Nearest neighbor balanced block designs for autoregressive errors

Mamadou Koné, Annick Valibouze

Version Ouverte
Version Editeur parue le 09 Avril 2020 dans Metrika 84, 281312 (2021)
Lien Editeur : https://doi.org/10.1007/s00184-020-00770-6

Nearest neighbor balanced block designs for autoregressive errors

Mamadou Koné · Annick Valibouze

September 8, 2021

Abstract In this paper we study the problem of finding neighbor optimal designs for a general correlation structure. We give universal optimality conditions for nearest-neighbor (NN) balanced block designs when observations on the same block are modeled by an autoregressive AR(m) process with arbitrary order m. The cases $m = 1, 2$ have been studied by Grondona and Cressie (1993) for AR(2) and by Gill and Shukla (1985) and Kunert (1987) for AR(1); we extend these results to the cases $m \geq 3$.

Keywords Autoregressive model · Block design · Generalized least squares estimation · Nearest-neighbor balanced · Universally optimal

1 Introduction

The systematic introduction of statistical designs is due to the British statistician R. A. Fisher (in the years 1925-1937) when he was appointed by Rothamsted Experimental Station to apply new statistical methods to the analysis of the accumulated results of the Rothamsted long-term agricultural experiments (Yates 1964). In these experimental results, Fisher began to consider the heterogeneity of the plots (considered as periods in our context) where the experiments take place, by comparing yields of different seed varieties; he introduced several types of designs including *complete block designs* (CBD), *incomplete block designs* (IBD) and *Latin squares*.

The classical theory of experimental designs is based on three principles, namely repetition, randomization and local control. Repetition is intended to estimate the residual variability and to increase the accuracy of the experiment. The purpose of

Mamadou Koné
Sorbonne Université, CNRS, LPSM, 75252 Paris Cedex 05, France
E-mail: mkone@math.cnrs.fr

Annick Valibouze (corresponding author)
Sorbonne Université, CNRS, LIP6, LPSM, 75252 Paris Cedex 05, France
Tel.: +33-1-44-27-88-51
E-mail: annick.valibouze@sorbonne-universite.fr

randomization is to remove bias and other sources of extraneous variation, which are uncontrollable. Local control aims to increase the accuracy of the experiments.

Over the decades that followed this initial work, the principles developed by Fisher in agronomy have been transposed to many other sectors of activity such as industry and services. Among the new concepts that have been introduced, we mention the concept of optimal design due to J. Kiefer (1958-1981). At the same time, the use of statistical methods in pharmacy and medicine has developed to the point that today these sectors are the main areas of application of experimental designs.

Recently, there has been considerable interest in the use of some particular methods of local control called *spatial* or mth *order nearest-neighbor*, abbreviated NN or NNm, where the integer $m > 0$ is the distance among neighbours in the model. Kiefer and Wynn (1981) studied the optimality of block designs under a first order (NN1) neighbor correlation model, using the ordinary least squares (OLS) estimator. In this context, they gave sufficient conditions of *weak universal optimality* for the estimation of treatment contrasts. Morgan and Chakravarti (1988) extended these conditions to the model NN2 and then these results were generalized to any correlation structure NNm, $m > 2$ (Koné and Valibouze 2011).

When the covariance structure is known, it is natural to construct the optimal experimental designs by making use of the generalized least squares (GLS) estimator. Several authors have used this approach for the correlation structures $\mathrm{AR}(1)$ and $\mathrm{AR}(2)$, the autoregressive processes of first and second order (Azzalini and Giovagnoli 1987; Gill and Shukla 1985a,b; Grondona and Cressie 1993; Kunert 1985, 1987; Martin and Eccleston 1991; Satpati, Parsad and Gupta 2007). Kiefer and Wynn (1981) justified the choice of the OLS estimator, rather than the GLS estimator, by showing that the loss of relative accuracy is lower with the use of OLS for the NN1 correlation model.

The NN methods can be refined by the concept of balancing. According to the nomenclature of Gill and Shukla (1985a) and Grondona and Cressie (1993) we qualify as NNm-balanced the experimental designs in incomplete blocks when these are balanced for the periods distant in time of m units, or less (see Definition 2).

In a context of medical experimentation such as clinical trial, time balancing procedure allows to remove from the experimental results the biases related to effects of interactions due to the proximity over time of the administration of certain treatments at a same patient.

The goal of this paper is to find, for any integer $m \geq 1$, conditions of *universal optimality* for NNm-balanced block designs when the correlation of the errors is modeled by an autoregressive AR(m) process for the estimation of treatment contrasts when GLS estimator is used.

This paper is organized as follows: Section 2 presents the designs and the correlation structure AR(m) that we consider. It also contains some results about them. Section 3 discusses the linear model that describes the correlation structure and then deals the information matrix $\mathbf{C}_d(V^*)$. This section ends with Proposition 3 which expresses the entries of $\mathbf{C}_d(V^*)$ for the AR(m) model. Section 4 recalls a fondamental result due to Kiefer (1975a) on the information matrices for universally optimal designs (see Proposition 4). Then this section states the main theorems, Optimality Theorem 1 and Theorem 2, which give sufficient conditions for universal optimality for AR(m) model. In Section 5, Theorems 1 and 2 are illustrated with the particular designs called *semi balanced arrays*. This section also contains examples of designs that illustrate our theorems. Section 6 is devoted to proofs.

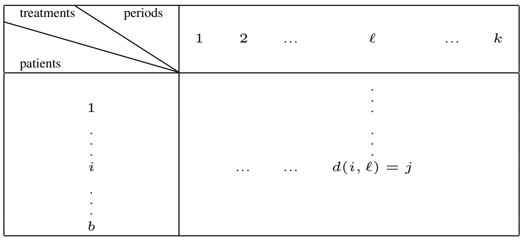
2 Experimental context

2.1 Designs for the considered experimental situation

We consider experimental situations in which $v \geq 2$ treatments can be applied to $b \geq 1$ patients during $k \geq 2$ distinct periods which are the distinct unities of time when the treatments are applied. In each period, the patient receives only one treatment which provides a single scalar experimental measurement. Assume that $k \leq v$. The number $\omega = \frac{2b}{v(v-1)}$ will be involved in many identities and will play a particular role in the case of semi balanced arrays in Section 5. We will reason within the framework of an experimental design in *incomplete blocks* where a given patient, represented by a block, receives exactly k (among v possible) distinct treatments. More precisely, such a block design d is defined as the following application:

$$d : (i, \ell) \in [\![1, b]\!] \times [\![1, k]\!] \to d(i, \ell) \in [\![1, v]\!]$$

where $d(i, \ell)$ is the treatment applied to the ith patient ($i \in [\![1, b]\!]$) at period ℓ ($\ell \in [\![1, k]\!]$). The following figure illustrates the design d:



We adopt the following first notations for the design d for all $j, j' \in [\![1, v]\!]$: $n_{d,j,i}$ is the number of times that the treatment j is applied to the ith patient, $r_{d,j}$ is the number of times that the treatment j is replicated in all of the experiment, $\lambda_{d,j,j'}$, $j \neq j'$, is the number of patients receiving both the two distinct treatments j and j', and $N^s_{d,j,j'}$ ($s \in [\![1, k-1]\!]$) is the number of patients in which j and j' are administered and are neighbors at distance s; that is, are separated by $s-1$ periods; $N^s_{d,j,j} = 0$. When d is fixed, the reference to d in these notations may be omitted. A design d is said *binary* if $n_{d,j,i} \in \{0, 1\}$ and *equireplicated* if $r_{d,j} = r_{d,j'} = r$. A binary equireplicated design d satisfies the following identities:

$$rv = kb \qquad \text{and} \tag{1}$$

$$\lambda_{d,j,j'} = \sum_{i=1}^{b} n_{d,j,i}\, n_{d,j',i} \quad . \tag{2}$$

We denote by $\Omega_{v,b,k}$ the set of incomplete blocks designs which are both binary and equireplicated.

Let us now define the specific plans called BIBD and CBD that were introduced by Yates during the years 1936 to 1940:

Definition 1 Let $d \in \Omega_{v,b,k}$. If for all distinct treatments j, j' the number $\lambda_{d,j,j'}$ is a constant λ then d is called a *balanced incomplete block design*, denoted by BIBD(v, b, r, k, λ). If moreover $k = v$, the design is called a *complete block design*, denoted by CBD(v, b).

A necessary condition for d in $\Omega_{v,b,k}$ to be a BIBD(v, b, r, k, λ) or a CBD(v, b) is:

$$\lambda = \lambda_{d,j,j'} = \omega\frac{k(k-1)}{2} \quad \forall j, j' \in [\![1, v]\!], j \neq j' \quad ; \tag{3}$$

recall that $\omega = \frac{2b}{v(v-1)}$; for a CBD$(v, b)$, we have $\lambda = b = r$. Section 5 contains an example with a BIBD and another with a CBD. Now introduce the NNm-*balanced* experimental designs that we will study among the BIBDs and the CBDs:

Definition 2 Let $d \in \Omega_{v,b,k}$. Let $m \in [\![1, k-1]\!]$. The design d is said *balanced for nearest-neighbor at distance* m, or NNm-balanced, if for any integer $s \in [\![1, m]\!]$ and for any two distinct treatments j, j' in $[\![1, v]\!]$, the value $N^s_{d,j,j'}$ does not depend on j, j' and it is the denoted by N^s_d.

Let $m \in [\![1, k-1]\!]$. A necessary condition for d in $\Omega_{v,b,k}$ to be a NNm-balanced design is:

$$N^s_d = N^s_{d,j,j'} = \omega(k-s) \quad \forall s \in [\![1, m]\!] \text{ and } \forall j, j' \in [\![1, v]\!], j \neq j' \quad . \tag{4}$$

When a NNm-balanced design is square (i.e. $k = v$), it must also satisfy the two identities (19) and (20) which will depend on new notations introduced in Section 3.3.

Example 1 Let d be the design in Table 1. Here $k = v = 4$, $b = 6$ and $\omega = 1$. The design d belongs to $\Omega_{4,6,4}$; in particular, it is binary and equireplicated. Let's see why it is NN2-balanced (i.e. $m = 2$): each pair of distinct treatments appears exactly $N^1_d = (k-1) = 3$ times at distance $s = 1$ and $N^2_d = (k-2) = 2$ times at distance $s = m = 2$. More precisely, the treatments 2 and 3 appear at distance $s = 1$ in the three lines 1, 3 and 6 and they appear at distance $s = 2$ in the two lines 4 and 5. It is the same for this others sets of treatments $\{1, 2\}, \{1, 3\}, \{1, 4\}, \{2, 4\}$ and $\{3, 4\}$. Note that d is also NN3-balanced.

Example 2 In Table 2, the design belongs to $\Omega_{5,10,4}$ and is NN3-balanced.

1	2	3	4
3	1	4	2
1	4	3	2
3	1	2	4
1	2	4	3
4	1	3	2

Table 1

1	2	3	4
2	3	4	5
3	4	5	1
4	5	1	2
5	1	2	3
1	3	5	2
2	4	1	3
3	5	2	4
4	1	3	5
5	2	4	1

Table 2

2.2 Autoregressive correlation structure AR(m)

We now describe the correlation structure considered in this paper. We suppose that the correlation between observations carried out on distinct patients equals zero.

Let $\varepsilon = (\varepsilon_{1,1}, \ldots, \varepsilon_{1,k}, \ldots, \varepsilon_{i,1}, \ldots, \varepsilon_{i,k}, \ldots, \varepsilon_{b,1}, \ldots, \varepsilon_{b,k})'$ be the bk-vector of random errors where $\varepsilon_{i,\ell}$ is the process of the error obtained at the ℓth period ($\ell \in [\![1, k]\!]$) on the ith patient ($i \in [\![1, b]\!]$) (see below (10), the model that we consider). We suppose that $\varepsilon_{i,\ell}$ is a partial realization of a mth order autoregressive process AR(m) characterized by the relations

$$\varepsilon_{i,\ell} - \sum_{r=1}^{m} \theta_r \varepsilon_{i,\ell-r} = w_{i,\ell} \quad \text{for} \quad \ell = 0, \pm 1, \pm 2, \ldots, \pm \min\{k, m\}, \tag{5}$$

where the θ_r are the parameters of the model and the $w_{i,\ell}$ are independent random variables, identically distributed, with zero mean and constant variance σ^2. Recall that the covariance function γ of a process AR(m) satisfies the following *difference equation* (see, for instance, Wei 1990):

$$\gamma(s) - \sum_{r=1}^{m} \theta_r \gamma(s-r) = \begin{cases} 0 & \text{for } s > 0 \\ \sigma^2 & \text{for } s = 0 \end{cases} \tag{6}$$

where for all i in $[\![1, b]\!]$ and for all $\ell \in [\![1, k]\!]$

$$\gamma(s) = \mathrm{Cov}(\varepsilon_{i,\ell}, \varepsilon_{i,\ell+s}) \;. \tag{7}$$

If we note ε_i the error vector $(\varepsilon_{i,1}, \ldots, \varepsilon_{i,k})'$ from the ith patient, then the variance-covariance matrix $V = \mathbb{V}\mathrm{ar}(\varepsilon_i)$ does not depend on the ith patient (it is the same for all the patients). The total variance-covariance matrix $V^* = \mathbb{V}\mathrm{ar}(\varepsilon)$ is given by:

$$V^* = \mathbf{I}_b \otimes V$$

where $\otimes$ is the Kronecker product and $\mathbf{I}_b$ is the $b \times b$ identity matrix.

Let $\mathbb{M}$ be the $(k \times k)$-matrix $\sigma^2 V^{-1}$, where σ^2 and V are defined above. The entries of $\mathbb{M}$ has been explicitly given by Wise (1955) and Siddiqui (1958). These entries are expressed in another way by Passi (1976). In the following, we express the entries of $\mathbb{M}$ in a form similar to those of Passi. This formulation will be convenient to calculate the information matrix $\mathbf{C}_d(V^*)$ defined in Section 3.

Proposition 1 *Assume $k \geq 3$. Let $m > 0$ be an integer such that $2m < k$. Put $\theta_0 = -1$ and $\theta_u = 0$ for all $u > m$. Then the entries of the matrix $\mathbb{M} = (\gamma_{\ell,\ell'})_{1 \leq \ell, \ell' \leq k} = \sigma^2 V^{-1}$ are given by:*

$$\gamma_{\ell,\ell'} = \sum_{u=0}^{\ell-1} \theta_u \theta_{u+(\ell'-\ell)} \quad \textit{for } \ell \in [\![1, k-m]\!] \textit{ and } \ell' \in [\![\ell, k]\!] \quad ; \tag{8}$$

more precisely, considering the zero values of the θ_i, the previous $\gamma_{\ell,\ell'}$ are given by:

$$(i)\ \gamma_{\ell,\ell} = \sum_{u=0}^{\ell-1} \theta_u^2 \quad \textit{for } \ell \in [\![1,m]\!]$$

$$(ii)\ \gamma_{\ell,\ell} = \sum_{u=0}^{m} \theta_u^2 \quad \textit{for } \ell \in [\![m+1,k-m]\!]$$

$$(iii)\ \gamma_{\ell,\ell+s} = \sum_{u=0}^{\ell-1} \theta_u\theta_{u+s} \quad \textit{for } \ell \in [\![1,m-1]\!], s \in [\![1,m-\ell]\!]$$

$$(iv)\ \gamma_{\ell,\ell+s} = \sum_{u=0}^{m-s} \theta_u\theta_{u+s} \quad \textit{for } \ell \in [\![1,k-m]\!], s \in [\![max(1,m-\ell+1),m]\!]$$

$$(v)\ \gamma_{\ell,\ell+s} = 0 \quad \textit{for } \ell \in [\![1,k-m]\!], s \in [\![m+1,k-\ell]\!].$$

The other entries not covered by (8) *can be deduced from these identities:*

$$\gamma_{\ell,\ell'} = \gamma_{\ell',\ell} = \gamma_{k-\ell+1,k-\ell'+1} \ \forall\ \ell,\ell' \in [\![1,k]\!] \tag{9}$$

which means that the matrix is symmetrical with respect to its two diagonals.

A formula on the sum c of the entries of $\mathbb{M}$ will be given in Proposition 3.

Example 3 For $m = 3$ and $k > 6 = 2m$, the matrix $\mathbb{M}$ is

$$\begin{pmatrix}
\theta_0^2 & -\theta_1 & -\theta_2 & -\theta_3 & 0 & \cdots & 0 & 0 \\
-\theta_1 & \theta_0^2+\theta_1^2 & -\theta_1+\theta_1\theta_2 & -\theta_2+\theta_1\theta_3 & -\theta_3 & \cdots & 0 & 0 \\
-\theta_2 & -\theta_1+\theta_1\theta_2 & \theta_0^2+\theta_1^2+\theta_2^2 & -\theta_1+\theta_1\theta_2+\theta_2\theta_3 & -\theta_2+\theta_1\theta_3 & \cdots & 0 & 0 \\
-\theta_3 & -\theta_2+\theta_1\theta_3 & -\theta_1+\theta_1\theta_2+\theta_2\theta_3 & \theta_0^2+\theta_1^2+\theta_2^2+\theta_3^2 & -\theta_1+\theta_1\theta_2+\theta_2\theta_3 & \cdots & 0 & 0 \\
\vdots & & & & & & & \vdots \\
0 & 0 & 0 & 0 & 0 & \cdots & \theta_0^2+\theta_1^2 & -\theta_1 \\
0 & 0 & 0 & 0 & 0 & \cdots & -\theta_1 & \theta_0^2
\end{pmatrix}$$

3 Information matrix

3.1 Description of the model

In our study, we consider the following classical linear model for a design d:

$$\mathbf{Y}_d = \mu\mathbf{1}_{bk} + (\mathbf{I}_b \otimes \mathbf{1}_k)\alpha + \mathbf{T}_d\beta + \varepsilon \tag{10}$$

where, for a non-zero integer a, $\mathbf{1}_a$ denotes the vector of length a filled with ones and where

- ε is the bk-vector of random errors which follows the AR(m) process with $\mathbb{E}(\varepsilon) = 0$ and $\mathbb{V}\mathrm{ar}(\varepsilon) = V^*$ (see Section 2.2);
- μ represents the overall mean, $\alpha = (\alpha_1, \ldots, \alpha_b)'$ is the vector of patient effects, β is the v-vector of (uncorrected) treatment effects;
- in $\mathbf{Y}_d = (Y_{1,1}, \ldots, Y_{1,k}, \ldots, Y_{i,1}, \ldots, Y_{i,\ell}, \ldots, Y_{i,k}, \ldots, Y_{b,1}, \ldots, Y_{b,k})'$, the element $Y_{i,\ell}$ is the response of the ith patient at period ℓ;
- the matrix $\mathbf{I}_b \otimes \mathbf{1}_k$ is interpreted as the $bk \times b$ *incidence matrix*;
- the $bk \times v$ *incidence matrix* $\mathbf{T}_d$ of *periods-treatments* is determined as follows:

$$\mathbf{T}_d = \begin{bmatrix} T_1 \\ \vdots \\ T_b \end{bmatrix} \quad \text{where } T_i = (\mathbf{t}_{\ell,j}(i))_{\substack{1\leq \ell \leq k \\ 1 \leq j \leq v}} \quad \text{and} \quad \mathbf{t}_{\ell,j}(i) = \delta_{j,d(i,\ell)} \tag{11}$$

($\delta_{a,b}$ denotes the Kronecker symbol). The entry $\mathbf{t}_{\ell,j}(i)$ of the submatrix T_i indicates when treatment j is or is not administered to the patient i at period ℓ.

Example 4 : For the design d:

$j \backslash \ell$ / i	1	2	3
1	1	1	2
2	2	3	3

, we have $v = k = 3$, $b = 2$ and:

$$(\mathbf{I}_b \otimes \mathbf{1}_k) = \begin{pmatrix} 1\,0 \\ 0\,1 \\ 1\,0 \\ 0\,1 \\ 1\,0 \\ 0\,1 \end{pmatrix} \quad \text{and} \quad \mathbf{T}_d = \begin{pmatrix} 1\,0\,0 \\ 1\,0\,0 \\ 0\,1\,0 \\ 0\,1\,0 \\ 0\,0\,1 \\ 0\,0\,1 \end{pmatrix}.$$

3.2 Information matrix

Consider the ith patient, $i \in [\![1, b]\!]$, and let $Y_i = (Y_{i,1}, \ldots, Y_{i,\ell}, \ldots, Y_{i,k})'$ be the vector of the k responses of the ith patient. In the linear model (10), the GLS estimator $\widehat{\beta}$ of the v-vector β of treatment effects satisfies the following reduced normal equations (Grondona and Cressie 1993):

$$T_i' \, \mathbb{W} \, T_i \beta = T_i' \, \mathbb{W} \, Y_i \quad \text{where} \quad \mathbb{W} = V^{-1} - (\mathbf{1}_k' V^{-1} \mathbf{1}_k)^{-1} V^{-1} \mathbf{1}_k \mathbf{1}_k' V^{-1} \quad . \tag{12}$$

Hence $\sigma^2 \mathbb{W} = \mathbb{M} - c^{-1} \mathbb{M} \mathbf{1}_k \mathbf{1}_k' \mathbb{M}$ where $c = \mathbf{1}_k' \mathbb{M} \mathbf{1}_k$ is the sum of entries of $\mathbb{M}$.

Let $\gamma \in \mathbb{R}^v$ and β be a treatment effects; the linear combination $\gamma' \cdot \beta = \sum_{j=1}^{v} \gamma_j \beta_j$ is called a *treatment contrast* if $\gamma' \cdot \mathbf{1}_v = 0$. A block design d is said to be *connected* if all treatment contrasts are estimable under d. We refer to Dey (2010, pages 11 and 12) for details about connected designs.

In the following, the set $\Omega_{v,b,k}$ is restricted to connected designs.

The vector $\gamma = (\beta_j - \frac{1}{v}\sum_{j=1}^{v}\beta_j)_{1\leq j\leq v}$ of corrected treatment effects is also written:

$$\gamma = (\mathbf{I}_v - \frac{\mathbf{1}_{v\times v}}{v})\beta \tag{13}$$

where $\mathbf{1}_{v\times v}$ denotes the matrix of dimension $v \times v$ filled with ones; this vector γ satisfies the identifiability constraint $\gamma' \cdot \mathbf{1}_v = 0$ and if $u \in \mathbb{R}^v$ such that $u' \cdot \mathbf{1}_v = 0$ then $u' \cdot \gamma = u' \cdot \beta$. Denote by $A^\dagger$ the Moore-Penrose inverse of a matrix A and by $\widehat{\gamma}$ the GLS estimator of a contrast γ. Then from (12) and (13):

$$\widehat{\gamma} = (\mathbf{I}_v - \frac{\mathbf{1}_{v\times v}}{v})(T_i'\mathbb{W}T_i)^\dagger T_i'\mathbb{W}Y_i = (T_i'\mathbb{W}T_i)^\dagger T_i'Y_i \quad . \tag{14}$$

From equation (14), for the ith patient, the variance-covariance matrix of $\widehat{\gamma}$ is given by: $\mathbb{V}\mathrm{ar}(\widehat{\gamma}) = (T_i'\mathbb{W}T_i)^\dagger$. Then we deduce the following known result used in Kunert (1987) and Grondona and Cressie (1993) (see Benchekroun (1993) for a proof):

Proposition 2 *Let $V^* = \boldsymbol{I}_b \otimes V$. In the covariance structure* (5), (6), (7), *the information matrix of the estimator $\widehat{\gamma}$ of treatment contrasts for the ith patient is given by $\boldsymbol{C}_{i,d}(V) = \mathbb{V}\mathrm{ar}(\widehat{\gamma})^\dagger = T_i'\mathbb{W}T_i$ and, for all the patients, the information matrix $\boldsymbol{C}_d(V^*)$ of dimension $v \times v$ is given by:*

$$\sigma^2\boldsymbol{C}_d(V^*) = \sum_{i=1}^{b}\sigma^2\boldsymbol{C}_{i,d}(V) = \sum_{i=1}^{b}T_i'\,\mathbb{M}\,T_i - c^{-1}\sum_{i=1}^{b}T_i'\,\mathbb{M}\boldsymbol{I}_k\boldsymbol{I}_k'\mathbb{M}\,T_i \tag{15}$$

where $c = \boldsymbol{I}_k'\mathbb{M}\boldsymbol{I}_k$ is the sum of entries of $\mathbb{M}$.

3.3 Coefficients of the information matrix in our experimental context

In this section we consider a (connected) block design d belonging to $\Omega_{v,b,k}$ with $k \geq 3$ and a strictly positive integer m such that $2m < k$. We will generalize the result of Grondona and Cressie (1993) which expresses for $m = 2$ the coefficients of the information matrix $\mathbf{C}_d(V^*)$ according to certain entities. We need some additional notations that generalize theirs for all $j, j' \in [\![1, v]\!]$:

$\phi^{\ell}_{d,j,i}$ is the number of times that treatment j is applied to the ith patient at either period ℓ or period $(k - \ell + 1)$ with $\ell \in [\![1, m]\!]$;

$\phi^{\ell}_{d,j}$ is the number of patients receiving treatment j at periods ℓ or $(k - \ell + 1)$ when $\ell \in [\![1, m]\!]$ and at the period ℓ when $\ell \in [\![m + 1, k - m]\!]$;

$\phi^{\ell*}_{d,j,j'}$ is the number of times that treatments j and j' occur to the same patient and for which at least one of j and j' is applied at period ℓ or at period $(k - \ell + 1)$ with $\ell \in [\![1, m]\!]$ (counted twice if j and j' are applied to both these periods);

$N^s_{d,j,j',i}$ is the number of times that j and j' are applied to the ith patient with a distance $s \in [\![1, k - 1]\!]$; with $N^s_{d,j,j,i} = 0$; we have $N^s_{d,j,j',i} \in \{0, 1\}$.

As an illustration, in Section 5, we will calculate the above quantities for explicit designs. We state below some results on these entities, sometimes immediate, that will be used later in the paper; the first one is due to Koné and Valibouze (2011), the second one comes from d equireplicated and the last comes from d binary:

$$\sum_{j=1}^{v} \phi_{d,j}^{\ell} = 2b \text{ for } \ell \in [\![1,m]\!] \quad , \tag{16}$$

$$r = r_{d,j} = \sum_{\ell=1}^{k-m} \phi_{d,j}^{\ell} \qquad \forall j \in [\![1,v]\!] \quad \text{and} \tag{17}$$

$$\phi_{d,j,i}^{\ell} = \delta_{j,d(i,\ell)} + \delta_{j,d(i,k-\ell+1)} \quad . \tag{18}$$

A square NNm-balanced design d in $\Omega_{v,b,v}$ must satisfies the two identities below for all $j, j' \in [\![1,v]\!]$ ($j \neq j'$) and for each $\ell \in [\![1,m]\!]$:

$$\phi_{d,j}^{\ell} = \frac{2b}{v} = \omega(v-1) \quad \text{and} \tag{19}$$

$$\phi_{d,j,j'}^{\ell *} = \frac{4b}{v} = 2\omega(v-1) \quad . \tag{20}$$

The two above identities proved in Section 6.6 apply to CBDs. The following proposition generalizes to any $m \geq 3$ the result for $m = 2$ of Grondona and Cressie (1993) on the information matrix:

Proposition 3 *Let v, k and m be integers such that $2 \leq 2m < k \leq v$ and let d be a design belonging to $\Omega_{v,b,k}$. Let's put*

$$a_\ell = \sum_{u=\ell}^{m} \theta_u \ , \ b_\ell = \sum_{u=\ell}^{m} \theta_u^2 \quad \textit{and} \quad \Theta_{t,s} = \theta_t\theta_{t+s} + \theta_{t+1}\theta_{t+1+s} + \cdots + \theta_{m-s}\theta_m \ .$$

Then, for the AR(m) model, the entries of the information matrix $\boldsymbol{C}_d := \boldsymbol{C}_d(V^*)$ are given by the following formulas:

- on the diagonal, for each treatment $j \in [\![1,v]\!]$:

$$\sigma^2 \boldsymbol{C}_{d,j,j} = s_0 r - s_1\phi_{d,j}^1 - s_2\phi_{d,j}^2 - \cdots - s_m\phi_{d,j}^m \tag{21}$$

where $s_\ell = b_\ell + c^{-1}a_0^2 a_\ell(a_\ell - 2a_0)$; in particular, $s_0 = b_0 - c^{-1}a_0^4$;

- out of the diagonal, for two distinct treatments $j' \neq j$ in $[\![1,v]\!]$:

$$\begin{aligned}\sigma^2 \boldsymbol{C}_{d,j,j'} = &\sum_{s=1}^{m} N_{d,j,j'}^{s} \Theta_{0,s} \\ &- \sum_{s=1}^{m-1}\sum_{t=1}^{m-s} \Theta_{t,s} \sum_{i=1}^{b} N_{d,j,j',i}^{s} (\phi_{d,j,i}^{t}\phi_{d,j',i}^{t+s} + \phi_{d,j',i}^{t}\phi_{d,j,i}^{t+s}) \\ &-c^{-1}a_0^2 \left\{ a_0^2\lambda_{d,j,j'} - a_0 \sum_{\ell=1}^{m} a_\ell \phi_{d,j,j'}^{\ell *} + \sum_{\ell=1}^{m}\sum_{\ell'=1}^{m} a_\ell a_{\ell'} \sum_{i=1}^{b} \phi_{d,j,i}^{\ell}\phi_{d,j',i}^{\ell'} \right\} .\end{aligned} \tag{22}$$

Moreover, the sum c of the entries of the matrix $\mathbb{M} = \sigma^2 V^{-1}$ *is given by:*

$$c = \boldsymbol{1}'_k \mathbb{M} \boldsymbol{1}_k = 2a_0 \sum_{\ell=0}^{m-1} (m-\ell)\theta_\ell + (k-2m)a_0^2 \quad . \tag{23}$$

Remark 1 **Consequence of Proposition 3**.
From Identity (16) and Proposition 3, the trace of the information matrix $\mathbf{C}_d$

$$\operatorname{tr}(\mathbf{C}_d) = \sum_{j=1}^{v} \mathbf{C}_{d,j,j} = \frac{s_0 vr - \sum_{u=1}^{m} s_u \sum_{j=1}^{v} \phi_{d,j}^u}{\sigma^2}$$

does not depend on the design $d \in \Omega_{v,b,k}$ and is given by the following identity:

$$\sigma^2 tr(\mathbf{C}_d) = s_0 vr - 2b(s_1 + s_2 + \cdots + s_m) \quad . \tag{24}$$

4 Universal optimality

To obtain strong optimality criteria we will study the information matrix $\mathbf{C}_d = \mathbf{C}_d(V^*)$ of the estimator $\widehat{\gamma}$.

4.1 Preliminary

Let $\mathcal{V} = \{\mathbf{C}_d : d \in \Omega_{v,b,k}\}$ be the set of information matrices of the estimator $\widehat{\gamma}$ for each design in $\Omega_{v,b,k}$. For each design $d \in \Omega_{v,b,k}$, the information matrix $\mathbf{C}_d$ is positive semi-definite of dimension $v \times v$ and satisfies these identities (Kiefer 1975b):

$$\mathbf{C}_d \mathbf{1}_v = \mathbf{C}_d^{'} \mathbf{1}_v = \mathbf{0}_v \tag{25}$$

where, for a non-zero integer a, $\mathbf{0}_a$ denotes the vector of length a filled with zeros; that is to say: in $\mathbf{C}_d$ the row and column sums are zero.

Definition 3 (Kiefer 1975a) A block design d belonging to $\Omega_{v,b,k}$ is said *universally optimal* if its information matrix $\mathbf{C}_d$ minimizes simultaneously all functions $\psi : \mathcal{V} \mapsto [-\infty, +\infty]$, called *criterions*, satisfying the three following conditions:

(i) for each $\mathbf{C} \in \mathcal{V}$, $\psi(\mathbf{C})$ is invariant under all permutations applied to the rows and columns of $\mathbf{C}$;
(ii) ψ is convex, i.e. $\psi\{a\mathbf{C}_1 + (1-a)\mathbf{C}_2\} \leq a\psi(\mathbf{C}_1) + (1-a)\psi(\mathbf{C}_2)$ for all $\mathbf{C}_1, \mathbf{C}_2 \in \mathcal{V}$ and $0 \leq a \leq 1$;
(iii) $\psi(a\mathbf{C}) \geq \psi(\mathbf{C})$ for all $\mathbf{C} \in \mathcal{V}$ and $0 < a < 1$.

Proposition 4 *(Kiefer 1975b) Suppose that there exists* $d^* \in \Omega_{v,b,k}$, *such that its information matrix* $\boldsymbol{C}_{d^*}$ *satisfies* (25) *and verifies:*

(i) $\boldsymbol{C}_{d^*}$ *is completely symmetric, i.e.* $\boldsymbol{C}_{d^*} = \alpha \boldsymbol{I}_v - \frac{\alpha}{v} \boldsymbol{1}_{v \times v}$ *where* α *is a scalar;*
(ii) the trace of $\boldsymbol{C}_{d^*}$ *is maximal on the set* $\mathcal{V}$.

Then the design d^* *is universally optimal in* $\Omega_{v,b,k}$.

By Identity (25), we just have to find a design whose information matrix meets conditions (i) and (ii) of Kiefer's Proposition 4.

4.2 Optimality conditions for the correlation structure AR(m)

We consider the (binary, equireplicated, connected) block designs in $\Omega_{v,b,k}$ with $3 \leq k \leq v$ and an integer $m > 0$ such that $2m < k$. We want to establish universal optimal conditions for the NNm-balanced BIBDs (resp. CBDs) existing in $\Omega_{v,b,k}$.

If no design d in $\Omega_{v,b,k}$ satisfies both Identities (3) and (4) then there is no NNm-balanced BIBD(v,b,r,k,λ) in $\Omega_{v,b,k}$ because these are necessary conditions for that. It is similar for the CBD: a NNm-balanced CBD(v,b) in $\Omega_{v,b,v}$ must satisfy $\lambda = b = r$ and Identities (4) (with $k = v$), (19) and (20).

Proposition 4 of Kiefer gives two sufficient conditions for a design to be universally optimal. Since all the designs in $\Omega_{v,b,k}$ have the same trace (see Remark 1), the condition (ii) of this Proposition is automatically satisfied. It is then enough to search for designs in $\Omega_{v,b,k}$ whose information matrix is completely symmetric. We can now establish our main Theorem:

Theorem 1 (Optimality Theorem) *Let v, k, m and $b > 0$ be integers. Assume that $2 \leq 2m < k < v$ and let's put $\omega = \frac{2b}{v(v-1)}$. If for the AR$(m)$ model there exists a NNm-balanced BIBD(v,b,r,k,λ) design d in $\Omega_{v,b,k}$, which also fulfills, for all distinct treatments j, j' in $[\![1,v]\!]$ and, for all $\ell, \ell' \in [\![1,m]\!]$, the following conditions:*

$$(i) \qquad \phi^{\ell *}_{d,j,j'} = 2\omega(k-1) \quad ,$$

$$(ii) \qquad \sum_{i=1}^{b} \phi^{\ell}_{d,j,i}\phi^{\ell'}_{d,j',i} = \omega(2-\delta_{\ell,\ell'}) \ ,$$

$$(iii) \quad \sum_{i=1}^{b} N^{|\ell-\ell'|}_{d,j,j',i}(\phi^{\ell}_{d,j,i}\phi^{\ell'}_{d,j',i} + \phi^{\ell}_{d,j',i}\phi^{\ell'}_{d,j,i}) = 2\omega \qquad \text{when } \ell \neq \ell'$$

then d is universally optimal over $\Omega_{v,b,k}$. ($\delta_{\ell,\ell'}$ denotes the Kronecker symbol.)

Note that when d is a NNm-balanced universally optimal BIBD(v,b,r,k,λ), Identities (3) and (4) must also be satisfied by d. Then, when d is universally optimal, Theorem 1 and Proposition 3 imply that the off-diagonal entries (for $j' \neq j$ in $[\![1,v]\!]$) of the information matrix $\mathbf{C}_d$ are given by:

$$\begin{aligned} \frac{\sigma^2}{\omega}\mathbf{C}_{d,j,j'} &= (k-s)\sum_{s=1}^{m}\Theta_{0,s} - 2\sum_{s=1}^{m-1}\sum_{t=1}^{m-s}\Theta_{t,s} \\ -\frac{c^{-1}a_0^2}{2}&\left\{a_0^2 k(k-1) - 4a_0(k-1)\sum_{\ell=1}^{m} a_\ell + 2\sum_{\ell=1}^{m}(a_\ell^2 + 2a_\ell \sum_{\substack{\ell'=1\\ \ell'\neq\ell}}^{m} a_{\ell'})\right\} \quad . \end{aligned} \tag{26}$$

When $v = k$, Condition (i) of Theorem 1 becomes Identity (20) which is always satisfied for a CBD(v,b). Then, in case of complete block designs, we obtain following theorem with one condition less:

Theorem 2 *Assume that b, v and m are strictly positive integers such that $2 \leq 2m < v$. If for the AR(m) model there exists a (square) design d in $\Omega_{v,b,v}$ which is a NNm-balanced CBD(v,b) then d is universally optimal over $\Omega_{v,b,v}$ if it fulfills Conditions (ii) and (iii) of Theorem 1.*

Remark 2 A necessary condition for the existence of designs satisfying Conditions (ii) of Theorem 1 is that $\omega = \frac{2b}{v(v-1)}$ is an integer and therefore $v(v-1)$ divides $2b$. A design is said *minimal* if the value of b is minimal for k and v fixed and if the design satisfies the associated optimality conditions. In Koné and Valibouze (2011) and Morgan and Chakravarti (1988), the authors showed that the minimal value b for which there exists a NN2-balanced $\mathrm{CBD}(v, b)$ is when $\omega = 1$; i.e. $2b = v(v-1)$.

As for Proposition 3, Theorems 1 and 2 imply the results of Kunert (1987), for $m = 1$, and the results of Grondona and Cressie (1993), for $m = 2$ [1].

5 Optimality Theorem and Semi-Balanced arrays

We will illustrate Optimality Theorems with designs called *semi-balanced arrays*. The concept of orthogonal arrays (OA) has been introduced in Rao (1946, 1947); later, in Rao (1961), appeared two variants called OA of Type I and OA of Type II; these two variants have been renamed respectively *transitive* arrays (TA) and *semi-balanced* arrays (SB) (for details, see also Hedayat, Sloane and Stufken 1999; Morgan and Chakravarti 1988; Rao 1973).

Definition 4 A $b \times k$ array of v symbols is an $\mathrm{SB}(b, k, v, t)$, where t is called the *strength*, if for any selection of t columns each unordered t-tuple has distinct symbols among v and appears exactly ω_t times, where $\omega_t \in \mathbb{N}$ is called the *index* of the array.

To define a transitive array, it is sufficient to replace "unordered t-tuples" by "ordered t-tuples" in the definition of an SB. Clearly, a $\mathrm{TA}(b, k, v, t)$ of index ω_t^* is an $\mathrm{SB}(b, k, v, t)$ of index $\omega_t = t!\,\omega_t^*$.

Remark 3 As the number of unordered t-tuples of symbols is $\binom{v}{t} = \frac{v!}{t!(v-t)!}$, the index of an $\mathrm{SB}(b, k, v, t)$ verifies $\omega_t = b/\binom{v}{t}$. Consequently, the existence of an $\mathrm{SB}(b, k, v, t)$ implies that b is a multiple of $\binom{v}{t}$. Note that for $t = 2$, the index ω_2 is the entity $\omega = \frac{2b}{v(v-1)}$ of Theorem 1.

In the context of our paper, b is the number of patients, k is the number of treatments received by each patient, and the v symbols represent the indices of the distinct treatments. We have chosen this particular context to clarify our explanations.

There exist many different methods to construct SBs and TAs designs (Morgan and Chakravarti 1988; Mukhopadhyay 1972; Ramanujacharyulu 1966; Stufken 1991, ...). In the context of this section, we will be interested only in the strength $t = 2$ and then the index is ω. In Rao (1961, 1973), the author showed that if a $\mathrm{TA}(v(v-1), k, v, 2)$ exists, then it can be constructed from $(k-1)$ mutually orthogonal latin squares of order v, and that if v is an odd prime power or an odd prime, an $\mathrm{SB}(v(v-1)/2, v, v, 2)$ can be constructed from $\mathrm{GF}(v)$, the finite Galois field with v elements.

[1] We bring attention on an error of their paper about one term of their formula (4.9) giving $\sigma^2 c_{l,m}$ for $l \neq m$: in the term $2(1-\phi_1-\phi_2)\phi_2 f^*_{l,m}$ of their paper, the factor 2 must be removed. The notations $e^*_{l,m}$ and $f^*_{l,m}$ of their paper correspond to the notations $\phi^{1*}_{d,l,m}$ and $\phi^{2*}_{d,l,m}$ of our paper.

Example 5 We built the following designs (a_i), $i \in [\![1,5]\!]$, using the cyclic shift method of Ahmed and Akhtar (2009) to build balanced neighbor designs of all orders. Their method generalizes that of Iqbal, Aman Ullah and Nasir (2006). The design d resulting from the superposition of Designs $(a_1), \dots (a_5)$ is an $\mathrm{SB}(55,7,11,2)$ of index $\omega = 1$.

1	2	3	4	5	6	7
2	3	4	5	6	7	8
3	4	5	6	7	8	9
4	5	6	7	8	9	10
5	6	7	8	9	10	11
6	7	8	9	10	11	1
7	8	9	10	11	1	2
8	9	10	11	1	2	3
9	10	11	1	2	3	4
10	11	1	2	3	4	5
11	1	2	3	4	5	6

(a_1)

1	3	5	7	9	11	2
2	4	6	8	10	1	3
3	5	7	9	11	2	4
4	6	8	10	1	3	5
5	7	9	11	2	4	6
6	8	10	1	3	5	7
7	9	11	2	4	6	8
8	10	1	3	5	7	9
9	11	2	4	6	8	10
10	1	3	5	7	9	11
11	2	4	6	8	10	1

(a_2)

1	4	7	10	2	5	8
2	5	8	11	3	6	9
3	6	9	1	4	7	10
4	7	10	2	5	8	11
5	8	11	3	6	9	1
6	9	1	4	7	10	2
7	10	2	5	8	11	3
8	11	3	6	9	1	4
9	1	4	7	10	2	5
10	2	5	8	11	3	6
11	3	6	9	1	4	7

(a_3)

1	5	9	2	6	10	3
2	6	10	3	7	11	4
3	7	11	4	8	1	5
4	8	1	5	9	2	6
5	9	2	6	10	3	7
6	10	3	7	11	4	8
7	11	4	8	1	5	9
8	1	5	9	2	6	10
9	2	6	10	3	7	11
10	3	7	11	4	8	1
11	4	8	1	5	9	2

(a_4)

1	6	11	5	10	4	9
2	7	1	6	11	5	10
3	8	2	7	1	6	11
4	9	3	8	2	7	1
5	10	4	9	3	8	2
6	11	5	10	4	9	3
7	1	6	11	5	10	4
8	2	7	1	6	11	5
9	3	8	2	7	1	6
10	4	9	3	8	2	7
11	5	10	4	9	3	8

(a_5)

Example 6 The following designs have been constructed by Deheuvels and Derzko (1991) .

1	3	4	5	2
2	4	5	1	3
3	5	1	2	4
4	1	2	3	5
5	2	3	4	1
1	2	5	3	4
2	3	1	4	5
3	4	2	5	1
4	5	3	1	2
5	1	4	2	3

(a)

1	4	3	2	5
2	5	4	3	1
3	1	5	4	2
4	2	1	5	3
5	3	2	1	4
1	5	2	4	3
2	1	3	5	4
3	2	4	1	5
4	3	5	2	1
5	4	1	3	2

(b)

1	3	4	5	2
2	4	5	1	3
3	5	1	2	4
4	1	2	3	5
5	2	3	4	1

(c)

1	2	5	3	4
2	3	1	4	5
3	4	2	5	1
4	5	3	1	2
5	1	4	2	3

(d)

Design (a), resulting from the superposition of the two quasi-complete Latin squares (c) and (d), is an $\mathrm{SB}(10,5,5,2)$ of index $\omega = 1$. Design (b) results from the superposition of the mirror images of designs (c) and (d). Design (e), resulting from the superposition of designs (a) and (b), yields a $\mathrm{TA}(20,5,5,2)$ of index 1 or an $\mathrm{SB}(20,5,5,2)$ of index 2.

Martin and Eccleston (1991) have introduced the concept of *strongly directionally equineighboured* designs (SDEN)[2]. They remarked that for $k \geq 3$ an SDEN(b,k,v) is equivalent to an SB$(b,k,v,2)$ and they constructed these designs from $\omega(v-1)$ latin squares of order v. The part (a) of their Theorem 2 implies that, for $k \geq 3$, if an SB$(b,k,v,2)$ exists then it is universally optimal within $\Omega_{v,b,k}$ for any variance-covariance matrix V, under GLS.

We are interested in SBs of strength $t = 2$ since if an SB$(b,k,v,2)$ exists then it can be interpreted as a BIBD(v,b,r,k,λ) (it is well kwown and easily provable). The following proposition applies Theorem 2 in Martin and Eccleston (1991). The correlation model that these authors use is broader than AR(m), but it applies only (for optimality) to a subset of designs among those we study in this article. Notice that this theorem also applies to non-binary designs, but we do not consider them here.

Proposition 5 *Let k and v be two integers such that $3 \leq k \leq v$. Suppose there exists a design d which is an SB($b,k,v,2$). Then for $k < v$ (resp. $k = v$), the design d is a BIBD(v,b,r,k,λ) (resp. a CBD(v,b)) and it satisfies Identity* (3) *for λ and*

$$r = \frac{k(v-1)}{2}\,\omega \tag{27}$$

where $\omega = \frac{2b}{v(v-1)}$ is the index of d. Moreover, for an integer $m > 0$ such that $2m < k$, the design d is NNm-balanced universally optimal for the AR(m) correlation structure. In particular, for $j, j' \in [\![1,v]\!]$, $j \neq j'$ and $\ell, \ell', s \in [\![1,m]\!]$, d satisfies Identity (4) *on N_d^s and Identities (i),(ii) and (iii) of Optimality Theorems 1.*

A similar result about weakly universally optimal BIBDs is given in Morgan and Chakravarti (1988) (Theorem 4.1) for the NN2 correlation structure and in Koné and Valibouze (2011) for the NNm ($m > 1$) correlation structures.

To illustrate Proposition 5 and Optimality Theorems 1 and 2, we end with two examples with SBs of strength 2: the first one is the simplest case with a CBD (Theorem 2) and the second one is with a BIBD (Theorem 1).

Example 7 Let us consider the design (a) of Example 6. This design is an SB$(b = 10, k = 5, v = 5, t = 2)$ of index $\omega = 1$. Following Proposition 5, it is a CBD$(v = 5, b = 10)$ with $r = b = \lambda = 10$ and $k = v = 5$. On this CBD, we consider an AR(m) correlation structure with $2m < k = 5$. We chose $m = 2$. Let $\ell, \ell' \in [\![1,2]\!] = [\![1,m]\!]$ and let $j, j' \in [\![1,5]\!] = [\![1,v]\!]$ be two distinct treatments.

To check Identity (4), we have to consider $s \in [\![1,2]\!] = [\![1,m]\!]$. For $s = 1$, we count in the design $d =$(a) the number of times that j and j' are applied consecutively to the same patient; we find $N^1_{d,j,j'} = 4$ and we check that $N^1_{d,j,j'} = \omega(k-s)$. For $s = 2$, the number of times that j and j' are applied to the same patient at distance $s = 2$ is found to be $N^2_{d,j,j'} = 3 = \omega(k-s)$. Hence, Identity (4) is satisfied.

[2] Deheuvels and Derzo coined the terms *totally balanced* for SDEN and SB, and *universally balanced* for TA.

Now, to check Identity (ii) of Theorem 1, consider the value $\phi^{\ell}_{d,j,i}$, the number of times that the treatment j is applied to the ith patient at period ℓ or $(k-\ell+1)$. When $\ell=\ell'$, the value $\sum_{i=1}^{10}\phi^{\ell}_{d,j,i}\phi^{\ell'}_{d,j',i}$ is the number of times that j and j' are applied to the same patient at the periods ℓ and $k-\ell+1$. By the definition of SBs of strength 2, this value is the index $\omega=1$ of Design (a) (that we can verify on the design itself). When $\ell\neq\ell'$, by symmetry, we can chose $\ell=1$ and $\ell'=2$. For example, $j=1$ and $j'=5$ appear 2 times on the same row (patients $i=1$ and $i=8$) with j at period $\ell=1$ or $k-\ell+1=5$ and j' is at period $\ell'=2$ or $k-\ell'+1=4$. In the same way, we could check $\sum_{i=1}^{10}\phi^{\ell}_{d,j,i}\phi^{\ell'}_{d,j',i}=2=2\omega$ for any j,j' with $j\neq j'$. Then Identity (ii) holds.

To finish our example, for Identity (iii) of Theorem 1, suppose that $\ell\neq\ell'$. Then necessarily $\mid\ell-\ell'\mid=1$ and we can chose $\ell=1$ and $\ell'=2$. The value $N^{|\ell-\ell'|}_{d,j,j',i}$ equals 1 if the treatments j and j' are applied consecutively to the ith patient; otherwise $N^{|\ell-\ell'|}_{d,j,j',i}=0$. For example, $j=1$ and $j'=5$ appear $\omega=1$ time together at periods $\ell=1$ and $\ell'=2$ (patient $i=10$) and $\omega=1$ time in periods $k-\ell+1=5$ and $k-\ell'+1=4$ (patient $i=8$). This could be checked for any j,j' with $j\neq j'$. Then, as stated in the Proposition 5, we obtain Identity (iii):

$$\sum_{i=1}^{10}N^{s}_{d,j,j',i}(\phi^{\ell}_{d,j,i}\phi^{\ell'}_{d,j',i}+\phi^{\ell}_{d,j',i}\phi^{\ell'}_{d,j,i})=2=2\omega\ ,\ \ell,\ell'\in[\![1,2]\!],s=\mid\ell-\ell'\mid=1\quad .$$

In the same way, we can check that Identity (iii) holds for each couple (j,j') where $j\neq j'$. Consequently, from Theorem 2, Design (a) is universally optimal.

Example 8 Let us consider the design d constructed in Example 5 with index $\omega=1$. By Proposition 5, d is also a BIBD$(11,55,35,7,21)$. We have $r=7\times5=35$ since each treatment appears once and only once in each column of each design (a_i). The number λ of times any one pair of distinct treatments is applied to the same patient is 21 which is actually the value $\omega\frac{k(k-1)}{2}$ expected in Identity (3). We let the reader check Identities (4), then (ii) and (iii) of Theorem 1 for $m=3$; we check only Identity (i). Let $\ell\in[\![1,3]\!]$ and let $j,j'\in[\![1,11]\!]$ be two distinct treatments. We have to count $\phi^{\ell*}_{d,j,j'}$, the number of times that j and j' occur to the same patient and for which at least one of j and j' is applied at period ℓ or at period $(k-\ell+1)$ (counted twice if j and j' are applied to both these periods). We find indeed Identity (i):

$$\phi^{\ell*}_{d,j,j'}=\sum_{u=1}^{5}\phi^{\ell*}_{(a_u),j,j'}=12=2\omega(k-1)\quad .$$

For example, for $\ell=1$ and $k-\ell+1=7$, we observe the first and the last columns. Let $(j,j')=(1,3)$. For $u=1$, the treatment $j=1$ appears in the first column of line $i=1$ with treatment 3 in the same line and it appears also in the last column of the line $i=6$ without the treatment 3 in the same line; the treatment $j'=3$ appears in the first column of line $i=3$ without the treatment 1 in the same line and it appears on the last column of the line $i=8$ with the treatment 1 in the same line. Then $\phi^{1*}_{(a_1),1,3}=2$. We count also $\phi^{1*}_{(a_2),1,3}=\phi^{1*}_{(a_3),1,3}=\phi^{1*}_{(a_5),1,3}=2$ and $\phi^{1*}_{(a_2),1,3}=4$. Then $\phi^{1*}_{d,1,3}=12$. In the same way, $\phi^{2*}_{d,1,3}=\phi^{3*}_{d,1,3}=12$. Consequently, applying Optimality Theorem 1, we conclude that Design d is universally optimal.

6 Appendix. Proofs

This appendix begins by the proof of formula (23) on $c = \mathbf{1}_k'\mathbb{M}\mathbf{1}_k$ in Proposition 3. To establish this formula we need the (essential) technical Lemma 1 on the sums of entries of a row of matrix $\mathbb{M}$ which is in Section 6.1 too. It is probably the difficulty in establishing this lemma that has long prevented the generalization to any m of the optimal conditions for the AR(m) process. The next four sections are devoted to the respective proofs of Propositions 3, Theorems 1 and 2 and Proposition 5. We will end in Section 6.6 with the proofs of Identities (3), (4), (19) and (20).

6.1 **Sum c of entries of matrix $\mathbb{M}$, Identity** (23)

We want establish the formula (23) of Proposition 3. This formula on c, the sum of entries of $\mathbb{M}$, is essentially based on Lemma 1 which gives the sum p_ℓ of entries of row $\ell \in [\![1, k]\!]$; it will be also used to establish Identity (44) in the proof of Proposition 3. We first prove Identity (23) using Lemma 1 that will come after.
By definition, $c = \mathbf{1}_k'\mathbb{M}\mathbf{1}_k = \sum_{\ell=1}^{k}\sum_{\ell'=1}^{k}\gamma_{\ell,\ell'} = 2\sum_{\ell=1}^{m} p_\ell + \sum_{\ell=m+1}^{k-m} p_\ell$. After that, from Formula $p_\ell = a_0(a_0 - a_\ell)$ of Lemma 1, we find:

$$\begin{aligned} c &= 2a_0\sum_{\ell=1}^{m}(a_0 - a_\ell) + \sum_{\ell=m+1}^{k-m} a_0^2 = 2a_0\sum_{\ell=1}^{m}(\theta_0 + \cdots + \theta_{\ell-1}) + (k-2m)a_0^2 \\ &= 2a_0\sum_{\ell=0}^{m-1}(m-\ell)\theta_\ell \ + \ (k-2m)a_0^2 \end{aligned}$$

because in the sum $\sum_{\ell=1}^{m}(\theta_0 + \cdots + \theta_{\ell-1})$ we count m times θ_0, $m-1$ times θ_1, and so on until only once θ_{m-1}. Thus Formula (23) is proved □

Lemma 1 *Assume $k > 2m \geq 2$. Let $p_\ell = \sum_{\ell'=1}^{k}\gamma_{\ell,\ell'}$ be the sum of the entries of row $\ell \in [\![1, k]\!]$ of matrix $\mathbb{M}$, $a_\ell = \sum_{u=\ell}^{m}\theta_u$ for $\ell \leq m$ and $a_\ell = 0$ for $\ell > m$. Then:*

$$p_\ell = a_0(a_0 - a_\ell) = (1 - \theta_1 - \cdots - \theta_m)(1 - \theta_1 - \cdots - \theta_{\ell-1}) \tag{28}$$

for $\ell \in [\![1, k-m]\!]$ and, as $\mathbb{M}$ is symmetric with respect to its second diagonal, $p_\ell = p_{k-\ell+1}$ for $\ell \in [\![k-m+1, k]\!]$.
In particular, $p_\ell = p_{m+1} = a_0^2$ for $\ell \in [\![m+1, k-m]\!]$.

Proof We consider the matrix $\mathbb{M} = (\gamma_{\ell,\ell'})_{1\leq\ell,\ell'\leq k}$ and we would like to express the sum $p_\ell = \sum_{\ell'=1}^{k}\gamma_{\ell,\ell'}$ of the entries of row ℓ in the form given in Lemma 1. By symmetry of $\mathbb{M}$ we can suppose that $\ell \in [\![1, k-m]\!]$. We write $p_\ell = \alpha_\ell + \beta_\ell$ where $\alpha_\ell = \sum_{\ell'=\ell}^{k}\gamma_{\ell,\ell'}$ and $\beta_\ell = \sum_{\ell'=1}^{\ell-1}\gamma_{\ell,\ell'}$.

First we compute $\alpha_\ell = \sum_{\ell'=\ell}^{k} \gamma_{\ell,\ell'}$. From Identity (8) of Proposition 1, we have the following expression of each $\gamma_{\ell,\ell'}$ for $\ell' \in [\![\ell, k]\!]$:

$$\gamma_{\ell,\ell+s} = \sum_{u=0}^{\ell-1} \theta_u \theta_{u+s} \quad \text{for } s \in [\![0, k-\ell]\!] \quad . \tag{29}$$

Then, as $\alpha_\ell = \sum_{s=0}^{k-\ell} \sum_{u=0}^{\ell-1} \theta_u \theta_{u+s}$, we obtain:

$$\alpha_\ell = \sum_{u=0}^{\ell-1} \left(\theta_u \sum_{s=0}^{k-\ell} \theta_{u+s} \right) = \sum_{u=0}^{\ell-1} \left(\theta_u \sum_{b=u}^{k+u-\ell} \theta_b \right) = \sum_{u=0}^{\ell-1} \left(\theta_u \sum_{b=u}^{m} \theta_b \right) \tag{30}$$

because for each $b > m$ we have $\theta_b = 0$ and for each $u \in [\![0, \ell-1]\!]$ we have $k + u - \ell \geq k - \ell \geq k - (k-m) = m$.

Now consider $\beta_\ell = \sum_{\ell'=1}^{\ell-1} \gamma_{\ell,\ell'} = \sum_{\ell'=1}^{\ell-1} \sum_{u=0}^{\ell'-1} \theta_u \theta_{u+(\ell-\ell')}$ and search to establish this formula:

$$\beta_\ell = \sum_{a=1}^{\ell-1} \theta_a \sum_{b=0}^{a-1} \theta_b \quad . \tag{31}$$

The expression $\beta_\ell = \sum_{\ell'=1}^{\ell-1} \sum_{u=0}^{\ell'-1} \theta_u \theta_{u+(\ell-\ell')}$ is a double sum and ℓ is fixed. Let us consider the square matrix $B = (b_{u,\ell'})$ of size $\ell - 1$ indexed by $\ell' \in [\![1, \ell-1]\!]$ for the columns and by $u \in [\![0, \ell-2]\!]$ for the rows. We define $b_{u,\ell'}$ as follows: $b_{u,\ell'} = \theta_u \theta_{u+(\ell-\ell')}$ for $u \leq \ell'$, otherwise $b_{u,\ell'} = 0$ (B is upper triangular). Note that $\sum_{u=0}^{\ell'-1} \theta_u \theta_{u+(\ell-\ell')}$ is both the inner sum of the double sum β_ℓ and the sum of the entries of column ℓ'; thus the sum of all the entries of B is β_ℓ.

To obtain the right member of (31), we will sum the entries for each diagonal of B. As B is upper triangular, each of the sums of the diagonals below the main diagonal is zero; for the $\ell - 1$ upper diagonals, let a be in $[\![1, \ell-1]\!]$; the sum of the entries of the diagonal at distance $\ell - 1 - a$ from the main diagonal is $\theta_a \sum_{b=0}^{a-1} \theta_b$. For example, for the main diagonal ($a = \ell - 1$ and the distance is 0), the sum of the entries equals $\theta_{\ell-1}(\theta_0 + \theta_1 + \cdots + \theta_{\ell-2})$; for the diagonal just above the main diagonal ($a = \ell - 2$ and the distance is 1), the sum of entries is $\theta_{\ell-2}(\theta_0 + \theta_1 + \cdots + \theta_{\ell-3})$; the last diagonal is reduced to the only one element $\theta_1\theta_0$ ($a = 1$ and the distance is $\ell - 2$). Then (31) is proved.

From (30) and (31), we deduce Formula (28) of Lemma 1:

$$p_\ell = \alpha_\ell + \beta_\ell = \sum_{u=0}^{\ell-1} \theta_u \sum_{b=0}^{m} \theta_b = a_0(a_0 - a_\ell)$$

with $a_\ell = \sum_{b=\ell}^{m} \theta_b$ for $\ell \in [\![1, m]\!]$ and $a_\ell = 0$ for $\ell > m$. In particular, for $\ell \in [\![m+1, k-m]\!]$, the formula becomes $p_\ell = p_{m+1} = a_0^2 = (1 - \theta_1 - \cdots - \theta_m)^2$. Consequently, Lemma 1 is proved □

6.2 Proof of Proposition 3 on entries of the information matrix

As the design d is fixed in $\Omega_{v,b,k}$, it will be omitted in the indices. In Section 6.1, we have already established Identity (23) on c. We still have to establish Identities (21) and (22) about the entries $\sigma^2\mathbf{C}_{j,j}$ and $\sigma^2\mathbf{C}_{j,j'}$ ($j \neq j'$) of the matrix $\sigma^2\mathbf{C}_d$. The information matrix is given by Identity (15) rewritten below:

$$\sigma^2\mathbf{C}_d = \sum_{i=1}^{b} T_i' \,\mathbb{M}\, T_i - c^{-1}\sum_{i=1}^{b} T_i' \,\mathbb{M}\, \mathbf{1}_k \mathbf{1}_k' \,\mathbb{M}\, T_i = \mathcal{A} - c^{-1}\mathcal{B} \tag{32}$$

where $T_i = (\mathbf{t}_1(i), \ldots, \mathbf{t}_v(i))$, $\mathcal{A} = \sum_{i=1}^{b} T_i' \,\mathbb{M}\, T_i$ and $\mathcal{B} = \sum_{i=1}^{b} T_i' \,\mathbb{M}\, \mathbf{1}_k \mathbf{1}_k' \,\mathbb{M}\, T_i$. The entries $\gamma_{\ell,\ell'}$ of the matrix $\mathbb{M} = \sigma^2 V^{-1}$ are described in Proposition 1. We will find:

$$\mathbf{C}_{j,j} = \tau - \omega_{j,j} \quad \text{and} \quad \mathbf{C}_{j,j'} = \mu - \omega_{j,j'}$$

where τ and μ come from $\mathcal{A}$ and $\omega_{j,j}$ and $\omega_{j,j'}$ come from $c^{-1}\mathcal{B}$. In the following, we will look for formulas on τ, μ, $\omega_{j,j}$ and $\omega_{j,j'}$ by first considering the matrix $\mathcal{A}$ and then the matrix $c^{-1}\mathcal{B}$. Before that, we introduce some necessary tools.

Preliminary notations and remarks

For $r \in [\![1,k]\!]$, $\boldsymbol{e}_r = (\boldsymbol{e}_{r,s})_{1\le s\le k}$ denotes the r-th canonical vector of $\mathbb{R}^k$, i.e. $\boldsymbol{e}_{r,s} = \delta_{r,s}$ (where δ is the Kronecker symbol). Note that each entry of a $k\times k$-matrix A is expressed in the form $A_{r,s} = \boldsymbol{e}_r'\, A\, \boldsymbol{e}_s$.

For each treatment $j \in [\![1,v]\!]$, the jth column vector $\mathbf{t}_j(i)$ of the matrix T_i defined in (11) can be expressed as follows: for each $i \in [\![1,b]\!]$, we set

$$\mathbf{t}_j(i) = \begin{cases} \boldsymbol{e}_\ell & \text{if } j \text{ is applied to } i\text{-th patient at period } \ell \in [\![1,k]\!] \\ \mathbf{0}_k & \text{otherwise.} \end{cases} \tag{33}$$

Hence, following notations of Section 3.3, for each period $\ell \in [\![1,k-m]\!]$, we find

$$\phi_j^\ell = \begin{cases} \#\{i : \mathbf{t}_j(i) \in \{\boldsymbol{e}_\ell, \boldsymbol{e}_{k-\ell+1}\}\} & \text{if } \ell \in [\![1,m]\!] \\ \\ \#\{i : \mathbf{t}_j(i) = \boldsymbol{e}_\ell\} & \text{if } \ell \in [\![m+1,k-m]\!] \end{cases} \quad . \tag{34}$$

Remark 4 For each treatment j, exactly r vectors $\mathbf{t}_j(i)$ are non-zero because exactly r patients receive the treatment j.

Remark 5 As the designs we consider in this paper are binary, each patient i receives at most one time the same treatment j; consequently, for each $\ell \in [\![1,m]\!]$ and because $\ell \neq k-\ell+1$ since $k > 2m$, we have:

$$\{i : \mathbf{t}_j(i) = \boldsymbol{e}_\ell\} \cap \{i : \mathbf{t}_j(i) = \boldsymbol{e}_{k-\ell+1}\} = \emptyset \quad .$$

Now we fix two distinct treatments j, j' in $[\![1,v]\!]$. To establish Identities (21) and (22) about $\sigma^2\mathbf{C}_{j,j}$ and $\sigma^2\mathbf{C}_{j,j'}$ of the matrix $\sigma^2\mathbf{C}_d$, we will examine separately the contributions of each of the two sums of the right member of (32), namely $\mathcal{A}$ (for τ and μ) then $\mathcal{B}$ (for $\omega_{j,j}$ and $\omega_{j,j'}$). Then we will achieve the proof.

Matrix $\mathcal{A} = \sum_{i=1}^{b} T_i' \, \mathbb{M} \, T_i$ of Identity (32):

Diagonal entry $\sigma^2 \mathbf{C}_{j,j}$: determination of τ

The contribution of $\mathcal{A}$ to the diagonal entry $\sigma^2 \mathbf{C}_{j,j}$ is the value $\tau = \sum_{i=1}^{b} \tau_i$ where $\tau_i = \mathbf{t}_j'(i) \, \mathbb{M} \, \mathbf{t}_j(i)$. From Definition (33) of vectors $\mathbf{t}_j(i)$, we have for each patient i:

$$\tau_i = \sum_{\ell=1}^{k} \sum_{\{i \,:\, \mathbf{t}_j(i) = \boldsymbol{e}_\ell\}} \boldsymbol{e}_\ell' \, \mathbb{M} \, \boldsymbol{e}_\ell = \sum_{\ell=1}^{m} \phi_j^\ell \, \boldsymbol{e}_\ell' \, \mathbb{M} \, \boldsymbol{e}_\ell + \sum_{\ell=m+1}^{k-m} \phi_j^\ell \, \boldsymbol{e}_\ell' \, \mathbb{M} \, \boldsymbol{e}_\ell \quad . \tag{35}$$

Combining the above identity (35) and Lemma 1 applied to the diagonal entries $\gamma_{\ell,\ell} = \boldsymbol{e}_\ell' \, \mathbb{M} \, \boldsymbol{e}_\ell$ of matrix $\mathbb{M}$, we obtain (recall that $\theta_0 = -1$):

$$\begin{aligned}
\tau &= \sum_{\ell=1}^{m} \phi_j^\ell \, (\theta_0^2 + \theta_1^2 \cdots + \theta_{\ell-1}^2) + \sum_{\ell=m+1}^{k-m} \phi_j^\ell \, (\theta_0^2 + \theta_1^2 \cdots + \theta_m^2) \\
&= \phi_j^1 \, \theta_0^2 + \phi_j^2 \, (\theta_0^2 + \theta_1^2) + \cdots + \phi_j^m \, (\theta_0^2 + \theta_1^2 + \cdots + \theta_{m-1}^2) \\
&\qquad + \sum_{\ell=m+1}^{k-m} \phi_j^\ell (\theta_0^2 + \theta_1^2 + \cdots + \theta_m^2) \\
&= \theta_0^2 \sum_{\ell=1}^{k-m} \phi_j^\ell + \theta_1^2 \sum_{\ell=2}^{k-m} \phi_j^\ell + \theta_2^2 \sum_{\ell=3}^{k-m} \phi_j^\ell + \cdots + \theta_m^2 \sum_{\ell=m+1}^{k-m} \phi_j^\ell \quad .
\end{aligned} \tag{36}$$

As $\sum_{\ell=1}^{k-m} \phi_j^\ell = r$ (see Identity (17)), we get:

$$\begin{aligned}
\tau &= \theta_0^2 r + \theta_1^2 (r - \phi_j^1) + \theta_2^2 (r - (\phi_j^1 + \phi_j^2)) + \cdots + \theta_m^2 (r - (\phi_j^1 + \cdots + \phi_j^m)) \\
&= r \sum_{u=0}^{m} \theta_u^2 - \phi_j^1 \sum_{u=1}^{m} \theta_u^2 - \phi_j^2 \sum_{u=2}^{m} \theta_u^2 - \cdots - \phi_j^\ell \sum_{u=\ell}^{m} \theta_u^2 - \cdots - \phi_j^m \theta_m^2 \quad .
\end{aligned}$$

Finally, the contribution τ of the term $\mathcal{A}$ to the diagonal entry $\sigma^2 \mathbf{C}_{j,j}$ is:

$$\tau = r b_0 - \phi_j^1 b_1 - \phi_j^2 b_2 - \cdots - \phi_j^m b_m \tag{37}$$

with $b_\ell = \sum_{u=\ell}^{m} \theta_u^2$ for $\ell \in [\![1, m]\!]$, as defined in Proposition 3.

Extra-diagonal entry $\sigma^2 \mathbf{C}_{j,j'}$: determination of μ

Similarly, let us now focus on the contribution μ of the sum $\mathcal{A} = \sum_{i=1}^{b} T_i' \, \mathbb{M} \, T_i$ to the extra-diagonal entry $\sigma^2 \mathbf{C}_{j,j'}$, where $\mu = \sum_{i=1}^{b} \mu_i$ with $\mu_i = \mathbf{t}_j'(i) \mathbb{M} \mathbf{t}_{j'}(i)$. For this purpose, we need to introduce the following notation: for $\ell, \ell' \in [\![1, k]\!]$, we denote by $\phi_{j,j'}^{\ell,\ell'}$ the number of patients who receive the distinct treatments j and j' at periods ℓ, ℓ':

$$\phi_{j,j'}^{\ell,\ell'} = \#\{ i \in [\![1, b]\!] \ : \ \mathbf{t}_j(i) + \mathbf{t}_{j'}(i) = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'} \} \quad . \tag{38}$$

Note that if $\ell' = \ell$ then $\mathbf{t}_j(i)+\mathbf{t}_{j'}(i) \neq \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ for each patient i because the distinct treatments j and j' cannot be applied simultaneously to the same patient i at the same period ℓ. Hence, for any $s \in [\![1, k-1]\!]$, we can write:

$$N^s_{j,j'} = \sum \phi^{\ell,\ell'}_{j,j'} \tag{39}$$

where the sum involves all the distinct periods ℓ, ℓ' in $[\![1, k]\!]$ and $s = |\ell - \ell'| \neq 0$.

From Definition of vectors $\mathbf{t}_j(i)$, as $j \neq j'$, the only non-zero $\mu_i = \mathbf{t}'_j(i)\mathbb{M}\mathbf{t}_{j'}(i)$ are such that $\mathbf{t}_j(i)+\mathbf{t}_{j'}(i) = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ for some periods ℓ and ℓ' which are necessarily distinct. Moreover, as the matrix $\mathbb{M}$ is symmetric, when the identity $\mathbf{t}_j(i) + \mathbf{t}_{j'}(i) = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ holds, we can suppose that $\mathbf{t}_j(i) = \boldsymbol{e}_\ell$ and $\mathbf{t}_{j'}(i) = \boldsymbol{e}_{\ell'}$ with $\ell < \ell'$.

Hence, by putting $u_{i,j} = \mathbf{t}_j(i) + \mathbf{t}_{j'}(i)$, $v_{\ell,\ell'} = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ and considering the element $\gamma_{\ell,\ell'} = \boldsymbol{e}'_\ell \, \mathbb{M} \, \boldsymbol{e}_{\ell'}$ of the matrix $\mathbb{M}$, we obtain:

$$\mu = \sum_{1 \leq \ell < \ell' \leq k} \; \sum_{\{i \,:\, u_{i,j} = v_{\ell,\ell'}\}} \boldsymbol{e}'_\ell \, \mathbb{M} \, \boldsymbol{e}_{\ell'} = \sum_{1 \leq \ell < \ell' \leq k} \gamma_{\ell,\ell'} \phi^{\ell,\ell'}_{j,j'} = \sum_{\ell'=2}^{k} \sum_{\ell=1}^{\ell'-1} \gamma_{\ell,\ell'} \phi^{\ell,\ell'}_{j,j'} \quad .$$

For sake of clarity we let $\phi^{\ell,\ell'} = \phi^{\ell,\ell'}_{j,j'}$ for the rest of this proof. We introduce in the expression of μ the values of the entries $\gamma_{\ell,\ell'}$ of the matrix $\mathbb{M}$ given in Proposition 1. Collecting the factors of each θ_ℓ and $\theta_\ell \theta_{\ell'}$, we obtain:

$$\begin{aligned}
\mu = -\; & \theta_1 \Big(\phi^{1,2} + \cdots + \phi^{k-1,k} \Big) - \cdots - \theta_s \Big(\phi^{\ell,\ell+s} + \phi^{\ell+1,\ell+s+1} + \cdots + \phi^{k-s,k} \Big) \\
& - \cdots - \theta_m \Big(\phi^{1,m+1} + \cdots + \phi^{k-m,k} \Big) \\
& + \sum_{s=1}^{m-1} \theta_1 \theta_{1+s} \Big(\phi^{2,2+s} + \cdots + \phi^{k-s-1,k-1} \Big) \\
& + \sum_{s=1}^{m-2} \theta_2 \theta_{2+s} \Big(\phi^{3,3+s} + \cdots + \phi^{k-s-2,k-2} \Big) + \cdots \\
& + \sum_{s=1}^{m-u} \theta_u \theta_{u+s} \Big(\phi^{u+1,u+1+s} + \phi^{u+2,u+2+s} + \cdots + \phi^{k-s-u,k-u} \Big) \\
& + \cdots + \sum_{s=1}^{2} \theta_{m-2} \theta_{m-2+s} \Big(\phi^{m-1,m-1+s} + \cdots + \phi^{k-s-(m-2),k-(m-2)} \Big) \\
& + \theta_{m-1} \theta_m \Big(\phi^{m,m+1} + \cdots + \phi^{k-m,k-m+1} \Big) \quad .
\end{aligned} \tag{40}$$

Recall that Identity (39) says that $N^s_{j,j'} = \phi^{1,1+s} + \phi^{2,2+s} + \cdots + \phi^{k-s-1,k-1} + \phi^{k-s,k}$. Putting

$$U_{t,s} = \phi^{t,t+s} + \phi^{k-t-s+1,k-t+1} \; ,$$

for $s \in [\![1, m-1]\!]$ and $t \in [\![1, m-s]\!]$, the expression (40) of μ becomes:

$$\begin{aligned}\mu = \sum_{s=1}^{m} \theta_0\theta_s N^s_{j,j'} &+ \sum_{s=1}^{m-1} \theta_1\theta_{1+s}(N^s_{j,j'} - U_{1,s})\\ &+ \sum_{s=1}^{m-2} \theta_2\theta_{2+s}(N^s_{j,j'} - (U_{1,s} + U_{2,s})) + \cdots\\ &+ \sum_{s=1}^{m-u} \theta_u\theta_{u+s}(N^s_{j,j'} - (U_{1,s} + U_{2,s} + \cdots + U_{u,s})) + \ldots \quad (41)\\ &+ \sum_{s=1}^{2} \theta_{m-2}\theta_{m-2+s}(N^s_{j,j'} - (U_{1,s} + U_{2,s} + \cdots + U_{m-2,s}))\\ &+ \ \theta_{m-1}\theta_m(N^1_{j,j'} - (U_{1,1} + U_{2,1} + \cdots + U_{m-1,1})) \quad .\end{aligned}$$

Collecting the factors of each $N^s_{j,j'}$ and each $U_{t,s}$, we obtain:

$$\mu = \sum_{s=1}^{m} N^s_{j,j'} \sum_{u=0}^{m-s} \theta_u\theta_{u+s} - \sum_{s=1}^{m-1}\sum_{t=1}^{m-s} U_{t,s} \sum_{u=t}^{m-s} \theta_u\theta_{u+s} \quad .$$

Indeed, for each $s \in [\![1, m-1]\!]$ and $t \in [\![1, m-s]\!]$, the component $\beta_{t,s}$ of μ which collects the terms $U_{t,s}\theta_{a,b}$ is the following:

$$\beta_{t,s} = -U_{t,s}(\theta_t\theta_{t+s} + \theta_{t+1}\theta_{t+1+s} + \cdots + \theta_{m-s}\theta_m) \; .$$

In addition, the double sum $\displaystyle\sum_{s=1}^{m-1}\sum_{t=1}^{m-s} \beta_{t,s}$ collects all the terms of the form $U_{t,s}\theta_{a,b}$ of the right-hand side of Identity (41). In order to complete the determination of μ, note that:

Remark 6 We have $\phi^\ell_{j,i} = \delta_{j,d(i,\ell)} + \delta_{j,d(i,k-\ell+1)}$ and $N^s_{j,j',i} \in \{0,1\}$ because d is binary (see Section 3.3); then, from Identity (38) about $\phi^{\ell,\ell'}_{j,j'}$, we find:

$$\begin{aligned}U_{t,s} &= \phi^{t,t+s}_{j,j'} + \phi^{k-t-s+1,k-t+1}_{j,j'}\\ &= \#\Big\{ i : \mathbf{t}_j(i) + \mathbf{t}_{j'}(i) \in \{\boldsymbol{e}_t + \boldsymbol{e}_{t+s}, \boldsymbol{e}_{k-t+1} + \boldsymbol{e}_{k-(t+s)+1}\}\Big\}\\ &= \sum_{i=1}^{b} N^s_{j,j',i}(\phi^t_{j,i}\phi^{t+s}_{j',i} + \phi^t_{j',i}\phi^{t+s}_{j,i}) \quad .\end{aligned}$$

Finally, the contribution μ of the term $\mathcal{A} = \sum_{i=1}^{b} T_i' \,\mathbb{M}\, T_i$ to the entry $\sigma^2\mathbf{C}_{j,j'}$ is:

$$\mu = \sum_{s=1}^{m} N^s_{j,j'}\Theta_{0,s} - \sum_{s=1}^{m-1}\sum_{t=1}^{m-s} \Theta_{t,s} \sum_{i=1}^{b} N^s_{j,j',i}(\phi^t_{j,i}\phi^{t+s}_{j',i} + \phi^t_{j',i}\phi^{t+s}_{j,i}) \qquad (42)$$

where $\Theta_{t,s} = \theta_t\theta_{t+s} + \theta_{t+1}\theta_{t+1+s} + \cdots + \theta_{m-s}\theta_m$.

Matrix $c^{-1}\mathcal{B} = c^{-1}\sum_{i=1}^{b} T_i'\,\mathbb{M}\,\mathbf{1}_k\mathbf{1}_k'\,\mathbb{M}\,T_i$ of Identity (32):

Introduce the following notation $\kappa_{j_1,i}$ for some treatment j_1 and some patient i:

$$\kappa_{j_1,i} = \mathbf{t}_{j_1}'(i)\,\mathbb{M}\,\mathbf{1}_k \quad .$$

As $\kappa_{j_1,i}$ is a scalar and $\mathbb{M} = \mathbb{M}'$ (i.e. $\mathbb{M}$ is symmetric), we also have:

$$\kappa_{j_1,i} = \mathbf{1}_k'\,\mathbb{M}\,\mathbf{t}_{j_1}'(i) \quad .$$

Then the contribution of $c^{-1}\mathcal{B}$ to the entry $\sigma^2\mathbf{C}_{j_1,j_2}$ for two treatments j_1, j_2, not necessarily distinct, is

$$\omega_{j_1,j_2} = c^{-1}\sum_{i=1}^{b}\kappa_{j_1,i}\kappa_{j_2,i} \quad . \tag{43}$$

In the following, we determine the quantities $\kappa_{j,i} = \mathbf{t}_j'(i)\,\mathbb{M}\,\mathbf{1}_k$ to find ω_{j_1,j_2}.

When the treatment j is not applied to the ith patient, $\kappa_{j,i} = 0$ because $\mathbf{t}_j(i) = \mathbf{0}_k$. Otherwise, it is applied only once, at some period ℓ and we have

$$\kappa_{j,i} = \mathbf{t}_j'(i)\mathbb{M}\mathbf{1}_k = \sum_{\ell'=1}^{k}\gamma_{\ell,\ell'} \quad .$$

Recall that the sum of the entries of row ℓ in matrix $\mathbb{M}$ is given in Lemma 1: for each $\ell \in [\![1, k-m]\!]$, the value $p_\ell = \sum_{\ell'=1}^{k}\gamma_{\ell,\ell'} = a_0(a_0 - a_\ell)$ (with $a_\ell = \sum_{u=\ell}^{m}\theta_u$ for $\ell \in [\![1, m]\!]$ and $a_\ell = 0$ for $\ell > m$) and $p_\ell = p_{k-\ell+1}$ for $\ell \in [\![k-m, k]\!]$. Remark that $p_\ell = p_{m+1} = a_0^2$ for all $\ell > m$. Thus $\forall\, \ell \in [\![1, m]\!] \cup [\![k-m+1, k]\!]$:

$$p_\ell - p_{m+1} = -a_0 a_\ell \quad . \tag{44}$$

Now, let's determine the values of $n_{j,i}$, defined in Section 2.1, and $\phi_{j,i}^{\ell}$ for all $\ell \in [\![1, m]\!]$. Recall that $\mathbf{t}_j(i) = \boldsymbol{e}_\ell$ if the treatment j is applied to the ith patient at period ℓ and $\mathbf{t}_j(i) = \mathbf{0}_k$ otherwise.

Case $\mathbf{t}_j(i) = \mathbf{0}_k$: $n_{j,i} = \phi_{j,i}^1 = \cdots = \phi_{j,i}^m = 0$ because the ith patient does not receive the treatment j.

Case $\mathbf{t}_j(i) = \boldsymbol{e}_\ell$ where $\ell \in [\![1, m]\!] \cup [\![k-m+1, k]\!]$: $n_{j,i} = \phi_{j,i}^{\ell} = 1$ and $\phi_{j,i}^1 = \cdots = \phi_{j,i}^{\ell-1} = \phi_{j,i}^{\ell+1} = \cdots = \phi_{j,i}^m = 0$.

Case $\mathbf{t}_j(i) = \boldsymbol{e}_\ell$ where $\ell \in [\![m+1, k-m]\!]$: $n_{j,i} = 1$ and $\phi_{j,i}^1 = \cdots = \phi_{j,i}^m = 0$.

If the treatment j is applied to the ith patient at some period ℓ for $\ell \in [\![1, k]\!]$ then $\kappa_{j,i} = p_\ell$. Otherwise, if the treatment j is not applied to the ith patient then $\kappa_{j,i} = 0$. Consequently, we can express the quantity $\kappa_{j,i}$ in the following form

$$\begin{aligned}\kappa_{j,i} = p_{m+1}n_{j,i} + \phi_{j,i}^1(p_1 - p_{m+1}) + \phi_{j,i}^2(p_2 - p_{m+1}) + \cdots \\ \cdots + \phi_{j,i}^m(p_m - p_{m+1}) \quad .\end{aligned} \tag{45}$$

From Formulas (28) and (44), we deduce that:

$$\begin{aligned}\kappa_{j,i} &= a_0(a_0 n_{j,i} - a_1\phi^1_{j,i} - a_2\phi^2_{j,i} - \cdots - a_m\phi^m_{j,i}) \\ &= a_0\left(a_0 n_{j,i} - \sum_{\ell=1}^{m} a_\ell \phi^\ell_{j,i}\right) \quad . \end{aligned} \tag{46}$$

Diagonal entry $\sigma^2\mathbf{C}_{j,j}$: determination of $\omega_{j,j}$

Recall that the contribution $c^{-1}\mathcal{B}$ to the entry $\sigma^2\mathbf{C}_{j,j}$ is the quantity $\omega_{j,j} = c^{-1}\sum_i \kappa^2_{j,i}$ (see Identity (43)). From Identity (46), we have:

$$\kappa^2_{j,i} = a_0^2\left\{a_0^2 n^2_{j,i} + \sum_{\ell=1}^{m} a_\ell^2\phi^\ell_{j,i} - 2a_0\sum_{\ell=1}^{m} a_\ell n_{j,i}\phi^\ell_{j,i}\right\}$$

because $\left(\phi^\ell_{j,i}\right)^2 = \phi^\ell_{j,i}\ \forall\, \ell \in [\![1,m]\!]$, and when $\ell \neq \ell'$, $\phi^\ell_{j,i}\phi^{\ell'}_{j,i} = 0$. From

$$\phi^\ell_j = \sum_{i=1}^{b}\phi^\ell_{j,i} = \sum_{i=1}^{b} n_{j,i}\phi^\ell_{j,i} \quad \text{and} \quad r = \sum_{i=1}^{b} n^2_{j,i},$$

we finally obtain:

$$\begin{aligned} c\,w_{j,j} = \sum_{i=1}^{b}\kappa^2_{j,i} &= a_0^2\left\{a_0^2 r + \sum_{\ell=1}^{m} a_\ell^2\phi^\ell_j - 2a_0\sum_{\ell=1}^{m} a_\ell\phi^\ell_j\right\} \\ &= -a_0^2\left\{a_0(a_0 - 2a_0)r - \sum_{\ell=1}^{m}\phi^\ell_j a_\ell(a_\ell - 2a_0)\right\} \quad . \end{aligned} \tag{47}$$

Extra-diagonal entry $\sigma^2\mathbf{C}_{j,j'}$: determination of $\omega_{j,j'}$

Let us determine the contribution $\omega_{j,j'} = c^{-1}\sum_{i=1}^{b}\kappa_{j,i}\kappa_{j',i}$, $j \neq j'$, to the entry $\sigma^2\mathbf{C}_{j,j'}$. From Identity (45), we have:

$$\begin{aligned}\kappa_{j,i}\kappa_{j',i} &= a_0^2\left(a_0 n_{j,i} - \sum_{\ell=1}^{m} a_\ell\phi^\ell_{j,i}\right)\left(a_0 n_{j',i} - \sum_{\ell'=1}^{m} a_{\ell'}\phi^{\ell'}_{j',i}\right) \\ &= a_0^2\left\{a_0^2 n_{j,i}n_{j',i} - a_0\left(\sum_{\ell=1}^{m} a_\ell n_{j,i}\phi^\ell_{j',i} + \sum_{\ell=1}^{m} a_\ell n_{j',i}\phi^\ell_{j,i}\right)\right. \\ &\quad \left. + \sum_{\ell=1}^{m}\sum_{\ell'=1}^{m} a_\ell a_{\ell'}\phi^\ell_{j,i}\phi^{\ell'}_{j',i}\right\} \quad . \end{aligned}$$

From $\lambda_{j,j'} = \sum_{i=1}^{b} n_{j,i}n_{j',i}$ (see Identity (2)) and

$$\phi^{\ell *}_{j,j'} = \sum_{i=1}^{b}(n_{j',i}\phi^\ell_{j,i} + n_{j,i}\phi^\ell_{j',i}) \quad \text{, for all } \ell \in [\![1,m]\!] \quad , \tag{48}$$

we finally obtain for $c\,\omega_{j,j'} = \sum_{i=1}^{b} \kappa_{j,i}\kappa_{j',i}$

$$c\,\omega_{j,j'} = a_0^4\lambda_{j,j'} - a_0^3 \sum_{\ell=1}^{m} a_\ell \phi_{j,j'}^{\ell *} + a_0^2 \sum_{\ell=1}^{m}\sum_{\ell'=1}^{m} \left(a_\ell a_{\ell'} \sum_{i=1}^{b} \phi_{j,i}^{\ell}\phi_{j',i}^{\ell'} \right) . \tag{49}$$

End of the proof of Proposition 3. From $\mathbf{C} = \mathcal{A} - c^{-1}\mathcal{B}$ (see Identity (32)), we find:

$$\mathbf{C}_{j,j} = \tau - \omega_{j,j} \quad \text{and} \quad \mathbf{C}_{j,j'} = \mu - \omega_{j,j'}$$

where τ and μ come from the matrix $\mathcal{A}$ and $\omega_{j,j}$ and $\omega_{j,j'}$ come from the matrix $c^{-1}\mathcal{B}$. Using the formulas on τ, μ, $\omega_{j,i}$ and $\omega_{j,j'}$ respectively establish in Identities (37), (42), (47) and (49), we complete the proof of Proposition 3.

6.3 **Proof of Theorem 1**

Consider $d \in \Omega_{v,b,k}$ a NNm-balanced BIBD(v,b,r,k,λ) for the AR(m) model with $k \geq 3$, $m \geq 1$ and $2m < k < v$ (this proof also holds for CBD when $k = v$).

In Remark 1, we have deduced from Proposition 3 that all the competitor designs have the same trace. Hence, from Proposition 4, the *universal optimality* of the design d is satisfied when the information matrix $\mathbf{C}_d$ of $\widehat{\gamma}$ is completely symmetric; which means that its extra-diagonal entries $\mathbf{C}_{d,j,j'}$ are all independent from j, j' $(j \neq j')$ because the sum by row (and by column) of $\mathbf{C}_d$ is null (see Identities (25)). According to the hypothesis of Theorem 1, we will prove that none of the five summation blocks of $\mathbf{C}_{d,j,j'}$ appearing in Identity (22) of Proposition 3 depends on j, j'.

As the design d is a NNm-balanced BIBD(v,b,r,k,λ), Identities (3) and (4) imply that two of the summation blocks of $\mathbf{C}_{d,j,j'}$ are independent from j, j': those depending on $\lambda = \lambda_{j,j'}$ and $N^s = N^s_{j,j'}$. Therefore, if Identities $(i), (ii)$ and (iii) of Theorem 1 hold then the three others summation blocks of $\mathbf{C}_{d,j,j'}$ are independent from j, j' (see Remark 7 for the case of (iii)).

Remark 7 On the right side of Identity (22), let's consider the summation block $\sum_{s=1}^{m-1}\sum_{t=1}^{m-s} \Theta_{t,s}\overline{\alpha}_{s,t}$ of $\mathbf{C}_{d,j,j'}$ where $\overline{\alpha}_{s,t} = N^s_{j,j',i}(\phi^t_{j,i}\phi^{t+s}_{j',i} + \phi^t_{j',i}\phi^{t+s}_{j,i})$. Let $\ell \neq \ell'$ in $[\![1,m]\!]$ and $\alpha_{\ell,\ell'} = N^{|\ell-\ell'|}_{j,j',i}(\phi^{\ell}_{j,i}\phi^{\ell'}_{j',i} + \phi^{\ell}_{j',i}\phi^{\ell'}_{j,i})$ be the left-hand side of Identity (iii) in Theorem 1. We claim that:

$$\{\alpha_{\ell,\ell'} \mid \ell \neq \ell' \text{ in } [\![1,m]\!]\} = \{\overline{\alpha}_{s,t} \mid s \in [\![1,m-1]\!] \text{ and } t \in [\![1,m-s]\!]\} \quad . \tag{50}$$

For " $\subset$ ", by symmetry between ℓ, ℓ' in $\alpha_{\ell,\ell'}$, we can suppose that $\ell < \ell'$ and express $\alpha_{\ell,\ell'}$ as follows: $\alpha_{\ell,\ell'} = N^{|\ell-\ell'|}_{j,j',i}(\phi^{\ell}_{j,i}\phi^{\ell+|\ell-\ell'|}_{j',i} + \phi^{\ell}_{j',i}\phi^{\ell+|\ell-\ell'|}_{j,i})$. Then $\alpha_{\ell,\ell'} = \overline{\alpha}_{s,t}$ with $s = |\ell-\ell'| \in [\![1,m-1]\!]$ and $\ell = t \in [\![1,m-s]\!]$ (as expected in the summation in the expression of $\mathbf{C}_{d,j,j'}$). Conversely, let $s \in [\![1,m-1]\!]$ and $t \in [\![1,m-s]\!]$. Then we have $\overline{\alpha}_{s,t} = \alpha_{\ell,\ell'}$ for the two distinct periods $\ell = t$ and $\ell' = t+s$ in $[\![1,m]\!]$.

In the following, we will prove Identities $(i), (ii)$ and (iii) of Theorem 1. More precisely, for each identity, we will suppose that the term in the left-hand side is a constant and we prove that it equals to the right-hand side. Recall that $\omega = \frac{2b}{v(v-1)}$.

Proof of Identity (i). For each treatment j, we first need to establish the following identity:

$$\sum_{j'\neq j} \phi^{\ell *}_{j,j'} = (k-2)\phi^{\ell}_{j} + 2r \quad . \tag{51}$$

Proof Develop $\sum_{j'\neq j} \phi^{\ell *}_{j,j'}$:

$$\sum_{j'\neq j} \phi^{\ell *}_{j,j'} = \sum_{j'\neq j}\sum_{i=1}^{b}(n_{j',i}\phi^{\ell}_{j,i} + n_{j,i}\phi^{\ell}_{j',i}) = \sum_{i=1}^{b}\phi^{\ell}_{j,i}\sum_{j'\neq j} n_{j',i} + \sum_{i=1}^{b} n_{j,i}\sum_{j'\neq j}\phi^{\ell}_{j',i} \; .$$

The first term of the right-hand side of the previous identity is

$$\alpha = \sum_{i=1}^{b}\phi^{\ell}_{j,i}\sum_{j'\neq j} n_{j',i} = \sum_{i=1}^{b}\phi^{\ell}_{j,i}\sum_{j'=1}^{v} n_{j',i} - \sum_{i=1}^{b}\phi^{\ell}_{j,i}n_{j,i} = k\,\phi^{\ell}_{j} - \phi^{\ell}_{j}$$

by definition of ϕ^{ℓ}_{j} and since each patient i receives k treatments. The second term is

$$\beta = \sum_{i=1}^{b} n_{j,i}\sum_{j'\neq j}\phi^{\ell}_{j',i} = \sum_{i=1}^{b} n_{j,i}\sum_{j'=1}^{v}\phi^{\ell}_{j',i} - \sum_{i=1}^{b} n_{j,i}\phi^{\ell}_{j,i} = 2\,r - \phi^{\ell}_{j}$$

because d is equireplicated (i.e. j appears r times in d) and only 2 treatments j' can be applied to a same patient i at periods ℓ and $(k-\ell+1)$ (i.e. $\phi^{\ell}_{j',i} = 1$ for these two treatments and 0 for the others). Summing α and β, we obtain Identity (51) □

From Formulas (51) and (16), we obtain finally:

$$\sum_{j=1}^{v}\sum_{j'\neq j}\phi^{\ell *}_{j,j'} = 2b(k-2) + 2rv = 2b(k-2) + 2bk = 4b(k-1) \tag{52}$$

because $rv = bk$. Suppose that each $\phi^{\ell *}_{j,j'}$ does not depend on j, j'. Then we have the equality $\sum_{j=1}^{v}\sum_{j'\neq j}\phi^{\ell *}_{j,j'} = v(v-1)\phi^{\ell *}_{j,j'}$. Thus from (52), we obtain Identity

$$(i)\ \phi^{\ell *}_{j,j'} = \tfrac{4b(k-1)}{v(v-1)} = 2\omega(k-1) \quad .$$

Proof of Identity (ii). Consider two distinct periods ℓ and ℓ' and fix a patient i. Four distinct treatments $j_1, \ldots, j_4$ are applied to this patient at the respective periods $\ell, k-\ell+1, \ell', k-\ell'+1$. Then $\phi^{\ell}_{j_1,i} = \phi^{\ell}_{j_2,i} = \phi^{\ell'}_{j_3,i} = \phi^{\ell'}_{j_4,i} = 1$ and the other values $\phi^{\ell}_{j,i}$ and $\phi^{\ell'}_{j',i}$ are zero; consequently:

$$\sum_{j=1}^{v}\sum_{j'\neq j}\phi^{\ell}_{j,i}\phi^{\ell'}_{j',i} = \phi^{\ell}_{j_1,i}(\phi^{\ell'}_{j_3,i} + \phi^{\ell'}_{j_4,i}) + \phi^{\ell}_{j_2,i}(\phi^{\ell'}_{j_3,i} + \phi^{\ell'}_{j_4,i}) = 4$$

and
$$\sum_{j=1}^{v}\sum_{j'\neq j}\phi^{\ell}_{j,i}\phi^{\ell}_{j',i}=\phi^{\ell}_{j_1,i}\phi^{\ell}_{j_2,i}+\phi^{\ell}_{j_2,i}\phi^{\ell}_{j_1,i}=2 \quad .$$

If the quantity $\sum_{i=1}^{b}\phi^{\ell}_{j,i}\phi^{\ell'}_{j',i}$ does not depend on j,j' then, by the same reasoning as for (i), we find ($\delta_{\ell,\ell'}$ is the Kronecker symbol):

$$(ii)\ \sum_{i=1}^{b}\phi^{\ell}_{j,i}\phi^{\ell'}_{j',i}=\frac{b(2+2(1-\delta_{\ell,\ell'}))}{v(v-1)}=\omega(2-\delta_{\ell,\ell'})\quad\text{for all }\ \ell,\ell'\in [\![1,m]\!] \quad .$$

Proof of Identity (iii). With reference to Remark 7, prove Identity (iii): $\alpha_{\ell,\ell'}=2\,\omega$ for $\ell\neq\ell'$ in $[\![1,m]\!]$ is equivalent to prove $\overline{\alpha}_{s,t}=2\,\omega$ for $s\in[\![1,m-1]\!]$ and $t\in[\![1,m-s]\!]$. Let's fix $s\in[\![1,m-1]\!]$ and $t\in[\![1,m-s]\!]$ and prove that $\overline{\alpha}_{s,t}=2\,\omega$. By the same reasoning as above, for a patient i, four distinct treatments $j_1,\dots,j_4$ are applied at the respective distinct periods $t, k-t+1, t+s, k-(t+s)+1$. Then

$$\begin{aligned}\beta_{t,s}&=\sum_{j=1}^{v}\sum_{j'\neq j}(\phi^{t}_{j,i}\phi^{t+s}_{j',i}+\phi^{t}_{j',i}\phi^{t+s}_{j,i})\\&=\sum_{j=1}^{v}\phi^{t}_{j,i}\sum_{j'\neq j}\phi^{t+s}_{j',i}+\sum_{j=1}^{v}\phi^{t+s}_{j,i}\sum_{j'\neq j}\phi^{t}_{j',i}\\&=2(\phi^{t}_{j_1,i}+\phi^{t}_{j_2,i})(\phi^{t+s}_{j_3,i}+\phi^{t+s}_{j_4,i})=8 \quad .\end{aligned}$$

But, in this sum, there are 4 cases in which two treatments among $j_1,\dots,j_4$ are applied at distance s and there are 4 cases in which two treatments among $j_1,\dots,j_4$ are applied at distance δ where $\delta\geq m>s$ because $k>2m$. For the firsts 4 cases, we have $N^{s}_{j,j',i}=1$ and for the 4 others cases we have $N^{s}_{j,j',i}=0$. Then

$$\sum_{j=1}^{v}\sum_{j'\neq j}N^{s}_{j,j',i}(\phi^{t}_{j,i}\phi^{t+s}_{j',i}+\phi^{t}_{j',i}\phi^{t+s}_{j,i})=\quad\frac{1}{2}\beta_{t,s}=4 \quad .$$

Hence, if each quantity $\overline{\alpha}_{s,t}=\sum_{i=1}^{b}N^{s}_{j,j',i}(\phi^{t}_{j,i}\phi^{t+s}_{j',i}+\phi^{t}_{j',i}\phi^{t+s}_{j,i})$ does not depend on j,j' ($j\neq j'$), the following identity holds for $\ell\neq\ell'$ in $[\![1,m]\!]$:

$$(iii)\ \alpha_{\ell,\ell'}=\overline{\alpha}_{s,t}=\tfrac{4b}{v(v-1)}=2\,\omega \quad .$$

Then Theorem 1 is proved.

6.4 **Proof of Theorem 2**

Theorem 2 is a straightforward consequence of the proof of Theorem 1 which also holds for $k=v$ and of Identities (19) and (20) for the NNm-balanced square designs.

6.5 **Proof of Proposition 5**

Recall that in case of the strength is $t = 2$, the index ω_2 is $\omega = \frac{2b}{v(v-1)}$ (see Remark 3). Since an SB$(b, k, v, 2)$ can be interpreted as a BIBD(v, b, r, k, λ), Identity (27) comes from the identities $v(v-1)\,\omega = 2b$ and $rv = bk$ (see Identity (1)).

Now consider an unordered pair (j, j') of two distinct treatments. For all $m \in [\![1, k-1]\!]$, the design d is NNm-balanced because $N^s_{d,j,j'}$, the number of times that (j, j') are applied to a same patient at distance $s \in [\![1, m]\!]$, is a constant N^s_d. More precisely, consider the $k - s$ possible pairs of periods ℓ and $\ell + s$ where ℓ runs in $[\![1, k-s]\!]$. Since the strength of d is two, we obtain Identity (4): $N^s_d = N^s_{d,j,j'} = \omega(k-s)$. To prove the rest of Proposition 5, we use item (a) of Theorem 2 in Martin and Eccleston (1991) which implies that d is universally optimal.

6.6 **Proofs of Identities** (3)**,** (4)**,** (19) **and** (20)

Proof of Identity (3)

Let $\beta = \sum_{j=1}^{v} \sum_{j' \neq j} \lambda_{d,j,j'}$. As d is a BIBD, we have $\beta = \sum_{j=1}^{v} \sum_{j' \neq j} \lambda = v(v-1)\lambda$. But we can express β differently: $\beta = bk(k-1)$ because there are b patients and exactly $k(k-1)$ distinct pairs of treatments for each of them (recall that $k \leq v$). The identification of the two expressions of β prove the wanted identity satisfied by λ:

$$\lambda = \lambda_{d,j,j'} = \frac{bk(k-1)}{v(v-1)} = \omega\,\frac{k(k-1)}{2} \qquad \forall j, j' \in [\![1, v]\!], j \neq j' \quad .$$

Proof of Identity (4)

Assume that design d is NNm-balanced. Let us fix $s \in [\![1, m]\!]$ and compute by two ways the sum

$$\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N^s_{d,j,j'} \quad .$$

Firstly, as the design is NNm-balanced, each $N^s_{d,j,j'}$ equals a constant N^s_d which does not depend on the choice j, j'. So we have:

$$\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N^s_d = v(v-1)\,N^s_d \quad .$$

Secondly, suppose that some patient i receives a given treatment j. Recall that j is administered at most once to a same patient. For the ith patient, if j is not applied in the first s or in the last s periods (i.e.when $\sum_{\ell=1}^{s} \phi^{\ell}_{d,j,i} = 0$) then there exist $2 = \sum_{j' \neq j} N^s_{d,j,j',i}$ treatments at distance s from j. Otherwise, if j is applied in the first s or in the last s periods then $\phi^{\ell}_{d,j,i} = 1$ for (only) one period $\ell \in [\![1, s]\!]$ (i.e. when

$\sum_{\ell=1}^{s} \phi_{d,j,i}^{\ell} = 1$) and there exists only $1 = \sum_{j' \neq j} N_{d,j,j',i}^{s}$ treatment at distance s from j. Therefore, in both cases, we obtain

$$\sum_{j' \neq j} N_{d,j,j',i}^{s} = 2 - \sum_{\ell=1}^{s} \phi_{d,j,i}^{\ell} \quad . \tag{53}$$

Moreover, as j appears exactly r times in the design d, by considering all patients i,

$$\sum_{j' \neq j} N_{d,j,j'}^{s} = 2r - \sum_{\ell=1}^{s} \phi_{d,j}^{\ell} \quad . \tag{54}$$

Let us sum the above equality for all j and from Identity (16), we obtain this second expression of α:

$$\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N_{d,j,j'}^{s} = \sum_{j=1}^{v} (2r - \sum_{\ell=1}^{s} \phi_{d,j}^{\ell}) = 2rv - 2bs \quad .$$

As $rv = kb$ (see Identity (1)), the identification of the two expressions of α implies the wanted identity (4) satisfied by N_d^s:

$$N_d^s = N_{d,j,j'}^{s} = \frac{2b(k-s)}{v(v-1)} = \omega\,(k-s) \quad \forall j, j' \in [\![1, v]\!], j \neq j' \quad .$$

Proof of Identities (19) **and** (20)

Let d be a NNm-balanced design with $k = v$ (i.e. the number of periods equals the number of treatments). We have also $r = b$ because $rv = kb$. We will prove that for each $\ell \in [\![1, m]\!]$ the quantities $\phi_{d,j}^{\ell}$ and $\phi_{d,j,j'}^{\ell *}$ do not depend on treatments j, j' ($j \neq j'$); we will express these quantities without j and j'.
Let $s \in [\![1, m]\!]$. Applying Identity (4), as d is a NNm-balanced design, $N_{d,j,j'}^{s} = N_d^s = 2b(k-s)/v(v-1) = 2b(v-s)/v(v-1)$ since $k = v$. Then from (54), we have:

$$\sum_{\ell=1}^{s} \phi_{d,j}^{\ell} = 2r - (v-1) N_d^s \quad .$$

As $r = b$, the previous equality becomes $\sum_{\ell=1}^{s} \phi_{d,j}^{\ell} = \frac{2bs}{v}$. Then, for each $s \in [\![1, m]\!]$, we find:

$$\phi_{d,j}^{s} = \sum_{\ell=1}^{s} \phi_{d,j}^{\ell} - \sum_{\ell=1}^{s-1} \phi_{d,j}^{\ell} = \frac{2b}{v}$$

which is Identity (19). We now prove the second identity. We know that each treatment is administered at most once for each patient; but, as moreover $k = v$, every patient will receive the v distinct treatments once and only once. That means $n_{d,j,i} = 1$ for all $j \in [\![1, v]\!]$. Therefore Identity (48) becomes Identity (20):

$$\phi_{d,j,j'}^{\ell *} = \phi_{d,j}^{\ell} + \phi_{d,j'}^{\ell} = \frac{4b}{v} \quad \forall\ \ell \in [\![1, m]\!]$$

and the two identities on NNm-balanced square designs are proved.

Acknowledgements We warmly thank Paul Deheuvels and Pierre Druilhet for their constructive suggestions which have improved the quality of this article. We would also like to thank the work of rewiewer.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Ahmed R and Akhtar M (2009) On construction of one dimensional all order neighbor balanced designs by cyclic shifts. Pak. J. Statist. 25(2):121–126

Azzalini A and Giovagnoli A (1987) Some optimal designs for repeated measurements with autoregressive errors. Biometrika 74(4):725–734

Benchekroun K (1993) Association-balanced arrays with applications to experimental design. Ph.D. thesis, Dept. of Statistics, The University of North Carolina, Chapel Hill

Deheuvels P and Derzko G (1991) Block designs for early-stage clinical trials. Technical report of the laboratory LSTA, Université Paris 6, France. HAL-CNRS Open archives. https://hal.archives-ouvertes.fr/hal-02068964. Accessed 15 Mar 2019

Dey A (2010) Incomplete Block Designs. Indian Statistical Institute, New Delhi, India

Gill PS and Shukla GK (1985) Efficiency of nearest neighbour balanced block designs for correlated observations. Biometrika 72(3):539–544

Gill PS and Shukla GK (1985) Experimental designs and their efficiencies for spatially correlated observations in two dimensions. Communications in Statistics - Theory and Methods 14(9):2181–2197

Grondona MO and Cressie N (1993) Efficiency of block designs under stationary second-order autoregressive errors. Sankhyā: The Indian Journal of Statistics, Series A 55(2):267–284

Hedayat NA, Sloane NJA and Stufken J (1999) Orthogonal Arrays: Theory and Applications. Springer, New York

Iqbal I, Aman Ullah M and Nasir J A (2006) The construction of second order neighbour designs. Journal of Research (Science), Bahauddin Zakariya University, Multan, Pakistan 17(3):191–199

Kiefer J (1975) Balanced block designs and generalized Youden designs. I. Construction (patchwork). Ann Stat 3:109–118

Kiefer J (1975) Construction and optimality of generalized Youden designs. in: A survey of statistical design and linear models (Proc. Internat. Sympos., Colorado State Univ., Ft. Collins, Colo., 1973), North-Holland, Amsterdam, pp 333–353

Kiefer J and Wynn HP (1981) Optimum balanced block and Latin square designs for correlated observations . Ann Stat 9(4):737–757

Koné M and Valibouze A (2011) Plans en blocs incomplets pour la structure de corrélation NNm. Annales de l'ISUP 55(2-3):65–88

Kunert J (1985) Optimal repeated measurements designs for correlated observations and analysis by weighted least squares. Biometrika 72(2):375–389

Kunert J (1987) Neighbour balanced block designs for correlated errors. Biometrika 74(4):717–724

Martin RJ and Eccleston JA (1991) Optimal incomplete block designs for general dependence structures. J Stat Plan Inference 28(1):67–81

Morgan JP and Chakravarti IM (1988) Block designs for first and second order neighbor correlations. Ann Stat 16(3):1206–1224

Mukhopadhyay AC (1972) Construction of BIBD's from OA's combinatorial arrangements analogous to OA's. Calcutta Statistical Association Bulletin 21:45–50

Passi RM (1976) A weighting scheme for autoregressive time averages. Journal of Applied Meteorology 15(2):117–119

Ramanujacharyulu C (1966) A new general series of balanced incomplete block designs. Proceeding of American Mathematical Society 17:1064–1068

Rao C (1946) Hypercubes of strength "d" leading to confounded designs in factorial experiments. Bulletin of the Calcutta Mathematical Society 38:67–78

Rao C (1947) Factorial experiments derivable from combinatorial arrangements of arrays. J. R. S. S., Suppl 09:128–139

Rao C (1961) Combinatorial arrangements analogous to orthogonal arrays. Sankhyā:The Indian Journal of Statistics, Series A:283–286

Rao CR (1973) Some combinatorial problems of arrays and applications to design of experiments. In: Survey of combinatorial theory (Proc. Internat. Sympos., Colorado State Univ., Ft. Collins, Colo., 1971), North-Holland, Amsterdam, pp 349–359

Satpati SK , Parsad R and Gupta VK (2007) Efficient block designs for dependent observations—a computer-aided search. Communications in Statistics - Theory and Methods 36(5-8):1187–1223

Siddiqui MM (1958) On the inversion of the sample covariance matrix in a stationary autoregressive process. The Annals of Mathematical Statistics 29:585–588

Stufken J (1991) Some families of optimal and efficient repeated measurements designs. J Stat Plan Inference 27:75-83

Wei WWS (1990) Time series analysis. Univariate and multivariate methods. Addison-Wesley Publishing Company Advanced Book Program, Redwood City, CA

Wise J (1955) The autocorrelation function and the spectral density function. Biometrika 42:151–159

Yates F (1964) Sir Ronald Fisher and the Design of Experiments. In Memoriam: Ronald Aylmer Fisher, 1890-1962. Biometrics 20(2):307–321