boldsymbol{w}' N_{1d} = \boldsymbol{w}' N_{2d} = \mathbf{0}. \tag{3.5}$$

Clearly, from (3.5) it follows that a necessary condition for an L-design to exist is that $k \equiv 0 \pmod 2$. Furthermore, Chai (2002) has shown that a necessary and sufficient condition for an L-design in $D(v = 2m, b, k, r)$ to exist is that $\frac{1}{2}k(m+1) \equiv 0 \pmod 2$. Thus, one cannot construct an L-design if either of the following conditions hold:

(i) $k \equiv 1 \pmod 2$;

(ii) $k \equiv 2 \pmod 4$ and $m \equiv 0 \pmod 2$.

When $k \equiv 2 \pmod 4$ and $m \equiv 0 \pmod 2$, Chai and Das (2001) defined a class of designs, called nearly L-designs. These designs allow the estimability of L_p and L_1 free from block effects. In this paper, we attempt to construct highly efficient block designs for parallel line assays when k is odd. In the rest of the paper, *we take $k > 2$ to be an odd integer*. We continue to call such designs nearly L-designs. Clearly, in such a case, $\mathbf{1}'_m N_{1d} \neq \mathbf{1}'_m N_{2d}$ and thus such designs do not allow the estimability L_p free from block effects. We formally define nearly L-designs considered in this paper.

Definition 2. *A block design $d \in D(v = 2m, b, k, r)$ with $k(> 2)$ odd is called a nearly L-design if the following are true :*

(a) $\mathbf{1}'_m N_{1d} = (\frac{k+1}{2}\mathbf{1}'_{\frac{b}{2}}, \frac{k-1}{2}\mathbf{1}'_{\frac{b}{2}})$;

(b) $\mathbf{1}'_m N_{2d} = (\frac{k-1}{2}\mathbf{1}'_{\frac{b}{2}}, \frac{k-1}{2}\mathbf{1}'_{\frac{b}{2}})$.

Furthermore if m is odd,

(c) $\boldsymbol{w}' N_{1d} = \boldsymbol{w}' N_{2d} = \mathbf{0}'$,

and, if m is even,

(c$'$) $\boldsymbol{w}' N_{1d} = \frac{1}{2}(\mathbf{1}'_{\frac{b}{4}}, -\mathbf{1}'_{\frac{b}{4}}, \mathbf{0}')$; $\boldsymbol{w}' N_{2d} = \frac{1}{2}(\mathbf{0}', \mathbf{1}'_{\frac{b}{4}}, -\mathbf{1}'_{\frac{b}{4}})$.

The normalized contrasts corresponding to L_p, L_1 and $L_1{}'$ are given respectively by $\boldsymbol{g}'_1\boldsymbol{\tau}, \boldsymbol{g}'_2\boldsymbol{\tau}, \boldsymbol{g}'_3\boldsymbol{\tau}$, where $\boldsymbol{g}_1 = (2m)^{-1/2}\ (\mathbf{1}'_m,\ \ -\mathbf{1}'_m)'$, $\boldsymbol{g}_2 = [m(m^2-1)/6]^{-1/2}\ (\boldsymbol{w}',\ \ \boldsymbol{w}')'$ and $\boldsymbol{g}_3 = [m(m^2-1)/6]^{-1/2}\ (\boldsymbol{w}',\ \ -\boldsymbol{w}')'$. Let $G = ((g_{ij}))$ be a $3 \times v$ matrix with rows $\boldsymbol{g}'_1$, $\boldsymbol{g}'_2$ and $\boldsymbol{g}'_3$.

Let $N_d = (N'_{1d}, N'_{2d})'$ be the incidence matrix of a nearly L-design $d \in D(v = 2m, b, k, r)$. Further, we restrict attention to a convenient family of nearly L-designs $\{d\}$ for which $N_{1d} = [M_{1d}, M_{2d}]$, $\ N_{2d} = [M_{2d}, M_{1d}]$ for some $m \times \frac{1}{2}b$ matrices M_{d1}, M_{d2}. Then, from Definition 2, we have

$$\mathbf{1}'_m M_{1d} = \frac{k+1}{2}\mathbf{1}'_{\frac{b}{2}};\ \mathbf{1}'_m M_{2d} = \frac{k-1}{2}\mathbf{1}'_{\frac{b}{2}}.$$

Let $G = VC_d$ for some $3 \times 2m$ matrix $V = \begin{bmatrix} \boldsymbol{v}'_{11} & \boldsymbol{v}'_{12} \\ \boldsymbol{v}'_{21} & \boldsymbol{v}'_{22} \\ \boldsymbol{v}'_{31} & \boldsymbol{v}'_{32} \end{bmatrix}$ where each $\boldsymbol{v}_{ij}$ is an $m \times 1$ vector (see pages 883-884 of Gupta and Mukherjee (1996)).

For an arbitrary $d \in D(v = 2m, b, k, r)$, the covariance matrix of $G\hat{\boldsymbol{\tau}}$, the best linear unbiased estimator of $G\boldsymbol{\tau}$, under d, is

$$Cov(G\hat{\boldsymbol{\tau}})_d = \sigma^2 V C_d V',$$

$$Cov(G\hat{\boldsymbol{\tau}}) - \frac{\sigma^2}{r} GG' = \sigma^2 V(C_d - r^{-1} C_d C_d') V'.$$

Hence,

$$Cov(G\hat{\boldsymbol{\tau}})_d = \sigma^2 r^{-1} GG' + \sigma^2 V(C_d - r^{-1} C_d^2) V' = \sigma^2 (r^{-1} GG' + (rk)^{-1} G N_d N_d' V'). \tag{3.6}$$

We consider two cases, according as m is odd or even.

Case (i). m is odd. We seek a nearly L-design d_0 for parallel line assays with parameters $k = 2k_1 + 1, m = 2m_1 + 1 (\Rightarrow v = 2m = 2(2m_1 + 1)), b = 2b_1, r = \frac{bk}{v} = \frac{b_1(2k_1+1)}{2m_1+1}$. Here, k_1 and m_1 are positive integers.

As a first step, we construct a linear trend-free design d^* with parameters $v^* = b, b^* = r, k^* = m, r_1^* = \cdots = r_{\frac{v^*}{2}}^* = k_1 + 1; r_{\frac{v^*}{2}+1}^* = \cdots = r_{v^*}^* = k_1$. Such a design can be a constructed, since $r_i^*(k^* + 1) \equiv 0 \pmod 2$ for $1 \leq i \leq v^*$.

From d^*, we construct a design d_0 as follows : Suppose, without loss of generality that k_1 is even, so that $k_1 + 1$ is odd. Write the blocks of d^* as columns of a $k^* \times b^*$ matrix, say Δ. Now construct a $k^* \times v^*$ matrix, N_{1d_0}, whose columns are indexed by the v^* treatments of d^* and the rows by the positions of the treatments in each column (block). If a treatment symbol j appears in the ith row of Δ n_{ij}^1 times, then the (i,j)th element of N_{1d_0} is n_{ij}^1 and, zero, otherwise. Let the $m \times \frac{1}{2}b$ matrix consisting of the first $\frac{1}{2}b$ columns of N_{1d_0} be denoted by M_{1d_0} and the matrix consisting of the last $\frac{1}{2}b$ columns of N_{1d_0} be M_{2d_0}. Then, $N_{1d_0} = [M_{1d_0}, M_{2d_0}]$. Define $N_{2d_0} = [M_{2d_0}, M_{1d_0}]$. The required nearly L-design $d_0 \in D(v = 2m, b, k, r)$ has incidence matrix $N_{d_0} = \begin{bmatrix} N_{1d_0} \\ N_{2d_0} \end{bmatrix}$. Then d_0 has the following properties :

(i) $N_{1d_0} = [M_{1d_0}, M_{2d_0}]$ and $N_{2d_0} = [M_{2d_0}, M_{1d_0}]$.
(ii) $\mathbf{1}_m' M_{1d_0} = (k_1 + 1)\mathbf{1}_{b_1}', \;\; \mathbf{1}_m' M_{2d_0} = k_1 \mathbf{1}_{b_1}', \;\; \boldsymbol{w}' M_{1d_0} = \mathbf{0}', \;\; \boldsymbol{w}' M_{2d_0} = \mathbf{0}'$.

From (i) and (ii) above, it follows that

$$\begin{aligned} &\frac{1}{rk} G N_{d_0} N_{d_0}' V' \\ = \;& \frac{1}{rk}\frac{1}{\sqrt{2m}} \begin{pmatrix} \mathbf{1}_{b_1}'(M_{1d_0} - M_{2d_0})'(\boldsymbol{v}_{11} - \boldsymbol{v}_{12}) & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \end{aligned}$$

Hence, under d_0,

$$Cov(G\hat{\boldsymbol{\tau}})_{d_0} = \sigma^2 \begin{pmatrix} \frac{1}{r} + \frac{1}{rk}\frac{1}{\sqrt{2m}} \mathbf{1}_{b_1}'(M_{1d_0} - M_{2d_0})'(\boldsymbol{v}_{11} - \boldsymbol{v}_{12}) & 0 & 0 \\ 0 & \frac{1}{r} & 0 \\ 0 & 0 & \frac{1}{r} \end{pmatrix}. \tag{3.7}$$

From (3.7), we have $\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_{d_0} = \sigma^2(\frac{1}{r}+\frac{1}{rk}\frac{1}{\sqrt{2m}}\mathbf{1}_{b_1}'(M_{1d_0}-M_{2d_0})'(\boldsymbol{v}_{11}-\boldsymbol{v}_{12})$ and $\mathrm{Var}(g_2'\hat{\boldsymbol{\tau}})_{d_0} = \mathrm{var}(g_3'\hat{\boldsymbol{\tau}})_{d_0} = \sigma^2 r^{-1}$, where for $i = 1,2,3$, $\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_{d_0}$ is the variance of the best linear unbiased estimator of $\boldsymbol{g}_i'\boldsymbol{\tau}$ under d_0. Since for an arbitrary design $d \in D(v = 2m, b, k, r)$, $\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_d \geq \sigma^2/r$, $i = 1,2,3$, it follows that the design d_0 estimates the contrasts L_1 and L_1' with full information.

Now let us concentrate on the contrast $\boldsymbol{g}_1'\boldsymbol{\tau}$. Let $d \in D(v = 2m, b, k, r)$ be arbitrary and as before, let $\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d$ denote the variance of the best linear unbiased estimator of $\boldsymbol{g}_1'\boldsymbol{\tau}$ under d. Then,

$$\sigma^{-2}\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d = \boldsymbol{g}_1'C_d^-\boldsymbol{g}_1 \geq (\boldsymbol{g}_1'C_d\boldsymbol{g}_1)^{-1} \geq \frac{1}{\max_{d\in D}\boldsymbol{g}_1'C_d\boldsymbol{g}_1}.$$

Now,

$$\begin{aligned}\max_{d\in D}\boldsymbol{g}_1'C_d\boldsymbol{g}_1 &= r - \min_{d\in D} k^{-1}\boldsymbol{g}_1'N_dN_d'\boldsymbol{g}_1 \\ &= r - (2mk)^{-1}\min_{d\in D}\sum_{j=1}^{b}(a_{d1j}-a_{d2j})^2,\end{aligned}$$

where $(a_{d11},\ldots,a_{d1b}) = \mathbf{1}_m'N_{1d}$, $(a_{d21},\ldots,a_{d2b}) = \mathbf{1}_m'N_{2d}$. The minimum of $\sum_{j=1}^{b}(a_{d1j}-a_{d2j})^2$ is attained when

$$|a_{d1j} - a_{d2j}| = 1, \text{for all } j = 1,\ldots,b, \tag{3.8}$$

as $k > 2$ is odd. Hence, when (3.8) holds, we have

$$\max_{d\in D}(\boldsymbol{g}_1'C_d\boldsymbol{g}_1) = r - b(2mk)^{-1} = r(1-k^{-2}).$$

Therefore,

$$\sigma^{-2}\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d \geq \frac{1}{r(1-k^{-2})}.$$

On the basis of the above analysis, one can obtain a *lower bound* to the efficiency factor of the contrast $\boldsymbol{g}_1'\boldsymbol{\tau}$ under a design d as

$$e_d = \sigma^2/\{\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d\, r(1-k^{-2})\}.$$

Also, a lower bound to the measure of an overall efficiency factor of a design d, based on all the three contrasts, is given by $\bar{e}_d = \frac{\sigma^2(3k^2-2)}{r(k^2-1)}/\sum_{1\leq i\leq 3}\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_d$.

Note that the proposed design d_0 satisfies (3.8) and also estimates $\boldsymbol{g}_i'\boldsymbol{\tau}$, $i = 2,3$ with efficiency one. Thus, it is expected that d_0 will have a high overall efficiency factor - in fact, in several examples, it is found that $\bar{e}_{d_0} > 0.95$. Thus when m is odd, the design d_0 allows the estimability of the contrasts $\boldsymbol{g}_2'\boldsymbol{\tau}$ and $\boldsymbol{g}_3'\boldsymbol{\tau}$ with efficiency one, while the efficiency factor of $\boldsymbol{g}_1'\boldsymbol{\tau}$ (L_p) is expected to be close to unity for appropriately chosen d_0.

Example 1. Let $m = 5, k = 5, b = 12, r = 6$. We first find a linear trend-free block design $d^* \in D(v^* = 12, b^* = 6, k^* = 5, r_1^* = \cdots = r_6^* = 3; r_7^* = \cdots = r_{12}^* = 2)$. Such a design, with columns as blocks, is shown below.

$$d^* \equiv \begin{array}{rrrrrr} 5 & 4 & 9 & 7 & 8 & 6 \\ 11 & 12 & 1 & 3 & 2 & 10 \\ 1 & 2 & 6 & 4 & 5 & 3 \\ 12 & 10 & 2 & 1 & 3 & 11 \\ 8 & 7 & 5 & 9 & 6 & 4 \end{array}$$

Following the method of construction of d_0 described in this section, we have

$$N_{1d_0} = \begin{bmatrix} 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \end{bmatrix}$$

$$N_{2d_0} = \begin{bmatrix} 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \end{bmatrix}$$

and $N_{d_0} = \begin{bmatrix} N_{1d_0} \\ N_{2d_0} \end{bmatrix}$ is the incidence matrix of $d_0 \in D(10, 12, 5, 6)$. The blocks of the design d_0 are

$$(2,3,4,6,10), (2,3,4,6,10), (2,3,4,6,10), (1,3,5,7,9), (1,3,5,7,9), (1,3,5,7,9),$$
$$(1,5,7,8,9), (1,5,7,8,9), (1,5,7,8,9), (2,4,6,8,10), (2,4,6,8,10), (2,4,6,8,10),$$

where $1, \ldots, 5$ are the standard doses and $6, \ldots, 10$ are the test doses. The efficiency factor for the contrast $\boldsymbol{g}_1' \boldsymbol{\tau}$ under this design is at least 0.9921 and the overall efficiency factor of the design is at least 0.9973.

Case (ii). m is even. Here the parameters of the design that we seek are $k = 2k_1 + 1, m = 2m_1 (\Rightarrow v = 2m = 4m_1), b = 4b_1, r = \frac{bk}{v} = \frac{4b_1(2k_1+1)}{4m_1} = \frac{b_1(2k_1+1)}{m_1}$.

As in Case (i), we assume that k_1 is even. Now, let d^* be a *nearly* linear trend-free design in $D(v^* = b, b^* = r, k^* = m, r_1^* = \cdots = r_{\frac{v^*}{2}}^* = k_1 + 1; r_{\frac{v^*}{2}+1}^* = \cdots = r_{v^*}^* = k_1)$. Note that a linear trend-free design cannot exist in this case, as $r_i^*(k^* + 1) \neq 0 \pmod 2$ for all $i, 1 \leq i \leq v^*$. Following the discussion in the last paragraph of Section 2, without loss of generality, we take a d^*, such that for $1 \leq i \leq \frac{1}{4}v^*$, $\sum_{j=1}^{b^*} \sum_{l=1}^{k^*} \delta_{jl}^i l = \frac{r_1^*(k^*+1)-1}{2}$, for $\frac{1}{4}v^* + 1 \leq i \leq \frac{1}{2}v^*$, $\sum_{j=1}^{b^*} \sum_{l=1}^{k^*} \delta_{jl}^i l = \frac{r_1^*(k^*+1)+1}{2}$ and for the remaining $\frac{1}{2}v^*$ treatments, $\sum_{j=1}^{b^*} \sum_{l=1}^{k^*} \delta_{jl}^i l = \frac{r_{v^*}^*(k^*+1)}{2} = \frac{(r_1^*-1)(k^*+1)}{2}$.

From d^*, we obtain the matrices N_{1d_0} and N_{2d_0} leading to the proposed design $d_0 \in D(v = 2m, b = 4b_1, k = 2k_1 + 1, r = \frac{b_1(2k_1+1)}{m_1})$, with incidence matrix $N_{d_0} = \begin{bmatrix} N_{1d_0} \\ N_{2d_0} \end{bmatrix}$, where N_{1d_0}, N_{2d_0} are obtained from d^* exactly in the same manner as in Case *(i)*. Then

$$N_{d_0} = \begin{bmatrix} M_{1d_0} & M_{2d_0} \\ M_{2d_0} & M_{1d_0} \end{bmatrix}$$

with

$$\mathbf{1}'_m M_{1d_0} = (k_1+1)\mathbf{1}'_{2b_1}, \mathbf{1}'_m M_{2d_0} = k_1 \mathbf{1}'_{2b_1}$$
$$\boldsymbol{w}' M_{1d_0} = \frac{1}{2}\left[\mathbf{1}'_{b_1}, -\mathbf{1}'_{b_1}\right] \text{ and } \boldsymbol{w}' M_{2d_0} = \mathbf{0}'.$$

For an arbitray design $d \in D(v = 2m, b, k, r)$, consider the matrix $GC_dG' = rGG' - k^{-1}GN_d{N_d}'G'$. Now,

$$\begin{aligned} GN_d &= \begin{bmatrix} (2m)^{-1/2}\mathbf{1}'_m & -(2m)^{-1/2}\mathbf{1}'_m \\ (m(m^2-1)/6)^{-1/2}\boldsymbol{w}' & (m(m^2-1)/6)^{-1/2}\boldsymbol{w}' \\ (m(m^2-1)/6)^{-1/2}\boldsymbol{w}' & -(m(m^2-1)/6)^{-1/2}\boldsymbol{w}' \end{bmatrix} \begin{bmatrix} N_{1d} \\ N_{2d} \end{bmatrix} \\ &= \begin{bmatrix} (2m)^{-1/2}(\mathbf{1}'_m N_{1d} - \mathbf{1}'_m N_{2d}) \\ (2m(m^2-1)/3)^{-1/2}(\boldsymbol{f}'N_{1d} + \boldsymbol{f}'N_{2d}) \\ (2m(m^2-1)/3)^{-1/2}(\boldsymbol{f}'N_{1d} - \boldsymbol{f}'N_{2d}) \end{bmatrix} \end{aligned}$$

where $\boldsymbol{f} = 2\boldsymbol{w}$.

As before, $\mathbf{1}'_m N_{1d} = (a_{d11}, \ldots, a_{d1b})$, $\mathbf{1}'_m N_{d_2} = (a_{d21}, \ldots, a_{d2b})$, and let $\boldsymbol{f}'N_{1d} = (c_{d11}, \ldots, c_{d1b})$ and $\boldsymbol{f}'N_{2d} = (c_{d21}, \ldots, c_{d2b})$. Then, since the design is equireplicate, $\sum_{j=1}^{b} c_{d1j} = \sum_{j=1}^{b} c_{d2j} = 0$. In order to maximize $\boldsymbol{g}'_i C_d \boldsymbol{g}_i$, $i = 1, 2, 3$ over $D(v = 2m, b, k, r)$, we need to minimize $\boldsymbol{g}'_i N_d N'_d \boldsymbol{g}_i$, since $\boldsymbol{g}'_i \boldsymbol{g}_i = 1$ is fixed. Now,

$$\begin{aligned} \boldsymbol{g}'_1 N_d N'_d \boldsymbol{g}_1 &= \sum_{j=1}^{b} (2m)^{-1}(a_{d1j} - a_{d2j})^2 \\ \boldsymbol{g}'_2 N_d N'_d \boldsymbol{g}_2 &= \sum_{j=1}^{b} (2m(m^2-1)/3)^{-1}(c_{d1j} + c_{d2j})^2 \\ \boldsymbol{g}'_3 N_d N'_d \boldsymbol{g}_3 &= \sum_{j=1}^{b} (2m(m^2-1)/3)^{-1}(c_{d1j} - c_{d2j})^2. \end{aligned}$$

To begin with, recall that as in Case *(i)*, $\boldsymbol{g}'_1 N_d N'_d \boldsymbol{g}_1$ is minimized when $|a_{d1j} - a_{d2j}| = 1$ for all $j = 1, \ldots, b$. Since m is even, $\boldsymbol{f}' = 2\boldsymbol{w}' = (-(m-1), -(m-3), \ldots, -3, -1, 1, 3, \ldots, m-3, m-1)$ and $\boldsymbol{\alpha}' = \boldsymbol{f}' + \mathbf{1}' = (-(m-2), -(m-4), \ldots, -4, -2, 0, 2, 4, \ldots, m-4, m-2, m)$. We now show that for $1 \le j \le b$, $c_{d1j} \pm c_{d2j} \ne 0$. To see this, if possible, let $c_{d1j} + c_{d2j} = 0$ for some j. Then, for this j, $c_{d1j} + c_{d2j} = \boldsymbol{f}'(\boldsymbol{n}_{1dj} + \boldsymbol{n}_{2dj}) = 0$, where $\boldsymbol{n}_{1dj}(\boldsymbol{n}_{2dj})$ is the jth column of $N_{1d}(N_{2d})$. Also, $\mathbf{1}'(\boldsymbol{n}_{1dj} + \boldsymbol{n}_{2dj}) = k = 2k_1 + 1$. Thus, $\boldsymbol{\alpha}'(\boldsymbol{n}_{1dj} + \boldsymbol{n}_{2dj}) = (\boldsymbol{f}' + \mathbf{1}')(\boldsymbol{n}_{1dj} + \boldsymbol{n}_{2dj}) = k$. But each element of $\boldsymbol{\alpha}$ is even and thus we have a contradiction. Again, if possible, let $c_{d1j} - c_{d2j} = 0$ for some j. Then, $c_{d1j} - c_{d2j} = \boldsymbol{f}'(\boldsymbol{n}_{1dj} - \boldsymbol{n}_{2dj}) = 0$. Also, $\mathbf{1}'(\boldsymbol{n}_{1dj} - \boldsymbol{n}_{2dj})$ is an odd integer. Thus, $\boldsymbol{\alpha}'(\boldsymbol{n}_{1dj} - \boldsymbol{n}_{2dj}) = (\boldsymbol{f}' + \mathbf{1}')(\boldsymbol{n}_{1dj} - \boldsymbol{n}_{2dj})$ is odd and the proof is complete.

The minimum of each of $\sum_{j=1}^{b}(c_{d1j}+c_{d2j})^2$ and $\sum_{j=1}^{b}(c_{d1j}-c_{d2j})^2$ is therefore attained when $c_{d1j}+c_{d2j}=\pm 1,\ 1\le j\le b$ and $c_{d1j}-c_{d2j}=\pm 1,\ 1\le j\le b$ respectively. With these values of $\{a_{dij}\},\ i=1,2$ and $\{c_{d1j}\pm c_{d2j}\},\ j=1,\ldots,b$, the minimum of $\boldsymbol{g}_i'N_dN_d'\boldsymbol{g}_i,\ i=1,2,3$ are given respectively by

$$\frac{b}{2m},\ \frac{3b}{2m(m^2-1)},\ \frac{3b}{2m(m^2-1)}.$$

Hence,

$$\max\nolimits_{d\in D}\,(\boldsymbol{g}_1'C_d\boldsymbol{g}_1)=r(1-k^{-2}),$$

$$\max\nolimits_{d\in D}\,(\boldsymbol{g}_2'C_d\boldsymbol{g}_2)=r(1-3k^{-2}(m^2-1)^{-1})=\max\nolimits_{d\in D}\,(\boldsymbol{g}_3'C_d\boldsymbol{g}_3),$$

and these maximum values are attained by the proposed design d_0.

Therefore, $\sigma^{-2}\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d\ \ge\ (r(1-k^{-2}))^{-1}$ and for $i=2,3$, $\sigma^{-2}\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_d\ \ge\ \{r(1-3k^{-2}(m^2-1)^{-1})\}^{-1}$. One can now obtain a *lower bound* to the efficiency factor of the contrasts $\boldsymbol{g}_i'\boldsymbol{\tau}$ under a design d as

$$e_{1d}=\sigma^2/\{\mathrm{Var}(\boldsymbol{g}_1'\hat{\boldsymbol{\tau}})_d\,r(1-k^{-2})\}$$

and

$$e_{id}=\sigma^2/\{\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_d\,r(1-3k^{-2}(m^2-1)^{-1})\},\ i=2,3.$$

Also, a lower bound to a measure of the overall efficiency factor of a design d is given by

$$\bar{e}_d=\frac{\sigma^2k^2\{(m^2-1)(3k^2-2)-3\}}{r(k^2-1)\{k^2(m^2-1)-3\}}\Big/\sum_{1\le i\le 3}\mathrm{Var}(\boldsymbol{g}_i'\hat{\boldsymbol{\tau}})_d.$$

For the proposed class of nearly L-designs, we find in several appropriately chosen examples that $\bar{e}_{d_0}>0.95$.

Example 2. Let $m=6,k=9,b=8,r=6$. We find a nearly linear trend-free block design $d^*\in D(v^*=8,b^*=6=k^*,r_1^*=\cdots=r_4^*=5;r_5^*=\cdots=r_8^*=4)$. The design d^*, with columns as blocks is shown below.

$$d^*\equiv\begin{array}{cccccc}2&3&6&5&4&1\\3&1&5&7&2&4\\7&4&8&3&6&8\\1&6&2&8&8&7\\4&2&7&1&3&5\\6&5&4&2&1&3\end{array}$$

Following the method of construction of d_0 described above, we have

$$N_{1d_0}=\left[\begin{array}{cccc|cccc}1&1&1&1&1&1&0&0\\1&1&1&1&1&0&1&0\\0&0&1&1&0&1&1&2\\1&1&0&0&0&1&1&2\\1&1&1&1&1&0&1&0\\1&1&1&1&1&1&0&0\end{array}\right]=[M_{1d_0}\,|\,M_{2d_0}]$$

$$N_{2d_0}=[M_{2d_0}\,|\,M_{1d_0}].$$

Then, $N_{d_0} = \begin{bmatrix} N_{1d_0} \\ N_{2d_0} \end{bmatrix}$ is the incidence matrix of the design $d_0 \in D(12, 8, 9, 6)$. For this design $\bar{e}_{d_0} = 0.9994$.

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Appendix

The following definition and lemmas are needed in the proof of Theorem 1.

Definition 3. *Given a block size k, two plots l and l' are said to be mirror-symmetric if $l + l' = k + 1$.*

Let $S_k = \{1, 2, \ldots, k\}$, $V_1 = \{1, 2, \ldots, t\}$ and $V_2 = \{t + 1, \ldots, v\}$.

Lemma 1. *Suppose $k = 2h$ and $p = 2l + 1, 3p < k$. Then there exists p sets of size 3, say $X_1, X_2, \ldots, X_p$, such that*

(i) $\bigcup_{i=1}^{p} X_i = S_k \backslash (\{1, 2, \ldots, (k-3p-1)/2\} \cup \{k/2+1\} \cup \{(k+3p+1)/2+1, (k+3p+1)/2+2, \ldots, k\})$;

(ii) $X_i \cap X_j = \emptyset$, *for all $i \neq j$, where $\emptyset$ is the null set ;*

(iii) For $1 \le i \le l$, $\sum_{x \in X_i} x = (3k+4)/2$ *and for* $l+1 \le i \le p$, $\sum_{x \in X_i} x = (3k+2)/2$.

Proof. Let $z = (k-3p-1)/2$. Define

$$X_i = \{i+z, 3l+3+i+z, 6l+5-2i+z\}\ ,\ 1 \le i \le l,$$

and

$$X_{l+j} = \{l+j+z, 2l+1+j+z, 6l+6-2j+z\}\ ,\ 1 \le j \le l+1.$$

The results (i), (ii) and (iii) follow easily from the construction of X_i's.

Lemma 1′. *Let* $\tilde{X}_i = \{k+1-x \mid x \in X_i\}$, *where* X_i*'s,* $1 \le i \le p$, *are constructed as in Lemma 1. Then*

(i) $\bigcup_{i=1}^{p} \tilde{X}_i = S_k \setminus (\{1, 2, \ldots, (k-3p-1)/2\} \cup \{k/2\} \cup \{(k+3p+1)/2+1, (k+3p+1)/2+2, \ldots, k\})$;

(ii) $\tilde{X}_i \cap \tilde{X}_j = \emptyset$, *for all* $i \neq j$;

(iii) For $1 \le i \le l$, $\sum_{x \in \tilde{X}_i} x = (3k+2)/2$ *and for* $l+1 \le i \le p$, $\sum_{x \in \tilde{X}_i} x = (3k+4)/2$.

Lemma 2. *Suppose* $k = 2h$ *and* $p = 2l$, $3p \le k$. *Then there exists* p *sets of size 3, say* $Y_1, Y_2, \ldots, Y_p$, *such that*

(i) $\bigcup_{i=1}^{p} Y_i = S_k \setminus (\{1, 2, \ldots, (k-3p)/2\} \cup \{(k+3p)/2+1, (k+3p)/2+2, \ldots, k\})$;

(ii) $Y_i \cap Y_j = \emptyset$, *for all* $i \neq j$;

(iii) For $1 \le i \le l$, $\sum_{y \in Y_i} y = (3k+4)/2$ *and for* $l+1 \le i \le p$, $\sum_{y \in Y_i} y = (3k+2)/2$.

Proof. Let $z = (k-6l)/2$. Define

$$Y_i = \{i+z, 3l+i+z, 6l+2-2i+z\}\ ,\ 1 \le i \le l.$$

and

$$Y_{l+j} = \{l+j+z, 2l+j+z, 6l+1-2j+z\}\ ,\ 1 \le j \le l.$$

The results (i), (ii) and (iii) follow easily from the construction of Y_i's.

Lemma 3. (Yeh *et al.* (1985)). *Suppose* k *is even. Then there exists a nearly linear trend-free block design* $d \in D(k, 3, k, 3)$.

Proof. The three blocks of d can be constructed as follows:

block 1: $(1, 2, \ldots, k/2, k/2+1, k/2+2, \ldots, k-1, k)$;

block 2: $(k, k-2, \ldots, 4, 2, k-1, k-3, \ldots, 3, 1)$;

block 3: $(k-1, k-3, \ldots, 3, 1, k, k-2, \ldots, 4, 2)$.

For $1 \leq i \leq k/2$, $\sum_{j=1}^{3}\sum_{l=1}^{k}\delta_{jl}^{2i-1} \cdot l = (3k+2)/2$ and $\sum_{j=1}^{3}\sum_{l=1}^{k}\delta_{jl}^{2i} \cdot l = (3k+4)/2$. Hence d is a nearly linear trend-free block design.

Next, we will prove that a nearly linear trend-free block design $d \in D(v, b, k, r_1, \ldots, r_v)$ exists when k is even and at least one of r_i's is odd. Suppose k is even and at least one of r_i's is odd. First, in Lemma 4, we handle the basic case of r_i equal to 2 or 3. Then in Theorem 1, we consider the general case $r_i \geq 2$.

The key idea for the proof of Lemma 4 is the following. Suppose $r_i = 3$, $i \in V_1$, and $r_j = 2$, $j \in V_2$.

Step I : With the help of Lemmas 1, 2 and 3, we can identify and fill those three proper plots with three replications of treatment i, $i \in V_1$, in an un-filled $k \times b$ array d such that (i) $\sum_{j=1}^{b}\sum_{l=1}^{k}\delta_{jl}^{i}l = (3k+2)/2$ or $(3k+4)/2$, $1 \leq i \leq t$; (ii) All remaining un-filled plots in d are mirror-symmetric in pairs, i.e., if a plot l in block j is unfilled, then there always exists another unfilled plot $k+1-l$ in some block j'.

Step II : Fill each pair of mirror-symmetric plots with two replications of treatment j, $j \in V_2$.

From the property of the mirror-symmetric plots, we get $\sum_{j=1}^{b}\sum_{l=1}^{k}\delta_{jl}^{i}l = r_i(k+1)/2 = 2(k+1)/2$, $t+1 \leq i \leq v$. Therefore, the filled array d is a nearly linear trend-free block design.

Lemma 4. *Suppose k is even, $r_i = 3$, $i \in V_1$, and $r_j = 2$, $j \in V_2$. Then a nearly linear trend-free block design $d \in D(v, b, k, r_1, \ldots, r_v)$ exists.*

Proof. Note that t is even since $t = bk - 2v$. Let $t = pk + q, 0 \leq q \leq k-1$ and $b = 3p + b_1$. Consequently q is even. Our desired nearly linear trend-free block design will be constructed as

$$d = \left[d_1 \vdots d_2 \vdots \cdots \vdots d_p \vdots d_{p+1} \vdots d_{p+2} \right],$$

where (i) for $1 \leq i \leq p, d_i \in D(k, 3, k, 3)$ is a nearly linear trend-free block design consisting of treatments $(i-1)k+1, (i-1)k+2, \ldots, ik$, constructed from Lemma 3; (ii) d_{p+1} is a $k \times h$ array and can be written as $\begin{bmatrix} d_{q_1} \\ d_q \\ d_{q_2} \end{bmatrix}$, where h could be 3, 2, 1 depending on cases. Furthermore in d_{p+1}, d_q occupies the middle ρ rows (ρ could be q, $3q/2$ or $3q$ depending on cases), contains treatments $pk+1, pk+2, \ldots, pk+q$ and maybe some treatments from V_2, d_{q_1} and d_{q_2} occupies the first $(k-\rho)/2$ rows and the last $(k-\rho)/2$ rows respectively, containing treatments from V_2 only; (iii) d_{p+2} has $b_1 - h$ blocks containing treatments from V_2 only. Our goal is to construct proper d_{p+1} and d_{p+2} to make d a nearly linear trend-free block design. We divide the proof into three cases.

Case 1. $b_1 \geq 3$. Here $h = 3$.
From Lemma 3, we can construct a nearly linear trend-free block design $d_q \in D(q,3,q,3)$ consisting of treatments $pk+1, pk+2, \ldots, pk+q$. Observe that all un-filled plots in d_{q_1}, d_{q_2} and d_{p+2} are mirror-symmetric in pairs. Hence, fill each pair of mirror-symmetric plots with two replications of treatment j, $j \in V_2$. From the property of mirror-symmetric plots, we get $\sum_{j=1}^{b}\sum_{l=1}^{k}\delta_{jl}^{i} l = r_i(k+1)/2 = 2(k+1)/2$, $t+1 \leq i \leq v$. The resulting design d is our desired nearly linear trend-free block design.

Case 2. $b_1 = 2$. Here $h = 2$ and d_{p+2} vanishes. Let $q = 2m$. Write d_q as

$$\begin{bmatrix} d_q^{m_1} & \vdots & d_q^{m_2} \end{bmatrix}$$

where $d_q^{m_i}$, $1 \leq i \leq 2$, is a $3m \times 1$ vector consisting of treatments $pk+(i-1)m+1, pk+(i-1)m+2, \ldots, pk+im$.
(a) m is odd. $d_q^{m_1}$ is constructed by inserting three replications of treatment $pk+j$ into the $(x)_{th}$ plot of an un-filled $3m \times 1$ vector, where $x \in X_j$, $1 \leq j \leq m$ and X_j's are obtained from Lemma 1 by letting $p = m$ and $k = 3m+1$. $d_q^{m_2}$ is constructed by inserting three replications of treatment $pk+m+j$ into the $(x)_{th}$ plot of an un-filled $3m \times 1$ vector, where $x \in \tilde{X}_j$, $1 \leq j \leq m$ and $\tilde{X}_j$'s are obtained from Lemma $1'$ by letting $p = m$ and $k = 3m+1$.
(b) m is even. $d_q^{m_i}$ is constructed by placing three replications of treatment $pk+(i-1)m+j$ into the $(y)_{th}$ plot of an un-filled $3m \times 1$ vector, where $y \in Y_j, 1 \leq i \leq 2, 1 \leq j \leq m$ and Y_j's are obtained from Lemma 2 by letting $p = m$ and $k = 3m$. Check the remaining unfilled plots in d_{p+1}, they are mirror-symmetric in pairs. Hence the desired design is constructed.

Case 3. $b_1 = 1$. Here $h = 1$ and d_{p+2} vanishes. d_q is a $3q \times 1$ vector consisting of treatments $pk+1, pk+2, \ldots, pk+q$. Now, let d_q act as the $d_q^{m_1}$ of Case 2(b), then the proof follows along the lines of Case 2(b).

The resulting designs in the above cases are nearly linear trend-free but not necessarily connected. Hence, we have to horizontally shift the positions of the treatments among d_i's to make d a connected design. That completes the proof.

Proof of Theorem 1. Without loss of generality, we assume r_i is odd, $1 \leq i \leq t$ and r_i is even, $t+1 \leq i \leq v$. For $1 \leq i \leq t$, we can write $r_i = 3 + 2r_{1i}$. Then r_i replications of treatment i can be renamed as 3 replications of one new treatment plus 2 replications of r_{1i} new treatments. For $t+1 \leq i \leq v$, we can write $r_i = 2r_{1i}$. Then r_i replications of treatment i can be renamed as 2 replications of r_{1i} new treatments. Let $v^* = t + \sum_{i=1}^{v} r_{1i}$. In other words, a design belonging to $D(v, b, k, r_1, r_2, \ldots, r_v)$ can be renamed as another design belonging to $D(v^*, b, k, r_1^*, \ldots, r_t^*, r_{t+1}^*, \ldots, r_{v^*}^*)$ with $r_i^* = 3,\ 1 \leq i \leq t$ and $r_i^* = 2,\ t+1 \leq i \leq v^*$. From Lemma 4, we know a nearly linear trend-free block design $d^* \in D(v^*, b, k, r_1^*, \ldots, r_{v^*}^*)$ exists. In d^*, revert new treatments back to the original treatments resulting into our required d. Obviously, $d \in D(v, b, k, r_1, \ldots, r_v)$ and for $1 \leq i \leq t$, $\sum_{j=1}^{b}\sum_{l=1}^{k} \delta_{jl}^{i} l = ((3(k+1)-1)/2$ or $(3(k+1)+1)/2) + r_{1i} \cdot 2(k+1)/2 = (r_i(k+1)-1)/2$ or $(r_i(k+1)+1)/2$ and for $t+1 \leq i \leq v$, $\sum_{j=1}^{b}\sum_{l=1}^{k} \delta_{jl}^{i} l = r_{1i} \cdot 2(k+1)/2 = r_i(k+1)/2$. Hence, d is a nearly linear trend-free block design.

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