NEAREST NEIGHBOR BALANCED BLOCK DESIGNS FOR AUTOREGRESSIVE ERRORS AR(m)

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ABSTRACT. The problem of findingneighbor optimal designs for a general correlation structure is studied. This paper gives optimality universal conditions for incomplete block designs when observations on the same block are modeled by an autoregressive process AR(m) of an arbitrary order m. It extends and generalizes existing results for models AR(1) and AR(2) as in such as those of Grondona and Cressie (1993) for AR(2) and those of Gill and Shukla (1985) and Kunert (1987) for AR(1).

Key words: block design, autoregressive model, nearest-neighbor balanced, generalized least squares estimation, universally optimal.

1. INTRODUCTION

The systematic introduction of statistical methods planning experience is due to the British statistician R. A. Fisher. In 1925-1937 years in agricultural research station Rothamsted (UK). In its results of experiments, Fisher began to consider the heterogeneity of the plots where the experiments take place, by comparing yields of different seed varieties which there were grown ; he introduced several types of designs including *complete block designs* (CBD), *incomplete block designs* and *Latin squares*.

The classic theory of designs of experiments is based on three principles, namely repetition, randomization and local control. The repetition is intended to allow an estimate of the residual variability, and increase the accuracy of the experiment. Randomization allows for unbiased estimators of the residual variability and the influence of treatments. As repetition, the goal of the local control is to increase the accuracy of the experiments.

Over the decades that followed this initial works, the principles developed by Fisher in agronomy have been transposed into various other sectors of activity, whose the industry and services sector. New concepts have been introduced, whose this one of optimal designs of J. Kieffer (1958-1981). At the same time, the use of statistical methods in the pharmacy and medicine has considerably developed, to the point that this one has came to

constitute, today, one of the main fields of application of experimental designs.

Recently, there has been considerable interest in the use of certain methods of local control called *spatial* or mth *order nearest-neighbor*, abbreviated by (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 have given sufficient conditions *weak universally optimality* for the estimation of treatment contrasts. Morgan and Chakravarti (1988) extend these conditions to the model NN2 and later Koné and Valibouze (2011) generalized this results to any correlation structure NNm, $m > 0$.
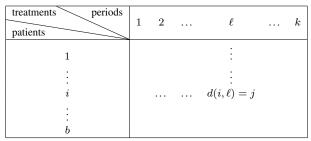
When the covariance structure is known, it is natural to construct the optimal experimental designs by making use of the generalized least squares (GLS) estimator. Kiefer and Wynn (1981) justified the choice of the OLS estimator, rather than the GLS estimator, in showing that the loss of accuracy relative resulting from the use of this estimator (OLS instead of the GLS) is quite low for the NN1 correlation models they consider. Among other authors, Kunert (1985, 1987), Azzalini and Giovagnoli (1987), Gill and Shukla (1985a,b), Martin and Eccleston (1991), Grondona and Cressie (1993) and Satpati and al. (2007) have used this approach for the correlation structures AR(1) et AR(2), the autoregressive processes of first and second order (see Definition in Section 2.2), and also for the model NN1.

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

Section 2 presents the experimental context : the design and the correlation structure AR(m). Section 3 is devoted to the presentation of the model describing the correlation structure. Section 4 presents a known result about universally optimal designs due to Kiefer (1975a) and Section 5 contains the main theorem, the Optimality Theorem 5.1, which gives sufficient conditions for universal optimality. In Section 6, our Optimality Theorem is illustrated with the particular designs called *semi balanced arrays*. Section 7 is devoted to proofs.

2. EXPERIMENTAL CONTEXT

2.1. **Designs for the considered experimental situation.** We consider experimental situations in which $v \geq 1$ treatments are applied to $b \geq 1$ patients during $k \geq 1$ distinct periods. The generic term of period means the distinct unities of times where the treatments are applied. The following figure illustrates a such designs d:

treatments / periods	1	2	...	ℓ	...	k
patients						
1				$\vdots$		
$\vdots$				$\vdots$		
i		...	...	$d(i,\ell)=j$		
$\vdots$						
b						

where $d(i, \ell) = j$ is one of the v treatments applied to the ith patient in the ℓth period.

The goal is to construct the best experimental structure, the effectiveness being measured by optimality criteria evaluating the precision with which one considers the average value of the effects. The precision is measured by the information matrix of the estimates.

We denote by $\Omega_{v,b,k}$ the set of the block designs of this type. More precisely, we will reason within the framework of an experimental structure in *incomplete blocks* where a given patient, represented by a block, receives exactly k distinct treatments distributed during the various periods. In each one of these periods, the patient receives only one of the v treatments. This gives a single scalar experimental measurement.

Following the nomenclature of Morgan and Chakravarti (1988) and Grondona and Cressie (1993), we qualify by NNm-*balanced* the experimental designs in incomplete block, when they are balanced for distinct periods in time at most m units (see lower exact Definition 1). In medical domain, the temporal balancing procedure can eliminate experimental results through the resulting effects interactions caused by the proximity in time of the administration of certain treatments on the same patient.

Definition 1. For an integer m ($m \geq 1$) fixed, a design will by said NNm-balanced (or a balanced design for nearest-neighbor at distance m) if for any integer $\delta \in [\![1, m]\!]$, the number of times that two distinct treatments administered to the same patient are neighbors at distance δ is independent of the choice of these two treatments; that is to say, this value depends only on δ and on the design.

Example 2. The design of Table 1 bellow is NN2-balanced. Indeed, here $m = 2$ and each pair of distinct treatments appears exactly three times at distance $\delta = 1$ and 2 times at distance $\delta = 2$.

TABLE 1. NN2-balanced design

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

2.2. **Autoregressive correlation structure AR(m).** Now describe the correlation structure considered in this paper. We suppose that the correlation between observations carried out on distinct patients is null.

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 error obtained at the ℓth period ($\ell \in [\![1, k]\!]$) on the ith patient ($i \in [\![1, b]\!]$) (see the model (6) that we consider). We suppose that $\varepsilon_{i,\ell}$ is a partial realization from a mth order autoregressive process AR(m) characterized by the relations

$$(1) \qquad \varepsilon_{i,\ell} - \sum_{r=1}^{m} \theta_r \varepsilon_{i,\ell-r} = w_{i,\ell} \quad \text{for} \quad \ell = 0, \pm 1, \pm 2, \ldots, \pm \infty,$$

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

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

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

$$(3) \qquad \gamma(s) = \mathrm{Cov}(\varepsilon_{i,\ell}, \varepsilon_{i,\ell+s}) \ .$$

In this paper, we will consider the variance-covariance matrix $V = \mathbb{V}\mathrm{ar}(\varepsilon_i)$ where $\varepsilon_i = (\varepsilon_{i,1}, \ldots, \varepsilon_{i,k})'$ is the error vector from the ith patient. The matrix V does not depend on the 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.

3. DESCRIPTION OF THE MODEL

A design $d \in \Omega_{v,b,k}$ will be defined as a function

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

where $d(i, \ell)$ is the treatment applied to the ith $(1 \leq i \leq b)$ patient in the ℓth $(1 \leq \ell \leq k)$ period. This design d is presented by a $b \times k$ table of indices of the treatment taken among the v possible values and applied to the different patients. In this table, the indices of the lines correspond to the b patients, those columns to the k periods of application and the treatment $d(i, \ell)$ is line i, column ℓ.

We adopt the following notations: for a design d, $n_{d,j,i}$, is the number of times that the treatment j is applied to the ith patient, $r_{d,j}$ is the number of times the treatment j is replicated in all of the experiment, $k_{d,i}$ is the total number of treatments received by the ith patient and $\lambda_{d,j,j'}$ is the number of patients for whom the distinct treatments j and j' are both applied. For a fixed design d, the designation of d in those notations would be omit.

If the design d is such that $n_{d,j,i} \in \{0, 1\}$, $r_{d,j} = r_{d,j'} = r$ or $k_{d,i} = k_{d,i'} = k$ it is respectively called *binary*, *equireplicated* and *proper*. For such designs the following identity holds

$$(4) \qquad\qquad\qquad rv = kb$$

because each member of this equality counts the cardinality of the design d.

Throughout this paper, we restrict $\Omega_{v,b,k}$ to the set of binary, proper and equireplicated block designs. In such designs, each treatment is replicated exactly $r = \frac{kb}{v}$ times in the whole design and the ith patient receives k distinct treatments $d(i, 1), \ldots, d(i, k)$ successively applied in the periods $1, \ldots, k$. Moreover we have:

$$(5) \qquad\qquad\qquad \lambda_{d,j,j'} = \sum_{i=1}^{b} n_{d,j,i}\, n_{d,j',i} \qquad .$$

For optimality criteria we will consider the particular cases of BIBD and CBD defined as follows:

Definition 3. A binary proper equireplicated block design d such that for each pair of distinct treatments j, j' the number $\lambda_{d,j,j'}$ is a constant λ is called a *balanced incomplete block design*, denoted by BIBD(v, b, r, k, λ). If moreover $k = v$ and $\lambda = r$, the design is called a *complete block design*, denoted by CBD(v, b).

The BIBD have been introduced and studied by Yates during the years 1936 to 1940.

In our study, we consider the following classical linear model:

$$(6) \qquad\qquad \mathbf{Y}_d \;=\; \mu \mathbf{1}_{bk} + (\mathbf{I}_b \otimes \mathbf{1}_k)\alpha + \mathbf{T}_d \beta + \varepsilon$$

where $\mathbf{1}_a$ and $\mathbf{1}_{a \times a}$ are respectively the a-vector and the $(a \times a)$-matrix composed entirely of one (for zero, we will adopt the same such notation with $\mathbf{0}_a$)

- ε is the bk-vector of random errors which follows the $\mathrm{AR}(m)$ process, zero mean: $\mathbb{E}(\varepsilon) = 0$ and of variance-covariance matrix $\mathbb{V}\mathrm{ar}(\varepsilon) = V^*$ (see Section 2.2);
- 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 in the ℓth period;
- 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;
- 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:

$$(7) \quad \mathbf{T}_d = \begin{bmatrix} T_1 \\ \vdots \\ T_b \end{bmatrix} \quad \text{where } T_i = (\mathbf{t}_{\ell,j}(i))_{1 \leq \ell \leq k,\ 1 \leq j \leq v} \quad \text{and} \quad \mathbf{t}_{\ell,j}(i) = \delta_{j,d(i,\ell)}$$

($\delta_{a,b}$ is the Kronecker symbol).

Example 4. : For $v = k = 3$ treatments and $b = 2$ patients, we have:

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

when the design d is:

j\\ℓ	1	2	3
i			
1	1	1	2
2	2	3	3

.

Let $\mathbb{M}$ be the $(k \times k)$-matrix $\sigma^2 V^{-1}$ whose general form was given by Wise (1955) and Siddiqui (1958). Passi (1976) gave another formulation of their result. In the following, we give a similar formulation that will prove convenient to calculate the information matrix when estimating a set of treatment contrasts defined in Section 4.

Lemma 5. *Let be an integer $m \geq 1$ and assume that $k > 2m$. Put $\theta_0 = -1$ and $\theta_u = 0$ for all $u > m$. Then the matrix $\mathbb{M} = (\gamma_{\ell,\ell'})_{1 \leq \ell,\ell' \leq k} = \sigma^2 V^{-1}$ is given by:*

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

More precisely and considering the zero values of the $\theta_i = 0$, we have:

$$
\gamma_{\ell,\ell'} : \begin{cases}
(i)\ \gamma_{\ell,\ell} = \displaystyle\sum_{u=0}^{\ell-1} \theta_u^2 & \text{for } \ell \in [\![1, m]\!] \\[2em]
(ii)\ \gamma_{\ell,\ell} = \displaystyle\sum_{u=0}^{m} \theta_u^2 & \text{for } \ell \in [\![m+1, k-m]\!] \\[2em]
(iii)\ \gamma_{\ell,\ell+s} = \displaystyle\sum_{u=0}^{\ell-1} \theta_u \theta_{u+s} & \text{for } \ell \in [\![1, m-1]\!] \text{ and } s \in [\![1, m-\ell]\!] \\[2em]
(iv)\ \gamma_{\ell,\ell+s} = \displaystyle\sum_{u=0}^{m-s} \theta_u \theta_{u+s} & \text{for } \ell \in [\![1, k-m]\!] \text{ and } s \in [\![max(1, m-\ell+1), m]\!] \\[2em]
(v)\ \gamma_{\ell,\ell+s} = 0 & \text{for } \ell \in [\![1, k-m]\!] \text{ and } s \in [\![m+1, k-\ell]\!].
\end{cases}
$$

The other elements not concerned by the formula (8) *are determined by:*

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

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

Example 6. For $m = 3$ and $k > 6 = 2m$, the matrix $\mathbb{M}$ of lemma 5 is given by

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

Now we present an essential lemma about the sum of elements of each line of the matrix $\mathbb{M}$:

Lemma 7. *Suppose $k > 2m$ and let $\ell \in [\![1, k]\!]$. Put $p_\ell = \displaystyle\sum_{\ell'=1}^{k} \gamma_{\ell,\ell'}$, the sum of the elements of the line ℓ of the matrix $\mathbb{M}$, $a_\ell = \displaystyle\sum_{u=\ell}^{m} \theta_u$ for $\ell \le m$ and $a_\ell = 0$ for $\ell > m$. Then:*

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

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 $\ell \in [\![k - m, k]\!]$. In particular, $p_\ell = p_{m+1} = a_0^2$ for $\ell \in [\![m + 1, k - m]\!]$.

Recall that Section 7 is devoted to the proofs.

The expression of p_ℓ given in Lemma 7 will be introduce in the proof of expressions of diagonal and extra-diagonal elements of the information matrix C_d that are given in Lemma 12; moreover, in this lemma, the coefficient c appearing in the expressions is the sum of all elements of the matrix $\mathbb{M}$ given by:

(11) $$c = \mathbf{1}'\mathbb{M}\mathbf{1} = 2a_0 \sum_{\ell=0}^{m-1}(m - \ell)\theta_\ell \; + \; (k - 2m)a_0^2$$

because

$$
\begin{aligned}
c &= \sum_{\ell=1}^{k}\sum_{\ell'=1}^{k}\gamma_{\ell,\ell'} = 2\sum_{\ell=1}^{m}p_\ell + \sum_{\ell=m+1}^{k-m}p_\ell \;\; = \;\; 2a_0\sum_{\ell=1}^{m}(a_0 - a_\ell) + \sum_{\ell=m+1}^{k-m}p_m \\
&= \; 2a_0\sum_{\ell=1}^{m}(\theta_0 + \theta_1 + \cdots + \theta_{\ell-1}) \;\; + \;\; (k - 2m)a_0^2 = 2a_0\sum_{\ell=0}^{m-1}(m - \ell)\theta_\ell \; + \; (k - 2m)a_0^2 \quad .
\end{aligned}
$$

4. ESTIMATION OF THE TREATMENT EFFECTS

In this section, we give the information matrix of a set of contrasts of effects related to the treatments.

Consider the ith patient, $i \in [\![1, b]\!]$, and put $Y_i = (Y_{i,1}, \ldots, Y_{i,\ell}, \ldots, Y_{i,k})'$, the vector of the k responses of the ith patient. In the model (6), the GLS estimator $\widehat{\beta}$ of the v-vector β of treatment effects satisfies the following reduced normal equations (see Benchekroun (1993)):

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

As said before Lemma 5 concerning the matrix $\mathbb{M}$, we are interested in the estimation of a set of treatment contrasts. Let $\gamma \in \mathbb{R}^v$. A linear combination $\gamma' \cdot \beta = \sum_{j=1}^v \gamma_j \beta_j$, where β is a treatment effects, is called a *treatment contrast* if $\gamma' \cdot \mathbf{1}_v = 0$. A block design d is said to *connected* if all treatment contrasts are estimable under d. We refer to Dey (2010) (pages 11 and 12) for the details of connected designs.

In the following, we restrict $\Omega_{v,b,k}$ at block designs which are binary, equireplicate, proper and connected.

As, the vector $\gamma = (\beta_j - \frac{1}{v} \sum_{j=1}^v \beta_j)_{1 \le j \le v}$ of corrected treatment effects satisfies the identifiability constraint $\gamma' \cdot \mathbf{1}_v = 0$, the optimality results of a design $d \in \Omega_{v,b,k}$ will be based on the set of contrasts

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

Observe that a such choice is suitable since $u' \cdot \gamma = u' \cdot \beta$ for any $u \in \mathbb{R}^v$ such that $u' \cdot \mathbf{1}_v = 0$. 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) (see Grondona and Cressie (1993)):

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

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, for the ith patient, the information matrix $\mathbf{C}_{i,d}(V) = \mathbb{V}\mathrm{ar}(\widehat{\gamma})^\dagger$ of $\widehat{\gamma}$ satisfies:

$$\mathbf{C}_{i,d}(V) = T_i' \mathbb{W} T_i \quad .$$

It follows this lemma stated by Kunert (1987) (see detailed proof in Benchekroun (1993)):

Lemma 8. *In the covariance structure (1, 2, 3), the information matrix of the estimator $\widehat{\gamma}$ of treatment contrasts is given by*

$$(15) \qquad\qquad \boldsymbol{C}_d(V^*) = \sum_{i=1}^{b} T_i' \, \mathbb{W} \, T_i$$

where $V^* = \mathbf{I}_b \otimes V$ and $\mathbb{W} = (w_{\ell,\ell'})_{1\leq \ell,\ell' \leq k} = V^{-1} - (\mathbf{1}_k' V^{-1} \mathbf{1}_k)^{-1} V^{-1} \mathbf{1}_k \mathbf{1}_k' V^{-1}.$

5. UNIVERSAL OPTIMALITY

The study of the information matrix associated with the estimator $\widehat{\gamma}$ of treatment contrasts can build strong optimality criteria.

5.1. **Preliminary.**

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

$$(16) \qquad\qquad \mathbf{C}_d \mathbf{1}_v = \mathbf{C}_d' \mathbf{1}_v = \mathbf{0}_v \quad .$$

which says that $\mathbf{C}_d$ has row- and column-zero for all $d \in \Omega_{v,b,k}$.

Definition 9. (Kiefer (1975a)) A block design d belonging to $\Omega_{v,b,k}$ is said *universally optimal* if its information matrix C_d minimizes simultaneously all fonctions $\psi : \mathcal{V} \mapsto \,]-\infty, +\infty]$, 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 $\mathbf{C} \in \mathcal{V}$ once $0 < a < 1$.

Proposition 10. *(Kiefer (1975b)) Suppose that there exists $d^* \in \Omega_{v,b,k}$, such that its information matrix $\boldsymbol{C}_{d^*}$ has row- and column-zero and verifies:* (i) $\boldsymbol{C}_{d^*}$ *is completely symmetric, i.e.* $\boldsymbol{C}_{d^*} = \alpha \boldsymbol{I}_v - \alpha/v \boldsymbol{I}_{v \times v}$ *where α is a scalar and* (ii) *the trace of $\boldsymbol{C}_{d^*}$ is maximum on the set $\mathcal{V}$. Then the design d^* is universally optimal in $\Omega_{v,b,k}$.*

By Identity (16), we just have to find a design whose the information matrix meets conditions (i) and (ii) of Kiefer's Theorem 10. We will seek them among the optimal designs.

5.2. **Optimality conditions for the correlation structure AR(m).**

Let d be a block design in $\Omega_{v,b,k}$ and the integer $m > 0$ such that $k > 2m$. We adopt the following notations which generalize those of Gill and Shukla (1985a) and Grondona and Cressie (1993) for the respective cases $m = 1$ and $m = 2$:

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

$\phi^{\ell}_{d,j}$ is the number of patients for which the treatment j is applied to the ℓth or to the $(k - \ell + 1)$th period when $\ell \in [\![1, m]\!]$ and to the ℓth period when $\ell \in [\![m + 1, k - m]\!]$;

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

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

$N^{s}_{d,j,j'}$ is the number of patients in which treatments j and j' occur as sth nearest neighbours (i.e. separate by $s - 1$ period); with $N^{s}_{d,j,j} = 0$.

Remark 11. When the design d is binary, we have: $\phi^{\ell}_{d,j,i} = \delta_{j,d(i,\ell)} + \delta_{j,d(i,k-\ell+1)}$ and

$$N^{s}_{d,j,j',i} = \begin{cases} 1 & \text{if } j \text{ and } j' \text{ are applied with a distance } s \text{ to the } i\text{th patient} \\ 0 & \text{otherwise} \end{cases}$$

When the design d is equireplicated, for each treatment $j \in [\![1, v]\!]$, we have:

$$(17) \qquad r_{d,j} = \sum_{\ell=1}^{k-m} \phi^{\ell}_{d,j} = r$$

In Example 23, some of this previous quantities are counted in a concret design.

The following lemma generalizes to any m the results (4.8) and (4.9) of Grondona and Cressie (1993) for $m = 2$:

Lemma 12. *Let be a design $d \in \Omega_{v,b,k}$, for an integer k which verifies $k > 2m$. Then, for the AR(m) model, the diagonal entries of the matrix $\boldsymbol{C}_d$ is given as follows for each treatment $j \in [\![1, v]\!]$:*

$$(18) \qquad \sigma^2 \boldsymbol{C}_{d,j,j}(V^*) = s_0 r - s_1 \phi^{1}_{d,j} - s_2 \phi^{2}_{d,j} - \cdots - s_m \phi^{m}_{d,j}$$

and taking $j' \neq j$ in $[\![1, v]\!]$, the off-diagonal entries are given by:

$$
\sigma^2 \boldsymbol{C}_{d,j,j'}(V^*) = \sum_{s=1}^{m} N_{d,j,j'}^s \sum_{u=0}^{m-s} \theta_u \theta_{u+s}
$$

$$
- \sum_{s=1}^{m-1} \sum_{t=1}^{m-s} \sum_{u=t}^{m-s} \theta_u \theta_{u+s} \sum_{i=1}^{b} N_{d,j,j',i}^s (\phi_{d,j,i}^t \phi_{d,j',i}^{t+s} + \phi_{d,j',i}^t \phi_{d,j,i}^{t+s})
$$

(19)
$$
-c^{-1} a_0^2 \left\{ a_0^2 \lambda_{d,j,j'} - a_0 \sum_{\ell=1}^{m} a_\ell \phi_{d,j,j'}^{\ell*} + \sum_{\ell=1}^{m} \sum_{\ell'=1}^{m} a_\ell a_{\ell'} \sum_{i=1}^{b} \phi_{j,i}^\ell \phi_{j',i}^{\ell'} \right\}
$$

where

$$
a_\ell = \sum_{u=\ell}^{m} \theta_u, \quad b_\ell = \sum_{u=\ell}^{m} \theta_u^2,
$$

$$
c = \boldsymbol{1}' \mathbb{M} \boldsymbol{1} = 2a_0 \sum_{\ell=0}^{m-1} (m - \ell) \theta_\ell + (k - 2m) a_0^2 \qquad and
$$

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

Remark 13. **Consequence of lemma 12**

The trace $\mathrm{tr}(\mathbf{C}_d) = \sum_{j=1}^{v} \mathbf{C}_{d,j,j}(V)$ of the information matrix $\mathbf{C}_d$ of $\widehat{\gamma}$ is independent of choice of the design in $d \in \Omega_{v,b,k}$ and is given by the identity

(20)
$$
\sigma^2 \mathrm{tr}(\mathbf{C}_d) = s_0 v r - 2b(s_1 + s_2 + \cdots + s_m) \quad .
$$

Indeed, following Lemma 12 and identity (21), we have:

$$
\sigma^2 \mathrm{tr}(\mathbf{C}_d) = s_0 v r - s_1 \sum_{j=1}^{v} \phi_{d,j}^1 - s_2 \sum_{j=1}^{v} \phi_{d,j}^2 - \cdots - s_m \sum_{j=1}^{v} \phi_{d,j}^m
$$

$$
= s_0 v r - 2b(s_1 + s_2 + \cdots + s_m)
$$

because (Koné and Valibouze, 2011):

(21)
$$
\sum_{j=1}^{v} \phi_{d,j}^\ell = 2b \text{ for } k > 2m \text{ and } \ell \in [\![1, m]\!] \quad .
$$

So all the designs which are potentially optimal in $\Omega_{v,b,k}$ have the same trace. It remains to identify the designs of $\Omega_{v,b,k}$ with an information matrix which is completely symmetric, i.e., the designs which are universally optimal in $\Omega_{v,b,k}$.

Before the main Theorem, we establish three lemmas concerning terms of expression of the terms $\mathbf{C}_{d,j,j'}$ given in Lemma 12. The first one in follows concerns the BIBD designs.

Lemma 14. *Assume $k \leq v$. For a BIBD(v, b, r, k, λ) design d, the number of times that two distinct treatments j, j' are administered to the same patient is a constant λ given by*

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

The second lemma concerns the NNm-balanced designs:

Lemma 15. *For a design d NNm-balanced and an integer $s \in [\![1, m]\!]$, there exists a constant N_d^s counting the number of times that two distinct treatments are applied to a same patient at a distance s and this constant is given by:*

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

The third lemma concerning the square NNm-balanced designs will be use for establishing Theorem 5.2:

Lemma 16. *Assume that the designs are square, i.e. the number k of periods equals the number v of treatments. Then a design d which is NNm-balanced satisfies not only identity (ii) of Lemma 15 but also the following:*

$$(22) \qquad \qquad \phi_{d,j,j'}^{\ell*} = \frac{4b}{v} \quad and$$

$$(23) \qquad \qquad \phi_{d,j}^{\ell} = \frac{2b}{v}$$

for each $j, j' \in [\![1, v]\!]$ ($j \neq j'$) and for each $\ell \in [\![1, m]\!]$.

We can now establish our main Theorem:

Theorem 5.1 (Optimality Theorem). *Assume $2m < k < v$.*
If a NNm-balanced BIBD(v, b, r, k, λ) $d \in \Omega_{v,b,k}$ for the model AR(m) exists, which also fulfills the conditions $(iii), (iv)$ and (v) below, for all distinct treatments j and j' in $[\![1, v]\!]$ and for $\ell, \ell' \in [\![1, m]\!]$, then d is universally optimal over $\Omega_{v,b,k}$;

$$(iii) \qquad \qquad \phi_{d,j,j'}^{\ell*} = \frac{4b(k-1)}{v(v-1)} \quad ,$$

$$(iv) \qquad \qquad \sum_{i=1}^{b} \phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} = \frac{2b(2-\delta_{\ell,\ell'})}{v(v-1)} \quad ,$$

$$(v) \qquad \sum_{i=1}^{b} N_{d,j,j',i}^{|\ell-\ell'|} (\phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} + \phi_{d,j',i}^{\ell} \phi_{d,j,i}^{\ell'}) = \frac{4b}{v(v-1)} \qquad \qquad when\ \ell \neq \ell'$$

where $\delta_{\ell,\ell'}$ is the Kronecker symbol.

When d is an NNm-balanced universally optimal BIBD(v, b, r, k, λ), Optimality Theorem implies that the off-diagonal entries of the matrix $\mathbf{C}_d$ are given by:

$$\sigma^2 \mathbf{C}_{d,j,j'}(V^*) = \frac{2b(k-s)}{v(v-1)} \sum_{s=1}^{m} \sum_{u=0}^{m-s} \theta_u \theta_{u+s} - \frac{4b}{v(v-1)} \sum_{s=1}^{m-1} \sum_{t=1}^{m-s} \sum_{u=t}^{m-s} \theta_u \theta_{u+s}$$

$$(24) \qquad - \frac{bc^{-1}a_0^2}{v(v-1)} \left\{ a_0^2 k(k-1) - a_0 4(k-1) \sum_{\ell=1}^{m} a_\ell + 2 \sum_{\ell=1}^{m} (a_\ell^2 + 2a_\ell \sum_{\substack{\ell'=1 \\ \ell' \neq \ell}}^{m} a_{\ell'}) \right\}$$

where $j' \neq j$ in $[\![1, v]\!]$,

$$a_\ell = \sum_{u=\ell}^{m} \theta_u \quad \text{and} \quad c = \mathbf{1}'\mathbb{M}\mathbf{1} = 2a_0 \sum_{\ell=0}^{m-1} (m-\ell)\theta_\ell + (k-2m)a_0^2 \quad .$$

In the case of a complete block design, we obtain the optimality following result:

Theorem 5.2. *Suppose $k > 2m$ and the designs are square: the number k of periods equals the number v of treatments. If a NNm-balanced CBD(v, b) $d \in \Omega_{v,b,k}$ for the AR(m) model exists then d is universaly optimal over $\Omega_{v,b,k}$ if it fulfills the conditions (iv) and (v) of Theorem 5.1.*

Remark 17. A necessary condition for the existence of the designs satisfying the condition conditions $(iii) - (v)$ of Theorem 5.1 and Theorem 5.2 is then $v(v-1)|2b$. A *minimal* design corresponds to the minimal value of b for k and v fixed satisfying the associated optimality conditions. Morgan and Chakravarti (1988) and Koné and Valibouze (2011) showed that the minimal value of b for wich the existe a NN2-balanced CBD is $b = v(v-1)/2$.

In Lemma 12, Theorem 5.1 and Theorem 5.2, for the value $m = 1$ we find the results of Kunert (1987) and for value $m = 2$ we find the results of Grondona and Cressie (1993) [1].

In the below section, the Optimality Theorem is illustrated with well-known designs called *semi balanced arrays*.

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[1] without one error of their paper in one element of the summation (4.9) giving $\sigma^2 c_{l,m}$ with $l \neq m$: according to their notations the factor 2 in $2(1 - \phi_1 - \phi_2)\phi_2 f^*_{l,m}$ must be removed and, moreover, their definitions of $f^*_{l,m}$ and $e^*_{l,m}$ must be modified as follows: $e^*_{l,m} := \phi^{1*}_{d,l,m}$ and $f^*_{l,m} := \phi^{2*}_{d,l,m}$.

6. OPTIMALITY THEOREM AND SEMI BALANCED ARRAYS

Rao (1946, 1947) introduced the concept of orthogonal arrays denoted by OA. Two variants of them are defined by Rao (1961): the OA of Type I and the OA of Type II which are renamed respectively *transitive* arrays, denoted by TA, and *semi balanced* arrays, denoted by SB. For more details, see Rao (1961, 1973), Morgan and Chakravarti (1988) and Hedayat, Sloane et Stufken (1999).

Definition 18. A $b \times k$ array of v symbols is an $\mathrm{SB}(b, k, v, t)$, where t is called its *strength*, if in every set of t columns each unordered t-tuples have distinct symbols among v and appears exactly ω times, where $\omega \in \mathbb{N}$ is called the *index* of the SB.

To define a TA, it suffices to replace "unordered t-tuples" by "ordered t-tuples" in the definition of a SB. Clearly, a $\mathrm{TA}(b, k, v, t)$ of index ω is an $\mathrm{SB}(b, k, v, t)$ of index $t! \, \omega$.

Remark 19. 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 $\omega = b / \binom{v}{t}$. By consequence, the existence of an $\mathrm{SB}(b, k, v, t)$ implies that b is the multiple $\omega \binom{v}{t}$ of $\binom{v}{t}$.

Note that in the context of our paper, b is the number of patients, k is the number of treatments received by patient, and the v symbols represent the indices of the distinct treatments. We have chosen this context to simplify our explanations.

Many methods for constructing SB and TA exist in the literature (Morgan and Chakravarti (1988), Mukhopadhyay (1972), Ramanujacharyulu (1966), Stufken (1991), ...). In context of this section, we will be interested only in the strength $t = 2$. Rao (1961, 1973) 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 Galois field with v elements.

Example 20. Below, the 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)

The design (a), obtained by superposition of the two quasi-complete Latin squares (c) and (d), is an $SB(10, 5, 5, 2)$ of index 1. The design (b) is superposition of mirror image of designs (c) and (d). The design (e) resulting to the superposition of designs (a) and (b) yields a $TA(20, 5, 5, 2)$ of index 1 or a $SB(20, 5, 5, 2)$ of index 2.

Martin and Eccleston (1991) have introduced SDEN designs (SDEN for *strongly directionally equineighboured*) [2]. They remark that for $k \geq 3$ a $SDEN(b, k, v)$ is equivalent to a $SB(b, k, v, 2)$ and construct these designs from $\omega(v - 1)$ latin squares of order v. The part (a) of they 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 have interested to SB's of strength $t = 2$ since if an $SB(b, k, v, 2)$ exists then it can be interpreted as a $BIBD(v, b, r, k, \lambda)$ (it is well kwown and easily provable). The following proposition applies Theorem 2 in Martin and Eccleston (1991), most general than $AR(m)$ for correlations structures but restricted for designs:

Proposition 21. *Suppose that there exists an SB($b, k, v, 2$) and call it d. Then d is a BIBD(v, b, r, k, λ) with*

$$(25) \quad \lambda = \frac{k(k - 1)}{2} \, \omega \quad and \quad r = \frac{k(v - 1)}{2} \, \omega \quad where \quad \omega = b\frac{2}{v(v - 1)}$$

is the index of d and it 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 verifies:

$$(26) \qquad\qquad N_d^s = N_{d,j,j'}^s \;\; = \;\; \omega(k - s)$$

$$(27) \qquad\qquad \phi_{d,j,j'}^{\ell*} \;\; = \;\; 2\omega(k - 1)$$

$$(28) \qquad\qquad \sum_{i=1}^{b} \phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} \;\; = \;\; \omega(2 - \delta_{\ell,\ell'})$$

$$(29) \qquad \sum_{i=1}^{b} N_{d,j,j',i}^{|\ell-\ell'|}(\phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} + \phi_{d,j',i}^{\ell} \phi_{d,j,i}^{\ell'}) \;\; = \;\; 2\omega \quad when \;\; \ell \neq \ell'.$$

Morgan and Chakravarti (1988) (Theorems 4.1) and Koné and Valibouze (2011) give a similar result in the case of the weakly universally optimal BIBD for respectively the NN2 and NNm (for all $m > 1$) correlation structure.

Remark 22. Let $j, j' \in [\![1, v]\!]$, $j \neq j'$ and $m < 2k$. Recall that a $BIBD(v, b, , k, \lambda)$ is NNm-balanced for the $AR(m)$ model if the quantity $N_{d,j,j'}^s$ is independent to j and j' (see

---

[2]Deheuvels and Derzko (1991) used the terms *totally balanced* for SDEN and SB, and *universally balanced* for TA.

Lemma 15) and it is universally optimal if moreover the three quantities at left of equalities (iii), (iv) and (v) of Optimality Theorem 5.1 are independent to j and j' and it this case the three equalities hold.

Proof. As it is known that an SB($b, k, v, 2$) can be interpreted as a BIBD(v, b, r, k, λ), the identities in (25) come from Remark (19) and Identities $rv = bk$ in (4) and $\lambda(v - 1) = r(k - 1)$ in Lemma 14. 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 $N_{d,j,j'}^s$, the number of times that (j, j') are applied to a same patient at distance $s \in [\![1, m]\!]$, is a constant N_d^s. More precisely, considering the $k - s$ pairs of periods ℓ and $\ell + s$ where ℓ runs in $[\![1, k - s]\!]$, as the strength of d is two, we obtain Identity (27): $N_d^s = N_{d,j,j'}^s = \omega(k - s)$. As $2b = \omega v(v - 1)$, N_d^s is obviously the same constant as that given in Lemma 15.

To prove the rest of Proposition 21, we apply (a) of Theorem 2 in Martin and Eccleston (1991) which implies that d is universally optimal and replace $2b$ by $\omega\, v(v - 1)$ in Identities (iii), (iv) and (v) of Optimality Theorem 5.1 (see Remark 22).

$\square$

We illustrate both our Optimality Theorem 5.1 and Proposition 21 by the following example.

Example 23. Verify identities of Proposition 21 on design (a) of Example 20. This design is an SB($b = 10, k = 5, v = 5, t = 2$) of index $\omega = 1$. We consider (a) as a BIBD($v = 5, b = 10, r = 10, k = 5, \lambda = 10$). On this BIBD, we will consider AR(m) correlation structures with necessarily $2m < k = 5$ (see Section 2.2). We chose $m = 2$. Let be two distinct treatments j and j' in $[\![1, 5]\!] = [\![1, v]\!]$ and $\ell, \ell' \in [\![1, 2]\!] = [\![1, m]\!]$.

To verify Identity (26), we have to consider $s \in [\![1, 2]\!]$. For $s = 1$, we count in (a) that $N_{d,j,j'}^1 = 4 = \omega(k - s)$, the number of times that j and j' are applied consecutively to the same patient. For $s = 2$, we count $N_{d,j,j'}^2 = 3 = \omega(k - s)$, the number of time that j and j' are applied to the same patient at distance $s = 2$. Hence, as in our proposition, the BIBD (a) is a NN2-balanced with $N_{d,j,j'}^s = \omega(k - s)$ for each $s \in [\![1, m]\!]$.

To verify (27), we have to count the value $\phi_{d,j,j'}^{\ell*}$ which is the number of times that the treatments j and j' occur together and j or j' are applied to the ℓth period or the $(k - \ell + 1)$th period. For example, for $\ell = 1$, we have $k - \ell + 1 = 5$; the treatment $j = 2$ appears 2 times in the first period (patients $i = 2$ and $i = 7$) and also 2 times in the last period. We find that j appears $4 = \omega(k - 1)$ times in the first or the last period. In the same way, any treatment j' appears 4 times in the first or the last period. Then $\phi_{d,j,j'}^{1*} = 8 = 2\omega(k - 1)$ as

in (27). We count also that $\phi^{2*}_{d,j,j'} = 8$ and Identity (iii) of Optimality Theorem holds.

Now, for Equality (28), consider the value $\phi^\ell_{d,j,i}$; i.e. the number of times that the treatment j is applied to the patient i at the 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' appear together at the periods ℓ <u>and</u> $k - \ell + 1$. By definition of SB of strength 2, this value is the index $\omega = 1$ of (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 together 2 times in the same line of (a) with j in period $\ell = 1$ or 5 and j' is in period $\ell' = 2$ or 4 (patients $i = 1$ and $i = 9$). It is the same for any j, j' with $j \neq j'$. Then $\sum_{i=1}^{10} \phi^\ell_{d,j,i} \phi^{\ell'}_{d,j',i} = 2 = 2\omega$ and as in our proposition $\sum_{i=1}^{10} \phi^\ell_{d,j,i} \phi^{\ell'}_{d,j',i} = \omega(2 - \delta_{\ell,\ell'})$. Then (iv) of Optimality Theorem holds.

Two finish with Equality (29), suppose that $\ell \neq \ell'$. Then necessarily $\mid \ell - \ell' \mid = 1$ and we can chose $\ell = 1$ and $\ell' = 2$. The value $N^{|\ell-\ell'|}_{d,j,j',i} = 1$ if the treatments j and j' are applied consecutively to the patient i and else $N^{|\ell-\ell'|}_{d,j,j',i} = 0$. For example, $j = 1$ and $j' = 5$ appear $\omega = 1$ times together in periods $\ell = 1$ and $\ell' = 2$ (patient $i = 10$) and $\omega = 1$ times in periods $k - \ell + 1 = 5$ and $k - \ell' + 1 = 4$ (patient $i = 8$). It is the same for any $j, j', j \neq j'$. Then, as in our proposition 21, we obtain

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

and Identity (v) of Optimality Theorem holds.

In consequence, by applying Optimality Theorem 5.1 or Proposition 21, we can conclude that the design (a) is universally optimal.

7. PROOFS

7.1. **Proof of Lemma 7.**

We consider the matrix $\mathbb{M} = (\gamma_{\ell,\ell'})_{1 \leq \ell, \ell' \leq k}$ and we search to express the sum $p_\ell = \sum_{\ell'=1}^{k} \gamma_{\ell,\ell'}$ of the elements of the line ℓ in the form given in the Lemma what we search to prove. By symmetry of matrix $\mathbb{M}$ we can suppose that $\ell \in [\![1, k - m]\!]$.

We will proceed in two steps. Let us first calculate the portion α_ℓ of this sum for $\ell' \geq \ell$ and then we calculate the rest β_ℓ. With the sum $p_\ell = \alpha_\ell + \beta_\ell$, we will find the appropriate formula.

First compute $\alpha_\ell = \sum_{\ell'=\ell}^{k} \gamma_{\ell,\ell'}$.
From Formula (8) of Lemma 5, we have the following expression of each $\gamma_{\ell,\ell'}$ for $\ell' \in [\![\ell, k]\!]$:

$$(30) \qquad \gamma_{\ell,\ell+s} = \sum_{u=0}^{l-1} \theta_u \theta_{u+s} \quad \text{for } s \in [\![0, k-\ell]\!] \quad .$$

Then

$$(31)\ \alpha_\ell = \sum_{s=0}^{k-\ell}\sum_{u=0}^{\ell-1} \theta_u\theta_{u+s} = \sum_{u=0}^{\ell-1}\theta_u \sum_{s=0}^{k-\ell} \theta_{u+s} = \sum_{u=0}^{\ell-1}\theta_u \sum_{b=u}^{k+u-\ell} \theta_b = \sum_{u=0}^{\ell-1}\theta_u \sum_{b=u}^{m} \theta_b \quad .$$

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

Now Compute $\beta_\ell = \sum_{\ell'=1}^{\ell-1} \gamma_{\ell,\ell'} == \sum_{\ell'=1}^{\ell-1} \gamma_{\ell',\ell}$, by symmetry. We have:

$$(32) \qquad \beta_\ell = \sum_{\ell'=1}^{\ell-1}\sum_{u=0}^{\ell'-1} \theta_u\theta_{u+(\ell-\ell')} = \sum_{a=1}^{\ell-1}\theta_a \sum_{b=0}^{a-1} \theta_b \quad .$$

To see this last identity, the reader can follows this method: write by column each element $\theta_u\theta_{u+(\ell-\ell')}$ forming the sum $\sum_{u=0}^{\ell'-1} \theta_u\theta_{u+(\ell-\ell')} = \gamma_{\ell',\ell}$; the first column for $\ell' = 1$, the second for $\ell' = 2$ and so on; the elements under the diagonal are all zero; then by the summation of the elements in each same parallel line over the diagonal we find $\theta_a \sum_{b=0}^{a-1} \theta_b$ if the parallel is at distance $\ell - 1 - a$ of the diagonal. There are $\ell - 2$ parallels. By example, the sum of the elements of the diagonal is $\theta_{\ell-1}(\theta_0 + \theta_1 + \cdots + \theta_{\ell-2})$ (i.e. $a = \ell - 1$ and the distance is 0), the sum of the parallel just over the diagonal is $\theta_{\ell-2}(\theta_0 + \theta_1 + \cdots + \theta_{\ell-3})$ (i.e. $v = \ell - 2$ and the distance is 0); the last parallel is reduced to the only one element $\theta_1\theta_0$ (i.e. $a = 1$ and the distance is $\ell - 2$).
We have finish because from (31) and (32), we obtain the announced identity in Lemma 7:

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

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 identity becomes $p_\ell = p_{m+1} = a_0^2 = (1 - \theta_1 - \cdots - \theta_m)^2$.
For the last lines, as $\mathbb{M}$ is symmetric with respect to its second diagonal, $p_\ell = p_{k-\ell+1}$ for $\ell \in [\![k-m+1, k]\!]$.

7.2. **Proof of Lemma 12.**

We introduce some tools before addressing the proof of Lemma 12. For $r \in [\![1, k]\!]$, $\boldsymbol{e}_r = (e_{r,s})_{1 \leq s \leq k}$ means the r-th canonical vector of $\mathbb{R}^k$, i.e. $e_{r,s} = \delta_{r,s}$ (where δ is the Kronecker symbol). Note that each element 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 (7) is expressed as follows: for each patient $i \in [\![1, b]\!]$, we set

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

Hence, by general notations, for each period $\ell \in [\![1, k - m]\!]$, we have

$$(34) \quad \phi_{d,j}^\ell = \begin{cases} \#\{i : \mathbf{t}_j(i) \in \{\boldsymbol{e}_\ell, \boldsymbol{e}_{k-\ell+1}\}\} & \text{if } \ell \in [\![1, m]\!] \\[2mm] \#\{i : \mathbf{t}_j(i) = \boldsymbol{e}_\ell\} & \text{if } \ell \in [\![m+1, k-m]\!]. \end{cases}$$

Remark 24. Exactly r vectors $\mathbf{t}_j(i)$ are nonzero because exactly r patients receive the treatment j.

Remark 25. As the considered designs are proper, each patient i receives at most one time the same treatment j; by consequence, for each $\ell \in [\![1, m]\!]$ and because $\ell \neq k - \ell + 1$ when $k > 2m$, we have:

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

We fix two distinct treatments j, j' in $[\![1, v]\!]$ and we seek identities on the elements $\sigma^2 C_{d,j,j}$ and $\sigma^2 C_{d,j,j'}$ of the matrix

$$(35) \quad \sigma^2 C_d = \sum_{i=1}^{b} T'_i \, \mathbb{M} \, T_i - \sum_{i=1}^{b} T'_i \, (\mathbf{1}'_k \, \mathbb{M} \, \mathbf{1}_k)^{-1} \, \mathbb{M} \, \mathbf{1}_k \mathbf{1}'_k \, \mathbb{M} \, T_i$$

where $\mathbb{M} = \sigma^2 V^{-1}$ (see Identity (15)), by considering independently the two terms in the right side of identity (35) respectively in Sections 7.2.1 and 7.2.2. We will conclude in Section 7.2.3 Also in the following the reference to the design d in index will be omit.

7.2.1. *The term $\sum_{i=1}^{b} T'_i \, \mathbb{M} \, T_i$ where $T_i = (\boldsymbol{t}_1(i), \ldots, \boldsymbol{t}_v(i))$.*

The contribution of $\sum_{i=1}^{b} T'_i \, \mathbb{M} \, T_i$ to the diagonal element $\sigma^2 C_{j,j}$ 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:

$$(36) \qquad \tau_i = \sum_{\ell=1}^{k} \sum_{\{i \,:\, \mathbf{t}_j(i)=e_\ell\}} e_\ell' \, \mathbb{M} \, e_\ell = \sum_{\ell=1}^{m} \phi_j^\ell \, e_\ell' \, \mathbb{M} \, e_\ell + \sum_{\ell=m+1}^{k-m} \phi_j^\ell \, e_\ell' \, \mathbb{M} \, e_\ell.$$

Combining the above identity (36) and Lemma 5 applied to elements $\gamma_{\ell,\ell} = e_\ell' \, \mathbb{M} \, e_\ell$ of the matrix $\mathbb{M}$ defined in Lemma 5, we obtain (recall that $\theta_0 = -1$):

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

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

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

Finally, the contribution τ of the term $\sum_{i=1}^{b} T_i' \, \mathbb{M} \, T_i$ to the element $\sigma^2 C_{j,j}$ is

$$(38) \qquad \tau \;=\; r b_0 - \phi_j^1 b_1 - \phi_j^2 b_2 - \cdots - \phi_j^m b_m$$

with $b_\ell = \sum_{u=\ell}^{m} \theta_u^2$ for $\ell \in [\![1, m]\!]$, as defined in Lemma 12.

In the same manner of the contribution of the term $\sum_{i=1}^{b} T_i' \, \mathbb{M} \, T_i$ to the diagonal elements, we now focus us on its contribution μ to the extra-diagonal element $\sigma^2 C_{j,j'}$ 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 new notation: for $\ell, \ell' \in [\![1, k]\!]$, we denote by $\phi_{j,j'}^{\ell,\ell'}$ the number of patients which receive the distinct treatments j and j' at the periods ℓ, ℓ', i.e.

$$(39) \qquad \phi_{j,j'}^{\ell,\ell'} = \#\{i \in [\![1, b]\!] \;:\; \mathbf{t}_j(i) + \mathbf{t}_{j'}(i) = e_\ell + e_{\ell'}\}.$$

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' can not be applied simultaneously to the same patient i at the same period ℓ. Hence we can write for $s \in [\![1, k-1]\!]$:

$$(40) \qquad N_{j,j'}^s = \sum \phi_{j,j'}^{\ell,\ell'}$$

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

By definition of vectors $\mathbf{t}_j(i)$, the value μ_i can be not equals zero only if $\mathbf{t}_j(i) + \mathbf{t}_{j'}(i) = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ for some periods ℓ', ℓ which are necessary 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 $u_{ij} = \mathbf{t}_j(i) + \mathbf{t}_{j'}(i)$, $u_{\ell\ell'} = \boldsymbol{e}_\ell + \boldsymbol{e}_{\ell'}$ and considering the element $\gamma_{\ell,\ell'} = \boldsymbol{e}_\ell' \mathbb{M} \boldsymbol{e}_{\ell'}$ of the matrix $\mathbb{M}$, we obtain:

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

For seeking of clarity in the following of this proof, we put $\phi^{\ell,\ell'} = \phi_{j,j'}^{\ell,\ell'}$. We introduce in the expression of μ the values of the elements $\gamma_{\ell,\ell'}$ of the matrix $\mathbb{M}$ given in Lemma 5. By summing the identical factors of each of the respective values θ_ℓ and $\theta_\ell \theta_{\ell'}$, we obtain:

$$\mu = -\theta_1\left(\phi^{1,2} + \cdots + \phi^{k-1,k}\right) - \cdots - \theta_s\left(\phi^{\ell,\ell+s} + \phi^{\ell+1,\ell+s+1} + \cdots + \phi^{k-s,k}\right) - \cdots$$

$$-\theta_m\left(\phi_{j,j'}^{1,m+1} + \cdots + \phi^{k-m,k}\right) +$$

$$(41) \quad \sum_{s=1}^{m-1} \theta_1\theta_{1+s}\left(\phi^{2,2+s} + \cdots + \phi^{k-s-1,k-1}\right) + \sum_{s=1}^{m-2} \theta_2\theta_{2+s}\left(\phi^{3,3+s} + \cdots + \phi^{k-s-2,k-2}\right)$$

$$+ \cdots + \sum_{s=1}^{m-u} \theta_u\theta_{u+s}\left(\phi^{u+1,u+1+s} + \phi^{u+2,u+2+s} + \cdots + \phi^{k-s-u,k-u}\right) + \cdots$$

$$+ \sum_{s=1}^{2} \theta_{m-2}\theta_{m-2+s}\left(\phi^{m-1,m-1+s} + \cdots + \phi^{k-s-(m-2),k-(m-2)}\right)$$

$$+ \theta_{m-1}\theta_m\left(\phi^{m,m+1} + \cdots + \phi^{k-m,k-m+1}\right).$$

Recall that identity (40) says that $N_{j,j'}^s = \phi^{1,1+s} + \phi^{2,2+s} + \cdots + \phi^{k-s-1,k-1} + \phi^{k-s,k}$. 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 (41) of μ becomes:

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

(42)

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

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

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 summation $\displaystyle\sum_{s=1}^{m-1}\sum_{t=1}^{m-s}\beta_{t,s}$ collects all the terms of the form $U_{t,s}\theta_{a,b}$ in the right side of Identity (42). In order to complete the determination of μ, note that:

Remark 26. Considering Identity (39) about $\phi_{j,j'}^{\ell,\ell'}$ and Remark 11 about the quantities $N_{j,j',i}^s$ and $\phi_{j,i}^{\ell}$, we find:

$$
\begin{aligned}
U_{t,s} &= \phi_{j,j'}^{t,t+s} + \phi_{i,j'}^{k-t-s+1,k-t+1} \\
&= \#\left\{ i : \mathbf{t}_j(i) + \mathbf{t}_{j'}(i) \in \{\boldsymbol{e}_t + \boldsymbol{e}_{t+s}, \boldsymbol{e}_{k-t+1} + \boldsymbol{e}_{k-(t+s)+1}\} \right\} \\
&= \sum_{i=1}^{b} N_{j,j',i}^s (\phi_{j,i}^t \phi_{j',i}^{t+s} + \phi_{j',i}^t \phi_{j,i}^{t+s}).
\end{aligned}
$$

Finally, the contribution μ of the term $\sum_{i=1}^{b} T_i' \, \mathbb{M} \, T_i$ to the element $\sigma^2 C_{j,j'}$ is:

$$
\begin{aligned}
\mu \;=\; & \sum_{s=1}^{m} N_{j,j'}^{s} \sum_{u=0}^{m-s} \theta_u \theta_{u+s} \;- \\
(43) \qquad & \sum_{s=1}^{m-1} \sum_{t=1}^{m-s} (\theta_t \theta_{t+s} + \theta_{t+1} \theta_{t+1+s} + \cdots + \theta_{m-s}\theta_m) \sum_{i=1}^{b} N_{j,j',i}^{s}(\phi_{j,i}^{t}\phi_{j',i}^{t+s} + \phi_{j',i}^{t}\phi_{j,i}^{t+s}) \quad .
\end{aligned}
$$

7.2.2. *Term $\sum_{i=1}^{b} T_i' \, (\mathbf{1}_k' \, \mathbb{M} \, \mathbf{1}_k)^{-1} \, \mathbb{M} \, \mathbf{1}_k \mathbf{1}_k' \, \mathbb{M} \, T_i$ on the right side of Identity (35).*

Note that the constant value $c = \mathbf{1}_k' \, \mathbb{M} \, \mathbf{1}_k$ in this summation is the sum of all elements of $\mathbb{M}$ given in Equation (11). So in the sequel we consider the term $c^{-1} \sum_{i=1}^{b} T_i' \, \mathbb{M} \, \mathbf{1}_k \mathbf{1}_k' \, \mathbb{M} \, T_i$.

Introduce the following notation for each treatment j_1 and each patient i :

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

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

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

Then the contribution of $c^{-1} \sum_{i=1}^{b} T_i' \, \mathbb{M} \, \mathbf{1}_k \mathbf{1}_k' \, \mathbb{M} \, T_i$ to the element $\sigma^2 C_{j_1,j_2}$ for two treatments j_1, j_2 not necessary distincts is

$$
(44) \qquad\qquad \omega_{j_1,j_2} = c^{-1} \sum_{i=1}^{b} k_{j_1,i} k_{j_2,i} \quad .
$$

Still with the aim of finding identities on the elements $C_{d,j,j}$ and $C_{d,j,j'}$ of the matrix C, we must determine the quantity $k_{j,i} = \mathbf{t}_j'(i) \, \mathbb{M} \, \mathbf{1}$.

When the treatment j is not applied to the ith patient, $k_{j,i} = 0$ because $\mathbf{t}_j(i) = \mathbf{0}_k$. Otherwise, it is applied only once, at some ℓth period and we have $k_{j,i} = \mathbf{t}_j'(i)\mathbb{M}\mathbf{1} = \sum_{\ell'=1}^{k} \gamma_{\ell,\ell'}$.

Recall that the sum of elements of the line ℓ in matrix $\mathbb{M}$ is given in Lemma 7: 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 $\forall \, \ell \in [\![1, m]\!] \cup [\![k-m+1, k]\!]$:

$$
(45) \qquad\qquad p_\ell - p_{m+1} = -a_0 a_\ell \quad .
$$

Now, let's determine the values of $n_{j,i}$ and $\phi_{j,i}^{\ell}$ for all $\ell \in [\![1, m]\!]$ that we have defined above. Recall that $\mathbf{t}_j(i) = \boldsymbol{e}_\ell$ if the treatment j is applied to the patient i at the ℓ-th period 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 patient i 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 patient i at one ℓth period for $\ell \in [\![1, k]\!]$ then $k_{j,i} = p_\ell$. Otherwise, if the treatment j is not applied to the patient i then $k_{j,i} = 0$. By consequence, we can express the quantity $k_{j,i}$ in the following form

$$
\begin{aligned}
k_{j,i} &= p_{m+1}n_{j,i} + \phi_{j,i}^1(p_1 - p_{m+1}) + \phi_{j,i}^2(p_2 - p_{m+1}) + \cdots \\
&\quad + \phi_{j,i}^m(p_m - p_{m+1}).
\end{aligned}
$$
(46)

By Formulas (10) and (45), we deduce that:

$$
\begin{aligned}
k_{j,i} &= a_0(a_0 n_{j,i} - a_1\phi_{j,i}^1 - a_2\phi_{j,i}^2 - \cdots - a_m\phi_{j,i}^m) \\
&= a_0\left(a_0 n_{j,i} - \sum_{\ell=1}^{m} a_\ell\phi_{j,i}^\ell\right) \quad .
\end{aligned}
$$
(47)

Recall that the contribution $\sum_{i=1}^{b} T_i'\,(\mathbf{1}_k'\,\mathbb{M}\,\mathbf{1}_k)^{-1}\,\mathbb{M}\,\mathbf{1}_k\mathbf{1}_k'\,\mathbb{M}\,T_i$ to element $\sigma^2 C_{j,j}$ is $\omega_{j,j} = c^{-1}\sum_i k_{j,i}^2$ (see (44)). By Identity (47), we have:

$$
k_{j,i}^2 = a_0^2\left\{a_0^2 n_{j,i}^2 + \sum_{\ell=1}^{m} a_\ell^2\phi_{j,i}^\ell - 2a_0\sum_{\ell=1}^{m} a_\ell n_{j,i}\phi_{j,i}^\ell\right\}
$$

because $\left(\phi_{j,i}^\ell\right)^2 = \phi_{j,i}^\ell \ \forall\, \ell \in [\![1, m]\!]$, and when $\ell \neq \ell'$, $\phi_{j,i}^\ell\phi_{j,i}^{\ell'} = 0$. By the facts

$$
\phi_j^\ell = \sum_{i=1}^{b} \phi_{j,i}^\ell = \sum_{i=1}^{b} n_{j,i}\phi_{j,i}^\ell \quad \text{and} \quad r = \sum_{i=1}^{b} n_{j,i}^2,
$$

we finally obtain:

$$c\, w_{j,j} = \sum_{i=1}^{b} k_{j,i}^2 \;=\; a_0^2 \left\{ a_0^2 r + \sum_{\ell=1}^{m} a_\ell^2 \phi_j^\ell - 2 a_0 \sum_{\ell=1}^{m} a_\ell \phi_j^\ell \right\}$$

(48)
$$= -a_0^2 \left\{ a_0(a_0 - 2a_0) r - \sum_{\ell=1}^{m} \phi_j^\ell a_\ell (a_\ell - 2a_0) \right\}$$

Now we search to determine the contribution $\omega_{j,j'} = c^{-1} \sum_{i=1}^{b} k_{j,i} k_{j',i}$, $j \neq j'$, to the element $\sigma^2 C_{j,j'}$. By Identity (46), we have:

$$k_{j,i} k_{j',i} \;=\; a_0^2 \left(a_0 n_{j,i} - \sum_{\ell=1}^{m} a_\ell \phi_{j,i}^\ell \right) \left(a_0 n_{j',i} - \sum_{\ell'=1}^{m} a_{\ell'} \phi_{j',i}^{\ell'} \right)$$

$$= a_0^2 \left\{ a_0^2 n_{d,j,i} n_{j',i} - a_0 \left(\sum_{\ell=1}^{m} a_\ell n_{j,i} \phi_{j',i}^\ell + \sum_{\ell=1}^{m} a_\ell n_{j',i} \phi_{j,i}^\ell \right) \right.$$

$$\left. \sum_{\ell=1}^{m} \sum_{\ell'=1}^{m} a_\ell a_{\ell'} \phi_{j,i}^\ell \phi_{j',i}^{\ell'} \right\}\,.$$

By the facts $\lambda_{j,j'} = \sum_{i=1}^{b} n_{j,i} n_{j',i}$ and

(49)
$$\phi_{j,j'}^{\ell*} = \sum_{i=1}^{b} (n_{j',i} \phi_{j,i}^\ell + n_{j,i} \phi_{j',i}^\ell) \quad \text{for all } \ell \in [\![1, m]\!] \quad,$$

we finally obtain:

$$c\, \omega_{j,j'} \;=\; \sum_{i=1}^{b} k_{j,i} k_{j',i}$$

(50)
$$= a_0^4 \lambda_{j,j'} - a_0^3 \sum_{\ell=1}^{m} a_\ell \phi_{j,j'}^{\ell*} + a_0^2 \sum_{\ell=1}^{m} \sum_{\ell'=1}^{m} a_\ell a_{\ell'} \sum_{i=1}^{b} \phi_{j,i}^\ell \phi_{j',i}^{\ell'} \quad.$$

7.2.3. *Conclusion of the proof of Lemma 12.*

From (35),we have:

$$C_{j,j} = \tau - \omega_{j,j} \quad \text{and} \quad C_{j,j'} = \mu - \omega_{j,j'} \quad.$$

where τ and μ come from the term $\sum_{i=1}^{b} T_i' \mathbb{M} T_i$ studied in Section 7.2.1 and $\omega_{j,j}$ and $\omega_{j,j'}$ come from the term $\sum_{i=1}^{b} T_i' (\mathbf{1}_k' \mathbb{M} \mathbf{1}_k)^{-1} \mathbb{M} \mathbf{1}_k \mathbf{1}_k' \mathbb{M} T_i$ studied in Section 7.2.2.

It suffice to collect the values of τ, μ, $\omega_{j,i}$ and $\omega_{j,j'}$ from Identities (38), (43), (48) and (50) to conclude that our Lemma 12 is true.

7.3. **Proof of Lemma 14.**

Firstly, as d is a BIBD, we have $\beta = \sum_{j=1}^{v} \sum_{j' \neq j} \lambda_{d,j,j'} = \sum_{j=1}^{v} \sum_{j' \neq j} \lambda = v(v-1)\lambda$
Secondly, we count β in this different manner:

$$\beta = \sum_{j=1}^{v} \sum_{j' \neq j} \lambda_{d,j,j'} = bk(k-1)$$

because there are b patients and exactly $k(k-1)$ distinct pairs of treatments by patient (recall that $k \leq v$) The identification of the two expressions of β prove the searched identity satisfied by λ:

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

7.4. **Proof of Lemma 15.**

We suppose that the design d is NNm-balanced. Then $N_{d,j,j'}^s$ is a constant N_d^s that we intend to establish.

We fix $s \in [\![1, m]\!]$. We compute with to manner the sum $\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N_{d,j,j'}^s$. Firstly, as the design is NNm-balanced, each $N_{d,j,j'}^s$ equals a constant N_d^s which does not depend on the choice j, j'. Then we have:

$$\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N_d^s = v(v-1) N_d^s \quad .$$

Secondly, we fixe one treatment j and suppose that a patient i receives this treatment. Recall that j is administered no more than once to a same patient. For the patient i, there exist $2 = \sum_{j' \neq j} N_{d,j,j',i}^s$ treatments at distance s to j if j is not applied in the first s or the last s periods (i.e.when $\sum_{\ell=1}^{s} \phi_{d,j,i}^\ell = 0$), otherwise $\phi_{d,j,i}^\ell = 1$ 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 to j . Then

$$(51) \qquad \sum_{j' \neq j} N_{d,j,j',i}^s = 2 - \sum_{\ell=1}^{s} \phi_{d,j,i}^\ell \quad .$$

Moreover j appears exactly r times in d. Then by considering firstly all patients i,

$$(52) \qquad \sum_{j' \neq j} N^s_{d,j,j'} = 2r - \sum_{\ell=1}^{s} \phi^\ell_{d,j}$$

and secondly Identity (21), we obtain the second expression of α:

$$\alpha = \sum_{j=1}^{v} \sum_{j' \neq j} N^s_{d,j,j'} = \sum_{j=1}^{v} (2r - \sum_{\ell=1}^{s} \phi^\ell_{d,j}) = 2rv - 2bs$$

As $rv = kb$ (see (4)), the identification of our two expressions of α implies the searched identity satisfied by N^s_d:

$$(ii) \qquad N^s_d = N^s_{d,j,j'} = \frac{2b(k-s)}{v(v-1)} \quad \forall j, j' \in [\![1, v]\!], j \neq j' \quad .$$

7.5. **Proof of Lemma 16.**

Let be an NNm-balanced design d with $k = v$ (i.e. the number of periods equals the number treatments). We have also $r = b$ because $rv = kb$.
We search to prove that for each $\ell \in [\![1, m]\!]$ the quantities $\phi^\ell_{d,j}$ and $\phi^{\ell*}_{d,j,j'}$ are independent of distinct treatments j, j' and to express them without j and j'.
Let be $s \in [\![1, m]\!]$. As d is an NNm-balanced design, from (ii) of Lemma 15 the quantity $N^s_{d,j,j'}$ is the constant $N^s_d = 2b(k-s)/v(v-1) = 2b(v-s)/v(v-1)$ since $k = v$.
From (52) and since $N^s_{d,j,j'}$ is the constant N^s_d for all $s \in [\![1, m]\!]$, we have:

$$(53) \qquad \sum_{\ell=1}^{s} \phi^\ell_{d,j} = 2r - (v-1)N^s_d \quad .$$

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

$$(54) \qquad \phi^s_{d,j} = \sum_{\ell=1}^{s} \phi^\ell_{d,j} - \sum_{\ell=1}^{s-1} \phi^\ell_{d,j} = \frac{2b}{v}$$

which is the identity expected by Lemma 16.
Now since $k = v$ and each treatment is administered at most once for each patient, each patient i receives each of the v distinct treatments once and only once. That means $n_{d,j,i} = 1$ for all $j \in [\![1, v]\!]$. Then Identity (49) becomes

$$(55) \qquad \phi^{\ell*}_{d,j,j'} = \phi^\ell_{d,j} + \phi^\ell_{d,j'} = \frac{4b}{v} \quad \forall \ \ell \in [\![1, m]\!]$$

and the Lemma is proved.

7.6. **Proof of Theorem 5.1.**

By the consequence of Lemma 12 (see remark 13), all the competitor designs have the same trace. Hence, by Proposition 10, the *universal optimality* of a design d for the model AR(m) is satisfied when the information matrix C_d of $\widehat{\gamma}$ is completely symmetric; that is to say that its extra-diagonal elements $C_{d,j,j'}$ are all independent of j, j' ($j \neq j'$) because the sum by line (and by column) of C_d is null (see (16)). According to hypothesis of Theorem 5.1, we will prove that each of the five terms of $C_{d,j,j'}$ in Lemma 12 is independent to j, j'.

As the design is NNm-balanced BIBD(v, b, r, k, λ), Identities (i) and (ii) of Lemmas 14 and 15 imply that two of the terms of $C_{d,j,j'}$ are independent to j, j'. If Identities $(iii), (iv)$ and (v) of Theorem 5.1 hold then the three others terms of $C_{d,j,j'}$ are independent to j and j'.

Remark 27. Note that, for a better presentation of Identity (v) in Theorem 5.1, we have replace the values s, t appearing in $C_{d,j,j'}$ by the values ℓ, ℓ'. This is possible as explained below. Suppose that Identity (v) holds for each ℓ and ℓ' such that $\ell \neq \ell' \in [\![1, m]\!]$. Then, by the symmetry in ℓ, ℓ' of the expression $\alpha_{\ell,\ell'} = N_{j,j',i}^{|\ell-\ell'|}(\phi_{j,i}^\ell \phi_{j',i}^{\ell'} + \phi_{j',i}^\ell \phi_{j,i}^{\ell'})$, we can suppose that $\ell < \ell'$ and we have $\alpha_{\ell,\ell'} = N_{j,j',i}^{|\ell-\ell'|}(\phi_{j,i}^\ell \phi_{j',i}^{\ell+|\ell-\ell'|} + \phi_{j',i}^\ell \phi_{j,i}^{\ell+|\ell-\ell'|})$. Then

$$(56) \qquad \alpha_{\ell,\ell'} = N_{j,j',i}^s(\phi_{j,i}^t \phi_{j',i}^{t+s} + \phi_{j',i}^t \phi_{j,i}^{t+s})$$

with $s = |\ell - \ell'| \in [\![1, m-1]\!]$ and $\ell = t \in [\![1, m-s]\!]$ as expected in the summation in the expression of $C_{d,j,j'}$. Conversely, let $s \in [\![1, m-1]\!]$ and $t \in [\![1, m-s]\!]$ as in the summation in $C_{d,j,j'}$. Then the two distinct periods $\ell = t$ and $\ell' = t + s$ in $[\![1, m]\!]$ verify Identity (56).

In the following, we will prove that Identities $(iii), (iv)$ and (v) of Theorem 5.1 are coherent. More precisely, for each identity, we will suppose that the term in the left side is a constant and we prove that it equals to the right side.

7.6.1. *Identity* (iii). For each treatment j, we first need to establish the following identity:

$$(57) \qquad \sum_{j' \neq j} \phi_{d,j,j'}^{\ell*} = (k-2)\phi_{d,j}^\ell + 2r \quad .$$

Proof. We develop $\sum_{j' \neq j} \phi_{j,j'}^{\ell*}$:

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

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

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

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

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

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 the ℓth and the $(k - \ell + 1)$th periods (i.e. $\phi_{j',i}^{\ell} = 1$ and not 0 for this two treatments). By the sum of α and β, Identity (57) is proved. $\qquad \square$

From Formulas (57) and (21), we obtain finally:

$$(58) \qquad \sum_{j=1}^{v} \sum_{j' \neq j} \phi_{d,j,j'}^{\ell*} = 2b(k-2) + 2rv = 2b(k-2) + 2bk = 4b(k-1)$$

because $rv = bk$. Suppose that each $\phi_{d,j,j'}^{\ell*}$ is independent to j, j'. Then $\sum_{j=1}^{v} \sum_{j' \neq j} \phi_{d,j,j'}^{\ell*} = v(v-1)\phi_{dj,i,j'}^{\ell*}$. Thus from (58), we obtain Identity

$$(iii) \quad \phi_{d,j,j'}^{\ell*} = \frac{4b(k-1)}{v(v-1)} \quad .$$

7.6.2. *Identity* (iv). Consider two distinct periods ℓ and ℓ' and set 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 $\phi_{d,j_1,i}^{\ell} = \phi_{d,j_2,i}^{\ell} = \phi_{d,j_3,i}^{\ell'} = \phi_{d,j_4,i}^{\ell'} = 1$ and the other values are zero; by consequence:

$$\sum_{j=1}^{v} \sum_{j' \neq j} \phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} = \phi_{d,j_1,i}^{\ell}(\phi_{d,j_3,i}^{\ell'} + \phi_{d,j_4,i}^{\ell'}) + \phi_{d,j_2,i}^{\ell}(\phi_{d,j_3,i}^{\ell'} + \phi_{d,j_4,i}^{\ell'}) = 4 \quad .$$

and

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

If the quantity $\sum_{i=1}^{b} \phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'}$ is independent of j, j' then, by the same reasoning as for (iii), we find:

$$(iv) \quad \sum_{i=1}^{b} \phi_{d,j,i}^{\ell} \phi_{d,j',i}^{\ell'} = \frac{b(2 + 2(1 - \delta_{\ell,\ell'}))}{v(v-1)} \quad \text{for all } \ell, \ell' \in [\![1, m]\!]$$

where $\delta_{\ell,\ell'}$ is the Kronecker symbol.

7.6.3. *Identity* (v). We fix $s \in [\![1, m-1]\!]$ and $t \in [\![1, m-s]\!]$. By the same reasoning as above, for a patient i, four distinct treatments $j_1, \ldots, j_4$ are applied at the respective distinct periods $t, k - t + 1, t + s, k - (t + s) + 1$. Then

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

But, in this sum, we have count 4 situations in which two treatments among $j_1, \ldots, j_4$ are applied at distance s and 4 situations in which two treatments among $j_1, \ldots, j_4$ are applied at distance $\geq m > s$ because $k > 2m$. For the firsts 4 situations, we have $N_{d,j,j',i}^{s} = 1$ for the 4 others we have $N_{d,j,j',i}^{s} = 0$. Then

$$
\begin{aligned}
\sum_{j=1}^{v} \sum_{j' \neq j} N_{d,j,j',i}^{s} (\phi_{d,j,i}^{t} \phi_{d,j',i}^{t+s} + \phi_{d,j',i}^{t} \phi_{d,j,i}^{t+s}) &= \sum_{j=1}^{v} \sum_{j' \neq j} N_{d,j,j',i}^{s} (\phi_{d,j,i}^{t} \phi_{d,j',i}^{t+s} + \phi_{d,j',i}^{t} \phi_{d,j,i}^{t+s}) \\
&= \frac{1}{2} \beta_{t,s} = 4 \quad .
\end{aligned}
$$

Hence, if each quantity $\sum_{i=1}^{b} N_{d,j,j',i}^{s} (\phi_{d,j,i}^{t} \phi_{d,j',i}^{t+s} + \phi_{d,j',i}^{t} \phi_{d,j,i}^{t+s})$ is independent to j, j' ($j \neq j'$), the following identity holds:

$$(v) \quad \sum_{i=1}^{b} N_{d,j,j',i}^{s} (\phi_{d,j,i}^{t} \phi_{d,j',i}^{t+s} + \phi_{d,j',i}^{t} \phi_{d,j,i}^{t+s}) = \frac{4b}{v(v-1)} \quad .$$

7.7. **Proof of Theorem 5.2.**

From Theorem 5.1 and Lemma 16 our Theorem is proved

Acknowledgments

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